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Bacille Calmette-Guérin Vaccination: A Review of Clinical Effectiveness and Guidelines

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Abbreviations

BCG	Bacillus Calmette-Guérin
BHIVA	British HIV Association
HTA	health technology assessment
NICE	National Institute for Health and Care Excellence
NRS	non-randomized study
RCT	randomized controlled trial
SR	systematic review
TB	tuberculosis

Context and Policy Issues

Tuberculosis (TB) is an infectious disease caused by the bacteria *Mycobacterium tuberculosis*, that is transmitted between humans mainly through the air.[1] TB usually affects a person's lungs (i.e., pulmonary TB) but can also spread to other parts of the body (i.e., extrapulmonary TB). Initial infection with *M. tuberculosis* results in a period of latency in the majority (i.e., around 95%) of people, known as latent TB infection.[2] People with latent TB do not have any symptoms, and cannot spread the TB infection to others, however, they can develop active TB disease.[1,3] Active TB disease occurs when the TB bacteria overwhelm the immune system and begin to multiply, resulting in TB disease,[3] which can occur soon after infection (in approximately 5% of cases) or it can develop long after infection, following a weakening of the immune system.[1,3] Symptoms of active TB disease include a bad cough, chest pain, fever, and weight loss.[4] People with active TB disease can spread the TB bacteria to others.[3]

TB is common in low and middle income countries, however, there are still cases of TB reported in high income countries.[5] Canada has one of the lowest rates of active TB in the world,[6] but new TB cases are still reported in Canada. Canada has had similar annual rates of active TB since the 1980s, and in 2017 the annual rate of active TB in Canada was 4.9 per 100,000 population.[6] Of the 1,796 cases of active TB reported in Canada in 2017, 72% of cases occurred in foreign-born individuals, and 17% of cases occurred in Indigenous peoples born in Canada.[6] These groups with high incidences of TB within an otherwise low TB burden country represent an opportunity for targeted approaches for preventing TB.

The Bacillus Calmette-Guérin (BCG) vaccine, is the only vaccine against TB in general use, and it is one of the most widely administered vaccines.[7] Nevertheless, there are still some questions with regards to the effectiveness of the BCG vaccine, particularly, the duration of the effect, and the ability to protect against pulmonary TB in adults.[8] A global registry updated in 2017 indicates that numerous countries still have a universal BCG vaccine strategy (e.g., most of the countries within South America, Africa, and Asia).[9] In Canada, the universal BCG vaccination policy was discontinued in the 1960s and 1970s, with the exception of specific high-risk groups (i.e., selective vaccination).[9] The selective vaccination groups for the BCG vaccine in Canada currently include infants residing in Indigenous communities or other areas with a high annual risk of TB infection (i.e., greater than 0.1% risk); and those working in areas with higher risk of exposure to TB (e.g., health care workers, prison workers, those working with people experiencing homelessness.[9,10] Other countries that have a selective BCG vaccination strategy include the United States, Australia, Spain, and France. In Greenland, the universal BCG vaccine policy was discontinued in 1990 and reintroduced in 1996.[9] Selective BCG vaccination in high-risk groups in otherwise low TB burden countries may pose challenges such as incomplete

coverage of at-risk individuals due to difficulties identifying or reaching these communities.[11]

The purpose of this report is to review and critically appraise the evidence pertaining to the effectiveness of the BCG vaccine in populations at risk of exposure to TB, including evidence from high and low TB burden countries. Additionally, evidence-based guidelines with recommendations regarding the use of the BCG vaccine will be reviewed. This information may be used to inform decision making relating to health policy on the use of the BCG vaccine.

This report is a component of a larger CADTH Condition Level Review on TB. A condition level review is an assessment that incorporates all aspects of a condition, from prevention, detection, treatment, and management. For more information on CADTH's Condition Level Review of TB, please visit the project page (https://www.cadth.ca/tuberculosis).

Research Questions

1. What is the clinical effectiveness of the use of Bacille Calmette-Guérin vaccination in populations at risk of exposure to pulmonary tuberculosis?
2. What are the evidence-based guidelines regarding the use of Bacille Calmette-Guérin vaccination in populations at risk of exposure to pulmonary tuberculosis?

Key Findings

One health technology assessment, three systematic reviews of primary studies, and two non-randomized studies were identified regarding the clinical effectiveness of the BCG vaccine for the prevention of TB. One systematic review of guidelines and four evidence-based guidelines were identified regarding the use of the BCG vaccine in populations at risk of exposure to TB.

The evidence included in this report was mostly low- to moderate-quality with considerable heterogeneity and may be considered outdated. However, in people who are immunocompetent, the BCG vaccine consistently demonstrated a lower risk of TB compared those unvaccinated with BCG, however, the duration of the vaccine effectiveness was less certain. The BCG vaccine was also associated with a lower risk of morality compared to the unvaccinated population. Insufficient evidence was found on the adverse effects of the BCG vaccine. The BCG vaccine is recommended for people who are immunocompetent who have a high risk of exposure to TB, including: those who live in countries or settings with a high incidence of TB; those who have a family history of TB; those with potential occupational exposure to TB; and those travelling to countries with a high incidence of TB. Revaccination with BCG is not recommended.

The evidence identified in this report suggests that the BCG vaccine is not effective in people with HIV, and the BCG vaccine is not recommended in adults with HIV. Recommendations concerning BCG vaccination of newborns with confirmed or suspected HIV is less certain, and may depend on the risk of exposure to TB.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline via Ovid, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were TB and BCG vaccination. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, any type of clinical trials or observational studies and guidelines. The search was also limited to English language documents published between Jan 1, 2015 and Mar 11, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	People of all ages at risk of exposure to pulmonary tuberculosis
Intervention	Administration of bacille Calmette-Guérin vaccine for the prevention of tuberculosis
Comparator	No administration of bacille Calmette-Guérin vaccine
Outcomes	Q1.Clinical effectiveness (e.g., development of latent pulmonary tuberculosis infection, development of active pulmonary tuberculosis disease, all cause mortality) and safety (e.g., injection site reactions, abscesses, ulcers, death) Q2. Recommendations regarding use of the Bacille Calmette-Guérin vaccine
Study Designs	Health technology assessments, systematic reviews, randomized controlled studies, non-randomized studies, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2015. Guidelines with unclear methodology were also excluded. We excluded studies where the BCG was administered for a reason other than the prevention of TB.

Critical Appraisal of Individual Studies

The included health technology assessment (HTA) and systematic reviews (SRs) were critically appraised by one reviewer using AMSTAR 2,[12] non-randomized studies (NRSs) were critically appraised using the Downs and Black checklist,[13] and guidelines were assessed with the AGREE II instrument.[14] Summary scores were not calculated for the

included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 683 citations were identified in the literature search. Following screening of titles and abstracts, 641 citations were excluded and 42 potentially relevant reports from the electronic search were retrieved for full-text review. Five potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 37 publications were excluded for various reasons, and 10 publications met the inclusion criteria and were included in this report. These comprised 1 HTA, 3 SRs of primary clinical studies, 1 SR of guidelines, 1 report that includes 2 non-randomized studies, and 4 evidence-based guidelines. Appendix 1 presents the PRISMA[15] flowchart of the study selection. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

One HTA,[16] three SRs of primary clinical studies,[11,17,18] one SR of guidelines,[19] two case-control studies published in Mangtani et al. (2017),[20] and four evidence-based guidelines[21-24] were identified and included in this review. Detailed characteristics are available in Appendix 2, Table 2, Table 3, and Table 4.

Study Design

The HTA[16] was published in 2015, and examined proposed changes to a national BCG vaccination program. The SR component of the HTA was conducted in January 2015 and was an update to a previous SR conducted in 2013; four randomized controlled trials (RCTs) and 10 case-control studies from the original search were included in the HTA and no new studies were identified in the updated search.[16] One SR published in 2019 examined the effectiveness of vaccines, including BCG, in children infected with HIV; this SR did not report the date range of the search and included two relevant case-control studies.[17] The second SR published in 2019 searched for evidence between 1988 and January 2018, and examined BCG vaccination in high-risk groups in low-incidence settings, and included seven relevant studies.[11] A 2016 SR with a meta-analysis examined the effects of three vaccines, including BCG, on all-cause mortality in children;[18] the search was conducted in November 2012 and there were 14 relevant studies included in this report. There were two overlapping primary studies between the HTA[16] and the 2016 SR.[18] In addition, a SR of guidelines published in 2016[19] examined European policies for TB prevention in health care workers and included 16 guidelines published between 2001 and 2013 that were relevant to this report.

This report includes one publication from 2017[20] that includes two case-control studies. The first case-control study examined BCG vaccination in infancy of high-risk groups and included 744 cases and 694 controls. The second case-control study examined BCG vaccination of low-risk school-aged children and included 677 cases and 1170 controls.

One guideline was developed in 2018 by the World Health Organization (WHO).[21] Two guidelines were published in 2016, and they were developed by the National Institute for Health and Care Excellence (NICE)[22] and the Italian Pediatric TB Study Group.[23] One

guideline was developed by the British HIV Association (BHIVA) and was published in 2015.[24]

Country of Origin

The HTA[16] was led by authors in Ireland. The SRs of primary clinical studies were led by authors in South Africa,[17] Canada,[11] and the UK.[18] The SR of guidelines was led by authors in Italy, and the included guidelines that were meant to apply to 13 different European countries.[19]

The report of the two case-control studies[20] was by authors in the UK, and the participants were recruited from England.

One guideline from the WHO is meant to apply globally,[21] the NICE guideline and the BHIVA guideline are meant to apply to the United Kingdom,[22,24] and the other guideline is specific to Italy.[23]

Patient Population

The HTA[16] included evidence related to BCG vaccination of neonates or infants less than one year of age; the sample size of the included studies ranged from 63 to 10,115 people. One SR included children who are HIV-positive, HIV-exposed, or HIV uninfected; the two relevant studies included 270 and 902 children.[17] Another SR included evidence from high-risk groups from low TB burden countries; the sample size of the included studies ranged from 474 people in a case-control study to over 700,000 people in a quasi-experimental study of regional vaccination.[11] The SR and meta-analysis included vaccinated and unvaccinated children (sample sizes ranged from 304 to 39,625 children).[18] The SR of guidelines[19] included European health care workers, and did not report the target population or the intended users of the individual guidelines.

For both case-control studies, the cases had a confirmed diagnosis of TB between 2003 and 2012, and the controls were from the same population, with no TB diagnosis, and age matched within 5 years.[20] The infant BCG case-control study included people (N = 744 cases, 694 controls) who are UK-born ethnic minorities who would have been eligible for the BCG vaccine in infancy. The school-aged case-control BCG study included people (N = 677 cases, 1170 controls) who are UK-born of white ethnicity who would have been eligible for the BCG vaccine around age 13.

The main target populations for the WHO and NICE guidelines[21,22] are unvaccinated neonates, children, and adults in areas of high and low TB burden. The main target population in the guideline by the Italian Pediatric Study Group is pediatric patients in Italy.[23] The target population of the BHIVA guideline is adults and adolescents who are HIV-positive.[24] The intended users of the WHO and NICE guidelines[21,22] are health care workers and key TB stakeholders. The guidelines by the Italian Pediatric Study Group and BHIVA did not specify the intended users.[23,24]

Interventions and Comparators

For the HTA,[16] the three SRs of clinical studies,[11,17,18] and the two case-control studies[20] the intervention of interest was the BCG vaccine compared to no BCG vaccination. The HTA,[16] and the infant case-control study[20] were specifically interested in BCG vaccination during infancy (i.e., less than one year of age). The school children case-control study[20] was specifically interested in BCG vaccination around age 13. The other studies did not specific the timing of the BCG vaccine.

For all four guidelines, and the SR of guidelines, the intervention of interest was the BCG vaccine.[19,21-24]

Outcomes

The HTA,[16] was interested in pulmonary TB and TB-related mortality. The SR of children with HIV[17] examined cases of TB (type of TB unspecified), and the reported vaccine efficacy or effectiveness (i.e., the proportionate reduction in disease among the vaccinated group[25]). The SR of high-risk groups[11] examined the reported vaccine efficacy or effectiveness (measured as a percentage), and adverse events. The SR and meta-analysis examined all-cause mortality.[18] The SR of guidelines included recommendations regarding BCG vaccination of European health care workers.[19]

Both case-control studies studied the level and duration of the effectiveness of the BCG vaccine in preventing TB calculated as a hazard ratio.[20] The infant BCG case-control study estimated the effectiveness of the BCG vaccine in five-year intervals post-vaccination up to 19 years after vaccination. The school-aged case-control BCG study estimated the effectiveness of the BCG vaccine in five-year intervals post-vaccination, from 10 to 29 years after vaccination.

For the WHO guideline,[21] the outcomes that were considered in the SRs and when formulating the recommendations were the prevention of TB infection and disease, and TB associated death. For the NICE guideline,[22] the outcomes that were considered were: pulmonary TB disease, TB deaths, TB meningitis, laboratory confirmed TB cases, disseminated TB, and cost-effectiveness. The guidelines by the Italian Pediatric Study Group and BHIVA did not report which outcomes were considered when developing the recommendations.[23,24]

Summary of Critical Appraisal

The critical appraisal of the included studies is summarized below and additional details regarding the strengths and limitations of included publications are provided in Appendix 3, Table 5, Table 6, and Table 7.

Health Technology Assessment and Systematic Reviews

The HTA and the three SRs of clinical studies had well described eligibility criteria.[11,16-18] The research question was clear in the HTA[16] and the SR with meta-analysis,[18] and it was unclear in the SR on HIV -infected children[17] and in the SR on high-risk groups.[11] Two SRs[17,18] referenced a written protocol available on the internet, the other SR explicitly stated that there was no registered protocol,[11] and the HTA did not mention whether there was a protocol.[16] The HTA and the three SRs included evidence from both RCTs and NRSs, as this type of research question lends itself to observational study designs.

The literature search used in the HTA[16] was comprehensive (e.g., multiple databases searched, complete search strategy provided) and was conducted less than a year prior to publication, ensuring the most recent evidence was captured. The SR and meta-analysis[18] was comprehensive (e.g., multiple databases searched, complete search strategy provided), but the search was conducted almost four years prior to publication, and may be considered out of date. The SR on HIV-infected children[17] searched multiple databases but it is unclear whether the search strategy was strong as the search strategy or key words were not provided. The SR on high-risk populations[11] searched two databases and provided the search strategy, but did not search references lists or grey literature. The

HTA[16] and the SR and meta-analysis[18] performed study selection and data extraction in duplicate. The SR on children with HIV[17] performed study selection in duplicate, but it was unclear whether data extraction was done in duplicate. The SR on high-risk groups[11] did not report how many people conducted study selection or data extraction which may impact the reliability of the results.

The HTA[16] and the SRs of clinical studies [11,16-18] provided minimal detail on the characteristics of the included studies; additional details regarding the populations, interventions, and study designs of the primary studies would help determine whether the findings of the SRs are generalizable to other settings and populations. These reviews used appropriate tools for assessing the risk of bias in the included RCTs and NRSs, although none of these publications reported the source of funding of the primary studies, which may be a source of bias in studies on a vaccine.

The HTA[16] and one of the SRs[18] analyzed the results using a meta-analysis. The other two SRs[11,17] provide narrative summaries of the results. The HTA[16] created separate forests plots for the findings from the RCTs and the NRSs, but also conducted an analysis that combined both types of study designs thus combining relative risk and odds ratios into one analysis. It was unclear whether combining these results was appropriate, as insufficient details were provided for the methods of analysis, and the analyses were associated with moderate to high statistical heterogeneity. In addition, the meta-analysis in the HTA did not account for the risk of bias in the individual studies, nor did the authors consider the risk of bias or the heterogeneity when discussing the results, or carry out an investigation of publication bias. In the SR with meta-analysis,[18] separate effect estimates were reported for the RCTs and the NRSs, and results were reported for both fixed and random effects analyses, however, the reporting for the random effect estimates was unclear, and there was moderate to high statistical heterogeneity in both analyses. The authors excluded studies with very high risk of bias from the analysis, and conducted a sensitivity analysis that only examined the studies with low risk of bias. The authors discussed the heterogeneity of the results of the review, and reported that they could not investigate publication bias due to the small number of studies in the review.[18]

The authors of the HTA and the three SRs of clinical studies declared no conflicts of interest. The three SRs made explicit statements that the reports were independent of the views of the funders.[11,17,18] No external source of funding was reported for the HTA, and it was not reported whether the HTA sponsor agency influenced the review.[16]

The SR of guidelines[19] clearly described the population and intervention of interest, however, the eligibility criteria was not clear with respect to what was considered a guideline, thus it is unclear whether the included guidelines were evidence-based clinical practice guidelines. This SR of guidelines did not report having a protocol, and did not have a comprehensive literature search (i.e., only searched one database, did not report date of search), thus there is uncertainty with the evidence in this report. It was not reported how many authors performed the study selection, and it was unclear whether data extraction was done in duplicate. There was a lack of detail on the guidelines; none of the methods for developing and appraising the recommendations were reported contributing to uncertainty in the recommendations. In addition, the SR authors did not assess the quality of the guidelines, reducing the certainty in the findings. The authors declared no conflicts of interest, and the funding source was not reported, thus it is unclear if the findings were influenced by the funder.

Non-Randomized Studies

The two NRS[20] included in this report were both case-control studies, which is a moderate strength study design.[26] In case-control studies, the people included in the study are selected based on whether they have the outcome of interest or not (e.g., do they have a diagnosis of TB), therefore this type of study design has a higher risk of selection bias. However, despite the moderate strength of the study design, the overall quality of these two case-control studies was high. The objective of these studies was clear, the main outcomes and intervention of interest were well described, and the definitions and sources of the cases and controls were well described. The possible confounders were reported in tables, and relevant confounders were included in the analysis of the results. The main findings were clearly presented and confidence intervals were provided to indicate the variability in the results. The cases and controls included in the study were representative of the populations of interest who would be eligible to receive the BCG vaccine. Due to the nature of study design, blinding of participants was not possible. The investigators were not blinded to the outcomes, however, strong efforts were made to ensure the accuracy of the assessment of whether participants were vaccinated or unvaccinated, reducing the likelihood that vaccination status would be misclassified. The investigators were well trained in identifying the scar associated with the BCG vaccine, and at least two methods were required to confirm vaccination status, including two types of vaccination or health records, participant recall, and the presence of the BCG scar. If vaccination status could not be determined, the data was considered missing, and the participants were not included in the analysis; similar levels of missing data occurred in the cases and the controls in both studies. Although one author declared serving as a member of the board that funded the study, there was an explicit statement that the funding body did not influence the results.

Guidelines

Three of the guidelines in this report were previously included in a CADTH report on guidelines for the prevention of TB.[27] The detailed critical appraisal of these guidelines can be found in that report.[27] In brief, for the WHO guideline, some of the details for the evidence collection were unclear and the guideline did not report the strength of the recommendation or the quality of the evidence, and was assessed to be moderate-quality.[21] The guideline by the Italian Pediatric Study Group did not report sufficient methods for developing the recommendations, creating uncertainty in the recommendations, and was assessed to be low-quality.[23] The NICE guideline was assessed to be high-quality; it followed a clear and detailed process for searching for evidence and formulating the recommendations.[22]

The BHIVA guideline[24] was assessed as low-quality. While the scope and target population of this guideline are clear, it did not provide many methodological details, and it is uncertain whether a systematic approach was used to search for and evaluate the evidence. The guideline references a development manual, but it is unclear whether the manual was followed as most of the methods sections were not reported in the guideline. The members of the guideline development group and their institutions were listed, but their roles and areas of expertise were not reported. A brief narrative summary of the evidence that contributed to the recommendation was reported, there was no explicit link between the evidence and the recommendations, it is unclear how the evidence was considered when formulating the recommendations. The guideline reported the level of evidence and the grade for each recommendation, but it did not report the risk of bias of the individual studies or include evidence-to-decision tables, thus it is unclear how the strengths and limitations of the evidence were incorporated into the evaluation of the recommendations. The guideline

development manual includes processes for external review and updating the guideline, but these were not reported for this guideline, thus the level of certainty in the recommendations is unclear. No external funding was received for this guideline. The development manual states that authors must complete a conflict of interest declaration, but these were not reported with the guideline and it is unclear whether there were any conflicts of interest from the authors.

Summary of Findings

Relevant study findings are summarized below, and a detailed summary of the findings, authors' conclusions, and recommendations are presented in Appendix 4, Table 8, Table 9, and Table 10.

Clinical Effectiveness of the BCG Vaccine

One HTA,[16] three SRs,[11,17,18] and two case-control studies (published in the same report)[20] were identified regarding the clinical effectiveness of the BCG vaccine.

Pulmonary TB

The HTA[16] reported on the risk of pulmonary TB in those who received the BCG vaccine compared to those who did not receive the vaccination. A meta-analysis of five RCTs assessed by the authors to have a high risk of bias due to randomization and blinding, found that those who received the BCG vaccine had a statistically significantly lower risk of pulmonary TB compared to the unvaccinated group. Evidence from six case-control studies found that the odds of pulmonary TB were statistically significantly lower in those who received the BCG vaccine compared to those who did not receive the BCG vaccine, however, all of the studies had a high risk of bias and there was substantial statistical heterogeneity in the analysis.[16]

TB (any type)

The clinical effectiveness of the BCG vaccine versus no BCG vaccine for preventing any type of TB was examined in the SR of children with HIV,[17] the SR of high-risk groups from low TB burden countries,[11] and both case-control studies.[20]

The SR of children with HIV[17] identified evidence the authors assessed to be very low-quality that the BCG vaccine was not effective in preventing TB in children with HIV. This SR also identified evidence that the BCG vaccine was effective in preventing TB in children who are not infected with HIV.[17]

The SR of high-risk groups from low TB burden countries[11] identified seven studies that examined the risk of TB in those who received the BCG vaccine versus those who did not receive the BCG vaccine. Two quasi-experimental and three NRSs reported findings for vaccine efficacy or effectiveness (i.e., the percent reduction in disease among the vaccinated group). Three studies reported measures of confidence of the findings for BCG vaccine effectiveness, which ranged from 49% to 57%, and was statistically significant in these three studies. In the other two studies the vaccine effectiveness was 80% and 85%, but the confidence in the findings was not reported. The other two quasi-experimental studies did not report vaccine efficacy, but one study reported more cases of TB in the area with lower vaccine coverage compared to the area with high BCG coverage, and the other study reported a statistically significantly higher rate of TB in the areas without universal neonatal BCG coverage compared to areas with universal coverage.

In the infant BCG case-control study, BCG vaccination in infancy was associated with a statistically significantly lower risk of TB between one and five years after vaccination, and between five and 10 years after vaccination when compared to the unvaccinated group. However, there was no significant difference in risk of TB between the vaccinated and unvaccinated groups 10 to 20 years post vaccination.[20]

The school aged BCG case-control study found that BCG vaccination around age 13 resulted in a statistically significantly lower risk of TB in the vaccinated group compared with the unvaccinated group between 10 to 15 years and between 15 to 20 years after vaccination, but no difference in risk between 20 to 30 years after vaccination.[20]

TB mortality

Evidence comparing mortality from TB between people who were vaccinated with BCG versus those who did not receive the BCG vaccine was available in one HTA.[16] Results from a meta-analysis of four RCTs found that BCG vaccination was associated with a statistically significantly lower risk of mortality from TB when compared to those who were not vaccinated with BCG.[16]

All cause mortality

Evidence comparing all cause mortality between people who received the BCG vaccine versus those who did not receive the BCG vaccine was reported in one SR with meta-analysis.[18] A meta-analysis of five clinical trials (3 RCTs, 2 quasi-RCTs) of low to moderate risk of bias, and a meta-analysis of 9 NRSs with high risk of bias, both found that the BCG vaccine was associated with a lower risk of all cause mortality when compared to those who were not vaccinated with BCG;[18] these analyses were associated with moderate and high levels of statistical heterogeneity, respectively.

Adverse Events

The SR of high-risk groups from low TB burden countries[11] aimed to examine adverse events of the BCG vaccine, and found that the reporting of adverse events was rare in studies comparing vaccinated and unvaccinated groups. The SR identified two studies that reported the number of adverse events due to the BCG vaccine but neither study conducted a comparative analysis. One RCT reported cases of osteomyelitis (0.005%) and BCGitis (0.001%) in the vaccinated group, and no cases in the unvaccinated group. A quasi-experimental study reported cases of lymphadenitis (1%) in the vaccinated group, and no cases in the unvaccinated group.

Guidelines for BCG Vaccination

Four evidence-based guidelines[21-24] included recommendations regarding BCG vaccination. In addition, a SR of guidelines[19] reported recommendations regarding BCG vaccination of health care workers from 15 guidelines, applying to 13 European countries.

BCG vaccination, general population

Three guidelines include recommendations regarding BCG vaccination of the general population.[21-23]

For high TB incidence countries, the moderate-quality guideline from the WHO[21] recommends that all healthy neonates receive the BCG vaccine at birth, or at the earliest opportunity, however the strength of the recommendation is unknown. NICE also recommends BCG vaccination of all neonates born in areas with a high incidence of TB

soon after birth, with the certainty that for most patients the vaccine will do more good than harm.[22] The WHO also recommends BCG vaccination for unvaccinated older children, adolescents and adults who test negative for TB, if they are living in or moving to a high TB incidence setting.[21]

In low TB burden countries, the high-quality NICE guideline,[22] the moderate-quality WHO guideline,[21] and the low-quality Italian pediatric guideline[23] recommend BCG vaccination to certain groups that are considered to have a higher risk of exposure to TB. These high-risk groups include those who are born in an area with high TB incidence, those whose parents or grandparents were born in a high-incidence country, or those with a family history of TB. With the exception of children who would have qualified for neonatal BCG vaccination, NICE does not recommend the BCG vaccine for children aged 10 to 14 years, as the intervention would not benefit most people.[22]

The Italian pediatric guideline strongly recommends against revaccination of previously vaccinated children.[23]

BCG vaccination in people with HIV infection

Three guidelines included recommendations specific to patients with an HIV infection (or a possible HIV infection).[21,23,24]

The moderate quality guideline from the WHO[21] includes four recommendations regarding the BCG vaccine in people with HIV infection or a possible HIV infection, however, this guideline did not grade the strength of the recommendations. According to the WHO, the BCG vaccine is contraindicated in people with HIV and other immunodeficiency syndromes.[21] The low-quality BHIVA guideline[24] also includes a strong recommendation (based on evidence the authors assessed as low-quality) against the administration of the BCG vaccine to adults and adolescents who are HIV-positive.

The low-quality Italian Pediatric guideline[23] recommends postponing BCG vaccination of newborns until the HIV status of the mother can be determined; this was a strong recommendation, based on moderate strength evidence.

For populations with a high prevalence of people infected with HIV, the WHO recommends BCG vaccination for neonates born to women of unknown HIV status, and neonates born to women with an HIV infection if the neonates does not have clinical evidence suggestive of an HIV infection.[21] In populations with a high prevalence of HIV, the WHO also recommends BCG vaccination of neonates with a confirmed HIV infection once they infant has started anti-retroviral therapy and is immunologically stable.[21]

BCG vaccination of health care workers

One guideline[22] and the SR of guidelines[19] include recommendations regarding BCG vaccination of health care workers.

The high-quality guideline by NICE[22] recommends BCG vaccination of health care workers who are likely to have direct contract with patients with TB; this recommendation was based off a SR that the authors determined to be high-quality.

The SR of guidelines[19] includes recommendations regarding BCG vaccination of health care workers for 13 European countries, however, the certainty of the recommendations is unclear as the SR did not assess the quality of the guidelines or report the strength of the recommendations. Four European countries recommend BCG vaccination for all health

care workers; one country recommends BCG vaccination for health care workers depending on their age; five countries recommend BCG vaccination for health care workers with a high risk of exposure to multi-drug resistant TB; and three countries do not recommend BCG vaccination for health care workers.[19]

BCG vaccination for other at-risk groups

Two guidelines[21,22] include recommendations regarding BCG vaccination for other at-risk groups, such as travellers and other occupations with a risk of exposure to TB.

The moderate-quality WHO guideline[21] recommends considering the BCG vaccine for travellers to countries with high TB incidence, with considerations for the duration and frequency of travel, and the country being visited, however, the strength of recommendations was not graded.

The high-quality NICE guideline[22] recommends BCG vaccination for people aged 35 and younger who have an increased risk of exposure to TB, including: staff who work with animal species known to be susceptible to TB; staff working with prisoners; staff in care homes for the elderly; staff at facilities for people who are homeless; and people travelling to high TB incidence countries for three months or more. NICE[22] also recommends BCG vaccination for contacts of people with TB, depending on their age, vaccination status, and their occupation. The NICE guideline development group is certain that for the majority of people in these groups, the BCG vaccine will do more good than harm. The moderate-quality WHO guideline also recommends BCG vaccination for those at risk of occupational exposure to TB.[21]

Limitations

There are various limitations associated with the evidence in this report on the BCG vaccine for the prevention of pulmonary TB.

A key limitation was the availability of high-quality comparative evidence. The HTA and SRs included in this report were limited by their search strategies and by not providing sufficient details on the characteristics of the primary studies, and they included evidence from studies the authors assessed to have mostly a moderate to high risk of bias, or to be very low quality. Two well conducted and well reported NRSs were also included in this report, however, the case-control study design is considered a moderately strong thus reducing the strength of the evidence. The overall low- to moderate-quality evidence reduces the certainty of the findings of this report.

Some of the evidence in this report may also be considered outdated given when the primary studies were published. The majority of the evidence found within the included HTA and SRs was published more than a decade ago (i.e., prior to 2010). In the HTA[16] three studies were published in the 1940s and one in the 1970s, and in the SR with meta-analysis[18] there was evidence from the 1930s, 1940s, and the 1980s. These older studies maybe have differences in study methodology and reporting practices which may have contributed to the lower overall quality of the evidence. Evidence published since 2010 includes the two case-control studies,[20] one quasi-experimental study in the SR of high-risk groups,[11] and one case-control study in the SR of children with HIV.[17] The BCG vaccine has been used in humans for almost 100 years,[7] and older evidence was expected, however, this older evidence may not be generalizable to current situations, particularly the use of the BCG vaccination in low TB burden countries.

The majority of the evidence in this report examines the effectiveness of the BCG vaccine with respect to all types of TB, rather than specifically relating to pulmonary TB. As such, the effectiveness of the BCG vaccine specifically for preventing pulmonary TB is less certain. The HTA[16] reported the relative risk of pulmonary TB, however, the evidence from the other studies either did not specify the type of TB or they included all types of TB in their analysis. Excluding evidence from studies that did not specifically examine pulmonary TB would have excluded a large portion of the findings from this report, thus these findings were retained for the report, however, it is important to interpret these findings appropriately.

This report is limited by the lack of findings specific to the Canadian context. Two of the primary studies within the HTA and SRs were conducted in Canada (one of which overlapped between the HTA[16] and a SR[18]), while the other primary studies were conducted in the US, Europe, Asia or Africa. In addition, while the guideline from the WHO[21] is meant to apply globally, the other guidelines are meant to apply to different European countries.[19,22-24] The 2014 TB standards published by Public Health Agency of Canada includes recommendations regarding the BCG vaccine,[10] however, this guideline has not been updated since 2014 and was not eligible for inclusion in this report. A previous CADTH report on the prevention of TB[27] includes a critical appraisal of this Canadian guideline. Overall, it is unknown if the studies conducted outside of Canada and the recommendations from guidelines developed outside of Canada are generalizable to Canadian clinical practice as there may be geographical differences in the risk of TB transmission in Canada.

Conclusions and Implications for Decision or Policy Making

This report was comprised of one HTA,[16] three SRs of primary studies,[11,17,18] and two case-control studies (published in one report)[20] regarding the clinical effectiveness of the BCG vaccine versus no BCG vaccination for the prevention of TB. One SR of guidelines[19] and four evidence-based guidelines[21-24] were summarized regarding the use of the BCG vaccine.

For the prevention of pulmonary TB, one HTA[16] with low methodological quality found evidence that receiving the BCG vaccine was associated with a lower risk of pulmonary TB compared to not receiving the BCG vaccine. The reduction in risk was observed in randomized and non-randomized studies, however, the evidence had a high risk of bias and substantial heterogeneity.

For the prevention of any type of TB in people who are immunocompetent, there was evidence from one SR[11] with low methodological quality, and two well conducted case-control studies[20] that demonstrated that the BCG vaccine was more effective in the prevention of TB compared to no BCG vaccine. The vaccine efficacy of the BCG vaccine ranged from 49% to 85% in high-risk groups in low TB burden countries,[11] however, the confidence in the findings was not reported in all studies, the studies varied in quality and study design, and they were not combined in a meta-analysis, thus the overall effect is unknown. Findings from both case-control studies published by Mangtani et al. (2017)[20] suggest that the effectiveness of the BCG vaccine may wane over time. BCG vaccination in infancy of a high-risk group was associated with a lower risk of TB for up to 10 years, but the benefit of the vaccine was not apparent 10 to 20 years after vaccination.[20] In addition, BCG vaccination of school aged children lowered the risk of TB between 10 and 20 years

after vaccination compared with those who were not vaccinated, but there was no difference in risk 20 to 30 years after vaccination.[20]

This report found evidence that receiving the BCG vaccine was associated with a reduction in mortality compared to the unvaccinated groups. A meta-analysis of RCTs in the HTA[16] found that the BCG vaccinated group was associated with a lower risk of mortality from TB compared to the unvaccinated group. Another SR with meta-analysis[18] found a lower risk of all-cause mortality in people vaccinated with BCG compared to those who did not receive the BCG vaccine, and the effect was observed in the RCTs and of the NRSs. However, two of the RCTs included in the HTA and the SR overlapped, and it is unclear to what extent the overlapping studies influenced the findings for mortality from TB and all-cause mortality.

The SR of high-risk groups from low TB burden countries[11] aimed to examine adverse effects of the BCG vaccine, but found that the reporting of adverse events was rare, and that even when adverse events were reported comparative analyses were not conducted.

Overall, people who received the BCG vaccine had a lower risk of pulmonary TB and other types of TB, and a lower risk of mortality from TB and all-cause mortality, compared to those who did not receive the BCG vaccine. There was insufficient comparative evidence on possible adverse effects of the BCG vaccine.

For the general population who are immunocompetent, the recommendations from the evidence-based guidelines[21-23] consistently recommended the BCG vaccine for the prevention of TB in people who have a high-risk of exposure to TB. The BCG vaccine is recommended for those living in high TB settings, with vaccination occurring preferably in the neonatal period.[21,22] For countries with low TB incidence, the BCG vaccine is recommended for populations at greater risk of exposure to TB based on factors such as family history of TB, place of birth of themselves or their parents, or whether they live in a setting with a high incidence of TB.[21-23] Revaccination of children was not recommended.[23] BCG vaccination is also recommended for people travelling to countries with a high TB incidence, depending on the duration and frequency of travel.[21,22]

For those with a risk of occupational exposure to TB, a high-quality guideline from 2016 recommends the BCG vaccine for health care workers who are likely to have direct contact with patients with TB.[22] In the SR of guidelines from 2016, guidelines for 10 of the 13 countries recommends the BCG vaccine for health care workers (depending on their age, and risk of exposure), but three did not recommend the BCG vaccine for health care workers.[19] The SR of guidelines did not evaluate the quality of the included guidelines, some of which may be considered out of date (they were published between 2001 and 2013), which could explain the difference in the recommendations for health care workers between the SR of guidelines and the high-quality guideline from NICE. BCG vaccination is also recommended for other groups at risk of occupational exposure, including staff in prisons, or care homes.[21,22]

For people with compromised immunity, there was evidence from two-case control studies identified in a SR with low methodological quality[17] that the BCG vaccine was not effective in preventing TB in children who are infected with HIV. The BCG vaccine is not recommended in adults with HIV infections.[21,24] However, for neonates born to women with suspected or confirmed HIV infection the recommendations are less consistent. One guideline recommends postponing the BCG vaccine until the HIV status of the mother is determined.[23] Another guideline suggests that in populations with a high prevalence of HIV that the BCG vaccine be given to neonates of mothers with known or unknown HIV status if

the neonate does not have appear to have an HIV infection, and also recommends the BCG vaccine for neonates with HIV once they are immunologically stable.[21] Thus in populations with a high prevalence of HIV, it is important to consider the likelihood of exposure to TB when considering the BCG vaccine.

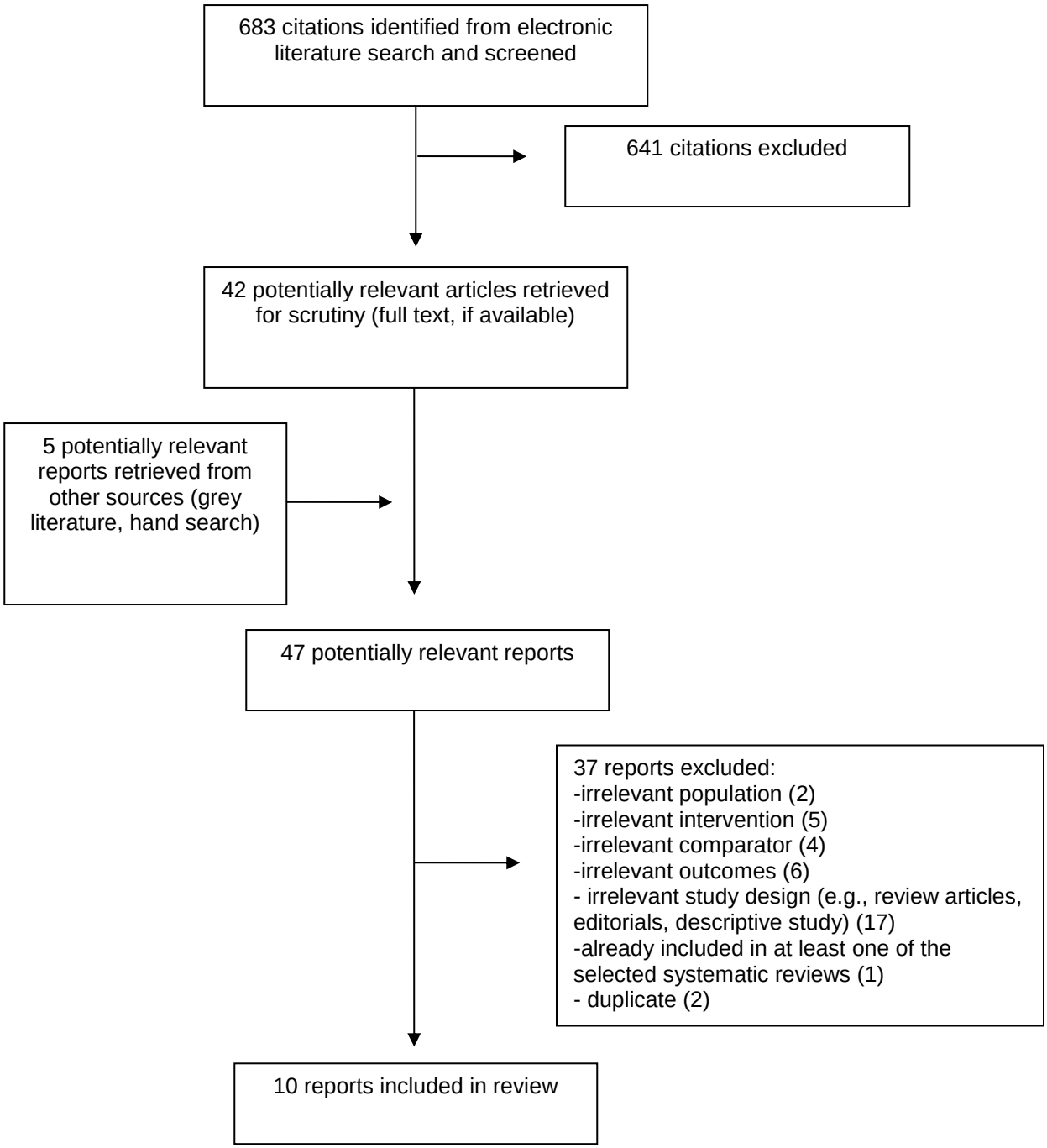
This report focused on the use of the BCG vaccine for the prevention of pulmonary TB, and includes evidence for all types of drug-susceptible TB. None of the studies or guidelines examined the BCG vaccine in the context of drug-resistant TB. Drug-resistant TB is on the rise,[28] and effective vaccines may be needed to prevent the spread. There are a number of new vaccines in development, which may help improve protection against TB, in particular pulmonary TB in adults and drug-resistant TB, however, these vaccines are still undergoing testing.[29]

The findings highlighted in this report come with a moderate degree of uncertainty and the limitations of the studies and guidelines included in this report should be considered when interpreting the findings. Although the findings in the report are limited by evidence that is mostly low- to moderate-quality and may be considered out of date (e.g., primary studies published in the 1930s to 1980s), most of the evidence included in this report demonstrated that people who are immunocompetent who receive the BCG vaccine had a lower risk of TB and mortality compared to those who are not vaccinated with the BCG vaccine. The BCG vaccine is consistently recommended for people who are immunocompetent and are likely to be exposed to TB. For people with HIV, the BCG vaccine in not recommended in adults, however, the evidence is less certain in infants born in populations with a high prevalence of HIV and TB.

References

1. Long R, Schwartzman K. Canadian Tuberculosis Standards, Chapter 2 - Pathogenesis and Transmission of Tuberculosis. 7th Ed ed. Ottawa: Public Health Agency of Canada; 2014: https://www.canada.ca/en/public-health/services/infectious-diseases/canadian-tuberculosis-standards-7th-edition/edition-14.html. Accessed 2020 Mar 6.
2. Global Tuberculosis Report 2019. Geneva: World Health Organization; 17 Oct 2019: https://www.who.int/tb/publications/global_report/en/. Accessed 2020 Jan 8.
3. The Difference Between Latent TB Infection and TB Disease Atlanta: Centers for Disease Control and Prevention; 2014: https://www.cdc.gov/tb/publications/factsheets/general/ltbiandactivetb.htm. Accessed 2020 Jan 8.
4. Tuberculosis: Symptoms and treatment. Ottawa: Public Health Agency of Canada; 2019: https://www.canada.ca/en/public-health/services/diseases/tuberculosis.html. Accessed 2020 Mar 6.
5. Halverson J, Ellis E, Gallant V, Archibald C. Canadian Tuberculosis Standards, Chapter 1 - Epidemiology of Tuberculosis in Canada. Ottawa: Public Health Agency of Canada; 2014: https://www.canada.ca/en/public-health/services/infectious-diseases/canadian-tuberculosis-standards-7th-edition/edition-13.html. Accessed 2020 Mar 6.
6. Tuberculosis: monitoring Ottawa: Public Health Agency of Canada; 2019: https://www.canada.ca/en/public-health/services/diseases/tuberculosis/surveillance.html. Accessed 2020 Jan 8.
7. von Reyn CF. Vaccines for prevention of tuberculosis. Waltham (MA): UpToDate; 2019: www.uptodate.com.
8. Principi N, Esposito S. The present and future of tuberculosis vaccinations. *Tuberculosis (Edinb).* 2015;95(1):6-13.
9. A Database of Global BCG Vaccination Policies and Practices. 2017: http://www.bcgatlas.org/. Accessed March 6, 2020.
10. Behr ME, K;. Canadian Tuberculosis Standards, Chapter 16 - Bacille Calmette-Guérin (BCG) Vaccination in Canada. 2014: https://www.canada.ca/en/public-health/services/infectious-diseases/canadian-tuberculosis-standards-7th-edition/edition-12.html.
11. Faust L, Schreiber Y, Bocking N. A systematic review of BCG vaccination policies among high-risk groups in low TB-burden countries: implications for vaccination strategy in Canadian indigenous communities. *BMC Public Health.* 2019;19(1):1504.
12. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *Bmj.* 2017;358:j4008.
13. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-384. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf. Accessed 2019 Jul 10.
14. Agree Next Steps Consortium. The AGREE II Instrument. [Hamilton, ON]: AGREE Enterprise; 2017: https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf. Accessed 2019 Jul 10.
15. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
16. Health technology assessment of a selective BCG vaccination programme. Dublin: Health Information and Quality Authority; 2015: https://www.higa.ie/sites/default/files/2017-01/BCG_technical_report.pdf Accessed 2020 Mar 9.
17. Adetokunboh OO, Ndwandwe D, Awotiwon A, Uthman OA, Wiysonge CS. Vaccination among HIV-infected, HIV-exposed uninfected and HIV-uninfected children: a systematic review and meta-analysis of evidence related to vaccine efficacy and effectiveness. *Hum Vaccin Immunother.* 2019;15(11):2578-2589.
18. Higgins JP, Soares-Weiser K, Lopez-Lopez JA, et al. Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. *Bmj.* 2016;355:i5170.
19. Bo M, Zotti CM. European policies on tuberculosis prevention in healthcare workers: Which role for BCG? A systematic review. *Hum Vaccin Immunother.* 2016;12(11):2753-2764.
20. Mangtani P, Nguipdop-Djomo P, Keogh RH, et al. Observational study to estimate the changes in the effectiveness of bacillus Calmette-Guerin (BCG) vaccination with time since vaccination for preventing tuberculosis in the UK. *Health Technol Assess.* 2017;21(39):1-54.
21. World Health O. BCG vaccine: WHO position paper, February 2018 - Recommendations. *Vaccine.* 2018;36(24):3408-3410.
22. Turnbull L, Bell C, Child F. Tuberculosis (NICE clinical guideline 33). *Archives of Disease in Childhood Education & Practice,.* 2017;102(3):136-142.
23. Montagnani C, Esposito S, Galli L, et al. Recommendations for pediatric tuberculosis vaccination in Italy. *Hum Vaccin Immunother.* 2016;12(3):644-650.
24. British HIV Assocation. British HIV Association guidelines on the use of vaccines in HIV-positive adults 2015. Letchworth Garden City (GB): British HIV Assocation; 2015: https://www.bhiva.org/vaccination-guidelines. Accessed 2020 Mar 12.
25. Principles of Epidemiology in Public Health Practice, Third Edition An Introduction to Applied Epidemiology and Biostatistics. *Lesson 3: Measures of Risk*. Atlanta: Centers for Disease Control and Prevention: https://www.cdc.gov/csels/dsepd/ss1978/lesson3/section6.html. Accessed 2020 Mar 31.
26. Public Health Agency of Canada. Prevention and Control Guidelines Critical Appraisal Tool Kit. Ottawa: Public Health Agency of Canada; 2014: http://publications.gc.ca/collections/collection_2014/aspc-phac/HP40-119-2014-eng.pdf. Accessed 2020 Mar 12.
27. Brett K, Dulong C, Severn M. Prevention of tuberculosis: a review of guidelines. *(CADTH rapid response report: summary with critical appraisal)*. Ottawa: CADTH; 2020: https://cadth.ca/prevention-tuberculosis-review-guidelines. Accessed 2020 Mar 31.
28. World Health Organization. What is multidrug-resistant tuberculosis (MDR-TB) and how do we control it? Geneva: World Health Organization: https://www.who.int/features/qa/79/en/. Accessed 2020 Feb 6.
29. Gong W, Liang Y, Wu X. The current status, challenges, and future developments of new tuberculosis vaccines. *Hum Vaccin Immunother.* 2018;14(7):1697-1716.
30. Abubakar I, Pimpin L, Ariti C, et al. Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette-Guerin vaccination against tuberculosis. *Health Technol Assess.* 2013;17(37):1-372, v-vi.
31. British HIV Association. British HIV Association (BHIVA) Guideline Development Manual. Letchworth Garden City(GB): British HIV Association; 2014: https://www.bhiva.org/GuidelineDevelopmentManual. Accessed 2020 Mar 10.
32. Public Health England. Tuberculosis: the green book, chapter 32. London (GB): Public Health England; 2018: https://www.gov.uk/government/publications/tuberculosis-the-green-book-chapter-32. Accessed 2020 March 25.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country, Funding	Literature Searched, and Numbers of Primary Studies Included	Eligibility criteria	Intervention and Comparator(s)	Relevant Clinical Outcomes, Length of Follow-Up
Health Technology assessments				
HIQA 2015[16] Ireland **Funding source:** HIQA	Clinical effectiveness chapter of the HTA. The SR was a quasi-update of a previous SR[30] that had a broader focus. **Search:** Updated the search of a previous SR[30] (conducted May 2009); new search conducted January 2015. Searched multiple databases and registries (MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, Clinical Trials Register, ClinicalTrials.gov, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database). Also searched reference lists. **Included studies:** 14 studies (all of which were identified in the previous 2009 SR[30]); includes 4 RCTs and 10 case-control studies	**Inclusion criteria:** Evidence related to BCG vaccination of neonates and infants aged less than 1 year, compared to no BCG vaccination. Included RCTs and case-control trials. Outcomes restricted to TB-related outcomes. **Exclusion criteria:** Evidence regarding older children, adolescents, and revaccinations. Vaccines other than BCG. Prevalence studies, TB control programmes, reviews.	**Intervention:** BCG vaccination in infants **Comparator:** No BCG vaccination	Restricted to TB related outcomes **Primary outcomes:** pulmonary TB **Secondary outcomes:** - TB-related mortality **Follow-up:** ranged from 2.5 to 23 years

First Author, Publication Year, Country, Funding	Literature Searched, and Numbers of Primary Studies Included	Eligibility criteria	Intervention and Comparator(s)	Relevant Clinical Outcomes, Length of Follow-Up
SRs of Primary clinical studies				
Adetokunboh 2019[17] South Africa **Funding source:** authors supported by National Research Foundation of South Africa, and National Institutes of Heath Research	Scope of this SR was broader than that of this report. **Search:** Searched Web of Science, Cochrane Library, MEDLINE via PubMed and Scopus databases, as well as references lists of identified papers. Also checked trial registries, and WHO position papers. No language or date restrictions. Search strategy not reported. **Included studies:** 2 case-control studies relevant to this report	**Inclusion criteria:** RCTs, cohort, and case-control trials on the effectiveness of vaccines in children (≤ 18 years) who are HIV-infected compared to HIV-exposed or uninfected. **Exclusion criteria:** populations > 18 years, non-human studies, reviews	**Intervention:** standard dose of the BCG vaccine **Comparator:** placebo, non-vaccinated groups	**Primary outcomes:** clinical or confirmed cases of TB **Secondary outcomes:** - vaccine efficacy or effectiveness **Follow-up:** not specified
Faust 2019[11] Canada **Funding source:** Indigenous Services Canada	**Search:** search of Medline and Embase conducted January 2018, for studies published in English or French after 1988. Detailed search strategy published online. **Included studies:** In the SR: 32 primary research studies (4 RCTs, 3 case-control, 5 quasi experimental, 8 cross-sectional, 7 cohorts, 4 modeling, 1 case report) 12 policy reports Relevant to the report: 7 studies provided relevant information on vaccine efficacy	**Inclusion criteria:** Studies regarding BCG vaccine efficacy, TB incidence under specific vaccination policies, and general BCG vaccination policy guidance for low-burden countries. Studies from a high-risk group in a low-burden country (i.e., < 100 TB cases per million population). Epidemiological studies, case studies, public health policy reports. **Exclusion criteria:** studies published before 1988; not taking place in high-risk group in a low-burden country	**Intervention:** BCG vaccine **Comparator:** no BCG vaccine	-BCG vaccine efficacy or effectiveness (reported as a %) - possible harms of vaccination **Follow-up:** not specified

First Author, Publication Year, Country, Funding	Literature Searched, and Numbers of Primary Studies Included	Eligibility criteria	Intervention and Comparator(s)	Relevant Clinical Outcomes, Length of Follow-Up
Higgins 2016[18] UK **Funding source:** WHO	Scope of this SR was broader than that of this report. **Search:** Medline and Embase (to November 2012), and Global Index Medicus and the WHO International Clinical Trials Registry Platform (to March 2013). Contact with experts was used to supplement the search. **Included studies:** 14 relevant studies for BCG vaccine	**Inclusion criteria:** clinical trials, cohort studies, and case-control studies comparing vaccinated and unvaccinated children. Vaccines of interest were BCG, DTP, and measles. Studies had to report mortality up to 5 years of age. Primary research only. **Exclusion criteria:** Reviews and meta-analyses, commentaries, or letters	**Intervention:** BCG vaccine **Comparator:** no BCG vaccine	**Primary outcomes:** All cause mortality **Follow-up:** up to 5 years
SR of Guidelines				
Bo 2016[19] Italy **Funding source:** Not reported	SR of guidelines **Search:** Pubmed searched, using keywords. No time or language limits. Reference lists also searched. Also searched online for relevant legislation, and consulted guideline databases. **Included studies:** 16 guidelines or policies published by public agencies addressing prevention and control of TB	**Inclusion criteria:** Reviews and original articles. Policy legislation. European national guidelines. Restricted to records that directly addressed current European legislation and practices of BCG vaccination of health care workers **Exclusion criteria:** Experimental studies and historical papers; BCG vaccination in populations other than health care workers; BCG vaccination in health care workers in a non-European Union countries; policies not yet implemented; papers not addressing BCG vaccine	**Intervention:** European national guidelines addressing national policies on BCG vaccination of health care workers **Comparator:** not applicable	**Primary outcomes:** Recommendations regarding BCG vaccination of health care workers **Secondary outcomes:** - the evidence supporting the recommendations

BCG = Bacillus Calmette-Guérin; DTP = diptheria-tetanus-pertussis; HIQA = Health Information and Quality Authority; HTA = health technology assessment; SR = systematic review; TB = tuberculosis

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country, Funding	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Mangtani 2017[20] UK **Funding source**: National Institute for Health Research	**Study design:** Two case-control studies. Study 1, Infant study: high-risk groups who were eligible for BCG vaccination as infants 0 to 19 years earlier Study 2, school children study: general population, low-risk children who were eligible for school-age BCG vaccination 10 to 29 years earlier For both studies: TB cases selected from UK national Enhanced TB Surveillance system from 2003 to 2012. Population-based age-matched controls were recruited. **Setting:** UK **Objective:** To assess the duration of the effect of BCG vaccination against TB	**Inclusion criteria:** Study 1: Cases = UK born ethnic minority patients (i.e. those with background from a high TB burden setting) with a confirmed TB episode between 2003 and 2012, aged 1 to 19; and who were vaccinated as infants. Recruitment restricted to areas in England with ≥ 30% of the population being Black or Asian minority Controls = people from the same target population as the cases with no diagnosis of TB, matched to cases within 5 years birth cohorts Study 2: Cases = UK born children from a white ethnic background with a confirmed TB episode, who were vaccinated around age 13 (range 10 to 15) residing in England at time of diagnosis, between 2003 and 2012; aged between 23 and 38 at time of diagnosis Controls = UK born people from a white ethnic background, residing in England, from the same birth cohorts as the cases, with no TB. Matched within 5 years of birth cohort. **Excluded:** patients with HIV were excluded as cases, but not controls; people from backgrounds other than the targeted ones, **Number of patients:** Study 1: Cases, N = 744 Controls, N = 694 Study 2:	**Intervention:** Study 1: BCG vaccine given in infancy Study 2: BCG vaccination given to TST-negative school children as part of the UK vaccination program (discontinued 2005) **Comparator:** no BCG vaccination	**Primary outcome:** Study 1: Effectiveness of BCG vaccine (level and duration) up to 19 years post vaccination Study 2: Effectiveness of BCG vaccine (level and duration) from 10 to 29 years post vaccination

First Author, Publication Year, Country, Funding	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		Cases, N = 677 Controls, N = 1170 **Sex, % male** Study 1: Cases, 44% Controls, 49.6% Study 2: Cases, 49.6% Controls, 40.2%		

BCG = Bacillus Calmette-Guérin; TB = tuberculosis

Table 4: Characteristics of Included Guidelines

Intended Users, Target Population (Country)	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
WHO, 2018[21]						
Primary users: National public health officials and managers of immunization programs Other users: international funding agencies, healthcare providers and researchers, vaccine advisory groups and manufacturers. Target population: neonates and unvaccinated children and adults in areas of high and low TB incidence, travelers (global)	BCG vaccination	Prevention of TB infection and disease TB associated death	Various SRs were conducted to inform the recommendations with varying search terms, databases, and dates searched. Unclear if SRs conducted for all questions. Evidence-to-recommendation tables were prepared, synthesizing the evidence, including the benefits and harms, values and preferences, resource use, equity, acceptability, feasibility, and the balance of the consequences.	GRADE methodology was used to assess the quality of the evidence, but the overall strength of the recommendations and quality of the evidence was not reported.	Draft recommendations were prepared by the working group. Decisions were reached by consensus, rather than voting, to ensure an in-depth discussion of the issues.	Reviewed by external experts, WHO staff, and reviewed and endorsed by the WHO Strategic Advisory Group of Experts on immunization. Decision to update the guideline will be made within two years, or sooner, if new evidence is available
Italian Pediatric Study Group, 2016[23]						
Intended users not specified. Target population: Pediatric population (Italy)	BCG vaccination	Not reported	SR of MEDLINE and the Cochrane Database of Systematic Reviews, from inception to December 2014. Also reviewed the international guidelines.	Primary studies were critically appraised using the Scottish Intercollegiate Guidelines Network methodological checklists. Methodology for evaluating the	Recommendations developed using the “Consensus Conference method”, but no reference available. Evidence and draft documents were provided to the panel prior to the meetings.	Final recommendations were revised based on discussions and reviewed by participants at the Consensus Conference for final approval.

Intended Users, Target Population (Country)	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
				quality of the evidence and the strength of the recommendations was not reported, but a grading scheme was reported.	Delphi method used to reach a consensus when the evidence did not provide consistent, clear recommendations.	External reviewers from Italy and other European countries evaluated the final report. Process for updating not reported.
NICE, 2016[22]						
Intended users: Health care professionals, TB multidisciplinary teams, substance misuse services, prisons and immigration removal centers, government, public health, volunteers, people with TB and their care givers Target population: neonates and unvaccinated children and adults in areas of high and low TB incidence, contacts of people with TB (United Kingdom)	BCG vaccination	Pulmonary TB disease TB deaths TB meningitis Laboratory confirmed TB cases Disseminated TB. Cost-effectiveness	Multiple SRs conducted to address the numerous research questions. Relevant databases searched from inception to December 2014. Detailed search strategies and eligibility criteria provided for each new SR. Meta-analyses were conducted where possible.	The NICE methodological checklists for RCTs and cohorts studies were used where appropriate for critically appraising the primary studies. GRADE evidence profiles were prepared to evaluated the body evidence. Criteria considered included risk of bias, inconsistency, indirectness, imprecision, and other considerations.	Recommendations were developed from the GRADE evidence profiles, focusing on linking the evidence to the recommendation, and balancing the trade off of benefits and harms. Consensus method was used to formulate the recommendations.	Published online for two formal rounds of public and stakeholder consultation. Involves responding to each comment and maintaining an audit trail. Standard NICE protocol for partial and full updates of guidelines: sections not updated in this version may be addressed within 2 years. Updates of specific areas may be reviewed if relevant evidence is published.
Bo 2016[19]						
Intended users: Health care	BCG vaccination	Not reported	Not reported	Not reported	Not reported	Not reported

Intended Users, Target Population (Country)	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
institutions, public health Target population: health care workers in public and private institutions in European countries (This publication was a SR of guidelines and additional details are available in Table 2)						
BHIVA, 2015[24]						
Intended users: not specified Target population: HIV-positive adults and adolescents (United Kingdom)	BCG vaccination	Not reported	Reported evidence from published peer-reviewed studies, and studies presented at conferences in the last two years was obtained. No search strategies or eligibility criteria reported.	Did not report the critical appraisal of primary studies. A modified GRADE system was used for the assessment, evaluation, and grading of the evidence and the development of the recommendation.	Recommendations developed following the BHIVA Guideline Development Manual[31] Based upon the GRADE instrument the authors aimed to reach a consensus on the strength of recommendation and level of supporting evidence.	Guideline validation not reported in the report, but the manual indicates that all guidelines are externally peer-reviewed and published online for public consultation. Does not report date of planned update.

BCG = Bacillus Calmette–Guérin; BHIVA = British HIV Association; GRADE = Grades of Recommendation, Assessment, Development and Evaluation; NICE = National Institute for Health and Care Excellence; NRS = non-randomized study; RCT = randomized controlled trial; SR = systematic review; TB= Tuberculosis; WHO= World Health Organization

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[12]

Strengths	Limitations
Health Technology Assessments	
HIQA 2015[16]	
• The research question and eligibility criteria clearly outlined the population, intervention, outcomes, and study designs of interest • Included both RCTs and NRS • Searched multiple databases, provided the complete search strategy, search was conducted less than year prior to publication • Study selection and data extraction performed in duplicate • Reasons for excluding studies was reported • Risk of bias assessment was conducted using appropriate tools in the original SR • Separate meta-analyses were conducted for the RCTs and the case-control studies • The authors declared no conflicts of interest	• No published or a priori protocol mentioned • This HTA provided minimal details about the included studies, such as year, country and sample size. The original SR includes more detail on the study characteristics, but the information is challenging to locate for the studies relevant to the current HTA. • Minimal detail of the risk of bias assessments reported within the HTA, all other information was in the original SR • Did not report source of funding for primary studies, which may be important for studies on vaccination • One meta-analysis combined the RCTs and case-controls studies and it was unclear if this was justified. Appears they combined odds ratios and relative risks in the forest plot, and no methods were provided with regards to how this meta-analysis was conducted. • Unclear whether the meta-analysis of the case-control studies used raw data or adjusted data • Risk of bias of the studies was not accounted for in the meta-analysis, and was not included in a discussion of the results • Heterogeneity was not discussed when interpreting the results • Publication bias was not assessed
SRs of Primary Clinical Studies	
Adetokunboh 2019[17]	
• Eligibility criteria provides clear descriptions of the population, intervention, comparators, and outcomes of interest • Study protocol registered online • Both RCTs and NRSs were eligible for inclusion • Searched multiple databases • Study selection performed in duplicate • Used an adapted Cochrane risk of bias tool for observational studies • The authors report no conflicts of interest • Some authors received funding, and it was stated that the views expressed are those of the authors not the funders	• Did not provide search strategy or key words thus unclear whether search was comprehensive • Did not report date of search, thus unclear when search was completed • Data extraction was conducted by two authors, but unclear if it was done in duplicate or how discrepancies were resolved, thus reducing certainty in the evidence • Did not report list of excluded studies, or reasons for exclusion • Minimal detail provided for included studies; missing information included the number of people in the two group (i.e., number of cases vs. the number of controls)

Strengths	Limitations
	• Uncertainty with risk of bias assessment due to color and symbol combinations not matching between the figure and the legend, thus is it unclear which symbols indicate which level of bias • Did not report source of funding for primary studies, which may be important for vaccine studies • The quality of the studies and potential heterogeneity was not considered when discussing the findings
Faust 2019[11]	
• Eligibility criteria provides clear descriptions of the population, outcomes, study designs • Included a variety of study designs • Searched two databases, and provide complete search strategy with date restrictions • Reasons for excluding studies was reported • Appropriate tools were used to asses risk of bias in the different study designs, and the results were presented for the individual studies and as a group • Declared that the funding body did not influence the report • The authors declared no conflicts of interest	• Research question unclear • Protocol was not registered a priori • Did not report searching reference lists or grey literature, which would have been relevant given the interest in policy reports • Did not report whether study selection or data extraction was performed in duplicate • Did not report source of funding for primary studies, which may be important for studies on vaccination • Insufficient study characteristics provided, including the study population details, the intervention and control groups, and the study design. Details that were provided were not presented clearly, reducing clarity of the evidence. • Did not include a discussion of risk of bias or heterogeneity when considering the results
Higgins 2016[18]	
• Research question and eligibility criteria provide clear descriptions of the population, intervention, comparator, and outcome of interest • SR protocol was published a priori, and included the eligibility criteria, search strategy, risk of bias assessment • Included RCTs and NRS due to the type of hypothesis • Comprehensive search strategy, including searching multiple databases and expert consultation • Study selection and data extraction performed in duplicate • Reasons for excluding studies was reported • Risk of bias was assessed using appropriate techniques for RCTs and NRS, and presented for each study. • Meta-analysis conducted separately for RCTs and NRS; NRS used adjust data rather than raw data. • Very high risk of bias studies excluded from the meta-analysis • Sources of heterogeneity were discussed • The authors declared no conflicts of interest • Funding was independent of the review	• Search may have been out of date; mainly conducted late 2012 or early 2013, but not published until September 2016 • Study characteristics were partially described; additional detail would have improved understanding of the body of evidence • Did not report source of funding for primary studies, which may be important for studies on vaccination • Results from meta-analysis presented for fixed effects and random effects models, however, unclear whether random effects model was done properly • Due to heterogeneity of follow-up time and country of origin, it is unclear whether the data should have been combined in a meta-analysis • Publication bias was not assessed as there were too few studies to perform a funnel plot

Strengths	Limitations
SR of Guidelines	
Bo 2016[19]	
• Population and intervention of interest were clear • Provided key words for the search, did not have date or language restrictions, and searched grey literature and reference lists • Reasons for excluding studies was reported • Discussion included possible reasons for the differences in recommendations across guidelines • The authors declared no conflicts of interest	• Eligibility criteria regarding what was considered a guideline was unclear, and it is unclear whether only evidence-based guidelines were included • No published or a priori protocol mentioned • Only searched one database and did not provide full search strategy • Did not report when the search was conducted, thus unclear whether the most recent evidence (at the time) was captured • Did not report whether study selection performed in duplicate • Unclear whether data extraction performed in duplicate; number of reviewers not reported, but mentions that disagreements resolved through consensus • Did not provide adequate description of the included guidelines; no methods or development process provided for the included guidelines • Did not assess the quality of the guidelines, creating uncertainty in the quality of the recommendations • No source of funding reported, thus unclear if a conflict exists from the funder

HIQA = Health Information and Quality Authority; NRS = non-randomized study; RCT = randomized control trial; SR = systematic review;

Table 6: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[13]

Strengths	Limitations
Mangtani 2017[20]	
• Objective of the study is clear • The characteristics of the cases and control groups, as well as the intervention were clearly described • Main findings well reported, with estimates of uncertainty (i.e., confidence intervals) and actual probability values (P values) reported • The cases and controls were recruited from the same population and are representative of the population to which the intervention would apply • Assessment of BCG vaccination status relied on more than one source of information (e.g., two types of health records), thus reducing the likelihood of bias in the assessment • Statistical analysis plan adjusted for multiple confounders and accounted for time since the intervention • Explicit statement that the views of the funding agency did not influence the report	• Due to the nature of a case-control study, it is not possible to blind the participants to the outcome (i.e., TB) or the intervention (i.e., vaccination status) • Investigators were not blinded, however, the assessment of the BCG scar was done by highly trained individuals. • Unable to determine BCG vaccination status of all individuals, these were considered missing data and not included in the analysis. Similar percentages of missing data in the cases and controls for both studies. • One author declared a competing interest (i.e., involvement with the board of the funding institution), and it was not addressed how this conflict was handled

BCG = Bacillus Calmette-Guérin; TB = tuberculosis.

Table 7: Strengths and Limitations of Guidelines using AGREE II[14]

Item	Guideline			
	WHO, 2018[21]	Italian Pediatric Study Group, 2016[23]	NICE, 2016[22]	BHIVA, 2015[24]
Domain 1: Scope and Purpose				
1. The overall objective(s) of the guideline is (are) specifically described.	Partially	Yes	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes	Yes	No
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Partially	Partially	Yes	Yes
Domain 2: Stakeholder Involvement				
4. The guideline development group includes individuals from all relevant professional groups.	Partially	Partially	Yes	Partially
5. The views and preferences of the target population (patients, public, etc.) have been sought.	No	No	Yes	No
6. The target users of the guideline are clearly defined.	Yes	No	Yes	No
Domain 3: Rigour of Development				
7. Systematic methods were used to search for evidence.	Partially	Yes	Yes	No
8. The criteria for selecting the evidence are clearly described.	Partially	No	Yes	No
9. The strengths and limitations of the body of evidence are clearly described.	Partially	No	Yes	No
10. The methods for formulating the recommendations are clearly described.	Partially	Partially	Yes	Partially
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Partially	Partially	Yes	No
12. There is an explicit link between the recommendations and the supporting evidence.	Partially	Partially	Yes	No
13. The guideline has been externally reviewed by experts prior to its publication.	Partially	Partially	Yes	Partially

Item	Guideline			
	WHO, 2018[21]	Italian Pediatric Study Group, 2016[23]	NICE, 2016[22]	BHIVA, 2015[24]
14. A procedure for updating the guideline is provided.	Yes	No	Yes	No
Domain 4: Clarity of Presentation				
15. The recommendations are specific and unambiguous.	Yes	Yes	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	NA	NA	Yes	NA
17. Key recommendations are easily identifiable.	Partially	Yes	Yes	Yes
Domain 5: Applicability				
18. The guideline describes facilitators and barriers to its application.	Yes	No	No	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	No	No	Partially	No
20. The potential resource implications of applying the recommendations have been considered.	Partially	No	Yes	No
21. The guideline presents monitoring and/or auditing criteria.	Yes	No	Yes	No
Domain 6: Editorial Independence				
22. The views of the funding body have not influenced the content of the guideline.	Yes	Partially	Partially	Yes
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	Yes	Yes	Partially

BHIVA = British HIV Association; NA = not applicable; NICE = National Institute for Health and Care Excellence; WHO = World Health Organization.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 8: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Health Technology Assessments	
HIQA 2015[16]	
Summary of studies included in the SR: Three RCTs conducted in North America, published in the 1940s, and one RCT conducted in India, published in 1976. One RCT included two sub studies, thus there are 5 RCT datasets. RCTs had lower risk of reporting bias and detection bias, and had higher risk of bias for randomization and blinding. The case-control studies were all published since 1980, and were published in India (n = 3), Indonesia, Thailand, Argentian, Myanmar, Brazil, and Mexico. All case-control studies were at high risk of bias for at least one of three criteria. **Pulmonary TB:** Evidence from RCTs: RR = 0.40, 95% CI, 0.26 to 0.60 Random effects, 5 RCT datasets, I^2 =20.3% Evidence from case control: OR = 0.47, 95% CI, 0.34 to 0.63 Random effects, 6 case-control studies, I^2 = 76.1% Evidence from all studies: RR = 0.44, 95% CI, 0.35 to 0.56 Random effects, 11 studies, I^2 = 60.6% **TB mortality** RR = 0.16, 95% CI, 0.05 to 0.50 Random effects, 4 RCT datasets, I^2 = not reported	"BCG vaccination is associated with substantial reductions in the risk of TB and TB mortality. The pooled estimates of RCT and case-control evidence suggest relative risks of 0.44 for pulmonary TB, 0.22 for extrapulmonary TB, 0.26 for TB meningitis, and 0.16 for TB mortality." (p. 71)
SRs of Primary Clinical Studies	
Adetokunboh 2019[17]	
Case-control study, 2015, HIV-infected children (Angola**)** Low risk of bias for: attrition bias, selection bias, origin of data, definition of outcomes, confounders GRADE = very low quality evidence N = 902 TB in HIV-infected children, BCG vaccinated vs. unvaccinated	"Vaccine effectiveness of BCG vaccine in preventing tuberculosis in HIV infected children was zero compared to 59% protection in HIV unexposed children" (p. 2584)

Main Study Findings	Authors' Conclusion
Vaccine effectiveness: 8%, 95% CI, –26 to 32 Adjusted vaccine effectiveness: 30%, –75 to 72 **Case-control study, 1993, HIV-infected and HIV-uninfected children (**Zambia) Low risk of bias for: attrition bias, selection bias, origin of data, definition of outcomes High-risk of bias for: confounders GRADE = very low quality evidence N = 270 <u>TB in HIV-infected children</u> BCG vaccinated vs. unvaccinated: OR = 1.00, 95% CI, 0.22 to 4.56 Vaccine effectiveness: 0%, 95% CI, –360 to 78 <u>TB in HIV-uninfected children</u> BCG vaccinated vs. unvaccinated: OR = 0.41, 95% CI, 0.18 to 0.92 Vaccine effectiveness: 59%, 95% CI, 8 to 82	
Faust 2019[11]	
BCG Vaccine efficacy 7 studies compared BCG vaccinated vs. unvaccinated individuals, and provided results on vaccine efficacy that was relevant to this report. Quasi-experimental study, Czech Republic, 1993, N = 148,560 ceased vaccination, N = 600,195 mass vaccination: vaccine efficacy = 80% Quasi-experimental study, France, 2011, N = not reported: vaccine efficacy = 105 TB cases with lower BCG coverage vs. 82 TB cases with higher BCG coverage Quasi-experimental study, Ireland, 1997, areas without neonatal BCG coverage vs. with universal coverage: incidence rate ratio TB = 1.92, 95% CI, 1.47 to 2.40 in 1986, and 2.12, 95% CI, 1.75 to 2.58 in 1991 Quasi-experimental, 2004, USA, N = 1483 BCG, N = 1309 placebo : vaccine efficacy = 52%, 95% CI, 27 to 69 Retrospective cohort, Sweden, 2006, routine vs. targeted vaccination, N = not reported: vaccine efficacy = 85% in 1969 to 1974 Case-control, UK, 1991, N = 111 with TB, N = 55 no TB: vaccine efficacy = 49%, 95% CI, 14 to 62	"Two arm studies comparing vaccinated to non-vaccinated groups (or areas with higher vs. lower vaccine coverage) generally report a higher incidence of TB in nonvaccinated (or low-coverage) groups compared to vaccinated (or high-coverage) groups. Despite this, reported vaccine efficacy however varied widely across studies, ranging from 49% (95%CI: 14–62%) in a study of Asian children living in the UK [53] to as high as 87.5% (95%CI: 30–98%) in a study of the general French population" (p. 9) "Findings that supported targeted vaccination among selected risk groups rather than universal vaccination included a high number of vaccinations needed to prevent one TB case in low-burden areas" (p. 9) "Given the variation in its reported efficacy and the high number of vaccinations needed to prevent one TB case in a low-incidence setting, there was general consensus among the reviewed studies that the replacement of universal screening with targeted screening of high-risk groups is justified in low-burden countries" (p. 27)

Main Study Findings	Authors' Conclusion
Case-control study, Canada, 1990, N = 160 with TB, N = 314 no TB: vaccine efficacy = 57%, 95% CI, 23.4 to 75.3 **BCG-associated adverse events** Two studies that compared BCG vaccination vs. no vaccination reported adverse events, but not comparative analyses were reported. One quasi-experimental study reported 8 cases of osteomyelitis (0.005%) and 2 cases of BCGitis (0.001%) in the vaccinated group, and no cases in the unvaccinated group. One RCT reported 23 cases of lymphadenitis (1%) in the vaccinated group, and no cases in the unvaccinated. Quality assessments: cohort studies were generally high quality; case-control studies insufficiently reported blinding of outcome assessors; quasi-experimental studies had insufficient details on the study groups.	
Higgins 2016[18]	
From the clinical trials: -3 RCTs, 2 quasi-RCTs **-** follow up ranged from 1 to 60 months -one from Canada, two from the US, from the 1930s and 1940s; two of which were conducted in Indigenous peoples (moderate risk of bias) - two from a country in West Africa in low birth weight babies from 2002 to 2008 (low risk of bias) BCG on mortality: RR = 0.76, 95% CI, 0.59 to 0.97 Fixed effects, P = 0.20, I^2 = 33% **From the observational studies:** -1 case-control, 8 cohort studies (all high risk of bias) - follow up ranged from 6 to 36 months - five studies from African countries, from the 1980s and 1990s - two studies from India, 1980s to 2002 - one study from Papua New Guinea BCG on mortality: RR = 0.49. 95% CI, 0.40 to 0.61 Fixed effects, P = 0.005, I^2 = 63% The results from four cohort studies were considered very high risk of bias and excluded from the meta-analysis	"Among the cohort studies of BCG vaccine, the mortality risk ranged from 1% over 12 months to 9% over 24 months. Assuming a 2% mortality risk over six months, vaccine relative risks of 0.5 and 0.75 would imply that there were 10 and five fewer deaths, respectively, per 1000 children during this period of time." (p. 11) "Evidence suggests that receipt of BCG … reduce overall mortality by more than would be expected through their effects on the disease prevent." (p. 1) "Findings from the studies included in this review are not necessarily applicable to infants and children globally. Follow-up periods were often of necessity short, mostly to less than 12 months of age for BCG and to less than 9 months of age for DTP. Many of the studies took place in communities with many years of use of these vaccines. In these studies, a combination of direct vaccine effects and herd immunity gave rise to low incidences of the diseases targeted by the vaccines, so that net benefits of routine use of these vaccines may not have been apparent." (p. 11)

Main Study Findings	Authors' Conclusion
SR of Guidelines	
Bo 2016[19]	
Evidence on which the recommendations in the guidelines were based was not reported in this SR of guidelines. 16 guidelines provided recommendations regarding the provision of the BCG vaccine for health care workers in European countries: 4 countries recommend BCG vaccination for all health care workers who have contact with patients with TB: Bosnia-Herzegovina, France, Norway, United Kingdom 1 country recommends BCG vaccination for all health care workers depending on their age: Ireland 5 countries recommend BCG vaccination for health care workers with a high risk of exposure to TB or multi-drug resistant TB : Belgium, Italy, Poland, Spain, Sweden 3 countries do not recommend BCG vaccination for health care workers: Germany, Portugal, Netherlands	"Differences still exist among European national policies regarding the immunization of health care workers against TB. In four countries, BCG is required or recommended for all previously unvaccinated Mantoux negative health care workers that may have contact with patients. In five other countries, immunization is only recommended for health care workers who are employed in high-risk sectors. In one country, the recommendations vary according to the health care workers' age. Finally, 4 countries do not currently recommend immunization against TB for health care workers." (p. 2756)

BCG = Bacillus Calmette-Guérin; CI = confidence interval; HIQA = Health Information and Quality Authority; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; TB = tuberculosis;

Table 9: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Mangtani 2017[20]	
Study 1, infant BCG vaccination: **Risk of TB, vaccinated vs. unvaccinated:** 1 to 5 years post BCG: HR = 0.34, 95% CI, 0.15 to 0.78, P = 0.011 5 to 10 years post BCG: HR = 0.25, 95% CI, 0.11 to 0.56, P = 0.001 10 to 15 years post BCG: HR = 0.64, 95% CI, 0.64 to 1.68, P = 0.361 15 to 20 years post BCG: HR = 2.26, 95% CI, 0.0.34 to 15.10, P = 0.400 Cases, N = 379; Controls, N = 378 Multivariate model adjusted for: number of people per bedroom, area-level deprivation quintile, and highest parental educational level. Study 2, school aged BCG vaccination: **Risk of TB, vaccinated vs. unvaccinated:** 10 to 15 years post BCG: HR = 0.49, 95% CI, 0.31 to 0.79, P = 0.003 15 to 20 years post BCG: HR = 0.43, 95% CI, 0.28 to 0.67, P < 0.001 20 to 25 years post BCG: HR = 0.75, 95% CI, 0.49 to 1.14, P = 0.174 25 to 30 years post BCG: HR = 0.99, 95% CI, 0.53 to 1.84, P = 0.97 Cases, N = 532; Controls, N = 993 Multivariate model adjusted for: area-level deprivation, educational level, lifestyle variables, history of homelessness, history of prison stays, and TB risk from regular travels abroad	Study 1: "Good evidence of a protective effect of the vaccine was noted in the < 5-year time period and in the 5- to 10-year period before and after adjusting for confounding. The evidence for a protective effect of the vaccine in the time period 10–15 years was weaker, both in the baseline analysis and more so in the adjusted analysis" (p. 34) Study 2: "There was strong evidence of a protective effect of the vaccine in each of the 5-year periods from 10 to 20 years post vaccination." (p. 40) Both studies: "The results from our studies of the duration of protection of BCG vaccination indicate that protection persists for at least 10 years for infant vaccination in a population at high risk for TB and for at least 20 years for school-age vaccination in a low-risk population." (p. 44)

BCG = Bacillus Calmette-Guérin; CI = confidence interval; HR = hazard ratio;

Table 10: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations, evidence that informed the recommendations
WHO, 2018[21]	
Recommendation 1: "BCG vaccination is recommended in countries or settings with a high incidence of TB (i.e., countries with high incidence of TB are those with a TB notification rate >40 TB cases (all forms) per 100 000 population per year)" (p. 92) Recommendation 2: "In countries or settings with a high incidence of TB (i.e., countries with high incidence of TB are those with a TB notification rate >40 TB cases (all forms) per 100 000 population per year) a single dose of BCG vaccine should be given to all healthy neonates at birth, for prevention of TB. If BCG vaccine cannot be given at birth, it should be given at the earliest opportunity thereafter and should not be delayed, in order to protect the child before exposure to infection occurs." (p. 93) Recommendation 3: "Countries with low incidence of TB (i.e., countries with low-incidence of TB are those with a TB notification rate of <10 TB cases (all forms) per 100 000 population per year) may choose to vaccinate neonates selectively in groups at high risk for TB. High-risk groups to be considered for vaccination include the following: neonates born to parents (or other close contacts/ relatives) with current or previous TB; neonates born in households with contacts to countries with high incidence of TB; neonates in any other locally identified risk group with TB." (p. 93) Recommendation 4: "BCG vaccination of older age groups is recommended for the following: unvaccinated TST- or IGRA-negative older children, adolescents and adults from settings with high incidence of TB; unvaccinated TST- or IGRA-negative older children, adolescents and adults moving from low to high TB incidence/ leprosy burden settings; unvaccinated TST- or IGRA-negative persons at risk of occupational exposure in low and high TB incidence areas (e.g. health-care workers, laboratory workers, medical students, prison workers, other individuals with occupational exposure) (p. 94) Recommendation 5: "An individual risk assessment based on duration of travel, and the TB incidence in the country to be visited, should be considered before vaccination of unvaccinated TST- or IGRA-negative travellers from non-TB endemic countries to TB endemic countries. Young unvaccinated children travelling to high TB incidence countries, particularly those likely to have repeated travel during childhood, should be vaccinated." (p. 95) Recommendation 6: "BCG vaccination is contraindicated for persons with congenital cell-mediated or severe combined immunodeficiency, immunodeficiency syndromes (e.g. HIV/AIDS, known or suspected congenital immunodeficiency, leukaemia,	Strength of the evidence and recommendations was not reported. Evidence for the effectiveness of the BCG vaccine against pulmonary TB from a SR and meta-analysis of 18 RCTs comparing the incidence of pulmonary TB in the vaccinated group versus the unvaccinated group found that the protection was 59% (RR 0.41, 95% CI: 0.29–0.58) for those vaccinated as neonates. When the BCG vaccine was given in childhood protection was 74% (RR 0.26, 95% CI: 0.18–0.37). A SR and meta-analysis of 12 cohort studies found that the protection against pulmonary TB ranged from 44% to 99% in 11 studies, with no protection in one study. Children with HIV have an increased risk of developing BCG disease after BCG vaccination, however, since populations with a high prevalence of HIV also have the greatest burden of TB, the potential benefits of BCG vaccine outweigh the risks associated from the vaccine.

Recommendations	Strength of Evidence and Recommendations, evidence that informed the recommendations
lymphoma or other malignant disease) and for patients undergoing immunosuppressive treatment (e.g. corticosteroids, alkylating agents, biological response modifiers, antimetabolites, radiation). Infants exposed to immunosuppressive treatment in utero or via breastfeeding should not receive BCG vaccination." (p. 94) In populations with a high-prevalence of HIV: Recommendation 7: "Neonates born to women of unknown HIV status should be vaccinated as the benefits of BCG vaccination outweigh the risks." (p. 95) Recommendation 8: "Neonates of unknown HIV status born to HIV infected women should be vaccinated if they have no clinical evidence suggestive of HIV infection, regardless of whether the mother is receiving ART." (p. 95) Recommendation 9: "Although evidence is limited, for neonates with HIV infection confirmed by early virological testing, BCG vaccination should be delayed until ART has been started and the infant confirmed to be immunologically stable (CD4 >25%)." (p. 95)	
Italian Pediatric Study Group, 2016[23]	
Recommendation 1: "BCG vaccination is recommended in Italy for all TST negative newborns/breastfeeding infants aged <6 months coming from areas in which TB is highly endemic, or whose parents come from areas in which TB is highly endemic" (p. 648) Recommendation 2: "BCG vaccination is recommended in Italy for all TST negative newborns/breastfeeding children aged <6 months who have come into contact with a family member affected by active TB and in whom the presence of the disease has been excluded" (p. 648) Recommendation 3: "BCG vaccination is recommended in Italy for all TST negative children aged from 6 months to at least 5 y coming from areas in which TB is highly endemic, or whose parents come from areas in which TB is highly endemic" (p. 648) Recommendation 4: "BCG vaccination is recommended in Italy for all TST negative children aged from 6 months to at least 5 y who have come into contact with a family member affected by active TB" (p. 648) Recommendation 5: "previously vaccinated children should not receive a second vaccination" (p. 648)	Recommendations 1, 2, 3, and 4: Moderate recommendation; based on high-quality evidence from more than one properly designed RCT or SR of RCTs Recommendation 5: Strong recommendation; based on high-quality evidence from more than one properly designed RCT or SR of RCTs Recommendation 6: Strong recommendation, based on evidence from cohort studies or their meta-analyis Evidence concerning the efficacy of the BCG vaccine was considered from 4 meta-analyses, 10 cohort studies, two RCTs, and one cost-efficacy study. Evidence concerning the duration of protection of the BCG vaccine was found in 2 meta-analyses, 2 RCTs, and one cohort study. The safety of the BCG vaccine was examined in six studies. The conclusions drawn from the evidence were: that the BCG vaccine offers a fair level of protection against pulmonary TB; the protective effect of the vaccine lasts at least 10 years; BCG vaccine is safe in immunocompetent people; the most frequent

Recommendations	Strength of Evidence and Recommendations, evidence that informed the recommendations
Recommendation 6: “before vaccinating a newborn, it is necessary to ascertain that the mother was screened for HIV during her pregnancy. If she was not screened, BCG vaccination should be postponed until HIV infection has been excluded” (p. 648)	adverse events are the abscesses and suppurative lymphoadenopathy.
NICE, 2016[22]	
BCG vaccination in neonates (0 to 4 weeks) Recommendation 1: “Preferably vaccinate babies at increased risk of TB before discharge from hospital or before handover from midwifery to primary care. Otherwise, vaccinate as soon as possible afterwards, for example, at the 6-week postnatal check.” (p. 10) Recommendation 2: “Primary care organizations with a high incidence of TB should consider vaccinating all neonates soon after birth.” (p. 10) “A high-incidence country or area has more than 40 cases of TB per 100,000 people per year. Public Health England lists high-incidence countries and areas of the UK on its website.” (p. 80) Recommendation 3: “In areas with a low incidence of TB, primary care organizations should offer BCG vaccination to selected neonates who: were born in an area with a high incidence of TB; or have 1 or more parents or grandparents who were born in a high-incidence country; or have a family history of TB in the past 5 years.” (p. 10) **BCG vaccination for infants (0 to 5 years) and older children (6 to 15 years)** Recommendation 4: “Routine BCG vaccination is not recommended for children aged 10–14 years. • Healthcare professionals should opportunistically identify unvaccinated children older than 4 weeks and younger than 16 years at increased risk of TB who would have qualified for neonatal BCG and provide Mantoux testing and BCG vaccination (if Mantoux-negative). • This opportunistic vaccination should be in line with the Green Book.[32]” (p. 11) **BCG vaccination for health care workers** Recommendation 5: “Offer BCG vaccination to healthcare workers and other NHS employees as advised in the Green Book.” (p. 12) • “Healthcare worker (HCW) or laboratory worker, who has either direct contact with TB patients or with potentially infectious clinical materials or derived isolates.” (p. 7, Green Book[32]) **BCG vaccination for contacts of people with active TB**	**BCG vaccination in neonates (0 to 4 weeks)** Recommendations 1 and 2: the benefit is less certain, and an intervention will do more good than harm for most patients. Recommendation 3: for the vast majority of patients, the intervention will do more good than harm Evidence from one meta-analysis, one cohort study, and one case control study, investigating the effectiveness of the BCG vaccination in neonates and infants compared to unvaccinated groups in relevant populations, was used to inform the recommendations. Neonatal BCG vaccine was significantly better than no vaccine for pulmonary disease, death, meningitis, laboratory-confirmed TB, and disseminated TB. **BCG vaccination for infants (0 to 5 years) and older children (6 to 15 years)** Recommendation 4: the intervention will not be of benefit for most patients Evidence from one RCT and two cohort studies that investigated the effectiveness of the BCG vaccine administered in school-aged children for preventing TB was used to inform the recommendation. BCG vaccination of school-aged children led to a reduction in the annual incidence of TB disease compared to unvaccinated children. However, given the low risk of TB exposure in school-aged children in the UK, and the high cost of the school program, it was determined that routine BCG vaccination of children aged 10 to 15 should be discontinued. **BCG vaccination for health care workers** Recommendation 5: for the vast majority of patients, the intervention will do more good than harm Evidence from one SR (assessed by the authors as high-quality) investigating the efficacy of the BCG vaccine in health care

Recommendations	Strength of Evidence and Recommendations, evidence that informed the recommendations
Recommendation 6: "Offer BCG vaccination to Mantoux-negative contacts of people with pulmonary and laryngeal TB if they: have not been vaccinated previously (that is, there is no adequate documentation or a BCG scar) and are aged 35 years or younger or are aged 36 years and older and a healthcare or laboratory worker who has contact with patients or clinical materials." (p. 12) **BCG vaccination for other groups** Recommendation 7: "Offer BCG vaccination to previously unvaccinated, Mantoux-negative people aged 35 years or younger in the following groups at increased risk of exposure to TB, in accordance with the Green Book: • veterinary and other staff such as abattoir workers who handle animal species known to be susceptible to TB, such as simians • prison staff working directly with prisoners • staff of care homes for older people • staff of hostels for people who are homeless and facilities accommodating refugees and asylum seekers • people going to live or work with local people for more than 3 months in a high-incidence country." (p. 13)	workers for preventing TB infection or disease showed a consistent trend to benefit of the BCG vaccine, but no meta-analysis was conducted due to heterogeneity **BCG vaccination for contacts of people with active TB** Recommendation 6: for the vast majority of patients, the intervention will do more good than harm One cohort study and four non-analytic studies that investigated the efficacy of BCG vaccination of people who are contacts of people with active TB disease compared to unvaccinated contacts of the same population were used to inform the recommendation. The evidence showed some protective effect of BCG vaccination prior to contact with people with TB, but no studies addressed the efficacy of the vaccine administered to people after exposure to TB. **BCG vaccination for other groups** Recommendation 7: for the vast majority of patients, the intervention will do more good than harm Recommendation is from the 2011 version of the NICE guideline; evidence not reported in this version.

Bo 2016[19]

Summary of the recommendations provided in the SR of guidelines. Minimal evidence (1 to 2 sentences) was provided for each guideline within the SR of guidelines. The recommendations were not graded.

Country, year(s) of guidelines	BCG vaccination of health care workers is recommended for:	Evidence cited in support of the recommendations
Bosnia-Herzegovina, 2008	• all unvaccinated and Mantoux-negative • those in contact with patients with TB	None
France, 2003	• all unvaccinated and Mantoux-negative • those in contact with patients with TB	Evidence of BCG efficacy in adults for pulmonary TB is unclear. Some studies suggest efficacy of BCG in adults.
Norway, 2006	• all unvaccinated and Mantoux-negative • those in contact with patients with TB	"The vaccine does not provide full protection against tuberculosis but does protect against the most dangerous forms of tuberculosis. The vaccine has not proven effective in people older than 35 years" (p. 2757)

Recommendations		Strength of Evidence and Recommendations, evidence that informed the recommendations
UK, 2011 and 2013	For those from the UK: • all who are unvaccinated and Mantoux-negative and have contact with patients with TB For those from high-incidence countries: • all who are unvaccinated and IGRA-negative • those who have had contact with patients in high-TB prevalence settings	• controlled studies showed a consistent trend of a benefit of BCG vaccine for health care workers • the efficacy of BCG in other settings suggests it is unlikely that the vaccine would not be effective for health care workers
Ireland, 2010	Those < 35 years: • unvaccinated and Mantoux-negative and have contact with patients with TB Those ≥ 35 years: • unvaccinated and Mantoux-negative depending on the country of origin and their role	BCG is probably most effective against TB meningitis and military TB Efficacy around 80%, and lasts 15 to 20 years
Belgium, 2013	• those with increased risk of exposure to multi-drug resistant TB • those who have spent long periods of time in high-prevalence countries	BCG efficacy ranged from 0 to 80% Protection lasted 10 to 15 years
Italy, 2013	• those with increased risk of exposure to multi-drug resistant TB • those with contraindications to TB therapy	"The efficacy of BCG among adults is discussed" (p. 2759) (no other information provided)
Poland, 2001	• those with increased risk of exposure to TB	"BCG has no effect on reducing the number of pulmonary TB cases in adults" (p. 2759)
Spain, 2010	• those with increased risk of exposure to multi-drug resistant TB	• efficacy of BCG in health care workers has not been proven • varying efficacy against pulmonary TB • BCG does not prevent TB infection
Sweden, 2013	• those with increased risk of exposure to multi-drug resistant TB	"The protective effect in adults is less documented than in children, but the risk of infection with MDR-TB enhances the recommendations for BCG BCG is rarely justified in the healthcare and social sectors" (p. 2760)
Germany, 2007	Not recommended	"BCG vaccination cannot prevent infection/illness" (p. 2760)
Poland, 2013	Not recommended	"The efficacy of BCG for preventing pulmonary TB is discussed." (p. 2760) (no other information provided)
Netherlands, 2009 and 2013	Not recommended	BCG does not provide absolute protection against TB, and can complicate the diagnosis

Recommendations	Strength of Evidence and Recommendations, evidence that informed the recommendations
BHIVA, 2015[24]	
"We recommend that the BCG vaccine be absolutely contraindicated in all HIV-positive persons regardless of CD4 cell count, ART use, viral load, and clinical status" (p. 83) Note: in this guideline 'persons' refer to adults and adolescents	Strong recommendation, based on low quality evidence. The evidence reported here suggest that the efficacy of the BCG vaccine in children and adults infected with HIV has not been determined. Fatal dissemination has been described following BCG vaccination in immunocompromised individuals. People with HIV are a greater risk of local and systemic complications including disseminated BCG. There is no clear benefit of the BCG vaccine in HIV-positive people that may offset the potential risk.

BCG = Bacillus Calmette–Guérin; BHIVA = British HIV Association; GRADE = Grades of Recommendation, Assessment, Development and Evaluation; IGRA = interferon-gamma release assay; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NRS = non-randomized study; RCT = randomized controlled trial; SR = systematic review; TB= Tuberculosis; TST= Tuberculin skin test; WHO= World Health Organization

Appendix 5: Additional References of Potential Interest

Irrelevant comparator

Thysen SM, Benn CS, Gomes VF, et al. Neonatal BCG vaccination and child survival in TB-exposed and TB-unexposed children: a prospective cohort study. BMJ Open. 2020;10(2):e035595.

> Control group was children without neonatal BCG, and included delayed BCG vaccination or no BCG vaccination. 87% of control group received the BCG vaccine after the neonatal period.

Alfawaz TS, Alshehri M, Alshahrani D. BCG related complications: A single center, prospective observational study. Int J Pediatr Adolesc Med. 2015;2(2):75-78.

> No comparator group, reported on complications following BCG vaccine.

Bolursaz MR, Lotfian F, Velayati AA. Bacillus Calmette-Guerin vaccine complications in Iranian children at a University Hospital. Allergol Immunopathol (Madr). 2017;45(4):356-361.

> No comparator group, reported on complications following BCG vaccine.

Barari-Savadkouhi R, Shour A, Masrour-Roudsari J. A study of the incidence of BCG vaccine complications in infants of Babol, Mazandaran (2011-2013). Caspian j. 2016;7(1):48-51.

> No comparator group, reported on complications following BCG vaccine.

Irrelevant study design

Abbott S, Christensen H, Welton NJ, Brooks-Pollock E. Estimating the effect of the 2005 change in BCG policy in England: a retrospective cohort study, 2000 to 2015. Euro Surveill. 2019;24(49).