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How do we solve a problem like tuberculosis?

Investment in a new tuberculosis vaccine is a landmark step forward, but continued efforts to advance treatments, diagnostics and biosocial issues are needed to meet targets to end the epidemic by 2035.

Mycobacterium tuberculosis, the causative agent of tuberculosis (TB), has been infecting humans for tens of thousands of years, although it is unclear exactly when and how *M. tuberculosis* emerged as a human pathogen[1]. The disease has had several names throughout history; Hippocrates named it phthisis around 460 BC, and it was known for centuries as consumption in common English due to the way that patients wasted away, as if being consumed. Descriptions of the characteristic cavities and abscesses that form during pulmonary TB were published in 1679 and, around 40 years later, the idea that consumption was caused by "wonderfully minute living creatures" was suggested by Benjamin Marten[2]. Following numerous efforts showing that the disease was contagious and could infect multiple body sites, Robert Koch finally isolated *M. tuberculosis* in 1882.

We now know that *M. tuberculosis* is an obligate human pathogen capable of causing a complex array of diseases. Tuberculous meningitis is the most severe, arising in 1–10% of cases, and particularly affecting the young and those living with HIV[3]. Untreated, it is always fatal, and even with treatment, mortality rates remain at 20%. Pulmonary TB is less severe and more common, yet still has a worryingly high mortality rate with global estimates at around 15% (ref. 4). The ability of *M. tuberculosis* to remain latent, surviving quiescently within its host in an asymptomatic manner, complicates diagnosis and treatment, while also creating a reservoir for transmission. The World Health Organization (WHO) estimates that one-quarter of the world's population has been infected with *M. tuberculosis* and, in 2021, 10.6 million people had active TB with 1.6 million people succumbing to infection[4]. After some years of decline, both cases and fatalities of this poverty-associated disease are on the rise again, especially in low- and middle-income countries.

The question arises as to why, after so long, TB remains the primary cause of death resulting from infectious disease globally, only briefly ceding centre stage to COVID-19. Although it is hard to pinpoint this to a single factor, issues at the diagnostic, treatment and prevention level are likely major contributors. Recently, Madhukar Pai and co-authors highlighted major gaps in TB diagnosis[5,6]. Approximately 40% of cases are going undiagnosed, a number that almost doubles when children are considered. If we aren't diagnosing TB effectively, it becomes increasingly difficult to treat infection or prevent transmission. Clearly more effort is needed at local, governmental and international levels to support the development and implementation of more effective, rapid and cost-effective diagnostics. These must include molecular approaches capable of distinguishing species and antibiotic resistance profiles, necessary training to ensure WHO guidelines are implemented, communication and education at the community level, and sufficient funding and outreach to ensure healthcare is available to those who need it most.

Considering treatments, options are also limited. Multidrug resistance and the ability of *M. tuberculosis* to form metabolically distinct, persistent subpopulations within the host hinders the efficacy of an already limited number of antibiotics. Side effects and lengthy treatment courses mean that some patients do not complete treatment, restricting the extent to which disease can be contained. Effective vaccines would help prevent disease. Surprisingly, however, for a disease with high global morbidity and mortality rates, there is only one licensed vaccine against TB. The Bacillus Calmette–Guérin (BCG) vaccine uses an attenuated strain of *Mycobacterium bovis*, a closely related species that causes bovine tuberculosis, and was first used in humans in 1921. We now have a better understanding of the strengths and weaknesses of this vaccine. BCG offers some protection against non-tuberculosis forms of mycobacterial infection such as leprosy, and also elicits trained immunity. Although it also offers some protection against TB in infants, its broader efficacy against TB is limited, especially against pulmonary tuberculosis in adults and adolescents[7].

Evidently, urgent advances in both treatments and vaccines are needed, but hope is on the horizon. At the end of June 2023, the Bill and Melinda Gates foundation, alongside the Wellcome Trust, pledged US$550 million to support phase III clinical trials testing safety and efficacy of a potential TB vaccine candidate, the M72/AS01$_E$ vaccine, in humans. If successful, this would be the first new vaccine targeting TB in more than a century. The vaccine comprises a recombinant fusion protein of two *M. tuberculosis* antigens: Mtb32A and Mtb39A, alongside an adjuvant, and efficacy in phase II trials reached 49.7%. Although this level may seem low, and higher vaccine efficacy is preferable to reach the WHO End TB Strategy's aim by 2035, this does represent a huge potential leap forward. By comparison, efficacy for BCG was recently estimated to be only 18% against all TB diseases across all age groups[7].

These results do signify, however, that a concerted effort is needed to find additional anti-TB approaches to address this disease from all sides. Further vaccine candidates are in the pipeline, some of which have shown protection in animal models, good immunogenicity and tolerance in phase II trials, although their efficacy in human populations remains to be established. Developments are also underway for new drugs and alternative therapies. A series of macrolides called sequanamycins that can overcome macrolide resistance in vitro, and treat acute and chronic TB in preclinical mouse models, have recently been reported[8]. Additionally, nutritional interventions have shown promise. In a controlled trial where 34% of individuals suffered from undernutrition, a high calorie, protein and micronutrient supplement in patients and household contacts was associated with reduced mortality and 39–48% reductions in TB incidence in patients and contacts, respectively[9,10]. Whether these approaches will translate beyond the lab and clinical trials is unclear, but they are promising components of a strategy that needs to be multi-pronged. By combining biosocial, therapeutic and vaccination measures, the probability of reaching the difficult goal of ending TB becomes more likely. A key

factor determining success is whether these measures will reach affected individuals. The recent announcement of a deal to make generic bedaquiline available to 44 low- and middle-income countries highlights how interventions need to be economical, accessible and deliverable in regions most affected by TB. As we move forwards, these factors must be forefront.

In order to solve a problem like *M. tuberculosis*, we must understand it. As a research community, we can address this through continued research into mycobacterial biology, metabolism and virulence, and interactions with the host. To paraphrase Carl Nathan as he writes on TB in this issue's Microbe Matters, by understanding the complex interplay between host and pathogen, tuberculosis teaches us not only about itself, but also about ourselves, educating us on wide-ranging principles of immunological function relevant to other infectious and non-infectious diseases. In tackling TB, we may well become equipped with tools to target multiple microbial sources of global morbidity and mortality. As a wider community, with support from policymakers, stakeholders, funders and governments, we also need to ensure that what we discover is ultimately made accessible to those who need it most.

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