

Effectiveness of interventions for TB control and prevention in countries of low TB incidence: full evidence synthesis from a systematic review of reviews

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OVERVIEW OF INCLUDED STUDIES

Direct effects: The 45 reviews spanned 11 intervention areas, including 13 reviews of vaccination, 9 reviews of TB prophylaxis, latent TB treatment or antiretroviral therapy in people with HIV and 8 reviews of latent TB treatment (**Table 1**). The remaining 15 reviews spanned 9 intervention areas, including treatment adherence, contact tracing plus prophylaxis, diagnostic tests for latent TB infection (LTBI), and approaches to TB detection and treatment (including screening). Quality assessment identified 17 core reviews (high confidence in the results of the review). Of the 28 supplementary reviews, 1 was rated as being of moderate quality, 6 as low quality and 21 as very low quality (**Appendix S4**).

Indirect effects: The 113 reviews covered 10 intervention areas, including 22 reviews of interventions related to treatment adherence, 17 reviews of interventions related to MDR-TB, 17 to treatment, 15 to diagnosis, and 15 to screening (**Table 1**). The other 27 reviews covered health and social care systems and vulnerable population groups, HIV/TB, contact tracing, healthcare-associated infection (healthcare workers and infection control), and prisons. Quality assessment identified 28 core reviews. Of the 85 supplementary reviews, 1 was rated as being of moderate quality, 25 as low quality and 59 as very low quality (**Appendix S4**).

Risk factors: Eleven of the 29 reviews were related to environmental and behavioural risk factors for TB, comprising 10 reviews of smoking, second hand tobacco smoke and indoor air pollution, and one of alcohol. The other 18 reviews covered travel, hospital infection control, pregnancy, and gender (**Table 1, Appendix S3**).

VACCINATION

Direct effects: A sufficient level of evidence for the effectiveness of BCG vaccination against TB was provided by four core reviews (Abubakar *et al.* 2013, Mangtani *et al.* 2014, Roy *et al.* 2014, Health Information and Quality Authority (HIQA) Ireland 2016), the largest of which was by Abubakar *et al.* 2013 (21 RCTs, 111 other studies, covering all age groups). Mangtani *et al.* investigated the effectiveness of BCG vaccination based only on RCT data (hence, 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), finding 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).

Indirect effects: No reviews identified. One supplementary review included under 'HEALTHCARE SYSTEMS' (NICE 2016) included a review of interventions to promote BCG uptake, concluding that there was evidence for staff training to increase uptake; only one of the six included studies was an RCT, which tested training clinical staff to identify people eligible for BCG vaccination, computer-based reminders to staff, and financial incentives to primary care practices for carrying out TB screening.

Risk factors: No reviews identified.

Conclusions: There is a sufficient level of evidence from systematic reviews to support the use of BCG vaccination, with good evidence of protective effects of up to 10 years. In countries with low TB incidence, selective BCG vaccination, for example, close contacts of active TB cases or infants in high risk groups such as immigrants from high TB incidence countries was recommended over universal vaccination although there was a lack of good evidence of cost-effectiveness.

SCREENING

Direct effects: No core reviews were identified as reporting direct effects of screening. 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 ‘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 provide direct evidence for targeted LTBI screening in primary care settings to improve quality of life or reduce active TB disease, transmission of TB, or disease specific or overall mortality among adults in high risk populations.

Indirect effects: The one core review (van't Hoog *et al.* 2013) was combined with two supplementary reviews (Kranzer *et al.* 2013, Shapiro *et al.* 2013) in WHO guidance for countries with medium to high TB incidence (WHO 2012) which recommended that: a) household contacts and other close contacts should be systematically screened for active TB; b) people living with HIV should be systematically screened for active TB at each visit to a health facility; and c) current and former workers in workplaces with silica exposure should be systematically screened for active TB. Of more relevance to low TB incidence countries were the eight supplementary reviews of migrant screening: two reviewing pre-entry screening/follow-up (Aldridge *et al.* 2014, Chan *et al.* 2017); one reviewing point-of-entry screening (Sammeh and Alsharif 2014); four post-entry screening (Arshad *et al.* 2010, Campbell *et al.* 2015, Campbell *et al.* 2015, Bozorgmehr *et al.* 2017); and one screening at all three points (Zenner *et al.* 2017). All of these reviews were supportive in principle of pre- or post-entry screening of migrants from high TB incidence countries, based mainly on case yield and risk of TB developing post-entry, but none compared the effectiveness of different approaches or provided conclusive evidence of cost-effectiveness, and all stressed the need for comparative studies and improved longitudinal data collection. Of the other supplementary reviews: one dismissed screening of non-immigrant visitors to the USA (Tan *et al.* 2001); one provided a wide range in case yield for

bi-directional screening in people with diabetes or TB (Jeon *et al.* 2010); one recommended ELISPOT over TST in screening for LTBI, particularly in patients taking immunosuppressant medication or those with previous BCG vaccination (Greveson 2009); and one estimated test positivity and treatment completion rates for a community-based targeted testing and treatment (TTT) intervention in a hypothetical (predominantly or majority foreign-born) US population (Malekinejad *et al.* 2017).

Risk factors: No reviews identified.

Conclusions: Whilst migrants from high TB incidence countries often have higher prevalence of active and latent TB than the general population in low TB incidence countries, there is insufficient evidence from systematic reviews either to support or discount the effectiveness of different approaches to screening in preventing TB cases, reducing TB incidence, reducing mortality or preventing transmission.

DIAGNOSIS

Direct effects: One core review was identified (Auguste *et al.* 2017), which did not find evidence (from 17 cohort studies) 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 better specificity of IGRAs instead of or to confirm TST results in low TB incidence countries, but the quality of this review was rated very low (Munoz and Santin 2013).

Indirect effects: Of the seven core reviews identified (Dinnes *et al.* 2007, Pinto *et al.* 2013, Steingart *et al.* 2014, Ayubi *et al.* 2015, Drobniowski *et al.* 2015, Auguste *et al.* 2016, Nathavitharana *et al.* 2017), three reviewed drug susceptibility testing (DST) for rifampicin and isoniazid resistance (Steingart *et al.* 2014, Drobniowski *et al.* 2015, Nathavitharana *et al.* 2017), two compared interferon-gamma release assay (IGRA) with tuberculin skin test (TST) (Ayubi *et al.* 2015, Auguste *et al.* 2016), and one each reviewed rapid diagnostic tests (Dinnes *et al.* 2007) and clinical scoring systems (Pinto *et al.* 2013).

The UK Health Technology Assessment (HTA) review of IGRA vs. TST (Auguste *et al.* 2016) found that IGRAs performed better than TST 10mm in identifying LTBI in children, IGRAs and TST performed better in people with low immunity at ruling out LTBI than identifying people who did have LTBI, and TST performed better than IGRAs at identifying LTBI in recently arrived immigrants from high TB incidence countries. Economic model showed that the best options were: in children, TST followed by IGRAs if negative; in people with low immunity, IGRAs followed by TST if negative; in the recently arrived population, TST alone. The core review of IGRA vs. TST in contacts of active TB cases found fair agreement between the two tests, meaning that no clear recommendation could be made as to the best option (Ayubi *et al.* 2015).

Evidence from low-prevalence countries strongly suggests that RD1-based assays are more accurate than TST- and PPD-based assays for diagnosis of LTBI. The review of clinical scoring systems found that chest radiograph scoring systems appeared to be useful in ruling out PTB in hospitals, but low specificity precludes ruling in PTB (Pinto *et al.* 2013).

The three core reviews of molecular DST included a UK HTA review of GenoType® MTBDRplus (isoniazid and rifampicin), INNO-LiPA Rif.TB® (rifampicin) and Xpert® MTB/RIF (rifampicin) (Drobniewski *et al.* 2015), a Cochrane review of the Xpert® MTB/RIF assay (Steingart *et al.* 2014) and a review of three commercial line probe assays (LPA) - Hain Genotype MTBDRplusV1, MTBDRplusV2 and Nipro NTM+MDRTB (Nathavitharana *et al.* 2017). The conclusion of all three reviews was that molecular tests had high sensitivity and specificity (regardless of HIV status) for rifampicin and isoniazid resistance, e.g. for rifampicin resistance detection, Xpert® MTB/RIF pooled sensitivity was 95%, specificity 98% (Steingart *et al.* 2014). Compared with smear microscopy, Xpert® MTB/RIF increased TB detection among culture-confirmed cases by 23%. The core (UK HTA) review of rapid diagnostic tests (Dinnes *et al.* 2007), including Nucleic Acid Amplification Tests (NAATs) and, for pleural TB and TB meningitis, adenosine deaminase (ADA) tests has been superseded by the more recent core reviews summarised above.

Risk factors: No reviews identified.

Conclusions: Diagnostic accuracy of TB diagnostic tests in different patient groups is increasingly well-characterised. Although there is insufficient review-level evidence either to support or discount direct effects of IGRAs compared with TST in diagnosing LTBI which progresses to active TB, there is sufficient review level evidence of indirect effects on TB incidence of molecular drug susceptibility testing.

TREATMENT

Direct effects: A sufficient level of evidence for the relative effectiveness of different drug regimens in treating latent TB infection (LTBI) to prevent progression to active TB was provided by four core reviews (Smieja *et al.* 2000, Ena and Valls 2005, Sharma *et al.* 2013, Zenner *et al.* 2017). The largest and most recent was a network 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, 3- to 4-month 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; shortened combined regimens of rifampicin with INH offered no advantage over longer INH regimens; a weekly regimen of rifapentine plus INH had higher completion rates and less liver toxicity, but more frequent treatment-limiting adverse events. 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), providing evidence for a slightly increased risk of isoniazid-resistant TB after isoniazid preventive therapy (compared to no treatment or placebo).

Indirect effects: The relatively large number of core reviews relating to TB treatment reflects the higher quality of systematic reviews of drug effectiveness (and their constituent studies): (Menzies *et al.* 2009, Mwandumba and Squire 2009, Kasozi *et al.* 2015, Gallardo *et al.* 2016, Grobler *et al.* 2016, Jeyashree *et al.* 2016, Mota *et al.* 2016, Gegia *et al.* 2017, Johnston *et al.* 2017). The findings of such reviews would inform clinical treatment guidelines, rather than providing an evidence base for interventions *per se*. Also, review-level evidence for the relative effectiveness of different drug regimens is more frequently updated than other intervention areas.

Fixed-dose combination therapy (FDC) was covered by one core review (Gallardo *et al.* 2016) and two supplementary reviews (Bangalore *et al.* 2007, Albanna *et al.* 2013); regimens for IH-resistant TB were covered by two core reviews (Menzies *et al.* 2009, Gegia *et al.* 2017), the 2017 review being an update of the earlier review; intermittent regimens were covered by four core reviews (Menzies *et al.* 2009, Mwandumba and Squire 2009, Kasozi *et al.* 2015, Johnston *et al.* 2017), the 2017 review being an update of the earlier review. The respective conclusions were that: overall there is little or no difference detected between FDCs and single-drug formulations for most outcomes reported (Gallardo *et al.* 2016); treatment of isoniazid-resistant tuberculosis with standardised regimens of first-line drugs resulted in suboptimal treatment outcomes (treatment failure, relapse, and acquired multidrug resistance) (Gegia *et al.* 2017); and thrice weekly dosing throughout therapy, and twice weekly dosing in the continuation phase appear to have worse microbiological treatment outcomes when compared with daily therapy (Johnston *et al.* 2017). A supplementary review of short-course regimens found insufficient evidence to draw conclusions regarding its effectiveness, mainly because of a lack of drug sensitivity results (Han 2006).

Therapeutic drug monitoring was covered by one core (Mota *et al.* 2016) and one supplementary review (Wilby *et al.* 2014), both describing discrepancies between recommended and actual drug concentrations but not providing sufficient evidence in support of routine measurement of drug concentrations. A supplementary review of daily dosing schedules favoured daily schedules in standard TB treatment regimens, especially during the initial phase in the presence of cavitation, isoniazid resistance and advanced HIV co-infection (Chang *et al.* 2011), whereas a supplementary review of toxicity monitoring in LTBI treatment failed to include any studies (Sotgiu *et al.* 2015).

One core (Grobler *et al.* 2016) and one supplementary review (Si *et al.* 2015) covered nutritional supplementation during treatment, concluding that there is insufficient evidence to know whether routinely providing free food or energy supplements improves tuberculosis treatment outcomes or, given low blood levels of some vitamins in people starting treatment for active tuberculosis, no

evidence that routinely supplementing above recommended daily amounts has clinical benefits. Similarly, a core review of smoking cessation found insufficient evidence for the effectiveness of cessation interventions in improving TB treatment outcomes (Jeyashree *et al.* 2016).

Risk factors: There was one review of mental health in relation to TB treatment (Doherty *et al.* 2013), which highlighted interactions between drugs used to treat TB and common mental illnesses, adverse psychiatric side-effects of anti-TB agents, and likely poor adherence in TB patients with comorbid mental illness. Diabetes was reported to increase the risk of treatment failure, death, and relapse among TB patients (Baker *et al.* 2011), with the authors suggesting a need for increased attention to treatment of TB in people with diabetes, including testing for diabetes, improved glucose control, and increased clinical and therapeutic monitoring.

Conclusions: There is a sufficient level of evidence from systematic reviews to support the treatment of LTBI to prevent progression to active TB. In high-income countries, 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 entirely dependent on related interventions, particularly screening. There is sufficient review-level evidence of indirect effects *via* sub-optimal outcomes related to treatment of isoniazid-resistant tuberculosis with standardised regimens of first-line drugs, and thrice weekly dosing throughout therapy and twice weekly dosing in the continuation phase compared with daily therapy. There is insufficient review-level evidence for other treatment-related ‘interventions’, including therapeutic drug monitoring, nutritional supplementation and smoking cessation. Whilst TB patients with diabetes appear to have worse outcomes, there is currently no evidence-base for specific interventions.

ADHERENCE

Direct effects: One core review was identified (M'Imunya J *et al.* 2012), which 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.

Indirect effects: Eight core reviews were identified (Lewin *et al.* 2010, Nglazi *et al.* 2013, Liu *et al.* 2014, Tian *et al.* 2014, Karumbi and Garner 2015, Lutge *et al.* 2015, Mbuagbaw *et al.* 2015, Weaver *et al.* 2015). There were two core reviews of directly-observed therapy (DOT) (Tian *et al.* 2014, Karumbi and Garner 2015). The Cochrane review authors (Karumbi and Garner 2015) concluded that there was insufficient evidence overall to either support or discount the effectiveness of DOT in terms of TB treatment completion or cure, although only 2/11 included studies were set in high-income countries (USA and Australia). A core review of incentive-based approaches (Lutge *et al.* 2015) which included 10 studies from the USA (out of 12 included studies) found that material incentives and enablers had little or no effect in improving the outcomes of patients on treatment for active TB, some effects on completion of prophylaxis for latent TB in some circumstances (but trial results were mixed), and some positive short term effects on clinic attendance for diagnostic test results and prophylaxis, particularly for marginal populations such as drug users, recently released prisoners, and the homeless, but that there was insufficient evidence to know if they can improve long term adherence to TB treatment. A Cochrane review of lay health worker-based interventions for the management of infectious diseases in primary care and the community (Lewin *et al.* 2010) included a subset of the USA studies from the Cochrane DOT review, and therefore found the same (insufficient) level of evidence. Evidence that mobile phone reminders improved adherence was lacking in two core reviews (Nglazi *et al.* 2013, Mbuagbaw *et al.* 2015) which included only one study from a low-medium TB incidence country (Argentina), whereas tentative evidence for the effectiveness of telephone-based reminder systems for clinic attendance during active TB treatment

(one USA study) and anti-TB prophylaxis (one study each in the USA and Spain) was found in a Cochrane review (Liu *et al.* 2014). The same review found that pre-appointment phone-calls or reminder cards for people undergoing screening for TB had little or no effect on the proportion of people returning to clinic for the result of their skin test (four USA trials, all using healthy volunteers). One supplementary review included under 'HEALTHCARE SYSTEMS' (NICE 2016) included a review of enhanced case management (ECM) strategies and DOT to increase the uptake of, or adherence to, treatment for people with active or latent TB, finding insufficient review-level evidence for either.

Risk factors: A qualitative review of determinants of non-adherence to TB treatment (Munro *et al.* 2007) identified four interacting factors: structural factors, including poverty and gender discrimination; social context; health service factors; and personal factors.

Conclusions: There is insufficient review-level evidence, particularly in high-income or low TB-incidence countries, to support or discount direct or indirect effects of treatment adherence interventions in reducing the incidence of active TB, including directly-observed treatment, incentives, lay health workers and reminder systems. Interventions to improve TB treatment adherence must address a host of complex and interacting barriers and facilitators.

HIV/TB

Direct effects: Of the three core reviews (Gray *et al.* 2009, Akolo *et al.* 2010, Suthar *et al.* 2012), one reviewed LTBI treatment in HIV+ adults (Akolo *et al.*, 12 RCTs) and 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). 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), whilst a third found tentative evidence for secondary preventive therapy to prevent recurrent TB in HIV patients previously treated for TB (Bruins and van Leth 2017).

Indirect effects: One core review was identified (Ayubi *et al.* 2016), reporting fair agreement between IGRA and TST for LTBI in HIV-positive patients, meaning that no clear recommendation for either test could be made (Ayubi *et al.* 2016), as supported by a supplementary review (Cattamanchi *et al.* 2011). The other four supplementary reviews covered: use of anti-retroviral therapy (ART) in TB patients on second-line anti-TB drug regimens (Arentz *et al.* 2012); the microscopic observation drug susceptibility (MODS) assay (an inexpensive, low-complexity, culture-based technique) for the diagnosis of TB infection and TB drug resistance in HIV-infected patients (Wikman-Jorgensen *et al.* 2014); integrated TB and HIV services in low- and middle-income countries (Legido-Quigley *et al.* 2013); and TST responses in people living with HIV in under-resourced settings (Kerkhoff *et al.* 2012). The first of these supplementary reviews suggested

that ART use during treatment of drug resistant TB appears to improve cure rates and decrease risk of death and found insufficient evidence to determine if ART use increases adverse drug interactions when used with second line TB drugs (Arentz *et al.* 2012), but data were pooled from various (not specified) ART and anti-TB regimens. The review of MODS reported good sensitivity and specificity in diagnosing TB, MDR-TB and smear negative-PTB in PLWH, albeit based on small numbers of studies in the low-income high HIV/TB prevalence settings for which this method was developed (Wikman-Jorgensen *et al.* 2014). Few studies of TB and HIV service integration (all of which were in LMICs) measured patient-relevant impacts, compared effectiveness or cost-effectiveness between models, or reported user or provider perspectives, meaning that there was no evidence to aid policy makers and service providers (Legido-Quigley *et al.* 2013). Also in a LMIC setting, IPT administered to PLWH pre-ART without assessment of TST status will only benefit a minority of those treated, especially among those with the lowest CD4 cell counts (who have the lowest prevalence of TST-positivity) (Kerkhoff *et al.* 2012).

Risk factors: No reviews identified.

Conclusions: There is sufficient review-level evidence to support LTBI treatment and ART to prevent active TB in people infected with HIV, although this evidence derives mainly from studies in low or middle income countries with medium to high TB incidence.

MDR-TB

Direct effects: Three core reviews were identified (Fraser *et al.* 2006, van der Werf *et al.* 2012, Langendam *et al.* 2013). 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. One supplementary review suggested that preventive treatments for MDR-TB contacts were effective, but the quality of this review was rated very low (Marks *et al.* 2017).

Indirect effects: No core reviews were identified. Most of the 17 supplementary reviews had treatment success as an outcome. Eight reviewed drug regimens (Orenstein *et al.* 2009, Ahuja *et al.* 2012, Ettehad *et al.* 2012, Chang *et al.* 2013, Falzon *et al.* 2013, Fox *et al.* 2016, Bastos *et al.* 2017, Fox *et al.* 2017), including three reviews of WHO Group 5 drugs (Chang *et al.* 2013, Fox *et al.* 2016, Fox *et al.* 2017) and one of paediatric MDR-TB (Ettehad *et al.* 2012). Pooled analysis indicated overall treatment success rates of 26% and 60% for XDR- and MDR-TB patients, respectively (Bastos *et al.* 2017). Although some reviews made specific recommendations, e.g. use linezolid for the treatment of XDR-TB or fluoroquinolone-resistant MDR-TB (Chang *et al.* 2013) and six- and four-drug combinations in the intensive and continuation phases of XDR-TB treatment (Falzon *et al.* 2013), the conclusion common to all reviews was the need for RCTs. Two reviewed DOT/DOTS+ (Yin *et al.* 2016, Kibret *et al.* 2017), one reporting that treatment success rates for studies using full DOT, intensive phase DOT, and self-administered therapy (SAT) were 67%, 67% and 47%, respectively, with no difference in success rates between DOT provided by healthcare workers and DOT provided by family members or between studies using health facility based DOT and home-based DOT (Yin *et al.* 2016). Reviews of decentralized (Ho *et al.* 2017), ambulatory (Bassili *et al.* 2013) and community-based care (Weiss *et al.* 2014), and strategies for reducing treatment default (Toczek *et al.* 2013) did not provide evidence in favour of any particular care model, whilst reviews

of DST (Bastos *et al.* 2014) and therapeutic drug monitoring (TDM) (Ghimire *et al.* 2016) indicated that further standardisation and validation of these methods was required. One supplementary review included under 'HEALTHCARE SYSTEMS' (NICE 2016) included a review of TB service organisation and delivery, which concluded (based on one observational study) that a comprehensive MDR-TB control programme can improve MDR-TB treatment completion and reduce mortality.

Risk factors: No reviews identified.

Conclusions: Overall treatment success is >60% for MDR-TB, but randomised drug-regimen trials are needed and there is insufficient review-level evidence for specific interventions in terms of reducing incidence, including LTBI treatment in contacts of MDR-TB cases.

CONTACTS AND TRANSMISSION

Direct effects: No core or supplementary reviews were identified.

Indirect effects: No core reviews were identified. Six supplementary reviews covered: contact investigations (Fair *et al.* 2012, Fox *et al.* 2013, Shah *et al.* 2014); whole genome sequencing (WGS) for detection of recent transmission and tracing of outbreaks (Hatherell *et al.* 2016, Nikolayevskyy *et al.* 2016); and active case finding in high-risk groups (Zenner *et al.* 2013). In the absence of sufficient evidence for specific interventions, review authors recommend investigating contacts of MDR-TB and HIV-positive TB cases, and LTBI treatment for child or HIV-positive contacts of all TB cases. Of the two WGS reviews, one (Nikolayevskyy *et al.* 2016) concluded that WGS has a higher discriminatory power compared to conventional genotyping, and detects transmission events missed by epidemiological investigations, whilst the other (Hatherell *et al.* 2016) highlighted current limitations of WGS, concluding that epidemiological data and clinical history remain critical to outbreak investigations, especially when *M. tuberculosis* genetic diversity is low. One supplementary review included under 'HEALTHCARE SYSTEMS' (NICE 2016) included a review of TB service organisation and delivery, which suggested (based on two observational studies) that cohort review can improve contact tracing, as can community health workers from immigrant communities working alongside public health nurses (one observational study).

Risk factors: There were two reviews of TB in relation to air travel specifically (Abubakar 2010, Kotila *et al.* 2016), both of which indicated a low risk of transmission, and one review of overseas travel in general (Freeman *et al.* 2010), which recommended targeted testing for long-term military and civilian travellers.

Conclusions: There is insufficient review-level evidence for specific interventions related to contact investigation, in terms of direct or indirect effects on TB incidence, but this does not preclude the implementation of pragmatic steps such as MDR-TB case contact investigation.

HEALTHCARE-ASSOCIATED INFECTION

Direct effects: No core reviews were identified. 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) (this review excluded a study of a pharmacy-based intervention for HCWs in the USA because it was not workplace-based/organised).

Indirect effects: A WHO policy statement on use of IGRAs in low- and middle-income countries comprising multiple systematic reviews (WHO 2011) was included as a core review. It recommended that IGRAs should not be used in HCW testing programmes (and should not replace TST for LTBI testing in adult and paediatric contacts or outbreak investigations). There were three supplementary reviews on TB screening in HCWs (Zwerling *et al.* 2012, Nienhaus *et al.* 2013, Lamberti *et al.* 2015). Lamberti *et al.* concluded that, in the absence of a gold-standard test, TB surveillance in HCWs needed to consider factors such as vaccination status, age and role, whilst Zwerling *et al.* commented that use of IGRAs for serial testing in HCWs is complicated by lack of data on optimum cut-offs. The two other supplementary reviews covered clinical prediction rules (CPR) for respiratory isolation of patients with suspected PTB (Wisnivesky *et al.* 2005, Solari *et al.* 2011), both reviews indicating that CPRs tend to have high sensitivity but low specificity, with inconclusive evidence for their utility in low TB incidence settings.

Risk factors: Four reviews were identified (Kramer *et al.* 2006, Ontario Medical Advisory 2012, Esquinas *et al.* 2014, Schepisi *et al.* 2015): Kramer *et al.* reviewed pathogen persistence on surfaces, reporting a range of 1 day to 4 months for *M. tuberculosis*; the Ontario HTA suggested that in-room air cleaning technology could prevent TB transmission, albeit based on a single experimental study using aerosolised *M. parafortuitum*; Esquinas *et al.* assessed infection risks to HCW managing patients under non-invasive mechanical ventilation (no reported infections); and Schepisi *et al.* reviewed TB transmission from HCWs to patients and co-workers.

Conclusions: There is insufficient review-level evidence for TB-specific interventions for HCWs or infection control, although this reflects a lack of systematic reviews in this area particularly in high-income country settings where hospital and HCW infection control practices are more likely to reflect best practice.

SOCIAL SUPPORT AND VULNERABLE GROUPS

Direct effects: One core review was identified which reviewed a wide range of interventions for diagnosis and treatment of TB in hard-to-reach populations (Heuvelings *et al.* 2017). This review extended and updated two earlier reviews by the UK National Institute for Health and Care Excellence (NICE 2011, NICE 2011). Of the 44 included primary studies, three had TB incidence or TB cases prevented as outcomes, two of which were included in other systematic reviews that we have reviewed under ‘SCREENING’. The remaining study was a non-randomized study of a social and health care programme for homeless people in Spain which 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 (Diez *et al.* 1996). This Spanish study was also identified in a review (very low quality) of community-based interventions for TB prevention and control (Arshad *et al.* 2014).

Indirect effects: The one core review in the area of health and social care (van Hoorn *et al.* 2016) concluded that psychosocial (PS) and socioeconomic (SE) support did improve treatment outcomes across a variety of settings and patient populations (of 25 studies, 9 were conducted in upper middle income countries, 7 in lower middle income countries, 6 in high income countries 3 in low income countries), with a tendency towards better outcomes with a PE or combined approach, but classified the quality of evidence as ‘very low’ (van Hoorn *et al.* 2016). The one supplementary review covered models of integrated HIV/TB care for people who inject drugs, concluding that successful interventions involved collaboration across services, a client-centred approach, and provision of social care (Grenfell *et al.* 2013). One supplementary review included under ‘HEALTHCARE SYSTEMS’ (NICE 2016) included reviews of enhanced case management (ECM) strategies and educational interventions to increase the uptake of, or adherence to, treatment for people with active or latent TB. The review of ECM identified several RCTs of interventions in injecting drug users (IDUs), finding some evidence for the effectiveness of incentives as an adjunct to directly observed

preventive therapy; the review of educational interventions found these to be less effective than incentives in increasing return rates for TB test reading among injecting drug or crack cocaine users. In one RCT among homeless people, peer support plus DOT was not more effective in increasing treatment completion than usual care plus SAT, and was less effective than incentives, follow-up calls and DOT.

Risk factors: No reviews identified.

Conclusions: There is insufficient review-level evidence to support or discount the effectiveness of TB-specific social support interventions or interventions in vulnerable groups.

HEALTHCARE SYSTEMS

Direct effects: No core or supplementary reviews were identified.

Indirect effects: No core reviews were identified. Four of the five supplementary reviews focused on healthcare systems in LMICs, including mixed public-private approaches (Lei *et al.* 2015), task-shifting (e.g. of treatment supervision to community health workers, laypersons, or family (Seidman and Atun 2017), evidence for scaling-up TB interventions such as IPT, clinical algorithms and second-line treatment (Cobelens *et al.* 2012), and evidence to support best practice in evaluating specialist HCW training (Wu *et al.* 2017). The fifth supplementary review (NICE 2016) included six separate reviews, two of which we included in their peer-reviewed published form under Diagnosis (Auguste *et al.* 2017) and Social support and Vulnerable Groups (Heuvelings *et al.* 2017). The other four reviews, collectively rated 'low' quality, covered a wide range of interventions, including: strategies to increase the uptake of BCG vaccination; enhanced case management and interventions to increase the uptake of, or adherence to, treatment for active or latent TB; strategies and interventions aimed at providing and delivering information and education to recipients and providers of care; and approaches to TB services in relation to reducing diagnostic delay for TB, improving TB contact tracing, and improving TB treatment completion. Evidence from these reviews is summarized in other sections of this Appendix. With regard to healthcare systems, the review of educational and information interventions found that intensive interventions with service providers, integrating clinician education with other components such as reminders, process improvement and incentives, were effective in improving service delivery outcomes, but that evidence on educational interventions alone was mixed and inconclusive.

Risk factors: There was one review of the potential impact of health economic analyses on TB control policy and practice (Floyd 2003). This review showed that the majority of cost and cost-effectiveness studies have been conducted in high-income low TB incidence countries, mainly on cost-effectiveness of screening and preventive therapy and the costs of treatment, but very few

(<5%) of the studies reported whether there had been any impact on policy and practice. The substantial losses at each step from detection to cure were described in a review of the ‘cascade of care’ (Alsdurf *et al.* 2016).

Conclusions: There is insufficient review-level evidence to support or discount the effectiveness of TB-specific interventions at the level of healthcare systems in low-incidence countries.

PREGNANCY AND GENDER

Direct effects: No core reviews were identified. One supplementary review of very low quality reviewed 35 non-randomised studies, 4 of which investigated treatment of LTBI with INH during pregnancy, none reporting progression to active TB (Nguyen *et al.* 2014).

Indirect effects: No reviews were identified. The review by Nguyen *et al.* cited above under ‘Direct effects’ included several interventions in pregnant women with indirect outcomes, including diagnosis/screening, treatment, adherence, and MDR-TB. The authors highlighted difficulties in diagnosing TB during pregnancy, treatment delays and poor adherence to IPT, and suggested that MDR-TB pregnant women can be cured and have a positive maternal outcome, and should therefore be given the option to continue with a pregnancy (if provided with attentive follow-up and appropriate therapy). However, all of the included studies were of limited quality.

Risk factors: Three reviews in relation to pregnancy (Moradi and Meshkat 2015, Repossi and Bothamley 2015, Malhame *et al.* 2016) suggested that: early diagnosis and prompt treatment can reduce the complications of congenital TB, especially neonatal mortality, prematurity and low birth weight; non-specific symptoms and extra pulmonary disease demand a higher level of suspicion of TB; standard first-line treatment is safe in pregnancy; and, although data on second-line drugs in pregnancy is limited, injectable drugs may affect the hearing and balance of the foetus. There were two reviews in relation to gender (van den Hof *et al.* 2010, Sudhakar and Admassu 2013): van den Hof *et al.* found no studies on the effects of gender-specific interventions to improve access to health care, TB diagnosis, treatment adherence, and outcomes; Sudhakar and Admassu reported gender-related differences in determinants of help seeking, perceived causes of tuberculosis infection and stigma.

Conclusions: There is insufficient review-level evidence for direct or indirect effects of specific pregnancy-related interventions relating to TB during pregnancy, beyond standard TB diagnosis and treatment procedures.

PRISONS

Direct effects: One supplementary 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 the effectiveness of LTBI treatment regimens in this setting.

Indirect effects: No core reviews were identified. One supplementary review (Vinkeles Melchers *et al.* 2013) identified limited accuracy of diagnostic algorithms and lack of adequate laboratory facilities as key limitations for TB control programmes in prisons. The authors reported that some prison settings allowed diagnostic testing and medical follow-up only for those presenting with symptoms, while quality control of smear examinations is not always present in local laboratories. Lack of well-organised health services or adequate referral was mentioned by one fifth of the 52 included studies. The authors suggested that poor health services may be related to limited infrastructure, equipment, staff or transport, as well as incomplete medical information systems and out-of-pocket payments, and that weak prison infrastructure limits infection control and adequate isolation of cases and neglects hard-to-reach populations (e.g. female and/or foreign-born inmates) who may encounter violence, discrimination or language barriers. One supplementary review included under 'HEALTHCARE SYSTEMS' (NICE 2016) included a review of education, information and support to increase the uptake of, or adherence to, treatment for people with active or latent TB, finding some evidence that educational interventions are effective in increasing uptake of and adherence to treatment among prisoners.

Risk factors: One review was identified (Baussano *et al.* 2010) which estimated that the median fraction of TB in the general population in a high-income country attributable to exposure in prisons was 8.5% (IQR: 1.9%-17.9%), suggesting that better TB control in prisons could reduce the national burden of TB, depending on country-specific epidemiology.

Conclusions: TB incidence is known to be much higher in correctional facilities but, beyond standard TB diagnosis and treatment procedures and infection control measures, there is insufficient review-level evidence for specific interventions in the context of prisons.

ENVIRONMENT AND BEHAVIOURS

Direct effects: No reviews identified

Indirect effects: No reviews identified

Risk factors: There were ten reviews of smoking, second hand tobacco smoke and/or indoor air pollution in relation to TB (Bates *et al.* 2007, Lin *et al.* 2007, Slama *et al.* 2007, Sumpter and Chandramohan 2013, Kurmi *et al.* 2014, Dogar *et al.* 2015, Jafta *et al.* 2015, Patra *et al.* 2015, Jayes *et al.* 2016, Underner *et al.* 2016), with consistent evidence pointing towards a causal association of smoking with TB, but less consistent evidence of an association between second hand tobacco smoke or indoor air pollution and TB. The authors of a review which reported an association between heavy alcohol consumption and active TB (Lonnroth *et al.* 2008) suggested that the association could be explained by social mixing patterns and/or immunological effects of alcohol and alcohol-related conditions.

Conclusions: Whilst plausible associations of smoking and heavy alcohol consumption and, to a lesser extent second hand tobacco smoke, with TB are supported by some reviews, there is as yet no review-level evidence to support the incorporation of smoking- or alcohol-related interventions into programmes for TB control and prevention.

REFERENCES

- Abubakar, I. (2010). "Tuberculosis and air travel: a systematic review and analysis of policy." *Lancet Infect Dis* **10**(3): 176-183.
- 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.
- Ahuja, S. D., et al. (2012). "Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients." *PLoS Med* **9**(8): e1001300.
- Akolo, C., et al. (2010). "Treatment of latent tuberculosis infection in HIV infected persons." *Cochrane Database Syst Rev*(1): CD000171.
- Al-Darraj, H. A., et al. (2012). "Isoniazid preventive therapy in correctional facilities: a systematic review." *Int J Tuberc Lung Dis* **16**(7): 871-879.
- Albanna, A. S., et al. (2013). "Fixed-dose combination antituberculosis therapy: a systematic review and meta-analysis." *Eur Respir J* **42**(3): 721-732.
- Aldridge, R. W., et al. (2014). "Pre-entry screening programmes for tuberculosis in migrants to low-incidence countries: a systematic review and meta-analysis." *Lancet Infect Dis* **14**(12): 1240-1249.
- Alsdurf, H., et al. (2016). "The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis." *Lancet Infect Dis* **16**(11): 1269-1278.
- Arentz, M., et al. (2012). "Use of anti-retroviral therapy in tuberculosis patients on second-line anti-TB regimens: a systematic review." *PLoS One* **7**(11): e47370.
- Arshad, A., et al. (2014). "Community based interventions for the prevention and control of tuberculosis." *Infect Dis Poverty* **3**(27): 27.
- Arshad, S., et al. (2010). "Active screening at entry for tuberculosis among new immigrants: a systematic review and meta-analysis." *Eur Respir J* **35**(6): 1336-1345.
- 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.
- Auguste, P., et al. (2016). "Accurate diagnosis of latent tuberculosis in children, people who are immunocompromised or at risk from immunosuppression and recent arrivals from countries with a high incidence of tuberculosis: systematic review and economic evaluation." *Health technology assessment (Winchester, England)* **20**(38): 1-678.
- 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.
- Ayubi, E., et al. (2015). "Do the tuberculin skin test and the QuantiFERON-TB Gold in-tube test agree in detecting latent tuberculosis among high-risk contacts? A systematic review and meta-analysis." *Epidemiol Health* **37**: e2015043.
- Ayubi, E., et al. (2016). "The Clinical Usefulness of Tuberculin Skin Test versus Interferon-Gamma Release Assays for Diagnosis of Latent Tuberculosis in HIV Patients: A Meta-Analysis." *PLoS One* **11**(9): e0161983.
- 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.
- Baker, M. A., et al. (2011). "The impact of diabetes on tuberculosis treatment outcomes: a systematic review." *BMC Med* **9**: 81.
- Balcells, M. E., et al. (2006). "Isoniazid preventive therapy and risk for resistant tuberculosis." *Emerg Infect Dis* **12**(5): 744-751.
- Bangalore, S., et al. (2007). "Fixed-dose combinations improve medication compliance: a meta-analysis." *Am J Med* **120**(8): 713-719.
- Bassili, A., et al. (2013). "A systematic review of the effectiveness of hospital- and ambulatory-based management of multidrug-resistant tuberculosis." *Am J Trop Med Hyg* **89**(2): 271-280.

- Bastos, M. L., et al. (2014). "Treatment outcomes of patients with multidrug-resistant and extensively drug-resistant tuberculosis according to drug susceptibility testing to first- and second-line drugs: an individual patient data meta-analysis." *Clin Infect Dis* **59**(10): 1364-1374.
- Bastos, M. L., et al. (2017). "An updated systematic review and meta-analysis for treatment of multidrug-resistant tuberculosis." *Eur Respir J* **49**(3).
- Bates, M. N., et al. (2007). "Risk of tuberculosis from exposure to tobacco smoke: a systematic review and meta-analysis." *Arch Intern Med* **167**(4): 335-342.
- Baussano, I., et al. (2010). "Tuberculosis incidence in prisons: a systematic review." *PLoS Med* **7**(12): e1000381.
- Bozorgmehr, K., et al. (2017). "Yield of active screening for tuberculosis among asylum seekers in Germany: a systematic review and meta-analysis." *Euro Surveill* **22**(12).
- 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.
- Campbell, J. R., et al. (2015). "Latent tuberculosis infection screening in immigrants to low-incidence countries: a meta-analysis." *Mol Diagn Ther* **19**(2): 107-117.
- Campbell, J. R., et al. (2015). "A systematic review on TST and IGRA tests used for diagnosis of LTBI in immigrants." *Mol Diagn Ther* **19**(1): 9-24.
- Cattamanchi, A., et al. (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): 230-238.
- Chan, I. H. Y., et al. (2017). "Post-migration follow-up of migrants identified to be at increased risk of developing tuberculosis at pre-migration screening: a systematic review and meta-analysis." *The Lancet Infectious Diseases* **17**(7): 770-779.
- Chang, K. C., et al. (2011). "Treatment of tuberculosis and optimal dosing schedules." *Thorax* **66**(11): 997-1007.
- Chang, K. C., et al. (2013). "WHO group 5 drugs and difficult multidrug-resistant tuberculosis: a systematic review with cohort analysis and meta-analysis." *Antimicrob Agents Chemother* **57**(9): 4097-4104.
- Cobelens, F., et al. (2012). "Research on implementation of interventions in tuberculosis control in low- and middle-income countries: a systematic review." *PLoS Med* **9**(12): e1001358.
- 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.
- Diez, E., et al. (1996). "Evaluation of a social health intervention among homeless tuberculosis patients." *Tuber Lung Dis* **77**(5): 420-424.
- Dinnes, J., et al. (2007). "A systematic review of rapid diagnostic tests for the detection of tuberculosis infection." *Health Technol Assess* **11**(3): 1-196.
- 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.
- Dogar, O. F., et al. (2015). "Second-hand smoke and the risk of tuberculosis: a systematic review and a meta-analysis." *Epidemiol Infect* **143**(15): 3158-3172.
- Doherty, A. M., et al. (2013). "A review of the interplay between tuberculosis and mental health." *General Hospital Psychiatry* **35**(4): no pagination.
- Drobniewski, F., et al. (2015). "Systematic review, meta-analysis and economic modelling of molecular diagnostic tests for antibiotic resistance in tuberculosis." *Health Technol Assess* **19**(34): 1-188, vii-viii.
- 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.
- Esquinas, A. M., et al. (2014). "Non-invasive mechanical ventilation in high-risk pulmonary infections: a clinical review." *European Respiratory Review* **23**(134): 427-438.

- Ettehad, D., et al. (2012). "Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis." Lancet Infect Dis **12**(6): 449-456.
- Fair, E., et al. (2012). "Systematic review of tuberculosis contact investigation in low and middle income countries." American Journal of Respiratory and Critical Care Medicine **185**: no pagination.
- Falzon, D., et al. (2013). "Resistance to fluoroquinolones and second-line injectable drugs: impact on multidrug-resistant TB outcomes." Eur Respir J **42**(1): 156-168.
- Floyd, K. (2003). "Costs and effectiveness--the impact of economic studies on TB control." Tuberculosis (Edinb) **83**(1-3): 187-200.
- Fox, G. J., et al. (2013). "Contact investigation for tuberculosis: a systematic review and meta-analysis." Eur Respir J **41**(1): 140-156.
- Fox, G. J., et al. (2017). "Group 5 drugs for multidrug-resistant tuberculosis: individual patient data meta-analysis." Eur Respir J **49**(1): 1600993-1600993.
- Fox, G. J., et al. (2016). "Propensity Score-Based Approaches to Confounding by Indication in Individual Patient Data Meta-Analysis: Non-Standardized Treatment for Multidrug Resistant Tuberculosis." PLoS One **11**(3): e0151724.
- 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.
- Freeman, R. J., et al. (2010). "Systematic review and meta-analysis of TST conversion risk in deployed military and long-term civilian travelers." J Travel Med **17**(4): 233-242.
- Gallardo, C. R., et al. (2016). "Fixed-dose combinations of drugs versus single-drug formulations for treating pulmonary tuberculosis." Cochrane Database Syst Rev **2016**(5): CD009913.
- Gegia, M., et al. (2017). "Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis." Lancet Infect Dis **17**(2): 223-234.
- Ghimire, S., et al. (2016). "Pharmacokinetic/pharmacodynamic-based optimization of levofloxacin administration in the treatment of MDR-TB." J Antimicrob Chemother **71**(10): 2691-2703.
- 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.
- Grenfell, P., et al. (2013). "Tuberculosis, injecting drug use and integrated HIV-TB care: a review of the literature." Drug Alcohol Depend **129**(3): 180-209.
- Greveson, K. (2009). "Can ELISpot replace the tuberculin skin test for latent tuberculosis?" Br J Nurs.
- Grobler, L., et al. (2016). "Nutritional supplements for people being treated for active tuberculosis." Cochrane Database Syst Rev(6): CD006086.
- Haas, M. K. and R. W. Belknap (2015). "A review of rifapentine for treating active and latent tuberculosis." Clinical Investigation **5**(11): 829-838.
- Han, T. (2006). "Effectiveness of standard short-course chemotherapy for treating tuberculosis and the impact of drug resistance on its outcome." Int J Evid Based Healthcare.
- Hatherell, H. A., et al. (2016). "Interpreting whole genome sequencing for investigating tuberculosis transmission: a systematic review." BMC Med **14**: 21.
- 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.
- Ho, J., et al. (2017). "Decentralized care for multidrug-resistant tuberculosis: a systematic review and meta-analysis." Bull World Health Organ **95**(8): 584-593.
- Jafta, N., et al. (2015). "Childhood tuberculosis and exposure to indoor air pollution: a systematic review and meta-analysis." Int J Tuberc Lung Dis **19**(5): 596-602.
- Jayes, L., et al. (2016). "SmokeHaz: Systematic Reviews and Meta-analyses of the Effects of Smoking on Respiratory Health." Chest **150**(1): 164-179.

- Jeon, C. Y., et al. (2010). "Bi-directional screening for tuberculosis and diabetes: a systematic review." Trop Med Int Health **15**(11): 1300-1314.
- Jeyashree, K., et al. (2016). "Smoking cessation interventions for pulmonary tuberculosis treatment outcomes." Cochrane Database Syst Rev(1): CD011125.
- Johnston, J. C., et al. (2017). "Effect of Intermittency on Treatment Outcomes in Pulmonary Tuberculosis: An Updated Systematic Review and Metaanalysis." Clin Infect Dis **64**(9): 1211-1220.
- 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.
- Karumbi, J. and P. Garner (2015). "Directly observed therapy for treating tuberculosis." Cochrane Database Syst Rev(5): CD003343.
- Kasozi, S., et al. (2015). "Intermittent Versus Daily Pulmonary Tuberculosis Treatment Regimens: A Meta-Analysis." Clin Med Res **13**(3-4): 117-138.
- Kerkhoff, A. D., et al. (2012). "Systematic review of TST responses in people living with HIV in under-resourced settings: implications for isoniazid preventive therapy." PLoS One **7**(11): e49928.
- Kibret, K. T., et al. (2017). "Treatment outcomes for multidrug-resistant tuberculosis under DOTS-Plus: a systematic review and meta-analysis of published studies." Infect Dis Poverty **6**(1): 7.
- Kotila, S. M., et al. (2016). "Systematic review on tuberculosis transmission on aircraft and update of the European Centre for Disease Prevention and Control risk assessment guidelines for tuberculosis transmitted on aircraft (RAGIDA-TB)." Euro Surveill **21**(4): 21357-21357.
- Kramer, A., et al. (2006). "How long do nosocomial pathogens persist on inanimate surfaces? A systematic review." BMC Infect Dis **6**: 130.
- Kranzer, K., et al. (2013). "The benefits to communities and individuals of screening for active tuberculosis disease: a systematic review." Int J Tuberc Lung Dis **17**(4): 432-446.
- Kurmi, O. P., et al. (2014). "Tuberculosis risk from exposure to solid fuel smoke: a systematic review and meta-analysis." J Epidemiol Community Health **68**(12): 1112-1118.
- Lamberti, M., et al. (2015). "Tuberculin skin test and Quantiferon test agreement and influencing factors in tuberculosis screening of healthcare workers: a systematic review and meta-analysis." J Occup Med Toxicol **10**: 2.
- 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.
- Legido-Quigley, H., et al. (2013). "Integrating tuberculosis and HIV services in low- and middle-income countries: a systematic review." Trop Med Int Health **18**(2): 199-211.
- Lei, X., et al. (2015). "Public-private mix for tuberculosis care and control: a systematic review." Int J Infect Dis **34**: 20-32.
- Lewin, S., et al. (2010). "Lay health workers in primary and community health care for maternal and child health and the management of infectious diseases." Cochrane Database Syst Rev **17**(3): CD004015.
- Lin, H. H., et al. (2007). "Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis." PLoS Med **4**(1): e20.
- Liu, Q., et al. (2014). "Reminder systems to improve patient adherence to tuberculosis clinic appointments for diagnosis and treatment." Cochrane Database Syst Rev(11): CD006594.
- Lonnroth, K., et al. (2008). "Alcohol use as a risk factor for tuberculosis: a systematic review." BMC Public Health **8**(289): (14 August 2008)-(2014 August 2008).
- 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.
- Lutge, E. E., et al. (2015). "Incentives and enablers to improve adherence in tuberculosis." Cochrane Database Syst Rev(9): CD007952.
- 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.

- Malekinejad, M., et al. (2017). "Yield of community-based tuberculosis targeted testing and treatment in foreign-born populations in the United States: A systematic review." *PLoS One* **12**(8): e0180707.
- Malhame, I., et al. (2016). "Latent Tuberculosis in Pregnancy: A Systematic Review." *PLoS One* **11**(5): e0154825.
- 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*.
- Mbuagbaw, L., et al. (2015). "Mobile phone text messaging interventions for HIV and other chronic diseases: an overview of systematic reviews and framework for evidence transfer." *BMC Health Serv Res* **15**(1): 33.
- Menzies, D., et al. (2009). "Standardized treatment of active tuberculosis in patients with previous treatment and/or with mono-resistance to isoniazid: A systematic review and meta-analysis." *PLoS Med*. **6**(9): 1-14.
- Moradi, B. and Z. Meshkat (2015). "Evaluation of tuberculosis infection in pregnant women and its effects on newborns: an overview." *Iranian Journal of Obstetrics, Gynecology and Infertility* **18**(178): Pe21-Pe36.
- Mota, L., et al. (2016). "Therapeutic drug monitoring in anti-tuberculosis treatment: a systematic review and meta-analysis." *Int J Tuberc Lung Dis* **20**(6): 819-826.
- 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.
- Munro, S. A., et al. (2007). "Patient adherence to tuberculosis treatment: a systematic review of qualitative research." *PLoS Med* **4**(7): e238.
- Mwandumba, H. C. and S. B. Squire (2009). "Fully intermittent dosing with drugs for treating tuberculosis in adults." *Cochrane Database of Systematic Reviews*.
- Nathavitharana, R. R., et al. (2017). "Accuracy of line probe assays for the diagnosis of pulmonary and multidrug-resistant tuberculosis: a systematic review and meta-analysis." *Eur Respir J* **49**(1).
- Nglazi, M. D., et al. (2013). "Mobile phone text messaging for promoting adherence to anti-tuberculosis treatment: a systematic review." *BMC Infect Dis* **13**: 566.
- Nguyen, H. T., et al. (2014). "Tuberculosis care for pregnant women: a systematic review." *BMC Infect Dis* **14**(617): 617.
- NICE (2011). Evidence review on the effectiveness and cost-effectiveness of interventions aimed at identifying people with tuberculosis and/or raising awareness of tuberculosis among hard-to-reach groups. London, National Institute for Health and Care Excellence (NICE).
- NICE (2011). Evidence review on the effectiveness and cost-effectiveness of interventions aimed at managing tuberculosis in hard-to-reach groups. London, National Institute for Health and Care Excellence (NICE).
- NICE (2016). Tuberculosis: NICE guideline NG33. London, National Institute for Health and Care Excellence (NICE).
- Nienhaus, A., et al. (2013). "IFN-gamma release assay versus tuberculin skin test for monitoring TB infection in healthcare workers." *Expert Rev Anti Infect Ther* **11**(1): 37-48.
- Nikolayevskyy, V., et al. (2016). "Whole genome sequencing of Mycobacterium tuberculosis for detection of recent transmission and tracing outbreaks: A systematic review." *Tuberculosis (Edinb)* **98**: 77-85.
- Ontario Medical Advisory, S. (2012). "Air cleaning technologies: an evidence-based analysis." *Ontario Health Technology Assessment Series* **5**(17): 1.
- Orenstein, E. W., et al. (2009). "Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis." *The Lancet Infectious Diseases* **9**(3): 153-161.
- 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.
- Patra, J., et al. (2015). "Exposure to second-hand smoke and the risk of tuberculosis in children and adults: a systematic review and meta-analysis of 18 observational studies." *PLoS Med* **12**(6): e1001835; discussion e1001835.
- Pinto, L. M., et al. (2013). "Scoring systems using chest radiographic features for the diagnosis of pulmonary tuberculosis in adults: A systematic review." *Eur Respir J* **42**(2): 480-494.
- Repossi, A. C. and G. H. Bothamley (2015). "Tuberculosis and Pregnancy: An Updated Systematic Review." *Pulmonary Research and Respiratory Medicine - Open Journal* **2**(1): 63-68.

- Roy, A., et al. (2014). "Effect of BCG vaccination against Mycobacterium tuberculosis infection in children: systematic review and meta-analysis." BMJ **349**: g4643.
- Sammeh, A. and M. Alsharif (2014). "Effectiveness and cost effectiveness of screening immigrants schemes for tuberculosis (TB) on arrival from high TB endemic countries to low TB prevalent countries." African Health Sciences **14**(3): 663-671.
- Schepisi, M. S., et al. (2015). "Tuberculosis transmission from healthcare workers to patients and co-workers: a systematic literature review and meta-analysis." PLoS One **10**(4): e0121639.
- Seidman, G. and R. Atun (2017). "Does task shifting yield cost savings and improve efficiency for health systems? A systematic review of evidence from low-income and middle-income countries." Hum Resour Health **15**(1): 29.
- Shah, N. S., et al. (2014). "Yield of contact investigations in households of patients with drug-resistant tuberculosis: systematic review and meta-analysis." Clin Infect Dis **58**(3): 381-391.
- Shapiro, A. E., et al. (2013). A systematic review of the number needed to screen to detect a case of active tuberculosis in different risk groups. Systematic screening for active tuberculosis: principles and recommendations. Geneva, World Health Organisation.
- 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.
- Si, Z. L., et al. (2015). "Adjuvant Efficacy of Nutrition Support During Pulmonary Tuberculosis Treating Course: Systematic Review and Meta-analysis." Chin Med J (Engl) **128**(23): 3219-3230.
- Slama, K., et al. (2007). "Tobacco and tuberculosis: a qualitative systematic review and meta-analysis." Int J Tuberc Lung Dis **11**(10): 1049-1061.
- Smieja, M. J., et al. (2000). "Isoniazid for preventing tuberculosis in non-HIV infected persons." Cochrane Database Syst Rev(2): CD001363.
- Solari, L., et al. (2011). "Evaluation of clinical prediction rules for respiratory isolation of inpatients with suspected pulmonary tuberculosis." Clin Infect Dis **52**(5): 595-603.
- Sotgiu, G., et al. (2015). "Monitoring toxicity in individuals receiving treatment for latent tuberculosis infection: a systematic review versus expert opinion." Eur Respir J **45**(4): 1170-1173.
- 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.
- Steingart, K. R., et al. (2014). "Xpert(R) MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults." Cochrane Database Syst Rev(1): CD009593.
- Sudhakar, M. and B. Admassu (2013). "Determinants of help seeking and treatment seeking behavior of tuberculosis patients - Gender perspective: A systematic review." JBI Database of Systematic Reviews and Implementation Reports **11**: 199-271.
- Sumpter, C. and D. Chandramohan (2013). "Systematic review and meta-analysis of the associations between indoor air pollution and tuberculosis." Trop Med Int Health **18**(1): 101-108.
- 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.
- Tan, L., et al. (2001). "Screening nonimmigrant visitors to the United States for tuberculosis: report of the Council on Scientific Affairs." Arch Intern Med **161**(3): 334-340.
- Thomas, R. E. (2000). "Preparing patients to travel abroad safely. Part 2: Updating vaccinations." Can Fam Physician **46**(MAR.): 646-652, 655-646.
- Tian, J. H., et al. (2014). "Effectiveness of directly observed treatment of tuberculosis: a systematic review of controlled studies." Int J Tuberc Lung Dis **18**(9): 1092-1098.
- Toczek, A., et al. (2013). "Strategies for reducing treatment default in drug-resistant tuberculosis: systematic review and meta-analysis." Int J Tuberc Lung Dis **17**(3): 299-307.
- Underner, M., et al. (2016). "[Smoking and adherence to anti-tuberculosis treatment]." Rev Mal Respir **33**(2): 128-144.

- van't Hoog, A. H., et al. (2013). A systematic review of the sensitivity and specificity of symptom- and chest-radiography screening for active pulmonary tuberculosis in HIV-negative persons and persons with unknown HIV status. Systematic screening for active tuberculosis: principles and recommendations. Geneva, World Health Organisation.
- van den Hof, S., et al. (2010). "A systematic review on the role of gender in tuberculosis control." KNCV Tuberculosis Foundation.
- 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.
- van Hoorn, R., et al. (2016). "The Effects of Psycho-Emotional and Socio-Economic Support for Tuberculosis Patients on Treatment Adherence and Treatment Outcomes - A Systematic Review and Meta-Analysis." PLoS One **11**(4): e0154095.
- Vinkeles Melchers, N. V., et al. (2013). "State of affairs of tuberculosis in prison facilities: a systematic review of screening practices and recommendations for best TB control." PLoS One **8**(1): e53644.
- Weaver, M. S., et al. (2015). "Interventions to improve adherence to treatment for paediatric tuberculosis in low- and middle-income countries: a systematic review and meta-analysis." Bull World Health Organ **93**(10): 700-711B.
- Weiss, P., et al. (2014). "Treatment outcomes from community-based drug resistant tuberculosis treatment programs: a systematic review and meta-analysis." BMC Infect Dis **14**: 333.
- WHO (2011). Use of tuberculosis interferon-gamma release assays (IGRAs) in low- and middle-income countries: policy statement. Use of tuberculosis interferon-gamma release assays (IGRAs) in low- and middle-income countries: policy statement. Geneva; Switzerland, World Health Organization: 70-70.
- WHO (2012). "Systematic screening for active tuberculosis." report to WHO.
- Wikman-Jorgensen, P., et al. (2014). "Microscopic observation drug susceptibility assay for the diagnosis of TB and MDR-TB in HIV-infected patients: a systematic review and meta-analysis." Eur Respir J **44**(4): 973-984.
- Wilby, K. J., et al. (2014). "Review of evidence for measuring drug concentrations of first-line antitubercular agents in adults." Clin Pharmacokinet **53**(10): 873-890.
- Wisnivesky, J. P., et al. (2005). "Validity of clinical prediction rules for isolating inpatients with suspected tuberculosis. A systematic review." J Gen Intern Med **20**(10): 947-952.
- Wu, S., et al. (2017). "Evaluating the impact of healthcare provider training to improve tuberculosis management: a systematic review of methods and outcome indicators used." Int J Infect Dis **56**: 105-110.
- 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.
- Yin, J., et al. (2016). "Association between Directly Observed Therapy and Treatment Outcomes in Multidrug-Resistant Tuberculosis: A Systematic Review and Meta-Analysis." PLoS One **11**(3): e0150511.
- Zenner, D., et al. (2017). "Treatment of Latent Tuberculosis Infection: An Updated Network Meta-analysis." Ann Intern Med **167**(4): 248-255.
- Zenner, D., et al. (2017). "Effectiveness and cost-effectiveness of screening migrants for active tuberculosis and latent tuberculous infection." Int J Tuberc Lung Dis **21**(9): 965-976.
- Zenner, D., et al. (2013). "Active TB case finding strategies in high-risk groups in low-incidence countries." European Respiratory Journal **42**: no pagination.
- Zwerling, A., et al. (2012). "Interferon-gamma release assays for tuberculosis screening of healthcare workers: a systematic review." Thorax **67**(1): 62-70.