Tuberculosis: The global killer

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Tuberculosis (TB) continues to claim close to 1.4 million lives from 8.7 million incident cases annually,[1] despite widespread vaccination and combinatorial antibiotic treatment. Rather than eradication, global trends suggest a marginal containment of disease in many high burden countries with an alarming increase in the frequency of drug resistance. South Africa has been ranked third amongst the high TB burden countries, preceded by India and China.[1] However, when corrected for population size, South Africa moves up to first place in the ranking – confirming that the TB epidemic in South Africa represents a public health concern of dramatic proportions. There are several factors that contribute to this current situation, some of which are described in this commentary along with some key interventions that are required to turn the tide on this disease.

Latent versus active infection

TB disease is the result of infection with *Mycobacterium tuberculosis* (Mtb), a Gram-positive, high G+C content member of the actinoymycetes.[2] Infection with Mtb results in one of two principle outcomes: (1) active cavitary disease which results in inflammation and lung necrosis leading to respiratory insufficiency or (2) the establishment of latent TB infection (LTBI) where the initial bacterial infection is contained by a strong immune response and the individual displays no symptoms of disease.[3,4] It has been hypothesised that LTBI is characterised by a dormant or metabolically quiescent population of Mtb and the lack of sufficient bacterial growth results in no gross lung damage[5]; however, very little substantive evidence exists to confirm this hypothesis. An alternative hypothesis is that LTBI is the result of a dynamic population of bacterial cells that are undergoing continuous growth and death.[6] Consistent with this idea, recent evidence suggests that LTBI represents a spectrum of disease states which range from complete latency to subclinical disease, the latter suggesting that some growth of Mtb occurs during latent infection.[7-9] The majority of infected individuals (~90% of those who develop disease after exposure) display this form of infection and, despite significant global effort, very little is known about mycobacterial physiology or the consequences of changes in the host immune response during LTBI[6]. Treatment of LTBI is particularly problematic because most of the current antitubercular drugs target those bacteria that are in the process of active growth and replication. Consequently, dormant bacteria are able to withstand current treatment protocols – a phenomenon that has driven a global search for new treatments that target non-replicating bacteria.

There has also been much activity recently in exploring the utility of preventative prophylaxis in individuals with LTBI, particularly isoniazid preventative therapy (IPT) with individuals that have a high risk of progressing to active disease. HIV-infected persons, particularly those with evidence of TB infection, who take continuous isoniazid preventive therapy have durable protection from TB for as long as they are taking it.[10] IPT taken with antiretroviral therapy further reduces the risk of TB without increasing the risk of side effects. Scale up of IPT in HIV clinics in Brazil has shown to reduce the rate of TB at a clinic-level.

TB–HIV co-infection

Recent estimates from the World Health Organization (WHO) indicate that southern Africa has the highest global prevalence of TB–HIV co-infection.[1] The synergy between these two diseases has been the principle underlying cause of the rampant spread of tuberculosis in this region. In high endemic regions, HIV-associated tuberculosis can account for up to 10% of cases.[10] The suppression of the innate immune response through HIV infection results in increased susceptibility to infection by Mtb and further increases the risk of progressing to active disease in those individuals with LTBI.[11,12] TB–HIV coinfection presents unique challenges for the diagnosis and treatment of TB disease. In most cases, clinical presentation of TB in immune-competent individuals is distinct to disease manifestation in HIV-infected individuals. The latter present with disseminated infection and limited cavitary disease in the lung,[13] which leads to a reduced number of bacteria in the sputum and results in inaccurate diagnosis with culture-based diagnostics and microscopy. Treatment of these co-morbidities is problematic from the perspective that some antiretroviral (ARV) drugs are antagonistic with frontline TB medication. Moreover, the reconstitution of the immune system which occurs with ARV treatment can lead to dramatic consequences for the control of TB infection. In some patients, ARV treatment results in worsening of the TB disease and severe inflammation, especially with disseminated disease – a phenomenon referred to as Immune Reconstitution Inflammatory Syndrome.[13] As a result, the timing of initiation of highly active antiretroviral treatment (HAART) has been intensely debated, with numerous recent studies demonstrating a positive effect of early initiation of HAART.[14] It seems clear that HIV infection will remain a significant confounder in controlling the TB epidemic[14] and new treatments that emerge for TB will need to dovetail with the management of HIV.

Drug treatment and adherence

Treatment for drug-sensitive TB requires 6 months of chemotherapy, stratified into a 2-month intensive phase of treatment (with rifampicin, isoniazid, ethambutol and pyrazinamide) and a further 4 months with rifampicin and isoniazid.[10] This daily treatment regimen is onerous on TB patients and is fraught with problems such as a lack of adherence, poor drug availability and drug side effects. Despite directly observed therapy, adherence remains a problem that is not easily overcome as a result of several factors including drug availability, socio-economic conditions, literacy and stigma. Thus, future drug development efforts need to focus on meaningful shortening of the duration of therapy with a concomitant reduction in the daily pill burden. The constant availability of drugs in all clinical settings, especially rural communities, remains a significant challenge. Another challenge is supporting and increasing the community-based directly observed therapy programme. Strong political will is needed, with decisive action, to have a meaningful impact on this disease.[15]

Drug resistance

The introduction of combination therapy for TB over five decades ago ushered in a new era for treatment of the disease, with the promise of eradication from human society. Unfortunately, the ability of Mtb to readily mutate and become resistant to drug treatment has limited the utility of antibiotics to eliminate TB. Resistance to individual TB drugs has been recorded in every country that reports an incidence of TB. Of greater concern is the emergence of multidrug-resistant (MDR) TB, defined as resistance to rifampicin and isoniazid, and, more recently, extensively drug resistant (XDR) TB, which is defined as MDR TB with additional resistance to a flouroquinolone and aminoglycosides. South Africa has seen a threefold increase in the prevalence of MDR TB between 2002 and 2010, which is indicative of deep-seated deficiencies in the TB control programme. In 2006, the outbreak of XDR TB in the Tugela Ferry region in KwaZulu-Natal, with a 16-day median survival time of infected patients, caused widespread panic in the country.[16] Since then, XDR TB has been recorded in all provinces in South Africa, suggesting that the prevalence of this form of drug resistance is increasing.[17] The WHO estimates a current global MDR incidence of 630 000 and has confirmed the presence of XDR TB in 84 countries.[1] Recent data show that MDR TB is spread by transmission in South Africa, confirming the notion that interruption of transmission is critical to limiting the spread of disease.[18, 19] In this regard, adequate infection control measures need to be implemented with diligence in hospitals and community health centres.[19] Rapid drug susceptibility testing is critical to limit the spread of drug-resistant TB.[20]

Diagnosis

Conventional diagnosis of TB infection is made by microscopic analysis of sputum samples for the presence of tubercle bacteria or by culture of bacteria directly from sputum. Mtb is classified as a slow-growing mycobacterial species and, depending on the culture conditions, is able to divide once every 17–24 hours. As a result, culture-based diagnostic tests routinely take 4–6 weeks to perform; drug susceptibility testing takes an equivalent amount of time. This results in a delay in treatment initiation and, in the case of drug-resistant patients, in prescribing the appropriate treatments, which fuels the evolution of further resistance. The introduction of novel molecular diagnostics such as the Hain Line Probe Assay and the GeneXpert promises to revolutionise TB diagnosis by providing diagnostic results in a shorter period of time (2–3 hours versus 4–6 weeks).[21]

Game-changing interventions needed for eradication of TB

The multitude of challenges presented above illustrates the fact that, despite the availability of drugs and a vaccine, elimination of TB remains a daunting task and will require a cross-disciplinary approach that integrates all aspects of patient management. The ever-increasing prevalence of drug resistance demands a new generation of novel TB treatments with faster clinical efficacy. Drugs that target non-replicating organisms are critical to ensure complete tissue sterilisation during treatment. Furthermore, drugs or interventions that limit the emergence of drug resistance will ensure the fidelity of current and future treatments. The implementation of rapid diagnostics is essential for limiting the spread of TB and to ensure that patients receive the correct treatment. A point-of-care rapid diagnostic platform is urgently needed. A new vaccine, with longer-lasting protection than the current BCG, will also be beneficial. Finally, sufficient integration of TB and HIV management is central to the eradication of TB in South Africa.

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