In the universe, there are things that are known, and things that are unknown, and in between, there are doors.

William Blake

Knowledge of what is, does not open the door directly to what should be.

Albert Einstein

A very little key will open a very heavy door.

Charles Dickens

There are so many doors to open. I am impatient to begin.

Charlie Gordon
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Introduction
Pulmonary tuberculosis (TB) has been identified in post-mortem examinations of Egyptian mummies from as early as ca. 2050 to 500 BC (1,2). The oldest statistics concerning TB are mortality records from cities in Europe (3), England and Wales (4) which extend back to the mid 18th and early 19th centuries. These records indicate TB as a major health burden with 25% of all deaths attributable to the disease, but only in 1882 did Robert Koch first present evidence that a specific microbe causes tuberculosis (5). Over subsequent decades TB incidence declined steadily (6). This decline occurred before there were effective antibiotics to treat TB (5) and was ascribed to the natural history of an epidemic on the downwards curve (7–9) and improved socio-economic conditions (8). Recently TB has continued to burden areas with poor socio-economic indicators (10) and a high concurrent HIV prevalence (5,11,12).

Pulmonary tuberculosis is a respiratory disease caused by *Mycobacterium tuberculosis* (*M. tb*) transmitted through droplet inhalation from person to person (13). Individuals with a high bacillary load, traditionally measured by sputum smear investigation, have been shown to be one of the drivers of the epidemic (12,14). In addition to bacillary load, the duration of exposure increases infection pressure and therefore the chance of transmission (15). The major transmission risk from an infectious (smear positive) individual is more likely before treatment is initiated and exposure to a household smear positive individual carries a 5-10 times higher risk in comparison to a smear negative individual due to the excess number of bacilli (16). The risk of transmission is also higher in crowded or slum areas (14,17) or areas with poor infection control (18,19).

The lifetime risk of developing TB disease once infected with *M. tb* is 10% (20) but in a HIV-positive individual the annual risk is 10% (21,22). Typical symptoms (13) of TB include chronic coughing defined as longer than two weeks (23), night sweats, loss of weight and appetite, chest pain and haemoptysis. The duration of untreated disease until self-cure or death is estimated to be three years although in a HIV positive person the mean survival of TB without treatment is less than 6 months (24). Current diagnostic tools include sputum smear microscopy and culture, chest x-ray and molecular diagnostic techniques, like line probe assays (LPA) (25) and the Xpert MTB/RIF test (Cepheid, USA) (26). In recurrent TB cases or other high risk groups (27), drug susceptibility tests are usually included in the diagnostic algorithm. Smear microscopy, although with a low sensitivity compared to culture (28), is used primarily because it is inexpensive (29,30) and can identify the most infectious cases (smear positive) (31) which is a key public health activity (16). Once a person is diagnosed with drug sensitive TB, treatment with a four drug combination (isoniazid, rifampicin, pyrazinamide, ethambutol) is initiated (27) to prevent the development of drug resistance, especially when using a rifampicin containing regimen (32). Good quality drugs and treatment monitoring are essential components of any TB treatment programme (27).
The widely used vaccine, Bacille Calmette Guerin (BCG) (33), protects mainly against complicated childhood disease namely disseminated TB and TB meningitis (34–37). If a person is infected with \textit{M.\textit{tuberculosis}} but without active disease, isoniazid prophylactic treatment (IPT) (27,38) may be initiated according to the country’s TB programme although its effectiveness has limitations (39–42) and therefore important other preventative measures are to reduce the force of transmission (17,43,44), to diagnose and treat TB early (43,44) and to prevent and/or treat HIV infection (17,45).

The vision of the Stop TB strategy (46) is a TB free world with the goal of reducing global TB by 2015 according to the Millennium Development Goals (47) and Stop TB partnership targets (46). These targets include: (i) to halt and reverse TB incidence by 2005, (ii) to reduce mortality and prevalence by 50% (compared to 1990) by 2015 and (iii) to eliminate TB as a public health problem by 2050. One of the objectives of the strategy is to ensure universal access to care for all people with TB through pursuing high quality directly observed therapy, short course (DOTS) expansion by improved case detection with quality assured bacteriology measured by a treatment success rate\(^1\) of >85%.

Progress has been made globally and the most recent global treatment success rate in new smear positive cases has been 87% (48) although case notification has stagnated. The global burden is however still enormous with 8.7 million incident cases in 2011, the largest estimated number of cases in Africa (26%) and Asia (59%) and 80% of the TB/HIV cases from Africa. New diagnostic techniques have been implemented (49–51) and new drugs (52,53) and vaccines (54–57) are promising. There are however funding gaps for TB care and control (48). US$1 billion is needed per annum (excluding TB/HIV) from international donors for low and middle income countries and an additional US$1 billion per annum for antiretroviral treatment in TB patients. Brazil, Russia, India, China and South Africa (the BRICS countries) are funding the bulk of their TB programmes nationally, but the funding is still insufficient for their respective TB control programmes. There are also funding gaps for research and development.

\section*{TB AND TB CONTROL IN SOUTH AFRICA}

South Africa is one of the 22 high burden countries in the world according to the WHO (27). TB mortality\(^2\) was 49/100000 (21-87/100000) in 2011, not including HIV positive individuals, with TB the main cause of death in South Africa (58). In 2011 TB prevalence\(^3\)

\footnotesize
\begin{itemize}
  \item \(\text{1\ Treatment success is achieved when a patient is cured (becomes smear negative) or completed treatment (was smear negative at diagnosis) in smear or culture positive patients (27).}\)
  \item \(\text{2\ TB mortality is defined as the number of deaths caused by TB in a given time period, usually one year.}\)
  \item \(\text{3\ TB prevalence is defined as the number of cases of TB at a given point in time.}\)
\end{itemize}

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Chapter 1

was estimated to be 768/100000 (399-1250/100000) and TB incidence 4 933/100000 (819-1180/100000) (48). Comparisons between the TB incidence in South Africa and globally, and other Southern African countries are shown in the figures below (Figures 1 and 2). These figures were compiled by professor Donald Enarson for a conference proceeding (used with permission) using the WHO Global Tuberculosis Report (59,60). From the figures it is obvious that although the global and African TB incidence is declining, it is still rising in South Africa.

Figure 1: Trend in tuberculosis incidence (global, Africa, South Africa)

Figure 2: Trend in tuberculosis incidence for selected countries in Africa

4 TB incidence is defined as the number of new and relapse cases of TB arising in a given time period, usually one year, as recorded and reported/notified.
A quarter of new and relapse\(^5\) notified cases in Africa are from South Africa (48). The case detection rate\(^6\) in 2011 was estimated to be 69% (58-83, 2.5-97.5 centile) with 47% of new cases smear positive\(^7\). The treatment success rate for all new cases in 2010 was 53%, but it was reported that because of missing data, this might have been an underestimation. 79% of new smear positive cases were successfully treated. The incidence and cure rates comparing the nine provinces of South Africa are shown in Table 1 (61). The HIV prevalence in incident TB cases was 65% (95%CI 65-66) and 83% of notified TB cases were tested for HIV in 2011 (48). South Africa is one of the five high TB/HIV burden countries globally in which 60% of all global HIV-associated TB is found.

South Africa is a high middle income country but the cost of treating one TB case with first line drugs is >US$1000 (48). Amongst the high burden countries it is only in Russia that treatment is more expensive. All the WHO policy guidelines for TB diagnosis have been incorporated into the South African TB programme since 2011. There are 244 smear facilities (0.5/100000 population), 15 culture/DST facilities (1.5/5 million population), 10 LPA facilities (1.0/5 million population), 55 Xpert Mtb/Rif facilities which use 37% of available modules and 53% cartridges globally, and a supranational reference laboratory in Pretoria.

South Africa’s contribution to global TB research efforts (48,55) includes research on vaccines for example MVA 85A (an attenuated vaccinia-vectored booster vaccine) phase 2b trials in infants and HIV-infected adults and an AERAS 402 phase 2b (an adeno-vectored, booster vaccine) trial. A new drug combination trial (NC-002) which investigates PA-824, bedaquiline, moxifloxacin and pyrazinamide for a shortened treatment period is also underway.

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5 New cases are defined as patients who never had treatment for TB or who have taken anti-TB drugs for less than one month. Relapse cases are defined as patients previously declared cured or treatment completed and diagnosed with bacteriologically-positive (sputum smear or culture) TB again (27).
6 The case detection rate is defined as an estimate of the ratio of notified:incident cases (48).
7 A smear positive patient is defined as a patient with one or more initial sputum smear examinations (direct smear microscopy) acid fast bacilli (AFB) positive (65).
Table 1: TB cure and incidence* rates in the nine South African provinces and in total (ZA) for 2005 and 2010

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<td>2005 TB register</td>
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*Defined as the number of new/relapse cases of TB in a given time period, usually one year, as recorded and reported/ notified


TB is acknowledged by the South African government as a major threat to the health of the South African population (62). TB is a notifiable disease and is recorded and reported (Health Act, Act No. 61 Of 2003) to the local, provincial and/or national Health Departments. The DOTS strategy was introduced in South Africa in 1999 (63) and the names and programmatic information of all TB cases on treatment are recorded in the paper-based TB treatment register at primary healthcare (PHC) facilities (64). The data are reported to the district and entered into an electronic TB register (ETR.net). District data are collated at provincial level before sent to national level and used for completing the WHO standard collection form (65).

All TB services, including diagnosis and treatment, are free of charge for the patients. For the diagnosis of TB, smears stained with fluorescent auramine-O (30,66) are primarily used to investigate sputum and diagnose smear positive TB (64) although the scale-up of TB diagnosis at public health facilities with Xpert as first line, which started in 2011, is expected to be completed in 2014 (67,68). Secondarily, sputum cultures are used to confirm the diagnosis, especially in patients with suspected smear negative or recurrent TB or other risk factors for drug resistant TB (64). At PHC level, sputum samples for bacteriological investigation are collected from TB suspects whose names are entered into the sputum register before the sputum is transported by courier to a centralised laboratory, the National Health Laboratory System (NHLS). Bacteriological investigations are requested using prescribed algorithms and standardised request forms. Results are returned to facilities per courier or fax. HIV testing is offered to TB suspects and rapid tests are done on site or at point of care according to the strategy of provider initiated HIV testing and counseling.

TB medication is procured by the TB programme through an official tender system and managed on provincial and district level (64). Ambulant TB patients on drug sensitive regimens receive daily treatment at healthcare facilities or in the community from
DOTS treatment supporters. Four drug fixed dose combination therapy is used for drug sensitive treatment, with a six month treatment period consisting of two months intensive phase (isoniazid, rifampicin, pyrazinamide, ethambutol) and four months continuation phase (isoniazid, rifampicin).

**RESEARCH QUESTIONS AND OVERVIEW OF THESIS**

TB case finding is a crucial area of enquiry since it identifies the source of infection in a community (16), indicating the individuals who are emitting bacilli. By treating these individuals and making them non-infectious, the transmission chain is cut. Adequate case finding minimises delay in treatment initiation (69). Case finding without treating the additional cases is irrational (16). Although cases are traditionally found by investigating those attending healthcare facilities complaining of symptoms of TB (passive case detection) (69), prevalence surveys aim to identify all prevalent cases, including those asymptomatic, and those who did not attend or were not investigated at healthcare facilities, in a community at a specific point in time (70). A prevalence survey from Viet Nam (71) for instance indicated 1.6 times more cases in the community than what was expected from notification rates and showed case detection was not as good as previously expected. Possible ways of case finding are illustrated in the ‘onion model’ (72) and Piot model (73) and can include the identification of patients who are initially lost to follow-up (74–77) and patients diagnosed in private healthcare systems (78,79).

The consequences of poor case finding include the continuous transmission of *M.tb* within households (80–83), communities (84) and in facilities (85), especially where airborne infection control measures are not implemented (86). Consequently people in health facilities, including healthcare workers (87,88), and people in the community continue to be infected with *M.tb*.

The overall aim of this thesis was to evaluate gaps regarding case finding in the South African National TB Programme according to the ‘onion model’ in order to develop interventions to address these gaps, thereby decreasing TB incidence and prevalence.
Chapter 1

The research questions are:

- What is the prevalence and predictors of culture positive tuberculosis in two communities in the Western Cape of South Africa?
- What proportion of patients who attend primary healthcare facilities has culture positive tuberculosis without being diagnosed?
- What proportion of smear positive TB patients are not started on treatment within a month of diagnosis, i.e. are initially lost to follow-up, and what are predictors of initial loss to follow-up at facility level?
- Is there an association between TB in healthcare workers and infection control measures at primary healthcare facilities in South Africa?
- What proportion of community healthcare researchers in the Western Cape develop TB in comparison to the general population?

Chapter 2 describes a prevalence survey in two communities in the Western Cape province of South Africa in 2005 with the aim to assess the completeness of case detection.

Chapter 3 describes an exit study completed at two primary healthcare facilities in the Western Cape province of South Africa in 2011. The participants in this study completed an exit interview after leaving the facilities in order to identify gaps in diagnosing TB among health facility attendees.

Chapter 4 describes a cross-sectional ecological study which aimed to determine initial loss to follow-up and determinants thereof at 133 primary healthcare facilities in five provinces of South Africa in 2009.

Chapter 5 describes, from the same set of primary healthcare facilities, the number of healthcare workers diagnosed with TB during a three-year period and the infection control practices at the facilities.

The study in chapter 6 aimed at determining TB incidence in community-based healthcare researchers from the Western Cape.

In chapter 7, the general discussion chapter, the implications of these studies are discussed.
REFERENCES

Chapter 1


Introduction


