New TB vaccines needed to tackle AMR

Tuberculosis (TB) is an airborne global pandemic. **In 2022, an estimated 10.6 million people became sick and 1.3 million people died from TB.** As an airborne bacterial pathogen, TB can infect anyone, but TB incidence is highest in low- and middle-income countries (LMICs).[i] Poverty and its causes and effects, such as overcrowding and undernourishment, increase the risk of TB transmission and disease.[ii]

The difficulty of diagnosing and successfully treating all people who have TB contributes significantly to antimicrobial resistance (AMR). TB also thrives in situations of displacement and social destabilization: humanitarian crises in countries with high (drug-resistant) TB burdens undermine provision of diagnostics, treatment, and prevention. Ukraine, for example, already had one of the world's highest rates of drug-resistant TB before the Russian invasion. The conflict has undermined access to health services; increasing rates of

TB infection and disease can be reasonably expected both in Ukraine and among the millions of people forced to flee.

Without further action, a projected 31.8 million TB deaths will occur by 2050, corresponding to an economic loss of US$17.5 trillion.[iii] Despite the huge threat posed by TB, political and financial support lags dangerously behind that of other communicable diseases. The world only spends one-fifth of the US$5 billion annual target governments committed to mobilize at the 2023 United Nations High-Level Meeting on TB to deliver the transformative technologies required to end the TB pandemic by the Sustainable Development Goal (SDG) deadline of 2030.[iv,v,vi]

New vaccines are needed to tackle this crisis. **Vaccines that prevent TB disease would save millions of lives, avert billions of dollars in treatment costs, and help curb the threat of AMR.**[vii] Developing new TB vaccines by 2030 is within reach if decision-makers prioritize TB vaccine R&D as a signature piece of global health and AMR agendas.

Key takeaways

TB is an airborne global pandemic that kills 1.3 million people each year, causes over 10.6 million people to fall sick, and results in catastrophic costs for patients and rising costs for health systems.

TB R&D is severely underfunded relative to the threat TB poses.

Drug-resistant TB is a major contributor to the global burden of antimicrobial resistance (AMR) and a significant cause of AMR deaths.

Without immediate corrective action by governments— including through additional funding for innovation—TB will cost the global economy a cumulative $US17.5 trillion by 2050.

Every $1 invested in the development and rollout of new TB vaccines for adolescents and adults will return $7 to the global economy over 25 years.

New vaccines against TB offer one of the best tools for stopping the spread of drug-resistant TB, saving lives, and mitigating the economic impact of TB-related AMR.

Decision makers must prioritize funding for TB vaccine R&D within all AMR initiatives.

Key terms

Mycobacterium tuberculosis (Mtb)
Mtb is a species of pathogenic bacteria and the causative agent of TB infection and disease.

Rifampicin-resistant TB (RR-TB)
TB resistant to rifampicin, one of the most effective first-line anti-TB drugs.

Isoniazid-resistant TB (Hr-TB)
TB resistant to isoniazid but susceptible to rifampicin.

Multidrug-resistant TB (MDR-TB)
TB resistant to rifampicin and isoniazid.

Pre-XDR-TB
TB that is resistant to rifampicin (and may also be resistant to isoniazid), and any fluoroquinolone drug agent (e.g., levofloxacin or moxifloxacin).

Extensively drug-resistant TB (XDR-TB)
TB caused by Mtb strains that fulfil the definition of MDR/RR-TB and which are also resistant to any fluoroquinolone and at least one additional Group A drug (e.g., bedaquiline or linezolid).

Group A drugs
The most potent group of drugs in the World Health Organization ranking of second-line medicines for the treatment of drug-resistant forms of TB.

Drug-resistant TB: A public health threat

Drug-resistant TB is an urgent global health crisis and a leading cause of death due to AMR.[viii] While the 2022 figures signal the start of a recovery in the global TB response following damaging COVID-19-related setbacks, current strategies to address drug-resistant TB are inadequate.

- In 2022, over 400,000 people fell ill with drug-resistant forms of TB.

- Most people who develop drug-resistant TB receive neither diagnosis nor treatment: less than 176,000 people were started on treatment in 2022—still below 181,500 in 2019.

- Based on these figures, the WHO estimates that treatment coverage (i.e., the number of people enrolled on treatment as a percentage of the number of people who developed MDR/RR-TB) is only 43%.

- Without treatment, most people with drug-resistant TB will die. Globally in 2020 (the latest patient cohort for which data are available), the treatment success rate for MDR/RR-TB with second-line regimens was 63%, up from 50% in 2012.

The majority of people who contract drug-resistant TB face catastrophic personal and health costs due to the duration, expense, and toxicity of treatment. Likewise, prevention and treatment of drug-resistant pathogens consumes large amounts of health resources worldwide, sometimes at the cost of national TB programs. It is estimated that drug-resistant TB services consume about half of all TB financing.[ix] **Addressing drug-resistant TB through treatment alone is both costly and insufficient.** New effective TB vaccines would make a major difference.
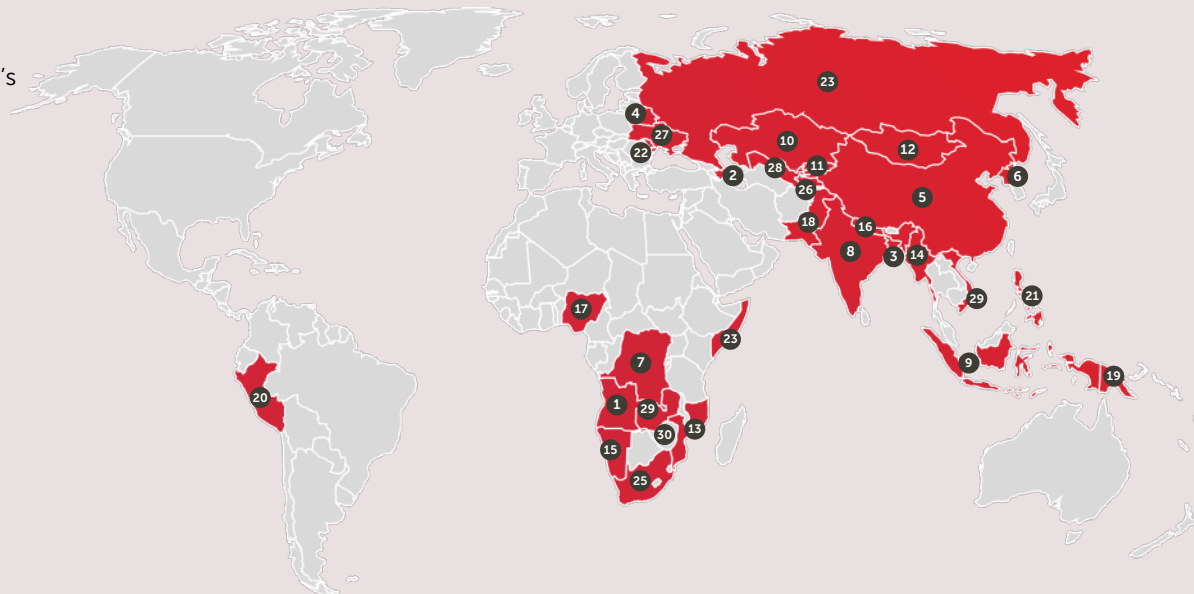
Treatment alone will not end drug-resistant TB

Drug-resistant TB treatment can last for months—or even years—with many debilitating and disabling side effects. Drug-resistant TB treatment regimens are very expensive for LMIC health systems (≥US$ 1000 per person). In 2022, WHO recommended a shorter six-month regimen for people with confirmed MDR-TB/RR-TB.[x,xi] However, this regimen is not accessible to all who need it and side effects, though improved compared to older therapies, can still be debilitating.[xii] Despite dramatic improvements in the standard of care, treatment for drug-resistant TB remains lengthy and dependent on the efficacy of a limited number of antibiotics. TB caused by bacteria which do not respond to second-line anti-TB drugs can leave patients without any further treatment options. Extensively drug-resistant TB has very poor treatment outcomes.

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By the end 2021, only 825,000 people (55%) of the UN target to treat 1.5 million people with MDR/RR-TB between 2018-2022 were reached.[i]

High burden countries

The World Health Organization (WHO) identifies 30 high burden MDR-TB countries[xiii]:

1. Angola
2. Azerbaijan
3. Bangladesh
4. Belarus
5. China
6. Democratic People's Republic of Korea
7. Democratic Republic of Congo
8. India
9. Indonesia
10. Kazakhstan
11. Kyrgyzstan
12. Mongolia
13. Mozambique
14. Myanmar
15. Namibia
16. Nepal
17. Nigeria
18. Pakistan
19. Papua New Guinea
20. Peru
21. Philippines
22. Republic of Moldova
23. Russian Federation
24. Somalia
25. South Africa
26. Tajikistan
27. Ukraine
28. Uzbekistan
29. Viet Nam
30. Zambia

Developing resistance

Anti-TB drugs have been used for decades. **Strains that resist one or more of the medicines have been documented in every country surveyed by the WHO.** On average, 20% of the people with MDR/RR-TB also have resistance to a fluoroquinolone, a key second line antibiotic.[xiv] Resistance is also developing to newer backbone medicines such as bedaquiline.[xv] Drug resistance emerges through simple mutation, incorrect prescription by health care providers, by use of poor-quality drugs, and when patients stop treatment prematurely, often due to the grueling nature of treatment regimens, insufficient treatment support, or interruptions to drug supply.

TB vaccines and AMR

Vaccination is one of the most effective ways to control and prevent AMR. Vaccines against bacterial pathogens—like those that prevent pneumonia and flu—have been very effective in reducing incidence of disease, use of antibiotics, and AMR, despite facing a number of hurdles to global access, implementation, and use.[xvi,xvii,xviii,xix] Yet, the only available TB vaccine is the century-old Bacillus Calmette-Guérin (BCG) vaccine, which is mostly ineffective in adolescents and adults, who are most at risk of developing and spreading TB.

A future TB vaccine could significantly help control drug-resistant TB, in a cost effective and affordable way.[xx,xxi,xxii] By preventing TB, new vaccines would reduce the need for antibiotics, and thus reduce the development of drug resistance and onward transmission. A TB vaccine for infants could avert an estimated 2.4–8.6 million treatments

India: the world's highest TB burden

India accounted for 29% of global TB deaths among HIV-negative people and 26% of the combined total number of TB deaths in people living with and without HIV in 2022. With almost 27% of all TB infections and almost 27% of MDR/RR-TB cases globally in 2022, India faces the world's highest burden of TB.[xxxiii] Urgent action is needed to prevent a major health crisis caused by widespread misuse of antibiotics.

MDR/RR-TB incidence (2022): 111,000

(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.**[vii]

Moreover, the mechanisms by which vaccines confer immunity likely differ from the mechanisms through which drug-resistance develops. Vaccines may also reduce the development of AMR in other pathogens exposed to antibiotics during TB treatment. Therapeutic vaccines, in combination with drugs, could reduce treatment duration, the risk of disease recurrence, and post-treatment health complications.

The cost of inaction wildly surpasses the cost of action. TB vaccines have been shown to be overwhelmingly cost-effective, particularly when targeted to adolescents and adults. Introduction of an adolescent/adult vaccine in most high drug-resistant TB burden countries could produce $283–474 billion in economic benefits by 2050.[xxiii] One study estimates that new TB vaccines could avert over a third of deaths attributable to bacterial AMR.[xxiv] New TB vaccines will help governments meet the WHO End TB Targets by 2030 which would save up to 23.8 million lives and avert $13.1 trillion in economic losses.[iii]

TB vaccines neglected in the AMR agenda

TB is commonly overlooked in AMR R&D programs, including CARB-X,[xxv] the world's largest and most diverse portfolio of early development antibacterial projects. Supporting early development of antibiotics, vaccines, rapid diagnostics and other life-saving products, CARB-X addresses other threats identified as "*Critical*" or "*High*" in the WHO's 2017 Priority Pathogen for R&D of new antibiotics list, but not TB.[xxvi] The European Commission's recent communication on the new EU global health strategy[xxvii] does mention TB among its priorities for health equity, and the ***European One Health Action Plan against Antimicrobial Resistance (AMR)***[xxviii] explicitly connects resistant strains of TB to AMR. However, the EU health security prevention and response agency, HERA, does not include TB research as part of the priority it places on AMR, and the ***2023-2024 Horizon Europe workplan for Health***[xxix] does not mention TB even once.

WHO calls for highest priority action on TB vaccines

In July 2022, WHO published an urgent call to use and develop new vaccines to tackle AMR, highlighting that the development of more effective vaccines against TB should be accelerated.[xxx] Given the urgent need, **the WHO calls for the accelerated development of more effective vaccines against TB, with the highest level of 'Priority 1: critical'**

in the 2020 *Action Framework on Leveraging Vaccines to Reduce Antibiotic Use and Prevent Antimicrobial Resistance.*[xxxi] In December 2022, WHO published an investment case presenting eight health and economic arguments for investing in new TB vaccines. **Every $1 invested in the development and rollout of new TB vaccines for adolescents and adults will return $7 to the global economy over 25 years.**[vii]

Funders, industry, governments, nongovernmental and supranational organizations, academic institutions, and researchers need to increase investments in TB vaccine R&D to address AMR globally. This includes creating new financing mechanisms for late-stage vaccine evaluation, vaccine introduction, manufacturing capacity development, and evaluation of new vaccine effectiveness and impact in real-world settings.

The potential of EU support for TB vaccine R&D

Europe's *One Health Action Plan against AMR* calls on the European Union (EU) and its Member States (MS) to invest in "infection prevention and control in vulnerable groups, in particular to tackle resistant TB strains," including investments for new vaccines. Europe has invested in TB research, but the EU and most MS are far behind their fair share targets. In fact, the majority barely cover half of their targets.[v]

The EU's *AMR Accelerator | Innovative Medicines Initiative (AMR | IMI)* invested the most in TB research in 2021: $31 million on TB drug development. While the AMR | IMI provides significant funding to TB drug development in support of the One Health Action Plan against AMR, it does not support TB vaccine research. The European Commission (EC) was the second-largest source of funds for TB research from the EU in 2021, at $30 million.[xxxii] The EDCTP came in third, at €29 million. Both the EC and EDCTP fund TB vaccine research – $4.4 million and $5.8 million respectively in 2021.

We call on EU member states to substantially increase their investments in TB vaccine R&D in line with their fair share targets. This will advance the TB vaccine pipeline and enable new TB vaccines to be available as early as 2028, saving money, saving lives, and preventing massive economic losses.

TB VAX ARM

The TB Vaccine Advocacy Roadmap (TB Vax ARM) represents a global coalition of TB stakeholders, including TB survivors, civil society organizations, and non-profits, invested in TB vaccine advocacy and research.

Summary of findings from *An investment case for new tuberculosis vaccines,* WHO (2022)

1 TB vaccines save lives

2 TB vaccines can help fight AMR

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

4 TB vaccines offer a substantial return on investment

5 Upfront costs of introducing TB vaccines are partially offset by savings to TB and HIV treatment

6 TB vaccines can advance health equity

7 There is a significant market for TB vaccines

8 TB vaccines can improve economic growth

Acknowledgements

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Learn more at www.newtbvaccines.org/advocacy

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