1 Appendix C: Search Strategies and Review Protocols

CLINICAL QUESTIONS

A.1.1 Scoping searches

Scoping searches were undertaken on the following websites and databases (listed in alphabetical order) in August 2012 to provide information for scope development and project planning. Browsing or simple search strategies were employed.

Guidelines/website	Systematic review/economic evaluations
• Canadian Medical Association Infobase • Centers for Disease Control and Prevention • Clinical Knowledge Summaries • Department of Health • Guidelines International Network (GIN) • Healthtalk Online • National Health and Medical Research Council (Australia) • National Institute for Health and Clinical Excellence (NICE) - published & in development guidelines • National Institute for Health and Clinical Excellence (NICE) - Topic Selection • National Institute for Innovation and Improvement • New Zealand Guidelines Group • NICE Evidence • Professional bodies/associations • Royal Colleges • Scottish Intercollegiate Guidelines Network (SIGN) • Trip Database • US National Guideline Clearinghouse • YouthHealth Talk	• Cochrane Database of Systematic Reviews (CDSR) • Database of Abstracts of Reviews of Effects (DARE) • DUETS (UK Database of Uncertainties about the Effects of Treatments) • Health Economic Evaluations Database (HEED) • Health Technology Assessment (HTA) Database • NHS Economic Evaluation Database (NHS EED) • NIHR Health Technology Assessment • NIHR Health Services and Delivery Research (HS&DR) Programme • PROSPERO • TRIP Database

A.1.2 Main searches

Sources searched for the guideline

- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley)
- Health Technology Assessment Database – HTA (Wiley)
- EMBASE (Ovid)
- MEDLINE (Ovid)

- MEDLINE In-Process (Ovid)

A.1.3 Identification of evidence for clinical questions

The searches were conducted between January 2013 and August 2014. The re-run searches took place on 2nd December 2014.The aim of the searches was to identify evidence for each of the clinical questions being asked.

The MEDLINE search strategies are presented below. These were translated for use in all of the other databases.

A.2 Review question search strategies

A.2.1 Search strategy review question B (2)

What is the most effective method of collecting respiratory samples from children unable to expectorate spontaneously?

Table 1: search strategy B (2)

Medline Strategy, searched 08/05/2014 **Database: Ovid MEDLINE(R) 1946 to April Week 5 2014** **Search Strategy:**
1 Mycobacterium tuberculosis/ (35828)
2 exp Tuberculosis/ (154666)
3 (tb* or tuberculos* or koch*).tw. (196409)
4 1 or 2 or 3 (250554)
5 Sputum/ (17162)
6 ((sputum* or mucus* or phlegm*) adj4 (induce* or induct*)).tw. (2883)
7 Gastric Lavage/ (1898)
8 (gastric* adj4 (irrigat* or lavage* or wash*)).tw. (1307)
9 Bronchoalveolar Lavage/ (2572)
10 ((bronchopulmonary or bronchial* or bronchioalveolar or bronchio alveolar or broncho alveolar or bronchoalveolar or lung*) adj4 (irrigat* or aspirat* or lavage* or wash*)).tw. (28918)
11 BAL.tw. (10738)
12 (tracheal* adj4 (lavage* or aspirat* or wash*)).tw. (1453)
13 diagnostic techniques, respiratory system/ or respiratory function tests/ or bronchoscopy/

Medline Strategy, searched 08/05/2014
Database: Ovid MEDLINE(R) 1946 to April Week 5 2014
Search Strategy:

(58179)

14 ((lung* or respiratory*) adj4 (test* or technique* or aspirat*)).tw. (16050)

15 (bronchoscop* or nebuliz* or nebulis*).tw. (25455)

16 ((cough* or laryng*) adj4 (swab* or plate* or smear*)).tw. (196)

17 ((nasal or nasopharyn*) adj4 (irrigat* or lavage* or aspirat* or swab* or wash*)).tw. (6872)

18 (chest adj2 (physio* or physical therap*)).tw. (766)

19 ((forced or directed) adj2 (exhalat* or expirat* or cough)).tw. (14455)

20 (chest* adj2 (shak* or percuss* or vibrat*)).tw. (166)

21 huff*.tw. (270)

22 or/5-21 (147442)

23 4 and 22 (10456)

24 animals/ not humans/ (3843498)

25 23 not 24 (10163)

26 limit 25 to english language (6604)

27 ADOLESCENT/ or MINORS/ (1600886)

28 (adolescen$ or teen$ or youth$ or young or juvenile? or minors or highschool$).ti,ab. (517783)

29 exp CHILD/ (1535207)

30 (child$ or schoolchild$ or "school age" or "school aged" or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab. (1031134)

31 exp INFANT/ (929906)

32 (infan$ or neonat$ or newborn$ or baby or babies).ti,ab. (532400)

33 exp PEDIATRICS/ or exp PUBERTY/ (57874)

34 (p?ediatric$ or pubert$ or prepubert$ or pubescen$ or prepubescen$).ti,ab. (237346)

35 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (3388089)

36 26 and 35 (1739)

A.2.2 Search strategy review questions C (3), D (4), E (5), G (7), H (8)

C: Apart from culture, what other tests are effective in establishing an accurate diagnosis of active respiratory TB in adults with suspected respiratory TB?

D: Apart from culture, what other tests are effective in establishing an accurate diagnosis of active respiratory TB in children and young people with suspected respiratory TB

E: In the presence of a negative culture, what other tests may support an accurate positive diagnosis in people with suspected respiratory TB?

G: Apart from culture, what other tests are effective in establishing an accurate diagnosis of active non-respiratory TB in people with suspected non-respiratory TB?

H: In the presence of a negative culture, what other tests may support a positive diagnosis in people with suspected active non-respiratory TB?

Table 2: search strategies C (3), D (4), E (5), G (7), H (8)

Medline Strategy, searched 16/12/2013 **Database: Ovid MEDLINE(R) 1946 to November Week 3 2013** **Search Strategy:**
1 exp Tuberculosis/ (158365)
2 (tb* or tuberculos* or koch*).tw. (203986)
3 1 or 2 (254071)
4 Microscopy/ (26751)
5 Radiography/ (24704)
6 X-Rays/ (16462)
7 Radiology/ (15249)
8 ((microscop* or x-ray* or "x ray*" or CT* genome* or radiolog* or radiograph*) adj4 diagnos*).tw. (30825)
9 Culture Techniques/ (47464)
10 Culture Media/ (105895)
11 Tuberculin test/ (12078)
12 Interferon gamma release tests/ (393)
13 ((Lowenstein adj4 Jensen) or Ogawa*).tw. (2056)
14 (serological adj4 (typ* or test* or assay* or diagnos* or technique* or analys*)).tw. (18264)
15 ((haemagglutination* or radioimmuno*) adj4 (typ* or test* or assay* or diagnos* or technique* or analys*)).tw. (11047)

Medline Strategy, searched 16/12/2013
Database: Ovid MEDLINE(R) 1946 to November Week 3 2013
Search Strategy:

16 (("enzyme linked" or enzyme-linked) adj1 (immunospot* or immunosorbent*)).tw. (63458)

17 ((ELISA* or Quantiferon* or ELISPOT* or T-SPOT* or "T SPOT*") adj4 (typ* or test* or assay* or diagnos* or technique* or analys*)).tw. (56786)

18 (automated adj4 liquid adj4 culture).tw. (54)

19 ("Blood culture*" or "Mycobacteria Growth Indicator*" or BACTEC* or MGIT*).tw. (19084)

20 (microculture* adj4 techniqu*).tw. (90)

21 ("septi-chek AFB" or difco* or probtec*).tw. (532)

22 ("mb bact*" or mb-bact*).tw. (89)

23 (ESP adj4 myco*).tw. (9)

24 ("Microscopic Observation Drug Susceptibility" or MODS).tw. (1246)

25 (colorimetric adj4 (typ* or test* or assay* or diagnos* or technique* or analys*)).tw. (6513)

26 "tuberculin skin test".tw. (2645)

27 neopterin*.tw. (2600)

28 Griess*.tw. (1858)

29 (MTT adj4 reduction* adj4 (typ* or test* or assay* or diagnos* or technique* or analys*)).tw. (441)

30 biopsy.tw. (207258)

31 ((C-reactive adj4 protein) or CRP).tw. (45817)

32 (("erythrocyte sedimentation*" or ESR) adj4 diagnos*).tw. (213)

33 ("interferon gamma" adj4 (typ* or test* or assay* or diagnos* or technique* or analys*)).tw. (2088)

34 IGRA.tw. (403)

35 Mantoux*.tw. (1349)

36 (phage-based* or "phage based" or mycobacteriophage* or "adenosine desaminase*" or ADA).tw. (7865)

37 (antigen adj4 detection* adj4 (typ* or test* or assay* or diagnos* or technique* or analys*)).tw.

Medline Strategy, searched 16/12/2013
Database: Ovid MEDLINE(R) 1946 to November Week 3 2013
Search Strategy:

(2190)

38 Nucleic acid amplification techniques/ (6954)

39 (("single stranded conformation polymorphism" or "nucleic acid*" or nucleic-acid* or NAAT* or "isothermal amplification" or "restriction enzyme fragmentation*") adj4 (typ* or test* or assay* or diagnos* or technique* or analys*)).tw. (6446)

40 (Genexpert or gene-xpert or "gene xpert").tw. (92)

41 (Polymerase adj2 reaction adj2 single adj2 strand adj2 conformation adj2 polymorphism*).tw. (1569)

42 (PCR-SSCP or PCR SSCP).tw. (2679)

43 (Amplicor adj4 MTB adj4 (typ* or test* or assay* or diagnos* or technique* or analys*)).tw. (40)

44 COBAS*.tw. (1658)

45 taqman.tw. (8139)

46 (("ligase chain reaction" or LCX*) adj4 (typ* or test* or assay* or diagnos* or technique* or analys*)).tw. (392)

47 (("Mycobacterium tuberculos*" or MTB) adj4 (typ* or test* or assay* or diagnos* or technique* or analys*)).tw. (3262)

48 ("BD-ProbeTec" or "BD ProbeTec" or Amplified-M or "Amplified M" or "Loop-mediated Isothermal Amplification" or LAMP or AccuProbe or GenoQuick or FluoroType or IS6110 or rif-lip or "rif lip").tw. (13361)

49 (("Gen Probe" or Gen-Probe or Genotype or "INNO LIPA" or INNO-LIPA or Genotype or "Mycobacterial interspersed repetitive*" or MIRU or MDR-TB) adj4 (typ* or test* or assay* or diagnos* or technique* or analys*)).tw. (11518)

50 Molecular Diagnostic Techniques/ (5779)

51 ("molecular diagnos*" adj4 (typ* or test* or assay* or diagnos* or technique* or analys*)).tw. (7862)

52 or/4-51 (724285)

53 3 and 52 (29127)

54 animals/ not humans/ (3974347)

Medline Strategy, searched 16/12/2013 Database: Ovid MEDLINE(R) 1946 to November Week 3 2013 Search Strategy:	
55	53 not 54 (26934)
56	limit 55 to english language (19753)

A.2.3 Search strategy review questions I (9)

In children with active TB receiving drug treatment, are intermittent dosing regimens as effective as daily drug treatment regimens in reducing mortality and morbidity?

Table 3: search strategy I (9)

Medline Strategy, searched 15/01/2013 Database: Ovid MEDLINE(R) 1946 to January Week 1 2013	
1	exp Tuberculosis/ (147685)
2	(tuberculosis* or tb or koch*).tw. (134341)
3	1 or 2 (183775)
4	Drug Administration Schedule/ (79476)
5	Antitubercular Agents/ad (3872)
6	Antibiotics, Antitubercular/ad (484)
7	((dose or dosage or dosing) adj3 (frequency* or frequencies or variation*)).tw. (4414)
8	((intermittent* or daily) adj3 (treatment* or regime* or chemotherap*)).tw. (15613)
9	(treatment adj regime*).tw. (19558)
10	ad.fs. (1024631)
11	or/4-10 (1068084)
12	3 and 11 (10251)
13	animals/ not humans/ (3653831)
14	12 not 13 (8943)
15	limit 14 to english language (5621)
16	ADOLESCENT/ or MINORS/ (1496701)

Medline Strategy, searched 15/01/2013 Database: Ovid MEDLINE(R) 1946 to January Week 1 2013
17 (adolescen$ or teen$ or youth$ or young or juvenile? or minors or highschool$).ti,ab. (474079)
18 exp CHILD/ (1452433)
19 (child$ or schoolchild$ or "school age" or "school aged" or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl?).ti,ab. (959013)
20 exp INFANT/ (884411)
21 (infan$ or neonat$ or newborn$ or baby or babies).ti,ab. (501096)
22 exp PEDIATRICS/ or exp PUBERTY/ (54230)
23 (p?ediatric$ or pubert$ or prepubert$ or pubescen$ or prepubescen$).ti,ab. (215213)
24 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 (3184932)
25 15 and 24 (1878)

A.2.4 Search strategy review question K (11),

How should the standard recommended regimen be adapted to accommodate comorbidities or co-existing conditions that affect the choice of regimen for the treatment of active respiratory and non-respiratory TB?

Table 4: search strategies K (11))

Medline Strategy, searched 10/10/2013 Database: Ovid MEDLINE(R) 1946 to September Week 4 2013 Search Strategy:
1 exp tuberculosis/ (157720)
2 (tuberculosis* or tb or koch*).tw. (148267)
3 1 or 2 (199049)
4 ANTITUBERCULAR AGENTS/ (27890)
5 ((tuberculostatic or antitubercular) adj4 (agent* or drug*)).tw. (1669)
6 4 or 5 (28367)
7 Isoniazid/ (13937)
8 isoniazid.tw. (11385)

Medline Strategy, searched 10/10/2013
Database: Ovid MEDLINE(R) 1946 to September Week 4 2013
Search Strategy:

9 (rifampicin or rifampin).tw. (17972)

10 Rifampin/ (15381)

11 Pyrazinamide/ (2689)

12 pyrazinamide.tw. (2800)

13 ethambutol.tw. (4013)

14 Ethambutol/ (3540)

15 Streptomycin/ (18172)

16 Streptomycin*.tw. (16090)

17 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (77612)

18 exp HIV/ (89687)

19 exp HIV Infections/ (239061)

20 (hiv* or aids*).tw. (293203)

21 (acquired adj4 immunodeficien* adj4 syndrome*).tw. (14999)

22 (human adj4 immunodeficien* adj4 virus*).tw. (73865)

23 (lymphadenopath* adj4 assoc* adj4 virus*).tw. (315)

24 (lav-htlv-iii or lav htlv iii).tw. (207)

25 (htlv-III or htlv iii).tw. (1655)

26 (human* adj4 t?cell* adj4 leuk?emia*).tw. (3)

27 (human* adj4 t?cell* adj4 lymphotrop*).tw. (1)

28 or/18-27 (344992)

29 exp Liver Diseases/ or exp Renal Insufficiency/ or exp acute kidney injury/ (556406)

30 ((renal or kidney* or liver) adj4 (fail* or insufficien* or injury or injuries or dysfunction* or disease*)).tw. (277225)

31 or/29-30 (681483)

32 exp Diabetes Mellitus/ (317677)

Medline Strategy, searched 10/10/2013
Database: Ovid MEDLINE(R) 1946 to September Week 4 2013
Search Strategy:

33 (diabete* or diabetic*).tw. (389381)

34 (Type* adj4 ("2" or "II" or two*) adj4 (diabete* or diabetic*)).tw. (75659)

35 (Type* adj4 ("1" or "I" or one*) adj4 (diabete* or diabetic*)).tw. (37338)

36 ((Ketosis-resistant* or stable*) adj4 (diabete* or diabetic*)).tw. (651)

37 ((Maturit* or adult* or slow*) adj4 onset* adj4 (diabete* or diabetic*)).tw. (2408)

38 ((Non-insulin* or Non insulin* or Noninsulin*) adj4 depend* adj4 (diabete* or diabetic*)).tw. (11470)

39 NIDDM.tw. (6756)

40 or/32-39 (442595)

41 exp SUBSTANCE-RELATED DISORDERS/ (373062)

42 ((substance* or drug*) adj4 (addict* or depend* or abus* or habit* or disorder*)).tw. (77371)

43 ((alcohol* or amphetamine* or cocaine or morphine or heroin or methadone or inhalant or marijuana or opioid* or phencyclidine* or psychoses or tobacco or cannabis or hashish or marihuana or narcotic* or tobacco or nicotine* or glue*) adj4 (abus* or habit* or disorder* or depend* or sniff*)).tw. (61090)

44 or/41-43 (424679)

45 exp pregnancy/ or exp Breast Feeding/ (734089)

46 (pregnan* or gestation*).tw. (426533)

47 (breast feeding or breastfeeding or "breast milk expression").tw. (22864)

48 (breast milk adj4 (expression* or pump* or collect*)).tw. (484)

49 or/45-48 (832724)

50 exp Eye Diseases/ or exp Vision Disorders/ (447643)

51 ((eye* or visual* or vision*) adj4 (impair* or disorder* or diabilit* or dysfunction* or disease*)).tw. (30378)

52 (metamorphopsia* or blind* or hemeralopia* or macropsia*).tw. (207728)

53 or/50-52 (643022)

Medline Strategy, searched 10/10/2013 Database: Ovid MEDLINE(R) 1946 to September Week 4 2013 Search Strategy:	
54	28 or 31 or 40 or 44 or 49 or 53 (3084054)
55	3 and 17 and 54 (7525)
56	Animals/ not Humans/ (3956431)
57	55 not 56 (7440)
58	limit 57 to english language (5702)

A.2.5 Search strategy review question L (12), M (13), P (16)

L: In adults with drug susceptible, active respiratory TB receiving drug treatment, what duration of regimen is the most effective in reducing mortality and morbidity?

i) Do regimens of less than 6 months present additional risks to the patient, and if so, in which patients?

ii) Do regimens of more than 6 months present additional benefits to the patient, and if so, in which patients?

M: In children and young people with drug susceptible, active respiratory TB receiving the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol), what duration of regimen is the most effective in reducing mortality and morbidity?

i) Do regimens of less than 6 months present additional risks to the patient, and if so, in which patients?

ii) Do regimens of more than 6 months present additional benefits to the patient, and if so, in which patients?

P: In people with drug susceptible, active non-respiratory TB receiving the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol), what duration of regimen is the most effective in reducing mortality and morbidity?

i) Do regimens of less than 6 months present additional risks to the patient

Table 5: search strategy L (12), M (13), P (16)

Medline Strategy, searched 11/03/2015 Database: Ovid MEDLINE(R1946 to February Week 4 2013 Search Strategy:	
1	exp Tuberculosis/ (148766)
2	(tuberculosis* or tb or koch*).tw. (135878)
3	1 or 2 (185453)
4	Isoniazid/ (13170)
5	isoniazid.tw. (10359)

Medline Strategy, searched 11/03/2015
Database: Ovid MEDLINE(R1946 to February Week 4 2013
Search Strategy:

6 4 or 5 (17416)

7 (rifampicin or rifampin).tw. (16211)

8 Rifampin/ (14184)

9 7 or 8 (21131)

10 6 and 9 (5761)

11 Pyrazinamide/ (2447)

12 pyrazinamide.tw. (2477)

13 11 or 12 (3659)

14 ethambutol.tw. (3624)

15 Ethambutol/ (3310)

16 14 or 15 (5074)

17 13 and 16 (1332)

18 10 and 17 (1104)

19 ((6 month* or six month* or six-month* or month* or 'short course*' or duration) adj3 (treatment* or regime* or chemotherap*)).tw. (66998)

20 18 or 19 (67827)

21 Meta-Analysis.pt. (37985)

22 Meta-Analysis as Topic/ (12497)

23 Review.pt. (1752900)

24 exp Review Literature as Topic/ (6591)

25 (metaanaly$ or metanaly$ or (meta adj2 analy$)).tw. (45376)

26 (review$ or overview$).ti. (240954)

27 (systematic$ adj4 (review$ or overview$)).tw. (40846)

28 ((quantitative$ or qualitative$) adj4 (review$ or overview$)).tw. (3146)

29 ((studies or trial$) adj1 (review$ or overview$)).tw. (6502)

30 (integrat$ adj2 (research or review$ or literature)).tw. (3124)

31 (pool$ adj1 (analy$ or data)).tw. (7703)

32 (handsearch$ or (hand adj2 search$)).tw. (4426)

33 (manual$ adj2 search$).tw. (2459)

34 or/21-33 (1890196)

35 animals/ not humans/ (3687915)

Medline Strategy, searched 11/03/2015 Database: Ovid MEDLINE(R1946 to February Week 4 2013 Search Strategy:
36 34 not 35 (1762141)

A.2.6 Search strategy review question N (14), Q (17)

N: In people with active TB receiving the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol), do corticosteroids as an adjunct to the antituberculosis drug treatment regimen decrease morbidity and mortality compared to the standard recommended regimen alone?

Q: In people with active non-respiratory TB receiving the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol), do corticosteroids as an adjunct to the antituberculosis drug treatment regimen decrease morbidity and mortality compared to the standard recommended regimen alone?

Table 4: Search strategy N (14), Q (17)

Medline Strategy, searched 22/05/2015 Database: Ovid MEDLINE(R) 1946 to May Week 2 2013 Search Strategy:
1 exp tuberculosis/ (151326)
2 (tuberculosis* or tb or koch*).tw. (139501)
3 1 or 2 (189466)
4 exp Adrenal Cortex Hormones/ (326166)
5 (corticoid* or corticosteroid* or glucorticoid*).tw. (73294)
6 ((hormone* adj1 adrenal adj1 cortex) or (adrenal adj1 cortex adj1 hormone*)).tw. (527)
7 or/4-6 (354848)
8 exp Prednisolone/ (43007)
9 exp Dexamethasone/ (42935)
10 exp Hydrocortisone/ (61390)
11 exp Adrenocorticotropic Hormone/ (44355)
12 (Prednisolon* or Dexamethason* or Corticotropin* or Corticotrophin* or Hydrocortison* or Adrenocorticotropic* or Adrenocorticotrophin* or acth* or fludrocortisone* or flupredisolone* or methylprednisolone* or prednimustine* or pregnadienetriol* or pregenedione*).tw. (121298)

Medline Strategy, searched 22/05/2015 Database: Ovid MEDLINE(R) 1946 to May Week 2 2013 Search Strategy:	
13	or/8-12 (206919)
14	7 or 13 (405256)
15	3 and 14 (3992)
16	Animals/ not Humans/ (3756152)
17	15 not 16 (3801)

A.2.7 Search strategy review question O (15), R (18), X (24)

O: In people with active TB receiving the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol), does surgery as an adjunct to an antituberculosis drug treatment regimen decrease morbidity and mortality compared to the standard recommended regimen alone?

R: In people with active non-respiratory TB receiving the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol), does surgery as an adjunct to the antituberculosis drug treatment regimen decrease morbidity and mortality compared to the standard recommended regimen alone?

X: In people with drug-resistant TB, does surgery as an adjunct to an antituberculosis drug treatment regimen decrease morbidity and mortality compared with an antituberculosis drug regimen alone?

Table 5: search strategy O (15), R (18), X (24)

Medline Strategy, searched 23/05/2015 Database: Ovid MEDLINE(R) 1946 to May Week 3 2013 Search Strategy:	
1	exp tuberculosis/ (151413)
2	(tuberculosis* or tb or koch*).tw. (139602)

Medline Strategy, searched 23/05/2015
Database: Ovid MEDLINE(R) 1946 to May Week 3 2013
Search Strategy:

3 1 or 2 (189577)

4 exp Tuberculosis/su [Surgery] (9052)

5 3 or 4 (189577)

6 General Surgery/ (32557)

7 Surgical Procedures, Operative/ (48210)

8 Pneumonectomy/ (19905)

9 (lung* adj1 volume adj1 reduction*).tw. (1081)

10 pneumonectom*.tw. (6192)

11 (excision adj3 lung*).tw. (173)

12 THORACIC SURGERY, VIDEO-ASSISTED/ (3835)

13 ((video-assist* or video assist*) adj3 (thoracic* or thoracoscop*)).tw. (3704)

14 (vatss or vats).tw. (2035)

15 Debridement/ (11407)

16 (debride* or reconstruct* or graft*).tw. (365815)

17 Thoracic surgery/ (10013)

18 (thoracic adj surg*).tw. (13186)

19 thoracoscopy/ (5686)

20 (thoracoscop* or pleuroscop*).tw. (8563)

21 (pleural adj1 endoscop*).tw. (6)

22 Lobectom*.tw. (12036)

23 ((surg* adj1 resection*) or shunt* or fixation*).tw. (165174)

24 Mediastinoscopy/ (1378)

25 Pleurodesis/ (1021)

26 Pericardiocentesis/ (608)

27 Pericardiectomy/ (859)

Medline Strategy, searched 23/05/2015
Database: Ovid MEDLINE(R) 1946 to May Week 3 2013
Search Strategy:

28 Curettage/ (3471)

29 Spinal Fusion/ (16137)

30 exp Decompression, Surgical/ (9648)

31 Spinal Cord Compression/ (9303)

32 (spinal adj3 compression*).tw. (5059)

33 (Mediastinoscop* or pleurodes* or Pleurectom* or Decortication* or Pericardiectom* or Pericardiocentes* or Pericardiotom* or Curettage* or pericardiectam* or decompression* or pericardot*).tw. (40090)

34 (Wedge adj1 resection).tw. (2263)

35 (Surg* adj1 excision).tw. (13251)

36 (lung adj1 resection).tw. (2555)

37 (laser adj1 photo adj1 coagulat*).tw. (17)

38 ((Bone or spine or spinal) adj3 fusion).tw. (5503)

39 (Abscess adj1 drainage).tw. (715)

40 (Bronchial adj (stent or stenosis*)).tw. (545)

41 or/6-40 (719642)

42 5 and 41 (8023)

43 Animals/ not Humans/ (3757869)

44 42 not 43 (7905)

A.2.8 Search strategy review question S (19)

In people with suspected or confirmed active TB, which relative risk factors are associated with a higher level of: i) multidrug resistance, or ii) any drug resistance?

Table 6: search strategy S (19)

Medline Strategy, searched 09/07/2014 **Database: Ovid MEDLINE(R) 1946 to June Week 4 2014** **Search Strategy**
1 exp Tuberculosis/ (156070)
2 Mycobacterium tuberculosis/ (36318)
3 (tb or tuberculos* or koch*).tw. (146257)
4 1 or 2 or 3 (201093)
5 tuberculosis, multidrug-resistant/ or extensively drug-resistant tuberculosis/ (4849)
6 exp Drug Resistance/ (243534)
7 treatment failure/ (26824)
8 Recurrence/ (160149)
9 Treatment Outcome/ (634734)
10 ((drug* or antibiotic* or penicillin* or med* or inject* or therap* or regimen* or multidrug* or multi-drug* or agent* or antituberculos* or anti-tubercolos*) adj4 (resist* or refractory or nonrespon* or non-respon* or respon* or recur* or relaps* or fail*)).tw. (411954)
11 (DR-TB or DRTB or DR TB).tw. (57)
12 (treatment* adj1 (fail* or outcome*)).tw. (43395)
13 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (1316182)
14 4 and 13 (23817)
15 animals/ not humans/ (3873259)
16 14 not 15 (22653)
17 limit 16 to english language (16955)
18 exp great britain/ (303686)
19 (britain$ or "united kingdom$" or uk or GB or england$ or northern ireland$ or wales$ or scotland$).tw,in,hw. (1107385)
20 (british or english or scottish or scots or welsh or northern irish).tw,in,hw. (1864361)
21 (london$ or birmingham$ or leeds$ or glasgow$ or sheffield$ or edinburg$ or liverpool$ or manchester$ or bristol$ or belfast$ or cardiff$ or nottingham$ or newcastle$ or aberdeen$).tw,in,hw. (681717)

Medline Strategy, searched 09/07/2014 Database: Ovid MEDLINE(R) 1946 to June Week 4 2014 Search Strategy
22 18 or 19 or 20 or 21 (3089903)
23 17 and 22 (1600)

A.2.9 Search strategy review question U (21), V (22), W (23)

U: In people with drug-resistant TB (excluding MDR- and XDR-TB), what is the most effective regimen of antituberculosis drugs for reducing mortality and morbidity?

V: In people with drug resistant TB (excluding MDR- and XDR-TB) receiving drug treatment, what duration of regimen is the most effective in reducing mortality and morbidity?

W: In people with drug-resistant TB, are intermittent dosing regimens as effective as daily drug treatment regimens in reducing mortality and morbidity?

Table 9: search strategy U (21), V (22), W (23)

Medline Strategy, searched 15/07/2013 Database: Ovid MEDLINE(R) 1946 to July Week 1 2013 Search Strategy:
1 exp Tuberculosis/ (156015)
2 (tuberculosis* or tb or koch*).tw. (146057)
3 or/1-2 (196562)
4 exp Drug Resistance, Multiple/ (24819)
5 ((drug* or treat* or med* or agent* or antibiotic* or penicillin* or inject* or therap* or regimen*) adj3 resist*).tw. (131679)
6 (DR-TB or DRTB or DR TB).tw. (48)
7 or/4-6 (145033)
8 3 and 7 (8505)
9 Tuberculosis, Multidrug-Resistant/ (4558)
10 or/8-9 (10229)
11 Isoniazid/ or Rifampin/ or Rifabutin/ or Pyrazinamide/ or Ethambutol/ or Streptomycin/ (42681)
12 (Isoniazid* or Rifampicin* or Rifampin* or Rifabutin* or Pyrazinamide* or Ethambutol* or Streptomycin*).tw. (40710)
13 Capreomycin/ or Cycloserine/ or Amikacin/ or Azithromycin/ or Clarithromycin/ (14017)
14 (Capreomycin* or Capreomicin* or Cycloserin* or Amikacin* or Azithromycin* or Clarithromycin* or Moxifloxacin*).tw. (21624)
15 or/11-14 (80195)
16 10 and 15 (3735)

Medline Strategy, searched 15/07/2013 Database: Ovid MEDLINE(R) 1946 to July Week 1 2013 Search Strategy:	
17	Animals/ not Humans/ (3906592)
18	16 not 17 (3603)
19	limit 18 to english language (2967)
20	Ofloxacin/ (6091)
21	(Ofloxacin* or Levofloxacin*).tw. (9755)
22	Ciprofloxacin/ (10935)
23	Ciprofloxacin*.tw. (17850)
24	Kanamycin/ (6068)
25	Kanam?cin*.tw. (7428)
26	Prothionamide/ (167)
27	(Prothionamid* or Protionamid*).tw. (189)
28	Linezolid*.tw. (3120)
29	Gatifloxacin*.tw. (1951)
30	Clofazimine/ (940)
31	Clofazimin*.tw. (926)
32	or/20-31 (42319)
33	10 and 32 (770)
34	Animals/ not Humans/ (3906592)
35	33 not 34 (727)
36	limit 35 to english language (601)

A.2.10 Search strategy review question Z (26)

For people receiving drug treatment for active TB who experience treatment interruptions, what approach to re-establishing appropriate treatment is the most effective in reducing mortality and morbidity?

Table10: search strategy Z (26)

Medline Strategy, searched 12/08/2014 Database: Ovid MEDLINE(R) 1946 to July Week 5 2014 Search Strategy:	
1	exp Tuberculosis/ (157146)
2	Mycobacterium tuberculosis/ (36611)

Medline Strategy, searched 12/08/2014
Database: Ovid MEDLINE(R) 1946 to July Week 5 2014
Search Strategy:

3 (tb or tuberculos* or koch*).tw. (147394)

4 1 or 2 or 3 (202551)

5 Isoniazid/ or Rifampin/ or Rifabutin/ or Pyrazinamide/ or Ethambutol/ or Streptomycin/ (42617)

6 (Isoniazid* or Rifampicin* or Rifampin* or Rifabutin* or Pyrazinamide* or Ethambutol* or Streptomycin*).tw. (40449)

7 5 or 6 (58376)

8 4 or 7 (239599)

9 Medication Adherence/ or Patient Compliance/ (55373)

10 Treatment failure/ (27142)

11 Drug administration schedule/ (86193)

12 Withholding treatment/ (9667)

13 Continuity of patient care/ (14711)

14 *Time factors/ (1126)

15 ((drug* or medicat* or treat* or regimen or therap*) adj2 (adher* or complian* or complying or refus* or declin* or drop-out or drop out or withhold* or withdraw*)).tw. (36117)

16 ((drug* or medicat* or treat* or regimen or therap*) adj2 (interrupt* or intermittent* or miss* or stop* or break* or cessation* or restart* or reintroduc* or re-introduc* or extend* or disturb* or disrupt* or suspend* or discontinue* or cease* or irregular*)).tw. (46224)

17 or/9-16 (252117)

18 "Drug-Related Side Effects and Adverse Reactions"/ (21885)

19 Antitubercular Agents/ae [Adverse Effects] (2684)

20 (hepatotoxic* or nephrotoxic*).tw. (31843)

21 ((undesirable or adverse) adj (reaction* or effect* or event* or outcome*)).tw. (197201)

22 ("side effect*" or side-effect*).tw. (167625)

23 ("poor absorb*" or "low absorb*" or (inadequate adj3 dos*)).tw. (976)

24 or/18-23 (397488)

Medline Strategy, searched 12/08/2014 Database: Ovid MEDLINE(R) 1946 to July Week 5 2014 Search Strategy:
25 17 or 24 (612217)
26 8 and 25 (10238)
27 animals/ not human/ (3900724)
28 26 not 27 (9667)
29 limit 28 to english language (7212)

A.2.11 Search strategy review question AA (27), BB (28)

AA: For people in congregate settings (including hospitals, schools, residential homes, homeless shelters, prisons and religious establishments) who have with suspected or confirmed active TB, what infection control measures are the most effective in preventing transmission of TB infection to others?

BB: For people who have active TB who are not in hospital but who are in congregate settings (for example schools, residential homes or homeless shelters), what infection control measures are the most effective in preventing transmission of TB infection to others?

Table 11: search strategy AA (27), BB (28)

Medline Strategy, searched 16/09/2014 Database: Ovid MEDLINE(R) 1946 to September Week 1 201 Search Strategy:
1 Mycobacterium tuberculosis/ (36976)
2 exp Tuberculosis/ (161104)
3 (tb or tuberculos* or koch*).tw. (149631)
4 1 or 2 or 3 (206953)
5 Infection Control/ (19200)
6 Cross Infection/ (46552)
7 Communicable Disease Control/ (18145)
8 infectious disease transmission, patient-to-professional/ or infectious disease transmission, professional-to-patient/ or Disease outbreaks/ or Disease Transmission, Infectious/ (72600)
9 Occupational Diseases/ (75189)

Medline Strategy, searched 16/09/2014
Database: Ovid MEDLINE(R) 1946 to September Week 1 201
Search Strategy:

10 ((infect* or disease* or contamin* or prevent* or minimi*) adj4 (transmit* or transmis* or communic*)).tw. (62473)

11 *mass screening/ (43577)

12 ((tuberculos* or tb) adj2 (screen* or surveillance*)).tw. (1814)

13 Respiratory Protective Devices/ (1651)

14 Patient Isolation/ (3218)

15 Patient Isolators/ (665)

16 Length of stay/ (60043)

17 Air Pollution, Indoor/ (9626)

18 Masks/ (3402)

19 Ventilation/ (4654)

20 Air microbiology/ (6529)

21 Time to treatment/ (817)

22 (time adj2 treat*).tw. (18768)

23 ((sputum or cough or respiratory or inhal* or expectorate*) adj4 (practice* or behaviour or behavior or etiquette* or hygiene or microbiology or procedure*)).tw. (2441)

24 ((face* or cough* or droplet*) adj4 shield*).tw. (144)

25 (aerosol-generat* or "aerosol generat*").tw. (501)

26 (patient* adj4 (isolat* or quarantine or separate or separation or separated or segregate or segregation or segregated)).tw. (51201)

27 ((isolat* or quarantine or separate or separation or separated or segregate or segregation or segregated) adj4 (time or duration or length or period*)).tw. (19749)

28 (airborne adj4 (precaution* or transmission* or isolation*)).tw. (539)

29 mask*.tw. (50900)

30 (respirator* adj4 (control* or protect* or filter* or atmosphere* or particulate* or purif* or equipment)).tw. (9446)

31 ((positive adj air adj pressure adj respirator*) or PAPR).tw. (61)

Medline Strategy, searched 16/09/2014
Database: Ovid MEDLINE(R) 1946 to September Week 1 201
Search Strategy:

32	(portable adj4 particulate adj4 filter*).tw. (4)
33	((isolation or isolated or single) adj4 (room* or ward* or bed* or area*)).tw. (7570)
34	(transmission adj4 (precaution* or control)).tw. (2945)
35	(negative adj1 pressure adj1 (room* or facilit*)).tw. (41)
36	(sputum adj4 booth*).tw. (2)
37	(ventilat* or air-flow* or airflow* or "air change").tw. (129549)
38	((ultraviolet or UV) adj4 (extract* or irradicat* or fan* or light*)).tw. (18849)
39	((High adj1 Efficiency adj1 Particulate adj1 Air*) or HEPA).tw. (1373)
40	("Ultraviolet Germicidal Irradiation" or UVGI).tw. (61)
41	((restrict* or reduce*) adj4 movement*).tw. (4723)
42	(infect* adj1 control* adj1 (team* or staff or consultant* or nurse* or doctor*)).tw. (659)
43	((barrier or infection*) adj4 nurse*).tw. (1081)
44	(auto* adj door* adj close*).tw. (4)
45	congregate.tw. (631)
46	((reduc* or avoid* or manag*) adj4 (overcrowd* or mass* or gathering*)).tw. (15013)
47	or/5-46 (689857)
48	4 and 47 (14718)
49	animals/ not human/ (3915350)
50	48 not 49 (14059)
51	limit 50 to english language (10326)

NOTE: Some references from a 2008 WHO Report were identified that had not been picked up by this strategy. On investigation, this was due to the study design filters that were added (as required by the Review Protocol). For the rerun searches it was decided to run the search without filters and with a date limit of 1st Jan 2008 – 2nd December 2014.

A.2.12 Search strategy review questions CC (29), DD (30)

CC: For people who have active TB, i) what duration of isolation is necessary to minimise the risk of infection to others, and ii) what prognostic factors help determine if a person poses a risk of infection to others and should remain in isolation?

DD: For people who have active TB that is suspected to be MDR-TB:

i) what prognostic factors help determine if a person poses a risk of infection to others and should remain in isolation?
ii) ii) what duration of isolation is necessary to minimise the risk of infection to others?

Table 12: search strategy CC (29), DD (30)

Medline Strategy, searched 27/08/2014 **Database: Ovid MEDLINE(R) 1946 to August Week 2 2014** **Search Strategy:**
1 Mycobacterium tuberculosis/ (36656)
2 exp Tuberculosis/ (157244)
3 (tb or tuberculos* or koch*).tw. (147541)
4 1 or 2 or 3 (202708)
5 Patient Isolation/ (3205)
6 Infection Control/ (19115)
7 "Predictive Value of Tests"/ (146096)
8 Length of stay/ (59782)
9 Risk Assessment/ (179479)
10 (risk* adj4 infect*).tw. (46856)
11 (patient* adj4 (isolat* or quarantine or separate or separation or separated or segregate or segregation or segregated)).tw. (50958)
12 ((isolat* or quarantine or separate or separation or separated or segregate or segregation or segregated) adj4 (time or duration or length or period*)).tw. (19664)
13 Prognosis/ (366323)
14 (prognosis or prognoses or prognostic).tw. (346052)
15 or/5-14 (989007)

Medline Strategy, searched 27/08/2014 Database: Ovid MEDLINE(R) 1946 to August Week 2 2014 Search Strategy:	
16	4 and 15 (11343)
17	animals/ not human/ (3904075)
18	16 not 17 (11123)
19	limit 18 to english language (7931)

A.2.13 Search strategy review question HH (34)

HH: According to their risk factors, which people with latent TB infection should receive drug treatment to prevent the development of active TB?

Table 13: search strategy HH (34)

Medline Strategy, searched 04/02/2014 Database: Ovid MEDLINE(R) 1946 to January Week 4 2014 Search Strategy:	
1	exp Tuberculosis/ (151509)
2	Mycobacterium tuberculosis/ (34665)
3	(latent adj4 (tb or tuberculos*)).tw. (2534)
4	(ltb or tb or tuberculos* or koch*).tw. (142112)
5	or/1-4 (195928)
6	exp Antitubercular Agents/ (51831)
7	((antitubercul* or anti-tubercul*) adj4 (drug* or agent*)).tw. (6102)
8	or/6-7 (53605)
9	5 or 8 (214547)
10	Risk/ or Risk Factors/ or Risk Assessment/ (746113)
11	risk?.tw. (1157957)
12	"Signs and Symptoms"/ (407)
13	(sign* adj2 symptom*).tw. (50571)

Medline Strategy, searched 04/02/2014 Database: Ovid MEDLINE(R) 1946 to January Week 4 2014 Search Strategy:	
14	or/10-13 (1491521)
15	9 and 14 (15048)
16	animals/ not human/ (3776805)
17	15 not 16 (14579)
18	limit 17 to english language (11586)

A.2.14 Search strategy review question II (35)

II a: For people with latent TB infection in which drug resistance is not suspected, which regimen is the most effective in preventing the development of active TB?

II b For people with latent TB infection in which drug resistance (excluding MDR- or XDR-TB) is suspected, which regimen is the most effective in preventing the development of active TB?

Table 14: search strategy II (35)

Medline Strategy, searched 21/01/2014 Database: Ovid MEDLINE(R) 1946 to January Week 2 2014 Search Strategy:	
1	exp Tuberculosis/ (151363)
2	Mycobacterium tuberculosis/ (34598)
3	(laten* adj4 (tb* or tubercul*)).tw. (2718)
4	ltb*.tw. (6812)
5	1 or 2 or 3 or 4 (172938)
6	Isoniazid/ (13381)
7	isoniazid.tw. (10659)
8	Rifampin/ (14537)
9	(rifampicin or rifampin).tw. (16706)
10	Pyrazinamide/ (2517)
11	pyrazinamide.tw. (2570)
12	or/6-11 (34724)

Medline Strategy, searched 21/01/2014 Database: Ovid MEDLINE(R) 1946 to January Week 2 2014 Search Strategy:
13 5 and 12 (15009)
14 limit 13 to english language (9768)
15 animals/ not human/ (3772463)
16 14 not 15 (9250)

A.3 Study Design Filters

The MEDLINE systematic reviews (SR), Randomized Controlled Trials (RCT) and Observational search filters were used where required for the review questions above are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

SR and RCT filters were appended to Review Questions: C (3), D (4), E (5), G (7), H (8), I (9), K (11), L (12), M (13), N (14), O (15), P (16), Q (17), R (18), U (21), V (22), W (23), X (24), Z (26), AA (27), BB (28), CC (29), DD (30), HH (34) (SR only), II (35)

Observational filters were appended to Review Questions: O (15), P(16), Q (17), R (18), X (24), Z (26), AA (27), BB (28), CC (29), DD (30), HH (34)

Table 15: Systematic Review Filter

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases. Economic evaluations
Systematic Review
1. Meta-Analysis.pt.
2. Meta-Analysis as Topic/
3. Review.pt.
4. exp Review Literature as Topic/
5. (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw.
6. (review$ or overview$).ti.
7. (systematic$ adj5 (review$ or overview$)).tw.
8. ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw.
9. ((studies or trial$) adj2 (review$ or overview$)).tw.
10. (integrat$ adj3 (research or review$ or literature)).tw.
11. (pool$ adj2 (analy$ or data)).tw.
12. (handsearch$ or (hand adj3 search$)).tw.
13. (manual$ adj3 search$).tw.
14. or/1-13

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

Economic evaluations

15. animals/ not humans/

16. 14 not 15

RCT

1. Randomized Controlled Trial.pt.

2. Controlled Clinical Trial.pt.

3. Clinical Trial.pt.

4. exp Clinical Trials as Topic/

5. Placebos/

6. Random Allocation/

7. Double-Blind Method/

8. Single-Blind Method/

9. Cross-Over Studies/

10. ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.

11. (random$ adj3 allocat$).tw.

12. placebo$.tw.

13. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.

14. (crossover$ or (cross adj over$)).tw.

15. or/1-14

16. animals/ not humans/

17. 15 not 16

Observational

1. Observational Study as Topic/

2. Observational Study/

3. Epidemiologic Studies/

4. exp Case-Control Studies/

5. exp Cohort Studies/

6. Cross-Sectional Studies/

7. Controlled Before-After Studies/

8. Historically Controlled Study/

9. Interrupted Time Series Analysis/

10. Comparative Study.pt.

11. case control$.tw.

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.
Economic evaluations
12. case series.tw.
13. (cohort adj (study or studies)).tw.
14. cohort analy$.tw.
15. (follow up adj (study or studies)).tw.
16. (observational adj (study or studies)).tw.
17. longitudinal.tw.
18. prospective.tw.
19. retrospective.tw.
20. cross sectional.tw.
21. or/1-20

A.4 Health economics search strategy

A.4.1 Economic evaluations and quality of life data

Sources searched to identify economic evaluations

- NHS Economic Evaluation Database – NHS EED (Wiley)
- Health Economic Evaluations Database – HEED (Wiley)
- Embase (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)
- PubMed

Search filters to retrieve economic evaluations and quality of life papers were appended to all of the search strategies to identify relevant evidence between February 2012 and August 2014. The re-run searches took place in December 2015.

Table 16: Health economics filters

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.	
Economic evaluations	
1	Economics/
2	exp "Costs and Cost Analysis"/
3	Economics, Dental/
4	exp Economics, Hospital/
5	exp Economics, Medical/
6	Economics, Nursing/
7	Economics, Pharmaceutical/
8	Budgets/

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.
Economic evaluations
9 exp Models, Economic/
10 Markov Chains/
11 Monte Carlo Method/
12 Decision Trees/
13 econom$.tw.
14 cba.tw.
15 cea.tw.
16 cua.tw.
17 markov$.tw.
18 (monte adj carlo).tw.
19 (decision adj2 (tree$ or analys$)).tw.
20 (cost or costs or costing$ or costly or costed).tw.
21 (price$ or pricing$).tw.
22 budget$.tw.
23 expenditure$.tw.
24 (value adj2 (money or monetary)).tw.
25 (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26 or/1-25
Quality of life
1 "Value of Life"/
2 Quality-Adjusted Life Years/
3 quality adjusted life.tw.
4 (qaly$ or qald$ or qale$ or qtime$).tw.
5 disability adjusted life.tw.
6 daly$.tw.
7 Health Status Indicators/
8 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
9 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
10 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
11 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
12 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
13 (euroqol or euro qol or eq5d or eq 5d).tw.
14 (hye or hyes).tw.
15 health$ year$ equivalent$.tw.
16 (health adj3 state adj3 utilit$).tw.
17 (utilit$ adj3 (health$ or valu$ or weight$ or scor$ or measure$)).tw.
18 (hui or hui1 or hui2 or hui3).tw.
19 disutili$.tw.
20 rosser.tw.
21 quality of wellbeing.tw.
22 quality of well-being.tw.
23 qwb.tw.
24 willingness to pay.tw.
25 standard gamble$.tw.
26 time trade off.tw.

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.	
Economic evaluations	
27	time tradeoff.tw.
28	tto.tw.
29	(preferen$ weight$ or health state preferen$).tw.
30	or/1-30

A.5 Review protocols – 2015 updated

A.5.1 REVIEW PROTOCOLS – CLINICAL

RQ A. What are the most effective methods for i) sputum smear microscopy and ii) sputum culture in establishing an accurate diagnosis of active pulmonary TB?

	Details	Additional comments
Review question A(i)	What are the most effective methods for sputum smear microscopy in establishing an accurate diagnosis of active respiratory TB?	The GDG felt a formal systematic review would not be necessary as there is already relevant information available – HPA Standard Operating Procedure – which outlines the minimum standards for clinical and public health microbiology. We thought an induction and sign posting to the HPA would be more appropriate.

	Details	Additional comments
Review question A(ii)	What are the most effective methods for sputum culture in establishing an accurate diagnosis of active respiratory TB?	As above

	Details	Additional comments
Review question B	What is the most effective method of collecting respiratory samples from children unable to expectorate spontaneously?	
Objectives	To establish which approach to sputum collection is the most acceptable to children unable to produce a sample spontaneously, and most effective in establishing an accurate diagnosis of TB.	
Type of review	Intervention	
Language	English	
Study design	Any comparative study	
Status	Published papers (full text only)	
Population	Children and young people with suspected respiratory TB	
Diagnostic tool(s)	Different approaches to collecting sputum samples	Includes: • sputum induction • gastric lavage • bronchoalveolar lavage/ bronchoscopy • cough swab • nasopharyngeal aspirate • chest physiotherapy
Comparator	Other approaches to collecting sputum samples	
Outcomes	• Smear-positive • Culture-positive • Genetic test-positive (PCR, NAAT) • Volume of sample • Number of collection events required to make a diagnosis • Time to diagnosis or treatment initiation (from start of symptoms or start of diagnostic efforts) • Acceptability of approach (from patient, carer and clinician perspectives) • Safety re: infection control • Adverse events • Health-related quality of life	

	• Resource use and cost	
Other criteria for inclusion/exclusion of studies	Include Papers comparing differing approaches to collecting sputum samples against each other Children and young people (<18 years) with suspected respiratory TB Exclude Adults Case studies, case series and narrative reviews	
Search strategies	Any comparative study	
Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Where a randomised crossover study is included, the data from the first treatment phase only will be extracted • Subgroup analysis will be undertaken by age, where appropriate	
Identified key studies	Systematic reviews Maciel EL, Brotto LD, Sales CM, Zandonade E & Sant'anna CC (2010) Gastric lavage in the diagnosis of pulmonary tuberculosis in children: a systematic review. Rev Saude Publica 44(4): 735-42 Studies Abadco DL & Steiner P (1992) Gastric lavage is better than bronchoalveolar lavage for isolation of Mycobacterium tuberculosis in childhood pulmonary tuberculosis. Pediatr Infect Dis J 11(9): 735-8 Baghaei P, Tabarsi P, Farnia P, Radaei AH, Kazempour M, Faghani YA, Mirsaeidi M, Novin A, Chitsaz E, Mansouri D, Masjedi MR & Velayati AA (2011) Utility of Gastric Lavage for Diagnosis of Tuberculosis in Patients who are Unable to Expectorate Sputum. J Glob Infect Dis 3(4): 339-43 Hatherill M, Hawkridge T, Zar HJ, Whitelaw A, Tameris M, Workman L, Geiter L, Hanekom WA & Hussey G (2009) Induced sputum or gastric lavage for community-based diagnosis of childhood pulmonary tuberculosis? Arch Dis Child	

	94(3): 195-201 Jones FL Jr (1966) The relative efficacy of spontaneous sputa, aerosol-induced sputa, and gastric aspirates in the bacteriologic diagnosis of pulmonary tuberculosis. Dis Chest 50(4): 403-8 Kang YA, Lee HW, Hwang SS, Um SW, Han SK, Shim YS & Yim JJ (2007) Usefulness of whole-blood interferon-gamma assay and interferon-gamma enzyme-linked immunospot assay in the diagnosis of active pulmonary tuberculosis. Chest 132(3): 959-65 Maciel EL, Peres RL, do Prado TN, Macedo CR, Palaci M, Vinhas SA, Dietze R, Johnson JL & Struchiner CJ (2010) Saline nebulization before gastric lavage in the diagnosis of pulmonary tuberculosis in children and adolescents. J Trop Pediatr 56(6): 458-9 Okutan O, Kartaloglu Z, Kilic E, Bozkanat E & Ilvan A (2003) Diagnostic contribution of gastric and bronchial lavage examinations in cases suggestive of pulmonary tuberculosis. Yonsei Med J 44(2): 242-8 Rahbar M & Hajia M (2007) Value of gastric lavage for diagnosis of pulmonary tuberculosis. Pak J Med Sci 23(1): 51-53 Singh M, Moosa NV, Kumar L & Sharma M (2000) Role of gastric lavage and broncho-alveolar lavage in the bacteriological diagnosis of childhood pulmonary tuberculosis. Indian Pediatr 37(9): 947-51 Somu N, Swaminathan S, Paramasivan CN, Vijayasekaran D, Chandrabhooshanam A, Vijayan VK & Prabhakar R (1995) Value of bronchoalveolar lavage and gastric lavage in the diagnosis of pulmonary tuberculosis in children. Tuber Lung Dis 76(4): 295-9 Zar H, Hanslo D, Apolles P, et al (2005) Induced sputum versus gastric lavage for microbiological confirmation if pulmonary tuberculosis in infants and young children: a prospective study. Lancet 365: 130 -134	

Review question C (3)	Apart from culture, what other tests are effective in establishing an accurate diagnosis of active respiratory TB in adults with suspected respiratory TB?	
Objectives	To establish which test is the most effective in adults in establishing an accurate diagnosis of active respiratory TB whilst the results of culture are awaited. To determine which diagnostic method is associated with the shortest time from start of symptoms or start of diagnostic efforts to diagnosis or treatment initiation.	
Type of review	Diagnostic	
Language	English	
Study design	Test-and-treat RCTs, quasi-RCTs, systematic reviews, cross-sectional studies (each test under examination is performed on every patient)	
Status	Published papers (full text only)	
Population	Adults with suspected respiratory TB	
Diagnostic tool(s)	Diagnostic tests for active respiratory TB	
Comparator	Culture	
Outcomes	• Diagnostic accuracy – sensitivity, specificity, positive predictive value, negative predictive value etc • Time to diagnosis or treatment initiation (from start of symptoms or start of diagnostic efforts) • Prognostic value of tests • Acceptability of approach to patent or healthcare worker • Adverse events • Downstream treatment outcomes, including mortality, cure, treatment success, treatment failure, relapse • Health-related quality of life • Resource use and cost	Time to diagnosis or treatment initiation (from start of symptoms or start of diagnostic efforts) – important to note service organisation (centralised vs localised)
Other criteria for inclusion/exclusion of studies	<u>Include</u> Papers comparing differing diagnostic methods against each other Adults with suspected TB Commercial tests	Diagnostic methods for active respiratory TB include: • culture techniques, such as: routine solid media (e.g. Lowenstein-Jensen, Ogawa), automated liquid culture (e.g. BACTEC, MGIT), microculture techniques (e.g. MODS, MABA),

	Sample size ≥30, unless pooled in a meta-analysis Test-and-treat RCTs, quasi-RCTs, systematic reviews, cross-sectional studies <u>Exclude</u> Children and young people (<18 years) Case-control, case studies, case series and narrative reviews Reference standard is not culture; others to be confirmed with GDG Tests are not conducted concomitantly In-house tests	colorimetric assays (e.g. nitrate reductase assay (Griess method), MTT reduction test, MABA, REMA, TEMA), blood culture, urine culture • microscopy • radiology: x-ray, CT • bronchial biopsy – histology and microbiology • blood tests – C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) • IGRA • tuberculin skin tests, such as the Mantoux test • molecular testing – methods include: PCR, single-stranded conformation polymorphism, nucleic acid probe, isothermal amplification, restriction enzyme fragmentation – HTA review will be incorporated • next-generation / whole genome sequencing • phage-based techniques • adenosine deaminase (ADA) • scoring systems (i.e. combined approaches) Means of collecting sputum samples in adults unable to expectorate spontaneously will not be assessed, although the accuracy of tests conducted upon induced samples will be considered alongside tests conducted upon spontaneously produced samples
Search strategies	Test-and-treat RCTs, quasi-RCTs, systematic reviews, cross-sectional studies	
Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and	

	further summarized in evidence statements • Where a randomised crossover study is included, the data from the first treatment phase only will be extracted • Analysis will be undertaken by site of disease, where possible • Subgroup analysis will be undertaken for people with HIV, where appropriate • Subgroup analysis will be undertaken for people with a negative culture, where appropriate	
Identified key studies	Systematic reviews Dinnes J et al. (2007) A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technology Assessment 11(3):1-196 Ling, D I, Flores LL et al. (2008) Commercial nucleic-acid amplification tests for diagnosis of pulmonary tuberculosis in respiratory specimens: meta-analysis and meta-regression. PLoS One 3: e1536 Pai M, Flores LL, Hubbard A et al. (2004) Nucleic acid amplifiaction tests in the diagnosis of tuberculous pleuritis: a systematic review and meta-analysis. BMC Infectious Diseases 4: 6 Kalantri S, Pai M, Pascopella L et al. (2005) Bacteriophage-based tests for the detection of Mycobacterium tuberculosis in clinical specimens: a systematic review and meta-analysis. BMC Infectious Diseases 5:59 Metcalfe JZ, Everett CK, Steingart KR et al. (2011) Interferon-gamma release assays for active pulmonary tuberculosis diagnosis in adults in low- and middle-income countries: systematic review and meta-analysis. Journal of Infectious Diseases 204: S1120-S1129 Sester M, Sotgiu G, Lange C et al. (2011) Interferon-release assays for the diagnosis of active tuberculosis: a systematic review and meta-analysis. European Respiratory Journal 37: 100-11 Flores LL, Steingart KR, Dendukuri N	

	et al. (2011) Systematic review and meta-analysis of antigen detection tests for the diagnosis of tuberculosis. Clinical and Vaccine Immunology: 1616-27 Liang QL, Shi HZ, Wang K et al. (2008) Diagnostic accuracy of adenosine deaminase in tuberculous pleurisy: a meta-analysis. Respiratory Medicine 102: 744-54 Studies van Cleeff MR, Kivihya Ndugga LE, Meme H et al. (2005) The role and performance of chest X-ray for the diagnosis of tuberculosis: a cost-effectiveness analysis in Nairobi, Kenya. BMC Infectious Diseases 5 Diel R, Loddenkemper R, Niemann S, Meywald-Walter K & Nienhaus A (2011) Negative and positive predictive value of a whole-blood interferon-γ release assay for developing active tuberculosis: an update. Am J Respir Crit Care Med 183(1): 88-95 Drobniewski FA (2000) A clinical, microbiological and economic analysis of a national service for the rapid molecular diagnosis of tuberculosis and rifampicin resistance in Mycobacterium tuberculosis. Journal of Medical Microbiology 49:271-278 Tu HZ, Chen YS, Lin YE et al. (2011) Combination of molecular assay and clinical evaluation for early confirmation of tuberculosis cases. Clinical Microbiology and Infection 17: 712-4 Michos AG, Daikos GL, Tzanetou K et al. (2006) Detection of mycobacterium tuberculosis DNA in respiratory and nonrespiratory specimens by the Amplicor MTB PCR. Diagnostic Microbiology and Infectious Disease 54: 121-6 Kibiki GS, Mulder B, van der Ven AJ, Sam N, Boeree MJ, van der Zanden A & Dolmans WM (2007) Laboratory diagnosis of pulmonary tuberculosis in TB and HIV endemic settings and the contribution of real time PCR for M. tuberculosis in bronchoalveolar lavage fluid. Trop Med Int Health 12(10): 1210-7	

	Details	Additional comments
Review question D (4)	Apart from culture, what other tests are effective in establishing an accurate diagnosis of active respiratory TB in children and young people with suspected respiratory TB?	
Objectives	To establish which test is the most effective in children and young people in establishing an accurate diagnosis of active respiratory TB whilst the results of culture are awaited. To determine which diagnostic method is associated with the shortest time from start of symptoms or start of diagnostic efforts to diagnosis or treatment initiation.	
Type of review	Diagnostic	
Language	English	
Study design	Test-and-treat RCTs, quasi-RCTs, systematic reviews, cross-sectional studies (each test under examination is performed on every patient)	
Status	Published papers (full text only)	
Population	Children and young people with suspected respiratory TB	
Diagnostic tool(s)	Diagnostic tests for active respiratory TB	
Comparator	Culture, or combined approach	
Outcomes	• Diagnostic accuracy – sensitivity, specificity, positive predictive value, negative predictive value etc • Time to diagnosis or treatment initiation (from start of symptoms or start of diagnostic efforts) • Prognostic value of tests • Acceptability of approach to patent or healthcare worker • Adverse events • Downstream treatment outcomes, including mortality, cure, treatment success, treatment failure, relapse • Health-related quality of life • Resource use and cost	Time to diagnosis or treatment initiation (from start of symptoms or start of diagnostic efforts) – important to note service organisation (centralised vs localised)
Other criteria for inclusion/exclusion of studies	<u>Include</u> Papers comparing differing diagnostic methods against each other Children and young people (< 18 years) with suspected TB Commercial tests	Diagnostic methods for active respiratory TB include: • culture techniques, such as: routine solid media (e.g. Lowenstein-Jensen, Ogawa), automated liquid culture (e.g. BACTEC, MGIT), microculture

	Sample size ≥30, unless pooled in a meta-analysis Test-and-treat RCTs, quasi-RCTs, systematic reviews, cross-sectional studies <u>Exclude</u> Adults Case-control, case studies, case series and narrative reviews Reference standard is not culture**,** or a combined approach confirmed with GDG Tests are not conducted concomitantly In-house tests	techniques (e.g. MODS, MABA), colorimetric assays (e.g. nitrate reductase assay (Griess method), MTT reduction test, MABA, REMA, TEMA), blood culture, urine culture • microscopy • radiology: x-ray, CT • bronchial biopsy • IGRA • tuberculin skin tests, such as the Mantoux test • molecular testing – methods include: PCR, single-stranded conformation polymorphism, nucleic acid probe, isothermal amplification, restriction enzyme fragmentation – HTA review will be incorporated • next-generation / whole genome sequencing • phage-based techniques • adenosine deaminase (ADA) • scoring systems (i.e. combined approaches), such as the Keith Edwards score
Search strategies	Test-and-treat RCTs, quasi-RCTs, systematic reviews, cross-sectional studies	
Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Where a randomised crossover study is included, the data from the first treatment phase only will be extracted • Analysis will be undertaken by site of disease, where possible • Subgroup analysis will be	

	undertaken for children and young people with HIV, where appropriate • Subgroup analysis will be undertaken for those under 5, where appropriate • Subgroup analysis will be undertaken for people with a negative culture, where appropriate	
Identified key studies	Systematic reviews Machingaidze S, Wiysonge CS, Gonzalez-Angulo Y, Hatherill M, Moyo S, Hanekom W & Mahomed H (2011) The utility of an interferon gamma release assay for diagnosis of latent tuberculosis infection and disease in children: a systematic review and meta-analysis. Pediatr Infect Dis J 30(8): 694-700 Pearce EC, Woodward JF, Nyandiko WM, Vreeman RC & Ayaya SO (2012) A systematic review of clinical diagnostic systems used in the diagnosis of tuberculosis in children. AIDS Research and Treatment 2012 Studies Delacourt C, Poveda JD, Chureau C, Beydon N, Mahut B, de Blic J, Scheinmann P, Garrigue G (1995) Use of polymerase chain reaction for improved diagnosis of tuberculosis in children. Journal of Pediatrics 126(5 pt 1): 703-9 Fauville-Dufaux M, Waelbroeck A, De Mol P, Vanfleteren B, Levy J, Debusschere P & Farber CM (1996) Contribution of the polymerase chain reaction to the diagnosis of tuberculous infections in children. European Journal of Pediatrics 155(2): 106-11 Wolf H, Mendez M, Gilman RH, Sheen P, Soto G, Velarde AK, Zimic M, Escombe AR, Montenegro S, Oberhelman RA, Evans CA (2008) Diagnosis of pediatric pulmonary tuberculosis by stool PCR. American Journal of Tropical Medicine and Hygiene 79(6): 893-8 Pierre C, Olivier C, Lecossier D, Boussougant Y, Yeni P, Hance AJ (1993) Diagnosis of primary tuberculosis in children by amplification and detection of mycobacterial DNA. American Review of Respiratory	

	Disease 147(2): 420-4 Ha DT, Lan NT, Wolbers M, Duong TN, Quang ND, Thi Van Thinh T, Thi Hong Ngoc L, Thi Ngoc Anh N, Van Quyet T, Thi Bich Tuyen N, Thi Ha V, Day J, Thi Thanh Hang H, Kiet VS, Thi Nho N, Hoa DV, Dung NH, Huu Lan N, Farrar J & Caws M (2009) Microscopic observation drug susceptibility assay (MODS) for early diagnosis of tuberculosis in children. PLoS One 4(12): e8341 Kampmann B, Whittaker E, Williams A, Walters S, Gordon A, Martinez-Alier N, Williams B, Crook AM, Hutton AM, Anderson ST (2009) Interferon-gamma release assays do not identify more children with active tuberculosis than the tuberculin skin test. European Journal of Pediatrics 33(6): 1374-82 Bamford A, Crook A, Clark J, et al (2010) Comparison of interferon-gamma release assays and tuberculin skin test in predicting active tuberculosis in children in the UK: a paediatric TB network study. Archive of Disease in Childhood 95: 180-186 Diel R, Loddenkemper R, Nienhaus A (2010) Evidence-based comparison of commercial interferon-gamma release assays for detecting active TB: a meta-analysis. Chest 137: 952-968 Hussey G, Kibel M, Dempster W (1991) The serodiagnosis of tuberculosis in children: an evaluation of an ELISA test using IgG antibodies to M. tuberculosis, strain H37 RV. Annals of Tropical Paediatrics 11(2): 113-8 Delacourt C, Gobin J, Gaillard JL, de Blic J, Veron M, Scheinmann P (1993) Value of ELISA using antigen 60 for the diagnosis of tuberculosis in children. Chest 104(2): 393-8 Turneer M, Van Nerom E, Nyabenda J, Waelbroeck A, Duvivier A, Toppet M (1994) Determination of humoral immunoglobulins M and G directed against mycobacterial antigen 60 failed to diagnose primary tuberculosis and mycobacterial adenitis in children. American Journal of Respiratory and Critical Care Medicine 150(6 pt 1): 1508-12 Montenegro SH, Gilman RH, Sheen P, Cama R, Caviedes L, Hopper T, Chambers R & Oberhelman RA (2003)	

	Improved detection of Mycobacterium tuberculosis in Peruvian children by use of a heminested IS6110 polymerase chain reaction assay. Clin Infect Dis 36(1): 16-23 Edwards DJ, Kitetele F & Van Rie A (2007) Agreement between clinical scoring systems used for the diagnosis of pediatric tuberculosis in the HIV era. Int J Tuberc Lung Dis 11(3): 263-9 Stegen G, Jones K & Kaplan P (1969) Criteria for guidance in the diagnosis of tuberculosis. Pediatrics 43(2): 260-3 Nair PM & Philip E (1981) A scoring system for the diagnosis of tuberculosis in children. Indian Pediatr 18: 299–303 Migliori GB, Borghesi A, Rossanigo P, Adriko C, Neri M, Santini S, Bartoloni A, Paradisi F & Acocella G (1992) Proposal of an improved score method for the diagnosis of pulmonary tuberculosis in childhood in developing countries. Tuber Lung Dis 73(3): 145-9	

	Details	Additional comments
Review question E (5)	In the presence of a negative culture, what other tests may support an accurate positive diagnosis in people with suspected respiratory TB?	Integrate as a subgroup for RQs C and D

	Details	Additional comments
Review question F (6)	What clinical signs, symptoms or risk factors are suggestive of a diagnosis of active non-respiratory TB?	The GDG felt that this is more about risk factors for having active TB, and wiill be covered therefore by RQ HH In terms of the clinical signs and symptoms suggestive of non-respiratory TB, the GDG also felt the information already exists and that this is more about educating healthcare workers about what to look for Perhaps do a high-level search with a narrative review? Awaiting confirmation from Commissioning.
Objectives	To establish which clinical signs, symptoms or risk factors are most predictive of a diagnosis of non-respiratory TB, and which may form a useful 'symptom screen' for initiating further diagnostic investigation.	
Type of review	Diagnostic	
Language	English	
Study design	High-level summary	Integrate the risk factors for progression to active TB identified in RQ HH
Status	Published papers (full text only)	
Population	People with suspected non-respiratory TB	Sites of interest include: • CNS • spinal • bone and joint • pericardial • peripheral lymph nodes • gastrointestinal • genitourinary • disseminated, including miliary
Diagnostic tool(s)	Clinical signs and symptoms or risk factors that indicate the presence of active non-respiratory TB	These may include: • lack of appetite or weight loss • high temperature or fever • night sweats • tiredness or fatigue • unexplained pain • duration of illness • tuberculin skin test <u>Site-specific signs or symptoms</u> CNS:

		• headaches • nausea • stiff neck • changes in mental state • blurred vision • seizures Peripheral lymph nodes: • swelling of the lymph nodes, which over time may release fluid through the skin Bone and joint: • curving of the affected bone or joint • loss of movement or feeling in the affected bone or joint • weakened bone that may fracture easily Gastrointestinal: • diarrheoa or constipation • rectal bleeding • chronic abdominal pain Genitourinary: • burning sensation when urinating • blood in urine • frequent urge to pass urine during the night
Comparator	Other clinical signs and symptoms or risk factors that indicate the presence of active non-respiratory TB	
Outcomes	• Diagnostic accuracy – sensitivity, specificity, positive predictive value, negative predictive value etc • Relationship between clinical sign, symptom or risk factor and the probability of a diagnosis of active non-respiratory TB • Resource use and cost	
Other criteria for inclusion/exclusion of studies	Include Papers considering the relationship between clinical signs, symptoms or risk factors and the diagnosis of active non-respiratory TB	
Search strategies	Test-and-treat RCTs, quasi-RCTs, non-randomised controlled trials, systematic reviews, observational	

	studies	
Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Where a randomised crossover study is included, the data from the first treatment phase only will be extracted • Subgroup analysis will be undertaken by site of disease, where appropriate • Subgroup analysis will be undertaken for children and young people, where appropriate • Subgroup analysis will be undertaken for people with HIV, where appropriate	
Identified key studies	Studies - CNS Farinha NJ, Razali KA, Holzel H, Morgan G, Novelli VM. Tuberculosis of the central nervous system in children: a 20-year survey. J Infect 2000;41(1):61e8 Kent SJ, Crowe SM, Yung A, Lucas CR, Mijch AM. Tuberculous meningitis: a 30-year review. Clin Infect Dis 1993;17(6): 987e94 Naz F; Malik MA; Malik N. Clinical profile of TBM children presenting in tertiary pediatric neurology unit. Pak Paediatr J 2008; 32(2): 105-10 Verdon R, Chevret S, Laissy JP, Wolff M. Tuberculous meningitis in adults: review of 48 cases. Clin Infect Dis 1996;22(6): 982e8 Kumar R, Singh SN, Kohli N. A diagnostic rule for tuberculous meningitis. Arch Dis Child 1999;81(3):221e4 Youssef FG, Afifi SA, Azab AM, Wasfy MM, Abdel-Aziz KM, Parker	

	TM, et al. Differentiation of tuberculous meningitis from acute bacterial meningitis using simple clinical and laboratory parameters. Diagn Microbiol Infect Dis 2006;55(4): 275e8 Srikanth SG, Taly AB, Nagarajan K, Jayakumar PN, Patil S. Clinicoradiological features of tuberculous meningitis in patients over 50 years of age. J Neurol Neurosurg Psychiatry 2007;78(5):536e8 Sultan T; Malik MA; Khan MMN; Ahmed TM. Clinical, laboratory and radiological indicators for the early diagnosis of tuberculous meningitis in children. Pak Paediatr J 2007; 31(3): 142-48 Studies – military TB Al-Jahdali H, Al-Zahrani K, Amene P, Memish Z, Al-Shimemeri A, Moamary M, Alduhaim A (2000) Clinical aspects of miliary tuberculosis in Saudi adults. Int J Tuberc Lung Dis 4(3): 252-5 Gurkan F, Bosnak M, Dikici B, Bosnak V, Yaramis A, Tas MA, Haspolat K (1998) Miliary tuberculosis in children: a clinical review. Scand J Infect Dis 30(4): 359-62 Wang JY, Hsueh PR, Wang SK, Jan IS, Lee LN, Liaw YS, Yang PC, Luh KT (2007) Disseminated tuberculosis: a 10-year experience in a medical center. Medicine (Baltimore) 86(1): 39-46 Stenius-Aarniala B & Tukiainen P (1979) Miliary tuberculosis. Acta Med Scand 206(5): 417-22 Mert A, Bilir M, Tabak F, Ozaras R, Ozturk R, Senturk H, Aki H, Seyhan N, Karayel T & Aktuglu Y (2001) Miliary tuberculosis: clinical manifestations, diagnosis and outcome in 38 adults. Respirology 6(3): 217-24	

	Details	Additional comments
Review question G (7)	Apart from culture, what other tests are effective in establishing an accurate diagnosis of active non-respiratory TB in people with suspected non-respiratory TB?	
Objectives	To establish which test is the most effective in adults in establishing an accurate diagnosis of active non-respiratory TB whilst the results of culture are awaited To determine which diagnostic method is associated with the shortest time from start of symptoms or start of diagnostic efforts to diagnosis or treatment initiation	
Type of review	Diagnostic	
Language	English	
Study design	Test-and-treat RCTs, quasi-RCTs, systematic reviews, cross-sectional studies (each test under examination is performed on every patient)	
Status	Published papers (full text only)	
Population	People with suspected respiratory TB	Sites of interest include: • CNS • spinal • bone and joint • pericardial • peripheral lymph nodes • gastrointestinal • genitourinary • disseminated, including miliary
Diagnostic tool(s)	Diagnostic tests for active non-respiratory TB	
Comparator	Culture	
Outcomes	• Diagnostic accuracy – sensitivity, specificity, positive predictive value, negative predictive value etc • Time to diagnosis or treatment initiation (from start of symptoms or start of diagnostic efforts) • Prognostic value of tests • Acceptability of approach to	Time to diagnosis or treatment initiation (from start of symptoms or start of diagnostic efforts) – important to note service organisation (centralised vs localised)

	patent or healthcare worker • Adverse events • Downstream treatment outcomes, including mortality, cure, treatment success, treatment failure, relapse • Health-related quality of life • Resource use and cost	
Other criteria for inclusion/exclusion of studies	<u>Include</u> Papers comparing differing diagnostic methods against each other People with suspected TB Commercial tests Sample size ≥30, unless pooled in a meta-analysis Test-and-treat RCTs, quasi-RCTs, systematic reviews, cross-sectional studies <u>Exclude</u> Case-control, case studies, case series and narrative reviews Reference standard is not culture; others to be confirmed with GDG Tests are not conducted concomitantly In-house tests	Diagnostic methods for active respiratory TB include: • culture techniques, such as: routine solid media (e.g. Lowenstein-Jensen, Ogawa), automated liquid culture (e.g. BACTEC, MGIT), microculture techniques (e.g. MODS, MABA), colorimetric assays (e.g. nitrate reductase assay (Griess method), MTT reduction test, MABA, REMA, TEMA), blood culture, urine culture • microscopy • radiology: x-ray, CT etc • biopsy – histology and microbiology • blood tests – C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) • IGRA • tuberculin skin tests, such as the Mantoux test • molecular testing – methods include: PCR, single-stranded conformation polymorphism, nucleic acid probe, isothermal amplification, restriction enzyme fragmentation – HTA review will be incorporated • next-generation / whole genome sequencing • phage-based techniques • scoring systems (i.e. combined approaches)
Search strategies	Test-and-treat RCTs, quasi-RCTs, systematic reviews, cross-sectional studies	
Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables	

	• Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Where a randomised crossover study is included, the data from the first treatment phase only will be extracted • Analyses will be conducted by site of disease • Subgroup analysis will be undertaken for children and young people, where appropriate • Subgroup analysis will be undertaken for people with HIV, where appropriate • Subgroup analysis will be undertaken for people with a negative culture, where appropriate	
Identified key studies	Systematic reviews - general Dinnes J et al. (2007) A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technology Assessment 11(3):1-196 Flores LL, Steingart KR, Dendukuri N et al. (2011) Systematic review and meta-analysis of antigen detection tests for the diagnosis of tuberculosis. Clinical and Vaccine Immunology: 1616-27 Steingart KR, Henry M, Laal S et al. (2007) A systematic review of commercial serological antibody detection tests for the diagnosis of extrapulmonary tuberculosis. Thorax 62: 911-8 Studies - general Michos AG, Daikos GL, Tzanetou K et al. (2006) Detection of mycobacterium tuberculosis DNA in respiratory and nonrespiratory specimens by the Amplicor MTB PCR. Diagnostic Microbiology and	

	Infectious Disease 54: 121-6 Systematic reviews – CNS Pai M, Flores LL, Pai N et al. (2003) Diagnostic accuracy of nucleic acid amplification tests for tuberculous meningitis: a systematic review and meta-analysis. Lancet Infectious Diseases 3: 633-43 Tuon FF, Higashino HR, Lopes MI et al. (2010) Adenosine deaminase and tuberculous meningitis: a systematic review with meta-analysis. Scandinavian Journal of Infectious Diseases 42: 198-207 Studies – CNS Kumar R, Singh SN, Kohli N. A diagnostic rule for tuberculous meningitis. Arch Dis Child 1999;81(3):221e4 Torok ME, Nghia HD, Chau TT, Mai NT, Thwaites GE, Stepniewska K, et al. Validation of a diagnostic algorithm for adult tuberculous meningitis. Am J Trop Med Hyg 2007; 77(3):555e9 Thwaites GE, Chau TT, Stepniewska K, Phu NH, Chuong LV, Sinh DX, et al. Diagnosis of adult tuberculous meningitis by use of clinical and laboratory features. Lancet 2002; 360(9342):1287e92 Sunbul M, Atilla A, Esen S, Eroglu C, Leblebicioglu H. Thwaites' diagnostic scoring and the prediction of tuberculous meningitis. Med Princ Pract 2005;14(3):151e4 Checkley AM, Njalale Y, Scarborough M. Sensitivity and specificity of an index for the diagnosis of TB meningitis in patients in an urban teaching hospital in Malawi. Trop Med Int Health; 2008 Systematic reviews – lymph nodes Daley P, Thomas S, Pai M (2007) Nucleic acid amplification tests for the diagnosis of tuberculous lymphadenitis: a systematic review. International Journal of Tuberculosis and Lung Disease	

	11: 1166-76 Systematic reviews – pericardial Tuon FF, Litvoc MN, Lopes M, I (2006) Adenosine deaminase and tuberculous pericarditis: a systematic review with meta-analysis. Acta Tropica 99: 67-74 Systematic reviews – abdominal Shah SR, Shenai S, Desai DC et al. (2010) Comparison of Mycobacterium tuberculosis culture using liquid culture medium and Lowenstein Jensen medium in abdominal tuberculosis. Indian Journal of Gastroenterology 29: 237-9 Studies – miliary Kwong JS, Carignan S, Kang E-Y, Müller NL & Fitzgerald JM (1996) Miliary Tuberculosis: Diagnostic Accuracy of Chest Radiography. Chest 110(2): 339-42	

	Details	Additional comments
Review question H (8)	In the presence of a negative culture, what other tests may support a positive diagnosis in people with suspected active non-respiratory TB?	Integrated as a subgroup for RQ G

	Details	Additional comments
Review question I (9)	In children and young people with active TB receiving drug treatment, are intermittent dosing regimens as effective as daily drug treatment regimens in reducing mortality and morbidity?	
Objectives	To establish whether intermittent dosing is as effective as daily dosing of treatment in reducing mortality and morbidity caused by active TB in children and young people. To determine whether there is variation between dosing frequencies in terms of adherence to the treatment regimen, as well as the incidence of treatment failure and relapse and/or the emergence of acquired drug resistance.	
Type of review	Intervention	
Language	English	
Study design	RCTs, quasi-RCTs, systematic reviews If there is insufficient evidence found, non-randomised controlled trials will be considered	'Insufficient evidence' is considered to be an evidence base that does not allow the GDG to make recommendations
Status	Published papers (full text only)	
Population	Children and young people with drug susceptible, active respiratory or non-respiratory TB	GDG confirmed that both respiratory and non-respiratory TB should be reviewed, though subgroup analyses to be conducted for each site of disease
Intervention	Treatment regimens of varying frequencies	One-, two- or three-times per week
Comparator	Daily dosing of treatment or other dosing frequency	
Outcomes	<u>Critical or important outcomes</u> 1. Cure: cure, treatment success or treatment failure 2. Adverse events 3. Mortality 4. Relapse 5. Adherence: adherence and treatment default 6. Changes in signs and symptoms 7. Emergence of acquired drug resistance <u>Adverse events of interest</u> Adverse events that are severe enough to require a modification, interruption or discontinuation in treatment, or one of the	Cure would optimally be defined by radiological improvement (e.g. commonly in the hilar lymph nodes), alone or in conjunction with culture or microscopy Culture or microscopy alone are not reliable means of diagnosing TB (i.e. defining a cure) in children Treatment success, as defined by WHO ("a patient who was cured or who completed treatment"), will only be reported where trials do not report the disaggregated data for cure or treatment completion

	following: 1. Mortality, treatment-related 2. Developmental impairment 3. Hepatotoxicity (liver toxicity) 4. Missed school (children) or work (adults) 5. Nausea and/or vomiting <u>Signs and symptoms of interest</u> 1. Weight loss 2. Cough 3. Fever 4. Inflammation 5. Fatigue, low energy or malaise	
Other criteria for inclusion / exclusion of studies	<u>Include</u> • Papers comparing treatment regimens of antituberculosis chemotherapy of differing dosing frequencies • Children and young people (< 18 years) with drug susceptible, active respiratory or non-respiratory TB • Follow-up for at least the full treatment period <u>Exclude</u> • Adults • People with latent TB or drug resistant TB • Papers with a focus on populations with comorbidities or coexisting conditions other than HIV that will affect the choice or management of treatment • Papers comparing dosing frequencies in regimens of different treatment durations and that contain different combinations of drugs • Papers using regimens that contain drugs other than the 4 drugs in the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol) • Papers considering the use of drugs not licensed in the UK • Observational, case series, case studies and narrative reviews	Age cut-off chosen for coherence with recommendations to be incorporated from CG117 (see CG117 scope, section 4.1.1)
Search	RCTs, quasi-RCTs, systematic reviews,	

strategies	non-randomised controlled trials	
Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Where a randomised crossover study is included, the data from the first treatment phase only will be extracted • Subgroup analysis will be undertaken for children aged 5 years or younger, where appropriate • Subgroup analysis will be undertaken by site of disease, where appropriate • Subgroup analysis will be undertaken for people who have previously experienced treatment failure or who have relapsed, where appropriate • Subgroup analysis will be undertaken for directly observed treatment, where appropriate	
Key papers	Kumar L, Dhand R, Singhi PD, Rao KLN, Katarya S. A randomized trial of fully intermittent vs daily followed by intermittent short course chemotherapy for childhood tuberculosis. Pediatr Infect Dis J 1990;9:802-6	

	Details	Additional comments
Review question J (10)	In people co-infected with drug susceptible, active TB and HIV receiving drug treatment for both infections, what are the key pharmacological considerations that should be taken into account when selecting a treatment regimen for treating active or latent TB?	
Objectives	To determine what pharmacological issues should be taken into consideration when selecting a treatment regimen for TB in people co-infected with drug susceptible TB and HIV who are receiving drug treatment for both infections.	
Type of review	Will not conduct a formal review, instead will produce a summary of the BNF and SPCs	Review of pharmacokinetic data is outside of NICE's scope; it is felt that the methods, expertise and remit to conduct a rigorous review are lacking
Language	English	
Study design	BNF and SPCs	
Status	BNF and SPCs	
Population	People co-infected with drug susceptible, active TB and HIV who are receiving drug treatment for both infections	
Intervention	Treatment regimens for drug susceptible TB and HIV	
Comparator	n/a	
Outcomes	n/a	
Other criteria for inclusion / exclusion of studies	BNF and SPCs	
Search strategies	• Information relating to the treatment of TB in people co-infected with HIV, and receiving treatment for HIV, will be extracted from the BNF and the Summary of Product Characteristics, and summarized in a table (i.e. narrative review)	
Review strategies		
Key papers		

	Details	Additional comments
Review question K	How should the standard recommended regimen be adapted to accommodate comorbidities or co-existing conditions that affect the choice of regimen for the treatment of active respiratory and non-respiratory TB?	
Objectives	To highlight the key issues associated with choosing a treatment regimen for people with active TB and a key comorbidity or co-existing condition. To identify possible ways in which the standard recommended regimen can be adapted to accommodate these comorbidities or co-existing conditions.	
Type of review	Intervention	
Language	English	
Study design	Review and summarise BNF and SPCs to highlight the issues that arise in the treatment of TB in people another comorbidity or co-existing condition RCTs, quasi-RCTs, systematic reviews If there is insufficient evidence found, non-randomised controlled trials will be considered	'Insufficient evidence' is considered to be an evidence base that does not allow the GDG to make recommendations
Status	Published papers (full text only)	
Population	People with a confirmed diagnosis of active, drug susceptible TB and one or more other comorbidity or co-existing condition	• HIV • Liver disease • Renal disease • Diabetes • Substance use, including methadone use • Pregnancy and breast-feeding • Impaired vision/eye disease
Intervention	Standard recommended regimen for active TB	
Comparator	Other treatment regimens for active TB	
Outcomes	<u>Critical or important outcomes</u> 1. Adverse events 2. Mortality 3. Cure: cure, treatment success or treatment failure 4. Relapse 5. Adherence: adherence and treatment default 6. Changes in signs and symptoms 7. Emergence of acquired drug	Treatment success, as defined by WHO ("a patient who was cured or who completed treatment"), will only be reported where trials do not report the disaggregated data for cure or treatment completion

	resistance Adverse events of interest Adverse events that are severe enough to require a modification, interruption or discontinuation in treatment, or one of the following: 1. Mortality, treatment-related 2. Hepatotoxicity (liver toxicity) 3. Visual impairment 4. Nausea and/or vomiting 5. Hospitalisation due to adverse event(s) Signs and symptoms of interest See 'TB signs and symptoms by site of disease' table	
Other criteria for inclusion / exclusion of studies	Include • Papers comparing different treatment regimens for TB in patients with active, drug susceptible TB and a defined comorbidity or co-existing condition • People with a confirmed diagnosis of active, drug susceptible TB • Follow-up for at least the full treatment period • Sample size ≥30 Exclude • People with latent TB or drug resistant TB • Papers considering the use of drugs not licensed in the UK • Observational study, case series, case studies and narrative reviews	
Search strategies	BNF and SPCs RCTs, quasi-RCTs, systematic reviews, non-randomised controlled trials, prospective cohort studies	
Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect	

	• All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Where a randomised crossover study is included, the data from the first treatment phase only will be extracted • Subgroup analysis will be undertaken for children and young people, where appropriate	
Key papers	Systematic reviews Mitchell I, Wendon J, Fitt S, Williams R: Antituberculous therapy and acute liver failure. Lancet 1995, 345:55–56 Studies Ungo JR, Jones D, Ashkin H, et al.: Antituberculosis druginduced hepatotoxicity: the role of hepatitis C virus and the human immunodeficiency virus. Am J Respir Crit Care Med 1998, 157:1871–1876 Devoto FM, González C, Iannantuono R, Serra HA, González CD, Sáenz C (1997) Risk factors for hepatotoxicity induced by antituberculosis drugs. Acta Physiol Pharmacol Ther Latinoam 47(4): 197-202 Sadaphal P, Astemborski J, Graham NM, Sheely L, Bonds M, Madison A, Vlahov D, Thomas DL, Sterling TR (2001) Isoniazid preventive therapy, hepatitis C virus infection, and hepatotoxicity among injection drug users infected with Mycobacterium tuberculosis. Clinical Infectious Diseases 33(10): 1687-91	

	Details	Additional comments
Review question L (12)	In adults with drug susceptible, active respiratory TB receiving drug treatment, what duration of regimen is the most effective in reducing mortality and morbidity? i) Do regimens of less than 6 months present additional risks to the patient, and if so, in which patients? ii) Do regimens of more than 6 months present additional benefits to the patient, and if so, in which patients?	
Objectives	To establish the optimum duration of treatment in adults with drug susceptible, active respiratory TB, with an emphasis on which patients may experience an additional risk of harm from the shorter regimens or an increased potential to benefit from the longer regimens	
Type of review	Intervention	
Language	English	
Study design	RCTs, quasi-RCTs, systematic reviews If there is insufficient evidence found, non-randomised controlled trials will be considered	'Insufficient evidence' is considered to be an evidence base that does not allow the GDG to make recommendations
Status	Published papers (full text only)	
Population	Adults with drug susceptible, active respiratory TB	
Intervention	• Treatment regimens of less than 6 months • Treatment regimens of more than 6 months	
Comparator	Treatment regimens of 6 months	
Outcomes	<u>Critical or important outcomes</u> 1. Cure: cure, treatment success or treatment failure 2. Adverse events 3. Mortality 4. Relapse 5. Adherence: adherence and treatment default 6. Changes in signs and symptoms 7. Emergence of acquired drug resistance <u>Adverse events of interest</u> Adverse events that are severe enough to require a modification, interruption or	Treatment success, as defined by WHO ("a patient who was cured or who completed treatment"), will only be reported where trials do not report the disaggregated data for cure or treatment completion Outcome data for relapse will be reported according to the period of follow-up after the end of the treatment period (e.g. odds ratios for relapse at 3 months after treatment end, at 6 months after treatment end, at 12 months after treatment end etc)

	discontinuation in treatment, or one of the following: 1. Mortality, treatment-related 2. Hepatotoxicity (liver toxicity) 3. Visual impairment 4. Nausea and/or vomiting 5. Hospitalisation due to adverse event(s) <u>Signs and symptoms of interest</u> See 'TB signs and symptoms by site of disease' table	
Other criteria for inclusion / exclusion of studies	<u>Include</u> • Papers comparing treatment regimens of antituberculosis chemotherapy of varying lengths • Adults with drug susceptible, active respiratory TB • Follow-up for at least the full treatment period <u>Exclude</u> • Children and young people (< 18 years) • People with active non-respiratory TB, latent TB or drug resistant TB • Papers with a focus on populations with comorbidities or coexisting conditions other than HIV that will affect the choice or management of treatment • Papers comparing treatment durations of varying length in regimens containing different combinations of drugs • Papers using regimens that contain drugs other than the 4 drugs in the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol) • Papers considering the use of drugs not licensed in the UK • Observational, case series, case studies, and narrative reviews	Comparisons that contain regimens without at least 3 drugs in the initial phase or without rifampicin for the full treatment period will be included only as supplementary evidence
Search strategies	RCTs, quasi-RCTs, systematic reviews If there is insufficient evidence found, non-randomised controlled trials will be considered	'Insufficient evidence' is considered to be an evidence base that does not allow the GDG to make recommendations
Review	• The NICE methodology checklists will be used as a guide to appraise the	

strategies	quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Where a randomised crossover study is included, the data from the first treatment phase only will be extracted • Analysis will be undertaken by site of disease (lungs, pleural cavity, mediastinal lymph nodes, larynx), where appropriate • Subgroup analysis will be undertaken by severity of disease, including smear negative disease or cavitatory disease, where appropriate • Subgroup analysis will be undertaken for people who have previously experienced treatment failure or who have relapsed, where appropriate • Subgroup analysis will be undertaken for people with HIV, where appropriate • Subgroup analysis will be undertaken for directly observed treatment, where appropriate	
Key papers	Systematic reviews El-Sadr WM, Perlman DC, Denning E, Matts JP & Cohn DL (2001) A review of efficacy studies of 6-month short-course therapy for tuberculosis among patients infected with human immunodeficiency virus: differences in study outcomes. Clinical Infectious Diseases 32(4): 623-32 Menzies D, Benedetti A, Paydar A et al. (2009) Effect of duration and intermittency of rifampin on tuberculosis treatment outcomes: a systematic review and meta-analysis. PLoS Medicine 6 Gelband H. Regimens of less than six months for treating tuberculosis. Cochrane Database of Systematic Reviews 1999, Issue 4. Article No. CD001362 Khan FA, Minion J, Pai M et al. (2010) Treatment of active tuberculosis in HIV-coinfected patients: a systematic review and meta-analysis. Clinical Infectious Diseases 50: 1288-99 Studies El-Sadr W, Perlman DC, Matts JP, et al (1998) The evaluation of an intensive intermittent induction regimen and short course duration of treatment for HIV-related pulmonary tuberculosis. Clin Infect Dis 26: 1148–58 Perriëns JH, St Louis ME, Mukadi YB, Brown C, Prignot J, Pouthier F, Portaels F, Willame JC, Mandala JK, Kaboto M, et al (1995) Pulmonary tuberculosis in HIV-infected patients in Zaire. A controlled trial of treatment for either 6 or 12 months.	

	New England Journal of Medicine 332(12): 779-84

	Details	Additional comments
Review question M (13)	In children and young people with drug susceptible, active respiratory TB receiving the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol), what duration of regimen is the most effective in reducing mortality and morbidity? i) Do regimens of less than 6 months present additional risks to the patient, and if so, in which patients? ii) Do regimens of more than 6 months present additional benefits to the patient, and if so, in which patients?	
Objectives	To establish the optimum duration of treatment in children and young people drug susceptible, with active respiratory TB, with an emphasis on which patients may experience an additional risk of harm from the shorter regimens or an increased potential to benefit from the longer regimens	
Type of review	Intervention	
Language	English	
Study design	RCTs, quasi-RCTs, systematic reviews If there is insufficient evidence found, non-randomised controlled trials will be considered	'Insufficient evidence' is considered to be an evidence base that does not allow the GDG to make recommendations
Status	Published papers (full text only)	
Population	Children and young people with drug susceptible, active respiratory TB	
Intervention	i) Treatment regimens of less than 6 months ii) Treatment regimens of more than 6 months	
Comparator	Treatment regimens of 6 months	
Outcomes	<u>Critical or important outcomes</u> 1. Cure: cure, treatment success or treatment failure 2. Adverse events 3. Mortality 4. Relapse 5. Adherence: adherence and treatment default 6. Changes in signs and symptoms 7. Emergence of acquired drug resistance <u>Adverse events of interest</u>	Cure would optimally be defined by radiological improvement (e.g. commonly in the hilar lymph nodes) alone, or in conjunction with culture or microscopy Culture or microscopy alone are not reliable means of diagnosing TB (i.e. defining a cure) in children Treatment success, as defined by WHO ("a patient who was cured or who completed treatment"), will only be reported where trials do not report the disaggregated data for cure or treatment completion Outcome data for relapse will be reported according to the period of

	Adverse events that are severe enough to require a modification, interruption or discontinuation in treatment, or one of the following: 1. Mortality, treatment-related 2. Developmental impairment 3. Hepatotoxicity (liver toxicity) 4. Missed school (children) or work (adults) 5. Nausea and/or vomiting <u>Signs and symptoms of interest</u> 1. Weight loss 2. Cough 3. Fever 4. Inflammation 5. Fatigue, low energy or malaise	follow-up after the end of the treatment period (e.g. odds ratios for relapse at 3 months after treatment end, at 6 months after treatment end, at 12 months after treatment end etc) Comparisons that contain regimens without at least 3 drugs in the initial phase or without rifampicin for the full treatment period will be included only as supplementary evidence
Other criteria for inclusion / exclusion of studies	<u>Include</u> • Papers comparing treatment regimens of antituberculosis chemotherapy of varying lengths • Children and young people (< 18 years) with drug susceptible, active respiratory TB • Follow-up for at least the full treatment period <u>Exclude</u> • Adults • Children and young people with active non-respiratory TB, latent TB or drug resistant TB • Papers with a focus on populations with comorbidities or coexisting conditions other than HIV that will affect the choice or management of treatment • Papers comparing treatment durations of varying length in regimens containing different combinations of drugs • Papers using regimens that contain drugs other than the 4 drugs in the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol) • Papers considering the use of drugs not licensed in the UK • Observational studies, case series,	

	case studies, and narrative reviews	
Search strategies	RCTs, quasi-RCTs, systematic reviews, non-randomised controlled trials	
Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Where a randomised crossover study is included, the data from the first treatment phase only will be extracted • Analysis will be undertaken by site of disease (lungs, pleural cavity, mediastinal lymph nodes, larynx), where appropriate • Subgroup analysis will be undertaken for children aged 5 years or younger, where appropriate • Subgroup analysis will be undertaken by severity of disease, including smear negative disease, where appropriate • Subgroup analysis will be undertaken for people who have previously experienced treatment failure or who have relapsed, where appropriate • Subgroup analysis will be undertaken for people with HIV, where appropriate • Subgroup analysis will be undertaken for directly observed treatment, where appropriate	
Key papers		

	Details	Additional comments
Review question N (14)	In people with active TB receiving the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol), do corticosteroids as an adjunct to the antituberculosis drug treatment regimen decrease morbidity and mortality compared to the standard recommended regimen alone?	
Objectives	To determine whether the addition of corticosteroids to the standard recommended regimen is effective in decreasing morbidity and mortality in people with active TB.	
Type of review	Intervention	
Language	English	
Study design	RCTs, quasi-RCTs, systematic reviews If there is insufficient evidence found, non-randomised controlled trials will be considered	
Status	Published papers (full text only)	
Population	People with active TB	
Intervention	Antituberculosis chemotherapy with corticosteroids	Corticosteroids include: • prednisolone • dexamethasone • hydrocortisone • ACTH • cortisol
Comparator	Antituberculosis chemotherapy alone	
Outcomes	<u>Critical or important outcomes</u> 1. Cure: cure, treatment success or treatment failure 2. Changes in signs and symptoms 3. Mortality 4. Adverse events 5. Relapse 6. Adherence: adherence and treatment default 7. Emergence of acquired drug resistance <u>Adverse events of interest</u> Adverse events that are severe enough to require a modification, interruption or discontinuation in treatment, or one of the following:	Treatment success, as defined by WHO ("a patient who was cured or who completed treatment"), will only be reported where trials do not report the disaggregated data for cure or treatment completion Outcome data for relapse will be reported according to the period of follow-up after the end of the treatment period (e.g. odds ratios for relapse at 3 months after treatment end, at 6 months after treatment end, at 12 months after treatment end etc)

	1. Mortality, treatment-related 2. Gastrointestinal bleeding 3. Hyperglycaemia or glycosuria 4. Obesity or weight gain 5. Nausea and/or vomitting <u>Signs and symptoms of interest</u> See 'TB signs and symptoms by site of disease' table	
Other criteria for inclusion / exclusion of studies	<u>Include</u> • Papers comparing the use of antituberculosis chemotherapy with corticosteroids to antituberculosis chemotherapy with alone • People receiving antituberculosis chemotherapy for drug susceptible or drug resistant active TB • Follow-up for at least the full treatment period <u>Exclude</u> • People with latent TB • People receiving corticosteroids in the absence of antituberculosis chemotherapy • Papers with a focus on populations with comorbidities or coexisting conditions other than HIV that will affect the choice or management of treatment • Papers comparing the use of corticosteroids or not in regimens containing different combinations of antituberculosis drugs • Papers considering the use of corticosteroids in regimens for drug susceptible TB that contain drugs other than the 4 drugs in the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol) • Papers considering the use of drugs not licensed in the UK • Observational studies, case series, case studies and narrative reviews	Comparisons that contain regimens without at least 3 drugs in the initial phase or without rifampicin for the full treatment period will be downgraded for indirectness
Search strategies	RCTs, quasi-RCTs, non-randomised controlled trials, systematic reviews	
Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of individual studies	

	• Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Where a randomised crossover study is included, the data from the first treatment phase only will be extracted • Analysis will be undertaken by site of disease • Subgroup analysis will be undertaken by drug susceptability • Subgroup analysis will be undertaken for children and young people, where appropriate • Subgroup analysis will be undertaken by severity of disease, including smear negative disease, where appropriate • Subgroup analysis will be undertaken for people with HIV, where appropriate • Subgroup analysis will be undertaken by duration of corticosteroid use, where appropriate	
Key papers	Systematic reviews - respiratory Smego RA, Ahmed N (2003) A systematic review of the adjunctive use of systemic corticosteroids for pulmonary tuberculosis. International Journal of Tuberculosis and Lung Disease 7: 208-13 Engel ME, Matchaba PT, Volmink J. Corticosteroids for tuberculous pleurisy. Cochrane Database of Systematic Reviews 2007, Issue 4. Article No: CD001876 Studies - respiratory Weinstein H J, Koler J J. Adrenocorticosteroids in the treatment of tuberculosis. N Engl J Med 1959; 260: 412–41 Horne N W. Prednisolone in treatment of pulmonary tuberculosis: A controlled trial—final report to the research committee of the tuberculosis society of Scotland. Br Med J 1960; 5215: 1751–1756 Bell W J, Brown P P. Prednisolone in the treatment of acute extensive pulmonary tuberculosis in West Africans. Tubercle 1960; 41: 341–351 Angel J H, Chu L S, Lyons H A. Corticotropin in the treatment of tuberculosis. A controlled study. Arch Intern Med 1961; 108: 75–91 Research Committee of the British Tuberculosis Association. A trial of corticotrophin and prednisone with chemotherapy in pulmonary tuberculosis. Tubercle 1961: 42: 391–412 Marcus H, Yoo O H, Akyol T, Williams M H Jr. A randomized study of the effects of corticosteroid therapy on healing of pulmonary tuberculosis as judged by clinical, roentgenographic and physiologic measurement. Am Rev Respir Dis 1962; 88: 55–	

	64 United States Public Health Service Tuberculosis Therapy Trial. Prednisolone in the treatment of pulmonary tuberculosis. Am Rev Respir Dis 1965; 91: 329–338 Johnson J R, Taylor B C, Morrissey J F, Jenne J W, MacDonald F M. Corticosteroids in pulmonary tuberculosis. Am Rev Respir Dis 1965; 92: 376–391 Malik S K, Martin C J. Tuberculosis, corticosteroid therapy and pulmonary function. Am Rev Respir Dis 1969; 100: 13–18 Tuberculosis Research Centre. India. Study of chemotherapy regimens of 5 and 7 months duration and the role of corticosteroids in the treatment of sputum-positive patients with pulmonary tuberculosis in South India. Tubercle 1983; 64: 73–91 Bilaceroglu S, Perim K, M. Büyüksirin, E. Çelikten. Prednisolone: a beneficial and safe adjunct to anti-tuberculous treatment? A randomized controlled trial. Int J Tuberc Lung Dis 1999; 3: 47–54 Bang JS, Kim MS, Kwak SM, Cho CH. Evaluation of steroid therapy in tuberculous pleurisy - A prospective, randomized study. Tuberculosis and Respiratory Disease 1997;44(1):52–8 Elliott AM, Luzze H, Quigley MA, Nakiyingi J, Kyaligonza S, Namujju PB, et al. A randomized, double-blind, placebo-controlled trial of the use of prednisolone as an adjunct to treatment in HIV- 1-associated pleural tuberculosis. Journal of Infectious Diseases 2004; 190(5):869–78 Galarza I, Canete C, Granados A, Estopa R, Manresa F. Randomised trial of corticosteroids in the treatment of tuberculous pleurisy. Thorax 1995;50(12):1305–7 Lee CH, Wang WJ, Lan RS, Tsai YH, Chiang YC. Corticosteroids in the treatment of tuberculous pleurisy. A double-blind, placebo- controlled, randomized study. Chest 1988;94(6):1256–9 Lee BH, Jee HS, Choi JC, Park YB, An CH, Kim JY, et al. Therapeutic effect of prednisolone in tuberculous pleurisy - A prospective study for the prevention of the pleural adhesion. Tuberculosis and Respiratory Disease 1999;46(4):481–8 Wyser C, Walzl G, Smedema JP, Swart F, van Schalkwyk EM, van de Wal BW. Corticosteroids in the treatment of tuberculous pleurisy. A double-blind, placebo-controlled, randomized study. Chest 1996;110(2):333–8 Park IW, Choi BW & Hue SH (1997) Prospective study of corticosteroid as an adjunct in the treatment of endobronchial tuberculosis in adults. Respirology 2(4): 275-81 Systematic reviews - CNS Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. Cochrane Database of Systematic Reviews 2008, Issue 1. Article No. CD002244 Studies - CNS Chotmongkol V, Jitpimolmard S, Thavornpitak Y (1996) Corticosteroid in tuberculous meningitis. Journal of the Medical Association of Thailand 79(2):83–90 Donald PR, Schoeman JF, van Zyl LE, de Villiers JN, Pretorius M, Springer P (1998) Intensive short course chemotherapy in the management of tuberculous meningitis. Int J Tuberc Lung Dis 2: 704–711 Girgis NI, Farid Z, Kilpatrick ME, Sultan Y, Mikhail IA (1991) Dexamethasone adjunctive treatment for tuberculous meningitis. Pediatric Infectious Disease Journal 10(3):179–83 Kumarvelu S, Prasad K, Khosla A, Behari M, Ahuja GK (1994) Randomized controlled trial of dexamethasone in tuberculous meningitis. Tubercle and Lung Disease 75(3):203–7 Lardizabal DV, Roxas AA. Dexamethasone as adjunctive therapy in adult patients with probable TB meningitis stage II and stage III: An open randomised controlled

	trial. Philippines Journal of Neurology 1998;4:4–10 O'Toole RD, Thornton GF, Mukherjee MK, Nath RL. Dexamethasone in tuberculous meningitis. Relationship of cerebrospinal fluid effects to therapeutic efficacy. Annals of Internal Medicine 1969;70(1):39–47 Schoeman JF, Van Zyl LE, Laubscher JA, Donald PR. Effect of corticosteroids on intracranial pressure, computed tomographic findings, and clinical outcome in young children with tuberculous meningitis. Pediatrics 1997;99(2):226–31 Simmons CP, Thwaites GE, Quyen NT, Chau TT, Mai PP, Dung NT, et al.The clinical benefit of adjunctive dexamethasone in tuberculous meningitis is not associated with measurable attenuation of peripheral or local immune responses. Journal of Immunology 2005;175(1):579–90 Thwaites GE, Nguyen DB, Nguyen HD, Hoang TQ, Do TT, Nguyen TC, et al (2004) Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med 351(17): 1741e51 Studies - peripheral lymph nodes Nemir RL, Cardona J, Lacoius A, David M (1963) Prednisone therapy as an adjunct in the treatment of lymph node-bronchial tuberculosis in childhood. A double-blind study. Am Rev Respir Dis 88:189-98 Systematic reviews - pericardial Mayosi BM. Interventions for treating tuberculous pericarditis. Cochrane Database of Systematic Reviews 2002, Issue 4. Article No. CD000526 Studies - pericardial Hakim J, Ternouth I, Mushangi E, Siziya S, Robertson V, Malin A. Double blind randomised placebo controlled trial of adjuvant prednisolone in the treatment of effusive tuberculous pericarditis in HIV seropositive patients. Heart 2000; 84: 183–8 Schrire V. Experience with pericarditis at Groote Schuur Hospital, Cape Town: An analysis of one hundred and sixty cases over a six- year period. South African Medical Journal 1959; 33: 810–7 Strang JIG, Kakaza HHS, Gibson DG, Girling DJ, Nunn AJ, Fox W. Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. Lancet 1987; 2 (8573): 1418–22 Strang JIG, Kakaza HHS, Gibson DG, Allen BW, Mitchison DA, Evans DJ, et al. Controlled clinical trial of complete open surgical drainage and of prednisolone in treatment of tuberculous pericardial effusion in Transkei. Lancet 1988; 2(8614): 759–64 Strang JI, Nunn AJ, Johnson DA, Casbard A, Gibson DG & Girling DJ (2004) Management of tuberculous constrictive pericarditis and tuberculous pericardial effusion in Transkei: results at 10 years follow-up. QJM 97(8): 525-35 Studies - genitourinary Horne NW & Tulloch WS (1975) Conservative management of renal tuberculosis. Br J Urol 47(5): 481-7 Studies – drug resistant TB Chan ED, Laurel V, Strand MJ, Chan JF, Huynh ML, Goble M, Iseman MD (2004) Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. Am J Respir Crit Care Med 169(10): 1103-9 Chiang CY, Yu MC, Bai KJ, Suo J, Lin TP & Lee YC (2001) Pulmonary resection in the treatment of patients with pulmonary multidrug-resistant tuberculosis in Taiwan. Int J Tuberc Lung Dis 5(3): 272-7 Iseman MD, Madsen L, Goble M & Pomerantz M (1990) Surgical intervention in the treatment of pulmonary disease caused by drug-resistant Mycobacterium tuberculosis. Am Rev Respir Dis 141(3): 623-5

	Park SK, Lee CM, Heu JP & Song SD (2002) A retrospective study for the outcome of pulmonary resection in 49 patients with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 6(2): 143-9 Park SK, Kim JH, Kang H, Cho JS & Smego RA Jr (2009) Pulmonary resection combined with isoniazid- and rifampin-based drug therapy for patients with multidrug-resistant and extensively drug-resistant tuberculosis. Int J Infect Dis 13(2): 170-5 Shiraishi Y, Katsuragi N, Kita H, Toishi M & Onda T (2008) Experience with pulmonary resection for extensively drug-resistant tuberculosis. Interact Cardiovasc Thorac Surg 7(6): 1075-8 Somocurcio JG, Sotomayor A, Shin S, Portilla S, Valcarcel M, Guerra D & Furin J (2007) Surgery for patients with drug-resistant tuberculosis: report of 121 cases receiving community-based treatment in Lima, Peru. Thorax 62(5): 416-21 Sung SW, Kang CH, Kim YT, Han SK, Shim YS & Kim JH (1999) Surgery increased the chance of cure in multi-drug resistant pulmonary tuberculosis. Eur J Cardiothorac Surg 16(2):187-93 Törün T, Tahaoğlu K, Ozmen I, Sevim T, Ataç G, Kir A, Güngör G, Bölükbaşi Y & Maden E (2007) The role of surgery and fluoroquinolones in the treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 11(9): 979-85 Treasure RL, Seaworth BJ (1995) Current role of surgery in Mycobacterium tuberculosis. Ann Thorac Surg 59(6): 1405-7 van Leuven M, De Groot M, Shean KP, von Oppell UO & Willcox PA (1997) Pulmonary resection as an adjunct in the treatment of multiple drug-resistant tuberculosis. Ann Thorac Surg 63(5): 1368-72

	Details	Additional comments
Review question O (15)	In people with active TB receiving the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol), does surgery as an adjunct to an antituberculosis drug treatment regimen decrease morbidity and mortality compared to the standard recommended regimen alone?	
Objectives	To determine whether the addition of surgery the standard recommended regimen is effective in decreasing morbidity and mortality in people with active TB.	
Type of review	Intervention	
Language	English	
Study design	RCTs, quasi-RCTs, systematic reviews, non-randomised controlled trials, observational	
Status	Published papers (full text only)	
Population	People with drug susceptible or drug resistant active TB	
Intervention	Antituberculosis chemotherapy with surgery	Interventions of interest include: • pneumonectomy • resection • video-assisted thoracic surgery • debridement • reconstruction • grafting • lobectomy • shunt • fixation
Comparator	Antituberculosis chemotherapy alone	
Outcomes	<u>Critical or important outcomes</u> 1. Mortality 2. Cure: cure, treatment success or treatment failure 3. Changes in signs and symptoms 4. Relapse 5. Adverse events 6. Adherence: adherence and treatment default 7. Emergence of acquired drug resistance	Treatment success, as defined by WHO ("a patient who was cured or who completed treatment"), will only be reported where trials do not report the disaggregated data for cure or treatment completion Outcome data for relapse will be reported according to the period of follow-up after the end of the treatment period (e.g. odds ratios for relapse at 3 months after treatment end, at 6 months after treatment end, at 12 months after treatment end etc)

	Adverse events of interest Adverse events that are severe enough to require a modification, interruption or discontinuation in treatment, hospitalisation, or one of the following: 1. Mortality, treatment-related 2. Failure of wound to heal 3. Infection of surgical site 4. Pain 5. Bleeding or blood loss Signs and symptoms of interest See 'TB signs and symptoms by site of disease' table	
Other criteria for inclusion / exclusion of studies	Include • Papers comparing the treatment regimens of antituberculosis chemotherapy with surgery to the treatment regimens of antituberculosis chemotherapy alone • People receiving antituberculosis chemotherapy for active TB • Follow-up for at least the full treatment period Exclude • People with latent TB • People undergoing surgery in the absence of antituberculosis chemotherapy • Papers with a focus on populations with comorbidities or coexisting conditions other than HIV that will affect the choice or management of treatment • Papers comparing the use of surgery or not in regimens containing different combinations of antituberculosis drugs • Papers using regimens for drug susceptible TB that contain drugs other than the 4 drugs in the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol) • Papers considering the use of drugs not licensed in the UK • Case studies and narrative reviews	Comparisons that contain regimens without at least 3 drugs in the initial phase or without rifampicin for the full treatment period will be downgraded for indirectness
Search strategies	RCTs, quasi-RCTs, systematic reviews, non-randomised controlled trials,	

	observational	

Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Where a randomised crossover study is included, the data from the first treatment phase only will be extracted • Analysis will be undertaken by drug susceptability • Analysis will be undertaken by site of disease • Analysis will be undertaken by intent of surgery (e.g. removal of infective material vs drainage) • Subgroup analysis will be undertaken for children and young people, where appropriate • Subgroup analysis will be undertaken for people with HIV, where appropriate • Subgroup analysis will be undertaken by severity of disease, where appropriate • Subgroup analysis will be undertaken for people who have previously experienced treatment failure or who have relapsed, where appropriate	
Key papers	<u>Studies - respiratory</u> Freixinet JG, Rivas JJ, Rodríguez De Castro F, Caminero JA, Rodriguez P, Serra M, de la Torre M, Santana N, Canalis E (2002) Role of surgery in pulmonary tuberculosis. Med Sci Monit 8(12):CR782-6 Hsu HS, Hsu WH, Huang BS & Huang MH (1997) Surgical treatment of endobronchial tuberculosis. Scand Cardiovasc J 31(2): 79-82 Lee YC, Luh SP, Wu RM, Lin TP, Luh KT (1994) Current role of surgery in the management of pleuropulmonary tuberculosis. J Formos Med Assoc. 1994 Oct;93(10):836-41 Perelman MI & Strelzov VP (1997) Surgery for Pulmonary Tuberculosis. World Journal of Surgery 21(5): 457-467 Takeda S, Maeda H, Hayakawa M, Sawabata N, Maekura R (2005) Current surgical intervention for pulmonary tuberculosis. The Annals of Thoracic Surgery 79(3): 959-963	

	Studies – CNS Agrawal D, Gupta A, Mehta VS. Role of shunt surgery in pediatric tubercular meningitis with hydrocephalus. Indian Pediatr 2005;42(3):245e50 Jha DK, Mishra V, Choudhary A, Khatri P, Tiwari R, Sural A, et al. Factors affecting the outcome of neuroendoscopy in patients with tuberculous meningitis hydrocephalus: a preliminary study. Surg Neurol 2007;68(1):35e41. discussion 41e2 Kemaloglu S, Ozkan U, Bukte Y, Ceviz A, Ozates M. Timing of shunt surgery in childhood tuberculous meningitis with hydrocephalus. Pediatr Neurosurg 2002; 37(4): 194e8 Lamprecht D, Schoeman J, Donald P, Hartzenberg H. Ventriculoperitoneal shunting in childhood tuberculous meningitis. Br J Neurosurg 2001;15(2):119e25 Mathew JM, Rajshekhar V, Chandy MJ. Shunt surgery in poor grade patients with tuberculous meningitis and hydrocephalus: effects of response to external ventricular drainage and other variables on long term outcome. J Neurol Neurosurg Psychiatry 1998; 65(1): 115e8 Palur R, Rajshekhar V, Chandy MJ, Joseph T, Abraham J. Shunt surgery for hydrocephalous in tubercular meningitis: A long-term follow up study. J Neurosurg 1991; 74: 64-69 Systematic reviews - spinal Jutte PC, van Loenhout-Rooyackers JH. Routine surgery in addition to chemotherapy for treating spinal tuberculosis. Cochrane Database of Systematic Reviews 2006, Issue 1. Article No: CD004532 Studies - spinal Bailey HL, Gabriel M, Hodgson AR & Shin JS (1972) Tuberculosis of the spine in children. Operative findings and results in one hundred consecutive patients treated by removal of the lesion and anterior grafting. J Bone Joint Surg Am 54(8): 1633-57 Chen WJ, Chen CH & Shih CH (1995) Surgical treatment of tuberculous spondylitis. 50 patients followed for 2-8 years. Acta Orthop Scand 66(2): 137-42 Guven O, Kumano K, YalVin S, Karahan M, Tsuji S. A single stage posterior approach and rigid fixation for preventing kyphosis in the treatment of spinal tuberculosis. Spine 1994;19:1039-43 Loembe PM. Tuberculosis of the lower cervical spine (C3-C7) in adults: Diagnostic and surgical aspects. Acta Neurochir (Wien) 1994;131:125-9 Louw JA (1990) Spinal tuberculosis with neurological deficit. Treatment with anterior vascularised rib grafts, posterior osteotomies and fusion. J Bone Joint Surg Br 72(4): 686-93 Medical Research Council Working Party on Tuberculosis of the Spine. Five-year assessments of controlled trials of ambulatory treatment, debridement and anterior spinal fusion in the management of tuberculosis of the spine. Studies in Bulawayo (Rhodesia) and in Hong Kong. Sixth report of the Medical Research Council Working Party on Tuberculosis of the Spine. Journal of Bone and Joint Surgery 1978;60-B(2):163–77 Nussbaum ES, Rockswold GL, Bergman TA, Erickson DL & Seljeskog EL (1995) Spinal tuberculosis: a diagnostic and management challenge. Journal of Neurosurgery 83(2): 243-7 Parthasarathy R, Sriram K, Santha T, Prabhakar R, Somasundaram PR, Sivasubramanian S. Short-course chemotherapy for tuberculosis of the spine. A comparison between ambulant treatment and radical surgery--ten-year report. Journal of Bone and Joint Surgery 1999;81-B(3):464–71 Rajasekaran S & Soundarapandian S (1989) Progression of kyphosis in tuberculosis of the spine treated by anterior arthrodesis. J Bone Joint Surg Am

	71(9): 1314-23 Yilmaz C, Selek HY, Gurkan I, Erdemli B, Korkusuz Z. Anterior instrumentation for the treatment of spinal tuberculosis. J Bone Joint Surg 1999;81:1261-7 Studies - peripheral lymph nodes Ammari FF, Bani Hani AH & Ghariebeh KI (2003) Tuberculosis of the lymph glands of the neck: a limited role for surgery. Otolaryngology: Head and Neck Surgery 128(4): 576-80 Studies - bone and joint Vohra R, Harinder SK, Dogra S, Saggar RR, Sharma R. Tuberculous osteomyelitis. J Bone Joint Surg Br 1997;79:562-6 Louw JA. Spinal tuberculosis with neurological deficit. Treatment with anterior vascularised rib grafts, posterior osteotomies and fusion. J Bone Joint Surg Br 1990;72-B:686-93. Systematic reviews - pericardial Mayosi BM. Interventions for treating tuberculous pericarditis. Cochrane Database of Systematic Reviews 2002, Issue 4. Article No. CD000526 Studies - pericardial Strang JI, Nunn AJ, Johnson DA, Casbard A, Gibson DG & Girling DJ (2004) Management of tuberculous constrictive pericarditis and tuberculous pericardial effusion in Transkei: results at 10 years follow-up. QJM 97(8): 525-35 Studies - abdominal Joshi MJ (1978) The surgical management of intestinal tuberculosis - a conservative approach. Indian J Surg 40: 79-83 Klimach OE & Ormerod LP (1985) Gastrointestinal tuberculosis: a retrospective review of 109 cases in a district general hospital. Q J Med 56(221): 569-78 Pujari BD (1979) Modified surgical procedures in intestinal tuberculosis. British Journal of Surgery 66(3):180-1 Studies - genitourinary Shin KY, Park HJ, Lee JJ, Park HY, Woo YN & Lee TY (2002) Role of early endourologic management of tuberculous ureteral strictures. J Endourol 16(10):755-8 Wong SH, Lau WY, Poon GP, Fan ST, Ho KK, Yiu TF & Chan SL (1984) The treatment of urinary tuberculosis. J Urol 131(2):297-301 Shammaa MZ, Hadidy S, al-Asfari R & Siragel-Din MN (1992) Urinary tuberculosis: experience of a teaching hospital in Syria. Int Urol Nephrol 24(5): 471-80 Gow JG (1966) The surgery of genito-urinary tuberculosis. Br J Surg 53(3):210-6

	Details	Additional comments
Review question P(16)	In people with drug susceptible, active non-respiratory TB receiving the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol), what duration of regimen is the most effective in reducing mortality and morbidity? i) Do regimens of less than 6 months present additional risks to the patient, and if so, in which patients? ii) Do regimens of more than 6 months	

	present additional benefits to the patient, and if so, in which patients?	

Objectives	To establish the optimum duration of treatment in adults with drug susceptible, active non-respiratory TB, with an emphasis on which patients may experience an additional risk of harm from the shorter regimens or an increased potential to benefit from the longer regimens	
Type of review	Intervention	
Language	English	
Study design	RCTs, quasi-RCTs, systematic reviews If there is insufficient evidence found, non-randomised controlled trials and then prospective cohort studies will be considered	'Insufficient evidence' is considered to be an evidence base that does not allow the GDG to make recommendations
Status	Published papers (full text only)	
Population	People with drug susceptible, active non-respiratory TB	Sites of interest include: • CNS • spinal • bone and joint • pericardial • peripheral lymph nodes • gastrointestinal • genitourinary • disseminated including miliary
Intervention	i) Treatment regimens of less than 6 months ii) Treatment regimens of more than 6 months	
Comparator	Treatment regimens of 6 months	
Outcomes	<u>Critical or important outcomes</u> 1. Cure: cure, treatment success or treatment failure 2. Adverse events 3. Mortality 4. Relapse 5. Adherence: adherence and treatment default 6. Changes in signs and symptoms 7. Emergence of acquired drug resistance <u>Adverse events of interest</u> Adverse events that are severe enough to require a modification, interruption or discontinuation in treatment, or one of	Treatment success, as defined by WHO ("a patient who was cured or who completed treatment"), will only be reported where trials do not report the disaggregated data for cure or treatment completion Outcome data for relapse will be reported according to the period of follow-up after the end of the treatment period (e.g. odds ratios for relapse at 3 months after treatment end, at 6 months after treatment end, at 12 months after treatment end etc)

	the following: 1. Mortality, treatment-related 2. Hepatotoxicity (liver toxicity) 3. Visual impairment 4. Nausea and/or vomiting 5. Hospitalisation due to adverse event(s) <u>Signs and symptoms of interest</u> See 'TB signs and symptoms by site of disease' table	
Other criteria for inclusion / exclusion of studies	<u>Include</u> • Papers comparing treatment regimens of antituberculosis chemotherapy of varying lengths • People with drug susceptible, active non-respiratory TB • Follow-up for at least the full treatment period <u>Exclude</u> • People receiving treatment for active respiratory TB, latent TB or drug resistant TB • Papers with a focus on populations with comorbidities or coexisting conditions other than HIV that will affect the choice or management of treatment • Papers comparing treatment durations of varying length in regimens containing different combinations of drugs • Papers using regimens that contain drugs other than the 4 drugs in the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol) • Papers considering the use of drugs not licensed in the UK • Observational, case series, case studies, and narrative reviews	Comparisons that contain regimens without at least 3 drugs in the initial phase or without rifampicin for the full treatment period will be included only as supplementary evidence
Search strategies	RCTs, quasi-RCTs, systematic reviews, non-randomised controlled trials Prospective observational studies in a separate search	
Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of individual studies • Data on all included studies will be	

	extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Where a randomised crossover study is included, the data from the first treatment phase only will be extracted • Analyses will be conducted by site of disease; an additional analysis will pool 'non-severe' sites (bone and joint TB, peripheral lymph node TB, gastrointestinal TB, and genitourinary TB) into an overarching analysis • Subgroup analysis will be undertaken for children and young people, where appropriate • Subgroup analysis will be undertaken by severity of disease, including smear negative disease, where appropriate • Subgroup analysis will be undertaken for people who have previously experienced treatment failure or who have relapsed, where appropriate • Subgroup analysis will be undertaken for people with HIV, where appropriate • Subgroup analysis will be undertaken for directly observed treatment, where appropriate	
Key papers	Systematic reviews - CNS van Loenhout-Rooyackers JH, Keyser A, Laheij RJ, Verbeek AL, van der Meer JW (2001) Tuberculous meningitis: is a 6-month treatment regimen sufficient? Int J Tuberc Lung Dis 5(11): 1028e35 Studies – CNS Doganay M, Calangu S, Turgut H, Bakir M, Aygen B (1995) Treatment of tuberculous meningitis in Turkey. Scand J Infect Dis 27: 135–138 Donald PR, Schoeman JF, van Zyl LE, de Villiers JN, Pretorius M, Springer P (1998) Intensive short course chemotherapy in the management of tuberculous meningitis. Int J Tuberc Lung Dis 2: 704–711 Jacobs RF, Sunakorn P, Chotpitayasunonah T, Pope S, Kelleher K (1992) Intensive short course chemotherapy for tuberculous meningitis. Pediatr Infect Dis J 11: 194–198 Systematic reviews - spinal van Loenhout-Rooyackers JH, Verbeek ALM, Jutte PC (2002) Chemotherapeutic	

	treatment for spinal tuberculosis. Int J Tuberc Lung Dis 6(3): 259-65 Studies - spinal Moon MS, Moon YW, Moon JL, Kim SS, Sun DH (2002) Conservative treatment of tuberculosis of the lumbar and lumbosacral spine. Clin Orthop Relat Res 398: 40-9 Nussbaum ES, Rockswold GL, Bergman TA, Erickson DL & Seljeskog EL (1995) Spinal tuberculosis: a diagnostic and management challenge. Journal of Neurosurgery 83(2): 243-7 Parthasarathy R, Sriram K, Santha T, Prabhakar R, Somasundaram PR & Sivasubramanian S (1999) Short-course chemotherapy for tuberculosis of the spine. A comparison between ambulant treatment and radical surgery--ten-year report. J Bone Joint Surg Br 81(3):464-71 Systematic reviews - peripheral lymph nodes van Loenhout-Rooyackers JH, Laheij RJF, Richter C, Verbeek ALM (2000) Shortening the duration of treatment for cervical tuberculous lymphadenitis. Eur Respir J 15:192-5 Studies - peripheral lymph nodes Campbell IA, Ormerod LP, Friend JA, Jenkins PA, Prescott RJ (1993) Six months versus nine months chemotherapy for tuberculosis of lymph nodes: final results. 87(8):621-3 Yuen APW, Wong SHW, Tam CM, Chan SL, Wei WI, Lau SK. Prospective randomized study of thrice weekly six-month and nine-month chemotherapy for cervical tuberculous lymphadenopathy. Otolaryngol Head Neck Surg 1997;116:189-92 Studies - abdominal Balasubramanian R, Nagarajan M, Balambal R, Tripathy SP, Sundararaman R, Venkatesan P (1997) Randomised controlled clinical trial of short course chemotherapy in abdominal tuberculosis: a five-year report. Int J Tuberc Lung Dis 1: 44-51 Studies - disseminated including miliary Lincoln EM & Hould F (1959) Results of specific treatment of miliary tuberculosis in children; a follow-up study of 63 patients treated with antimicrobial agents. N Engl J Med 261(3): 113-20 Studies - genitourinary Gokce G, Kilicarslan H, Ayan S, Tas F, Akar R, Kaya K & Gultekin EY (2002) Genitourinary tuberculosis: a review of 174 cases. Scand J Infect Dis 34(5): 338-40

	Details	Additional comments
Review question Q (17)	In people with active non-respiratory TB receiving the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol), do corticosteroids as an adjunct to the antituberculosis drug treatment regimen decrease morbidity and mortality compared to the standard recommended regimen alone?	Review has been integrated into review question N

	Details	Additional comments
Review question R (18)	In people with active non-respiratory TB receiving the standard recommended regimen (isoniazid, rifampicin, pyrazinamide and ethambutol), does surgery as an adjunct to the antituberculosis drug treatment regimen decrease morbidity and mortality compared to the standard recommended regimen alone?	Review has been integrated into review question O

	Details	Additional comments
Review question S (19)	In people with suspected or confirmed active TB, which relative risk factors are associated with a higher level of: i) multidrug resistance, or ii) any drug resistance?	
Objectives	To establish which risk factors are associated with drug-resistant TB, and which may form a useful screen for initiating rapid drug susceptibility testing, or for whom infection control measures and treatment appropriate to drug resistant disease should be initiated	
Type of review	Prognostic	
Language	English	
Study design	Prognostic (cohort etc) on recent UK data; if insufficient evidence is found, an analysis of national surveillance data for UK-specific risk factors will be undertaken International surveillance data (from WHO) to highlight countries with a high incidence of drug resistance	
Status	Published papers (full text only)	
Population	People with suspected or confirmed active TB	UK filter applied after discussions between IS analyst and reviewer
Prognostic factors	Clinical signs and symptoms or risk factors to predict the presence of i) multidrug resistance, or ii) any drug resistance	Might include: • prior TB drug treatment • treatment failure (for example, signified by no improvement after 2 months of treatment, or persistence of a positive culture result at the end of treatment) • contact with a known case of drug-resistant TB • birth in a foreign country, particularly high-incidence countries • HIV • residence in London • age profile, with highest rates between ages 25 and 44 • male gender
Outcomes	• Identification of i) multidrug resistance, or ii) any drug resistance • Resource use and cost	
Other criteria for	Include	Additional inclusion criteria

inclusion/exclusion of studies	Papers examining clinical signs, symptoms or risk factors for i) multidrug resistance, or ii) any drug resistance Exclude Papers examining formal diagnostic investigations to confirm drug resistance Case studies, case series and narrative reviews	Papers about UK populations and settings Additional exclusion criteria? Studies without multivariate analysis, unless insufficient data found
Search strategies	Prognostic (cohort etc) on recent UK data; if insufficient evidence is found, an analysis of national surveillance data for UK-specific risk factors will be undertaken International surveillance data (from WHO) to highlight countries with a high incidence of drug resistance	
Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • Data will be displayed in tables by prognostic factor • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements	
Identified key studies	Studies Djuretic T, Herbert J, Drobniewski F, Yates M, Smith EG, Magee JG, Williams R, Flanagan P, Watt B, Rayner A, Crowe M, Chadwick MV, Middleton AM & Watson JM (2002) Antibiotic resistant tuberculosis in the United Kingdom: 1993-1999. Thorax 57(6): 477-82 Irish C, Herbert J, Bennett D, Gilham C, Drobniewski F, Williams R, Smith EG, Magee JG, Watt B, Chadwick M, Watson JM (1999) Database study of antibiotic resistant tuberculosis in the United Kingdom, 1994-6. BMJ 318(7182): 497-8 Surveillance data Tuberculosis in the UK: Annual report on tuberculosis surveillance in the UK, 2013. London: Public Health England, August 2013. World Health Organization (2010) Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response. WHO: Geneva	

	Details	Additional comments
Review question T (20)	Other than review of a patient's risk factors for drug resistance, what diagnostic methods should be used for the identification of drug resistance?	Use HTA
Objectives	To establish which test is the most effective in accurately identifying drug resistance. To determine which diagnostic method is associated with the shortest time from start of drug susceptibility testing to identification of drug resistance or initiation of appropriate treatment.	
Type of review	Diagnostic	
Language	English	
Study design	Test-and-treat RCTs, quasi-RCTs, systematic reviews, cross-sectional studies (each test under examination is performed on every patient)	
Status	Published papers (full text only)	
Population	People with confirmed active TB	
Diagnostic tool(s)	Drug susceptibility tests	
Comparator	Culture	
Outcomes	• Diagnostic accuracy – sensitivity, specificity, positive predictive value, negative predictive value etc • Time to identification of drug resistance or initiation of appropriate treatment (from start of drug susceptibility testing) • Prognostic value of tests • Acceptability of approach • Adverse events • Health-related quality of life • Downstream treatment outcomes, including mortality, cure, treatment success, treatment failure, relapse • Resource use and cost	
Other criteria for inclusion/exclusion of studies	<u>Include</u> Papers comparing differing diagnostic methods against each other People with confirmed active TB Commercial tests Sample size ≥30, unless pooled in a meta-analysis Test-and-treat RCTs, quasi-RCTs, systematic reviews, cross-sectional studies	Diagnostic methods for drug resistance include: • culture techniques, such as: routine solid media, automated liquid culture (e.g. BACTEC, MGIT), microculture techniques (e.g. MODS, MABA), colorimetric assays (e.g. nitrate reductase assay (Griess method), MTT reduction test, MABA, REMA, TEMA), blood culture, urine

	Exclude People with latent TB Reference standard is not culture Case-control, case studies, case series and narrative reviews Tests are not conducted concomitantly In-house tests	culture • molecular testing – methods include: PCR, single-stranded conformation polymorphism, nucleic acid probe, isothermal amplification, restriction enzyme fragmentation • phage-based techniques
Search strategies	Test-and-treat RCTs, quasi-RCTs, systematic reviews, cross-sectional studies	
Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Where a randomised crossover study is included, the data from the first treatment phase only will be extracted	
Identified key studies	Systematic reviews Piersimoni C, Olivieri A, Benacchio L & Scarparo C (2006) Current perspectives on drug susceptibility testing of Mycobacterium tuberculosis complex: the automated nonradiometric systems. J Clin Microbiol 44(1): 20-8 Studies Angeby KA, Klintz L & Hoffner SE (2002) Rapid and inexpensive drug susceptibility testing of Mycobacterium tuberculosis with a nitrate reductase assay. J Clin Microbiol 40(2): 553-5 Arias M, Mello FC, Pavón A, Marsico AG, Alvarado-Gálvez C, Rosales S, Pessôa CL, Pérez M, Andrade MK, Kritski AL, Fonseca LS, Chaisson RE, Kimerling ME, Dorman SE (2007) Clinical evaluation of the microscopic-observation drug-susceptibility assay for detection of tuberculosis. Clin Infect Dis 44(5): 674-80 Carrière C, Riska PF, Zimhony O, Kriakov J, Bardarov S, Burns J, Chan J & Jacobs WR Jr (1997) Conditionally replicating luciferase reporter phages:	

	improved sensitivity for rapid detection and assessment of drug susceptibility of Mycobacterium tuberculosis. J Clin Microbiol 35(12): 3232-9 Caviedes L, Lee TS, Gilman RH, Sheen P, Spellman E, Lee EH, Berg DE & Montenegro-James S (2000) Rapid, efficient detection and drug susceptibility testing of Mycobacterium tuberculosis in sputum by microscopic observation of broth cultures. The Tuberculosis Working Group in Peru. J Clin Microbiol 38(3): 1203-8 Flament-Saillour M, Robert J, Jarlier V & Grosset J (1999) Outcome of multi-drug-resistant tuberculosis in France: a nationwide case-control study. Am J Respir Crit Care Med 160(2): 587-93 Montoro E, Lemus D, Echemendia M, Martin A, Portaels F, Palomino JC (2005) Comparative evaluation of the nitrate reduction assay, the MTT test, and the resazurin microtitre assay for drug susceptibility testing of clinical isolates of Mycobacterium tuberculosis. Journal of Antimicrobial Chemotherapy 55(4): 500-5 Moore DA, Mendoza D, Gilman RH, Evans CA, Hollm Delgado MG, Guerra J, Caviedes L, Vargas D, Ticona E, Ortiz J, Soto G, Serpa J; Tuberculosis Working Group in Peru (2004) Microscopic observation drug susceptibility assay, a rapid, reliable diagnostic test for multidrug-resistant tuberculosis suitable for use in resource-poor settings. J Clin Microbiol 42(10): 4432-7 Moore DA, Evans CA, Gilman RH, Caviedes L, Coronel J, Vivar A, Sanchez E, Piñedo Y, Saravia JC, Salazar C, Oberhelman R, Hollm-Delgado MG, LaChira D, Escombe AR, Friedland JS (2006) Microscopic-observation drug-susceptibility assay for the diagnosis of TB. N Engl J Med 355(15): 1539-50 Palaci M, Ueki SY, Sato DN, Da Silva Telles MA, Curcio M & Silva EA (1996) Evaluation of mycobacteria growth indicator tube for recovery and drug susceptibility testing of Mycobacterium tuberculosis isolates from respiratory specimens. J Clin Microbiol 34(3): 762-4 Palomino JC & Portaels F (1999) Simple procedure for drug susceptibility testing of Mycobacterium tuberculosis using a commercial colorimetic assay. Eur J Clin	

	Microbiol Infect Dis 18(5): 380-3 Palomino JC, Traore H, Fissette K & Portaels F (1999) Evaluation of Mycobacteria Growth Indicator Tube (MGIT) for drug susceptibility testing of Mycobacterium tuberculosis. Int J Tuberc Lung Dis 3(4): 344-8 Park WG, Bishai WR, Chaisson RE & Dorman SE (2002) Performance of the microscopic observation drug susceptibility assay in drug susceptibility testing for Mycobacterium tuberculosis. J Clin Microbiol 40(12): 4750-2 Rastogi N, Goh KS & David HL (1989) Drug susceptibility testing in tuberculosis: a comparison of the proportion methods using Lowenstein-Jensen, Middlebrook 7H10 and 7H11 agar media and a radiometric method. Res Microbiol 140(6): 405-17 Roberts GD, Goodman NL, Heifets L, Larsh HW, Lindner TH, McClatchy JK, McGinnis MR, Siddiqi SH, Wright P (1983) Evaluation of the BACTEC radiometric method for recovery of mycobacteria and drug susceptibility testing of Mycobacterium tuberculosis from acid-fast smear-positive specimens. J Clin Microbiol 18(3): 689-96 Shiferaw G, Woldeamanuel Y, Gebeyehu M, Girmachew F, Demessie D & Lemma E (2007) Evaluation of microscopic observation drug susceptibility assay for detection of multidrug-resistant Mycobacterium tuberculosis. J Clin Microbiol 45(4): 1093-7 Siddiqi SH, Libonati JP & Middlebrook G (1981) Evaluation of rapid radiometric method for drug susceptibility testing of Mycobacterium tuberculosis. J Clin Microbiol 13(5): 908-12 Siddiqi SH, Hawkins JE & Laszlo A (1985) Interlaboratory drug susceptibility testing of Mycobacterium tuberculosis by a radiometric procedure and two conventional methods. J Clin Microbiol 22(6): 919-23 van Klingeren B, Dessens-Kroon M, van der Laan T, Kremer K & van Soolingen D (2007) Drug susceptibility testing of Mycobacterium tuberculosis complex by use of a high-throughput, reproducible, absolute concentration method. J Clin Microbiol 45(8): 2662-8 Van Rie A, Warren R, Mshanga I,	

	Jordaan AM, van der Spuy GD, Richardson M, Simpson J, Gie RP, Enarson DA, Beyers N, van Helden PD & Victor TC (2001) Analysis for a limited number of gene codons can predict drug resistance of Mycobacterium tuberculosis in a high-incidence community. J Clin Microbiol 39(2): 636-41 Wilson SM, al-Suwaidi Z, McNerney R, Porter J & Drobniewski F (1997) Evaluation of a new rapid bacteriophage-based method for the drug susceptibility testing of Mycobacterium tuberculosis. Nat Med 3(4): 465-8	

	Details	Additional comments
Review question U (21)	In people with drug-resistant TB (excluding MDR- and XDR-TB), what is the most effective regimen of antituberculosis drugs for reducing mortality and morbidity?	
Objectives	To establish what regimen of antituberculosis drugs is most effective in reducing mortality and morbidity caused by drug-resistant TB (excluding MDR- and XDR-TB)	Regimens may vary by: • dosing frequency • duration • combination of drugs
Type of review	Intervention	
Language	English	
Study design	RCTs, quasi-RCTs, non-randomised controlled trials, systematic reviews If there is insufficient evidence found, prospective cohort studies will be considered	'Insufficient evidence' is considered to be an evidence base that does not allow the GDG to make recommendations
Status	Published papers (full text only)	
Population	People with drug-resistant TB, excluding MDR-TB or XDR-TB	Drug resistances of interest include, but are not limited to: • isoniazid • rifampicin • pyrazinamide • ethambutol • streptomycin • streptomycin and isoniazid
Intervention	Varying regimens of antituberculosis drugs	Regimens may vary by: • dosing frequency • duration • combination of drugs
Comparator	Other regimens of antituberculosis drugs	
Outcomes	<u>Critical or important outcomes</u> 1. Cure: cure, treatment success or treatment failure 2. Adverse events 3. Mortality 4. Relapse 5. Adherence: adherence and treatment default 6. Changes in signs and symptoms 7. Emergence of acquired drug	Treatment success, as defined by WHO ("a patient who was cured or who completed treatment"), will only be reported where trials do not report the disaggregated data for cure or treatment completion Outcome data for relapse will be reported according to the period of follow-up after the end of the treatment period (e.g. odds ratios for relapse at 3 months after treatment end, at 6 months after treatment end, at 12 months after treatment end etc)

	resistance Adverse events of interest Adverse events that are severe enough to require a modification, interruption or discontinuation in treatment, or one of the following: 1. Mortality, treatment-related 2. Hepatotoxicity (liver toxicity) 3. Visual impairment 4. Nausea and/or vomiting 5. Hospitalisation due to adverse event(s) Signs and symptoms of interest See 'TB signs and symptoms by site of disease' table	
Other criteria for inclusion / exclusion of studies	Include • Papers comparing different combinations of antituberculosis drugs • People with drug-resistant TB • Follow-up for at least the full treatment period Exclude • People with MDR-TB or XDR-TB, unless reported separately from data for people with non-MDR- or non-XDR-TB • People with drug susceptible TB or latent TB • Papers with a focus on populations with comorbidities or coexisting conditions other than HIV that will affect the choice or management of treatment • Papers comparing regimens that include drugs not licensed in the UK • Observational, case series, case studies and narrative reviews	
Search strategies	RCTs, quasi-RCTs, non-randomised controlled trials, systematic reviews. If there is insufficient evidence found, prospective cohort studies	

	will be considered	
Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Where a randomised crossover study is included, the data from the first treatment phase only will be extracted • The analysis will be conducted by type of drug resistance, dosing frequency, duration and the combination and number of drugs used, where possible. • Subgroup analysis will be undertaken by site of disease, where possible • Subgroup analysis will be undertaken by site of disease, where possible • Subgroup analysis will be undertaken for children and young people, where appropriate • Subgroup analysis will be undertaken for people with HIV, where appropriate	
Key papers		

	Details	Additional comments
Review question V (22)	In people with drug resistant TB (excluding MDR- and XDR-TB) receiving drug treatment, what duration of regimen is the most effective in reducing mortality and morbidity?	Integrated into review question U

	Details	Additional comments
Review question W (23)	In people with drug-resistant TB, are intermittent dosing regimens as effective as daily drug treatment regimens in reducing mortality and morbidity?	Non-MDR-TB has been integrated into review question U; MDR-TB has been integrated into review question Y

	Details	Additional comments
Review question X (24)	In people with drug-resistant TB, does surgery as an adjunct to an antituberculosis drug treatment regimen decrease morbidity and mortality compared with an antituberculosis drug regimen alone?	Review has been integrated into review question O

	Details	Additional comments
Review question Y (25)	What management strategies are most effective for managing all cases of MDR-TB ?	
Objectives	To identify the broad treatment principles or elements of care that should be applied to the management of all cases of MDR-TB	
Type of review	Intervention	
Language	English	
Study design	RCTs, quasi-RCTs, systematic reviews, non-randomised controlled trials, observational	The GDG determined that, given the breadth of this review area, the review question would best be answered by a **position paper** by a group of **topic experts** from the GDG
Status	Published papers (full text only)	
Population	People with MDR-TB	Drug resistances of interest include: • isoniazid • rifampicin • pyrazinamide • ethambutol • streptomycin • streptomycin and isoniazid • MDR-TB • XDR-TB
Intervention	Broad treatment principles or elements of care in the management of drug-resistant TB	Might include: • never add a single drug to a failing regimen • standardised vs individualised regimens • use of drug susceptibility data to design regimens • number of anti-tuberculosis drugs required • advisable length of the initial phase of treatment • treatment decisions only by experienced clinicians • dosing frequency • treatment of latent TB in which the source case is suspected to have MDR-TB
Comparator	Other treatment principles or elements of care in the management of drug-resistant TB	
Outcomes	Critical or important outcomes	Treatment success, as defined by WHO (“a patient who was cured or who completed

	1. Cure: cure, treatment success or treatment failure 2. Adverse events 3. Mortality 4. Relapse 5. Adherence: adherence and treatment default 6. Changes in signs and symptoms 7. Emergence of acquired drug resistance <u>Adverse events of interest</u> Adverse events that are severe enough to require a modification, interruption or discontinuation in treatment, hospitalisation, or one of the following: 1. Mortality, treatment-related 2. Hepatotoxicity (liver toxicity) 3. Discontinuation or interruption of tx 4. Visual impairment 5. Nausea and/or vomiting <u>Signs and symptoms of interest</u> See 'TB signs and symptoms by site of disease' table	treatment"), will only be reported where trials do not report the disaggregated data for cure or treatment completion Outcome data for relapse will be reported according to the period of follow-up after the end of the treatment period (e.g. odds ratios for relapse at 3 months after treatment end, at 6 months after treatment end, at 12 months after treatment end etc)
Other criteria for inclusion / exclusion of studies	<u>Include</u> • Papers examining treatment principles or elements of care in the management of MDR-TB <u>Exclude</u> • Case studies and narrative reviews	
Search strategies	RCTs, quasi-RCTs, systematic reviews, non-randomised controlled trials, observational	
Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will	

	be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Where a randomised crossover study is included, the data from the first treatment phase only will be extracted	
Key papers	Systematic reviews Jacobson KR, Tierney DB, Jeon CY, Mitnick CD & Murray MB (2010) Treatment outcomes among patients with extensively drug-resistant tuberculosis: systematic review and meta-analysis. Clin Infect Dis 51(1): 6-14 Johnston JC, Shahidi NC, Sadatsafavi M & Fitzgerald JM (2009) Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. PLoS One 4(9): e6914 Studies Cox HS, Kalon S, Allamuratova S, Sizaire V, Tigay ZN, Rüsch-Gerdes S, Karimovich HA, Kebede Y & Mills C (2007) Multidrug-resistant tuberculosis treatment outcomes in Karakalpakstan, Uzbekistan: treatment complexity and XDR-TB among treatment failures. PLoS One 2(11): e1126 Geerligs WA, Van Altena R, De Lange WCM, Van Soolingen D & Van Der Werf TS (2000) Multidrug-resistant tuberculosis: long-term treatment outcome in the Netherlands. Int J Tuberc Lung Dis 4(8): 758-64 Kim HJ, Kang CH, Kim YT, Sung SW, Kim JH, Lee SM, Yoo CG, Lee CT, Kim YW, Han SK, Shim YS & Yim JJ (2006) Prognostic factors for surgical resection in patients with multidrug-resistant tuberculosis. Eur Respir J 28(3): 576-80 Kwon YS, Kim YH, Suh GY, Chung MP, Kim H, Kwon OJ, Choi YS, Kim K, Kim J, Shim YM & Koh WJ (2008) Treatment outcomes for HIV-uninfected patients with multidrug-resistant and extensively drug-resistant tuberculosis. Clin Infect Dis 47(4): 496-502 Leimane V, Riekstina V, Holtz TH, Zarovska E, Skripconoka V, Thorpe LE, Laserson KF & Wells CD (2005) Clinical outcome of individualised treatment of multidrug-resistant tuberculosis in Latvia: a retrospective cohort study. Lancet 365(9456): 318-26 Mirsaeidi SM, Tabarsi P, Khoshnood K, Pooramiri MV, Rowhani-Rahbar A, Mansoori SD, Masjedi H, Zahirifard S, Mohammadi F, Farnia P, Masjedi MR & Velayati AA (2005) Treatment of multiple drug-resistant tuberculosis (MDR-TB) in Iran. Int J Infect Dis 9(6): 317-22 Nathanson E, Gupta R, Huamani P, Leimane V, Pasechnikov AD, Tupasi TE, Vink K, Jaramillo E & Espinal MA (2004) Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. Int J Tuberc Lung Dis 8(11): 1382-4 Park SK, Lee CM, Heu JP & Song SD (2002) A retrospective study for the outcome of pulmonary resection in 49 patients with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 6(2): 143-9 Suárez PG, Floyd K, Portocarrero J, Alarcón E, Rapiti E, Ramos G, Bonilla C, Sabogal I, Aranda I, Dye C, Raviglione M & Espinal MA (2002) Feasibility and cost-effectiveness of standardised second-line drug treatment for chronic	

	tuberculosis patients: a national cohort study in Peru. Lancet 359(9322): 1980-9 Tahaoğlu K, Törün T, Sevim T, Ataç G, Kir A, Karasulu L, Ozmen I & Kapakli N (2001) The treatment of multidrug-resistant tuberculosis in Turkey. N Engl J Med 345(3): 170-4

	Details	Additional comments
Review question Z (26)	For people receiving drug treatment for active TB who experience treatment interruptions, what approach to re-establishing appropriate treatment is the most effective in reducing mortality and morbidity?	Separate searches for each cause (i.e. 1 for poor adherence and 1 for drug toxicity)
Objectives	To establish the most effective approach to re-establishing treatment for active TB following treatment interruptions.	
Type of review	Intervention	
Language	English	
Study design	RCTs, quasi-RCTs, systematic reviews, non-randomised controlled trials, observational	
Status	Published papers (full text only)	
Population	People receiving drug treatment for drug susceptible active TB receiving the standard recommended regimen who have experienced treatment interruptions	A treatment interruption is defined as break in treatment for 2 weeks or more, or more than 20% of prescribed doses missed intermittently throughout the regimens Different causes of treatment interruption might indicate different management options. The causes of treatment interruption might include: • poor adherence • side effects arising from drug toxicity • poor absorption eg severe diarrhoea • started treatment in another country using regime that we would consider inferior Further differentiated by: • duration of interruption • where in the regimen the interruption falls • dosing frequency prescribed
Intervention	Different approaches to re-establishing appropriate treatment	Approaches (for intermittently poor adherence) might include: • extending the treatment period • restarting the treatment regimen from the

		beginning Approaches (for prolonged poor adherence) might include: • extending the treatment period • restarting the treatment regimen from the beginning Approaches (for interruptions due to drug toxicity) might include: • extending the treatment period • restarting the treatment regimen from the beginning • sequential reintroduction
Comparator	Different approaches to re-establishing appropriate treatment	
Outcomes	<u>Critical or important outcomes</u> 1. Mortality 2. Cure: cure, treatment success or treatment failure 3. Changes in signs and symptoms 4. Relapse 5. Adverse events 6. Adherence: adherence and treatment default 7. Emergence of acquired drug resistance <u>Adverse events of interest</u> Adverse events that are severe enough to require a modification, interruption or discontinuation in treatment, or one of the following: 1. Mortality, treatment-related 2. Hepatotoxicity (liver toxicity) 3. Visual impairment 4. Nausea and/or vomiting 5. Hospitalisation due to adverse event(s) <u>Signs and symptoms of interest</u> See 'TB signs and symptoms by site of disease' table	

Other criteria for inclusion/exclusion of studies	Include • Papers examining approaches to re-establishing appropriate treatment in people who have experienced treatment interruptions • People receiving antituberculosis chemotherapy for active TB who have experienced treatment interruptions • Follow-up for at least the full treatment period Exclude • Papers considering the use of drugs not licensed in the UK • Case series, case studies and narrative reviews	IS strategy: (TB OR standard regimen) AND (treatment interruptions OR adverse events) AND (Obs, RCT, SR filters)
Search strategies	RCTs, quasi-RCTs, systematic reviews, non-randomised controlled trials, observational	
Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Where a randomised crossover study is included, the data from the first treatment phase only will be extracted • Analysis and searches to be conducted by type of treatment interruption (e.g. treatment interruptions associated with poor adherence vs treatment interruptions associated with side effects of treatment) • Subgroup analysis will be undertaken by duration and timing (initiation vs continuation phase) of treatment interruption, where possible • Subgroup analysis will be undertaken by site of disease, where possible • Subgroup analysis will be undertaken by severity of disease, where possible • Subgroup analysis will be undertaken for children and young people, where appropriate • Subgroup analysis will be undertaken	

	for people with HIV, where appropriate	
Identified key studies	Systematic reviews Brasil PE & Braga JU (2008) Meta-analysis of factors related to health services that predict treatment default by tuberculosis patients. Cad Saude Publica 24(Suppl 4): s485-502 Studies Breen RA, Miller RF, Gorsuch T, Smith CJ, Schwenk A, Holmes W, Ballinger J, Swaden L, Johnson MA, Cropley I & Lipman MC (2006) Adverse events and treatment interruption in tuberculosis patients with and without HIV co-infection. Thorax 61(9): 791-4 Driver CR, Matus SP, Bayuga S, Winters AI & Munsiff SS (2005) Factors associated with tuberculosis treatment interruption in New York City. J Public Health Manag Pract 11(4): 361-8 Sloan JP & Sloan MC (1981) An assessment of default and non-compliance in tuberculosis control in Pakistan. Trans R Soc Trop Med Hyg 75(5): 717-8	

	Details	Additional comments
Review question AA (27)	For people in congregate settings (including hospitals, schools, residential homes, homeless shelters, prisons and religious establishments) who have with suspected or confirmed active TB, what infection control measures are the most effective in preventing transmission of TB infection to others?	AA initially hospitals only; AA and BB (other congregate settings) integrated Subgroup analysis to be performed by setting
Objectives	To establish the best approach to minimising the transmission of TB from people with active, drug susceptible TB to others in the hospital in which they are staying. Special consideration will be given to the prevention of transmission in settings in which people who are immunocompromised or children may be particularly exposed, or instances in which MDR- or XDR-TB is suspected.	(infect$ or colonis$ or coloniz$ or contaminat$)
Type of review	Intervention	
Language	English	
Study design	RCTs, quasi-RCTs, systematic reviews, non-randomised controlled trials If there is insufficient evidence found, prospective observational studies will be considered	
Status	Published papers (full text only)	
Population	People exposed to TB in congregate settings	
Intervention	Measures for preventing the transmission of TB in congregate settings	Might include: • personal: mask-wearing, cough hygiene/behaviour • administrative: isolation or reduction in patient movements, reduced time to diagnosis/initiation of treatment, sample collection in isolation rooms, dedicated infection control staff, restricting/screening of visitors • engineering: isolation rooms (including negative pressure isolation rooms, autodoor-closers, sputum induction booths), droplet shields, improved ventilation (including extraction fans, laminar airflow), UV lights
Comparator	Other measures for preventing the transmission of TB in congregate settings	
Outcomes	• Risk of tuberculosis infection or	Acceptability of approach should

	disease: number of cases of TB identified/number of people at risk or tested • Acceptability of approach • Risk of exposure: amount of contact with a case of TB • Resource use and cost • Health-related quality of life	be inclusive, taking into account, for example, views of both patients and staff
Other criteria for inclusion/exclusion of studies	Include • Papers examining the effectiveness of infection control measures in preventing TB transmission in hospitals • RCTs, quasi-RCTs, systematic reviews, non-randomised controlled trials; if there is insufficient evidence found, prospective observational studies will be considered Exclude • Case series, case studies, descriptions of nosocomial outbreaks, narrative reviews, modeling studies • Studies that utilised questionnaire responses to ascertain prevalence or incidence of latent or active TB	
Search strategies	RCTs, quasi-RCTs, systematic reviews, non-randomised controlled trials, observational studies	
Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Where a randomised crossover study is included, the data from the first treatment phase only will be extracted • Subgroup analysis will be undertaken by setting, where appropriate • Subgroup analysis will be undertaken for non-respiratory TB, where appropriate • Subgroup analysis will be undertaken for settings in which children are particularly exposed, where	

	appropriate • Subgroup analysis will be undertaken for settings in which people who are immunocompromised are particularly exposed, where appropriate • Subgroup analysis will be undertaken for women who are pregnant, where appropriate • Subgroup analysis will be undertaken for suspected MDR- or XDR-TB, where appropriate	
Identified key studies	Systematic reviews Menzies D, Joshi R & Pai M (2007) Risk of tuberculosis infection and disease associated with work in health care settings. Int J Tuberc Lung Dis 11(6): 593-605 Studies Bangsberg D R, Crowley K, Moss A, Dobkin J F, McGregor C, Neu H C (1997) Reduction in tuberculin skin-test conversions among medical house staff associated with improved tuberculosis infection control practices. Infect Control Hosp Epidemiol 18: 566–570 Behrman A J, Shofer F S. Tuberculosis exposure and control in an urban emergency department. Ann Emerg Med 1998; 31: 370–375 Blumberg H M, Watkins D L, Jeffrey P A-C, et al (1995) Preventing the nosocomial transmission of tuberculosis. Ann Intern Med 122: 658–663 Escombe AR, Moore DA, Gilman RH, Navincopa M, Ticona E, Mitchell B, Noakes C, Martínez C, Sheen P, Ramirez R, Quino W, Gonzalez A, Friedland JS & Evans CA (2009) Upper-room ultraviolet light and negative air ionization to prevent tuberculosis transmission. PLoS Med 6(3): e43 Fella P, Rivera P, Hale M, Squires K, Sepkowitz K (1995) Dramatic decrease in tuberculin skin test conversion rate among employees at a hospital in New York City. Am J Infect Control 23: 352–356 Fraser VJ, Johnson K, Primack J, Jones M, Medoff G & Dunagan WC (1993) Evaluation of rooms with negative pressure ventilation used for respiratory isolation in seven midwestern hospitals. Infect Control Hosp Epidemiol 14(11): 623-8 Fridkin S K, Managan L, Boyard R N	

	(1995) SHEA-CDC TB survey, Part II. Efficacy of TB infection control programs at member hospitals, 1992. Infect Control Hosp Epidemiol 16: 135–140 Knirsch CA, Jain NL, Pablos-Mendez A, Friedman C & Hripcsak G (1998) Respiratory isolation of tuberculosis patients using clinical guidelines and an automated clinical decision support system. Infect Control Hosp Epidemiol 19(2): 94-100 Maciel EL, Viana MC, Zeitoune RC, Ferreira I, Fregona G & Dietze R (2005) Prevalence and incidence of Mycobacterium tuberculosis infection in nursing students in Vitória, Espírito Santo. Rev Soc Bras Med Trop 38(6): 469-72 Maloney S A, Pearson M L, Gordon M T, Del Castillo R, Boyle J F, Jarvis W R (1995) Efficacy of control measures in preventing nosocomial transmission of multidrug-resistant tuberculosis to patients and health care workers. Ann Intern Med 122: 90–95 Marier RL & Nelson T (1993) A ventilation-filtration unit for respiratory isolation. Infect Control Hosp Epidemiol 14(12): 700-5 Menzies D, Fanning A, Yuan L & FitzGerald JM (2000) Hospital ventilation and risk for tuberculous infection in canadian health care workers. Canadian Collaborative Group in Nosocomial Transmission of TB. Ann Intern Med 133(10): 779-89 Moro M L, Errante I, Infuso A, et al (2000) Effectiveness of infection control measures in controlling a nosocomial outbreak of multidrug- resistant tuberculosis among HIV patients in Italy. Int J Tuberc Lung Dis 4: 61–68 Nolan CM, Elarth AM, Barr H, Saeed AM & Risser DR (1991) An outbreak of tuberculosis in a shelter for homeless men. A description of its evolution and control. Am Rev Respir Dis 143(2): 257-61 Riley RL (1994) Ultraviolet air disinfection: rationale for whole building irradiation. Infect Control Hosp Epidemiol 15(5): 324-5 Stead WW, Lofgren JP, Warren E & Thomas C (1985) Tuberculosis as an endemic and nosocomial infection among the elderly in nursing homes. N Engl J Med 312(23): 1483-7	

	Stroud LA, Tokars JI, Grieco MH, Crawford JT, Culver DH, Edlin BR, Sordillo EM, Woodley CL, Gilligan ME, Schneider N, et al (1995) Evaluation of infection control measures in preventing the nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis in a New York City hospital. Infect Control Hosp Epidemiol 16(3): 141-7 Tokars JI, McKinley GF, Otten J, Woodley C, Sordillo EM, Caldwell J, Liss CM, Gilligan ME, Diem L, Onorato IM & Jarvis WR (2001) Use and efficacy of tuberculosis infection control practices at hospitals with previous outbreaks of multidrug-resistant tuberculosis. Infect Control Hosp Epidemiol 22(7): 449-55 Wenger P N, Otten J, Breeden A, Orfas D, Beck-Sague C M, Jarvis W R (1995) Control of nosocomial transmission of multidrugresistant Mycobacterium tuberculosis among health care workers and HIV-infected patients. Lancet 345: 235–240	

	Details	Additional comments
Review question BB (28)	For people who have active TB who are not in hospital but who are in congregate settings (for example schools, residential homes or homeless shelters), what infection control measures are the most effective in preventing transmission of TB infection to others?	Combined with AA (same evidence base) Additional settings – prisons, religious establishments?

	Details	Additional comments
Review question CC (29)	For people who have active TB, i) what duration of isolation is necessary to minimise the risk of infection to others, and ii) what prognostic factors help determine if a person poses a risk of infection to others and should remain in isolation?	CCi combined with CCii, DDi and DDii (CCi previously: 'For people who have active TB that is not suspected to be MDR-TB, what prognostic factors help determine if a person poses a risk of infection to others and should remain in isolation?')
Objectives	To establish the duration that a person with active TB should remain in isolation in order to minimise the risk of infection to others To determine what factors are predictive of the level of infectiousness of a person with active TB, and can be used to determine if a person should remain in isolation in order to minimise the risk of infection to others	
Type of review	i) intervention, ii) prognostic	
Language	English	
Study design	Systematic reviews, RCTs, quasi-RCTs, non-randomised controlled trials, cohort (prospective and retrospective), longitudinal studies, cross-sectional, case-control	
Status	Published papers (full text only)	
Population	People who have active TB	People with confirmed active TB, broken down into the following subgroups: • non-MDR-TB (drug susceptible and isolated/combined resistances) • suspected MDR-TB • confirmed MDR-TB
Intervention	i) isolation periods of varying duration ii) clinical signs, symptoms or measurements that indicate whether a person with active TB poses a continued risk of infection to others	Examples of clinical signs, symptoms or measurements that indicate whether a person with active TB poses a continued risk of infection to others may include: • number of sputum samples showing sputum conversion (e.g. 3 consecutive samples) • acid-fast bacilli counts (e.g. concentrated *vs* unconcentrated) • time to smear conversion • time to culture positivity

		• frequency of coughing • severity of disease – e.g. presence of cavitary disease • site of disease • previous or current treatment – has this been adequate? • duration of isolation so far • NAAT result
Comparator	i) other durations of isolation ii) other clinical signs, symptoms or measurements that indicate whether a person with active TB poses a continued risk of infection to others	
Outcomes	• Risk of tuberculosis infection or disease: number of cases of TB identified/number of people at-risk or tested • Risk of exposure: amount of contact with a case of TB • Acceptability of approach • Relationship between clinical factor and risk of a diagnosis (microbiological) of active or latent TB in another person • Resource use and cost • Health-related quality of life	Acceptability of approach should be inclusive, taking into account, for example, views of both patients and staff Do not correlate microbiological status in both outcomes *and* interventions – only one
Other criteria for inclusion/exclusion of studies	<u>Include</u> • Papers examining varying periods of isolation as means of infection control in people with active respiratory TB • Papers considering the predictive value of clinical signs, symptoms or measurements in indicating whether a person with active TB poses a risk of infection to others • Papers considering the relationship between clinical signs, symptoms or measurements of people with active TB and the risk of a diagnosis of active or latent TB in another person • Systematic reviews, RCTs, quasi-RCTs, non-randomised controlled trials, cohort (prospective and retrospective), longitudinal studies, cross-sectional, case-control • Full text papers • English language <u>Exclude</u>	

	• Case series, case studies, descriptions of nosocomial outbreaks, narrative reviews, modeling studies	
Search strategies	Systematic reviews, RCTs, quasi-RCTs, non-randomised controlled trials, cohort (prospective and retrospective), longitudinal studies, cross-sectional, case-control	
Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Where a randomised crossover study is included, the data from the first treatment phase only will be extracted • Subgroup analysis will be undertaken for children, where appropriate • Subgroup analysis will be undertaken for people with HIV, where appropriate • Subgroup analysis will be undertaken for non-MDR-TB, suspected MDR-TB and confirmed MDR-TB, where appropriate	
Identified key studies	Studies Aguilar J, Yang JJ, Brar I & Markowitz N (2009) Clinical prediction rule for respiratory isolation of patients with suspected pulmonary tuberculosis. Infectious Diseases in Clinical Practice 17(5): 317-22 Bock NN, McGowan JE Jr, Ahn J, Tapia J & Blumberg HM (1996) Clinical predictors of tuberculosis as a guide for a respiratory isolation policy. Am J Respir Crit Care Med 154(5): 1468-72 Brooks SM, Lassiter NL & Young EC (1973) A pilot study concerning the infection risk of sputum positive tuberculosis patients on chemotherapy. Am Rev Respir Dis 108(4): 799-804 Fortún J, Martín-Dávila P, Molina A, Navas E, Hermida JM, Cobo J, Gómez-	

	Mampaso E & Moreno S (2007) Sputum conversion among patients with pulmonary tuberculosis: are there implications for removal of respiratory isolation? J Antimicrob Chemother 59(4): 794-8 Gaeta TJ, Webheh W, Yazji M, Ahmed J & Yap W (1997) Respiratory isolation of patients with suspected pulmonary tuberculosis in an inner-city hospital. Acad Emerg Med 4(2): 138-41 Gunnels JJ, Bates JH, Swindoll H (1974) Infectivity of sputum-positive tuberculous patients on chemotherapy. Am Rev Respir Dis 109:323-30 Horne DJ, Johnson CO, Oren E, Spitters C & Narita M (2010) How soon should patients with smear-positive tuberculosis be released from inpatient isolation? Infect Control Hosp Epidemiol 31(1): 78-84 Loudon RG & Spohn SK (1969) Cough frequency and infectivity in patients with pulmonary tuberculosis. Am Rev Respir Dis 99(1): 109-11 Mixides G, Shende V, Teeter LD, Awe R, Musser JM & Graviss EA (2005) Number of negative acid-fast smears needed to adequately assess infectivity of patients with pulmonary tuberculosis. Chest 128(1): 108-15 Rakoczy KS, Cohen SH & Nguyen HH (2008) Derivation and validation of a clinical prediction score for isolation of inpatients with suspected pulmonary tuberculosis. Infect Control Hosp Epidemiol 29(10): 927-32 Redd JT & Susser E (1997) Controlling tuberculosis in an urban emergency department: a rapid decision instrument for patient isolation. Am J Public Health 87(9): 1543-7 Ritchie SR, Harrison AC, Vaughan RH, Calder L & Morris AJ (2007) New recommendations for duration of respiratory isolation based on time to detect Mycobacterium tuberculosis in liquid culture. Eur Respir J 30(3): 501-7 Shaw JB & Wynn-Williams N (1954) Infectivity of pulmonary tuberculosis in relation to sputum status. Am Rev Tuberc 69(5): 724-32 Solari L, Acuna-Villaorduna C, Soto A & van der Stuyft P (2011) Evaluation of clinical prediction rules for respiratory isolation of inpatients with suspected	

	pulmonary tuberculosis. Clin Infect Dis 52(5): 595-603 Telzak EE, Fazal BA, Pollard CL, Turett GS, Justman JE & Blum S (1997) Factors influencing time to sputum conversion among patients with smear-positive pulmonary tuberculosis. Clin Infect Dis 25(3): 666-70 Yeager H Jr, Lacy J, Smith LR & LeMaistre CA (1967) Quantitative studies of mycobacterial populations in sputum and saliva. Am Rev Respir Dis 95(6): 998-1004	

	Details	Additional comments
Review question CCii (29)	For people who have active TB that is not suspected to be MDR-TB, what duration of isolation is necessary to minimise the risk of infection to others?	Combined with CCi, DDi and DDii

	Details	Additional comments
Review question DDi (30)	For people who have active TB that is suspected to be MDR-TB, what prognostic factors help determine if a person poses a risk of infection to others and should remain in isolation?	Combined with CCi, CCii and DDii

	Details	Additional comments
Review question DDii (30)	For people who have active TB that is suspected to be MDR-TB, what duration of isolation is necessary to minimise the risk of infection to others?	Combined with CCi, CCii and DDi

	Details	Additional comments
Review question EE (31)	Which diagnostic strategy is most effective in establishing an accurate diagnosis of latent TB in children?	Update searches from CG117
Objectives	To establish which diagnostic strategy is the most effective in children in establishing an accurate diagnosis of latent TB, in the absence of a gold standard To determine the appropriate diagnostic thresholds for Mantoux, as well as the impact of HIV and BCG status	
Type of review	Diagnostic	
Language	English	
Study design	Update searches from CG117	
Status	Published papers (full text only)	
Population	Children and young people	
Intervention	IGRA alone or with Mantoux	IGRAs available in the UK are: • QuantiFERON-TB Gold In tube • T-SPOT.TB Where possible, relative effectiveness of each IGRA will be assessed individually
Comparator	Mantoux alone	
Outcomes	• Association between test results and the risk of having latent TB: discordance, concordance, odds ratios, ratios of odds ratios • Prognostic value of tests • Acceptability of approach • Adverse events • Likelihood of indeterminate result • Health-related quality of life • Resource use and cost	
Other criteria for inclusion/exclusion of studies	Include Papers comparing differing approaches to diagnosing latent TB Children and young people (<18 years) Exclude Adults Case studies, case series and narrative reviews	Tuberculin skin tests other than Mantoux will be downgraded for indirectness
Search strategies	Update searches from CG117	
Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of	

	individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Where a randomised crossover study is included, the data from the first treatment phase only will be extracted • Subgroup analysis will be undertaken for contacts of those with active respiratory TB, and the time from initial exposure to test, where appropriate • Subgroup analysis will be undertaken by age, where appropriate • For seriel tesing strategies, subgroup analysis will be undertaken for issues relating to test interaction, such as duration of period between tests, where appropriate • Subgroup analysis will be undertaken by threshold of Mantoux interpretation (≥5mm, ≥10mm, ≥15mm), where appropriate • Subgroup analysis will be undertaken by BCG status, where appropriate	
Identified key studies	Systematic reviews Machingaidze S, Wiysonge CS, Gonzalez-Angulo Y, Hatherill M, Moyo S, Hanekom W & Mahomed H (2011) The utility of an interferon gamma release assay for diagnosis of latent tuberculosis infection and disease in children: a systematic review and meta-analysis. Pediatr Infect Dis J 30(8): 694-700 Studies Adetifa IM, Ota MO, Jeffries DJ, Hammond A, Lugos MD, Donkor S, Patrick O, Adegbola RA & Hill PC (2010) Commercial interferon gamma release assays compared to the tuberculin skin test for diagnosis of latent Mycobacterium tuberculosis infection in childhood contacts in the Gambia. Pediatr Infect Dis J 29(5): 439-43 Bianchi L, Galli L, Moriondo M, Veneruso G, Becciolini L, Azzari C, Chiappini E, de Martino M (2009) Interferon-gamma release assay improves the diagnosis of tuberculosis in children. J Pediatr Infect Dis J 28(6): 510-4 Chun JK, Kim CK, Kim HS, Jung GY, Lee TJ, Kim KH & Kim DS (2008) The role of a whole blood interferon-gamma assay for the detection of latent tuberculosis infection in Bacille	Make sure CG117 inclusions have been considered

	Calmette-Guérin vaccinated children. Diagn Microbiol Infect Dis 62(4): 389-94 Connell TG, Curtis N, Ranganathan SC & Buttery JP (2006) Performance of a whole blood interferon gamma assay for detecting latent infection with Mycobacterium tuberculosis in children. Thorax 61(7): 616-20 Connell TG, Ritz N, Paxton GA, Buttery JP, Curtis N & Ranganathan SC (2008) A three-way comparison of tuberculin skin testing, QuantiFERON-TB gold and T-SPOT.TB in children. PLoS One 3(7): e2624 Davies MA, Connell T, Johannisen C, Wood K, Pienaar S, Wilkinson KA, Wilkinson RJ, Zar HJ, Eley B, Beatty D, Curtis N & Nicol MP (2009) Detection of tuberculosis in HIV-infected children using an enzyme-linked immunospot assay. AIDS 23(8):961-9 Diel R, Loddenkemper R, Niemann S, Meywald-Walter K & Nienhaus A (2011) Negative and positive predictive value of a whole-blood interferon-γ release assay for developing active tuberculosis: an update. Am J Respir Crit Care Med 183(1): 88-95 Dogra S, Narang P, Mendiratta DK, Chaturvedi P, Reingold AL, Colford JM Jr, Riley LW & Pai M (2007) Comparison of a whole blood interferon-gamma assay with tuberculin skin testing for the detection of tuberculosis infection in hospitalized children in rural India. J Infect 54(3): 267-76 Hansted E, Andriuskeviciene A, Sakalauskas R, Kevalas R & Sitkauskiene B (2009) T-cell-based diagnosis of tuberculosis infection in children in Lithuania: a country of high incidence despite a high coverage with bacille Calmette-Guerin vaccination. BMC Pulm Med 9: 41 Haustein T, Ridout DA, Hartley JC, Thaker U, Shingadia D, Klein NJ, Novelli V & Dixon GL (2009) The likelihood of an indeterminate test result from a whole-blood interferon-gamma release assay for the diagnosis of Mycobacterium tuberculosis infection in children correlates with age and immune status. Pediatr Infect Dis J 28(8): 669-73 Hill PC, Brookes RH, Adetifa IM, Fox A, Jackson-Sillah D, Lugos MD, Donkor SA, Marshall RJ, Howie SR, Corrah T, Jeffries DJ, Adegbola RA & McAdam KP (2006) Comparison of enzyme-linked immunospot assay and tuberculin skin test in healthy children exposed to Mycobacterium tuberculosis. Pediatrics 117(5): 1542-8 Kampmann B, Whittaker E, Williams A, Walters S, Gordon A, Martinez-Alier N, Williams B, Crook AM, Hutton AM, Anderson ST (2009) Interferon-gamma release assays do not	

	identify more children with active tuberculosis than the tuberculin skin test. J Eur Respir J 33(6): 1374-82 Lighter J, Rigaud M, Eduardo R, Peng CH & Pollack H (2009) Latent tuberculosis diagnosis in children by using the QuantiFERON-TB Gold In-Tube test. Pediatrics 123(1): 30-7 Lucas M, Nicol P, McKinnon E, Whidborne R, Lucas A, Thambiran A, Burgner D, Waring J & French M (2010) A prospective large-scale study of methods for the detection of latent Mycobacterium tuberculosis infection in refugee children. Thorax 65(5): 442-8 Mandalakas AM, Hesseling AC, Chegou NN, Kirchner HL, Zhu X, Marais BJ, Black GF, Beyers N & Walzl G (2008) High level of discordant IGRA results in HIV-infected adults and children. Int J Tuberc Lung Dis 12(4): 417-23 Nicol MP, Davies MA, Wood K, Hatherill M, Workman L, Hawkridge A, Eley B, Wilkinson KA, Wilkinson RJ, Hanekom WA, Beatty D & Hussey G (2009) Comparison of T-SPOT.TB assay and tuberculin skin test for the evaluation of young children at high risk for tuberculosis in a community setting. Pediatrics 123(1): 38-43 Tsiouris SJ, Austin J, Toro P, Coetzee D, Weyer K, Stein Z & El-Sadr WM (2006) Results of a tuberculosis-specific IFN-gamma assay in children at high risk for tuberculosis infection. Int J Tuberc Lung Dis 10(8): 939-41	

	Details	Additional comments
Review question FF (32)	Which diagnostic strategy is most effective in establishing an accurate diagnosis of latent TB in people who are immunocompromised or at risk from immunosuppression?	
Objectives	To establish which diagnostic strategy is the most effective in people who are immunocompromised or at risk from immunosuppression in establishing an accurate diagnosis of latent TB, in the absence of a gold standard To determine the appropriate diagnostic thresholds for Mantoux, as well as the impact of BCG status	
Type of review	Diagnostic	
Language	English	
Study design	Update searches from CG117	
Status	Published papers (full text only)	
Population	People who are immunocompromised or at risk from immunosuppression	May include: • people with HIV • people with renal disease • people with diabetes • people with liver disease • people with haematological disease • people with haematological and solid cancers • people with autoimmune disease • people on or about to start anti-TNF-α treatment • people who have had prolonged steroid use (equivalent to 15mg daily prednisolone for at least a month) • people who have had or are about to have a transplant and are or will be using anti-rejection therapy such as cyclosporin
Intervention	IGRA alone or with Mantoux	IGRAs available in the UK are: • QuantiFERON-TB

		Gold In tube • T-SPOT.TB Where possible, relative effectiveness of each IGRA will be assessed
Comparator	Mantoux alone	
Outcomes	• Association between test results and the risk of having latent TB: discordance, concordance, odds ratios, ratios of odds ratios • Prognostic value of tests • Acceptability of approach • Adverse events • Likelihood of indeterminate result • Health-related quality of life • Resource use and cost	
Other criteria for inclusion/exclusion of studies	Include Papers comparing differing approaches to diagnosing latent TB People who are immunocompromised or at risk from immunosuppression Exclude Case studies, case series and narrative reviews	Tuberculin skin tests other than Mantoux will be downgraded for indirectness
Search strategies	Update searches from CG117 *PLUS* new search for those at risk of immunosuppression – those about to start anti-TNF-alpha (people with Crohns, rheumatoid arthritis, psoriasis, IBD, autoimmune diseases) and people who are about to have a transplant	
Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Where a randomised crossover study is included, the data from the first treatment phase only will be extracted • Subgroup analysis will be undertaken by type of immunosuppression, where	

	appropriate • Subgroup analysis will be undertaken by use of immunomodulators (that is, anfliximab, adalimumab, methotrexate, steroids, etanercept, azathioprine), where appropriate • Subgroup analysis will be undertaken by age, where appropriate • Subgroup analysis will be undertaken by threshold of Mantoux interpretation (≥5mm, ≥10mm, ≥15mm), where appropriate • Subgroup analysis will be undertaken by BCG status, where appropriate	
Identified key studies	Mixed – studies Richeldi L, Losi M, D'Amico R, Luppi M, Ferrari A, Mussini C, Codeluppi M, Cocchi S, Prati F, Paci V, Meacci M, Meccugni B, Rumpianesi F, Roversi P, Cerri S, Luppi F, Ferrara G, Latorre I, Gerunda GE, Torelli G, Esposito R & Fabbri LM (2009) Performance of tests for latent tuberculosis in different groups of immunocompromised patients. Chest 136(1): 198-204 HIV – systematic reviews Cattamanchi A, Smith R, Steingart KR, Metcalfe JZ, Date A, Coleman C, Marston BJ, Huang L, Hopewell PC & Pai M (2011) Interferon-gamma release assays for the diagnosis of latent tuberculosis infection in HIV-infected individuals: a systematic review and meta-analysis. J Acquir Immune Defic Syndr 56(3): 230-8 HIV - studies Davies MA, Connell T, Johannisen C, Wood K, Pienaar S, Wilkinson KA, Wilkinson RJ, Zar HJ, Eley B, Beatty D, Curtis N & Nicol MP (2009) Detection of tuberculosis in HIV-infected children using an enzyme-linked immunospot assay. AIDS 23(8):961-9 Luetkemeyer AF, Charlebois ED, Flores LL, Bangsberg DR, Deeks SG, Martin JN & Havlir DV (2007) Comparison of an interferon-gamma release assay with tuberculin skin testing in HIV-infected individuals. Am J Respir Crit Care Med 175(7): 737-42 Mandalakas AM, Hesseling AC, Chegou NN, Kirchner HL, Zhu X, Marais BJ, Black GF, Beyers N & Walzl G (2008) High level of discordant IGRA results in HIV-infected adults and children. Int J Tuberc Lung Dis 12(4): 417-23 Rangaka MX, Wilkinson KA, Seldon R, Van Cutsem G, Meintjes GA, Morroni C, Mouton P,	Make sure CG117 inclusions have been considered.

	Diwakar L, Connell TG, Maartens G & Wilkinson RJ (2007) Effect of HIV-1 infection on T-Cell-based and skin test detection of tuberculosis infection. Am J Respir Crit Care Med 175(5): 514-20 Stephan C, Wolf T, Goetsch U, Bellinger O, Nisius G, Oremek G, Rakus Z, Gottschalk R, Stark S, Brodt HR & Staszewski S (2008) Comparing QuantiFERON-tuberculosis gold, T-SPOT tuberculosis and tuberculin skin test in HIV-infected individuals from a low prevalence tuberculosis country. AIDS 22(18): 2471-9 Talati NJ, Seybold U, Humphrey B, Aina A, Tapia J, Weinfurter P, Albalak R & Blumberg HM (2009) Poor concordance between interferon-gamma release assays and tuberculin skin tests in diagnosis of latent tuberculosis infection among HIV-infected individuals. BMC Infect Dis 9: 15 Haematological disease – studies Piana F, Codecasa LR, Cavallerio P, Ferrarese M, Migliori GB, Barbarano L, Morra E & Cirillo DM (2006) Use of a T-cell-based test for detection of tuberculosis infection among immunocompromised patients. Eur Respir J 28(1): 31-4 Renal disease – studies Chung WK, Zheng ZL, Sung JY, Kim S, Lee HH, Choi SJ & Yang J (2010) Validity of interferon-γ-release assays for the diagnosis of latent tuberculosis in haemodialysis patients. Clin Microbiol Infect 16(7): 960-5 Lee SS, Chou KJ, Su IJ, Chen YS, Fang HC, Huang TS, Tsai HC, Wann SR, Lin HH & Liu YC (2009) High prevalence of latent tuberculosis infection in patients in end-stage renal disease on hemodialysis: Comparison of QuantiFERON-TB GOLD, ELISPOT, and tuberculin skin test. Infection 37(2): 96-102 Passalent L, Khan K, Richardson R, Wang J, Dedier H & Gardam M (2007) Detecting latent tuberculosis infection in hemodialysis patients: a head-to-head comparison of the T-SPOT.TB test, tuberculin skin test, and an expert physician panel. Clin J Am Soc Nephrol 2(1): 68-73 Triverio PA, Bridevaux PO, Roux-Lombard P, Niksic L, Rochat T, Martin PY, Saudan P & Janssens JP (2009) Interferon-gamma release assays versus tuberculin skin testing for detection of latent tuberculosis in chronic haemodialysis patients. Nephrol Dial Transplant 24(6): 1952-6 Liver disease – studies Manuel O, Humar A, Preiksaitis J, Doucette K,	

	Shokoples S, Peleg AY, Cobos I & Kumar D (2007) Comparison of quantiferon-TB gold with tuberculin skin test for detecting latent tuberculosis infection prior to liver transplantation. Am J Transplant 7(12): 2797-801 Autoimmune diseases – studies Bartalesi F, Vicidomini S, Goletti D, Fiorelli C, Fiori G, Melchiorre D, Tortoli E, Mantella A, Benucci M, Girardi E, Cerinic MM & Bartoloni A (2009) QuantiFERON-TB Gold and the TST are both useful for latent tuberculosis infection screening in autoimmune diseases. Eur Respir J 33(3): 586-93 Gogus F, Gunendi Z, Karakus R, et al. Comparison of tuberculin skin test and QuantiFERON-TB gold in tube test in patients with chronic inflammatory diseases living in a tuberculosis endemic population. Clin Exp Med 2009; 10:173–177 Marques CD, Duarte AL, de Lorena VM, et al. Evaluation of an interferon gamma assay in the diagnosis of latent tuberculosis infection in patients with rheumatoid arthritis. Rheumatol Int 2009 30(1):57-62 Matulis G, Juni P, Villiger PM, Gadola SD. Detection of latent tuberculosis in immunosuppressed patients with autoimmune diseases: performance of a Mycobacterium tuberculosis antigen-specific interferon gamma assay. Ann Rheum Dis 2008; 67:84–90 Schoepfer AM, Flogerzi B, Fallegger S, et al. Comparison of interferon-gamma release assay versus tuberculin skin test for tuberculosis screening in inflammatory bowel disease. Am J Gastroenterol 2008; 103:2799–2806 About to start anti-TNF-α – studies Bocchino M, Matarese A, Bellofiore B, Giacomelli P, Santoro G, Balato N, Castiglione F, Scarpa R, Perna F, Signoriello G, Galati D, Ponticiello A & Sanduzzi A (2008) Performance of two commercial blood IFN-gamma release assays for the detection of Mycobacterium tuberculosis infection in patient candidates for anti-TNF-alpha treatment. Eur J Clin Microbiol Infect Dis 27(10): 907-13 Cobanoglu N, Ozcelik U, Kalyoncu U, et al. Interferon-gamma assays for the diagnosis of tuberculosis infection before using tumour necrosis factor-alpha blockers. Int J Tuberc Lung Dis 2007; 11:1177–1182 Kwakernaak AJ, Houtman PM, Weel JF, et al. A comparison of an interferongamma release assay and tuberculin skin test in refractory inflammatory disease patients screened for	

	latent tuberculosis prior to the initiation of a first tumor necrosis factor alpha inhibitor. Clin Rheumatol 2011; 30:505–510 Laffitte E, Janssens JP, Roux-Lombard P, et al. Tuberculosis screening in patients with psoriasis before antitumour necrosis factor therapy: comparison of an interferon-gamma release assay vs. tuberculin skin test. Br J Dermatol 2009; 161:797–800 Martin J, Walsh C, Gibbs A, et al. Comparison of interferon gamma release assays and conventional screening tests before tumour necrosis factor alpha blockade in patients with inflammatory arthritis. Ann Rheum Dis 2010; 69: 181-185 Ponce de Leon D, Acevedo-Vasquez E, Alvizuri S, Gutierrez C, Cucho M, Alfaro J, Perich R, Sanchez-Torres A, Pastor C, Sanchez-Schwartz C, Medina M, Gamboa R & Ugarte M (2008) Comparison of an interferon-gamma assay with tuberculin skin testing for detection of tuberculosis (TB) infection in patients with rheumatoid arthritis in a TB-endemic population. J Rheumatol 35(5): 776-81 Vassilopoulos D, Stamoulis N, Hadziyannis E, Archimandritis AJ. Usefulness of enzyme-linked immunosorbent assay (Elispot) compared to tuberculin skin testing for latent tuberculosis screening in rheumatic patients scheduled for antitumor necrosis factor treatment. J Rheumatol 2008; 35:1271–1276 On anti-TNF-α – studies Behar SM, Shin DS, Maier A, et al. Use of the T-SPOT.TB assay to detect latent tuberculosis infection among rheumatic disease patients on immunosuppressive therapy. J Rheumatol 2009; 36:546–551 Chen DY, Shen GH, Hsieh TY, Hsieh CW & Lan JL (2008) Effectiveness of the combination of a whole-blood interferon-gamma assay and the tuberculin skin test in detecting latent tuberculosis infection in rheumatoid arthritis patients receiving adalimumab therapy. Arthritis Rheum 59(6): 800-6 Takahashi H, Shigehara K, Yamamoto M, Suzuki C, Naishiro Y, Tamura Y, Hirohashi Y, Satoh N, Shijubo N, Shinomura Y & Imai K (2007) Interferon gamma assay for detecting latent tuberculosis infection in rheumatoid arthritis patients during infliximab administration. Rheumatol Int 27(12): 1143-8	

	Details	Additional comments
Review question GG (33)	Which diagnostic strategy is most effective in establishing an accurate diagnosis of latent TB in people from regions with a high incidence of TB?	Update searches from CG117
Objectives	To establish which diagnostic strategy is the most effective in adults who are recent arrivals from countries with a high incidence of TB in establishing an accurate diagnosis of latent TB, in the absence of a gold standard To determine the appropriate diagnostic thresholds for Mantoux, as well as the impact of HIV and BCG status	
Type of review	Diagnostic	
Language	English	
Study design	Update searches from CG117	
Status	Published papers (full text only)	
Population	People who are recent arrivals from high-incidence countries People born in high-incidence countries	High incidence = 40/100,000 [WHO]
Intervention	IGRA alone or with Mantoux	IGRAs available in the UK are: • QuantiFERON-TB Gold In tube • T-SPOT.TB Where possible, relative effectiveness of each IGRA will be assessed
Comparator	Mantoux alone	
Outcomes	• Association between test results and the risk of having latent TB: discordance, concordance, odds ratios, ratios of odds ratios • Prognostic value of tests • Acceptability of approach • Adverse events • Likelihood of indeterminate result • Health-related quality of life • Resource use and cost	GDG to confirm key adverse events
Other criteria for inclusion/exclusion of studies	Include Papers comparing differing approaches to diagnosing latent TB Adults who are recent arrivals from high-incidence countries or who were born in high-incidence countries Exclude	Tuberculin skin tests other than Mantoux will be downgraded for indirectness

	Case studies, case series and narrative reviews	
Search strategies	Update searches from CG117	
Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Where a randomised crossover study is included, the data from the first treatment phase only will be extracted • Subgroup analysis will be undertaken by age, where appropriate • Subgroup analysis will be undertaken by threshold of Mantoux interpretation (≥5mm, ≥10mm, ≥15mm), where appropriate • Subgroup analysis will be undertaken by BCG status, where appropriate • Subgroup analysis will be undertaken by prevalence in the country of origin (40-150, 150-250 and >250/100,000), where appropriate	
Identified key studies	Studies Carvalho AC, Pezzoli MC, El-Hamad I, Arce P, Bigoni S, Scarcella C, Indelicato AM, Scolari C, Carosi G & Matteelli A (2007) QuantiFERON-TB Gold test in the identification of latent tuberculosis infection in immigrants. J Infect 55(2): 164-8 Harstad I, Winje BA, Heldal E, Oftung F & Jacobsen GW (2010) Predictive values of QuantiFERON-TB Gold testing in screening for tuberculosis disease in asylum seekers. Int J Tuberc Lung Dis 14(9): 1209-11 Kik SV, Franken WP, Mensen M, Cobelens FG, Kamphorst M, Arend SM, Erkens C, Gebhard A, Borgdorff MW & Verver S (2010) Predictive value for progression to tuberculosis by IGRA and TST in immigrant contacts. Eur Respir J 35(6): 1346-53 Mulder C, van Deutekom H, Huisman EM, Toumanian S, Koster BF, Meijer-Veldman W, van Loenhout-Rooyackers JH, Appel M, Arend SM, Borgdorff MW & van Leth F (2012) Role of the QuantiFERON(R)-TB Gold In-Tube assay in screening new immigrants for tuberculosis infection. Eur Respir J 40(6): 1443-9	Make sure CG117 inclusions have been considered.

	Orlando G, Merli S, Cordier L, Mazza F, Casazza G, Villa AM, Codecasa L, Negri E, Cargnel A, Ferrarese M & Rizzardini G (2010) Interferon-gamma releasing assay versus tuberculin skin testing for latent tuberculosis infection in targeted screening programs for high risk immigrants. Infection 38(3): 195-204 Pareek M, Watson JP, Ormerod LP, Kon OM, Woltmann G, White PJ, Abubakar I & Lalvani A (2011) Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis. Lancet Infect Dis 11(6): 435-44 Saracino A, Scotto G, Fornabaio C, Martinelli D, Faleo G, Cibelli D, Tartaglia A, Di Tullio R, Fazio V, Prato R, Monno L & Angarano G (2009) QuantiFERON-TB Gold In-Tube test (QFT-GIT) for the screening of latent tuberculosis in recent immigrants to Italy. New Microbiol 32(4): 369-76 Winje BA, Oftung F, Korsvold GE, Mannsåker T, Jeppesen AS, Harstad I, Heier BT & Heldal E (2008) Screening for tuberculosis infection among newly arrived asylum seekers: comparison of QuantiFERONTB Gold with tuberculin skin test. BMC Infect Dis 8: 65	

	Details	Additional comments
Review question HH (34)	According to their risk factors, which people with latent TB infection should receive drug treatment to prevent the development of active TB?	
Objectives	To establish which risk factors are associated with greater potential benefit from the treatment of latent TB or greater potential harm	
Type of review	Prognostic	
Language	English	
Study design	Cohort (prospective and retrospective), cross-sectional, case-control	
Status	Published papers (full text only)	
Population	People with latent TB infection	
Endpoints	Significant benefit from the treatment of latent TB Significant harm from the treatment of latent TB	Benefits may be greater: • for people with a higher risk of progressing from latent to active TB, or of developing more severe disease • where people pose a greater risk of infecting others – to be considered in the health economic analysis Harms may be greater for people: • with a higher risk of hepatotoxicity during treatment
Prognostic factors	Risk factors that predict significant benefit from the treatment of latent TB Risk factors that predict significant harm from the treatment of latent TB	Risk factors for progressing to active TB might include: • recent contact with active TB, or time since exposure • age – in particular neonates/under 2s, and those over 35 • old fibrotic lesions • BCG • immunocompromised or at risk of immunosuppression, including HIV, people on/about to start biological therapies (Crohn's disease, rheumatoid arthritis, steroid use etc) • chronic lung diseases – silicosis • liver disease • renal disease • diabetes • malignancy • malnutrition • smoking

		• alcohol or substance use • drug resistance • homelessness Risk factors for hepatotoxicty from treatment might include: • age – in particular over 35s and over 50s • liver disease, including viral hepatitis • alcohol or substance use • people with HIV
Other criteria for inclusion / exclusion of studies	<u>Include</u> • Papers examining factors to predict risk of progressing from latent to active TB • Papers examining risk factors to predict hepatoxicity from the treatment of latent TB • Multivariate analysis <u>Exclude</u> • Case studies, case series and narrative reviews	
Search strategies	Cohort (prospective and retrospective), cross-sectional, case-control	
Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements by prognostic factor • Subgroup analysis will be conducted by regimen used, where appropriate	
Identified key studies	<u>Factors associated with a higher risk of progressing to active TB</u> Bruce RM & Wise L (1977) Tuberculosis after jejunoileal bypass for obesity. Ann Intern Med 87(5): 574-6	

	Buskin SE, Gale JL, Weiss NS & Nolan CM (1994) Tuberculosis risk factors in adults in King County, Washington, 1988 through 1990. Am J Public Health 84(11): 1750-6 Chia S, Karim M, Elwood RK & FitzGerald JM (1998) Risk of tuberculosis in dialysis patients: a population-based study. Int J Tuberc Lung Dis 2(12): 989-91 Jeon CY & Murray MB (2008) Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PLoS Med 5(7): e152 Kim HA, Yoo CD, Baek HJ, Lee EB, Ahn C, Han JS, Kim S, Lee JS, Choe KW & Song YW (1998) Mycobacterium tuberculosis infection in a corticosteroid-treated rheumatic disease patient population. Clin Exp Rheumatol 16(1): 9-13 Körner MM, Hirata N, Tenderich G, Minami K, Mannebach H, Kleesiek K & Körfer R (1997) Tuberculosis in heart transplant recipients. Chest 111(2): 365-9 Lönnroth K, Williams BG, Stadlin S, Jaramillo E & Dye C (2008) Alcohol use as a risk factor for tuberculosis - a systematic review. BMC Public Health 8: 289 Morán-Mendoza O, Marion SA, Elwood K, Patrick D & FitzGerald JM (2010) Risk factors for developing tuberculosis: a 12-year follow-up of contacts of tuberculosis cases. Int J Tuberc Lung Dis ;14(9): 1112-9 Muñoz P, Palomo J, Muñoz R, Rodríguez-Creixéms M, Pelaez T & Bouza E (1995) Tuberculosis in heart transplant recipients. Clin Infect Dis 21(2): 398-402 Pablos-Méndez A, Blustein J & Knirsch CA (1997) The role of diabetes mellitus in the higher prevalence of tuberculosis among Hispanics. Am J Public Health 87(4): 574-9 Schatz M, Patterson R, Kloner R & Falk J (1976) The prevalence of tuberculosis and positive tuberculin skin tests in a steroid-treated asthmatic population. Ann Intern Med 84(3): 261-5 Selwyn PA, Hartel D, Lewis VA, Schoenbaum EE, Vermund SH, Klein RS, Walker AT & Friedland GH (1989) A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med 320(9): 545-50 Selwyn PA, Sckell BM, Alcabes P, Friedland GH, Klein RS & Schoenbaum EE (1992) High risk of active tuberculosis in HIV-infected drug users with cutaneous anergy. JAMA 268(4): 504-9 Steiger Z, Nickel WO, Shannon GJ, Nedwicki EG & Higgins RF (1976) Pulmonary tuberculosis after gastric resection. Am J Surg 131(6): 668-71 Westerholm P, Ahlmark A, Maasing R & Segelberg I (1986) Silicosis and risk of lung cancer or lung tuberculosis: a cohort study. Environ Res 41(1): 339-50 Young F, Wotton CJ, Critchley JA, Unwin NC & Goldacre MJ (2012) Increased risk of tuberculosis disease in people with diabetes mellitus: record-linkage study in a UK population. J Epidemiol Community Health 66(6): 519-23 Factors associated with adverse events Devoto FM, González C, Iannantuono R, Serra HA, González CD, Sáenz C (1997) Risk factors for hepatotoxicity induced by antituberculosis drugs. Acta Physiol Pharmacol Ther Latinoam 47(4): 197-202 Fountain FF, Tolley E, Chrisman CR & Self TH (2005) Isoniazid hepatotoxicity associated with treatment of latent tuberculosis infection: a 7-year evaluation from a public health tuberculosis clinic. Chest 128(1): 116-23 Gordin FM, Cohn DL, Matts JP, Chaisson RE & O'Brien RJ; Terry Beirn Community Programs for Clinical Research on AIDS; Adult AIDS Clinical Trials Group; Centers for Disease Control and Prevention (2004) Hepatotoxicity of rifampin and pyrazinamide in the treatment of latent tuberculosis infection in HIV-infected persons: is it different than in HIV-uninfected persons? Clin Infect Dis

	39(4): 561-5 Jasmer RM, Saukkonen JJ, Blumberg HM, Daley CL, Bernardo J, Vittinghoff E, King MD, Kawamura LM & Hopewell PC; Short-Course Rifampin and Pyrazinamide for Tuberculosis Infection (SCRIPT) Study Investigators (2002) Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial. Ann Intern Med 137(8): 640-7 Lee AM, Mennone JZ, Jones RC & Paul WS (2002) Risk factors for hepatotoxicity associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection: experience from three public health tuberculosis clinics. Int J Tuberc Lung Dis 6(11): 995-1000 Lobato MN, Reves RR, Jasmer RM, Grabau JC, Bock NN & Shang N; 2RZ Study Group (2005) Adverse events and treatment completion for latent tuberculosis in jail inmates and homeless persons. Chest 127(4): 1296-303 Pande JN, Singh SP, Khilnani GC, Khilnani S & Tandon RK (1996) Risk factors for hepatotoxicity from antituberculosis drugs: a case-control study. Thorax 51(2): 132-6 Stout JE, Engemann JJ, Cheng AC, Fortenberry ER & Hamilton CD (2003) Safety of 2 months of rifampin and pyrazinamide for treatment of latent tuberculosis. Am J Respir Crit Care Med 167(6): 824-7

	Details	Additional comments
Review question IIa (35)	For people with latent TB infection in which drug resistance is not suspected, which regimen is the most effective in preventing the development of active TB?	
Objectives	To determine which antituberculosis regimen is most effective in people with latent TB infection in which drug resistance is not suspected	
Type of review	Intervention	
Language	English	
Study design	RCTs, quasi-RCTs, systematic reviews If there is insufficient evidence found, non-randomised controlled trials will be considered	'Insufficient evidence' is considered to be an evidence base that does not allow the GDG to make recommendations
Status	Published papers (full text only)	
Population	People with latent TB infection in which drug resistance is not suspected	
Intervention	Varying regimens of antituberculosis drugs	Might include: • 9 months isoniazid • 6 months isoniazid • 4-6 months rifampicin • 3 months rifampicin + isoniazid • 3 months rifapentine + isoniazid (rifapentine not licensed in the UK, so this can only be discussed in the evidence base (as a comparator) – cannot make recommendations on its use)
Comparator	Other regimens of antituberculosis drugs or placebo	
Outcomes	<u>Critical or important outcomes</u> 1. Progression to active TB: the number in which this occurs and the time it takes 2. Adverse events 3. Adherence: adherence, treatment completion and treatment default <u>Adverse events of interest</u> Adverse events that are severe enough to require a modification, interruption or discontinuation in treatment, or one of the following: 1. Hepatotoxicity 2. Treatment-related mortality 3. Rash	

	4. Allergy 5. Nausea and/or vomiting	
Other criteria for inclusion / exclusion of studies	Include • Papers comparing different regimens of antituberculosis drugs or placebo • People with latent TB infection in which drug resistance is not suspected • Follow-up for at least the full treatment period Exclude • People with latent TB infection in which drug resistance is suspected • Observational, case series, case studies and narrative reviews	
Search strategies	RCTs, quasi-RCTs, systematic reviews, non-randomised controlled trials	
Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Where a randomised crossover study is included, the data from the first treatment phase only will be extracted • Subgroup analysis will be undertaken for children and young people, including children under 5 years, where appropriate • Subgroup analysis will be undertaken for people over the age of 35, where appropriate • Subgroup analysis will be undertaken for people with HIV, where appropriate • Subgroup analysis will be undertaken for other people who are immunocompromised or at risk of immunosuppression, where appropriate; this will be conducted by underlying cause immunosuppression • Substance misusers, homeless people, detained populations • Subgroup analysis will be undertaken	

	for directly observed treatment, where appropriate • Subgroup analysis will be undertaken for dosing frequency, where appropriate • Subgroup analysis will be undertaken for dosing significantly more or less than recommended (see BNF), where appropriate	
Key papers	Systematic reviews Akolo C, Adetifa I, Shepperd S & Volmink J (2010) Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev: CD000171 Ena J & Valls V (2005) Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a meta-analysis. Clin Infect Dis 40(5): 670-6 Gao XF, Wang L, Liu GJ, Wen J, Sun X, Xie Y & Li YP (2006) Rifampicin plus pyrazinamide versus isoniazid for treating latent tuberculosis infection: a meta-analysis. Int J Tuberc Lung Dis 10(10): 1080-90 Studies Fitzgerald DW, Severe P, Joseph P, Mellon LR, Noel E, Johnson WD, Pape JW. No effect of isoniazid prophylaxis for purified protein derivative-negative HIV infected adults living in a country endemic tuberculosis: results of a randomized trial. Journal of Acquuired Immune Deficiency Syndromes 2001;28(3):305–307 Gordin FM, Matts JP, Miller C, Brown LS, Hafner R, John SL, Klein M, Vaughn A, Besch CL, Perez G, Szabo S, El-Sadr W. A controlled trial of isoniazid in persons with anergy and human immunodeficiency virus infection who are at high risk for tuberculosis. NEJM 1997;337:315–320 Gordin F, Chaisson RE, Matts JP, et al. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-Infected persons. An international randomized trial. JAMA 2000;283:1445–1450 Halsey NE, Coberly JS, Desormeaux J, Losikoff P, Atkinson J, Moulton LH, Contave M, Johnson M, Davis H, Geitre L, Johnson E, Huebner R, Boulos R, Chaisson R. Randomized trial of isoniazid versus rifampicine and pyrazinamide for prevention of tuberculosis in HIV-1 infection. The Lancet 1998;351(9105):786–792 Hawken MP, Meme HK, Elliot LC, Chakaya JM, Morris JS, Githui WA, Juma ES, Odhiambo JA, Thiong'o LN, Kimari JN, Ngugi EN, Bwayo JJ, Gilks CF, Plummer FA, Porter JDH, Nunn PP, McAdam KPWJ. Isoniazid preventive therapy for tuberculosis in HIV-1 infected adults: results of a randomized controlled trial. AIDS 1997;11:875–882 Jasmer RM, Saukkonen JJ, Blumberg HM, Daley CL, Bernardo J, Vittinghoff E, King MD, Kawamura LM & Hopewell PC; Short-Course Rifampin and Pyrazinamide for Tuberculosis Infection (SCRIPT) Study Investigators (2002) Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial. Ann Intern Med 137(8): 640-7 Johnson JL, Okwera A, Hom DL, Mayanja H, Mutuluuza Kityo C, Nsubuga P, Nakibali JG, Loughlin AM, Yun H, Mugyenyi PN, Vernon A, Mugerwa RD, Ellner JJ & Whalen CC; Uganda-Case Western Reserve University Research Collaboration (2001) Duration of efficacy of treatment of latent tuberculosis infection in HIV-infected adults. AIDS 15(16): 2137-47 Lim HJ, Okwera A, Mayanja-Kizza H, Ellner JJ, Mugerwa RD, Whalen CC. Effect of Tuberculosis Preventive Therapy on HIV Disease Progression and Survival in HIV-Infected Adults. HIV Clin Trials 2006;7(4):172–183	

	Mohammed A, Myer L, Ehrlich R, Wood R, Cilliers F, Maartens G. Randomised controlled trial of isoniazid preventive therapy in South African adults with advanced HIV disease. Int J Tuberc Lung Dis 2007;11(10):1114–1120 Mwinga A, Hosp M, Godfrey-Fusset P, Quigley M, Mwaba P, Mugala BN, Nyirenda O, Luo N, Pobee J, Elliot AM, McAdam KPWJ, Porter JDH. Twice weekly tuberculosis preventive therapy in HIV infection in Zambia. AIDS 1998;12:2447–57 Pape JW, Jean SS, Ho JL, Hafner A, Johnson WD. Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. The Lancet 1993;342:268–72 Quigley MA, Mwinga A, Hosp M, Lisse I, Fuchs D, Porter JDH, Godfrey-Fausett P. Long-term effect of preventive therapy for tuberculosis in a cohort of HIV-infected Zambian Adults. AIDS 2001;15:215–222 Rivero A, Lopez-Cortes L, Castillo R, Lozano F, Gracia MA, Diez F, Escribano JC, Canueto J, Pasquau J, Hernandez JJ, Polo R, Martinez-Marcos FJ, Kindelan JM, Rey R. A randomized trial of three regimens to prevent tuberculosis in HIV-infected patients with anergy. Enferm Infecc Microbiol Clin 2003;21(6):287–292 Rivero A, López-Cortés L, Castillo R, Verdejo J, García MA, Martínez-Marcos FJ, Díez F, Escribano JC, Canueto J, Lozano F, Pasquau J, Hernández JJ, Márquez M, Kindelán JM. A Randomized clinical trial investigating three chemoprophylaxis regimens for latent tuberculosis infection in HIV-infected patients. Enferm Infecc Microbiol Clin 2007;25(5):305–310 Schechter M, Zajdenverg R, Falco G, Barnes GL, Faulhaber JC, Coberly JS, Moore RD & Chaisson RE (2006) Weekly rifapentine/isoniazid or daily rifampin/pyrazinamide for latent tuberculosis in household contacts. Am J Respir Crit Care Med 173(8): 922-6 Spyridis NP, Spyridis PG, Gelesme A, Sypsa V, Valianatou M, Metsou F, Gourgiotis D & Tsolia MN (2007) The effectiveness of a 9-month regimen of isoniazid alone versus 3- and 4-month regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children: results of an 11-year randomized study. Clin Infect Dis 45(6): 715-22 Whalen CC, Johnson JL, Okwera A, Hom DL, Huebner R, Mugyenyi P, Mugerwa RD, Ellner JJ, Nsubuga P, Vjecha M, Myanja H, Kityo C, Loughlin A, Milberg J, Pekovic V. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. NEJM 1997;337:801–808 Whalen CC, Johnson JL, Okwera A, Hom DL, Huebner R, Mugyenyi P, Mugerwa RD, Ellner JJ, Nsubuga P, Vjecha M, Myanja H, Kityo C, Loughlin A, Milberg J, Pekovic V. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus.. NEJM 1997;337:801–808

	Details	Additional comments
Review question IIb	For people with latent TB infection in which drug resistance (excluding MDR- or XDR-TB) is suspected, which regimen is the most effective in preventing the development of active TB?	
Objectives	To determine which antituberculosis regimen is most effective in people with latent TB infection in which drug resistance (excluding MDR- or XDR-TB) is suspected	
Type of review	Intervention	
Language	English	

Study design	RCTs, quasi-RCTs, systematic reviews If there is insufficient evidence found, non-randomised controlled trials will be considered	'Insufficient evidence' is considered to be an evidence base that does not allow the GDG to make recommendations
Status	Published papers (full text only)	
Population	People with latent TB infection in which drug resistance (excluding MDR- or XDR-TB) is suspected	
Intervention	Varying regimens of antituberculosis drugs	
Comparator	Other regimens of antituberculosis drugs or placebo	
Outcomes	Critical or important outcomes 4. Progression to active TB: the number in which this occurs and the time it takes 5. Adverse events 6. Adherence: adherence, treatment completion and treatment default Adverse events of interest Adverse events that are severe enough to require a modification, interruption or discontinuation in treatment, or one of the following: 6. Hepatotoxicity 7. Treatment-related mortality 8. Rash 9. Allergy 10. Nausea and/or vomiting	
Other criteria for inclusion / exclusion of studies	Include • Papers comparing different regimens of antituberculosis drugs or placebo • People with latent TB infection in which drug resistance is suspected • Follow-up for at least the full treatment period Exclude • People with latent TB infection in whom MDR-TB is suspected in the source case • People with latent TB infection in which drug resistance is not suspected • Observational, case series, case studies and narrative reviews	
Search strategies	RCTs, quasi-RCTs, systematic reviews, non-randomised controlled trials	
Review strategies	• The NICE methodology checklists will be used as a guide to appraise the quality of	

	individual studies • Data on all included studies will be extracted into evidence tables • Where statistically possible, a meta-analytical approach will be used to give an overall summary effect • All key outcomes from evidence will be presented in GRADE profiles or modified profiles and further summarized in evidence statements • Where a randomised crossover study is included, the data from the first treatment phase only will be extracted • Analysis will be undertaken by the type of drug resistance suspected in the source case, where appropriate • Subgroup analysis will be undertaken for children and young people, including children under 5 years, where appropriate • Subgroup analysis will be undertaken for people over the age of 35, where appropriate • Subgroup analysis will be undertaken for people with HIV, where appropriate • Subgroup analysis will be undertaken for other people who are immunocompromised or at risk of immunosuppression, where appropriate; this will be conducted by underlying cause immunosuppression • Substance misusers, homeless people, detained populations • Subgroup analysis will be undertaken for directly observed treatment, where appropriate • Subgroup analysis will be undertaken for dosing frequency, where appropriate • Subgroup analysis will be undertaken for dosing significantly more or less than recommended (see BNF), where appropriate	
Key papers	Systematic reviews Fraser A, Paul M, Attamna A & Leibovici L (2006) Treatment of latent tuberculosis in persons at risk for multidrug-resistant tuberculosis: systematic review. Int J Tuberc Lung Dis 10(1): 19-23	

TB signs and symptoms by site of disease

Respiratory TB	Pleural TB	CNS TB	Spinal TB	Bone & joint
Cough Fever or night sweats Radiographic changes Anorexia or appetite loss Shortness of breath or respiratory function Weight change	Pleural effusion Fever Anorexia or appetite loss Pain	Coma Neurological deficit Disability Hydrocephalus or oedema Lesions (tuberculoma) Nausea and/or vomiting	Bone and joint disturbances Fever Disability or neurological involvement Pain Inflammation	Disability or reduced activity levels Bone and joint disturbances Pain Inflammation or swelling Fever
Peripheral lymph node	**Pericardial**	**Gastrointestinal TB**	**Genitourinary TB**	**Disseminated TB**
Lymph node enlargement or glands Sinuses & abscesses Fever Inflammation Anorexia or appetite loss	Pericardial effusion or cardiac tamponade Constrictive pericarditis Pericardial adhesion Fever Shortness of breath or reduced activity levels	Abdominal TB Fever GI obstruction Nausea and/or vomiting Anorexia or appetite loss Weight loss	Fertility Ureteral stricture or obstruction Pain Fever Bleeding Weight loss	Nausea and/or vomiting Fever Abscess Weight loss Headache Fatigue

PUBLIC HEALTH QUESTIONS

A.5.2 RQ JJ - search strategy and review protocol

This document is a protocol for a public health evidence review which is being developed by London School of Hygiene & Tropical Medicine (LSHTM) and the Centre for Public Health (CPH) at NICE to inform the joint clinical and public health guidance on TB.

Review question

What strategies and interventions are effective and cost effective in increasing the uptake of BCG vaccination among people at increased risk of developing active or latent TB?

Methods

The review will be carried out according to the methodological guidance set out in the current (third) edition of *Methods for the development of NICE public health guidance*. The review will be registered with PROSPERO when the protocol is finalized.

Searching

Database sources

The following sources will be searched from 1993 to the most recent records:

ASSIA via ProQuest
British Nursing Index (BNI) via ProQuest
CINAHL via EBSCO
Conference Proceedings Citation Index- Science (CPCI-S) via ISI*
Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH) via ISI*
EMBASE via OVID
ERIC via ProQuest
HMIC via OVID+
MEDLINE in Process via OVID
MEDLINE via OVID
NCJRS via ProQuest
OpenGrey via www.opengrey.eu
PsycINFO via OVID
Science Citation Index Expanded (SCI-EXPANDED) via ISI*
Social Policy and Practice via OVID+
Social Sciences Citation Index (SSCI) via ISI*
Sociological Abstracts via ProQuest
The Cochrane Library via www.thecochranelibrary.com
the date range of these two resources will be 2011-Current

+ indicates resources with good access to grey and report literature

A search of PubMed will also be run limited to electronic, advanced publication articles.

Web searching

The following websites will be hand-searched:

NICE via www.nice.org.uk
Public Health Observatory via www.apho.org.uk
Public Health England via www.gov.uk/government/organisations/public-health-england
We will also search Google using a simplified version of the search string used for the database searches and scanning the first 100 results. This will identify published reports which are not indexed on the bibliographic databases.

Supplementary searching

All items included on full-text will be citation chased. Backwards citation chasing will be conducted manually (one generation) and forwards citation will conducted in Web of Science.

A search of BL Ethos (http://ethos.bl.uk/) will be used to identify theses.

Search strategy

(tuberculosis) AND (BCG vaccination) AND (uptake OR interventions OR settings OR effectiveness)

The first two clusters are straightforward and will need few synonyms. The 'uptake' cluster will contain a number of synonyms, possibly including both direct synonyms for 'uptake' (e.g. 'receipt', 'compliance') and terms for population-level vaccination status as an outcome (e.g. 'coverage'). The 'interventions' and 'settings' clusters will contain terms for specific types of intervention (e.g. information) and settings (e.g. primary care) and people potentially delivering interventions. The 'effectiveness' cluster will be a brief set of terms to identify effectiveness studies (e.g. 'trial', 'effectiveness'). The combination of 'uptake' terms with a generic effectiveness filter will help to ensure the sensitivity of the search. Some of the non-health-focused sources may be searched using the first two clusters only.

No language restrictions will be placed on the search. A filter will be used to exclude studies on animals.

Screening

EPPI-Reviewer 4 software will be used to manage data. A random sample of 10% of titles and abstracts will be screened by two reviewers independently and differences resolved by discussion. If agreement is adequate at this stage, subsequent abstracts will be screened by one reviewer. The full text of all studies which meet criteria, or where it is unclear whether they meet the criteria, will be retrieved and screened by two reviewers independently.

The inclusion criteria will be as follows:

Is the study an outcome evaluation of an intervention? (Initially any study design including an intervention and at least some pre- and

post-test outcome data will be included here, i.e. trials, one-group before-after studies, and retrospective or observational studies which report clear pre and post data.)

Does the study measure uptake of BCG vaccination as an outcome?

Was the study conducted in a high-income country (current OECD member)? [a]

Any type of intervention will be included. In particular, we will include both provider-focused interventions such as clinician education or service reorganisation, and public-focused interventions such as reminders or information programmes.

Quality assessment and data extraction

Quality assessment and data extraction will be conducted using the tools in the methods manual. All studies will be quality assessed and data extracted by one reviewer, with all data checked in detail by a second reviewer.

Data synthesis

Data will be synthesized narratively in the first instance. If sufficiently homogenous and high-quality data are located, meta-analysis may be considered, although this is unlikely.

[a] These are: Australia, Austria, Belgium, Canada, Chile, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Luxembourg, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, UK, USA

A.5.3 RQ KK - search strategy and review protocol

This is a draft protocol for a public health evidence review which is being developed by London School of Hygiene & Tropical Medicine (LSHTM) and the Centre for Public Health (CPH) at NICE to inform the joint clinical and public health guidance on TB.

Review question

What is known from systematic reviews concerning high-risk populations (see below for definition) about the effectiveness of interventions to promote vaccination, barriers or determinants of vaccine uptake?

Methods

The review will be carried out according to the methodological guidance set out in the current (third) edition of *Methods for the development of NICE public health guidance*.

Searching

The following sources will be searched:

MEDLINE via OVID;
MEDLINE in Process via OVID;
EMBASE via OVID; and,
The Cochrane Library: CDSR, HTA and DARE via www.thecochranelibrary.com
We will also search PROSPERO to identify any in-process unpublished reviews and contact authors of unpublished reviews which meet inclusion criteria.

The following web-sites will be searched to locate any UK reviews:

NICE Web-site via www.nice.org.uk
Public Health Observatory via www.apho.org.uk
Public Health England via www.gov.uk/government/organisations/public-health-england
Google Scholar will also be searched using a limited version of the search strategy and the first 100 hits screened.

The search strategy will take the following form: (vaccination) AND (review filter). See Search Annex for full details of the database search strategy.

We will restrict searching to studies published in the last 10 years, as reviews published in this timeframe will contain a substantial body of older primary data. The search will be restricted to human populations. No language restriction will be applied.

Screening

EPPI-Reviewer 4 software will be used to manage data. A random sample of 10% of titles and abstracts will be screened by two reviewers independently and differences resolved by discussion. If agreement is adequate at this stage, subsequent abstracts will be screened by one reviewer. The full text of all studies which meet criteria, or where it is unclear whether they meet the criteria, will be retrieved and screened by two reviewers independently.

The inclusion criteria will initially not include any population concept. We will conduct a first round of screening of title and abstracts using the criteria below, and when this is complete, consider whether restriction by population is appropriate.

> Does the study report data on vaccination / immunization to prevent disease in humans? (Exclude vaccines used for immunotherapeutic treatment of disease and animal studies. Exclude studies of epidemiology or prevalence intended to inform vaccination programmes, but which do not report actual data regarding vaccination.)
>
> Is the study a systematic review (i.e. does it report at least some information on both search strategy and inclusion criteria)?
>
> Does the review include at least some data from high-income countries (OECD member)? [b]
>
> Does the review include data on at least one of the following? (Exclude reviews of clinical effectiveness or safety data only, or descriptive data only.)

Effectiveness or cost-effectiveness of interventions to increase uptake of vaccination (code IN_EFF)
Determinants (correlates) of uptake of vaccination (code IN_DET); or
Views / attitudes / beliefs regarding vaccination (code IN_VIEW)?
We will separate included reviews into three streams according to the three categories above. Depending on volume of included reviews and available resource, and in consultation with the NICE team, we may further restrict inclusion to studies of effectiveness and cost-effectiveness, or at least prioritise these for synthesis.

Quality assessment and data extraction

Quality assessment and data extraction will be conducted using the tools in the methods manual. All studies will be quality assessed and data extracted by one reviewer, with all data checked in detail by a second reviewer.

Data synthesis

Data will be synthesized narratively.

[b] These are: Australia, Austria, Belgium, Canada, Chile, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Luxembourg, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, UK, USA

A.5.4 RQ LL and MM – search strategy and review protocol

This document is a protocol for a public health evidence review which is being developed by London School of Hygiene & Tropical Medicine (LSHTM) and the Centre for Public Health (CPH) at NICE to inform the joint clinical and public health guidance on TB.

Review questions

What case management strategies and interventions are effective and cost effective in increasing the uptake of, or adherence to, treatment for people with active or latent TB?

What is known from studies of case management interventions about the barriers to uptake and adherence to treatment for active or latent TB?

Methods

The review will be carried out according to the methods set out in the current (third) edition of *Methods for the development of NICE public health guidance*. The review will be registered with PROSPERO when the protocol is finalized.

Search sources

The following sources are proposed and will be searched from 1993 to the most recent records:

- ASSIA via ProQuest
- British Library Electronic Theses Online via http://ethos.bl.uk
- British Nursing Index (BNI) via ProQuest
- CINHAL via Ebsco
- Cochrane Database of Systematic Reviews (CDSR) via http://www.thecochranelibrary.com
- Cochrane Health Technology Assessment database via http://www.thecochranelibrary.com
- Conference Proceedings Citation Index- Science (CPCI-S) via ISI*
- Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH) via ISI*
- Database of Abstracts of Reviews of Effects (DARE) via http://www.thecochranelibrary.com
- Embase via OVID
- Embase via OVID
- EPPI Centre Trials Register of Promoting Health Interventions (TRoPHI) via http://eppi.ioe.ac.uk/webdatabases/Intro.aspx?ID=5
- ERIC via ProQuest
- HMIC via OVID
- MEDLINE in Process via OVID
- MEDLINE via OVID
- NHS Economic Evaluation Database via http://www.thecochranelibrary.com
- OpenGrey via http://www.opengrey.eu/
- Science Citation Index Expanded (SCI-EXPANDED) via ISI
- Social Policy and Practice via OVID
- Social Sciences Citation Index (SSCI) via ISI

- Sociological Abstracts via ProQuest

* the date range of these two resources will be 2011-Current

A search of PubMed will also be run limited to electronic, advanced publication articles.

Web searching

The following general websites will be hand-searched:

- Campbell Collaboration via http://www.campbellcollaboration.org/
- McMaster University Health Evidence via http://www.healthevidence.org/
- National Guideline Clearinghouse http://www.guideline.gov/
- NICE via http://www.nice.org.uk/
- Public Health England via https://www.gov.uk/government/organisations/public-health-england
- Public Health Observatory via http://www.apho.org.uk/

The following websites will be hand-searched:

- British Infection Association via http://www.britishinfection.org/drupal/
- British Thoracic Society via http://www.brit-thoracic.org.uk/
- Chartered Institute of Environmental Health via http://www.cieh.org/
- Cochrane Infectious Diseases Group Specialized Register via http://cidg.cochrane.org/specialized-register
- Department of Health, Social Services and Public Safety of Northern Ireland via http://www.dhsspsni.gov.uk/
- Health Protection Scotland via http://www.hps.scot.nhs.uk/
- Health Quality Improvement Partnership via http://www.hqip.org.uk/
- Infection Prevention Society via http://www.ips.uk.net/
- Local Government Association via http://www.local.gov.uk
- Stop TB UK via http://www.stoptbuk.org/
- Target Tuberculosis via http://www.targettb.org.uk
- TB Alert via http://www.tbalert.org

A search will be made of Google using Google advanced search limited to PDFs or word document files.

Supplementary searching

All items included on full-text will be citation traced. Backwards citation tracing will be conducted manually (one generation) and forwards citation tracing will be conducted in Web of Science.

Search terms

The draft search terms (for Medline) are shown below. The logic of the strategy is: (tuberculosis) AND (terms for uptake / adherence outcomes) AND (terms for case management interventions).

1 (Tuberculosis or TB).ti,ab,kw.
2 exp Tuberculosis/
3 1 or 2
4 *Directly Observed Therapy/
5 (DOT$ or (directly observ$ adj3 (therap$ or treat$))).ti,ab,kw.
6 (short course adj3 (therap$ or treat$)).ti,ab,kw.
7 ((observ$ or supervis$ or watch$ or witness$ or see$ or monitor$ or check$) adj3

(therap$ or treat$)).ti,ab,kw.
8 ((record$ or report$) adj3 (therap$ or treat$)).ti,ab,kw.
9 or/4-8
10 Case Management/
11 ((case or care or treatment) adj3 manage$).ti,ab,kw.
12 ((manag$ or supported or plan$) adj3 care).ti,ab,kw.
13 Managed Care Programs/
14 ("patient centered" or "patient centred").ti,ab,kw. or Patient-Centered Care/
15 ((Tuberculosis or TB) adj5 (nurse or staff or team or multidisciplinary or outreach or centre or center or clinic)).ti,ab,kw.
16 ((case or link) adj3 worker).ti,ab,kw.
17 ("treatment partner" or "treatment supporter").ti,ab,kw.
18 "Continuity of Patient Care"/
19 social support/
20 or/10-19
21 9 or 20
22 (uptake or up-take or (up adj1 tak$) or takeup or take-up).ti,ab,kw.
23 (adher$ or nonadheren$ or (non adj1 adheren$) or access or refusal or compliance or comply$ or compli$ or concordan$ or default$ or dropout or drop out or interrupt$ or complet$ or finish$ or follow up or (miss$ adj2 appointment)).ti,ab,kw.
24 *Medication Adherence/
25 *Patient Compliance/
26 *Patient Dropouts/
27 *Treatment Refusal/
28 or/22-27
29 3 and 21 and 28
30 limit 29 to yr="1993 -Current"
31 limit 30 to english language
32 exp animals/ not humans.sh.
33 31 not 32
34 (cow or cows or cattle or bovine or calves or badger or badgers or hedgehog or hedgehogs or mice or mouse or rat or rats).mp.
35 33 not 34

Screening

EPPI-Reviewer 4 software will be used to manage data. A random sample of 10% of titles and abstracts will be screened by two reviewers independently and differences resolved by discussion. If agreement is adequate at this stage, subsequent abstracts will be screened by one reviewer. The full text of all studies which meet criteria, or where it is unclear whether they meet the criteria, will be retrieved and screened by two reviewers independently.

The inclusion criteria will be as follows:

1) Does the study measure uptake of, or adherence to, tuberculosis treatment as an outcome, or concern an intervention aiming to increase uptake or adherence? (This will include: uptake of diagnostic testing; receipt of diagnostic test results; starting therapy after diagnosis; clinic attendance; any measure of treatment adherence; treatment completion or non-completion. The following outcomes will be excluded: number of cases of tuberculosis found; tuberculosis recurrence; drug-resistance.)

2) Does the study present primary data regarding an intervention, either concerning outcomes or processes? (For outcome evaluation studies, any study design including an intervention and at least some pre- and post-test outcome data will be included here initially, i.e. trials, one-group before-after studies, and retrospective or observational studies which cover the time period of an intervention and report clear pre and post data on an outcome which is relevant as per criterion (1). Cost-effectiveness studies will also be included here. Studies of process data (data on barriers, acceptability etc., e.g. qualitative research) will be included only if they clearly relate to a specific intervention programme. That is, studies about barriers or acceptability in general terms without reference to an intervention, or with reference to a hypothetical intervention not actually implemented, or to usual processes of care without reference to a defined intervention, will be excluded. This latter criterion will be applied strictly at abstract stage.)

3) Was the study conducted in a country which is a current OECD member? [c]

4) Does the intervention include case management (CM), defined as an approach where a designated case manager facilitates access and adherence to treatment or engagement with services?[d] This may include, for example, needs assessment, risk assessment, assistance in developing a programme of care or with accessing services, and/or observation of therapy, and includes both standard and enhanced CM. The intervention need not be exclusively focused on TB, and could include more broadly based interventions for those with complex needs, as long as they use a CM approach and the study measures some adherence-related outcome as per criterion (1). Directly observed therapy (DOT / DOTS) will be included in the definition of case management. Interventions will not be excluded depending on who delivers the intervention (i.e. interventions delivered by lay people or other professionals, as well as clinicians or healthcare professionals, will be included.) The following will be excluded: interventions which mainly comprise information or education, or general social support [which are included in the other review]; programmes to engage the general population with services (e.g. population screening); novel drug regimens or drug delivery forms.

Criterion (4) may be subject to further refinement in consultation with the team at NICE conducting searching and screening for the review of education and social support..

Quality assessment and data extraction

Quality assessment and data extraction will be conducted using the tools in the CPH methods manual. All studies will be quality assessed and data extracted by one reviewer, with all data checked in detail by a second reviewer.

Data synthesis

Data will be synthesised narratively in the first instance. If sufficiently homogeneous and high-quality data are located, meta-analysis may be considered, although this is unlikely.

[c] These are: Australia, Austria, Belgium, Canada, Chile, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Luxembourg, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, UK, USA

[d] Cf. the definitions of case management in the glossary to PH37.

A.5.5 RQ NN and OO – search strategy and review protocol

Review question 3a

What information, education or other support-based interventions are currently used in practice to support the diagnosis, treatment and management of TB?

Review question 3b

How effective and cost effective are strategies and interventions aimed at providing and delivering information and education about the symptoms and risk of TB, clinical management of the illness and broader social support to people affected by TB?

Protocol for a public health evidence review developed by Centre for Public Health (CPH) at NICE and the London School of Hygiene & Tropical Medicine (LSHTM) to inform the joint clinical and public health guidance on TB.

- Introduction

Current UK guidance on vaccination for tuberculosis (TB)[e] recommends that Bacillus Calmette-Guérin (BCG) vaccine should be offered to the following groups:

- infants living in high-prevalence areas of the UK[f], infants and children up to 16 years with a parent or grandparent born in a high-prevalence country, who are contacts of cases of respiratory TB, who were born in or have lived for at least three months in a high-prevalence country.
- healthcare workers and laboratory staff who will have contact with patients or clinical materials; veterinary and staff such as abattoir workers who handle animal species known to be susceptible to TB and staff of prisons, care homes for the elderly, hostels for homeless people and facilities accommodating refugees and asylum seekers.

In addition to those classified as high risk and eligible for BCG vaccination a number of additional groups are recognised at increased risk of TB infection:

- people who are homeless
- substance misusers
- prisoners
- people who are immunocompromised
- those who are hard to reach – as defined by PH37
- those who have migrated from or have visited a country classified as a high prevalence area, having resided there for a minimum of 3 months.

All of the above groups are particularly important when providing guidance on the testing, diagnosis, treatment, management, prevention and control of TB and are considered the '**relevant groups**' for whom information, education and support approaches are required.

It is likely a range of information, education and support approaches are currently employed in practice to support the diagnosis, treatment and management of TB in relevant groups.

In order to identify what those approaches are the Centre for Public Health at NICE issued a call for evidence. Specifically, stakeholders were asked to submit links to published and unpublished reports relating to a number of questions including '*What information, education or other support-based*

[e] Salisbury D, Ramsay M, Noakes K, eds. (2006). *Immunisation against infectious disease: The green book* (London: TSO/DH), pp. 397-8. Cf. also the current NICE Clinical Guideline on TB (CG117).

[f] annual incidence greater than or equal to (≥) 40/100,000

interventions are currently used in practice to support the diagnosis, treatment and management of TB?' The results of the call for evidence will be supplemented by searches for literature (in particular grey literature) on current practice.

A range of information, education and support approaches are currently employed in practice in the UK to support the testing, diagnosis, treatment, management, prevention and control of TB among relevant groups. These will be summarised in Review 3a based on a call for evidence issued by CPH at NICE, a search of the NICE shared learning portal and a search of the literature undertaken by NICE using current practice search terms to provide an overview of current UK practice focussed on information, education and support approaches to facilitate the diagnosis, treatment and management of TB. The evidence on current practice will be collated and may provide a benchmark for current UK practice against which to consider other effective interventions from appropriate non-UK countries (i.e. OECD members).

Where inclusion criteria are met, the evidence for Review 3a (current practice) will feed directly into Review 3b (effectiveness and cost effectiveness) for quality appraisal, data extraction and synthesis. This latter element of Review 3b will be conducted by a team based at LSHTM, with advice from the CPH team.

Review 3b is intended to support the development of clinical and public health guideline by providing an overview and synthesis of the evidence on the effectiveness and cost effectiveness of interventions focussed on information, education and support currently being employed to facilitate the testing, diagnosis, treatment, management, prevention and control of TB within current practice in countries applicable to UK practice. These will be identified in Review 3b based on a search of the NICE shared learning portal and a search of the published and grey literature.

- The evidence will be identified and assessed for inclusion by a team from CPH – NICE.
- The evidence appraisal, extraction and synthesis will be conducted by a team based at LSHTM, with advice from CPH.

- Methods

The review will be carried out according to the methodological guidance set out in the current (third) edition of *Methods for the development of NICE public health guidance*.

- **Searching**

  Search approach

The searches will be consistent with the methods set out in Chapter 4 of the CPH methods manual.

The purpose of the search is to identify both journal articles and grey literature (such as reports and surveys). Four approaches to identifying the evidence will be used:

1. specific searches in bibliographic databases covering both health and social science
2. targeted online searches for grey literature
3. supplementary searches to locate additional evidence not indexed on databases
4. a call for evidence which gave stakeholders the opportunity to submit relevant evidence.

The searches for Review 3a will focus on retrieving evidence published in or about the UK, with the sources chosen according to their coverage of the UK literature[g]). The searches for Review 3b will cover the international literature. The database strategies will be as specific as possible (following

[g] Cooper C, O'Mara-Eves A, Rogers M, Bethel A, Lowe J, Crathorne L, et al. (2012) The best of the UK? A report on the value and future of UK databases in the health and social care fields: a systematic map protocol. *BMJ Open* 1;2(3).

testing) to ensure that sufficient time is available for grey literature and other supplementary searching.

The searches will focus on current practice, effectiveness and cost effectiveness directly relating to tuberculosis. Studies relating to information, education or other support outside the TB arena (such as other infectious diseases) will not be specifically searched for but may be passed to the reviewers when identified.

The search strategy will be developed by an Information Specialist in NICE Guidance Information Services (gIS). The strategy will be peer reviewed by another gIS Information Specialist before being run. The Information Specialist will consult with the authors of the search strategies for the other reviews prepared for this joint guidance to ensure consistency.

The initial search strategy will be developed in MEDLINE (Ovid Interface). Appropriate steps will be taken to translate this strategy for use with other databases.

Search sources

Bibliographic databases

The following sources will be searched for the reviews on current practice and effectiveness:

- Applied Social Sciences Index and Abstracts (ASSIA) via ProQuest
- British Library Electronic Theses Online (EThOS) via http://ethos.bl.uk
- British Nursing Index (BNI) via ProQuest
- Cumulative Index to Nursing and Allied Health (CINHAL) via Ebsco
- Cochrane Central Register of Controlled Trials (CENTRAL) via http://www.thecochranelibrary.com
- Cochrane Database of Systematic Reviews (CDSR) via http://www.thecochranelibrary.com
- Cochrane Health Technology Assessment database (HTA) via http://www.thecochranelibrary.com
- Database of Abstracts of Reviews of Effects (DARE) via http://www.thecochranelibrary.com
- Embase via OVID
- EPPI Centre Database of Education Research via http://eppi.ioe.ac.uk/webdatabases/Intro.aspx?ID=6
- EPPI Centre Trials Register of Promoting Health Interventions (TRoPHI) via http://eppi.ioe.ac.uk/webdatabases/Intro.aspx?ID=5
- Education Resource Information Center (ERIC) via ProQuest
- Health Management Information Consortium (HMIC) via OVID
- MEDLINE in Process via OVID
- MEDLINE via OVID
- OpenGrey via http://www.opengrey.eu/
- Social Care Online (SCO) via http://www.scie-socialcareonline.org.uk/
- PsycINFO via OVID
- Social Policy and Practice (SPP) via OVID
- Sociological Abstracts (SA) via ProQuest

Cost effectiveness evidence searches

A separate file of references will be compiled for the cost effectiveness evidence using three methods. 1. The following sources will be searched again with the validated cost effectiveness filter from the Centre for Reviews and Dissemination applied:

- Embase via OVID

- MEDLINE in Process via OVID
- MEDLINE via OVID

2. ASSIA, EThOS, BNI, CINHAL, CENTRAL, CDSR, HTA, DARE, EPPI, ERIC, HMIC, OpenGrey, SCO, SPP, SA and the websites listed below will not be searched again. A single search will be used on these sources and the screening process will identify papers relevant to both the effectiveness and cost effectiveness reviews.

3. The following resources will be used to identify additional cost effectiveness papers:

- CEA Registry via https://research.tufts-nemc.org/cear4/
- EconLit via Dialog
- EconPapers via http://econpapers.repec.org/
- Health Economic Evaluations Database (HEED) via http://onlinelibrary.wiley.com/book/10.1002/9780470510933
- NHS Economic Evaluations Database (NHS EED) via http://www.thecochranelibrary.com

Web searching

Websites will be searched and/or browsed as appropriate for current practice, effectiveness and cost effectiveness evidence.

The following general websites will be used:

- Campbell Collaboration via http://www.campbellcollaboration.org/
- McMaster University Health Evidence via http://www.healthevidence.org/
- National Guideline Clearinghouse via http://www.guideline.gov/
- NICE via http://www.nice.org.uk/
- NICE Evidence Search https://www.evidence.nhs.uk/
- Public Health Observatory via http://www.apho.org.uk/
- Public Health England via https://www.gov.uk/government/organisations/public-health-england
- Turning Research Into Practice via http://www.tripdatabase.com/

The following subject specific websites will be used:

- African Health Forum via http://www.africanhealthforum.org.uk/index.htm
- Black Health Agency via http://www.thebha.org.uk
- British Infection Association via http://www.britishinfection.org/drupal/
- British Society for Antimicrobial Chemotherapy via http://bsac.org.uk
- British Thoracic Society via http://www.brit-thoracic.org.uk/
- Centers for Disease Control and Prevention resources on TB via http://www.cdc.gov/tb/
- Chartered Institute of Environmental Health via http://www.cieh.org/
- Cochrane Infectious Diseases Group Specialized Register via http://cidg.cochrane.org/specialized-register
- Department of Health, Social Services and Public Safety of Northern Ireland via http://www.dhsspsni.gov.uk/
- Education for Health via http://www.educationforhealth.org/
- Health Protection Scotland via http://www.hps.scot.nhs.uk/
- Health Quality Improvement Partnership via http://www.hqip.org.uk Infection Prevention Society via http://www.ips.uk.net
- Local Government Association via http://www.local.gov.uk/

- Public Health Wales via http://www.publichealthwales.wales.nhs.uk/
- Race Equality Foundation via http://www.raceequalityfoundation.org.uk
- South Asian Health Foundation via http://www.sahf.org.uk
- Stop TB UK via http://www.stoptbuk.org/
- Target Tuberculosis via http://www.targettb.org.uk/
- TB Alert via http://www.tbalert.org/

Google searches will also be used via http://www.google.co.uk/

This search will focus on UK materials, for example the following commands might be used to restrict the results:

Site: gov.uk

Site: nhs.uk

Limit to pages from the UK

It may also be necessary to restrict the search results to particular file types, such as PDF or Word formats.

Supplementary searching

A set of items will be selected for supplementary searching to identify effectiveness and cost effectiveness evidence. This will include:

- Items identified through the call for evidence and scoping searches prior to the database searching
- Items identified as relevant to the review identified through the screening process.

The supplementary searching will be conducted in three ways:

- Backwards reference harvesting: studies will be extracted from the bibliographies of the papers identified and will be added to Reference Manager if the titles are relevant and/or they are not methodology papers (e.g. the Cochrane Handbook).
- Forwards citation searching: the Science Citation Index and the Social Science Citation Index via Web of Science (http://apps.webofknowledge.com) will be used to look for later papers citing the references of interest. All citations will be added to Reference Manager
- Related item searching using PubMed via http://www.ncbi.nlm.nih.gov/pubmed/
  If there are 1-100 references they will all be downloaded into Reference Manager. If there are 101 or more references they will be sorted by relevance and then the first 100 will be downloaded into Reference Manager.

Note that some of the supplementary searching cannot take place until after completion of the earlier rounds of searching. This searching will proceed alongside data screening from the initial searching steps and so will be more tailored at that point as the team has a clearer idea of where the evidence lies and any gaps that have emerged.

Search strategy

The search strategy will be developed following test searches and consultation with the NICE CPH team and the committee as appropriate.

The current practice strategy is likely to take the form:

(Tuberculosis OR TB) AND (education OR information dissemination OR social support) AND (current UK practice)

The effectiveness strategy is likely to take the form:

(Tuberculosis OR TB) AND (education OR information dissemination OR social support) AND (outcomes)

The cost effectiveness strategy is likely to take the form:

(Tuberculosis OR TB) AND (education OR information dissemination OR social support) AND (validated economic filter)

Terms for diagnosis, treatment and management will not be added, as the test searches show that they are not necessary, given the number of results being returned in MEDLINE. The search will cover both the education of patients and health professionals.

The search will not incorporate any population terms for patients and people at high risk of TB. As there will be no limitations specifying population, evidence on education, information or social support returned in the search could relate to professionals, other workers and lay and/or peer groups as well as patients, family, communities and the public – providing the evidence relates to TB.

Search limits

An English language restriction will be placed on the search.

A filter will be used to exclude studies on animals consistent with the other public health reviews.

No filters for study type will be applied, except in the cost effectiveness component of the searching.

Terms will be applied to remove editorials, news items and letters.

Validated filters for identifying cost effectiveness evidence will be applied as appropriate.

Databases will be searched from 1993 to the most recent records.

In the case of current practice (Review 3a), initial screening (see next section) of search results from 2003 will be prioritised, as (according to GDG expertise) TB services underwent changes between 2003-2005 thus, evidence from before this period may be less relevant to current practice.

Search results

Full search histories, including the full strategy used on each database, will be retained in line with Appendix C of the CPH Methods Manual.

Database results will be downloaded and de-duplicated in Reference Manager (version 12).

The results of the web searches will be recorded in Microsoft Word. Bibliographic details will be added to Reference Manager when requested by the CPH reviewers.

- *Screening*

Reference Manager software will be used to manage search results. An initial sample of 10% of titles and abstracts will be screened by two reviewers independently and differences resolved by discussion. The reviewers will consider all inclusion and exclusion decisions and discuss differences. If agreement is adequate at this stage, the CPH team will consider if subsequent title/abstracts may be screened by one reviewer.

All full text records which meet the inclusion criteria, or where it is unclear whether they meet the criteria, will be retrieved and screened by two reviewers independently. Differences in screening decisions will be discussed, recorded and consensus agreed, with the involvement of other reviewers as necessary. Screening decisions at full text will be recorded and listed in the review appendix and can made available to the GDG during review development as required.

The full text of all studies which meet criteria for Review 3b, or where it is unclear whether they meet the criteria, will be retrieved. These studies will be passed onto the external review team for quality assurance, extraction and synthesis.

The inclusion criteria (for Review 3a) will be as follows:

1) Does the report describe (what appears to be) current UK practice[h] for interventions or strategies focussed on information, education and other support?

Initially the summary of current UK practice will have no study design limits, the only limit imposed will relate to which evidence subsequently filters into the effectiveness and cost effectiveness review and will be incorporated based on the inclusion criteria described in part b.

2) Does the report describe:

Information, education and/or support, covering but not limited to:

- knowledge and awareness of TB among people who have, or who are at high-risk of TB, and relevant staff, including:
  - how to recognise symptoms
  - the need for rapid diagnosis
  - referral and access to specialist TB services
  - the need for prompt, complete treatment
  - health, social and economic outcomes for people affected by TB

3) Does the study/document report on practice in the UK (or, can information be extracted relevant to UK practice, if wider)?

- **Extraction and synthesis (review 3a)**

Details on current practice will be extracted into evidence tables and a narrative synthesis of current practice taking place within the UK will be undertaken. Any reports or studies which also meet the inclusion criteria described for Review 3b (effectiveness and cost effectiveness) will be passed onto the review team at LSHTM as appropriate for quality assurance, data extraction and data synthesis.

The inclusion criteria for (review 3b) will be as follows:

1) Intervention: Does the study include an outcome evaluation of a strategy or intervention providing and delivering information and/or education about:
   a. the symptoms and risk of TB
   b. clinical management of the illness
   c. broader social support for people affected by TB?

Comparison: Initially any study design including an intervention/strategy that is intended to support uptake and adherence and at least some data before and after the intervention are reported. Study design could include controlled trials, before-after studies, retrospective or observational studies which report clear pre and post data

2) Populations:
   Adults, young people and children who have or suspected to have **active** TB, who have **latent** TB, who are at increased risk of infection from and/or progression to active disease.

   Consideration for specific sub-groups for whom diagnosis and management of TB may vary will also be given.

   See scope section 5.1.1 (page 7–8 and relevant groups outlined above) for details.

[h] With reference to this review 'current UK practice' means evidence of practice in any UK setting

3) Outcomes: Does the study measure change in knowledge or awareness; uptake of diagnostic testing or uptake and adherence to treatment/management of TB as an outcome?

4) Applicability: Was the study conducted in a high-income country (that is, a current OECD member)? [i]

Any type of intervention will be included: both provider-focused interventions such as clinician education (training for clinicians to develop their practice/se), and public-focused interventions such as awareness raising, reminders or information programmes.

The above inclusion criteria may be subject to further refinement in consultation with the team at LSHTM undertaking the review of factors to support adherence and uptake of treatment.

To supplement the above reviewing activity, recommendations from NICE in relevant areas (i.e. TB hard to reach groups [PH37], HIV increasing uptake of testing [PH 33 and 34] Hepatitis B and C – ways to promote and offer testing [PH43]) in relation to the range of activities, interventions and groups considered in this review will be identified. Recommendations and underpinning evidence statements that appear to be potentially relevant to elements of this review will be indicated and a 'map' of these linkages presented to the GDG for consideration.

The CPH team will also note where evidence on information, education and support (Review 3a) relates to the care pathway for people affected by TB. In particular, linking evidence identified to points in CG117 (and the update, as appropriate) where it is recommended that service providers 'inform' and 'advise'.

Steps to this point will be provided by NICE CPH and NICE Guidance Information Services (gIS), subsequent steps will be provided by LSHTM.

Quality assessment and data extraction

Quality assessment and data extraction will be conducted in line with the Centre for Public Health Methods for the Development of NICE Public Health Guidance (3rd Edition - 2012). All studies will be appraised for quality and data extracted by one reviewer, with all data checked by a second reviewer.

Data synthesis (review part 3b)

Data will be synthesised narratively in the first instance. If sufficiently homogenous and good-quality data are located, meta-analysis will be considered.

[i] These are: Australia, Austria, Belgium, Canada, Chile, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, South Korea, Luxembourg, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, UK, USA

A.5.6 RQ PP – search strategy and review protocol

• Review objectives

Describe commissioning models, service models, and service structures that are in place in countries[j], regions and cities that have seen a positive shift in TB incidence and prevalence, in particular how services are commissioned, organised and delivered where possible in relation (but not limited) to:

- Reducing diagnostic delay for TB
- Improving TB contract tracing
- Improving TB treatment completion

Analysis of the evidence will focus on extracting information on elements of particular relevance to the UK context such as: demographics, geography, variations due to differences in TB rates[k], and accountability arrangements. It will summarise, where available, the evidence on:

- The effectiveness of different service models (in relation to the outcomes above), and where possible the factors that contribute to this
- The cost and cost effectiveness of different approaches
- Implementation issues relevant to different approaches

• Methods

The guideline development group for TB are in the process of developing recommendations for the effective identification, management and control of TB, based on the best available evidence of effectiveness and cost effectiveness. The review questions driving the development focus on the effectiveness and cost effectiveness of relevant interventions, and evidence being used to inform the recommendations is derived largely from systematic reviews of effectiveness.

The service delivery element of the guideline is concerned with identifying the optimal service models for delivering relevant interventions across a clinical pathway. Relevant evidence is likely to come from a variety of sources that may not be captured by a standard systematic review approach. Following discussion with the GDG chairs and Service Delivery Group members, it has been agreed that a standard systematic review of effectiveness may not be the most appropriate approach to identifying and synthesising the evidence in this area. Instead, the review will take a mixed method approach to identifying, interrogating and presenting the evidence, comprising of a systematic literature review focusing on a set of pre-identified cities and countries. All review work will be conducted in line with NICE methods and principles.

• *Identifying the evidence*

• Approach

A call for evidence will be made to stakeholders for the guidance, including members of the GDG and the Service Delivery Group (SDG) for recommendations on relevant published and

[j] See country of study section below
[k] Incidence, prevalence, population density, transmission rates etc…

unpublished literature, which fit the inclusion criteria described below. The call for evidence will run from 04-03-2014 to 01-04-2014.

The literature search approach will be iterative and emergent. The search will focus on identifying a cluster of documents relevant to the case study cities and countries. The cluster will then be used to inform the next steps in the search to retrieve related information using the berrypicking method[I]. A small number of bibliographic databases will be used where appropriate with search strategies focussed on the relevant case studies. See Appendix 1 for further details.

The searches will be developed by an Information Specialist in NICE Guidance Information Services (gIS) and the main strategy will be quality assured by a Senior Information Manager in gIS. Additional search strategies will be peer reviewed by another gIS Information Specialist before being run.

Full search histories, including the strategy used on each database, will be retained in line with Appendix C of the CPH Methods Manual.

Database results will be downloaded and de-duplicated in Reference Manager (version 12). The results of the web searches will be recorded in Microsoft Word. Bibliographic details will be added to Reference Manager when requested by the CPH reviewers.

- **Screening**

The evidence identified via the SDG, the call for evidence and the literature search will be compiled in a suitable format (Word for smaller volumes or MS Access if the volume is large) and then screened for inclusion using the criteria described below in the “Inclusion Criteria” section.

It will be screened by one reviewer using a standard two stage approach of title and abstract screening, followed by full-text screening of all potentially relevant literature. A conservative approach will be taken, whereby any literature for which there is uncertainty will be screened by a second reviewer (at both abstract and full text stage). A third reviewer will be consulted if disagreements arise.

- ***Inclusion criteria***

Study design

There will be no limit on study design but the following will be prioritised: comparative studies, quantitative studies (particularly time series analysis), case studies, or evaluations of TB services that focus on our key intervention and outcome sections below.
We will also include economic analyses, including cost-benefit, cost-effectiveness, cost-utility, modelling studies, or cost-impact analyses.

If excessive numbers of studies or reports are located, we will consider restricting inclusion based on relevance of the setting or context to the UK health service, and adopting more restrictive criteria for economic analyses (e.g. regarding perspective, country or type of evaluation).

[I] Booth A et al. Towards a methodology for cluster searching to provide conceptual and contextual "richness" for systematic reviews of complex interventions: case study (CLUSTER). *BMC Medical Research Methodology*. 2013 Sep;13(1): 118.

Population

Anyone with active or latent TB, or at risk of TB who is in scope for the guideline update (see section 5.1 in the final scope).

Studies of the general population and specific sub-population groups will be included and be reported at sub-population level if they present clearly disaggregated data on members of different eligible groups, however, the focus will be on service models that can cater for the needs of all those affected by tuberculosis as Public Health Guidance (PH37) recommendations are already available on 'Identifying and managing tuberculosis among hard to reach groups'.

Service and commissioning models, and service structures (interventions)

The report will aim to collate key characteristics/ factors of successful interventions, services and service models.

In order to capture interventions/service models relevant to the review in the screening process, we have conceived a number of potentially relevant interventions in a very broad sense. These will include but are not limited to:

Any organisational-level intervention which has shown a marked improvement in improving the speed of TB diagnosis, contact tracing for TB, or treatment completion in eligible population groups.

This may include:

- the centralisation of TB services;
- the provision of new services, such as outreach clinics;
- changes to service delivery or accessibility to reduce wider structural and social barriers to accessing TB services;
- changes to components of TB services;
- the provision of services in new settings or by different providers;
- the adoption of new information or knowledge management methods to facilitate service delivery;
- the use of different protocols, processes or methods for example in contact tracing;
- the provision of different service configurations to meet the needs of different groups at need, different areas of prevalence/incidence or geographies;
- the provision of services via and education/training of non-traditional healthcare workforces to meet varying population needs such as lay health workers;
- different approaches to providing peer support to people with a positive diagnosis upon starting treatment.

Settings

Any setting in which health or public services for TB are received, provided or commissioned in the public, private and voluntary sectors.

Outcomes

The outcomes of interest will include, but not be limited to, service models/delivery interventions or evaluations that report on:

- number of TB diagnoses and time that elapses between symptomatic TB infection and diagnosis;
- changes in transmission rates of TB;
- associated with delayed diagnosis, contact tracing or treatment completion in response to service delivery changes;
- change in awareness and uptake of TB screening services in response to service changes (which could include anti stigma initiatives);
- service providers' use of or adherence to contact tracing tools;
- number of people completing treatment for TB in response to service changes;
- changes in multi-drug-resistant TB cases in response to service changes;
- the availability and reach of TB diagnosis and treatment services, such as the number of screening opportunities offered; use of different providers for screening;
- referrals into TB services and/or referral to other services (i.e support services) in response to service changes;
- economic outcomes, such as costs, cost-effectiveness, cost-benefit, and cost-utility measures).

Economic perspective (where relevant)

Any perspective will be considered for the economic evaluation studies. However, if the volume of evidence is large, the perspective will be limited to that of the public sector, including the NHS, personal social services and local authorities (and other public sector agencies as appropriate).

Country of study

The emphasis will be on evidence from the UK and a subset of relevant countries and cities within the OECD that have been identified by the SDG as being successful in managing TB, and that have some applicability to the UK context. Focus will be on those perspectives that have the greatest similarities and applicability to the UK in such things as service delivery, health care system and epidemiology (i.e. low vs. high prevalence).

The following places have been identified as most relevant in discussion with the SDG and finalised in consultation with the chairs:

- New York (useful analogy for London),
- Netherlands (mixed urban/rural),
- Barcelona (good example of a smaller urban setting)
- Canada (well organised and dispersed population analogous to our more rural areas).

Date of publication

Studies published in 2003 or later will be included. This date range is considered to be more appropriate as it will capture any relevant service or policy changes that have occurred in the UK (such as the end of universal BCG vaccination in 2005) or, that may have occurred during or after the production of NICE guidance CG33, CG117 and PH37.

Language of study

English-language studies only will be included.

Quality assessment and data extraction

All included studies will be quality-assessed and data extracted using the tools specified in the NICE methods manual. Quality assessment and data extraction will be carried out by one reviewer and checked by a second, and any disagreements resolved by discussion. Evidence tables for all included studies will be created and included as appendices to the final review report.

Data synthesis and reporting

Identified literature (published and grey) that describes TB services (including multidisciplinary and third sector services) with a positive change in relevant outcomes will be synthesised to describe:

- How the service is structured?
- How the service is commissioned and funded?
- How the service is organised?
- Who does the service treat?
- Who delivers the service?
- Who is accountable for the service?
- How does the service perform in relation to our key outcomes?
- What aspects/factors of the service have been shown to contribute to improved outcomes?

A narrative will aim to describe how different the programmes are from the UK, and whether the UK can deliver services in a similar way. Any information located on the effectiveness or cost effectiveness of the service will also be described.

The appendix will present structured evidence tables, and where possible (but not limited to) grouping studies or reports into the 3 areas noted above: delayed diagnosis, contact tracing, treatment completion. Studies may also be grouped by commissioning structures or model, type of service delivery configuration and population, as appropriate. Economic studies will be presented separately using structured tables and grouping by the type of economic study and type of service delivery change under evaluation, as appropriate. If appropriate and feasible, different service configurations will be diagrammatically presented.

Search Strategy

The search will follow the "berrypicking" model of identifying a cluster of relevant documents and then exploring how they relate to other papers in an iterative process. It is difficult to predict in advance where the relevant evidence might lie. The types of evidence required for this review are likely to be found in grey literature. Sensitive searches of bibliographic databases would not be an efficient use of time to locate this type of evidence. The documents submitted by SDG members will form the initial cluster and help to direct where the search progresses.

- **Website searching**

Websites could be a productive source of evidence on the case study countries and cities, as well as of UK materials. A wide spread of websites has been proposed to conduct an initial broad search. A selection of websites may be chosen for more focussed searching later in the process when any gaps in the evidence have been identified.

The following websites will be searched and browsed to help identify the initial cluster of relevant documents:

- African Health Forum via http://www.africanhealthforum.org.uk/index.htm
- Agency for Health Care Research and Quality via http://www.ahrq.gov/
- Audit Commission via http://www.audit-commission.gov.uk
- Australian Clinical Practice Guidelines Portal via http://www.clinicalguidelines.gov.au/
- Black Health Agency via http://www.thebha.org.uk
- British Infection Association via http://www.britishinfection.org/drupal/
- British Society for Antimicrobial Chemotherapy via http://bsac.org.uk
- British Thoracic Society via http://www.brit-thoracic.org.uk/
- Campbell Collaboration via http://www.campbellcollaboration.org/
- Centers for Disease Control and Prevention resources on TB via http://www.cdc.gov/tb/
- Chartered Institute of Environmental Health via http://www.cieh.org/
- Cochrane Infectious Diseases Group Specialized Register via http://cidg.cochrane.org/specialized-register
- Department of Health via http://www.gov.uk
- Department of Health, Social Services and Public Safety of Northern Ireland via http://www.dhsspsni.gov.uk/
- European Centre of Disease Prevention and Control via http://www.ecdc.europa.eu
- Find TB Resources via http://www.findtbresources.org/
- Guidelines & Audit Implementation Network via http://www.gain-ni.org/
- Health & Social Care Information Centre via http://www.hscic.gov.uk/
- Health Protection Scotland via http://www.hps.scot.nhs.uk/
- Health Quality Improvement Partnership via http://www.hqip.org.uk
- Healthcare Quality Improvement Partnership via http://www.hqip.org.uk/
- Infection Prevention Society via http://www.ips.uk.net
- Institute for Clinical Systems Improvement via https://www.icsi.org
- KNCV Tuberculosis Foundation via http://www.kncvtbc.org
- Local Government Association via http://www.local.gov.uk/
- McMaster University Health Evidence via http://www.healthevidence.org/
- National Audit Office via http://www.nao.org.uk/

- National Guideline Clearinghouse via http://www.guideline.gov/
- New York City Department of Health and Mental Health via http://www.nyc.gov/html/doh/html/diseases/tb.shtml
- NHS England via http://www.england.nhs.uk/
- NHS Health Scotland via http://www.healthscotland.com/resources/publications/search-result.aspx
- NICE via http://www.nice.org.uk/
- NICE Evidence Search https://www.evidence.nhs.uk/
- NIHR Health Services & Delivery Research Programme via NIHR Service Delivery and Organisation programme
- Nuffield Trust via http://www.nuffieldtrust.org.uk/
- OpenGrey via http://www.opengrey.eu/
- Public Health Agency of Canada via http://www.phac-aspc.gc.ca/index-eng.php
- Public Health England via https://www.gov.uk/government/organisations/public-health-england
- Public Health Observatory via http://www.apho.org.uk/
- Public Health Wales via http://www.publichealthwales.wales.nhs.uk/
- Quality, Innovation, Productivity and Prevention via http://www.evidence.nhs.uk/qipp
- Race Equality Foundation via http://www.raceequalityfoundation.org.uk
- Royal College of Nursing via https://www.rcn.org.uk/
- Royal College of Physicians via http://www.rcplondon.ac.uk/
- South Asian Health Foundation via http://www.sahf.org.uk
- Stop TB UK via http://www.stoptbuk.org/
- Target Tuberculosis via http://www.targettb.org.uk/
- TB Alert via http://www.tbalert.org/ and http://www.thetruthabouttb.org/
- Turning Research Into Practice via http://www.tripdatabase.com/
- World Health Organization via http://www.who.int/en/

- **Google searches**

Google searches will also be used to locate materials on the case studies via http://www.google.co.uk/
This search will focus on concepts, projects or authors identified in the initial cluster of relevant materials. The search will aim for precision rather than recall, for example only the highest ranking search results may be investigated, or the following commands might be used to restrict the results:

Site: gov.uk
Site: nhs.uk
Limit to pages from the UK

It may also be necessary to restrict the search results to particular file types, such as PDF or Word formats.

- **Non-database searching**

Papers relating to those in the initial cluster will be retrieved in three ways:

- Backwards reference harvesting: studies will be extracted from the bibliographies of the relevant papers if they are relevant to the scope.
- Forwards citation searching: the Science Citation Index and the Social Science Citation Index via Web of Science (http://apps.webofknowledge.com) will be used to

look for later papers citing the references of interest. All citations will be added to Reference Manager

- Related item searching using PubMed via http://www.ncbi.nlm.nih.gov/pubmed/
  If there are 1-100 references they will all be downloaded into Reference Manager if they are relevant to the scope. If there are 101 or more references they will be sorted by relevance and then the first 100 will be downloaded into Reference Manager. if they are relevant to the scope. Relevant to the scope means TB or tuberculosis is in the title.

- **Bibliographic databases**

Appropriate bibliographic databases will be subject to targeted searches focussing on the case studies and any evidence gaps identified in the earlier stages of the search process. The searches could target the concepts, projects, organisations or authors identified in the initial cluster of documents.

The following databases have been chosen for their relevance to TB and coverage of grey literature based on previous experience of searching for TB and grey literature for NICE public health guidance.

Relevance to TB

- Embase via OVID
- MEDLINE in Process via OVID
- MEDLINE via OVID
- PsycINFO via OVID

UK and grey literature

- Health Management Information Consortium (HMIC) via OVID
- Social Policy and Practice (SPP) via OVID

Social science and grey literature

- Applied Social Sciences Index and Abstracts (ASSIA) via ProQuest
- Cumulative Index to Nursing and Allied Health (CINHAL) via HDAS

Cochrane Library

- Cochrane Central Register of Controlled Trials (CENTRAL) via http://www.thecochranelibrary.com
- Cochrane Database of Systematic Reviews (CDSR) via http://www.thecochranelibrary.com
- Database of Abstracts of Reviews of Effects (DARE) via http://www.thecochranelibrary.com
- NHS Economic Evaluations Database (NHS EED) via http://www.thecochranelibrary.com

Cost effectiveness

- CEA Registry via https://research.tufts-nemc.org/cear4/
- EconLit via Ovid
- EconPapers via http://econpapers.repec.org/

- **Search strategy**

The search strategy will be developed following test searches and consultation with the NICE CPH team and the SDG as appropriate. The initial search strategy will be developed in

MEDLINE (Ovid Interface) and appropriate steps will be taken before using this in the other databases. It is likely that an iterative approach will be taken to strategy development, where a series of short searches are developed to target specific issues, rather than developing one sensitive strategy.

Terms for tuberculosis will be taken from the searches done for Review 3. The search will not incorporate any population terms for patients and people at high risk of TB.

- An English language restriction will be placed on the database searches.
- A filter will be used to exclude studies on animals.
- No filters for study type will be applied.
- Terms will be applied to remove editorials, news items and letters (as in review 3).

Databases will be searched from 2003 to the most recent records.