Editorial

New Approaches to the Treatment of Tuberculosis

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Tuberculosis (TB) remains one of the world's most important infectious diseases, with an estimated 10 million cases and 1.7 million deaths per year—the leading cause of death globally from a single infectious agent.[1] It is an especially important disease in Asia, accounting for almost 60% of the global cases. Multidrug-resistant TB (MDR-TB) —characterised by resistance to rifampicin and isoniazid, 2 of the key firstline drugs—affects around 500,000 people annually. Extensively drug-resistant TB (XDR-TB)—where resistance to 2 of the key secondline drugs is also present—is now emerging as an important threat to TB control as the extensive resistance profile makes it almost impossible to construct an effective treatment regimen. TB is the leading cause of death related to antimicrobial resistance. Although incidence rates have been declining globally, the overall rate of decrease is just 2% per year and in Singapore, rates have fluctuated around 40 per 100,000 for the last decade, with no suggestion of a declining trend.

In response to this recalcitrant problem, the World Health Organization (WHO) launched a new strategy in 2015. The End TB Strategy aims to accelerate the rate of decline of new cases to 10% per year by 2025, and to 17% per year thereafter with the ultimate goal of ending the TB epidemic by 2035.[2] Whilst these targets are clearly aspirational, and rely heavily on "intensified research and innovation" which is only just beginning to bear fruit, there are reasons to hope that there will be significant advances made through ongoing clinical research that could possibly be game-changing.

Improving firstline treatment for drug-sensitive disease is a high priority and this is one area in which there have been significant research-led advances in recent years. Standard "short-course" chemotherapy was established in the 1980s and has changed little since then. It comprises 6 months' treatment with a combination of drugs, each of which may cause side-effects. Adherence to long courses of treatment is challenging for many patients and poor adherence promotes the development of drug resistance. Identifying curative firstline treatment regimens that are shorter in duration— preferably 2 months or less—is an important objective for decreasing the failure rate of treatment in a programme setting, and for reducing the pressure for development of drug-resistant TB.

One approach to shortening treatment is to find new drugs that have improved activity against the persistent forms of TB bacilli—these bacilli are hard to eradicate with standard treatment and drive the need for the current protracted courses of treatment. As with antibiotic research and development in general, pharmaceutical industry investment is constrained by the perceived lack of financial return that would follow the successful development of a new TB drug. Nonetheless, after a hiatus of 40 years, 2 new drugs have been developed —bedaquiline[3] and delamanid[4]—that have recently received (accelerated) licences for the treatment of TB. Bedaquiline in particular appears to have potent activity against persistent bacilli, and also has the potentially attractive property of a very long half-life. The drug was evaluated in trials in MDR-TB but studies are now underway examining its role in combinations for the treatment of drug-sensitive TB.

Aside from the expensive quest to develop new drugs specific for TB, there has been considerable interest in repurposing drugs, i.e. finding drugs (usually antibiotics) that have been shown to be effective for other diseases (usually infections) that fortuitously have activity against TB. One class of drugs with particular promise is the beta-lactams. Penicillins, the first drugs to be identified in this class, are known to be inactive against TB because they are inactivated by penicillinase (beta-lactamase) produced by TB bacteria. However, when co-administered with clavulanic acid (a beta-lactamase inhibitor), penicillins may retain some anti-TB activity. Several studies evaluating carbapenems in a mouse model of TB infection have found evidence of efficacy, with improved survival and decreased bacterial load.[5,6] A recent 14-day trial showed that meropenem—an injectable carbapenem widely used in serious hospital-acquired infections—reduced TB bacterial counts when used as monotherapy.[7] A further impetus to this approach of repurposing beta-lactams for TB came with the recent identification of synergistic activity between beta-lactams and rifampicin,[8] one of the standard TB drugs. There are now several early-phase studies underway looking at various

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beta-lactam and rifampicin combinations as potential treatment-shortening approaches for drug-sensitive TB.

An even more straightforward approach than evaluating repurposed drugs would be to make changes to enhance the efficacy of drugs in the standard TB treatment regimen. Rifampicin is the most important sterilising drug in standard combination therapy, but the usual clinical dose of 10 mg/kg is known to lie at the lower end of the dose-response curve. Recent studies have tested increased doses of rifampicin (up to a dose of 35mg/kg) and shown substantial improvements in bacterial clearance in the first 8 weeks of treatment.[9] This increase in dose may be accompanied by higher rates of gastro-intestinal intolerance, but it does not appear to be associated with higher incidence of hepatotoxity, which was initially raised as a theoretical concern. Further trials are underway testing high dose rifampicin in short-duration treatment combinations.

Another previously neglected treatment approach that is now receiving substantial attention is the use of immunomodulatory drugs to enhance TB clearance. The human immune system is capable, in the majority of cases, of controlling TB infection even without the assistance of antibiotics. Given the limitations of standard TB drugs in clearing persistent organisms, pharmacologic enhancement of the immune response to TB could be beneficial as an adjunct that may allow shortening of the duration of antibacterial treatment.[10] This is similar to the approach that has transformed oncology treatment in recent years and several trials are now underway evaluating host-directed therapies in TB. In one such study conducted in Singapore, pascolizumab (a monoclonal antibody directed against interleukin-4) is being tested for safety and efficacy as an adjunct to standard therapy in drug-sensitive TB.

In summary, although TB remains an apparently intractable problem, there are encouraging advances in clinical research that may lead to significant improvements in TB treatment in the coming few years. Equally important for the control of TB will be: advances in diagnostic approaches that allow more people with clinical TB (or with latent TB at high risk of clinical progression) to be identified and subsequently offered effective treatment; and advances in preventive approaches including vaccines, as well as innovative ways to deliver treatment in programme settings, that may increase treatment adherence and retention in care.

REFERENCES

1. World Health Organisation. Global Tuberculosis Report. 2017.
2. World Health Organisation. The End TB Strategy. 2015.
3. Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasilyeva I, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med 2014;371:723-32.
4. Gler MT, Skripconoka V, Sanchez-Garavito E, Xiao H, Cabrera-Rivero JL, Vargas-Vasquez DE, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. N Engl J Med 2012;366:2151-60.
5. Chambers HF, Turner J, Schecter GF, Kawamura M, Hopewell PC. Imipenem for treatment of tuberculosis in mice and humans. Antimicrob Agents Chemother 2005;49:2816-21.
6. England K, Boshoff HI, Arora K, Weiner D, Dayao E, Schimel D, et al. Meropenem-clavulanic acid shows activity against Mycobacterium tuberculosis in vivo. Antimicrob Agents Chemother 2012;56:3384-7.
7. Diacon AH, van der Merwe L, Barnard M, von Groote-Bidlingmaier F, Lange C, García-Basteiro AL, et al. β-Lactams against tuberculosis – new Trick for an old dog? N Engl J Med 2016;375:393-4.
8. Kaushik A, Makkar N, Pandey P, Parrish N, Singh U, Lamichhane G. Carbapenems and rifampin exhibit synergy against mycobacterium tuberculosis and mycobacterium abscessus. Antimicrob Agents Chemother 2015;59:6561-7.
9. Boeree MJ, Heinrich N, Aarnoutse R, Diacon AH, Dawson R, Rehal S, et al. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial. Lancet Infect Dis 2017;17:39-49.
10. Wallis RS, Hafner R. Advancing host-directed therapy for tuberculosis. Nat Rev Immunol 2015;15:255-63.