



TB research and innovation in Latin America

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The current epidemiological status of TB in Latin America, with its high morbidity and mortality due to TB and MDR-TB, does not match the development of R&D in TB and MDR-TB in the region
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ABSTRACT The production of tuberculosis (TB) research and innovation in Latin America during the past decade has notably improved. Its role in the acceleration of the decline of the average annual TB incidence rate by 2.5% from 2017 to 2018 is still unclear, but it is looking promising that the region will meet the End TB Strategy targets set for 2030.

Well performed and high-quality research and evidence is critical for improving national TB control programme outcomes. In Latin America, this need is most apparent when responding to the multidrug-resistant TB epidemic.

There is an urgent need for technological breakthroughs to accelerate by an average of 17% per year if the decline in TB incidence rate is to meet the target set for 2030. Intensified research and innovation, identified as one of the three essential pillars of the End TB Strategy, has scarcely been achieved in the region due to political and economic context. This will be analysed further in this article.

Introduction

The production of tuberculosis (TB) research, innovation and biotechnology in health in Latin America during the past two decades has notably improved. Although its role in the acceleration of the decline of the average annual TB incidence rate by 2.5% [1] from 2017 to 2018 is still unclear, such research has great promise in ensure the region meets the 2030 End TB Strategy targets.

Well performed, high-quality TB research and evidence is critical for improving national TB control programme outcomes, particularly in response to the multidrug-resistant (MDR)-TB epidemic [2].

Technological breakthroughs are needed to accelerate on average by 17% [1] annually if the decline in TB incidence is to meet the 2030 TB elimination targets. Yet the region's political and economic context has hampered the type of intensified research and innovation identified as one of the three essential pillars of the End TB Strategy.

Research priorities include: 1) development of rapid point-of-care TB diagnostics, including those for drug resistance; 2) a TB vaccine effective both before and after exposure to lower the risk of infection; 3) new drug treatment to cut the risk of TB disease in 18.3% of the population already latently infected in the region [3]; and 4) simpler, shorter drug regimens for treating TB disease.

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Boosting TB research and development in Latin America will allow countries to reinsert those affected by TB as social assets and promote economic development. TB research in the past decade has driven the early detection of resistant strains, increased social TB knowledge, enhanced the ability to solve complex TB programmatic problems, and addressed some social determinants of TB [4].

Recently, Latin American countries have been investing more into TB research, especially in Brazil, Argentina, Uruguay, Colombia, Mexico and Chile where a connection has been demonstrated between improving TB research and development and the efficacy of TB programmes. In other countries, funding shortfalls reflect a lack of understanding of the key role research plays in disease control. Greater investments in the past may have led to far better tools to help improve TB control today [5].

TB programmes and TB clinical research are two sides of the same coin, a symbiosis, with high relevance for each other. Countries are making progress in the identification of locally relevant TB research priorities and in turning these into coherent TB research roadmaps. The World Health Organization has defined India, Brazil, South Africa, Peru, Vietnam and Indonesia as pathfinder countries in developing national strategic plans for TB research [6]. This effort should be expanded to Bolivia, Honduras, Ecuador, El Salvador and Venezuela, and also should ensure that national strategic plans include mechanisms for holding countries accountable for honouring new commitments to TB research. One option would be to reserve dedicated funding for civil society groups to monitor the implementation of national strategic plans.

Numerous TB research needs and gaps still remain. Countries have achieved remarkable success in increased detection rates, improved laboratory quality assurance, and better systematic management of cases of MDR-TB. Yet, few efforts correspond with domestic development of biotechnology in Latin America [7].

Research and development in TB and MDR-TB in Latin America is still dependent on foreign external technical and financial partners, reducing capability to locally produce patents, and perpetuating dependence on external research and development priorities [8].

Latin American countries need to build strong policies dedicated to TB research, with appropriate funding levels [9]. Policy implementation must allow countries to effectively structure and fund their TB research priorities (Brazil, Mexico, Peru and Ecuador are leading this process).

Funding, research and MDR TB in Latin America

Latin America is ideal for large-scale research development in TB. The MDR-TB epidemic has spurred investor interest in research and biotechnology development, which has grown annually from 16.86% in 2005–2006 to 88.03% in 2015–2017 [10].

The region currently attracts TB research and development investors, including large pharmaceutical companies, and Product Development Partners initiatives for the development of TB vaccines, biotechnology in TB and development of new therapeutic alternatives. Latin America accounts for 3% of all cases worldwide [10] and has well-implemented health systems, a critical mass of human resources with proper training, and well-established TB prevention and control programmes.

The most relevant Product Development Partners in Latin America during the past two decades have been: 1) the TB Alliance, focused on developing new drugs and drug regimens to treat drug-susceptible-TB and drug resistant-TB; 2) Aeras and TBVI, which conduct preclinical and clinical trials of TB vaccines; and 3) FIND, which supports a range of diagnostic developers.

Most research and development funding has come from external sources including DFID, USAID, DGIS, NORAD and the Bill and Melinda Gates Foundation, with little support from Latin American governments.

Relationship between national expenditures on TB research and development and incidence of MDR/rifampicin-resistant TB in Latin America

To understand the relationship between TB and MDR-TB rates, and the percentage of national expenditures on research and innovation, we followed the World Bank [5] in examining the Human Development Index, gross domestic product (GDP) per capita, public expenditure on health as a percentage of GDP, and the percentage of GDP devoted to innovation and development activities in Latin America and MDR/rifampicin-resistance TB rates (table 1) [11].

Argentina and Chile had the highest Human Development Indexes (0.83 and 0.847, respectively), while Honduras and Peru had the lowest (0.623 and 0.75, respectively).

The number of patents granted per million inhabitants in 2000–2005 was generally low, with the highest number awarded to residents of Argentina and Cuba [12]. The percentage of GDP devoted to innovation

TABLE 1 Percentage of gross domestic product (GDP) per capita devoted to research and development and incidence of tuberculosis (TB) and multidrug-resistant (MDR)/rifampicin-resistant (RR) TB in Latin America

Country	HDI	Position over 189 countries	GDP per capita	% GDP devoted to R&D	Total TB incidence number (thousands)	MDR/RR TB incidence number (thousands)
Brazil	0.76	79	8920.76	0.9	95	2.5
Argentina	0.83	48	11 683.98	0.65	12	0.56
Chile	0.84	42	15 925.36	0.5	3.4	0.095
Uruguay	0.808	57	17 277.97	3.5	1.2	0.01
El Salvador	0.674	121	4 058.25	0.1	4.5	0.1
Honduras	0.623	132	2 500.11	0.1	3.5	0.081
Peru	0.75	89	6 750	0.75	39	3.2
Colombia	0.761	79	6 667.79	0.4	16	0.58
Mexico	0.767	76	9 673.44	0.36	29.6	0.95

HDI: Human Development Index; R&D: research and development. Data from [11].

and development activities was <1.0% in all countries except Brazil. Science and technology costs also varied widely, with the largest investments made in Argentina, Brazil and Chile.

The GDP per capita was highest for Uruguay, Chile, Argentina, Mexico and Brazil, but does not correspond to the percentage of GDP devoted to innovation and development activities. With the exception of Uruguay, this was <1.0% in all countries. Brazil devoted 0.90% of GDP to research and development. Health-oriented scientific production per million inhabitants was highest in Chile, Argentina, Uruguay and Brazil and lowest in El Salvador, Honduras and Peru. Based on this analysis, we correlated this data with TB and MDR-TB rates. We consider these rates to be an indicator of the severity of the spread of TB, complexity of the management, and unmet need for TB control. The countries with the highest Human Development Index (Chile, Argentina, Uruguay, in that order) were also the countries with the highest GDP. Uruguay is a special case, because economic growth matched with lowest TB and MDR-TB rates. For Mexico, Peru and Brazil no relationship exists between GDP devoted to research and innovation and low TB and MDR-TB rates. For Brazil and Peru this is understandable given that the increase in the GDP devoted to research and innovation is quite a recent occurrence, specifically as part of a TB reduction strategy.

Trends in TB knowledge and TB biotechnology production in Latin America

Health biotechnology is an important field of technology globally, representing 60% of the biotechnology market. Health biotechnology in Latin America is expected to generate economic benefits while also solving local health problems not prioritised by high-income countries. Several successful cases of Latin American health biotechnology investment exist. Together, the academy and industry of Argentina have achieved the use of synthesised biological health products by applying recombinant DNA technology. Brazilian universities developed and patented Neutral Protamine Hagedorn. Chile has commercialised an immune-enzymatic assay for the detection of serum antibodies against *Trypanosoma cruzi* and Colombia is evaluating a diagnostic assay that uses biomarkers for TB detection. There is a lack of information about the levels and main characteristics of the production of scientific knowledge in health biotechnology in Latin America that is necessary to understand the best way to harness the technology for the region.

Stewardship structure and investment in TB research and innovation in Latin America

To articulate a research and development strategy for TB in Latin America, an evolutionary form of research stewardship was formally structured in 1970. An articulated system exists with actors in defined roles and with proper stewardship, governance, management and legal framework. This precondition offers the opportunity to strategically promote TB research and innovation in the region.

However, this network of formal structures for research and innovation in Latin America has so far fallen short in linking research and development with formal domestic policy making bodies. A more efficient integration of formal research and development structures for TB research is necessary.

In table 2, we summarise the formal structure for TB research, the main funders, the amount devoted to TB research and development and the rank for each country [5, 6, 13, 14].

TABLE 2 Stewardship structure and investment in tuberculosis (TB) research and innovation in selected countries in Latin America

Country	Research and innovation stewardship structure	Tuberculosis R&D funder	TB R&D funds provided annually	Rank according to amount spent on R&D investment over 114 countries
Argentina	National Agency for Science and Technology Promotion National Council on Scientific and Technical Research National Commission on Health Research (Salud Investiga)	Argentinian Ministry of Science, Technology and Productive Innovation	US\$ 132.406	82
Brazil	Federal: Secretariat of Science, Technology and Strategic Inputs, Ministry of Health; National Council on Scientific and Technical Research; Coordination for the Improvement of Higher Education Personnel State: State Health Ministry; State Ministry of Science and Technology	Brazilian NTP Brazilian Development Bank	US\$ 873244 US\$ 500000	49
Cuba	Office of Science and Technology	Ministry of Economy and Planning	US\$ 5331 100	16
Venezuela	Ministry of Popular Power for Health, Executive Management of Research and Education Board	Ministry of Popular Power for Health Venezuelan Institute for Social Security	US\$ 681 PPA Par Price Power of Acquisition Dollars	109
Peru	National Institute of Health CONCYTEC FONDECYT, NTP-TB Research Network	Ministry of Economy Ministries Conseil Presidence CONCYTEC Ministry of Health INS	US\$ 348417	68
Chile	National Conseil of Research in Health CONIS	Chilean National Commission for Health and Social Protection	US\$ 263796	70
Colombia	Colombian Ministry of Health and Social Protection	Colombian Ministry of Health and Social Protection	US\$ 350519	67

R&D: research and development; NTP: national TB control programmes. Data from [13].

Almost all Latin American countries have formal governance and management structures for TB research (table 2). In Brazil, Cuba, Chile, Peru, Venezuela, Colombia and Argentina [12], both governance and management structures are led by the Ministry of Health, while Argentina, Cuba, Ecuador and Venezuela have mixed structures in which the Ministry of Health and the Ministry of Science and Technology play important roles. In Argentina and Brazil [15], the Ministries of Science And Technology are responsible for management functions [16].

Prioritisation of TB research

The World Health Organization has established four new global TB targets for the 5-year period from 2018 to 2022 [4], these are: 1) to treat 40 million people for TB disease; 2) reach at least 30 million people with TB preventive treatment for a latent TB infection; 3) mobilise at least US\$ 13 billion annually for universal access to TB diagnosis, treatment and care by 2022; and 4) mobilise US\$ 2 billion annually for TB research [14]. Almost all Latin American countries have policies listing TB research priorities, indicating that a process exists to prioritise, evaluate and adopt TB research. Based on official national TB control programme documents, this priority lists includes the following. 1) Biology and other basic

science: to discover fundamental knowledge about latent TB infection, especially in children, *Mycobacterium tuberculosis* and closely related mycobacterial organisms. 2) MDR-TB diagnostics: to produce better and less toxic TB drugs and to improve preclinical and clinical research on treatments and treatment strategies for TB disease and infection. 3) Vaccines: preclinical and clinical research on TB vaccines, including both preventive and immunotherapeutic vaccines. 4) Operational research including randomised trials, surveillance, and epidemiological and observational studies to evaluate new or existing TB control tools and strategies for vulnerable and key populations.

Discussion and conclusions

- Specific TB research priorities should be defined by the national TB control programmes in Latin American countries themselves and not by external entities. Strategies for defining the lines of TB research in Latin America must include dialogue, participation and interaction of all stakeholders, including the affected communities.
- National TB control programmes must lead the stewardship for TB research and development, with the support of other national science and technology institutions, to establish TB research and development priorities and identify strategies for developing and strengthening TB research and innovation in Latin America to enhance and ensure the academic excellence of the systems.
- While the significance of these systems is widely acknowledged, much remains to be done in order to strengthen local capacity for research and innovation in Latin America.
- In Latin America, visible progress has been made on increasing GDP per capita, but poor correlation with the GDP devoted to TB innovation and research. Closer linkage of TB research and development activities among countries in the region is needed.
- The level of human and technological development is not a limiting factor in establishing a formal structure for the stewardship of TB research. However, it is essential to create conditions for job security and adequate salaries to ensure continuity of work and the appropriate human resource capacity.

Conflict of interest: S. Manga has nothing to disclose.

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