COST-EFFECTIVENESS ANALYSIS OF MVA85A VACCINE: A NEW TB VACCINE CANDIDATE

by

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Date: 08 July 2013
Dedications

To Dr Fareed Abdullah (affectionately known as “Dr”), thank you for taking a chance on me in 2003, for expanding my “pharmacist” horizons, for taking an interest in my professional development, and for investing in it, too! Without you, I would never have been exposed to the concepts of health economics, contemplated a degree in Public Health, or embarked upon a career in international health (financing!). My gratitude is endless; you are, truly, one of my heroes.
Abstract

Tuberculosis (TB) remains a major public health concern. The BCG vaccine is, currently, the only vaccine against TB and, although it provides some protection against disseminated forms of TB, its effectiveness in preventing primary infection and disease progression to pulmonary TB is highly varied.

A number of potential new TB vaccine candidates have been identified and are, currently, undergoing clinical trials. One such candidate is MVA85A.

This study aims to assess the potential cost-effectiveness of a new TB vaccine, the MVA85A vaccine. The study compares two TB vaccine strategies, from the perspective of the South African Government:

i. BCG, given at birth, which is the current standard of care in South Africa; and

ii. BCG, given at birth, together with a booster vaccine (MVA85A) given at 4 months, which is the potential new strategy.

The study employs Decision Analytical Modelling, through the use of a Markov model, to estimate the costs and outcomes of the two strategies. The cumulative costs and outcomes of each intervention are used to calculate the cost-effectiveness ratio (CER) (i.e. the cost per TB case averted and the cost per TB death averted) for each intervention. These two cost-effectiveness ratios are compared using an incremental cost-effectiveness ratio (ICER), which represents the additional cost per additional benefit received.

The results of the cost-effectiveness analysis indicate that the MVA85A strategy is both more costly and more effective – there are fewer TB cases and deaths from TB – than BCG alone. The Government would need to spend an additional USD 1,105 for every additional TB case averted and USD 284,017 for every additional TB death averted.
Given the disappointing results of the MVA85A vaccine clinical trial – showing an efficacy of only 17.3%, this study will predominantly contribute to establishing an efficacy threshold for future vaccines.

Our research also contributes to the body of knowledge on economic evaluations involving new TB vaccines as – to the best of our knowledge – this is the first cost-effectiveness analysis conducted using trial data involving a novel TB vaccine and providing a direct comparison with BCG vaccination.

Furthermore, it provides a standardized Markov model, which is relatively simple to adapt to local settings and, which could be used in the future, to estimate the potential cost-effectiveness of new TB vaccines in children between the ages of 0–10 years.
Acknowledgements

Thank you to the various staff of the Provincial Government, Western Cape, Department of Health; most notably, those working in the HIV/AIDS & TB, Comprehensive Health Programmes, Professional Support Services, and Health Impact Assessment Directorates, and to the Senior Pharmacist of the City of Cape Town who generously provided support and the information necessary to complete this work.

To the members of the “Expert Group” – Professor Willem Hanekom, Dr Mark Hatherill, Professor Anneke Hesseling, Dr Helen McShane, Dr Hassan Mohammed, Dr Roxana Rustomjee, and Dr Michele Tameris – your constructive feedback, valuable insights, and willingness to participate and share your expertise remains highly appreciated.

Mrs Lorraine Burton, I treasure your enthusiasm and commitment to ensuring a professional looking end-product as well as your unending emotional support. Thank you.

To my family and friends who have endured my continuous “sorry, I can’t, I’m working on my thesis”, thank you for all your love and support and for celebrating with me during the good times and sustaining me through the low times. Finally, it is done!

Dr Edina Sinanovic, thank you. Thank you for agreeing to be my supervisor, for guiding and supporting me through this exciting project, for sharing your knowledge and your professional network so willingly, for pointing me in the right direction when I was lost, for cheering me on when times were tough, and for being the voice of calm and reason when I was freaking-out. I have learnt so many new skills during our time together.
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<td>ARI</td>
<td>Annual Risk of Infection</td>
</tr>
<tr>
<td>BCG</td>
<td>Bacille Calmette–Guérin</td>
</tr>
<tr>
<td>CBA</td>
<td>Cost Benefit Analysis</td>
</tr>
<tr>
<td>CEA</td>
<td>Cost-Effectiveness Analysis</td>
</tr>
<tr>
<td>CER</td>
<td>Cost Effectiveness Ratio</td>
</tr>
<tr>
<td>CMA</td>
<td>Cost Minimization Analysis</td>
</tr>
<tr>
<td>CPI</td>
<td>Consumer Price Index</td>
</tr>
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<td>CUA</td>
<td>Cost Utility Analysis</td>
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<tr>
<td>DOTS</td>
<td>Directly Observed Therapy, Short-Course)</td>
</tr>
<tr>
<td>DTP3</td>
<td>Diphtheria-Tetanus-Pertussis</td>
</tr>
<tr>
<td>EPI</td>
<td>Expanded Programme of Immunization</td>
</tr>
<tr>
<td>FIND</td>
<td>Foundation for Innovative New Diagnostics</td>
</tr>
<tr>
<td>GDP</td>
<td>Gross Domestic Product</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental Cost Effectiveness Ratio</td>
</tr>
<tr>
<td>IPT</td>
<td>Isoniazid Preventive Therapy</td>
</tr>
<tr>
<td>MCV</td>
<td>Measles-containing vaccine</td>
</tr>
<tr>
<td>MDG</td>
<td>Millennium Development Goals</td>
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<tr>
<td>MDR-TB</td>
<td>Multidrug Resistant Tuberculosis</td>
</tr>
<tr>
<td>mTB</td>
<td>Miliary Tuberculosis</td>
</tr>
<tr>
<td>MVA85A</td>
<td>Modified Vaccinia Ankara 85A</td>
</tr>
<tr>
<td>NGO</td>
<td>Non-Government Organization</td>
</tr>
<tr>
<td>OETC</td>
<td>Oxford Emergent Tuberculosis Consortium</td>
</tr>
<tr>
<td>PTB</td>
<td>Pulmonary Tuberculosis</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality-Adjusted Life-Year</td>
</tr>
<tr>
<td>StatsSA</td>
<td>Statistics South Africa</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
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<tr>
<td>TBM</td>
<td>Tuberculosis Meningitis</td>
</tr>
<tr>
<td>TBVI</td>
<td>TB Vaccine Initiative</td>
</tr>
<tr>
<td>TST</td>
<td>Tuberculin Skin Test</td>
</tr>
<tr>
<td>UCT</td>
<td>University of Cape Town</td>
</tr>
<tr>
<td>USD</td>
<td>U.S. Dollars</td>
</tr>
<tr>
<td>WHA</td>
<td>World Health Assembly</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>ZAR</td>
<td>South African Rand</td>
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Part A

PROTOCOL
1. Introduction

1.1. Problem statement

Global Epidemiology of TB

Globally, it is estimated that, in 2010, there were 8.8 million new cases and 12 million prevalent cases of tuberculosis (TB) and 1.45 million deaths associated with TB. Furthermore, 2 billion – or a third of the world’s population – is believed to be latently infected with TB (World Health Organization 2012).

Although Asia had the highest number of new cases – 59% compared to Africa at 26% – Africa still has the highest proportion of cases per population – 276/100,000 compared to 193/100,000 in Asia and 128/100,000 globally. Africa also accounts for 82% of all TB cases amongst people living with HIV (World Health Organization 2012).

Since 2000, 22 countries have been identified as “high-burden countries” and have been prioritised globally. These 22 countries account for approximately 80% of TB cases worldwide. South Africa is included in the 22 countries and, in 2010, was one of five countries with the highest number of incident cases; the others being China, India, Pakistan, and Indonesia. South Africa is the only country, of the 22, showing an increase in the incidence rate (World Health Organization 2012).

The numbers affecting children are not readily available and tend to be unreliable for a variety of reasons, including the difficulties in diagnosing TB in children and the lack of standardised data collection. The latest estimates are that 520,000 (490,000 – 550,000) new cases and 64,000 (58,000 – 71,000) deaths occurred in children in 2010 (Sismanidis 2012). This represents 6% of new cases globally; although previous estimates were around 10% (Marais, Gie et al. 2006). The World Health Organization is in the process of preparing new estimates that will be released in 2012.
Global Targets

The Millennium Declaration in 2000 established the 8 Millennium Development Goals (MDGs) to be achieved by 2015, which included targets for TB control.

- MDG target 6.C: Have halted by 2015 and begun to reverse the incidence of malaria and other major diseases
  - Indicator 6.4 Incidence, prevalence and death rates associated with tuberculosis
  - Indicator 6.5 Proportion of tuberculosis cases detected and cured under directly observed treatment short course

The Global Partnership to STOP TB (STOP TB Partnership), founded in 2001 and hosted by the World Health Organization, brings together various stakeholders (e.g. technical agencies, government,
nongovernmental organizations (NGOs), academia, and the private sector) in support of the fight against TB.

- The STOP TB Partnership has endorsed the following targets linked to the MDGs.
  
  • by 2015: reduce prevalence and deaths due to TB by 50% compared with a baseline of 1990
  
  • by 2050: eliminate TB as a public health problem

*Global Efforts to develop a new TB vaccine*

In the mid-2000’s, modelling studies showed that existing strategies alone would not be sufficient to achieve the 2050 target of elimination of TB as a public health concern. It was recognized that new strategies for prevention (e.g. new tools for diagnosis and a new vaccine) and treatment (e.g. shorter, more effective regimens) would be needed (Dye, Garnett et al. 1998, Abu-Raddad, Sabatelli et al. 2009). Particularly, it was acknowledged that new vaccines that both prevented infection (pre-exposure) and disease (post-exposure) progression are needed (Young, Dye 2006).

Following the successful sequencing of the Mycobacterium Tuberculosis (M.tuberculosis) genome as well as progress in sequencing bacille Calmette–Guérin (BCG), a number of potential new TB vaccine candidates have been identified and are currently in clinical trials. One such candidate is MVA85A.

1.2. Literature Review

**BCG Vaccine**

The BCG vaccine was first used in humans in 1921 and was included in the World Health Organization’s Expanded Programme of Immunization (EPI) schedule in 1974 (Kaufmann, Hussey et al. 2010). The BCG vaccine is, currently, the only vaccine against tuberculosis. Data on its effectiveness in preventing primary infection and disease progression to
pulmonary TB is highly varied – ranging from 0–80% (Brewer 2000, Colditz, Berkey et al. 1995, Colditz, Brewer et al. 1994, Fine 1995, Rodrigues, Diwan et al. 1993). However, there is a general consensus that BCG is protective against disseminated forms of TB, including military and meningeal TB (Brewer 2000, Colditz, Berkey et al. 1995, Colditz, Brewer et al. 1994, Fine 1995, Rodrigues, Diwan et al. 1993). Data on the duration of protective effect is also mixed, but it appears that it is limited to approximately 10 years (Sterne, Rodrigues et al. 1998).

Revaccination with BCG does not enhance its effectiveness or extend is duration of protectiveness (Rodrigues, Pereira et al. 2005).

The World Health Organization recommends the immunization of all infants in high TB burden countries, except those known to have a compromised immune system (e.g. HIV), with the BCG vaccine.

South Africa: BCG vaccination coverage

South Africa introduced universal BCG vaccination for all infants at birth in 1972 (van Rie, Beyers et al. 1999). According to the Department of Health’s 2010/2011 Annual Report, 89.4% of children less than one-year old are fully immunized (Department of Health 2011). Given that children under one receive a number of vaccinations over a period of 0–9 months, it is possible that BCG coverage is higher. A study conducted in the Western Cape Province, showed a coverage rate of 99% (Corrigall, Coetzee et al. 2008).

MVA85A

MVA85A is a “post-exposure” sub-unit vaccine that is designed to boost the immunological response of BCG. MVA stands for “modified vaccinia Ankara”, which is the delivery system used to present the mycobacterial antigen 85A to the immune system. It has undergone a number of Phase I and Phase II Clinical Studies which has shown that it is well tolerated, has no significant safety concerns, is highly immunogenic, and is effective in increasing the immune response to
antigen 85A in people who have previously been vaccinated with BCG (McShane 2011, Odutola, Owolabi et al. 2012, Scriba, Tameris et al. 2011).

MVA85A is, currently, being tested in a Phase IIb Clinical Trial in HIV-negative Children in Worcester, Western Cape, South Africa.

**Cost-Effectiveness Analysis**

A Cost-Effectiveness Analysis (CEA) is one of four types of economic evaluation in which health outcomes are expressed in natural units (e.g. patients cured, infections avoided, lives saved) and the results as the “cost per unit of outcome”. A CEA addresses questions of technical efficiency as it compares alternative ways of achieving the same objective. CEA is an appropriate framework to compare two interventions where one is the current standard of care and the other is a new intervention, as it provides information on the relative value provided by the “innovation” (Walley, Haycox et al. 2004).

Decision analytic modelling may be used to generate the costs and health outcomes for a CEA as it provides a structure in which evidence from a variety of sources can be incorporated; allows for the extrapolation of data beyond the trial follow-up period; and allows for the inclusion and management of uncertainty (Drummond 2005). In this study, Markov modelling is applicable as TB is a chronic infectious disease which has a number of possible and recurring health states.

**Cost-Effectiveness of BCG vaccination**

“Immunization remains one of the most cost-effective health interventions, even with newer, more expensive vaccines” (World Health Organization, UNICEF et al. 2009).

Despite the controversies on the effectiveness of BCG and its role in TB control, a cost-effectiveness analysis of the effect of BCG vaccination on TB meningitis and miliary TB, conducted in 2006, declared it to be “highly cost-effective” (Trunz, Fine et al. 2006). A review of published
economic evaluations involving vaccination against TB, including potential new vaccines, also concluded that universal BCG vaccination, in developing countries with a high burden of TB, is cost effective (Tu, Vu et al. 2012).

Cost-Effectiveness of MVA85A vaccination

Although presentations pertaining to market studies and a cost-effectiveness study were identified, no studies evaluating the cost-effectiveness of MVA85A have been identified in the published literature.

1.3. Rationale and justification for research

Resources are scarce and governments, as well as international financing organizations (e.g. the Global Fund, GAVI Alliance), need to make informed decisions about where best to allocate resources in order to maximize population health benefits.

A number of new vaccines (e.g. pneumococcal, rotavirus, and human papillomavirus) have been developed over the past decade which increases the competition for these limited resources in developing countries (Kim, Goldie 2008).

This work will contribute to global discussions on the development of new TB vaccines and, specifically, will add to the Oxford-Emergent Tuberculosis Consortium’s (OETC) body of knowledge when deciding whether or not to take forward the development of MVA85A.

If MVA85A is formulated into a “finished pharmaceutical product”, this study could help to establish the launch price of MVA85A in South Africa and, possibly, other developing countries.

Furthermore, specifically in South Africa, the study will contribute to the policy discussion on whether or not to incorporate MVA85A into the EPI schedule by providing policy makers with information, in a transparent
and simplified manner, on the relative value of MVA85A vaccination for the prevention of TB disease in children.

1.4. Research aim and objectives

Overall aim
To examine the potential cost-effectiveness of adding the MVA85A vaccine to the BCG vaccine in HIV negative children from the perspective of the South African Government.

Specific objectives
(a) To develop a Markov state transition model that simulates the natural history of tuberculosis infection and disease in general and, where appropriate, in the South African context.

(b) To estimate the economic and health outcomes, over a 10-year period of two vaccination strategies aimed at reducing the incidence and mortality of tuberculosis disease. The two strategies are:
   – BCG at birth
   – BCG at birth plus a booster vaccine (MVA85A) at 4–6 months

(c) To estimate the incremental cost effectiveness ratio of adding a booster vaccine (MVA85A) to BCG in terms of cost per TB case averted and per TB death averted.

2. Methodology

Overview
This study is Cost-Effectiveness Analysis (CEA) employing Markov modelling, using the TreeAge Pro Suite® 2012 software. The model will follow the natural history of tuberculosis (TB) disease in children.

The study will be conducted from the perspective of the South African Government as vaccines in the EPI schedule are provided free of
charge to all health-care institutions (Loots, personal communication 2012, July 6; Johnson and Arnot, personal communication 2012, July 13).

**Description of alternatives**

The study examines the potential cost-effectiveness of adding a new TB booster vaccine – MVA85A – to the current BCG vaccine.

The two alternatives being compared are:

- the current standard of care, which is vaccinating all those who are HIV-negative; and
- the current standard of care plus a booster vaccine given at 4–6 months.

2.1. Decision model

**Model structure**

The proposed structure draws on structures used in other studies on tuberculosis control and prevention strategies, which employed decision analysis (Clark, Cameron 2006, Mandalakas, Hesseling et al. 2013, Tseng, Oxlade et al. 2011).

This model will be a static, deterministic, population-based, closed, and discrete model.

The costs and consequences/outcomes of the two strategies will be compared. The costs and consequences will be estimated through modelling the vaccination of a hypothetical cohort of HIV-negative newborns and following them from birth through to 10 years of age. A time horizon of 10 years was chosen as this represents the time period over which there is a unique pathway of TB in children. Beyond 10 years, the course of TB tends to mimic that of adults. To extend the time horizon beyond 10 years would require having two model structures – one for 0-10 years and one for 10 years and beyond.
Modelling is employed to extend the costs and consequences/outcomes of the two interventions beyond the trial time-horizon of 2 years.

Six-month cycles will be employed as this period is associated with treatment of both active and latent TB. The model will run for 10 years, following the natural history of TB, the duration of effectiveness of BCG, and to allow for all relevant differences in future costs and consequences to accrue for the two interventions.

Consistent with recommendations and published studies, all future costs and consequences will be discounted at 3% (Weinstein, Siegel et al. 1996).

Herd immunity is not considered in this model as humans have a natural immunity to infection with M.tuberculosis, which is not further enhanced by BCG and, at this time, is not being studied for MVA85A.

**Health states**

The Markov model will follow the natural history of tuberculosis (TB) disease in children. The disease is classified into mutually exclusive health states, which represent the clinically and economically significant events of the disease.

The states are mutually exclusive as patients can only be in one health state at any given time. Transition between states is permitted according to specific transition probabilities and specific criteria. Patients may remain in certain health states (e.g. uninfected). “Death” is considered to be an absorbing state i.e. once a patient has entered it, the patient cannot leave. This model assumes that once a patient is infected with TB, the patient can never be “uninfected”, again. All patients will start out in the “uninfected” health state. The following health states are included:

- Uninfected
- Infected
- Re-infected
- Pulmonary TB (PTB)
- Miliary TB (mTB)
- TB Meningitis (TBM)
- Death from TB
- Death from other causes

**Health states and possible transition between states**

<table>
<thead>
<tr>
<th>Health state</th>
<th>Possible transitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninfected</td>
<td>Remain uninfected, become infected, or die from causes unrelated to TB</td>
</tr>
<tr>
<td>Infected</td>
<td>Remain infected, become reinfected, progress to one of the three TB disease states, or die from causes unrelated to TB</td>
</tr>
<tr>
<td>Reinfected</td>
<td>Go back to being infected, progress to one of the three TB disease states, or die from causes unrelated to TB</td>
</tr>
<tr>
<td>Pulmonary TB (PTB)</td>
<td>Go back to being infected, become reinfected, die from TB, or die from causes unrelated to TB</td>
</tr>
<tr>
<td>Miliary TB (mTB)</td>
<td>Go back to being infected, become reinfected, die from TB, or die from causes unrelated to TB</td>
</tr>
<tr>
<td>TB Meningitis (TBM)</td>
<td>Go back to being infected, become reinfected, die from TB, or die from causes unrelated to TB</td>
</tr>
<tr>
<td>Death (all cause)</td>
<td>Remain dead (absorbing state)</td>
</tr>
<tr>
<td>Death (TB-related)</td>
<td>Remain dead (absorbing state)</td>
</tr>
</tbody>
</table>

Refer to **Annex 1** for a graphical representation of the health states and the possible transitions amongst them.

### 2.2. Data inputs

*Effectiveness data*
Effectiveness will be expressed as TB cases averted and TB deaths averted. In order to generate these, the model will be populated with parameters relevant to the natural course of the disease and which reflect the probability of moving between various health states.

Age-specific risks for progression to three different TB disease states – pulmonary TB (PTB), miliary TB (mTB), and TB meningitis (TBM) – and the risk of death from these disease states will be reflected in the model together with the risk of TB infection. These data will be taken from the published literature, expert opinion, and government data bases such as the South African electronic TB register.

Data on all-cause mortality rates were taken from WHO 2009 Life-Tables and were adjusted to remove the age-specific risk of dying from one of three TB disease states.

Data on the efficacy of MVA85A vaccine will be taken from the Phase IIb Clinical Trial currently underway in Worcester, Western Cape, South Africa. The trial database closes on 31 December 2012 and data will be made available for this study within the first quarter of 2013. This trial received its ethics approval from the UCT Ethics Committee on 17 December 2008 (REC REF 291/2008).

Assumptions on up-take or coverage rates for MVA85A will be obtained through consultation with experts. No decision on whether or not to include adverse effects has yet been made. Given that studies to-date have not shown any significant side effects, it is likely that these will be excluded.

Cost data

Costs are the value of resources used to achieve a particular outcome. They are calculated by identifying all the relevant inputs, determining “quantity” of each input, and the unit cost of each input. Which costs are included in a CEA depend on the perspective taken. As this study is taken from the perspective of the South African Government, only
costs to the South African Government which are associated with providing the vaccine and treating TB disease will be considered.

This data will be obtained from published and unpublished studies as well as directly from the Department of Health. Emergent will provide information on the potential cost of the MVA85A vaccine. Costs will be represented in 2012 US dollars.

Proposed parameters

<table>
<thead>
<tr>
<th>Type</th>
<th>Parameter</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td>Age-specific mortality rates</td>
<td>The World Health Organization’s Life-Tables</td>
</tr>
<tr>
<td>Epidemiological</td>
<td>Annual risk of infection (ARI)</td>
<td>Published literature (local studies); expert opinion</td>
</tr>
<tr>
<td>Natural history</td>
<td>Age specific: Risk of disease progress – pulmonary &amp; disseminated TB; Risk of death – pulmonary &amp; disseminated TB</td>
<td>e-TB register; StatsSA mortality data</td>
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<tr>
<td>Vaccine</td>
<td>Drop-out rate DTP3 and MCV; duration of protective effect</td>
<td>Published literature</td>
</tr>
<tr>
<td>Cost</td>
<td>Vaccine, TB treatment</td>
<td>Published and unpublished literature; tender awards; personal communication</td>
</tr>
<tr>
<td>Economic</td>
<td>Discount rate</td>
<td>Published literature</td>
</tr>
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</table>

Refer to Annex 2 for a more detailed list of the parameters and their values.

2.3. Outcomes
Health outcomes

The health outcomes that will be measured are TB cases averted and TB deaths averted. Given that very limited information is available on the utilities associated with the various health states for TB in children, as well as the difficulty in determining these, the Quality-Adjusted Life-Year (QALY) will not be used.

Economic outcomes

The cost per TB case averted and the cost per TB death averted will be estimated from the Markov model for each intervention.

According to the World Health Organization’s Choosing Interventions that are Cost-Effective (CHOICE) project, interventions are considered to be highly cost-effective at less than GDP (Gross Domestic Product) per capita, cost-effective at 1–3 times GDP per capita, and not cost-effective at more than 3 times GDP per capita (World Health Organization CHOICE 2012).

An incremental cost-effectiveness ratio (ICER) will also be calculated. This ratio represents the additional cost per additional unit of effect.

2.4. Model validation

Once constructed, the model will be validated through consultation with experts in paediatric TB, TB vaccine development, and economic evaluation.

2.5. Sensitivity analysis

Sensitivity analysis involves varying the value of parameters that are important and, possibly, uncertain over a plausible range to determine the impact on the cost-effectiveness ratios (Walley, Haycox et al. 2004).

Our study will employ one-way sensitivity analysis wherein the value of one parameter will be varied at a time.
A threshold analysis for efficacy will also be done.

3. Work plan and logistics

This study will be carried out over a period of 12 months. The results form part of a dissertation for a Master of Public Health in Health Economics that is planned for submission in August 2013.

4. Budget

This study is self-funded and forms part of a dissertation for a Master of Public Health in Health Economics.

5. Ethical considerations

Ethics approval will be obtained from the University of Cape Town Ethics Committee. However, as this study does not involve human subjects, no major ethical conflicts are anticipated.

Data used to populate the model will be taken from published literature and, where necessary, expert opinion. Data on the efficacy of the MVA85A vaccine will be sourced from the Phase IIb Clinical Trial, which received its ethics approval from the UCT Ethics Committee on 17 December 2008 (REC REF 291/2008).

6. Dissemination of study findings

The results of this study form part of a dissertation for a Master of Public Health in Health Economics.

It is hoped that this study will be published in a journal and the policy brief disseminated both locally and amongst the global community.
In addition, the findings will be shared with OETC, who are developing MVA85A for the global market, and the Western Cape Department of Health, who have made their data available.
References


Annex 1: Health states and possible transitions (State diagram)
## Annex 2: Disease parameters

<table>
<thead>
<tr>
<th>Parameters</th>
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<td>3-5 years</td>
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<sup>1</sup> Expert opinion provided by: Professor Willem Hanekom, Dr Mark Hatherill, Professor Anneke Hesseling, Dr Helen McShane, Dr Hassan Mohammed, Dr Roxana Rustomjee, and Dr Michele Tameris.
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<td>&lt; 3 years</td>
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<td>12.3 – 22.3</td>
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<td>99.0 – 99.5</td>
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<td>13.43 – 14.28</td>
<td>Published and unpublished literature (Mandalakas, Hesseling et al. 2013)</td>
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</table>

1 Expert opinion provided by: Professor Willem Hanekom, Dr Mark Hatherill, Professor Anneke Hesseling, Dr Helen McShane, Dr Hassan Mohammed, Dr Roxana Rustomjee, and Dr Michele Tameris.
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References


Part B

STRUCTURED LITERATURE REVIEW
Introduction

This study employs Decision Analytic Modelling, through the use of a Markov model, to estimate the potential Cost-Effectiveness of a new TB vaccine, which is still under development. As such, the objectives of the literature review were to identify information on:

- tuberculosis (TB), as a public health concern, and its global impact;
- the natural course of tuberculosis (TB) in children, including the childhood-specific risks associated with acquiring TB infection, developing TB disease, and the outcomes of TB disease;
- BCG vaccine and new TB vaccines under development; and
- the approaches taken by others when conducting an economic evaluation, employing modelling, of a TB-related intervention, specifically, or other vaccines, generally.

Literature was identified by searching PUBMED and Google Scholar and through using the references cited in the articles identified. Given the limited amount of information available in the formal literature, Google was also employed to search for grey literature, such as presentations and reports.

The literature contributed to an understanding of tuberculosis and the global impact of this disease and informed the development of the model structure as well as the identification of model parameters.

What follows is a summary of the literature as it pertains to the research topic as well as different aspects of the model. The first section provides an overview of the current global and South African TB situation; from there we explain what TB is and some of the challenges in addressing it; before going on to describing TB in children. The second section looks at the history of TB control globally, the existing tools for preventing and combatting the disease, and the tools currently under development. Section three summarises the role of economic evaluation, including the use of modelling, in the evaluation of vaccines. It briefly touches on aspects such as discounting and cost-effectiveness thresholds, before describing the use of economic
evaluations and their role in decision making. We conclude with a summary of the review.

Global Tuberculosis Report 2012 with a focus on South Africa

According to the World Health Organization (WHO) Global Tuberculosis Control Report 2012, “TB remains a major global health problem” and is the second foremost cause of death from an infectious disease, second only to HIV (World Health Organization 2012).

In 2011, worldwide, there were an estimated 8.7 million incident cases of TB, 12 million prevalent cases, and 1.4 million deaths associated with TB. Approximately 13% (1.1 million) of incident cases occurred in HIV-positive individuals; 79% of which were from Africa. Of the 1.4 million deaths, 990,000 occurred in HIV-negative individuals and 430,000 in HIV-positive individuals (World Health Organization 2012).

There were 5.8 million case notifications, representing 66.67% of incident cases. China and India accounted for 40% of these notifications and Africa 24%, of which South Africa accounted for 25%. It is estimated that 88% of the 5.8 million cases notified occurred in the age group 15–64 years and 6% among children <15 years (World Health Organization 2012).

Since 2000, 22 countries have been identified by WHO as “high TB burden countries” and have been prioritised globally for support. These 22 countries contribute approximately 80% of TB cases worldwide. South Africa is included in the 22 countries and, in 2011, was one of five countries with the highest number of incident cases; the others being China, India, Pakistan, and Indonesia (World Health Organization 2012).

Compared to the global incidence of TB of 125 per 100,000 population in 2011, South Africa had an incidence of 993 per 100,000 population. This translates into roughly 500,000 new cases each year. Approximately 65% of all TB cases in South Africa occur in HIV-positive individuals (World Health Organization 2012).
South Africa is also one of 27 high MDR-TB burden countries. Approximately 1.8% of “new TB cases” have MDR-TB and 6.7% of “previously treated TB cases” have MDR-TB. This compares with the global estimates of 3.7% and 20%, respectively (World Health Organization 2012).

**Tuberculosis (TB)**

Tuberculosis (TB) is an airborne infectious disease mainly caused by *Mycobacterium tuberculosis* (*M* tuberculosis). It is spread by people, who have active pulmonary TB disease, when they cough or sneeze; releasing the Mycobacterium into the air. If inhaled, the bacillus is deposited in the alveoli of the lungs where it elicits a localized immune response. The bacilli may be destroyed or contained at this point or may spread via the local lymphatic system or bloodstream to other parts of the body such as the brain and bones. If the bacilli spread, a systemic immune response occurs. The body can either contain the bacilli – which results in latent TB infection – or can fail to arrest proliferation in which case the bacilli rapidly multiply and the individual progresses to disease. It is also possible for an individual to have latent TB, which is reactivated (endogenous reactivation) at a later stage due to a variety of reasons including suppression of the immune system or for an individual to be reinfected (exogenous reinfection) (Dye, Floyd 2006, Vynnycky, Fine 1997).

The major type of TB disease is pulmonary TB. However, other forms of TB exist such as miliary TB, TB meningitis, TB of the kidney, and TB in the bones and joints. These forms of TB are classified as extrapulmonary TB (Dye, Floyd 2006).

TB remains a complex disease. Despite the discovery of the bacillus in 1882 by Robert Koch, relatively little is known of the bacillus and the human immune response to it. This lack of understanding poses challenges to the development of new tools for prevention, diagnosis, and treatment. However, as technology advances, our knowledge of the pathogenesis of the disease
and how the immune system responds to the organism grows (Lawn, Zumla 2011).

The sequencing of the \textit{M tuberculosis} genome in the late 1990s was considered a major breakthrough as it led to the discovery of specific antigens, which have now been targeted in the development of new diagnostic tests and vaccines as well as the identification of biomarkers for tuberculosis (Lawn, Zumla 2011, Hussey, Hawkridge et al. 2007, Collins, Kaufmann 2001, Ziv, Daley et al. 2004).

Not everyone who breathes in the infectious particles will become infected with TB and, of those infected; only a small proportion of people will actually develop TB disease. It is estimated that, worldwide, there are 2 billion people latently infected with \textit{M tuberculosis} (Lawn, Zumla 2011).

It is estimated that only about 30\% of those exposed to \textit{M tuberculosis} will actually become infected (McShane 2009). Amongst those infected, there is a 10\% lifetime risk of developing TB disease; however, this increases to a 10\% annual risk in those who are infected with the human immunodeficiency virus (HIV). The 10\% lifetime risk is also not evenly distributed – there is an ebb and flow in progressing to TB disease – it is approximately 5\% in the first 18–24 months after initial infection and then approximately 5\% for the remaining lifetime (Zumla, Raviglione et al. 2013)(Dye, Floyd 2006, Marais 2008).
This demonstrates that a natural resistance and herd immunity to TB disease exists (Young, Dye 2006). This fact alone makes TB different from other vaccine preventable diseases (McShane 2009, Marais 2008).

TB exists as various health states such as primary TB infection, latent TB, TB reactivation, and active disease. These states exist on a continuous spectrum and not as discrete health states (Lawn, Zumla 2011, Lin, Flynn 2010). They are affected by, amongst other things, the status of the host’s immune system and the mycobacterial bacillary load (Lawn, Zumla 2011). The mechanisms associated with reactivation and reinfection are not well understood and the risks associated with infection and progression to disease appear to be age-dependent and vary over time (Vynnycky, Fine 1997, Marais, Gie et al. 2004a, Flynn, Chan 2001).

There is a lack of consensus as to whether TB can be eliminated from the body with the currently existing tools or whether, once infected, a person will remain infected for life (Lin, Flynn 2010, Flynn, Chan 2001).
The Annual Risk of Infection (ARI) is the probability of acquiring TB infection or TB re-infection over a period of one year. The ARI is derived from data generated through tuberculin skin test (TST) surveys among children. There is a lack of consensus about whether age-specific ARIs exist and whether the ARI for new infections is the same as for reinfection (Marais, Gie et al. 2004a).

While data on the risk of infection and the risk of progression to disease exists, no data on the risk of reactivation has been identified. This is partially due to the inability of scientists to differentiate between recent infection and reactivation of latent infection with existing diagnostic technologies (Lin, Flynn 2010, Marais, Parker et al. 2009).

TB generally affects adults in the economically productive age groups (age 15–49 years) and men are more likely to develop TB than women (World Health Organization 2011a). The morbidity and mortality associated with TB constitutes a significant economic burden for individuals, families, and countries (Laxminarayan, Klein et al. 2007).

Studies have also shown that TB is strongly associated with socioeconomic status (Davies 2005, Lienhardt, Fielding et al. 2005, Rasanathan, Sivasankara Kurup et al. 2011, Shetty, Shemko et al. 2006)(Marais, Obihara et al. 2005). In 2005, WHO developed guidance on how TB programmes could include measures for addressing poverty as one dimension of TB control. In its guidance, WHO stated “while TB is not exclusively a disease of the poor, the association between poverty and TB is well established and widespread” and represented the vicious cycle between TB and poverty (Figure 2) (Chauhan, Dara et al. 2005).
Figure 2: The vicious cycle between TB and poverty

![Diagram of the vicious cycle between TB and poverty]

The poor lack:
- Food security
- Access to water, sanitation and health care
- Income stability

Income poverty → TB disease → TB may lead to:
- Loss of 20-30% of annual wages among the poor
- Global economic costs: US$ 12 billion annually

Childhood TB

TB in children provides an indirect measure of how well the TB control programme is functioning as it signifies recent transmission in the community (Marais, Obihara et al. 2005, Nelson, Wells 2004). The true extent of the burden of TB disease in children is not known (Nelson, Wells 2004, Kabra, Lodha et al. 2004, Swaminathan, Rekha 2010)(Donald 2002), but it is estimated to be around 490,000 cases and 64,000 deaths, annually (World Health Organization 2012). Childhood TB remains a relatively neglected disease as children are not considered infectious and, therefore do not contribute significantly to the burden and spread of the disease (Marais, Obihara et al. 2005, Swaminathan, Rekha 2010, Marais, Gie et al. 2006, Brent, Anderson et al. 2008, Donald, Maher et al. 2007). However, once infected they represent a reservoir for future transmission (Nelson, Wells 2004).
Infants – defined as 0–12 months – have the highest risk of progression to disease after infection. Children infected between the ages of 1–5 years remain at relatively high risk of progression; whereas children infected between the ages between 5–10 years have the lowest level of risk in children. After 10 years of age, the risk of progression to disease and the type of TB disease mimics that of adolescents and adults (Marais, Gie et al. 2004a, Nelson, Wells 2004, Marais, Gie et al. 2006, Marais, Gie et al. 2004b, van Rie, Beyers et al. 1999, Moyo, Verver et al. 2010, Mandalakas, Hesseling et al. 2013).

The accurate diagnosis of TB in children is generally difficult to establish as children tend to have paucibacillary TB and are commonly unable to produce sputum, which is the necessary for traditional smear microscopy as well as newer diagnostic technologies. Therefore, the majority of children are treated based on clinical symptoms, patient history and a high degree of suspicion (Marais 2008, Nelson, Wells 2004).

Children tend to develop TB disease after infection more rapidly than adults and develop the more severe forms of TB such as miliary TB and TB meningitis resulting in significant morbidity and mortality (Nelson, Wells 2004, Swaminathan, Rekha 2010, Donald 2002, Brent, Anderson et al. 2008). It is only recently that public health officials have begun to look at child-friendly diagnostics and medicines as well as child-friendly treatment regimens.

In adults the notion of reactivation of latent TB exists; however, this does not seem to be relevant to children (Marais, Parker et al. 2009). The primary mode of TB disease is from TB infection and TB reinfection (Marais, Parker et al. 2009).

Information on childhood TB remains limited. A review of the literature revealed a fair amount of information from the pre-chemotherapy era. However, very little information is available, particularly from developing countries, about childhood TB in the chemotherapy era; how these disease risks have changed and the natural course of childhood TB.
History of TB Control

The steady decline in TB mortality in industrialized countries in the 20th century is attributed to improvements in socioeconomic conditions, better nutrition and living standards, and the isolation of infection patients coupled with the discovery of the Bacillus Calmette-Guérin (BCG) vaccine in 1921 and the discovery of various antibiotics to treat TB from the 1940’s. The advent of HIV and multi-drug resistant TB in the 1980’s and 1990’s resulted in TB control efforts being hampered. The significant increase in the burden of TB disease in developing countries in the early 1990’s is attributed to HIV co-infection, the emergence of drug resistance, and, in the eastern European region, to the collapse of the Soviet Union (Lienhardt, Glaziou et al. 2012).

In 1991, the World Health Organization (WHO) at its Forty-fourth World Health Assembly (WHA), recognizing the global increase in new cases and deaths related to tuberculosis (TB), adopted a new strategy for addressing TB in countries and established two targets to be attained by 2000: to diagnose 70% of all people with infectious TB, and to cure 85% of those diagnosed. The new strategy comprised of 5 core elements and reflected the change to “short-course” regimens and the adoption of “directly observed therapy” and became known as DOTS (directly observed therapy, short-course). In 1993, WHO declared tuberculosis a global public health emergency and published its first annual TB Control Report in 1997 (Lienhardt, Glaziou et al. 2012).

At its Fifty-third WHA, in 2000, Member States acknowledged that the targets would not be achieved and deferred their achievement to 2005. The WHA also endorsed the establishment of the Global Partnership to STOP TB (STOP TB Partnership) which brings together stakeholders in support of strategies that will help achieve the targets. Furthermore, the Millennium Declaration in 2000 established the 8 Millennium Development Goals (MDGs) to be achieved by 2015. In response to MDG 6, the STOP TB Partnership established two targets: halving the 1990 prevalence and mortality rates.
The STOP TB Partnership’s ultimate goal is the elimination of TB as a public health concern by 2050 (Lienhardt, Glaziou et al. 2012).

In 2006, WHO together with the STOP TB Partnership, launched an updated STOP TB Strategy consisting of 6 pillars, including the need for the development of new tools for the prevention, detection, and treatment of TB (World Health Organization 2006b).

Up until the mid-1990's it was widely believed that the existing tools for the prevention, detection, and treatment of TB were sufficient and that they need to be applied consistently and at a larger scale in order to achieve the MDG targets as well as the goal of elimination (Lienhardt, Glaziou et al. 2012). Slowly, individual groups began recognizing that new tools would be necessary, especially given the emerging challenges of TB/HIV co-infection and drug resistant TB. In the mid-2000’s, modelling studies confirmed that existing strategies alone would not be sufficient to achieve the 2050 target of elimination of TB as a public health concern. It was recognized that new strategies for prevention (e.g. new tools for diagnosis and a new vaccine) and treatment (e.g. shorter, more effective regimens) would be needed (Dye, Garnett et al. 1998) (Abu-Raddad, Sabatelli et al. 2009). Particularly, it was acknowledged that new vaccines that both prevented infection (pre-exposure) and disease (post-exposure) progression are needed (Young, Dye 2006).

**Currently existing tools**

*Isoniazid Preventative Therapy (IPT)*

Isoniazid preventative therapy (IPT) is recommended in children <5 years (World Health Organization 2006a) and HIV-positive individuals who are infected with TB, but do not have active TB disease (World Health Organization 2011b).

Isoniazid preventative therapy decreases the risk of progression to active TB disease. No data has been identified, which suggests that IPT can completely eliminate the bacilli from the body.
TB Vaccine – BCG

The bacillus Calmette-Guérin (BCG) vaccine was discovered by French bacteriologist, Albert Calmette and French veterinarian, Charles Guérin and first administered in 1921 (Lienhardt, Glaziou et al. 2012, McShane 2011). It was incorporated into the expanded programme on immunization (EPI) in 1974 (Lienhardt, Glaziou et al. 2012). It is one of the most widely used vaccines; being administered in the majority of countries worldwide. In 2011, global coverage at birth with BCG was at 90.88% (UNICEF, WHO 2012).

The BCG vaccine is a live attenuated vaccine and is, currently, the only vaccine against tuberculosis (Hussey, Hawkridge et al. 2007).

In the early 1990’s, two separate meta-analyses of the published literature on BCG vaccination were published.

The first paper, published in 1993, reflected the inclusion of ten randomised control trials and eight case-control studies. The meta-analysis looked at the protective effect of BCG against pulmonary TB and against meningeal and miliary TB. For pulmonary TB, it was not possible to calculate a summary measure from either the randomised control trials or the case-control studies as the results from these studies were so disparate showing a protective effect from negative to 100%. However, for miliary and meningeal TB, the protective effect from randomised control trials was 86% and from case-control studies was 75% (Rodrigues, Diwan et al. 1993).

The second paper, published in 1994, included fourteen prospective trials and 12 case-control studies. The summary effect from the prospective trials showed an overall protective effect against TB of 51%, a protective effect of 63% against pulmonary TB and 71% against death from TB. The results of the case-control studies showed an overall protective effect against TB of 55%, a protective effect of 50% against pulmonary TB, 64% against meningeal TB, and 78% against disseminated TB (Colditz, Brewer et al. 1994).

In 2006, a paper published by Trunz, Fine, and Dye used the data from these two meta-analyses to recalculate the protective effect of BCG against
TB meningitis and miliary TB and found it to be 73% and 77%, respectively (Trunz, Fine et al. 2006).

Overall, the data on BCG’s efficacy in preventing disease progression to pulmonary TB after initial infection is highly varied – ranging from 0–80%. However, generally, there is consensus that BCG does provide protection against severe forms of TB, including miliary and meningeal TB.

The reasons for the varied effect of BCG that have been put forward include differences between the different brands of the vaccine, population differences in exposure to environmental mycobacteria, human genetics, and differences between different strains of *M tuberculosis* (Fine 1995, Department of Vaccines and Biologicals 1999).

Due to BCG’s efficacy in preventing severe forms of TB, WHO, in 2004, recommended that countries should continue to give BCG to all neonates at-birth in countries with a high prevalence of TB as well as to children in high-risk groups in low TB prevalence countries (World Health Organization: Weekly Epidemiological Record 2004). In 2007, WHO updated this recommendation to exclude children who are known to be HIV-infected due to the increased risk of disseminated TB disease (World Health Organization: Weekly Epidemiological Record 2007).

No data on BCG’s ability to prevent TB infection has been identified.

Historically it was thought that BCG did not directly impact on the risk of dying from TB; rather it decreased the risk of developing disease and, therefore, indirectly contributed to lowering the number of TB deaths. Recently, a few studies have been published from the West Africa region, which suggests that BCG may also have a direct effect on lowering all-cause mortality (Aaby, Roth et al. 2011, Roth, Stensballe et al. 2006); although the findings of these studies are disputed (Fine, Smith et al. 2012).

There is inconsistent evidence on the duration of protective effect offered by BCG as well as whether this protection is consistent or whether it declines over time. A paper published in 1998, based on a review of 10 randomized
control trials, concluded that “there is not good evidence that BCG provides protection more than ten years after vaccination”. This same paper showed mixed results regarding consistency in protection – of the ten papers reviewed, seven showed a declining efficacy over time and three showed an increase in efficacy (Sterne, Rodrigues et al. 1998).

There is no evidence to suggest that revaccination with BCG enhances its effectiveness or extends its duration of protectiveness (McShane 2009, Rodrigues, Pereira et al. 2005). For this reason, WHO does not recommend giving booster doses of BCG (World Health Organization 2006a).

Despite the controversies on the effectiveness of BCG and its role in TB control, a cost-effectiveness analysis of the effect of BCG vaccination on TB meningitis and miliary TB, conducted in 2006, declared it to be “highly cost-effective” (Trunz, Fine et al. 2006). A review of published economic evaluations involving vaccination against TB, including potentially new vaccines, also concluded that universal BCG vaccination, in developing countries with a high burden of TB, is cost effective (Tu, Vu et al. 2012).

**TB Treatment**

Treatment for TB is also a relatively new innovation. The first medicines – Streptomycin and Para-aminosalicylic acid (PAS) – for the treatment of TB were discovered in 1944. Based on the results of a clinical trial conducted by the UK Medical Research Council, dual therapy was introduced in the late 1940’s. Shortly thereafter, Isoniazid was discovered and triple therapy was introduced. Ethambutol replaced PAS in the 1960’s and Rifampicin was introduced in the 1970’s. Pyrazinamide replaced Streptomycin in the 1980’s. These changes allowed for the introduction of short-course treatment involving Rifampicin, Isoniazid, Pyrazinamide, Ethambutol, and, in some cases, Streptomycin for drug susceptible TB; reducing the duration of treatment from 18–24 months to 6–8 months (Lienhardt, Glaziou et al. 2012). Short-course treatment using standardized regimens remains the cornerstone of TB control efforts.
The first treatment guidelines for MDR-TB treatment were issued in 1997 by WHO and relied on medicines not being used for drug susceptible TB, but which demonstrated bactericidal and bacteriostatic activity against *M tuberculosis* (World Health Organization 1997). Since then one or two new fluoroquinolones have been added, but, besides, there have been no new developments.

**New tools under development**

“The establishment of the Bill & Melinda Gates Foundation (in 1994) coincided with the establishment of other public–private partnerships that have played a major part in resurrecting TB research and development.” (Lienhardt, Glaziou et al. 2012) As of today, the Bill & Melinda Gates Foundation provides funding support for TB drug development (e.g. through The Global Alliance for TB Drug Development), for new TB diagnostics (e.g. through FIND – the Foundation for Innovative New Diagnostics), and for new TB vaccines (e.g. through AERAS and the TB Vaccine Initiative (TBVI)).

**New medicines**

New medicines to treat both drug susceptible and drug resistant TB are needed because current regimens involve taking a significant number of tablets; treatment courses are long; medicines have significant side-effects; some of the existing medicines are not compatible with antiretroviral treatment; are not appropriate for children; and do not address latent TB infection.

As of November 2012, there were 8 molecules in pre-clinical development, 9 Phase II Clinical Studies and 4 Phase III Clinical Studies (Figure 3).
**New diagnostics**

The increasing numbers of TB cases due to the emergence of HIV and drug resistant TB means that new diagnostics are needed in order to speed up the detection of both drug-susceptible and drug-resistant TB and to determine what TB medicines the bacillus is resistant to. A number of new diagnostic technologies have been launched in the past 5 years (Figure 4).
New vaccines

According to the STOP TB Partnership’s Working Group on new TB vaccines, two or three different vaccines are needed to address the different challenges of TB Control. A vaccine is not only needed to prevent infection with \textit{M tuberculosis} (pre-exposure vaccine), but given the extent of existing latent infection (almost a third of the world’s population) and low efficacy of BCG vaccine, new vaccines to boost existing BCG or to replace BCG that prevent progression to disease as well as vaccines to act as an adjunct to treatment to shorten the duration of treatment and increase its effectiveness, are also needed.

The vaccines that are the most advanced in their development can be broadly classified according to two categories:

1. Live attenuated vaccines; and
2. Subunit vaccines.

The first category looks at replacing the existing BCG vaccine through either a recombinant BCG or genetic attenuation of \textit{M tuberculosis}. The second
category looks at boosting the efficacy of the current BCG vaccine (McShane 2011, Kaufmann, Hussey et al. 2010, Rowland, McShane 2011).

As of 2011, 12 vaccine candidates were in various states of clinical studies (Figure 5).

**Figure 5: Global TB Vaccine Pipeline**
(http://stoptb.org/wg/new_vaccines/assets/documents/Global%20TB%20Vaccine%20Pipeline_Aug%202012.ppt)

**Global TB Vaccine Pipeline**

One vaccine candidate currently being developed is MVA85A. MVA85A is a “post-exposure” subunit vaccine that is designed to boost the immunological response of BCG. MVA stands for “modified vaccinia Ankara”, which is the delivery system used to present the mycobacterial antigen 85A to the immune system. It has undergone a number of Phase I and Phase II Clinical Studies which has shown that it is well tolerated, has no significant safety concerns, is highly immunogenic, and is effective in increasing the immune response to antigen 85A in people who have previously been vaccinated with BCG (McShane 2011, Odutola, Owolabi et al. 2012, Scriba, Tameris et al. 2011).
The findings of a Phase IIb Clinical Study conducted in South Africa involving HIV-negative infants, where MVA85A was given at 4–6 months as a booster to the BCG vaccine, were published in February 2013. The results of this study were disappointing; showing an efficacy of only 17.3% (Tameris, Hatherill et al. 2013).

Economics
Economics is a social science that studies the production, distribution, and consumption of goods and services by individuals, governments, and societies in the presence of scarcity. Given that people, governments, and societies tend to always want more than is available, it analyses how choices are made in allocating scarce resources to maximize welfare (Guinness, Wiseman 2011, Haycox, Noble 2009).

Health Economics
Health Economics is a sub-discipline of Economics. It uses the methods and theories from Economics to analyse the healthcare industry (Guinness, Wiseman 2011, Haycox, Noble 2009).

Economic Evaluation
Economic Evaluation is one tool that can be used, by decision makers, to compare alternative approaches to addressing the same problem by looking at the costs and outcomes of each (Drummond 2005). Economic Evaluation aims to either maximize health gains from a specified basket of resources or to achieve a predefined result for the least amount of resources (Haycox, Noble 2009). There are four types of “full” economic evaluations. Each type assesses costs in a similar manner, but differs in the way outcomes are measured and valued (Drummond 2005).

A Cost Minimization Analysis (CMA) is used if evidence exists that shows the two alternatives being compared produce exactly the same outcomes. This may be the case when comparing originator and generic medicines or when
comparing medicines from the same pharmacological class. In this case, the choice between alternatives can be made based purely on a cost comparison and the least costly alternative would be chosen. There is controversy on whether, or not, a CMA is a full or a partial economic evaluation (Drummond 2005).

A Cost Effectiveness Analysis (CEA) is an economic evaluation in which health outcomes are expressed in natural units (e.g. patients cured, infections avoided, lives saved) and the results are expressed as the “cost per unit of outcome”. CEA is an appropriate framework to compare two interventions where one is the current standard of care and the other is a new intervention, as it provides information on the relative value provided by the “innovation”. A CEA addresses questions of technical efficiency as it compares alternative ways of achieving the same objective (Drummond 2005, Gray, Clarke et al. 2011).

A Cost Utility Analysis (CUA) is similar to a CEA except that it incorporates the idea of quality into the outcome measure. Generally, the outcomes are measured as quality adjusted life years (QALYs) or disability adjusted life years (DALYs). QALYs consider not only the quantity of life years gained from an intervention, but also the quality of these life years gained. CUA is useful when quality of life is an important outcome, for example when looking at different options for cancer treatment. By changing natural units into a common unit of measure, it is possible to compare interventions across different diseases. In this way a CUA can address questions of not only technical efficiency, but of allocative efficiency, too (Guinness, Wiseman 2011, Drummond 2005).

A Cost Benefit Analysis (CBA) values health outcomes in monetary terms. This method is not often used in the evaluation of health programmes as people tend to have difficulty in valuing health and human life in monetary terms. As all outcomes are measures in monetary terms, it is possible to use a CBA to compare interventions across sectors (Guinness, Wiseman 2011, Drummond 2005).
When conducting an economic evaluation it is important to decide up-front the perspective or viewpoint from which the study will be undertaken. These may range from a narrow perspective of the Ministry of Health or individual patients to the broadest perspective being that of society. The viewpoint chosen will impact on which costs are included in the costing of interventions (Drummond 2005).

**Decision Analytic Modelling**

Decision analytic modelling can be used when there is insufficient evidence available from a single source on which to base a decision and there is uncertainty on which course of action to pursue (Drummond 2005). In 2003, the International Society for Pharmacoconomics and Outcomes Research (ISPOR), through its task force on Good Research Practices for Modelling Studies, defined a health care evaluation model as “an analytic methodology that accounts for events over time and across populations, that is based on data drawn from primary and/or secondary sources, and whose purpose is to estimate the effects of an intervention on valued health consequences and costs” (Weinstein, O'Brien et al. 2003). A model, thus, allows for the synthesis of evidence on outcomes and costs by providing a structure in which evidence from a variety of sources can be incorporated, allowing for the extrapolation of data beyond the trial follow-up period, and allowing for the inclusion and management of uncertainty (Drummond 2005, Gray, Clarke et al. 2011, Briggs, Claxton et al. 2011).

In the case of this study, decision analytic modelling in the case of new vaccines allows us to extend the costs and outcomes of the two interventions beyond the trial time horizon of 2 years.

In employing decision analytic modelling in cost effectiveness analyses we acknowledge that the purpose is to aid decision making rather than provide an explicit and absolute result (Gray, Clarke et al. 2011, Briggs, Claxton et al. 2011). This is due to the inherent subjective nature of models. When developing a model a number of assumptions have to be made. These
include assumptions on the structure of the model, the parameters chosen and their respective values, and value judgements, for example which parameters to vary during sensitivity analyses. A well conducted study will present these assumptions transparently and will express any conclusions as being dependent upon the assumptions made.

ISPOR listed a number of principles as “good practice” when using models for economic evaluation (Weinstein, O'Brien et al. 2003).

**Markov models**

Markov models are a particular type of decision analytical model (Briggs, Claxton et al. 2011). According to Sonneberg and Beck, Markov models “are useful when a decision problem involves risk that is continuous over time, when the timing of events is important, and when important events may happen more than once” (Sonneberg, Beck 1993). These complex interrelated aspects are difficult to analyse through a standard decision tree. Markov modelling is an appropriate framework for modelling childhood TB as TB is a chronic infectious disease which has a number of possible and recurring health states with transition probabilities that vary with age.

Markov models require that discrete and mutually exclusive health states be defined. Patients can only be in one health state at any given time and transitions between health states are governed by defined probabilities that are either constant or vary over time. The cycle length and time horizon of the model should reflect the natural course of the disease. Each health state is associated with a cost and a reward. These accrue at the end of each cycle and the cumulative result represents the costs and outcomes of each intervention once the model has finished running (Gray, Clarke et al. 2011, Briggs, Claxton et al. 2011, Sonnenberg, Beck 1993, Briggs, Sculpher 1998).

**Discounting**

It is generally accepted that for studies with a time-horizon of longer than twelve months, discounting of both costs and outcomes should be employed.
This is because individuals do not value costs and outcomes that occur in the future the same way as those that occur immediately. Discounting allows for the future costs and outcomes to be presented at present day value (Drummond 2005). There is no consensus on which discount rate to use, whether the same discount rate should be applied to both costs and outcomes, and whether the discount rate should vary over time or remain constant (Severens, Milne 2004, Torgerson, Raftery 1999, Langer, Holle et al. 2012). A review in 2000 of 147 studies showed that the same discount rates were used for both costs and outcomes and that the rate ranged from 1–8%, with the most frequent being 3% and 5% (Smith, Gravelle 2000)(Smith, Gravelle 2000).

Cost-Effectiveness Threshold

Cost-effectiveness thresholds were first proposed by Weinstein and Zeckhauser in 1973. They proposed that for a given fixed budget in situations of perfect divisibility and constant returns to scale of all programmes, it is possible to specify a critical ratio – termed lambda – at which point all programmes equal to or less than should be implemented (Gafni, Birch 2006). This theory has been criticized due to its impracticality in implementing it in the healthcare sector (Gafni, Birch 2006).

Advocates of the threshold note that the threshold reflects the amount of money a particular entity, country, or region is willing to spend for the outcome received. The threshold can either be a fixed value or a range of values. They consider that the thresholds provide a practical way to objectively and transparently assess new technologies in a consistent manner (Shillcutt, Walker et al. 2009).

Countries with defined, either implicitly or explicitly, thresholds include (Gafni, Birch 2006, McCabe, Claxton et al. 2008, Devlin, Parkin 2004, Bridges, Onukwugha et al. 2010):

- USA (US Dollars 50,000)
• UK (British Pounds 20,000 – 30,000)
• Canada (Canadian Dollars 20,000 – 100,000)

The WHO convened, Commission on Macroeconomics and Health, has also proposed the following (World Health Organization CHOICE 2012):

• Interventions are considered to be highly cost-effective at less than GDP (Gross Domestic Product) per capita;
• Cost-effective at 1–3 times GDP per capita; and
• Not cost-effective at more than 3 times GDP per capita.

However, they remain controversial as the establishment of a particular threshold is “a value judgement that depends on several factors” such as “who is making the decision; what the purpose of the analysis is; how the decision maker values health, money, and risk; and what the available resources are” (Owens 1998).

The main argument against threshold values is that there is no rational basis for the current values (Gafni, Birch 2006, Shillcutt, Walker et al. 2009, Bridges, Onukwugha et al. 2010).

South Africa is in the initial stages of implementing pharmacoconomic evaluation. The guidelines were issued at the beginning of 2013 (Department of Health: Republic of South Africa 2013). The guidelines do not state how decisions on cost-effectiveness will be made.

**Economic Evaluation of Vaccines**

Although immunization remains one of the most cost effective health interventions (World Health Organization, UNICEF et al. 2009), a number of new vaccines have been launched in the past decade. These newer vaccines are significantly more expensive than their predecessors and policy makers need a standardized way of assessing their additional costs and benefits in order to make informed decisions (Immunization 2008).
In 2008, two publications, providing surprising similar frameworks for describing models for cost effectiveness analysis of immunization interventions, were published (Immunization 2008, Kim, Goldie 2008). Most notably, WHO, in an attempt to ensure consistency in how new vaccines were being evaluated, issued guidance on the standardization of economic evaluations of immunization programmes (Immunization 2008).

These documents describe five basic attributes that health economists should consider when designing a model to evaluate a vaccine. They are:

1. Whether the risk of being infected is static (stays the same) or dynamic (changes over time)?
2. Whether the transition probabilities are deterministic (established and consistent at the population level) or stochastic (random and variable)?
3. Whether simulation occurs at a cohort or individual level?
4. Whether events occur at discrete intervals or over a continuum?
5. Whether the model is open (individuals are allowed to enter) or closed?

**Methods for the Economic Evaluation of vaccines**

The WHO guidance document from 2008, indirectly, recommends the use of Cost Utility Analysis for economic evaluations of vaccines by recommending that outcomes be expressed as Disability Adjusted Life Years (DALYs) (Immunization 2008).

A review of published literature involving TB vaccines was conducted in 2012. The study identified thirteen articles of which twelve looked at BCG vaccine and one looked at BCG and a potential new TB vaccine. Seven studies employed Cost Effectiveness Analysis, five employed Cost Benefit Analysis, and one used both Cost Effectiveness and Cost Benefit Analyses. None employed Cost Utility Analysis (Tu, Vu et al. 2012). This could be attributed
to the difficulty in obtaining utility values for young children who are generally the ones receiving vaccines.

No published Cost-Effectiveness Analyses of the MVA85A vaccine were identified.

**Use of Economic Evaluations**

As the need to contain the ever increasing cost of health care grows, so does the need for economic evaluations. Increasingly governments are requiring economic data either prior to the registration of a new product or prior to listing a product for reimbursement (Clemens, Garrison et al. 1993). The purpose of these evaluations is to demonstrate the new medicine or vaccine represents a reasonable level of “value for money”. Value for money is a “term used to assess whether or not an organisation has obtained the maximum benefit from the goods and services it acquires and/or provides, within the resources available to it”. It can be “described in terms of the 'three Es' – economy, efficiency and effectiveness” (Jackson 2012, Imperial College London n.d.). Figure 6 provides a schematic framework within which value for money could be considered.

**Figure 6: Value for Money Framework (UK AID 2011)**

As a result, pharmaceutical companies are increasingly investing in the production of economic evaluations at the time of clinical studies.
The role of Economic Evaluation in decision making

Economic evaluation is one tool that can assist in decision making. However, other aspects, such as affordability, capacity of the health system to implement the new technology, equity, and need (e.g. neglected or rare diseases), should also be taken into consideration during the decision making process. In this regard, the results of an economic evaluation remain only one factor that should be taken into consideration by decision makers when deciding whether to adopt a new technology or approach (Guinness, Wiseman 2011).

Conclusion

Tuberculosis remains a global health concern even though tools to prevent and treat TB have been around since the early 1900s. The advent of HIV and multi-drug resistant TB in the 1980’s and 1990’s resulted in TB control efforts being hampered. Existing tools for the prevention and treatment of tuberculosis are old and, largely, ineffective – the BCG vaccine doesn’t provide complete protection, diagnostics are slow and not 100% accurate, and TB treatment involves taking many tablets over a long period of time, some of which, have severe side-effects.

TB remains a complex disease. Despite the discovery of the bacillus in 1882 by Robert Koch, relatively little is known of the bacillus and the human immune response to it. This poses challenges to the development of new tools for prevention, diagnosis, and treatment.

Since the early 2000’s, the TB community has been working with various stakeholders to advocate for new tools to fight the disease. These include new diagnostics (e.g. GeneXpert®), new medicines (e.g. bedaquiline), and new vaccines.

Childhood TB remains a relatively neglected disease as children are not considered infectious and, therefore do not contribute significantly to the burden and spread of the disease.
The BCG vaccine is a live attenuated vaccine and is, currently, the only vaccine against tuberculosis. No data on BCG’s ability to prevent TB infection has been identified. Overall, the data on BCG’s efficacy in preventing disease progression to pulmonary TB after initial infection is highly varied – ranging from 0–80%. Generally, however, there is consensus that BCG does provide protection against severe forms of TB, including miliary and meningeal TB. There is inconsistent evidence on the duration of protective effect offered by BCG as well as whether this protection is consistent or whether it declines over time. There is no evidence to suggest that revaccination with BCG enhances its effectiveness or extends its duration of protectiveness.

From an epidemiological perspective, there is a clear need for a new, more effective TB vaccine. As of 2011, 12 vaccine candidates were in various states of clinical studies and a number of vaccines are entering into the final phases of development.

Although immunization remains one of the most cost effective health interventions, a number of new vaccines have been launched in the past decade. These newer vaccines are significantly more expensive than their predecessors and policy makers need a standardized way of assessing their additional costs and benefits in order to make informed decisions.

Economic Evaluation is one tool that can be used, by decision makers, to compare alternative approaches to addressing the same problem by looking at the costs and outcomes of each. A Cost Effectiveness Analysis (CEA) is an economic evaluation in which health outcomes are expressed in natural units (e.g. patients cured, infections avoided, lives saved) and the results are expressed as the “cost per unit of outcome”. CEA is an appropriate framework to compare two interventions where one is the current standard of care and the other is a new intervention, as it provides information on the relative value provided by the “innovation”.

Decision analytic modelling can be used when there is insufficient evidence available from a single source on which to base a decision and there is
uncertainty on which course of action to pursue. A model allows for the synthesis of evidence on outcomes and costs by providing a structure in which evidence from a variety of sources can be incorporated, allowing for the extrapolation of data beyond the trial follow-up period, and allowing for the inclusion and management of uncertainty. Markov models are a particular type of decision analytical model.

To-date there is no standardized and widely-recognized model to estimate the potential costs and outcomes of new TB vaccines relative to the BCG vaccine. In addition, no studies looking at the potential cost-effectiveness of the MVA85A vaccine in any populations or age-groups have been identified. This study will contribute to the development of a standardized Markov model, which could be used, in the future, to estimate the potential cost-effectiveness of new TB vaccines in children between the ages of 0–10 years. Furthermore, it will provide information on the potential cost-effectiveness of the MVA85A vaccine. Given the disappointing results of the MVA85A vaccine clinical trial, this study will predominantly contribute to establishing an efficacy threshold for future vaccines.

There is a paucity of published information available on TB in children, including specific data on their risk of infection and their risk of progression to disease. A review of the literature revealed a fair amount of information from the pre-chemotherapy era. However, when this information was compared with routinely available data, there appeared to be a disconnect. A search for information from the chemotherapy era, revealed that very little information is available, particularly from developing countries; how these disease risks have changed and the natural course of childhood TB. These data, preferably by country or by region, are needed to ensure a robust and reliable model, which produces results which are generalizable.
References


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Part C

JOURNAL ARTICLE
ABSTRACT

Background

TB remains the second foremost cause of death from an infectious disease; second only to HIV. Existing tools are largely inadequate. It is acknowledged that new vaccines that both prevent infection (pre-exposure) and disease (post-exposure) progression are needed. A number of potential new TB vaccine candidates have been identified and are, currently, in Clinical Trials. One such candidate is MVA85A. This study aimed to examine the potential cost-effectiveness of adding the MVA85A vaccine to the BCG vaccine in children from the perspective of the South African Government.

Methods

The cost-effectiveness was assessed by employing Decision Analytic Modelling, through the use of a Markov model. The model compared the existing strategy of BCG vaccination to a new strategy in which infants receive BCG and a booster vaccine, MVA85A, at 4–6 months of age. The costs and outcomes of the two strategies are estimated through modelling the vaccination of a hypothetical cohort of newborns and following them from birth through to 10 years of age, employing 6-monthly cycles.

Results

The results of the cost-effectiveness analysis indicate that the MVA85A strategy is both more costly and more effective – there are fewer TB cases and deaths from TB – than BCG alone. The Government would need to spend an additional USD 1,105 for every additional TB case averted and USD 284,017 for every additional TB death averted. The threshold analysis also shows that, if the efficacy of the MVA85A vaccine was 41.361% (instead of the current efficacy of 17.3%), the two strategies would have the same cost but more cases of TB and more deaths from TB would be prevented by
adding the MVA85A vaccine to the BCG vaccine. In this case, the Government should consider the MVA85A strategy.

Conclusions

At the current level of efficacy, the MVA85A vaccine is neither effective nor cost-effective and, therefore, not a good use of limited resources.

Keywords

Cost-Effectiveness Analysis, new TB vaccine, Markov modelling, Childhood TB, South Africa
Background

TB remains the second foremost cause of death from an infectious disease; second only to HIV (World Health Organization 2012).

Globally, it is estimated that, in 2011, there were 8.7 million new cases and 12 million prevalent cases of tuberculosis (TB) and 1.4 million deaths associated with TB (World Health Organization 2012). Furthermore, 2 billion – or a third of the world’s population – is believed to be latently infected with TB (Lawn, Zumla 2011).

The true extent of the burden of TB disease in children is not known (Kabra, Lodha et al. 2004, Swaminathan, Rekha 2010, Nelson, Wells 2004)(Donald 2002), but it is estimated to be around 490,000 cases and 64,000 deaths, annually (World Health Organization 2012).

The BCG vaccine is, currently, the only vaccine against tuberculosis. Data on its effectiveness in preventing primary infection and disease progression to pulmonary TB is highly varied – ranging from 0–80%. However, there is consensus that BCG is protective against disseminated forms of TB, including military and meningeal TB (Brewer 2000, Colditz, Berkey et al. 1995, Colditz, Brewer et al. 1994, Fine 1995, Rodrigues, Diwan et al. 1993).

In the mid-2000’s, modelling studies showed that existing strategies alone would not be sufficient to achieve the 2050 target of elimination of TB as a public health concern. It was recognized that new strategies for prevention (e.g. new tools for diagnosis and a new vaccine) and treatment (e.g. shorter, more effective regimens) would be needed (Dye, Garnett et al. 1998, Abu-Raddad, Sabatelli et al. 2009). Particularly, it was acknowledged that new vaccines that both prevented infection (pre-exposure) and disease (post-exposure) progression are needed (Young, Dye 2006).

Following the successful sequencing of the Mycobacterium Tuberculosis (M.tuberculosis) genome as well as progress in sequencing bacilli Calmette–Guérin (BCG), a number of potential new TB vaccine candidates
have been identified and are, currently, in Clinical Trials. One such candidate is MVA85A.

MVA85A is a “post-exposure” sub-unit vaccine that is designed to boost the immunological response of BCG (McShane 2011, Odutola, Owolabi et al. 2012, Scriba, Tameris et al. 2011).

Resources for TB control are limited and have been further constrained due to the global financial crisis. In addition, a number of new vaccines (e.g. pneumococcal, rotavirus, and human papillomavirus) have been developed over the past decade which increases the competition for these limited resources.

This study aimed to examine the potential cost-effectiveness of adding the MVA85A vaccine to the BCG vaccine in children from the perspective of the South African Government. Modelling is employed to estimate the cost-effectiveness of a new vaccination strategy as it allows us to extend the costs and outcomes of the two interventions beyond the trial time-horizon of 2 years.

**Methods**

*Strategies compared in the model*

Our study compared two strategies: BCG at birth, which is the current standard of care in South Africa, and BCG at birth plus a booster vaccine (MVA85A) at 4–6 months, which is the potential new strategy.

*Modelling*

The cost-effectiveness was assessed by employing Decision Analytic Modelling, through the use of a Markov model. Markov modelling is an appropriate framework for modelling childhood TB as TB is a chronic infectious disease which has a number of possible and recurring health states with transition probabilities that vary with age.
A Markov state transition model was developed in TreeAge Pro Suite® 2012 to reflect the natural course of TB in children. The model compared the existing strategy of BCG vaccination to a new strategy in which infants receive BCG and a booster vaccine, MVA85A, at 4–6 months of age (Figure 1).

Eight mutually exclusive health (Markov) states representing the natural history of tuberculosis (TB) disease in children were used. They are uninfected, infected, reinfection, pulmonary TB, miliary TB, TB meningitis, death all causes, death TB-related (Figure 2). Transitions amongst health states were permitted according to specific transition probabilities and specific criteria. Patients could remain in certain health states (e.g. uninfected). “Death” was considered to be an absorbing state i.e. once a patient had entered it, the patient could not leave.

The model is a static, deterministic, closed, and discrete model.

- Static: one Annual Risk of Infection (ARI) has been used for the entire duration of the model.
- Deterministic: set parameters are used to determine how the cohort moves through the model.
- Population-based: a single cohort moves through the model.
- Closed: new individuals cannot enter the model over the 10-year period.
- Discrete: events occur at 6-monthly intervals.

The costs and outcomes of the two strategies were estimated through modelling the vaccination of a hypothetical cohort of newborn children and following them from birth through to 10 years of age, employing 6-monthly cycles.

A time horizon of 10 years was chosen as this represents the time period over which there is a unique pathway of TB in children. Beyond 10 years, the course of TB tends to mimic that of adults.
Age-specific risks for progression to three different TB disease states – pulmonary TB (PTB), miliary TB (mTB), and TB meningitis (TBM) – and the risk of death from these disease states were reflected in the model together with the risk of TB infection. These data have been taken from the published literature, expert opinion, and government data bases such as the South African electronic TB (e-TB) register.

Data on all-cause mortality rates were taken from WHO 2009 Life-Tables (World Health Organization Global Health Observatory (GHO) 2012) and were adjusted to remove the age-specific risk of dying from one of three TB disease states.

Data on the efficacy of MVA85A was taken from the results of the Phase IIb Clinical Trial in Worcester, South Africa, which showed the efficacy rate against tuberculosis in infants to be 17.3% (Tameris, Hatherill et al. 2013). This cost-effectiveness study was designed before the findings of the vaccine efficacy became available.

The model parameters are reflected in Table 1.

**Model Assumptions**

- All children started out uninfected and, once infected, a child could never be uninfected.
- A single Annual Risk of Infection (ARI) of 3% was used throughout the duration of the model, for all age groups, and for both the risk of “TB infection” and “TB reinfection”.
- Three age groups (0–2 years, 3–5 years, and 6–10 years) were represented in the model. These represented the ages at which the risks associated with progression to disease and mortality was significantly different.
- The efficacy of BCG vaccine was indirectly included in the model by virtue of the fact that the TB data used in the model has been taken from a setting in which BCG has been routinely administered since
the 1970’s (van Rie, Beyers et al. 1999) and up-take – defined as the proportion of children eligible to receive the vaccine who actually receive the vaccine – is in excess of 95% (Corrigall, Coetzee et al. 2008).

- The efficacy of BCG remained constant over the 10-year period and BCG did not have a direct effect on all-cause mortality.

- The drop-out rate between the DTP3 vaccine (given at 14 weeks) and the MCV vaccine (given at 9 months) was taken as the proxy for MVA85A vaccine up-take. Vaccine up-take was used together with efficacy to calculate the effectiveness.

**Excluded from the model**

- Herd immunity, as humans seem to have a natural resistance to infection with M.tuberculosis and to progression to TB disease, which doesn’t appear to be further enhanced by the BCG vaccine (Young, Dye 2006) and is not being studied for the MVA85A vaccine.

- Isoniazid preventive therapy (IPT), as the effect would have been equal in both arms.

- BCG disseminated disease (a side-effect of BCG vaccination), as the effect would have been equal in both arms.

**Costing method**

Costs were taken from the perspective of the South African Government and were calculated using an ingredients-based costing methodology. All cost data, except for the price of MVA85A, was taken from South African data. The majority of information has been taken from the costing work down by Mandalakas et al (Mandalakas, Hesseling et al. 2013). These costs, available as South African Rand (ZAR) 2009, were inflated using consumer price index (CPI) figures (Statistics South Africa 2012a) to 2012 values, and then converted to US dollars (USD) at the average exchange rate USD to ZAR for 2012 of USD 1 = ZAR 8.12. The Oxford Emergent TB Consortium
(OETC) provided the cost of MVA85A vaccine in USD. All costs were reflected in 2012 USD.

The cost for vaccination, diagnosis, and treatment are reflected in Table 2.

**Effectiveness measurement**

As the vaccine was designed to prevent progression from TB infection to TB disease, we calculated the absolute difference in the number of TB cases and TB deaths between the two interventions i.e. BCG alone versus BCG + MVA85A.

Given that very limited information is available on the utilities associated with the various health states for TB in children, as well as the difficulty in determining these, the Quality-Adjusted Life-Year (QALY) was not used.

**Cost-effectiveness analysis**

The model was designed to determine the number of TB cases averted and the number of TB deaths averted. At the end of the 10-year period the cumulative costs and outcomes of each intervention were used to calculate the cost-effectiveness ratio (CER) (i.e. the cost per TB case averted and the cost per TB death averted) for each intervention. These two cost-effectiveness ratios were compared using an incremental cost-effectiveness ratio (ICER), which represent the additional cost per additional benefit received.

**Discounting**


**Model Calibration and Validation**

There is no standardized Markov model for the evaluation of new TB vaccines. Therefore, calibration of the study model was not possible.
However, the structure and model inputs were validated through an expert consultation group.

**Dealing with uncertainty**

By its very nature modelling is considered subjective and involves a degree of uncertainty (Drummond 2005). We, therefore, conducted a one-way sensitivity analysis to check for uncertainty around the discount rate, MVA85A vaccine efficacy, vaccine cost, vaccine coverage, and annual risk of infection.

We also performed a threshold analysis to determine the level of efficacy at which the cost of the MVA85A vaccine strategy would equal the cost of the BCG strategy, but produce additional benefits.

**Results**

Table 3 represents the discounted and undiscounted 10-year costs, the absolute number of TB cases and TB deaths, and incremental cost-effectiveness ratios (ICERs) associated with adding MVA85A vaccine to the existing strategy of BCG at birth, from the perspective of the South African Government.

Both the discounted and discounted results show that adding the MVA85A vaccine to the BCG vaccine is both more effective and more costly.

The base-case scenario reveals ICERs of USD 1,105 per TB case averted and USD 284,017 per TB death averted.

**Sensitivity Analyses**

A summary of the sensitivity analyses for key parameters is provided in Table 4. The results showed that the outcomes were robust; being most sensitive to the ARI, MVA85A vaccine efficacy, and the MVA85A vaccine price.

The threshold analysis shows that at an efficacy of 41.361%, the MVA85A vaccine produces more benefits, but at a cost equal to the BCG vaccine.
Discussion

This cost-effectiveness study was designed while the vaccine clinical trial was still ongoing. The recently published results of the Phase IIb Clinical Trial conducted in Worcester, South Africa, showed that the efficacy of the MVA85A vaccine in preventing TB in infants to be 17.3% (Tameris, Hatherill et al. 2013). Therefore, the vaccine has very poor effectiveness. This has had a noticeable effect on the outcomes of the cost-effectiveness analysis.

The results of the cost-effectiveness analysis indicate that the MVA85A strategy is both more costly and more effective – there are fewer TB cases and deaths from TB – than BCG alone. The Government would need to spend an additional USD 1,105 for every additional TB case averted and USD 284,017 for every additional TB death averted.

South Africa is in the initial stages of implementing pharmacoeconomic evaluation and has not defined an explicit acceptability threshold. However, if we consider the recommendations made by the Commission on Macroeconomics and Health (World Health Organization CHOICE 2012), then at South Africa’s GDP per capita of USD 8,070 (World Bank 2013), the vaccine would be considered highly cost-effective in terms of TB cases averted. For TB deaths averted it would, however, not be considered cost-effective.

Irrespective of these results, our research contributes to the body of knowledge on economic evaluations involving new TB vaccines as – to the best of our knowledge – this is the first cost-effectiveness analysis conducted using trial data involving a novel TB vaccine and providing a direct comparison with BCG vaccination. While economic evaluations involving the modelling of new TB vaccines have been done, those published, have relied on assumptions of efficacy (Tseng, Oxlade et al. 2011, Ziv, Daley et al. 2004).

In addition, this study provides a model structure, which could be used for future modelling studies and which is relatively simple to adapt to local settings.
The threshold analysis also shows that, if the efficacy of the MVA85A vaccine was 41.361% (instead of the current efficacy of 17.3%), the two strategies would have the same cost but more cases of TB and more deaths from TB would be prevented by adding the MVA85A vaccine to the BCG vaccine. In this case, the Government should consider the MVA85A strategy.

The sensitivity analyses suggest that the ICER is sensitive to the price at which the vaccine will be made available, the annual risk of being infected with TB, and the efficacy of the vaccine.

The limitations of this study arise from the paucity of data on childhood TB during the chemotherapy era and our inability to access the full South African e-TB register dataset. For these reasons, parameters have been derived from the Western Cape’s e-TB register. As the Western Cape has the third highest number of TB cases in South Africa (Day, Barron et al. 2012), we do not believe that this has distorted the results. The study assumed an annual risk of infection of 3% and has applied this to the e-TB register data in order to establish the risk of progressing to disease. It was also assumed that the e-TB register data reflected the effectiveness of the BCG vaccine in the population given that the Western Cape has routinely administered BCG since the 1970’s (van Rie, Beyers et al. 1999) and up-take is in excess of 95% (Corrigall, Coetzee et al. 2008).

**Conclusion**

Our findings indicate that, due to its low efficacy, adding MVA85A as a booster to BCG against infant and childhood TB is not cost-effective, and, therefore, not a viable use of limited resources.

Nevertheless, our research contributes to developing a standardized Markov model, which could be used, in the future, to estimate the potential cost-effectiveness of new TB vaccines compared to the BCG vaccine, in children between the ages of 0–10 years.
It also provides an indicative threshold of vaccine efficacy, which could guide future development.
List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARI</td>
<td>Annual Risk of Infection</td>
</tr>
<tr>
<td>BCG</td>
<td>Bacille Calmette–Guérin</td>
</tr>
<tr>
<td>CER</td>
<td>Cost Effectiveness Ratio</td>
</tr>
<tr>
<td>CPI</td>
<td>Consumer Price Index</td>
</tr>
<tr>
<td>DTP3</td>
<td>Diphtheria-Tetanus-Pertussis</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental Cost Effectiveness Ratio</td>
</tr>
<tr>
<td>IPT</td>
<td>Isoniazid Preventive Therapy</td>
</tr>
<tr>
<td>MCV</td>
<td>Measles-containing vaccine</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>Multidrug Resistant Tuberculosis</td>
</tr>
<tr>
<td>mTB</td>
<td>Miliary Tuberculosis</td>
</tr>
<tr>
<td>MVA85A</td>
<td>Modified Vaccinia Ankara 85A</td>
</tr>
<tr>
<td>OETC</td>
<td>Oxford Emergent Tuberculosis Consortium</td>
</tr>
<tr>
<td>PTB</td>
<td>Pulmonary Tuberculosis</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TBM</td>
<td>Tuberculosis Meningitis</td>
</tr>
<tr>
<td>USD</td>
<td>U.S. Dollars</td>
</tr>
<tr>
<td>ZAR</td>
<td>South African Rand</td>
</tr>
</tbody>
</table>

Competing Interests

None – financial support was received from OETC, but this was limited to funding the expert consultation meeting and the TreeAge® software.
### Table 1: Model parameters: base-case estimates and source

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
<th>Range</th>
<th>References</th>
</tr>
</thead>
</table>
| ARI and annual risk of re-infection (%)        | 3      | 2 – 4 | • Published literature (Kritzinger, den Boon et al. 2009, Middelkoop, Bekker et al. 2008, Shanaube, Sismanidis et al. 2009, Wood, Liang et al. 2010)  
• Expert opinion¹ |
| Risk of dying from “other causes”              |        |       | • Electronic database (World Health Organization Global Health Observatory (GHO) 2012) and adjusted to remove the risk of dying from TB  
• Expert opinion¹ |
| 0–1 years                                      | 0.04295312 |       |                                                                             |
| 1–2 years                                      | 0.00475194 |       |                                                                             |
| 3–4 years                                      | 0.00490931 |       |                                                                             |
| 5 years                                        | 0.00143069 |       |                                                                             |
| 6–10 years                                     | 0.00143080 |       |                                                                             |
| 10 years                                       | 0.00120560 |       |                                                                             |
| Risk of progressing to pulmonary TB (%)        |        |       | • Electronic database (Provincial Government Western Cape Department of Health 2012) and calculated assuming an ARI of 3%  
• Expert opinion¹ |
| 0–2 years                                      | 54.1929 |       |                                                                             |
| 3–5 years                                      | 20.3757 |       |                                                                             |
| 6–10 years                                     | 6.6028  |       |                                                                             |
| Risk of progressing to miliary TB (%)          |        |       |                                                                             |
| 0–2 years                                      | 0.2227  |       |                                                                             |
| 3–5 years                                      | 0.1022  |       |                                                                             |
| 6–10 years                                     | 0.0388  |       |                                                                             |
| Risk of progressing to TB meningitis (%)       |        |       |                                                                             |
| 0–2 years                                      | 0.5241  |       |                                                                             |
| 3–5 years                                      | 0.1394  |       |                                                                             |
| 6–10 years                                     | 0.0970  |       |                                                                             |

¹ Expert opinion provided by: Professor Willem Hanekom, Dr Mark Hatherill, Professor Anneke Hesseling, Dr Helen McShane, Dr Hassan Mohammed, Dr Roxana Rustomjee, and Dr Michele Tameris.
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
<th>Range</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of death from pulmonary TB (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3 years</td>
<td>0.74952</td>
<td></td>
<td>Electronic databases (Provincial Government Western Cape Department of Health 2012, Statistics South Africa 2012b)</td>
</tr>
<tr>
<td>3-5 years</td>
<td>0.09120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 6 years</td>
<td>0.58766</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of death from miliary TB (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3 years</td>
<td>23.52941</td>
<td></td>
<td>Calculated using average for 2005-2009 and e-TB data</td>
</tr>
<tr>
<td>3-5 years</td>
<td>9.09091</td>
<td></td>
<td>Expert opinion</td>
</tr>
<tr>
<td>&gt; 6 years</td>
<td>16.66667</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of death from TB meningitis (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3 years</td>
<td>25.00000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-5 years</td>
<td>26.66667</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 6 years</td>
<td>20.00000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVA85A efficacy against TB disease (%)</td>
<td>17.3</td>
<td>12.3 – 22.3</td>
<td>Published literature (Tameris, Hatherill et al. 2013)</td>
</tr>
<tr>
<td>Up-take BCG (%)</td>
<td>99.0</td>
<td>99.0 – 99.5</td>
<td>Published literature (Corrigall, Coetzee et al. 2008, Department of Health; Republic of South Africa 2011)</td>
</tr>
<tr>
<td>Up-take MVA85A</td>
<td>85.0</td>
<td>76.4 – 89.5</td>
<td>Calculated</td>
</tr>
<tr>
<td>Drop-out rate DTP3 to MCV</td>
<td>14.0</td>
<td>9.5 – 23.1</td>
<td>Published literature and electronic database (Saloojeei, Bamfordii 2006, Health Systems Trust 2007)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Expert opinion</td>
</tr>
<tr>
<td>Discount rate costs (%)</td>
<td>3</td>
<td>0 – 6</td>
<td></td>
</tr>
</tbody>
</table>

---

1 Expert opinion provided by: Professor Willem Hanekom, Dr Mark Hatherill, Professor Anneke Hesseling, Dr Helen McShane, Dr Hassan Mohammed, Dr Roxana Rustomjee, and Dr Michele Tameris.
Table 2: Cost of vaccination, diagnosis and treatment\(^1\) in USD 2012: base-case estimates and source

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
<th>Range</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of BCG vaccination (USD 2012)(^2)</td>
<td>13.57</td>
<td>13.43 – 14.28</td>
<td>• Published and unpublished literature (Mandalakas, Hesseling et al. 2013)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Personal Communication (Anot, Hayes 2012)</td>
</tr>
<tr>
<td>Cost of MVA85A vaccination (USD 2012)(^2)</td>
<td>28.22</td>
<td>20.22 – 48.22</td>
<td>• Personal Communication Oxford Emergent Tuberculosis Consortium (OETC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Published and unpublished literature (Mandalakas, Hesseling et al. 2013)</td>
</tr>
<tr>
<td>Costs of diagnosis and treatment PTB (USD 2012)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2 years</td>
<td>406.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–5 years</td>
<td>433.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–10 years</td>
<td>459.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costs of diagnosis and treatment mTB (USD 2012)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2 years</td>
<td>3,184.76</td>
<td></td>
<td>• Personal Communication (Anot, Hayes 2012, von Zeil 2012)</td>
</tr>
<tr>
<td>3–5 years</td>
<td>3,213.57</td>
<td></td>
<td>• Published and unpublished literature (Mandalakas, Hesseling et al. 2013)</td>
</tr>
<tr>
<td>6–10 years</td>
<td>3,241.54</td>
<td></td>
<td>• Published report (Statistics South Africa 2012a)</td>
</tr>
<tr>
<td>Costs of diagnosis and treatment TBM (USD 2012)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–2 years</td>
<td>29,782.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–5 years</td>
<td>29,844.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–10 years</td>
<td>29,881.88</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) TB treatment costs: an average weight of 10kg was used for the age group 0–2 years, 20kg for 3–5 years, and 30kg for 6–10 years. As per the South African TB guidelines treatment is given daily (7 days a week) for 6 months (2 months intensive phase and 4 months continuation phase) for pulmonary TB and miliary TB, whereas treatment is given daily for 6–9 months (single phase of treatment) for TB meningitis. Other costs include costs associated with various diagnostics and laboratory monitoring as well as hospital and clinic costs.

\(^2\) The cost of BCG vaccine includes the cost per dose, which includes 40% wastage, the cost for a needle and syringe, and the cost of a clinic visit.

\(^3\) The cost of MVA85A vaccine includes the cost per dose (provided by OETC), the cost for a needle and syringe, and the cost of a clinic visit.
### Table 3: Cost-effectiveness of adding the MVA85A vaccine to the BCG vaccine

<table>
<thead>
<tr>
<th>Strategy</th>
<th>10-year costs (USD 2012)</th>
<th>Absolute Number of TB cases</th>
<th>Absolute Number of TB deaths</th>
<th>ICER Per TB case averted (USD 2012)</th>
<th>ICER Per TB deaths averted (USD 2012)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASE CASE RESULTS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discounted (3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCG alone</td>
<td>84.17</td>
<td>0.09101</td>
<td>0.0003501817</td>
<td></td>
<td></td>
</tr>
<tr>
<td>plus MVA85A</td>
<td>98.23</td>
<td>0.07828</td>
<td>0.0003006626</td>
<td>1,105</td>
<td>284,017</td>
</tr>
<tr>
<td>Undiscounted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCG alone</td>
<td>97.65</td>
<td>0.10627</td>
<td>0.0004174069</td>
<td></td>
<td></td>
</tr>
<tr>
<td>plus MVA85A</td>
<td>109.80</td>
<td>0.09138</td>
<td>0.0003583168</td>
<td>816</td>
<td>205,603</td>
</tr>
<tr>
<td>Discounted (6%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCG alone</td>
<td>73.53</td>
<td>0.07885</td>
<td>0.0002969804</td>
<td></td>
<td></td>
</tr>
<tr>
<td>plus MVA85A</td>
<td>89.10</td>
<td>0.06785</td>
<td>0.0002550313</td>
<td>1416</td>
<td>371,271</td>
</tr>
</tbody>
</table>
Table 4: Effect of differing assumptions on the base-case ICER

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Increase/Decrease in ICER (TB cases averted)</th>
<th>Increase/Decrease in ICER (TB deaths averted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual Risk of Infection (ARI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2%</td>
<td>+ 79.86%</td>
<td>+ 79.71%</td>
</tr>
<tr>
<td>4%</td>
<td>- 39.88%</td>
<td>- 39.83%</td>
</tr>
<tr>
<td>MVA85A vaccine cost(^1) (USD 2012)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20.22</td>
<td>- 48.35%</td>
<td>- 48.35%</td>
</tr>
<tr>
<td>48.22</td>
<td>+ 120.87%</td>
<td>+ 120.87%</td>
</tr>
<tr>
<td>MVA85A vaccine up-take</td>
<td></td>
<td></td>
</tr>
<tr>
<td>76.4%</td>
<td>+ 0.14%</td>
<td>+ 0.12%</td>
</tr>
<tr>
<td>89.5%</td>
<td>- 0.07%</td>
<td>- 0.06%</td>
</tr>
<tr>
<td>MVA85A vaccine efficacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.3%</td>
<td>+ 69.90%</td>
<td>+ 69.81%</td>
</tr>
<tr>
<td>22.3%</td>
<td>- 38.55%</td>
<td>- 38.52%</td>
</tr>
<tr>
<td>Discounting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>-26.15%</td>
<td>- 27.61%</td>
</tr>
<tr>
<td>6%</td>
<td>28.14%</td>
<td>+ 30.72%</td>
</tr>
</tbody>
</table>

\(^1\) Vaccine price provided by OETC: base-case USD 15 per dose; low USD 7 per dose; high USD 35 per dose
Figure 1: One arm of the Markov model (BCG + MVA85A)
Figure 2: Health States and Possible Transitions (State Diagram)
References


Part D

APPENDICES
Appendix 1: Ethics approval

UNIVERSITY OF CAPE TOWN

20 August 2012

HREC REF: 424/2012

Ms L Channing
c/o Dr E Sinanovic
Public Health & Family Medicine
Health Economics Unit

Dear Ms Channing

PROJECT TITLE: COST-EFFECTIVENESS ANALYSIS OF MVA85A: A NEW TB VACCINE CANDIDATE

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has formally approved the above-mentioned study.

Approval is granted for one year till the 30th August 2013

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6; Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.
Appendix 2: Journal Instructions

Instructions for Authors

Submission Process

The submitted manuscript must be accompanied by a cover letter (from the corresponding author) containing the name and contact information for all authors, along with a brief summary of the article. The cover letter should include a statement that the manuscript has not been published elsewhere and is not under consideration by another journal. The cover letter should also indicate that all authors have approved the final manuscript.

The manuscript should be submitted electronically via the journal’s online submission system. Authors are encouraged to use a plagiarism detection tool to ensure that the manuscript is original and has not been published elsewhere.

The manuscript should be formatted according to the journal’s style guide. The journal’s style guide can be found on the journal’s website.

The journal’s editorial board will review each manuscript and make a decision on its suitability for publication. The decision may be a rejection, a request for revisions, or an acceptance for publication.

The accepted manuscript will undergo copyediting and proofreading before publication.

Researchers and readers may access the journal’s articles through the journal’s website or through a subscription service.

Research Activities

The journal encourages research and development in the field of study and welcomes contributions from researchers and practitioners.

Cost, Efficiency, and Resource Allocation

The journal focuses on the efficient allocation and management of resources in various fields, including economics, finance, and health care.

The journal’s goal is to promote research that contributes to the efficient use of resources and the achievement of cost savings.

The journal publishes research on topics such as cost-benefit analysis, resource allocation models, and the efficient use of resources in various sectors.

The journal’s impact factor is 1.68, reflecting the high quality and relevance of the research published in the journal.

The journal’s scope includes topics such as cost-effectiveness analysis, resource optimization, and the efficient use of resources in various sectors.

The journal’s editorial board consists of experts in the field, ensuring the quality and relevance of the research published.

The journal is indexed in major academic databases, making it easily accessible to researchers and practitioners.

The journal’s publication frequency is quarterly, ensuring timely dissemination of research findings.

The journal’s subscription service ensures that researchers and practitioners can access the latest research findings in the field.

The journal’s open access policy guarantees that researchers and practitioners can access the latest research findings in the field at no cost.
Title page
The title page should:
- provide the title of the article
- list the full names, institutional addresses and email addresses for all authors
- indicate the corresponding author

Please note:
- the title should include the study design, for example “A versus B in the treatment of C: a randomized controlled trial” in the abstract
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The abstract of the manuscript should not exceed 350 words and must be structured into separate sections: Background, the context and purpose of the study; Methods, how the study was performed and statistical tests used; Results, the main findings; Conclusions, brief summary and potential implications. Please minimize the use of abbreviations and do not cite references in the abstract. Trial registration. If your manuscript reports the results of a controlled clinical trial, please list your trial registry, along with the unique identifying number (e.g., Trial registration: Current Controlled Trials [RCT]/NCT01234567). Please note that there should be no space between the letters and numbers of your trial registration number. We recommend manuscripts that report randomized controlled trials follow the CONSORT extension for abstracts.

Keywords
Three to ten keywords representing the main content of the article.

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The background section should be written in a way that is accessible to researchers without specialist knowledge in that area and must clearly state - and, if helpful, illustrate - the background to the research and its aims. Reports of clinical research should, where appropriate, include a summary of a search of the literature to indicate why this study was necessary and what it aimed to contribute to the field. The section should end with a brief statement of what is being reported in the article.

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**Units**

SI units should be used throughout (liter and molar are permitted, however).
Appendix 3: Markov model structure and inputs in TreeAge® 2012

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**Figure 1:** Decision node and two strategies being compared

```
Infants
ARI = 0.03
Age = iniAge
+_stage
cBCG = 13.57
cDR = 0.03
cMVA85A = 28.22
eMVA85A = 0.173
iniAge = 0
oDR = 0.03
oTBcase = 1
oTBcaseAverted = 1
oTBdeath = 1
oTBdeathAverted = 1
uBCG = 0.99
uMVA85A = 0.85
```
Figure 2: BCG arm

Uninfected

- Markov Information
  - Init Cost: dbCG*ubCG
  - Inc Cost: 0
  - Final Cost: 0
  - Inc TB cases: 0
  - Final TB cases: 0

Infected

- Markov Information
  - Init Cost: 0
  - Inc Cost: 0
  - Final Cost: 0
  - Inc TB cases: 0
  - Final TB cases: 0

Re-infected

- Markov Information
  - Init Cost: 0
  - Inc Cost: 0
  - Final Cost: 0
  - Inc TB cases: 0
  - Final TB cases: 0

PTB

- Markov Information
  - Init Cost: 0.5 * (discount(dPTBdxTx[Age];cDR; stage/2))
  - Inc Cost: 0.5 * (discount(dPTBdxTx[Age];cDR; stage/2))
  - Final Cost: 0.5 * (discount(dPTBdxTx[Age];cDR; stage/2))
  - Inc TB cases: 0
  - Final TB cases: 0

mTB

- Markov Information
  - Init Cost: 0.5 * (discount(dMTBdxTx[Age];cDR; stage/2))
  - Inc Cost: 0.5 * (discount(dMTBdxTx[Age];cDR; stage/2))
  - Final Cost: 0.5 * (discount(dMTBdxTx[Age];cDR; stage/2))
  - Inc TB cases: 0
  - Final TB cases: 0

TBM

- Markov Information
  - Init Cost: 0.5 * (discount(dTMBdxTx[Age];cDR; stage/2))
  - Inc Cost: 0.5 * (discount(dTMBdxTx[Age];cDR; stage/2))
  - Final Cost: 0.5 * (discount(dTMBdxTx[Age];cDR; stage/2))
  - Inc TB cases: 0
  - Final TB cases: 0

Death TB disease

- Markov Information
  - Init Cost: 0
  - Inc Cost: 0
  - Final Cost: 0
  - Inc TB cases: 0
  - Final TB cases: 0

Death all cause

- Markov Information
  - Init Cost: 0
  - Inc Cost: 0
  - Final Cost: 0
  - Inc TB cases: 0
  - Final TB cases: 0
Figure 3: BCG + MVA85A arm

BCG at birth
--- Markov Information
Term (obj._STAGE = 20)

Uninfected
--- Markov Information
Init Cost: 0
Incr Cost: 0
Final Cost: 0
Init TB cases: 0
Incr TB cases: 0
Final TB cases: 0

Infected
--- Markov Information
Init Cost: 0
Incr Cost: 0
Final Cost: 0
Init TB cases: 0
Incr TB cases: 0
Final TB cases: 0

Re-infected
--- Markov Information
Init Cost: 0
Incr Cost: 0
Final Cost: 0
Init TB cases: 0
Incr TB cases: 0
Final TB cases: 0

PTB
--- Markov Information
Init Cost: 0.5 * (discount * (PTB0xTx[Age]:cDR_stage/2))
Incr Cost: (discount * (PTB0xTx[Age]:cDR_stage/2))
Final Cost: 0.5 * (discount * (PTB0xTx[Age]:cDR_stage/2))
Init TB cases: 0
Incr TB cases: 0
Final TB cases: 0

mTB
--- Markov Information
Init Cost: 0.5 * (discount * (mTB0xTx[Age]:cDR_stage/2))
Incr Cost: (discount * (mTB0xTx[Age]:cDR_stage/2))
Final Cost: 0.5 * (discount * (mTB0xTx[Age]:cDR_stage/2))
Init TB cases: 0
Incr TB cases: 0
Final TB cases: 0

TBM
--- Markov Information
Init Cost: 0.5 * (discount * (TBMDxTx[Age]:cDR_stage/2))
Incr Cost: (discount * (TBMDxTx[Age]:cDR_stage/2))
Final Cost: 0.5 * (discount * (TBMDxTx[Age]:cDR_stage/2))
Init TB cases: 0
Incr TB cases: 0
Final TB cases: 0

Death_TB disease
--- Markov Information
Init Cost: 0
Incr Cost: 0
Final Cost: 0
Init TB cases: 0
Incr TB cases: 0
Final TB cases: 0

Death_all cause
--- Markov Information
Init Cost: 0
Incr Cost: 0
Final Cost: 0
Init TB cases: 0
Incr TB cases: 0
Final TB cases: 0
Figure 4a: BCG arm. Number of TB cases
Figure 4b: BCG arm_Number of TB deaths
Figure 5a: BCG + MVA85A arm_Number of TB cases
Figure 5b: BCG + MVA85A arm_Number of TB deaths

- **Uninfected**
  - Initial Information
  - Initial Cost: 0
  - Incr Cost: 0
  - Final Cost: 0
  - Initial TB deaths: 0
  - Incr TB deaths: 0
  - Final TB deaths: 0

- **Infected**
  - Initial Information
  - Initial Cost: 0
  - Incr Cost: 0
  - Final Cost: 0
  - Initial TB deaths: 0
  - Incr TB deaths: 0
  - Final TB deaths: 0

- **Re-infected**
  - Initial Information
  - Initial Cost: 0
  - Incr Cost: 0
  - Final Cost: 0
  - Initial TB deaths: 0
  - Incr TB deaths: 0
  - Final TB deaths: 0

- **PTB**
  - Initial Information
  - Initial Cost: 0
  - Incr Cost: 0
  - Final Cost: 0
  - Initial TB deaths: 0
  - Incr TB deaths: 0
  - Final TB deaths: 0

- **MNB**
  - Initial Information
  - Initial Cost: 0
  - Incr Cost: 0
  - Final Cost: 0
  - Initial TB deaths: 0
  - Incr TB deaths: 0
  - Final TB deaths: 0

- **TBM**
  - Initial Information
  - Initial Cost: 0
  - Incr Cost: 0
  - Final Cost: 0
  - Initial TB deaths: 0
  - Incr TB deaths: 0
  - Final TB deaths: 0

- **Death from TB disease**
  - Initial Information
  - Initial Cost: 0
  - Incr Cost: 0
  - Final Cost: 0
  - Initial TB deaths: 0
  - Incr TB deaths: 0
  - Final TB deaths: 0

- **Death from all cause**
  - Initial Information
  - Initial Cost: 0
  - Incr Cost: 0
  - Final Cost: 0
  - Initial TB deaths: 0
  - Incr TB deaths: 0
  - Final TB deaths: 0

- **Remain uninfect**
  - Become infected
  - Prob to prob(RI;12)

- **Remain infected**
  - Become re-infected
  - Prob to prob(RI;12)

- **Alive**
  - Become uninfected
  - Prob to prob(RI;12)

- **Cured & remain infected**
  - Die from PTB
    - Prob to prob(PDyirgPTB;12)
  - Prob to prob(PDyirgMNB;12)
  - Prob to prob(PDyirgTBm;12)

- **Remain cured & re-infected**
  - Prob to prob(RI;12)

- **Remain cured & immediately re-infected**
  - Prob to prob(RI;12)

- **Remain cured & re-infected**
  - Prob to prob(RI;12)

- **Cured & re-infected**
  - Immediate re-infected
  - Prob to prob(RI;12)

- **Cured & immediately re-infected**
  - Prob to prob(RI;12)

- **Cured & re-infected**
  - Immediate re-infected
  - Prob to prob(RI;12)

- **Cured & re-infected**
  - Immediate re-infected
  - Prob to prob(RI;12)

- **Cured & re-infected**
  - Immediate re-infected
  - Prob to prob(RI;12)

- **Cured & re-infected**
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- **Cured & re-infected**
  - Immediate re-infected
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- **Cured & re-infected**
  - Immediate re-infected
  - Prob to prob(RI;12)

- **Cured & re-infected**
  - Immediate re-infected
  - Prob to prob(RI;12)

- **Cured & re-infected**
  - Immediate re-infected
  - Prob to prob(RI;12)

- **Cured & re-infected**
  - Immediate re-infected
  - Prob to prob(RI;12)

- **Cured & re-infected**
  - Immediate re-infected
  - Prob to prob(RI;12)

- **Cured & re-infected**
  - Immediate re-infected
  - Prob to prob(RI;12)
Part E

POLICY BRIEF
PREVENTING TB IN CHILDREN IN SOUTH AFRICA

Is it cost-effective to add the MVA85A vaccine to the BCG vaccine?

Key points

- South Africa has a high burden of TB. Existing tools to prevent and treat TB are, largely, ineffective. New vaccines that prevent TB infection and progression to TB disease are needed.
- MVA85A is intended to enhance the effectiveness of the BCG vaccine and is, currently, being studied in various Clinical Trials.
- In HIV-negative infants, MVA85A vaccine is not effective in preventing TB when given as a booster to the BCG vaccine.
- Adding MVA85A as a booster to BCG against infant and childhood TB is not cost-effective, and therefore not a good use of limited resources.
- A new TB vaccine with an efficacy of, at least, 41.361% would potentially be cost-effective.

Introduction

South Africa is considered, internationally, as both a high TB burden country and a high MDR-TB burden country. Annually, there are an estimated 500,000 new cases of TB, of which, approximately 10,000 have MDR-TB. TB/HIV co-infection is a key driver of the epidemic (World Health Organization 2012).

The tools for preventing and combatting tuberculosis are old and, largely, ineffective. The BCG vaccine doesn’t provide complete protection, the diagnostics are slow and not 100% accurate, and the treatment involves taking many tablets over a long period of time, some of which, have severe side-effects. Since the early 2000’s, the TB community has been working with various stakeholders to advocate for new tools to fight the disease. These include new diagnostics (e.g. GeneXpert®), new medicines (e.g. bedaquiline), and new vaccines (Lienhardt, Glaziou et al. 2012).
The new TB vaccines being developed are designed to either prevent infection (pre-exposure vaccine) or to prevent progression to active disease (post-exposure vaccine), or both. South Africa has approved a number of clinical trials, involving new TB vaccines. One such trial took place in Worcester, Western Cape, and looked at the safety and efficacy of the MVA85A vaccine in preventing TB infection and progression to disease in HIV-negative infants (Tameris, Hatherill et al. 2013).

The Government of South Africa must continuously consider how best to invest the resources available for health to address the quadruple burden of disease. Over the past 10 years, a number of new vaccines have been developed (e.g. pneumococcal, rotavirus, and human papillomavirus). The Ministry of Health needs to consider whether to introduce these new vaccines. One aspect of this decision making process is looking at “cost-effectiveness” i.e. whether the resources that will be invested in delivering these vaccines will produce sufficient health outcomes (e.g. prevent cases, deaths or disability) to justify the investment.

Objectives

Our study compared the costs and health outcomes of two TB vaccine strategies:

i. BCG, given at birth, which is the current standard of care in South Africa; and

ii. BCG, given at birth, together with a booster vaccine (MVA85A) given at 4 months, which is the potentially new strategy.

The aim was to determine, which of these two strategies was more cost-effective from the perspective of the South African Government.

1 HIV & TB; Maternal & Child morbidity & mortality; non-communicable diseases; violence, injuries & trauma
Methods

To estimate the costs and health outcomes of the two strategies, a model was developed using TreeAge® Pro 2012 software. The model followed a hypothetical group of infants over a period of 10 years. The risks of being infected with TB (Kritzinger, den Boon et al. 2009, Middelkoop, Bekker et al. 2008, Shanaube, Sismanidis et al. 2009, Wood, Liang et al. 2010, developing TB disease (Provincial Government Western Cape Department of Health 2012), dying from TB (Statistics South Africa 2012), and dying from causes other than TB (World Health Organization Global Health Observatory (GHO) 2012) was taken from South African data; as was the data on the cost of BCG vaccination and the cost of diagnosing and treating three types of childhood TB (pulmonary, miliary, and meningeal) (Mandalakas, Hesseling et al. 2013). The efficacy (how well the vaccine works) of the MVA85A vaccine was taken from the published trial data (Tameris, Hatherill et al. 2013).

The model was used to calculate the absolute difference in the number of TB cases and TB deaths between the two interventions i.e. BCG alone versus BCG + MVA85A. At the end of the 10-year period the cumulative costs and outcomes of each intervention were used to calculate the cost-effectiveness ratio (CER) (i.e. the cost per TB case averted and the cost per TB death averted) for each intervention. These two cost-effectiveness ratios were compared using an incremental cost-effectiveness ratio (ICER), which represent the additional cost per additional benefit received.

Results

Unfortunately, the MVA85A trial data only showed an efficacy of 17.3% in preventing TB in HIV-negative infants when given as a booster to the existing BCG vaccines. This has heavily impacted on the results of this cost-effectiveness study.

The results indicate that the MVA85A strategy is both more costly and more effective – there are fewer TB cases and deaths from TB – than BCG alone. The Government would need to spend an additional USD 1,105 for every additional TB case averted and USD 284,017 for every additional TB death averted (Table 1).
Table 1: Cost-effectiveness of adding the MVA85A vaccine to the BCG vaccine from the perspective of the South African Government

<table>
<thead>
<tr>
<th>Strategy</th>
<th>10-year costs (USD 2012)</th>
<th>Absolute Number of TB cases</th>
<th>Absolute Number of TB deaths</th>
<th>ICER Per TB case averted (USD 2012)</th>
<th>ICER Per TB deaths averted (USD 2012)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discounted (3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCG alone</td>
<td>84.17</td>
<td>0.09101</td>
<td>0.0003501817</td>
<td></td>
<td></td>
</tr>
<tr>
<td>plus MVA85A</td>
<td>98.23</td>
<td>0.07828</td>
<td>0.0003006626</td>
<td>1,105</td>
<td>284,017</td>
</tr>
<tr>
<td>Undiscounted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCG alone</td>
<td>97.65</td>
<td>0.10627</td>
<td>0.0004174069</td>
<td></td>
<td></td>
</tr>
<tr>
<td>plus MVA85A</td>
<td>109.80</td>
<td>0.09138</td>
<td>0.0003583168</td>
<td>816</td>
<td>205,603</td>
</tr>
</tbody>
</table>

South Africa does not have a defined acceptability threshold. If we consider the recommendations made by the Commission on Macroeconomics and Health, then at South Africa’s GDP per capita of USD 8,070, the vaccine would be considered highly cost-effective in terms of TB cases averted.

The sensitivity analyses suggest that the results are sensitive to the price at which the vaccine will be made available, the annual risk of being infected (ARI) with TB, and the efficacy of the vaccine.

The threshold analysis shows that, if the efficacy of the MVA85A vaccine was 41.361% (instead of the current efficacy of 17.3%), the two strategies would have the same cost but more cases of TB and more deaths from TB would be prevented by adding the MVA85A vaccine to the BCG vaccine. In this case, Government should consider the MVA85A strategy.

Policy Recommendations

This cost-effectiveness study shows that adding the MVA85A vaccine to the BCG vaccine is both more costly and more effective in preventing TB disease and deaths from TB than using BCG alone. However, the clinical study shows that, in HIV-negative infants, the MVA85A vaccine’s efficacy is very low, when given as a booster to the BCG
vaccine. Therefore, adding MVA85A as a booster to BCG against infant and childhood TB is not cost-effective, and is not a good use of Government’s limited resources.

Furthermore, the study indicates that, a new TB vaccine with an efficacy of, at least, 41.361% and provided at the same price as the MVA85A vaccine, would have the same cost to Government as using the BCG vaccine, but prevent more cases of childhood TB and more deaths from TB. In this case, the Government should consider investing in the new vaccine.
References


