Tuberculosis control has failed in South Africa – time to reappraise strategy

Robin Wood, Stephen D Lawn, Simon Johnstone-Robertson, Linda-Gail Bekker

South Africa's rate of tuberculosis (TB) has increased over the last 20 years, to now having the third-highest TB burden in the world. The TB control programme has primarily focused on effective case management of passively presenting TB cases, and progress has been recorded towards international treatment targets. While outcomes for notified TB cases have improved, this strategy failed to contain the TB epidemic. South Africa has the highest per capita annual risk of TB disease of comparably sized countries globally, and its communities have extremely high TB transmission rates. The rates of TB infection of children and adolescents are now similar to those reported 100 years ago in Europe long before chemotherapy became available. High rates of HIV testing of TB patients in Cape Town allows analysis of TB notification data stratified by age, type of TB and HIV status, and a better understanding of TB epidemiology. TB infection prevalence data from Cape Town communities allow estimation of the prevailing force of TB infection and, together with TB notification and prevalence data, the effective number of secondary infections and case finding proportions can be estimated. This better understanding of the major drivers of the TB epidemic allows reasons to be identified for failure of the present strategy. New control strategies can also be identified, that must be accompanied by novel TB control targets.

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South African reports to the World Health Organization (WHO) indicate that its tuberculosis (TB) notifications have increased fivefold over the last 20 years; in 2008, South Africa (SA) had the third-highest TB burden, after India and China.[1] SA and Swaziland now have the highest TB notification rates in the world, with about 1% of their populations developing TB annually.[1,2] SA was responsible for approximately 25% of the global burden of HIV-associated TB cases in 2007.[2]

While a worsening epidemic is revealed, data give little insight into understanding why TB control is failing. To better understand the epidemiology of TB control, the national and available community and city level data must be integrated; understanding this provides insights into the weaknesses of existing strategies and permits the development of additional rational interventions to regain TB control.

Desmond Tutu HIV Centre, and Institute of Infectious Diseases and Molecular Medicine, Faculty of Health Sciences, University of Cape Town
Robin Wood, MB BCh, BSc, FCP
Stephen D Lawn, BMedSci, MB BS, MRCPMD, DTM&H, Dip HIV Med
Simon Johnstone-Robertson, BSc, BSc (Hons), PDS
Linda-Gail Bekker, MB ChB, FCP, PhD

Department of Medicine, Faculty of Health Sciences, University of Cape Town
Robin Wood, MB BCh, BSc, FCP
Linda-Gail Bekker, MB ChB, FCP, PhD

Department of Science and Technology/National Research Foundation, Centre of Excellence in Epidemiological Modeling and Analysis, Stellenbosch University
Robin Wood, MB BCh, BSc, FCP
Simon Johnstone-Robertson, BSc, BSc (Hons), PDS

Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK
Stephen D Lawn, MMedSci, MB BS, MRCPMD, DTM&H, Dip HIV Med

Corresponding author: *Linda-Gail Bekker (Linda-Gail.Bekker@hiv-research.org.za)*

TB notifications

In 2007, 315 000 cases of TB were notified in South Africa – a rate of new and recurrent disease of 649 per 100 000 population.[2] Approximately 40% of nationally notified cases were tested for HIV infection, of which 73% were estimated to be positive, but this high prevalence may be affected by selection bias. The 2009 Cape Town (population 3.4 million) notification of 31 095 TB cases[3] represents double the number of TB cases reported in the USA (population >300 million people).[2]

Provider-initiated HIV testing in Cape Town TB clinics has increased to over 85%, allowing analysis of data stratified by age and HIV status, and providing a better understanding of the epidemiology of TB in a large urban population. Using denominators from the Cape Town population structure (Calle Hedberg, City of Cape Town and Stats SA) and TB notification data, age-specific TB notification rates stratified by HIV status were derived (Fig. 1). HIV-associated TB accounted for 44% of the total case burden. The peak TB notification

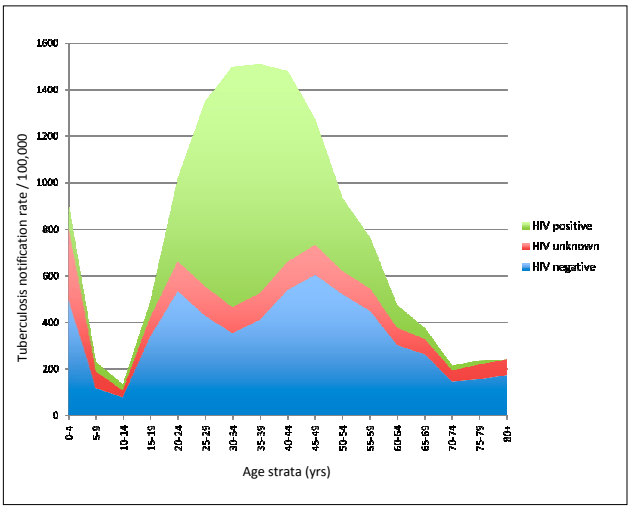

Fig. 1. TB notifications in 2009 for the City of Cape Town stratified by 5-year age groups and by provider-initiated HIV testing results. The demominators for age strata derived from National Department of Health/Health Information System Programme by disaggregating StatsSA district estimates (November 2009) using data from the `Small Area Layer` (StatsSA, 2004).

rate was among young adults, exceeding 1 400 per 100 000 population (Fig. 1). Of those aged between 25 years and 45 years, 63% of TB cases were HIV-associated. Of particular concern is that about 1% of children <5 years old were notified as having TB. Since children rapidly progress from TB infection to TB disease, childhood TB disease indicates recent ongoing TB transmission.[4,5] These data strongly indicate very high transmission rates in the community.

The cumulative lifetime risk of new and recurrent TB of HIV-uninfected individuals living in Cape Town was calculated by cumulatively adding the annual incidence of each 5-year age grouping (Fig. 2). The denominators for these calculations are the total age strata populations. As the HIV-infected population is included in the denominator, the resultant rate estimations are conservative. With the *status quo*, 1 in 5 individuals resident in Cape Town who remain HIV-uninfected will be at risk for developing TB before reaching the age of 60 years. This modern lifetime risk is unprecedented and is approximately twice that for individuals acquiring TB infection in the UK in the 1950s.[6] The cumulative risk of TB disease for those who become HIV-infected is considerably higher. Therefore our TB control strategies have failed, resulting in the highest reported global rates of TB disease in children and HIV-infected and uninfected adults.

TB infection

The epidemiological transitions relevant to the pathogenesis of TB from exposure to death or cure are outlined in Fig. 3. As with other infectious diseases, the key primary event is the initial acquisition of infection. While there have been no recent systematic attempts to measure TB infection rates in South Africa, data from Cape Town report extremely high prevalence rates of TB infection among children and adolescents.[7-10]

In 2005, the prevalence of a positive (>10 mm induration) tuberculin skin test (TST) among 7 457 primary school children (median age 8.6 years) was 37.4%.[7] A TST survey in a Cape Town school in 2005 reported TB prevalence to be 26.2% in 5 - 8-year-olds, increasing to 52.5% in 14 - 17-year-olds.[8] The prevalence of TB infection increased from 20% at school entry to 52% at 15 years, and reached 75% at 25 years in another study including HIV-negative adolescents and adults.[9] Note also that a further 8% of the population will have developed TB disease by the age of 25 years (Fig. 2) and they were excluded from the prevalence surveys. In 2 neighboring urban communities with low HIV prevalence, a high prevalence of TB infection in children (6 - 9 years) was reported.[10] Transmission rates

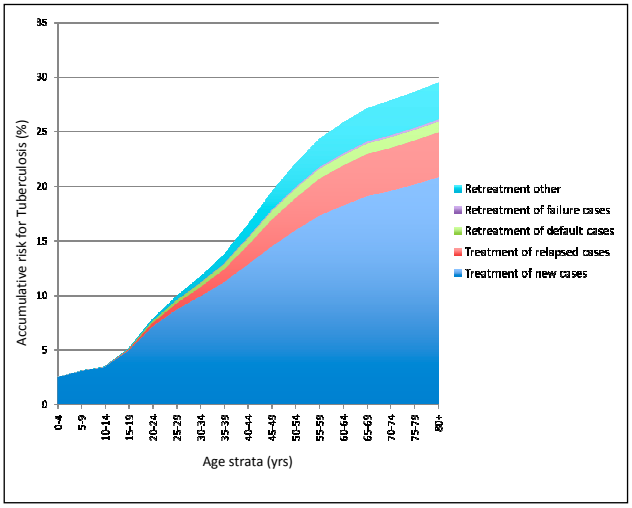

Fig. 2. The accumulated life-time risk of being notified with new or relapsed TB calculated for HIV-negative individuals. Values are based on cumulative 2009 age-specific TB notification rates for Cape Town.

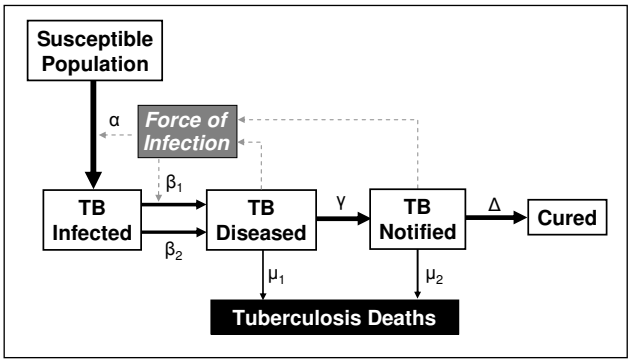

Fig. 3. An outline of TB transition states for a susceptible population from initial infection to disease and treatment outcome or death. The force of infection is shown as a function of prevalent untreated TB disease and determines the rate of primary TB infection (α) and the rate of multiple infection exposures (β_1) of latently infected individuals. β_2 is the progression rate from latent to active disease, γ the case-finding proportion, Δ the cure rate, and μ_1 and μ_2 the off- and on-chemotherapy mortality rates respectively.

increased between 1998 and 2005 and remained among the highest (4.1 - 5.8% per annum) in the world.[10]

Collectively, these studies indicate an extremely high prevalence of TB infection in Cape Town acquired during childhood, and that high rates of acquisition of TB infection continue throughout adolescence and into young adulthood. These high rates of TB transmission predate the HIV epidemic and have not declined over the last decade. Together with increasing TB notification rates, these data clearly indicate a failure of TB control.

Force of TB infection

The force of infection is the proportion of TB-uninfected individuals newly infected per annum, and is principally determined by the prevalence of infectious TB cases and the effective number of secondary cases infected by each infectious case. A TB prevalence survey of a random sample of the general population was conducted in a Cape township in 2005. The prevalence of laboratory-proven TB among HIV-uninfected and infected adults was 0.47% and 5.2% respectively.[11] After the community scale-up of antiretroviral therapy (ART), the prevalence of TB among the HIV-uninfected population did not change, but the prevalence among HIV-infected adults decreased from 5.2% to 1.3%.[12]

Cape Town studies estimated the force of TB infection to be between 4% and 8% per annum.[7-10] In historical perspective, these values are similar to the force of infection estimated for the UK population in the early decades of the 20th century, which was long before TB chemotherapy was developed. In 1900 in the UK, the force of infection was 10% per annum, declining to 1% around 1950 and to <0.01% by 2000.[13]

Fig. 4 shows the relationship between increasing force of infection and the proportion of the population with primary TB infection and the proportion multiply exposed to TB infection. Effective TB control interventions that produced small reductions in the force of infection in Cape Town could produce large benefits in transmission reduction. Reduction of the force of infection to 1% would decrease the proportion of the population exposed to multiple TB exposures from over 50% to <0.5% (β_1 in Fig. 3) and the proportion acquiring primary infection would decrease from 75% to <30% (α in Fig. 3).

Effective contact number

An effective TB contact is defined as a contact between an infectious pulmonary case and a susceptible individual, sufficient to result in TB infection.[14] The number of individuals infected by each case (the

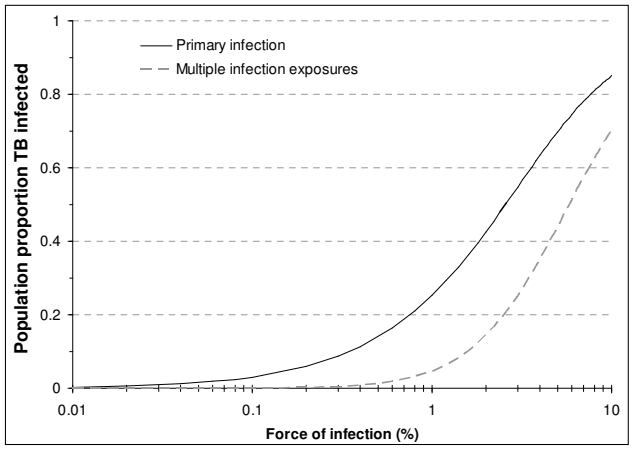

Fig. 4. The relationship between 'force of tuberculosis infection' and proportion of population acquiring primary TB infection and multiple infectious exposures. The prevalence of primary infection is defined as $P_1=[^{60}\Sigma_{x=0}(1-\exp(-Fx)]/61$ *and the prevalence of multiple infection exposures is defined as* $P_2=[^{60}\Sigma_{x=0}(1-\exp(-Fx)-(Fx)\exp(-Fx)]/61$ *where F is force of TB infection and x is age.*

effective contact number) is determined by the ratio of the force of infection and the prevalence of infectious pulmonary TB cases. The ratio between a force of infection of 4 - 8% (4 000 - 8 000/100 000) TB infection rate and a prevalence of smear-positive pulmonary cases notified during 2009 in Cape Town of 370/100 000 indicates an effective contact number of between 11 and 22. Historically, the effective contact number in the UK declined from 22 in 1900, to 10 in 1950 and to 1 in 1990.[13]

For long-term control of an epidemic, the effective contact number must be lower than the number of individuals who can be expected to produce a single new case of infectious pulmonary TB during a lifetime. As the lifetime risk in Cape Town of developing smear-positive pulmonary TB among HIV-negative residents is approximately 10%, the effective contact number must be reduced to <10 to achieve a reduction in the TB epidemic. Current interventions are not achieving this.

Impact of the HIV epidemic

The South African HIV epidemic has expanded markedly over 20 years, and it was recognised early that TB was a major cause of morbidity and mortality.[15,16] A pertinent question is the degree to which the HIV-associated TB epidemic has caused the failure to control TB or the manifestation of the failure to contain TB transmission. Although 44% of the total TB case load in Cape Town in 2009 was HIV-related, only 14.3% of smear-positive pulmonary disease was HIV-related. It therefore appears likely that the HIV epidemic disproportionately increases TB case load rather than TB transmission.

There is no strong evidence that HIV-associated immune suppression affects the acquisition of TB infection (α Fig. 3). Instead, HIV infection appears to be associated with a marked increase in risk of progression from latent infection to TB disease, following either a primary (β_2 Fig. 3)[17-19] or recurrent exposure (β_1 Fig. 3).[20,21] Case-finding proportions (γ Fig. 3) were reduced in HIV-infected individuals (44%) compared with HIV-uninfected (57%) in a Cape Town township.[7] However, the population case-finding proportion improved following introduction of an ART programme (64%).[8] TB case fatality (μ_1 and μ_2 Fig. 3) is increased particularly in those with low CD4 cell counts.[22] ART partially reverses immune suppression[23] and can reduce risk of TB progression after recent TB exposure (β_1 Fig. 3) and, together with isoniazid preventive therapy, can decrease the progression from latent to active disease (β_2 Fig. 3).[24] Active case-finding within ART programmes markedly improves TB case finding.[12,25-28]

Why is TB control failing?

Broad existing strategies for TB control are case-finding and treatment of active disease, treatment of latent TB infection, and vaccination with bacille Calmette-Guérin (BCG).[25] Universal BCG vaccination of all infants protects against progression to miliary TB and TB meningitis but does not affect TB transmission.[29] Treatment of latently infected individuals with isoniazid prophylaxis has not been widely implemented in either HIV-infected or uninfected populations in SA.[2]

The SA TB control strategy predominantly focuses on the quality of case management of patients passively presenting to TB clinics. Passive case-finding is detection of active TB disease among symptomatic patients presenting to medical services, and is promoted in developing countries as part of the WHO-recommended DOTS strategy.[30,31] Consequently, the primary targets and reporting statistics of the SA TB control programme has been the proportion of TB cases which are effectively treated under DOTS with anti-TB chemotherapy.[1,2] SA national DOTS coverage increased from 77% to 100% and the treatment success rate from 61% to 74% between 2001 and 2006.[1,2] However, TB notifications doubled in the same period.[1,2]

The TB burden was decreasing in industrialised countries before effective chemotherapy was introduced, with reductions in the force of infection from approximately 10% to 1% in the early 20th century.[13] Introducing effective chemotherapy in the 1950s consolidated these trends in improved TB control. While effective TB case management is necessary in TB control, it was, however, predicted that it would be insufficient for TB control in scenarios such as South Africa with a high force of infection, high proportion of latently infected individuals and a generalised HIV epidemic.[32] The DOTS strategy is insufficient in high HIV-burdened settings.[33] In high transmission settings where effective contact numbers are high, lower case-finding rates and delays in diagnosis and initiation of chemotherapy result in ongoing transmission.

Development of a new TB control strategy

The benefits of improved case-finding depend on the prevailing epidemiology of TB transmission. In a setting with a force of infection <1.0, detecting a case of TB will mainly benefit that individual alone. In contrast, the benefit of early detection of a TB case where there is an effective contact number >10 will additionally prevent up to 10 secondary cases. The benefits of increased and earlier case-finding on TB transmission are therefore significantly amplified in high-transmission settings. Decreasing TB infection rates is fundamental to achieving the long-term aim of TB control of a steady decline of disease in successive generations. Reducing the high force of TB infection, especially in high-density townships, should therefore become a primary target for long-term TB control. Historical TB control measures using community-based interventions such as enhanced and intensified case-finding strategies must be re-explored in view of the additional benefits accruing for decreasing transmission.[25,34,35]

Reducing the time period of infectiousness also directly influences the prevalence of infectious TB. The period of infectiousness results from delays including health-seeking behaviour, diagnostic delays and health systems delays in initiating effective chemotherapy. Intensified

case-finding can increase awareness of typical symptoms of TB disease, thereby improving health-seeking behaviour. Diagnostic delays can be reduced by using newer molecular diagnostic technologies, and improved health systems efficiencies can further decrease time to initiation of effective TB therapy.

High-risk communities should be specifically targeted, and age-specific interventions are necessary to interrupt TB transmission to infants and young children, school-age children and adolescents, and both HIV-negative and positive adult populations. A change in priority focus from case management to TB transmission reduction should be accompanied by incorporating new outcome measures that reflect ongoing TB transmission at national and sentinel sites. A reduction in TB disease rates among young children, and a steady decrease in the number of latently infected children at school entry and subsequently, would reflect a decrease of TB transmission to children. TB control among adults would be reflected by a decrease in the proportion of recent infections, a decrease in the effective contact number, and eventually a decrease in lifetime risk of TB disease. In HIV-infected patients, full implementation of existing ART guidelines will reduce the pre-ART TB disease burden. The TB infection rates of patients on ART probably reflect the current force of TB infection. The effectiveness of 6-month isoniazid prophylaxis therapy (IPT) to reduce TB disease in already latently infected individuals is very likely undermined where the force of TB infection is high and consistent with southern African data indicating little or no lasting benefit after 6 months IPT.[36,37]

Changing the emphasis from individual benefit to population benefit has parallels with the concept of using ART as prevention, which has been modelled as a potential strategy to control the HIV epidemic.[38,39] This may have an additional effect on control of HIV-associated TB.[40] The HIV force of infection is the result of prevalent community levels of HIV load and sexual networking, which can be reduced by widespread HIV testing and initiation of ART. Similarly for the TB epidemic, the drivers of the high force of infection are population prevalence of infectious TB cases and the effective contact number. Reducing the high force of TB infection, especially in high-density townships, should therefore become a primary target for long-term TB control.

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