Tuberculosis: yesterday, today and tomorrow

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Abstract. Tuberculosis (TB) remains an important public health challenge globally and in Australia. For the more than 10 million people who become sick with TB each year, the disease can cause immense personal and economic hardship, including loss of income and education through ill health, prolonged and arduous treatment, and stigmatisation – perpetuating a cycle of disadvantage. Past efforts to control TB have taught us much about modern disease control and public health. As the world grapples with the coronavirus (COVID-19) pandemic, the response to TB provides valuable lessons which can inform our response to COVID-19.

Yesterday

Tuberculosis (TB), the disease caused by the closely related group of mycobacteria within the *Mycobacterium tuberculosis* complex, is spread person-to-person through infectious aerosols generated within the lungs of persons with pulmonary TB disease. *M. tuberculosis* emerged as a human pathogen in pre-historic times. It has been hypothesised that changes in early human behaviour around the use of controlled fire may have facilitated the evolution of *M. tuberculosis* from an environmental organism to human pathogen[1,2]. Through history, TB has caused more deaths than any single other infectious disease[3].

TB is facilitated by economic disadvantage – overcrowded living conditions and substandard housing aid its spread. Modern changes in human behaviour brought on by the industrial revolution during the 18th and 19th centuries were exploited by the organism. At a time before the advent of effective treatments, the concentration of human populations within urban centres and large factories, characterised by cramped and overcrowded quarters, and poor sanitation and ventilation facilitated the amplification of TB spread[4]. These factors led to a peak in deaths from TB during the 1800s, when the disease is believed to have been responsible for around a quarter of all deaths in Europe[5].

In 1882, Koch discovered the bacillus responsible for TB disease[5]. The early 20th century saw progress in reducing disease rates through improvements in sanitation and living standards, pasteurisation of milk – effective in controlling disease caused by *M. bovis*[6] – and development of the Bacille Calmette Guérin (BCG) vaccine in the 1920s[7]. In the late 1940s, streptomycin and para-aminosalicylic acid were first used as anti-tuberculous treatments, followed by isoniazid, pyrazinamide, ethambutol and rifampicin – the four drugs which still constitute the standard first-line regimen for TB treatment[8].

As in the Northern hemisphere, TB was a leading cause of death in Australia at the turn of the 20th century[9]. Between 1948 and 1976, the Australian Tuberculosis Campaign provided free diagnostic and treatment services, and social support to those with TB. Anti-tuberculous drugs, once available, were also provided free[10]. The period of the Australian Tuberculosis Campaign saw a marked decrease in TB incidence in Australia; the program ended in 1976. The success of the Campaign highlights the role of active case finding in disease control. Australia has since maintained a low TB incidence, with <10 cases per 100 000 population reported annually[11]. This has led many to consider TB a disease of the past.

Today

Despite the advent of effective modern treatments, TB has exploited modern circumstances and remains a major global

public health threat. The emergence of HIV, which increases the risk of activation of TB disease approximately 20-fold, became a driver of the TB epidemic, particularly in sub-Saharan Africa[12,13]. Meanwhile, drug-resistance has become a dangerous threat to TB control, with resistance emerging faster than the drug development pipeline. Increasing frequency of global travel and migration has aided disease spread across borders and meant that Australia and other low-burden countries must maintain robust systems for early detection of TB disease in high-risk groups[14].

In 2015, the World Health Organization (WHO) published its Global End TB Strategy – marking a redirection from past TB control efforts to a more pro-active elimination strategy. The Strategy included ambitious targets to reduce TB-related deaths by 95% and the global incidence of TB by 90%, and to ensure that no TB-affected family faces catastrophic costs associated with TB treatment by 2035[15]. In 2018, the President of the United Nations General Assembly took the exceptional measure of convening a United Nations High Level Meeting on TB to garner political commitment to achieve the Strategy[16]. Despite significant efforts, the world is not on track to meet the End TB Strategy Targets. The WHO reported an estimated 10 million incident cases of TB and 1.5 million TB deaths in 2018[17].

Following the reduction in Australia's TB incidence during the Australian Tuberculosis Campaign, progress has plateaued – with essentially no reduction in TB incidence seen in the past three decades[18]. To achieve further progress, Australia must: scale up prevention of TB among those most likely to be infected who may go on to develop future TB disease; close the gap in TB burden faced by vulnerable and higher risk groups within the population; and contribute to addressing the TB epidemic at its source – beyond Australia's borders.

A hallmark of *M. tuberculosis* is its ability to achieve a dormant state and cause asymptomatic infection in exposed hosts. This greatly complicates diagnosis and control. Previously termed 'latent TB', the preference is now to describe this as 'TB infection' to emphasise its importance and justify treatment. Nearly one-quarter of the world's population is estimated to be infected with TB[19], and approximately 10% will go on to develop TB disease[20]. Treatment of TB infection is effective at preventing activation of TB disease, but testing and treatment of TB infection is limited by poor diagnostic and treatment options, and incomplete reach to at-risk populations. Scaling up management of TB infection among high risk groups such as recently arrived migrants from high-burden countries would reduce the pool of people at risk of becoming new TB cases in the future.

The incidence of TB among Aboriginal and Torres Strait Islander Australians remains around six times higher than that of the Australian born non-Indigenous population. The failure to close this gap highlights ongoing socioeconomic inequities and shortcomings in the health system's ability to provide patient-centred, culturally sensitive care. Social factors such as overcrowded housing and medical factors such as delayed diagnosis of TB and worse treatment outcomes among Aboriginal and Torres Strait Islander patients, contribute to continued transmission of disease in some communities[21].

Cross-border spread of TB, including drug-resistant TB, from Papua New Guinea to Australia's Torres Strait Islands has been documented[22]. This demonstrates that whilst having strong systems for detection and treatment of TB within Australia is important, it is insufficient to eliminate TB. As a high-resource setting with access to vast expertise in TB control, Australia has a responsibility to support its neighbours in the Asia-Pacific, where there is a large burden of disease and limited resources for TB control. Investment in regional TB control is likely to have direct benefits for Australia too. In the United States, it has been estimated that strategic investment in TB control in other countries could lead to a reduction in TB morbidity and mortality and overall cost savings in the United States[23]. Australian researchers and TB experts are making significant contributions to regional TB control through collaborative efforts with countries in the region[24–26].

Tomorrow

Tomorrow undoubtedly holds new challenges and opportunities on the path towards TB elimination. Globally there remains a large pool of people with latent TB infection. Given aging populations and the increasing burden of diabetes and other non-communicable disease which may increase the risk of progression to active TB disease, we may expect to see a shift in the burden of TB towards older people with more complex health needs. Drug-resistant TB continues to emerge as an epidemic within an epidemic – facilitated by major gaps in case detection and treatment[17].

Effective diagnostics and treatments are available for TB, yet these have not enabled us to overcome the global TB epidemic. Future efforts to eliminate TB will require both new tools and better use of existing ones. Molecular diagnostics such as GeneXpert® nucleic acid amplification test have improved detection of *M. tuberculosis* and rifampicin resistance and are now recommended first-line in place of microscopy[27]. However, access remains limited in many settings. Safer and more effective

drugs would be welcomed for drug-resistant TB, but meanwhile, there are opportunities to improve the use of existing drugs. Several significant changes in drug-resistant TB treatment have been recently recommended by WHO, including a shorter (9-12 month) all-oral regimen for treatment of multi-drug resistant TB and a new 6–9 month regimen for multi-drug resistant TB with resistance to fluoroquinolones[28]. Shorter rifamycin-based regimens for treatment of latent TB infection are being increasingly utilised, with potential to improve uptake and completion of preventive therapy. Significant efforts are being made to develop new, more effective TB vaccines, with around 16 candidate vaccines currently in the pipeline[29]. One of these candidates – *M72/AS01E,* shows promise for the prevention of TB disease among adults who already have evidence of TB infection[30].

Reflecting on progress made in reducing the global burden of TB provides relevant lessons for the response to COVID-19 and other communicable disease threats. It is clear that TB burden is intrinsically linked to the social determinants of health; addressing these underlying social and economic factors is critical. Public health responses should be guided by the principles of equity and social justice and services for diagnosis, treatment and care should be universally accessible and patient centred. Specifically, free testing for communicable diseases is essential; charging individuals for diagnostic tests diminishes case-finding and fosters disease transmission. Also, economic support is needed to keep people away from work – mandatory time off work while contagious with TB or COVID-19 is impossible for those on low incomes[31]. Early diagnosis through active case finding and appropriate procedures for isolation of infectious cases and infection control in health facilities is needed to prevent transmission both in communities and healthcare facilities. Finally, and perhaps most importantly, what we know from TB is the need for affected communities to be engaged and active in the response – to support one another, protect the most vulnerable and eliminate stigma and discrimination.

Conflicts of interest

The authors declare no conflicts of interest.

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