ARTICLE
https://doi.org/10.22239/2317-269X.02322

Overview of the main clinical studies on tuberculosis drugs in Brazil and around the world

Panorama dos principais estudos clínicos sobre medicamentos contra tuberculose no Brasil e no mundo

Sílvia Pereira da Silva Santos[I]

Flavia Maria Lins Mendes[II]

Wanise Borges Gouvea Barroso[III,*]

ABSTRACT

Introduction: This article provides a comprehensive overview of tuberculosis (TB) drug clinical trials conducted in Brazil and globally. TB is highlighted as one of the leading lethal infectious diseases, facing the growing challenge of drug resistance. **Objective:** The study aims to map recent advances and identify gaps and challenges in the search for effective treatments for TB, emphasizing Brazil's contribution, which is known for its research in tropical diseases. **Method:** An analysis of clinical trials related to TB was conducted, focusing on the geographical diversity of the studies and the intersectoral collaboration between governments, academic institutions, and non-governmental organizations. The survey covered research at both national and international levels. **Results:** The results indicate a significant increase in the number of clinical trials, reflecting a growing interest and investment in research and development (R&D) aimed at combating TB. Regions with high disease incidence have received special attention. Collaboration between different sectors has been crucial in promoting progress. **Conclusions:** Despite the advances, the study underscores important challenges, such as the need for more R&D investments and the urgency of public policies to facilitate access to new drugs. The article highlights the importance of continuous and collaborative efforts in developing safe and accessible treatments, as well as the effective integration of innovations into the healthcare system, with special attention to vulnerable populations.

KEYWORDS: Tuberculosis; Drug; Clinical Trials; Landscape

RESUMO

INTRODUÇÃO: Este artigo oferece uma visão abrangente dos estudos clínicos sobre medicamentos contra a tuberculose (TB) realizados no Brasil e globalmente. A TB é destacada como uma das principais doenças infecciosas letais, enfrentando o desafio crescente da resistência aos medicamentos. **Objetivo:** O objetivo do estudo é mapear os avanços recentes e identificar lacunas e desafios na busca por tratamentos eficazes contra a TB, com ênfase na contribuição do Brasil, conhecido por sua pesquisa em doenças tropicais. **Método:** Foi realizada uma análise de estudos clínicos relacionados à TB, com foco na diversidade geográfica dos estudos e na colaboração intersetorial entre governos, instituições acadêmicas e organizações não governamentais. O levantamento abrangeu a pesquisa tanto em âmbito nacional quanto internacional. **Resultados:** Houve um aumento significativo no número de estudos clínicos, refletindo um crescimento do interesse e dos investimentos em pesquisa e desenvolvimento (P&D) voltados para o combate à TB. Regiões com alta incidência da doença têm recebido atenção especial. A colaboração entre diferentes setores tem sido crucial para promover avanços. **Conclusões:** Apesar dos avanços, o estudo sublinha desafios importantes, como a necessidade de mais investimentos em P&D e a urgência de políticas públicas para facilitar o acesso a novos medicamentos. O artigo destaca a importância de esforços contínuos e colaborativos no desenvolvimento de tratamentos seguros e acessíveis, além da integração eficaz de inovações no sistema de saúde, com atenção especial às populações vulneráveis.

PALAVRAS-CHAVE: Tuberculose; Medicamento; Pesquisa Clínica; Prospecção Tecnológica

[I] Instituto de Tecnologia em Fármacos, Fundação Oswaldo Cruz (Farmanguinhos/Fiocruz), Rio de Janeiro, RJ, Brasil

[II] Fiocruz Mato Grosso do Sul, Fundação Oswaldo Cruz (Fiocruz), Campo Grande, MS, Brasil

[III] Instituto de Ciência e Tecnologia em Biomodelos/Fiocruz | Instituto de Tecnologia em Fármacos, Fundação Oswaldo Cruz (Farmanguinhos/Fiocruz), Rio de Janeiro, RJ, Brasil

* **E-mail:** wanise.barroso@fiocruz.br

Received: Apr 16, 2024
Approved: Aug 30, 2024

How to cite: Santos SPS, Mendes FML, Barroso WBG. Overview of the main clinical studies on tuberculosis drugs in Brazil and around the world. Vigil Sanit Debate, Rio de Janeiro, 2024, v.12: e02322. https://doi.org/10.22239/2317-269X.02322

INTRODUCTION

Tuberculosis (TB) remains one of the most lethal infectious diseases in the world. Without treatment, its mortality rate is approximately 50%, representing a significant challenge for global public health. Despite advances in medicine and the development of control strategies, TB continues to affect millions of individuals every year, with a disproportionate burden in developing countries[1]. According to the World Health Organization's (WHO) Global Tuberculosis Report 2023, 7.5 million people will be diagnosed with TB in 2022.[1]

Many strains of *Mycobacterium tuberculosis*, the causative agent of TB, are becoming increasingly resistant to available drugs, which makes certain forms of the disease difficult to treat. This highlights the urgent need to search for new therapeutic approaches. In this sense, clinical trials[2] are essential in identifying and developing new therapies that can effectively combat resistant strains, offering hope to patients facing forms of TB previously considered incurable.[1]

Clinical trials are fundamental tools for assessing the efficacy, safety and tolerability of new drugs and treatment regimens. From these, new treatments, vaccines and medicines are developed, tested and eventually approved for public use. In general, and simplified terms, the process for developing a new drug goes through the pre-clinical, clinical, regulatory approval, marketing, and post-marketing phases. In the case of clinical studies, these are divided into four phases with specific objectives ranging from preliminary assessment of safety and efficacy to providing the data needed for regulatory approval for marketing and clinical use.

Brazil has played a significant role in developing and conducting clinical research. The existence of a solid research infrastructure in many areas of medicine, with research centers, universities, and hospitals, as well as a diverse population and favorable regulations, means that the country has established several international partnerships for this type of study.

The recent enactment of Law No. 14.874, of May 28, 2024, which "provides for research with human beings and establishes the National System of Ethics in Research with Human Subjects", represents a significant milestone for clinical research in Brazil. This legislation establishes strict guidelines to guarantee ethics and safety in research involving human subjects, promoting transparency and the protection of participants.

In addition, the creation of the National System of Ethics in Research with Human Subjects strengthens supervision and compliance with international standards. This ensures that studies carried out in the country meet the highest criteria of scientific integrity and respect for human rights. The implementation of this law is crucial for the advancement of clinical research in Brazil, especially in critical areas such as the development of new treatments for TB, guaranteeing a robust and reliable research environment. In this way, the country is recognized for its ability to conduct high-quality research into tropical diseases, along with other countries around the world, and has been playing a crucial role in conducting clinical studies aimed at combating TB.[1]

The aim of this study is to draw up an overview of clinical trials on TB drugs in Brazil and worldwide, focusing on presenting the following information: geographical distribution, distribution of clinical trials by research area, classification of clinical drug trials in terms of recruitment status, eligibility criteria (age group), study phases, type of funders, and sponsors/collaborators.

Tuberculosis

TB is a communicable disease that is a serious global public health problem and one of the leading causes of death worldwide. Until 2020, before the coronavirus pandemic, TB was the leading cause of death from a single infectious agent, above HIV/AIDS, and was among the 10 leading causes of death worldwide, according to the WHO.[1]

TB can be caused by any of the seven species that make up the *Mycobacterium tuberculosis* (Mtb) complex, namely: M. tuberculosis, M. bovis, M. africanum, M. canetti, M. microti, M. pinnipedi, and M. caprae, with *M. tuberculosis*, also known as Koch's bacillus (KB), being the most important species.[3]

The disease is transmitted by air, from a person with pulmonary or laryngeal TB, who eliminates bacilli in the environment (source case), to another person, by exhaling aerosols from coughing, talking, or sneezing. Thus, TB primarily affects the lung, which is also the entry point for most cases.[3]

TB generally affects the lungs (pulmonary TB) and can affect other parts of the body (extrapulmonary TB). Most people (around 90%) who develop the disease are adults, with more cases among men than women. As a result, it is estimated that a quarter of the world's population is infected with *M. tuberculosis*.[1]

In 2014, during the World Health Assembly at the WHO[4], with the participation of 194 member countries, the new global strategy for tackling TB was approved, with the vision of a TB-free world by 2035.

In 2015, the WHO released its End TB Strategy[4], which included a 95% reduction in the incidence of TB worldwide by 2030. To achieve this bold goal, in addition to advocating early diagnosis and treatment of active disease, prevention must also be prioritized, to reduce the transmission of M. tuberculosis (Mtb).

In Brazil, the National Plan to End Tuberculosis as a Public Health Problem, proposed by the Brazilian Ministry of Health, also has preventive TB treatment among its priorities[5]. The country had the leading role in being the main proponent of the strategy in the prevention and treatment of TB, due to its experience with the Unified Health System (SUS) and the Brazilian Tuberculosis Research Network (Rede-TB).[5]

Brazil has followed the global downward trend in new TB cases, i.e. in 2019, the incidence rate was 40.26 new cases per 100,000 inhabitants, falling to 35.64 per 100,000 inhabitants in 2020, within the context of the COVID-19 pandemic. In 2021, according to DATASUS data, Brazil registered 67,292 new TB cases, with an incidence rate of 35.28 cases per 100,000 inhabitants[1], i.e. even with the COVID-19 pandemic in 2020 and 2021, there was a reduction in TB cases in the country.

The 2030 Agenda, with its Sustainable Development Goals (SDGs), sets out an ambitious global plan to eradicate poverty, protect the environment and ensure prosperity for all[6]. In the context of TB, this plan highlights the importance of strengthening the SUS in Brazil, with a view to achieving the goal of health and well-being for all, especially regarding the prevention and effective treatment of TB.[5]

Integration between the global agenda and national public health policies is essential to drive innovations in treatment, improve access to health services, and guarantee equal treatment for all. Thus, the commitment to the 2030 Agenda and the strengthening of the SUS represents decisive steps towards the eradication of TB, reflecting the joint effort needed to overcome public health challenges in the 21st century.

Drugs for the treatment of tuberculosis in Brazil

TB is a disease with a high cure rate (85%) when treatment is carried out. TB drug treatment usually takes place over six months and if the patient doesn't adhere to it, the disease can return, and treatment and recovery become much more difficult.[3]

The drugs used to treat TB are called anti-tuberculosis drugs or tuberculostatics. The SUS provides these drugs free of charge, guaranteed by the National Tuberculosis Control Program (PNCT) and they are not available for sale.[7]

Brazil was the first country in the world to standardize the six-month regimen in the public health network, with all drugs administered orally and distributed free of charge[5,7]. To this day, these drugs are widely distributed in the public health network, delivered to the patient upon presentation of the completed notification form.[3]

Medications for the treatment of TB are divided into first-line drugs and second-line drugs. First-line drugs are chosen to make up the basic treatment regimen and second-line drugs are reserved for the treatment of resistant TB or situations that make it impossible to use the basic regimen.[3]

According to the 2022 National Drug List (Rename), the Ministry of Health provides 17 drugs for TB treatment[8] in their various forms of concentration and/or composition, as shown in Chart 1.

Adherence to TB treatment is crucial to its success, and lack of adherence is one of the main causes of low effectiveness, which can manifest as abandonment, incorrect or irregular use of medication.[8]

The WHO recommends new approaches in the treatment regimen, including new drugs such as bedaquiline and linezolid, to improve results. Medicines are essential for treating diseases and relieving symptoms, and it is vital to guarantee access to them. Technological tools can help in the effective management of health resources[1]. Medicines are fundamental in the treatment and prevention of diseases, interrupting their course or relieving symptoms, highlighting the essentiality of access to these therapeutic resources. This scenario reiterates the importance of access to medicines.[9,10,11]

Deficiencies in the production and distribution of medicines seriously affect public health[12]. This highlights the need for careful investment, especially in technology, for effective management of therapeutic resources.

Development of new medicines

The validation of the safety and efficacy of medicines takes place through studies over 10 to 15 years, from the development of the molecule to its introduction onto the market. This development is commonly divided into four main phases, as described by Mendes[13] and Pontes Junior.[14]

Chart 2 shows the phases of new drug development, from discovery to post-marketing (pharmacovigilance), including an overview of the stages and the participants involved in development.

In the first stage of drug development, "Compound Discovery", researchers examine five to 10 thousand molecules to identify potential new therapeutic substances.[13]

The second stage (Pre-Clinical Phase) consists of structural identification of the drugs and chemistry, biology, pharmacology, and toxicology tests to assess safety and efficacy.[13]

Pre-clinical drug trials assess the safety of the new drug, using animal models or human tissue cultures to evaluate toxic doses and potential pharmacological actions using pharmacokinetic studies.[13]

As the Research and Development (R&D) phase can take up to 10 years, the company needs to be able to protect its intellectual property to ensure a financial return on its investment. At this stage, the number of compounds studied is reduced to around 250.[14]

The third stage is clinical trials, where the drug is tested on humans. The number of compounds studied at this stage is up to five. Clinical trials are divided into phases:

Phase I: The test is carried out on a small number of individuals, around 20 to 100 healthy volunteers, and aims to verify the first parameters of safety, pharmacokinetics, and drug interaction with alcohol and other drugs.[13,15]

Phase II: The safety, pharmacological activity, and dose-response relationship of the drug are evaluated, i.e. the efficacy of the drug. The drug is tested on a larger number of individuals, from 100 to 300 volunteers, with the disease or condition for which the procedure is being studied.[13,15]

Chart 1. Medicines made available by the Unified Health System and included in the 2022 National Drug List for the treatment of tuberculosis.

NO.	Generic name	Concentration/ Composition	Pharmaceutical form	ATC code	Component
1	araminosalicylic acid	4 g	oral granules	J04AA01	Strategic
2	bedaquiline	100 mg	tablet	J04AK05	Strategic
3	capreomycin	1 g	powder for solution for injection	J04AB30	Strategic
4	ethambutol hydrochloride	400 mg	tablet	J04AK02	Strategic
5	delamanid	50 mg	tablet	J04AK06	Strategic
6	ethionamide	250 mg	tablet	J04AD03	Strategic
7	rifabutin	150 mg	capsule	J04AB04	Strategic
8	rifapentine	150 mg	tablet	J04AB05	Strategic
9	terizidone	250 mg	capsule	J04AK03	Strategic
10	clofazimine	50 mg	capsule	J04BA01	Strategic
		100 mg	capsule	J04BA01	Strategic
11	dapsone	50 mg	tablet	J04BA02	Strategic
		100 mg	tablet	J04BA02	Strategic
12	isoniazid	100 mg	tablet	J04AC01	Strategic
		300 mg	tablet	J04AC01	Strategic
13	pyrazinamide	500 mg	tablet	J04AK01	Strategic
		30 mg/mL	oral suspension	J04AK01	Strategic
		150 mg	dispersible tablet	J04AK01	Strategic
14	rifampicin	300 mg	capsule	J04AB02	Basic
		150 mg	capsule	J04AB02	Strategic
15	rifampicin + isoniazid	150 mg + 75 mg	tablet	J04AM02	Strategic
		300 mg + 150 mg	tablet	J04AM02	Strategic
		75 mg + 50 mg	dispersible tablets	J04AM02	Strategic
16	rifampicin + isoniazid + pyrazinamide	75 mg + 50 mg + 150 mg	dispersible tablets	J04AM05	Strategic
17	rifampicin + isoniazid + pyrazinamide + ethambutol hydrochloride	150 mg + 75 mg + 400 mg + 275 mg	tablet	J04AM06	Strategic

Source: Prepared by the authors, 2024.

Phase III: From 300 to 3,000 people with the disease are involved, a larger number of individuals are needed for the drug being tested. These studies take place over a longer period than the previous phases and are usually carried out in more than one study center (multicenter studies). In this phase, data is obtained on safety, efficacy, the most common adverse reactions, and drug interactions. This information contributes to the preparation of the drug's label and package leaflet.[13,15]

Phase IV: In this phase, studies are carried out to monitor the use of the drug in uncontrolled situations. The aim is to identify adverse reactions that have not yet been detected, as well as drug interactions and additional details on the safety and effectiveness of the product.[13,15]

The fourth stage is the review and approval of the government body responsible for releasing the new drug for production and marketing. This stage also includes large-scale production and marketing. Only one drug reaches this last stage of the process.[15]

According to Mendes[13], each of these stages must be successfully completed to proceed to the next, and only when all of them have been completed is the medicine reached.

It is important to note that phase IV corresponds to the post-marketing phase, in which the drug, already approved by the health authorities, is monitored in regular use to detect long-term effects. Monitoring clinical studies in their various phases allows for targeted investments or the redefinition of strategies.

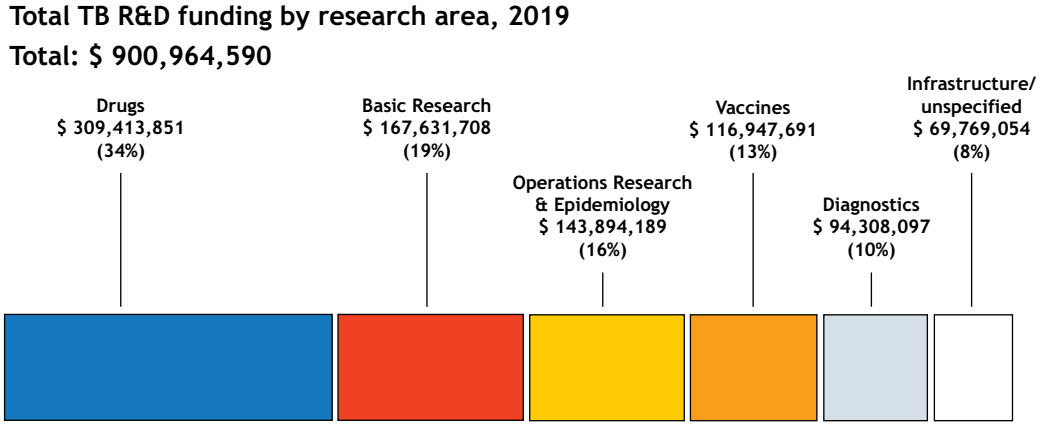
According to the WHO, in 2019, more than a third of total TB R&D investments were allocated to TB drug research, as illustrated in Figure 1, corresponding to approximately 309 million dollars. It is crucial to note that, of the total invested in 2019, 160 million dollars corresponds to the three largest funders of TB drug research: the National Institute of Allergy and Infectious Diseases (NIAID), the Gates Foundation and Company X.[16]

Since the Treatment Action Group (TAG) began surveying investments in TB research, it has been observed that investments in

Chart 2. Phases of drug development.

Phase	Description	Number of people
Compound discovery	• Biological and pathophysiological assessment of the disease • Identifies protein biomarkers • Identifies and validates pharmacological targets • Design, screening and optimization of the molecule • Laboratory tests	Not applicable
Pre-clinical phase *In vitro* and *in vivo* tests	• Safety and toxicity studies • Assessment of organ damage, carcinogenesis, teratogenesis, etc. • Initial formulation • Evaluation of pharmacokinetics and pharmacodynamics	Not applicable
Clinical Phase I	• Dose and safety assessment • Discovery of markers for safety and toxicity • Determines appropriate and optimal dose to be tested • Evaluation of pharmacokinetics	20 to 100 healthy volunteers
Clinical Phase II	• Evaluation of efficacy and safety potential • Explore the activity and measure preliminary effectiveness • Investigate the occurrence of short-term adverse effects • Discovery of prognostic biomarkers • Determine dose and dosage • Very strict inclusion and exclusion criteria • Short duration	100 to 300 volunteers with the disease
Clinical Phase III	• Evaluation of efficacy, safety, interactions, contraindications, and medium term • Confirmation of the efficacy and safety profile • Often multicenter, multinational, comparative studies • Strict inclusion and exclusion criteria	300 to 3,000 volunteers with the disease
Clinical Phase IV Post-marketing (pharmacovigilance)	• Post-marketing evaluation • Evaluates effectiveness, safety, risks and long-term benefit • Makes it possible to identify rare adverse effects	Large number of individuals

Source: Prepared by the authors based on Mendes[13], 2024.



Source: TAG, 2020.

Figure 1. Total Funding for TB R&D by Funder Category.

drug research constitute the largest share when compared to investments in diagnostics and vaccines. Although the amounts invested are surprising in their volume, the WHO emphasizes that this category still requires significantly more resources to reach the revised five-year target of the Global Plan to End TB. When adding up the investments for 2018 and 2019, funding totaled US$ 645 million, which corresponds to only 9% of the US$ 6.8 billion target set for the period from 2018 to 2022, as illustrated in Figure 2[16], where the data refers to global data.

As illustrated in Figure 3, Brazil is one of the countries that did not reach the target for investment in research and development for TB, according to information updated by the WHO in 2019. In this context, Brazil only met 3% of the target set.[16]

ClinicalTrials.gov database

ClinicalTrials.gov[17] is a comprehensive repository of clinical studies conducted worldwide, encompassing research funded by public and private sources. This database provides information on clinical trials online, enabling patients, families, healthcare professionals, researchers, and the general public to access data on studies that have been completed, are ongoing, or are planned worldwide. In March 2024, ClinicalTrials.gov registered 488,952 studies from 223 countries[18]. Table 1[19] shows the percentage of studies registered on ClinicalTrials.gov carried out by residents and non-residents of the United States of America (USA) by March 2024.

It was found that 265,252 studies conducted exclusively by non-US residents were registered, representing 54% of the total studies. Studies conducted only in the US account for 30%, those conducted both in the US and abroad represent 5%, and 11% were not specified.

The information on ClinicalTrials.gov is managed by the National Library of Medicine (NLM), part of the National Institutes of Health (NIH), and is provided and updated by the sponsors or principal investigators of the clinical studies themselves.

When studies are started, they are submitted and indexed on the site, with updates made throughout their execution. This database of clinical studies also serves as a results registry, where in some cases the results are posted after the studies have been completed.

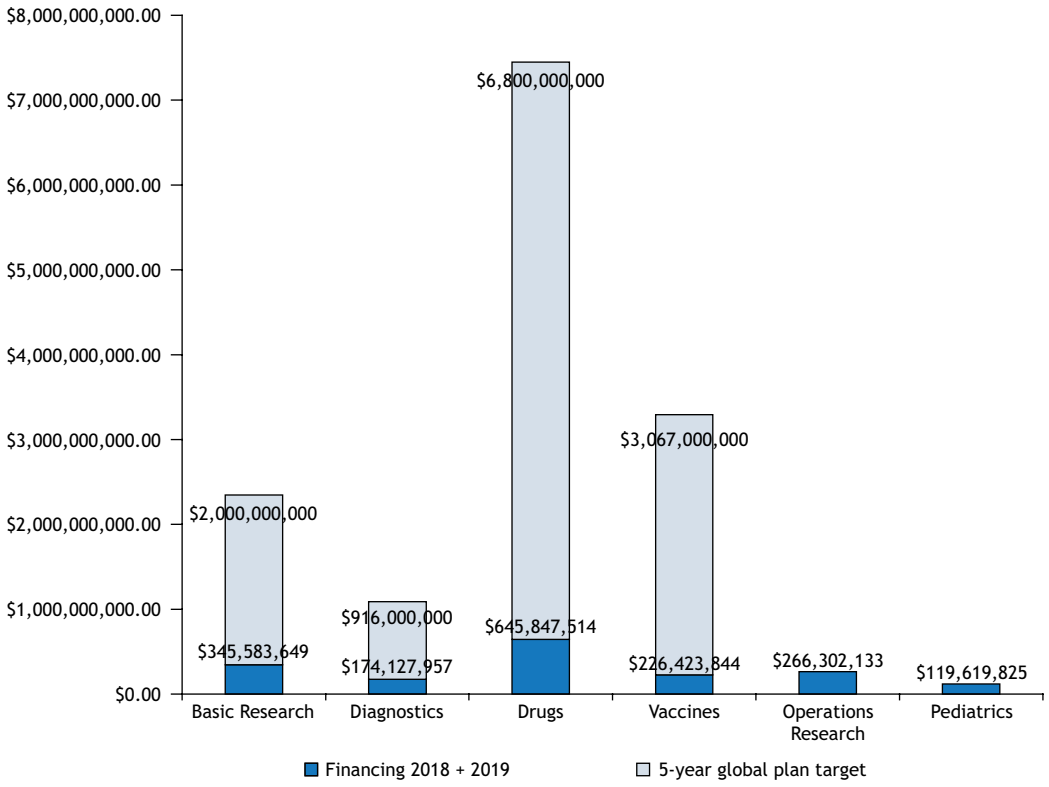
METHOD

The search was carried out in March 2024 and considered all the information in the clinical trials repository on ClinicalTrials.gov (2024), regardless of when it was indexed. The classic website (Go to the classic website) was accessed using the advanced search for the word "tuberculosis", to check the total number of clinical trials related to this disease, without restrictions on the type of product investigated in the search carried out and to identify the geographical distribution of the trials.

Typing "tuberculosis" into the "Condition or Disease" field automatically brought up several expressions as search options, namely: "tuberculosis pulmonary", "tuberculosis infection", "tuberculosis meningeal", "tuberculosis pleural", "tuberculosis multidrug-resistant", "tuberculosis spinal", "tuberculosis miliary", "tuberculosis MDR", and "Tuberculosis, Extrapulmonary". Only the word "tuberculosis" was kept for the opportunity to associate it with the most diverse types of studies associated with the disease. A total of 1,385 clinical studies on TB were found.

To refine the search, we kept the word "tuberculosis" and in the "Other terms" field we searched separately for the words "drug"; "vaccine"; "diagnostic", "kit" to identify the number of tests in these areas.

Next, the search was kept to "drug" and the search was refined using the filters provided by the repository.



Source: Prepared by the authors, 2024.

Figure 2. Progress on the TB Research Funding Targets of the five-year Global Plan.[16]

Rank	Country	2019 financing	Annual fair share target	Percentage of target reached in 2019
1	United States of America	$397,123,557	$444,500,000	89%
2	United Kingdom	$56,317,780	$40,400,000	139%
3	European Union	$38,844,007	$202,400,000	19%
4	India	$28,570,953	$46,500,000	61%
5	Germany	$24,290,971	$99,700,000	24%
6	South Korea	$19,554,816	$64,000,000	31%
7	Canada	$19,277,700	$25,300,000	76%
8	Australia	$12,148,939	$21,200,000	57%
9	Japan	$8,129,865	$154,900,000	5%
10	France	$7,393,331	$55,400,000	13%
11	Sweden	$4,542,620	$13,700,000	33%
12	The Netherlands	$4,394,265	$15,100,000	29%
13	Switzerland	$3,325,545	$13,400,000	25%
14	South Africa	$3,142,906	$4,600,000	68%
15	Norway	$2,724,073	$5,300,000	51%
16	Philippines	$2,349,973	$700,000	336%
17	New Zealand	$1,856,506	$1,800,000	103%
18	Ireland	$1,397,485	$3,300,000	42%
19	Brazil	$1,196,568	$35,000,000	3%

Source: TAG, 2020.

Figure 3. Funding targets for tuberculosis (TB) research and development achieved by countries.

Table 1. Percentage of studies registered on ClinicalTrials.gov carried out by US residents and non-US residents.[19]

Location	Number of studies registered and percentage of total number of studies registered and percentage of total
Non-US residents	265,252 (54%)
US residents	147,748 (30%)
Both in the USA and outside the USA	23,537 (5%)
Not informed	52,415 (11%)
Total	488,952 (100%)

Source: Prepared by the authors based on ClinicalTrials.

Thus, the search combining "tuberculosis and drug" found 979 trials. The results were analyzed according to the distribution of clinical trials by research area, recruitment status, eligibility criteria - age group, study phases, type of funders, type of sponsors/collaborators.

RESULTS AND DISCUSSION

The analysis of TB clinical trials on ClinicalTrials.gov shows current trends, geographical distribution, research investments, and the diversity of treatments and diagnoses, highlighting advances, gaps and areas for future research in the fight against the disease.

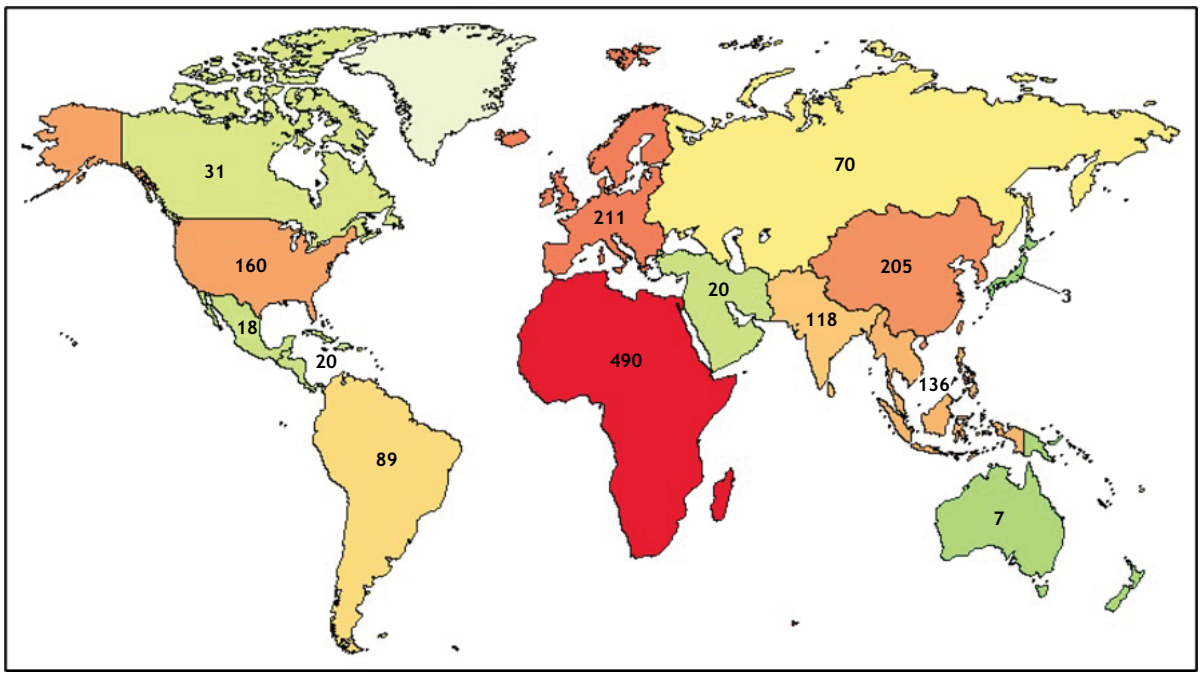
Distribution by geographical area

A search of the data available on ClinicalTrials.gov revealed the existence of 1,385 clinical studies using the term "tuberculosis". The global geographical distribution of these studies is visually outlined in the map presented in Figure 4, reflecting the panorama of studies up to March 2024, showing the international framework of trials in the fight against TB.

The analysis shows that the African continent leads in terms of numbers, with a total of 490 trials, reflecting the urgency and priority given to the disease in this location. Next, China reports 205 trials, and Europe contributes 211 trials, demonstrating a substantial effort in TB research in these countries. The USA recorded 160 studies, followed by Indonesia with 136, India with 118, and Brazil with 89, all reflecting a global commitment to finding solutions against TB.

Table 2 details the global distribution of TB-related clinical trials, highlighting both the total number of studies and the specific distribution by country and region.

Analysis of the data reveals a significant emphasis on conducting TB research on the African continent (490) and in Asia (East



Source: Prepared by the authors, 2024.

Figure 4. Map showing the number of clinical trials in each country for the term "tuberculosis".

205, North 70, South 118, Southeast 136, Japan 3, Middle East 20), followed by Europe (211) and North America (189). This geographical focus on clinical trials reflects the varying disease burden in different parts of the world, but also the efforts of international scientific communities to address specific public health needs. In addition, this geographical distribution of trials may indicate areas of intense research and development activity, suggesting regions where strategic partnerships and investments in research infrastructure may be particularly fruitful in the global fight against TB.

Distribution by research area

Among the total of 1,385 clinical trials carried out focusing on TB, 979 trials were dedicated to drug development, reflecting the intense search for new therapies. In addition, 179 trials focused on vaccines, highlighting the ongoing effort to prevent the disease.

In the field of diagnostics, 573 trials aimed to improve the detection and monitoring of TB, and 23 trials explored the development of kits, essential tools to facilitate and speed up diagnosis. This analysis underlines the breadth and multifaceted focus of scientific research into TB, from prevention and diagnosis to treatment.

Table 3 details the number of clinical trials related to vaccines, drugs, and diagnostics. The combined total of trials for these three categories exceeds the total number of studies, which suggests that some trials may have been categorized in more than one area of research.

Table 2. Number of clinical tests for tuberculosis by country and region.

Name of region	Number of studies
Total in the world	1,385
Africa	
Africa	490
Americas	
Central America	20
North America	189
South America	89
Canada	31
USA	160
Mexico	18
Asia	
East Asia	205
North Asia	70
South Asia	118
Southeast Asia	136
Japan	3
Middle East	20
Europe	
Europe	211
Oceania	
Australia	7

Source: Prepared by the authors, 2024.

Considering that the main objective of our study is to analyze clinical trials related to medicines, the following analyses are pertinent to this category.

Classification by recruitment status

Chart 3 presents a classification of clinical trials focused on TB drugs, as registered on ClinicalTrials.gov, categorized according to their recruitment status and progress.

An analysis of the data on the status of clinical trials reveals significant insights into the current panorama of TB clinical research. The large number of completed studies (562) serves as a positive indication of progress in research, suggesting ample data generation and potential advances in the investigated area. On the other hand, the presence of 156 studies with unknown status highlights challenges in managing and monitoring clinical trials. This could indicate difficulties in updating records or completing studies.

The number of studies not yet recruited (27) and in the recruitment phase (124) highlights the continued interest and investment in new research.

The studies enrolled by invitation (4) and active but not recruiting (45), together with those suspended (4), illustrate the diversity of situations that clinical trials can face, from specific selection of participants to pauses necessary for a variety of reasons.

The number of studies closed (35) and withdrawn (20) reflects the challenges inherent in clinical research, in which not all trials reach their conclusion for reasons that can range from the lack of efficacy of treatments to operational or financial issues.

Eligibility criteria - age group

In the Eligibility criteria of trials for drugs to treat TB, volunteers were classified by age group, revealing that 281 trials were conducted with children (0-17 years), 912 with adults (18-64 years), and 721 with the elderly (over 65 years).

This distribution suggests an inclusive and comprehensive approach to study design, seeking to understand the effects of potential treatments across a broad demographic. The significant number of studies involving adults and the elderly may reflect a concentration of research efforts on conditions prevalent in these age groups, while the inclusion of children highlights the importance of evaluating the safety and efficacy of treatments across a younger age spectrum.

Clinical study phases

An analysis of data from ClinicalTrials.gov, as detailed in Chart 4, reveals the panorama of ongoing efforts to combat TB through drug development. To date, four Phase 0 studies have been registered, which are exploratory and involve very limited exposure to the drug in humans, aiming to understand how or if a drug affects the body. In Phase I, which focuses on the safety of the drug, 152 studies have been registered.

In Phase II, in which 236 studies were carried out, the efficacy of the drug in individuals with the disease or condition to be treated is verified. In Phase III, 149 studies were carried out, which expand the evaluation of efficacy and monitoring of safety

Table 3. Number of clinical trials for "tuberculosis" by research area.

Classification	Quantity
Total	1,385
Drug	979
Vaccine	179
Diagnosis	573
Kit	23

Source: Prepared by the authors, 2024.

Chart 3. Number and status of clinical trials of TB drugs.

No.	Status (quantity)	Quantity	Status description
1	Not yet recruiting	27	The study has not started recruiting participants.
2	Recruitment	124	The study is currently recruiting participants.
3	Registration by invitation	4	The study selects participants from a specific group defined by the researchers and is not open to all those eligible, but only to the individuals invited from that group.
4	Active, not recruiting	45	The study is ongoing, and participants are receiving an intervention or being examined, but potential participants are not being recruited or enrolled at the moment.
5	Suspended	4	The study was stopped early but may start again.
6	Closed	35	The study was stopped early and will not be started again. The participants are no longer being examined or treated.
7	Completed	562	The study has ended normally, and the participants are no longer being examined or treated (i.e. the last visit of the last participant has taken place).
8	Withdrawn	20	The study stopped before enrolling its first participant.
9	Unknown	156	A study on ClinicalTrials.gov whose last known status was recruiting; not yet recruiting; or active, not recruiting, but past the completion date and the status has not been checked for the last two years.

Source: Prepared by the authors, 2024.

Chart 4. The phase of clinical studies organized by quantity and definition.

Study phase	Quantity	Phase Definition
Phase 0 (zero)	4	Exploratory studies to understand the impact of the drug on the body, with very limited exposure.
Phase I	152	It tests the safety of the drug, usually with healthy volunteers, to determine the body's response.
Phase II	236	It assesses the effectiveness of the drug in people with the target condition, as well as monitoring safety.
Phase III	149	It expands the evaluation of safety and efficacy in larger populations and different dosages.
Phase IV	87	Carried out after the approval of the drug, it collects additional data on safety and effective use.
Not applicable	206	It encompasses studies that do not fit into the traditional phases, including device trials or behavioral interventions.

Source: Prepared by the authors, 2024.

in larger populations, often comparing the drug to existing standard treatments.

Phase IV, carried out after the approval of the drug, involves 87 studies, which collect additional information on the risks, benefits and optimal use of the drug.

Finally, a significant number of studies (206 studies) were classified as "Not applicable", covering those that do not fit into the traditionally defined phases, including device trials or behavioral interventions.

Chart 5 shows the number of clinical trials in phase III related to "tuberculosis and drugs" by global region. The total of 149 registered studies in this phase indicates a significant international effort to combat TB. Africa leads the way with 69 studies, reflecting the urgency of responding to the prevalence of the disease on the continent. East Asia, South Asia, and Southeast Asia also show a high concentration of research activities, with 29, 30 and 30 studies respectively, highlighting the importance of TB as a public health issue in these regions.

Meanwhile, North America (including the USA, Canada, and Mexico) and South America show considerable involvement, with 23 and 16 studies respectively. The Middle East shows less activity, with only two studies. This distribution reflects public health priorities, the burden of disease and the focus of clinical research in different regions of the world.

Chart 5. Number of phase III clinical trials by country and region.

Name of region	Number of studies
World	149
Africa	
Africa	69
Americas	
Central America	4
North America	23
South America	16
Canada	8
USA	12
Mexico	3
Asia	
East Asia	29
North Asia	16
South Asia	30
Southeast Asia	30
Middle East	2
Europe	
Europe	15
Oceania	
Australia	3

Source: Prepared by the authors, 2024.

Type of funders

ClinicalTrials.gov classifies clinical trial funders into four categories: NIH, another US federal agency, industry, and others (including individuals, universities, and organizations).

Focusing on clinical trials for TB and drugs, a total of 979 studies were found, with the NIH and industry being the main funders, both with 163 studies each.

Other US federal agencies contributed 49 studies. The "other" category (individuals, universities, organizations) comprises the largest share, with 625 studies, highlighting the diversity of funding sources that support TB and drug research, from government funding to contributions from private and academic entities.

This panorama indicates the importance of collaboration between different sectors and the varied contribution of funding sources in the research and development of new treatments for TB.

Type of sponsors/collaborators

A search on ClinicalTrials.gov using the terms "tuberculosis" and "drug", focusing on sponsors and collaborators, revealed an interesting distribution of clinical studies, as shown in Chart 6.

Within the Clinical Research Network, 18 studies were identified, with the Center for the AIDS Program of Research in South Africa and the Tuberculosis Network European Trials group standing out, demonstrating international collaboration in TB research.

On the government side, excluding the US federal government, a total of 74 studies were registered, with the European and Developing Countries Clinical Trials Partnership (EDCTP) (15 studies) and ANRS, Emerging Infectious Diseases (12) leading the funding, reflecting the government's commitment to TB research outside the US.

Universities and organizations account for 457 studies, and the main ones are the University of Cape Town (41 studies), the Global Alliance for TB Drug Development (30), and the University of Oxford (30) among the main contributors, highlighting the importance of academic institutions and non-profit organizations at the forefront of TB research.

This analysis highlights the diversity of global efforts and the vital role of various entities, from clinical research networks to governments and universities, in advancing knowledge and developing new therapies against TB.

The research on TB clinical trials and drugs carried out in Brazil, as detailed in Chart 7, shows active participation from both the government sector and universities and organizations.

From the government, excluding the US federal government, three studies were registered, with notable collaborations from ANRS, Emerging Infectious Diseases, the Communicable Disease Program of Brazil, and the Brazilian Ministry of Health,

Chart 6. Number of tests for "tuberculosis" and "drugs" by sponsors and collaborators.

Clinical Research Network	
Sponsors/Collaborators	**Number of studies**
Total studies in the Clinical Research Network	18
Centre for the AIDS Programme of Research in South Africa	7
Tuberculosis Network European Trialsgroup	4
PENTA Foundation	2
Andalusian Society of Infectious Diseases	2
THINK TB & HIV Investigative Network	2
Jiangsu Province Centers for Disease Control and Prevention	1

Government, excluding the US federal government	
Sponsors/Collaborators (only the top five are listed)	**Number of studies**
Total government studies, excluding the US federal government	74
European and Developing Countries Clinical Trials Partnership (EDCTP)	15
ANRS, Emerging Infectious Diseases	12
Tuberculosis Research Center, India	8
National Institute of Health and Medical Research, France	6
Shanghai Public Health Clinical Center	6

Universities and Organizations	
Sponsors/Collaborators (only the top five are listed)	**Number of studies**
Total studies by universities and organizations	457
University of Cape Town	41
Global Alliance for TB Drug Development	30
University of Oxford	30
London School of Hygiene and Tropical Medicine	23
University of Stellenbosch	19

Source: Prepared by the authors, 2024.

evidencing the direct involvement of the Brazilian government in the fight against TB.

A total of 16 studies were carried out by universities and organizations, with the Oswaldo Cruz Foundation making a significant contribution with four studies, followed by Johns Hopkins University and the Bill and Melinda Gates Foundation, among others. This underlines the importance of partnerships between national and international academic institutions, foundations and government entities in advancing research and development of effective treatments against TB in Brazil.

This distribution of clinical studies reflects the collaborative and multidisciplinary effort needed to tackle the challenges of TB, a critical public health issue in the country.

CONCLUSIONS

This study provides a detailed and up-to-date analysis of global and national efforts in TB clinical research, with a particular focus on the development of new drugs based on data collected from ClinicalTrials.gov.

There has been an increase in the number of clinical studies covering different geographies and population contexts, aimed at developing new drugs for TB, reflecting the growing investment and interest in the area, evidencing a significant commitment from a variety of funders and collaborators.

This collective effort reflects the universal recognition of TB as a public health priority and the urgency of the search for innovative therapeutic solutions, especially in the face of the challenge of resistant strains, as proposed by the 2030 Agenda.

The wide geographical distribution of clinical studies shows a global commitment to finding solutions to combat TB. Regions with a high burden of the disease, such as Africa and Asia, have shown a significant number of studies, highlighting local and international efforts to tackle this problem.

Chart 7. Number of tests carried out in Brazil by sponsors and collaborators.

Government, excluding the US federal government	
Sponsors/Collaborators (only the top five are listed)	Number of studies
Total government studies, excluding the US federal government	3
ANRS, Emerging Infectious Diseases	1
Communicable Disease Program, Brazil	1
Ministry of Health, Brazil	1

Universities and Organizations	
Sponsors/Collaborators (only the top five are listed)	Number of studies
Total studies by Universities and Organizations	16
Oswaldo Cruz Foundation	4
Johns Hopkins University	3
Bill and Melinda Gates Foundation	2
McGill University	2
Ataulpho de Paiva Foundation	1
Consortium to Respond Effectively to the AIDS/Tuberculosis Epidemic	1
Federal University of Mato Grosso	1
Federal University of Rio Grande do Sul	1
Dr. Heitor Vieira Dourado Tropical Medicine Foundation	1
Global Alliance for TB Drug Development	1
Hospital de Clínicas de Porto Alegre	1
Ceará Society of Infectious Diseases	1
Stanford University	1
Federal University of Rio de Janeiro	1
University Medical Center Groningen	1
University of Miami	1

Source: Prepared by the authors, 2024.

The participation of a diversity of funders and collaborators, including governments, academic institutions, and non-governmental organizations, underlines the importance of collaborative and multidisciplinary approaches in advancing research.

On the other hand, despite the advances, the study highlights the need to increase investment in R&D for TB, especially for the development of drugs that can combat resistant forms of the disease.

Turning research findings into practical and accessible treatments remains a significant obstacle. It is essential to create public policies and targeted strategies to make new drugs available and integrate innovations efficiently into the healthcare system.

It is important to intensify clinical studies that consider the specificities of vulnerable populations, such as children and the elderly, ensuring that treatments are safe and effective for all segments of the population.

The study reinforces the importance of continuing and expanding clinical research for TB drug development, with a special focus on innovation, global collaboration and sustainable financing. To achieve the vision of a TB-free world by 2035, as set out by the WHO, it is imperative that joint efforts in research, development, and the implementation of public policies are intensified. In addition, it is essential to guarantee equitable access to the drugs and treatments developed, promoting the health and well-being of all populations affected by TB.

This study paves the way for future research and strategic actions aimed at eradicating TB as a global public health challenge.

As a suggestion for future studies, it is proposed to delve deeper into the 87 studies identified in Phase 4 during the search on ClinicalTrials. This phase, dedicated to gathering additional information on the risks, benefits and optimal use of drugs, offers a valuable opportunity to evaluate in detail the TB drugs available on the market, which are under pharmacovigilance monitoring.

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Authors' Contribution

Santos SPS, Mendes FML, Barroso WBG - Conception, planning (study design), data acquisition, analysis, interpretation, and manuscript writing. All the authors approved the final version of the paper.

Conflict of Interest

The authors inform that there is no potential conflict of interest with peers and institutions, political or financial, in this study.