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Title :

Health economic evaluation of current vaccination strategies and new vaccines against tuberculosis: a systematic review

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Abstract

Introduction: Bacillus Calmette-Guérin (BCG) is the only licensed vaccine for tuberculosis, but its effectiveness is limited and varies by age. New candidate vaccines are currently being investigated. In response to the declining incidence of TB, practices relating to BCG vaccination have changed in various countries in recent years. A valid cost-effectiveness study is therefore needed in order to assist decision-makers in the implementation of cost-effective strategies for BCG vaccination.

Areas covered: Studies involving economic evaluations of BCG vaccination were reviewed in order to present current findings concerning a range of BCG vaccination strategies in a variety of regions, target populations, and vaccine types. The Quality of Health Economic Studies (QHES) instrument was used to assess the quality of the studies included in the analysis.

Expert Opinion: Most of the studies showed a favorable economic profile of BCG vaccination. Selective strategies seem the most cost-effective option for low-incidence areas. Varying results on revaccination strategies did not lead to any conclusive finding on the cost-effectiveness of the strategies. A novel vaccine – either a BCG replacement or booster vaccine that provides better protection, especially in adults – has the potential to enhance the cost-effectiveness of vaccinating against tuberculosis.

Keywords: tuberculosis, economic evaluation, Bacillus Calmette-Guérin (BCG), vaccination, strategies

1. Introduction

Tuberculosis (TB) is an infectious disease that caused 1.3 million deaths in 2017[1]. Although both the mortality and incidence rates are decreasing by 3% and 2% per year, respectively, the global burden of the disease has remained high, with around 10.4 million new cases in 2016

[2]. Meeting the Sustainable Development Goals (SDGs) and the WHO "End TB Strategy" target will require further reductions in these rates: by 2035, a 95% reduction in mortality and a 90% reduction in incidence, relative to baseline in 2015 [3,4]. One essential component of efforts to achieve these goals is a prevention program utilizing a strategy involving existing or improved vaccines [1].

The Bacillus Calmette-Guérin (BCG) vaccine is the only vaccine available on the market to date. The efficacy of this vaccine is limited, however, and it varies by age. Although it is effective in infants, the duration of protection is limited and declines over time, for an average of no longer than 10 years [5]. It thus provides little, if any protection in adults, even though adult pulmonary TB is almost exclusively responsible for the transmission of the disease [6,7]. Millions of dollars have been invested in research and development aimed at finding a more effective and universally applicable TB vaccine [8]. At present, almost 20 candidate vaccines are being investigated, with only a few products entering the clinical trial pipeline [9].

In recent years, BCG vaccination practices in various countries have changed in response to the declining incidence of TB [10]. According to a survey conducted in 2015, almost half of all European countries had changed their vaccination policies during the preceding decade [11]. For high-incidence countries, the World Health Organization (WHO) still recommends vaccinating all children at an early age (a universal strategy). Low-incidence countries may decide to vaccinate only high-risk populations, which consist predominantly of infants of immigrant parents originally from high-incidence countries (a selective strategy) [12]. In the United States, BCG vaccination is administered selectively to people who meet the criteria based on an expert TB examination, as recommended by the Centers for Disease Control and Prevention (CDC) [13]. If the resources available for the healthcare program are constrained, public health decisions concerning BCG vaccination policies should be based on both clinical outcomes and a health-economic evaluation.

According to a review published in 2012, despite the sub-optimal efficacy of the vaccine, universal strategies have been suggested as the most cost-effective strategies for low and middle-income countries, while selective strategies could be considered in more affluent, low-incidence countries 14]. This review also revealed wide variations in the methodologies used – accompanied by potential variations in quality – in the studies addressed [14]]. Given the large number of more recent health-economic evaluation studies, an updated review is warranted. The aim of this study is to present current findings by systematically detailing and comparing the outcomes of economic evaluation studies involving various BCG vaccination strategies in a variety of regions, target populations, and vaccine types. The review also includes a quality assessment of the studies based on the Quality of Health Economic Studies (QHES) tool.

2. Methods

2.1 Search strategy

We performed a comprehensive search of the literature using the PUBMED and EMBASE databases, with no limitation on years or study population. The main keywords chosen for this study were quite similar to those used in the previous review [14]: “tuberculosis,” “vaccination,” and “economic evaluation.” We extended the search terms slightly, however, and we did not restrict the search to any particular type of tuberculosis (for details, see Appendix 2). One of the researchers (AM) developed and ran the database search. The final search was run on September 24, 2018. In addition, a snowball search strategy involving the retrieval of potential additional studies in the reference sections of the papers identified in the main search was performed, in order to identify previously undetected papers.

2.2 Eligibility criteria

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The inclusion criteria were as follows: studies were required to include a cost-effectiveness analysis (CEA), a cost-benefit analysis (CBA), or a cost-utility analysis (CUA), in addition to reporting the evaluations of cost and effectiveness separately; the types of BCG vaccines covered were the BCG vaccine that is currently applied, or a hypothetical, novel, or booster vaccine applied in humans; and the full text had to be available and written in English. There were no restrictions on study designs with regard to data collection and analysis: observational, modelling, and mathematical-calculation designs were all included. We excluded any study that lacked complete information on how the analysis was performed, as well as reviews and systematic reviews, editorial letters, guidelines, protocols, comments, news, correspondence, book chapters, and abstracts for posters or oral presentations.

2.3 Study selection

Two of the researchers (AM and SP) independently screened the titles, abstracts, and full text of the identified articles based on the inclusion and exclusion criteria. Any disagreements were discussed with the other authors until consensus was reached concerning the eligibility of the papers to be included.

2.4 Data extraction

Data extraction was performed by AM and verified by SP with regard to the following aspects: author names, year of publication, country of study, population, incidence of disease, vaccination coverage or uptake, strategy comparator, type of economic evaluation, immunization approach, type of study, perspective, discount rates, effectiveness outcomes, time horizon, currency and year, vaccine efficacy, duration of protection, cost per vaccination, cost per TB case, effectiveness, incremental cost-effectiveness ratio (ICER), and sensitivity

analysis. In this case as well, consensus was achieved to resolve any discrepancies on data interpretation and verification of the validity of the extracted information.

2.5 Quality assessment

We used the Quality of Health Economic Studies (QHES) tool to assess the quality of the studies included. The QHES instrument is a validated method for assessing the quality of health-economic analyses, including 16 questions, each with specific weight values ranging from 1 to 9 [15]. Each score is multiplied by the weight to produce a total score, with a maximum score of 100. To minimize problems of interpretation, we assigned only full points in the assessment; no partial grading of individual criteria was done, even though several criteria consist of sub-items or subjective appreciations. Separate QHES evaluations were conducted independently by AM and SP. Any disagreements were discussed until the two reviewers reached consensus on the same interpretation.

3. Results

3.1 Selection Criteria

The initial search of PUBMED and EMBASE yielded a total of 3481 titles. After removing duplications, 2373 articles were screened based on titles and abstracts, after which 48 articles were eligible for full-text review.

After reviewing the 48 full-texts, 25 articles were excluded, leaving 23. Of the 25 articles excluded, 12 were excluded because the interventions did not meet the criteria. Notably, TB vaccination strategies were not specifically assessed in the study. An additional 10 studies were excluded due to partial evaluation; five evaluated only the cost and five described only the effectiveness of BCG vaccination. We further excluded one study that evaluated the

effectiveness of BCG vaccine in chain distribution rather than explicitly considering the economic aspects [16], one study in which the input parameters for the economic evaluation of BCG vaccination program could not be retrieved [17], and one that did evaluate the cost-effectiveness of BCG vaccination but that was rather a review than it was original research [18]. Details are provided in Figure 1.

The previous review by Tu and colleagues et al. included 13 studies [14]. We included all but one of the papers from this study [19], as we deemed the cost evaluation included in that paper incomplete according to present standards in health economics. Based on broader search terms, our review included two additional articles [20,21] published during the time-period of the previous review [14] as well as nine new articles published after 2011 through 2018. As mentioned, this study addresses a total of 23 articles.

3.2 Characteristics of the studies included

While four studies focused on non-specific countries (worldwide setting), most of the studies (19 of 23) were performed in country-specific settings: eight in European countries [22–29], four in Africa [30–33], four in Asia [20,34–36], and three in the United States [37–39]. In most cases, BCG vaccination was applied at a very young age: in 16 studies, it was applied in infants [21–23,25–27,30–35,40], in nine studies in school-aged children, either as a first vaccination[20,21,24,27,28,37,41] or as a revaccination [26,31,32,35], and two studies targeted children without specific age grouping [41,42]. Four studies reported BCG vaccination strategies aimed at adults, with a specific focus on healthcare workers [39], homeless people living in a shelter [38], and HIV-negative adolescents [27,40]. Most of the studies included economic evaluations of a licensed BCG vaccine available on the market, while two studies evaluated the MVA85A vaccine [30,33] (a potential candidate BCG booster vaccine), and four studies evaluated a hypothetical BCG vaccine with an assumed level of efficacy [31,32,39,40].

3.3 Methodologies used in the included studies

Nearly all of the studies (21 of 23) adopted a model-based design (i.e., decision-tree model, Markov model, or mathematical calculation) to perform an economic evaluation of BCG vaccination. Two remaining studies performed a trial-based cost-effectiveness analysis [23,37].

In most cases (19 of 23), the analysis was conducted from a third-payer perspective: healthcare institutes [20,22–25,27,29,31], governments [30,36], employers [39], or un-specified payers [26,34,35,38,42]. Four studies were performed from the societal perspective [21,28,32,33], and one study reported from an incomplete societal perspective [37]. Two studies analyzed both healthcare and societal perspectives for purposes of comparison or performance in scenario analysis [40,41]. Most of the studies (19 of 23) included cost-effectiveness analyses (CEA), while three included cost-benefit analyses (CBA) [26,27,43], one study included both a CEA and a CBA [35], and one study provided a comparison of costs and benefits [28]. The most common clinical outcomes used within the studies were the number of cases averted and the number of deaths averted (15 of 21 studies). Other clinical outcomes included life years gained (LYG) [22,29,38,39,42], disability-adjusted life years (DALYs) [24,31,36,40], quality-adjusted life years (QALYs) [29] and hospitalization rates [23]. Of the model-based studies, various input parameters were observed, such as vaccine efficacy, duration of protection, cost of vaccination, and time horizon. The vaccine efficacy varied depending on the vaccination strategy and type of vaccine. The duration of protection varied from 5 to 40 years, with 15 years applied most often and 40 years used for a best scenario analysis in one study [36]. The cost per vaccination varied from USD 1 to 10; with the range USD 1-3 used most often, for a universal strategy. The studies applied higher cost per vaccination for selective and targeted strategies, ranging from USD 5 to 50; even more variation was found for revaccination or new (hypothetical) vaccines. The time horizon varied between 5 years [42], 10 years [30,33–35,37,40,41], and 15 years [20–23,25,26,28,29]. Three studies were based on longer time

horizons: 30 years [32], 50 years [39], and lifetime [24,36]. Three studies did not state the time horizon [27,31,38]. Details are provided in Table 2. 3.4 Vaccination approach

Three main BCG vaccination approaches can be distinguished in the studies: 1) a universal strategy (11 studies) [20–22,25,27,28,34,36,37,41,42], which involves vaccinating the entire population; 2) targeted or other specific strategies (7 studies) [22–25,29,38,39], which involve vaccinating specific high-risk populations; and 3) revaccination strategies (3 studies) [26,31,35], which involve delivering a second or higher-order vaccination after the first vaccination. Seven studies assessed the cost-effectiveness of new and/or hypothetical vaccines [30,32,33,38–41]. Most studies addressed a low-incidence setting, with only five studies addressed high-incidence countries mainly focusing on the assessment of the new vaccines [30,32,33], one study on revaccination strategy [31], and one study on a universal strategy [20]. For studies evaluating two or more different populations and vaccination approaches, all analyses were included. Details are provided in Table 1.

3.5 Universal vaccination strategies

Universal BCG vaccination strategies were analyzed in 11 studies, either as the main intervention [21,27,28,34,37,38,41,42] or in comparison to selective strategies [22,25,29], no vaccination strategy [36], revaccination strategies [30,32,33], a proposed new TB vaccine [40], or other TB prevention strategies [20,38]. Universal strategies were most commonly applied in infants, with only four studies specifically addressing the vaccination of school-aged children [20,28,37,40]. All of the studies used model-based evaluations, except for one trial-based study by Pereira et al. [37].

The input parameters used in the model-based studies were diverse. In the model-based studies, the BCG vaccine-efficacy rates used for the base case varied from 25% to 80% in infants. Some studies adopted efficacy rates that were lower (5% to 10%) or higher (100%) for the scenario

analyses or as comparators. Most of the studies used protection periods of 10 years [30,33,34,37,40,41] and 15 years [20–22,25,28], with two divergent studies using periods of 5 years [42] and 30 years [32], respectively. One study did not specify the duration of BCG vaccine protection [27]. The ICER values were reported in various currencies, price years and outcome measures.

When applied in high-incidence countries with TB-incidence rates above the threshold established by the International Union Against Tuberculosis and Lung Disease (IUATLD), a universal BCG vaccination against severe TB diseases was considered highly cost-effective at USD 206 (2002 USD) (CI 150–272)/LYG in a worldwide setting [42]. In 1980, a study conducted in Indonesia showed that combining universal BCG vaccination with other vaccination programs was more cost-effective than implementing the program independently: USD 101 vs USD 455 (1978 USD) per death prevented, respectively [20]. Meanwhile, the ICER values reported were higher when the strategy was applied in low-incidence countries: USD 35,950–USD 175,862 (2001 USD) per case prevented in Japan [34]; EUR 204,373 (2012 EUR) per LYG[22] and EUR 139,557 (2014 EUR) per QALY[29] in Ireland, and USD 38,311 (2001 USD) per case averted in Finland [25]. A model-based study in Taiwan, a moderate TB-incidence country with 43 cases per 100,000 persons, reported that discontinuing universal vaccination would produce a small but robustly negative health impact, reflected by a projected increase of 82.9 cases within 10 years [36].

In addition, some studies evaluated universal strategies that were applied for both infants and older/school-aged children and, in some cases, adults. A study conducted in Brazil indicated that BCG vaccination of school-aged children as a catch-up strategy was cost-effective, even with an average vaccine-effectiveness rate of only 34% (8%–53%). The study demonstrated that it would cost less to vaccinate 381 children than it would to treat one patient with tuberculosis, with a cost-effectiveness ratio of 0.69 (vaccination vs treatment) [37]. A

mathematical calculation study conducted in Austria showed that the cost savings from preventing the disease could compensate for the costs of vaccination for a strategy of universal vaccination in infants, with a ratio of 1.2, with a higher value (3.3) when applied in older children [27]. A 1976 study based on a societal perspective, however, reported that the costs of vaccination in school-aged children exceeded its monetary benefit [28].

3.6 Selective strategies

Seven studies assessed selective strategies for BCG vaccination – all performed in notably low-incidence TB countries in Europe and the United States. While two studies examined a hypothetical BCG vaccination on specific high-risk adult populations – healthcare workers [39] and homeless people older than 35 years [38], the rest of the studies assessed selective strategies applying BCG vaccination only in infants at high risk of TB.

A wide range of ICER values were reported for selective strategies. The ICER value reported in a study conducted in a Dutch setting was EUR 4500 (2005 EUR)/QALY, when the target of vaccination was expanded beyond immigrant infants from high-incidence countries to include immigrant infants from low-incidence countries but with high numbers of immigrants [24]. As noted by the authors, however, relevant uncertainties (e.g., with regard to vaccine efficacy and incidence) impede generalization of the results [24]. Two studies from Ireland reported that selective strategies were not considered cost-effective relative to no-vaccination strategies, with ICER values of EUR 143,233/LYG and EUR 340,520/LYG in studies conducted in 2016[22] and 2018 [29], respectively. Compared to universal vaccination, the selective strategy was substantially less costly (EUR 1,055,692), although it exhibited marginally reduced effectiveness, with 4.8 life-years lost relative to the universal strategy in Ireland [22]. A trial-based study conducted in the Local Health Unit of Prato (Italy) indicated that a selective vaccination strategy had a positive effect, relative to the no-vaccination strategy, by

significantly reducing the TB hospitalization rate [23]. A study conducted in Finland, which has a low incidence of TB (0.56 per 100,000 cases per year) reported that a universal strategy was not cost-effective relative to a selective strategy, with an ICER value of at USD 38,311 (2001 USD) per case averted [25].

In addition, when targeted at high-risk adults, BCG vaccination was reported to be a cost-saving strategy, even with effectiveness of only 40% (e.g., for people living in crowded shelters) [38]. Another study concluded that a hypothetical BCG vaccine with an assumed effectiveness rate of 50% would be more cost-effective than tuberculin testing followed by preventive therapy in preventing TB cases among healthcare workers [39].

3.7 Revaccination strategies

Of the six studies evaluating revaccination in school-aged children, three evaluated revaccination strategies using a licensed BCG vaccine that was available in the market [26,31,35]. Two were conducted in low-incidence countries (i.e., Czech Republic [26] and Japan [35]), with incidence rates ranging from 1.1 to 20.2 per 100,000, depending on the age group. Another revaccination study was modelled according to the situation in South Africa, which is characterized by a high rate of TB transmission [31]. The vaccine-efficacy rate for revaccination strategies reported in the studies varied, with the highest efficacy assumed to be 80% [31], the lowest being 0% [26], and a moderate efficacy rate of around 50% applied in some scenarios [31,35]. Two studies were based on a 10-year protection period [31,35], and one study applied a longer protection period of 15 years [26]. The two earlier studies (published in 1999 and 2002) concluded that revaccination with BCG was not a favorable strategy, as the costs exceeded the benefits [26] and the ICER value was high, at USD 108,378 (1999 USD) per case averted [35]. As demonstrated in the more recent model-based study, however, revaccination could be beneficial (with vaccine-efficacy rates ranging from 10% to 80%),

especially when considering the prevention of TB transmission, with ICER values ranging from USD 52 to USD 4540 (2011 USD) per DALY averted [31].

3.8 Economic evaluation of new vaccines

The three model-based studies evaluated a novel booster vaccine to be applied after the first BCG vaccination at birth [30,32,33]. The two studies conducted in South Africa assessed the MVA85A vaccine, which was applied at the age of 4 months and assumed to provide protection for 10 years [30,33]. However, each of these studies used a different vaccine-efficacy rate as an input parameter: a low efficacy rate of 17.3% (12.3%–22.3) [30] and a moderate rate of 60% (40%–70%) [33]. The first study concluded that adding a booster to the BCG vaccine alone was not a cost-effective strategy, based on the efficacy of MVA85A at that time (17.3%), although an efficacy rate of at least 41.3% would make the booster cost-effective [30]. The second study reported that, with a moderate vaccine-efficacy of 60% (40%–70%) and considering a societal perspective, MVA85A resulted in cost savings: around USD 14.82 million (USD 7.69–USD 16.68) (2012 USD) [33]. The third study compared a hypothetical BCG replacement vaccine to the existing TB control program (i.e., current BCG vaccine at birth and DOTS [directly observed treatment, short course]). The study reported that the addition of a prime-booster vaccine, applied at age 10, was more cost-saving than a replacement vaccine applied only at birth, albeit with an assumed efficacy of 70%, as reflected in the net societal cost-saving results: USD 5.6 vs USD 3.6 million [32]. Similar findings were also reported by Knight et al*.,* who demonstrated that a new TB vaccine targeting adolescents and adults – with 60% vaccine effectiveness and a 10-year protection period - would prevent more TB cases and yield lower ICER values than would a strategy targeting infants alone: 17 (11–24) vs 0.89 (0.42–1.58) million TB cases prevented and USD 378 (USD 150–USD 881) vs USD 1,692 (USD 634–USD 4,603) per DALY averted, respectively [40]. It was also predicted that such investments in a better novel vaccine with an efficacy of 75% and a 10-year protection period would be

profitable, with even higher values when considering productivity lost throughout the world setting [41].

3.9 Key drivers of the analysis

The key drivers of cost-effectiveness were derived from the sensitivity analyses reported in the studies included in this review. Of the studies included, four did not include sensitivity analyses [21,23,24,27], and one of these was a trial-based study [23]. Nine studies that did involve sensitivity analyses reported the key parameters influencing the cost-effectiveness analysis [22,25,30,32,34,35,37,38,41]. Other studies reported only the robustness of the results, due to changes in some parameters in certain scenarios (e.g., best-case or worst-case scenarios) [20,28,32,33]. Three studies reported multi-variate sensitivity analyses and described the range of the ICER values [33,42] or the probability of being cost-effective [26]. As expected, vaccine efficacy was the most commonly reported parameter influencing cost-effectiveness [22,25,30,32,34,35,37,38], with the second most commonly reported parameters being vaccine price or cost of vaccination [30,37,41]. Other parameters reported as key drivers were duration of vaccine protection; incidence of TB cases or TB deaths; vaccination coverage; and cost of TB cases. Details are provided in Table 1.

3.10 Quality assessments

We used the QHES tool to assess the quality of the studies included in this review. With a maximum score of 100, studies with scores above 50 are usually adequate for publication [15]. The quality of most of the studies included in this review were considered adequate; 15 studies scored above 75 [22,24–26,29,30,32–38,40,42], 6 scored between 50 and 75 [21,23,28,31,39,41], and only two studies scored below 50 [20,27]. The complete final QHES scores for each study are provided in a supplementary appendix.

The two items having the lowest scores in this review had to do with the sources of the estimates of relevant parameters and reporting of potential biases. The sources of estimates were fulfilled in only nine studies [22,23,26,29,30,34,36,37,42], with the rest of studies merely relying on assumptions for some parameters rather than deriving them from randomized control trials or previously published studies. Most of the studies (12 of 23) did not explicitly discuss the potential biases of the analysis [23,25,31–34,37,40,42].

4. Discussion

4.1 Main Findings

Three main vaccination approaches were evaluated in the studies and reviewed in our analysis: universal strategies, selective strategies, and revaccination strategies. Universal strategies targeting either infants or older children were identified as the most cost-effective option when applied in high-incidence countries. This finding suggests that the current BCG vaccine, although showing inconsistent efficacy, is still providing adequate protection in controlling TB in high-incidence countries. When applied to low-incidence countries, however, universal strategies were less cost-effective than no-vaccination or selective strategies. Nevertheless, in moderate-incidence countries (e.g., Taiwan), universal vaccination programs that are already in place remain beneficial as compared to no-vaccination policies: discontinuing BCG vaccination in such situations would still give rise to a small negative health impact which could not be neglected [36]. The IUATLD recommends that countries switch from a universal vaccination strategy if the incidence of TB is less than 5 cases per 100,000 population [36,44]. Although the WHO recommends BCG vaccination for infants, in some settings, universal strategies targeting adolescents or school-aged children were reported to be cost-effective as well [20,37,40]. A recent case-control study also indicated that BCG vaccination for school-aged children could provide up to 20 years of moderate protection [45]. Vaccinating high-risk adult

populations (e.g., healthcare workers or adults living in crowded shelters) was also identified as a cost-saving strategy [38,39].

Various studies recommend the application of selective strategies, in most cases, as a replacement for universal strategies in low-incidence countries. In extremely low-incidence settings – such as the Netherlands (3 cases per 100,000) and Finland (0.56 cases per 100,000) – the selective vaccination of infants at high risk of TB was deemed beneficial, with the benefits exceeding the costs of vaccination [24,25]. For Ireland, with a TB incidence of around 7 cases per 100,000 population, the studies included in this review reported very high ICER values when comparing selective strategies to universal strategies [22,29]. As mentioned before, one limitation of these studies is that the very low incidence of TB makes it more difficult to generalize the results, due to uncertainty with regard to the efficacy of the BCG vaccine [24]. For switching from a universal strategy to a selective strategy, low-incidence countries, therefore, should carefully consider the IUALTD recommendation and a high-quality economic evaluation, which incorporates country-specific TB profiles, transmission effects, and societal impacts of the strategies.

The current review suggests that revaccination strategies might not be cost-effective in low-incidence countries [26,35], although a model-based study demonstrated that they could be beneficial in high-incidence countries [31], especially when accounting for the prevention of transmission. Although the studies conducted in low-incidence countries were deemed outdated (i.e., published in 1999 and 2002), they did provide an overview for the decision-makers in these countries at that time [26,35]. These studies were also in line with the WHO recommendation stating that, while repeating BCG vaccination does not confer any additional protection, it could incur more costs [46]. This recommendation was not based on cost-effectiveness analysis, however, and many studies nevertheless argued that the benefits and safety of revaccination would outweigh the costs [47–49]. In one study, however, Roth et al.

report that routine BCG revaccination, combined with other vaccination programs, was associated with an increase in overall mortality [50]. However, a recent phase 2 randomized control trial (RCT) study reported an encouraging result on the revaccination strategy in preventing TB infection in a high-transmission setting [51].Revaccination was intended to provide enhanced protection within the population of adults who are vulnerable to contracting TB, thereby posing a risk of transmission. Despite the potential benefits of revaccination strategies, the safety and high burden of vaccination in adolescents should be taken into consideration.

In comparing the findings of this review with the earlier one [14], it appears that some conclusions remain unchanged, applying a universal strategy can be considered the optimal strategy when applied in high-incidence countries, while a selective strategy can be considered an appropriate choice in developed, low-incidence, countries. However, some notable findings are included in this updated review. For example, a selective strategy can only be considered cost-effective in developed countries if TB incidence is extremely low, considerably below 5 per 100 000 inhabitants. Another novelty was found for revaccination strategy, previously not considered to be cost-effective in developed countries – it has potential benefits, if applied in high-incidence and high-transmission settings [31].

Our results indicate that a new, improved vaccine that would provide greater protection in older children and adults would be a more cost-effective strategy. This finding is in line with those of another review study on modelling a future TB vaccine, which predicts that a novel TB vaccine targeting older age groups (with pre-exposure and/or post-exposure efficacy) would have a better and more rapid epidemiological impact than would neonatal vaccination only[52]. Most new vaccines have been intended as prime boosters and applied in adolescence, with the expectation that they would provide additional protection beyond that of the current BCG vaccine, with the drawbacks associated with its waning effects [53]. The only new vaccine

assessed in the studies analyzed in this review is MVA85A. According to a randomized controlled trial, however, MVA85A has no significant efficacy [54]. Meanwhile, currently, two potential new TB vaccines have entered phase 2b trials. Firstly, H4:IC31 which showed a moderate efficacy of 30.4% against *M. tuberculosis* infection in a high-transmission setting [51]. Secondly, M72/AS01$_E$ which showed a vaccine efficacy of 50.4% against progression of *M. tuberculosis* infection into active pulmonary TB [55]. The modelling studies in this review consistently indicate that the new vaccine would be cost-effective if its vaccine efficacy against TB were to be at least around 40% [30,32,33]. Given that we found vaccine efficacyto be one of the key drivers of the cost-effectiveness of vaccines, further research and economic evaluations of the two aforementioned new vaccines are warranted. Further (cost-effectiveness) research would also need to focus on the other main drivers of cost-effectiveness: the duration of protection, especially within the adult population, and the pricing of the new vaccines.

In all, 23 studies were eligible for analysis in this review. Considering that we did not apply any restrictions on publication date or geographical area in our search, this is a relatively low number of economic evaluation studies. In the past seven years, however, a relatively large number of articles have been published, and the number of articles published since the previous review has doubled [14]. The most common objective of economic evaluations of BCG vaccination has been to assist decision-makers in re-evaluating the vaccination strategies in their countries (e.g., by shifting from a universal or revaccination strategy to a selective strategy, or even discontinuing BCG vaccination altogether). This could be the reason why most of the studies were conducted in low-incidence countries. Nevertheless, economic evaluation of BCG vaccination in high-incidence countries, which are known to have the highest use of BCG vaccination, is also needed in order to evaluate the current strategies of BCG policies and to predict the best vaccine profiles, with optimal cost-benefit ratios in light of limited resources, as is generally the case in low-income, high-incidence countries.

Almost all of the studies addressed in this review were modelling studies. Such studies have become a useful assessment tool for predicting the impact of potential future TB vaccines [52]. The aspect that received the lowest QHES score among all studies included had to do with the sources of parameter estimates. Given that the efficacy of the BCG vaccine varies considerably across populations and regions, as established in clinical trials and observational studies [5], future economic-evaluation studies should review the best available age-specific and country-specific evidence in order to estimate the input parameters for the analysis. This finding also highlights a clear need for broader research on the current efficacy and effectiveness of the BCG vaccine, representing the best estimates in low-incidence and high-incidence countries, thereby potentially improving the reliability of country-specific analyses. In addition, static modelling was most often applied within the included studies, represents a straightforward calculation of the cost-effectiveness analysis. However, dynamic modelling, which incorporates effects on TB transmissions, could provide better estimates for the analysis, apparently for critical strategies such as switching to a universal strategy in low-to-moderate incidence countries, applying a revaccination strategy in high-incidence high-transmission countries, or assessing the new vaccines. Moreover, most studies in this review used a third payer perspective for the analysis which does not capture the potential effects on society, such as productivity losses and some catastrophic costs.

4.2 Strengths and Limitations

This review involved a systematic search of two large databases – PubMed and EMBASE – following PRISMA guidelines. In addition, we applied strict inclusion criteria and did not impose any limitations on the year of publication. We therefore expected to find all studies containing relatively complete economic evaluations since the introduction of the BCG vaccination in 1921. We also assessed the quality of the studies included using a validated instrument: QHES. Despite its strengths, however, this systematic review is also subject to

limitations. First, the studies included in the review had flaws in terms of methodology and the input parameters used in the analyses. It is therefore difficult to make direct comparisons and to draw straightforward conclusions from our review. However, combined with transferability assessments, this review could assist decision-makers in countries with limited resources in making such economic evaluations, by providing an overview of the cost-effectiveness strategies applied in BCG policies in country-specific settings. Second, because the review was limited to studies from peer-reviewed publications, which excluded those published by manufacturers or marketing agencies, as well as some abstracts for which the full text could not be retrieved. We also might have missed some studies in locally or regionally reputed journals in low-income countries, as we included only studies that were indexed in PUBMED and EMBASE.

5. Conclusions

Most of the studies included in our analysis exhibited a favorable economic profile for the use of BCG vaccination against TB. Universal strategies remain the most cost-effective for high-incidence countries. Although strategies clearly targeting infants are considered cost-effective, the vaccination of adolescents as a catch-up strategy might also be cost-effective in some settings. Countries with low to moderate incidence rates might consider selective strategies, as they appear to be more cost-effective than discontinuing vaccination altogether. Given the variations in the results reported for revaccination strategies, we are unable to draw conclusions on the cost-effectiveness of BCG revaccination. In the future, a new vaccine that offers better protection within the adult population would be the most cost-effective investment in research and development.

6. Expert opinion

Based on the 23 studies on the economic evaluation of BCG vaccination included in this review, we have demonstrated that universal vaccination at birth remains the most cost-effective strategy for high-incidence countries. Given that no new vaccines replacing BCG have been licensed and made ready to enter the market to date, the current BCG vaccine will continue to be the most cost-effective strategy for universal application in infants for the next five years. At the same time, given that the incidence of TB is declining in most developed countries, some countries with incidence rates lower than that recommended by the IUATLD (5 cases per 100,000)-particularly in the European region, the United States, and some Asian countries or parts thereof- might need to re-evaluate their current BCG policies, thus considering to reallocate the budget to strengthening other components of their TB control programs (i.e., early diagnosis and appropriate treatment). Subject of further research should include the efficacy of BCG vaccination in adult populations, or the cost-effectiveness of vaccinating adolescents or adults in some settings, as with catch-up strategies for school-aged children or as a preventive measure in high-risk adult populations (e.g., healthcare workers or people living in crowded shelters). In addition, given the lack of evidence on the efficacy of revaccination, this strategy is not considered cost-effective for low-incidence countries. At the same time, however, second BCG vaccination could be beneficial in high-incidence countries, especially in light of the high transmission rate. Further evaluation is required, taking into account the best evidence concerning the safety and burden of revaccination strategies. In addition to targeting the potential replacement of BCG vaccinations for infants, there is an urgent need for novel vaccines that meet the SDGS and WHO targets, in order to reduce the TB burden worldwide. Future research and development with regard to novel vaccines should address the shortcomings of the current BCG vaccine: waning protective effect over time, thereby resulting in little or no protection in adult populations, in addition to the low overall efficacy of the vaccine in settings characterized by a high TB burden. Such boosters or replacement vaccines

that could provide better protection, especially in adults have been predicted to be the most cost-effective.

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Article Highlights

- Universal BCG vaccination remains cost-effective for high-incidence countries.
- Countries with low to moderate incidence rates should carefully consider applying a selective strategy by vaccinating high risk-infants, in light of the recommendations of IUATLD and based on country-specific economic-evaluation studies.
- Further evaluation is needed regarding the implementation of vaccination for older children or adult populations for first vaccination or second vaccination (i.e., revaccination).
- Future research on novel TB vaccines could focus on a new, improved vaccine that could provide better protection to infants, as well as within the adult population.

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