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MVA85A vaccine to enhance BCG for preventing tuberculosis (Protocol)

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[Intervention Protocol]

MVA85A vaccine to enhance BCG for preventing tuberculosis

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess and summarize the effects of the MVA85A vaccine boosting BCG in humans.

BACKGROUND

Description of the condition

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis*. In 2016, 6.3 million new cases of tuberculosis were reported. Tuberculosis now ranks first, followed by human immunodeficiency virus (HIV), as the leading cause of death from an infectious disease worldwide killing an estimated 1.8 million people in 2016, including 370,000 people living with HIV. Over 95% of these people were living in low- and middle-income countries (WHO 2017).

Tuberculosis can be classed as active when people experience signs or symptoms of tuberculosis or have radiological evidence of it. Tuberculosis can also be classified as latent tuberculosis infection (LTBI) where immunological evidence of previous exposure to *M. tuberculosis* exists without clinical or radiological evidence of the disease (CDC 2000). Of healthy adults with immunological evidence of previous exposure to *M. tuberculosis*, the overall lifetime risk of progressing to active disease if not treated for the infection is 5% to 10% (Harries 2006). Often this happens months or years after the initial infection in response to a weakening of the body's immune system. The probability of developing active disease is higher in HIV-positive, diabetic patients, and young children (Baker 2011; Perez-Velez 2012; Tiemersma 2010). Fifty percent of infants with evidence of LTBI will progress to active disease if untreated (Marais 2004). People with LTBI require early diagnosis and treatment to reduce the pool of active tuberculosis cases. This is particularly important in high-risk groups, such as those co-infected with HIV (Sharma 2012). Tuberculosis can be treated with long courses of multiple antibiotics, but the rise of HIV and spread of multi-drug resistant tuberculosis (MDR-TB) means that tuberculosis is still one of the largest threats to public health worldwide (WHO 2017). Structural determinants such as rapid urbanization of populations and economic inequalities, social determinants such as poverty and poor housing, alongside biological factors such as HIV and drug-resistant strains of tuberculosis play a vital role in the spread of tuberculosis through vulnerable populations (Daftary 2012).

The Bacillus Calmette-Guérin (BCG) vaccine is currently the only

available vaccine. Epidemiological studies indicate that it has a protective effect against tuberculosis disease in children, particularly against the more severe forms of the disease such as tuberculosis meningitis or miliary tuberculosis (Roy 2014). The effectiveness of BCG differs greatly depending on location and site of infection. It has consistent protection against tuberculosis meningitis and miliary disease in children but variable protection against pulmonary tuberculosis (Abubakar 2013; Colditz 1995). As a result, despite many areas achieving high coverage of BCG vaccination, the disease remains a problem, and a new tuberculosis vaccine remains an important global research priority (WHO 2017).

Previously it has been impossible to ascertain reliably whether the BCG vaccine protected against active disease or infection with *M. tuberculosis*. This was due to the tuberculin skin test being unable to distinguish between cases of LTBI and people who had been vaccinated with BCG (Roy 2014). An important development was therefore the development and use of interferon gamma release assays (IGRA), which can distinguish between tuberculosis infection and vaccination. This has allowed researchers to establish that BCG vaccination reduces the risk of *Mycobacterium* infection in some settings (Eisenhut 2009).

Description of the intervention

Many researchers and policy makers emphasize that a new effective vaccine could be a major contribution to tuberculosis control and elimination as a public health problem (de Cassan 2010). There are 13 vaccine candidates in clinical trials: nine in Phase II or Phase III, and four in Phase I. They include candidates to prevent the development of tuberculosis, and candidates to help improve the outcomes of treatment for tuberculosis disease (WHO 2017; Table 1).

The modified Vaccinia Ankara virus expressing antigen 85A (MVA85A) is a viral vector vaccine. It is based on the modified Vaccinia Ankara (MVA) virus used as a vector. MVA is an attenuated virus that does not replicate in human tissue and, as such, has been used as a platform to encode multiple antigens and allowing development of multivalent vaccines (Altenburg 2014). In this case, MVA has had pieces of DNA from *M. tuberculosis* inserted into it, so that it expresses the antigen 85A. This antigen complex is an enzyme that is involved in the cell wall biosynthesis of *M. tuberculosis* and constitutes a vital part of the way in which the bacteria forms its outer mycomembrane. This is important for the viability of the mycobacterium and works as an effective barrier to drug therapies by repelling some antibiotics and preventing them from entering the cell (Favrot 2013).

Immunological studies have shown that a prime boost strategy, where MVA85A is used to boost the effects of BCG, is effective in expanding immune responses specific to *M. tuberculosis* (Beveridge 2007). Thus MVA85A was proposed primarily as a booster to individuals already vaccinated with BCG (Tameris 2013). Further studies have also assessed MVA85A in other regimens including in combination with other viral vector vaccines (Sheehan 2015).

How the intervention might work

MVA85A is the first vaccine since 1968 to be tested in efficacy trials (Tameris 2013). It has been tried with a promise of prolonged antimycobacterial immunity in human UK trials (McShane 2004), and in tuberculosis-endemic areas (Hawkridge 2008). The intention is that MVA85A would boost the immune response to tuberculosis above that which is afforded by vaccination with BCG (Roy 2014). MVA85A is administered as a single intradermal dose in people who have already received BCG vaccine (Tameris 2013). Other routes have been studied in animal studies, such as aerosol and intravenous administration (Kashangura 2015), and are being considered in humans (Satti 2014).

The researchers who developed the vaccine have evaluated its effects in animals and conducted Phase 1 studies in humans. Early literature and reviews by the team noted the vaccine was safe and produced an immune response in a number of populations (McShane 2004; Rowland 2012).

An independent systematic review of the animal studies, carried out by some members of this Cochrane Review team, raised questions about whether these animal studies provided evidence of efficacy in the various animal models used (Kashangura 2015), when clinical and pathological endpoints were examined in a variety of animal models subjected to challenge studies. These studies gave BCG, BCG and MVA85A, or no vaccine and exposed animals to tuberculosis challenge. Clearly progression to clinical trial is not solely based on evidence derived from preclinical efficacy studies, but preclinical studies are an important component of the tuberculosis vaccine development paradigm (McShane 2014 Barker 2012).

The safety of the vaccine in human subjects has been evaluated in a number of Phase 1 studies. The standard approach for Cochrane Reviews within the Cochrane Infectious Diseases Group is to only summarize efficacy trials. Given the interest over the balance between benefits and harms, we thought it helpful to summarize the considerable number of Phase 1 studies that the researchers carried out to exclude severe adverse effects attributable to the vaccine in humans, and summarize the data from Phase 1 studies in this Background section. We searched registered clinical trial databases (ClinicalTrials.gov, World Health Organiziation (WHO) International Clinical Trials Registry Platform (ICTRP), Pan African Trials Registry, EU Clinical Trials Register) in June 2017 and summarized the Phase 1 studies identified in Table 2. We found 21 separate studies as registered (prospectively and retrospectively) dating from 2003 with the most recent studies scheduled to complete follow-up in 2018. In addition, we found an existing narrative review of Phase 1 studies (Rowland 2012), which summarizes Phase 1 safety data relating to selected trials including unpublished data and compares this to selected trials in yellow fever and BCG.

The 21 studies included 712 participants investigated from 2002 with follow-up expected to be completed by 2018. The studies covered a diverse population in the UK, South Africa, Senegal, and The Gambia with HIV-positive and HIV-negative individuals as well as infants, children, and adults. Intramuscular, intradermal, and aerosolized delivery routes were all investigated. The summary shows most of the adverse events related to vaccination were mild and were contained locally to the injection site. There were very few serious adverse events; erythema and mild pain were the most common.

Why it is important to do this review

Summarizing the evidence to date will be useful to the public, scientists, and to others interested in innovation in tuberculosis. As of November 2017, there are ongoing studies looking at aerosolized delivery of the vaccine (NCT02532036). In 2017 studies have been published that address the immunogenicity of what the study authors termed "the candidate TB vaccine MVA85A" in *Schistosomiasis*-infected teenagers (Wajja 2017), and a further efficacy study in HIV-exposed infants (Nemes 2017). This Cochrane Review will help maintain a summary of various patient groups, routes, and purposes for which the vaccine is being evaluated.

OBJECTIVES

To assess and summarize the effects of the MVA85A vaccine boosting BCG in humans.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) that include measures of clinical efficacy (Phase II clinical trials).

Types of participants

Any person regardless of age or HIV status.

Types of interventions

Intervention

MVA85A vaccine regardless of vaccination schedule, dosage, route, or formulation given with BCG.

Control

BCG alone.

Types of outcome measures

Primary outcomes

Active tuberculosis, defined by either:

- clinical signs and symptoms fulfilling an algorithm defined in the trial;
- clinical signs and symptoms plus confirmation by microscopy, culture, or GeneXpert®;
- clinical signs and symptoms plus radiological evidence of tuberculosis as defined in the trial.

Secondary outcomes

Latent tuberculosis, diagnosed by IGRA or Mantoux without clinical or radiological evidence of active disease.

Adverse outcomes

Adverse effects of any severity, defined as "an adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility" (Loke 2011).

Serious adverse effects, defined as an adverse event attributable to the intervention "leading to death, are life threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, or result in persistent or significant disability or incapacity" (ICH 1994).

Adverse events of any severity, defined as "any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment" (WHO-ART 2008).

Abnormal haematological tests during the follow-up period after being vaccinated.

Abnormal biochemical tests during the follow-up period after being vaccinated.

Search methods for identification of studies

We will attempt to identify all potential studies regardless of language or publication status (published, unpublished, in press, and in progress).

Electronic searches

We will search the following databases using the search terms and strategy described in Appendix 1: the Cochrane Infectious Diseases Group Specialized Register; Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library; MEDLINE (Pubmed); Embase (OVID); Science Citation Index-Expanded, Social Sciences Citation index, Conference proceedings (Web of Science); and CINAHL (EBSCOHost). We will also search the WHO ICTRP (www.who.int/ictrp/en/) and ClinicalTrials.gov (https://clinicaltrials.gov/ct2/home), using the search terms: MVA85A, "modified vaccinia virus Ankara", Ag85A , "Antigen 85A", and tuberculosis OR TB OR BCG. If trials are reported as completed in a trial registry and data are not in the public domain within two years of the last patient last visit (LPLV) we will contact the authors to ask when the data will be available.

Searching other resources

We will search the proceedings and abstracts of the following tuberculosis conferences: Union World Conference on Lung Health, European Respiratory Society, and the International Conference of the American-Thoracic-Society (ATS), for the past five years. We will handsearch reference lists of relevant papers, and contact researchers working in the field.

Data collection and analysis

Selection of studies

Two review authors will independently screen all abstracts retrieved by the search strategy above using predefined eligibility criteria designed and piloted by the review authors. We will exclude clearly irrelevant studies. We will search for multiple publications using studies from the same data set. Full-text copies will be retrieved for all trials thought to be potentially relevant. Two review authors will then independently assess all identified trials for inclusion in the review using the pre-defined inclusion criteria.

We will resolve any disagreements in assessment through discussion. In cases of unresolved differences, a third review author will adjudicate. We will keep records of the initial results and the changes after discussion. We will list all studies excluded after full-text assessment in a 'Characteristics of excluded studies' table. We will illustrate the study selection process in a PRISMA diagram.

Data extraction and management

We will design and pilot data extraction forms. Data extraction and management will be done independently and in duplicate. We will gather information from each included trial separately on trial characteristics. This will include:

- study setting, design, study duration, population sample size, and power calculations;
- baseline characteristics of study population including age, sex, weight, prematurity, HIV, other comorbidity, whether breastfeeding,race, HIV status, antiretroviral therapy (ART), CD4 count, and viral load;
- the intervention and control group vaccine dosages, routes of administration, and times of vaccination;
- time of outcome measure after administering MVA85A;
- duration of follow-up, any participants who withdrew from the study, and reasons why.

All outcomes are dichotomous so we will tabulate numbers of participants who developed tuberculosis disease or an adverse event (n) with the total sample size number (N) in each of the comparison groups. We will document the different definitions of outcomes in the trials for further consideration.

Two review authors will compare data extracted and resolve discrepancies through discussion with a third review author. We will later combine the separate reports on a multiple data collection sheet including key elements of each study. We will then transfer this information to Review Manager 5 (RevMan 5) for analysis (RevMan 2014). Authors of included studies will be contacted for missing information and any other queries.

Three review authors (RK, SoJ, and SaJ) will screen studies, design, and pilot extraction forms and extract data.

Assessment of risk of bias in included studies

We will assess the study quality for RCTs using the Cochrane 'Risk of bias' tool (Higgins 2011).

All studies will be assessed for risk of bias independently and in duplicate. We will resolve any disagreement through discussion and, where necessary, through consultation with a third review author.

Two review authors will initially pilot the 'Risk of bias' assessments on four included trials to check for consistency and to ensure all methodological issues have been understood. Sequence generation (if predictable method used) and allocation concealment will assess for selection bias and detection bias will be assessed by looking at blinding methods. We will consider both the intention of blinding and the success of blinding for each outcome. If there is no description of the procedure, for example how randomization was done, we will mark it as unclear.

In addition, we will examine the objectivity of outcome measures, use of intention-to-treat (ITT) analysis, loss to follow-up, and selective outcome reporting in order to assess the risk of bias in included studies. We will also assess whether outcome measures are specified *a priori* and whether the published endpoints match those specified in study protocols.

We will assess incomplete outcome data in each included trial to determine the proportion of missing results and whether it affects the results or not in terms of event risk and effect size. We will

assess if reasons for missing data are related to adverse events or death from MVA85A and if missing data balanced in the two experimental groups in order to have an overall decision on risk associated with incomplete outcome data.
Other forms of high risk of bias will include influence by funders, extreme differences in baseline characteristics, and stopping of the trial before it is finished for unclear reasons.
For adverse effects and events we will use methods used in previous systematic reviews, as outlined in Table 3. We will assess the included trials for risk of bias by examining if monitoring was active or passive; whether participants and outcome assessors were blinded; whether the outcome data reporting was complete; whether all participants were included; and whether data analysis was independent of pharmaceutical companies (Bukirwa 2014).
If there is insufficient information to assess risk of bias we will contact authors to obtain information needed to adequately assess risk of bias.

Measures of treatment effect

We will analyse all data using RevMan 5 (RevMan 2014). If appropriate, we will present and combine dichotomous data using risk ratios (RR) with their corresponding 95% confidence intervals (CI); and we will express continuous outcomes as standardized mean differences with 95% CIs.

Unit of analysis issues

If we identify studies for inclusion that have multiple intervention arms, we will include data from these studies by either combining treatment arms, or by splitting the control group so that participants are only included in the meta-analysis once.
Where studies undertook multiple observations on the same participants we will stratify the analysis by time point.

Dealing with missing data

We will assess missing data to see if it is related to outcome. If missing data from trial reports restricts the use of the study, we will contact trial authors for more information. It is anticipated that for older publications it may not be possible to reach the trial author. If data are missing at random, we will analyse only the available data. If the amount of incomplete outcome data is such that the trial is thought to be at a high risk of bias, we may use imputation and perform sensitivity analyses to investigate the impact of this missing data.
We will use ITT analysis for all outcomes except adverse effects where a treatment received analysis will be done.

Assessment of heterogeneity

We will assess extracted data from included trials to find key differences in population groups, study setting, intervention and control groups, dosages and route of vaccine administration, or timing between BCG and boosting. Degree of risk of bias, when and how the outcome was measured, and variation in treatment effects will also be assessed.
We will determine the level of heterogeneity by inspecting forest plots for overlapping CIs. We will judge a Chi² P value significance level of ≤ 0.1 as likely heterogeneity. An I^2 statistic value of less than 40% will be regarded as not showing any significant heterogeneity.

Assessment of reporting biases

If applicable, we will use funnel plot analysis or statistical tests such as an Egger regression test, or both, to assess for publication bias.

Data synthesis

We will use the fixed-effect Mantel-Haenszel model for meta-analysis. The intention for meta-analysis of adverse outcomes will be to limit it to three to five of the most frequent adverse effects and all those that were considered to be serious. However, due to different methods of monitoring adverse effects that in turn lead to different results, meta-analysis might not be done and a narrative report given instead.
If appropriate, we will perform statistical adjustments for sample size and variance for any cluster randomized trials before meta-analysis according to methods described in the *Cochrane Handbook for Systematic Review of Interventions* (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

We will explore heterogeneity by:

- subgroup by children and adults;
- background prevalence of tuberculosis (or tuberculosis incidence in the control group);
- HIV status; and
- geographical location.

We will consider random-effects meta-analysis if subgroup analysis does not explain the heterogeneity. The I^2 statistic will be applied according to guidance of: less than 40% as not significant heterogeneity; 30% to 60% representing moderate heterogeneity; 50% to 90% representing substantial heterogeneity; and 75% to 100% considerable heterogeneity (Higgins 2011). We will regard a Chi² P value significance level of ≤ 0.1 and an I^2 statistic value of > 40% as showing significant heterogeneity, in which case we will either consider a random-effects model or we will not perform meta-analysis. In case of extensive qualitative heterogeneity, we will not carry out meta-analysis.

We will report the term used for any adverse effect in each trial. Where trials use different terminology for similar adverse events and adverse effects, we will code them using the preferred term based on Medical Dictionary for Regulatory Activities (MedDRA) terminology (for example, sleepiness, somnolence) and analyse them together (MedDRA 2016).

Sensitivity analysis

We will perform sensitivity analysis for imputed data and any other peculiarities between the trials identified during the review process If high risk of bias is identified in some trials, we will perform sensitivity analysis by assessing results after excluding trials that are at high or unclear risk of bias. Methodological quality summaries will show review author judgements about each 'Risk of bias' assessment item for each included trial and also weighting of each item across all included trials.

Certainty of the evidence

We will assess the certainty of the evidence using the GRADE approach (Langer 2012). We will construct a 'Summary of findings' table, which will show the main review findings for outcomes listed under the 'Types of outcome measures' section.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Novel vaccines undergoing trials for tuberculosis prevention

Category	Vaccine	Clinical trial stage
Protein/adjuvant	M72/AS01	Phase IIb

Table 1. Novel vaccines undergoing trials for tuberculosis prevention (*Continued*)

	H4/IC31	Phase IIa
	H56/IC31	Phase IIa
	ID93/GLA-SE	Phase IIa
Viral vector	MVA85A (Aerosol)	Phase I
	ChAdOx185A	Phase I
	Ad5Ag85A	Phase I
	TB FLu -04L	Phase II
Live *Mycobacteria*	MTBVAC	Phase I
	VPM1002	Phase IIb
Mycobacteria whole cell/extract	Dar-901 booster	Phase IIb
	RUTI	Phase IIa
	Vaccae	Phase III

Table adapted from WHO 2017.

Table 2. Summary of Phase 1 studies

NCT trial number	Route	Dates	Intervention and schedule details	Country	Participants (age)	HIV	Adverse events	Reference
NCT0042350	ID	2002-3	MVA85A; 1 dose	UK	14 adults (18 to 45 years)	-ve	7 trials (112 participants); combined in one report: no serious AE attributable to the vaccine	McShane 2004, Rowland 2012
NCT0042383	ID	2003-5	MVA85A; 1 dose, 2 doses (5 x 10^7 PFU)	Gambia	21 adults	N/R	No serious AE attributable to the vaccine	Brookes 2008; Ibanga 2006; Owiafe 2012
NCT0042783	ID	2003-5	MVA85A; 1 dose (5 x 10^7	UK	21 adults	-ve	No serious AE attributable to the	McShane 2004; Pathan 2007;

Table 2. Summary of Phase 1 studies (*Continued*)

			PFU)				vaccine	Rowland 2012; Tanner 2014; Whelan 2009
NCT004274[illegible]	ID	2003-5	MVA85A; 1 dose (5 x 10^7 PFU)	UK	10 adults	-ve	No serious AE attributable to the vaccine	Pathan 2007; Rowland 2012
NCT004561[illegible]	ID	2005-7	MVA85A, (5 x 10^7 PFU)	UK	12 adults with latent tuberculosis	-ve	No vaccine related serious adverse events 7 trials (112 participants; data combined in one report)	Rowland 2012; Sander 2009; Tanner 2014
NCT004654[illegible]	ID	2005-7	MVA85A; 1 dose (1 x 10^8 PFU for 12 participants, and 1 x 10^7 PFU for 12 participants)	UK	24 adults	-ve	No serious AE attributable to the vaccine	Griffiths 2011; Matsumiya 2013; Pathan 2012; Rowland 2012
NCT004605[illegible]	ID	2005-8	MVA85A, (5 x 10^7 PFU)	South Africa	36 adults and adolescents	-ve	No vaccine related serious adverse events	Hawkridge 2008; Scriba 2010; Tameris 2014; Tanner 2014
NCT004804[illegible]	ID	2006-9	MVA85A; 1 dose MVA85A (2.5 x 10^7 PFU, 5 x 10^7 PFU) Groups 1. EPI vaccines: 2. MVA85A + EPI: 3. MVA85A + EPI 1 week later	The Gambia	214 infants (4 months)	N/R	No serious AE judged to be related to the vaccine	Odutola 2012; Ota 2011
NCT003957[illegible]	ID	2006-10	MVA85A; 1 dose (5 x 10^7PFU for 10	UK	20 adults	+ve	No serious AE attributable to the vaccine	Minassian 2011

Table 2. Summary of Phase 1 studies (*Continued*)

			participants, and 1 x 10^8 PFU for 10 participants)					
NCT0048055	ID	2007-11	MVA85A; 1 dose (5 x 10^7 PFU) 4 groups with background of 1. MTB 2. HIV 3. MTB + HIV 4. HIV on ART	South Africa	48 adults (18 to 50 years)	+ve	No vaccine related serious adverse effects	Scriba 2012; Tanner 2014; Tameris 2014
NCT0065377	ID	2007-10	FP85A, MVA85A (5 x 10^7 PFU)	UK	31 adults	-ve	No serious AE attributable to the vaccine	Rowland 2013
NCT0054844	ID	2007-10	MVA85A; 1 dose (1 x 10^8 PFU), administered as 2 injections (5 x 10^7 PFU each injection)	UK	12 adults	-ve	7 trials (112 participants) ; data combined in one report: no serious AE attributable to the vaccine	Porter (unpublished data: source Rowland 2012)
NCT0073147	ID	2008-11	MVA85A; 2 doses (spaced by 6 to 12 months) (1 x 10^8 PFU)	Senegal	24 adults	+ve	No serious AE attributable to the vaccine	Dieye 2013
NCT0118185	ID IM	2010-1	MVA85A; 1 dose (1 x 10^8 PFU)	UK	24 adults	-ve	No serious AE attributable to the vaccine	Matsumiya 2013; Meyer 2013
NCT0119418	ID	2010-2	MVA85A, BCG; 1 dose (1 x 10^8 PFU) Group A: BCG naïve, no MVA85A	UK	49 adults recruited (48 completed study)	-ve	No serious AE attributable to the vaccine	Harris 2014a; Harris 2014b; Matsumiya 2013

Table 2. Summary of Phase 1 studies (*Continued*)

			Group B: BCG naïve, MVA85A Group C: BCG vaccinated, no MVA85A Group D: BCG vaccinated, MVA85A.					
NCT014977(	Aerosol ID	2011-3	MVA85A; 1 dose: 1 x 10^8, 1 x 10^7 PFU	UK	24 adults	-ve	No vaccine related serious adverse effects.	Satti 2014
NCT016837	ID	2012-4	AERAS-402 MVA85A; Group A: 2 doses AERAS-402 then MVA85A Group B: 1 dose AERAS-402 then MVA85A	UK	40 adults	-ve	No vaccine related serious adverse effects	Sheehan 2015
NCT018791(	ID	2013-4	MVA85A IMX313; Group A: low dose MVA85A-IMX313 (1 x 10^7 PFU) Group B: dose MVA85A-IMX313 (5 x 10^7 PFU) Group C: MVA85A (5 x 10^7 PFU)	UK	30 BCG vaccinated adults	-ve	No vaccine related serious AE	Minhinnick 2016
NCT018294(	IM	2013-6	MVA85A, ChAdOx1 85A; Group A: 1 dose ChA-	UK	42 adults	-ve	No data reported yet	No publication NCT01829490

Table 2. Summary of Phase 1 studies (*Continued*)

			dOx1 85A Group B: 1 dose ChA-dOx1 85A then MVA85A Group C: 2 doses ChA-dOx1 85A then MVA85A (1 x 10^8 PFU)					
NCT0195450	Aerosol ID	2013-6	MVA85A; Group 1: aerosol then ID Group 2: ID then aerosol Group 3: ID then ID (5 x 10^7 PFU)	UK	37 adults	-ve	No data reported yet	Manjaly Thomas 2016 (conference abstract)
NCT0253203	Aerosol ID	2015-8	MVA85A; 1 x 10^7 PFU aerosol inhaled, 5 x 10^7 aerosol and ID	UK	15 adults	-ve	No data reported yet	NCT02532036

Abbreviations: -ve: negative; +ve: positive; intradermal: ID; intramuscular: IM; plaque-forming unit: PFU; adverse event: AE; not reported: N/R.

Table 3. Adverse events risk of bias methods

Criterion	Assessment	Explanation
Patient-reported symptoms		
Was monitoring active or passive?	Active Passive Unclear	We will classify monitoring as 'active' when authors reviewed participants at set time points and enquired about symptoms
Was blinding for participants and outcome assessors adequate?	Adequate Inadequate Unclear	We will classify blinding as 'adequate' when both participants and outcome assessors were blinded to the intervention group, and the methods of blinding (including use of a placebo) were described

Table 3. Adverse events risk of bias methods (*Continued*)

Was outcome data reporting complete or incomplete?	Complete Incomplete Unclear	We will classify outcome data reporting as 'complete' when data was presented for all the time-points where it was collected
Were all participants included in reporting?	Yes No	We will report the percentage of randomised participants included in adverse event reporting
Was the analysis independent of study sponsor?	Yes No Unclear	We will classify the analysis of trials sponsored by pharmaceutical companies as independent of the sponsor when it was clearly stated that the sponsor had no input to the trial analysis
Laboratory tests		
Number of tests undertaken	-	We will extract the type and number of laboratory tests were taken
Timing of tests: was number and timing of tests adequate?	Adequate Inadequate	We will classify the number and timing of tests as 'adequate', when tests were taken at baseline, plus two other time points within the first week after treatment, plus the last day of the study. We will class the number of test taken as "inadequate", if either the laboratory controls in the first week or controls at four weeks were not performed
Reporting of test results: was reporting of test results complete?	Complete Incomplete	We will classify reporting as 'complete' when test results of all time points were reported. For the trials with inadequate number of tests taken, we will consider completeness of reporting as inconsequential, and therefore did not record a judgement
Independence of data analysis: was data analysis independent?	Yes No Unclear	We will classify the analysis of trials sponsored by pharmaceutical companies as independent of the sponsor when it is clearly stated that the sponsor had no input to the trial analysis

Adapted from Bukirwa 2014.

APPENDICES

Appendix 1. Sample MEDLINE (PubMed) search terms

#7	Search #3 and #6[1]
#6	Search 4 or 5
#5	"antigen 85A" OR Ag85A OR "modified vaccinia ankara" OR MVA85A Field: Title/Abstract
#4	"antigen 85A, Mycobacterium tuberculosis" [Supplementary Concept] or "MVA 85A" [Supplementary Concept])
#3	Search 1 or 2
#2	(("BCG Vaccine"[Mesh]) OR "bcg vaccin*" or "bacille Calmette-Guérin" Field: Title/Abstract
#1	"Tuberculosis"[Mesh] or tuberculosis or TB Field: Title/Abstract

[1]We will use search terms in combination with the search strategy for retrieving trials developed by Cochrane (Lefebvre 2011). This is the preliminary search strategy for MEDLINE (PubMed). We will adapt it for searching other electronic databases. All search strategies will be reported in full in the final version of the review.

CONTRIBUTIONS OF AUTHORS

RK drafted the protocol and collated Phase 1 data and responded to referee comments.

Sophie Jullien (SoJ) collated Phase 1 data and helped draft the protocol.

PG and TY contributed to the methods, coherence, and writing of the protocol.

Samuel Johnson (SaJ) coordinated and helped draft the protocol, responded to referee comments, and collated Phase 1 data.

DECLARATIONS OF INTEREST

RK has no known conflicts of interest.

SoJ worked for the Cochrane Infectious Diseases Group at the Liverpool School of Tropical Medicine from September 2015 to April 2016, which is funded by UK aid from the UK Government for the benefit of low- and middle-income countries (Grant: 5242).

PG is the Director of the Effective Health Care Research Programme Consortium, a DFID-funded research programme to support people carrying out Cochrane reviews for the benefit of the poor in low- and middle-income countries (Grant: 5242). DFID had no part in writing this protocol.

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