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**Gordon Institute
of Business Science**
University of Pretoria

A framework for tuberculosis research and development expenditure based on the
return on investment criterion

Babalwa Jongihlati

Student Number: 12356019

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Abstract

Research and development (R&D) covering diseases that disproportionately affect developing nations is grossly inadequate. In particular it has been noted over a long period that governments of countries with high tuberculosis (TB) disease burden under invest in TB R&D, despite having 40% of the world's notified TB cases. For instance, South Africa's (SA) annual expenditure on TB R&D, of US\$1,2 million in 2012, is insignificant relative to its disease burden, of 1 003 per 100,000 population. New tools are required to stop TB; these tools require R&D investment.

However a recent report has noted that for the first time in eight years, global spending on TB R&D decreased in 2012 compared with the previous year. This drop in R&D investment threatens to undermine the possibility of any future insights from TB research. The important question remains: how can public investment in TB R&D be stimulated or incentivised, especially within those countries of high prevalence and sizeable R&D budgets (such as India, SA, China and Russia)?

In an attempt to answer such a question, this research followed a quantitative, case study methodology based on secondary data analysis of information from the World Health Organisation (WHO) and the SA National Strategic Plan (NSP) 2012-2016, looking at the costs associated with TB treatment in SA and identified areas of potential savings as a consequence of well directed R&D. For additional information on external funding and TB R&D investment, the study used the Organisation for Economic and Development (OECD) and Treatment Action Group (TAG) data. A return on investment estimation method for suitable R&D projects was then used to compute the optimal TB R&D investment range.

The results of the research show that there are higher returns on the optimization of TB drug regimens versus new drug development. The argument proposed by this research is that further TB R&D expenditure can be justified from a purely economic return on investment consideration, considering that expenditure of public funds on TB treatment is high and significant savings can be made through improvements to the current drug regimen optimisation. This report will help policy makers in increasing public health R&D expenditure from present levels to those targets set by the World Health Organisation's Consultative Expert Working Group (CEWG) and others. This return on investment will only be realised if public-funded R&D is focussed more directly on public health priorities.

Key Words

Health R&D

Return on Investment

Tuberculosis

Neglected Diseases

Declaration

I declare that this research project is my own work. It is submitted in partial fulfilment of the requirements for the degree of Master of Business Administration at the Gordon Institute of Business Science, University of Pretoria. It has not been submitted before for any degree or examination in any other University. I further declare that I have obtained the necessary authorisation and consent to carry out this research.

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Chapter 1 Introduction to the Research Problem

1.1 Research Topic

This research was designed to develop a methodological framework to determine the required public health research and development (R&D) expenditure based on a return on investment (RoI) criterion. The research builds a strong argument in favour of literature that supports higher expenditure in tuberculosis (TB) R&D investment, especially to develop new tools for diseases that primarily affect the poor and for which patents provide insufficient market incentives (Rottingen & Chamas, 2012). The research develops justifiable targets for national TB R&D investment, using TB research in South Africa (SA) as a case study. A RoI factor was used to determine the target for national TB R&D investment. The developed methodology will be useful to add to the work by Walwyn (2013) and the World Health Organisation's (WHO) Consultative Expert Working Group (CEWG) work in estimating the scale of a country's investment in TB R&D as a function of TB disease burden and per capita income. Even though TB research was used as an example, the designed methodological framework can be practical equally well to the broader therapeutic area of neglected diseases (Walwyn, 2013).

Estimating the return on health R&D investment is relatively new (September, 2003). As such, there are very few global studies that have assessed the return on investing in health R&D (September, 2003). A few studies have addressed the burden of disease but the direct link to savings made through R&D expenditure has not been extensively measured (September, 2003). Walwyn (2013) argues that high TB disease burden countries could realise a considerable return on investment from TB and other neglected disease R&D through savings to public expenditure as a consequence of better and improved diagnostics, drug regimens and vaccines. This research contributes to theory on the impact of increased R&D investment within mid-level developing countries.

This research focuses on the benefits and returns on investment of health R&D, which will be of value to policy-makers. It will also contribute to the national debate on health policy and health economics.

The development of a framework to calculate the potential return on investment for public health R&D programmes will help in increasing public health R&D expenditure from current levels to global goal targets. This return on investment will only be realised if public-

funded R&D is focussed more directly on public health priorities. Each year annual spending toward research for new and improved TB tools falls far from the \$2 billion global target defined by the Stop TB Partnership's Global Plan to Stop TB 2011–2015 (Jimenez-Levi, 2012). The Global Plan to Stop TB 2011-2015 sets out the goals and associated investments required in order to achieve the global targets for TB control (Logan, 2013).

R&D for new tools to treat, diagnose and prevent TB, especially multidrug-resistant TB (MDR-TB) is moving forward far too slowly (WHO, 2012). Current strategies and tools to prevent and control TB are becoming less and less effective (Jimenez-Levi, 2012). Much greater investment is needed in health R&D to ensure that patients have access to the best diagnostic tests and preventive and curative therapies. Jimenez Levi (2012) further states that a lack of investment and political will has resulted in a pipeline for new TB diagnostics, treatments and vaccines that is anaemic when compared to those for human immunodeficiency virus (HIV).

The current rise of drug resistant TB has added to the sense of urgency to global efforts to find new TB tools (Logan, 2013).

Despite some welcome increases in global R&D investment in recent years, it is agreed that research for the diseases that disproportionately affect developing countries are grossly inadequate (Nwaka *et al.*, 2010). There is a great need for more discussion on how developing countries, like South Africa, can build up their fragile health systems and develop their own capacity to conduct health research as every country benefits from having a strong health research policy (Whitworth, Kokwaro & Kinyanjui, 2008).

Governments need to strengthen their national health systems to ensure the realisation of the right to health (Mugabe, 2013). The rising treatment costs and R&D challenges put health-care budgets under immense strain. Given the strains on the health system, there is an increasing need for better alignment of funding (CEWG, 2012). Loddenkemper, Sotgiu and Mitnick (2012) suggest health economic analyses should be used to estimate the value and the economic impact of different healthcare interventions in order to adequately allocate public money and resources. However, the authors argue that instead, policy makers in the public sector adopt health economic evaluations to increase the efficacy of their choices to respond to public health issues. R&D should be a focus of health disease research, especially in high burden countries (Walwyn, 2013).

Mugabe (2013) highlights the threat to Africa's long-term economic growth and sustainability by high burden disease. African countries with particularly high burden diseases such as HIV have suffered up to a 1.7% reduced economic welfare per year. An example is that of Botswana, which has experienced more than a 5% decrease in economic welfare per year in the past decade due to HIV (Mugabe, 2013).

Returns on investments in R&D and other innovation assets are a subject of considerable interest to policy makers (Hall, Mairesse & Mohnen, 2011). This is because investment in R&D and innovation is expensive and one would like to be sure that there is a positive return. Policy makers are especially interested in the social or economy-wide returns to R&D investment, which can be greater or less than the private returns to individual firms (Hall *et al.*, 2011). Public policy makers have to choose goals, values and practices to improve social and economic welfare with the aim of making everyone better off (Hillman & Keim, 1995). Public policy makers are challenged to take into account the divergent views of interested parties (Hillman & Keim, 1995). When the public policy decision making process is evidence based, it is better informed, more effective and less expensive as the main aim is to improve decision making through rigorous analysis of policy options (Colebatch, 1988).

The present expenditure of public funds on health R&D is not linked directly to an improvement in the efficiency of health services provided by the state. The investment of public funds in health R&D is recognised as an important antecedent to the development of new health products or services by the private sector, the benefit from which accrues mainly to private health patients. As a consequence, the incentive for the public sector to invest directly in the development of new products and services to improve healthcare delivery or outcomes in the public sector is not widely recognised.

Public health remains largely neglected because even though the bulk of health R&D is financed by the public sector, the benefits accrue largely to private patients. As such, research to accelerate global TB R&D is gravely underfunded (Jimenez-Levi, 2012). The scientific gains achieved in the last decade for drug, vaccine, and diagnostics development mean more resources are needed to see these new tools actually come to fruition (Jimenez-Levi, 2012).

1.2 Research Problem

The WHO (2012) report states that innovations that address factors covering diseases that affect developing nations are often biased against the poor as these innovations are often held back by underinvestment by the public sector and market failure. This is because governments in many low and middle income countries underinvest in public health R&D for various reasons, such as the perceived high risk/return ratio, and the lengthy and expensive process of developing a new product / diagnostic tool to the market (WHO, 2012).

Health R&D, when strategically targeted to cost-effective high priority R&D areas, is an investment with exceptional returns and the potential to alleviate the burden of illness and costs placed on the health system (September, 2003).

There have been positive efforts to tackle the above stated issues, including the establishment of diverse public–private product development partnerships like the Medicines for Malaria Venture (MMV) and Drugs for Neglected Diseases initiative (DNDi). The MMV is a not-for-profit public-private partnership which was established as a foundation with a mission to reduce the burden of malaria in disease-endemic countries by discovering, developing and facilitating the delivery of new, effective and affordable antimalarial drugs (MMV, 2013). The DNDi is a collaborative, non-profit drug R&D organisation that is developing new treatments for neglected diseases (DNDi, 2013)].

However, the above-mentioned efforts have only treated the symptoms exhibited by the system failures and not the root causes (Medecins Sans Frontieres (MSF), 2012).

This research was undertaken to address the following three problems:

- a) South Africa is reported to under invest public funds in TB R&D (Frick & Jimenez-Levi, 2013)
- b) There is no suitable methodological framework for determining national TB R&D expenditure. Little information is available to policymakers about the costs of diagnosing and treating TB, with even very recent analyses rely on unit-cost estimates made before the rollout of antiretroviral therapy for HIV (Rosen, 2013).

- c) As a consequence, even if the TB R&D expenditure were to be increased, we cannot say how much it should be increased.

The need for robust, low-cost and safe point-of-care diagnostics and drug treatments for various health diseases, such as TB, require dramatic increases in research investment to identify appropriate biomarkers and capitalise on technological breakthroughs to create innovative test platforms (Weyer *et al.*, 2012).

Figure 1.1 below outlines 2011 investment levels against the funding targets set by the Global Plan. The chart illustrates a somber reality about the global progress toward eliminating TB as a public health threat, with an annual funding gap of \$1.35 billion (Jimenez-Levi, 2012).

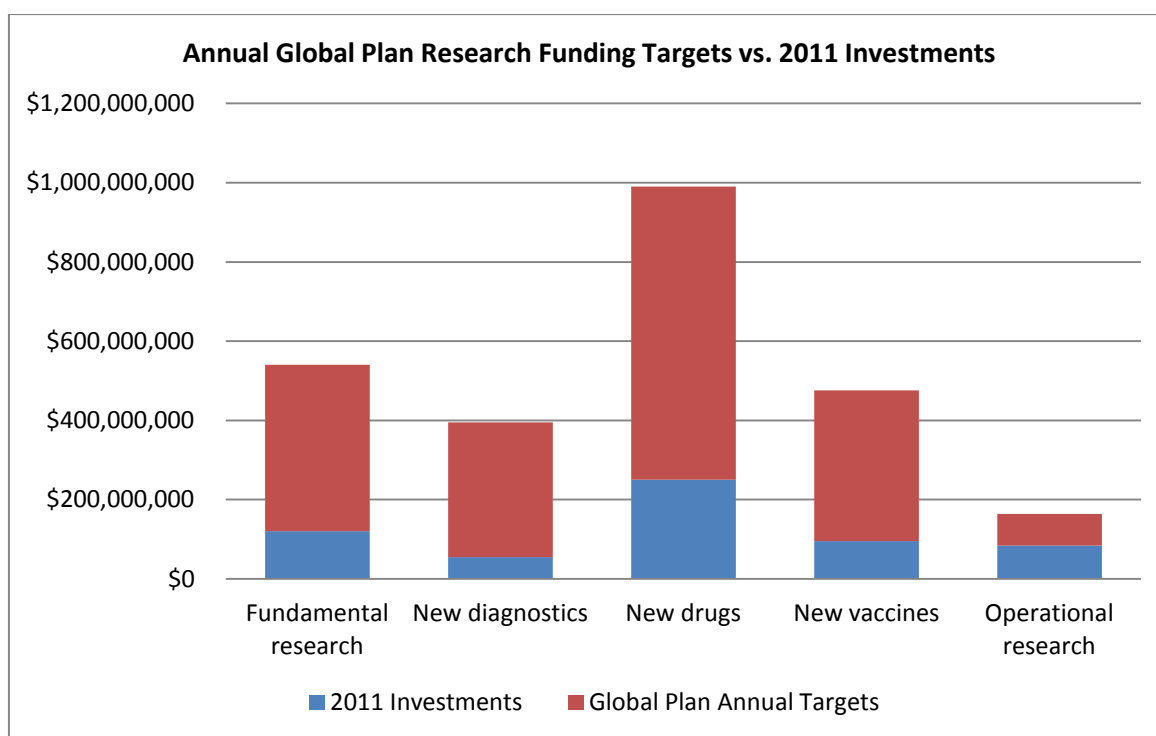


Figure 1.1 Annual Global Research Funding Targets vs. 2011 Investments.

Source: Jimenez-Levi, 2012

South Africa faces one of the world's worst epidemics of TB and drug-resistant TB. The country's decision to roll out Xpert TB/RIF (rifampicin) technology for diagnosing TB and rifampicin resistance has added greater urgency to the need for up-to-date cost estimates to use for policymaking and budgeting (Rosen, 2013). Xpert MTB/RIF is a rapid molecular test that can diagnose TB and rifampicin resistance within 100 minutes. South Africa is the

leader amongst low and middle income countries that have adopted the test (37% of purchased test) (WHO, 2012).

Numerous publications have stressed the dramatic increase of MDR and extensively drug-resistant TB (XDR-TB) in the world, confirming that drug-resistant TB is an important problem, especially as it is well known to be associated with a relatively low treatment success rate and a significant increase in treatment cost (Diel *et al.*, 2013; Pooran, Pieterse, Davids, Theron, 2013; Dheda, 2013). MDR-TB is defined as resistance to at least two of the most powerful first line anti-TB drugs, isoniazid and rifampicin. XDR-TB is adding resistance to any fluoroquinolone and at least one of the three injectable anti-TB drugs (amikacin, capreomycin or kanamycin) to MDR (Diel *et al.*, 2013). According to the WHO, 3.7% of the 8.7 million new TB cases in 2011 had MDR-TB and 58,000 cases had XDR-TB (WHO, 2012).

1.3. Research Objective

The first objective of this research was to evaluate the costs associated with TB disease management.

The second objective was to develop a methodologically sustainable framework based on a RoI criterion, to determine the required TB R&D expenditure. The framework contributes to ongoing efforts seeking to assess the relevance and impact of health R&D through innovations.

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1.4 Research Propositions

The two key propositions driving this research are that:

- a) Health R&D will reduce the disease burden and cost of treatment, through both direct and indirect economic benefits
- b) The greatest gains are to be made in the highest disease burden areas.

Chapter 2: Literature Review

2.1 Introduction

R&D is defined as systematic work undertaken in order to increase knowledge and the use of this knowledge to develop new tools and applications (Organisation for Economic Co-operation and Development (OECD), 1994). Health R&D is defined as a scientific inquiry into the nature and causes of diseases and subsequent use of scientific knowledge to develop vaccines, diagnostics and medicines (Mugabe, 2013). The WHO (2011) highlights the importance of knowledge production leading to health gain, as the key linkage between the two is often the impact that the results of research have on health-care policy. Health R&D is also critical in order to reduce the burden of disease and improve public health as it advances the understanding of specific diseases, thereby improving prevention, diagnosis, treatment, and reducing the costs of healthcare (Mugabe, 2013).

Medical research is a source of new growth and has done a considerable amount to extend work and life expectancy, first with the introduction of antibiotics and later with the introduction of new classes of drugs and medical devices (Stephan, 2010).

A health research system is located at the intersection between the health system and the research system of a country. In SA, the health system is the responsibility of the Department of Health whereas the research system falls under the Departments of Science and Technology, and Higher Education and Training (Senkubuge & Mayosi, 2013). The National Health Research Committee, which is a statutory body established in terms of the National Health Act (Act 61 of 2003), is located under the Department of Health and is mandated to ensure that there is coordination between the activities of public institutions (such as the Departments of Health, Science and Technology, and Higher Education and Training) in the development and management of the national health research system (Senkubuge & Mayosi, 2013).

2.3 Health Research and Development

Health R&D is acknowledged as a crucial element in improving health and stimulating economic development. It contributes to global knowledge about prevalent diseases in terms of prevention and treatment (Academy of Science of South Africa (ASSAf), 2009). Buxton, Hanney and Jones (2004) also acknowledge health R&D as an investment that plays a central role in addressing the prevention and control of diseases and conditions that afflict populations.

The knowledge produced by health research contributes to the improvement of the health of individuals and populations, especially when products are commercialised (Mugabe, 2013). This knowledge also contributes to the development of evidence-informed policies and the enhancement of performance of health systems (Senkubuge & Mayosi, 2013). It is crucial that health research includes a focus on local priorities (NSP, 2012-2016). The establishment of a local research agenda, linked more closely to the country's specific needs and in line with its strategic objectives and with the necessary funding is a critical step (NSP, 2012-2016). According to Mugabe (2013), Africa, compared to other regions, has not effectively invested in, nor reaped the benefits of, health R&D for health security, development and profit.

Senkubuge and Mayosi (2013) identify the two intrinsic goals of a health research system as the advancement of scientific knowledge and the utilisation of this knowledge to improve health and equity.

Botchkarev and Andru (2011) estimate that half of the past benefits in health span are due to health R&D – as opposed to public health awareness and prevention programmes. The National Institute of Health (NIH) report also states the U.S. nation has gained about one year of longevity every six years since 1990, due in large part to health R&D (Ehrlich, 2012). However, the health status of the African population remains behind that of populations in Europe and North America, as well as many other developing regions with similar affluence. This is independent of economic development, as measured by Gross Domestic Product (GDP) per capita (Nwaka *et al.*, 2010). In order to correct this, Pooran *et al.* (2013) recommend more accurate budget allocation methodology by policy makers for rational allocation of resources, to prioritise and inform future cost-effectiveness analyses.

Hall *et al.* (2011) conducted an in-depth literature review and economic research to determine the return on investing in R&D, the social rate of return and whether there are spill-overs. They concluded that the rates of return for R&D are positive in many countries, and usually higher than those for ordinary capital. The R&D executed in one country often triggers new avenues of research, inspire new research projects or finds new applications in other sectors or countries. This concept, defined as R&D spill-over, is very relevant for growth and development, because it lays the foundation for further knowledge creation and diffusion and is further intertwined with social R&D returns, as social returns are estimated to be substantially greater than private returns (Hall *et al.*, 2011).

Health research leads to direct cost savings in the healthcare system by means of new therapies that reduce either the number of patients needing treatment or the overall cost of treatment per patient (Buxton, Hanney, & Jones, 2004). Research based approaches that result in shorter and/or more effective treatments may also result in savings in non-medical direct costs, such as custodial care, transportation, special equipment, and community support programmes run by governments (Buxton, *et al.*, 2004).

Innovations in TB are needed to fuel discovery of drugs, vaccines and diagnostics, and to develop improved treatment and prevention regimens using current and new drugs (NSP, 2012-2016). The NSP on TB (2012–2016) is the strategic guide for the national response to TB for the next five years. The plan addresses the drivers of the TB epidemics and builds on the achievements of the previous NSPs to achieve its goals (NSP, 2012-2016).

The development of new drugs and regimes is expensive, time consuming and inherently high risk and can fail at any point along the lengthy development and stringent approval process (Walwyn, 2013). However, it is these exact conditions that make public R&D investment fundamental. While public health professionals highlight that prevention is better than cure, there is a need to keep pushing investments to develop new/better treatment drugs, along with diagnostic tests and vaccines for the patients who do become infected (Logan, 2013).

Countries that have a high TB disease burden have the most to gain from TB R&D, as a result of savings to national funds. The argument is made that new and better effective tools should lead to significant savings in TB management costs (Walwyn, 2013).

The benefits of health R&D are illustrated in Figure 2.1 below.

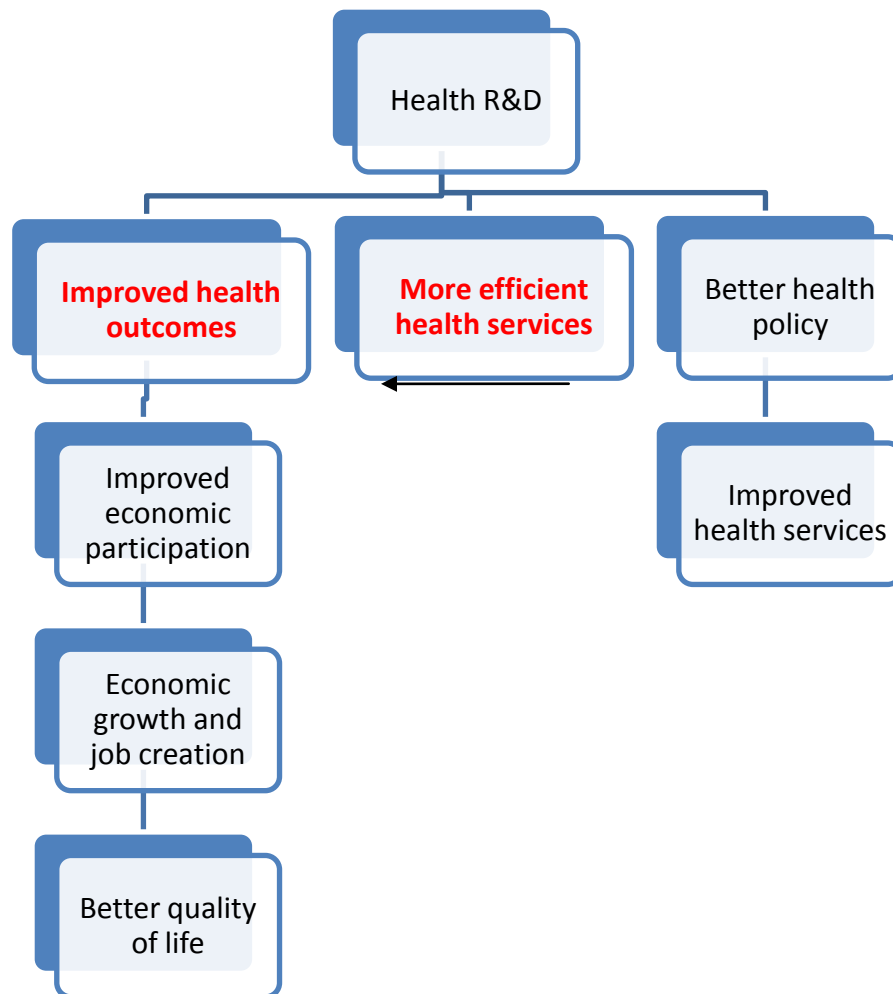


Figure 2.1 Health R&D Benefits.

2.3. Health Research and Development Funding

Governments have a moral obligation to fulfil human rights and protect the health of their own citizens (CEWG, 2012). The efforts of high income countries do not relieve developing countries of their responsibility towards their citizens (Walwyn, 2013). Adequate support for health research should remain a priority in the allocation of national funds within affected countries. While donor grants and external funding aid continue to be a critical funding source for health R&D, international evidence suggests that domestic funding for health services is the key to long-term sustainability (G-FINDER, 2011). Also, economic problems in donor countries since 2007 have put pressure on external resources, and scrutiny of value for money has increased (Floyd, Fitzpatrick, Pantoja, & Raviglione, 2013). Floyd *et al.* (2013) state that South Africa is amongst the list of high burden countries that could mobilise almost all the requisite resources from domestic sources whereas, in other low income high burden countries international donor funding is needed.

The MSF (2013) reports little private sector investment or activity in the field of neglected diseases. The report highlighted the failure of governments to adequately intervene and steer R&D towards the greatest needs, noting that governments of developing countries with high levels of neglected diseases have invested inadequately little towards neglected disease research (MSF, 2013). Philanthropic actors like the BMGF, Wellcome Trust, and Rockefeller Foundation play an increasingly large role in funding public/private partnerships, leading to concerns that governments are abdicating their responsibility (MSF, 2013).

Floyd *et al.* (2013) further report that much more funding is needed for a full response to the TB epidemic in low-income and middle-income countries, especially domestic resources from countries with a high disease burden and high, increasing political and economic profile including South Africa. A high TB burden equates to a high social and economic cost, especially to the national treasury since most countries (including South Africa) cover TB treatment within their respective public health programmes (Walwyn, 2013).

WHO began monitoring government and international donors for TB in 2002, which built on a system that was established in 1995 for yearly collection of data from national TB control programmes (Floyd *et al.*, 2013). Floyd *et al.* (2013) assessed long-term trends in

government and international donor funding for care and control of TB in low-income and middle-income countries. Their findings were that funding grew substantially between 2002 and 2011 and that domestic funding has underpinned progress in countries with a similar GDP to South Africa. International donor funding for TB control has also increased by 50% since 2006, from US\$ 0.4 billion to an expected US\$ 0.6 billion in 2012, but still falls far short of funding for malaria (US\$ 1.8 billion in 2009) and HIV (US\$ 6.9 billion in 2010) (WHO, 2011).

The Global Funding of Innovation for Neglected Diseases (G-FINDER) survey (funded by the Bill and Melinda Gates Foundation (BMGF) annually assesses global R&D funding for neglected diseases (G-FINDER, 2011). It surveys investments that meet the following three criteria:

- 1) Where the disease disproportionately affects the poor in developing countries
- 2) Where there is a need for new products or diagnostic tools and,
- 3) Where there is a market failure.

The latest G-FINDER survey report (2012) finding is that there has been an increase in funding from foundations, from US\$ 60 million in 1986 to US\$ 568 million in 2010. Of this, 80% of funds came from the philanthropic fund, the BMGF. The majority of these funds were towards product development partnerships (PDPs). A PDP is an innovative collaboration model for R&D for neglected diseases in the form of public-private partnerships (PPPs) (G-FINDER, 2011). PDPs are created from a desire to generate innovative approaches to alleviate the global burden of neglected diseases by taking the expertise and knowledge of both the private and public sectors, and exploiting each of their strengths to find the most efficient and effective solutions (G-FINDER, 2011).

The WHO and the Global Fund (2013) suggest for domestic contributions to cover the bulk of financing required for TB care and control in high burden countries. Countries that have a high TB prevalence and sizeable R&D budgets would need to have TB funding increases in line with economic growth and for increased political commitment (WHO, 2013). This is especially relevant for countries like South Africa that currently underperform in comparison to their ability to pay (WHO, 2013).

Figure 2.2 below shows that over 58% of the estimated US\$ 1.6 billion needed for donor financing is for WHO's African Region. The gaps for other WHO regions are: 12% in the European Region, 9% in the Western-Pacific Region, 10% in the Eastern-Mediterranean Region, 9% in the South-East Asia Region, and 2% in the Region of the Americas (WHO and The Global Fund, 2013).

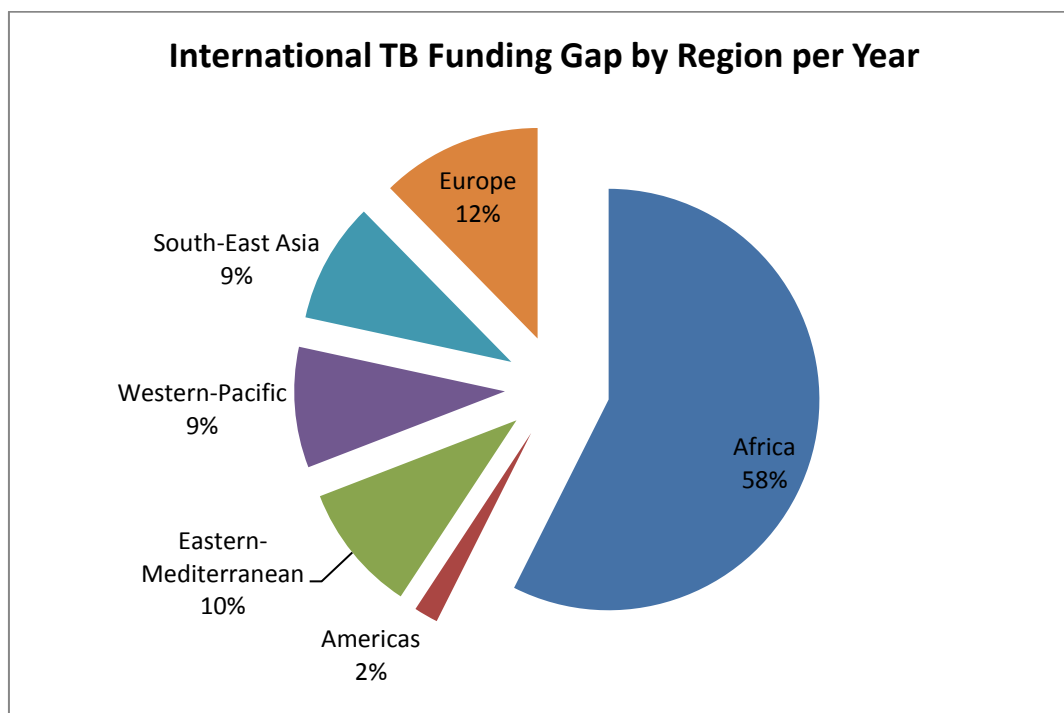


Figure 2.2 International Funding Gaps by Region per year.

(Source: WHO and the Global Fund, 2013)

In 2011, 81 donors invested \$649.6 million in TB R&D, an 82% increase from the baseline year of 2005, but only a 3% increase over 2010 funding (Jimenez-Levi, 2012). The top ten donors disbursed \$506.7 million of the \$649.6 million total, or 78% of the global share. While the 2011 global investment figure was the largest total ever recorded, it was still \$1.35 billion short of the annual \$2 billion funding target recommended by the Global Plan (Jimenez-Levi, 2012).

Jimenez-Levi (2012) reports that of the \$649.6 million global R&D total, the top ten donors spent 78% of the global share (\$506.7 million). The largest investments – over \$100 million

each- originated from the National Institute of Allergy and Infectious Diseases (NIAID) and the BMGF, whose combined investments represent 42% of the global total. In 2011, TB drug development received the largest share of global R&D investment. However, the \$250 million TB drug figure represents only 34% of the \$740 million annual target (Jimenez-Levi, 2012).

There is consensus that the health research system of SA is severely underfunded from local public and private sources. The National Health Research Committee has estimated that the National Department of Health spent 0.37% (R416.5 million) of its health budget (R112.6 billion) in health research in the 2010/2011 financial year, which falls far short of the recommendation of the health research policy in SA of 2001 and subsequent undertakings by the Ministry of Health in Mexico and Bamako to invest 2% of the health budget in health research (Senkubuge & Mayosi, 2013).

Increasing R&D activities for under researched diseases and promoting collaborative networks in countries like South Africa will require robust local-based funding mechanisms to complement current funding that is coming mostly from outside Africa (Nwaka *et al.*, 2010). The Third World Academy of Sciences recommends that two percent of the GDP of developing countries is a necessary minimum investment in R&D, with health research receiving 10% of that amount. South Africa is spending more on R&D than before, but this is still less than one percent of GDP (Mayosi *et al.*, 2011).

The CEWG report proposes a minimum commitment of 0.05% to 0.1% of GDP be devoted towards national funded R&D for developing countries with research capacity (CEWG, 2011). The Commission on Health Research for Development (CHRD) was among the first to recommend that lower- and middle-income countries should spend at least 2% of their health programme budgets on health research and that donors should match this with an allocation of 5% of their health programme funding (Senkubuge & Mayosi, 2013).

Health research in developing countries further lacks well defined national research priorities (Walwyn, 2013). The declarations by several African governments and non-governmental bodies cited above are summarised in table 2.1 in the next page.

Table 2.1 Health R&D Policy Statements in Declarations.*(Source: Mugabe, 2013)*

Declaration/Communique	Examples of Policy Statements
Bangkok Declaration on Health R&D (2000)	Health research is important for improvements in social and economic development; and R&D is critical for the attainment of health as a fundamental human right
African Union Summit (2007)	Heads of States and governments pledged to increase expenditure on R&D to at least 1% of GDP
Bamako Communique of the Global Ministerial Forum on Research for Health (2008)	At least 2% of national health budgets devoted to research.
Algiers Declaration of the Ministerial Conference on Research for Health in the African Region (2008)	Countries should allocate at least 2% of national health expenditure and at least 5% of external aid for health projects to research and research capacity building

The targets indicated have not been met by several African countries, including South Africa (Mugabe, 2013). Possible explanations for the weak policy implementation during the last decade include insufficient human and financial resources, unrealistic policy targets and supposition that the health sector has suffered from a lack of political commitment (Mugabe, 2013). The Bamako Communique and Algiers Declaration commit governments to invest at least 2% of their national health budgets in health R&D.

South Africa's health R&D expenditure is estimated to be 0.8% of its total annual health budget while Kenya's is about 2% (Mugabe, 2013). Furthermore, African countries are spending less than 1% of their GDP on R&D, falling short of the African Union Summit (2007) pledge. In 2008, South Africa's expenditure on R&D was 0.9% of GDP, Botswana 0.5%, Kenya 0.4% and Zambia 0.37%. In comparison, Brazil's expenditure on R&D in the same 2007/2008 period was 1.10%, India 0.8% and China 1.5% of GDP (Mugabe, 2013). This further highlights the need for African countries to increase their investments in health research and innovation in order to reduce the burden of disease and spur economic growth. There has been considerable increase in the number of firms engaged in health innovation activities in Brazil and China due to incentive measures deliberately introduced

by their governments. The countries have also created innovation mechanisms for funding start-up companies. The three countries invested significantly in establishing world class research institutes specialising in different areas of R&D. The success of Brazil, India and China highlights the benefit of putting emphasis on R&D for innovation, building and endowing national centres of excellence in health R&D for innovation (Mugabe, 2013). Political commitment by national governments is needed to foster national and international partnerships. Evidence of this is seen in Brazil, India, and China, as stated in the text above.

The substantial investment of public funding with the expressed intent of benefiting society warrants a focus on government-operated R&D programmes (Stone & Lane, 2012). Mayosi *et al.* (2011) suggest funding resources be allocated to national health priorities. Government commitment and partnership, strategic planning, and coordination are needed to revitalise health research (ASSAf, 2009; Collins, 2012). South African health research on TB is widely recognised as being world-class; however, much of the current research done by South African researchers is determined by the agendas of international donor agencies that provide the bulk of research funding, rather than through a well coordinated, global R&D framework (NSP, 2012-2016).

Differing investment patterns between sectors affect the type of research that is funded for a given disease, with an average of over 70% of total funding invested into product development for the semi-commercial diseases, compared to an average 60% for diseases with a significant philanthropic stake, and an average 45% for diseases that rely heavily on the public sector (G-FINDER, 2012). For high-funded diseases this is less of an issue, but if a disease has both low funding and a low focus on product development, outcomes are likely to be poor. PDPs appear to be diversifying their funding sources towards science and technology agencies, but remain highly dependent on the BMGF and donor agencies (G-FINDER, 2012).

There is growing consensus that the South African public health sector is inadequately resourced and there appears to be a commitment on the part of government to gradually increasing public funding of health services (NSP, 2012-2016). While donor grants and external aid will continue to be a critical funding source for many of the interventions outlined in the NSP, international evidence suggests that domestic funding for health services is the key to long-term sustainability. In addition, while substantial donor funding

is available to support the scaling up of many NSP-related interventions, this amounts to approximately only 2% of the overall resource envelope available in the public health system (NSP, 2012-2016).

The global R&D actions to address the challenges of developing nations can no longer rely on unsustainable voluntary funding contributions alone (WHO, 2012). The severity of the economic crisis facing many traditional donors further complicates issues. The NSP (2012-2016) has proposed four steps to address this:

- A national research agenda needs to be developed on the basis of detailed knowledge of the burden of disease
- Researchers and policy-makers must commit to a common understanding of the country's TB response
- Regular interaction must occur between researchers, policy-makers and the leaders of public-health programmes to ensure that the TB policies and programmes take account of the latest science
- Local funding of TB research must increase substantially.

This research especially focused on the last step above, with the aim of developing a framework for calculating the required TB R&D expenditure based on a RoI criterion.

2.4 Neglected Disease Research and Development

A disease is considered neglected when treatment options are inadequate or don't exist, and when their drug-market potential is insufficient to readily attract private sector response (MSF, 2013). Infectious diseases like TB that predominantly affect people in developing countries are most commonly understood by the term "neglected diseases", but even within this category a distinction is often made, based roughly on levels of R&D activity, between "neglected" diseases such as HIV/AIDS and TB (where there is more commercial R&D activity) and "most neglected" diseases, such as sleeping sickness (where there has typically been little to no R&D activity and few resources) (MSF, 2013).

Neglected diseases are distinct from “global diseases,” such as non-communicable diseases, for which both the public health needs and R&D activity are significant. The shortcomings for neglected diseases extend to areas such as antibiotics, where new medicines need to be developed (MSF, 2013). Low and middle income countries now face a double burden of disease, with both infectious diseases and, increasingly, non-communicable diseases. These are areas where the existing health system has failed to meet public health needs which should be addressed (MSF, 2013).

Regardless of how great the needs may be, where commercial potential is weak, there is little “pull” to develop new technologies (MSF, 2013). Governments have not filled the vacuum left by industry, particularly for the “most neglected” diseases (MSF, 2013). The MSF report (2013) notes that even when there is enough of a profit incentive to drive innovation – for example when diseases affect both developed and developing countries alike – the resulting products are too often out of reach for poor communities. What is needed, therefore, is not just innovation – but both innovation and access.

Governments must put in place an R&D framework that monitors, coordinates, and finances medical innovation for neglected diseases (MSF 2013; Walwyn, 2013). However, global commissions have shown that health research is not given its rightful place in improving health, equity and development in low- and middle-income countries.

According to the G-FINDER (2012) report, public funding remains the mainstay of neglected disease R&D, accounting for 65.6% of total funding across the last five years. Figure 2.3 in the next page illustrates this point, using the case of TB.

The G-FINDER survey is regarded as the most rigorous neglected disease R&D survey conducted to date in terms of its scope, methodology, and breadth of participation. It is intended to report accurate, comparable R&D investment figures across the spectrum of neglected diseases. It does not seek to analyse whether investment is best spent, or to make recommendations on funding allocation, nor does it attempt the task of ascertaining how much R&D funding is “enough” (Moran *et al.*, 2009).

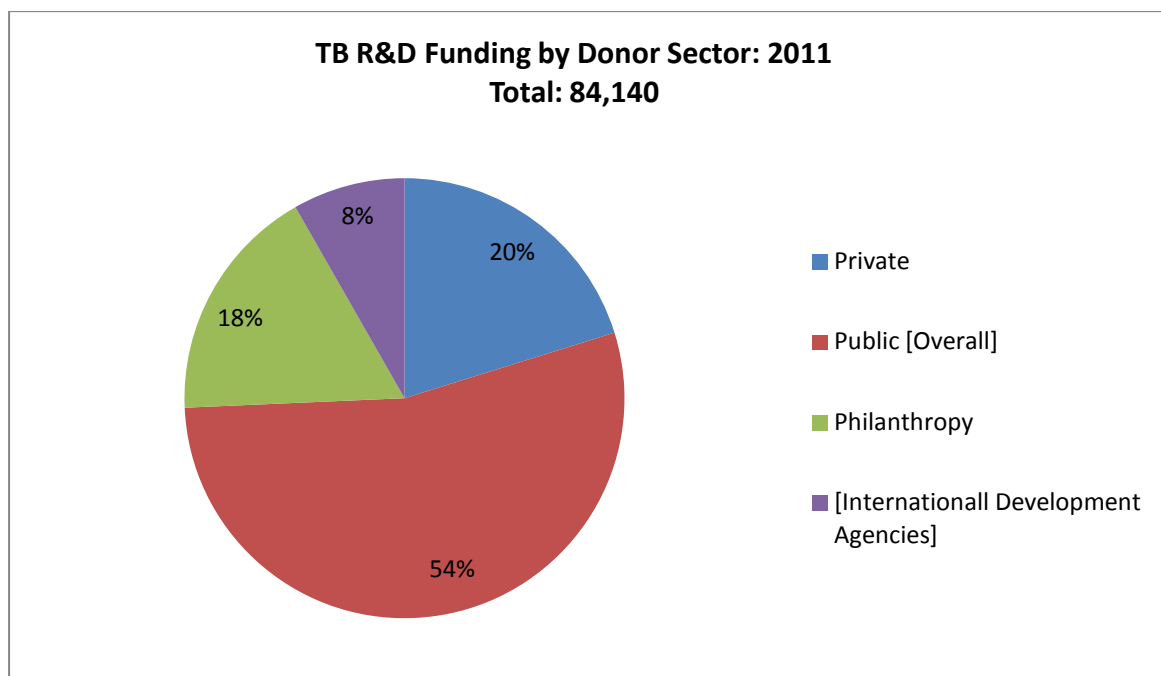


Figure 2.3 TB R&D Funding by Donor Sector.

Source: Jimenez-Levi, 2012.

The latest G-FINDER (2012) report notes that public funding has shifted substantially from product development to basic research, which accounted for 31.2% of total public funding in 2011 compared to 26.0% in 2007, with an additional \$124.2m invested in basic research. Philanthropic funding for neglected diseases has dropped significantly since the global financial crisis, driven by large drops in the BMGF funding since 2008 (down \$169.1m, -27.4%). This had a pronounced impact on PDPs in particular since the BMGF provided over half (53.6%) of global PDP funding.

The BMGF, the primary driver of philanthropic funding, attributes this decrease to funding cycles and the completion of large multi-year grants (G-FINDER, 2012). Philanthropic funding plays a contributing rather than dominant role overall – unlike the public sector – with the philanthropic share of funding for each disease ranging from 6.4% of total funding for dengue, through to salmonella and HIV/AIDS (12.1% and 12.4% respectively), up to 23.5% for TB, and around 30% of total funding for most other diseases (G-FINDER, 2012).

Figure 2.4 below shows sources of R&D funding for neglected diseases.

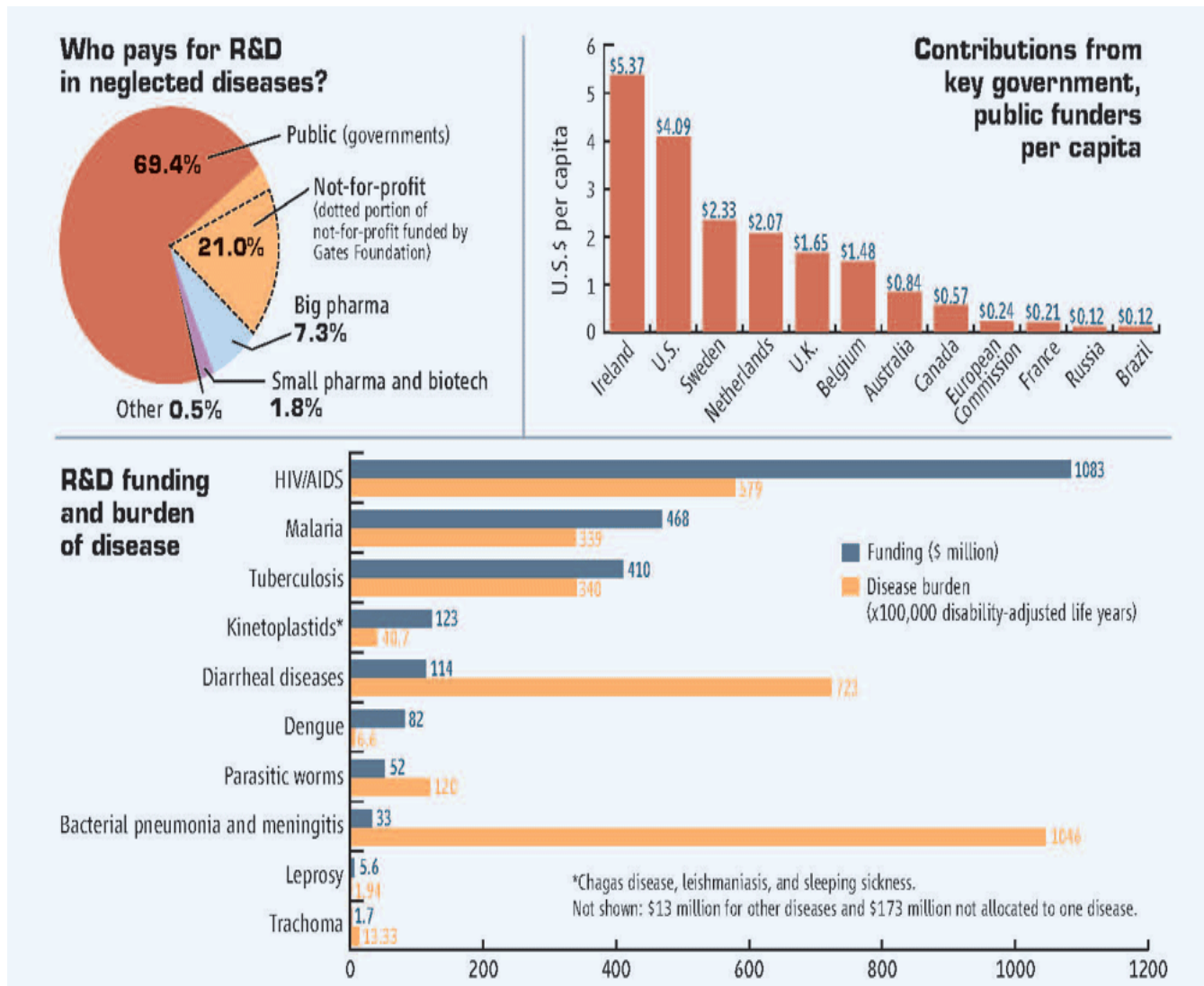


Figure 2.4 R&D Funding for Neglected Diseases.

Source: <http://www.sciencemaq.org/content/323/5915/700/F1.expansion>

The G-FINDER (2012) report further states that up until 2009 global investment in neglected disease R&D had been increasing steadily, but has been in gradual decline thereafter as the impact of the global financial crisis became evident. This further highlights the need for governments to fill in the gap and increase their health R&D investments.

The 2012 Report on Tuberculosis Research Funding Trends, 2005–2011, found that out of 132 surveyed institutions, 81 reported investing \$649.6 million in TB R&D funding, a 3% increase from 2010's \$630.4 million investment (Jimenez-Levi, 2012). Of the \$649.6 million in TB R&D funding reported for 2011, the top ten donors invested 78% of the global total. The largest investments—over \$100 million each—originated from the NIH's National Institute of Allergy and Infectious Diseases (NIAID) and the BMGF, whose combined investments represent 42% of the global total (Jimenez-Levi, 2012). The South African Department of Science and Technology (SA DST) was ranked as number 24, amongst a total of 79 TB R&D funders in 2011, with an investment of \$4,000,000 (Jimenez-Levi, 2012). However, in the latest 2013 report, the SA DST investment had gone down to only \$1,217,500. The SA DST ranking also went down to number 43 (Frick & Jimenez-Levi, 2013). This is despite an increase in TB incidence in South Africa, in the same period (WHO, 2013).

The need for new pharmaceutical tools to prevent and treat neglected diseases is widely accepted (Moran *et al.*, 2009). The 2000 Global Forum for Health Research report highlighted that only 10% of the world's health R&D was dedicated to illnesses that affect 90% of the global disease burden – a “fatal imbalance” often referred to as the “10/90 gap”. The DNDi and MSF conducted a study to reassess the state of R&D for neglected diseases in the period 2000 – 2011. The results of the study showed a somewhat mixed picture with important progress had been made in neglected product development, but that it was very uneven (WHO, 2012). Of the 756 new drugs approved between 2000 and 2011, 29 (3.8%) were indicated for neglected diseases, even though the global burden of disease is estimated at 10.5% (CEWG, 2012).

2.5 Tuberculosis

This research has used TB as a case study. TB is an infectious disease that is caused by the pathogenic bacteria *Mycobacterium tuberculosis* (WHO, 2011). The bacteria usually attack the lungs but can affect any part of the body. TB is easily spread through the air from one person to another when a person with TB disease of the lungs or throat coughs (Logan, 2013). It remains a major public health crisis in sub-Saharan Africa despite declining global TB incidence rates and the availability of highly efficacious treatment for decades (Pooran *et al.*, 2013; WHO, 2011). TB is a leading cause of morbidity and mortality worldwide, with 8.7 million incident cases of TB and 1.4 million deaths estimated

in 2011 (Weyer *et al.*, 2012). It is the second leading cause of death from an infectious disease worldwide (after HIV, which caused an estimated 1.7 million deaths in 2011 (Floyd *et al.*, 2013). The 2013 WHO TB report suggests that incidence rates are falling in 10 countries, are approximately stable in 11 countries and are increasing in South Africa (WHO, 2013). There is a wide variation in TB prevalence across age, race, gender, socio-economic status and geographical location. It is estimated that 80% of the South African population is infected with the TB bacillus; however, not everyone who is infected will progress to active TB disease (NSP, 2012-2016). However, the probability of developing TB is much higher among people infected with HIV (WHO, 2013). The TB epidemic in South Africa is threatening its social and economic well-being through both the direct cost of treatment and the loss of productive economic activity (Walwyn, 2013). South Africa currently ranks third highest in the world in terms of the TB burden, with an incidence that has increased by 400% over the past 15 years (NSP, 2012).

TB has remained as a high public health problem, mainly for two reasons: co-infection with HIV and the development of complex mycobacterial drug resistance patterns (Loddenkemper, *et al.*, 2012). The HIV epidemic is exacerbating the problem by increasing the number of TB patients and the use of isoniazid prophylactic therapy (IPT) that all HIV patients are recommended to receive.

In order for TB to be eliminated as a global health problem in the foreseeable future, improved detection of patients, earlier diagnosis and timely identification of drug resistance will be critical (Weyer *et al.*, 2012). The current TB treatment guidelines recommend six months of medication for treatment of drug-sensitive TB and minimum of 18 months for drug resistant TB, making patient adherence challenging, leading to drug resistance and eventually treatment failure (Walwyn, 2013). There is a need for rapid acting, potent anti-tubercular drugs that are efficacious against multidrug-resistant and extensively drug-resistant TB (MDR-TB and XDR-TB), as well as being safe to co-administer with antiretroviral therapies for HIV (G-FINDER, 2012).

There are multiple drug candidates in development, including a novel three-drug combination (*PA-824, moxifloxacin and pyrazinamide*) which has shown promising results against both drug sensitive and MDR-TB. The new drug combination could shorten the treatment of drug-resistant TB from two years to four months (G-FINDER, 2012). The

WHO (2012) report also points to the promise of medical breakthroughs from new TB drugs – the first in over 40 years.

The only available TB vaccine, the BCG, is over 100 years old. BCG vaccine is a vaccine that is highly effective only against disseminated TB in children. It is however ineffective in preventing the infectious pulmonary TB that occurs mainly in adults and remains the primary source of TB transmission (Jimenez-Levi, 2012). A new vaccine is needed, which should have greater efficacy than BCG, whilst matching or improving its safety profile.

There are also some vaccine candidates in clinical trials, with the most advanced being the *Mycobacterium indicus pranii* (MIP) candidate developed by the Indian Department of Biotechnology (DBT) and Cadila Pharmaceuticals Ltd, which is in Phase III trials (G-FINDER, 2012).

Existing TB point-of-care diagnostics are also inadequate, detecting less than half the active TB cases. There is a recognised need for cheap, rapid, easy-to-use diagnostics that can distinguish between active and latent disease, with or without HIV co-infection (G-FINDER, 2012). The most widely used diagnostic tool – sputum smear microscopy is neither sensitive nor specific for *M. Tuberculosis* (Rajalahti, Ruokonen, Kotomaki, Sintonen, & Nieminen, 2004). Cultures are more accurate but take several weeks to confirm diagnosis (Jimenez-Levi, 2012).

There is praise for the recent worldwide roll-out of a new diagnostic device that can test patients for TB, including drug-resistant TB, in just 100 minutes (WHO, 2012). The fully automated nucleic acid amplification test (NAAT), which can diagnose TB and rifampicin-resistant disease, is available in 67 low- and middle-income countries, including South Africa (WHO, 2012). Adoption of the ‘while you wait’ test is expected to further accelerate, following a recent 41% fall in the price of the test (WHO, 2012).

Despite the above development, there is a US\$ 1.4 billion funding gap per year for health R&D (WHO, 2012).

With the current trends, the African region is unlikely to achieve the United Nations Millennium Development goal to halve the TB disease burden by 2015 (WHO, 2011). In order to achieve this goal, the WHO calls for the region to advocate for and participate in research to develop new anti-TB drugs, on top of better diagnostics and new vaccines

(WHO, 2013). Reduction of the burden of TB disease requires adequate and sustained financing for many years (Floyd, *et al.*, 2013).

The Department of Health of SA has committed to a number of TB-specific objectives including a reduction in the TB burden of disease and an improvement in the TB treatment success rate (National Department of Health, 2010).

The WHO (2012) report warns that apart from the US\$ 1.4 billion funding gap for research, there is a further US\$ 3 billion per year funding shortfall between 2013 and 2015 which could have severe consequences for TB control. This gap threatens to hold back delivery of TB care to patients and weaken measures that prevent and control the spread of TB, with low-income countries at most risk (WHO, 2012). To address this, WHO is calling for targeted international donor funding and continued investments by countries themselves to safeguard recent gains and ensure continued progress (WHO, 2012).

Figure 2.5a and 2.5b below and in the next page illustrate the total TB R&D funding trend from 2005 to 2011.

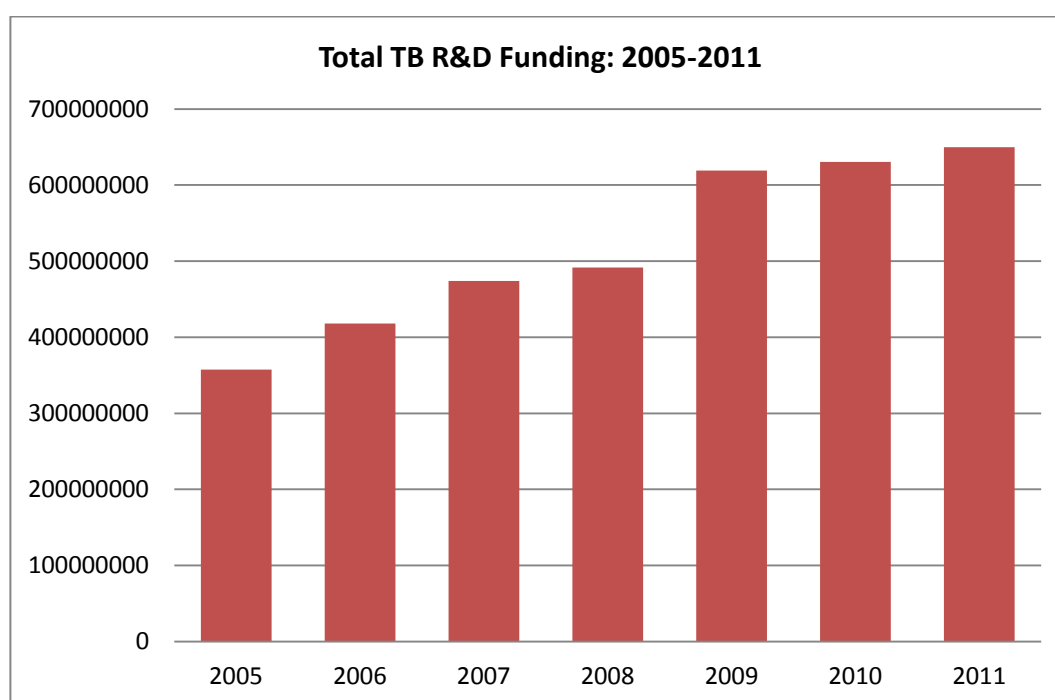


Figure 2.5a Total TB R&D Funding: 2005-2011.

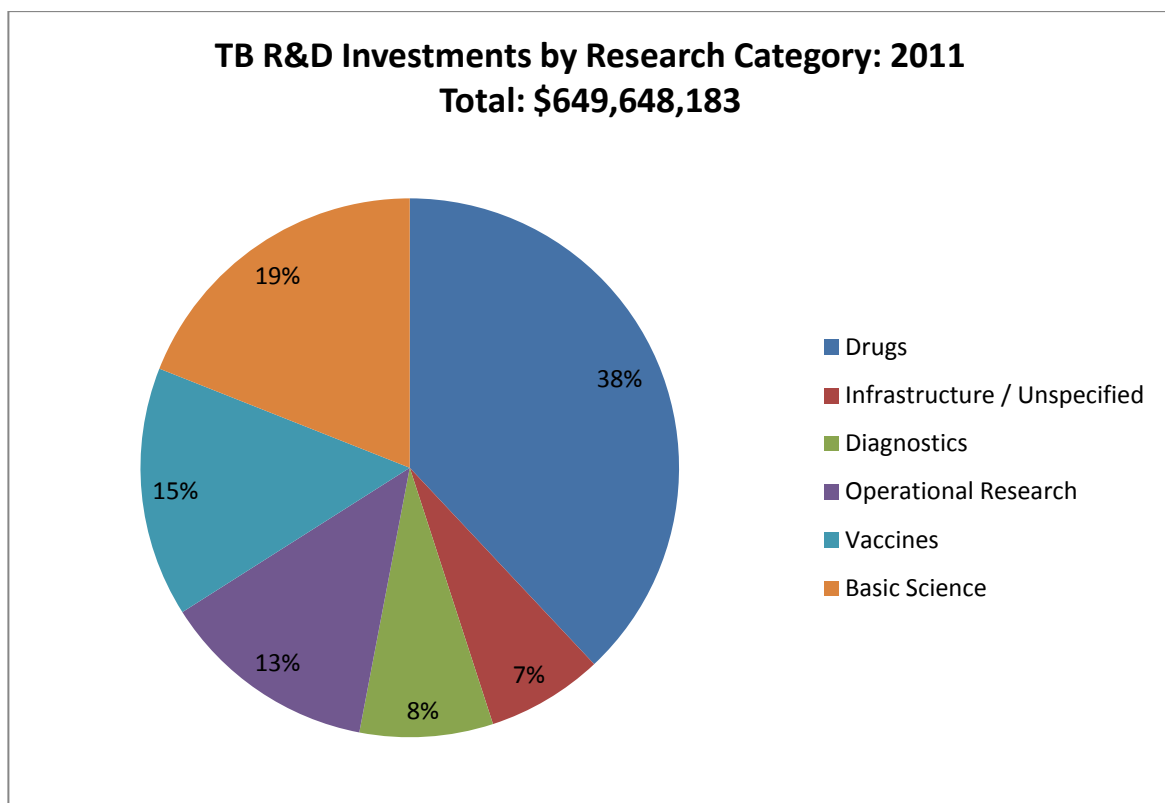


Figure 2.5b Total TB R&D Funding: 2005-2011.

2.6 Cost of Tuberculosis Management

The NSP (2012–2016) reflects the progress made by the SA government in achieving a clearer understanding of the challenges posed by HIV, Sexually Transmitted Infections (STIs) and TB epidemics and the increasing unity of purpose among all the stakeholders, who are driven by a shared vision to attain the highest impact of policies towards the long term vision of zero new HIV and TB infections.

A high TB burden is costly to the national treasury as TB case management costs in South Africa are covered within the public sector budget. New technologies and products should therefore result in significant savings in treatment costs (Walwyn, 2013). Yet, despite this potential return, TB R&D has failed historically to attract sufficient funding from either the public or the private sector (Walwyn, 2013).

Pooran *et al.* (2013) performed a cost analysis on the costs associated with the diagnosis and treatment of TB in South Africa. The main findings by Pooran *et al.* (2013) were that

despite drug resistant TB comprising a small proportion of the total case burden, it consumed a disproportionately large amount of the total national TB budget.

Diel *et al.* (2013) conducted a comprehensive cost-per-case study for TB in the European Union (EU). This was the first time that such costs had been estimated for TB. The total treatment cost of drug-susceptible, MDR, and XDR TB cases across the EU in 2011 was €536 890 315. However, the researchers note that this figure is probably a substantial underestimate, since factors such as locating and treating close contacts and vaccination strategies with the BCG vaccine were not included. A suggestion was made that these additional elements could treble the total cost of tuberculosis treatment (Diel *et al.*, 2013).

Diel *et al.* (2013) conclude that without better vaccines, it is unlikely that TB will ever be eliminated. An investment of about €560 million was considered necessary by the authors, in order to develop new, effective TB treatments in the EU, suggesting that this investment is essential because the costs of the current economic burden far outweigh the cost of investing in new treatments.

Diel *et al.* (2013) further propose that the investment required from the EU is not only urgent but has to be at least double the estimated amount because, although the figures mentioned above might be underestimates, a large proportion of MDR and XDR tuberculosis remains undiagnosed because of poor-quality tuberculosis services and access to quality laboratory services.

2.7 Return on Investment

The expenditure on medical research provides a huge economic return on investment – whether measured in terms of monetary value of lives saved, health costs saved, or jobs created (Senkubuge & Mayosi, 2013).

Most of the literature that measures the returns on R&D, whether at the micro or macro level, relies on a production function framework, where the output of an economy is related to its stock of R&D or knowledge capital (Hall *et al.*, 2010). September (2003) recommends using mortality and morbidity measures as attributes to health R&D benefits.

However, there are challenges with exclusively attributing medical breakthroughs to gains in life expectancy, as other factors such as better education and policy regulations interact

with health R&D advances. These factors also contribute to gains in life expectancy (September, 2003).

Returns on investment in health R&D lead to three types of savings: direct savings, indirect savings and overall health-span gains (September, 2003). Direct savings results in savings to the costs of the health care system. Examples of direct savings include lower health care costs, hospitalisations, and savings through the development of new drugs and diagnostics (September, 2003).

Indirect savings are savings as a result of a 'healthy' nation. Examples of indirect savings include savings made through lowered morbidity and improved productivity of the population. A reduction of the burden on insurers and welfare payments are also examples of indirect savings (September, 2003).

Quality of life gains are calculated by disability-adjusted life years (DALYs) (September, 2003). DALYs are used to calculate extensions in health-span, including quality of life measurement. It is however more challenging to put a value on DALYs. The formula for calculating DALYs is adding the years of life lost (YLL) and the years lost due to disability (YLD), within a nation: $DALY = YLL + YLD$ (September, 2003). Africa is especially affected by a series of infectious diseases that are responsible for more than half of its disability-adjusted life years (DALYs) and over 6 million deaths (Nwaka, *et al.*, 2010). The G-FINDER reports that research funding is highly concentrated and has little correlation with the burden of diseases, as measured by DALYs (Moran *et al.*, 2009). This observation should, however, not be construed as a belief that funding levels should be based only on disease DALYs. DALYs are the most widely accepted quantitative indicator of burden of disease, but remain an imperfect measure as they do not reflect the impact of co-morbidities (Moran *et al.*, 2009; Nwaka, *et al.*, 2010).

A less significant rate of return on R&D is reported for public rather than private R&D, both at the private and social level (Hall *et al.*, 2010). This is possibly explained by the fact that a large share of public funds is spent precisely in areas where the risk is higher or where there is a public goods problem. Public R&D has subsequently been identified to encourage private R&D and hence have an indirect rate of return (Hall *et al.*, 2010).

Private returns are measured by the profits to the innovator, net costs of producing, marketing and carrying out the innovation, and net profits the innovator would have earned

on products displaced by the innovation, with an adjustment for the unsuccessful R&D. Social benefits are obtained by adding to the private benefits the change in consumer surplus arising from the possible price reduction and profits made by the imitators and by subtracting the R&D costs toward the same innovation incurred by other firms (Hall *et al.*, 2010). Mansfield in Hall *et al.* (2010) reports the social rate of return of innovations generally exceeds the private rates of return by a substantial margin. The median social rate of return is about 56% against a median private rate of return of about 25%.

2.8 ROI for Direct Savings

The current business model for life sciences R&D is significantly more complex compared with a decade ago. Confronted with a steep rise in the cost of product innovation – that has far outpaced commercialisation success rates – nations and companies are fundamentally reconfiguring how they approach drug development. Increasingly, health ministers and heads of R&D are expected to justify R&D investment and returns (Deloitte and Thompson Reuters, 2010).

Research often provides answers to un-posed questions, however answers to the simple questions such as ‘What is the private rate of return on investing in R&D?’ ‘What is the social rate of return?’ ‘Are there spill-overs?’ turn out to be very complex (Hall *et al.*, 2010).

The conventional wisdom holds that because of problems related to appropriability, public goods would be under produced if left to the private sector (Stephan, 2010). Hence, health research must be subsidised by government or philanthropic institutions. The main goal of research on TB in South Africa, as stated in the NSP (2012-2016), is to provide scientific evidence to guide policy and enhance the country’s response to TB.

Deloitte and Thompson Reuters (2010) undertook a proprietary analysis into an Internal Rate of Return (IRR) approach to value measurement. The ‘whole R&D business’ assessment of R&D returns report indicates that the top 12 research-based pharmaceutical companies (measured by R&D spend) were each achieving a positive return ranging from 8% to 18%. The report concludes that alongside existing R&D returns measures, an IRR approach can improve decision making in R&D.

R&D performance can be measured using a variety of indicators. The most commonly used indicator has been the Gross Expenditure on R&D (GERD) / GDP ratio (OECD,

1994). The use of the GERD/GDP as an indicator can, however, underestimate the extent to which a country has increased its actual R&D expenditures (OECD, 1994). This can happen when the growth in GDP increases at a greater rate than the increase in R&D expenditures. A significant increase in the investment that a country makes in R&D might not be registered, because the growth in GERD/GDP ratio can be affected by many factors, not just the growth in R&D. For example, if a country experiences an economic slowdown but continues to commit a set amount to R&D, its GERD/GDP ratio may actually improve (OECD, 1994).

An alternative indicator to measure a country's R&D performance is the absolute increase in the proportion of GDP allocated to R&D over a given period of time (OECD, 1994). This is a measure that more fully reflects the increasing commitment that a country makes to R&D as a proportion of GDP over time (OECD, 1994).

2.9 Conclusion to the Literature Review

This research was designed with the objective of making a constructive contribution to public debate and decision making on the issue of health care costs, focusing on South Africa and TB disease. Despite being preventable and treatable, TB remains a leading cause of death and a major public health concern worldwide. Furthermore, MDR and XDR TB are spreading at an alarming rate globally. The lack of robust R&D funding by investors and government into TB R&D is threatening to undermine historical gains made. In particular it has been noted over a long period that governments of countries with high TB disease burden under invest in TB R&D, despite having 40% of the world's notified TB cases. To help reduce the burden of disease and meet constitutional obligations, African countries need to increase their investment in health research and innovation.

Globally, governments formulate, and implement a wide range of policy regulations and legislation to accelerate health R&D for innovation. A recent report has noted that for the first time in eight years, global spending on TB R&D decreased in 2012 compared with the previous year. This drop in R&D investment threatens to undermine the possibility of any future insights from TB research. A strong political will and commitment for innovation-oriented health R&D is essential to ensure commercialisation of locally generated knowledge and technologies.

The recent economic history of countries such as Brazil, China and India demonstrates how important investment in health R&D is for industrial production of medicines and diagnostics and the knock-on benefits for the economy. However, the same countries are underrepresented among the top TB R&D donors, despite having the highest TB disease burden and a sizeable R&D budget

Evidence from the literature accessed shows that a large economic return on investments can be observed when medical research is invested in at country level (English & Padarath, 2013). The fact that neglected diseases impact most heavily on the poorest is perhaps one of the reasons that governments like SA should play a role in supporting TB research due to the potential return on investment. The pipeline for new TB drugs and diagnostics is likely to remain weak unless government and other donors recommit to meeting the target funding levels required to accelerate TB R&D.

Chapter 3: Research Questions

This research specifically focused on South Africa and the case of TB drug development. Until very recently, no new TB drugs have been developed in over half a century. The current TB treatment regimen is very lengthy, especially for drug resistant TB, taking up to two years, including a daily injection for the first eight months (MSF, 2013). A safe, effective, oral, short-course of drug regimen that is affordable and adapted for the remote and rural places is needed (MSF, 2013).

In South Africa, TB cases are managed in the public sector. Newer, optimised treatment options will benefit the government through shorter duration in treatment time and a reduction in the number of drugs. Most recent drugs and regimen options in development contain fewer drugs and are promising efficacy in shorter time durations.

This research was designed to answer the following four questions:

1. **What is SA's TB disease burden?**
2. **What does this TB disease burden 'cost' SA?**
3. **What is SA's TB R&D expenditure?**
4. **Given the cost of TB disease, what should SA be spending on TB R&D?**

The burden of disease caused by TB can be measured in terms of incidence (defined as the number of new and relapsed cases of TB arising during a given time period, usually one year), prevalence (defined as the number of cases of TB at a given point in time) and mortality (defined as the number of deaths caused by TB in a given time period, usually one year) (WHO, 2011). It can also be expressed in terms of the DALYs lost (WHO, 2011). This research seeks to determine TB R&D investments that the SA national government must do to improve government output.

South Africa's commitment to re-engineering the health system has been driven by the country's overwhelming quadruple burden of disease fuelled by a range of risk factors – such as alcohol, tobacco smoking, obesity; unsafe sex and sexually transmitted disease; interpersonal violence; maternal and childhood malnutrition; and decreased physical activity, amongst other factors (English & Padarath, 2013). The high prevalence of these

and other risk factors, including rising non-communicable disease rates, has turned policymakers' attention to addressing the social determinants of disease. Combating HIV and AIDS and decreasing the burden of disease from TB have been substantially prioritised by the South African National Department of Health, supported by the release of a raft of plans and national strategies intended to be implemented on a wide scale (English & Padarath, 2013).

A key recommendation for improving health R&D funding is for developing countries to spend at least 2% of their health programme budgets on health research, with donors adding at least 5% (English & Padarath, 2013). However, it is not clear how these targets were determined and their relation to priorities (Walwyn, 2013). This research seeks to determine justifiable and realistic targets for TB R&D.

Chapter 4: Research Methodology

4.1 Introduction

This chapter describes the research methodology that was used in this research study. It explains the systematic process employed in sourcing, collecting, analysing, and interpreting data in order to develop a new theory and answer the research questions stated in chapter three above. The literature review and anticipated type of data needed to respond to the research questions provided a basis for the research methodology.

4.2 Research Method and Design

This research followed a quantitative, case study methodology based on empirical analysis of secondary data, looking at the details of TB treatment in SA and identified areas of potential savings as a consequence of well-directed R&D. The argument was that further R&D expenditure can be justified from an economic return on investment consideration. Where the state is currently spending a lot of money on TB disease treatment, this research proposes that government can save money if certain innovations are made. An inductive, descriptive, empirical approach was used to develop a new theory in order to develop a framework based on expected savings.

The three common research approaches are quantitative, qualitative, and mixed methods (Williams, 2007). Research can also be exploratory, descriptive as well as explanatory (Saunders & Lewis, 2012).

This study adopted a descriptive quantitative case study methodology in order to develop a RoI framework for setting South Africa's TB R&D target. Saunders and Lewis (2012) define descriptive research as a form of a research study which intends to study the accurate information about events or situations.

Quantitative studies' great strength is providing data that is descriptive (Madrigal & McClain, 2012). According to Saunders and Lewis (2012), quantitative research tends to have more statistical power than qualitative research when it comes to verifying information/trends. The authors suggest a quantitative study when one seeks to describe events or situations accurately.

Williams (2007) classifies quantitative research into three broad groups, namely: descriptive, experimental and causal comparative. The descriptive research approach, which was employed in this research, is a research method that examines the situation, as it exists in its current state (Williams, 2007).

Saunders and Lewis (2012) recommend case studies for enabling the researcher to get a detailed understanding of the context of the research. Case studies enable researchers to understand and learn about a poorly understood condition (Williams, 2007). The fact that little information is available to policymakers about the costs of diagnosing and treating TB, with even very recent analyses relying on unit-cost estimates made before the rollout of antiretroviral therapy for HIV which was the basis for adopting a case study methodology (Rosen, 2013).

The broad research topic was on health R&D, with a focus on neglected disease R&D, specifically TB R&D. TB was chosen as a disease of focus because it remains a major global health problem. TB is ranked as the second leading cause of death from an infectious disease worldwide, after HIV. WHO declared TB a global public health emergency in 1993 (WHO, 2012).

South Africa was used as a case study because of the high TB disease burden in the country. The burden of TB is highest in Asia and Africa (WHO, 2012). South Africa had the third largest number of incident cases in 2011 (0.4 million – 0.6 million) (WHO, 2012).

Reasonable access to data was another factor that led to using South Africa as the country of choice for the case study. A number of good quality data sources for the data used were known to the researcher, such as the WHO website, the OECD, the SA government website, the NSP document, and the TAG report to name a few.

The disadvantage with a case study methodology is the external validity, i.e. the extent to which it can be generalised to the broader issue, e.g. what should South Africa be spending on health R&D, not just TB. Some criticise the case study strategy because one case, or even a small number of cases, may be no basis for placing faith in the findings (Saunders & Lewis, 2012). For this reason the case study is dismissed as useful only as an exploratory tool. But a well designed and skilfully executed case study yields insights not possible in more descriptive strategies (Saunders & Lewis, 2012).

4.3 Data Collection

The researcher accessed the latest, reliable databases to source the most recent statistics.

Data to calculate the burden of TB disease in South Africa, the cost of diagnosis, treatment and management of TB in South Africa was accessed from the TB NSP for South Africa 2012 - 2016 document, and was supplemented with data from the WHO (2012 and 2013) TB reports on Global TB Control, and the recent work by Pooran *et al.* (2013) and Walwyn (2013). The data was used to understand the costs associated with TB treatment in SA and to identify areas of potential savings as a consequence of well directed R&D.

For additional information on external funding and TB R&D investment, the study used the Organisation for Economic and Development (OECD) and Treatment Action Group (TAG) data.

These documents are freely available and downloadable from the National Department of Health, the WHO websites, the OECD website and published journals.

Governments and non-governmental agencies now allow open access to data they have collected, making it available for anyone to use. The advantage of having access to this huge variety of large, high quality secondary data is the research opportunity which would otherwise be outside of the researcher's reach. It is extremely unlikely that the researcher would have either the time or the financial resources to collect the data available in the agencies stated above.

4.4 Data Analysis

The WHO global TB report (2012 and 2013) data was used to analyse the TB disease burden as it is one the high quality, most reliable source of information. The WHO data is data that is reported by the countries. Estimates of disease burden are produced by WHO in consultation with countries.

The NSP (2012-2016) report was also used in the analysis of SA's disease burden. The NSP (2012-2016) report was chosen as it the latest comprehensive SA government strategic document that details SA's response to the dual epidemics of HIV and TB. The plan addresses the drivers of the TB epidemic and aims to inform all stakeholders on

strategic directions to be taken into consideration on applicable decisions (NSP, 2012-2016).

The general approach to calculating costs is to estimate the number of people in need of an intervention from the epidemiological and demographic data, together with the coverage of the service, based on the coverage targets (NSP, 2012 – 2016). The unit cost of each intervention is then calculated by estimating the physical ingredients of the intervention (e.g. TB drugs, diagnostic tests) and multiplying this by the cost of each component (NSP, 2012-2016). Costing was undertaken from the government's perspective and focused only on the costs incurred by the government. Costs incurred by patients (such as travelling costs to and from facilities) were not considered (NSP, 2012-2016).

The collected data was used to identify areas in the main drivers of TB costs and potential savings as a consequence of well directed R&D. The likelihood of achieving these savings and the impact of such savings was also calculated from the secondary data. The collected data was further used to calculate the net present value (NPV) of the savings and estimated a target of how much government should invest per year to achieve these savings, based on current health expenditure and GDP.

Quantification of TB R&D expenditure benefits was considered as the NPV of the savings over the anticipated duration of the innovation and risk adjusted NPV (rNPV) of future savings. The NPV is defined as the "difference amount" between the sums of discounted cash inflows and cash outflows (Svennebring & Wikberg, 2013). It compares the present value of money today to the present value of money in the future, taking inflation and returns into account (Svennebring & Wikberg, 2013). The rNPV is defined as a method to value risky future cash flows and is regarded as an indicator of project profitability (Walwyn, 2013). rNPV modifies the standard NPV calculation of discounted cash flow analysis by adjusting (multiplying) each cash flow by the estimated probability that it occurs (the estimated success rate) (Svennebring & Wikberg, 2013). rNPV is the standard valuation method in the drug development industry, where sufficient data exists to estimate success rates for all R&D phases (Svennebring & Wikberg, 2013).

The following cost components for drug-susceptible (DS) TB, MDR-TB and XDR-TB were gathered from the following publications: Pooran *et al.*, 2013; WHO, 2012; WHO, 2013 and NSP, 2012-2016):

- Hospital inpatient stay cost
- Hospital outpatient visit cost
- Primary Care Clinic visit cost
- Cost of TB medication
- Diagnostic / Monitoring Test
- Other costs (Costs associated with adverse drug reaction, surgery and death).

The most current version of cost calculations was chosen for this research as the aim of this research was to show current TB costs.

The costs of public health surveillance, preventive treatment of people latently infected by *Mycobacterium tuberculosis* and costs representing productivity loss because of TB-induced sick days off work were out of the scope of this research analysis.

Data to accurately estimate the total TB programme budget was compared between the three latest reliable sources stated above.

The NSP (2012-2016) document is the latest government document which reports on current TB treatment and screening costs to the government. The document also reports projected treatment and screening costs, up to year 2016/2017. The costing that is reported in the NSP (2012-2016) is viewed as reliable by the researcher. This is because the costing reported in the NSP (2012-2016) is an indication of the potential magnitude of the anticipated costs, based on use of high-level costing tools such as the National TB Cost Model.

Pooran *et al.* (2013) analysed the cost diagnosis and treatment of DS-TB, MDR-TB and XDR-TB, based on National South African TB guidelines. The researcher used the data

from the Pooran *et al.* (2013) work in order to understand the key cost drivers for the three different TB types, i.e. DS-TB, MDR-TB and XDR-TB.

The total national TB programme budget figure used in this research was from the latest WHO global TB report (2013). The WHO is regarded as a reliable source and of high quality.

The TB cost breakdown analysis for MDR TB was based on DR-TB guidelines, where the recommendation is for the majority of MDR-TB cases to be treated as outpatients, while the remainder are hospitalised for severe illness. Conversely, the assumption was that all XDR-TB cases require hospitalisation. The figures used for the national TB figures were from the NSP (2012 – 2016) document and the WHO (2013) TB report as these represent the latest TB figures. The NSP (2012 – 2016) document however does not provide a breakdown of the contribution of the key cost drivers towards the total budget. The percentage contribution of key cost drivers was taken from the Pooran *et al.* (2013) article, as this was the latest report showing the contribution of all key cost components.

In developing the methodological framework for determining the TB R&D target, the following factors were taken into account:

- SA's TB disease burden as measured by the incidence rate per 100,000 population
- SA's capacity to invest, i.e. GDP per capita
- The size of SA's total TB treatment programme

The OECD database was used to analyse and do a comparison of the GDP and GERD for South Africa, Russia, China, India, UK and US. The first four countries were chosen as they are all part of the BRICS countries (the latest data for Brazil was not on the OECD database). The UK and US were selected as they are amongst the top funders for TB R&D.

The ratio of GERD to gross GDP was plotted against GDP per capita, in order to show the correlation and the national R&D intensity of various countries. GDP per capita is regarded as an indication of a country's capacity to support R&D, with a direct relationship, where high levels of GDP are linked with higher GERD (Walwyn, 2013).

The current and historical TB R&D funding statistics was sourced from the 2011 and 2012 TAG reports. TAG tracks annual spending on TB R&D and compares investments in different areas of research with the funding targets set by the Stop TB Partnership Global Plan. The South African TB R&D funding data reported in the TAG report and the OECD data were used to compute TB R&D per capita and the proposed TB R&D per capita.

The researcher used data from the extensive work done by DiMasi, Hansen & Grabowski (2003) and Mahmoud, Danzon, Barton, and Mugerwa (2006) to estimate the cost of developing a new TB drug, new diagnostic tool and TB treatment regimen optimisation.

For purposes of this research, the researcher limited the outcomes of R&D investment to at least three new innovations:

1. An optimised TB treatment regimen, using the current available drugs.
2. A new TB drug or vaccine development.
3. A new TB diagnostic tool.

The data from DiMasi *et al.* (2003) and Mahmoud, *et al.* (2006) was also used to estimate the success rate of various R&D projects and the expected savings to the national treasury based on each R&D project.

Based on the above calculations, the RoI Factor and total affordable TB R&D figure were then estimated for the South African national TB R&D programme.

The RoI of three proposed R&D outcomes mentioned above were compared, based on the framework that is discussed in the next chapters.

4.5 Assumptions

For purposes of this research, a figure of 15% was used as a guide in the evaluation of project profitability where R&D outcomes are assumed to achieve a minimum 15% hurdle rate. It is reported that managers of public health use a figure of about 15% when evaluating the cost of implementing a project, where below 15% the cost of implementation is considered to exceed the extent of the savings (Walwyn, 2013).

The discount rate was assumed to be 8%. The discount rate is the expected return that the investors or the national treasury in this case, forego during development when an investment is made toward TB R&D instead of an equally risky investment (DiMasi, *et al.*, 2003). The discount rate of 8% was based on the SA government bond 10 years rate, reported as 7.96% (World Bank).

For purposes of this research, the average duration of a drug discovery project was assumed to be 15 years. An important aspect of a new drug R&D is the length of time it takes. Mahmoud, *et al.*, (2006) indicate that the average time for a new drug or vaccine to proceed from discovery through preclinical testing, clinical trials, and regulatory approval is longer than a decade,

A drug development clinical study/project is a lengthy, highly risky process with the possibility of compounds failing at anytime during the process (DiMasi, *et al.*, 2003), In this research, a new drug development project was assumed to have a high risk with a weighted average success rate of about 30%. The 30% success rate is supported by work by DiMasi, *et al.*, (2003); Walwyn (2013) given that it is never certain that development of a investigational compound will be successful.

Another assumption made was that TB R&D investment would lead to development of a new TB drug or a new improved treatment regimen. The current TB drug regimes under investigation are likely to reduce TB treatment times from six months to two months, with the number of drugs reduced from four to two (TB Alliance, 2013). The net cost savings to the National Treasury from these new drug regimens were assumed to be a reduction in drug costs, treatment times and hospitalisation. These were assumed to result in at least a third reduction from current TB budget. This assumption is considered reasonable as the savings figure is based on lower drug costs and a reduction in hospitalisation costs for DR-

TB. Also, the newer TB regimens currently being tested are effective in shorter time periods and contain fewer drugs (Mitnick, McGee & Peloquin, 2009).

It is estimated that a new, shorter TB drug regimen will improve the treatment success rate. In the year 2012, the WHO estimates that 52 586 patients were retreatment cases, from the 323 664 total new and relapsed cases treated. This is equivalent to a 6% retreatment rate of all SA TB patients treated per annum (WHO, 2013). This study assumed that the retreatment rate will contract to at least 5% with a better, optimised TB regimen, thereby providing another saving to the government. The new estimated lower retreatment rate is considered reasonable given the target retreatment rate of 5% as stated in the South Africa's national TB control programme goals and strategies (Department of Health, 2012).

4.6 Research Limitations

The first limitation of this study is that of external validity as the research methodology followed was a case study. Triangulation of the findings with a Delphi survey could not be conducted due to time constraints and resource capacity.

A further limitation of this research is that it relied on secondary data. One of the possible pitfalls of using secondary data is the verification or the accuracy of the data as the purpose of the original research data may be vastly different to the researcher's purpose. There are many potential sources of uncertainty associated with estimates of TB incidence, prevalence, and mortality, as well as measurement of case detection and treatment success rates (WHO, 2012). TB cases may be underreported, misclassified or over-reported (WHO, 2012).

This research evaluated the effectiveness of current TB management strategy, with more focus on cost analysis and current R&D investment. The study used data from the latest national budget document, i.e. the NSP (2012 – 2016 document), and the WHO (2013) TB report but also based the key cost driving contributions to the total budget on the Pooran *et al.* (2013) study which used data from Brooklyn Chest Hospital (BCH). BCH may not be representative of the rest of other South African hospitals, in terms of hospital costs. Treatment policies and regimens may also vary slightly across South African provinces. As such, the percentages from Pooran, *et al.* (2013) article were assumed to be realistic but may not accurately reflect current disease outcomes. The other factor which led to

adopting the percentages in the Pooran, *et al.* (2013) paper is that the cost driver contributions were based on the latest South African national TB guidelines.

The other limitation of this study is that the total national TB budget costs exclude certain costs, such as those incurred by patients. As such, the presented costs may be somehow underestimated as the analyses considered by this research only focused on costs associated with diagnosis and treatment. Nevertheless, despite the limitations of this project, the best available cost data needed for budgeting and financing the expansion of TB R&D were used.

Chapter 5: Results

5.1 Introduction

The layout of the data results will be as per the research questions stated in chapter three. The data will be presented starting with the epidemiology of TB in SA, followed by the outcomes of the current TB regimen, the current TB budget and key cost drivers, the correlation between GDP per capita and TB incidence, GERD/GDP and GDP per capita, and finally a calculation of the optimal TB R&D expenditure based on the RoI factor and three possible R&D projects (i.e. optimised TB regimen, new TB drug development, and new TB diagnostic tool).

5.2. South Africa's TB disease burden

Figure 5.1 and table 5.1 in the next two pages show SA's growing burden of TB disease, based on the number of cases notified and the incidence rate of all TB cases in SA during the period 1999–2010.

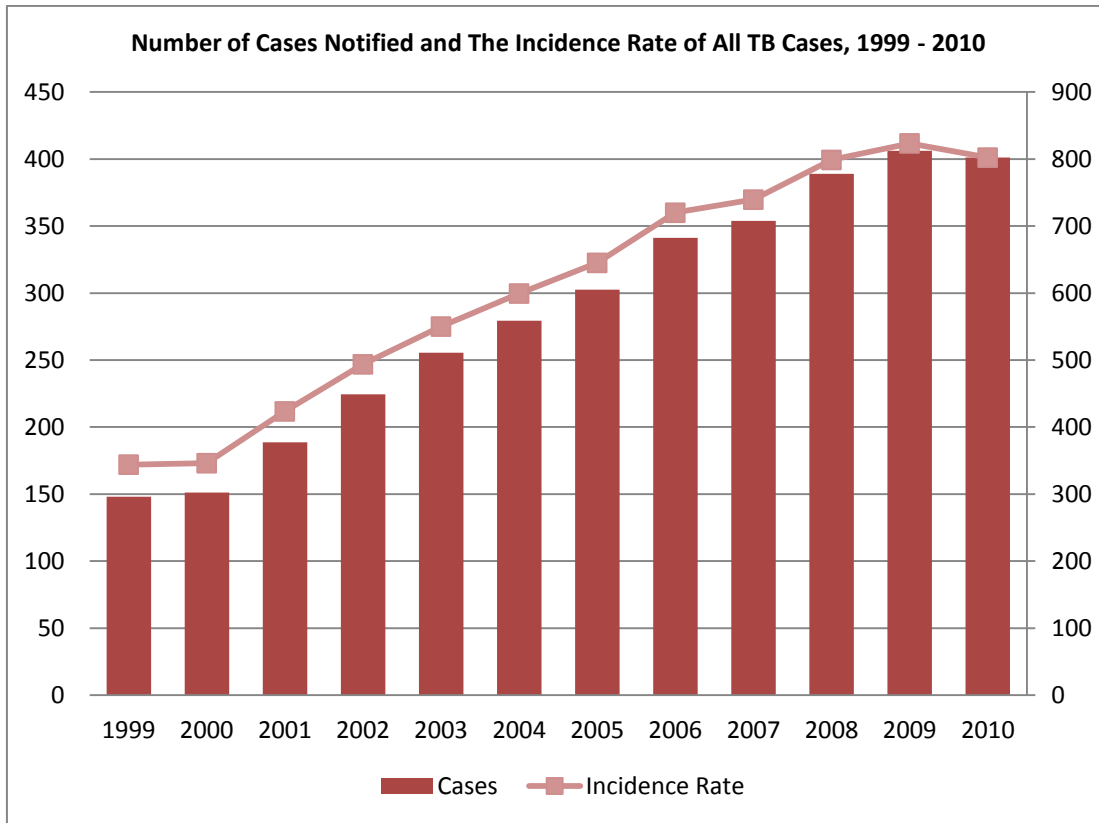


Figure 5.1 Number of Cases Notified and the Incidence Rate of all TB Cases in South Africa, 1999–2010.

Source: National Strategic Plan on HIV, STIs and TB: 2012-2016

Table 5.1 Number of Cases Notified and the Incidence Rate of all TB Cases in South Africa, 1999–2010.

Source: National Strategic Plan on HIV, STIs and TB: 2012-2016

	1999	2000	2001	2002	2003	2004
Cases	148.16	151.23	188.69	224.42	255.42	279.26
Incidence Rate	344.1	346.2	423.5	493.7	550.1	599.4

	2005	2006	2007	2008	2009	2010
Cases	302.46	341.16	353.87	388.88	406.08	401.04
Incidence Rate	645.1	719.9	739.5	798.7	823.4	802.2

A summary of the latest, key epidemiological TB statistics for South Africa is presented in Table 5.2 below. These statistics highlight the enormous TB burden faced by SA.

Table 5.2 TB statistics for South Africa (2012).

Source: WHO, 2013.

	Total Number	Rate (per 100,000 population)
Mortality (excludes HIV + TB)	31,000	59
Prevalence (includes HIV+TB)	450,000	857
Incidence (includes HIV+TB)	530,000	1003
Incidence (HIV+TB only)	330,000	631
Case Detection, all forms (%)	62,000	

Figure 5.2 below and table 5.3 in the next page show the treatment outcomes of the current TB regimen for new TB cases, for the period 2000–2009. The data shows an improvement in the success and cure rates, albeit these are still below the target percentages.

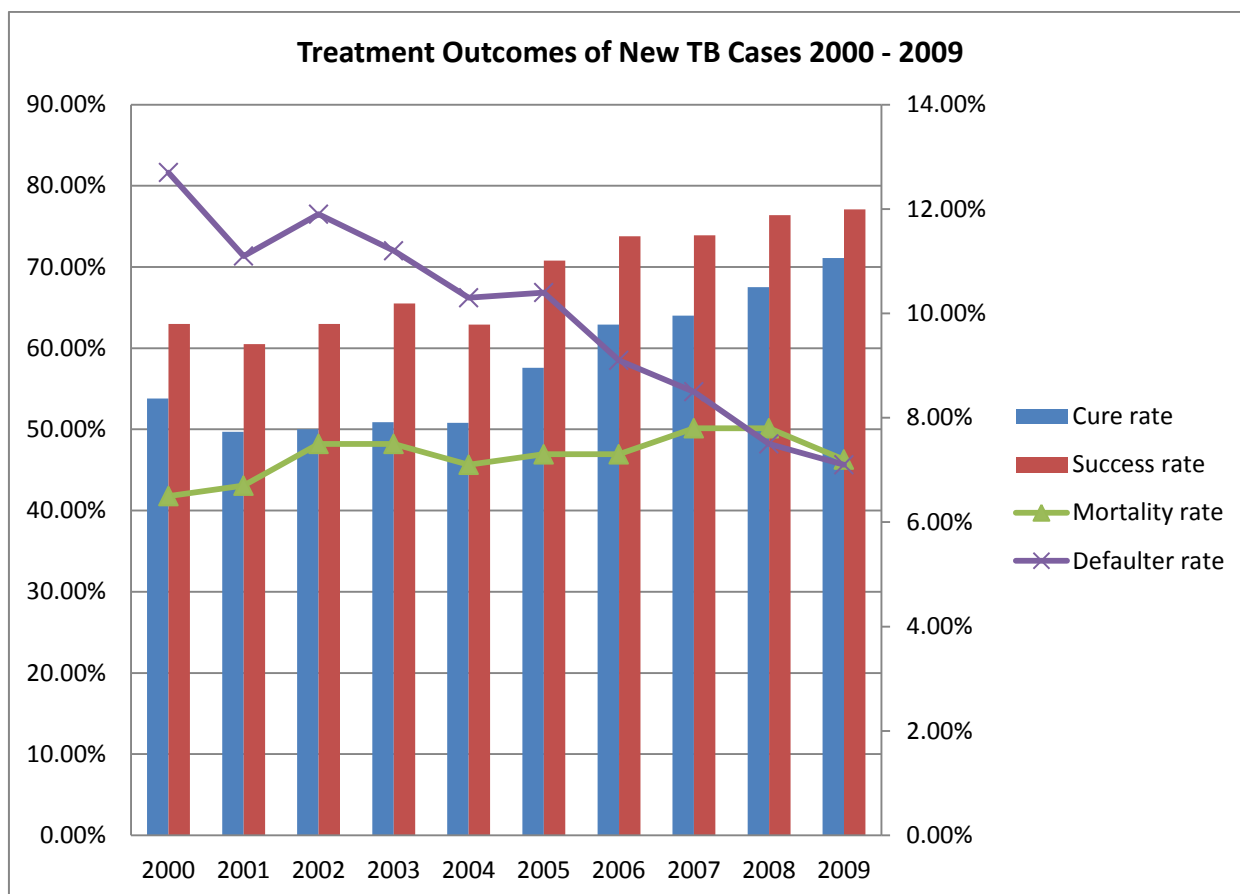


Figure 5.2 Treatment Outcomes of New TB Cases 2000–2009.

Source: National Strategic Plan on HIV, STIs and TB: 2012-2016

Table 5.3 Treatment Outcomes of New TB Cases 2000–2009.*Source: National Strategic Plan on HIV, STIs and TB: 2012-2016*

	2000 %	2001 %	2002 %	2003 %	2004 %	2005 %	2006 %	2007 %	2008 %	2009 %
Cure rate	53.80	49.70	50	50.90	50.80	57.60	62.90	64	67.50	71.10
Success rate	63	60.50	63	65.50	62.90	70.80	73.80	73.90	76.40	77.10
Mortality rate	6.50	6.70	7.50	7.50	7.10	7.30	7.30	7.80	7.80	7.20
Defaulter rate	12.70	11.10	11.90	11.20	10.30	10.40	9.10	8.50	7.50	7.10

The costs associated with financing the national TB programme in SA (adapted from the NSP, (2012-2016) and WHO (2013) are shown in figure 5.3 below and 5.4, including table 5.4 and 5.5 in the next pages.

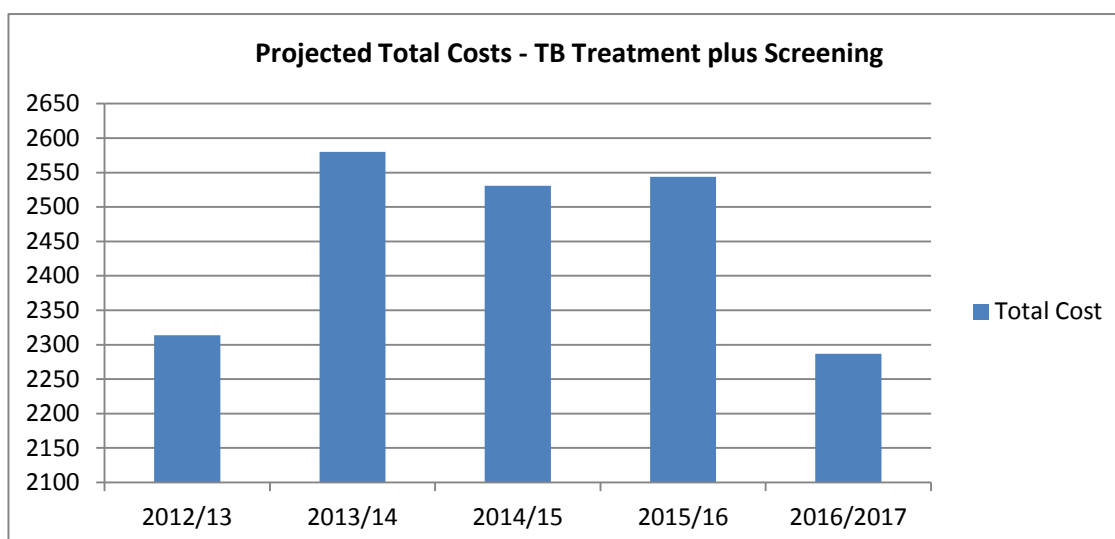
**Figure 5.3 South Africa's Department of Health budget for TB treatment (2012–2017). Annual costs (ZAR millions at 2011 prices).***Adapted from: National Strategic Plan on HIV, STIs and TB: 2012 – 2016.*

Table 5.4 South Africa's Department of Health budget for TB treatment (2012–2017). Annual costs (ZAR millions at 2011 prices).

Adapted from: National Strategic Plan on HIV, STIs and TB: 2012 – 2016.

	2012/13	2013/14	2014/15	2015/16	2016/2017
TB treatment	1329	1337	1356	1253	869
TB screening	985	1243	1175	1291	1418
Total Cost	2314	2580	2531	2544	2287

The total TB budget programme for financing TB control in SA, as reported to WHO for the WHO (2013) TB reported is shown in figure 5.4 and table 5.5 below. The figures show that SA has a large TB treatment programme, however TB R&D funding is still small, as will shown later in this report. The data for the year 2012 was not reported to the WHO.

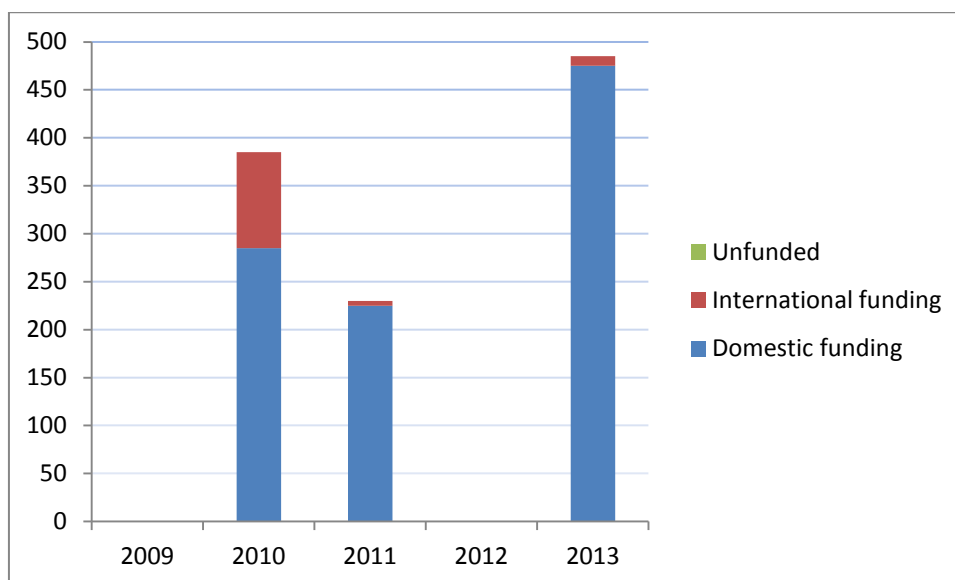
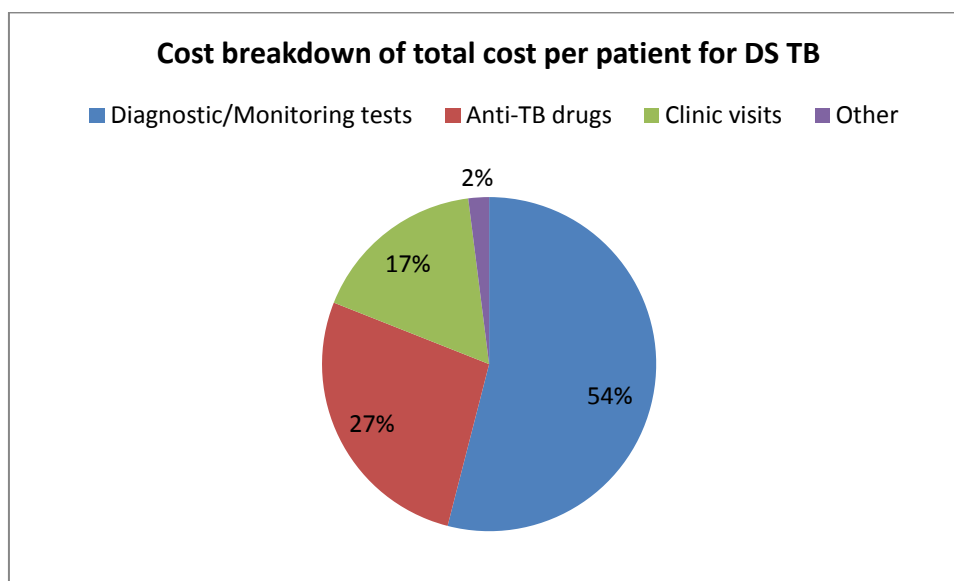


Figure 5.4 Financing TB control. (Source: WHO, 2013)

Table 5.5 Financing TB control 2013. (Source: WHO, 2013)

National TB programme budget (US\$ millions)	475
% Funded domestically	97%
% Funded internationally	3%
% Unfunded	0%

Figure 5.5a to 5.5c below show the cost breakdown of the total cost per patient for DS-TB, MDR-TB and XDR-TB in South Africa, adapted from the Pooran et al. (2013) report. A small proportion of these were MDR-TB (2%) and XDR-TB (0.2%). These DR-TB cases however contributed to a significant proportion of the total TB costs (32% and 13%, respectively), with anti-TB drugs being a major contributor to the total cost of TB diagnosis and treatment. DR-TB drugs made up 58% of anti-TB drug costs (Pooran, *et al.*, 2013).

**Figure 5.5a The Total Cost Breakdown of the Cost per Patient for DS-TB in South Africa.**

(Adapted from Pooran et al., 2013).

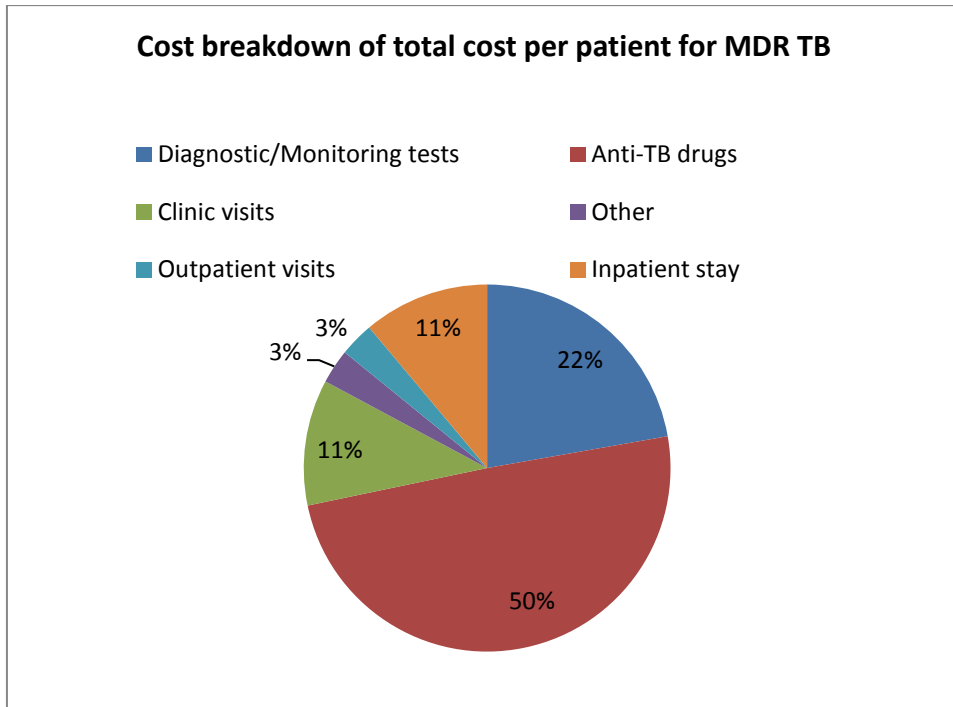


Figure 5.5b The Total Cost Breakdown of the Cost per Patient for MDR-TB in S. Africa.

(Adapted from Pooran et al., 2013).

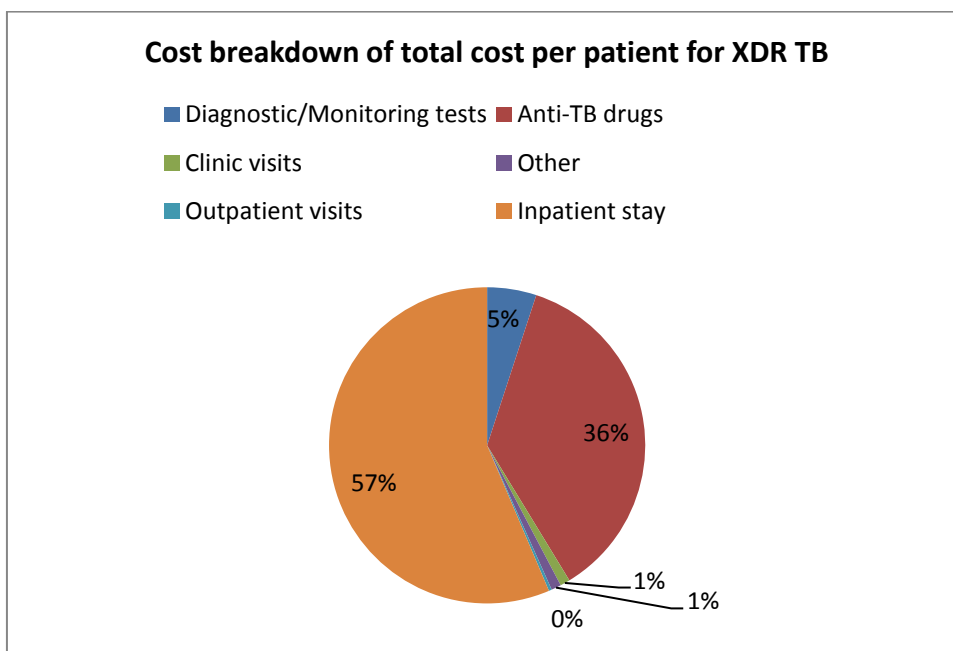


Figure 5.5c The Total Cost Breakdown of the Cost per Patient for XDR-TB in South Africa.

(Adapted from Pooran et al., 2013).

The breakdown of key cost drivers is given in Table 5.6 below, with the contribution of each cost component towards the total budget.

Table 5.6 Key Cost Drivers.

(Adapted from Pooran et al., 2013 and WHO, 2013)

Budget Item	Contribution to Total Costs %	Amount (\$ millions)
Anti TB Drugs	35	166
Outpatient / Clinic visits	14	67
Diagnostic/Monitoring Tests	37	176
TB Hospitalisation / Inpatient	11	52
Other	3	14
Total	100	475

Figure 5.6 in the next page shows the total drug cost percentages of notified cases of DS-TB, MDR-TB, and XDR-TB, using data from Pooran *et al.* (2013) paper. This shows that anti-TB drugs were a major contributor to the total cost of TB treatment.

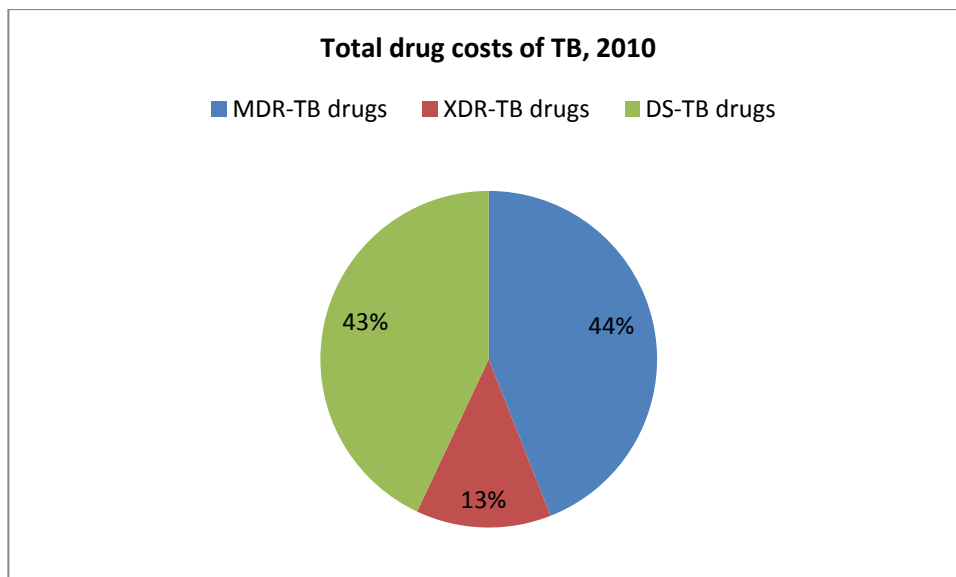


Figure 5.6 The Total Drug Cost of Notified Cases of Drug Sensitive (Ds-Tb), Multi-Drug Resistant (Mdr-Tb) and Extensively Drug-Resistant Tuberculosis (Xdr-Tb) Reported in 2010.

Adapted from Pooran, et al. (2013).

Data from the TAG, WHO and G-FINDER reports were used to do a correlation between TB R&D, TB disease burden and GDP per capita. The ratio of GERD to gross GDP was plotted against GDP per capita (figure 5.7 in the next page), in order to show the correlation and the national R&D intensity of various countries. GDP per capita is regarded as indication of a country's capability to invest in R&D, where high levels of GDP are associated with higher research expenditure (Walwyn, 2013). This is however not the case with South Africa.

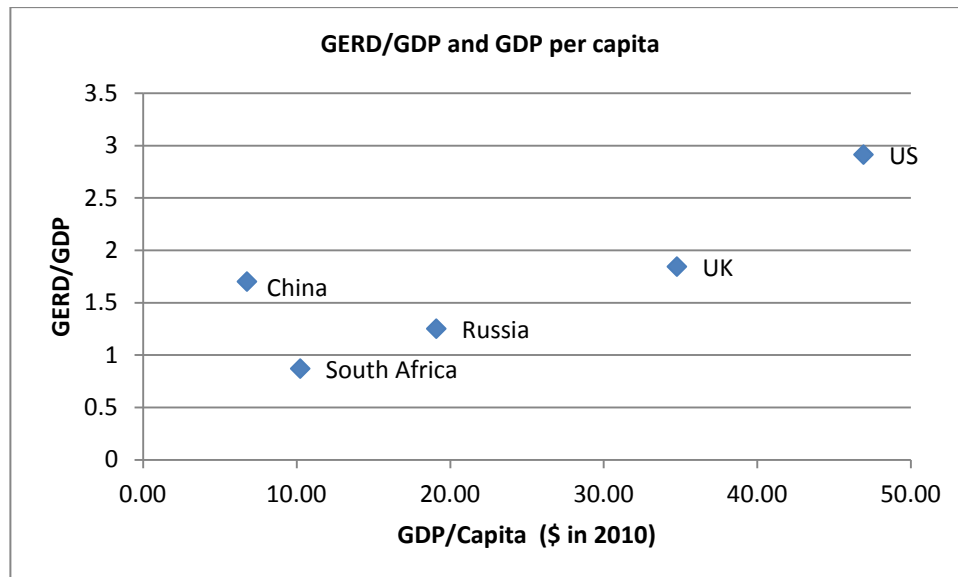


Figure 5.7 National R&D Intensity Correlates with GDP per Capita.

Source: OECD

The correlation between GDP per capita and TB incidence of various nations is shown Figure 5.8 below. The graph highlights the observation that a higher GDP per capita is associated with a lower TB incidence.

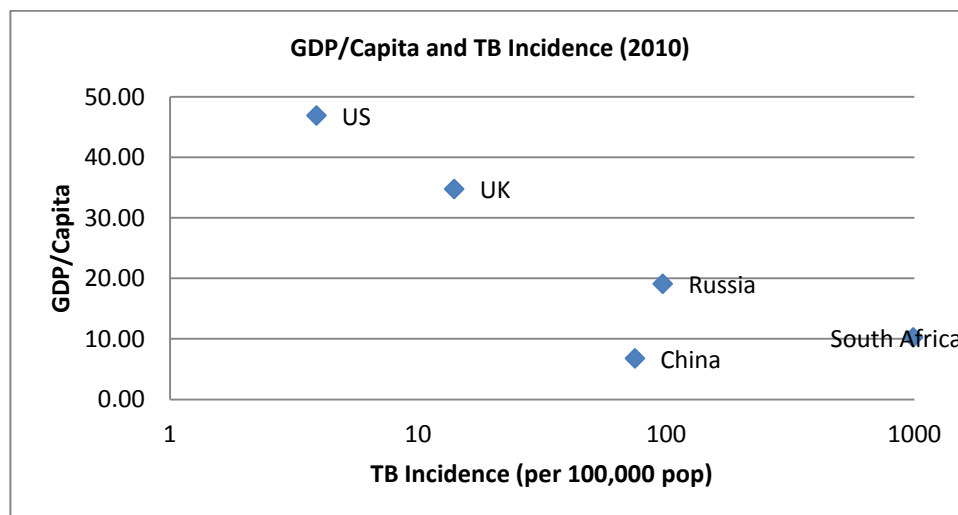


Figure 5.8 GDP per Capita Relative to TB Incidence.

Source: WHO, G-FINDER and OECD.

The optimal TB R&D expenditure was calculated, taking into account the TB burden and the affordability of such expenditure from the national treasury's programme.

The current TB programme budget was calculated from the WHO data and the NSP 2012-2016 data on incidence and treatment costs per TB patient. The full national TB programme budget as reported in the WHO global TB 2013 report was estimated to be \$US 475 million per annum.

The first source of possible savings with a new or optimised TB drug regimen was identified as a reduction in TB treatment time and the number of TB drugs. A reduction in the TB treatment time from the current 6 months and the number of drugs from four was estimated to result in a 1/3 reduction of the current treatment costs and result in net cost savings to the National Treasury of about \$158 million per annum. This assumption is considered reasonable as the savings figure is based on lower drug costs and a reduction in hospitalisation costs for DR-TB. Also, the newer TB regimens currently being tested are effective in shorter time periods and contain fewer drugs (Mitnick, McGee & Peloquin, 2009). The calculations are presented in Appendix 1.

Another source of cost saving with a new or optimised drug regimen was identified as an improvement in treatment outcomes. The current treatment success rate of new infectious TB cases is 77.1%, with a total retreatment rate of 6% of the patients treated per annum (a total of 52 586 patients were retreated in 2012). The target success rate for SA is >85% and a low rate of retreatment to 5% or below. A new or optimised drug regimen can improve the retreatment rate from the current 6% to the target 5%, saving the National Treasury \$17 million per annum in retreatment costs. This assumption is considered reasonable considering the retreatment rate of comparable bacterial infections and the target retreatment rate of 5% as stated in the SA national TB control programme goals and strategies document (Department of Health, 2012). In addition and to support the assumption made above is that the NSP (2012-2016) document has projected the TB cure rate will improve to the following percentages by the years indicated:

- 2012/13: 75% cure rate
- 2013/14: 77% cure rate
- 2014/15: 80% cure rate
- 2016/17: 85% cure rate

The value of the proposed TB R&D investment project was calculated as the NPV of the future savings over the 15 year new drug clinical development project duration. The assumption was that the R&D outcomes will achieve the minimum 15% hurdle rate required by public health programmes. A 15 year period is the expected reasonable average duration for a new drug development project.

To calculate the rNPV of future savings, the discount rate was assumed to be 8%, the expected duration of a new drug innovation as 15 years and the expected success rate of a new drug discovery project as 30%.

A success rate is the probability of a compound, diagnostic tool or regimen that enters the clinical testing pipeline will eventually be approved for marketing (DiMasi, *et al.*, 2003). The probabilities and assumptions in this research are based on the extensive work done by DiMasi *et al.* (2003) on the clinical drug development process.

For purposes of this research, R&D investment is expected to lead to at least three new innovations:

4. An optimised TB treatment regimen, using the current available drugs.
5. A new TB drug or vaccine development.
6. A new TB diagnostic tool.

The average cost of developing a new drug has been extensively researched and reported. It is estimated to be 250 million US\$. The most detailed evidence on the average cost of developing new compound to market, within a developing/low income country set-up is from Mahmoud *et al.* (2006), who estimate the cost at US\$ 250 million to US\$ 300 million per compound if they are developed by PPPs with foundation or government funding,

The cost of improving/optimising TB treatment regimen was estimated to be 15 million US\$, whilst the cost of developing a new diagnostic is estimated to be 60 million US\$. Mahmoud, *et al.*, (2006) indicate that the timelines and the costs of developing diagnostics are significantly lower than a new drug development, even though the process of developing diagnostics is similar to the drugs or vaccines development. The costs of developing new diagnostics depend on the type of diagnostic tool; the duration from

discovery to approval, technology, clinical trials, marketing and support costs (Mahmoud, *et al.*, 2006).

The R&D costs for regimen optimisation are lower because fewer trials, fewer patients, or both per trial may be needed to prove safety and efficacy as some data would have been established already for the compounds (Mahmoud, *et al.*, 2006).

The costs of developing new drugs and diagnostics reflect both the technical complexities of product development and the rising costs related to regulatory approval, which require large clinical trials to establish product safety and efficacy (Mahmoud *et al.*, 2006).

The success factor percentages used in this research (30%, 50% and 80%) are in line with the findings in the study by DiMasi, *et al.* (2003), where they found success rates of 75.0%, 56.1% and 36.3% for new drug development at the various stages of R&D.

The framework that is developed in this research considers the likely success factor of the R&D projects and the expected savings to the National Treasury, using the rNPV calculation. The research analyzed the effects of changes in the success rate at various expected savings percentages, keeping the discount rate at 8% and the duration of the R&D project over a 15 year development period. The net benefit to the national treasury varies from negative benefits of \$67 million (for a new drug development) to positive benefit of \$148 million savings (with TB treatment optimisation). Using the rNPV, expected savings and success factor methodology as described above, the net benefits of each R&D project are presented in table 5.7, 5.8 and 5.9 below.

For example, if 15 million US\$ is invested into optimisation of the current TB treatment regimen, with expected 5% minimum savings and a success factor of 80%, the RoI for the national treasury is estimated to be \$148 million. This approach is the best R&D investment approach that gives the most benefit to the government and is illustrated in table 5.7 in the next page.

Table 5.7 Calculation of the rNPV and Net Benefit using the TB treatment regimen optimisation.

Savings	5%	
Duration	15	Years
Discount Factor	8%	
Success Factor	80%	
Total	356.25	\$ million
NPV	203.29	\$ million
rNPV	163	\$ million
Development Costs	15	\$ million
Rol	148	\$ million

The investments needed for developing a new diagnostic tool are on average, US\$ 60 million. A realistic probability of a success factor, based on the figures reported by Mahmoud, *et al.* (2006) is 50%, and the expected savings to the government are 10%, the Rol for the government is expected to be US\$ 143 million. The calculations are given in table 5.8 below.

Table 5.8 Calculation of the rNPV for a new TB diagnostic.

Savings	10%	
Duration	15	Years
Discount Factor	8%	
Success Factor	50%	
Total	712.5	\$ million
NPV	406.58	\$ million
rNPV	203	\$ million
Development Costs	60	\$ million
Rol	143	\$ million

A new TB drug development clinical project on average costs US\$250 million. A new drug development project is inherently a risky project. Diel *et al.* (2003) calculated an average clinical success rate for a new drug development project as 22%. Based on this average success rate, if the success factor is estimated at 30% (i.e. the chances of the project being successful are only 30%), and the 15% expected savings figure used by health managers is met, the RoI for the government is a negative outflow (loss) of US\$67 million.

The calculations are presented in table 5.9 in the next page.

Table 5.9 Calculation of the Net Benefit for a new drug development.

Savings	15%	
Duration	15	Years
Discount Factor	8%	
Success Factor	30%	
Total	1068.75	\$ million
NPV	609.86	\$ million
rNPV	183	\$ million
Development Costs	250	\$ million
RoI	-67	\$ million

The various expected savings in rNPV terms, based on the current SA TB budget and the different scenarios of success rate percentages and expected savings percentages are given in table 5.10 and 5.11 in the next page and are also attached in appendix 1. The calculations are based on a discount rate of 8%, 15 year R&D project, the current NTP budget of 475 US\$ million dollars per annum. The expected savings (in rNPV terms) in table 5.10 to the national treasury are in US\$ million per annum.

Table 5.10 Calculation of the savings in rNPVs term of TB R&D projects.

		Success Factor		
Savings		80%	50%	30%
	5%	163	102	61
	10%	325	203	122
	15%	488	305	183

Table 5.11 below shows the most likely returns (based on the calculations presented above) for each of the three proposed R&D options. It is clear from the calculations that investments towards optimisation of the current TB treat regimen using public R&D funds is justifiable and the most attractive option as it yields the highest returns.

R&D investment towards new diagnostic tool is the next best R&D project to invest in with positive returns. However, the costs for developing are higher than the regimen optimisation and the success rate is lower.

R&D investment towards a new TB drug development has the least returns, compared to the other mentioned R&D options.

Table 5.11 Calculation of the RoI for different R&D proposals.

	Optimised TB treatment regimen	New diagnostic tool	New TB drug
Cost	15	60	250
RoI	148	143	- 67

Chapter 6 Discussion of Results

This research was designed to facilitate planning and resource allocation, and will form part of studies that will inform future TB R&D investment targets. This is because, despite progress made recently in TB care and control, reaching the proposed 2015 and post 2015 goal to end the global TB epidemic will require major technological breakthroughs from the R&D pipeline. Short, effective and well tolerated treatments for TB, improved diagnostics and effective vaccines are of key importance to end the global TB epidemic (WHO, 2013).

The layout of this chapter will follow the sequence of the research questions. Each research question will be answered and discussed on its own.

6.1 South Africa's TB disease burden

Despite being preventable, treatable, and curable, TB remains the second leading cause of death from an infectious disease worldwide after HIV (Frick & Jimenez-Levi, 2013). A wide range of factors affects TB risk. Variables such as GDP per capita, population structure, and HIV prevalence have been reported by Akachi, Zumla and Atun (2012) as some of the key risk factors affecting the national trends in TB burden.

The WHO annually produces estimates of TB disease burden (calculated in terms of incidence, prevalence, and mortality), as shown in table 5.2 above. The WHO data is produced using information gathered through expert opinion, surveillance systems, and consultation with respective countries (Akachi, *et al.*, 2012; WHO, 2013). Incidence has been the most commonly used indicator for measuring TB burden (Akachi, *et al.*, 2012). However, it may not be the most responsive indicator for measuring short-term changes in the TB burden attributable to changes in health service performance (Akachi, *et al.*, 2012). Akachi, *et al.* (2012) argue TB incidence can remain stable or even increase when case detection and treatment success rates are rising, if the risk of developing TB at the population level is increasing. This is possibly one of the reasons why the SA TB incidence rate for 2012 was reported as having increased, based on the recent adoption of the GeneXpert MTB/RIF diagnostic test by the SA government. It is further stated that TB mortality declines more rapidly than TB incidence because drug treatment reduces not only transmission but also the case-fatality rate (Akachi, *et al.*, 2012).

The TB disease burden results reported in figure 5.1, table 5.1 and 5.2 above, support the literature that SA TB disease burden is increasing. The number of cases detected for all forms of TB has steadily increased from 148 16 in 1999 to 401 048 in 2010 (NSP, 2012-2016). The TB epidemic is further compounded by drug resistant TB and HIV co-infection. The findings from the secondary data analysis in this research confirm literature reports that TB incidence is increasing in South Africa, and that drug resistant strains are on the rise, bringing an increase in cost of treatment.

South Africa also finds itself amongst the list of countries that have a high TB burden, a high TB-HIV co-infection burden and a high MDR-TB burden (WHO, 2013). The 22 high burden countries accounted for 81% of all estimated global TB incident cases. The reported incidence rate for SA is that at least 1 in every 100 people develops TB each year (WHO, 2013). The most recent decline in the incidence rate for SA was seen between 2009 and 2010. The current and forecast prevalence rate suggests that South Africa is unlikely to meet the Stop TB Partnership target of halving TB prevalence 1990 levels by 2015.

The TB cure rate, as reported in figure 5.2 and table 5.3 above, has improved from 54% in 2000 to 71.1% in 2009. The treatment success rate of new infectious TB cases has also improved to 77.1% (NSP, 2012-2016). However, this is still below the global target of >85% treatment success rate. This observation confirms literature reports by Mitnick *et al.*, (2009); Walwyn (2013); and Frick and Jimenz-Levi (2013) that new tools are required to stop TB. These tools require R&D investment.

6.2 Cost of South Africa's TB disease burden

One of the first objectives of this research was to review the available evidence on the costs and cost components that may act as cost drivers for TB care and management in South Africa.

The treatment of active TB disease requires combination drug therapy to avoid the development of drug-resistant TB. TB represents a high cost for South Africa, summing up to US\$ 475 million per annum according to the latest WHO report (WHO, 2013), shown in figure 5.4 and table 5.5 above. Figure 5.3 also highlights the sizeable NTP budget for SA. However, the TB R&D investment portion is much smaller in comparison.

These NTP budget calculations possibly underestimate the real overall cost of TB in South Africa. Diel *et al.* (2013) estimate that as much as 61% of costs due to TB management are mainly due to surrounding costs such as surveillance, screening of high risk groups, follow up and treating of contacts and BCG vaccination.

The comparison of costs between treatments for DS-TB, MDR-TB & XDR-TB, as shown in figures 5.5a to 5.5c highlights the disproportionate contribution of drugs and hospitalisation to the overall cost for drug-resistant TB. The drug costs for MDR-TB and XDR-TB are considerably higher than those for DS-TB. This is, in part, due to the longer treatment duration of MDR-TB and XDR-TB and the complex, more expensive drugs used in the latter two cases. Similarly, the cost of hospitalisation comprised 10% to 60% of total treatment costs.

The analysis done in this research also shows that DR-TB consumed about 32% of the 2011 national TB budget, despite the fact that it only accounted for about 2% of all TB cases. The need for extensive, specialised supervised patient care for DR-TB patients possibly contributes to the high cost of diagnosing, treating, and managing DR-TB patients.

This research supports the latest literature by Diel *et al.* (2013) that without innovative tools to control TB disease, it is unlikely the cost of TB will go down. Taking into account the current costs of TB disease, there is no doubt that the economic burden of TB provides good rationale for investing in the optimisation of current TB regimen and development of new, safe and efficacious TB drugs and vaccines. In line with the NSP goals for TB care, higher investments towards TB R&D could clearly contribute towards achieving the United Nations Millennium Development goal to improve TB treatment cure rate to > 85% and halve the 1990 levels of burden of TB in the African region by 2015 and beyond (Pooran *et al.*, 2013, and WHO, 2011).

Drug resistant TB is all too often a death sentence for many people globally, due to inadequate access to treatment and the complex, toxic, and lengthy treatment (Logan, 2013). The cost difference to treat resistant strains is also staggering.

This research supports the findings by Logan (2013); Walwyn (2013); and the WHO (2013) TB report suggesting for TB funding to increase in line with economic growth and for

increased political commitment, especially in BRICS countries that currently underperform in comparison to their ability to pay.

This research identified three potential areas of cost savings. These are:

- i. A reduction in the incidence of TB cases (number of new infections)
- ii. A reduction in TB treatment costs (per patient costs)
- iii. An improvement in the TB treatment success rate

These savings can be achieved with TB drug regimen optimisation, as calculations in table 5.7 to 5.9 above show. This research adds to theory that explores a wide range of therapeutic strategies that might be employed to stem the rising tide of TB in the world. Over the past several decades, TB treatment and policy have relied largely on a single, standardized regimen which is not going to end the epidemic alone (Mitnick, *et al.*, 2009).

The six month TB treatment regimen was selected as having the greatest potential for reducing the global burden of TB as clinical trials demonstrated cure in more than 95% of patients receiving regimens comprising isoniazid, rifampin, pyrazinamide, and ethambutol. However, most countries, including South Africa struggle to achieve a cure rate of 80%, let alone the target cure rate of >85%. Further, many HIV-infected TB patients are not adequately treated with a six month regimen, leading to treatment extension to nine months for such patients. In resource poor, developing nations such as South Africa, nine month regimens significantly tax an already overburdened healthcare system (Mitnick, *et al.*, 2009). The search for newer TB regimens is urgently needed, given the emergence of MDR and XDR-TB which are not effectively treated by the current standard TB regimen (Mitnick, *et al.*, 2009)

New strategies, better diagnostic tests, new drug regimens and vaccines are all urgently needed (Frick & Jimenez-Levi, 2013). This research proposes the R&D investment projects presented in tables 5.7 to 5.9, with the various expected savings figures. These new developments however need political will and adequate funding. Frick and Jimenez-Levi (2013) report South Africa will not meet its Millennium Development Goals of halving the number of TB deaths by 2015 and halving TB prevalence. In 2012, the TB incidence rate was estimated to be rising in SA, with the African region having the highest (75%) TB/HIV burden (WHO, 2013). Countries with a high burden of MDR-TB, like SA, are urged

to recognise TB as a public health crisis, which can be solved if country-specific research for new tools and strategies are accelerated, with findings translated into practice to facilitate better diagnosis, treatment and prevention of TB (WHO, 2013).

The analysis of TB cost data in this research shows that MDR-TB and XDR-TB contribute a considerable portion of the total TB programme, despite being only a small proportion of TB cases. This is possibly due to the higher cost of managing MDR-TB and XDR-TB. Pooran *et al.* (2013) reported that high DR-TB drug prices and the need for extensive supervised patient care contribute to the high cost of diagnosing and treating MDR-TB.

The MDR-TB burden in 2012 was estimated to be 1.8 % of all TB cases. Drugs for TB were a major contributor to the total cost of TB diagnosis and treatment, with DR-TB contributing the most to these costs (Pooran, *et al.*, 2013).

The cost of treating DR-TB is also likely to increase, given the recent adoption and implementation of the Xpert MTB/RIF which is likely to increase the detection rate of DR-TB. New strategies to manage DR-TB are therefore urgently needed in order to deal with this expected rise in DR-TB cases.

Secondary analysis of TB treatment care data shows that DR-TB management in SA is extremely expensive (Pooran, *et al.*, 2013). The key cost drivers in TB management are the anti-TB drugs, diagnostic/monitoring tests, and hospitalisation costs for DR-TB.

6.3 South Africa's current TB R&D expenditure

The South African Department of Science and Technology (SA DST) invested \$1,217,500 towards TB R&D in 2012 (Jimenez-Levi, 2012). This is a huge reduction compared to the \$4,000,000 TB R&D investment in 2011 (Frick & Jimenez-Levi, 2013). This drop in investment also moved the SA DST ranking from no.24 in 2011 down to no.43 in the 2012 TB R&D funders ranking. Frick and Jimenez-Levi (2013) highlight the conspicuous absence of the BRICS countries from the top funders list despite having 40% of the world's notified TB cases and 60% of its estimated MDR-TB cases.

The WHO (2013) has recognised that much more effort, substantial investment and innovation for new TB diagnostic development is essential to ensure availability of tests that are reliable, easy to use, affordable, and accessible. The current recommended TB treatment regimen for new cases of drug susceptible TB, with first line drugs is highly

efficacious. Nonetheless, it requires six months of treatment (WHO, 2013). The current recommended regimens for treatment of MDR-TB are associated with lower cure rates and multiple, serious adverse effects (WHO, 2013). Optimised drug combinations and/or new drugs are required to shorten and simplify treatment, to improve the efficacy and tolerability of treatment for TB (WHO, 2013).

The role that existing drugs and new compounds could have in shortening or improving treatment for tuberculosis has been reviewed by Mitnick, *et al.* (2009). The results of this research are in agreement with the findings by Mitnick *et al.* (2009) in that more potential options for improved TB treatment exist. It is now the right time for governments to invest in ways to optimise current TB treatment regimens. The key to current TB treatment shortening appears to be sterilizing activity, or the ability of drugs to kill the *tuberculous mycobacteria* that persist after the initial days of multidrug treatment (Mitnick, *et al.*, 2009).

This research proposes three TB R&D investment strategies for improving TB care and treatment. These can broadly be divided into treatments that use current TB and other existing drugs, those that will incorporate TB drugs and vaccines in development and TB diagnostic tools in development. While awaiting the advent of new agents and tools—which is unlikely in the near future, given the latest TAG report—this research advocates a strong commitment to optimising dosages of current TB regimen. Mitnick, *et al.* (2009) suggest in particular, optimizing the doses of rifampin and rifapentine, as they hold the greatest promise for ensuring better outcomes and may also permit shorter therapy, perhaps four months or less. Mitnick, *et al.* (2009) further propose use of existing drugs without a TB indication, such as moxifloxacin, can potentially improve treatment of drug-susceptible and drug-resistant TB and might increase the probability of TB cure over the course of six months. Additionally, these drugs may permit shorter regimens, at least in selected patients.

The increasing TB incidence and the growing problem of MDR-TB highlight the critical need for higher TB R&D investment to find new tools to fight the TB epidemic. Based on the GDP per capita and the TB disease burden, South Africa should invest more than the current \$1,217,500 towards TB R&D investment. The section below proposes how much these target investments should be.

6.4 South Africa's target TB R&D expenditure

In a study by Akachi, *et al.* (2012), a higher GDP per capita was significantly associated with reductions in TB incidence and mortality. An increase in funding for national TB programmes was also significantly associated with a downward trend in the TB burden. The proposal for the SA government to increase its TB R&D funding is based on the GDP per capita and the current TB incidence, as shown in figure 5.7 and 5.8.

South Africa is amongst the list of countries that underperform in TB domestic financing relative to their TB disease burden and income levels (i.e. ability to pay). The results of this research support the literature findings that high-burden countries will benefit from TB R&D investments in developing improved TB treatments. In South Africa, the National Treasury covers TB treatment within the public health programme. The use of science to develop new TB therapies is expected to reduce costs in the long term (WHO, 2013). To highlight the crucial role of R&D in ending the global TB epidemic, the WHO post-2015 global strategy includes 'intensified research and innovation' as one of three strategic pillars. TB care and control requires adequate funding sustained over many years (WHO, 2013).

The results of this research show that there are higher returns on the optimization of TB drug regimens versus new drug development. The argument proposed by this research is that further TB R&D expenditure can be justified from a purely economic return on investment consideration, considering that expenditure of public funds on TB treatment is high and significant savings can be made through improvements to the current drug regimen optimisation. This report will help policy makers in increasing public health R&D expenditure from present levels to those targets set by the WHO's CEWG and others. This return on investment will only be realised if public-funded R&D is focussed more directly on public health priorities. This research further contributes to ongoing efforts that seek to assess the impact of health R&D (Kuruvilla, *et al.*, 2006).

This research proposes three TB R&D investment projects, with success rate of each project ranging from 30% to 80%. The success rate is based on the perceived risk of the project. A new drug development project has a higher risk compared to a regimen optimisation project using current available drugs. A success rate of 30% is considered likely for a high risk project, such as a new drug discovery project. A success rate of 80%

is considered for a project that is very likely to be successful, such as a TB drug regimen optimisation project. The justification for these assumptions was discussed in chapter four above.

The expected savings rates used in this research range from 5% to 15%. A figure of 15 % is used by managers of public health programmes as a guide in the evaluation of a proposed new programme (Walwyn, 2013). To be conservative, this research assumed the maximum savings percentage to be 15% although the annual savings in the proposed R&D investments are likely to be higher. This is because, optimisation of the current TB regimen is likely to reduce the duration of treatment and the number of drugs, thereby reducing the treatment cost per patient (Mitnick, *et al.*, 2009).

The rNPV of future savings for the three different R&D projects, across the various success rate percentages and expected savings percentages are presented in table 5.7 in chapter six and appendix 1.

The 2012 TB R&D investment by the SA government was reported as \$1,217,500 in the latest TAG report (Frick & Jimenez-Levi, 2013). This is a huge under investment compared to the previous year (2011) investment of \$4,000,000 and considering the growing TB disease burden and a sizeable GDP per capita.

The optimal South African TB R&D budget is calculated to be about in the range of 15 million US\$ and 60 million US\$, using the success factor, expected savings and rNPV framework. When using the RoI factor analysis and TB regimen optimisation investment approach, the optimal TB R&D budget should be US\$ 58 million per annum. These calculations are presented in table 5.7 to 5.11 and in appendix 1.

The proposal this research makes is for the SA government to invest at least or a minimum of US\$15 million towards TB R&D drug optimisation drug regimen. This is the approach that is likely to give higher returns with a higher success rate and lower investment upfront. Higher TB R&D investments, up to US\$ 58 million per annum are justifiable based on GDP per capita. Regimen optimisation using public R&D funds is justifiable and the most attractive option.

The analysis and calculations in this research support the observation by Jimenez-Levi (2012) and Walwyn (2013) that middle income countries that have massive TB disease burden and a significant GERD and GDP, like South Africa, will benefit from higher TB R&D investments.

The proposed goal of the post-2015 global TB strategy is to end the global TB epidemic. However, despite the historical major progress in TB care and control, reaching this goal will require major technological breakthroughs from the R&D pipeline, such as short, effective and well-tolerated treatments, point-of-care diagnostic test, and an effective post-exposure vaccine.

These tools will be of key importance to end the global TB epidemic (Frick & Jimenez-Levi, 2013). As South Africa is amongst the list of countries with a high TB rate and high burden of TB-HIV co-infection, greater engagement between the government, NGOs and the private sector is urgently needed. Collaboration between stakeholders, especially in middle and low income countries play a big role in spearheading research for new diagnostics, drugs, and vaccines.

The results of the research show that there are higher returns on the optimization of TB drug regimens versus new drug development. The argument proposed by this research is that further TB R&D expenditure can be justified from a purely economic return on investment consideration, considering that expenditure of public funds on TB treatment is high and significant savings can be made through improvements to the current drug regimen optimisation. This report will help policy makers in increasing public health R&D expenditure from present levels to those targets set by the World Health Organisation's Consultative Expert Working Group (CEWG) and others. This return on investment will only be realised if public-funded R&D is focussed more directly on public health priorities.

Chapter 7 Conclusion

TB R&D continues to suffer from a shallow sense of shared urgency and political will among government and corporate funders in high, middle, and low income countries. Decreased TB R&D funding delays the development, approval, and implementation of better diagnostic tests, new drug regimens, new drugs and vaccines that are urgently needed to fight and ultimately end the global TB epidemic (WHO, 2012). Frick and Jimenez-Levi (2013) highlight how the BRICS countries (Brazil, Russia, India, China, and South Africa) are underrepresented among the top 30 donors towards TB R&D funding—despite having 40% of the world's notified TB cases and 60% of its estimated MDR-TB cases.

TB R&D relies heavily on ten funders, who in 2012 provided 78% of the global total, indicating a shallow sense of urgency and political will globally (Frick & Jimenez-Levi, 2013). TB R&D remains an endeavour financed primarily by philanthropic and public institutions in the U.S. and the U.K. The top two funders (the BMGF and the U.S. National Institute of Allergy and Infectious Diseases (NIAID)) each spent over \$100 million and together comprise 45% of the global total (Frick & Jimenez-Levi, 2013). Walwyn (2013) reported that the BRICS countries invested less than 0.05% of their total R&D spending to TB, despite the heavy burden of TB in those countries. This research adds on to that theory and observation and seeks to find optimal TB R&D targets for the SA government.

This research highlights literature findings which call for robust R&D investment and financial commitments to support lifesaving research. The latest TAG report reveals that funding for TB R&D dropped by \$30.4 million in 2012 compared with 2011 (Frick & Jimenez-Levi, 2013). This was the first year since TAG began reporting in 2005 that the global funding total decreased compared with the previous year. The South African public TB R&D funding also saw a drop from \$4,000,000 to a mere \$ 1,217,500 for the SA DST, despite an increasing TB disease burden (Frick & Jimenez-Levi, 2013).

The latest TAG report shows that globally, TB R&D funding fell in four of the six research areas (Frick & Jimenez-Levi, 2013). The gap between the actual and desired spending seems to be widening in most TB research categories. It was also the first year since 2005 that funding for drug research declined, falling 6.7% (Frick & Jimenez-Levi, 2013). The gap between actual and required spending is largest for drug development.

With this setback, the total spending on TB R&D in 2012 was below the investment levels seen in 2011 and 2010, and represents only 31.4% of the \$2 billion annual funding target outlined in the 2011–2015 Global Plan (Frick & Jimenez-Levi, 2013). Frick and Jimenez-Levi (2013) also call for a dramatic increase in funding in order for advancement of promising new tools.

This research focused on developing a framework to determine the required TB R&D expenditure based on improving the current TB treatment regimen. The framework developed considers the likely success factor/rate, the expected savings in rNPV terms, the GDP per capita, GERD and the TB disease burden. The framework percentages/assumptions are based on extensive work done on new drug, regimen optimisation and diagnostic development costs by DiMasi *et al.* (2003) and Mahmoud, *et al.* (2006). TB treatment regimen optimisation is the R&D investment option that is likely to give higher returns and is less risky is the most attractive option and justifiable.

The research also focused on how the existing agents, and new compounds, may be used to improve standard anti-TB therapy and the likely savings to the National Treasury thereof. Shortened regimens, failures or relapses would be the measure of improved standard TB treatment.

This research proposes that optimisation of the current TB regimen is possible through new drug dosages, new combinations, or new formulations of existing drugs.

This research adds to theory by Mitnick, *et al.*, (2009) amongst others, which states that it is quite likely that other treatment approaches based on the currently available TB drugs may yield superior regimens. Mitnick *et al.* (2009) calls for renewed focus on improving the efficacy and shortening the duration of tuberculosis treatment researching treatment combinations other than the current standard TB regimen (Mitnick, *et al.*, 2009).

Recent progress has been made in South Africa in improving access to TB diagnostic tools, for example the adoption of Xpert MTB/RIF. Further strengthening of the TB treatment regimens could help to accelerate this progress.

The results of this research also support the findings by Akachi *et al.* (2012); which state that increased investment in TB national programmes and R&D lead to improved case detection rate and treatment success rate.

7.1 Research Limitations

The researcher acknowledges the limitation of this research, as it is difficult to estimate the value of a new optimised regimen or new drug before its use in the market, because both positive and negative effects may be discovered (Mahmoud, *et al.*, 2006).

The limitations of this research are further compounded by the unknown accuracy of the data used and the assumptions made in the calculations. Some of the data used in this research calculation was based on actual, retrospective data, whereas the estimates used in the RoI calculations are prospective estimates, i.e. best guesses based on literature for TB drug development costs. However, the data used was sourced from the most reliable sources and relied on the latest, quality data. The literature used to support the assumptions made in the calculations was also the most extensive work done on R&D costing and analyses.

7.2 Recommendation to the South African Government

The SA government has made recent good progress in response to the dual epidemics of HIV and TB. The NSP (2012-2016) document reflects the progress made in achieving a clearer understanding of the challenges posed by HIV, TB and STIs. What is needed now is political will and commitment to sustain and improve the recent gains.

An increase in unity of purpose among all the stakeholders who are driven by a shared vision towards the long-term vision of zero new HIV and TB infections is urgently needed.

The SA government must endeavour to respond to the TB disease burden not only as an emergency that needs to be controlled and managed, but also as an investment in the health of its people, the SA citizens.

The secondary data analysis, RoI calculations, and the optimal TB R&D investment from the government perspective used in this report strongly recommend and call for higher TB R&D funding investments than the current \$1,217,500 investment, as reported in the latest TAG report by Frick and Jimenez-Levi (2013).

The optimal South African TB R&D budget is calculated to be in the range of US\$15,000,000 and US\$ 60, 000,000 when using the success factor, expected savings

and rNPV framework. When using the RoI factor analysis and TB regimen optimisation investment approach, the optimal TB R&D budget should be US\$ 58, 000, 000 per annum.

The rising incidence of TB and MDR justifies the call for higher TB R&D spending.

The justifiable and most attractive R&D investment option is regimen optimisation as it results in higher returns and has lower risks. Importantly, a strong political will and commitment to fight and stop TB is needed.

While awaiting the advent of new agents and tools—which is unlikely in the near future, given the latest TAG report—this research advocates a strong commitment to optimising dosages of current TB regimen.

7.3 Recommendation for the Private Sector and other Stakeholders

Collaboration among all stakeholders who are driven by a shared vision towards the long-term vision of zero new TB infections is urgently needed.

7.4 Recommendation for SA citizens

All South African citizens need to maintain the positive response to the national theme *I am Responsible. We are Responsible, South Africa is Taking Responsibility* (NSP, 2012-2016). SA citizens need to unite with the efforts by the government and other stakeholders to reduce new infections and to create an environment that is enabling for all.

7.5 Conclusion

With the current high TB treatment costs and rising TB incidence, several potential strategies exist for improving TB treatment and care. This research proposes public fund R&D investments which can broadly be divided into treatments that optimize use of the current/existing TB drugs, those that will incorporate new TB drugs & vaccines in development and those involving new diagnostic tools. However, whilst awaiting the advent of new agents (new drugs, new vaccines or new diagnostic tools)—which is unlikely in the near future—this research advocates a strong commitment to the approach of optimizing the existing TB treatment regimen. The increase in TB R&D investment from the South African government will boost efforts to develop new tools to fight TB with developing country settings in mind.

Reference List

- Academy of Science of South Africa. (2009). *Consensus report on revitalising clinical research in South Africa*. Retrieved from <http://www.assaf.co.za/wp-content/uploads/2009/09/ASSAf-Clinical-Report-2009.pdf>. Accessed on 10 August 2013.
- Akachi, Y., Zumla, A., & Atun, R. (2012). Investing in improved performance of national tuberculosis programs reduces the tuberculosis burden: analysis of 22 high-burden countries, 2002-2009. *Journal of Infectious Diseases*, 15, Supplement 2:S284–92.
- Botchkarev, A., & Andru, P. (2011). A return on investment as a metric for evaluating information systems: taxonomy and application. *Interdisciplinary Journal of Information, Knowledge, and Management*. 6, 245-269.
- Buxton, M., Hanney, S., & Jones, T. (2004). Estimating the economic value to societies of the impact of health research: a critical review. *Bulletin of the World Health Organisation* 82(10), 733 – 737.
- CEWG: *Research and development to meet health needs in developing countries: strengthening global financing and coordination*. Geneva: WHO; 2012 [http://www.who.int/phi/news/cewg_2011/en/]. Accessed on 15 August 2013.
- Colebatch, H.K. (1998). *Policy* (1st ed.). Buckingham: Open University Press.
- Collins, F.S. (2012). Testimony before the health subcommittee of the energy and commerce committee United States House of Representatives. U.S. Department of Health and Human Services.
- Deloitte & Thompson Reuters (2010). *R&D value measurement. Is R&D earning its investment?* London: The Creative Studio. Deloitte.
- Department of Health (South Africa). (2001). *Health research policy in South Africa*. Pretoria.
- Department of Health (South Africa). (2012). *The national TB control programme goals and strategies*. Pretoria.

- Diel, R., Vandeputte, J., de Vries, G., Stillo, J., Wanlin, M., & Nienhaus, A. (2013). Costs of tuberculosis disease in the EU – a systematic analysis and cost calculation. *European Respiratory Society*. 1-23. doi:10.1183/09031936.00079413.
- DiMasi J. A., Hansen R. W., & Grabowski H. G. (2003). The price of innovation: new estimates of drug development costs. *Journal of Health Economics*. 22:151–85.
- Drugs for Neglected Diseases initiative. (2013). *About us / Overview*. Retrieved from <http://www.dndi.org/about-us/overview-dndi.html>. Accessed on 20 September 2013.
- Ehrlich, E. (2012). NIH's role in sustaining the U.S. economy. A 2011 update. United for medical research. Retrieved from <http://www.unitedformedicalresearch.com/wp-content/uploads/2012/03/NIH-Role-in-Sustaining-the-US-Economy-2011.pdf>. Accessed on 10 September 2013.
- English, R. & Padarath, A. (2013). Editorial. In Padarath A & English R (Eds.), *South African Health Review 2012/13*, pp. vii – xi. Durban: Health Systems Trust.
- Frick, M. & Jimenez-Levi, E. (2013). 2013 Report on tuberculosis research funding trends, 2005 – 2012. 2nd Ed. New York, Treatment Action Group/Stop TB Partnership, 2013.
- Floyd, K., Fitzpatrick, C., Pantoja, A., & Raviglione, M. (2013). Domestic and donor financing for tuberculosis care and control in low-income and middle-income countries: an analysis of trends, 2002—11, and requirements to meet 2015 targets. *Lancet Global Health*; 1: e105-e115
- G-FINDER. (2012). Public Search Tool. London: Policy Cures; 2012 <http://www.policycures.org/g-finder2012.html>. Accessed on 20 October 2013.
- G-FINDER. (2011). *Neglected disease research and development: is innovation under threat?* London: Policy Cures; 2011 <http://policycures.org/index.html> Accessed on 20 October 2013.
- Global Alliance for TB Drug Development. (2013). *TB Alliance Pipeline*. Geneva: TB Alliance; 2013 <http://www.tballiance.org/downloads/Pipeline/TBA-Pipeline-Q3-2013.pdf>. Accessed on 21 October 2013.

- Hall, B.H, Mairesse, M., & Mohnen, P. (2010). Measuring the returns to R&D. In *Handbook in Economics*. (pp 1034–1074). California, USA: Elsevier B.V.
- Hillman, A.J., & Keim, G.D. (1995). International variation in the business-government interface. *Academy of Management Review*, 20(1), 193.
- Jimenez-Levi, E. (2012). 2012 Report on tuberculosis research funding trends, 2005 – 2011. 2nd Ed. New York, Treatment Action Group/Stop TB Partnership, 2012.
- Kuruvilla, S., Mays, N., Pleasant, A., & Walt, G. (2006). Describing the impact of health research: a research impact framework. *BMC Health Services Research* 6(134), 1–18.
- Loddenkemper, R., Sotgiu, G., & Mitnick, C.D. (2012). Cost of tuberculosis in the era of multidrug resistance: will it become unaffordable? *European Respiratory Journal*, 40, 9-11. doi: 10.1183/09031936.00027612.
- Logan, S. (2013). *Drug resistant tuberculosis: old disease – new threat*. All Party Parliament Group on Global Tuberculosis. Retrieved from <http://www.appg-tb.org.uk/images/reports/Report%20on%20TB%2011.04.2013%20-MTA.pdf>. Accessed on 21 October 2013.
- Madrigal, D. & McClain, B. (2012). Strengths and weaknesses of quantitative and qualitative research. Retrieved from <http://www.uxmatters.com/mt/archives/2012/09/strengths-and-weaknesses-of-quantitative-and-qualitative-research.php>. Accessed on 9 August 2013.
- Mahmoud, A., Danzon, P.M., Barton, J.H., & Mugerwa, R.D. (2006). Product development priorities. In Jamison, D.T., Breman, J.G., & Measham, A.R. (Eds.), *Disease control priorities in developing countries*. Retrieved from <http://www.ncbi.nlm.nih.gov/books/NBK11718/#A722>. Accessed on 1 November 2013.
- Mayosi, B.M., Mekwa, N.J., Blackburn J., Coovadia, H., Friedman, I.B., Jeenah, M., ... Paruk, F. (2011). *National health research summit report: strengthening research for health, development and innovation in South Africa*. Pretoria.

- Medicines for Malaria Venture (2013). *Defeating malaria together. About us*. Retrieved from <http://www.mmv.org/about-us>. Accessed on 25 October 2013.
- Meyer-Rath G., Bistline K., Long L., MacLeod, W., Sanne, I., Stevens, W., & Rosen, S. (2011). *The incremental cost of introducing Xpert® MTB/RIF into the South African national tuberculosis programme: Results of the National TB Cost Model 2011/12 - 2016/17*. Johannesburg: HE²RO Policy Brief Number 1, Health Economics and Epidemiology Research Office.
- Mitnick, C.D., McGee, B., & Peloquin, C.A. (2009). Tuberculosis pharmacotherapy: strategies to optimize patient care. *Expert Opinion Pharmacotherapy*; 10(3): 381-401.
- Moran, M., Guzman, J., Ropars, A.L., McDonald, A., Jameson, N., Omune, B., Ryan, S. & Wu, L. (2009). Neglected disease research and development: How much are we really spending? *PLoS Med* 6(2): e1000030, 0137 – 0146.
- Moran, M., Guzman, J., Abela-Oversteegen, L., Liyanage, R., Omune, B., Wu, L., Chapman, N., & Gouglas, D. (2011). *G-Finder report 2011: Neglected disease research and development: Is innovation under threat?* Policy Cures, London, 2011 (http://www.policycures.org/downloads/g-finder_2011.pdf). Accessed on 10 August 2013
- Medecins Sans Frontieres. (2012). Medical innovation for neglected patients. 2012.
- Mugabe, J. O. (2013). *Accelerating health research for Africa's development. An assessment of the effectiveness of national policies in Eastern and Southern Africa*. Pretoria: International Aids Vaccine Initiative (IAVI), University of Pretoria.
- National Department of Health: *National Health Research Summit Report*. Pretoria, 2011 [<http://www.doh.gov.za/docs/reports/2012/summitreport.pdf>]. Accessed on 12 August 2013
- Nwaka, S., Ilunga, TB., Da Silva, J.S., Rial Verde, E., Hackley, D., De Vre, R., Mboya-Okeyo, T., & Ridley, R.G. (2010). Developing ANDI: A novel approach to health product R&D in Africa. *PLoS Medicine* 7(6): e1000293.

- OECD. (1994). *The measurement of scientific & technological activities*. Paris. Organisation for Economic Cooperation & Development.
- Pooran, A., Pieterse E., Davids, M., Theron, G., & Dheda, K. (2013). What is the cost of diagnosis and management of drug resistant tuberculosis in South Africa? *PLoS ONE* (8)1: e54587.
- Rajalahti, I., Ruokonen, E-L., Kotomaki, T., Sintonen, H., & Nieminen, M.M. (2004). Economic evaluation of the use of PCR assay in diagnosing pulmonary TB in a low-incidence area. *European Respiratory Journal*, 23, 446-451. doi: 10.1183/09031936.04.0000.9704
- Rosen, S. (2013). *The costs of diagnosing and treating tuberculosis in South Africa*. Institute for Health Metrics and Evaluation. Retrieved from: <http://www.healthmetricsandevaluation.org/news-events/seminar/costs-diagnosing-and-treating-tuberculosis-south-africa>. Accessed on 18 September 2013.
- Røttingen J-A, Chamas C (2012) A new deal for global health R&D? The recommendations of the Consultative Expert Working Group on Research and Development (CEWG). *PLoS Med* 9(5): e1001219.
- Saunders, M. & Lewis, P. (2012). *Doing research in business and management*. United Kingdom: Pearson Education.
- Senkobe, F. & Mayosi, B.M. (2013). The state of the national health research system in South Africa. In Padarath, A. & English, R. (Eds.), *South African Health Review 2012/13*, pp. 141-150. Durban: Health Systems Trust.
- September, C. (2003). *Exceptional returns: the value of investing in health R&D in Australia*. The Australian society for medical research.
- Stephan, P. (2010). The economics of science. In *Handbook in Economics*, pp.1034–1074. California, USA: Elsevier B.V.
- Stone, V.I., & Lane, J.P. (2012). Modeling technology innovation: How science, engineering, and industry methods can combine to generate beneficial socioeconomic impacts. *Implementation Science* (7)44, 1-19.

- Svennebring, A. M., & Wikberg, J. E. S. (2013). *Net present value approaches for drug discovery*. SpringerPlus 2013 2:140.
- The World Bank. GDP per capita (current US\$). Accessed from <http://data.worldbank.org/indicator/NY.GDP.PCAP.CD>. Accessed on 2 October 2013.
- Walwyn, D. (2013). Determining quantitative targets for public funding of tuberculosis research and development. *Health Research Policy and Systems*, (11)10, 1-8.
- Weyer, K., Mirzayev, F., Migliori, G.B., Van Gemert, W., D'Ambrosio, L., Zignol, M., ... Raviglione, M. (2012). Rapid molecular TB diagnosis: evidence, policy making and global implementation of Xpert MTB/RIF. *European Respiratory Journal*, 42, 252-271. doi: 10.1183/09031936.00157212
- Whitworth, J. A. G., Kokwaro, G & Kinyanjui, S. (2008). Strengthening capacity for health research in Africa. *Lancet*. 372, 1590-1593.
- Williams, C. (2007). Research methods. *Journal of Business & Economic Research*. (5)3, 65-72.
- World Health Organisation (2006). *Public health, innovation and intellectual property rights report of the commission on intellectual property rights, innovation and public health*. Geneva: World Health Organisation. Retrieved from: <http://www.who.int/intellectualproperty/report/en/index.html>. Accessed on 2 October 2013.
- World Health Organisation (2011). *Global tuberculosis control: WHO report 2011*. Geneva: World Health Organisation.
- World Health Organisation (2012). *Global tuberculosis report 2012*. Geneva: World Health Organisation.
- World Health Organisation (2013). *Global tuberculosis report 2013*. Geneva: World Health Organisation.

World Health Organisation and Global Fund (2013) Tuberculosis financing and funding gaps. Retrieved from: http://www.who.int/tb/WHO_GF_TB_financing_factsheet.pdf. Accessed on 31 October 2013.

Appendix 1

1(a) rNPV savings – TB regimen optimisation

Savings	5%	
Duration	15	years
Discount Factor	8%	
Success Factor	80%	
Total	356.25	\$ mill
NPV	203.29	\$ mill
rNPV	163	\$ mill

1 (b) Calculation of the savings in rNPV terms of TB R&D projects,

		Success Factor		
		80%	50%	30%
Savings	5%	163	102	61
	10%	325	203	122
	15%	488	305	183

1 (c) Net Returns

Cost	Regimen Optimisation	New Diagnostic	New TB Drug
	15	60	250
Net Returns	148	143	-67

1 (d)

GDP/ Capita and GERD/GDP calculations for the selected various countries (Source: OECD)

2009	2009	Year
GDP/Capita	GERD/GDP	Country
34.78	1.844944905	<u>United Kingdom</u>
46.93	2.914543505	<u>United States</u>
6.78	1.701982672	<u>China</u>
19.11	1.251917343	<u>Russian Federation</u>
10.25	0.870789033	<u>South Africa</u>

1 (e) GDP/ Capita and GERD/GDP calculations for the selected various countries and TB epidemiology data (Source: OECD; WHO, 2013)

Country	GDP/Capita (2010)	GERD/GDP (2010)	Total Population (2011)	TB Prevalence Rate (per 100, 000 population)	TB Incidence Rate (per 100,000 population)
<u>United Kingdom</u>	34777	1.844944905	62,000,000	19	14
<u>United States</u>	46927	2.914543505	313,000,000	4,7	3,9
<u>China</u>	6781	1.701982672	1,348,000,000	104	75
<u>Russian Federation</u>	19109	1.251917343	143,000,000	124	97
<u>South Africa</u>	10251	0.870789033	52,000,000	857	1003
India			1,241,000,000	249	181

1 (f) TB funding and epidemiology data (Source: OECD; WHO, 2013)

Country	TB Mortality Rate (per 100 000 population)	TB Prevalence	TB Incidence	Total TB Budget (US\$ millions, 2013)	per pt cost (US\$) (Source: WHO, 2013)
<u>United Kingdom</u>	0.35,000	12,000	9,000		
<u>United States</u>	0.42,000	15,000	12,000	140	
<u>China</u>	47,000	1,400,000	1,000,000	367	
<u>Russian Federation</u>	22,000	180,000	140,000	1562	
<u>South Africa</u>	168,000	450,000	530,000	475	600
India	300,000	3,100,000	2,200,000	219	

1 (g) TB R&D funding data (Source: Frick and Jimenez-Levi, 2013; OECD)

Country	TB R&D funding (US\$ millions, 2013)	GDP (2012) US\$ current PPPs, millions	TB R&D/capita	Proposed TB R&D/capita
<u>South Africa</u>	1.2	569,529.80	0.02	0.03
India	9,5			

1 (h) TB epidemiology and funding (Source: WHO, 2013)

Country	Cost Savings from 1/3 Rx Cost Reduction (US\$ millions)	Total new and relapse (no. of cases, 2013) WHO	Total retreatment (no. of cases, 2013) WHO	Total retreatment (no. of cases, 2013) WHO	Retreatment cost (US\$)
<u>South Africa</u>	158	323,664.00	52,586.00	52,586.00	31,551,600.00

1 (i) TB R&D calculations

Country	Cost Savings from improving success rate (Retreatment cases drop from 6% to 5%)	Possible Savings	ROI Factor	National Wealth Index	Total Affordable TB R&D	Actual TB R&D	Factor
<u>South Africa</u>	29,974,020.00	356.25	57,936.97	1.4	57,938.41	1.2	48281.0