Early Detection and Integrated Management of Tuberculosis in Europe

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Early diagnosis of tuberculosis

D7.2
Policy review (evidence base)

WP 7 – Strengthening national TB programmes

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1.0	02-12-2017	DH PHE	First version

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Key word list

TB prevention
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Definitions and acronyms

Acronyms	Definitions
ART	Anti-Retroviral Therapy
DOTS	Directly Observed Therapy – Short course
ECDC	European Centre for Disease Prevention and Control
HCW	Health Care Worker
INH	Isoniazid
IGRA	Interferon Gamma Release Assay
LTBI	Latent TB Infection
RCT	Randomised Controlled Trial
TST	Tuberculin Skin Test

1. Introduction

The objective of this Work Package 7 deliverable (D7.2) is to identify evidence of best practice for high impact TB control interventions, to inform national TB strategy development in the EU/ EEA. The evidence summarised in this report will be combined with the results of a survey of national TB control plan development and implementation in EU/EEA Member States (deliverable D7.1) to identify gaps and design targeted and appropriate support. A structured meeting with national TB programme leads and other experts (deliverable D7.3), supported by the results of the survey, the present review, and a review of barriers to TB development and implementation, will help to prioritise the summarised evidence within the context of EU/EEA countries. The outcome of this meeting will be a toolkit (deliverable D7.4) to aid national TB plan development and implementation based on best evidence, expert views and experience from individual member states.

1.1. General context

High income countries may have an advantage, compared with low-income countries, in reaching WHO End TB strategic targets (Lönnroth and Raviglione 2016). National TB control strategies in countries of low (<10/100,000 per year) to medium (<20/100,000 per year) TB incidence in the general population typically include actions targeted at vulnerable and high risk groups, alongside wider health system efforts to improve treatment, prevent drug resistance, and implement new technologies (Lonnroth *et al.* 2015). Ideally, these actions are described in a national plan for TB control and prevention, which is then implemented in a programme coordinated by a national TB control board or committee with representation from all stakeholders (World Health Organisation 2015).

National TB control programmes across the European Union (EU) and European Economic Area (EEA) benefit from synchronisation of strategies and monitoring of outcomes at a supranational level (ECDC 2010). However, projected trends indicate that considerable intensification of efforts is needed across Europe if the 2035 End TB goal is to be attained (ECDC 2017). It is of fundamental importance that these efforts are underpinned by a strong evidence base regarding the effectiveness of interventions (D'Ambrosio *et al.* 2014).

Systematic reviews of reviews are a recognised method of compiling and assessing the findings from multiple systematic reviews into an accessible and usable summary, which can then be used to identify gaps in the evidence base and to prioritise future research (Cochrane 2011, Li *et al.* 2012). The aim of the present study was to identify systematic reviews of interventions for TB control and prevention relevant to settings of low-medium TB incidence, to assess the quality of the reviews, and to summarise the strength of evidence for each intervention.

1.2. Deliverable objectives

The specific objective of this deliverable was to conduct a systematic search and review of the evidence base for TB control and prevention interventions in low and medium TB incidence countries. The aim of the review is to provide national TB programme leads and experts with an evidence-based framework for discussion of future strategy in a structured meeting, by identifying interventions (and gaps in evidence) in relation to priority action areas within national TB strategies (whether current or under development).

2. Methodological approach

2.1. Search strategy and selection criteria

Our review protocol was defined in advance and registered with PROSPERO (Collin *et al.* 2017).

2.1.1. Inclusion criteria

All systematic reviews of interventions for TB control and prevention relevant to settings of low (<10/100,000) or medium (<20/100,000) TB incidence were eligible. A systematic review was defined as one that made a documented attempt to identify systematically studies addressing a research question of interest, with or without a statistical summary of included studies (meta-analysis).

2.1.2. Interventions of interest

We defined 'interventions for TB control and prevention' as any population level, public health or clinical (at primary, secondary or tertiary level) approach which aims to prevent cases of TB or reduce the incidence of TB at local, national or regional level. For the purpose of this report, our analysis was restricted to reviews which reported a quantifiable direct effect of a clearly defined intervention (reported as a primary or secondary outcome in the systematic review), i.e. TB cases prevented or TB incidence reduced. We also retrieved reviews of interventions which were clearly defined but which had an indirect effect on TB cases/incidence, i.e. the review reported an outcome other than cases prevented/incidence reduced, but excluded these for analysis here. We also retrieved reviews where an intervention was not evaluated but the review described risk groups or technologies which, if targeted/deployed in a hypothetical intervention, could prevent TB cases or reduce incidence. We included all defined types of intervention without pre-specification.

2.1.3. Search methods for identification of reviews

The following databases were searched from inception to May 2017: MEDLINE, EMBASE, CINAHL, Scopus, Global Health, Trip, Cochrane Library, Social Policy and Practice, HMIC (Health Management Information Consortium), DoPHER (Database of promoting health effectiveness reviews), Health Systems Evidence, National Guideline Clearinghouse. In addition, the PROSPERO systematic reviews register and International Journal of TB and Lung Disease were searched within the same period. Full search strategies are shown in **Appendix 1**. In brief, we used a search filter developed by Lee *et al.* to identify systematic reviews of public

health interventions (Lee *et al.* 2012), combined with MeSH and title word terms for tuberculosis/TB. To search databases of reviews, health evidence or guidelines, we simply used terms for tuberculosis/TB. No language or date restrictions were imposed.

2.1.4. Selection of reviews

Citations identified by the search were imported into EndNote (EndNote X8; Clarivate Analytics, Boston, MA 02210, USA) for de-duplication, and then imported into to EPPI-Reviewer (EPPI-Reviewer 4; EPPI-Centre Software; Social Science Research Unit, UCL Institute of Education, London, UK) for further de-duplication. Two reviewers conducted screening of references by title and abstract independently and in parallel, with any disagreements resolved by discussion with a third reviewer. Full texts of all articles identified in the second screen by title and abstract were retrieved, requesting copies from authors if necessary. Irretrievable articles, i.e. not accessible from any source or from the authors were excluded. The full texts of retrieved articles were screened for final inclusion independently and in parallel by two reviewers using an inclusion checklist (**Appendix 2**), with any disagreements resolved by discussion with a third reviewer. When several versions of reviews were identified, only the most recent was included. If there was more than one publication of an identical review (e.g. a Cochrane review and a journal version including the same papers), the reference with the most detail was included.

2.1.5. Inclusion/exclusion classification

Reviews were included for our primary analysis if they reported evidence of a direct effect in controlling or preventing TB, i.e. preventing cases or reducing incidence, either as a primary or secondary outcome measure of the review. Reviews were flagged for future analysis if they evaluated an intervention which had a plausible indirect effect in preventing TB cases or reducing TB incidence (regardless of the outcome measures reported in the review), or if an intervention was not evaluated but the review described risk groups or technologies which, if targeted/deployed in a hypothetical intervention, could prevent TB cases or reduce TB incidence. Pre-specified reasons for excluding reviews were: not a systematic review; no intervention evaluated; no direct, indirect or hypothetical effect in preventing TB cases/reducing TB incidence; economic evaluation only; or any other reason. Although our focus was on TB control and prevention in countries with low-medium overall TB incidence, we did not exclude reviews based mainly (or partly) on studies in countries with high TB incidence if evidence of effectiveness could plausibly be generalizable to a low-medium TB incidence setting and there were no reviews based on studies in low-medium incidence countries.

2.1.6. Data extraction and management

The following data were extracted: bibliographic details (author, year, title); category (type of intervention); outcomes reported; number of included studies and/or patients; main results and key findings; authors' conclusions. Extracted data were entered into a spreadsheet.

2.1.7. Assessment of methodological quality of the systematic reviews

The quality of included reviews was assessed using the AMSTAR 2 tool, a 16-item measurement tool specifically used to assess systematic reviews that include randomised or non-randomised studies of healthcare interventions (or both) (Shea *et al.* 2017) (**Appendix 3**). Five domains from the 16 items were considered to be 'critical': 1) the adequacy of the literature search; 2) assessment of risk of bias in included studies; 3) appropriate meta-analytical methods; 4) consideration of risk of bias in interpreting the results of the review; 5) assessment of presence and impact of publication (small study) bias. The other 10 domains were considered to be 'non-critical'. Confidence in the results of the review was classified as 'high' if it had ≤3 non-critical weaknesses, 'moderate' if >2 non-critical weaknesses and <1 critical weakness, 'low' if 1 critical weakness, and 'very low' if ≥2 critical weaknesses.

2.2. Data analysis

All included reviews were summarised descriptively by category of intervention, including the number and type of primary studies (RCTs or 'other' studies, including non-randomised trials or observational studies). Reviews were categorised into either high-quality 'core' reviews (high confidence in the results of the review according to AMSTAR 2 criteria) which formed the basis of evidence used to assess interventions, or 'supplementary' reviews which were not considered to be of sufficient quality to rely on the authors' conclusions but which potentially provided information to complement the core reviews (MacArthur *et al.* 2014). For each type of intervention we extracted information on the review authors' assessment of the evidence and the design and findings of primary studies included in that review. The overall level of evidence in support of, or discounting, the effectiveness of an intervention was classified as 'sufficient', 'tentative', 'insufficient' or 'no' review-level evidence, using a framework based on the design and findings of the primary studies included in reviews, and concluding statements made by authors of core reviews (**Table 1**).

Table 1: Classification of level of evidence in support of, or discounting, the effectiveness of an intervention

Sufficient review-level evidence to either support or discount the effectiveness of an intervention: Clear and consistent statement from one or more core reviews based on multiple robust studies, or Consistent evidence across multiple robust studies within one or more core reviews, in the absence of a clear and consistent statement in the review(s).
Tentative review-level evidence to either support or discount the effectiveness of an intervention: A tentative statement from one or more core reviews based on consistent evidence from a small number of robust studies, or Consistent evidence from a small number of robust studies or multiple weaker studies within one or more core reviews, in the absence of a clear and consistent statement in the review(s), or Conflicting evidence from one or more core reviews, with the stronger evidence weighted towards one side (either supporting or discounting effectiveness) and a plausible reason for the conflict, or Consistent evidence from multiple robust studies within one or more supplementary reviews, in the absence of a core review.
Insufficient review-level evidence to either support or discount the effectiveness of an intervention: A statement of insufficient evidence from a core review, or Insufficient evidence to either support or discount the effectiveness of an intervention (either because there is too little evidence or the evidence is too weak), in the absence of a clear and consistent statement of evidence from a core review(s), or Anything less than consistent evidence from multiple robust studies within one or more supplementary reviews. No review-level evidence: no core or supplementary reviews of the topic identified, possibly due to a lack of primary studies.
No review-level evidence: No core or supplementary reviews of the topic identified, possibly due to a lack of primary studies.

3. Summary of activities and research findings

3.1. Search results

We identified 11,578 references, including 1,654 from MEDLINE, 2,796 from EMBASE, 250 from CINAHL, 2,949 from Scopus, 1,059 from Global Health, 2,040 from Trip, and 92 from Cochrane. Of these, 7,499 were removed by de-duplication, leaving 4,079 to be screened by title and abstract. Screening by title and abstract eliminated 3,813 unique references, leaving 266 references for full text review (**Figure 1**). Of these, 45 reviews of interventions reporting a direct effect were included. A further 113 reviews reporting interventions with an indirect effect and 29 reviews related to hypothetical effects were not included in this report, but may be revisited at a later stage (**Table 2**).

Figure 1: Study selection flowchart

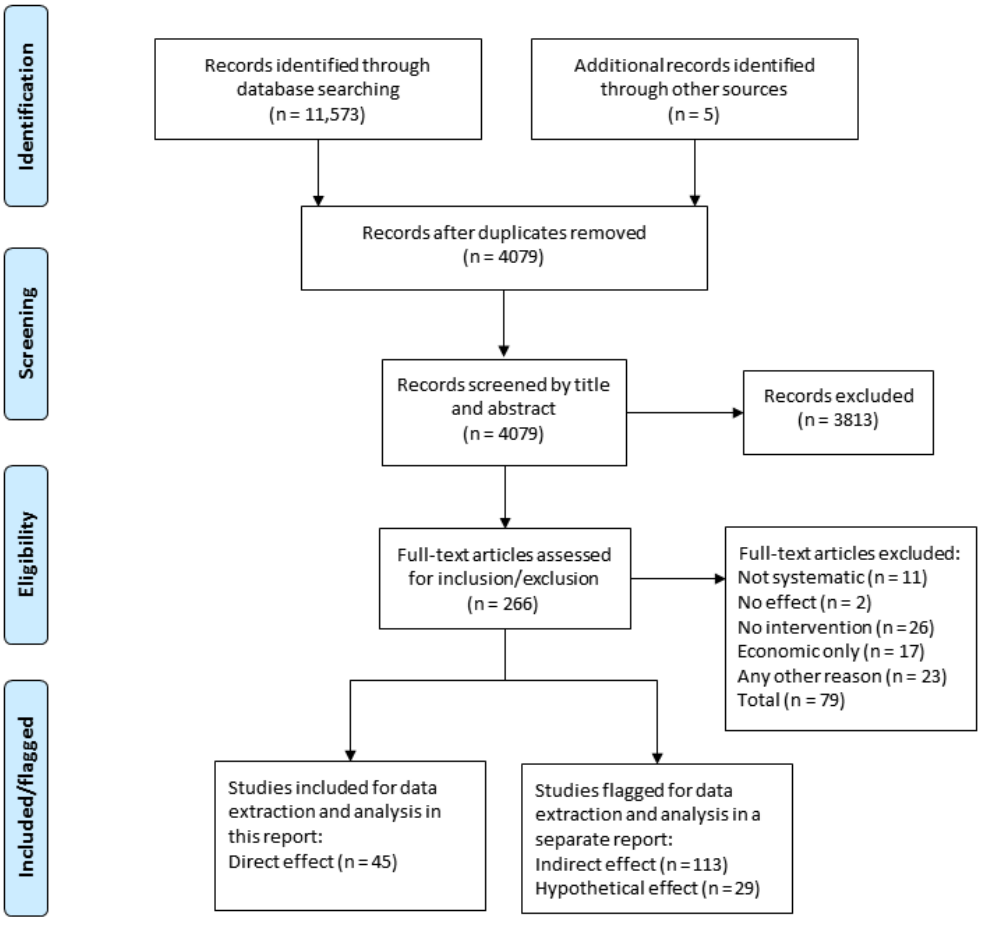

Table 2: Categorization of studies included, flagged (for future analysis) or excluded after full text review

	Included	Excluded from this review			Total
Category	Direct effect	Indirect effect	Hypothetical effect*	Excluded	
Adherence	1	23	1	5	30
Contacts and transmission	0	5	3	4	12
Diagnosis	2	16	0	4	22
Economic	0	0	0	3	3
HCW and infection control	1	4	4	9	18
HIV/TB	9	6	0	7	22
High risk	0	0	0	2	2
MDR-TB	4	18	0	8	30
Pregnancy	1	0	3	1	5
Prisons	1	1	1	1	4
Risk factors*	0	0	16	1	17
Screening	3	16	0	9	28
Systems	2	7	1	11	21
Treatment	8	17	0	10	35
Vaccination	13	0	0	4	17
Total	45	113	29	79	266

* Studies which reported risk groups or technologies which if targeted/deployed in a hypothetical intervention could have an effect in controlling or preventing TB.

3.2. Interventions with a direct effect on TB incidence

The 45 reviews of interventions considered to have a direct effect in preventing TB cases or reducing TB incidence covered 12 intervention areas, with the majority covering topics of vaccination (n=13), Interventions in HIV infected persons including LTBI prophylaxis and ART treatment (n=9), and latent TB treatment (n=8, **Table 2**). Other intervention areas included adherence, contact tracing plus prophylaxis, diagnostic tests for latent TB infection (LTBI), and approaches to TB detection and treatment (including screening). Our quality assessment identified 16 core reviews (high confidence in the results of the review) and 29 supplementary reviews. Of the latter category, two were rated as being of moderate quality, four as low quality and 23 as very low quality (**Appendix 4**).

3.2.1. Vaccination

Core review(s): (Abubakar *et al.* 2013, Mangtani *et al.* 2014, Roy *et al.* 2014, Health Information and Quality Authority (HIQA) Ireland 2016)

Summary: A sufficient level of evidence for the effectiveness of BCG vaccination was provided by four core reviews, the largest of which was Abubakar *et al.* 2013 (21 RCTs, 111 other studies, covering all age groups. Mangtani *et al.* investigated the effectiveness of BCG vaccination limited to RCT data (a subset of studies included in the review by Abubakar *et al.*). The Irish HIQA review was an update of Abubakar *et al.* (restricted to neonatal and infant vaccination), but found no additional studies. Roy *et al.* investigated the effectiveness of BCG vaccination in protecting children against *M tuberculosis* infection, as opposed to disease, in settings where children can be presumed to have been exposed to *M tuberculosis*. Confidence in the results of all but one of the nine supplementary reviews was rated 'very low', including two reviews of vaccination for travellers (Thomas 2000, Steffen *et al.* 2015) and one investigating co-administration of BCG and oral polio vaccine (Tamuzi *et al.* 2017).

Conclusion: There is a sufficient level of evidence from systematic reviews to support the use of BCG vaccination, particularly in those age <35 years, with good evidence of protective effects up to 10 years. In countries with low TB incidence, selective BCG vaccination of contacts and high-risk groups is likely to be more appropriate (and more cost-effective) than universal vaccination.

3.2.2. Screening

Core review(s): None.

Summary: There were two supplementary reviews of chest radiography for active TB case finding in homeless populations (Paquette *et al.* 2014, Curtis 2016), but both were rated 'very low' quality. A recent review of primary care screening and treatment for LTBI (Kahwati *et al.* 2016) on behalf of the US Preventive Services Task Force (5 RCTs, 67 other studies) was rated 'low' quality, and none of the included studies could be used to answer the question "Is there direct evidence that targeted screening for LTBI in primary care

settings in asymptomatic adults at increased risk for developing active TB improves quality of life or reduces active TB disease, transmission of TB, or disease specific or overall mortality?"

Conclusion: There is insufficient evidence from systematic reviews either to support or discount the effectiveness of screening in preventing active TB cases or reducing active TB incidence.

3.2.3. Diagnosis

Core review(s): (Auguste *et al.* 2017)

Summary: A core review by Auguste *et al.* (17 cohort studies) did not find evidence that IGRA performed better than TST in diagnosing LTBI when the outcome was progression to active TB in children (5 studies), immunocompromised people (10 studies), or people who had recently arrived from high TB burden countries (2 studies). A supplementary review suggested tentative evidence for better specificity of IGRAs instead of or to confirm TST in low TB incidence countries, but the quality of this review was rated very low (Munoz and Santin 2013).

Conclusion: There is insufficient review-level evidence either to support or discount the effectiveness of IGRAs *vs* TST in diagnosing LTBI which progresses to active TB.

3.2.4. Treatment of latent TB infection (LTBI)

Core review(s): (Smieja *et al.* 2000, Ena and Valls 2005, Sharma *et al.* 2013, Zenner *et al.* 2017)

Summary: A sufficient level of evidence for the relative effectiveness of different drug regimens in treating latent TB infection to prevent progression to active TB was provided by four core reviews. The largest and most recent was a meta-analysis by Zenner *et al.* 2017 (61 RCTs, all age groups), which found evidence for the efficacy and safety (compared to no treatment or placebo) of 6-month isoniazid (INH) monotherapy, rifampicin monotherapy, and combination therapies with 3-4 months of INH and rifampicin, regardless of age and HIV status. Sharma *et al.* (10 RCTs, all age groups) concluded that shortened regimens using rifampicin alone had not demonstrated higher rates of active TB when compared to longer INH regimens, with probably better treatment completion and fewer adverse events. Longer INH regimens offered no advantage over shortened combined regimens of rifampicin with INH . A weekly regimen of rifapentine plus INH had higher completion rates, and less liver toxicity.

Confidence in the results of all but one of the four supplementary reviews was rated 'very low', including a review of the long-term efficacy of DOTS regimens (Cox *et al.* 2008) and a review of rifapentine for treating LTBI (Haas and Belknap 2015). The other supplementary review was of moderate quality (Balcells *et al.* 2006), finding insufficient evidence for a slightly increased risk of development of isoniazid-resistant TB after isoniazid preventive therapy (compared to no treatment or placebo).

Conclusion: There is a sufficient level of evidence from systematic reviews to support the treatment of LTBI to prevent progression to active TB. Drug regimens can be optimised to minimise adverse events and cost,

and to maximise adherence and completion. The impact of LTBI treatment on TB incidence at population level has not been evaluated because its overall effectiveness is dependent on related interventions, particularly screening.

3.2.5. Adherence

Core review(s): (M'Imunya J *et al.* 2012)

Summary: M'Imunya *et al.* reviewed studies of patient education and counselling for promoting adherence to TB treatment, finding 3 trials which reported LTBI treatment completion rates (children in Spain, adolescents in the USA, and prisoners in the USA), none of which measured progression to active TB.

Conclusion: There is insufficient review-level evidence either to support or discount the effectiveness of treatment adherence interventions in reducing the incidence of active TB.

3.2.6. HIV/TB

Core review(s): (Gray *et al.* 2009, Akolo *et al.* 2010, Suthar *et al.* 2012)

Summary: A core review of LTBI treatment in HIV+ adults (Akolo *et al.*, 12 RCTs) found a reduced risk of active TB comparing any drug with placebo, particularly among in patients with a positive TST. The equivalent core review in HIV+ children by Gray *et al.* also reported a marked reduction in risk of active TB, but based on a single RCT. Suthar *et al.* (3 RCTs, 8 other studies) reviewed antiretroviral therapy (ART) for prevention of TB in adults, and found a substantial reduction in TB incidence based on studies from low and middle-income countries. The six supplementary reviews were of low (2/6) or very low (4/6) quality. Two reviews described a substantial protective effect of ART in HIV+ children based mainly on cohorts in high TB incidence countries (B-Lajoie *et al.* 2016, Dodd *et al.* 2017), similar to effects reported in adults (Suthar *et al.* 2012, Low *et al.* 2016). Core review evidence for the effectiveness of isoniazid prophylaxis in preventing TB in TST+ HIV patients was reported in two supplementary reviews (Bucher *et al.* 1999, Ayele *et al.* 2015), and one supplementary review found tentative evidence for secondary preventive therapy to prevent recurrent TB in HIV patients previously treated for TB (Bruins and van Leth 2017).

Conclusion: There is sufficient review-level evidence to support LTBI treatment and ART to prevent active TB in people infected with HIV. This evidence is based mainly on studies in countries with medium to high TB incidence.

3.2.7. MDR-TB

Core review(s): (Fraser *et al.* 2006, van der Werf *et al.* 2012, Langendam *et al.* 2013)

Summary: Fraser *et al.* found no RCTs on the effectiveness of treatments for LTBI in people exposed to MDR-TB, and van der Werf *et al.* concluded that there was insufficient evidence on preventive treatments for contacts of MDR-TB cases from an analysis of three cohort studies. Langendam *et al.* found insufficient evidence of adverse effects related to preventive treatments. A supplementary review suggested tentative evidence for the effectiveness of preventive treatments for MDR-TB contacts, but the quality of this review was rated very low (Marks *et al.* 2017).

Conclusion: There is insufficient review-level evidence either to support or discount the effectiveness of LTBI treatment in contacts of MDR-TB cases.

3.2.8. Healthcare workers

Core review(s): None.

Summary: One supplementary review of very low quality included 3 non-randomised studies of workplace interventions to provide HCWs with HIV and/or TB diagnosis and/or treatment services, all in sub-Saharan African countries (Yassi *et al.* 2013). One study of a pharmacy-based intervention for HCWs in the USA was excluded because it was not workplace-based/organised.

Conclusion: There is insufficient review-level evidence for interventions to prevent TB in HCWs.

3.2.9. Pregnancy

Core review(s): None

Summary: One supplementary review of very low quality reviewed 35 non-randomised studies, 4 of which investigated treatment of LTBI with INH during pregnancy - none reported progression to active TB (Nguyen *et al.* 2014).

Conclusion: There is insufficient review-level evidence for interventions to prevent TB during pregnancy.

3.2.10. Prisons

Core review(s): None

Summary: A review of studies of isoniazid preventive therapy in prisons identified 4 studies which reported TB incidence as an outcome (Al-Darraji *et al.* 2012). The review was of very low quality, and no conclusion could be drawn regarding efficacy of LTBI treatment regimens in this setting.

Conclusion: There is insufficient review-level evidence for interventions to prevent TB in prisons.

3.2.11. Healthcare system-level interventions

Core review(s): None.

Summary: A supplementary review of moderate quality reviewed interventions for diagnosis and treatment of TB in hard-to-reach populations, including 5 RCTs and 40 other studies (Heuvelings *et al.* 2017). Of the included studies, one non-randomised study of a social and health care programme for homeless people in Spain reported pre/post-intervention TB incidence compared with a non-intervention area as an outcome, but no reliable conclusion could be drawn regarding the programme's effectiveness. The Spanish study was also identified in a review (very low quality) of community-based interventions for TB prevention and control (Arshad *et al.* 2014)

Conclusion: There is insufficient evidence from systematic reviews for healthcare system-level interventions to prevent TB.

3.3. Interventions with an indirect effect on TB incidence

The 113 reviews of interventions considered to have an indirect effect in preventing TB cases or reducing TB incidence covered 10 areas, including 23 reviews of interventions related to adherence, 18 reviews of interventions related to MDR-TB, 17 related to treatment, 16 to diagnosis, and 16 to screening (**Table 2**). The other 23 reviews covered 5 intervention areas, including healthcare systems, HIV/TB, contact tracing, HCWs and infection control, and prisons. These reviews are not included in this report.

3.4. Hypothetical interventions

The majority of hypothetical interventions (16/29) related to risk factors for TB (**Table 2**), of which 11/16 were potentially modifiable including smoking (5 studies), second hand tobacco smoke (7 studies), indoor air pollution (4 studies), alcohol (1 study), and diabetes (1 study). The remaining 13 studies covered areas of hypothetical intervention related to contacts and infection control (5 studies), travel (3 studies), pregnancy (3 studies), prisons (1 study), determinants of adherence (1 study), and the impact of health economic analyses on TB control policy and practice (1 study). These reviews will be graded and summarised in a separate report.

4. Conclusions and future steps

The review of interventions for the prevention of TB cases or reduction of TB incidence presented in this report has identified three intervention areas that are sufficiently supported by review-level evidence, namely vaccination, treatment of latent TB infection (LTBI) and treatment of HIV. Other interventions for TB control and prevention, including screening, did not have sufficient review-level evidence. The results of this review of reviews will be triangulated with information obtained from a survey of national TB programme leaders in the 31 EU/EEA member states and with a review of barriers to the implementation of TB control interventions in these countries. The combined information will be presented to national TB programme leaders ahead of a structured meeting, which has as its ultimate outcome the formulation of a 'toolkit' to assist EU/EEA member states in developing and/or implementing action plans for TB control and prevention.

5. Bibliographical references

Abubakar, I., et al. (2013). "Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette-Guerin vaccination against tuberculosis." Health Technol Assess **17**(37): 1-372, v-vi.

Akolo, C., et al. (2010). "Treatment of latent tuberculosis infection in HIV infected persons." Cochrane Database Syst Rev(1): CD000171.

Al-Darraji, H. A., et al. (2012). "Isoniazid preventive therapy in correctional facilities: a systematic review." Int J Tuberc Lung Dis **16**(7): 871-879.

Arshad, A., et al. (2014). "Community based interventions for the prevention and control of tuberculosis." Infect Dis Poverty **3**(27): 27.

Auguste, P., et al. (2017). "Comparing interferon-gamma release assays with tuberculin skin test for identifying latent tuberculosis infection that progresses to active tuberculosis: systematic review and meta-analysis." BMC Infect Dis **17**(1): 200.

Ayele, H. T., et al. (2015). "Isoniazid Prophylactic Therapy for the Prevention of Tuberculosis in HIV Infected Adults: A Systematic Review and Meta-Analysis of Randomized Trials." PLoS One **10**(11): e0142290.

B-Lajoie, M. R., et al. (2016). "Incidence and prevalence of opportunistic and other infections and the impact of antiretroviral therapy among HIV-infected children in low- and middle-income countries: a systematic review and meta-analysis." Clinical Infectious Diseases **62**(12): 1586-1594.

Balcells, M. E., et al. (2006). "Isoniazid preventive therapy and risk for resistant tuberculosis." Emerg Infect Dis **12**(5): 744-751.

Bruins, W. S. and F. van Leth (2017). "Effect of secondary preventive therapy on recurrence of tuberculosis in HIV-infected individuals: a systematic review." Infect Dis (Lond) **49**(3): 161-169.

Bucher, H. C., et al. (1999). "Isoniazid prophylaxis for tuberculosis in HIV infection: a meta-analysis of randomized controlled trials." AIDS **13**(4): 501-507.

Cochrane (2011). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. J. P. Higgins and S. Green, The Cochrane Collaboration.

Collin, S., et al. (2017) "Effectiveness of interventions for TB control and prevention in countries of low and medium TB incidence: a systematic review of reviews." PROSPERO 2017 CRD42017060096 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017060096

Cox, H. S., et al. (2008). "Long term efficacy of DOTS regimens for tuberculosis: systematic review." BMJ **336**(7642): 484-487.

Curtis, J. (2016). "Impact of x-ray screening programmes for active tuberculosis in homeless populations: a systematic review of original studies." J Public Health (Oxf) **38**(1): 106-114.

D'Ambrosio, L., et al. (2014). "Tuberculosis elimination: theory and practice in Europe." Eur Respir J **43**(5): 1410-1420.

Dodd, P. J., et al. (2017). "The impact of HIV and antiretroviral therapy on TB risk in children: a systematic review and meta-analysis." Thorax **72**(6): 559-575.

ECDC (2010). Progessing towards TB elimination: A follow-up to the Framework Action Plan to Fight Tuberculosis in the European Union. Stockholm, ECDC.

ECDC (2017). Tuberculosis surveillance and monitoring in Europe 2017. Stockholm, ECDC.

Ena, J. and V. Valls (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): 670-676.

Fraser, A., et al. (2006). "Drugs for preventing tuberculosis in people at risk of multiple-drug-resistant pulmonary tuberculosis." Cochrane Database Syst Rev(2): CD005435.

Gray, D. M., et al. (2009). "Impact of tuberculosis preventive therapy on tuberculosis and mortality in HIV-infected children." Cochrane Database Syst Rev(1): CD006418.

Haas, M. K. and R. W. Belknap (2015). "A review of rifapentine for treating active and latent tuberculosis." Clinical Investigation **5**(11): 829-838.

Health Information and Quality Authority (HIQA) Ireland (2016). "Health technology assessment of a selective BCG vaccination programme." Health Technology Assessment (HTA) Database.

Heuvelings, C. C., et al. (2017). "Effectiveness of interventions for diagnosis and treatment of tuberculosis in hard-to-reach populations in countries of low and medium tuberculosis incidence: a systematic review." Lancet Infect Dis **17**(5): e144-e158.

Kahwati, L. C., et al. (2016). "Primary Care Screening and Treatment for Latent Tuberculosis Infection in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force." JAMA **316**(9): 970-983.

Langendam, M. W., et al. (2013). "Adverse events in healthy individuals and MDR-TB contacts treated with anti-tuberculosis drugs potentially effective for preventing development of MDR-TB: a systematic review." PLoS One **8**(1): e53599.

Lee, E., et al. (2012). "An optimal search filter for retrieving systematic reviews and meta-analyses." BMC Med Res Methodol **12**: 51.

Li, T., et al. (2012). "What comparative effectiveness research is needed? A framework for using guidelines and systematic reviews to identify evidence gaps and research priorities." Ann Intern Med **156**(5): 367-377.

Lonnroth, K., et al. (2015). "Towards tuberculosis elimination: an action framework for low-incidence countries." Eur Respir J **45**(4): 928-952.

Lönnroth, K. and M. Raviglione (2016). "The WHO's new End TB Strategy in the post-2015 era of the Sustainable Development Goals." Transactions of the Royal Society of Tropical Medicine and Hygiene **110**(3): 148-150.

Low, A., et al. (2016). "Incidence of Opportunistic Infections and the Impact of Antiretroviral Therapy Among HIV-Infected Adults in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis." Clin Infect Dis **62**(12): 1595-1603.

M'Imunya J, M., et al. (2012). "Patient education and counselling for promoting adherence to treatment for tuberculosis." Cochrane Database Syst Rev **5**(5): CD006591.

MacArthur, G. J., et al. (2014). "Interventions to prevent HIV and Hepatitis C in people who inject drugs: a review of reviews to assess evidence of effectiveness." Int J Drug Policy **25**(1): 34-52.

Mangtani, P., et al. (2014). "Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials." Clin Infect Dis **58**(4): 470-480.

Marks, S. M., et al. (2017). "Systematic Review, Meta-Analysis, and Cost Effectiveness of Treatment of Latent Tuberculosis Infection to Reduce Progression to Multidrug-Resistant Tuberculosis." Clin Infect Dis.

Munoz, L. and M. Santin (2013). "Interferon-gamma release assays versus tuberculin skin test for targeting people for tuberculosis preventive treatment: an evidence-based review." J Infect **66**(4): 381-387.

Nguyen, H. T., et al. (2014). "Tuberculosis care for pregnant women: a systematic review." BMC Infect Dis **14**(617): 617.

Paquette, K., et al. (2014). "Chest radiography for active tuberculosis case finding in the homeless: a systematic review and meta-analysis." Int J Tuberc Lung Dis **18**(10): 1231-1236.

Roy, A., et al. (2014). "Effect of BCG vaccination against Mycobacterium tuberculosis infection in children: systematic review and meta-analysis." BMJ **349**: g4643.

Sharma, S. K., et al. (2013). "Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB." Cochrane Database of Systematic Reviews **5**(7): no pagination.

Shea, B. J., et al. (2017). "AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both." BMJ **358**: j4008.

Smieja, M. J., et al. (2000). "Isoniazid for preventing tuberculosis in non-HIV infected persons." Cochrane Database Syst Rev(2): CD001363.

Steffen, R., et al. (2015). "Vaccine-preventable travel health risks: What is the evidence - What are the gaps?" Journal of Travel Medicine **22**(1): 1-12.

Suthar, A. B., et al. (2012). "Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis." PLoS Med **9**(7): e1001270.

Tamuzi, J. L., et al. (2017). "Co-administration of oral polio vaccine and Bacillus Calmette Guerin in infants: systematic review of low- and middle-income countries." International Annals of Medicine.

Thomas, R. E. (2000). "Preparing patients to travel abroad safely. Part 2: Updating vaccinations." Can Fam Physician **46**(MAR.): 646-652, 655-646.

van der Werf, M. J., et al. (2012). "Lack of evidence to support policy development for management of contacts of multidrug-resistant tuberculosis patients: two systematic reviews." Int J Tuberc Lung Dis **16**(3): 288-296.

World Health Organisation (2015). Toolkit to develop a National Strategic Plan for TB prevention, care and control. Geneva, WHO.

Yassi, A., et al. (2013). "Workplace programmes for HIV and tuberculosis: a systematic review to support development of international guidelines for the health workforce." AIDS Care **25**(5): 525-543.

Zenner, D., et al. (2017). "Treatment of Latent Tuberculosis Infection: An Updated Network Meta-analysis." Ann Intern Med **167**(4): 248-255.

6. Appendices

Appendix 1: Search strings

EMBASE

1. ("tubercul$" or "mycobacter$" or "TB").ti.
2. exp tuberculosis/
3. 1 or 2
4. MEDLINE.tw.
5. exp systematic review/ or systematic review.tw.
6. meta-analysis/
7. intervention$.ti.
8. 4 or 5 or 6 or 7
9. 3 and 8

MEDLINE

1. tubercul$.ti.
2. mycobacter$.ti.
3. TB.ti.
4. tuberculosis.xm.
5. 1 or 2 or 3 or 4
6. MEDLINE.tw.
7. systematic review.tw.
8. meta-analysis.pt.
9. intervention$.ti.
10. 6 or 7 or 8 or 9
11. 5 and 10

CINAHL

((tubercul*).ti OR (mycobacter*).ti OR (TB).ti OR exp "MYCOBACTERIUM INFECTIONS"/) AND ((MEDLINE).ti OR (MEDLINE).ab OR exp "LITERATURE REVIEW"/ OR (systematic review).ti OR (systematic review).ab OR exp "META ANALYSIS"/ OR (intervention*).ti)

Global Health

(TI tubercul* OR TI mycobacter* OR TI TB OR SU tuberculosis) AND (TI MEDLINE OR AB MEDLINE OR SU systematic review OR TI systematic review OR AB systematic review OR SU meta-analysis OR TI intervention*)

Scopus

(TITLE-ABS(tubercul*) OR TITLE-ABS(mycobacter*) OR TITLE-ABS(TB)) AND (TITLE-ABS(MEDLINE) OR TITLE-ABS(systematic review) OR TITLE(meta-analysis) OR TITLE(intervention*))

Trip

(tubercul* or mycobacter* or TB)

Appendix 2: Inclusion/exclusion checklist for full text review

First author (year):								
Inclusion/exclusion criteria:						Yes	No	Unsure
1.	Is this a systematic review?							
2.	Is this an economic evaluation?							
3.	Is an intervention clearly defined?							
4.	Is it relevant to TB control and prevention in countries of low and medium TB incidence?							
5.	Does the study report a direct effect (preventing cases/reducing incidence) as a PRIMARY outcome?							
6.	Does the study report a direct effect (preventing cases/reducing incidence) as a SECONDARY outcome?							
7.	Does the intervention have a plausible INDIRECT effect (preventing cases/reducing incidence)?							
Classification (circle):	INCLUDE		FLAG (FOR FUTURE)		EXCLUDE			
	1° DIRECT (1, 3, 4, 5 = Yes)	2° DIRECT (1, 3, 4, 6 = Yes)	INDIRECT (1, 3, 4, 7 = Yes)	HYPOTHETICAL (1, 4, 7 = Yes)	Not systematic (1 & 2 = No)	Not defined (3 = No)	Not relevant (4 = No)	
Comment:					Economic only (2, 3, 4 = Yes)	No effect (5, 6 or 7 = No)	Any other reason	

Appendix 3: AMSTAR 2 Checklist (Shea *et al.* 2017)

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:

- ☐ Population
- ☐ Intervention
- ☐ Comparator group
- ☐ Outcome

Optional (recommended)

- ☐ Timeframe for follow up

- ☐ Yes
- ☐ No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:

- ☐ review question(s)
- ☐ a search strategy
- ☐ inclusion/exclusion criteria
- ☐ a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:

- ☐ a meta-analysis/synthesis plan, if appropriate, and
- ☐ a plan for investigating causes of heterogeneity
- ☐ a plan for investigating causes of heterogeneity

- ☐ Yes
- ☐ Partial Yes
- ☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:

- ☐ Explanation for including only RCTs
- ☐ OR Explanation for including only NRSI
- ☐ OR Explanation for including both RCTs and NRSI

- ☐ Yes
- ☐ No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):

- ☐ searched at least 2 databases (relevant to research question)
- ☐ provided key word and/or search strategy
- ☐ justified publication restrictions (e.g. language)

For Yes, should also have (all the following):

- ☐ searched the reference lists / bibliographies of included studies
- ☐ searched trial/study registries
- ☐ included/consulted content experts in the field
- ☐ where relevant, searched for grey literature
- ☐ conducted search within 24 months of completion of the review

- ☐ Yes
- ☐ Partial Yes
- ☐ No

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:

- ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- ☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.

- ☐ Yes
- ☐ No

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:

- ☐ at least two reviewers achieved consensus on which data to extract from included studies
- ☐ OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.

- ☐ Yes
- ☐ No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:

- ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:

- ☐ Justified the exclusion from the review of each potentially relevant study

- ☐ Yes
- ☐ Partial Yes
- ☐ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):

- ☐ described populations
- ☐ described interventions
- ☐ described comparators
- ☐ described outcomes
- ☐ described research designs

For Yes, should also have ALL the following:

- ☐ described population in detail
- ☐ described intervention in detail (including doses where relevant)
- ☐ described comparator in detail (including doses where relevant)
- ☐ described study's setting
- ☐ timeframe for follow-up

- ☐ Yes
- ☐ Partial Yes
- ☐ No

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from	For Yes, must also have assessed RoB from:	
☐ unconcealed allocation, and	☐ allocation sequence that was not truly random, and	☐ Yes ☐ Partial Yes ☐ No ☐ Includes only NRSI
☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	

NRSI

For Partial Yes, must have assessed RoB:	For Yes, must also have assessed RoB:	
☐ from confounding, and	☐ methods used to ascertain exposures and outcomes, and	☐ Yes ☐ Partial Yes ☐ No ☐ Includes only RCTs
☐ from selection bias	☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes

☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	☐ Yes ☐ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:

☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. ☐ AND investigated the causes of any heterogeneity	☐ Yes ☐ No ☐ No meta-analysis conducted

For NRSI

For Yes:

☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present ☐ AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available ☐ AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	☐ Yes ☐ No ☐ No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes:

☐ included only low risk of bias RCTs ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	☐ Yes ☐ No ☐ No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:

☐ included only low risk of bias RCTs ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	☐ Yes ☐ No

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes:

☐ There was no significant heterogeneity in the results ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	☐ Yes ☐ No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes:

☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☐ Yes ☐ No ☐ No meta-analysis conducted

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:

☐ The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest	☐ Yes ☐ No

Appendix 4: Methodological quality of the included systematic reviews

Vaccination

Author	Year	Title	AMSTAR 1	AMSTAR 2	AMSTAR 3	AMSTAR 4	AMSTAR 5	AMSTAR 6	AMSTAR 7	AMSTAR 8	AMSTAR 9	AMSTAR 10	AMSTAR 11	AMSTAR 12	AMSTAR 13	AMSTAR 14	AMSTAR 15	AMSTAR 16	Confidence (high, moderate, low, very low)	Core or supplementary review	Number of randomised studies	Number of non-randomised studies	Total number of included studies	Level of evidence
Abubakar	2013	Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette-Guerin vaccination against tuberculosis	1.0	1.0	0.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	High	Core	21	111	132	Sufficient
Brewer	2000	Preventing tuberculosis with bacillus Calmette-Guerin vaccine: a meta-analysis of the literature	1.0	0.0	0.0	0.5	0.0	0.0	0.0	0.0	0.5	0.0	1.0	1.0	1.0	1.0	0.0	0.0	Very low	Supplementary	7	19	26	Tentative
Colditz	1995	The efficacy of bacillus Calmette-Guerin vaccination of newborns and infants in the prevention of tuberculosis: meta-analyses of the published literature	1.0	0.0	0.0	0.5	0.0	0.0	0.0	0.0	0.5	0.0	1.0	1.0	1.0	1.0	0.0	0.0	Very low	Supplementary	3	9	12	Tentative
HIQA Ireland	2016	Health technology assessment of a selective BCG vaccination programme	1.0	1.0	1.0	1.0	1.0	1.0	0.5	1.0	1.0	0.0	1.0	1.0	1.0	1.0	1.0	1.0	High	Core	4	10	14	Sufficient
Knuf	1996	Efficacy of BCG vaccination	1.0	0.0	0.0	0.5	0.0	0.0	0.0	0.5	0.0	0.0	-	-	0.0	0.0	-	0.0	Very low	Supplementary	0	15	15	Insufficient
Mangtani	2014	Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials	1.0	1.0	1.0	1.0	1.0	1.0	0.5	1.0	1.0	0.0	1.0	1.0	1.0	1.0	1.0	1.0	High	Core	18	0	18	Sufficient
Ortqvist	2010	Vaccination of children - a systematic review	1.0	0.0	0.0	0.0	0.0	0.0	1.0	1.0	1.0	0.0	-	-	1.0	0.0	-	1.0	Low	Supplementary	5	26	31	Tentative
Roy	2014	The protective effect of BCG vaccination against mycobacterium tuberculosis infection in children: A systematic review	1.0	0.0	0.0	1.0	1.0	0.0	0.0	1.0	1.0	0.0	1.0	1.0	1.0	1.0	1.0	1.0	High	Core	0	14	14	Sufficient
Schmitz	2013	Meta-analysis of BCG vaccine efficacy for infants in Ireland	1.0	0.0	0.0	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	Very low	Supplementary	5	19	24	Insufficient
Steffen	2015	Vaccine-preventable travel health risks: What is the evidence - What are the gaps?	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.5	0.0	-	-	0.0	0.0	-	1.0	Very low	Supplementary	0	0	0	Insufficient
Sterne	1998	Does the efficacy of BCG decline with time since vaccination?	1.0	0.0	0.0	1.0	0.0	0.0	0.0	1.0	0.0	0.0	1.0	0.0	1.0	1.0	0.0	1.0	Very low	Supplementary	10	0	10	Tentative
Tamuzi	2015	Co-administration of oral polio vaccine and Bacillus Calmette Guerin in infants: systematic review of low- and middle-income countries	1.0	0.0	0.0	1.0	1.0	1.0	0.0	1.0	1.0	0.0	1.0	1.0	0.0	1.0	0.0		Very low	Supplementary	3	3	6	Insufficient
Thomas	2000	Preparing patients to travel abroad safely. Part 2: Updating vaccinations	1.0	0.0	0.0	0.5	0.0	0.0	0.0	0.0	0.0	0.0	-	-	0.0	0.0	-	0.0	Very low	Supplementary	0	0	0	Insufficient

Screening

Author	Year	Title	AMSTAR 1	AMSTAR 2	AMSTAR 3	AMSTAR 4	AMSTAR 5	AMSTAR 6	AMSTAR 7	AMSTAR 8	AMSTAR 9	AMSTAR 10	AMSTAR 11	AMSTAR 12	AMSTAR 13	AMSTAR 14	AMSTAR 15	AMSTAR 16	Confidence (high, moderate, low, very low)	Core or supplementary review	Number of randomised studies	Number of non-randomised studies	Total number of included studies	Level of evidence
Curtis	2016	Impact of x-ray screening programmes for active tuberculosis in homeless populations: a systematic review of original studies	1.0	0.0	0.0	1.0	0.0	0.0	0.0	1.0	1.0	0.0	-	-	0.0	0.0	-	0.0	Very low	Supplementary	0	14	14	Insufficient
Kahwati	2016	Primary Care Screening and Treatment for Latent Tuberculosis Infection in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force	1.0	0.0	0.0	0.5	1.0	1.0	0.5	1.0	1.0	0.0	-	-	0.0	1.0	-	1.0	Low	Supplementary	5	67	72	Insufficient
Paquette	2014	Chest radiography for active tuberculosis case finding in the homeless: a systematic review and meta-analysis.	1.0	0.0	0.0	1.0	0.0	1.0	0.5	0.5	1.0	0.0	-	-	0.0	1.0	-	0.0	Very low	Supplementary	0	16	16	Insufficient

Diagnosis

Author	Year	Title	AMSTAR 1	AMSTAR 2	AMSTAR 3	AMSTAR 4	AMSTAR 5	AMSTAR 6	AMSTAR 7	AMSTAR 8	AMSTAR 9	AMSTAR 10	AMSTAR 11	AMSTAR 12	AMSTAR 13	AMSTAR 14	AMSTAR 15	AMSTAR 16	Confidence (high, moderate, low, very low)	Core or supplementary review	Number of randomised studies	Number of non-randomised studies	Total number of included studies	Level of evidence
Auguste	2017	Comparing interferon-gamma release assays with tuberculin skin test for identifying latent tuberculosis infection that progresses to active tuberculosis:	1.0	0.0	1.0	1.0	1.0	1.0	0.5	1.0	1.0	0.0	1.0	1.0	1.0	1.0	1.0	1.0	High	Core	0	17	17	Insufficient
Munoz	2013	Interferon-gamma release assays versus tuberculin skin test for targeting people for tuberculosis preventive treatment: an evidence-based review	1.0	0.0	0.0	0.0	1.0	1.0	0.5	1.0	1.0	0.0	-	-	0.0	0.0	-	0.0	Very low	Supplementary	0	11	11	Insufficient

Treatment of latent TB infection (LTBI)

Author	Year	Title	AMSTAR 1	AMSTAR 2	AMSTAR 3	AMSTAR 4	AMSTAR 5	AMSTAR 6	AMSTAR 7	AMSTAR 8	AMSTAR 9	AMSTAR 10	AMSTAR 11	AMSTAR 12	AMSTAR 13	AMSTAR 14	AMSTAR 15	AMSTAR 16	Confidence (high, moderate, low, very low)	Core or supplementary review	Number of randomised studies	Number of non-randomised studies	Total number of included studies	Level of evidence
Acuna-Villaorduna	2013	Systematic review of shorter 2-3 months regimens for treatment of latent tuberculosis	1.0	0.0	0.0	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	Very low	Supplementary	16	0	16	Tentative
Balcells	2006	Isoniazid preventive therapy and risk for resistant tuberculosis	1.0	0.0	0.0	1.0	0.0	1.0	0.0	1.0	0.5	0.0	1.0	1.0	1.0	1.0	1.0	1.0	Moderate	Supplementary	12	1	13	Insufficient
Cox	2008	Long term efficacy of DOTS regimens for tuberculosis: systematic review	1.0	0.0	1.0	1.0	0.0	0.0	0.5	1.0	0.0	0.0	-	-	0.0	1.0	-	1.0	Very low	Supplementary	6	10	16	Insufficient
Ena	2005	Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for	1.0	0.0	0.0	1.0	1.0	1.0	0.5	1.0	0.5	0.0	1.0	1.0	1.0	1.0	1.0	1.0	High	Core	5	0	5	Sufficient
Haas	2015	A review of rifapentine for treating active and latent tuberculosis	1.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.0	0.0	-	-	0.0	0.0	-	1.0	Very low	Supplementary	12	0	12	Tentative
Sharma	2013	Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-	1.0	1.0	0.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	High	Core	10	0	10	Tentative
Smieja	2000	Isoniazid for preventing tuberculosis in non-HIV infected persons	1.0	1.0	0.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	High	Core	11	0	11	Sufficient
Zenner	2017	Treatment of latent tuberculosis infection: an updated network meta-analysis	1.0	1.0	0.0	1.0	1.0	1.0	0.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	High	Core	61	0	61	Tentative

Adherence

Author	Year	Title	AMSTAR 1	AMSTAR 2	AMSTAR 3	AMSTAR 4	AMSTAR 5	AMSTAR 6	AMSTAR 7	AMSTAR 8	AMSTAR 9	AMSTAR 10	AMSTAR 11	AMSTAR 12	AMSTAR 13	AMSTAR 14	AMSTAR 15	AMSTAR 16	Confidence (high, moderate, low, very low)	Core or supplementary review	Number of randomised studies	Number of non-randomised studies	Total number of included studies	Level of evidence
M'Imunya	2012	Patient education and counselling for promoting adherence to treatment for tuberculosis	1.0	1.0	0.0	1.0	1.0	1.0	1.0	1.0	1.0	0.0	-	-	1.0	1.0	-	1.0	High	Core	3	0	3	Insufficient

HIV/TB

Author	Year	Title	AMSTAR 1	AMSTAR 2	AMSTAR 3	AMSTAR 4	AMSTAR 5	AMSTAR 6	AMSTAR 7	AMSTAR 8	AMSTAR 9	AMSTAR 10	AMSTAR 11	AMSTAR 12	AMSTAR 13	AMSTAR 14	AMSTAR 15	AMSTAR 16	Confidence (high, moderate, low, very low)	Core or supplementary review	Number of randomised studies	Number of non-randomised studies	Total number of included studies	Level of evidence
Akolo	2010	Treatment of latent tuberculosis infection in HIV infected persons	1.0	1.0	0.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	High	Core	12	0	12	Sufficient
Ayele	2015	Isoniazid Prophylactic Therapy for the Prevention of Tuberculosis in HIV Infected Adults: A Systematic Review and Meta-Analysis of Randomized Trials	1.0	0.0	0.0	1.0	0.0	0.0	1.0	1.0	1.0	0.0	1.0	0.0	0.0	1.0	0.0	1.0	Very low	Supplementary	10	0	10	Tentative
B-Lajoie	2016	Incidence and prevalence of opportunistic and other infections and the impact of antiretroviral therapy among HIV-infected children in low- and middle-income countries: a systematic review and meta-analysis	1.0	0.0	0.0	1.0	1.0	0.0	0.0	1.0	0.0	0.0	1.0	0.0	0.0	0.0	0.0	1.0	Very low	Supplementary	0	12	12	Tentative
Bruins	2017	Effect of secondary preventive therapy on recurrence of tuberculosis in HIV-infected individuals: a systematic review	1.0	0.0	0.0	1.0	1.0	0.0	0.0	0.5	1.0	0.0	-	-	0.0	0.0	-	1.0	Low	Supplementary	3	1	4	Tentative
Bucher	1999	Isoniazid prophylaxis for tuberculosis in HIV infection: a meta-analysis of randomized controlled trials	1.0	0.0	0.0	1.0	1.0	0.0	0.0	1.0	0.5	0.0	1.0	1.0	1.0	0.0	0.0	0.0	Low	Supplementary	7	0	7	Tentative
Dodd	2014	The impact of HIV and antiretroviral therapy on TB risk in children: a systematic review and meta-analysis	1.0	1.0	0.0	1.0	1.0	1.0	0.5	1.0	1.0	0.0	1.0	0.0	0.0	0.0	0.0	1.0	Very low	Supplementary	0	22	22	Tentative
Gray	2009	Impact of tuberculosis preventive therapy on tuberculosis and mortality in HIV-infected children	1.0	1.0	0.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	-	-	1.0	-	-	1.0	High	Core	1	0	1	Insufficient
Low	2016	Incidence of Opportunistic Infections and the Impact of Antiretroviral Therapy Among HIV-Infected Adults in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis	1.0	0.0	0.0	1.0	1.0	0.0	0.0	1.0	0.0	0.0	1.0	0.0	0.0	1.0	0.0	1.0	Very low	Supplementary	2	31	33	Insufficient
Suthar	2012	Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis	1.0	1.0	0.0	1.0	1.0	1.0	0.5	1.0	1.0	0.0	1.0	0.0	1.0	1.0	1.0	1.0	High	Core	3	8	11	Sufficient

MDR-TB

Author	Year	Title	AMSTAR 1	AMSTAR 2	AMSTAR 3	AMSTAR 4	AMSTAR 5	AMSTAR 6	AMSTAR 7	AMSTAR 8	AMSTAR 9	AMSTAR 10	AMSTAR 11	AMSTAR 12	AMSTAR 13	AMSTAR 14	AMSTAR 15	AMSTAR 16	Confidence (high, moderate, low, very low)	Core or supplementary review	Number of randomised studies	Number of non-randomised studies	Total number of included studies	Level of evidence
Fraser	2006	Drugs for preventing tuberculosis in people at risk of multiple-drug-resistant pulmonary tuberculosis	1.0	1.0	0.0	1.0	1.0	-	-	-	-	-	-	-	-	-	-	1.0	High	Core	0	0	0	None
Langendam	2013	Adverse events in healthy individuals and MDR-TB contacts treated with anti-tuberculosis drugs potentially effective for preventing development of MDR-TB: a systematic review	1.0	0.0	0.0	1.0	1.0	1.0	0.0	1.0	1.0	0.0	-	-	1.0	1.0	-	1.0	High	Core	16	4	20	Insufficient
Marks	2017	Systematic Review, Meta-Analysis, and Cost Effectiveness of Treatment of Latent Tuberculosis Infection to Reduce Progression to Multidrug-Resistant Tuberculosis	1.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.0	0.0	-	-	0.0	0.0	-	1.0	Very low	Supplementary	0	21	21	Tentative
van der Werf	2012	Lack of evidence to support policy development for management of contacts of multidrug-resistant tuberculosis patients: two systematic reviews	1.0	0.0	0.0	1.0	1.0	1.0	1.0	1.0	1.0	0.0	-	-	1.0	1.0	-	1.0	High	Core	0	3	3	Insufficient

Healthcare workers

Author	Year	Title	AMSTAR 1	AMSTAR 2	AMSTAR 3	AMSTAR 4	AMSTAR 5	AMSTAR 6	AMSTAR 7	AMSTAR 8	AMSTAR 9	AMSTAR 10	AMSTAR 11	AMSTAR 12	AMSTAR 13	AMSTAR 14	AMSTAR 15	AMSTAR 16	Confidence (high, moderate, low, very low)	Core or supplementary review	Number of randomised studies	Number of non-randomised studies	Total number of included studies	Level of evidence
Yassi	2013	Workplace programmes for HIV and tuberculosis: a systematic review to support development of international guidelines for the health workforce	1.0	0.0	0.0	0.5	1.0	1.0	0.0	1.0	1.0	0.0	-	-	0.0	0.0	-	0.0	Very low	Supplementary	0	3	3	Insufficient

Pregnancy

Author	Year	Title	AMSTAR 1	AMSTAR 2	AMSTAR 3	AMSTAR 4	AMSTAR 5	AMSTAR 6	AMSTAR 7	AMSTAR 8	AMSTAR 9	AMSTAR 10	AMSTAR 11	AMSTAR 12	AMSTAR 13	AMSTAR 14	AMSTAR 15	AMSTAR 16	Confidence (high, moderate, low, very low)	Core or supplementary review	Number of randomised studies	Number of non-randomised studies	Total number of included studies	Level of evidence
Nguyen	2014	Tuberculosis care for pregnant women: a systematic review	1.0	0.0	0.0	1.0	1.0	0.0	0.0	1.0	1.0	0.0	-	-	0.0	0.0	-	1.0	Very low	Supplementary	0	35	35	Insufficient

Prisons

Author	Year	Title	AMSTAR 1	AMSTAR 2	AMSTAR 3	AMSTAR 4	AMSTAR 5	AMSTAR 6	AMSTAR 7	AMSTAR 8	AMSTAR 9	AMSTAR 10	AMSTAR 11	AMSTAR 12	AMSTAR 13	AMSTAR 14	AMSTAR 15	AMSTAR 16	Confidence (high, moderate, low, very low)	Core or supplementary review	Number of randomised studies	Number of non-randomised studies	Total number of included studies	Level of evidence
Al-Darraji	2012	Isoniazid preventive therapy in correctional facilities: a systematic review	1.0	0.0	0.0	0.5	1.0	1.0	0.0	1.0	0.0	0.0	-	-	0.0	0.0	-	1.0	Very low	Supplementary	3	15	18	Insufficient

Healthcare system-level interventions

Author	Year	Title	AMSTAR 1	AMSTAR 2	AMSTAR 3	AMSTAR 4	AMSTAR 5	AMSTAR 6	AMSTAR 7	AMSTAR 8	AMSTAR 9	AMSTAR 10	AMSTAR 11	AMSTAR 12	AMSTAR 13	AMSTAR 14	AMSTAR 15	AMSTAR 16	Confidence (high, moderate, low, very low)	Core or supplementary review	Number of randomised studies	Number of non-randomised studies	Total number of included studies	Level of evidence
Arshad	2014	Community based interventions for the prevention and control of tuberculosis	1.0	0.0	0.0	1.0	0.0	0.0	0.0	1.0	1.0	0.0	1.0	0.0	0.0	0.0	0.0	1.0	Very low	Supplementary	34	7	41	Insufficient
Heuvelings	2017	Effectiveness of interventions for diagnosis and treatment of tuberculosis in hard-to-reach populations in countries of low and medium tuberculosis incidence: a systematic review	1.0	1.0	0.0	1.0	1.0	1.0	0.0	1.0	0.5	0.0	-	-	1.0	1.0	-	1.0	Moderate	Supplementary	5	40	45	Insufficient