The case for assessing the full value of new tuberculosis vaccines

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A multidisciplinary framework is needed to guide the research needed for making economic and health impact arguments for tuberculosis vaccine development and uptake http://bit.ly/2stNDok

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Tuberculosis (TB) ranks as the leading cause of death among infectious diseases in human history, claiming over a billion lives in the past two centuries alone [1, 2]. Although a number of important advances have been made to control TB in the past decade, an estimated 10 million people fell ill with TB and 1.5 million died from the disease in 2018 alone [1]. The only licensed TB vaccine, bacille Calmette–Guérin (BCG), provides partial protection against severe forms of TB in infants and young children (averting thousands of paediatric deaths annually), but fails to stop transmission of pulmonary tuberculosis in adults [3, 4]. The World Health Organization (WHO)'s End TB Strategy stipulates that more effective vaccines are needed to end the TB epidemic, which will subsequently bolster efforts to achieve broader global health ambitions under universal health coverage, and a number of other sustainable development goal targets, particularly the targets focused on eradicating poverty in all its forms, ending the AIDS epidemic, strengthening health systems, and reducing premature mortality among women and children [5, 6]. By preventing TB disease, an effective vaccine would also reduce the need for antibiotics, an essential step for curbing antimicrobial resistance. Recognising this, member states during the United Nations General Assembly high level meeting on TB, held in New York in 2018, have committed to increase investment in and accelerate research for the development of more effective TB vaccines that are affordable and accessible by all countries that need them [7].

To accelerate efforts, WHO, through a wide consensus-generating consultation, has developed preferred product characteristics for new TB vaccines, to articulate attributes of products suitable for end users, and to guide scientists, funding agencies and industry groups developing TB vaccine candidates intended for WHO prequalification and policy recommendations [8, 9]. There are several challenges to developing more effective TB vaccines. From a scientific perspective, significant challenges include a lack of validated, predictive animal models of TB infection and disease; a lack of validated biomarkers that can act as prospective signatures of the risk of developing TB or as correlates of protection; and an incomplete understanding of the nature of protective immunity to TB. From a developer perspective, market uncertainties, as well as the long and expensive research timeline, make TB vaccine development challenging. There is also the impending challenge of developing a product that is affordable to low-and-middle income countries; acceptable to communities; and feasible to sustainably implement

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under low resource settings. Despite these difficulties, there is cause for optimism. Recently, an experimental TB vaccine candidate ($M72/AS01_E$) was found to be significantly protective against pulmonary TB in a phase IIb trial conducted in Kenya, South Africa and Zambia, in individuals with latent TB infection [10, 11]. An increasing number of signatures that predict risk of disease progression are also emerging [12]. At least 14 other vaccine candidates are being tested for prevention of infection; prevention of TB disease (in persons with or without evidence of past exposure); or as an immunotherapeutic agent for shortening TB treatment or reducing the risk of recurrence following treatment completion [1, 5].

Further development and validation of candidate vaccines in the clinical pipeline is conditional on collaboration between research funders, governments, public private partnerships, international agencies, affected communities and the pharmaceutical industry. Partnerships are particularly important in order to finance multi-country clinical trials needed to gather evidence for licensure. Beyond clinical trials, broader research in areas of social, economic, and population health impact are also needed to guide vaccine introduction and implementation [13]. Recognising this complexity, countries weigh in different factors before adding a vaccine to their national immunisation programmes that oftentimes involves a trade off with investing in other vaccines or alternative strategies [14]. These include 1) the disease burden and its political priority at national and global platforms; 2) relative effectiveness of alternative strategies; 3) safety, efficacy, and equity impact of the vaccine; 4) sufficient vaccine supply; 5) the vaccine's economic and financial attributes (cost, affordability, and cost-effectiveness); and 6) the capacity of the immunisation programme and underlying health system to successfully introduce and sustainably deliver the vaccine. For TB, additional evidence needs include studies on how to align vaccine implementation with ongoing TB prevention efforts (particularly among populations eligible for TB preventive therapy), and how to use the vaccine among vulnerable groups such as children, diabetics, people living with HIV, and pregnant women. Because future TB vaccines will likely target adults and adolescents who are not part of traditional

TABLE 1 Framework for assessing the full value of new tuberculosis (TB) vaccines

Category	Needs
Health gains	Estimated potential impact of new TB vaccines on disease burden and transmission (including drug-resistant TB (DR-TB) and co-infection with HIV), as measured by incidence, mortality and morbidity (in the context of alternative strategies)
Value for money	Estimated societal cost-effectiveness/cost-utility and return on investment for new TB vaccines from the perspective of both the healthcare payer and society
Equity and financial risk protection impact	Estimated impact of a new TB vaccine on equity (in the context of health gains by income distribution and vulnerability) and reduced household financial vulnerability (catastrophic costs and impoverishment)
Economic impact	Estimated impact of new TB vaccines on medical and other expenses, as well as on gross domestic product and its rate of growth; estimated impact of new TB vaccines on government expenditure (including expenditure through the HIV response, as applicable) and on sustainability of financing over the long term
Global health security impact	An estimated impact of a new TB vaccine on antimicrobial stewardship (reducing antibiotic use, mitigating the reduced effectiveness of antimicrobials from continued use, reducing DR-TB disease incidence, reducing human and programmatic costs of DR-TB management, and improving health outcomes)
Market	Estimated potential demand for new TB vaccines
Vaccine characteristics and implementation scenario assumptions	The various parameters above should be evaluated under different vaccine characteristics and implementation scenario assumptions (target population, geographical scope and vaccine characteristics) In addition, the interaction between a new vaccine and alternative strategies (optimal use of current and future alternative interventions) on key outputs should be considered

immunisation programmes, programme innovation will also be needed to achieve acceptable coverage and equity in these populations [8].

Considering these broad areas of need, a framework would be helpful to guide research and evidence necessary for making economic and health impact arguments for TB vaccine development and uptake (table 1). Evidence aligned to such a framework can help boost investments by vaccine developers, traditional health institutions, such as ministries of health or GAVI, the Vaccine Alliance, and ministries of finance or their equivalent [15, 16]. Preliminary modelling works have already shown that new TB vaccines will be highly cost-effective, and will offer substantial cost savings to healthcare systems and society [17]. In addition, mathematical modelling using data from 183 countries suggests that a new TB vaccine for prevention of disease that is 60% efficacious and delivered to just 20% of adolescents and adults globally could avert 25–35 million cases in its first 20 years of use [18]. A significantly improved infant vaccine (relative to BCG) would avert about an additional 4–6 million new cases of TB over the same period. Expanding on this work by modelling additional disease dynamics and scenarios, as outlined above, will help resolve complexities around late stage research needs and provide better understanding of the demand around TB vaccines, for stakeholders engaged in vaccine development, production and implementation.

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