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World Health Organization

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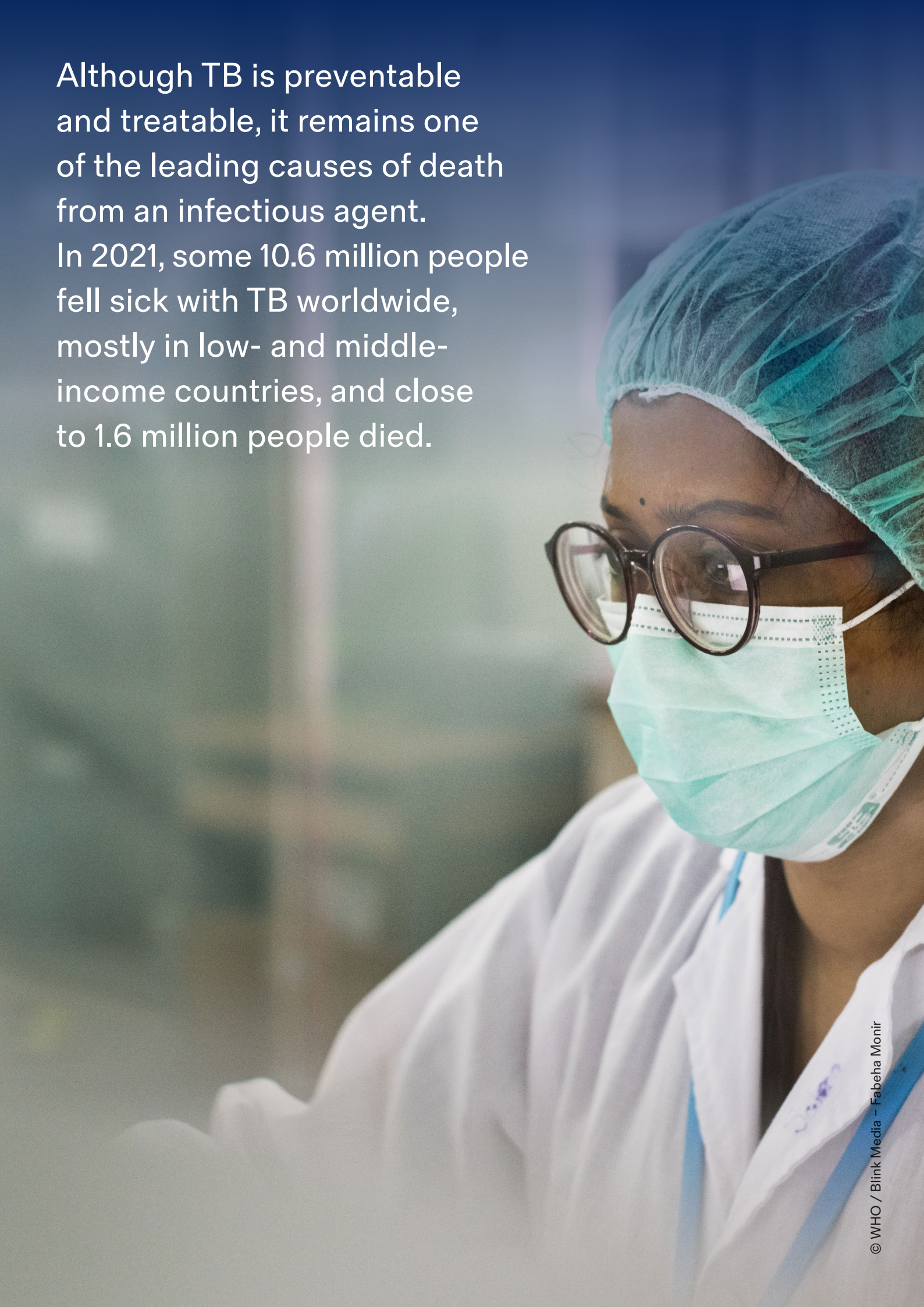
An investment case for new tuberculosis vaccines

Although TB is preventable and treatable, it remains one of the leading causes of death from an infectious agent.
In 2021, some 10.6 million people fell sick with TB worldwide, mostly in low- and middle-income countries, and close to 1.6 million people died.



INTRODUCTION

Although tuberculosis (TB) is preventable and treatable, it remains one of the leading causes of death from an infectious agent. In 2021, some 10.6 million people fell sick with TB worldwide, mostly in low- and middle-income countries, and close to 1.6 million people died.[1] The World Health Organization (WHO) End TB Strategy states that, to end the TB epidemic by 2030, major technological breakthroughs must be introduced by 2025, such as a vaccine that is effective both before and after exposure. This would dramatically accelerate the rate at which TB incidence falls from past levels.

WHO has developed "preferred product characteristics" to promote the development of vaccine candidates intended for WHO prequalification and policy recommendation.[2,3] Today, there are at least 16 candidates under active clinical development; however, a more robust, diverse pipeline is necessary to deliver impact. New approaches and technologies are providing unprecedented scientific opportunities, including drawing on lessons from vaccines against SARS-CoV-2; however, constrained funding is slowing progress.

To make the case for investment, WHO commissioned a full value assessment of new TB vaccines that meet WHO preferred product characteristics. Such an assessment includes estimating long-term effect of the vaccines on health, productivity, equity, antibiotic stewardship, costs, cost–effectiveness and return on investment, as applicable. The results of the assessment predict high health and economic returns, particularly in the case of vaccines for adolescent and adult populations.

This document summarizes the results of the WHO-commissioned full value proposition for new TB vaccines. It is for use by national and global decision-makers involved in vaccine development and implementation.

WHO gratefully acknowledges the financial support of the Kingdom of Netherlands to complete this work.

[1] Global TB Report. Geneva: See World Health Organization; 2022 (https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022).

[2] WHO preferred product characteristics for new tuberculosis vaccines. Geneva: World Health Organization; 2018 (https://www.who.int/publications/i/item/WHO-IVB-18.06).

[3] Preferred product characteristics for therapeutic vaccines to improve tuberculosis treatment outcomes. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/handle/10665/330448).

Why did WHO commission this assessment?

The assessment was commissioned to provide early evidence for national and global decision-makers involved in TB vaccine development and implementation, who include stakeholders involved in vaccine research, financing, regulation and policy-making, manufacturing, introduction and procurement. The goal is to accelerate development of effective vaccines against TB and their rapid introduction into countries.

Why do we need new TB vaccines?

TB is one of the leading causes of death from an infectious agent. The WHO End TB Strategy states that, to end the epidemic by 2030, major technological breakthroughs must be introduced by 2025 to accelerate the rate of decrease in disease incidence. These include a new vaccine that is effective both before and after exposure. The only licensed TB vaccine, bacille Calmette-Guérin (BCG), provides moderate-to-good protection against severe forms of TB in infants and young children (averting thousands of paediatric deaths annually), but it does not adequately protect adolescents and adults, who account for most transmission of TB infection and disease burden. New vaccines that are effective against all forms of TB in all age groups are essential to end the TB epidemic.

What is the status of development of new TB vaccines?

Currently, at least 16 candidate vaccines are under active clinical development. There is, however, little antigenic and immunological diversity among the current candidates, whereas novel antigenic targets that can induce different immunological characteristics are necessary to improve the chances of efficacy. Furthermore, few of the candidates will advance through late-stage product development because of the high level of attrition inherent to vaccine development and insufficient investment in late-stage clinical research. Preliminary results only for the M72/AS01E vaccine meet the WHO preferred product characteristics,[4] and larger studies are planned to confirm the findings. It is therefore imperative that funders continue to invest in both early- and late-stage research to ensure that candidates advance to full-scale development.

[4] Tait DR, Hatherill M, Van Der Meeren O, Ginsberg AM, Van Brakel E, Saluan B et al. Final analysis of a trial of M72/AS01E vaccine to prevent tuberculosis. N Engl J Med. 2019;381(25):2429–39 (doi: 10.1056/NEJMoa1909953).

What are the challenges in developing new TB vaccines?

→ The greatest scientific challenge to TB vaccine development remains the lack of biomarkers, which are signs of the prospective risk of developing TB or correlates of protection. Identification of biomarkers could accelerate vaccine research and development on TB by allowing investigators to detect signals of efficacy at earlier stages of development.

→ Inadequate funding for research and development and lack of industry engagement constrain progress. The Stop TB Partnership's Global Plan to End TB, 2018–2022 calls for approximately US$ 790 million per year to advance TB vaccines; however, the average annual investment in the past 5 years (2018–2020) has been only US$ 115 million.

→ A political environment that stimulates demand for effective TB vaccines and initiatives that reduce market uncertainty could incentivize stronger engagement from industry, biotechnology firms and manufacturers.

HOW WAS THIS ASSESSMENT DONE?

The potential health and economic impact of vaccines that meet the technical specifications of the WHO preferred product characteristics for new TB vaccines, as shown in the table below, was estimated for 105 low- and middle-income countries, accounting for 93% of the global TB burden.

Vaccine Age Group	Infection status at time of vaccination required for efficacy	Prevents	PPC parameters used for the assessment reported in this document — *Results for other parameters have been published.*		
			Vaccine efficacy (%)	Duration of protection	Dose
Adolescents and adults (≥9 years)	Any (before and after infection)	Disease	50%	10 years	Single
Infants	Uninfected (before infection)	Disease	80%	10 years	Single

01. VACCINATION SCENARIOS DESCRIBED IN THIS DOCUMENT

Base-case: routine vaccination of 9-year-olds and a one-dose vaccination campaign for people aged ≥ 10 at nationally specified age at introduction (based on national data on previous vaccine introduction) between 2028 and 2047, with a 5-year scale-up to ensure coverage. The results are presented according to the following immunization coverage targets at 5 years: 85% for neonates, 80% for 9-year-olds and 70% for ≥ 10-year-olds.

Accelerated Scale-up: similar to the base case, but all countries introduce the vaccine in 2025 with instant scaling up. Results for other scenarios have been published.[5]

Vaccine prices: The price negotiated for human papillomavirus vaccine (US$ 4.60) in low- and middle-income countries was used. Scenarios with other vaccine prices and with high–middle-tier vaccine pricing have been published.[6]

02. THE HEALTH IMPACT OF NEW TB VACCINES

A compartmental age-stratified dynamic TB infection transmission model was used to evaluate the reductions in incidence and mortality rates achieved by 2050 with different vaccine profiles and vaccination strategies as compared with the status quo (no new vaccine). The cumulative numbers of TB treatments, deaths and cases averted between vaccine introduction and 2050 were calculated for each vaccine scenario and compared with the numbers predicted for the status quo in order to demonstrate health impact.[5] The time horizon of the analysis was 2025–2050.

03. THE ECONOMIC IMPACT OF NEW TB VACCINES

The costs, cost-effectiveness (from both the health system and societal perspective), budget impact and incremental net monetary benefit of TB vaccine introduction were estimated for each scenario.[6] To estimate the implications for equity, TB outcomes were stratified by income quintile within each country, and out-of-pocket costs borne by households were calculated.[7] Longer-term economic benefits were estimated for 2025–2080 in a macroeconomic model to simulate changes in gross domestic product in the modelled countries due to introduction of a new TB vaccine.[8]

[5] Clark RA, Mukandavire C, Portnoy A, Weerasuriya CK, Doel A, Scarponi D et al. The impact of alternative delivery strategies for novel tuberculosis vaccines in low- and middle-income countries: a modelling study. medRxiv. 2022 (doi: 10.1101/2022.04.16.22273762).

[6] Portnoy A, Clark RA, Quaife M, Weerasuriya CK, Mukandavire C, Bakker R et al. The cost and cost–effectiveness of novel tuberculosis vaccines in low- and middle-income countries: a modelling study. medRxiv. 2022 (doi: 10.1101/2022.05.04.22274654).

[7] Portnoy A, Clark RA, Weerasuriya CK, Mukandavire C, Bakker R et al. The potential impact of novel tuberculosis vaccines on health equity and financial protection in low- and middle-income countries. medRxiv. 2022 (doi: 10.1101/2022.10.29.22281678).

[8] Portnoy A, Arcand JL,Clark RA, Weerasuriya CK, Mukandavire C, Bakker R et al. The potential impact of novel tuberculosis vaccine introduction on economic growth in low- and middle-income countries. medRxiv. 2022 (doi.org/10.1101/2022.11.23.22282690).

SUMMARY OF FINDINGS

1 TB vaccines save lives

Over 2025–2050, a TB vaccine for infants could avert 5.8–18.8 million cases and 0.8–2.6 million deaths, while a vaccine for adolescents and adults that is 50% effective in preventing disease could cumulatively avert 37.2–76.0 million cases and 4.6–8.5 million deaths. A vaccine that is 75% effective could avert 54–110 million new TB cases and 6.7–12·3 million TB deaths.

2 TB vaccines can help fight antimicrobial resistance

A TB vaccine for infants could avert an estimated 2.4–8.6 million treatments (up to US$ 299 million in treatment costs saved), while one for adolescents and adults could avert 21.9–42.3 million treatments, saving up to US$ 3.2 billion in treatment costs.

3 TB vaccines can be highly cost-effective and cost-saving

Vaccine products for both infants and adolescents/adults were estimated to be cost–effective in nearly all high TB-burden countries and cost-saving from a societal perspective.

4 TB vaccines offer a substantial return on investment

The value of novel TB vaccines in monetary terms was estimated globally as US$ 68.6 (44.5–100.0) billion for introduction of a vaccine for infants and US$ 372 (283–474) billion for one for adolescents and adults.

5 Projected costs and budgetary impact of TB vaccines

For US$ 11.8 billion costs for vaccine introduction and scale-up, a vaccine for infants could reduce TB diagnosis and treatment costs by 1.7% with an associated 0.01% increase in costs for antiretroviral therapy. For US$ 50.5 billion costs for introduction and scaling-up, a vaccine for adolescents and adults could reduce TB diagnosis and treatment costs by 16.8% with an associated 0.21% increase in costs for antiretroviral therapy.

6 TB vaccines can advance health equity

A vaccine for infants could avert US$ 5.3–6.5 billion in TB-related household expenditure, while one for adolescents and adults could avert US$ 36.6–41.5 billion, including 66% of total catastrophic costs averted for the poorest 40% of the population.

7 There is a significant market for TB vaccines

The population that requires vaccination could be up to 1.32–1.43 billion infants and 4.64–5.18 billion adolescents and adults.

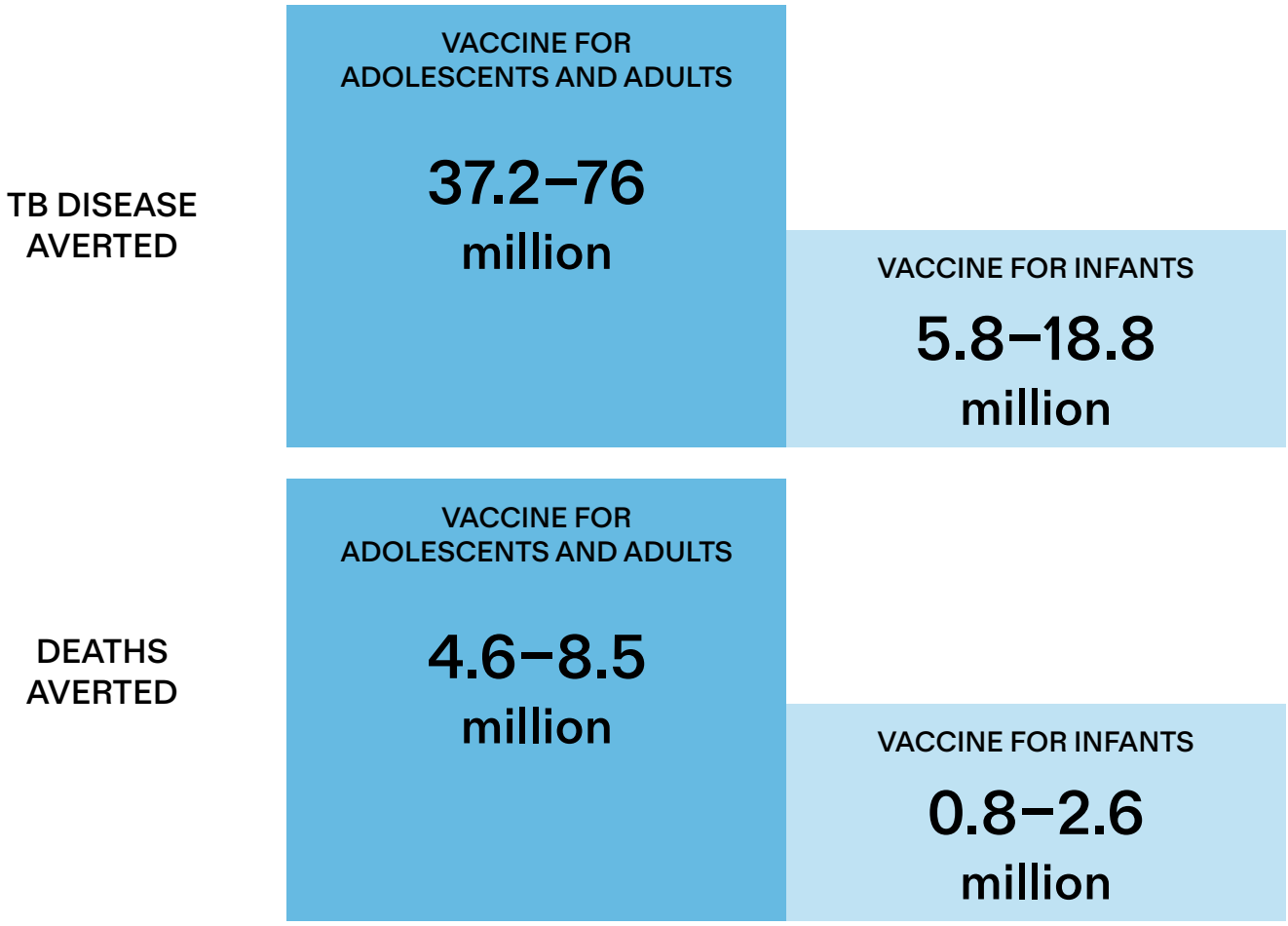
8 TB vaccines can improve economic growth

TB vaccines could have longer-term macroeconomic benefits. Absolute gains in gross domestic product of US$ 1.6 (0.8–3.0) trillion were projected with use of a vaccine for adolescents and adults and US$ 0.2 (0.1–0.4) trillion with a vaccine for infants.

1 TB vaccines save lives

On average, a TB vaccine for adolescents and adults could avert about 37.2–76.0 million cases and 4.6–8.5 million deaths by 2050. A vaccine for infants could avert approximately 5.8–18.8 million cases and 0.8–2.6 million deaths during the same period. A vaccine that is 75% effective could avert 54–110 million new TB cases and 6.7–12.3 million TB deaths.

The findings indicate that TB vaccines could significantly reduce TB incidence and mortality, a vaccine for adolescents and adults having a greater impact than one for infants. The impact of a vaccine depends on its efficacy, duration of protection, the age group targeted, coverage and the delivery strategy.[9]



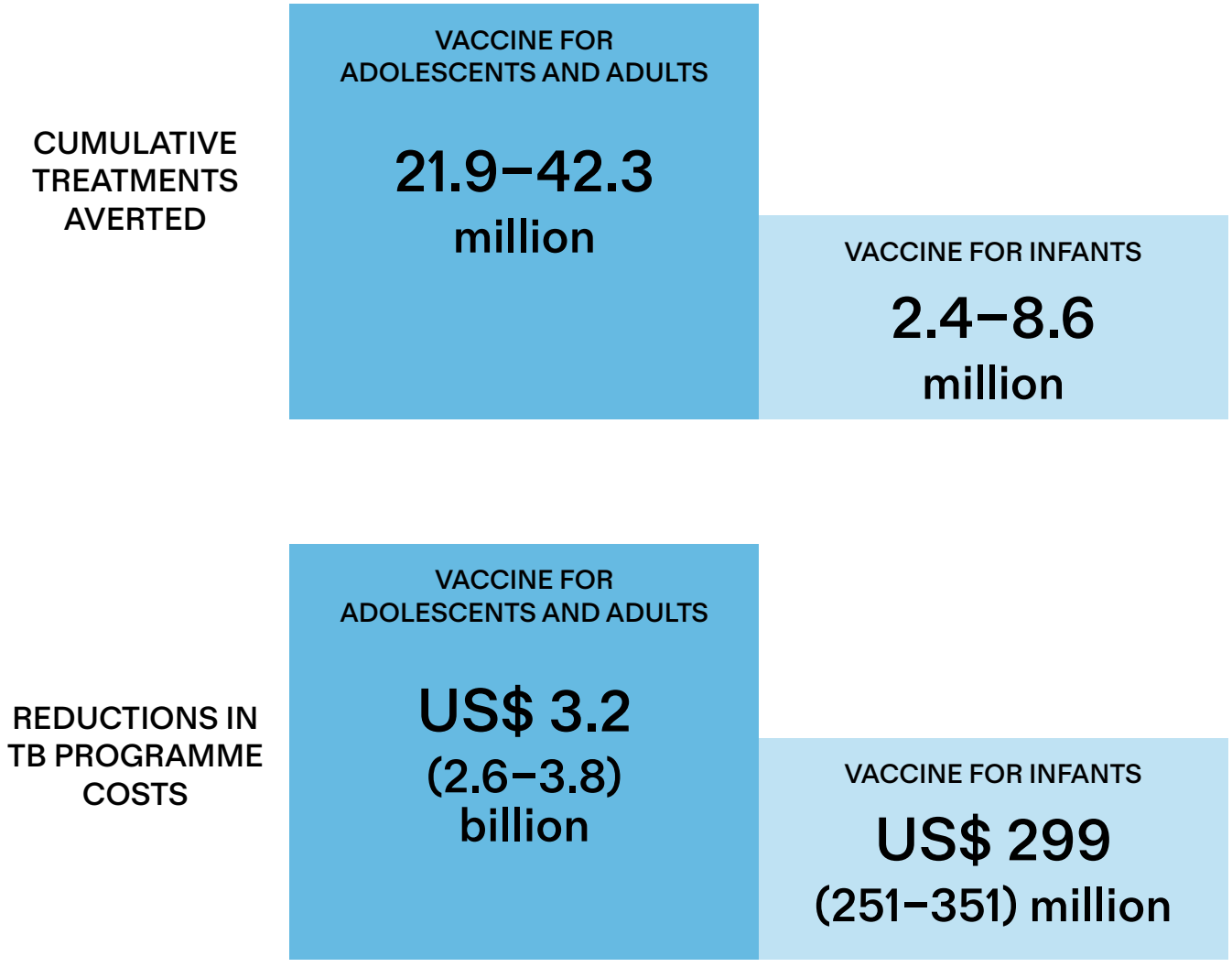
[9] Clark RA, Mukandavire C, Portnoy A, Weerasuriya CK, Doel A, Scarponi D et al. The impact of alternative delivery strategies for novel tuberculosis vaccines in low- and middle-income countries: a modelling study. medRxiv 2022 (doi: 10.1101/2022.04.16.22273762).

TB vaccines could significantly reduce TB incidence and mortality, a vaccine delivered to adolescents and adults having a greater, more immediate impact than one for infants.

2 TB vaccines can help fight antimicrobial resistance

Antimicrobial resistance poses a serious threat to global public health. Introduction of an effective TB vaccine would not only save lives but also provide wider societal benefits by reducing the use of antibiotics.

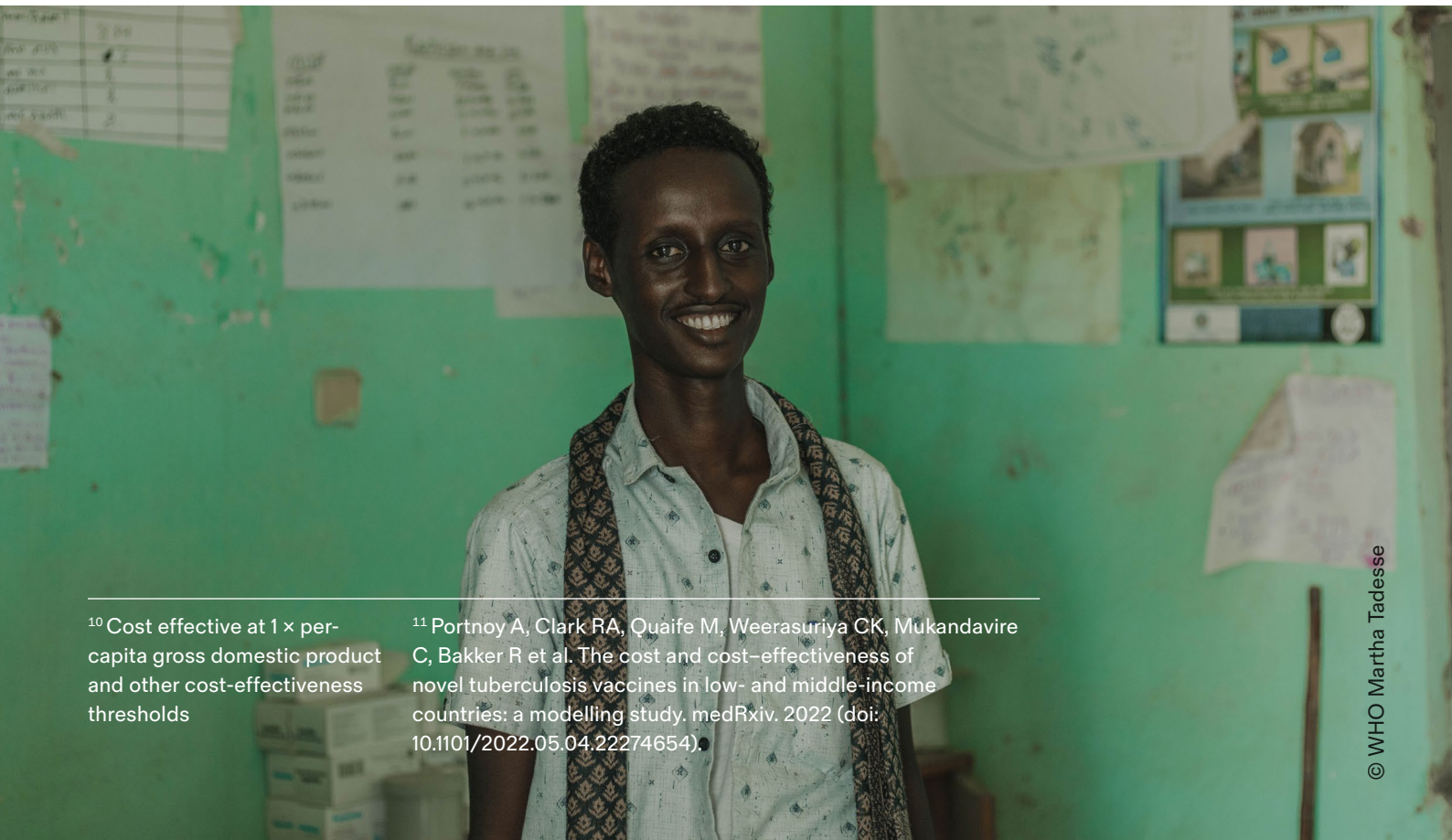
As TB vaccines are assumed to affect drug-susceptible and drug-resistant TB equally, they could contribute to reducing the programme costs associated with treatment of drug-resistant TB.



3 TB vaccines are cost-effective and can be cost-saving

Vaccines are highly cost-effective in most countries.[10, 11] In the base-case scenario, vaccine products for both infants and for adolescents and adults were estimated to be cost–effective in nearly all high-TB burden countries. Accelerated introduction made vaccine products cost–effective or cost-saving in all the modelled countries. When costs were assessed from a societal perspective, introduction of vaccines saved costs in nearly all high-TB burden countries.

- → **TB vaccines are highly cost-effective in countries with a high TB burden and can be cost-saving.**
- → **For every US$ 1 invested in the full set of interventions for the adolescent and adult vaccine scenario, we expect US$ 7 in health and economic benefits to be returned to the economy over 25 years, with the highest return on investments and the lowest costs per disability-adjusted life year averted in lower–middle-income countries.**



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[10] Cost effective at 1 × per-capita gross domestic product and other cost-effectiveness thresholds

[11] Portnoy A, Clark RA, Quaife M, Weerasuriya CK, Mukandavire C, Bakker R et al. The cost and cost–effectiveness of novel tuberculosis vaccines in low- and middle-income countries: a modelling study. medRxiv. 2022 (doi: 10.1101/2022.05.04.22274654).

4 TB vaccines offer a substantial return on investment

Estimation of the value of global investment in immunization programmes is critical to help decision-makers prioritize and coordinate implementation of health interventions. To derive the return on investment, costs assessed from the societal perspective were subtracted from monetized health benefits of vaccine introduction. In countries where vaccination is cost–effective at 1 × per-capita gross domestic product, a cumulative US$ 68.6 (44.5–100) billion incremental net monetary benefit was estimated globally for introduction of a vaccine for infants and US$ 372 (283–474) billion for a vaccine for adolescents and adults. The return on investment was concentrated in world regions with a higher disease burden.[12]

VACCINE FOR ADOLESCENTS AND ADULTS

US$ 372 (283–474) billion averted

VACCINE FOR INFANTS

US$ 68.6 (44.5–100) billion averted

[12] Portnoy A, Clark RA, Quaife M, Weerasuriya CK, Mukandavire C, Bakker R et al. The cost and cost–effectiveness of novel tuberculosis vaccines in low- and middle-income countries: a modelling study. medRxiv. 2022 (doi: 10.1101/2022.05.04.22274654).

5 Projected costs and budget impact of TB vaccines

Over the period 2025–2050, in a scenario with no new vaccine, the total undiscounted costs of TB diagnosis and treatment were estimated to be US$ 20.7 (12.8–31.2) billion for drug-susceptible TB and US$ 19.2 (15.6–23.1) billion for drug-resistant TB. The costs of vaccine introduction and scale-up and the related impact on the costs of TB diagnosis and treatment and of antiretroviral therapy due to longer survival of people living with HIV were estimated for this timeline.

COSTS AND BUDGET IMPACT Timeline: 2025–2050 Vaccine price, US$ 4.60	VACCINE FOR INFANTS (80% efficacy, 85% routine coverage, 10-year protection, base-case scenario)	VACCINE FOR ADOLESCENTS AND ADULTS (50% efficacy, 80% routine and 70% campaign coverage, 10-year protection, base-case scenario)
Global costs of vaccine introduction	US$ 11.8 (9.6–16.9) billion	US$ 50.5 (38.1–75.9) billion
Averted costs for drug-susceptible TB diagnosis and treatment	US$ 342 (223–489) million	US$ 3.5 (2.2–5.2) billion
Averted costs for drug-resistant TB diagnosis and treatment	US$ 299 (251–351) million	US$ 3.2 (2.6–3.8) billion
Costs incurred for antiretroviral therapy	US$ 13.4 (9.5–19.2) million	US$ 362 (281–466) million

OTHER SCENARIOS

Halving the price of the vaccine for infants to US$ 2.30 decreased the costs of infant vaccination from US$ 11.8 to US$ 7.6 (36% decrease), while doubling the price of the vaccine to US$ 9.20 increased the costs to US$ 20.2 billion (71% increase).

Halving the price of the vaccine for adolescents and adult to US$ 2.30 decreased the costs of vaccinating adolescents and adults from US$ 50.5 to US$ 36.4 billion (28% decrease), while doubling the price of the vaccine to US$ 9.20 increased costs to US$ 78.8 billion (56% increase).

Alternative high–middle-tier vaccine pricing schemes were also modelled.[13]

[13] Portnoy A, Clark RA, Quaife M, Weerasuriya CK, Mukandavire C, Bakker R et al. The cost and cost–effectiveness of novel tuberculosis vaccines in low- and middle-income countries: a modelling study. medRxiv. 2022 (doi: 10.1101/2022.05.04.22274654).

6 TB vaccines can advance health equity

One of the issues that policy-makers consider in prioritizing health interventions for financing is their impact on health equity. A significant proportion of TB patients in low- and middle-income countries face substantial economic burdens before, during and even after TB care. According to surveys, almost half of TB patients and their households experience catastrophic costs due to TB. Furthermore, nearly 20% of global TB incidence is attributable to undernutrition.

The vaccine for infants could avert approximately 3.3–4.1 million cases of catastrophic cost faced by TB-affected households, corresponding to US$ 5.3–6.5 billion in savings. A vaccine for adolescents and adults could avert approximately 21.4–24.5 million cases of catastrophic cost, corresponding to US$ 36.6–41.5 billion in savings. The number of TB cases averted by the introduction of vaccines for both adolescents and adults and for infants was highest for lower-income quintiles (about 56% of benefits in the poorest two quintiles).[14]

VACCINE FOR ADOLESCENTS AND ADULTS

US$ 36.6–41.5 billion averted

VACCINE FOR INFANTS

US$ 5.3–6.5 billion averted

[14] Portnoy A, Clark RA, Weerasuriya CK, Mukandavire C, Quaife M, Bakker R et al. The potential impact of novel tuberculosis vaccines on health equity and financial protection in low- and middle-income countries. medRxiv. 2022 (doi: 10.1101/2022.10.29.22281678).

7 There is a significant market for TB vaccines

Forecasts of the demand for vaccines in a population provide an incentive for countries to develop and/or manufacture effective TB vaccines. Such forecasts also give countries the bargaining power to negotiate the price of the vaccine in the long run.

Adding up all the individuals who would be eligible to receive a vaccine in a country in which the vaccine was found to be cost–effective from a societal perspective, the market would be 1.431 (1.430–1.432) billion doses for the vaccine for infants and 5.182 (5.180–5.183) billion for that for adolescents and adults between 2025 and 2050. If the estimate includes only eligible vaccinees in countries in which the vaccine is cost-saving from the societal perspective, the market size would be 1.316 (1.315–1.317) billion for the vaccine for infants and 4.642 (4.617–4.644) billion for that of adolescents and adults between 2025 and 2050.[15]

DOSES OF VACCINE FOR ADOLESCENTS AND ADULTS

4.64 – 5.18 billion

DOSES OF VACCINE FOR INFANTS

1.32–1.43 billion

[15] Portnoy A, Clark RA, Quaife M, Weerasuriya CK, Mukandavire C, Bakker R et al. The cost and cost–effectiveness of novel tuberculosis vaccines in low- and middle-income countries: a modelling study. medRxiv. 2022 (doi: 10.1101/2022.05.04.22274654).

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8 TB vaccines can increase economic growth

TB vaccines can have longer-term economic benefits by improving public health, life expectancy and work performance. Between 2025 and 2080, gains in gross domestic product were estimated to be US$ 1.6 (0.8–3.0) trillion with the vaccine for adolescents and adults and US$ 0.2 (0.1–0.4) trillion with the vaccine for infants. Gains in gross domestic product resulting from vaccine introduction were concentrated in countries with high TB incidence that implemented early vaccine introduction.[16]

VACCINE FOR ADOLESCENTS AND ADULTS

US$ 0.8–3.0 trillion

VACCINE FOR INFANTS

US$ 0.1–0.4 trillion

[16] Portnoy A, Arcand JL,Clark RA, Weerasuriya CK, Mukandavire C, Bakker R et al. The potential impact of novel tuberculosis vaccine introduction on economic growth in low- and middle-income countries. medRxiv. 2022 (doi.org/10.1101/2022.11.23.22282690).

KEY MESSAGES AND WAY FORWARD

TB vaccines could significantly reduce TB incidence and mortality and development of antimicrobial resistance, with a vaccine for adolescents and adults projected to have a greater, more immediate impact than one for infants. The health impact of TB vaccines depends on their efficacy, duration of protection, the age group targeted, coverage and the delivery strategy.

There is a strong economic argument for investing in new TB vaccines. TB vaccines would be highly cost–effective in nearly all countries with a high TB burden and in most other low- and middle-income countries and could offer a significant return on investment. It was estimated that the substantial resources required for introduction of a vaccine would be offset by future cost savings due to the averted TB burden.

TB vaccines can improve health equity and contribute to the achievement of several Sustainable Development Goals (SDGs) by averting TB-related costs in affected households and by preventing development of the disease in poor, vulnerable groups. Thus, TB vaccines could contribute substantially to achievement of universal health coverage by narrowing income-based disparities in the health and the economic consequences of TB in low- and middle-income countries, helping to achieve several SDG targets, such as eradicating poverty (SDG 1), eradicating hunger (SDG 2), promoting decent work and growth (SDG 8) and promoting good health and well-being (SDG 3).

Increased investment in research and development will be instrumental to ensure rapid development and availability of effective TB vaccines, with more diverse funding sources and alignment of funders to address the most pressing needs. Rapid, equitable introduction and scaling-up of use of vaccines will have high public health and economic impacts. Thus, both the public and the private sectors must work together to maintain the affordability of and global access to TB vaccines once they become available.

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