Task Force 6
Accelerating SDGs: Exploring New Pathways to the 2030 Agenda

INVESTMENT TOOLBOX TO ADVANCE TB VACCINE DEVELOPMENT THROUGH JOINT ACTION

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Abstract

Tuberculosis (TB), which continues to be a global pandemic, is a pressing public health, human rights, and economic concern. At least one new TB vaccine must be licensed and approved by 2025 to meet the World Health Organization's (WHO) goal of ending TB by 2030. The G20 includes many countries with a high burden of TB and is uniquely positioned to lead TB vaccine development and delivery through joint, sustained, and scaled-up investments. This Policy Brief outlines recommendations for G20 members to act together to accelerate TB vaccine development. An "investment toolbox" is proposed, adaptable to each country's economic and research capacities and disease burden.

The Challenge

1

The TB Pandemic: Public Health and Economic Impacts

Globally, tuberculosis (TB) will soon overtake COVID-19 to once again become the leading cause of death from infectious disease. COVID-19-related setbacks have reversed a decade of progress on TB. In 2021, 10.5 million people fell ill with TB and 1.6 million lost their lives to the disease, mostly in low- and middle-income countries (LMICs).[1] New cases of multi-drug-resistant TB rose by 3 percent to an estimated 450,000 cases in 2021, contributing to the growing health and security threat of antimicrobial resistance (AMR).[2] While the standard of care for treating drug-susceptible and drug-resistant TB has substantially improved, treatment remains lengthy and dependent on a limited arsenal of effective drugs, with often debilitating side effects. Addressing TB through treatment alone is insufficient to meet the global goal of ending TB by 2030. Multiple TB vaccines are needed to achieve this aim.

Without immediate action, almost 32 million TB deaths will occur between 2020 and 2050, resulting in global economic losses of US$17.5 trillion. Conversely, meeting the global 'End TB' target to reduce TB mortality by 90 percent by 2030 would save 23.8 million lives and avoid US$13.1 trillion in economic losses.[3,4] Improved TB vaccines would have even greater impact, considering the catastrophic costs of TB treatment, and subsequent TB-related disabilities. Half of TB-affected households incur catastrophic TB-related expenses: this is more than half their annual income over the course of TB illness.[5]

The Promise of New TB Vaccines

Universally accessible TB vaccines would fight AMR, advance health equity, avert millions from household catastrophic costs, improve affected countries' macroeconomic prospects, and advance infrastructure for pandemic preparedness and response (PPR). The rapid development and roll-out of multiple COVID-19 vaccines contributed significantly to controlling the pandemic. A similar response is required to end TB.

The only available TB vaccine is the century-old Bacille Calmette–Guérin (BCG), which offers important yet limited protection to infants and young children. Unfortunately, it is largely

ineffective in adolescents and adults, who are most at risk of developing and spreading TB. Today, after decades of hard-fought scientific progress and public and philanthropic investments, 15 TB vaccine candidates are under clinical investigation worldwide. With five candidates currently in Phase III clinical trials, the pipeline presents a historic opportunity to bring at least one new TB vaccine through licensure and ensure global access in the current decade.[6] This will only be possible if governments substantially increase funding for TB vaccine R&D without delay.

Developing new TB vaccines is a smart economic investment. While substantial upfront financing is needed to ensure success, including for the mass vaccination campaigns that should follow, even a single new TB vaccine would produce substantial public health and economic gains in high-burden countries, comparable to recent high-impact health interventions in those same countries.[7] New TB vaccines would be highly cost-effective in nearly all high TB burden countries and in most other LMICs as well. Every dollar invested in delivering a new vaccine for adolescents and adults should generate seven dollars in health and economic returns over 25 years.[8]

Why TB Vaccine R&D Is Still Not Prioritised

TB vaccine R&D remains chronically underfunded. Long-term financing is not guaranteed.[9] Insufficient action by governments and minimal private-sector investment – amounting to only US$9 million in 2021 – has led to stop-start research with protracted and costly delays across the clinical development continuum, particularly in late-stage testing. There is also a dearth of candidates in the pipeline.

The potential market for TB vaccines is large. However, the market is considered insufficiently predictable and is not seen to offer attractive returns on investment for industry as it is concentrated in LMICs or among low-income populations in upper-middle-income countries.[10,11] Further, compared to drugs, vaccines are inherently more complex and riskier to develop. On their own, market forces will not bring TB vaccine R&D to fruition.

So far, TB vaccine R&D has depended on limited funding streams. Over 80 percent of investments come from

just three donors—United States (US) National Institutes of Health (NIH), the Bill and Melinda Gates Foundation, and the European and Developing Countries Clinical Trials Partnership (EDCTP). The European Union (EU) and most other wealthy countries prioritise health investments on diseases which have high prevalence in their own territories—which excludes TB. Indeed, TB vaccine R&D is overlooked by existing multilateral and global health funding mechanisms both for TB and for vaccine R&D, be it the Global Fund for Aids, Tuberculosis and Malaria, the global vaccine alliance Gavi, the Coalition for Epidemic Preparedness Innovations (CEPI), or the World Bank's Pandemic Fund.

At the 2018 United Nations (UN) High-Level Meeting to End TB, world leaders pledged to invest US$2 billion annually in TB research over five years.[12] By 2021, only 30 percent of the target had been invested—for vaccines, the figure was only 15 percent. Funding for TB vaccine development has never exceeded US$121 million per year, against an annual target of US$613 million. The Global Plan to End TB 2023-2030 now estimates that TB vaccine R&D will require US$10 billion over eight years, plus US$13 billion for vaccine delivery.[13]

The World Health Organization (WHO) and the Stop TB Partnership have called for at least one new vaccine against TB to be licensed and approved by 2025.[14] Coordinated financial and political action by G20 states is thus urgently needed to correct market inefficiencies, de-risk investments, and attract industry engagement in TB vaccine R&D.

The G20's Role

2

The G20 is uniquely positioned to advance TB vaccine development and delivery through joint, sustained, and scaled-up investments. To achieve this, two preconditions must be fulfilled.

a. Concrete political commitment

Some G20 countries have already signalled laudable commitments to ending TB. Four high-TB burden countries will hold consecutive G20 presidencies across 2022-2025. India, holding the 2023 presidency, has invested in TB vaccine research, including multiple Phase III trials. Indonesia, during its presidency in 2022, issued a call to action on financing TB response.[15] The presidencies of Brazil and South Africa will follow, offering an unparalleled opportunity for scaled-up G20 political commitment for TB vaccine development to catalyse joint investments across G20 states and demonstrate to manufacturers and other stakeholders and funders that TB vaccine development is a priority.

b. Joint undertaking

No single country or institution can develop new TB vaccines on its own. Multilateral cooperation is essential to mitigate the risk borne by individual funders and maximise efficient use of investments across the continuum of vaccine development and introduction. G20 support for concrete financing mechanisms and for a multi-country, multi-site, and multi-stakeholder approach can advance TB vaccine development efficiently and effectively.

Recommendations to the G20

3

The TB Vaccine Investment Toolbox for Joint Action

To meet the funding and resource needs of the TB vaccine pipeline, this Policy Brief proposes a pragmatic approach for the G20 based on two key recommendations: (1) mobilise joint financial support; and (2) establish an enabling environment for TB vaccine development.[16]

1. Mobilise joint financial support

The investment toolbox' that follows can be segmented by market. G20 members can together employ existing and innovative financing and resourcing mechanisms tailored to a country's economic and research capacities and disease burden (see Figures 1 and 2). Substantial upfront investments will remain critical.

Figure 1

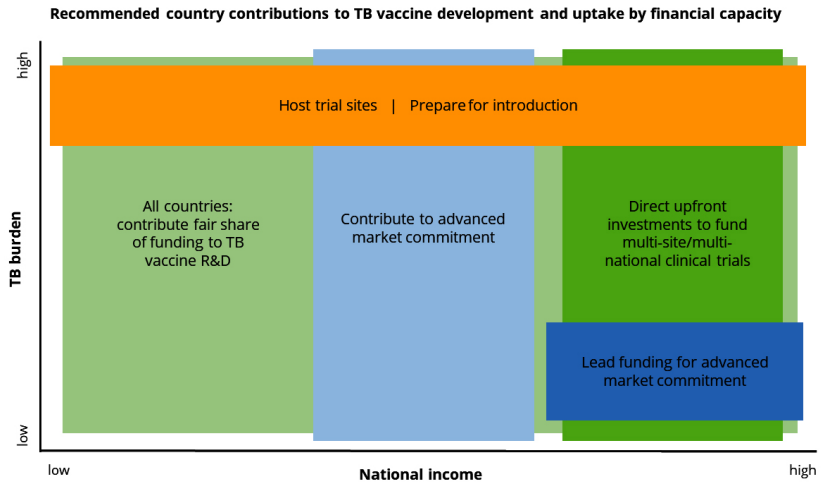
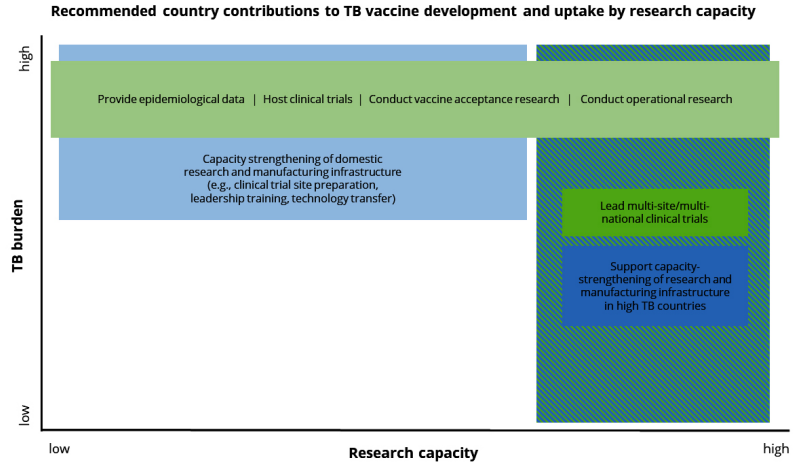


Figure 2



G20 members should accordingly assess the most appropriate and efficient financing mechanisms and research platforms to raise joint funding.

All G20 countries should fund their 'fair share' of TB R&D and direct investments towards vaccine R&D.

All countries, including G20 states, can contribute a 'fair share' to TB R&D. If each country dedicates at least 0.1 percent of its national expenditure on R&D to TB, funding gaps will close.[17] Funnelling a greater portion of this to TB vaccine R&D specifically will accelerate vaccine development. South Africa is already meeting this fair-share target. Other G20 members are close: the US met 94 percent of its target in 2021, Canada, 67 percent, and India, 50 percent. Such targets enable tracking progress toward meeting shared commitments.

Business and investment cases for middle-income, high-burden countries

Middle-income, high-burden countries such as Brazil, India, Indonesia, and South Africa are in a good position to not only invest their fair share of domestic resources in TB vaccine R&D, but also to utilise existing domestic research, regulatory, and manufacturing infrastructure and capabilities. Country-specific business cases can identify how and where investments will produce meaningful economic, societal, and public health returns. G20 states should concurrently support efforts to define a clear path to commercialisation by using market-shaping tools such as forecasting, volume and procurement guarantees, and the identification of commercial partners to stimulate industry engagement.[18]

Advanced Market Commitment for low- and middle-income, high-burden countries

Advanced Market Commitments (AMC) can demonstrate markets and secure access. Generally implemented during the final phases of clinical development, AMCs reward successful outputs rather than supporting more speculative research.[19] AMCs legally bind vaccine manufacturers to sell a future vaccine at a particular price. The price should take into account public financing for R&D and reflect cost-of-goods, plus a reasonable mark-up to generate revenues and support sustainable supply. Contributing countries,

including G20 members, should pay this price for up to a certain number of doses. Middle-income countries could contribute to the AMC or make parallel supportive investments, such as expanding production capacity among domestic manufacturers. The volumes purchased through an AMC should be enough to support mass vaccination campaigns in affected countries. Once initial volumes are met, manufacturers would be obligated to maintain an affordable price for eligible countries.[20] Hard-won lessons from previous AMCs for vaccines should inform the design of future financing mechanisms for TB.

Other tools

G20 members should consider other tools in tandem to deliver additional capital:

- High-income countries could match funding to incentivise and supplement LMIC investments (analogous to how the US matches a dollar for every two dollars other partners pledge to the Global Fund for Aids, Tuberculosis and Malaria).[21]

- The Global Plan to End TB 2023–2030 outlines several other tools that could be applied to TB vaccine R&D, including impact bonds, blended finance, micro-levies/taxes, and corporate social responsibility.

- Development banks could provide loans at competitive or below-market rates or in the form of credits as long-term loans funded largely by direct contributions from donor countries.[22]

- Tools such as debt relief restructuring and global public investments could increase the fiscal space for targeted investments for TB vaccines R&D.

(2) Establish an enabling environment for R&D.

An enabling environment for TB vaccine R&D addresses redundancies and maximises efficiencies across the pipeline with an end-to-end perspective to make the best use of the time, money, and resources available. The recommendations that follow complement those made earlier:

Leverage global partnerships with robust leadership and accountability.

Funders from G20 countries have provided invaluable long-term investments to TB vaccine R&D,

including the US NIH, the Bill and Melinda Gates Foundation, and the EDCTP. The governments of India, South Korea, and the United Kingdom (UK) have also contributed. G20 leaders must now engage with other players to increase and deliver on commitments to secure the future of the pipeline.

More visible leadership and coordination is vital. G20 leaders should, for example, participate in the WHO TB Vaccine Accelerator Council to catalyse strategic alignment, drive accountability, and overcome barriers to vaccine development.[23] They should start by raising significant additional financing for TB vaccine R&D. An independent monitoring and accountability mechanism should be instituted alongside to track fulfilment of resulting commitments which should include active participation of community and civil society representatives.

Political leadership by G20 states has likewise been key to establishing multilateral global health funding mechanisms and bringing vaccine candidates through to licensure that otherwise lacked viable commercial markets. The UK was instrumental, for instance, in bringing the Meningococcus C vaccine to market to prevent meningitis, while Canada, Italy, Russia, and the UK were key players in Gavi's Pneumococcal vaccine AMC initiative to prevent pneumonia, meningitis, and sepsis in children. G20 countries, including those most affected by TB, should mobilise increased investments and incentivise investments from other countries and stakeholders.

Multi-ministerial engagement will be vital to the successful development and introduction of new TB vaccines. The G20 should involve all relevant ministries encompassing different G20 tracks, including Development, Health, Research and Innovation Initiative Gathering (RIIG), and the Joint Finance and Health Task Force. The G20 also can support member countries' health and finance ministries, regulatory bodies, and immunisation programmes to prepare for vaccine introduction. This should include plans to appropriately finance rollout, stock maintenance, training of healthcare workers, and engaging communities.

Attach conditionalities to public funding to ensure equitable access.

Recognising that public funding will comprise the bulk of the funding for TB vaccine development, G20 investments

must include conditionalities to ensure equitable access to resulting products. The inequities seen in access to COVID-19 vaccines should not be repeated for TB. They are avoidable if governments act to maximise public returns on public investments. Conditionalities should promote *transparency* (of clinical trial results, cost-of-goods, product pricing, and contract terms), *sharing* (of data and knowledge, including the transfer of know-how and technology to enable regional or domestic manufacturing), and *inclusivity* (of decision making and priority setting, participation from civil society and communities, and equitable and fair access to marginalised and vulnerable populations). Provisions attached to public funding should promote access to the means, methods, and materials necessary for scientific discovery, to the know-how required for manufacturing, and to timely and affordable access to new TB vaccines for people who urgently need them.

Maximise efficiencies in financing and R&D practices

Lengthy interruptions between clinical trial phases, especially during late-stage efficacy testing, impose unnecessary and costly delays. G20 countries should, as a standard practice, provide flexible, long-term funding guarantees to ensure seamless transition of a vaccine candidate to the next phase of clinical development if data supports advancing. To further mitigate delays, aggressive timelines for reviewing applications for TB vaccine trials can be adopted by all G20 states, such as the six-month funding horizon for the US-NIH HIV-related grants.[24]

Joint calls for TB vaccine trials and clinical research initiatives could leverage existing bilateral collaborations among G20 members in TB R&D to catalyse new funding for TB vaccines. There are many which can be used, including the US-South Africa Programme for Collaborative Biomedical Research, the Regional Prospective Observational Research for Tuberculosis (RePORT) International, and the India-South Africa collaborative research programme on HIV/AIDS and TB.

The COVID-19 response demonstrated the huge potential for innovation in vaccine development. The TB vaccine pipeline is poised to benefit from similar innovations, including adaptive trial designs, pooled epidemiology, and harmonised clinical trial protocols. In

recent years, a range of frameworks have been developed to support an accelerated and efficient TB vaccine pipeline, including the 2021 Global TB Vaccine R&D Roadmap, published by the EDCTP and the Amsterdam Institute for Global Health and Development, and the WHO Evidence Considerations for Vaccine Policy. These should be used as guiding frameworks for all future efforts, including those under the WHO TB Vaccine Accelerator Council.

Integrate TB into PPR and AMR Agendas

Investing in TB vaccine R&D can build local and global research capacities across the vaccine research continuum that are flexible, adaptable, and sustainable in support of the global PPR agenda.[25] Countries with R&D and manufacturing capacity must lead acceleration of TB vaccine R&D and access. This will address TB while ensuring the world has the infrastructure to address future threats. New TB vaccines could also significantly help control drug-resistant TB in a cost-effective way.[26,27]

TB vaccines remain neglected across AMR agendas, despite WHO calling for the highest priority action on TB vaccine development to prevent AMR.[28] G20 members must prioritise TB vaccine R&D as a signature piece of the PPR and AMR agendas at all levels.

To end TB, the world urgently needs new and effective TB vaccines that work across all populations. New TB vaccines are within reach this decade but only with significantly scaled-up and joint investments. G20 members must come together to fulfil their commitments to end TB by implementing appropriate and efficient financing mechanisms to raise the funding and resources required. With bold, coordinated, and sustained efforts, G20 members can provide the financing, policy leadership, enabling research environments, manufacturing capacity, and access and delivery systems needed to deliver effective vaccines to transform the global TB response. Doing so will save millions of lives and trillions of dollars—a worthy return on investment.

Attribution: Shaun Palmer et al., “Interventions for TB Vaccine Development,” *T20 Policy Brief*, July 2023.

Endnotes

1 WHO, "Global Tuberculosis Report 2022," Accessed April 5, 2023, https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022.

2 WHO, "Tuberculosis deaths and disease increase during the COVID-19 pandemic," Accessed April 5, 2023, https://www.who.int/news/item/27-10-2022-tuberculosis-deaths-and-disease-increase-during-the-covid-19-pandemic.

3 Sachin Silva et al., "Economic impact of tuberculosis mortality in 120 countries and the cost of not achieving the Sustainable Development Goals tuberculosis targets: a full-income analysis," *The Lancet Global Health* 9, no.10 (2019): e1372-e1379.https://doi.org/10.1016/S2214-109X(21)00299-0.

4 WHO, "The end TB strategy," Accessed April 5, 2023, https://www.who.int/teams/global-tuberculosis-programme/the-end-tb-strategy.

5 Tadayuki Tanimura et al., "Financial burden for tuberculosis patients in low- and middle-income countries: a systematic review," *European Respiratory Journal* 43, no. 6 (2014): 1763-1775. https://doi.org/10.1183/09031936.00193413.

6 Treatment Action Group, "Pipeline Report 2022: Tuberculosis Vaccines," Accessed April 4, 2023, https://www.treatmentactiongroup.org/wp-content/uploads/2022/10/2022_pipeline_TB_vaccines_final.pdf.

7 Rebecca C Harris et al., "Potential impact of tuberculosis vaccines in China, South Africa, and India," *Science Translational Medicine*12, no.564 (2020. https://doi.org/10.1126/scitranslmed.aax4607.

8 WHO, "An investment case for new tuberculosis vaccines," Accessed March 24, 2023, https://www.who.int/publications/i/item/9789240064690.

9 Treatment Action Group, "Tuberculosis Research Funding Trends, 2005–2021," Accessed April 3, 2023, https://www.treatmentactiongroup.org/resources/tbrd-report/tbrd-report-2022/.

10 David Webber and Michael Kremer, "Perspectives on stimulating industrial research and development for neglected infectious diseases," *Bulletin of the World Health Organization* 79 (2001): 735-741. https://scielosp.org/pdf/bwho/v79n8/v79n8a09.pdf.

11 EDCTP and Amsterdam Institute for Global Health and Development, "Global roadmap for research and development of tuberculosis vaccines," Accessed March 23, 2023, http://www.edctp.org/web/app/uploads/2021/04/EDCTP-TB-vaccine-roadmap-full-version-final.pdf.

12 UN, "Political Declaration of the UN General Assembly High-Level Meeting on the Fight Against Tuberculosis," Accessed March 23, 2023, https://cdn.who.int/media/docs/default-source/documents/tuberculosis/political-declaration-un-general-assembly-tb-tuberculosis77cd7a27-7e8d-4fbb-9729-a5dbd505798f.pdf?sfvrsn=4f4090dc_1&download=true.

13 Stop TB Partnership, “Global Plan to End TB 2023-2030,” Accessed March 24, 2023, https://www.stoptb.org/global-plan-to-end-tb/global-plan-to-end-tb-2023-2030.

14 Stop TB Partnership, “United to End Tuberculosis: An Urgent Global Response to a Global Epidemic: Key Asks from TB Stakeholders and Communities,” Accessed May 26, 2023, https://stoptb.org/assets/documents/global/advocacy/KEYASKS.PDF.

15 Indonesian G20 Presidency, “Chair’s Summary: Health Minister’s Meeting of the G20 – Call to Action on Financing for TB Response,” October 28, 2022, http://www.g20.utoronto.ca/2022/Chairs-Summary-G20-Health-Ministers-Meeting-27-28-October-2022.pdf.

16 Rino Rappuoli, Steven Black, and David E Bloom, “Vaccines and global health: In search of a sustainable model for vaccine development and delivery,” *Science Translational Medicine* 11, no. 497 (2019),https://doi.org/10.1126/scitranslmed.aaw2888.

17 Sarah Steingrüber, “European Commitments to TB R&D Investments: Promises Made to Be Broken?,” *Treatment Action Group* (2022), https://www.treatmentactiongroup.org/wp-content/uploads/2022/02/TAG_eu_tb_funding-report_final.pdf.

18 MedAccess,“Market shaping,” Accessed April 5, 2023, https://medaccess.org/innovative-finance/market-shaping/.

19 Theolis Costa Barbosa Bessa et al., “R&D in Vaccines Targeting Neglected Diseases: An Exploratory Case Study Considering Funding for Preventive Tuberculosis Vaccine Development from 2007 to 2014,” *BioMed Research International* (2017), https://doi.org/10.1155/2017/4765719.

20 IAVI, “Policy Brief: Advance Market Commitments: Helping to accelerate AIDS vaccine development,” 2004, https://assets.publishing.service.gov.uk/media/57a08c6740f0b652dd0012ea/policybrief_advance_market_commitments.pdf.

21 KFF, “The U.S. & the Global Fund to Fight AIDS, tuberculosis and malaria,” Accessed April 5, 2023, https://www.kff.org/global-health-policy/fact-sheet/the-u-s-the-global-fund-to-fight-aids-tuberculosis-and-malaria/.

22 Council on Foreign Relations, “The World Bank and International Development Lenders,” Accessed April 6, 2023, https://www.cfr.org/backgrounder/world-bank-and-international-development-lenders.

23 WHO, “WHO announces plans to establish a TB Vaccine Accelerator council,” Accessed April 5, 2023, https://www.who.int/news/item/17-01-2023-who-announces-plans-to-establish-a-tb-vaccine-accelerator-council.

24 Richard E Chaisson, Mike Frick, and Payam Nahid, “The scientific response to TB – the other deadly global health emergency,” *The International Journal of Tuberculosis and Lung Disease* 26, No. 3 (2022): 186-189, https://doi.org/10.5588/ijtld.21.0734.

25 Janika Hauser, Matt Oliver, ‘’Ready Next Time. Beating TB today and preparing for pandemics tomorrow,*” Campaigns in Global Health, Cambridge, United kingdom*, https://www.cghproject.org.

26 Han Fu et al., “Modelling the global burden of drug-resistant tuberculosis avertable by a post-exposure vaccine,” *Nature Communications* 12, No. 424 (2021), https://doi.org/10.1038/s41467-020-20731-x.

27 Chathika K Weerasuriya et al., “The epidemiologic impact and cost-effectiveness of new tuberculosis vaccines on multidrug-resistant tuberculosis in India and China,” *BMC Medicine* 19, 60 (2021), https://doi.org/10.1186/s12916-021-01932-7.

28 WHO, “Urgent call for better use of existing vaccines and development of new vaccines to tackle AMR,” Accessed March 23, 2023, https://www.who.int/news/item/12-07-2022-urgent-call-for-better-use-of-existing-vaccines-and-development-of-new-vaccines-to-tackle-amr.

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