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

by

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DECLARATION

I, Liezl Bonnin Channing (student number CHNLIE001), hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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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.

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List of Abbreviations

Abbreviation	Description
ARI	Annual Risk of Infection
BCG	Bacille Calmette–Guérin
CBA	Cost Benefit Analysis
CEA	Cost-Effectiveness Analysis
CER	Cost Effectiveness Ratio
CMA	Cost Minimization Analysis
CPI	Consumer Price Index
CUA	Cost Utility Analysis
DOTS	Directly Observed Therapy, Short-Course)
DTP3	Diphtheria-Tetanus-Pertussis
EPI	Expanded Programme of Immunization
FIND	Foundation for Innovative New Diagnostics
GDP	Gross Domestic Product
HIV	Human Immunodeficiency Virus
ICER	Incremental Cost Effectiveness Ratio
IPT	Isoniazid Preventive Therapy
MCV	Measles-containing vaccine
MDG	Millennium Development Goals
MDR-TB	Multidrug Resistant Tuberculosis
mTB	Miliary Tuberculosis
MVA85A	Modified Vaccinia Ankara 85A
NGO	Non-Government Organization
OETC	Oxford Emergent Tuberculosis Consortium
PTB	Pulmonary Tuberculosis
QALY	Quality-Adjusted Life-Year
StatsSA	Statistics South Africa
TB	Tuberculosis

Abbreviation	Description
TBM	Tuberculosis Meningitis
TBVI	TB Vaccine Initiative
TST	Tuberculin Skin Test
UCT	University of Cape Town
USD	U.S. Dollars
WHA	World Health Assembly
WHO	World Health Organization
ZAR	South African Rand

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.

South African Picture (Kaiser Family Foundation: U.S. Global Health Policy 2012)

Indicators	Data/Date Range	Type of Data	World	South Africa
Tuberculosis HBCs	2011	Text	22	Yes
New TB Cases	2010	#	8,800,000	490,000
New TB Smear Positive Cases	2008	#	4,300,000	200,000
New TB Case Rate	2010	Rate per 100,000	128	981
People living with TB	2010	#	12,000,000	400,000
TB Prevalence Rate	2010	Rate per 100,000	178	795
TB Smear Positive Case Rate	2008	Rate per 100,000	64	410
TB Deaths	2010	#	1,100,000	25,000
TB Death Rate	2010	Rate per 100,000	15	50
TB Incidence in HIV People	2010	#	1,100,000	300,000
TB Incidence in HIV People per 100,000 Population	2010	Rate per 100,000	16	591
HIV Prevalence in Incident TB Cases	2010	%	23.00%	60.00%
TB Prevalence in HIV People	2007	#	687,024	167,799
TB Prevalence in HIV People per 100,000 Population	2007	Rate per 100,000	10	345
TB Mortality in HIV People	2007	#	456,218	93,702
TB Mortality in HIV People per 100,000 Population	2007	Rate per 100,000	7	193
DOTS Coverage	2007	%	94%	100%
DOTS Detection Rate	2007	%	63%	78%
DOTS Treatment Success	2006	%	85%	74%
Population	2011	#	6,928,198,253	49,004,031
Population Under Age 15	2011	%	27%	30%
Death Rate (overall)	2011	Rate per 1,000	8.12	17.09
Infant Mortality Rate	2011	Rate per 1,000	41.61	43.2
Under-Five Mortality Rate	2010	Rate per 1,000	57	57
GDP Per Capita	2010	$	$11,125	$10,565
Country Income Classification	As of July	Text	(NA)	Upper middle

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

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

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

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

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

ABU-RADDAD, L.J., SABATELLI, L., ACHTERBERG, J.T., SUGIMOTO, J.D., LONGINI, I.M.,JR, DYE, C. and HALLORAN, M.E., 2009. Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics. *Proceedings of the National Academy of Sciences of the United States of America,* **106**(33), pp. 13980-13985.

BREWER, T.F., 2000. Preventing tuberculosis with bacillus Calmette-Guerin vaccine: a meta-analysis of the literature. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America,* **31 Suppl 3**, pp. S64-7.

CLARK, M. and CAMERON, D.W., 2006. The benefits and risks of bacille Calmette-Guerin vaccination among infants at high risk for both tuberculosis and severe combined immunodeficiency: assessment by Markov model. *BMC pediatrics,* **6**, pp. 5.

COLDITZ, G.A., BERKEY, C.S., MOSTELLER, F., BREWER, T.F., WILSON, M.E., BURDICK, E. and FINEBERG, H.V., 1995. The efficacy of bacillus Calmette-Guerin vaccination of newborns and infants in the prevention of tuberculosis: meta-analyses of the published literature. *Pediatrics,* **96**(1 Pt 1), pp. 29-35.

COLDITZ, G.A., BREWER, T.F., BERKEY, C.S., WILSON, M.E., BURDICK, E., FINEBERG, H.V. and MOSTELLER, F., 1994. Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. *JAMA : the journal of the American Medical Association,* **271**(9), pp. 698-702.

CORRIGALL, J., COETZEE, D. and CAMERON, N., 2008. Is the Western Cape at risk of an outbreak of preventable childhood diseases? Lessons from an evaluation of routine immunisation coverage. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde,* **98**(1), pp. 41-45.

DEPARTMENT OF HEALTH, 2011. *Annual Report 2010/2011.*

DRUMMOND, M.F., 2005. *Methods for the economic evaluation of health care programmes.* 3 edn. Oxford ; New York: Oxford University Press.

DYE, C., GARNETT, G.P., SLEEMAN, K. and WILLIAMS, B.G., 1998. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. Directly observed short-course therapy. *Lancet,* **352**(9144), pp. 1886-1891.

FINE, P.E., 1995. Variation in protection by BCG: implications of and for heterologous immunity. *Lancet,* **346**(8986), pp. 1339-1345.

KAISER FAMILY FOUNDATION: U.S. GLOBAL HEALTH POLICY, 2012-last update, Country Data: Custom Data Sheet. Available: http://www.globalhealthfacts.org/data/factsheet/stepone.aspx [July 9, 2012].

KAUFMANN, S.H., HUSSEY, G. and LAMBERT, P.H., 2010. New vaccines for tuberculosis. *Lancet,* **375**(9731), pp. 2110-2119.

KIM, S.Y. and GOLDIE, S.J., 2008. Cost-effectiveness analyses of vaccination programmes: a focused review of modelling approaches. *PharmacoEconomics,* **26**(3), pp. 191-215.

MANDALAKAS, A.M., HESSELING, A.C., GIE, R.P., SCHAAF, H.S., MARAIS, B.J. and SINANOVIC, E., 2013. Modelling the cost-effectiveness of strategies to prevent tuberculosis in child contacts in a high-burden setting. *Thorax,* **68**(3), pp. 247-255.

MARAIS, B.J., GIE, R.P., SCHAAF, H.S., BEYERS, N., DONALD, P.R. and STARKE, J.R., 2006. Childhood pulmonary tuberculosis: old wisdom and new challenges. *American journal of respiratory and critical care medicine,* **173**(10), pp. 1078-1090.

MCSHANE, H., 2011. Tuberculosis vaccines: beyond bacille Calmette-Guerin. *Philosophical transactions of the Royal Society of London.Series B, Biological sciences,* **366**(1579), pp. 2782-2789.

ODUTOLA, A.A., OWOLABI, O.A., OWIAFE, P.K., MCSHANE, H. and OTA, M.O., 2012. A new TB vaccine, MVA85A, induces durable antigen-specific responses 14 months after vaccination in African infants. *Vaccine,* **30**(38), pp. 5591-5594.

RODRIGUES, L.C., DIWAN, V.K. and WHEELER, J.G., 1993. Protective effect of BCG against tuberculous meningitis and miliary tuberculosis: a meta-analysis. *International journal of epidemiology,* **22**(6), pp. 1154-1158.

RODRIGUES, L.C., PEREIRA, S.M., CUNHA, S.S., GENSER, B., ICHIHARA, M.Y., DE BRITO, S.C., HIJJAR, M.A., DOURADO, I., CRUZ, A.A., SANT'ANNA, C., BIERRENBACH, A.L. and BARRETO, M.L., 2005. Effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: the BCG-REVAC cluster-randomised trial. *Lancet,* **366**(9493), pp. 1290-1295.

SCRIBA, T.J., TAMERIS, M., MANSOOR, N., SMIT, E., VAN DER MERWE, L., MAUFF, K., HUGHES, E.J., MOYO, S., BRITTAIN, N., LAWRIE, A., MULENGA, H., DE KOCK, M., GELDERBLOEM, S., VELDSMAN, A., HATHERILL, M., GELDENHUYS, H., HILL, A.V., HUSSEY, G.D., MAHOMED, H., HANEKOM, W.A. and MCSHANE, H., 2011. Dose-finding study of the novel tuberculosis vaccine, MVA85A, in healthy BCG-vaccinated infants. *The Journal of infectious diseases,* **203**(12), pp. 1832-1843.

SISMANIDIS, B., 2012. Background document 10: Epidemiological estimates of global childhood TB burden, B. SISMANIDIS, ed. In: *5th WHO Global Task Force on TB Impact Measurement, Geneva, Switzerland*, 9-10 May 2012 2012.

STERNE, J.A., RODRIGUES, L.C. and GUEDES, I.N., 1998. Does the efficacy of BCG decline with time since vaccination? *The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease,* **2**(3), pp. 200-207.

TRUNZ, B.B., FINE, P. and DYE, C., 2006. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. *Lancet,* **367**(9517), pp. 1173-1180.

TSENG, C.L., OXLADE, O., MENZIES, D., ASPLER, A. and SCHWARTZMAN, K., 2011. Cost-effectiveness of novel vaccines for tuberculosis control: a decision analysis study. *BMC public health,* **11**, pp. 55.

TU, H.A., VU, H.D., ROZENBAUM, M.H., WOERDENBAG, H.J. and POSTMA, M.J., 2012. A review of the literature on the economics of vaccination against TB. *Expert review of vaccines,* **11**(3), pp. 303-317.

VAN RIE, A., BEYERS, N., GIE, R.P., KUNNEKE, M., ZIETSMAN, L. and DONALD, P.R., 1999. Childhood tuberculosis in an urban population in South Africa: burden and risk factor. *Archives of Disease in Childhood,* **80**(5), pp. 433-437.

WALLEY, T., HAYCOX, A. and BOLAND, A., eds, 2004. *Pharmacoeconomics.* London: Churchill Livingstone.

WEINSTEIN, M.C., SIEGEL, J.E., GOLD, M.R., KAMLET, M.S. and RUSSELL, L.B., 1996. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. *JAMA : the journal of the American Medical Association,* **276**(15), pp. 1253-1258.

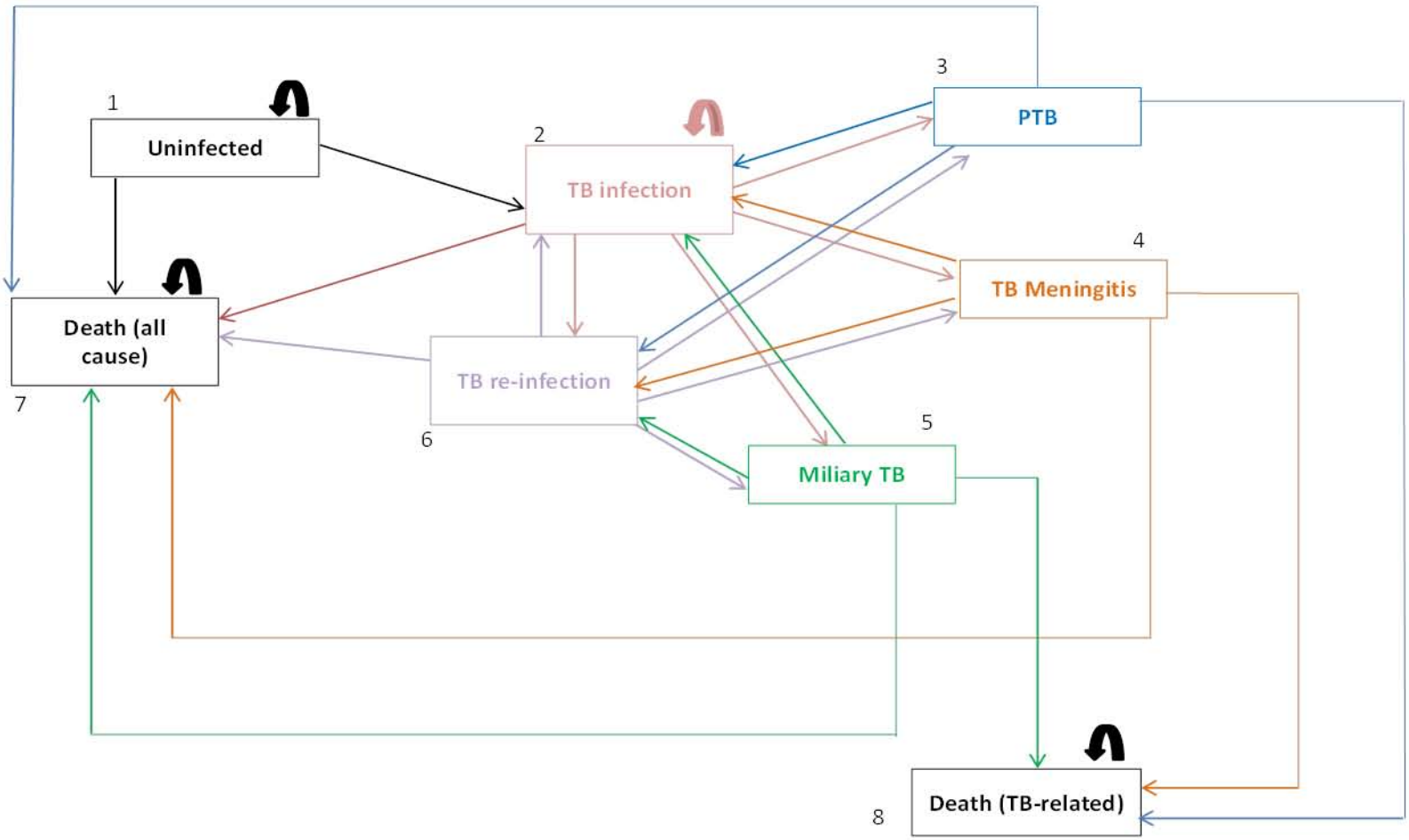
WORLD HEALTH ORGANIZATION, 2012. *The Global Tuberculosis Control Report 2012.* Geneva, Switzerland: World Health Organization.

WORLD HEALTH ORGANIZATION CHOICE, 2012-last update, Cost-effectiveness thresholds. Available: http://www.who.int/choice/costs/CER_thresholds/en/index.html [July 26, 2012].

WORLD HEALTH ORGANIZATION, UNICEF and WORLD BANK, 2009. *State of the world's vaccines and immunization, 3rd ed.* Geneva: World Health Organization.

YOUNG, D. and DYE, C., 2006. The development and impact of tuberculosis vaccines. *Cell,* **124**(4), pp. 683-687.

Annex 1: Health states and possible transitions (State diagram)



Annex 2: Disease parameters

Parameters	Value	Range	References
Annual Risk of Infection (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 opinion[1]
Risk of dying from "other causes"			
0-1 years	0.04295312		• Electronic database (World Health Organization Global Health Observatory (GHO) 2012) and adjusted to remove the risk of dying from TB • Expert opinion[1]
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 (%)			
0-2 years	54.1929		• Electronic database (Provincial Government Western Cape Department of Health 2012) and calculated assuming an ARI of 3% • Expert opinion[1]
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.

Parameters	Value	Range	References
Risk of death from pulmonary TB (%)			
< 3 years	0.74952		• Electronic databases (Provincial Government Western Cape Department of Health 2012, Statistics South Africa 2012b) • Calculated using average for 2005-2009 and e-TB data • Expert opinion[1]
3-5 years	0.09120		
> 6 years	0.58766		
Risk of death from miliary TB (%)			
< 3 years	23.52941		
3-5 years	9.09091		
> 6 years	16.66667		
Risk of death from TB meningitis (%)			
< 3 years	25.00000		
3-5 years	26.66667		
> 6 years	20.00000		
MVA85A efficacy against TB disease (%)	17.3	12.3 – 22.3	• Published literature (Tameris, Hatherill et al. 2013)
Up-take BCG (%)	99.0	99.0 – 99.5	• Published literature (Department of Health: Republic of South Africa 2011, Corrigall, Coetzee et al. 2008)
Up-take MVA85A	85.0	76.4 – 89.5	• Calculated
Drop-out rate DTP3 to MCV	14.0	9.5 – 23.1	• Published literature and electronic database (Saloojeei, Bamfordii 2006, Health Systems Trust 2007) • Expert Opinion[1]
Cost of BCG vaccination (USD 2012)	13.57	13.43 – 14.28	• Published and unpublished literature (Mandalakas, Hesseling et al. 2013) • Personal Communication (Arnot, Hayes 2012)
Cost of MVA85A vaccination (USD 2012)	28.22	20.22 – 48.22	• Personal Communication Oxford Emergent Tuberculosis Consortium (OETC) • Published and unpublished literature (Mandalakas, Hesseling et al. 2013)

[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.

Parameters	Value	Range	References
Costs of diagnosis and treatment PTB (USD 2012)			
0-2 years	406.13		• Personal Communication (Arnot, Hayes 2012, von Zeil 2012) • Published and unpublished literature (Mandalakas, Hesseling et al. 2013) • Published report (Statistics South Africa 2012a)
3-5 years	433.13		
6-10 years	459.29		
Costs of diagnosis and treatment mTB (USD 2012)			
0-2 years	3,184.76		
3-5 years	3,213.57		
6-10 years	3,241.54		
Costs of diagnosis and treatment TBM (USD 2012)			
0-2 years	29,782.98		
3-5 years	29,844.60		
6-10 years	29,881.88		
Discount rate_outcomes (%)	3	0 – 6	• Published literature (Weinstein, Siegel et al. 1996, Severens, Milne 2004, Torgerson, Raftery 1999, Langer, Holle et al. 2012, Smith, Gravelle 2000)
Discount rate_costs (%)	3	0 – 6	

References

ARNOT, M. and HAYES, H., 2012. *BCG and TB medicine tenders and treatment guidelines.* Cape Town: Provincial Government of the Western Cape, Department of Health.

CORRIGALL, J., COETZEE, D. and CAMERON, N., 2008. Is the Western Cape at risk of an outbreak of preventable childhood diseases? Lessons from an evaluation of routine immunisation coverage. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde,* **98**(1), pp. 41-45.

DEPARTMENT OF HEALTH: REPUBLIC OF SOUTH AFRICA, 2011. *Annual Report 2010/11.* Pretoria, South Africa: Department of Health.

HEALTH SYSTEMS TRUST, July, 2007-last update, Immunisation drop out rate (DTP3-measles), [Online]. Available: http://indicators.hst.org.za/healthstats/239/data [May 18, 2013].

KRITZINGER, F.E., DEN BOON, S., VERVER, S., ENARSON, D.A., LOMBARD, C.J., BORGDORFF, M.W., GIE, R.P. and BEYERS, N., 2009. No decrease in annual risk of tuberculosis infection in endemic area in Cape Town, South Africa. *Tropical medicine & international health : TM & IH,* **14**(2), pp. 136-142.

LANGER, A., HOLLE, R. and JOHN, J., 2012. Specific guidelines for assessing and improving the methodological quality of economic evaluations of newborn screening. *BMC health services research,* **12**, pp. 300.

MANDALAKAS, A.M., HESSELING, A.C., GIE, R.P., SCHAAF, H.S., MARAIS, B.J. and SINANOVIC, E., 2013. Modelling the cost-effectiveness of strategies to prevent tuberculosis in child contacts in a high-burden setting. *Thorax,* **68**(3), pp. 247-255.

MIDDELKOOP, K., BEKKER, L., MYER, L., DAWSON, R. and WOOD, R., 2008. Rates of Tuberculosis Transmission to Children and Adolescents in a Community with a High Prevalence of HIV Infection among Adults. *Clinical Infectious Diseases,* **47**(3), pp. 349-355.

PROVINCIAL GOVERNMENT WESTERN CAPE DEPARTMENT OF HEALTH, 2012. *e-TB register 2008.* Electronic Database edn. Cape Town: Provincial Government Western Cape Department of Health.

SALOOJEEI, H. and BAMFORDII, L., 2006. Chapter 11: Key Childhood Health Promotion and Disease Prevention Programmes. In: P. IJUMBA and A. PADARATH, eds, *South African Health Review 2006.* Durban: Health Systems Trust.

SEVERENS, J.L. and MILNE, R.J., 2004. Discounting health outcomes in economic evaluation: the ongoing debate. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research,* **7**(4), pp. 397-401.

SHANAUBE, K., SISMANIDIS, C., AYLES, H., BEYERS, N., SCHAAP, A., LAWRENCE, K.A., BARKER, A. and GODFREY-FAUSSETT, P., 2009. Annual risk of tuberculous infection using different methods in communities with a high prevalence of TB and HIV in Zambia and South Africa. *PloS one,* **4**(11), pp. e7749.

SMITH, D. and GRAVELLE, H., 2000. *The Practice of Discounting Economic Evaluation of Health Care Interventions.* CHE Technical Paper Series 19. York: The University of York, Centre for Health Economics.

STATISTICS SOUTH AFRICA, 2012a. *Consumer Price Index (CPI).* P0141. Pretoria: Statistics South Africa.

STATISTICS SOUTH AFRICA, 2012b. *Western Cape TB Mortality Data Children 0-10 years (2005-2009).* Electronic Database edn. Pretoria: Statistics South Africa.

TAMERIS, M.D., HATHERILL, M., LANDRY, B.S., SCRIBA, T.J., SNOWDEN, M.A., LOCKHART, S., SHEA, J.E., MCCLAIN, J.B., HUSSEY, G.D., HANEKOM, W.A., MAHOMED, H., MCSHANE, H. and THE MVA85A 020 TRIAL STUDY TEAM, 2013. Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial. *Lancet, Epub ahead of print*.

TORGERSON, D.J. and RAFTERY, J., 1999. Economic notes. Discounting. *BMJ (Clinical research ed.),* **319**(7214), pp. 914-915.

VON ZEIL, M., 2012. *Childhood TB Treatment guidelines, practice guidelines to accomodate TB medicines on tender.* Cape Town: City of Cape Town, Department of Health.

WEINSTEIN, M.C., SIEGEL, J.E., GOLD, M.R., KAMLET, M.S. and RUSSELL, L.B., 1996. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. *JAMA : the journal of the American Medical Association,* **276**(15), pp. 1253-1258.

WOOD, R., LIANG, H., WU, H., MIDDELKOOP, K., ONI, T., RANGAKA, M.X., WILKINSON, R.J., BEKKER, L.G. and LAWN, S.D., 2010. Changing prevalence of tuberculosis infection with increasing age in high-burden townships in South Africa. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease,* **14**(4), pp. 406-412.

WORLD HEALTH ORGANIZATION GLOBAL HEALTH OBSERVATORY (GHO), 2012. *South Africa Life-Tables 2009.* Electronic Database edn. Geneva: World Health Organization.

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

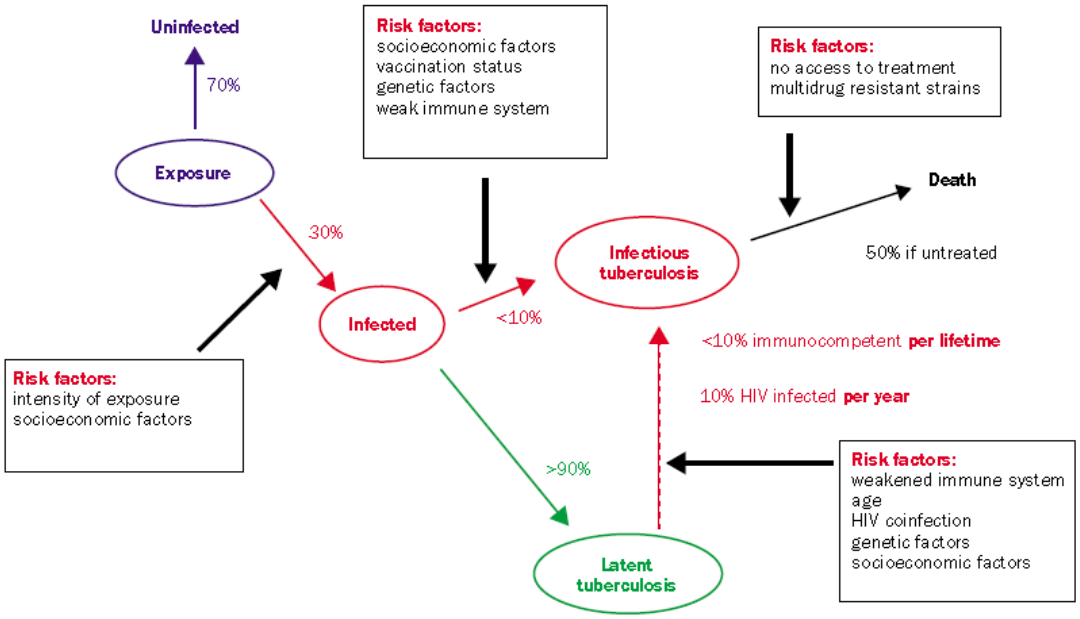
and how the immune system responds to the organism grows (Lawn, Zumla 2011).

The sequencing of the *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 *M tuberculosis* (Lawn, Zumla 2011).

It is estimated that only about 30% of those exposed to *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).

Figure 1: Risk of infection and progression to disease and the associated risk factors (taken from (Collins, Kaufmann 2001))



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).

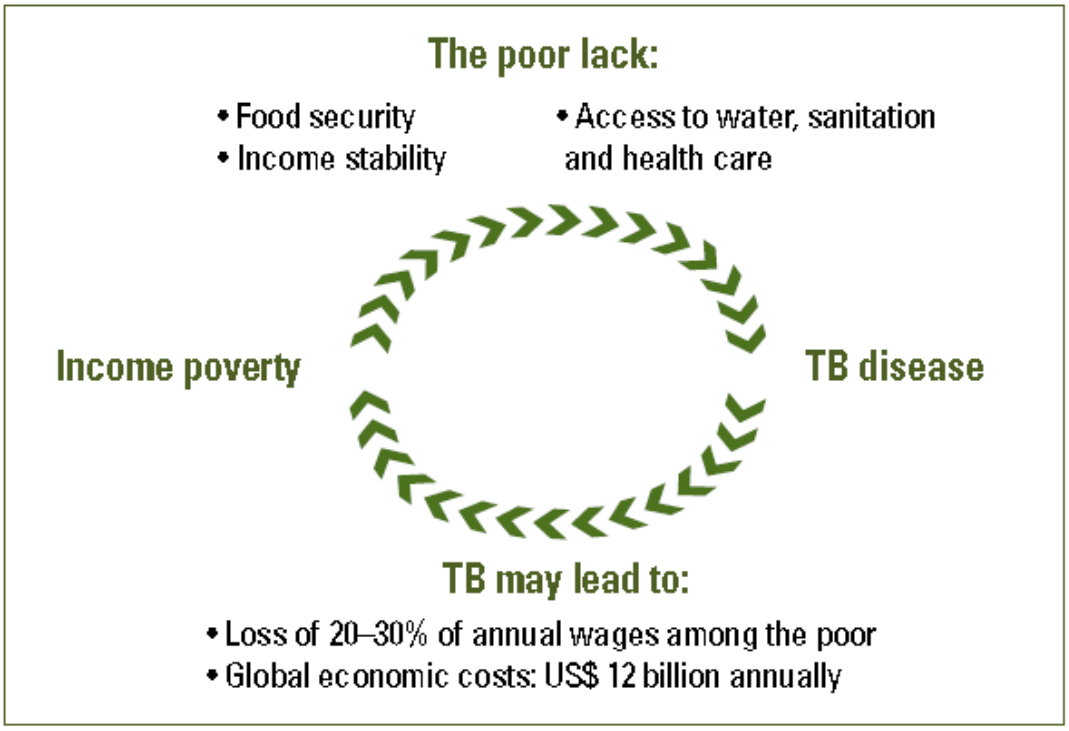
The Annual Risk of Infection (ARI) is the probability of acquiring TB infection or TB re-infection over a period of one year. The ARI is derived from data generated through tuberculin skin test (TST) surveys among children. There is a lack of consensus about whether age-specific ARIs exist and whether 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



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

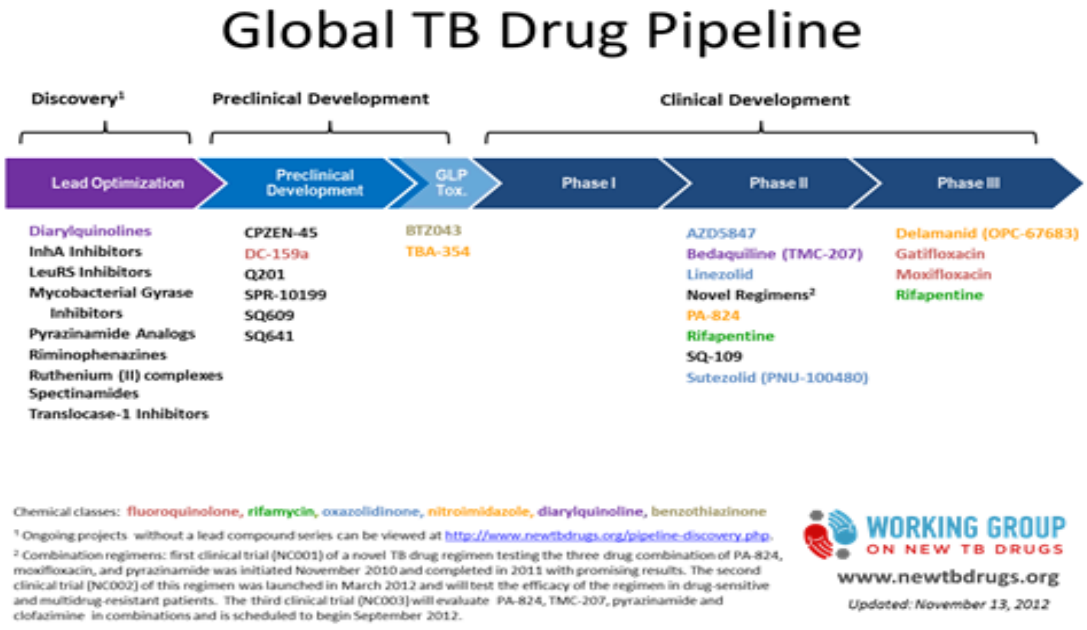
"The establishment of the Bill & Melinda Gates Foundation *(in 1994)* coincided with the establishment of other public–private partnerships that have played a major part in resurrecting TB research and development." (Lienhardt, Glaziou et al. 2012) As of today, the Bill & Melinda Gates Foundation provides 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).

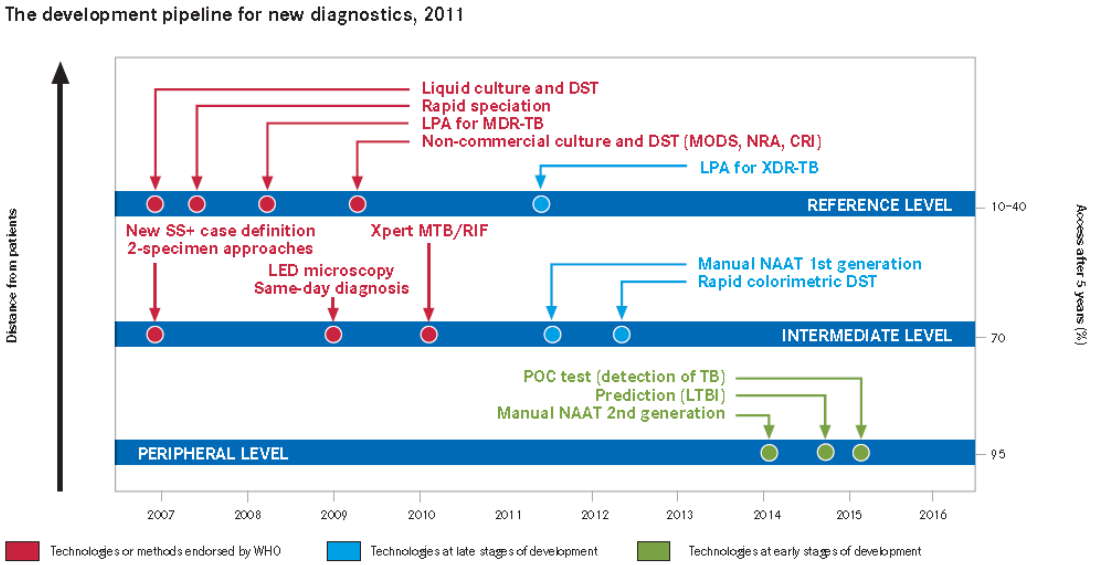
Figure 3: Global TB Drug Pipeline (http://www.newtbdrugs.org/pipeline.php)



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).

Figure 4: Global Diagnostic Pipeline (http://stoptb.org/wg/new_diagnostics/objectives.asp)



Abbreviations: **DST** Drug susceptibility test; **NAAT** Nucleic acid amplification test; **LTBI** Latent TB infection; **POC** Point of care; **MODS** Microscopic observation drug-susceptibility; **NRA** Nitrate reductase assay; **CRI** Colorimetric redox indicator assay; **LED** Light-emitting diode; **LPA** Line probe assay

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 *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:

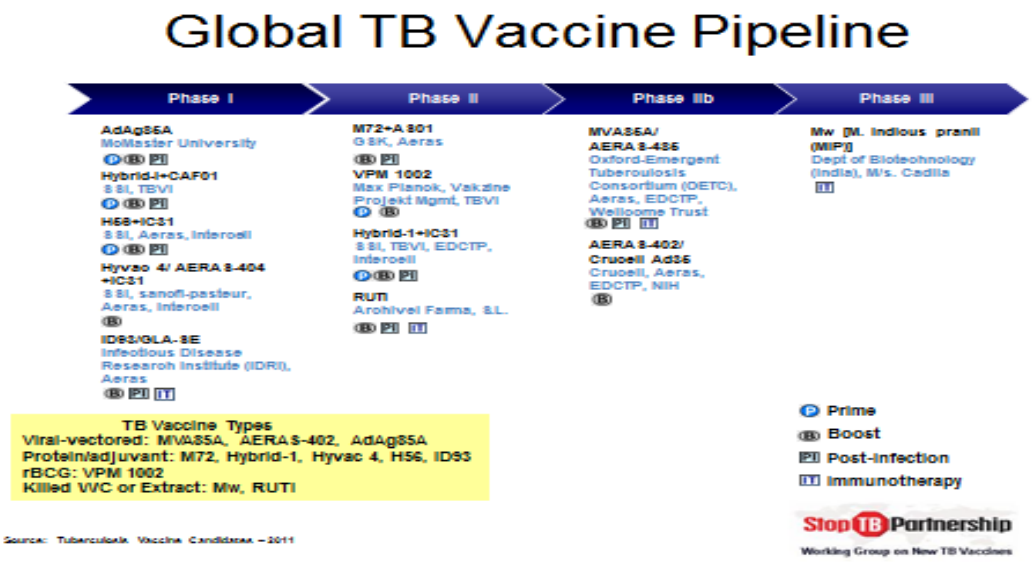
1. Live attenuated vaccines; and
2. Subunit vaccines.

The first category looks at replacing the existing BCG vaccine through either a recombinant BCG or genetic attenuation of *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)



MVA85A

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 Pharmacoeconomics 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” (Sonnenberg, 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 pharmacoeconomic 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

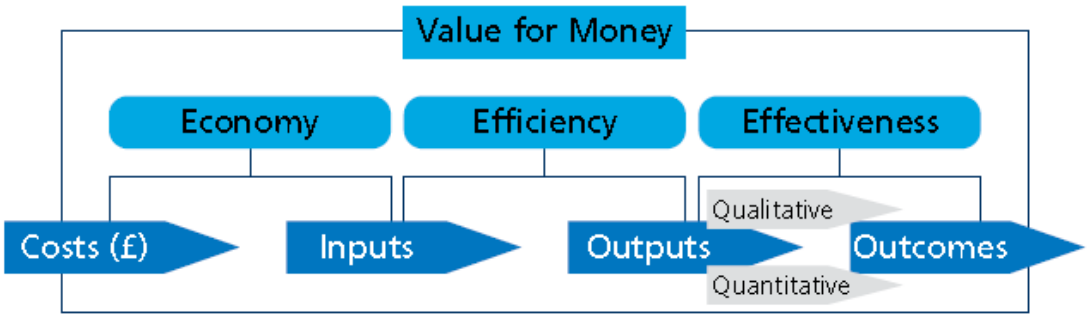
to the difficulty in obtaining utility values for young children who are generally the ones receiving vaccines.

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

AABY, P., ROTH, A., RAVN, H., NAPIRNA, B.M., RODRIGUES, A., LISSE, I.M., STENSBALLE, L., DINESS, B.R., LAUSCH, K.R., LUND, N., BIERING-SORENSEN, S., WHITTLE, H. and BENN, C.S., 2011. Randomized trial of BCG vaccination at birth to low-birth-weight children: beneficial nonspecific effects in the neonatal period? *The Journal of infectious diseases,* 204(2), pp. 245-252.

ABU-RADDAD, L.J., SABATELLI, L., ACHTERBERG, J.T., SUGIMOTO, J.D., LONGINI, I.M.,JR, DYE, C. and HALLORAN, M.E., 2009. Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics. *Proceedings of the National Academy of Sciences of the United States of America,* 106(33), pp. 13980-13985.

BRENT, A.J., ANDERSON, S.T. and KAMPMANN, B., 2008. Childhood tuberculosis: out of sight, out of mind? *Transactions of the Royal Society of Tropical Medicine and Hygiene,* 102(3), pp. 217-218.

BRIDGES, J.F., ONUKWUGHA, E. and MULLINS, C.D., 2010. Healthcare rationing by proxy: cost-effectiveness analysis and the misuse of the $50,000 threshold in the US. *PharmacoEconomics,* 28(3), pp. 175-184.

BRIGGS, A., CLAXTON, K. and SCULPHER, M., 2011. *Decision Modelling for Health Economic Evaluation.* 1st edn. Oxford: Oxford University Press.

BRIGGS, A. and SCULPHER, M., 1998. An introduction to Markov modelling for economic evaluation. *PharmacoEconomics,* 13(4), pp. 397-409.

CHAUHAN, L.S., DARA, M., FIGUEROA-MUÑOZ, J., HANSON, C., MARTINEZ, L., SALANIPONI, F., SQUIRE, B., SUNDARAM, C., VAN CLEEFF, M. and WEIL, D., 2005. *Addressing Poverty in TB Control: Options for National TB Control Programmes.* WHO/HTM/TB/2005.352. Geneva: World Health Organization.

CLEMENS, K., GARRISON, L.P.,JR, JONES, A. and MACDONALD, F., 1993. Strategic use of pharmacoeconomic research in early drug development and global pricing. *PharmacoEconomics,* 4(5), pp. 315-322.

COLDITZ, G.A., BREWER, T.F., BERKEY, C.S., WILSON, M.E., BURDICK, E., FINEBERG, H.V. and MOSTELLER, F., 1994. Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. *JAMA : the journal of the American Medical Association,* 271(9), pp. 698-702.

COLLINS, H.L. and KAUFMANN, S.H., 2001. Prospects for better tuberculosis vaccines. *The Lancet infectious diseases,* 1(1), pp. 21-28.

DAVIES, P.D., 2005. Risk factors for tuberculosis. *Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace / Fondazione clinica del lavoro, IRCCS [and] Istituto di clinica tisiologica e malattie apparato respiratorio, Universita di Napoli, Secondo ateneo,* 63(1), pp. 37-46.

DEPARTMENT OF HEALTH: REPUBLIC OF SOUTH AFRICA, 2013. *Guidelines for Pharmacoeconomic Submissions.* Government Gazette 36118. Pretoria, South Africa: National Department of Health.

DEPARTMENT OF VACCINES AND BIOLOGICALS, 1999. *Issues relating to the use of BCG in immunization programmes: A discussion document.* WHO/V&B/99.23. Geneva: World Health Organization.

DEVLIN, N. and PARKIN, D., 2004. Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis. *Health Economics,* 13(5), pp. 437-452.

DONALD, P.R., 2002. Childhood tuberculosis: out of control? *Current opinion in pulmonary medicine,* 8(3), pp. 178-182.

DONALD, P.R., MAHER, D. and QAZI, S., 2007. A research agenda to promote the management of childhood tuberculosis within national tuberculosis programmes. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease,* 11(4), pp. 370-380.

DRUMMOND, M.F., 2005. *Methods for the economic evaluation of health care programmes.* 3 edn. Oxford ; New York: Oxford University Press.

DYE, C. and FLOYD, K., 2006. Chapter 16: Tuberculosis. In: D.T. JAMISON, J.G. BREMAN, A.R. MEASHAM, G. ALLEYNE, M. CLAESON, D.B. EVANS, P. JHA, A. MILLS and P. MUSGROVE, eds, *Disease Control Priorities in Developing Countries.* 2nd edn. New York: Oxford University Press & World Bank, pp. 289.

DYE, C., GARNETT, G.P., SLEEMAN, K. and WILLIAMS, B.G., 1998. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. Directly observed short-course therapy. *Lancet,* 352(9144), pp. 1886-1891.

FINE, P.E., 1995. Variation in protection by BCG: implications of and for heterologous immunity. *Lancet,* 346(8986), pp. 1339-1345.

FINE, P.E., SMITH, P.G. and EVANS, S.J., 2012. Non-specific effects of BCG? *The Journal of infectious diseases,* 205(3), pp. 515; author reply 517-8.

FLYNN, J.L. and CHAN, J., 2001. Tuberculosis: latency and reactivation. *Infection and immunity,* 69(7), pp. 4195-4201.

GAFNI, A. and BIRCH, S., 2006. Incremental cost-effectiveness ratios (ICERs): the silence of the lambda. *Social science & medicine (1982),* 62(9), pp. 2091-2100.

GRAY, A.M., CLARKE, P.M., WOLSTENHOLME, J.L. and WORDSWORTH, S., 2011. *Applied Methods of Cost-Effectiveness Analysis in Health Care.* 1st edn. Oxford: Oxford University Press.

GUINNESS, L. and WISEMAN, V., eds, 2011. *Introduction to Health Economics.* 2nd edn. Berkshire: Open University Press.

HAYCOX, A. and NOBLE, E., 2009. *What is Health Economics?* London: Hayward Medical Communications.

HUSSEY, G., HAWKRIDGE, T. and HANEKOM, W., 2007. Childhood tuberculosis: old and new vaccines. *Paediatric respiratory reviews,* 8(2), pp. 148-154.

IMMUNIZATION, V.A.B., 2008. *WHO guide for standardization of economic evaluations of immunization programmes.* WHO/IVB/08.14. Geneva: World Health Organization.

IMPERIAL COLLEGE LONDON, n.d. n.d.-last update, Value for Money Policy, [Online]. Available: http://www3.imperial.ac.uk/purchasing/externalvalueformoney [April 20, 2013].

JACKSON, P., 2012. *Value for Money and International Development: Deconstructing Myths to Promote a More Constructive Discussion*. Paris: OECD.

KABRA, S.K., LODHA, R. and SETH, V., 2004. Some current concepts on childhood tuberculosis. *The Indian journal of medical research,* 120(4), pp. 387-397.

KAUFMANN, S.H., HUSSEY, G. and LAMBERT, P.H., 2010. New vaccines for tuberculosis. *Lancet,* 375(9731), pp. 2110-2119.

KIM, S.Y. and GOLDIE, S.J., 2008. Cost-effectiveness analyses of vaccination programmes : a focused review of modelling approaches. *PharmacoEconomics,* 26(3), pp. 191-215.

LANGER, A., HOLLE, R. and JOHN, J., 2012. Specific guidelines for assessing and improving the methodological quality of economic evaluations of newborn screening. *BMC health services research,* 12, pp. 300.

LAWN, S.D. and ZUMLA, A.I., 2011. Tuberculosis. *The Lancet,* 378(9785), pp. 57-72.

LAXMINARAYAN, R., KLEIN, E., DYE, C., FLOYD, K., DARLEY, S. and ADEYI, O., 2007. *Economic Benefit of Tuberculosis Control.* WPS4295. Washington D.C.: The World Bank.

LIENHARDT, C., FIELDING, K., SILLAH, J.S., BAH, B., GUSTAFSON, P., WARNDORFF, D., PALAYEW, M., LISSE, I., DONKOR, S., DIALLO, S., MANNEH, K., ADEGBOLA, R., AABY, P., BAH-SOW, O., BENNETT, S. and MCADAM, K., 2005. Investigation of the risk factors for tuberculosis: a case-control study in three countries in West Africa. *International journal of epidemiology,* 34(4), pp. 914-923.

LIENHARDT, C., GLAZIOU, P., UPLEKAR, M., LONNROTH, K., GETAHUN, H. and RAVIGLIONE, M., 2012. Global tuberculosis control: lessons learnt and future prospects. *Nature reviews.Microbiology,* 10(6), pp. 407-416.

LIN, P.L. and FLYNN, J.L., 2010. Understanding latent tuberculosis: a moving target. *Journal of immunology (Baltimore, Md.: 1950),* 185(1), pp. 15-22.

MANDALAKAS, A.M., HESSELING, A.C., GIE, R.P., SCHAAF, H.S., MARAIS, B.J. and SINANOVIC, E., 2013. Modelling the cost-effectiveness of strategies to prevent tuberculosis in child contacts in a high-burden setting. *Thorax,* 68(3), pp. 247-255.

MARAIS, B.J., 2008. Tuberculosis in children. *Pediatric pulmonology,* 43(4), pp. 322-329.

MARAIS, B.J., GIE, R.P., SCHAAF, H.S., BEYERS, N., DONALD, P.R. and STARKE, J.R., 2006. Childhood pulmonary tuberculosis: old wisdom and new challenges. *American journal of respiratory and critical care medicine,* 173(10), pp. 1078-1090.

MARAIS, B.J., GIE, R.P., SCHAAF, H.S., HESSELING, A.C., OBIHARA, C.C., NELSON, L.J., ENARSON, D.A., DONALD, P.R. and BEYERS, N., 2004a. The clinical epidemiology of childhood pulmonary tuberculosis: a critical review of literature from the pre-chemotherapy era. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease,* 8(3), pp. 278-285.

MARAIS, B.J., GIE, R.P., SCHAAF, H.S., HESSELING, A.C., OBIHARA, C.C., STARKE, J.J., ENARSON, D.A., DONALD, P.R. and BEYERS, N., 2004b. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease,* 8(4), pp. 392-402.

MARAIS, B.J., OBIHARA, C.C., WARREN, R.M., SCHAAF, H.S., GIE, R.P. and DONALD, P.R., 2005. The burden of childhood tuberculosis: a public health perspective. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease,* 9(12), pp. 1305-1313.

MARAIS, B.J., PARKER, S.K., VERVER, S., VAN RIE, A. and WARREN, R.M., 2009. Primary and postprimary or reactivation tuberculosis: time to revise confusing terminology? *AJR.American journal of roentgenology,* 192(4), pp. W198; author reply W199-200.

MCCABE, C., CLAXTON, K. and CULYER, A.J., 2008. The NICE cost-effectiveness threshold: what it is and what that means. *PharmacoEconomics,* 26(9), pp. 733-744.

MCSHANE, H., 2011. Tuberculosis vaccines: beyond bacille Calmette-Guerin. *Philosophical transactions of the Royal Society of London.Series B, Biological sciences,* 366(1579), pp. 2782-2789.

MCSHANE, H., 2009. Vaccine strategies against tuberculosis. *Swiss medical weekly,* 139(11-12), pp. 156-160.

MOYO, S., VERVER, S., MAHOMED, H., HAWKRIDGE, A., KIBEL, M., HATHERILL, M., TAMERIS, M., GELDENHUYS, H., HANEKOM, W. and HUSSEY, G., 2010. Age-related tuberculosis incidence and severity in children under 5 years of age in Cape Town, South Africa. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease,* 14(2), pp. 149-154.

NELSON, L.J. and WELLS, C.D., 2004. Global epidemiology of childhood tuberculosis. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease,* 8(5), pp. 636-647.

ODUTOLA, A.A., OWOLABI, O.A., OWIAFE, P.K., MCSHANE, H. and OTA, M.O., 2012. A new TB vaccine, MVA85A, induces durable antigen-specific responses 14 months after vaccination in African infants. *Vaccine,* 30(38), pp. 5591-5594.

OWENS, D.K., 1998. Interpretation of cost-effectiveness analyses. *Journal of general internal medicine,* 13(10), pp. 716-717.

RASANATHAN, K., SIVASANKARA KURUP, A., JARAMILLO, E. and LONNROTH, K., 2011. The social determinants of health: key to global tuberculosis control. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease,* 15 Suppl 2, pp. S30-6.

RODRIGUES, L.C., DIWAN, V.K. and WHEELER, J.G., 1993. Protective effect of BCG against tuberculous meningitis and miliary tuberculosis: a meta-analysis. *International journal of epidemiology,* 22(6), pp. 1154-1158.

RODRIGUES, L.C., PEREIRA, S.M., CUNHA, S.S., GENSER, B., ICHIHARA, M.Y., DE BRITO, S.C., HIJJAR, M.A., DOURADO, I., CRUZ, A.A., SANT'ANNA, C., BIERRENBACH, A.L. and BARRETO, M.L., 2005. Effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: the BCG-REVAC cluster-randomised trial. *Lancet,* 366(9493), pp. 1290-1295.

ROTH, A.E., STENSBALLE, L.G., GARLY, M.L. and AABY, P., 2006. Beneficial non-targeted effects of BCG--ethical implications for the coming introduction of new TB vaccines. *Tuberculosis (Edinburgh, Scotland),* 86(6), pp. 397-403.

ROWLAND, R. and MCSHANE, H., 2011. Tuberculosis vaccines in clinical trials. *Expert review of vaccines,* 10(5), pp. 645-658.

SCRIBA, T.J., TAMERIS, M., MANSOOR, N., SMIT, E., VAN DER MERWE, L., MAUFF, K., HUGHES, E.J., MOYO, S., BRITTAIN, N., LAWRIE, A., MULENGA, H., DE KOCK, M., GELDERBLOEM, S., VELDSMAN, A., HATHERILL, M., GELDENHUYS, H., HILL, A.V., HUSSEY, G.D., MAHOMED, H., HANEKOM, W.A. and MCSHANE, H., 2011. Dose-finding study of the novel tuberculosis vaccine, MVA85A, in healthy BCG-vaccinated infants. *The Journal of infectious diseases,* 203(12), pp. 1832-1843.

SEVERENS, J.L. and MILNE, R.J., 2004. Discounting health outcomes in economic evaluation: the ongoing debate. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research,* 7(4), pp. 397-401.

SHETTY, N., SHEMKO, M., VAZ, M. and D'SOUZA, G., 2006. An epidemiological evaluation of risk factors for tuberculosis in South India: a matched case control study. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease,* 10(1), pp. 80-86.

SHILLCUTT, S.D., WALKER, D.G., GOODMAN, C.A. and MILLS, A.J., 2009. Cost effectiveness in low- and middle-income countries: a review of the debates surrounding decision rules. *PharmacoEconomics,* 27(11), pp. 903-917.

SMITH, D. and GRAVELLE, H., 2000. *The Practice of Discounting Economic Evaluation of Health Care Interventions.* CHE Technical Paper Series 19. York: The University of York, Centre for Health Economics.

SONNENBERG, F.A. and BECK, J.R., 1993. Markov models in medical decision making: a practical guide. *Medical decision making: an international journal of the Society for Medical Decision Making,* 13(4), pp. 322-338.

STERNE, J.A., RODRIGUES, L.C. and GUEDES, I.N., 1998. Does the efficacy of BCG decline with time since vaccination? *The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease,* 2(3), pp. 200-207.

SWAMINATHAN, S. and REKHA, B., 2010. Pediatric tuberculosis: global overview and challenges. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America,* 50 Suppl 3, pp. S184-94.

TAMERIS, M.D., HATHERILL, M., LANDRY, B.S., SCRIBA, T.J., SNOWDEN, M.A., LOCKHART, S., SHEA, J.E., MCCLAIN, J.B., HUSSEY, G.D., HANEKOM, W.A., MAHOMED, H., MCSHANE, H. and THE MVA85A 020 TRIAL STUDY TEAM, 2013. Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial. *Lancet, Epub ahead of print*.

TORGERSON, D.J. and RAFTERY, J., 1999. Economic notes. Discounting. *BMJ (Clinical research ed.),* 319(7214), pp. 914-915.

TRUNZ, B.B., FINE, P. and DYE, C., 2006. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. *Lancet,* 367(9517), pp. 1173-1180.

TU, H.A., VU, H.D., ROZENBAUM, M.H., WOERDENBAG, H.J. and POSTMA, M.J., 2012. A review of the literature on the economics of vaccination against TB. *Expert review of vaccines,* 11(3), pp. 303-317.

UK AID, 2011. *Multilateral Aid Review: Ensuring Maximum Value for Money for UK AID through Multilateral Organizations.* London, UK: DFID.

UNICEF and WHO, July 14, 2012-last update, Immunization Summary: A Statistical Reference containing data through 2011, [Online]. Available: http://apps.who.int/immunization_monitoring/en/globalsummary/timeseries/tswucoveragebcg.htm [April 1, 2013].

VAN RIE, A., BEYERS, N., GIE, R.P., KUNNEKE, M., ZIETSMAN, L. and DONALD, P.R., 1999. Childhood tuberculosis in an urban population in South Africa: burden and risk factor. *Archives of Disease in Childhood,* 80(5), pp. 433-437.

VYNNYCKY, E. and FINE, P.E., 1997. The natural history of tuberculosis: the implications of age-dependent risks of disease and the role of reinfection. *Epidemiology and infection,* 119(2), pp. 183-201.

WEINSTEIN, M.C., O'BRIEN, B., HORNBERGER, J., JACKSON, J., JOHANNESSON, M., MCCABE, C., LUCE, B.R. and ISPOR TASK FORCE ON GOOD RESEARCH PRACTICES--MODELING STUDIES, 2003. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modeling Studies. *Value in health: the journal of the International Society for Pharmacoeconomics and Outcomes Research,* 6(1), pp. 9-17.

WORLD HEALTH ORGANIZATION, 2012. *The Global Tuberculosis Control Report 2012.* Geneva, Switzerland: World Health Organization.

WORLD HEALTH ORGANIZATION, 2011a. *Global Tuberculosis Control 2011.* Geneva: World Health Organization.

WORLD HEALTH ORGANIZATION, 2011b. *Guidelines for Intensified Tuberculosis Case-Finding and Isoniazid Preventive Therapy for People Living with HIV in Resource-Constrained Settings.* 978 92 4 150070 8. Geneva: World Health Organization.

WORLD HEALTH ORGANIZATION, 2006a. *Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children.* WHO/HTM/ TB/2006.371 & WHO/FCH/CAH/2006.7. Geneva: World Health Organization.

WORLD HEALTH ORGANIZATION, 2006b-last update, The STOP TB Strategy, [Online]. Available: http://www.who.int/tb/strategy/en/index.html [July 3, 2012].

WORLD HEALTH ORGANIZATION, 1997. *Guidelines for the Management of Drug-Resistant Tuberculosis.* WHO/TB/96.210 (Rev.1). Geneva: World Health Organization.

WORLD HEALTH ORGANIZATION CHOICE, 2012-last update, Cost-effectiveness thresholds. Available: http://www.who.int/choice/costs/CER_thresholds/en/index.html [July 26, 2012].

WORLD HEALTH ORGANIZATION: WEEKLY EPIDEMIOLOGICAL RECORD, 2007. Global Advisory Committee on Vaccine Safety, 29–30 November 2006: Safety of BCG vaccine in HIV-infected children. *Weekly Epidemiological Record,* 82(3), pp. 22.

WORLD HEALTH ORGANIZATION: WEEKLY EPIDEMIOLOGICAL RECORD, 2004. BCG Vaccine. *Weekly Epidemiological Record,* 79(4), pp. 27.

WORLD HEALTH ORGANIZATION, UNICEF and WORLD BANK, 2009. *State of the world's vaccines and immunization, 3rd ed.* Geneva: World Health Organization.

YOUNG, D. and DYE, C., 2006. The development and impact of tuberculosis vaccines. *Cell,* 124(4), pp. 683-687.

ZIV, E., DALEY, C.L. and BLOWER, S., 2004. Potential public health impact of new tuberculosis vaccines. *Emerging infectious diseases,* 10(9), pp. 1529-1535.

ZUMLA, A., RAVIGLIONE, M., HAFNER, R. and VON REYN, C.F., 2013. Tuberculosis. *The New England journal of medicine,* 368(8), pp. 745-755.

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, reinfected, 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

Consistent with recommendations and published studies, all future costs and outcomes were discounted at 3% (Weinstein, Siegel et al. 1996, Severens, Milne 2004, Torgerson, Raftery 1999, Langer, Holle et al. 2012, Smith, Gravelle 2000).

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

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

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

Parameters	Value	Range	References
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 opinion[1]
Risk of dying from "other causes"			
0–1 years	0.04295312		• Electronic database (World Health Organization Global Health Observatory (GHO) 2012) and adjusted to remove the risk of dying from TB • Expert opinion[1]
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 (%)			
0–2 years	54.1929		• Electronic database (Provincial Government Western Cape Department of Health 2012) and calculated assuming an ARI of 3% • Expert opinion[1]
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.

Parameters	Value	Range	References
Risk of death from pulmonary TB (%)			
< 3 years	0.74952		• Electronic databases (Provincial Government Western Cape Department of Health 2012, Statistics South Africa 2012b) • Calculated using average for 2005-2009 and e-TB data • Expert opinion[1]
3-5 years	0.09120		
> 6 years	0.58766		
Risk of death from miliary TB (%)			
< 3 years	23.52941		
3-5 years	9.09091		
> 6 years	16.66667		
Risk of death from TB meningitis (%)			
< 3 years	25.00000		
3-5 years	26.66667		
> 6 years	20.00000		
MVA85A efficacy against TB disease (%)	17.3	12.3 – 22.3	• Published literature (Tameris, Hatherill et al. 2013)
Up-take BCG (%)	99.0	99.0 – 99.5	• Published literature (Corrigall, Coetzee et al. 2008, Department of Health: Republic of South Africa 2011)
Up-take MVA85A	85.0	76.4 – 89.5	• Calculated
Drop-out rate DTP3 to MCV	14.0	9.5 – 23.1	• Published literature and electronic database (Saloojeei, Bamfordii 2006, Health Systems Trust 2007) • Expert opinion[1]
Discount rate outcomes (%)	3	0 – 6	• Published literature (Weinstein, Siegel et al. 1996, Severens, Milne 2004, Torgerson, Raftery 1999, Langer, Holle et al. 2012, Smith, Gravelle 2000)
Discount rate costs (%)	3	0 – 6	

[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

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

[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

Strategy	10-year costs (USD 2012)	Absolute Number of TB cases	Absolute Number of TB deaths	ICER Per TB case averted (USD 2012)	ICER Per TB deaths averted (USD 2012)
BASE CASE RESULTS					
Discounted (3%)					
BCG alone	84.17	0.09101	0.0003501817		
plus MVA85A	98.23	0.07828	0.0003006626	1,105	284,017
Undiscounted					
BCG alone	97.65	0.10627	0.0004174069		
plus MVA85A	109.80	0.09138	0.0003583168	816	205,603
Discounted (6%)					
BCG alone	73.53	0.07885	0.0002969804		
plus MVA85A	89.10	0.06785	0.0002550313	1416	371,271

Table 4: Effect of differing assumptions on the base-case ICER

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

[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)

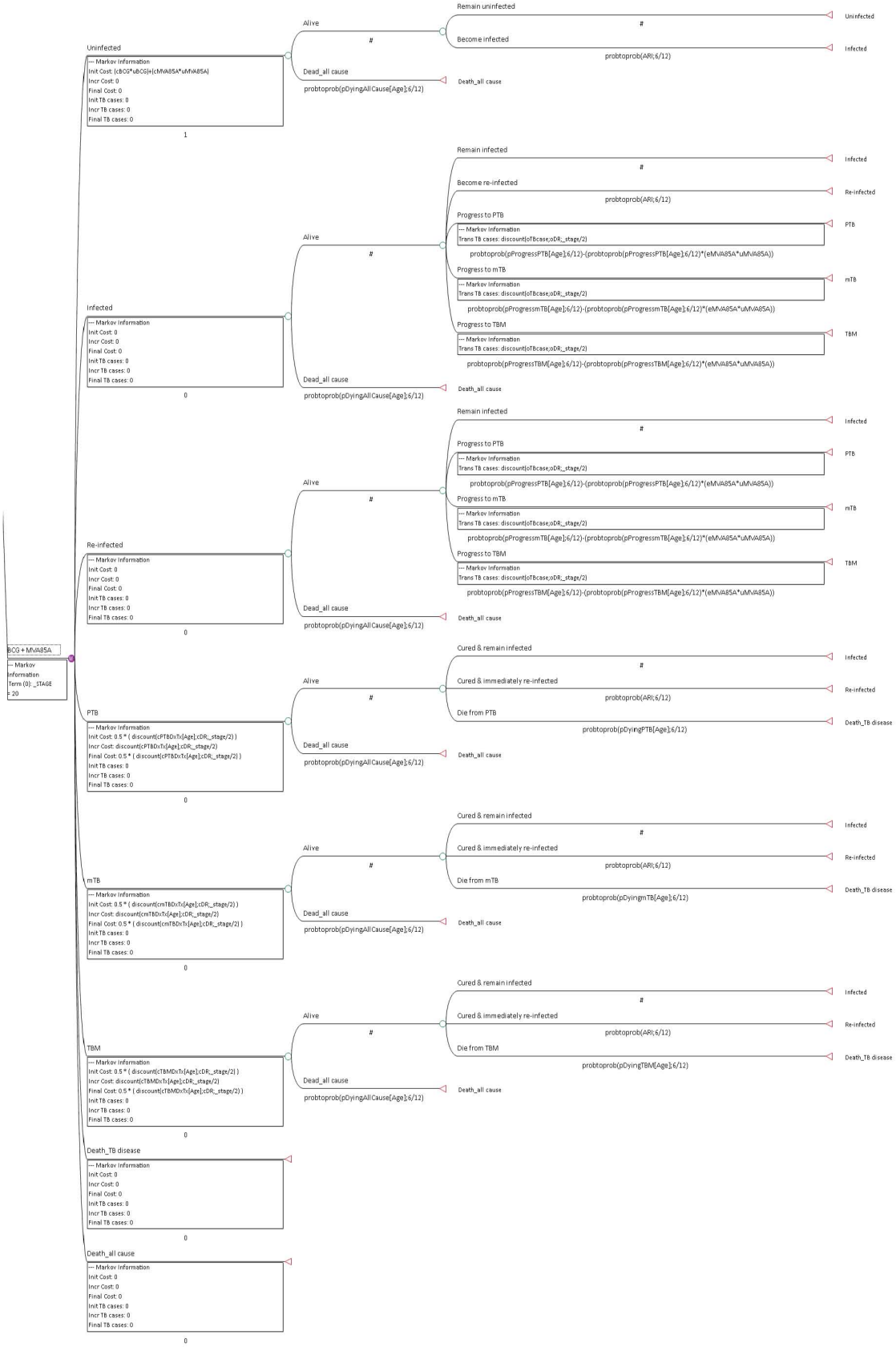
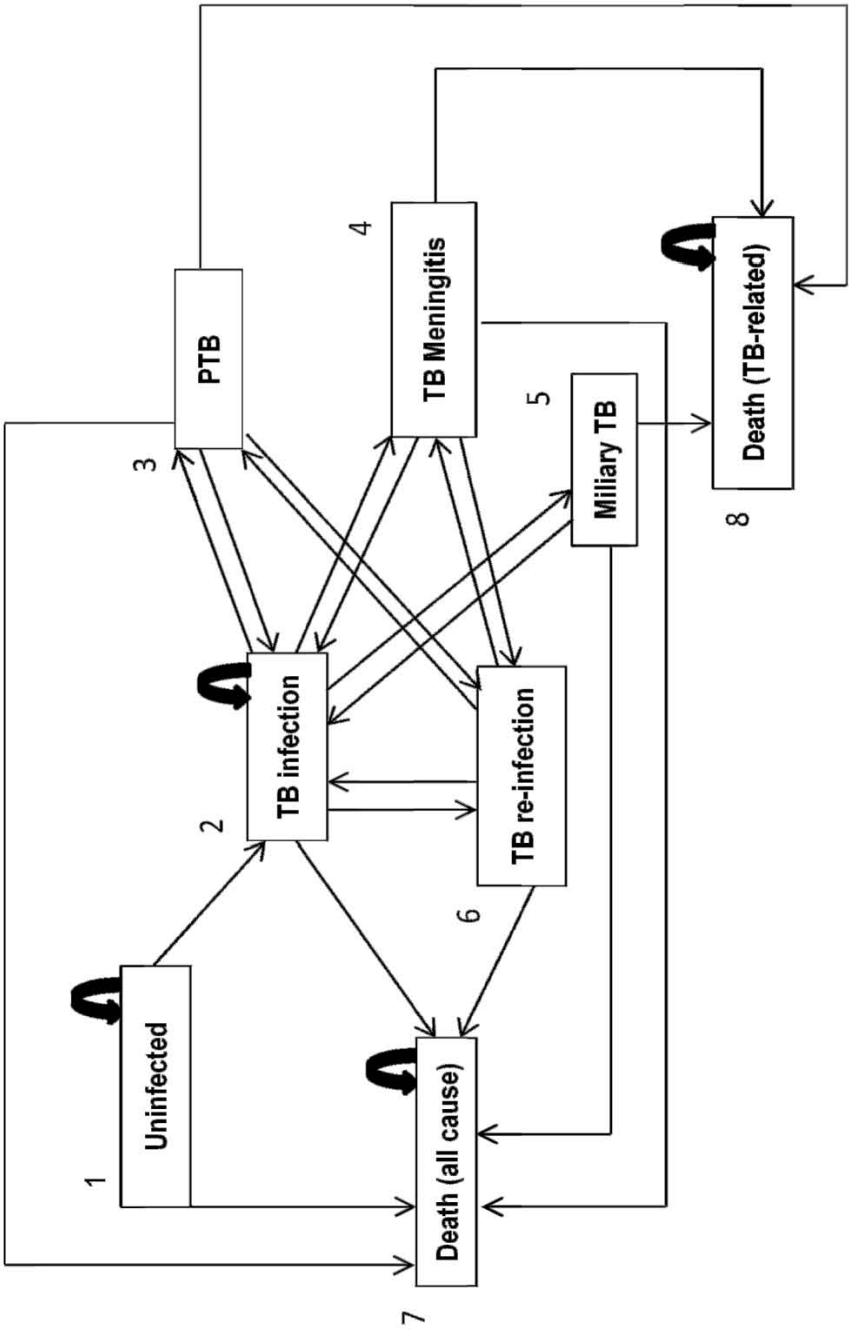


Figure 2: Health States and Possible Transitions (State Diagram)



References

ABU-RADDAD, L.J., SABATELLI, L., ACHTERBERG, J.T., SUGIMOTO, J.D., LONGINI, I.M.,JR, DYE, C. and HALLORAN, M.E., 2009. Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics. *Proceedings of the National Academy of Sciences of the United States of America,* **106**(33), pp. 13980-13985.

ARNOT, M. and HAYES, H., 2012. *BCG and TB medicine tenders and treatment guidelines.* Cape Town: Provincial Government of the Western Cape, Department of Health.

BREWER, T.F., 2000. Preventing tuberculosis with bacillus Calmette-Guerin vaccine: a meta-analysis of the literature. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America,* **31 Suppl 3**, pp. S64-7.

COLDITZ, G.A., BERKEY, C.S., MOSTELLER, F., BREWER, T.F., WILSON, M.E., BURDICK, E. and FINEBERG, H.V., 1995. The efficacy of bacillus Calmette-Guerin vaccination of newborns and infants in the prevention of tuberculosis: meta-analyses of the published literature. *Pediatrics,* **96**(1 Pt 1), pp. 29-35.

COLDITZ, G.A., BREWER, T.F., BERKEY, C.S., WILSON, M.E., BURDICK, E., FINEBERG, H.V. and MOSTELLER, F., 1994. Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature. *JAMA : the journal of the American Medical Association,* **271**(9), pp. 698-702.

CORRIGALL, J., COETZEE, D. and CAMERON, N., 2008. Is the Western Cape at risk of an outbreak of preventable childhood diseases? Lessons from an evaluation of routine immunisation coverage. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde,* **98**(1), pp. 41-45.

DAY, C., BARRON, P., MASSYN, N., PADARATH, A. and ENGLISH, R., eds, 2012. *District Health Barometer 2010/2011.* Durban: Health Systems Trust.

DEPARTMENT OF HEALTH: REPUBLIC OF SOUTH AFRICA, 2011. *Annual Report 2010/11.* Pretoria, South Africa: Department of Health.

DONALD, P.R., 2002. Childhood tuberculosis: out of control? *Current opinion in pulmonary medicine,* **8**(3), pp. 178-182.

DRUMMOND, M.F., 2005. *Methods for the economic evaluation of health care programmes.* 3 edn. Oxford ; New York: Oxford University Press.

DYE, C., GARNETT, G.P., SLEEMAN, K. and WILLIAMS, B.G., 1998. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. Directly observed short-course therapy. *Lancet,* **352**(9144), pp. 1886-1891.

FINE, P.E., 1995. Variation in protection by BCG: implications of and for heterologous immunity. *Lancet,* **346**(8986), pp. 1339-1345.

HEALTH SYSTEMS TRUST, July, 2007-last update, Immunisation drop out rate (DTP3-measles), [Online]. Available: http://indicators.hst.org.za/healthstats/239/data [May 18, 2013].

KABRA, S.K., LODHA, R. and SETH, V., 2004. Some current concepts on childhood tuberculosis. *The Indian journal of medical research,* **120**(4), pp. 387-397.

KRITZINGER, F.E., DEN BOON, S., VERVER, S., ENARSON, D.A., LOMBARD, C.J., BORGDORFF, M.W., GIE, R.P. and BEYERS, N., 2009. No decrease in annual risk of tuberculosis infection in endemic area in Cape Town, South Africa. *Tropical medicine & international health : TM & IH,* **14**(2), pp. 136-142.

LANGER, A., HOLLE, R. and JOHN, J., 2012. Specific guidelines for assessing and improving the methodological quality of economic evaluations of newborn screening. *BMC health services research,* **12**, pp. 300.

LAWN, S.D. and ZUMLA, A.I., 2011. Tuberculosis. *The Lancet,* **378**(9785), pp. 57-72.

MANDALAKAS, A.M., HESSELING, A.C., GIE, R.P., SCHAAF, H.S., MARAIS, B.J. and SINANOVIC, E., 2013. Modelling the cost-effectiveness of strategies to prevent tuberculosis in child contacts in a high-burden setting. *Thorax,* **68**(3), pp. 247-255.

MCSHANE, H., 2011. Tuberculosis vaccines: beyond bacille Calmette-Guerin. *Philosophical transactions of the Royal Society of London.Series B, Biological sciences,* **366**(1579), pp. 2782-2789.

MIDDELKOOP, K., BEKKER, L., MYER, L., DAWSON, R. and WOOD, R., 2008. Rates of Tuberculosis Transmission to Children and Adolescents in a Community with a High Prevalence of HIV Infection among Adults. *Clinical Infectious Diseases,* **47**(3), pp. 349-355.

NELSON, L.J. and WELLS, C.D., 2004. Global epidemiology of childhood tuberculosis. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease,* **8**(5), pp. 636-647.

ODUTOLA, A.A., OWOLABI, O.A., OWIAFE, P.K., MCSHANE, H. and OTA, M.O., 2012. A new TB vaccine, MVA85A, induces durable antigen-specific responses 14 months after vaccination in African infants. *Vaccine,* **30**(38), pp. 5591-5594.

PROVINCIAL GOVERNMENT WESTERN CAPE DEPARTMENT OF HEALTH, 2012. *e-TB register 2008.* Electronic Database. Cape Town: Provincial Government Western Cape Department of Health.

RODRIGUES, L.C., DIWAN, V.K. and WHEELER, J.G., 1993. Protective effect of BCG against tuberculous meningitis and miliary tuberculosis: a meta-analysis. *International journal of epidemiology,* **22**(6), pp. 1154-1158.

SALOOJEEI, H. and BAMFORDII, L., 2006. Chapter 11: Key Childhood Health Promotion and Disease Prevention Programmes. In: P. IJUMBA and A. PADARATH, eds, *South African Health Review 2006.* Durban: Health Systems Trust.

SCRIBA, T.J., TAMERIS, M., MANSOOR, N., SMIT, E., VAN DER MERWE, L., MAUFF, K., HUGHES, E.J., MOYO, S., BRITTAIN, N., LAWRIE, A., MULENGA, H., DE KOCK, M., GELDERBLOEM, S., VELDSMAN, A., HATHERILL, M., GELDENHUYS, H., HILL, A.V., HUSSEY, G.D., MAHOMED, H., HANEKOM, W.A. and MCSHANE, H., 2011. Dose-finding study of the novel tuberculosis vaccine, MVA85A, in healthy BCG-vaccinated infants. *The Journal of infectious diseases,* **203**(12), pp. 1832-1843.

SEVERENS, J.L. and MILNE, R.J., 2004. Discounting health outcomes in economic evaluation: the ongoing debate. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research,* **7**(4), pp. 397-401.

SHANAUBE, K., SISMANIDIS, C., AYLES, H., BEYERS, N., SCHAAP, A., LAWRENCE, K.A., BARKER, A. and GODFREY-FAUSSETT, P., 2009. Annual risk of tuberculous infection using different methods in communities with a high prevalence of TB and HIV in Zambia and South Africa. *PloS one,* **4**(11), pp. e7749.

SMITH, D. and GRAVELLE, H., 2000. *The Practice of Discounting Economic Evaluation of Health Care Interventions.* CHE Technical Paper Series 19. York: The University of York, Centre for Health Economics.

STATISTICS SOUTH AFRICA, 2012a. *Consumer Price Index (CPI).* P0141. Pretoria: Statistics South Africa.

STATISTICS SOUTH AFRICA, 2012b. *Western Cape TB Mortality Data Children 0-10 years (2005-2009).* Electronic Database edn. Pretoria: Statistics South Africa.

SWAMINATHAN, S. and REKHA, B., 2010. Pediatric tuberculosis: global overview and challenges. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America,* **50 Suppl 3**, pp. S184-94.

TAMERIS, M.D., HATHERILL, M., LANDRY, B.S., SCRIBA, T.J., SNOWDEN, M.A., LOCKHART, S., SHEA, J.E., MCCLAIN, J.B., HUSSEY, G.D., HANEKOM, W.A., MAHOMED, H., MCSHANE, H. and THE MVA85A 020 TRIAL STUDY TEAM, 2013. Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial. *Lancet, Epub ahead of print*.

TORGERSON, D.J. and RAFTERY, J., 1999. Economic notes. Discounting. *BMJ (Clinical research ed.),* **319**(7214), pp. 914-915.

TSENG, C.L., OXLADE, O., MENZIES, D., ASPLER, A. and SCHWARTZMAN, K., 2011. Cost-effectiveness of novel vaccines for tuberculosis control: a decision analysis study. *BMC public health,* **11**, pp. 55.

VAN RIE, A., BEYERS, N., GIE, R.P., KUNNEKE, M., ZIETSMAN, L. and DONALD, P.R., 1999. Childhood tuberculosis in an urban population in South Africa: burden and risk factor. *Archives of Disease in Childhood,* **80**(5), pp. 433-437.

VON ZEIL, M., 2012. *Childhood TB Treatment guidelines, practice guidelines to accomodate TB medicines on tender.* Cape Town: City of Cape Town, Department of Health.

WEINSTEIN, M.C., SIEGEL, J.E., GOLD, M.R., KAMLET, M.S. and RUSSELL, L.B., 1996. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. *JAMA: the journal of the American Medical Association,* **276**(15), pp. 1253-1258.

WOOD, R., LIANG, H., WU, H., MIDDELKOOP, K., ONI, T., RANGAKA, M.X., WILKINSON, R.J., BEKKER, L.G. and LAWN, S.D., 2010. Changing prevalence of tuberculosis infection with increasing age in high-burden townships in South Africa. *The international journal of tuberculosis and lung disease: the official journal of the International Union against Tuberculosis and Lung Disease,* **14**(4), pp. 406-412.

WORLD BANK, April 16, 2013-last update, World Development Indicators, 2011, [Online]. Available: http://data.worldbank.org/data-catalog/world-development-indicators [May 19, 2013].

WORLD HEALTH ORGANIZATION, 2012. *The Global Tuberculosis Control Report 2012.* Geneva, Switzerland: World Health Organization.

WORLD HEALTH ORGANIZATION CHOICE, 2012-last update, Cost-effectiveness thresholds. Available: http://www.who.int/choice/costs/CER_thresholds/en/index.html [July 26, 2012].

WORLD HEALTH ORGANIZATION GLOBAL HEALTH OBSERVATORY (GHO), 2012. *South Africa Life-Tables 2009.* Electronic Database edn. Geneva: World Health Organization.

YOUNG, D. and DYE, C., 2006. The development and impact of tuberculosis vaccines. *Cell,* **124**(4), pp. 683-687.

ZIV, E., DALEY, C.L. and BLOWER, S., 2004. Potential public health impact of new tuberculosis vaccines. *Emerging infectious diseases,* **10**(9), pp. 1529-1535.

Part D

APPENDICES

Appendix 1: Ethics approval

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

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 Signature removed

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.

s.thomas

Appendix 2: Journal instructions

COST EFFECTIVENESS AND RESOURCE ALLOCATION

BioMed Central IMPACT FACTOR 1.68

Instructions for authors

Research Articles

Submission process | Preparing main manuscript text | Preparing illustrations and figures | Preparing tables | Preparing additional files | Style and language

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Preparing main manuscript text

General guidelines of the journal's style and language are given below.

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Manuscripts for Research Articles submitted to *Cost Effectiveness and Resource Allocation* should be divided into the following sections (in this order):

Title page
Abstract
Keywords
Background
Methods
Results and discussion
Conclusions
List of abbreviations used (if any)
Competing interests
Authors' contributions
Authors' information
Acknowledgements
Endnotes
References
Illustrations and figures (if any)
Tables and captions
Preparing additional files

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Book with institutional author
Advisory Committee on Genetic Modification: ***Annual Report.*** London; 1999.

PhD thesis
Kohavi R: **Wrappers for performance enhancement and oblivious decision graphs.** *PhD thesis.* Stanford University, Computer Science Department; 1995.

Link / URL
The Mouse Tumor Biology Database [http://tumor.informatics.jax.org/mtbwi/index.do]

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Appendix 3: Markov model structure and inputs in TreeAge® 2012

Page

Figure 1: Decision node and two strategies being compared

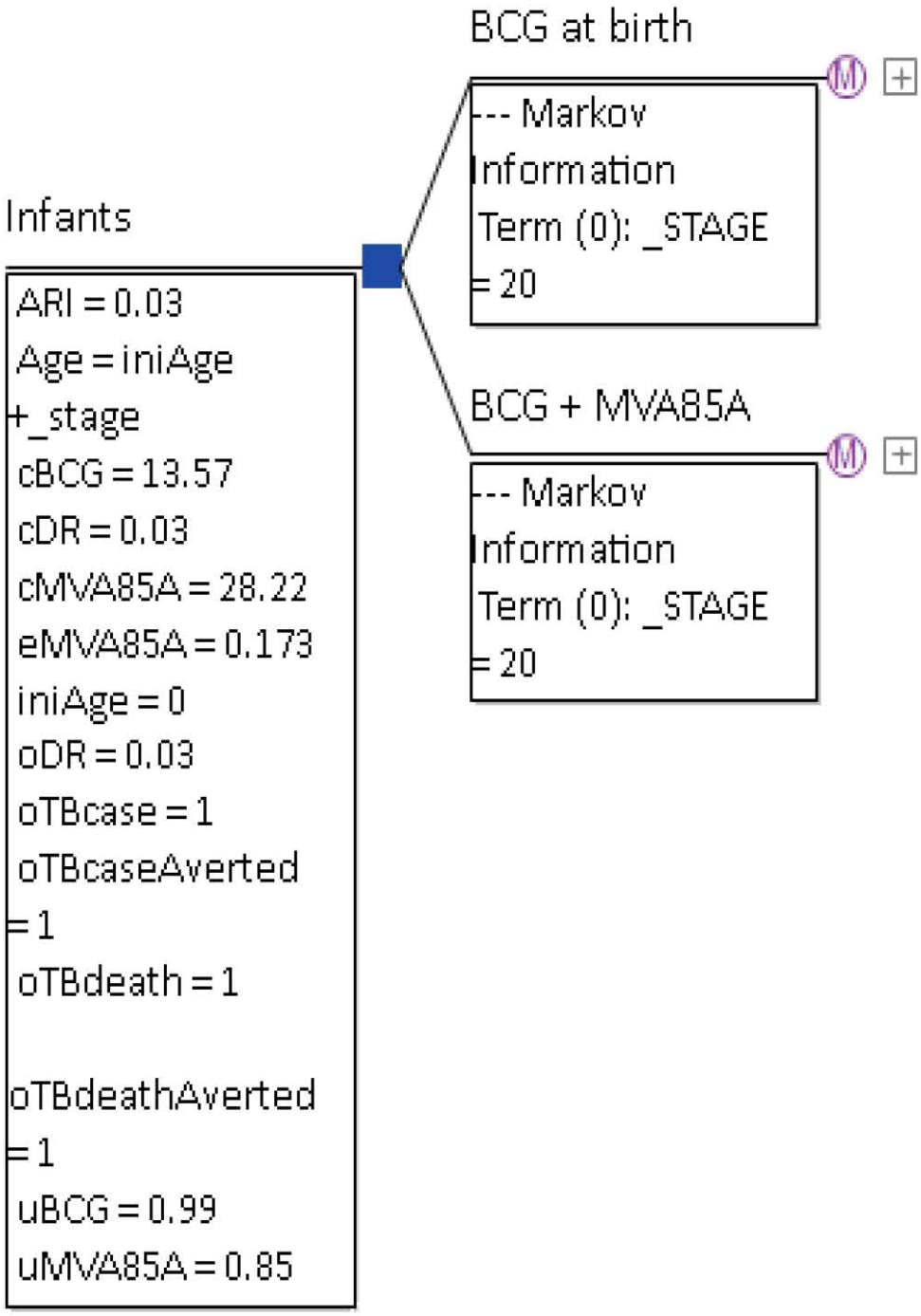


Figure 2: BCG arm

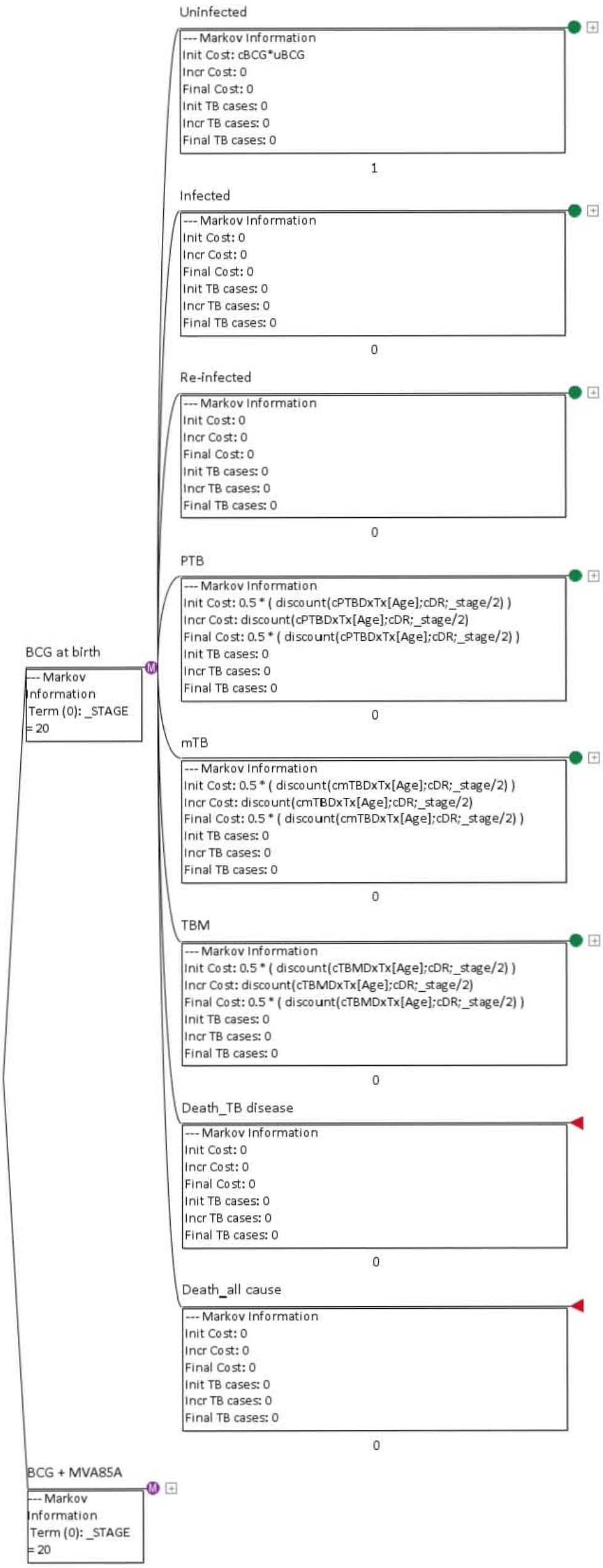


Figure 3: BCG + MVA85A arm

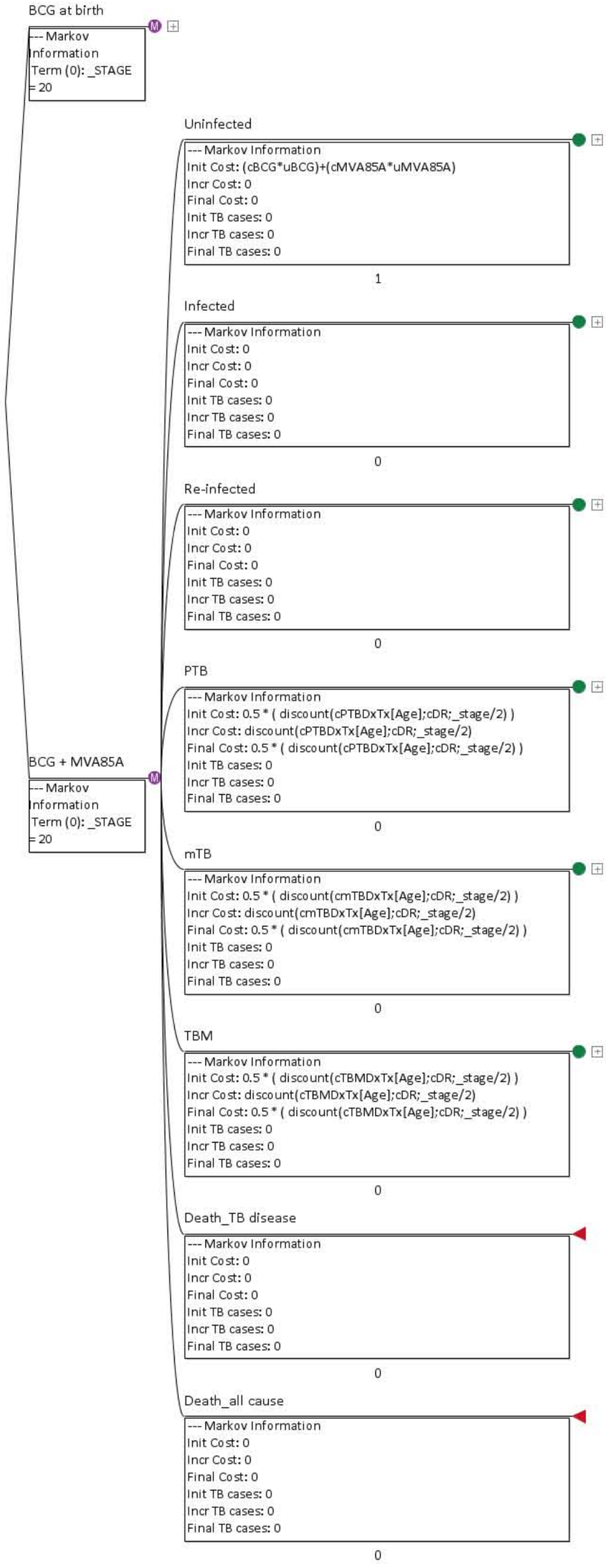


Figure 4a: BCG arm_Number of TB cases

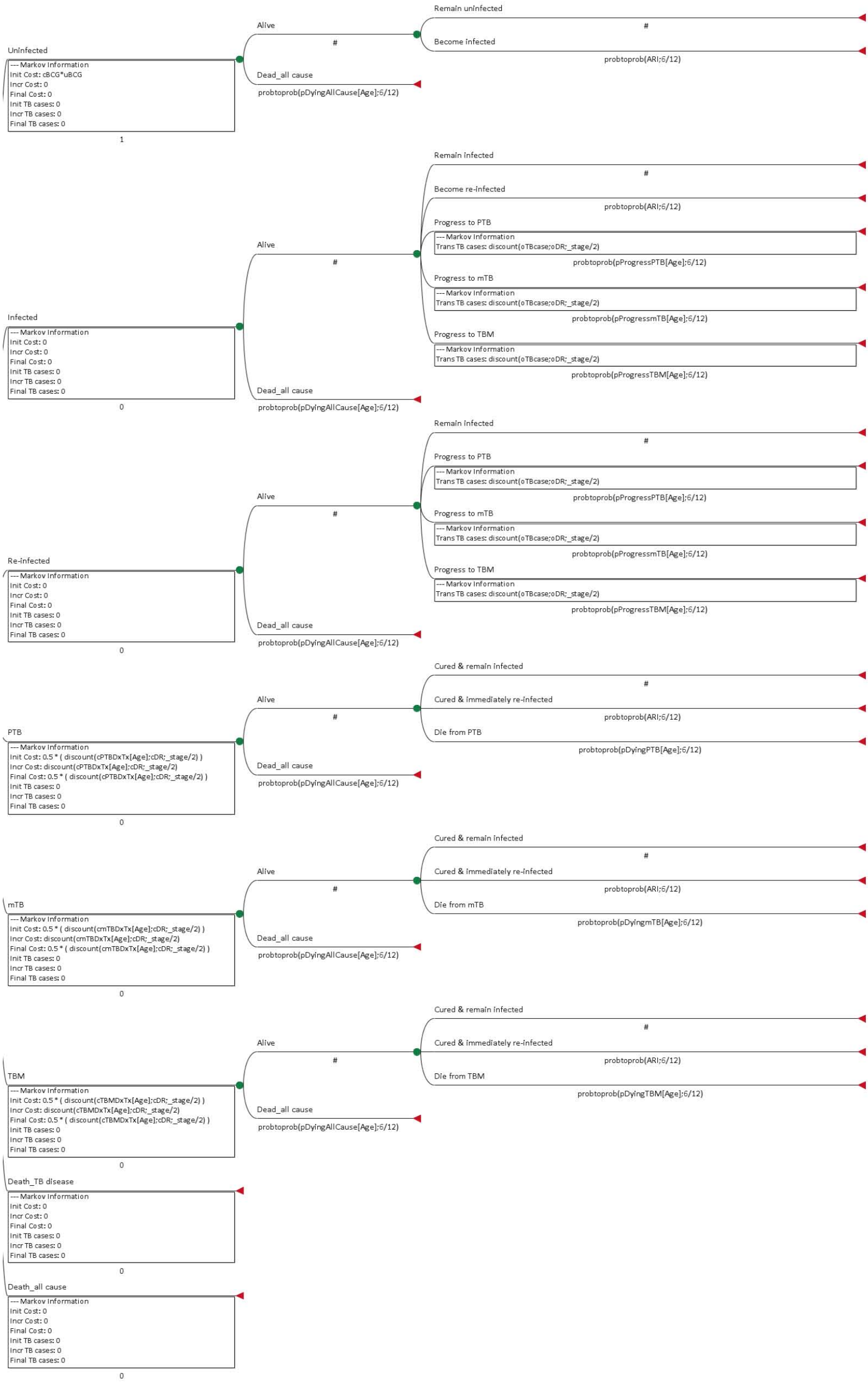


Figure 4b: BCG arm_Number of TB deaths

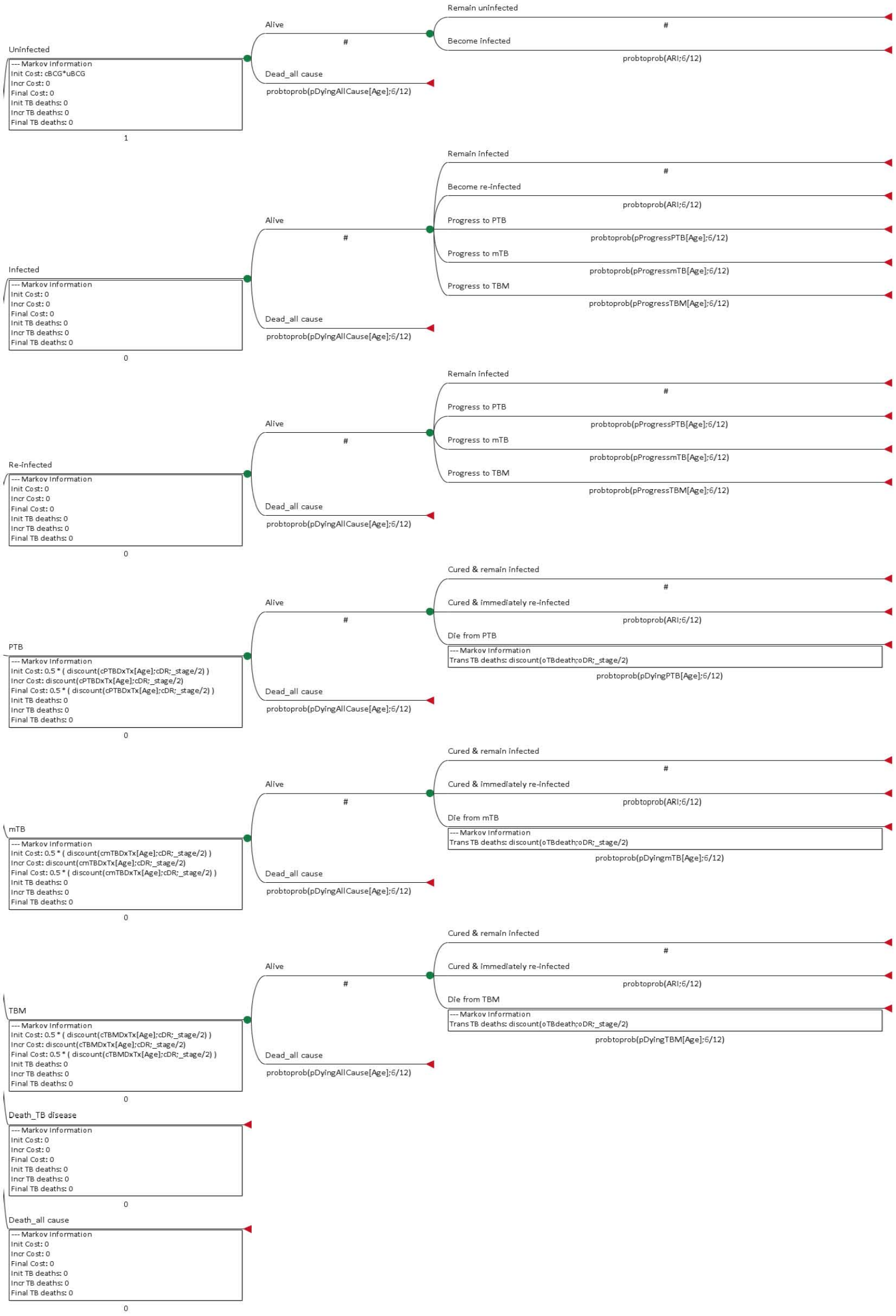


Figure 5a: BCG + MVA85A arm_Number of TB cases

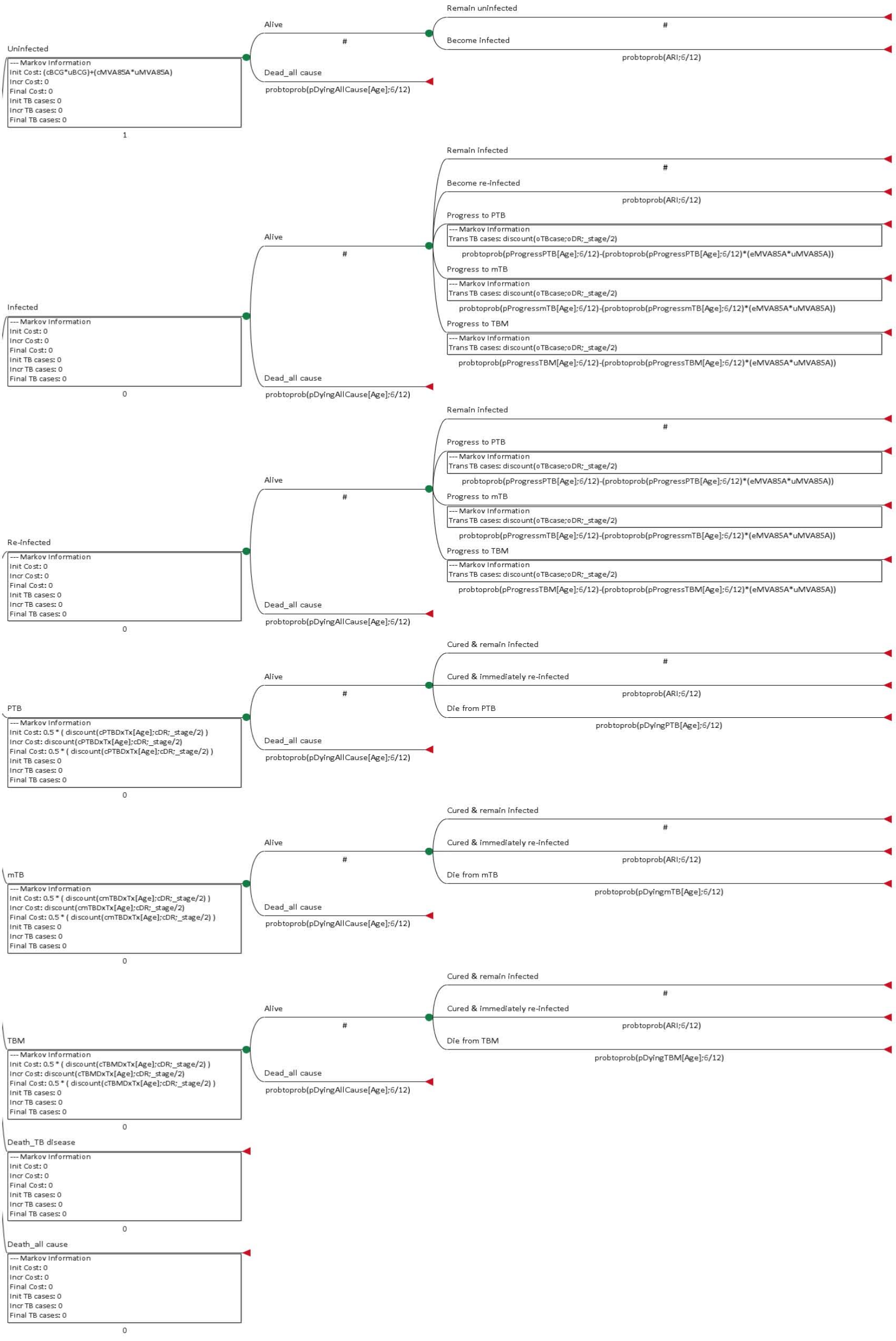
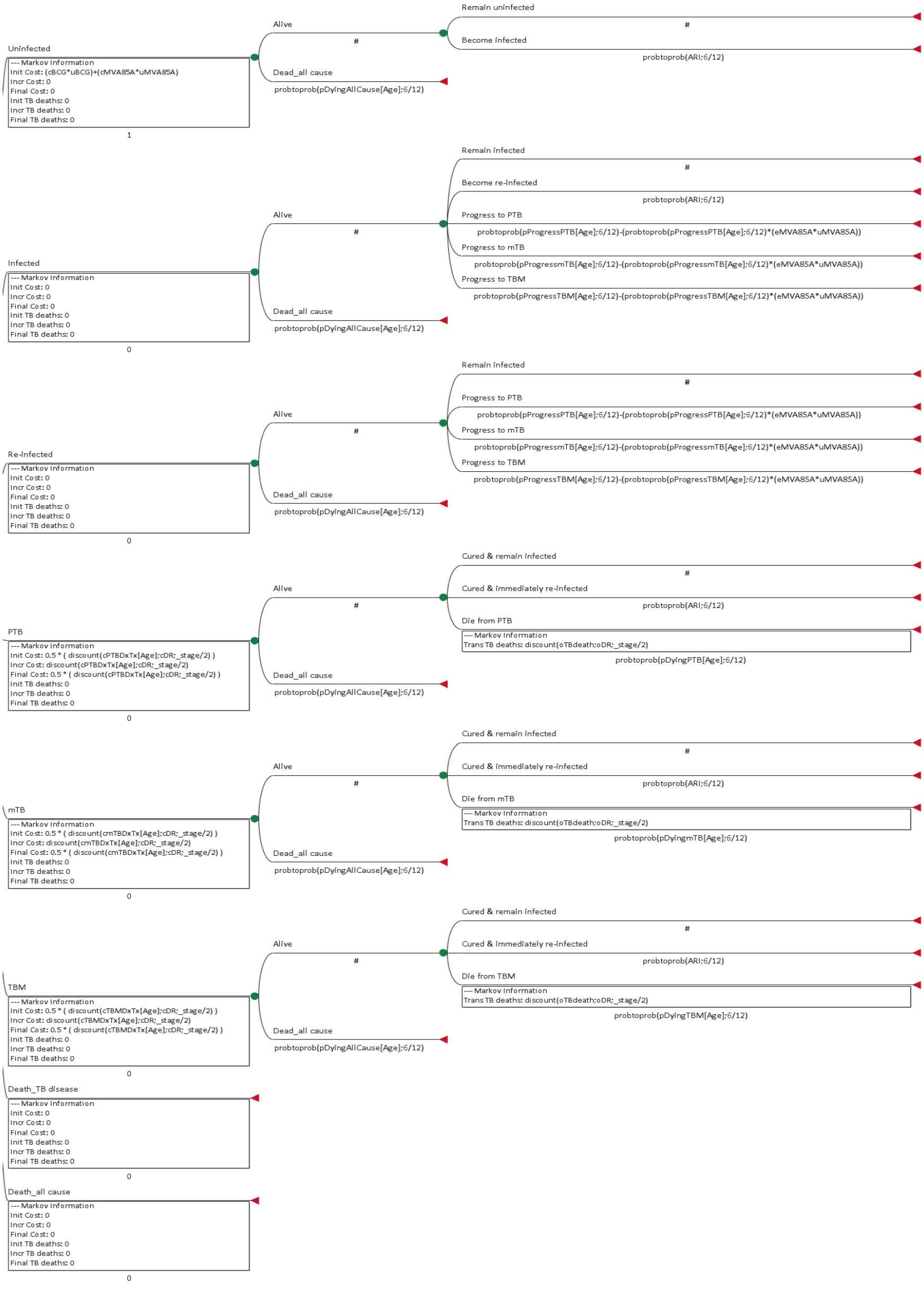


Figure 5b: BCG + MVA85A arm_Number of TB deaths



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[1]. 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***

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

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

LIENHARDT, C., GLAZIOU, P., UPLEKAR, M., LONNROTH, K., GETAHUN, H. and RAVIGLIONE, M., 2012. Global tuberculosis control: lessons learnt and future prospects. *Nature reviews.Microbiology,* **10**(6), pp. 407-416.

MANDALAKAS, A.M., HESSELING, A.C., GIE, R.P., SCHAAF, H.S., MARAIS, B.J. and SINANOVIC, E., 2013. Modelling the cost-effectiveness of strategies to prevent tuberculosis in child contacts in a high-burden setting. *Thorax,* **68**(3), pp. 247-255.

PROVINCIAL GOVERNMENT WESTERN CAPE DEPARTMENT OF HEALTH, 2012. *e-TB register 2008.* Electronic Database. Cape Town: Provincial Government Western Cape Department of Health.

STATISTICS SOUTH AFRICA, 2012. *Western Cape TB Mortality Data Children 0-10 years (2005-2009).* Electronic Database. Pretoria: Statistics South Africa.

TAMERIS, M.D., HATHERILL, M., LANDRY, B.S., SCRIBA, T.J., SNOWDEN, M.A., LOCKHART, S., SHEA, J.E., MCCLAIN, J.B., HUSSEY, G.D., HANEKOM, W.A., MAHOMED, H., MCSHANE, H. and THE MVA85A 020 TRIAL STUDY TEAM, 2013. Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial. *Lancet, Epub ahead of print*.

WORLD HEALTH ORGANIZATION, 2012. *The Global Tuberculosis Control Report 2012.* Geneva, Switzerland: World Health Organization.

WORLD HEALTH ORGANIZATION GLOBAL HEALTH OBSERVATORY (GHO), 2012. *South Africa Life-Tables 2009.* Electronic Database edn. Geneva: World Health Organization.