Effectiveness of interventions for reducing TB incidence in countries with low TB incidence: a systematic review of reviews

Simon M. Collin[1], Fatima Wurie[1], Morris C. Muzyamba[1], Gerard de Vries[2], Knut Lönnroth[3], Giovanni Battista Migliori[4], Ibrahim Abubakar[5], Sarah R. Anderson[1] and Dominik Zenner[5]

Affiliations: [1]TB Unit, National Infection Service, Public Health England, London, UK. [2]KNCV Tuberculosis Foundation, Den Haag, Netherlands. [3]Karolinska Institutet, Stockholm, Sweden. [4]Istituti Clinici Scientifici Maugeri IRCCS, Tradate, Italy. [5]UCL Institute for Global Health, London, UK.

Correspondence: Simon Collin, TB Unit, National Infection Service, Public Health England, London, NW9 5EQ, UK. E-mail: simon.collin@phe.gov.uk

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Whilst vaccination and treatment of latent TB infection are supported by review level evidence, there is a need for a stronger evidence base in other intervention areas to support decisions when formulating TB control policy in low-incidence countries. http://ow.ly/Y4vA50p4Hfv

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ABSTRACT

Aims: What is the evidence base for the effectiveness of interventions to reduce tuberculosis (TB) incidence in countries which have low TB incidence?

Methods: We conducted a systematic review of interventions for TB control and prevention relevant to low TB incidence settings (<10 cases per 100 000 population). Our analysis was stratified according to "direct" or "indirect" effects on TB incidence. Review quality was assessed using AMSTAR2 criteria. We summarised the strength of review level evidence for interventions as "sufficient", "tentative", "insufficient" or "no" using a framework based on the consistency of evidence within and between reviews.

Results: We found sufficient review level evidence for direct effects on TB incidence/case prevention of vaccination and treatment of latent TB infection. We also found sufficient evidence of beneficial indirect effects attributable to drug susceptibility testing and adverse indirect effects (measured as sub-optimal treatment outcomes) in relation to use of standardised first-line drug regimens for isoniazid-resistant TB and intermittent dosing regimens. We found insufficient review level evidence for direct or indirect effects of interventions in other areas, including screening, adherence, multidrug-resistant TB, and healthcare-associated infection.

Discussion: Our review has shown a need for stronger evidence to support expert opinion and country experience when formulating TB control policy.

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TABLE 1 Stratification of systematic reviews of interventions

Direct effect	Evidence that intervention has a direct effect in controlling or preventing TB, *i.e.* preventing cases or reducing incidence, reported as a primary or secondary outcome of the review
Indirect effect	No direct effect reported, but intervention has a plausible indirect effect in preventing TB cases or reducing TB incidence, for example *via* improvements in diagnosis, detection, treatment outcomes and reductions in transmission and resistance

TB: tuberculosis.

Introduction

Projected trends indicate that a substantial strengthening of efforts to reduce tuberculosis (TB) incidence is needed if the World Health Organization (WHO) End TB strategy is to be met in countries of low TB incidence [1]. Whilst frameworks to accelerate the reduction in TB incidence can be reached by expert consensus [2, 3], it is fundamental that these are underpinned by a robust and up-to-date evidence base for the effectiveness of specific interventions. Such an evidence base also allows for harmonisation of best-practice approaches to TB control between countries which have shared (or open) borders, such as across the European Union/European Economic Area (EU/EEA) [4–6].

Systematic reviews are a recognised method for compiling and assessing the findings of multiple systematic reviews into one accessible and usable summary of the evidence base [7, 8]. The objective of the present review was: 1) to identify systematic reviews of interventions to reduce TB incidence and prevent TB cases in settings of low TB incidence; 2) to assess the quality of the reviews in relation to direct and indirect effects of the interventions on TB incidence; and 3) to summarise the overall strength of evidence for each reviewed intervention. We focused on reviews of interventions for which reduction in TB incidence and prevention of TB cases was a measurable outcome, but our broad definition of "intervention" also encompassed approaches to TB diagnosis and treatment which could have an indirect impact on TB incidence. The overall aim of the review was to provide an evidence base to inform the development and implementation of national TB plans.

Methods

This systematic review was conducted as part of the European Commission funded E-DETECT TB (Early Detection and Integrated Management of Tuberculosis in Europe) project, which aims to improve TB control efforts across Europe through translational research designed to reach high-risk groups in EU/EEA countries, as well as the development of a practical evidence-based toolkit to support development and implementation of national TB plans [9, 10]. The review protocol was defined in advance and registered with PROSPERO (www.crd.york.ac.uk/prospero/ CRD42017060096).

Inclusion and exclusion criteria

Systematic reviews of interventions for TB control and prevention in settings of low TB incidence (<10 cases per 100 000 population) were eligible [11]. We defined "intervention" as any population level, public health or clinical (at primary, secondary or tertiary level) activity which prevents further cases of active TB or latent TB infection (LTBI), and which has the potential to reduce the incidence of TB at local, regional or national level. This broad definition of "intervention" would include: actions specifically designed for/ targeted at TB control/case prevention; clinical approaches, such as different diagnostic methods and drug regimens; areas of activity defined by particular patient groups, *e.g.* HIV co-infected, multidrug-resistant (MDR)-TB, vulnerable groups, pregnant women, or settings such as healthcare facilities and prisons; and areas of action defined by level of intervention, *e.g.* social and healthcare systems. Our analysis was stratified by type of effect, distinguishing reviews of interventions which reported a quantifiable "direct effect" from those which had an "indirect effect" on reducing TB incidence or preventing TB cases (table 1). Pre-specified reasons for excluding reviews were: not a systematic review; no intervention evaluated; no direct or indirect effect in preventing TB cases/reducing TB incidence; and economic evaluation only (see Appendix S2 for inclusion checklist). We did not exclude systematic reviews which included studies set in countries with high TB incidence if the review included at least one study in a low TB-incidence setting. As an adjunct to our main analysis, we included reviews of "risk factors" which could modify the effects of interventions or which, if targeted in a hypothetical intervention, could lead to a reduction in TB incidence. Our aim with regard to risk factors was to highlight possible future areas for intervention, particularly those which currently fall outside conventional TB-focused public health or clinical approaches to reducing TB incidence or which could reduce or enhance the effectiveness of conventional interventions.

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 and National Guideline Clearinghouse. In addition, the PROSPERO systematic reviews register and the *International Journal of Tuberculosis and Lung Disease* were searched within the same period. Full search strategies are shown in Appendix S1. In brief, we used a search filter developed by Lee *et al.* [12], combined with MeSH and title word terms for tuberculosis, mycobacterium and TB. To search databases of reviews, health evidence or guidelines, we simply used terms for tuberculosis/TB. No language or date restrictions were imposed.

Selection of reviews

Citations identified by the search were imported into EndNote (EndNote X8; Clarivate Analytics, Boston, MA, USA) for de-duplication, and then imported into to EPPI-Reviewer 4 (EPPI-Centre Software, Social Science Research Unit, UCL Institute of Education, London, UK) for further de-duplication and for screening. Two reviewers screened references by title and abstract, 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. The full texts of retrieved articles were screened for final inclusion independently and in parallel by two reviewers, 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.

Data extraction and management

The following data were extracted: bibliographic details (author, year, title); category (area of intervention); type of intervention; outcomes reported; number of included studies and/or participants; key findings; and authors' conclusions. Areas and types of intervention were not pre-defined, but emerged thematically and were rationalised during the screening process.

Assessment of methodological quality of the systematic reviews

Quality of included reviews was assessed using the AMSTAR2 tool, a 16-item measurement tool specifically used to assess systematic reviews that include randomised or non-randomised studies of healthcare interventions (or both) [13]. 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; and 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 <4 non-critical and no critical weaknesses, "moderate" if ⩾4 non-critical but no critical weaknesses, "low" if one critical weakness, and "very low" if ⩾2 critical weaknesses [14]. Reviews of "risk factors" were not assessed for methodological quality.

Data analysis

Included reviews (direct or indirect effects) were summarised descriptively by category (area) of intervention, including the number and type of primary studies (randomised controlled trials (RCTs) or "other" studies, meaning non-randomised and observational studies). Areas of intervention were not specified *a priori*, but emerged by inspection of the topics covered by the included reviews, with the aim of defining areas which had the least amount of overlap. Reviews were categorised into either high-quality "core" reviews (high confidence in the results of the review according to AMSTAR2 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 provided additional information to complement the core reviews. 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 consistency of evidence within and between reviews, and concluding statements made by the authors (table 2).

Results

We identified 11 578 references, including 1654 from MEDLINE, 2796 from EMBASE, 250 from CINAHL, 2949 from Scopus, 1059 from Global Health, 2040 from Trip, and 92 from Cochrane. Of these, 7499 were removed by de-duplication, leaving 4079 to be screened by title and abstract. Screening by title and

TABLE 2 Framework to classify review level evidence

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 cautious 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 review, 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

abstract eliminated 3813 references, leaving 266 references for full text review (figure 1). Of these, 187 were included, covering 13 areas of intervention (table 3) and comprising 45 reviews of interventions reporting a direct effect, 113 an indirect effect, and 29 describing risk or contextual factors (Appendix S3). Quality assessment rated direct effect (17 (37.8%) out of 45) and indirect effect (28 (24.8%) out of 113) reviews as high-quality core reviews (table 4 and Appendix S4). A full textual data synthesis for each category of intervention stratified by effect is provided in Appendix S5. The results below summarise the overall (review level) evidence in support of, or discounting, the effectiveness of interventions.

Sufficient review level evidence for direct or indirect effects of interventions

Vaccination

There was a sufficient level of evidence from systematic reviews to support the use of bacille Calmette–Guerin (BCG) vaccination, with evidence of protective effects against pulmonary and extrapulmonary TB of up to 10 years' duration. Vaccine efficacy varied by age and tuberculin sensitivity status at time of vaccination, and was greatest when comparing naïve individuals with naïve unvaccinated individuals. These results derived from four core reviews [15–18], the largest of which included 21 RCTs and 111 other studies, covering all age groups [15]. An update of this review, but restricted to neonatal and infant vaccination, found no additional studies [16]. These last two reviews recommended selective BCG vaccination, for example, of infants born to immigrants from high TB-incidence countries or close contacts of active TB cases, whilst acknowledging a lack of evidence for cost-effectiveness compared with universal vaccination.

Diagnosis

Diagnostic accuracy of TB diagnostic tests in different patient groups is increasingly well-characterised. There is insufficient review level evidence either to support or discount direct effects of interferon γ-release assays (IGRAs) compared with tuberculin skin test (TST) in predicting which cases of LTBI would progress to active TB, *i.e.* the two tests are similar in predictive value (high negative predictive value, low positive predictive value). There is sufficient review level evidence of indirect effects on TB incidence of performing molecular drug susceptibility testing. This assessment was based on three core reviews of molecular drug susceptibility testing: 1) a UK HTA review of GenoType MTBDRplus (isoniazid (INH) and rifampicin), INNO-LiPA Rif.TB (rifampicin) and Xpert MTB/RIF (rifampicin) [51]; 2) a Cochrane review of the Xpert MTB/RIF assay [54]; and 3) a review of three commercial line probe assays, Hain Genotype MTBDRplusV1, MTBDRplusV2 and Nipro NTM+MDRTB [52]. The conclusion of all three reviews was that molecular tests had high sensitivity and specificity (regardless of HIV status) for rifampicin and INH resistance, *e.g.* for rifampicin resistance detection Xpert MTB/RIF pooled sensitivity and specificity were 95% and 98%, respectively [54].

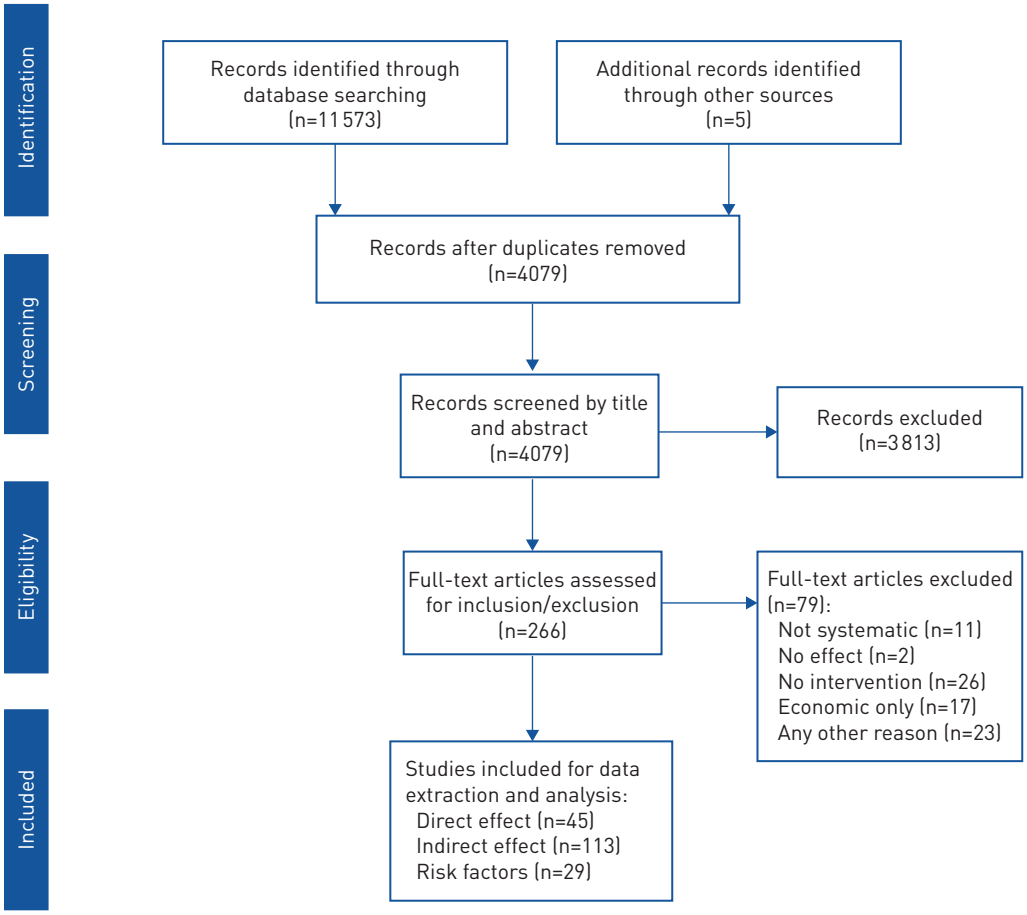

FIGURE 1 Study selection (PRISMA flow diagram).

Treatment

A sufficient level of evidence for the relative effectiveness of different drug regimens in treating LTBI to prevent progression to active TB was provided by four core reviews [63–66]. The largest and most recent was a network meta-analysis based on 61 RCTs covering all age groups, which found evidence for the efficacy and safety (compared to no treatment or placebo) of 6 months of INH monotherapy, 3–4 months of rifampicin monotherapy, and combination therapies with 3–4 months of INH and rifampicin, regardless of age and HIV status [66]. Sharma *et al.* [64] (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, probably with better treatment completion and fewer adverse events; and that shortened combined regimens of rifampicin with INH offered no advantage over longer INH regimens. 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 INH-resistant TB with standardised regimens of first-line drugs, and three times 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 changes to TB treatment regimens.

HIV/TB

There is sufficient review level evidence to support LTBI treatment and antiretroviral therapy (ART) to prevent active TB in people infected with HIV, although this evidence derives mainly from studies in low- or middle-income countries. Of the three core reviews: one reviewed LTBI treatment in HIV-positive adults based on 12 RCTs, finding a reduced risk of active TB comparing various anti-TB drug regimens with placebo, particularly among patients with a positive TST [115]; another review in HIV-positive

TABLE 3 Specific interventions evaluated by included reviews (not an exhaustive list)

Intervention area	Specific interventions evaluated by included reviews
Vaccination	BCG vaccination: universal or selective (contacts and high-risk groups)
Screening	Pre-, post- and point-of-arrival testing for active TB or LTBI in migrants
	Active case finding in primary care settings, and in high-risk and vulnerable population groups
Diagnosis	Diagnostic accuracy of TST *versus* IGRA
	Drug susceptibility testing
Treatment	Efficacy and safety of drug regimens for treating LTBI
	Therapeutic drug monitoring
	Nutritional supplementation
	Diabetes
Adherence	Directly observed treatment, incentives, lay healthcare workers and reminder systems
HIV/TB	Efficacy and safety of antiretroviral therapy for treating HIV and/or drug regimens for treating LTBI
	Diagnostic accuracy of TST *versus* IGRA
	Drug susceptibility testing
	Service integration
MDR-TB	Efficacy and safety of drug regimens for treating MDR-TB
	Efficacy and safety of drug regimens for preventing MDR-TB in contacts of MDR-TB cases
	Directly observed therapy and care models
Contacts and transmission	Contact investigation
	Whole genome sequencing
	Air travel
Healthcare-associated infection	Serial screening for TB in healthcare workers
	Clinical prediction rules
Social support and vulnerable groups	Socioeconomic and psychosocial support
	Reaching vulnerable groups
Healthcare systems	Integrated care models
	Scaling up
	Task shifting
Pregnancy and sex	Efficacy and safety of drug regimens for treating active TB, LTBI and MDR-TB
	Sex-specific approaches to TB diagnosis and treatment
Prisons	Isoniazid preventive therapy
Environment and behaviours	Smoking, second-hand tobacco smoke and indoor air pollution
	Alcohol

TB: tuberculosis; MDR-TB: multidrug-resistant TB; BCG: bacille Calmette–Guerin; LTBI: latent TB infection; TST: tuberculin skin test; IGRA: interferon γ-release assay.

children also reported a marked reduction in risk of active TB, but based on a single RCT [116]; and a review of ART for prevention of TB in adults based on three RCTs and eight other studies found a substantial reduction in TB incidence [117].

Insufficient review level evidence for direct or indirect effects of interventions

Screening

Whilst migrants from high TB incidence countries often have a higher prevalence of active and latent TB than the general population in low TB incidence countries, there was insufficient evidence from systematic reviews to either support or discount the effectiveness of different screening approaches to prevent TB cases, reducing TB incidence, reducing mortality or preventing transmission. Eight supplementary reviews of migrant screening (two reviewing pre-entry screening/follow-up [32, 34], one point-of-entry screening [42], four post-entry screening [33, 36–38] and one screening at all three points [45]) favoured pre- or post-entry screening of migrants from high TB-incidence countries (based mainly on case yield and risk of TB developing post-entry) compared with no screening, but none compared the effectiveness of different approaches or provided conclusive evidence of cost-effectiveness. All eight reviews stressed the need for comparative studies and improved longitudinal data collection.

TABLE 4 Studies included and excluded after full text review

Intervention area	Included reviews									Excluded reviews	Full text screen total
	Direct effects[#]				Indirect effects[#]				Risk factors		
	High	Moderate	Low	Very low	High	Moderate	Low	Very low			
Vaccination	4 [15–18]	0	1 [19]	8 [20–27]	0	0	0	0	0	4	17
Screening	0	0	3 [28–30]	0	1 [31]	0	4 [32–35]	10 [36–45]	0	11	30
Diagnosis	1 [46]	0	0	1 [47]	7 [48–54]	0	5 [55–59]	3 [60–62]	0	4	22
Treatment	4 [63–66]	1 [67]	0	3 [68–70]	9 [71–79]	0	4 [80–83]	4 [84–87]	2 [88, 89]	10	36
Adherence	1 [90]	0	0	0	8 [91–98]	0	2 [99–101]	12 [102–113]	1 [114]	5	30
HIV/TB	3 [115–117]	0	2 [118, 119]	4 [120–123]	1 [124]	0	2 [125, 126]	3 [127–129]	0	7	22
Multidrug-resistant TB	3 [130–132]	0	0	1 [133]	0	0	3 [134–136]	14 [137–150]	0	9	30
Contacts and transmission	0	0	0	0	0	1 [151]	2 [152, 153]	3 [154–156]	3 [157–159]	4	13
Healthcare-associated infection	0	0	0	1 [160]	1 [161]	0	1 [162]	4 [163–166]	4 [167–170]	9	17
Social support and vulnerable groups	1 [171]	0	0	1 [172]	1 [173]	0	0	1 [174]	0	1	5
Healthcare systems	0	0	0	0	0	0	1 [175]	4 [176–179]	2 [180, 181]	12	19
Pregnancy and sex	0	0	0	1 [182]	0	0	0	0	5 [183–187]	1	7
Prisons	0	0	0	1 [188]	0	0	0	1 [189]	1 [190]	1	4
Environment and behaviours	0	0	0	0	0	0	0	0	11 [191–201]	1	13
Subtotals	17	1	6	21	28	1	25	59	29	79	266

Direct effect: evidence that intervention has a direct effect in preventing cases or reducing incidence, reported as a primary or secondary outcome measure of the review; indirect effect: intervention has a plausible indirect effect in preventing tuberculosis (TB) cases or reducing TB incidence, regardless of the outcome measures reported in the review; risk factors: no intervention was evaluated but the review described risk (or contextual) factors which could modify the effects of interventions or which, if targeted in a hypothetical intervention, could lead to a reduction in TB incidence. [#]: the AMSTAR2 criteria were used to categorise the included reviews as either "core" reviews (providing an evidence base for interventions) of high quality or "supplementary" reviews (providing additional information) of moderate, low or very low quality.

Adherence

There is insufficient review level evidence, particularly in high-income/low TB-incidence countries, to support or discount direct or indirect effects of treatment adherence interventions to reduce the incidence of active TB, including directly observed treatment (DOT), incentives, lay healthcare workers (HCWs) or reminder systems. Interventions to improve TB treatment adherence must address a host of complex and interacting barriers and facilitators. This assessment was based on nine core reviews, one relating to direct effects [90] and eight relating to indirect effects [91–98]. M'Imunya *et al.* [90] reviewed studies of patient education and counselling for promoting adherence to TB treatment, finding three trials which reported LTBI treatment completion rates (children in Spain, adolescents in the USA, and prisoners in the USA). Although incidence of active TB was a stated outcome of the review, no studies were identified which measured progression to active TB. There were two core reviews of DOT [91, 97]. The Cochrane review authors [91] 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 two out of 11 included studies were set in high-income countries (USA and Australia). A core review of incentive-based approaches [94] 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 insufficient evidence to know if they can improve long-term adherence to TB treatment.

MDR-TB

Pooled analysis indicates overall treatment success rates of 26% and 60% for extensively drug-resistant (XDR)- and MDR-TB patients, respectively [139]. No core reviews were found in relation to approaches to MDR-TB treatment (*e.g.* drug regimens). Some of the supplementary reviews of drug regimens made specific recommendations, *e.g.* linezolid for the treatment of XDR-TB or fluoroquinolone-resistant MDR-TB [135] and six- and four-drug combinations in the intensive and continuation phases of XDR-TB treatment [141], but the common conclusion was the urgent need for more RCTs of MDR- and XDR-TB treatments. Three core reviews were identified in relation to preventive treatments for contacts of MDR-TB cases, two of which found no evidence of effectiveness [130, 132]; a third was focused on adverse events, finding no evidence of these [131]. Overall, there is insufficient review level evidence for effects of interventions on MDR-TB incidence in MDR-TB cases or contacts.

Contacts and transmission

No core reviews were identified, and there is insufficient review level evidence from supplementary reviews for specific interventions to improve contact investigation, in terms of direct or indirect effects on TB incidence. The supplementary reviews recommend pragmatic actions such as investigating contacts of MDR-TB cases, and LTBI treatment for child or HIV-positive contacts of active TB cases [152, 154–156], or describing potential benefits of whole genome sequencing to support epidemiological investigations [151, 153]. Two reviews of TB in relation to air travel indicated a low risk of transmission in airplanes [157, 159].

Healthcare-associated infection

There is insufficient review level evidence for TB-specific interventions for HCWs or infection control in healthcare settings, although this reflects a lack of systematic reviews in this area particularly in high-income countries. There were three supplementary reviews on TB screening in HCWs [164–166]. Lamberti *et al.* [164] 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.* [166] commented that use of IGRAs for serial testing in HCWs is complicated by lack of data on optimum cut-offs. Two supplementary reviews analysed clinical prediction rules for respiratory isolation of patients with presumptive pulmonary TB [162, 163], both reviews indicated that clinical prediction rules tend to have high sensitivity but low specificity, with inconclusive evidence for their utility in low TB-incidence settings.

Social support and vulnerable groups

There is insufficient review level evidence to support or discount the effectiveness of TB-specific social support interventions or interventions in vulnerable groups. One core review by Heuvelings *et al.* [171] was identified, which reviewed a wide range of interventions for diagnosis and treatment of TB in hard-to-reach populations. This review extended and updated two earlier reviews by the UK National Institute for Health and Care Excellence (NICE) [202, 203]. Of the 44 included primary studies, three had reduction of TB incidence or number of TB cases prevented as outcomes; two of these studies were included in other systematic reviews that we have reviewed under "screening". The remaining study was a non-randomised study of a social and healthcare 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 [204]. A core review of psychosocial and socioeconomic support found that these appeared to improve treatment outcomes across a variety of settings and patient populations, but the authors rated the quality of the primary studies as very low [173].

Healthcare systems

There is insufficient review level evidence to support or discount the effectiveness of TB-specific interventions at the level of healthcare systems in high-/low-incidence countries. Four of the five supplementary reviews focused mainly on healthcare system interventions in low and middle-income countries, including mixed public–private approaches [177], task-shifting (*e.g.* of treatment supervision to community health workers, laypersons or family [178]), scaling-up of TB interventions such as isoniazid preventive therapy, clinical algorithms and second-line treatment [176], and best practice in evaluating specialist HCW training [179]. The fifth supplementary review comprised six separate reviews commissioned to inform UK NICE guidelines for TB [175], including a review of information and education interventions for service providers which concluded that intensive interventions integrating clinician education with other components such as reminders, process improvement and incentives could be effective in improving service delivery outcomes, particularly TB screening.

Pregnancy

There is insufficient review level evidence for direct or indirect effects of specific interventions relating to TB during pregnancy. One supplementary review of 35 non-randomised studies included two which investigated treatment of LTBI with INH during pregnancy (neither reported progression to active TB as an outcome), 14 reported treatment of active TB and four reported treatment of MDR-TB [182]. The authors highlighted delays in diagnosing and treating TB during pregnancy, poor adherence to INH preventive therapy (and a possible elevated risk of INH toxic hepatitis), but the reviewed studies showed no association between child abnormality and mother's exposure to first- or second-line anti-TB drugs.

Prisons

TB incidence is often higher in correctional facilities than in the general population, 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. One supplementary review of studies of INH preventive therapy in prisons identified four studies which reported TB incidence as an outcome [188]. The review was of very low quality, and no conclusion could be drawn regarding the effectiveness of LTBI treatment regimens in prison settings. A supplementary review identified limited accuracy of diagnostic algorithms and lack of adequate laboratory facilities as key limitations for TB control programmes in prisons [189].

Environment and behaviours

Whilst plausible associations of smoking and heavy alcohol consumption and, to a lesser extent, second-hand tobacco smoke and indoor air pollution with TB were supported by a number of reviews [191–201], there is as yet no review level evidence to support either the incorporation of smoking- or alcohol-related interventions into programmes for TB control and prevention or to address these factors in relation to treatment outcomes.

Discussion

Our review focused on interventions for which reduction in TB incidence and prevention of TB cases was a directly measurable outcome, or could be inferred indirectly from another reported outcome, based on evidence from systematic reviews. Clearly, we recognise the basic obligation to provide TB patients with high-quality evidence-based clinical care that reduces suffering and mortality, and to make this standard of care accessible to everyone. From this point of departure, our review identified two interventions supported by sufficient review level evidence of direct effects in reducing TB incidence and preventing TB cases, namely BCG vaccination and treatment of LTBI to prevent progression to active TB.

The insufficient review level evidence of direct effects in other intervention areas is a consequence of two related factors: 1) the lack of good quality primary studies; and 2) the lack of good quality systematic reviews. The first of these may be because policymakers perceive no added value in testing interventions which, by simple logic, should have a beneficial impact (or where effectiveness, *e.g.* of drug regimens for uncomplicated TB, is not disputed). Such testing may be unethical or would require RCTs of complex interventions at large enough scale and of sufficient duration to detect an effect on TB incidence. The second factor follows from the first or, where experimental evidence is available, reflects the difficulty of synthesising evidence with substantial heterogeneity in settings, interventions and outcomes. In the

absence of a comprehensive, consistent and robust review level evidence base, the choice of interventions for TB control plans and programmes will continue to be pragmatic, at best supported by evidence from individual studies, but otherwise based on local TB epidemiology, expert opinion and accumulated national and international experience.

One of the main challenges to building an evidence base in TB control and prevention at national level is the interconnectedness of interventions along the "cascade of care" from detection of TB through to successful completion of treatment [181]. This implies that interventions need to be evaluated in a joined-up rather than standalone manner. Also, the biggest impact on TB incidence over time has come from societal, socioeconomic and wider healthcare improvements, which are beyond the remit of a TB control plan. These changing factors, together with non-static populations, preclude before-and-after studies as an unbiased method for evaluating TB-specific interventions [205]. Without substantial investment to strengthen the evidence base, the pragmatic alternative is to accept that "good" interventions may not be supported by "hard" evidence, and to trust that implementing a range of common-sense interventions, alongside population-level improvements in social determinants and risk factors and continual improvements in the effectiveness and quality of clinical care, will eventually lead to elimination of TB. A persuasive counter-argument can be made that interventions deemed to be "good" even by the application of logic may not be as effective as thought, or could be made more effective, hence why more investment in research is essential. This research may require methodological innovation, such as using a factorial trial design to add interventions, *e.g.* screening and reminder systems, to an optimised programme of diagnosis and treatment, and measuring transmission (using molecular methods) as an outcome [206].

Our findings in context

Vaccination

We reported sufficient evidence of protection against TB by BCG vaccination from four reviews. These indicate that an important role remains for vaccination targeted at high-risk groups who are most likely to benefit because of higher risk of exposure, with recent research suggesting >15 years' duration of protection by BCG [207, 208]. Although RCT evidence for the use of BCG in high-risk groups is unlikely to be forthcoming for ethical reasons, TB control programmes should probably adopt this approach whilst the search for a new and more effective TB vaccine continues [209].

Diagnosis and treatment

Perhaps unsurprisingly, these two areas accounted for the highest number of high-quality core reviews (21 out of 45 core reviews in total; eight in diagnostics, 13 in treatment). This reflects the relative ease with which comparative clinical studies of diagnostic methods and treatment regimens can be designed, conducted and systematically reviewed, compared with evaluations of complex interventions. Clinical studies tend to capture outcomes such as treatment success and diagnostic accuracy, hence the majority were categorised as having indirect effects on TB incidence that were not quantified as an outcome of the included systematic review. Translating outcomes such as treatment efficacy into effects on TB incidence is an area where modelling can be of some use [210]. That we found review level evidence for direct effects on TB incidence of LTBI treatment and indirect effects of DST and sub-optimal treatment highlights the importance of continuing to build a high-quality evidence base to support best practice in clinical care, and of continuing to develop more accurate diagnostic tests and more efficacious and safer drugs.

Screening and LTBI

We found that evidence for the efficacy of LTBI treatment in contacts and persons with certain comorbidities is robust, whilst evidence for LTBI screening, especially population-based programmes, is much weaker. This lack of evidence is particularly important in view of south–north migration [211–214]. The recent push towards TB elimination in low-incidence countries in keeping with the ambitious End TB Strategy has increased interest in systematic LTBI screening and treatment, because most TB disease in these countries is a result of LTBI reactivation. It is worth noting that WHO issued strong recommendations for LTBI treatment of persons with certain comorbidities, such as underlying immunosuppressive diseases or medications, whilst only issuing conditional recommendations for wider screening of migrants from high-incidence countries [215]. The trade-off and tension between provision of LTBI treatment to only a few high-risk patients who have high likelihood of individual benefit from treatment, but with little or no effect on country-level incidence, *versus* provision of screening to a larger group at lower risk (such as migrants) with lower expected individual benefit but higher likelihood of reducing population-level incidence, remains unresolved. Ultimately, national TB strategic planning must base decisions about screening programmes on context, cost considerations and local TB epidemiology, including the rate of MDR TB, for which LTBI treatment is still in its infancy.

Adherence

Many variants on interventions to improve treatment adherence have been evaluated, particularly in higher TB burden settings. Recent WHO guidelines [216] recommend that treatment should be based on an assessment of individual patients' needs, providers' resources and conditions for implementation. The paucity of review level evidence for direct effects on reducing the incidence of active TB in low-incidence countries suggests the need for evaluation studies that can account for the complex and intersecting determinants of poor adherence, which can vary both within an individual and over the course of treatment. Under the auspices of the End TB Strategy there is a need to intensify efforts to design and test public health interventions that explicitly target modifiable social and behavioural determinants of adherence, thereby supporting high-risk groups in accessing and engaging with patient-centred care.

Strengths and limitations

The main strength of our study is the consistent methodology applied to all reviewed systematic reviews, covering a wide range of interventions. We applied rigorous quality assessment criteria, the results of which are consistent with an earlier assessment of the quality of systematic reviews on TB [217]. The main limitation of a "review of reviews" approach is that evidence from primary studies will not be assessed if those studies have not been systematically reviewed. Where studies have been reviewed, some "detail" may be lost because we are synthesising evidence which has already been synthesised. We did report some pertinent details from individual studies included in systematic reviews, where these primary studies provided the only evidence for a particular intervention, but unreplicated single-study evidence must be interpreted with caution. It has also been argued that systematic reviews may fail to capture effects of complex interventions, such as DOT, particularly where simplified outcome measures are used [218]. This is an area where qualitative systematic reviews could potentially contribute to evidence of effectiveness. Where we found sufficient evidence for effects of interventions on TB incidence, we did not attempt to quantify the magnitude of these effects. For example, BCG vaccination of infants in high-risk groups will have little impact on overall TB incidence and case numbers in low-incidence countries because children represent a small proportion of TB cases. As a public health intervention in low-incidence countries, BCG will be more effective in preventing life-threatening paediatric TB cases, *e.g.* meningitis, than in reducing overall TB incidence.

Implications of our findings for TB control plans and strategies

The objective of our review was to synthesise an evidence base for the effectiveness of interventions for TB control and prevention in low-incidence settings. Our aim was to use this evidence to inform the development of a TB Strategy Toolkit for EU/EEA countries, which will include guidance on the prioritisation of interventions within national TB control plans. The toolkit will be developed through a consensus approach, incorporating other types of evidence including a survey of current practices and priorities in EU/EEA countries [6], qualitative reviews of barriers and enablers to TB control [219, 220], current international standards, and WHO and ECDC guidelines [221]. This consensus process will address questions such as how to link national TB plans, which need to focus on strategic choices around interventions to reduce the overall burden of TB in the population, with continually evolving guidelines and evidence around best practice in TB patient care. Our review has shown the need for more evidence to support expert opinion and to support local experience when making policy decisions in TB control and prevention.

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