Review Article

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Global Research Trends on Tuberculosis: A Bibliometric and Visualized Study of Clinical Trials

Mansoureh Feizabadi [1], Esmaeil Vaziri [2], Seyed Mohammad Reza Nejatollahi [3], Elham Sadati [4], Arman Hasanzade [5], Masoud Shafaghi [6], Fariba Ghorbani [7]

[1] Iranian Research Center on Healthy Aging, Sabzevar University of Medical Sciences, Sabzevar, Iran, [2] Department of Information Science and Knowledge Studies, Faculty of Humanities, University of Zabol, Zabol, Iran, [3] Department of Hepato-Pancreato-Biliary and Transplant Surgery, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [4] Pediatric Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [5] Lung Transplantation Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [6] Strategic Planning and Executive Office Manager, International Federation of Inventors' Associations, Geneva, Switzerland, [7] Tracheal Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

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Correspondence to: Ghorbani F
Address: Tracheal Diseases Research Center, NRITLD, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Email address: dr.f.ghorbani@gmail.com

Tuberculosis stands as a prominent global infectious disease, ranking among the leading causes of mortality. Its complex pathogenesis and significant resistance to existing treatments have made the eradication of this disease challenging. Over the 20th century and into the present, numerous endeavors have been undertaken to comprehensively understand various aspects of this disease and find a proper solution to this challenge.

This scientometric study employs the content analysis method to provide an overview of existing clinical trials in the tuberculosis field. We conducted a comprehensive review using the World Health Organization Clinical Trials Registry database, covering studies registered between 1998 and 2021.

A total of 1,590 tuberculosis-related clinical trials were registered across global clinical trial registries through the end of 2021.Significant joint initiatives were observed, notably between South Africa and India (53 studies), South Africa and Peru (47 studies), and South Africa and Uganda (40 studies). There was a predominant focus on Human Immunodeficiency Virus (HIV) diseases (14.15% of trials). Pulmonary tuberculosis with 316 (19.87%) trials and multidrug-resistant tuberculosis with 92 (5.76%) trials were the most evaluated topics. Drug-based interventions led with 942 studies (58.25), and Isoniazid was evaluated in 261 trials (16.42%).

Conclusion: Scientometric analyses provide valuable insights into research trends across diverse fields, helping researchers identify knowledge gaps and guide future investigations. The steadily increasing annual registration of clinical trials, together with persistent gaps in our understanding of tuberculosis pathogenesis, prevention, and treatment, and the substantial global burden of disease, underscores the need for continued research in this field.

Keywords: Bibliometric; Clinical Trials; *Mycobacterium tuberculosis*; Scientometric; Scientometric Mapping; Tuberculosis

INTRODUCTION

Tuberculosis (TB), caused by the bacterium *Mycobacterium tuberculosis* (MTB), remains a significant global health concern. In the late twentieth century, TB emerged as a major cause of mortality worldwide, leading to a World Health Organization (WHO) declaration of a global emergency in 1993 (1,2). Despite subsequent efforts, TB persists as the second leading cause of death from a single infectious disease, claiming 1.3 million lives in 2022 (3). TB manifests with a spectrum of clinical presentations, ranging from asymptomatic infections to severe, life-threatening illnesses. Common symptoms include cough,

fever, weight loss, and nocturnal hyperhidrosis (1). While MTB predominantly affects the pulmonary system, it can also impact various organs, such as the brain, bone, liver, spleen, skin, urogenital system, adrenals, and muscles (1,4). The pathogenesis of TB involves complicated interactions among the host, the organism, and the environment (5). Despite numerous studies, the complete understanding of TB's pathogenesis and immunology remains uncertain (1). The complexity of TB extends beyond its pathogenesis, presenting challenges in the treatment of this disease. Various combination therapy regimens exist for active and latent TB, including four main medications: Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol. Unfortunately, resistance to all these medications is prevalent worldwide, particularly resistance to Rifampicin and Isoniazid. This widespread resistance poses a significant obstacle to globally defeating TB (1,5). Accordingly, ongoing research aims to elucidate TB resistance mechanisms and discover new drugs to address this challenging infectious disease (1). The complexity of TB, spanning from its complex pathogenesis to the challenges in treatment, underscores the necessity for research efforts to enhance our understanding and ultimately improve global TB management.

Clinical trials serve as a pivotal tool in advancing clinical knowledge (6). Recognizing their significance, the International Committee of Medical Journal Editors (ICMJE) issued a joint statement in September 2004, advocating for the mandatory registration of all clinical trial studies. This initiative aimed to create an accessible database of clinical trial information, encouraging researchers to register their trials before initiating patient recruitment (7). Conducting experimental and interventional research, with clinical trials at the forefront, plays a crucial role in enhancing community public health. These trials, recognized as a standard method for evaluating therapeutic effects, constitute a reliable research approach in medical sciences. Emphasizing the importance of full study registration, it is a gesture of gratitude toward the numerous participants who willingly assume risks to contribute to these studies altruistically. Complete registration serves the purpose of ensuring that information from such studies becomes universally accessible. Research participants deserve the assurance that the findings generated through their altruistic participation will be used to inform decisions about patient care. This approach aligns with the principle that decisions in patient care should be based on all available evidence, not just the selective reporting of trial results (7–9). Beyond the ICMJE, the WHO endeavors to establish a global standard for the information that authors of clinical trial studies must provide and disclose. Registering a clinical trial contributes to transparency by elucidating the landscape of ongoing intervention studies involving human subjects. This collective effort aims to uphold ethical standards, enhance research integrity, and ultimately benefit patient care decision-making processes (8).

Scientometric reviews involve a statistical and quantitative evaluation of literature, aiming to uncover various aspects of research within a specific field. These reviews serve the purpose of exploring the structure, scientific impacts, publication dynamics, citation networks, trending topics, and research productivity of the targeted field. One notable scientometric technique, the creation of a scientific map, contributes to understanding the landscape of published research within the field (10). Therefore, the objective of our study was to facilitate a comprehensive understanding of trials in the tuberculosis field and analyze evolving trends across different periods. Using scientometric techniques and vocabulary co-occurrence methods, our approach aimed to provide insights into the overall research landscape. This endeavor was anticipated to contribute valuable information for researchers, enabling them to navigate the current state of knowledge and inform their choices for future studies in the realm of tuberculosis research.

METHODS

This scientometric approach entailed a quantitative study employing the content analysis method. Content

analysis was utilized to discern the status of studies, analyze trends, investigate countries with the highest registered trials, explore scientific, national, and international collaborations, and examine the authoring network of clinical trial researchers in the realm of tuberculosis.

To gather comprehensive global clinical trial data, information was sourced from the international clinical trial registration portal website, accessible at "https://www.who.int/clinical-trials-registry-platform". The dataset encompassed 18 systems, including the Australian New Zealand Clinical Trials Registry, Chinese Clinical Trial Registry, ClinicalTrials.gov, EU Clinical Trials Register (EU-CTR), International Standard Randomised Controlled Trial Number (ISRCTN), The Netherlands National Trial Register, Brazilian Clinical Trials Registry (ReBEC), Clinical Trials Registry - India, Clinical Research Information Service - Republic of Korea, Cuban Public Registry of Clinical Trials, German Clinical Trials Register, Iranian Registry of Clinical Trials, Japan Registry of Clinical Trials, Pan African Clinical Trial Registry, Sri Lanka Clinical Trials Registry, Thai Clinical Trials Registry (TCTR), Peruvian Clinical Trials Registry (REPEC), and Lebanese Clinical Trials Registry (LBCTR).

To ensure data integrity, all systems involved adhere to the WHO standard, encompassing 24 essential fields. These include Primary Registry and Trial Identifying Number, Date of Registration in the Primary Registry, Secondary Identifying Numbers, Source(s) of Monetary or Material Support, Primary Sponsor, Secondary Sponsor(s), Contact for Public Queries, Contact for Scientific Queries, Public Title, Scientific Title, Countries of Recruitment, Health Condition(s) or Problem(s) Studied, Intervention(s), Key Inclusion and Exclusion Criteria, Study Type, Date of First Enrollment, Sample Size, Recruitment Status, Primary Outcome(s), Ethics Review, Completion date, Summary Results, and IPD sharing statement.

The investigation covered additional fields such as the sponsoring organization of the study, type of organization, date of study registration in the system, name of the clinical trial registration system, patient status, patient gender, sample size, study objective, study phase, type of intervention, the country where the study is conducted, and the type of disease.

To retrieve information, a comprehensive search strategy was implemented using the following terms:

(MDR-TB OR Tuberculosis, Multidrug-Resistant OR XDR-TB OR Extensively Drug-Resistant Tuberculosis OR tuberculosis OR tuberculosis* OR TB OR "Latent TB" OR "LTBI OR MTB OR "*Mycobacterium tuberculosis* bacteria" OR drug-sensitive TB OR "drug-sensitive tuberculosis" OR DS-TB)

This strategy was applied in the search section of the portal at https://trialsearch.who.int for data extraction.

The choice of the international clinical trial registration portal was driven by its comprehensive coverage of information from 17 global clinical trial registration systems. The search, conducted until December 31, 2021, revealed a total of 2118 registered studies, from which 1590 interventional studies were included after removing duplicates and observational studies.

For data on tuberculosis prevalence, the 2021 World Health Organization report was referenced at "https://www.who.int/teams/global-tuberculosis-programme/data". Population and incidence rates in countries were extracted from the "TB country, regional, and global profiles" section of "https://worldhealthorg.shinyapps.io/tb_profiles".

Descriptive statistics and scientometric visualization techniques were employed for result analysis. Bib Excel software facilitated data pre-processing and file output for map creation. To ensure uniformity in document types across databases, Bib Excel standardized indexed documents. VOS Viewer software generated density maps and clustering visualizations based on distance-based techniques, while NetDraw 2.153 software illustrated scientific cooperation maps between countries. Standardization of study phase, intervention type, and disease name was carried out by three researchers, using the Primary Purpose system of the U.S. Clinical Trial Registry clinical trial registration system.

RESULTS

In this study, 1590 tuberculosis-related trial studies registered in diverse global clinical trial registration systems until the end of 2021, retrievable through the international clinical trial registration portal, were analyzed. Notably, the highest number of studies, 196 in total, was documented in 2021, whereas 2002 marked the lowest, with no registered clinical trials in the tuberculosis domain. These findings are graphically depicted in Figure 1, illustrating a consistent annual growth in the number of registered clinical trials.

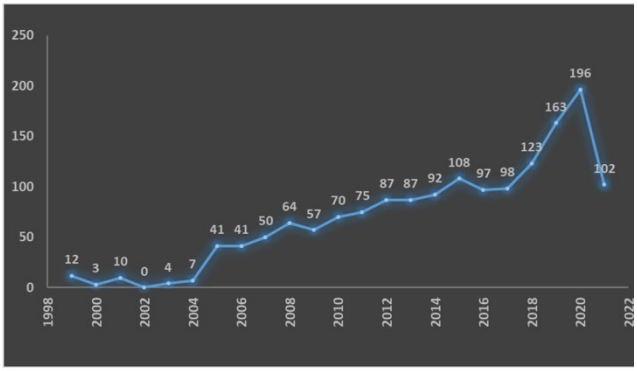

Figure 1. Distribution of Registered Clinical Trials in the Field of Tuberculosis

According to the TB clinical trial registration system, 878 cases (55.22%) were registered in the American registration system, with the lowest registration observed in Cuba's clinical trial registration system, accounting for only one study (0.06%). Table 1 details the study status, patient status, investigated gender, sample size, study phase, and age groups associated with the respective registering systems.

Among the countries engaged in tuberculosis studies, a total of 116 were identified. South Africa led with 294 clinical trials, while the fewest trials were associated with Morocco, Madagascar, Kyrgyzstan, Yemen, Algeria, Uruguay, Armenia, Guatemala, Slovenia, Somalia, Paraguay, Croatia, Serbia, Cuba, Dominican Republic, Niger, Ecuador, Papua New Guinea, Denmark, North Korea, each contributing one study. Notably, among the 30 high-burden tuberculosis countries, including Lesotho, Gabon, Central African Republic, Philippines, Namibia, Mongolia, Mozambique, Angola, Zambia, Congo, Liberia, Myanmar, Indonesia, Sierra Leone, Pakistan, Kenya, Tanzania, Nigeria, Bangladesh, Uganda, India, Vietnam, Thailand, Ethiopia, China, Brazil, four nations had no registered clinical trials. An assessment of countries with a high TB incidence rate, based on the 2021 WHO report, revealed that among the top 20 countries with the most trials, 11 had a high incidence rate. Table 2 provides details on the 20 countries with the highest number of registered clinical trial studies.

In terms of collaborative efforts in conducting clinical trial studies on tuberculosis, significant joint initiatives were observed, notably between South Africa and India (53 studies), South Africa and Peru (47 studies), and South Africa and Uganda (40 studies). Figure 2 illustrates the scientific collaborations among 51 countries with a minimum of 10 clinical trial studies. It's important to note that a country might have numerous studies, but if it lacks collaboration in clinical trial endeavors with other nations, including Iran, it won't be represented on the map.

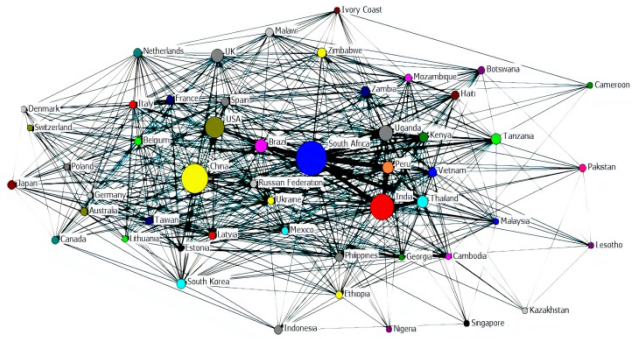

Figure 2. Visualization of International Collaboration in TB Clinical Trials

The extensive scope of these studies involved 592 organizations contributing to the 1590 conducted studies. Table 3 presents the list of these organizations based on their frequency of participation in the trials.

Clinical trials on tuberculosis revealed a predominant focus on Human Immunodeficiency Virus (HIV) diseases (14.15% of trials). Regarding the TB types, Pulmonary Tuberculosis with 316 (19.87%) trials and Multidrug-resistant tuberculosis with 92 (5.76%) trials were the most evaluated topics (Table 4).

Table 1. Overview of registered clinical trials in the field of tuberculosis

	Item	N	%
Source	U.S. Clinical Trial Registry (ClinicalTrials.gov)	878	55.22%
	Chinese Clinical Trial Registry (ChiCTR)	167	10.50%
	Clinical Trials Registry- India (CTRI)	129	8.11%
	WHO and ICMJE clinical trial registry (ISRCTN)	104	6.54%
	Pan African Clinical Trials Registry (PACTR)	92	5.79%
	European Union Clinical Trials Register (EU Clinical Trials Register)	55	3.46%
	Iranian Registry of Clinical Trials (IRCT)	34	2.14%
	Peruvian Clinical Trials Registry (REPEC)	30	1.89%
	Australia, New Zealand Clinical Trials Registry (ANZCTR)	26	1.64%
	Japan Primary Registries Network (JPRN)	26	1.64%
	Thai Clinical Trials Registry (TCTR)	21	1.32%
	Brazilian Clinical Trials Registry (REBEC)	13	0.82%
	Clinical Research Information System, South Korea (CRIS)	6	0.38%
	German Clinical Trials Register (German Clinical Trials Register)	5	0.31%
	Netherlands Trial Register	3	0.19%
	Cuban Public Registry of Clinical Trials	1	0.06%
Recruitment Status	Authorized	24	1.51%
	N/A	8	0.50%
	Not recruiting	1180	74.21%
	Recruiting	378	23.77%
Included gender	Female	21	1.32%
	Male	37	2.33%
	Male; Female	1367	85.97%
	N/A	165	10.38%
Sample Size	< 100	610	38.36
	101- 1000	668	42.01
	1001-10000	203	12.77
	10001-100000	23	1.45
	100000 >	12	0.75
	N/A	74	4.65
Age group	Adult	251	15.79%
	Adult; Older Adult	639	40.19%
	Child	82	5.16%
	Child; Adult	48	3.02%
	Child; Adult; Older Adult	179	11.26%
	N/A	391	24.59%
Phase	N/A	660	41.51%
	Phase 2	230	14.47%
	Phase 3	192	12.08%
	Phase 1	187	11.76%
	Phase 4	182	11.45%
	Phase 2; Phase 3	42	2.64%
	Phase 1; Phase 2	31	1.95%
	Other	28	1.76%
	Diagnostic of New Technique	14	0.88%
	Phase 0	11	0.69%
	New Treatment Measure Clinical Study	6	0.38%
	Phase 3; Phase 4	4	0.25%
	Retrospective study	2	0.13%
	Clinical pre-test	1	0.06%

Table 2. Top twenty countries with registered clinical trials; *countries among the thirty highest TB incidence countries; **based on the countries' TB profile on WHO

Country	N	%	Population 2020**	TB incidence	% Of Population
South Africa*	294	18.49	59,000,000	328000	0.56
China*	245	15.41	1,439,000,000	842000	0.06
India*	207	13.02	1,380,000,000	2590000	0.19
USA	166	10.44	331,000,000	7900	0.00
Uganda*	106	6.67	46,000,000	90000	0.20
Brazil*	83	5.22	213,000,000	96000	0.05
UK	80	5.03	68,000,000	4700	0.01
Peru	67	4.21	33,000,000	38000	0.12
Thailand*	65	4.09	70,000,000	105000	0.15
Tanzania*	59	3.71	60,000,000	133000	0.22
Kenya*	48	3.02	54,000,000	139000	0.26
South Korea	43	2.70	51,000,000	25000	0.05
Zambia*	42	2.64	18,000,000	59000	0.33
Iran	40	2.52	84,000,000	11000	0.01
Zimbabwe	40	2.52	15,000,000	29000	0.19
Malawi	39	2.45	19,000,000	27000	0.14
Philippines*	36	2.26	110,000,000	591000	0.54
Spain	35	2.20	47,000,000	3400	0.01
Netherlands	34	2.14	17,000,000	710	0.00
Indonesia*	33	2.08	274,000,000	824000	0.30

Table 3. Twenty organizations providing the most financial support for TB clinical trials

Organization	N	%
National Institute of Allergy and Infectious Diseases (NIAID)	75	4.72
Capital Medical University	38	2.39
University of Oxford	38	2.39
Fudan University	38	2.39
University of Cape Town	34	2.14
TB Alliance	28	1.76
Johns Hopkins University	28	1.76
Tongji University	27	1.70
Aeras	27	1.70
Centers for Disease Control and Prevention	26	1.64
University of London	23	1.45
All India Institute of Medical Sciences	22	1.38
GlaxoSmithKline	22	1.38
University College London	21	1.32
Shahid Beheshti University of Medical Sciences	19	1.19
Otsuka Pharmaceutical Development & Commercialization, Inc.	13	0.82
Statens Serum Institut	13	0.82
Anhui Zhifei Longcom Biologic Pharmacy Co., Ltd.	13	0.82
University of California San Francisco	13	0.82
Seoul National University	12	0.75

In terms of intervention types, drug-based interventions led with 942 studies (58.25). The evaluation of each specific intervention revealed the highest frequency for the isoniazid drug, examined in 261 trials (16.42%). The next three frequently assessed interventions in clinical trials were also medication-related, including placebo, pyrazinamide, and rifampicin, respectively (Table 5).

Among the interventions, 167 studies explored various tuberculosis vaccines, with 76 trials (4.21% of all) specifically related to BCG vaccine. The distribution of vaccine-related trials is presented in Table 6.

In Figure 3, the co-occurrence of keywords is illustrated. The terms “telephone calls”, “rifapentine”, “VPM1002 vaccine”, “BCG”, and “PPD” exhibited high frequency and were located in the hotspot area. Conversely, the terms "prednisolone", "ethionamide”, “ritonavir", "zidovudine", and "text messages" were situated in the cold zone.

Table 4. Various types of TB, evaluated in registered clinical trials

Type of Tuberculosis	N	%
Tuberculosis	892	56.10
Pulmonary Tuberculosis	316	19.87
Multidrug-Resistant Tuberculosis	92	5.79
Latent Tuberculosis	77	4.84
Drug-resistant Tuberculosis	33	2.08
Pleural Tuberculosis	12	0.75
Spinal tuberculosis	11	0.69
Mycobacterium Tuberculosis	9	0.57
Meningeal Tuberculosis	7	0.44
Miliary Tuberculosis	7	0.44
Lymph Node Tuberculosis	6	0.38
intestinal tuberculosis	5	0.31
Tuberculosis of specified organs	5	0.31
Bone and joint tuberculosis	4	0.25
Extensively Drug-Resistant Tuberculosis (XDR-TB)	4	0.25
Genital Tuberculosis	4	0.25
Tracheobronchial Tuberculosis	4	0.25
Endobronchial tuberculosis (EBTB)	2	0.13
Recurrent Tuberculosis	2	0.13
Central Nervous System Tuberculosis	1	0.06
Chest Wall Tuberculosis	1	0.06
Disseminated Tuberculosis	1	0.06
inactive tuberculosis	1	0.06
Isoniazid-Resistant Tuberculosis	1	0.06
Military tuberculosis	1	0.06
Minimal Tuberculosis in Children	1	0.06
relapse Tuberculosis	1	0.06
renal tuberculosis	1	0.06
Silicosis Tuberculosis	1	0.06
Tuberculosis of ear	1	0.06
Tuberculosis of eye	1	0.06
Tuberculosis of larynx	1	0.06
Tuberculosis of skin	1	0.06

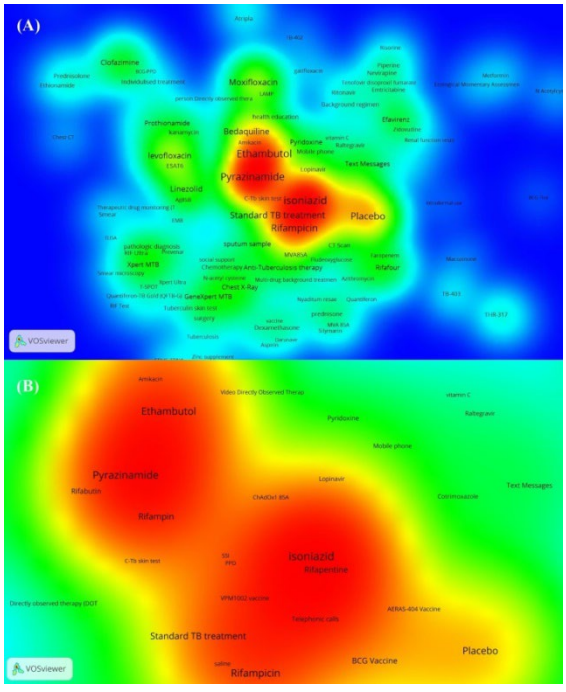

Figure 3. Co-occurrence of Keywords in TB Clinical Trials. (A) hot and cold zones; (B) A deep layer of the hot area

Table 5. Predominant interventions investigated in TB clinical trials

Intervention	N	%
Isoniazid	261	16.42
Placebo	213	13.40
Pyrazinamide	162	10.19
Rifampicin	133	8.36
Ethambutol	131	8.24
Standard TB treatment	103	6.48
Rifapentine	70	4.40
Rifampin	70	4.40
Moxifloxacin	69	4.34
Bedaquiline	65	4.09
BCG vaccine	58	3.65
Linezolid	42	2.64
Rifabutin	41	2.58
Levofloxacin	40	2.52
Clofazimine	34	2.14
Efavirenz	32	2.01
Pretomanid	27	1.70
Delamanid	27	1.70
Text Messages	25	1.57
Vitamin D	21	1.32
Xpert MTB	21	1.32
MVA85A	20	1.26
counseling	17	1.07
Anti-Tuberculosis Therapy	16	1.01
GeneXpert MTB	16	1.01
Pyridoxine	16	1.01
Mobile phone	16	1.01
Ritonavir	14	0.88
Chest X-Ray	14	0.88
Chemotherapy	14	0.88

Table 6. Types of vaccines assessed in TB clinical trials

Vaccine	N	%
BCG vaccine	67	4.21
MVA85A/AERAS-485 Vaccine	20	1.26
AERAS 402 Vaccine	14	0.88
VPM1002 vaccine	9	0.57
AERAS-404 Vaccine	7	0.44
GLA-SE vaccine	7	0.44
MVA 85A vaccine	7	0.44
RUTI vaccine	6	0.38
AEC/BC02 Vaccine	5	0.31
Ag85B vaccine	4	0.25
ChAdOx1 85A vaccine	3	0.19
GamTBvac vaccine	3	0.19
Ad5Ag85A Vaccine	2	0.13
DAR-901 vaccine	2	0.13
Vaccae vaccine	2	0.13
AERAS-422 Vaccine	1	0.06
AS01B vaccine	1	0.06
M72/AS01E vaccine	1	0.06
CAF01 vaccine	1	0.06
CIMAvax-EGF vaccine	1	0.06
FP85A vaccine	1	0.06
GX-70 vaccine	1	0.06
IMMUVAC vaccine	1	0.06
ESAT-6 vaccine	1	0.06

DISCUSSION

This scientometric study focuses on tuberculosis, evaluating clinical trials registered until the end of 2021. The analysis reveals a notable increasing trend in annual trial registrations, peaking at 196 studies in 2020. Assessing the origin countries of these trials highlights active participation from both developing nations with high TB rates and developed nations with lower TB prevalence. South Africa emerges as a leader with 294 registered trials, constituting 18.49% of the total. Remarkably, South Africa, a country with a high burden of TB, aligns with the WHO's 2023 report, showcasing a 50% reduction in TB incidence between 2015 and 2022 (3). Moreover, our evaluation of international collaboration indicates that South Africa predominantly collaborates with countries such as India, Peru, and Uganda. Beyond TB, the majority of trials are associated with pulmonary tuberculosis and HIV. Drug therapy emerges as the most explored intervention, with Isoniazid being the focus of numerous drug-related trials. TB vaccination also garners attention, with the BCG vaccine being the most extensively examined. This comprehensive assessment sheds light on the dynamic landscape of tuberculosis research, emphasizing trends in trial registration, global collaboration patterns, and the prevalence of specific interventions and diseases within the research domain.

Bibliometrics and scientometrics, widely employed systematic methods for evaluating research output, employ mathematical and statistical approaches to analyze pertinent literature. These analyses have been applied across diverse scientific fields to map literature, unveil historical developments in research fields, and assess the research productivity of scientists, organizations, countries, and journals. Presently, the terms "bibliometrics" and "scientometrics" are nearly synonymous. Within bibliometric and scientometric analyses, science mapping is a method utilized to visually depict the structural and dynamic aspects of scientific knowledge in a specific research field. This involves performance analysis, the identification of intellectual connections, and graphic plotting (10). While our study represents, to the best of our knowledge, the first scientometric analysis in the field of tuberculosis (TB) focusing on clinical trials, there have been related prior studies. In 2015, Groneberg et al. evaluated all publications in the TB field, analyzing 58,319 publications from 1900 to 2012 using the Web of Science (WoS) database. Their study revealed the participation of 132 countries in this field (11). Similarly, Chang et al. conducted a scientometric study on original and review articles resulting from international collaboration between 1998 and 2017, utilizing the WoS database (12). Both studies, similar to ours, reported an annual increase in the number of publications. Additionally, they identified the USA as having the highest number of publications, whereas our analysis of clinical trials placed South Africa in the first and the USA in the fourth position, with 166 trials (10.44%). Interestingly, in the ranking of the highest number of publications, South Africa was the fifth country after the USA, UK, India, and France (11). The USA also led in citations in this field for both overall and collaborative publications. However, Denmark ranked highest in the number of citations per publication in both overall and collaborative studies (11,12), while the USA ranked 11th with 27.6 citations per publication (11). A notable disparity exists concerning international collaboration between trials and all publications. While our observation showed more collaboration with other countries by South Africa, particularly with India, Groneberg et al. reported more collaboration related to the USA, followed by the UK and South Africa. They also reported that the most collaboration occurred between the USA and the UK, then the USA and South Africa, followed by South Africa and the UK (11). Confirming these outcomes, Chang et al.'s evaluation demonstrated higher numbers of cooperation with other countries from the USA, but the strongest and most stable collaboration was between the UK and South Africa (12).

HIV stands out as a significant risk factor for tuberculosis (TB), with HIV and TB coinfection comprising 12.0% of the 9.65 million worldwide TB cases and

contributing to 15.5% of the 1.40 million TB-related deaths in 2019 (13). According to the WHO's 2019 report, HIV infection was identified as the second most common risk factor for new TB cases after nutrition, resulting in 0.76 million new cases (14). Additionally, HIV is recognized as a primary risk factor for TB reactivation (15). Given this strong association, it is reasonable that a substantial number of TB clinical trials focus on HIV infection. A recent scientometric study assessed publications on HIV and MTB coinfection from 2017 to 2022, based on WoS results. The evaluation revealed a declining trend in annual publications, with a shift in study design from randomized controlled trials to open-label trials. The USA, UK, and South Africa emerged as leaders in the number of publications in this field, with South Africa, particularly the University of Cape Town, contributing significantly to collaborative studies. This insight underscores the ongoing efforts to understand and address the complex dynamics of TB and HIV coinfection through research and clinical trials (16).

The dominance of drug therapy as the primary focus in TB clinical trials, constituting 59.25% of all studies, is rationalized by the persistent challenge in treating TB, particularly due to resistance against key anti-TB medications. Cases of Rifampicin-resistant (RR-TB) and Multidrug-resistant TB (MDR-TB), resistant to both Rifampicin and Isoniazid, were frequently reported. WHO's report of 206,030 MDR/RR-TB cases in 2019, a 10% increase from 2018 (14), underscores the urgency in addressing TB drug therapies. Researchers' significant attention to TB drug therapies aligns with a scientometric evaluation of MTB focusing on drug discovery and microbial pathogenesis. This study revealed a 3.95% annual growth in publications from 1999 to 2020, highlighting a substantial interest in this field (17). Analysis of publication records in PubMed and PubTator across different publication types identified drug resistance as the most extensively studied research topic, with rifampin and isoniazid emerging as the most frequently investigated drugs. This research landscape is not confined to specific countries, as both developed and developing nations contribute significantly. The USA leads in this field, with South Africa ranking fourth after China and India. However, South Africa exhibits extensive collaboration, with the University of Cape Town being the most affiliated center. This global participation underscores the collective effort to address the pressing challenges of TB drug discovery and resistance, reflecting a collaborative approach among nations in advancing research in this critical domain (17).

CONCLUSION

In this article, we conducted a comprehensive evaluation of various facets within clinical trials of tuberculosis. Employing content analysis, we provided insights into the current status of clinical trials, analyzed trends, identified countries leading in registered trials, examined scientific, national, and international collaborations, explored authoring networks, and assessed the co-occurrence of interventions in tuberculosis clinical trial studies. Despite numerous studies addressing various aspects of tuberculosis, the increasing trends in registered clinical trials and persisting unanswered questions related to TB's pathogenesis, prevention, and treatment underscore the imperative for future research endeavors in this critical field.

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