Evidence reviews to support the update of NICE guidance on Tuberculosis: clinical diagnosis and management of tuberculosis and measures for its prevention and control

Review 1a: Effectiveness and cost-effectiveness of strategies to increase the uptake of BCG vaccination among people at increased risk of developing active or latent TB

FINAL REPORT

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Theo Lorenc, Elizabeth Tyner, Chris Cooper

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Declaration of authors' competing interests

No authors have any competing interests.

Abbreviations used in the report

BA	before-after (study)
BCG	Bacillus Calmette-Guérin
CI	confidence interval
CPH	Centre for Public Health [at NICE]
ITS	interrupted time series
NA	not applicable
NICE	National Institute for Health and Care Excellence
NR	not reported
OECD	Organisation for Economic Co-operation and Development
QA	quality assessment
RCT	randomised controlled trial
TB	tuberculosis

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1 Executive summary

This report presents the findings of a systematic review commissioned by the NICE Centre for Public Health to support the development of updated guidance on tuberculosis. The review question is:

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

We searched a range of database sources, including both health and non-health databases, from 1993 to 2013. We included any outcome evaluation study which measured BCG uptake as an outcome and was conducted in a high-income (OECD) country. Quality assessment and data extraction were carried out using standardised forms from the NICE methods manual. Data were synthesized narratively.

Eight studies were included in the review. One study was graded as high quality (++), and the other seven as low quality (–). Six studies were conducted in the UK, one in Sweden and one in Turkey. The findings of the studies are summarised in the evidence statements below.

Evidence statement 1: Staff training

There is evidence from six studies (four UK and two from other countries) that interventions involving staff training may increase the uptake of BCG vaccination. One RCT (Griffiths et al., 2007 (++)) shows significantly higher uptake in the intervention group, with an odds ratio of 9.52 (95% CI 4.0–22.7). Five BA studies showed some increase in uptake (Athavale et al., 2006 (–); Gill and Scott, 1998 (–); Romanus, 2005 (–); Tseng et al., 1997 (–); Uskun et al., 2008 (–)), although in only two cases was statistical significance measured, and in neither of these did the increase reach significance (Tseng et al., 1997 (–); Uskun et al., 2008 (–)). The RCT involved 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. The BA studies generally focused mainly on staff training and did not use incentives.

Applicability

Most evidence is applicable to BCG vaccination in the UK. Four studies in this category (Athavale et al., 2006 (–); Gill and Scott, 1998 (–); Griffiths et al., 2007 (++); Tseng et al., 1997 (–)) were carried out in the UK, and one (Romanus, 2005 (–)) in Sweden, which has broadly similar patterns of TB infection and BCG policy to the UK. One study (Uskun et al., 2008 (–)) was carried out in Turkey, which has a policy of universal neonatal BCG vaccination, and may be less applicable.

Evidence statement 2: Reminders to clinical staff

One BA study (Chappel and Fernandes, 1996 (–)) appears to show that computerised reminders to hospital staff can increase the uptake of BCG vaccination. However, the data are difficult to interpret as the criteria for eligibility for BCG were defined differently at pre- and post-test.

Applicability

This evidence is directly applicable to BCG vaccination in the UK as the study was conducted in the UK.

Evidence statement 3: Contact tracing interventions

There is inconclusive evidence from one BA study (Ansari et al., 1998 (–)) as to whether revised contact tracing protocols can increase the uptake of BCG vaccination.

Applicability

This evidence is directly applicable to BCG vaccination in the UK as the study was conducted in the UK.

2 Background

Current UK guidance on vaccination for tuberculosis (TB)[1] recommends that Bacillus Calmette-Guérin (BCG) vaccine should be offered to the following groups:

- infants living in high-prevalence areas of the UK (annual incidence ≥40/100,000);
- infants and children up to 16 years with a parent or grandparent born in a high-prevalence country;
- children up to 16 years who are contacts of cases of respiratory TB;
- children up to 16 years who were born in or have lived for at least three months in a high-prevalence country;
- healthcare workers and laboratory staff who will have contact with patients or clinical materials;
- veterinary and staff such as abattoir workers who handle animal species known to be susceptible to TB, e.g. simians;
- staff of prisons, care homes for the elderly, hostels for homeless people and facilities accommodating refugees and asylum seekers.

This policy has been in place since 2005. Prior to that date, there was a universal programme of BCG vaccination for adolescents, in addition to selective vaccination for neonates and contacts of TB cases along similar lines to the post-2005 policy.

A range of strategies may be employed to increase the uptake of BCG vaccination among relevant groups. The aim of this review is to synthesize evidence from outcome evaluation studies about the effectiveness of interventions to increase BCG uptake. This review is supplemented by the review of reviews produced for the same phase of this project, which synthesizes review-level evidence on interventions to increase the uptake of vaccination in general.

3 Methods

This review was conducted according to the methods guidance set out in the current (third) edition of *Methods for the development of NICE public health guidance.*

3.1 Review question

The review question is:

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

3.2 Searching

3.2.1 Database searches

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

A comprehensive search strategy was developed in consultation with the CPH team and the Guideline Development Group. The following database sources were searched in July 2013. The searches were limited from 1993 to the most recent records (with the exception of SCI, SSCI and Conference Proceedings Citation Index, which were run from 2011-current to access recent grey literature and conference proceedings).

- ASSIA
- British Education Index
- British Nursing Index
- CINAHL
- Cochrane Library
- Conference Proceedings Citation Index
- Embase
- ERIC
- HMIC
- Medline
- Medline In Process
- NCJRS
- OpenGrey
- PsycINFO
- Science Citation Abstracts
- Social Policy and Practice
- Sociological Abstracts

The search strategy took the following form:

(TB) AND (BCG) AND (terms for uptake OR terms for specific intervention types, personnel or settings OR terms for effectiveness study methods)

A filter was used to exclude studies on animals. No language restriction was placed on the searches (although in subsequent screening, non-English-language references were excluded). The full database search records can be found in Appendix 1.

3.2.2 Other searches

We searched the following websites for unpublished data:

- NICE via www.nice.org.uk
- Public Health Observatory via www.apho.org.uk
- Public Health England via www.gov.uk/government/organisations/public-health-england

We searched Google using a simplified version of the search string used for the database searches and scanned the first 100 results. We searched PubMed using a time-limited search to identify any new items. We chased citations from all items included on full text, and conducted forward citation chasing on Web of Science. We also searched the British Library's Ethos database (http://ethos.bl.uk/) using a simplified search string to identify unpublished theses.

3.3 Screening

EPPI-Reviewer 4 software was used to manage data. The following inclusion criteria were applied:

1) Is the study an outcome evaluation of an intervention? (To be included here a study had to: (a) involve some intervention (of any kind, e.g. including practice changes, strategies, protocols etc.); and (b) report at least some pre- and post-test outcome data (or use random assignment to intervention and comparison groups), i.e. trials, one-group before-after studies, and retrospective or observational studies which reported clear pre and post data were included.)

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

3) Was the study conducted in a high-income country (current OECD member)? [2]

4) Is the study report in English?

5) Was the study report published in 1993 or later?

An initial random sample of 10% of titles and abstracts was screened by two reviewers independently, with differences resolved by discussion. Agreement at this stage was 99.2%, with kappa = 0.85. On the basis of this agreement, subsequent titles and abstracts were screened by one reviewer alone. The full text of all references which met criteria, or where it was unclear if they met the criteria, was retrieved and re-screened to the same criteria by two reviewers independently, with differences resolved by discussion.

3.4 Quality assessment, data extraction and synthesis

Review quality was assessed, and data extracted, using the tools in the methods manual (NICE, 2012). Quality assessment and data extraction were conducted by one reviewer and checked in detail by a second reviewer. Data were synthesized narratively.

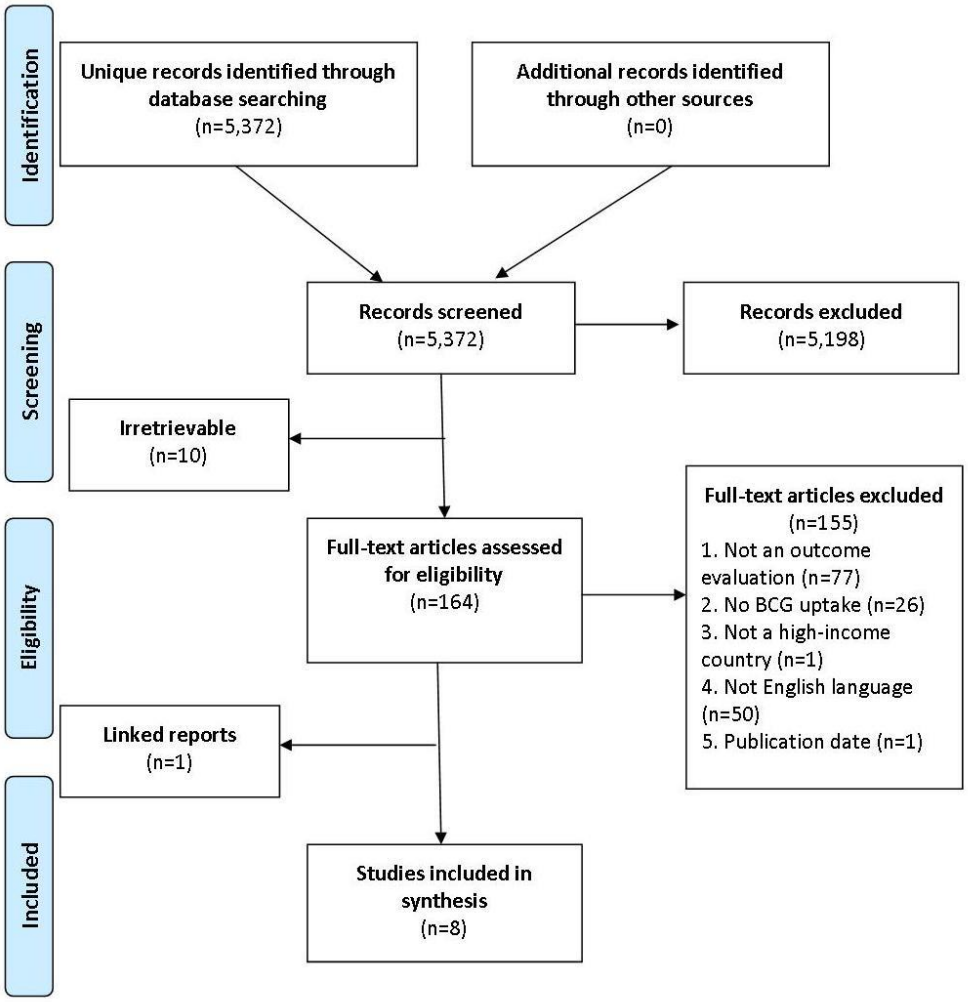
4 Results

4.1 Flow of literature through the review

Eight studies were included. Figure 1 shows the flow of literature through the review.

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

Figure 1. Flow of literature through the review



4.2 Results of quality assessment

The QA tool (NICE, 2012) rates each study on a number of domains and gives an overall rating (high, medium or low) to each study on internal and external validity. With one exception, all studies received a low internal validity rating, largely due to poor reporting of methods, and the use of non-comparative designs. Five studies received medium external validity ratings (although this was interpreted liberally, to include any study providing more than minimal information about its context or population), two low and one high. Table 1 provides a summary of the QA results.

Table 1. Quality of the included studies

		Population			Method of allocation to intervention/comparison										Outcomes						Analysis						Summary	
	Design	1.1	1.2	1.3	2.1	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	2.10	3.1	3.2	3.3	3.4	3.5	3.6	4.1	4.2	4.3	4.4	4.5	4.6	5.1	5.2
Ansari 1998	BA	+	+	–	NA	+	NA	NA	–	NA	NA	NA	++	+	+	+	+	+	NA	+	NA	NA	NR	–	–	NA	–	+
Athavale 2006	BA	+	+	–	NA	+	NA	NA	–	NA	NA	NA	++	++	+	+	+	++	NA	++	NA	NA	NR	NR	–	NA	–	+
Chappel 1996	BA	–	+	–	NA	+	NA	NA	–	NA	NA	NA	++	+	–	+	+	++	NA	++	NA	NA	NR	–	+	NA	–	–
Gill 1998	BA	+	+	+	NA	+	NA	NA	–	NA	NA	NA	++	+	–	+	+	++	NA	++	NA	NA	NR	NR	–	NA	–	+
Griffiths 2007	RCT	+	+	+	++	++	++	+	+	NR	++	++	++	++	+	+	++	++	+	+	++	++	++	++	++	++	++	++
Romanus 2006	BA	+	+	++	NA	–	NA	NA	–	NA	NA	NA	+	+	+	+	+	++	NA	++	NA	NA	NR	NR	–	NR	–	+
Tseng 1997	BA	+	++	–	NA	–	NA	NA	–	NA	NA	NA	++	++	+	+	+	++	NA	+	NA	NA	NR	+	+	+	–	–
Uskun 2008	BA	+	–	–	NA	+	NA	NA	++	NA	NA	NA	–	+	+	+	++	++	NA	+	NA	NA	NR	+	–	+	–	+

Key to questions:

1.1 Is the source population or source area well described?
1.2 Is the eligible population or area representative of the source population or area?
1.3 Do the selected participants or areas represent the eligible population or area?
2.1 Allocation to intervention (or comparison). How was selection bias minimised?
2.2 Were interventions (and comparisons) well described and appropriate?
2.3 Was the allocation concealed?
2.4 Were participants and/or investigators blind to exposure and comparison?

2.5 Was the exposure to the intervention and comparison adequate?
2.6 Was contamination acceptably low?
2.7 Were other interventions similar in both groups?
2.8 Were all participants accounted for at study conclusion?
2.9 Did the setting reflect usual UK practice?
2.10 Did the intervention or control comparison reflect usual UK practice?
3.1 Were outcome measures reliable?
3.2 Were all outcome measurements complete?
3.3 Were all important outcomes assessed?
3.4 Were outcomes relevant?
3.5 Were there similar follow-up times in exposure and comparison groups?
3.6 Was follow-up time meaningful?
4.1 Were exposure and comparison groups similar at baseline? If not, were these adjusted?
4.2 Was Intention to Treat (ITT) analysis conducted?
4.3 Was the study sufficiently powered to detect an intervention effect (if one exists)?
4.4 Were the estimates of effect size given or calculable?
4.5 Were the analytical methods appropriate?
4.6 Was the precision of intervention effects given or calculable? Were they meaningful?
5.1 Are the study results internally valid? (i.e. unbiased)
5.2 Are the study results generalisable to the source population? (i.e. externally valid)

Key to sections 1-4:
++ The study has been designed/conducted in such a way as to minimise the risk of bias
+ Either the answer to the checklist question is not clear from the way the study is reported, or the study may not have addressed all potential sources of bias
- Significant sources of bias may persist
NR The study fails to report this particular question
NA Not applicable given the study design

Key to section 5:
++ All or most of the checklist criteria have been fulfilled; where they have not been, the conclusions are very unlikely to alter
+ Some of the checklist criteria have been fulfilled, where they have not, or not adequately described, the conclusions are unlikely to alter
- Few or no checklist criteria have been fulfilled and the conclusions are likely to alter

4.3 Characteristics of the included studies

Full details of the included studies are given in the evidence tables in Appendix 2. Table 2 shows in which country the studies were conducted, and gives a brief summary of the interventions, populations and settings investigated in the studies.

Table 2. Characteristics of the studies

First author, year	Design	Country	Setting	BCG population	Intervention	QA rating
Ansari et al., 1998	BA	UK	TB clinic	Contacts of cases	Revised protocol for TB contact screening: contacts discharged or referred to chest clinic after initial screening	–
Athavale et al., 2006	BA	UK	Maternity ward	Neonates	Staff training to offer BCG vaccination to neonates at risk of TB; reminders to mothers; promotion of BCG incorporated in pre-discharge neonatal examination	–
Chappel and Fernandes, 1996	BA	UK	Maternity ward	Neonates	Computer reminders to obstetric staff, with details of BCG eligibility	–
Gill and Scott, 1998	BA	UK	Antenatal clinic and maternity ward	Neonates	Training for health visitors and midwives to offer BCG vaccination; at-risk mothers identified at antenatal visits, given information about BCG and asked for consent to vaccination; primary responsibility for vaccination shifted from community medical officers to health visitors /	–

					midwives	
Griffiths et al., 2007	RCT	UK	Primary care	General population (London)	Staff training (based on social influence theory) – educational visits to practices by research GP and nurse to promote TB screening and raise awareness of guidelines; computer reminders incorporated into practice systems; telephone support from nurse; financial incentives for practices	++
Romanus, 2006	BA	Sweden	Child health centres	Neonates	Information to nurses about change from universal to selective vaccination and definitions for BCG eligibility	–
Tseng et al., 1997	BA	UK	Primary care; health visitor service	Neonates	Health visitors trained to identify and refer at-risk children; leaflets about BCG for parents and health professionals	–
Uskun et al., 2008	BA	Turkey	Primary care	Neonates	Training for primary healthcare workers, including information about vaccination, vaccination schedules, monitoring and recording; training sessions lasted 3 days and attendance was compulsory	–

4.4 Study findings

As can be seen from the summaries above, only one study (Griffiths et al., 2007 (++)) used any kind of comparative design; this study was a high-quality study which used a prospective, cluster randomised controlled trial design. The other seven studies, which have been described as 'before-after' studies in the tables, generally used retrospective methods to analyse impacts of changes in policy at the level of particular practices (many also had very substantial limitations in design and reporting).

Most studies (Athavale et al., 2006 (–); Gill and Scott, 1998 (–); Griffiths et al., 2007 (++); Romanus, 2005 (–); Tseng et al., 1997 (–); Uskun et al., 2008 (–)) concerned interventions with a substantial component of staff training. These have been counted as 'staff training interventions' below (although several interventions also contain other components). The intervention in one study (Chappel and Fernandes, 1996 (–)) has been categorised as 'reminders', and the final one (Ansari et al., 1998 (–)) as 'screening policy change'.

4.4.1 Staff training interventions

Comparative study

Griffiths et al. (2007 (++)) is considered first in this section, as it was the only comparative study; non-comparative studies are considered further below. Griffiths et al. (2007 (++)) evaluated an intervention in primary care in Hackney, London, an ethnically mixed and socio-economically deprived area. The study design used was a cluster-randomised controlled trial, with randomisation at the level of GP practices. A total of 50 practices were included at baseline, with outcomes measured on all new patients registering with those practices over a two-year period (a total sample of N=93,970), although data on the BCG uptake outcome were available only for 43 practices. The included population was ethnically mixed (approx. 43% white, 23% black, 10% Asian), and included a substantial number of new immigrants (approx. 260 per practice registered over the 2 year study period). However, outcome measures were not disaggregated by group.

The main goal of the intervention was to promote screening for TB, rather than BCG uptake alone. A specialist nurse and researcher GP carried out educational visits to intervention practices to promote TB screening and raise awareness of guidelines, and made a follow-up phone call after the visit (on-going telephone support was also available). This component of the intervention was based on the social influence theory of behaviour change. Reminders were also incorporated into intervention practices' computer systems. Practices were also provided with equipment for TB testing and financial incentives for carrying out tests (£7 each).

The relevant outcome for this review was BCG coverage in people aged 5 years or older (although it is not entirely clear whether this refers to total coverage in the population or new vaccinations carried out; it would appear the latter). Over the period of the study, BCG coverage was 2.68% in patients of intervention practices (N of practices = 22), and 0.38% in patients of control practices (N=21), giving an odds ratio of 9.52 (95% CI 4.0–22.7).

This was a methodologically robust study, with appropriate checks in place to reduce bias. It found that a staff training intervention had the effect of increasing BCG uptake rates in an ethnically mixed population. However, the study has some limitations for the purposes of this review. The intervention did not mainly focus on increasing BCG uptake, and detailed data for this outcome were

not provided in the report. In addition, the intervention had a number of components, including practice-level incentives as well as training and support, and it is unclear which components may have made the greatest contribution to the success of the intervention.

Non-comparative studies

The findings from the observational studies are considerably less reliable from a methodological perspective, since they do not include control groups, and hence any change in outcome cannot be securely attributed to the intervention. This type of study may, however, provide some useful indicative evidence of the possible effects of interventions in real-life settings, withstanding some of the limitations of these studies as described below.

Athavale et al. (2009 (–)) evaluated an intervention in a maternity hospital in Glasgow serving a deprived population with a substantial proportion of immigrants (full demographic detail was not reported). The study used a retrospective before-after design. The intervention involved training staff to identify neonates at risk of TB, and recommending BCG to eligible mothers as part of the routine pre-discharge examination; a specialist vaccination clinic was also set up in the hospital outpatient area. Baseline measures in this study found a low uptake of BCG (N=5 over 1 year, percentage not reported). After the intervention, 606 infants were identified as eligible for BCG, of whom 557 were vaccinated in the specialist clinic and a further nine in the community (93%). Statistical significance was not reported.

Gill and Scott (1998 (–)) evaluated an intervention at antenatal clinics and a maternity ward in a Bolton, an area where approximately 8% of the population is from ethnic minority groups, most from the Indian subcontinent. Approximately 20% of infants born each year are considered eligible for BCG vaccination. The study used a retrospective before-after design. The intervention comprised of moving the responsibility for BCG vaccination from community health officers to midwives and health visitors. Specifically, midwives identified women whose infant would be indicated for BCG vaccination at her first visit to the antenatal clinic. At following visits the women were given additional information about the vaccination (details not reported) and asked to give consent for the infant to be vaccinated on the maternity ward following birth. To support these changes, midwives and health visitors attended training sessions focussed on tuberculosis, administration of BCG, anaphylaxis, and paediatric resuscitation. All those who completed the course received a certificate of attendance and a copy of the BCG vaccination policy.

The primary outcome of interest was the number of children for whom BCG was indicated who had received it within the first three months of life. The outcomes show a large increase in the number of eligible infants receiving BCG: 1993 (pre) 6%; 1994 (post) 88%; 1995 (post) 90%; 1996 (post) 89%. However, statistical significance is not reported. Again, it is unclear how the denominator of the fraction (i.e. the number of eligible infants) was calculated, and whether it was consistent between pre and post measures.

Romanus (2009 (–)) describes the impact of the selective vaccination programme in Sweden, where approximately 12% of the population is foreign-born, using a retrospective before-after design. The study is mainly concerned with epidemiological monitoring data, but does include limited information about a policy change regarding BCG vaccination. BCG vaccination policy changed from universal to selective (mainly targeting children of foreign-born parents) in 1975, leading to a drop in

coverage from “at least 95%” to “below 2%” (full outcome data are not reported). A programme was then implemented in which nurses at child health centres were given information about the reasons for the change to selective vaccination, and in particular, about the case definition for risk groups to be vaccinated (no further details of the intervention are reported). This led to an increase in coverage, with coverage reaching 15% total among cohorts born from 1998 to 2002 (estimated at 88% among eligible groups). Statistical significance was not reported.

Tseng et al. (1997 (–)) evaluated the implementation of a new BCG policy in South London (Lewisham, Southwark and Lambeth), an ethnically diverse area where TB notification is highest in people of black African and Indian subcontinent ethnicity. The study used a retrospective before-after design. The nature and timing of the intervention in this study are not clearly reported, but it appeared to include the following components: a consultant in communicable disease control met with clinical directorates of acute hospitals to encourage them to ensure BCG was available for at-risk neonates; health visitors received training in order to identify and refer eligible infants to BCG vaccination clinics; and leaflets about BCG were distributed to parents and healthcare professionals.

The primary outcomes of interest were the number of BCG vaccinations given and the proportion of eligible infants given BCG. Prior to the intervention 11% of eligible infants received BCG (36 of 342), and 15% following the intervention (30 of 210). The authors report that this change was not statistically significant.

Uskun et al. (1996 (–)) evaluated an intervention designed to increase knowledge of primary healthcare workers and vaccination coverage Isparta, Turkey, where BCG vaccination is recommended universally as part of the standard vaccination schedule. The intervention focused on training healthcare providers. Three-day workshops for primary healthcare providers, which included both lectures and activities, were implemented. The content included vaccines, national vaccination schedule, cold-chain management, planning and regulation of immunization, tracking the trends and increase in vaccination coverage, and immunization recording. Attendance and participation in the workshops was mandatory.

In the pre-test period, BCG coverage was 25.4% (1,287 of 5,057), and at post-test 25.8% (1,294 of 5,020). The study authors report that this increase was statistically significant (at $p<0.001$), but no details of the analysis are given, and recalculation of the reported data would suggest that it is not significant at $p<0.05$, so there appears to be some error in the reported analysis. The results of this study may not be applicable to the UK context as BCG vaccination is recommended for all infants in Turkey, rather than being targeted as in the UK.

Evidence statement 1: Staff training

There is evidence from six studies (four UK and two from other countries) that interventions involving staff training may increase the uptake of BCG vaccination. One RCT (Griffiths et al., 2007 (++)) shows significantly higher uptake in the intervention group, with an odds ratio of 9.52 (95% CI 4.0–22.7). Five BA studies showed some increase in uptake (Athavale et al., 2006 (–); Gill and Scott, 1998 (–); Romanus, 2005 (–); Tseng et al., 1997 (–); Uskun et al., 2008 (–)), although in only two cases was statistical significance measured, and in neither of these did the increase reach significance (Tseng et al., 1997 (–); Uskun et al., 2008 (–)). The RCT involved 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. The BA studies generally focused mainly on staff training and did not use incentives.

Applicability

Most evidence is applicable to BCG vaccination in the UK. Four studies in this category (Athavale et al., 2006 (–); Gill and Scott, 1998 (–); Griffiths et al., 2007 (++); Tseng et al., 1997 (–)) were carried out in the UK, and one (Romanus, 2005 (–)) in Sweden, which has broadly similar patterns of TB infection and BCG policy to the UK. One study (Uskun et al., 2008 (–)) was carried out in Turkey, which has a policy of universal neonatal BCG vaccination, and may be less applicable.

4.4.2 Reminders to clinical staff

Chappel and Fernandes (1996 (–)) evaluated an intervention in the obstetric unit of a district hospital in Milton Keynes. The study used a retrospective before-after design. The intervention involved the installation of a computer which provided automated reminders to staff to offer BCG to eligible infants. The outcomes were the number of vaccinations conducted, and the proportion of eligible infants vaccinated. However, the latter outcome are difficult to interpret as the number of eligible infants was estimated differently at pre-test and at post-test, with the pre-test number extrapolated from Census data, and the post-test number derived from the data recorded on the computer. The outcomes, presented in Table 3, show a significant increase in the number of BCG vaccinations given, and, with the caveat above, appear to show an increase in the proportion of the eligible population vaccinated.

Table 3. Outcome data from Chappel and Fernandes (1996 (–))

Year	N of BCG vaccinations given	Estimated eligible population	Estimated BCG coverage (%)	95% CI (%)
1988	42	176	23.9	17.7-30.3
1989	31	169	18.3	12.5-24.2
1990	33	171	19.3	13.4-25.2
1991 – new system introduced	140	NR	NR	NR
1992	234	445	52.6	47.9-57.2
1993	354	457	77.5	73.6-81.3

Evidence statement 2: Reminders to clinical staff

One BA study (Chappel and Fernandes, 1996 (–)) appears to show that computerised reminders to hospital staff can increase the uptake of BCG vaccination. However, the data are difficult to interpret as the criteria for eligibility for BCG were defined differently at pre- and post-test.

Applicability

This evidence is directly applicable to BCG vaccination in the UK as the study was conducted in the UK.

4.4.3 Contact tracing interventions

Ansari et al. (1998 (–)) focused on a revised protocol for TB contact tracing, implemented in a specialist clinic in South Glamorgan, Wales (an area of mostly white ethnicity and low TB prevalence). The study design used was a retrospective before-after design. Unfortunately the previous protocol is not described in this study, so the intervention cannot be readily characterised, although the new protocol is described as 'simplified'.

The main outcome used in this study was number of BCG vaccinations carried out; the authors also report when BCG was given 'inappropriately' and when it was omitted 'inappropriately' (i.e., respectively, given when it should not have been, and not given when it should have been), although it is unclear what eligibility criteria were used. The study findings are presented in Table 4. Statistical significance was not reported, so the effectiveness of the intervention cannot readily be evaluated, although there appears to have been some decline in the number of patients for whom BCG was inappropriately omitted.

Table 4. Outcome data from Ansari et al. (1998 (–))

	Pre	Post
BCG given	119 (20%)	161 (22.8%)
BCG given appropriately	119 (100%)	153 (95%)
BCG given inappropriately	0 (0%)	8 (5%)
BCG inappropriately omitted	38 (6.4%)	2 (0.3%)

Evidence statement 3: Contact tracing interventions

There is inconclusive evidence from one BA study (Ansari et al., 1998 (–)) as to whether revised contact tracing protocols can increase the uptake of BCG vaccination.

Applicability

This evidence is directly applicable to BCG vaccination in the UK as the study was conducted in the UK.

5 Discussion

5.1 Overview of findings

One reasonably robust cluster-RCT finds that an intervention in primary care including training of staff, financial incentives to practices, and computer reminders can increase the number of BCG vaccinations carried out in a deprived and ethnically diverse area (Griffiths et al., 2007 (++)). Two BA studies find that staff training in conjunction with a special vaccination clinic (Athavale et al., 2006 (–)) or staff training in conjunction with a policy change making midwives and health visitors primarily responsible for vaccination (Gill and Scott, 1998 (–)), may be effective in increasing BCG uptake. However, two further BA studies (Tseng et al., 1997 (–); Uskun et al., 2008 (–)) suggest that education of staff alone may be ineffective in increasing BCG uptake.

One study (Chappel and Fernandes, 1996 (–)) suggests that computerised reminders may be effective in increasing BCG uptake. There is no usable evidence on any other intervention types. No studies of cost-effectiveness of any intervention were located.

The findings thus tentatively suggest that interventions involving the provision of information to clinical staff are likely to be effective if they are carried out in conjunction with other components, such as changes to clinical policy, automated reminders, financial incentives or on-going support for healthcare providers. This is broadly in line with the findings of the review of reviews carried out in parallel to this review. However, the evidence is insufficient to give a detailed understanding of how different intervention components may interact.

5.2 Strengths and weaknesses of the review

This systematic review was carried out in accordance with NICE Centre for Public Health methods guidance and incorporated a range of strategies to reduce bias. We carried out comprehensive, systematic searches, including a range of database sources to ensure coverage of the literature. Screening, quality assessment and data extraction were carried out in accordance with clearly defined *a priori* criteria and tools.

Most studies were carried out in the UK, and hence these should be broadly applicable to current UK practice, although detailed information on populations and contexts was usually lacking. The studies reflect some local variability in which groups were considered eligible for BCG (and, again, less than completely clear reporting), although this is unlikely to be a major barrier to applicability.

The main limitations of this review relate to the quantity and quality of the primary evidence. As discussed in section 4.2 above, all the included studies except one received low quality ratings for internal validity. Several limitations are seen across the studies, relating particularly to study design (specifically the absence of control groups), the reporting of population characteristics and intervention content, and data analysis. In addition, as noted above, one specific issue not reflected in the QA tool is the confusion (and sometimes clear inconsistency) in how eligibility for BCG was evaluated and recorded. Since this affects the denominator of the fraction representing BCG coverage rates, it results in serious ambiguities in how the latter outcome variable should be interpreted in several studies.

6 References

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7 Appendix 1. Search strategies

#	Database	Hits
1	Medline	1777
2	Medline in Process	86
3	PsycINFO	14
4	Social Policy and Practice	12
5	HMIC	50
6	Embase	3527
7	CINAHL	110
8	British Nursing Index	24
9	ASSIA	30
10	ERIC	0
11	NCJRS	0
12	Sociological Abstracts	8
13	The Cochrane Library	162
14	Science Citation Abstracts	2367
15	Conference Proceedings Citation Index	5
16	Open Grey	3
17	British Education Index	0
	Total	8175
	- De-duplication	-2866
	Unique Records	5309

1.
Database: Medline
Host: OVID
Data Parameters: 1946 to June Week 3 2013
Date Searched: Wednesday July 3rd 2013
Hits: 1777
Strategy:

#	Searches	Results
1	(Tuberculosis or TB).ti,ab,kw.	140658
2	exp Tuberculosis/	153696
3	1 or 2	189102
4	("Bacille Calmette-Guerin" or "Bacillus Calmette-Guerin" or BCG).ti,ab,kw.	19611
5	BCG Vaccine/	16436
6	or/4-5	24551
7	(uptake or up-take or (up adj1 take) or takeup or take-up).ti,ab,kw.	241878
8	((increas$ or improv$ or inform$ or impact$ or encourag$ or enhanc$ or support$ or	955063

	adopt$ or assist$) adj5 (demand or impact$ or respon$ or satisf$ or accept$ or respon$ or referr$ or self-referr$ or follow up or identification or identify$ or finding or compliance or comply or complie$ or adher$ or access$ or avail$ or provision or administrat$ or receiv$ or monitoring)).ti,ab,kw.	
9	((increas$ or improv$ or impact$ or encourag$ or enhanc$ or support$ or adopt$ or assist$) adj3 (coverage or cover or target$ or receipt or particip$ or efficacy or effectiveness)).ti,ab,kw.	90505
10	exp Patient Acceptance of Health Care/	159182
11	exp Immunization/	133754
12	*Immunization Programs/	4725
13	or/7-12	1489125
14	(promot$ or educat$).ti,ab,kw.	879473
15	((increas$ or improv$ or encourag$ or raising) adj3 awareness).ti,ab,kw.	15939
16	((advert$ or campaign or policy) adj5 (aware$ or increas$ or improv$ or encourag$ or support$ or involv$ or adopt$ or assist$ or promot$ or utilize or utilise or receive or optimiz$ or optimis$)).ti,ab,kw.	14693
17	(e-mail or email or electronic mail or letter$ or invite or reminder$ or invitation$ or written or telephone or text or mobile or SMS or twitter or tweet or facebook or social media or social marketing or mass media or marketing or target$ or chat room$ or billboard or flyer or poster or hand out or leaflet$ or radio or television or TV or workshop$ or outreach or incentiv$).ti,ab,kw.	1074401
18	*Health education/	29126
19	*Health promotion/	32482
20	Mass Media/	8600
21	or/14-20	1874631
22	exp Health Personnel/	357655
23	((patient or person or doctor$ or physician$ or GP or general practi$ or hospital or nurse) and (vaccinat$ or Immunisation or vaccination or inoculation)).ti,ab,kw.	13149
24	((health or healthcare) adj3 (worker$ or personnel or staff)).ti,ab,kw.	35028
25	(medical adj3 (worker$ or personnel or staff)).ti,ab,kw.	16074
26	(hospital adj3 (worker$ or personnel or staff or volunteer)).ti,ab,kw.	8647
27	(Midwife or midwives or midwifery).ti,ab,kw.	14466
28	(allied health adj3 (staff or worker$ or professional$ or personnel)).ti,ab,kw.	1343
29	(lay health adj3 (staff or worker$ or professional$ or personnel)).ti,ab,kw.	152
30	((laboratory or lab) adj3 staff).ti,ab,kw.	945

31	(organisation or delivery or shortage$).ti,ab,kw.	276505
32	(vet$1 or veterinary or veterinarian).ti,ab,kw.	29438
33	(farm$1 or farmer$ or abattoir).ti,ab,kw.	37118
34	student$.ti,ab,kw.	153942
35	exp Delivery of Health Care/	766701
36	((vaccination or inoculation or immunisation) and delivery).ti,ab,kw.	4097
37	(school$ or outreach or university or work or (out adj1 reach$) or (out adj2 hours) or mobile or home or communi$).ti,ab,kw.	1374978
38	((peer or community) adj1 led).ti,ab,kw.	542
39	((selective adj3 (vaccinat$ or inoculat$ or immuni$)) or (case adj3 (finding or detection))).ti,ab,kw.	5935
40	(free adj3 (vaccin$ or inoculat$ or immuni?$ or clinic or session or appointment$)).ti,ab,kw.	2310
41	((vaccin$ or inoculat$ or immuni?$) adj3 clinic$).ti,ab,kw.	5566
42	(integrated adj3 (vaccin$ or inoculat$ or immuni?$ or clinic or session or appointment$ or healthcare or service or organisation)).ti,ab,kw.	1701
43	(screen$ or surveillance).ti,ab,kw. or *Mass Screening/	510042
44	or/22-43	2944452
45	Randomized Controlled Trial.pt.	367158
46	Trial.ti,ab.	328756
47	effectiveness.ti.	54530
48	or/45-47	606258
49	13 or 21 or 44	5100971
50	48 or 49	5480628
51	3 and 6 and 50	4811
52	exp animals/ not humans.sh.	3910958
53	51 not 52	3818
54	(cow or cows or cattle or bovine or bovis or calves or badger or badgers or hedgehog or hedgehogs or mice or mouse or rat or rats).mp.	2918597
55	53 not 54	2823
56	limit 55 to yr="1993 -Current"	1777

Notes: N/A
File Name: TB MEDLINE Endnote RIS.txt

2.
Database: Medline in Process
Host: OVID
Data Parameters: July 02, 2013
Date Searched: Wednesday July 3rd 2013
Hits: 86
Strategy:

#	Searches	Results
1	(Tuberculosis or TB).ti,ab,kw.	9151
2	exp Tuberculosis/	0
3	1 or 2	9151
4	("Bacille Calmette-Guerin" or "Bacillus Calmette-Guerin" or BCG).ti,ab,kw.	644
5	BCG Vaccine/	0
6	or/4-5	644
7	(uptake or up-take or (up adj1 take) or takeup or take-up).ti,ab,kw.	12965
8	((increas$ or improv$ or inform$ or impact$ or encourag$ or enhanc$ or support$ or adopt$ or assist$) adj5 (demand or impact$ or respon$ or satisf$ or accept$ or respon$ or referr$ or self-referr$ or follow up or identification or identify$ or finding or compliance or comply or complie$ or adher$ or access$ or avail$ or provision or administrat$ or receiv$ or monitoring)).ti,ab,kw.	76188
9	((increas$ or improv$ or impact$ or encourag$ or enhanc$ or support$ or adopt$ or assist$) adj3 (coverage or cover or target$ or receipt or particip$ or efficacy or effectiveness)).ti,ab,kw.	7588
10	exp Patient Acceptance of Health Care/	0
11	exp Immunization/	0
12	*Immunization Programs/	0
13	or/7-12	93277
14	(promot$ or educat$).ti,ab,kw.	58425
15	((increas$ or improv$ or encourag$ or raising) adj3 awareness).ti,ab,kw.	1435
16	((advert$ or campaign or policy) adj5 (aware$ or increas$ or improv$ or encourag$ or support$ or involv$ or adopt$ or assist$ or promot$ or utilize or utilise or receive or optimiz$ or optimis$)).ti,ab,kw.	1122
17	(e-mail or email or electronic mail or letter$ or invite or reminder$ or invitation$ or written or telephone or text or mobile or SMS or twitter or tweet or facebook or social media or social marketing or mass media or marketing or target$ or chat room$ or billboard or flyer or poster or hand out or leaflet$ or radio or television or TV or	94355

	workshop$ or outreach or incentiv$).ti,ab,kw.	
18	*Health education/	0
19	*Health promotion/	0
20	Mass Media/	0
21	or/14-20	145293
22	exp Health Personnel/	0
23	((patient or person or doctor$ or physician$ or GP or general practi$ or hospital or nurse) and (vaccinat$ or Immunisation or vaccination or inoculation)).ti,ab,kw.	789
24	((health or healthcare) adj3 (worker$ or personnel or staff)).ti,ab,kw.	2549
25	(medical adj3 (worker$ or personnel or staff)).ti,ab,kw.	793
26	(hospital adj3 (worker$ or personnel or staff or volunteer)).ti,ab,kw.	413
27	(Midwife or midwives or midwifery).ti,ab,kw.	1012
28	(allied health adj3 (staff or worker$ or professional$ or personnel)).ti,ab,kw.	114
29	(lay health adj3 (staff or worker$ or professional$ or personnel)).ti,ab,kw.	11
30	((laboratory or lab) adj3 staff).ti,ab,kw.	41
31	(organisation or delivery or shortage$).ti,ab,kw.	18769
32	(vet$1 or veterinary or veterinarian).ti,ab,kw.	2609
33	(farm$1 or farmer$ or abattoir).ti,ab,kw.	3149
34	student$.ti,ab,kw.	11392
35	exp Delivery of Health Care/	2
36	((vaccination or inoculation or immunisation) and delivery).ti,ab,kw.	282
37	(school$ or outreach or university or work or (out adj1 reach$) or (out adj2 hours) or mobile or home or communi$).ti,ab,kw.	120077
38	((peer or community) adj1 led).ti,ab,kw.	49
39	((selective adj3 (vaccinat$ or inoculat$ or immuni$)) or (case adj3 (finding or detection))).ti,ab,kw.	375
40	(free adj3 (vaccin$ or inoculat$ or immuni?$ or clinic or session or appointment$)).ti,ab,kw.	132
41	((vaccin$ or inoculat$ or immuni?$) adj3 clinic$).ti,ab,kw.	347
42	(integrated adj3 (vaccin$ or inoculat$ or immuni?$ or clinic or session or appointment$ or healthcare or service or organisation)).ti,ab,kw.	144
43	(screen$ or surveillance).ti,ab,kw. or *Mass Screening/	35723
44	or/22-43	178643
45	Randomized Controlled Trial.pt.	700

46	Trial.ti,ab.	20486
47	effectiveness.ti.	3306
48	or/45-47	23620
49	13 or 21 or 44	340855
50	48 or 49	354036
51	3 and 6 and 50	124
52	exp animals/ not humans.sh.	5
53	51 not 52	124
54	(cow or cows or cattle or bovine or bovis or calves or badger or badgers or hedgehog or hedgehogs or mice or mouse or rat or rats).mp.	68371
55	53 not 54	89
56	limit 55 to yr="1993 -Current"	86

Notes: N/A
File Name: TB MIP Endnote RIS.txt

3.
Database: PsycINFO
Host: OVID
Data Parameters: 1806 to July Week 1 2013
Date Searched: Wednesday July 3rd 2013
Hits: 14
Strategy:

#	Searches	Results
1	(Tuberculosis or TB).ti,ab,sh.	2048
2	("Bacille Calmette-Guerin" or "Bacillus Calmette-Guerin" or BCG).ti,ab,sh.	63
3	1 and 2	18
4	(cow or cows or cattle or bovine or bovis or calves or badger or badgers or hedgehog or hedgehogs or mice or mouse or rat or rats).mp.	171166
5	3 not 4	16
6	limit 5 to yr="1993 -Current"	14

Notes: N/A
File Name: TB PsycINFO Endnote RIS.txt

4.
Database: Social Policy and Practice
Host: OVID

Data Parameters: 201304
Date Searched: Wednesday July 3rd 2013
Hits: 12
Strategy:

#	Searches	Results
1	(Tuberculosis or TB).ti,ab,sh.	178
2	("Bacille Calmette-Guerin" or "Bacillus Calmette-Guerin" or BCG).ti,ab,sh.	21
3	1 and 2	19
4	(cow or cows or cattle or bovine or bovis or calves or badger or badgers or hedgehog or hedgehogs or mice or mouse or rat or rats).mp.	154
5	3 not 4	19
6	limit 5 to yr="1993 -Current"	12

Notes: N/A
File Name: TB SPP Endnote RIS.txt

5.
Database: HMIC
Host: OVID
Data Parameters: 1979 to March 2013
Date Searched: Wednesday July 3rd 2013
Hits: 50
Strategy:

#	Searches	Results
1	(Tuberculosis or TB).ti,ab,sh.	898
2	("Bacille Calmette-Guerin" or "Bacillus Calmette-Guerin" or BCG).ti,ab,sh.	113
3	1 and 2	74
4	(cow or cows or cattle or bovine or bovis or calves or badger or badgers or hedgehog or hedgehogs or mice or mouse or rat or rats).mp.	1022
5	3 not 4	73
6	limit 5 to yr="1993 -Current"	50

Notes: N/A
File Name: TB HMIC Endnote RIS.txt

6.
Database: EMBASE
Host: OVID

Data Parameters: 1980 to 2013 Week 26
Date Searched: Wednesday July 3rd 2013
Hits:
Strategy:

#	Searches	Results
1	(Tuberculosis or TB).ti,ab,kw.	158557
2	exp Tuberculosis/	179093
3	1 or 2	219525
4	("Bacille Calmette-Guerin" or "Bacillus Calmette-Guerin" or BCG).ti,ab,kw.	21727
5	BCG vaccine/	27776
6	4 or 5	34719
7	(uptake or up-take or (up adj1 take) or takeup or take-up).ti,ab,kw.	287031
8	((increas$ or improv$ or inform$ or impact$ or encourag$ or enhanc$ or support$ or adopt$ or assist$) adj5 (demand or impact$ or respon$ or satisf$ or accept$ or respon$ or referr$ or self-referr$ or follow up or identification or identify$ or finding or compliance or comply or complie$ or adher$ or access$ or avail$ or provision or administrat$ or receiv$ or monitoring)).ti,ab,kw.	1245048
9	((increas$ or improv$ or impact$ or encourag$ or enhanc$ or support$ or adopt$ or assist$) adj3 (coverage or cover or target$ or receipt or particip$ or efficacy or effectiveness)).ti,ab,kw.	116738
10	exp patient attitude/	232066
11	*preventive health service/	10156
12	7 or 8 or 9 or 10 or 11	1782539
13	(promot$ or educat$).ti,ab,kw.	1064022
14	((increas$ or improv$ or encourag$ or raising) adj3 awareness).ti,ab,kw.	22130
15	((advert$ or campaign or policy) adj5 (aware$ or increas$ or improv$ or encourag$ or support$ or involv$ or adopt$ or assist$ or promot$ or utilize or utilise or receive or optimiz$ or optimis$)).ti,ab,kw.	17582
16	(e-mail or email or electronic mail or letter$ or invite or reminder$ or invitation$ or written or telephone or text or mobile or SMS or twitter or tweet or facebook or social media or social marketing or mass media or marketing or target$ or chat room$ or billboard or flyer or poster or hand out or leaflet$ or radio or television or TV or workshop$ or outreach or incentiv$).ti,ab,kw.	1418838
17	*Health education/	30630
18	*Health promotion/	28048
19	exp mass communication/	340542

20	13 or 14 or 15 or 16 or 17 or 18 or 19	2616185
21	exp health care personnel/	804028
22	((patient or person or doctor$ or physician$ or GP or general practi$ or hospital or nurse) and (vaccinat$ or Immunisation or vaccination or inoculation)).ti,ab,kw.	18037
23	((health or healthcare) adj3 (worker$ or personnel or staff)).ti,ab,kw.	42013
24	(medical adj3 (worker$ or personnel or staff)).ti,ab,kw.	20946
25	(hospital adj3 (worker$ or personnel or staff or volunteer)).ti,ab,kw.	10684
26	(Midwife or midwives or midwifery).ti,ab,kw.	15857
27	(allied health adj3 (staff or worker$ or professional$ or personnel)).ti,ab,kw.	1820
28	(lay health adj3 (staff or worker$ or professional$ or personnel)).ti,ab,kw.	164
29	((laboratory or lab) adj3 staff).ti,ab,kw.	1297
30	(organisation or delivery or shortage$).ti,ab,kw.	360690
31	(vet$1 or veterinary or veterinarian).ti,ab,kw.	36911
32	(farm$1 or farmer$ or abattoir).ti,ab,kw.	42447
33	student$.ti,ab,kw.	190996
34	exp health care delivery/	1752010
35	((vaccination or inoculation or immunisation) and delivery).ti,ab,kw.	5249
36	(school$ or outreach or university or work or (out adj1 reach$) or (out adj2 hours) or mobile or home or communi$).ti,ab,kw.	1816391
37	((peer or community) adj1 led).ti,ab,kw.	674
38	((selective adj3 (vaccinat$ or inoculat$ or immuni$)) or (case adj3 (finding or detection))).ti,ab,kw.	7271
39	(free adj3 (vaccin$ or inoculat$ or immuni?$ or clinic or session or appointment$)).ti,ab,kw.	2636
40	((vaccin$ or inoculat$ or immuni?$) adj3 clinic$).ti,ab,kw.	6347
41	(integrated adj3 (vaccin$ or inoculat$ or immuni?$ or clinic or session or appointment$ or healthcare or service or organisation)).ti,ab,kw.	2241
42	(screen$ or surveillance).ti,ab,kw. or *Mass Screening/	662857
43	or/21-42	4687449
44	randomized controlled trial/	345100
45	Trial.ti,ab.	426818
46	effectiveness.ti.	68922
47	44 or 45 or 46	696424
48	12 or 20 or 43	7346108

49	47 or 48	7706249
50	3 and 6 and 49	6128
51	exp animal/ not exp human/	3939260
52	50 not 51	5434
53	(cow or cows or cattle or bovine or bovis or calves or badger or badgers or hedgehog or hedgehogs or mice or mouse or rat or rats).mp.	3067423
54	52 not 53	4444
55	limit 54 to yr="1993 -Current"	3527

Notes: N/A
File Name: TB Embase Endnote RIS.txt

7.
Database: CINAHL
Host: Ebsco Host
Data Parameters: 1937-Current
Date Searched: Wednesday July 3rd 2013
Hits: 110
Strategy:
((Tuberculosis or TB) AND (("Bacille Calmette-Guerin") or ("Bacillus Calmette-Guerin") or BCG))

Notes: Search limited by date (1993-Current). A server side de-duplication was undertaken to remove MEDLINE hits
File Name: TB CINAHL Endnote RIS.txt

8.
Database: British Nursing Index (BNI)
Host: ProQuest
Data Parameters: 1994-Current
Date Searched: Wednesday July 3rd 2013
Hits: 24
Strategy:
((Tuberculosis or TB) AND (("Bacille Calmette-Guerin") or ("Bacillus Calmette-Guerin") or BCG))

Notes: N/A
File Name: TB BNI Endnote RIS.txt

9.
Database: ASSIA
Host: ProQuest
Data Parameters: 1987-Current
Date Searched: Wednesday July 3rd 2013

Hits: 30
Strategy:
((Tuberculosis or TB) AND (("Bacille Calmette-Guerin") or ("Bacillus Calmette-Guerin") or BCG))

Notes: Search limited by date (1993-Current)
File Name: TB ASSIA Endnote RIS.txt

10.
Database: ERIC
Host: ProQuest
Data Parameters: 1966-Current
Date Searched: Wednesday July 3rd 2013
Hits: 0
Strategy:
((Tuberculosis or TB) AND (("Bacille Calmette-Guerin") or ("Bacillus Calmette-Guerin") or BCG))

Notes: N/A
File Name: N/A

11.
Database: NCJRS
Host: ProQuest
Data Parameters: 1975-Current
Date Searched: Wednesday July 3rd 2013
Hits: 0
Strategy:
((Tuberculosis or TB) AND (("Bacille Calmette-Guerin") or ("Bacillus Calmette-Guerin") or BCG))

Notes: N/A
File Name: N/A

12.
Database: Sociological Abstracts
Host: ProQuest
Data Parameters: 1952-Current
Date Searched: Wednesday July 3rd 2013
Hits: 8
Strategy:
((Tuberculosis or TB) AND (("Bacille Calmette-Guerin") or ("Bacillus Calmette-Guerin") or BCG))

Notes: N/A
File Name: TB Soc Abs Endnote RIS.txt

13.
Database: The Cochrane Library
Host: http://www.thecochranelibrary.com/view/0/index.html

Data Parameters: CENTRAL 6 of 12 (June 2013) CDSR, DARE, NHS EEDS and HTA issue 2 of 4 April.
Date Searched: Wednesday July 3rd 2013
Hits: CDSR: 9; DARE 8; CENTRAL 114; METHODS 2; HTA 4. (Total 162)
Strategy:

ID	Search	Hits
#1	(Tuberculosis or TB):ti,ab,kw (Word variations have been searched)	2813
#2	MeSH descriptor: [Tuberculosis] explode all trees	1507
#3	#1 or #2	2820
#4	(("Bacille Calmette-Guerin") or ("Bacillus Calmette-Guerin") or BCG)	1250
#5	MeSH descriptor: [BCG Vaccine] this term only	660
#6	#4 or #5	1250
#7	#3 and #6 from 1993 to 2013	162

Notes: N/A
File Name: TB Cochrane Endnote RIS.txt

14.
Database: Science Citation Index Expanded (SCI-EXPANDED) & Social Sciences Citation Index (SSCI)
Host: ISI
Data Parameters: 1900 & 1956 - Current
Date Searched: Wednesday July 3rd 2013
Hits: 2367
Strategy:
Topic=(((Tuberculosis) AND (("Bacille Calmette-Guerin") or ("Bacillus Calmette-Guerin") or BCG))) NOT Topic=((cow or cows or cattle or bovine or bovis or calves or badger or badgers or hedgehog or hedgehogs or mice or mouse or rat or rats))

Notes: N/A
File Name: TB WOS Endnote RIS.txt

15.
Database: Conference Proceedings Citation Index- Science (CPCI-S) & Conference Proceedings Citation Index- Social Science & Humanities (CPCI-SSH)
Host: ISI
Data Parameters: 1990-Current
Date Searched: Wednesday July 3rd 2013
Hits: 5
Strategy: Wednesday July 3rd 2013
Topic=(((Tuberculosis) AND (("Bacille Calmette-Guerin") or ("Bacillus Calmette-Guerin") or BCG)))

Notes: This search was date limited 2011-Current
File Name: TB ISI Conference Abs Endnote RIS.txt

16.
Database: Open Grey

Host: http://www.opengrey.eu/
Date Searched: Wednesday July 3rd 2013
Hits: 3
Strategy:
(Tuberculosis) AND (BCG)

Notes: N/A
File Name: TB Grey Endnote RIS.txt

17.
Database: British Education Index
Host: ProQuest
Data Parameters: 1994-Current
Date Searched: Wednesday July 3rd 2013
Hits: 0
Strategy:
((Tuberculosis or TB) AND (("Bacille Calmette-Guerin") or ("Bacillus Calmette-Guerin") or BCG))

Notes: N/A
File Name: N/A

8 Appendix 2. Evidence tables

Study Details	Population and setting	Method of allocation to intervention/control	Outcomes and methods of analysis:	Results	Notes
Authors: Ansari et al. **Year:** 1998 **Citation:** Ansari, S., Thomas, S., Campbell, I. A., et al., 1998. Refined tuberculosis contact tracing in a low incidence area. *Respiratory Medicine.* 92(9), 1127-1131. **Country of study:** Wales **Aim of study:** To evaluate the efficacy of a revised	**Source population/s:** Contact tracing clinic in South Glamorgan **Eligible population:** Recruitment: not applicable (retrospective case record study) **Selected population:** Contact of someone identified to have TB within South Glamorgan **Excluded population:** Not reported **Sample characteristics:** No information on study sample. In broader population: South Glamorgan population of 408,600 (95.2% whites, 1.9% of Indian subcontinent origin, 0.5% black Africans); low TB incidence area, 103 index cases of TB over 3 year period; 1987-1989 TB	**Method of allocation:** Not applicable **Intervention/s description:** New, 'simplified' protocol for TB contact screening (Figure1, p.1128), previous protocol not described in any detail in study report **Control/comparison/s description:** Not applicable **Sample sizes:** Pre-test: 611 for old protocol; Post-test: 732 for new protocol **Baseline comparisons:** Not applicable **Study sufficiently powered?** Not reported	**Outcomes:** Primary of interest: number of BCG vaccinations given (appropriately, inappropriately, inappropriately omitted) **Follow up periods:** unclear **Method of analysis:** descriptive statistics	**Results for all relevant outcomes:** BCG given: previous protocol 119 persons or 20% (all given it appropriately); current protocol 161 persons or 22% (95% given it appropriately and 5% inappropriately) and 5 failed to attend for vaccination (0.7%) and 1 refused (0.1%). Inappropriately omitted: previous protocol 38 persons or 6.4%; current protocol 2 persons or 0.3%. **Results on inequalities:** Not reported, but approximately half the index cases were from ethnic minority backgrounds **Total sample:** Baseline: 611 Endpoint: 732 **Attrition details:** Not	**Limitations identified by author:** Not reported **Limitations identified by review team:** Non-comparative design. Poorly reported time frame. Somewhat limited information on population. Study is not focused on our review question, just happens to report relevant BCG data. Previous protocol not described. **Evidence gaps and/or recommendations for future research:** Not reported **Source of funding:** Not reported

tuberculosis contact tracing procedure in South Glamorgan **Study design:** BA **Quality Score:** – **External validity:** +	diagnosed in 1% of contacts			applicable	

Study Details	Population and setting	Method of allocation to intervention/control	Outcomes and methods of analysis:	Results	Notes
Authors: Athavale et al. **Year:** 2006 **Citation:** Athavale, D., McCullough, S. & Mactier, H., 2006. Implementing the new BCG vaccination guidelines - A maternity hospital-based clinic approach. *Journal of Public Health.* 28(2), 133-136. **Country of study:** Scotland **Aim of study:** To describe	**Source population/s:** (out-patient) BCG clinic at Princess Royal Maternity (PRM) in Glasgow **Eligible population:** Recruitment: mothers whose infants were eligible for BCG were given verbal explanation of BCG policy before discharged from hospital after giving birth; women who agreed to have child immunised given appointment card and additional written information **Selected population:** Women with infants at higher risk of TB and delivering at Princess Royal Maternity **Excluded population:** Not reported **Sample characteristics:** No information on study sample. Hospital in	**Method of allocation:** Not applicable **Intervention/s description:** Pilot project: junior medical staff individually advised of indications for BCG immunization and encouraged to identify / offer immunization to infants at higher risk of TB infection; mother informed of recommendation for immunization and given details of a clinic appointment by letter, telephone or via her Health Visitor. Full intervention: "clear guidelines for infants at risk of TB made available to the postnatal ward staff, verbal explanation of the BCG immunization policy given to mother	**Outcomes:** BCG immunisation rate **Follow up periods:** Baseline: (data from local audit) April 2002 – March 2003 ; Pilot project carried out March-June 2003 ; Revised protocol (intervention) implemented from July 2003 onwards-- post-test data collected over 18 months following **Method of analysis:** Descriptive statistics	**Results for all relevant outcomes:** Baseline (April 2002 to March 2003) 5 infants received BCG immunization prior to discharge from the postnatal ward, number of infants eligible for BCG vaccination not reported; Pilot study (March-June 2003) 39 infants identified as eligible for BCG vaccination, 82% immunised; Full intervention (July 2003-December 2004) 606 infants identified as eligible for BCG vaccination, 93% immunised **Results on inequalities:** not reported, but those at high-risk for TB include BME populations **Total sample:** 5,200 births at Princess Royal Maternity per annum, on average Pilot: 39 infants eligible for	**Limitations identified by author:** Audit does not determine how many eligible infants failed to be identified in the maternity hospital. Maternity case records provide some data regarding maternal ethnicity, but paternal ethnicity, family history of TB and intended travel abroad not documented which makes complete ascertainment of missed cases impossible. **Limitations identified by review team:** Non-comparative design. Very limited information on characteristics of identified infants. Number of infants eligible for BCG (and so coverage rate) at pre-

experience of improving BCG provision in Glasgow **Study design:** BA (2 pre-intervention time points) **Quality Score:** – **External validity:** +	deprived area with a large immigrant and asylum-seeking population; has approximately 5,200 deliveries per year.	at routine pre-discharge baby examination, if she agrees to immunization handwritten appointment card for next BCG clinic given immediately, with a leaflet explaining BCG immunization; interpreters present and non-English pamphlets available **Control/comparison/s description:** Not applicable **Sample sizes:** 5,200 births at Princess Royal Maternity per annum, on average Pilot: 39 infants eligible for BCG vaccination Full intervention: 606 infants identified as eligible for BCG vaccination (over 18 months) **Baseline comparisons:** Not applicable **Study sufficiently**		BCG vaccination Full intervention: 606 infants identified as eligible for BCG vaccination (over 18 months) **Attrition details:** Not applicable	test not reported. **Evidence gaps and/or recommendations for future research:** Not reported **Source of funding:** Not reported

		powered? Not reported			

Study Details	Population and setting	Method of allocation to intervention/control	Outcomes and methods of analysis:	Results	Notes
Authors: Chappel and Fernandes. **Year:** 1996 **Citation:** Chappel, D. & Fernandes, V., 1996. Improving the coverage of neonatal BCG vaccination. *Journal of Public Health Medicine.* 18(3), 308-312. **Country of study:** UK **Aim of study:** To audit BCG vaccination programme and develop means to improve	**Source population/s:** District hospital in Milton Keynes **Eligible population:** Recruitment: not applicable (retrospective case record study), assume all women giving birth in selected hospital eligible in principle **Selected population:** Implicitly, all births to minority ethnic parents in selected site **Excluded population:** Not reported **Sample characteristics:** No information on study sample. Population of Milton Keyes 190,000, approximately 3000 deliveries a year, nearly all in the district hospital, 5.4% of population were in ethnic groups other than white	**Method of allocation:** Not applicable **Intervention/s description:** 1991 installed a computer in the obstetric department at the Milton Keynes district hospital so staff could enter whether neonate was likely to be in a higher-risk group; if neonate was in high-risk group a form requesting BCG vaccination was automatically printed out, staff to provide the BCG vaccination and return form to community child health department where it was entered their computer; if baby not vaccinated then mother offered appointment to return for vaccination **Control/comparison/s**	**Outcomes:** Number of vaccinations given; percent coverage (defined as vaccinations given divided by eligible population, although this is defined differently at different time points) **Follow up periods:** Last follow-up ~2 years after implementation of new system **Method of analysis:** Descriptive statistics, with 95% CIs	**Results for all relevant outcomes:** 1988 (pre) 42 vaccinations given, 23.9% coverage (95% CI 17.7%-30.3%); 1989 (pre) 31 vaccinations given, 18.3% coverage (12.5%-24.2%); 1990 (pre) 33 vaccinations given, 19.3% coverage (13.4%-25.2%); 1992 (post) -234 vaccinations given, 52.6% coverage (47.9%-57.2%); 1993 (post) 354 vaccinations given, 77.5% coverage (73.6%-81.3%) **Total sample:** Not reported as such, somewhere under 3,000 births per year **Results on inequalities:** Population of study as a whole is BME people, although not totally clear how defined **Attrition details:** Not applicable	**Limitations identified by author:** Not reported **Limitations identified by review team:** Non-comparative, retrospective design. Very little information on methods or context (and what is reported is sometimes unclear). Because pre and post outcome measures are calculated differently, the quantitative findings cannot be regarded as meaningful. **Evidence gaps and/or recommendations for future research:** Not reported **Source of funding:** Not reported.

vaccination coverage and monitoring **Study design:** BA (or ITS: 5 time points) **Quality Score:** – **External validity:** –		**description:** Not applicable **Sample sizes:** Hard to define due to retrospective nature of study. Milton Keynes has about 3000 deliveries a year, nearly all in the district hospital and authors' estimates of eligible population range from 169-457 per year (problematic estimates). **Baseline comparisons:** Not applicable **Study sufficiently powered?** Not reported			

Study Details	Population and setting	Method of allocation to intervention/control	Outcomes and methods of analysis:	Results	Notes
Authors: Gill and Scott. **Year:** 1998 **Citation:** Gill, J. & Scott, J., 1998. Improving the uptake of selective neonatal BCG immunisation. *Communicable Disease & Public Health.*1(4), 281-282. **Country of study:** UK **Aim of study:** To describe the impact of a new local policy on BCG **Study design:** BA (or ITS; 4	**Source population/s:** Antenatal clinic and maternity ward in a hospital in Bolton **Eligible population:** Recruitment: questionnaires given in all new birth packs and distributed to health visitors by the community trust's health department **Selected population:** Implicitly, all giving birth in selected hospitals (data collected from health visitors.) Response rates : response rates: 96%, 98%, 93%, 87%. **Excluded population:** Not reported **Sample characteristics:** No information on study sample. Bolton: population: 270,000, 8% ethnic minorities (largely from Indian subcontinent),	**Method of allocation:** Not applicable **Intervention/s description:** Responsibility for vaccination moved from community medical officers to midwives and health visitors. Training sessions for midwives and health visitors on tuberculosis, advice about the vaccination, percutaneous administration of BCG vaccine, contraindications, anaphylaxis, and paediatric resuscitation; midwives and nurses receive certificate of attendance and copy of the neonatal vaccination policy. Women whose infant indicated for BCG were identified by midwife at first visit to antenatal clinic and given	**Outcomes:** Primary of interest: number of children for whom BCG was indicated and had been given it within the first three months of life **Follow up periods:** 1 year increments: 1993 (pre-intervention); 1994, 1995 and 1996 (post-intervention) **Method of analysis:** Descriptive statistics	**Results for all relevant outcomes:** Infants for whom BCG was indicated who received it by 3 months (sig NR): 1993 (pre-intervention) 6% ;1994 88%, 1995 90%, 1996 89% (post-intervention) **Results on inequalities:** not explicitly discussed, but policy targeted those born to parents from Indian subcontinent **Total sample:** Baseline: 576; Year 2: 590; Year 3: 555; Year 4: 521 **Attrition details:** Not applicable	**Limitations identified by author:** Not reported **Limitations identified by review team:** Non-comparative design. Significance of findings not reported. Limited detail on characteristics of included population and healthcare workers. Data collection and measures unclear. **Evidence gaps and/or recommendations for future research:** Not reported **Source of funding:** Not reported

time points) **Quality Score:** – **External validity:** +	between 2/3s and 3/4s of TB cases in Bolton are in people from Indian subcontinent, incidence of TB in persons from Indian subcontinent is 40 times higher than in white British persons, approximately 3,500 babies born per year and approximately 20% of them eligible for BCG vaccination.	information about BCG vaccination (verbally and in mother language); at subsequent visits before birth women given more information and asked to give consent for vaccination (to be done on maternity unit after birth or within 3 months by a health visitor and after that at the Department of Thoracic Medicine at local hospital). **Control/comparison/s description:** Not applicable **Sample sizes:** Baseline: 576 Total: 2,242 across 4 time points **Baseline comparisons:** Not applicable **Study sufficiently powered?** Not reported			

Study Details	Population and setting	Method of allocation to intervention/control	Outcomes and methods of analysis:	Results	Notes
Authors: Griffiths et al. **Year:** 2007 **Citation:** Griffiths, C., Sturdy, P., Brewin, P., et al., 2007. Educational outreach to promote screening for tuberculosis in primary care: a cluster randomised controlled trial. *The Lancet.* 369 (9572), 1528-1534. **Country of study:** UK **Aim of study:** To evaluate a programme	**Source population/s:** Primary care in Hackney, London **Eligible population:** Recruitment (at practice level) all but one practice in Hackney were invited to participate (the other one was a pilot for the study). Recruitment by researchers, by letter. Individual patients were recruited on an opt-out basis, i.e. they were shown information about the study by practice receptionists, and were assumed to consent to participation if they did not object. 96% of eligible practices agreed to participate; participation numbers not reported for individual patients **Selected population:** Newly registered patients with all GP practices in Hackney	**Method of allocation:** Cluster randomised by GP practice (N=50). Randomisation used a minimization method with respect to several aspects of the practice. **Intervention/s description:** Educational visits to practices by a specialist nurse and GP to promote TB screening and raise awareness of relevant guidelines, with follow-up phone call (educational programme based on social influence theory). Incorporation of reminders into practice computer systems. Provision of equipment for TB testing. Telephone support from specialist nurse. Financial incentives to practices for TB tests	**Outcomes:** Primary of interest: BCG coverage in people 5 years or older (taken from practice records - unclear if this refers to total coverage, or number of vaccinations conducted). **Follow up periods:** Unclear; data were collected from June 2002 - Sept 2004, but timing of intervention implementation with respect to this is not clearly reported. **Method of analysis:** Poisson regression, adjusted for cluster randomisation	**Results for all relevant outcomes:** BCG coverage over study period 26.8 per 1000 intervention, 3.8 per 1000 control; odds ratio 9.52 (95% CI 4.0–22.7). **Results on inequalities:** not reported, but population was ethnically mixed and low-SES **Total sample:** Baseline: N=50 practices; End point: N=48 practices (of which N=43 reported BCG data) **Intervention group(s):** Baseline: N=25 practices; Endpoint: N=25 practices, N=44,986 patients **Control group(s):** Baseline: N=25 practices; Endpoint: N=23 practices, N=48,984 patients **Attrition details:** 2 practices merged in the study period. BCG data	**Limitations identified by author:** Insufficient power to measure impact on proportion of cases identified, rather than changes in identification rate. Not everyone registers in primary care or attends health checks. **Limitations identified by review team:** Methodologically robust study. Some minor flaws in reporting (follow-up time, definition of BCG coverage outcome). **Evidence gaps and/or recommendations for future research:** Evaluate programmes using more effective means of testing; evaluate effectiveness and cost-effectiveness of programmes with different types of

to promote screening for TB in primary care **Study design:** Cluster RCT **Quality Score:** ++ **External validity:** ++	**Excluded population:** None **Sample characteristics:** Mean age intervention (I) 29, control (C) 26; I male 47%, C 46%; I 45% white, 22% black, 9% Asian, C 42% white, 24% black, 10% Asian; I N=248 mean immigrants per practice, C N=272.	(£7 each). **Control/comparison/s description:** Usual care **Sample size at baseline:** N =50 practices, N=93,970 patients **Baseline comparisons:** Checked for differences at practice level in terms of: number of doctors; % patients attending registration checks; practices registering new patients at trial outset (open lists); practice nurse; whether approved for training doctors; whether had an EMIS computer system; list size; N of patients; ethnicity of patients; N of new immigrants registering; rank of multiple deprivation [unclear how measured]; sex of patients; age of patients. **Study sufficiently**		unavailable from 7 practices.	screening method, settings and targeted populations. **Source of funding:** UK Department of Health

		powered? Yes			

Study Details	Population and setting	Method of allocation to intervention/control	Outcomes and methods of analysis:	Results	Notes
Authors: Romanus. **Year:** 2006 **Citation:** Romanus, V., 2006. Selective BCG vaccination in a country with low incidence of tuberculosis. *Eurosurveillance*. 11(3), 14-17. **Country of study:** Sweden **Aim of study:** To describe the impact of the selective vaccination programme in Sweden **Study design:**	**Source population/s:** Child health centres in Sweden **Eligible population:** Recruitment: not applicable (surveillance data) **Selected population:** All newborns in Sweden **Excluded population:** None **Sample characteristics:** No information on study sample. For population as a whole, 12% foreign born, 3.7% from Africa or Asia (2004 figures).	**Method of allocation:** Not applicable **Intervention/s description:** Nurses at child health centres given more information and education about the reasons for the change to selective vaccination, and in particular, about the case definition for risk groups to be vaccinated. **Control/comparison/s** **description:** Not applicable **Sample sizes:** Annual number of births 90,000 to 124,000 **Baseline comparisons:** Not applicable **Study sufficiently powered?** Not reported	**Outcomes:** Number of vaccinations; percentage of eligible population receiving vaccination **Follow up periods:** Timing of intervention unclear, but approximately 25-30 years **Method of analysis:** Descriptive statistics	**Results for all relevant outcomes:** Incomplete reporting. Cohorts born in first five-year period (1976-1981) following change in BCG policy vaccination coverage of newborns fell from at least 95% (before 1975) to below 2%; 1982 onwards gradual increase of vaccination coverage reaching levels above 15%, among cohorts born in 1998 and later; BCG coverage of children in the defined risk groups was estimated at about 88% among children born during the period 1998 to 2002. **Results on inequalities:** not reported **Total sample:** Not reported **Attrition details:** Not applicable	**Limitations identified by author:** Not reported **Limitations identified by review team:** Non-comparative design. Study is not conceptualized as an outcome evaluation (it can be interpreted as such, but this is problematic.) Very limited reporting on any dimension, including results and intervention content. **Evidence gaps and/or recommendations for future research:** Not reported **Source of funding:** Not reported

BA **Quality Score:** – **External validity:** +					

Study Details	Population and setting	Method of allocation to intervention/control	Outcomes and methods of analysis:	Results	Notes
Authors: Tseng et al. **Year:** 1997 **Citation:** Tseng, E., Nesbitt, A. & O'Sullivan, D., 1997. Audit of the implementation of selective neonatal BCG immunisation in south east London. *Communicable Disease Report.* 7(11), R165-168. **Country of study:** UK **Aim of study:** To audit the implementation of BCG	**Source population/s:** Primary care; health visiting service in south London (Lambeth, Southwark, Lewisham) **Eligible population:** Recruitment: by medical officers for pre-test and by health visitors for post-test (not clearly stated; limited information overall.) Response rates 81% pre, 86% post, although unclear how much non-response represents participant refusal. **Selected population:** Implicitly, all infants born in selected area **Excluded population:** Not reported **Sample characteristics:** No information on study sample other than whether they met BCG eligibility criteria (Table 3). In source	**Method of allocation:** Not applicable **Intervention/s description:** Unclear what formed part of the standard policy (at pre-test) and what was changed between pre and post-test. Consultant in communicable disease control met with clinical directorates of acute hospitals to encourage them to improve the availability of BCG to neonates at risk. Health visitors trained to identify and refer eligible infants to designated local clinics where BCG vaccination is offered, and leaflets about BCG for parents and health professionals were distributed. **Control/comparison/s**	**Outcomes:** Vaccinations given; proportion of eligible infants vaccinated **Follow up periods:** Unclear, approximately 18 months between two time points, but timing of intervention relative to these (or even definition of intervention) is unclear **Method of analysis:** Descriptive statistics and odds ratio with 95% CI	**Results for all relevant outcomes:** Pre 11% (36 of 342 eligible); post 14% (30 of 210). Analysis by site shows most of this to be accounted for by one of the four sites. "[T]he difference was not statistically significant (odds ratio=0.6; 95% confidence interval 0.34-1.07)"; this appears to be incorrect. **Results on inequalities:** not reported, but most infants eligible for BCG (88% at baseline) were eligible by being born outside of Europe / North America / Australia / NZ / Japan. **Total sample:** Baseline: 804; Endpoint: 527 **Attrition details:** Not applicable	**Limitations identified by author:** Not reported as such, authors report as a process finding that applying BCG eligibility criteria may not be reliable - this would also be a limitation of the data. **Limitations identified by review team:** Non-comparative design. Unclarity in definition and timing of intervention. Limited information on participants or context. Apparent error in reporting findings. **Evidence gaps and/or recommendations for future research:** Not reported **Source of funding:** Not reported

policy in the selected area **Study design:** BA **Quality Score:** – **External validity:** –	population: 26% of population and 42% of 0-4yo children were of non-White ethnicity; TB notification rate of 32 per 100,000, highest in people of black African and Indian subcontinent ethnicity.	**description:** Not applicable **Sample sizes:** Baseline: 804; Total: 1,604 over two time points **Baseline comparisons:** Not applicable **Study sufficiently powered?** Not reported			

Study Details	Population and setting	Method of allocation to intervention/control	Outcomes and methods of analysis:	Results	Notes
Authors: Uskun et al. **Year:** 2008 **Citation:** Uskun, E., Uskun, S.B., Uysalgenc, M., et al., 2008. Effectiveness of a training intervention on immunization to increase knowledge of primary healthcare workers and vaccination coverage rates. *Public Health.* 122 (9), 949-958. **Country of study:** Turkey	**Source population/s:** Primary health centres in Isparta, Turkey **Eligible population:** Recruitment of healthcare workers : those in primary health centres were invited to participate (unclear how, and if this was all of them) ; For population vaccinated: presume from record review, so not applicable **Selected population:** Healthcare workers: people with responsibility for providing vaccination within primary care, if all were invited 18% participated; Population vaccinated: implicitly, all children <1yo **Excluded population:** Not reported **Sample characteristics:** Limited information on population receiving	**Method of allocation:** Not applicable **Intervention/s description:** 18 intensive immunization workshops (3 full days) were conducted that comprised instructive lectures, activities designed to elicit discussion of participants' knowledge about immunization; The workshop content included vaccines, national vaccination schedule, cold chain and management, planning and regulation of immunization, tracking the trends and increase in vaccination coverage, and immunization recording. Full participation and attendance compulsory, materials provided by the MoH for EPI training were given to the study	**Outcomes:** Primary of interest: vaccination coverage for BCG, (also hepatitis B and DTP/OPV, not extracted here) **Follow up periods:** ~3 mo (intervention implemented March-May 2004, follow-up data collected June-August) **Method of analysis:** Chi-squared	**Results for all relevant outcomes:** Pre-test: N=1,287 vaccinations carried out; 25.4% coverage; Post-test: N=1,294 vaccinations carried out; 25.8% coverage. Study authors report that this is significant at p<0.001 (seems questionable.) **Results on inequalities:** not reported **Total sample:** Baseline: N=229 HCWs, N=5,057 children eligible for vaccination; Endpoint: unclear for HCWs, N=5,020 children eligible for vaccination **Attrition details:** Not clearly reported for HCWs; not applicable for children	**Limitations identified by author:** Duration of the intervention [unclear what this means; intervention may not be feasible in all settings?]. No results on cost-effectiveness. Findings may not be generalisable to HCWs without primary responsibility for vaccination. **Limitations identified by review team:** Non-comparative design. Limited information on population receiving vaccination. Some unclarities in analysis. Main focus of analysis is knowledge and attitudinal outcomes, and changes in coverage rates are addressed only in passing; effect size in the latter is extremely small (and p-value

Aim of study: To examine the effectiveness of an intervention to increase knowledge of primary healthcare workers and vaccination coverage **Study design:** BA **Quality Score:** – **External validity:** +	vaccination, either in study sample or in broader context. Healthcare workers: N=89 GPs, N=14 nurses, N=88 midwives, N=38 health officers; mean age 31, mean years experience 8, 62% female	participants. **Control/comparison/s description:** Not applicable **Sample sizes:** Baseline: N=229 HCWs; N=5,057 children eligible for vaccination ; Total sample size: N=10,077 children eligible for vaccination across 2 time points **Baseline comparisons:** Not applicable **Study sufficiently powered?** Not reported			reported is implausible). **Evidence gaps and/or recommendations for future research:** Not reported **Source of funding:** None declared

9 Appendix 3. Call for evidence

Stakeholder Organisation	Full Reference	Inclusion/Exclusion
Central Manchester University Hospitals NHS Foundation Trust	Vaccines in Practice. December 2012. Volume 5, Issue 3. www.vaccinesinpractice.co.uk	EX2: BCG vaccination not measured as an outcome
London TB Commissioning Board	Altass, L., Minnion, L., and Farran, S., 2013. Report on BCG policy and provision in London, February 2013. National Health Service: London Health Programmes.	EX1: report is not an outcome evaluation of an intervention
North Bristol NHS Trust	Van Tongeren, L., Nolan, S., Cook, V.J., FitzGerald, J.M., and Johnston, JC., 2013. Therapeutic drug monitoring in the treatment of tuberculosis: a retrospective analysis. *Int J Tuberc Lung Dis.*17(2),221-4.	Not relevant to this review
Royal College of General Practitioners	Lutge, E.E., Wiysonge, C.S., Knight, S.E., and Volmink, J., 2012. Material incentives and enablers in the management of tuberculosis. *The Cochrane Library,* 1.	Not relevant to this review
Royal College of General Practitioners	M'Imunya, J.M., Kredo, T., and Volmink, J., 2012. Patient education and counselling for promoting adherence to treatment for tuberculosis. *The Cochrane Library,* 5.	Not relevant to this review
Royal College of General Practitioners	Gallardo, C.R., Rigau Comas, D., Valderrama Rodríguez, A., Roqué i Figuls, M., Parker, L.A., Caylà, J., and Bonfill Cosp, X., 2012. Fixed-dose combinations of drugs versus single drug formulations for treating pulmonary tuberculosis. *The Cochrane Library,* 5.	Not relevant to this review
Royal College of General Practitioners	Steingart, K.R., Sohn, H., Schiller, I., Kloda, L.A., Boehme, C.C., Pai, M., and Dendukuri, N., 2013. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. *The Cochrane Library,* 1.	Not relevant to this review
Royal College of General Practitioners	Sharma, S.K., Sharma, A., Kadhiravan, T., and Tharyan, P., 2013. Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB. *The Cochrane Library,* 7.	Not relevant to this review
Royal College of General Practitioners	Adamu, B., Abdu, A., Abba, A.A., Borodo, M.M., and Tleyjeh, I.M., 2010. Antibiotic prophylaxis for preventing post solid organ transplant tuberculosis. *The Cochrane Library,* 7.	Not relevant to this review

Royal College of General Practitioners	Sinclair, D., Abba, K., Grobler, L., and Sudarsanam, T.D., 2011. Nutritional supplements for people being treated for active tuberculosis. *The Cochrane Library,* 11.	Not relevant to this review
Royal College of General Practitioners	Ziganshina, L.E., Titarenko, A.F., and Davies G.R., 2013. Fluoroquinolones for treating tuberculosis (presumed drug-sensitive). *The Cochrane Library,* 6.	Not relevant to this review
Royal College of General Practitioners	Arentz, M., Horne, D.J., and Walson, J.L. , 2011. Treatment of drug-resistant tuberculosis in patients with HIV-1 infection. *The Cochrane Library,* 12.	Not relevant to this review
Royal College of General Practitioners	Rosa, B., Cavalcanti, R.V., Alves da Cunha, A.J.L, Fernandes de Paulo, R., Medronho, R.A., and Atallah, A.N., 2012. TMC207 for treatment of people with pulmonary tuberculosis. *The Cochrane Library,* 10.	Not relevant to this review
Royal College of General Practitioners	Fox, G.J., Dobler, C.C., and Marks, G.B., 2011. Active case finding in contacts of people with tuberculosis. *The Cochrane Library,* 9.	Not relevant to this review
Royal College of General Practitioners	Marrone, M., Venkataramanan, V., Goodman, M., and Mase, S., 2011. Surgical interventions for treating multidrug and extensively-drug resistant pulmonary tuberculosis. *The Cochrane Library,* 2.	Not relevant to this review
Royal College of General Practitioners	Royce, S., Anglemyer, A., Horvath, T., McCarthy, E., Rutherford, G., Baggaley, R., Suthar, A., and Negussie, E., 2013. Tuberculosis clinics providing or referring for antiretroviral therapy (protocol). PROSPERO 2013:CRD42013004238.	Not relevant to this review
Royal College of General Practitioners	Mulder, C., Erkens, C.G.M., Kouw, P.M., Huisman, E.M., Meijer, V., Wieneke, M.V., Borgdorff, M.W., and, van Leth, F., 2012. Missed opportunities in tuberculosis control in The Netherlands due to prioritization of contact investigations. *European Journal of Public Health*. 22(2), 177-182.	EX1: report is not an outcome evaluation of an intervention
Royal College of General Practitioners	Nicol, M.P., Workman, L., Isaacs, W., Munro, J., and Black, F., 2011. Accuracy of the Xpert MTB/RIF test for the diagnosis of pulmonary tuberculosis in children admitted to hospital in Cape Town, South Africa: a descriptive study *Lancet Infectious Diseases*. 11(11), 819-824.	Not relevant to this review

Royal College of General Practitioners	Department of Health., 2011. Tuberculosis: the disease, its treatment and prevention. London: Department of Health.	EX1: leaflet is not an outcome evaluation of an intervention
Royal College of General Practitioners	van Rie, A., Westreich, D., and Sanne, I., 2011. Tuberculosis in patients receiving antiretroviral treatment: incidence, risk factors and prevention strategies. *Journal of Acquired Immune Deficiency Syndromes*. 56(4), 349-355.	EX1: study is not an outcome evaluation of an intervention
Royal College of General Practitioners	Basu, S., Stuckler, D., Bitton, A., Glantz, S, A., 2011. Projected effects of tobacco smoking on worldwide tuberculosis control: mathematical modelling analysis. *British Medical Journal.* 343(d5506).	Not relevant to this review
Royal College of General Practitioners	Glaziou, P., Floyd, K., Korenromp, E.L., and Sismanidis, C., 2011. Lives saved by tuberculosis control and prospects for achieving the 2015 global target for reducing tuberculosis mortality. *Bulletin of the World Health Organization*. 89(8): 573-582.	EX2: BCG vaccination not measured as an outcome
Royal College of General Practitioners	Bothamley, G.H., Kruijshaar, M.E., and Kunst, H., 2011. Tuberculosis in UK cities: workload and effectiveness of tuberculosis control programmes. *BMC Public Health.* 11(896).	EX1: study is not an outcome evaluation of an intervention
Royal College of General Practitioners	Cayla, J.A., and Orcau, A., 2011. The control of tuberculosis in large cities in developed countries: an organisational problem. *BMC Medicine.* 127.	EX1: study is not an outcome evaluation of an intervention
Royal College of General Practitioners	Malmborg, R., Mann, G., and Squire, S.B., 2011. Systematic assessment of the concept and practice of public-private mix for tuberculosis care and control. *International Journal for Equity in Health* 2011. 10(49).	EX2: BCG vaccination not measured as an outcome
Royal College of General Practitioners	World Health Organisation., 2011. Collaborative framework for care and control of tuberculosis and diabetes. Geneva: World Health Organisation.	EX1: study is not an outcome evaluation of an intervention
Royal College of General Practitioners	World Health Organisation., 2011. Global tuberculosis control 2011. Geneva: World Health Organisation.	EX1: study is not an outcome evaluation of an intervention
Royal College of General Practitioners	Abubakar, I., Lipman, M., Anderson, C., Davies, P., and Zumla, A., 2011. Tuberculosis in the UK: time to regain control. *BMJ*. 343(7818):293-296.	EX1: study is not an outcome evaluation of an intervention
Royal College of General Practitioners	le Polain, O., Maguire, H., and Pedrazzoli, D. Unpublished. Epidemiology of TB in children in London, 2009 – 2011. Are	Full text irretrievable

	opportunities for prevention being missed? London: Health Protection Agency.	
Royal College of General Practitioners	Nguipdop-Djomo, P., Mangtani, P., Pedrazzoli, D., Rodrigues, L.C., and Abubakar, I., 2013. Uptake of neonatal BCG vaccination in England: performance of the current policy recommendations. *Thorax.* 0:1-3.	EX1: study is not an outcome evaluation of an intervention
Royal College of General Practitioners	Pilger, D., Nguipdop-Djomo, P., Abubakar, I., Elliman, D., Rodrigues, L.C., Watson, J.M., Eastman, V., and Mangtani, P., 2012. BCG vaccination in England since 2005: a survey of policy and practice. *BMJ Open.* 2*:*e001303.	EX1: study is not an outcome evaluation of an intervention
TB Alert	Patient Information Forum (PiF)., 2013. Making the Case for Information: the evidence for investing in high quality health information for patients and the public. London: Patient Information Forum.	EX1: study is not an outcome evaluation of an intervention
TB Alert	Craig, G.M., Booth, H., Story, A., Hayward, A., Hall, J., Goodburn, A. and Zumla, A., 2007. The impact of social factors on tuberculosis management. *Journal of Advanced Nursing.* 58(5):418-424.	EX1: study is not an outcome evaluation of an intervention
TB Alert	Wanless, D., 2004. Securing good health for the whole population-final report. London: HMG Stationary Office.	EX1: study is not an outcome evaluation of an intervention
TB Alert	Akugizibwe, P. and Ramakant, B., 2010. Challenges for community role in tuberculosis response. *The Lancet.* 375(9731):2059-2061.	EX1: study is not an outcome evaluation of an intervention
TB Alert	Basri, C., Bergström, K., Walton, W., Surya, A., Voskens, J., and Metha, F., 2009. Sustainable scaling up of good quality health worker education for tuberculosis control in Indonesia: a case study. *Human Resources for Health.* 7:85.	EX2: BCG vaccination not measured as an outcome
TB Alert	Whitehead, M., 2007. A typology of actions to tackle social inequalities in health. *J Epidemiol Community Health*. 61(6), 473–478.	EX1: study is not an outcome evaluation of an intervention

10 Appendix 4. Quality appraisal example

Checklist items are worded so that 1 of 5 responses is possible:

++	Indicates that for that particular aspect of study design, the study has been designed or conducted in such a way as to minimise the risk of bias.
+	Indicates that either the answer to the checklist question is not clear from the way the study is reported, or that the study may not have addressed all potential sources of bias for that particular aspect of study design.
–	Should be reserved for those aspects of the study design in which significant sources of bias may persist.
Not reported (NR)	Should be reserved for those aspects in which the study under review fails to report how they have (or might have) been considered.
Not applicable (NA)	Should be reserved for those study design aspects that are not applicable given the study design under review (for example, allocation concealment would not be applicable for case control studies).

Each study is then awarded an overall study quality grading for internal validity (IV) and a separate one for external validity (EV):

++	All or most of the checklist criteria have been fulfilled, where they have not been fulfilled the conclusions are very unlikely to alter.
+	Some of the checklist criteria have been fulfilled, where they have not been fulfilled, or not adequately described, the conclusions are unlikely to alter.
–	Few or no checklist criteria have been fulfilled and the conclusions are likely or very likely to alter.

Study identification:	Griffiths, C., Sturdy, P., Brewin, P., et al., 2007. Educational outreach to promote screening for tuberculosis in primary care: a cluster randomised controlled trial. *The Lancet.* 369 (9572), 1528-1534.	
Study design:	Cluster RCT	
Guidance topic:	Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control (update)	
Assessed by:	Theo Lorenc	
Section 1: Population		
1.1 Is the source population or source area well described? Was the country (e.g. developed or non-developed, type of healthcare system), setting (primary schools, community centres etc.), location (urban, rural), population demographics etc. adequately described?	**Score:** **+**	**Comments:** Fairly brief description of source
1.2 Is the eligible population or area representative of the source population or area? Was the recruitment of individuals, clusters or areas well defined (e.g. advertisement, birth register)? Was the eligible population representative	**Score:** **+**	**Comments:** All attending GP practices in Hackney eligible, so can be assumed representative, although detailed figures NR

of the source? Were important groups under-represented?		
1.3 Do the selected participants or areas represent the eligible population or area? Was the method of selection of participants from the eligible population well described? What % of selected individuals or clusters agreed to participate? Were there any sources of bias? Were the inclusion or exclusion criteria explicit and appropriate?	**Score:** **+**	**Comments:** Clear at practice level, less clear at individual patient level
Section 2: Method of allocation to intervention (or comparison)		
2.1 Allocation to intervention (or comparison). How was selection bias minimised? Was allocation to exposure and comparison randomised? Was it truly random ++ or pseudo-randomised + (e.g. consecutive admissions)? If not randomised, was significant confounding likely (−) or not (+)? If a cross-over, was order of intervention randomised?	**Score:** **++**	**Comments:** Cluster randomised, full description of randomisation procedure
2.2 Were interventions (and comparisons) well described and appropriate? Were interventions and comparisons described in sufficient detail (i.e. enough for study to be replicated)? Was comparisons appropriate (e.g. usual practice rather than no intervention)?	**Score:** **++**	**Comments:** Full description of intervention
2.3 Was the allocation concealed? Could the person(s) determining allocation of participants or clusters to intervention or comparison groups have influenced the allocation? Adequate allocation concealment (++) would include centralised allocation or computerised allocation systems.	**Score:** **++**	**Comments:** See p28, column 2
2.4 Were participants or investigators blind to exposure and comparison? Were participants and investigators – those delivering or assessing the intervention kept blind to intervention allocation? (Triple or double blinding score ++) If lack of blinding is likely to cause important bias, score −.	**Score:** **+**	**Comments:** Participants and deliverers couldn't be blinded due to nature of intervention. Outcome assessors (record coders) were blinded; see end p29.
2.5 Was the exposure to the intervention and comparison adequate? Is reduced exposure to intervention or control related to the intervention (e.g.	**Score:** **+**	**Comments:** Not described in detail, although some checks appear to have been in place

adverse effects leading to reduced compliance) or fidelity of implementation (e.g. reduced adherence to protocol)? Was lack of exposure sufficient to cause important bias?		
2.6 Was contamination acceptably low? Did any in the comparison group receive the intervention or vice versa? If so, was it sufficient to cause important bias? If a cross-over trial, was there a sufficient wash-out period between interventions?	**Score:** **NR**	**Comments:** Not really discussed - could assume not because people aren't usually registered with >1 GP.
2.7 Were other interventions similar in both groups? Did either group receive additional interventions or have services provided in a different manner? Were the groups treated equally by researchers or other professionals? Was this sufficient to cause important bias?	**Score:** **++**	**Comments:** Broadly - they do say "Several [practices in the control group] were doing some tuberculin skin testing before the study and continued to do so."
2.8 Were all participants accounted for at study conclusion? Were those lost-to-follow-up (i.e. dropped or lost pre, during or post-intervention) acceptably low (i.e. typically <20%)? Did the proportion dropped differ by group? For example, were drop-outs related to the adverse effects of the intervention?	**Score:** **++**	**Comments:** At practice level, appear to have lost 2 practices because they merged with others (table 3 note). At individual patient level, NA
2.9 Did the setting reflect usual UK practice? Did the setting in which the intervention or comparison was delivered differ significantly from usual practice in the UK? For example, did participants receive intervention (or comparison) condition in a hospital rather than a community-based setting?	**Score:** **++**	**Comments:**
2.10 Did the intervention or control comparison reflect usual UK practice? Did the intervention or comparison differ significantly from usual practice in the UK? For example, did participants receive intervention (or comparison) delivered by specialists rather than GPs? Were participants monitored more closely?	**Score:** **++**	**Comments:** The intervention works within the existing UK primary care paradigm, and wouldn't demand radical changes to practice
Section 3: Outcomes		
3.1 Were outcome measures reliable? Were outcome measures subjective or objective (e.g. biochemically validated nicotine levels ++ vs self-reported smoking –)?	**Score:** **+**	**Comments:** Assume that clinical records are reliable, although this is not discussed explicitly

How reliable were outcome measures (e.g. inter- or intra-rater reliability scores)? Was there any indication that measures had been validated (e.g. validated against a gold standard measure or assessed for content validity)?		
3.2 Were all outcome measurements complete? Were all or most study participants who met the defined study outcome definitions likely to have been identified?	**Score:** **+**	**Comments:** Stated that BCG data were not available from 7 out of 50 practices (table 3 note), although unclear why
3.3 Were all important outcomes assessed? Were all important benefits and harms assessed? Was it possible to determine the overall balance of benefits and harms of the intervention versus comparison?	**Score:** **++**	**Comments:**
3.4 Were outcomes relevant? Where surrogate outcome measures were used, did they measure what they set out to measure? (e.g. a study to assess impact on physical activity assesses gym membership – a potentially objective outcome measure – but is it a reliable predictor of physical activity?)	**Score:** **++**	**Comments:**
3.5 Were there similar follow-up times in exposure and comparison groups? If groups are followed for different lengths of time, then more events are likely to occur in the group followed-up for longer distorting the comparison. Analyses can be adjusted to allow for differences in length of follow-up (e.g. using person-years).	**Score:** **+**	**Comments:** Not entirely clear
3.6 Was follow-up time meaningful? Was follow-up long enough to assess long-term benefits or harms? Was it too long, e.g. participants lost to follow-up?	**Score:** **+**	**Comments:** Unclear: data were collected from June 2002 - Sept 2004, but timing of intervention implementation with regards to this doesn't seem to be reported. But follow-up time is reasonable on the assumption that something was already happening at the beginning of that period.
Section 4: Analyses		
4.1 Were exposure and comparison groups similar at baseline? If not, were these adjusted? Were there any differences between groups in important confounders at baseline? If so, were these adjusted for in the analyses (e.g. multivariate analyses or stratification). Were there likely to be any residual differences of relevance?	**Score:** **++**	**Comments:** Full detail given

4.2 Was intention to treat (ITT) analysis conducted? Were all participants (including those that dropped out or did not fully complete the intervention course) analysed in the groups (i.e. intervention or comparison) to which they were originally allocated?	**Score:** **++**	**Comments:** Yes
4.3 Was the study sufficiently powered to detect an intervention effect (if one exists)? A power of 0.8 (that is, it is likely to see an effect of a given size if one exists, 80% of the time) is the conventionally accepted standard. Is a power calculation presented? If not, what is the expected effect size? Is the sample size adequate?	**Score:** **++**	**Comments:** Power calculation reported
4.4 Were the estimates of effect size given or calculable? Were effect estimates (e.g. relative risks, absolute risks) given or possible to calculate?	**Score:** **++**	**Comments:** Effect sizes reported
4.5 Were the analytical methods appropriate? Were important differences in follow-up time and likely confounders adjusted for? If a cluster design, were analyses of sample size (and power), and effect size performed on clusters (and not individuals)? Were subgroup analyses pre-specified?	**Score:** **++**	**Comments:**
4.6 Was the precision of intervention effects given or calculable? Were they meaningful? Were confidence intervals or p values for effect estimates given or possible to calculate? Were CI's wide or were they sufficiently precise to aid decision-making? If precision is lacking, is this because the study is under-powered?	**Score:** **++**	**Comments:**
Section 5: Summary		
5.1 Are the study results internally valid (i.e. unbiased)? How well did the study minimise sources of bias (i.e. adjusting for potential confounders)? Were there significant flaws in the study design?	**Score:** **++**	**Comments:**
5.2 Are the findings generalisable to the source population (i.e. externally valid)? Are there sufficient details given about the study to determine if the findings are	**Score:** **++**	**Comments:**

generalisable to the source population? Consider: participants, interventions and comparisons, outcomes, resource and policy implications.		