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Comparative effectiveness of vaccines for tuberculosis in endemic countries: a systematic review and meta-analysis

Abstract

Tuberculosis is a highly contagious disease (global 50% prevalence), especially in low-resource areas where adequate treatment is limited. No current vaccine has shown efficacy after infancy.

Objectives: The primary outcome was to determine if newly available vaccines were effective in providing immunity from morbidity associated with Tuberculosis. The protocol for this review is published on Prospero and can be located by using the following record number, CRD42015017238.

Search methods: Searches of the Cochrane Library, Trip Database, PDQ-Evidence, PubMed, and Science Direct were completed. The search included common terms related to vaccine effectiveness and safety for tuberculosis.

Selection criteria: Randomized controlled trials comparing tuberculosis vaccines with placebo, in adults and children were screened for eligibility for compliance with inclusion criteria.

Data collection and analysis: Clinical outcomes data were reported for adverse events, safety and immunogenicity endpoints with 95% confidence intervals (CI). Vaccine efficacies were reported however, none of the vaccines in this review achieved an efficacy rate higher than 17.3% (95% CI -31.9 to 48.2). Cytokine CD4 cell expression was observed.

Main results: This review includes 7 group comparisons with data from 5 clinical trials. There was significant heterogeneity between studies with respect to study population size, testing validation methods, and baseline characteristics. There was also considerable statistical heterogeneity (I2 = 75.3%). None of the included studies demonstrated efficacy or effectiveness against Tuberculosis, the highest efficacy rate being 17.3% (95% CI -31.9 to 48.2). Positive Quantiferon conversion was observed at a rate of (RR, 2.72 95% CI 0.94, 7.85). Cytokine Positive CD4 T-cell expressing IFN-y growth was observed (Std. Mean Diff 1.92 95% CI 1.19 to 2.65) in 4 studies. There is potential in the tolerability of the vectors explored in this review possess to be potential delivery pathways for future vaccines in this disease area.

Keywords: Tuberculosis vaccine, BCG, MVA85A, IC31, SATVI, TB vaccine review

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Abbreviations: BCG, bacille calmette-guerin vaccine; CI, confidence interval; CD4, CD8, a type of white blood cell help to defend the body from infections; DNA, deoxyribonucleic acid; EPI, expanded program on immunizations; GAVI, global alliance for vaccines and immunization; HIV, human immunodeficiency virus; IAVI, international aids vaccine initiative; IFN, inteferon; LMIC, low to middle income countries; MDR-TB, multi-drug resistant tuberculosis; PATH, program for appropriate technology in health; QFT, quantiferon; RR, risk ratio; SABIN, sabin vaccine institute; SATVI, south african tuberculosis vaccine initiative; Std, standard; TB, tuberculosis; WHO, world health organization; XDR-TB, extremely drug-resistant tuberculosis

Introduction

Tuberculosis is a highly contagious disease which currently has a standard of care which presents side effects which rival the symptoms of the disease it is targeted to prevent. The current treatment regimen for TB consists of four drugs (isoniazid, rifampin, pyrazinamide and ethambutol-for 2months, followed by 4 months of isoniazid and rifampin) which are delivered in tablet form, in most countries. Treatment regimens for more complicated forms of the disease can involve an elevated number of drugs as well as an extended duration of treatment. Due to the high probability of relapse, disease acceleration, and drug resistance monitored treatment periods have become the standard. These factors complicate addressing infected patients and successful treatment, especially in low-resource areas where adequate treatment may not be available.[1] The current standard of care, the Bacillus Calmette-Guerin (BCG) vaccine, is the oldest vaccine in current use in the world. This vaccine been administered throughout the developed and developing world for tuberculosis in all countries, except for the United States and Netherlands, since the 1960s.[2] Despite the clinical evidence that supports the wide administration of the BCG vaccine, the side effects associated with this vaccine present the patient with a difficult decision; take a vaccine which possesses potential adverse events such as; reversion to an infectious bacterial state, wildly differing strains resulting in no increased immunity, topical lesions at injection sites, and in severe cases, outbreaks of lymphadenitis have occurred when a new strain of BCG was introduced.[1] There are many simultaneous efforts in different parts of the world to develop a vaccine which can provide immunity with an improved quality of life for the patient post immunization. Continuous 7 evaluations of ongoing efforts to identify a solution is necessary

for collective advancements in the vaccine research community. From an ethical perspective, any current trials which are evaluating technologies which have been determined to be ineffective, or found to expose participants to unnecessary level of risk could be stopped if certain endpoints were reached in other trials. Vaccines solutions for neglected diseases are a global effort. Systematic reviews are a useful tool in determining whether an evaluation of an intervention should be explored or abandoned.

Objectives

The aim of this review is to determine if any of the vaccines that have been developed in the last two years are viable vaccine candidates for preventative immunization against TB in [P] disease naïve patients, who experience onset of tuberculosis in endemic countries (these countries will be identified using criteria established by WHO for high TB burden countries). These populations are concentrated in sub-Saharan Africa, Eastern Europe, Central Asia and Western South America.I The prospective vaccine candidates will be evaluated against [C] Bacille Calmette-Guerin, also known as the BCG vaccine, which is the current standard of care in use for countries where tuberculosis is endemic. This vaccine is usually administered shortly after birth. [O] The primary outcome is to determine if newly available vaccines are effective in providing immunity from morbidity associated with Tuberculosis (protection in presence of disease in a clinical setting). The results of this review will be used to identify vaccines and/or viable approaches and methodologies which indicate promise of improving immunization to Tuberculosis. The protocol for this review is published on Prospero and can be located by using the following record number, CRD42015017238[3–20] (Tables 1-16) (Figures 1-3).

Table 1 Characteristics of Included Studies: Table 1. Aeras-402 Tameris et al.,[3]

Methods	Multi-center, double-blind, randomized, placebo-controlled, The primary outcome was safety, and included all solicited, unsolicited and serious adverse events in all participants who received at least one dose of study vaccine. The percentage of participants with AEs was presented by MedDRA Preferred Term. For categorical data, analysis was performed using the Chi-square test; and for AE grading analysis the Chi-square test for linear trend was used. Statistical significance was assigned to $p \leq 0.05$.
Participants	Infants were eligible for enrolment only if the parent or legal guardian provided written informed consent. We enrolled healthy infants, aged 16–26 weeks, who had received BCG more than 3 months prior to randomization, who had received appropriate routine immunizations at least 14 days before randomization, and whose mother's HIV status was known. HIV-uninfected infants of HIV-infected mothers were eligible.
Interventions	An adenovector encoding a fusion protein of Mycobacterium tuberculosis antigens 85A, 85B, and TB10.4
Outcomes	The primary outcome was safety, and included all solicited, unsolicited and serious adverse events in all participants who received at least one dose of study vaccine. Dose-finding and Immunogenicity
Notes	The quality control had significant issues meeting quality standards and was forced to abandon the primary efficacy endpoint due to difficulty concerning the validity of clinical lab data.

Table 2 Risk of Bias (Aeras-402 Tameris et al.,[3]

Bias	Author's Judgment	Support for Judgment
Random Sequence Generation (Selection Bias)	Low Risk	Infants were randomized to receive two intramuscular doses ofAERAS-402 or placebo on study days 0 and 28 using a paper-based system in Groups 1–3 and an interactive voice response system (IVRS) in Groups 4–5.
Allocation Concealment (Selection Bias)	Low Risk	Group allocation was sequential, subsequent to Data Monitoring Committee (DMC) review of safety data. Dose selection for Group 5 was determined by sponsor review of cumulative safety and immunogenicity data for Groups 1–4 and all previous trials ofAERAS-402 in both adults and infants.[11–13] The selection of the highest dose strength, 1 × 1011vp, was based on these data and supported by the protocol which states that in case of ambiguous data the highest dose should be selected.
Blinding of Participants and Personnel (performance bias)	Low Risk	Participants' parents or legal guardians and all clinical study staff were blinded to the assigned intervention group. Randomization in Groups 1–3 was in a 3:1 ratio (AERAS- 402: placebo),Group 4 in a 1:1:1:1 ratio to receive one of three dose levels ofAERAS-402 (1.5 × 1010, 3.0 × 1010, or 1 × 1011 viral particles (vp)) or placebo, and Group 5 in a 1:1 randomization ratio (1 × 1011vp: placebo).
Blinding of Outcome Assessment (detection bias)	Unclear Risk	No Information Provided
Incomplete Outcome Data (attrition bias)	Unclear Risk	No Information Provided
Selective Reporting (reporting bias)	Unclear Risk	No Information Provided
Other bias	Unclear Risk	The trial was funded by Aeras, the manufacturer of the vaccine candidate MVA85A, one of the clinical sites was SATVI. 3 of the 5 trials utilized this site. Same lead author as MVA85A Tameris et al.,[3]

Table 3 Characteristics of Included Studies: H1/IC31 Reither et al.,[4]

Methods	HIV-infected adults with CD4+ T cell counts. 350/mm3 and without evidence of active tuberculosis were enrolled and followed until day 182. H1/IC31 vaccine or placebo was randomly allocated in a 5:1 ratio. The vaccine was administered intramuscularly at day 0 and 56. Safety assessment was based on medical history, clinical examinations, and blood and urine testing. Immunogenicity was determined by a short-term whole blood intracellular cytokine staining assay.

Table Continued...

Participants	Participants were eligible if they were between 18 and 55 years of age, HIV infected with CD4+ lymphocyte counts greater than 350/mm3, antiretroviral therapy naive, generally healthy, had no evidence of active TB, had no history of receiving immunosuppressive medication, immunoglobulins, blood products or known hypersensitivity to any of the vaccine components. Women of child bearing potential were eligible if pregnancy was excluded and they agreed to use at least two forms of acceptable contraception from 21 days prior to administration of the study vaccine through to the end of the study.
Interventions	The Hybrid 1 (H1) vaccine is a recombinant fusion protein of the antigens Ag85B and ESAT-6 (Ag85B–ESAT-6), developed and manufactured by the Statens Serum Institut (Denmark). The adjuvant IC31 was developed by Intercell AG (Austria) and consists the cationic poly-amino acid KLK, which is composed of the amino acids lysine (K) and leucine (L), and ODN1a, a single stranded oligodeoxynucleotide with alternating sequences of the nucleic acids inosine and cytidine. A volume of 0.5mL was administered providing a dose of 50 mg Ag85B-ESAT6 (antigen) and 500 nmol KLK +20 nmol ODN1a (adjuvant) or 0.5 mL Tris buffer (placebo).
Outcomes	H1/IC31 was well tolerated and safe in HIV-infected adults with a CD4+ Lymphocyte count greater than 350 cells/mm3. The vaccine did not have an effect on CD4+ T cell count or HIV-1 viral load. H1/IC31 induced a specific and durable Th1 immune response
Notes	The quality control had significant issues meeting quality standards and was forced to abandon the primary efficacy endpoint due to difficulty concerning the validity of clinical lab data.

Table 4 Risk of Bias (H1/IC31 Reither et al.,[4]

Bias	Author's Judgment	Support for Judgment
Random Sequence Generation (Selection Bias)	Low Risk	Participants were randomly allocated in a 5:1 ratio to receive either H1/IC31 vaccine or placebo according to a pharmacist prepared the vaccination according the pre-prepared study randomization list.
Allocation Concealment (Selection Bias)	Low Risk	Participants were randomly allocated in a 5:1 ratio to receive either H1/IC31 vaccine or placebo according to a computer-generated randomization list. The pharmacist prepared the vaccination according the pre-prepared study randomization list.
Blinding of Participants and Personnel (performance bias)	Low Risk	The study monitors, investigators, and participants were blinded to study product. The study pharmacists prepared the investigational product. Syringes were masked with red tape in order to conceal a slight difference in the appearance of the H1/IC31 and placebo.
Blinding of Outcome Assessment (detection bias)	Unclear Risk	No Information Provided
Incomplete Outcome Data (attrition bias)	Unclear Risk	No Information Provided
Selective Reporting (reporting bias)	Unclear Risk	No Information Provided
Other bias	Unclear Risk	Ingrid Kromann, Peter Bang, and Søren T. Hoff are employed by the Statens Serum Institut, a Danish not-for-profit governmental research institution which holds intellectual property rights on H1 as a vaccine construct. Peter Andersen is a co-inventor on a patent application covering the use of H1 as a vaccine (Patent No. WO9844119; Nucleic acid fragments and polypeptide fragments derived from M. tuberculosis). All rights have been assigned to Statens Serum Institut. The patent does not alter the authors' adherence to PLOS ONE policies on sharing data. This study also used SATVI as a clinical site 3 of 5 studies.

Table 5 Characteristics of Included Studies: MVA85A Ndaiye et al.,[5]

Methods	We did a randomized, double-blind, placebo-controlled, phase 2 trial of MVA85A in adults infected with HIV-1, at two clinical sites, in Cape Town, South Africa and Dakar, Senegal.
Participants	Eligible participants were aged 18–50 years, had no evidence of active tuberculosis, and had baseline CD4 counts greater than 350 cells per μL if they had never received antiretroviral therapy or greater than 300 cells per μL (and with undetectable viral load before randomization) if they were receiving antiretroviral therapy; participants with latent tuberculosis infection were eligible if they had completed at least 5 months of isoniazid preventive therapy, unless they had completed treatment for tuberculosis disease within 3 years before randomization.
Interventions	The modified vaccinia virus Ankara expressing the major M tuberculosis antigen 85A (MVA85A) is a clinically advanced candidate vaccine.10–12 MVA85A is well tolerated and immunogenic in adults infected and not infected with HIV-1, and in infants not exposed to HIV-1.10–14 MVA85A adds to BCG-induced protection against mycobacterial challenge in some preclinical animal models.
Outcomes	Tuberculosis disease endpoint 1 was defined as culture or GeneXpert MTB/RIF positivity; endpoint 2 included endpoint 1 and a composite clinical endpoint (which included a single acid-fast bacilli smear from a sterile body site; two smears from pulmonary and gastric sampling, and compatible clinical symptoms and radiological signs); and endpoint 3 was participant commencement on anti-tubercular chemotherapy (see the study protocol for more information; appendix). The M tuberculosis infection endpoint was defined as conversion from negative QFT at baseline to positive QFT at the final visit.
Notes	N/A

Table 6 Risk of Bias (MVA85A Ndaiye et al.,[5]

Bias	Author's Judgment	Support for Judgment
Random Sequence Generation (Selection Bias)	Low Risk	Participants were randomly assigned (1:1) in blocks of four by randomly generated sequence to receive two intradermal injections of either MVA85A or placebo. Randomization was stratified by antiretroviral therapy status and study site.
Allocation Concealment (Selection Bias)	Low Risk	Participants, nurses, investigators, and laboratory staff were masked to group allocation.
Blinding of Participants and Personnel (performance bias)	Low Risk	Participants were randomly assigned (1:1) in blocks of four by a randomly generated sequence of participant identification numbers via an interactive voice response system to receive two intradermal injections of either 1×10^8 pfu MVA85A or placebo (Candida skin test antigen [Candin], Allermed Laboratories, San Diego, CA, USA).
Blinding of Outcome Assessment (detection bias)	Unclear Risk	No Information Provided
Incomplete Outcome Data (attrition bias)	Unclear Risk	No Information Provided
Selective Reporting (reporting bias)	Unclear Risk	No Information Provided
Other bias	Unclear Risk	HM was previously a shareholder in the Oxford-Emergent Tuberculosis Consortium (OETC), a joint venture established for the development of MVA85A (OETC no longer exists). KH has a patent (US 5736524 A) related to the development of a DNA vaccine against Mycobacterium tuberculosis. RJW received grants from the European & Developing Countries Clinical Trials Partnership, the Welcome Trust, the UK Medical Research Council, and the European Union during the conduct of the study, and personal fees from GlaxoSmithKline unrelated to this work. The study was funded by the European & Developing Countries Clinical Trials Partnership (IP.07.32080.002), Aeras, Bill & Melinda Gates Foundation, the Wellcome Trust (095780, 084323, and 088316), and the Oxford-Emergent Tuberculosis Consortium. Quintiles (Bloemfontein, South Africa) were used for the statistical analysis, and Aeras paid for this service.

Table 7 Characteristics of Included Studies: MVA85A Tameris et al.,[3]

Methods	In our double-blind, randomized, placebo-controlled phase 2b trial, we enrolled healthy infants (aged 4–6 months) without HIV infection who had previously received BCG vaccination. We randomly allocated infants (1:1), according to an independently generated sequence with block sizes of four, to receive one intradermal dose of MVA85A or an equal volume of Candida skin test antigen as placebo at a clinical facility in a rural region near Cape Town, South Africa. We actively followed up infants every 3 months for up to 37 months. The primary study outcome was safety (incidence of adverse and serious adverse events) in all vaccinated participants, but we also assessed efficacy in a protocol-defined group of participants who received at least one dose of allocated vaccine. The primary efficacy endpoint was incident tuberculosis incorporating microbiological, radiological, and clinical criteria, and the secondary efficacy endpoint was M tuberculosis infection according to QuantiFERON TB Gold In-tube conversion (Cellestis, Australia). This trial was registered with the South African National Clinical Trials Register (DOH-27-0109-2654) and with ClinicalTrials.gov on July 31, 2009, number NCT00953927
Participants	We enrolled healthy infants, aged 4–6 months and who had received BCG (Danish 1331, Statens Serum Institut, Denmark) within 7 days of birth. Infants had to have received all age-appropriate routine immunizations, and two doses of pneumococcal conjugate vaccine at least 28 days before study vaccination (amended to 14 days during enrolment). All infants had to be HIV ELISA negative, QuantiFERON-TB Gold In-tube test (QFT; Cellestis, Australia) negative, and have had no substantial exposure to a patient with known tuberculosis
Interventions	MVA85A is a recombinant strain of modified Vaccinia Ankara virus expressing the immune-dominant M tuberculosis protein, antigen 85A. MVA85A has been developed as a heterologous boost for BCG. Boosting BCG with MVA85A improved BCG-induced protection against mycobacterial challenge in animals. MVA85A was well tolerated in clinical trials in infants. Furthermore, a BCG prime-MVA85A boost immunization regimen in infants induced antigen-specific Th1 and Th17 cells, which are regarded as important in protection against tuberculosis.
Outcomes	The primary safety outcome was incidence of adverse and serious adverse events. The primary efficacy outcome was incidence of endpoint. The secondary efficacy outcome was infection with M. Tuberculosis.
Notes	N/A

Table 8 Risk of Bias (MVA85A Tameris et al.,[3]

Bias	Author's Judgment	Support for Judgment
Random Sequence Generation (Selection Bias)	Low Risk	In our double-blind, randomized, placebo-controlled phase 2b trial, we enrolled healthy infants (aged 4–6 months) without HIV infection who had previously received BCG vaccination. We randomly allocated infants (1:1), according to an independently generated sequence with block sizes of four, to receive one intradermal dose of MVA85A or an equal volume of Candida skin test antigen as placebo.

Table Continued...

Bias	Author's Judgment	Support for Judgment
Allocation Concealment (Selection Bias)	Low Risk	We randomly allocated infants in a 1:1 ratio, with a block size of four, by use of an interactive voice/online response system to receive one intradermal dose of MVA85A (1×10^8 plaque-forming units in 0·06 mL) or an equal volume of Candida skin test antigen (Candin, AllerMed, USA) as placebo.
Blinding of Participants and Personnel (performance bias)	Unclear Risk	No Information Provided
Blinding of Outcome Assessment (detection bias)	Low Risk	Doses were prepared and labelled in masked syringes by an unmasked study pharma cist. An independent statistician prepared the randomization schedule. The parents or legal guardians of study participants, study staff administering vaccinations or undertaking follow-up clinic assessments, and lab oratory staff were masked to intervention group assignment.
Incomplete Outcome Data (attrition bias)	Unclear Risk	Exact figures were not provided, but stated that the number of participants lost did not affect the final analysis
Selective Reporting (reporting bias)	Unclear Risk	No Information Provided
Other bias	Unclear Risk	SL and JES are employees of Emergent BioSolutions and own shares and stock options in the company. HMcS is a shareholder in the Oxford-Emergent Tuberculosis Consortium (a joint venture between Emergent BioSolutions and the University of Oxford). This study also used SATVI as a clinical site 3 of 5 studies. Same lead author as Aeras-402.

Table 9 Characteristics of Included Stories: RUTI Nell et al.,[6]

Methods	Double-blind, randomized, placebo-controlled Phase II Clinical Trial (95 patients randomized). Three different RUTI doses and placebo were tested, randomized both in HIV-positive (n = 47) and HIV-negative subjects (n = 48), after completion of one month isoniazid (INH) pre-vaccination. Each subject received two vaccine administrations, 28 Days apart.
Participants	Study inclusion criteria were men and women 18–50 years of age, without evidence of active TB, positive tuberculin skin test (TST+) [5mm induration] and Quantiferon TB Gold positive result. Additional inclusion criteria in the HIV-positive group were: HIV antibody positive, CD4 count 350 cells/mL and clinically stable subjects if on anti-retroviral treatment.
Interventions	The Hybrid 1 (H1) vaccine is a recombinant fusion protein of the antigens Ag85B and ESAT-6 (Ag85B–ESAT-6), developed and manufactured by the Statens Serum Institut (Denmark). The adjuvant IC31 was developed by Intercell AG (Austria) and consists the cationic poly-amino acid KLK, which is composed of the amino acids lysine (K) and leucine (L), and ODN1a, a single stranded oligodeoxynucleotide with alternating sequences of the nucleic acids inosine and cytidine. A volume of 0.5mL was administered providing a dose of 50mg Ag85B-ESAT6 (antigen) and 500 nmol KLK +20 nmol ODN1a (adjuvant) or 0.5 mL Tris buffer (placebo). Each vial of placebo contents: sucrose (50,000.0mg/mL), soy lecithin (2,114.4mg/mL), sodium cholate 230.0mg/mL and sodium chloride 52.1mg/mL, which is exactly the same composition of RUTI vaccine, excepting the content of drug substance.
Outcomes	To evaluate the H1/IC31® TB vaccine in HIV-infected adults for: Safety, Induction of cellular and humoral immunity To describe the effect of the H1/IC31®, TB vaccine in HIV-infected adults on: CD4+ lymphocyte counts, HIV viral loads, To evaluate innate and adaptive immune response to H1/IC31®, TB vaccine in HIV-infected adults using transcriptomics.
Notes	The major deviation was recorded for one patient (HIV-negative group 5mg RUTI) at Day 63, PBMC blood samples were delivered to the laboratory with a delay of more than 4 hours. Additional samples had to be collected next day. Three patients took theophylline in the pretreatment phase which was a prohibited concomitant medication according the exclusion criteria.

Table 10 Risk of Bias (RUTI Nell et al.,[6]

Bias	Author's Judgment	Support for Judgment
Random Sequence Generation (Selection Bias)	Low Risk	The medication (RUTI vials) was prepared giving the RUTI or placebo after the random attribution to a serial number generated using the RANDPLAN, a locally developed SAS validated macro utilizing the PROC PLAN procedure in SAS.
Allocation Concealment (Selection Bias)	Low Risk	The medication (RUTI vials) was prepared giving the RUTI or placebo after the random attribution to a serial number generated using the RANDPLAN, a locally developed SAS validated macro utilizing the PROC PLAN procedure in SAS
Blinding of Participants and Personnel (performance bias)	Low Risk	The randomization list was sent to the persons responsible of the medication storage and labelling and the rest of the personnel were kept blinded.
Blinding of Outcome Assessment (detection bias)	Unclear Risk	Medication was transferred to pharmacists at each trial site with the correspondent sealed envelope labelled with the serial number containing information on the nature of the medication inside. The envelopes were maintained in a locked secure place throughout the whole study while still allowing access for emergency code breaking only.
Incomplete Outcome Data (attrition bias)	Unclear Risk	No Information Provided

Table Continued...

Bias	Author's Judgment	Support for Judgment
Selective Reporting (reporting bias)	Unclear Risk	No Information Provided
Other bias	Unclear Risk	Competing Interests: The following statement was included in the cover letter: Jordi Picas and Merce` Amat are employees of ArchivelFarma S.L., Pere-Joan Cardona is consultant of ArchivelFarma S.L., Andre S. Nell and Eva D'lom are employees of PAREXEL (South Africa) and PAREXEL International (Spain), respectively. Patrick Bouic is employee of Synexa Life Sciences (SouthAfrica), Ramon Bosser is employee of Janus Developments (Spain), and Montserrat Sabate´ is an employee of TFS Develop (Spain). This does not alter the authors' adherence to all the PLOS ONE policies on sharing data and materials. Pere Joan Cardona is editor of PLOS ONE.

Table 11 Characteristics of Excluded Studies: Justification for Excluded Studies

Study Identification	Reason for Exclusion
ID93/GLA-SE	Evaluation of an adjuvanted vaccine against a clinical strain of M. Tuberculosis in a laboratory
M72/AS01 Day et al.	Patients were actively infected with TB at screening
M72/AS01 Idoko et al.	Vaccine is administered as a booster vaccine shortly after receiving BCG in infants
M72/AS01 Kumarasamy et al.	Not at least a Phase II study
M72/AS01 Montoya et al.	Dose-finding study, did not report efficacy or safety outcomes

Table 12 Summary of Findings- Effectiveness Outcomes

Experimental Vaccines Compared with Placebo for Tuberculosis

Patient or population: Patients in low to middle income countries where Tuberculosis is endemic
Settings: Clinical Trials site hospital or clinic
Intervention: Tuberculosis-targeted vaccine
Comparison: Placebo, equal amount of buffer

Outcomes	Illustrative comparative risks* (95% CI) Assumed Risk	Corresponding Risk	Relative effect (95%CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
Positive Quantiferon Conversion Rate Prior=r to study completion	**Low risk population** **10 per 1000**	**1 Per 1000** (0 to 3)	**RR 2.72** (0.94 to 7.85)	3328 (3)	⊕⊕⊕⊖ **moderate**	QFT results study data was unavailable for two studies. The test was performed in both cases, but was not reported.
Cytokine Positive CD4 Positive T-Cells Expressing IFN-y Range: >350 cells per µL testing performed at predetermined intervals post-immunization to determine immune response	The mean 18% cells per µL ranged across control groups from 0.02 to 0.5% cells per µL	The mean 1.02% cells per µL in the intervention groups was 0.75 to 1.15% per µL		4025 (4)	⊕⊕⊕⊖ **moderate**	Results were reported using different scales so figures needed t be adjusted to allow for a comparison across studies.

Table 13 Summary of Findings Table-Safety Outcomes

Serious Adverse Events When SAEs are identified they should investigated, recorded and categorized immediately. Medical care should be provided immediately to address the patient's needs. If necessary a determination if the event was related to the intervention can be made at a later data.	**Medium Risk Population** **44 per 1000**	**48 per 1000** (1-257)	**RR. 1.22** (1.08 to 1.38)	4073 (5) ⊕⊕⊕⊕ **high**	Deaths occurred during the execution of the trails, however no deaths were a result of the investigational vaccines.
Total Related Adverse Events After clinical evaluation, post event resolution, Prior to study closeout.	**Low Risk Population** **49 per 1000**	**63 per 1000** (0 to 307)	**RR 1.05** (1.02 to 1.09)	4073 (5) ⊕⊕⊕⊕ **high**	The majority of the adverse events were due to redness and swelling at the injection site and classified as minor or moderate

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **Corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** (Risk Ratio); [other abbreviations, eg. OR, etc]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Table 14 Efficacy and Outcomes

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
Positive Quantiferon Conversion Rate	3	3328	Risk Ratio (M-H, Random, 95% CI)	2.72 [0.94, 7.85]
Cytokine Positive CD4 Positive T-Cells Expressing IFN-y	4	4025	Std. Mean Difference (IV, Random, 95% CI)	1.92 [1.19, 2.65]

Table 15 Safety Outcomes Data

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
Serious Adverse Events	5	4073	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [1.08, 1.38]
Total Related Adverse Events	5	4073	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [1.02, 1.09]

Table 16 Baseline Characteristics Outcomes Data

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
Female Participant Allocation	5	4073	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.95, 1.18]
HIV Positive Participants	3	1020	Risk Ratio (M-H, Random, 95% CI)	2.02 [0.14, 28.19]
Age > 18 years	3	792	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.99, 1.01]

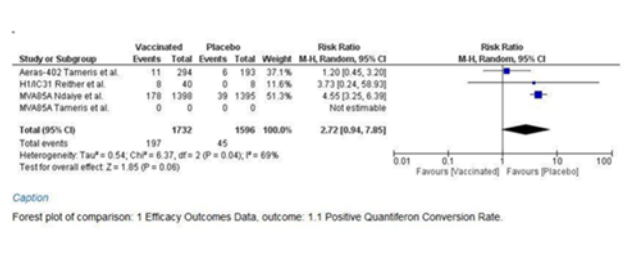

Figure 1 Efficacy outcome – Positive Quantiferon Conversion Rate.

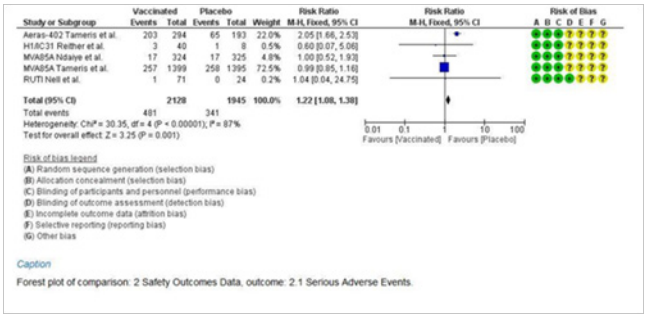

Figure 2 Safety Outcome – Serious Adverse Events.

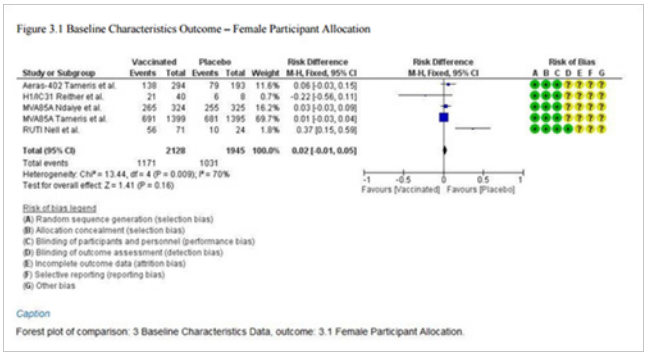

Figure 3 Baseline Characteristics Outcome – Female Participant Allocation.

Conclusion

There is promise that the vector types explored in this review possess potential vial delivery pathways for future vaccines in this area. These vaccines could be used as boosters to BCG in infants or as new interventions to improve responses in patients with co-morbidities closely associated with Tuberculosis, such as HIV and Meningitis.[21–26] There is a case that the immune responses which were observed immediately after immunization could be sustained if dosages were increased at levels which maintain the safety profiles observed in these trials.

Acknowledgements

Dr Jeremy Howick for providing guidance on the design and planning necessary to execute this systematic review.

Conflicts of interest

Author declares there are no conflicts of interest.

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