

# Investigating Empirical evidence on the Epidemiology, Diagnosis and Bibliometric analysis of the 100 topmost cited publications on Tuberculosis Disease

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**Received:** 16<sup>th</sup> December 2022; **Accepted:** 17<sup>th</sup> February 2023; **Published:** 30<sup>th</sup> March 2023

**DOI:** <https://doi.org/10.47787/pasj.v1i03.11>

## Abstract

Tuberculosis (TB) disease remains a growing threat in public health globally. This study explored the epidemiology, diagnosis, management, and bibliometric analysis of the top 100 most cited articles on TB. The study adopted a narrative review and bibliometric analysis to explore publications on TB disease. Publications in the Web of Science were retrieved to provide extensive selection process. The present study of top 100 articles which are mostly cited are reported between 1969 to 2018. Reported documents were published in 37 journals, and a total of 1058 authors contributed with 10.5 authors per document, and 12 countries contributed, with most of TB research originating from the US (N=51) articles. We found 1058 occasional authors, and of these, 971 authors (0.003%) presented only three articles, followed by 11 authors (0.010%) and 18 authors (0.017%), respectively. About (n=34) research was published in General & Internal Medicine and Science & Technology. New England Journal of Medicine with 14 was top journal. The lead research institution was the University of Cape Town. The significant correlations were found between the number of citations and documents per year ( $r=0.9579$ ,  $p<0.0001$ ), countries ( $r=0.9570$ ,  $p<0.0001$ ), article per journal ( $r=0.8721$ ,  $p<0.0001$ ), and authors ( $r=0.4601$ ,  $p<0.0001$ ), and documents per [Institution](#) ( $r=0.6159$ ,  $p<0.0001$ ). A new insight into TB scientific production was through social network. The evidence from this study provides a template for understanding the epidemiology of TB and the trends in research. It also exposes the hotspot of research along with research gaps for future studies.

**Keywords:** Tuberculosis; Epidemiology; Bibliometrics; Drug-Resistance

Tuberculosis (TB) is an airborne disease caused by *Mycobacterium tuberculosis* (MTB), and it is one of the world's leading infectious diseases spiking global mortality [1]. TB remains the leading cause of death among adults worldwide [2]. There has been intensified research effort on TB in the last four years on transmission, diagnosis, and treatment; much remains to be discovered to effectively provide a lasting solution to its prevalence [1]. TB treatment remains a challenge, especially in the resource developing countries that are most impacted[3,4]. Similarly, with the medical efforts, there has been painful slow eradication progress due to drug resistance. Thus, TB is considered an international crisis from its challenges, such as the inadequacy of a vaccine, drug resistance, and inconsistent protection to pulmonary TB patients [5,6]. TB is still a significant infectious disease that affects most African region countries transcending to a significant global health problem.

Consequently, approximately 8.8 million new cases and 1.45 million deaths annually [7], and evidence of TB in Africa show the prevalence is high among the poor people, or people whose lives are closely linked to both overcrowding and malnutrition, making it one of the primary diseases of poverty [8,9]. Other burdens sprouting from TB's global prevalence are the inadequate socioeconomic capacity of infected people, which leads patients to abandon treatment, develop drug resistance, and subsequently lead to mortality [10,11]. Poverty and political instability in developing countries have inhibited progress in implementing effective TB control measures.

The burden of TB in Sub-Saharan Africa is far more significant today but the principal reason for the resurgence of TB in Africa is not the deterioration of control programs [12]. A decade ago, the problem of TB in Africa attracted little attention [12,13]. The rapid increase of research productivity on TB globally could be associated with the importance of the disease as a global health issue with the annual risk of infection rate and mortality reported globally [14–16]. According to the World Health Organization (WHO), there were nearly 2 million deaths from TB

in 2017, and an estimated 10 million individuals became morbid [17]. TB's occurrence for 2.5% of global burden disease with more than 90% of total cases occurring in developing countries, and about 1.67 million people died from TB infection in 2016 [18]. African countries contribute 31% of new cases, mainly concentrated in Nigeria and Ethiopia [19,20]. Only 5-10% of all carriers will develop active disease during their lifetime, influenced by several risk factors directly or indirectly associated with infection susceptibility [21].

The aggregation of research on TB will provide information on research productivity and produce new data, leading to promising progress in developing improved tuberculosis diagnostics, biomarkers of disease activity, drugs and support health policy in controlling, treating, and prevention. Many researchers have used bibliometrics analysis to follow many scientific research fields [22–24]. However, there is little known about the current state of research productivity and its evolution over time in tuberculosis-related publication. Therefore, using bibliometric for assessing the top 100 cited articles on TB is essential in evaluating and better understanding the research progress and scientific research production done over the years. The study gives a comprehensive analysis of TB research characteristics such as epidemiology, diagnosis, vaccines, and bibliometric analysis of the 100 top-cited publications on TB Disease. The study further analyzed authorship, keywords, active countries, institutions, funding agencies, and most productive journals of articles indexed in the Web of Science (WoS).

## 1.1 Epidemiology of Tuberculosis

Tuberculosis is the top killer disease, responsible for 25% of adult deaths in developing countries [17]. The global burden of TB in 2017 was 10.0 million cases; 5.8 million were men, 3.2 million women, and 1.0 million children; with overall 90% were adults, and 9% were people living with

HIV infection. Surprisingly, 72% of them are from African countries [25]. Differences in TB incidence rates between countries vary due to different risk factors and disparities in health care facilities, case registration, diagnosis, notification, and control [26]. Sudan ranks among the high prevalence countries in the Eastern Mediterranean region with a total TB burden of 14.6% [27]. The estimated TB incidence rate in Sudan in 2017 was 77 per 100,000 individuals, with several 20,438 new and relapse TB cases, including HIV co-infected [28]. In 2016, only 17% of all notified TB cases were screened for HIV; almost 99% of patients who were HIV positive started antiretroviral therapy (Elegail). In a study conducted to determine the TB control status in conflict region Darfur and the non-conflict region of Eastern Sudan, Extrapulmonary Tuberculosis (EPTB) was the most common type comprising 35% of the new TB cases [29].

## 1.2 The risk associated with tuberculosis

The risk of progression from infection to disease is controlled by several factors, directly or indirectly related to the host. The host's related factor is concerned with socioeconomic and behavioral factors such as smoking, tobacco, alcohol addicts, indoor air pollution like firewood or biomass smoke in developing countries as they are recognized as independent risk factors for disease [17]. Age, gender increase TB incidence; women are more susceptible to TB than men, and low-income persons are more vulnerable to developing the disease [30]. Physiological factors increase the risk of progression to active infection or reactivation of latent MTB in patients with prior infection with HIV, diabetes, malnutrition, default of Bacillus Calmette-Guérin (BCG) vaccination [17]. The concentration of bacilli in TB patients' sputum is positively correlated with the disease's infectivity [30]. Close contacts to TB infected, such as household contacts and health care workers, are at a higher risk of becoming infected with *Mycobacterium tuberculosis* and developing the primary active disease.

Sociodemographic factors, such as age, lifestyle, and poor socioeconomic condition with low diagnostic capacity, were associated with increased disease transmission, TB drug resistance, chronic pulmonary impairment, and increased mortality rates [29,31]. Loss of treatment follow-up was significantly associated with disease severity, especially in the conflict zone in which there were low primary health care coverage, inadequate health system accessibility, and depleted human resources [32].

Significant risk factors for Multidrug-resistant TB (MDR-TB) were HIV co-infection, previous history of treatment found in 67.9% of MDR-TB cases, interruption due to the prolonged treatment, and long-distance to health care units. Smoking is a predictor for MDR-TB patients and education level [28].

### **1.3 Treatment, prevention, and Control of Tuberculosis**

TB is a significant contributor to the global burden of disease globally and has received substantial attention in the latest years, particularly in developing countries with low-income [37]. The treatment remains a challenge due to the need to consider when approaching it in the context of individual and collective health [3]. International health regulations towards TB reported that Food and Drug Administration approved the first-line drugs (Isoniazid (INH), Rifampin (RIF), Ethambutol (EMB), and Pyrazinamide (PZA)) were used for the treatment of all types of TB. The standard regimen calls for daily use of each of the first-line medications for eight weeks, followed by daily INH and RIF for 18 months. For latent TB infection, a daily nine-month regimen of INH is indicated. In cases of MDR-TB, EMB is recommended along with a combination of Fluoroquinolones (Levofloxacin, Moxifloxacin) and aminoglycosides (Amikacin, Streptomycin, Kanamycin) [38].

Treatment adherence is a particular problem in TB. Although TB is not a chronic disease, its prevention and cure usually involve taking antibiotics for several months, ranging between 6 to 24 months. Further reports show that multiple medications for TB patients are needed, but the regimens may be complicated [3,37,39].

The treatment burden in the world has become an issue for WHO, especially for developing countries, and it is significantly prevented from the end of the tuberculosis epidemic in the world [40]. Care and treatment facilities are provided to TB patients free of charge following the WHO-recommended directly observed treatment short-course TB control strategy (DOTS). In developing countries such as Sudan, many hospitals provide care and treatment for TB patients, such as Abu Anja Specialized TB Hospital and other State hospitals [35,41]. The intense program to prevent and control TB infection includes; early detection, successful diagnosis, treatment, and screening of high-risk groups [42]. Successful application of the DOTS program, which is implemented for treatment follow-up, can achieve TB elimination worldwide.

Moreover, assessment and management of comorbid conditions, including malnutrition, could improve anti-tuberculosis treatment response [43]. In addition, TB disease could be controlled by advances in diagnosis with the use of rapid molecular testing and whole-genome sequencing in both sputum and non-sputum samples, which could change this situation of the TB reported cases in the world [44]. Besides, further studies of protected and susceptible populations are necessary to guide the development of novel tuberculosis vaccines that could facilitate WHO's goal to eliminate deaths from TB, especially among childhood [45].

#### **1.4 Tuberculosis drug-resistant**

The treatment of TB infection starts with the first-line four drugs consisting: Rifampicin (RIF), Isoniazid (INH), Pyrazinamide (PZA), and Ethambutol (EMB). Each regiment has an initial phase

of 2 months with an intensive phase followed by several options for the continuation phase of either 4 or 7 months [33]. Multidrug-resistance TB (MDR-TB) is defined as resistance to first-line anti-TB drugs, mostly Rifampicin (RIF) and Isoniazid (INH) [33,34]. The first report on MDR-TB prevalence was published in 1997 by WHO. In 2017, 558.000 people developed resistance to the first-line drug Rifampicin (RR-TB), and 82% of the cases had MDR-TB. Rifampicin resistance (RR-TB) is caused by a mutation in the (b) subunit of RNA polymerase, which is encoded by the *rpoB* gene [33]. Globally, 3.5% of new cases, 18% of previously treated patients had MDR/RR-TB with 230.000 deaths [25]. Three countries accounted for half of the world's TB drug resistance; India (24%), China (13%), and the Russian Federation (10%) [25,33]. Classification of Second-line drugs according to WHO as follows; Aminoglycosides (Kanamycin and Amikacin), Polypeptides (Capreomycin, Viomycin, and Enviomycin), Fluoroquinolones (Ofloxacin, Ciprofloxacin, and Gatifloxacin), D-cycloserine and Thionamides (Ethionamide and Prothionamide), used to treat MDR-TB cases for 6 to 9 months [33]. In 2017, 8.5% of cases of MDR-TB patients were Extensively Drug-resistant (XDR-TB). XDR-TB is a unique form of MDR-TB resistant to fluoroquinolones and at least one of three second-line injectable agents: Capreomycin, Amikacin Kanamycin [25,34,35]. The term "totally drug resistance (TDR-TB) was recently used to describe the resistance for all TB treatment regimens. In Sudan, the prevalence of patient resistance to Rifampicin and Isoniazid was 38%, while the percentage of MDR-TB among previously treated patients was 13% and among newly diagnosed patients was 2.9% [25,36].

### 1.5 Economic Impacts of Tuberculosis Disease

Although much is known about the epidemiology of TB, relatively little is known of its economic and social impacts. In many regions of the world, TB is a growing problem.



While TB is on the increase, economic difficulties in some countries are putting pressure on health budgets. Because of a combination of economic decline there is insufficient application of control measures social security payments for patients undergoing treatment. Besides, the fear and stigma associated with TB have a more significant impact on women than men [46]. Poverty is widely recognized as an essential risk factor for TB disease, where even the epidemiology among the minority groups is poorly understood [47]. Therefore, there is the need to refocus international attention on the continuing problems as it is a greater risk for many people living in poverty [48].

## 2. MATERIALS AND METHODS

### 2.1 Data Sources

The study used bibliometric analysis techniques commonly used by many scholars over the past year [49,50] to measure scientific progress in various disciplines by using the Web of Science database (updated on 10 May 2021). Ethical approval was not required since data retrieved were publicly available and did not involve human or animal subjects.

### 2.2 Search Strategy

The following research was developed as on the previous studies [49–52] by using Medical Subject Headings (MeSH) 2021 to maximize the accuracy of the retrieved research. For this review, we selected articles using the Keyword following the query: Title (Koch's Disease\* OR Kochs Disease\* OR *Mycobacterium tuberculosis* Infection\* OR tuberculosis\*) indexed by the National Library of Medicine and revised on 17 June 2021. Indexes: Web of Science Core Collection: Citation Indexes (Social Sciences Citation Index (SSCI)) and Science Citation Index Expanded (SCI-Expanded)). Refine by document type published in English: "Original article"



and “Review” were only included for analysis, while other document types were excluded from the analysis. Overall documents published in the English language within Timespan: 1900-2020 were subjected to final analysis. Approximately 62,283 documents were screened base on the document’s title, and later the top 100 cited articles based on the Keywords Terms in title and Citation order were retrieved by two researcher (THM and HHM) independently screened the top 100 articles on 18 June to prevent biases due to the daily databases updates. All articles were downloaded and stored as TXT format files, including titles, keywords, authors, abstracts, descriptors, identifiers. Information includes authors, years of publications, titles, Keywords, journal, institution, country of origin, organizations, and funding organizations.

## 2.3 Data Analysis

Bibliometric analysis of retrieved documents was analyzed using Bibliometrix, an R package [53], and HistCite[54], and VOSviewer.Var1.6.6 is a Scientometric software tool for creating bibliometric networks (Leiden University, Leiden, The Netherlands) [55]. GraphPad Prism 5 [56] was used The Pearson correlation coefficient was calculated using the Spearman correlation coefficient (r). A P-value of less than 0.05 was considered statistically significant.

## 3. RESULTS

### General. Information top 100 articles on TB related publications

A total of 100 most cited TB articles were analyzed. Between 1969 and 2018, averages of 20.9 articles were published annually. A total of 37 journals, 1049 authors were contributed from 12 countries in the world. The general information of other study variables was presented in Table 1.

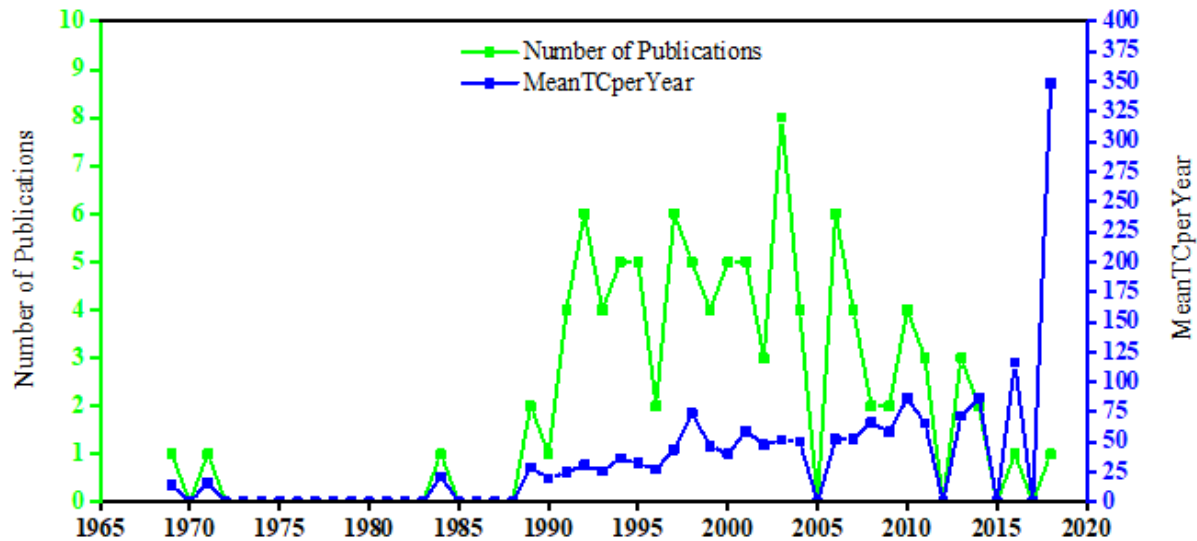
**Table 1:** Main characteristics of the metadata on TB related publications

Description	Results
Timespan	1969:2018
Sources (Journals, Books, etc)	37
Documents	100
Total citations	90,190
Average years from publication	20.9
Average citations per documents	901.9
Average citations per year per doc	47.77
References	5092
Countries	12
<b>Document types</b>	
Article	79
Review	21
Document contents	
Keywords Plus (ID) <sup>a</sup>	508
Author's Keywords (DE) <sup>b</sup>	57
<b>Authors</b>	
Authors	1058
Author Appearances (AA) <sup>c</sup>	1182
Authors of single-authored documents	5
Authors of multi-authored documents	1044
<b>Authors collaboration</b>	
Single-authored documents	5
Documents per Author	0.095
Authors per Document	10.5
Co-Authors per Documents	11.8
Collaboration Index (CI) <sup>d</sup>	11

<sup>a</sup>: Frequency distribution of keywords associated to the document by Clarivate Analytics Web of Science; <sup>b</sup>:Frequency distribution of the authors' keywords'; <sup>c</sup>:Number of author appearances; <sup>d</sup>:The scientific collaboration on the social process by which two or more researchers is work together sharing their intellectual and material resources to produce new scientific knowledge.

## The dynamics and trends of the topmost 100 cited articles on TB

The rapid growths of interest of the scientific community were increased slowly between 1970 to 1990; after that, the growth became exponential between 2000-2005 (**Figure 1**).



**Figure 1:** Annual distribution and the average of the number of citations time per year on TB related publications, 1965-2018

### Top 100 most cited articles in TB

The 100 most cited articles published on TB are presented in Table S1. Interestingly, the most cited article was published in Nature under the title “Deciphering the biology of *Mycobacterium tuberculosis* from the complete genome sequence” in 1998, which reached 5878 citations [57]. The second ranked paper was published in New England Journal of Medicine under title “TB associated with infliximab, a tumor necrosis factor (alpha)-neutralizing agent” in the year 2001, which reached 2622 citations [58]. Among the top 100 articles, 24 articles were considered classical publications with more than 1000 citations, as shown in Table 2.

**Table 2:** The 100 topmost cited articles in TB

SCR	Title	Journals	TC	PY
1	Deciphering the biology of <i>Mycobacterium tuberculosis</i> from the complete genome sequence	Nature	5878	1998
2	Tuberculosis associated with infliximab, a tumor necrosis factor (alpha)-neutralizing agent	New England Journal of Medicine	2622	2001
3	Global burden of tuberculosis - Estimated incidence, prevalence, and mortality by country	Jama-Journal of the American Medical Association	2322	1999
4	Simultaneous detection and strain differentiation of <i>Mycobacterium tuberculosis</i> for diagnosis and epidemiology	Journal of Clinical Microbiology	2227	1997
5	The growing burden of tuberculosis - Global trends and interactions with the HIV epidemic	Archives of Internal Medicine	1885	2003
6	Immunology of tuberculosis	Annual Review of Immunology	1580	2001
7	Autophagy is a defense mechanism inhibiting BCG and <i>Mycobacterium tuberculosis</i> survival in infected macrophages	Cell	1554	2004
8	Efficacy of BCG Vaccine In the Prevention of Tuberculosis - Metanalysis of the published Literature	Jama-Journal of the American Medical Association	1459	1994
9	Rapid Molecular Detection of Tuberculosis and Rifampin Resistance	New England Journal of Medicine	1427	2010
10	Microplate Alamar blue assay versus BACTEC 460 system for high-throughput screening of compounds against <i>Mycobacterium tuberculosis</i> and <i>Mycobacterium avian</i>	Antimicrobial Agents and Chemotherapy	1361	1997
11	American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of tuberculosis	American Journal of Respiratory and Critical Care Medicine	1323	2003
12	A Prospective-Study of the Risk of Tuberculosis among Intravenous Drug-Users with Human Immunodeficiency Virus-Infection	New England Journal of Medicine	1313	1989
13	Diagnostic standards and classification of tuberculosis in adults and children	American Journal of Respiratory and Critical Care Medicine	1273	2000
14	Tumor-Necrosis-Factor-Alpha is Required In the Protective Immune-Response Against <i>Mycobacterium-Tuberculosis</i> in Mice	Immunity	1265	1995

15	Global Epidemiology of Tuberculosis - Morbidity and Mortality of A Worldwide Epidemic	Jama-Journal of the American Medical Association	1236	1995
16	Tuberculosis - Commentary on a Reemergent Killer	Science	1196	1992
17	Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa	Lancet	1151	2006
18	An interferon-inducible neutrophil-driven blood transcriptional signature in human tuberculosis	Nature	1119	2010
19	Inha, A Gene Encoding A Target For Isoniazid And Ethionamide In <i>Mycobacterium-Tuberculosis</i>	Science	1091	1994
20	Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis	Lancet Infectious Diseases	1046	2018
21	Transcriptional adaptation of <i>Mycobacterium tuberculosis</i> within macrophages: Insights into the phagosomal environment	Journal of Experimental Medicine	1022	2003
22	A new evolutionary scenario for the <i>Mycobacterium tuberculosis</i> complex	Proceedings of the National Academy of Sciences ,USA	1008	2002
23	The Epidemiology of Tuberculosis In San-Francisco - A Population-Based study using Conventional and Molecular Methods	New England Journal of Medicine	1007	1994
24	The Catalase Peroxidase Gene and Isoniazid Resistance of <i>Mycobacterium-Tuberculosis</i>	Nature	1002	1992
25	Persistence of <i>Mycobacterium tuberculosis</i> in macrophages and mice requires the glyoxylate shunt enzyme isocitrate lyase	Nature	992	2000
26	Proposal for standardization of optimized mycobacterial interspersed repetitive unit-variable-number tandem repeat typing of <i>Mycobacterium tuberculosis</i>	Journal of Clinical Microbiology	983	2006
27	Detection of Rifampicin-Resistance Mutations in <i>Mycobacterium-Tuberculosis</i>	Lancet	983	1993
28	Evaluation of a nutrient starvation model of <i>Mycobacterium tuberculosis</i> persistence by gene and protein expression profiling	Molecular Microbiology	983	2002
29	IL-23 and IL-17 in the establishment of protective pulmonary CD4(+) T cell responses after vaccination and during <i>Mycobacterium tuberculosis</i> challenge	Nature Immunology	974	2007

30	Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: An update	annals of internal medicine	959	2008
31	Tuberculosis in Patients with Human-Immunodeficiency-Virus Infection	New England Journal of Medicine	938	1991
32	An outbreak of Tuberculosis with accelerated Progression among persons Infected with the Human-Immunodeficiency-Virus - an Analysis using Restriction-Fragment-Length-Polymorphisms	New England Journal of Medicine	866	1992
33	The spectrum of latent tuberculosis: rethinking the biology and intervention strategies	Nature Reviews Microbiology	843	2009
34	Killing of Virulent <i>Mycobacterium-Tuberculosis</i> by Reactive Nitrogen Intermediates Produced by Activated Murine Macrophages	Journal of Experimental Medicine	841	1992
35	Restricted structural gene polymorphism in the <i>Mycobacterium tuberculosis</i> complex indicates evolutionarily recent global dissemination	Proceedings of the National Academy of Sciences of The United States of America	811	1997
36	Identification of nitric oxide synthase as a protective locus against tuberculosis	Proceedings of the National Academy of Sciences of the United States of America	810	1997
37	Response of Cultured Macrophages to <i>Mycobacterium-Tuberculosis</i> , With Observations on Fusion of Lysosomes With Phagosomes	Journal of Experimental Medicine	804	1971
38	An in vitro model for sequential study of shift down of <i>Mycobacterium tuberculosis</i> through two stages of non-replicating persistence	Infection and Immunity	802	1996
39	Structure of the MscL homolog from <i>Mycobacterium tuberculosis</i> : A gated mechanosensitive ion channel	Science	801	1998
40	Occurrence And Stability of Insertion Sequences in <i>Mycobacterium-Tuberculosis</i> Complex Strains - Evaluation of An Insertion Sequence-Dependent DNA Polymorphism as a Tool in the Epidemiology of Tuberculosis	Journal of Clinical Microbiology	797	1991
41	<i>Mycobacterium tuberculosis</i> complex genetic diversity: mining the fourth international spoligotyping database (SpolDB4) for classification, population genetics and epidemiology	BMC Microbiology	793	2006

42	Ruminant Para-Tuberculosis (Johnes Disease) - The Current Status And Future-Prospects	Cornell Veterinarian	787	1984
43	The Emergence of Drug-Resistant Tuberculosis in New-York-City	New England Journal of Medicine	768	1993
44	Meta-analysis: New tests for the diagnosis of latent tuberculosis infection: Areas of uncertainty and recommendations for research	Annals of Internal Medicine	761	2007
45	Diabetes mellitus increases the risk of active tuberculosis: A systematic review of 13 observational studies	PloS Medicine	758	2008
46	Transmission of Tuberculosis In New-York-city -An Analysis by DNA-Fingerprinting And Conventional Epidemiologic Methods	New England Journal of Medicine	752	1994
47	A small-molecule nitroimidazopyran drug candidate for the treatment of tuberculosis	Nature	740	2000
48	The challenge of new drug discovery for tuberculosis	Nature	739	2011
49	Resazurin Microtiter assay plate: Simple and inexpensive method for detection of drug resistance in <i>Mycobacterium tuberculosis</i>	Antimicrobial Agents and Chemotherapy	738	2002
50	An outbreak of Multidrug-Resistant Tuberculosis Among Hospitalized-Patients ith the Acquired-Immunodeficiency-Syndrome	New England Journal of Medicine	736	1992
51	Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk - A multicenter active-surveillance report	Arthritis and Rheumatism	731	2003
52	Rapid, low-technology MIC determination with clinical <i>Mycobacterium tuberculosis</i> isolates by using the microplate Alamar Blue assay	Journal of Clinical Microbiology	724	1998
53	Advances In Techniques of Testing Mycobacterial Drug Sensitivity, And Use of Sensitivity Tests In Tuberculosis Control Programmes	Bulletin of the World Health Organization	718	1969
54	Interferonn assays-gamma in the Immunodiagnosis of tuberculosis: a systematic review	Lancet Infectious Diseases	710	2004
55	Tuberculosis	Lancet	698	2003
56	Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study	Lancet	691	2011



57	Multidrug-resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis	Lancet	690	2010
58	Major Histocompatibility Complex Class-I-Restricted T-Cells Are Required For Resistance to <i>Mycobacterium-Tuberculosis</i> Infection	Proceedings of the National Academy of Sciences of the United States of America	686	1992
59	Inhibition of respiration by nitric oxide induces a <i>Mycobacterium tuberculosis</i> dormancy program	Journal of Experimental Medicine	682	2003
60	Variable host-pathogen compatibility in <i>Mycobacterium tuberculosis</i>	Proceedings of the National Academy of Sciences of the United States of America	680	2006
61	Human toll-like receptors mediate cellular activation by <i>Mycobacterium tuberculosis</i>	Journal of Immunology	672	1999
62	Xpert (R) MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults	Cochrane Database of Systematic Reviews	662	2014
63	The Global Tuberculosis Situation and the new Control Strategy of The World-Health-Organization	Tubercle	655	1991
64	Specific immune-based diagnosis of tuberculosis	Lancet	654	2000
65	M-tuberculosis and M-leprae translocate from the phagolysosome to the cytosol in myeloid cells	Cell	634	2007
66	Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial	Lancet	631	2013
67	Dynamical models of tuberculosis and their applications	Mathematical Biosciences and Engineering	610	2004
68	Global Tuberculosis Incidence and mortality during 1990-2000	Bulletin of the World Health Organization	607	1994
69	Polymerase Chain-Reaction Amplification of A Repetitive DNA-Sequence Specific for <i>Mycobacterium-Tuberculosis</i>	Journal of Infectious Diseases	605	1990
70	Treatment of 171 Patients with Pulmonary Tuberculosis Resistant To Isoniazid And Rifampin	New England Journal of Medicine	602	1993
71	Variations in the Nrampi gene and susceptibility to tuberculosis in West Africans	New England Journal of Medicine	586	1998
72	Nonreplicating persistence of <i>Mycobacterium tuberculosis</i>	Annual Review of Microbiology	584	2001

73	Sex differences in Tuberculosis Burden and Notifications in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis	PloS Medicine	580	2016
74	Regulation of the <i>Mycobacterium tuberculosis</i> hypoxic response gene encoding alpha-crystallin	Proceedings of the National Academy of Sciences of the United States of America	579	2001
75	Tuberculosis in New-York-City - Turning the tide	New England Journal of Medicine	572	1995
76	Predominance of A Single Genotype of <i>Mycobacterium-Tuberculosis</i> in countries of East-Asia	Journal of Clinical Microbiology	571	1995
77	resurgent tuberculosis in new-York-city - human-immunodeficiency-virus, homelessness, and the decline of tuberculosis-control programs	American Review of Respiratory Disease	570	1991
78	Complex lipid determine tissue specific replication of <i>Mycobacterium tuberculosis</i> in mice	Nature	568	1999
79	Rapid Detection of <i>Mycobacterium tuberculosis</i> and Rifampin Resistance by use of on-Demand, Near-Patient Technology	Journal of Clinical Microbiology	566	2010
80	The Diarylquinoline TMC207 for Multidrug-Resistant Tuberculosis	New England Journal of Medicine	566	2009
81	IL-17 production is dominated by gamma delta T cells rather than CD4 T cells during <i>Mycobacterium tuberculosis</i> infection	Journal of Immunology	566	2006
82	Influence of vitamin D deficiency and vitamin D receptor polymorphisms on tuberculosis among Gujarati Asians in west London: a case-control study	Lancet	561	2000
83	<i>Mycobacterium tuberculosis</i> pathogenesis and molecular determinants of virulence	Clinical Microbiology Reviews	560	2003
84	Immunogenicity and protective efficacy of a tuberculosis DNA vaccine	Nature Medicine	560	1996
85	Cutting edge: Vitamin D-mediated human antimicrobial activity against <i>Mycobacterium tuberculosis</i> is dependent on the induction of cathelicidin	Journal of Immunology	557	2007
86	Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management	Lancet Infectious Diseases	555	2003
87	Advances in the development of new tuberculosis drugs and treatment regimens	Nature Reviews Drug Discovery	553	2013

88	A glycolipid of hyper virulent tuberculosis strains that inhibits the innate immune response	Nature	552	2004
89	Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013	Lancet	552	2014
90	Transmission of <i>Mycobacterium tuberculosis</i> from patients smear-negative for acid-fast bacilli	Lancet	548	1999
91	Interleukin 12 (IL-12) is crucial to the development of protective immunity in mice intravenously infected with <i>Mycobacterium tuberculosis</i>	journal of experimental medicine	548	1997
92	Modification of the NADH of the isoniazid target (InhA) from <i>Mycobacterium tuberculosis</i>	Science	547	1998
93	<i>Mycobacterium tuberculosis</i> : Here today, and here tomorrow	Nature Reviews Molecular Cell Biology	546	2001
94	Characterization of the <i>Mycobacterium-Tuberculosis</i> Phagosome And Evidence That Phagosomal Maturation Is Inhibited	Journal of Experimental Medicine	545	1995
95	Out-of-Africa migration and Neolithic co expansion of <i>Mycobacterium tuberculosis</i> with modern humans	Nature Genetics	542	2013
96	Drug-Therapy - Treatment of Multidrug-Resistant Tuberculosis	New England Journal of Medicine	541	1993
97	Role of the major antigen of <i>Mycobacterium tuberculosis</i> in cell wall biogenesis	Science	540	1997
98	Tuberculosis	Lancet	539	2011
99	Stimulation of A Major Subset of Lymphocytes Expressing T-Cell Receptor-Gamma-Delta by an Antigen Derived From <i>Mycobacterium-Tuberculosis</i>	Cell	535	1989
100	Toward the structural genomics of complexes: Crystal structure of a PE/PPE protein complex from <i>Mycobacterium tuberculosis</i>	Proceedings of the National Academy of Sciences of the United States of America	535	2006

SCR, Standard Competition Ranking; NP: Number of articles; TC: Total Number of citations reported per documents

## Authorship analysis

The research study shows that 1049 authors contributed to the top 100 cited documents. The first ranking author was Bloom BR (NP = 5, TC=4740), followed by Jacobs WR from Howard Hughes Medical Institute, Department of Microbiology and Immunology (Table 3).

**Table 3:** Authors with  $\geq 4$  h\_index on TB related publications

SCR	Author (n=1058)	Co-author's Affiliations <sup>a</sup>	h_index	TC	NP
1	Bloom BR	Howard Hughes Medical Institute, Albert Einstein College of Medicine,	5	4740	5
2	Jacobs WR	Howard Hughes Medical Institute, Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, New York 10461, USA.	5	4064	5
3	Schoolnik GK	Medical Service, San Francisco General Hospital Medical Center, Calif.	5	4156	5
4	Alland D	Department of Medicine, Montefiore Medical Center, North Central Bronx Hospital, N.Y. 10467.	4	3436	4
5	Barry CE	Tuberculosis Research Section, Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA.	4	8013	4
6	Flynn JL	Department of Molecular Genetics and Biochemistry, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15261, USA	4	4097	4
7	Hopewell PC	Department of Medicine, Stanford Medical School, Calif. 94305.	4	3101	4
8	Kreiswirth BN	Section of Molecular Pathobiology, Department of Pathology, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA.	4	2896	4
9	Kremer K	Unité de Génétique Moléculaire Bactérienne, Laboratoire de Génomique des Microorganismes Pathogènes, and Centre National de Référence des Mycobactéries, Institut Pasteur, 25-28 Rue du Docteur Roux, 75724 Paris Cedex 15, France.	4	3464	4
10	Niemann S	Genomics and Health Unit, Centre for Public Health Research (CSISP-FISABIO), Valencia, Spain. CIBER (Centros de Investigación Biomédica en Red) in Epidemiology and Public Health, Barcelona, Spain.	4	2998	4
11	Pai M	McGill University and Montreal Chest Institute, Montreal, Quebec, Canada.	4	3092	4
12	Schnappinger D	Department of Pathobiology, University of Washington, Seattle, WA 98195, USA	4	3126	4

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13	Small PM	Medical Service, San Francisco General Hospital Medical Center, Calif.	4	3101	4
14	Van soolingen D	Department of Medicine, Albert Einstein College of Medicine and Montefiore Medical Center,	4	3474	4

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SCR, Standard Competition Ranking; TC: Total Number of citations reported per documents, NP: Number of publications.

### Most Influential Journals

The impact factor was used to evaluate the influences, and Journals with  $\geq 3$  h\_index on TB-related publications in journals with high impact factors. Our study revealed that 96 TB type documents were published in the top 10 journals in the past 49 years, where there were 37 information sources reported in the top 100 articles on TB. New England Journal of Medicine with Number of documents and Impact factor (NP=14, IF-2019=74.699), followed by Lancet (NP=11, IF-2019=60.39), Nature (NP=8, IF-2019=42.779) were the best three journals. The journal's quality is an indicator of the quality of research output, and it is assessed using Journal quartile and Journal h\_index. More than 65% of the documents were published in a journal in the Q1 range, which are high-quality journals. **(Table 4).**

### Country collaborative analysis

A total number of 12 countries or regions contributed to the top 100 most cited publications on TB. The United States is the leader in this field which produced 51 articles and was actively involved in international cooperation presenting in Single Country Publication with (NP=38 publications) documents a, and Multiple country Publication with (NP=13 publications). Accordingly, countries' collaboration in TB studies is described by the lines (links) that join the countries as presented in (Table 5).

**Table 4:** Journals with  $\geq 3$  h\_index on TB related publications

SCR	Journal (n=37)	NP	(%)	TC	h_index	IF (2019)	Quartile
1	New England Journal of Medicine	<a href="#">14</a>	14.0	13296	14	74.699	Q1
2	Lancet	<a href="#">11</a>	11.0	7698	11	60.39	Q1
3	Nature	<a href="#">8</a>	8.0	11590	8	42.779	Q1
4	Proceedings of the National Academy of Sciences of the United States of America	<a href="#">7</a>	7.0	5109	7	NA	NA
5	Journal of Clinical Microbiology	<a href="#">6</a>	6.0	5868	6	5.897	Q1
6	Journal of Experimental Medicine	<a href="#">6</a>	6.0	4442	6	11.743	Q1
7	Science	<a href="#">5</a>	5.0	4175	6	41.846	Q1
8	Cell	<a href="#">3</a>	3.0	2723	3	38.637	Q1
9	Jama-Journal of the American Medical Association	<a href="#">3</a>	3.0	5017	3	45.54	Q1
10	Journal of Immunology	<a href="#">3</a>	3.0	1795	3	4.886	Q1
11	Lancet Infectious Diseases	<a href="#">3</a>	3.0	2311	3	24.446	Q1

**SCR:** Standard Competition Ranking; **NP:** Number of publications; **TC:** Total Number of citations reported per documents; **Q:** Journal Quartile –range; **TC:** **NP:** Number of articles; NA: Not available.

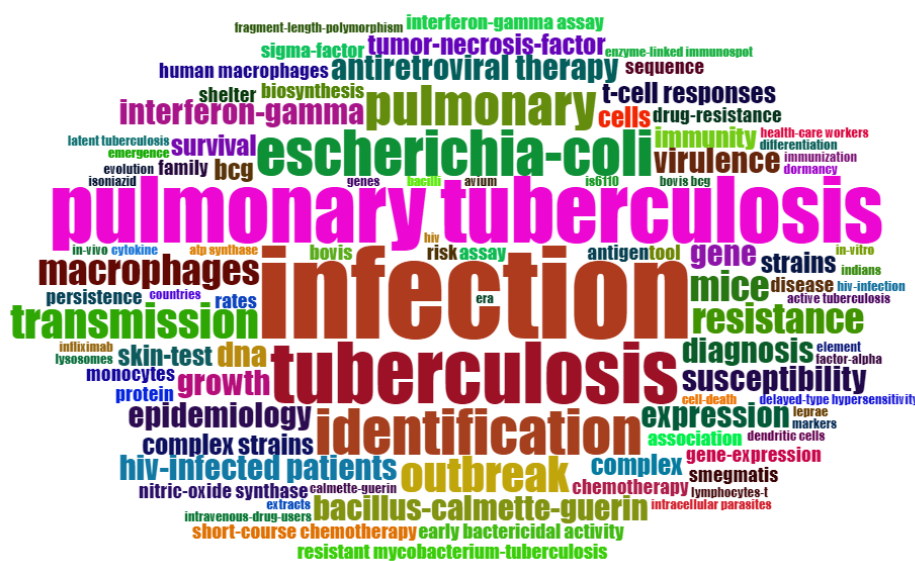
**Table 5:** Most productive countries in the productions with  $\geq 2$  TB related articles

SCR	Country (N=12)	NP	TC	ACPY	SCP <sup>b</sup>	MCP <sup>c</sup>	MCP_Ratio
1	USA	51	40948	803	38	13	0.255
2	United Kingdom	10	12753	1275	1	9	0.900
3	Switzerland	8	9752	1219	3	5	0.625
4	Canada	4	2823	706	1	3	0.750
5	Belgium	2	1477	738	0	2	1.000
6	France	2	1991	996	0	2	1.000
7	Spain	2	1273	636	1	1	0.500

**SCR:** Standard Competition Ranking; **NP:** Number of Publications; **TC:** Total citation; **GDP:** Gross Domestic; **TC:** The number of times each manuscript has been cited;<sup>b&c</sup>; **Country collaborations:** The intra-country (SCP) and inter-country (MCP) collaboration indices; **TC:** Total Citations; **ACPY:** Average Citations Per Year

## Research hotspots

The frequency distribution of keywords associated with the document by Clarivate Analytics Web of Science Keyword using WordCloud (Figure 2). Among the 100 keyword Plus identified the most frequent occurrence of keywords by using WorldClude were mycobacterium-tuberculosis (28), followed by infection (18), human-immunodeficiency-virus (13), pulmonary tuberculosis (13), tuberculosis (12), escherichia-coli (9), identification (9), pulmonary (8), outbreak (7), and transmission (7).



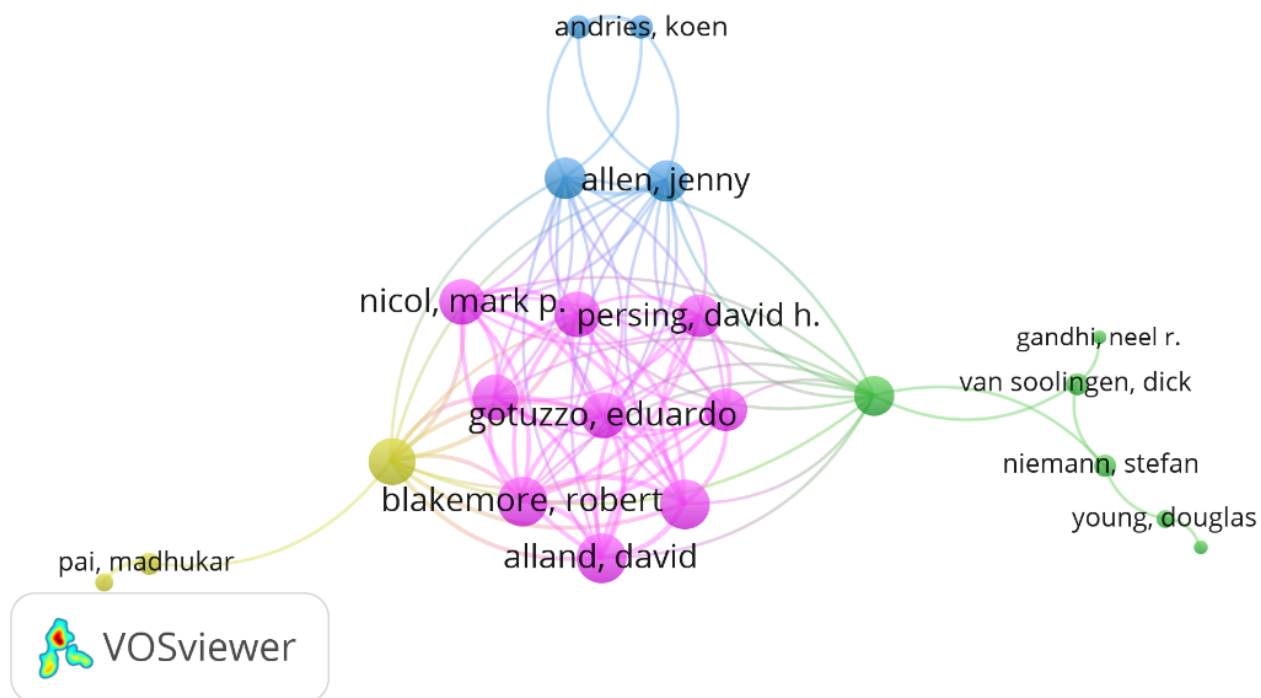
**Figure 2:** Graphical analysis of Keyword plus (ID) by using WordCloud on TB related publications

## The social structure of knowledge of authors and Organizations

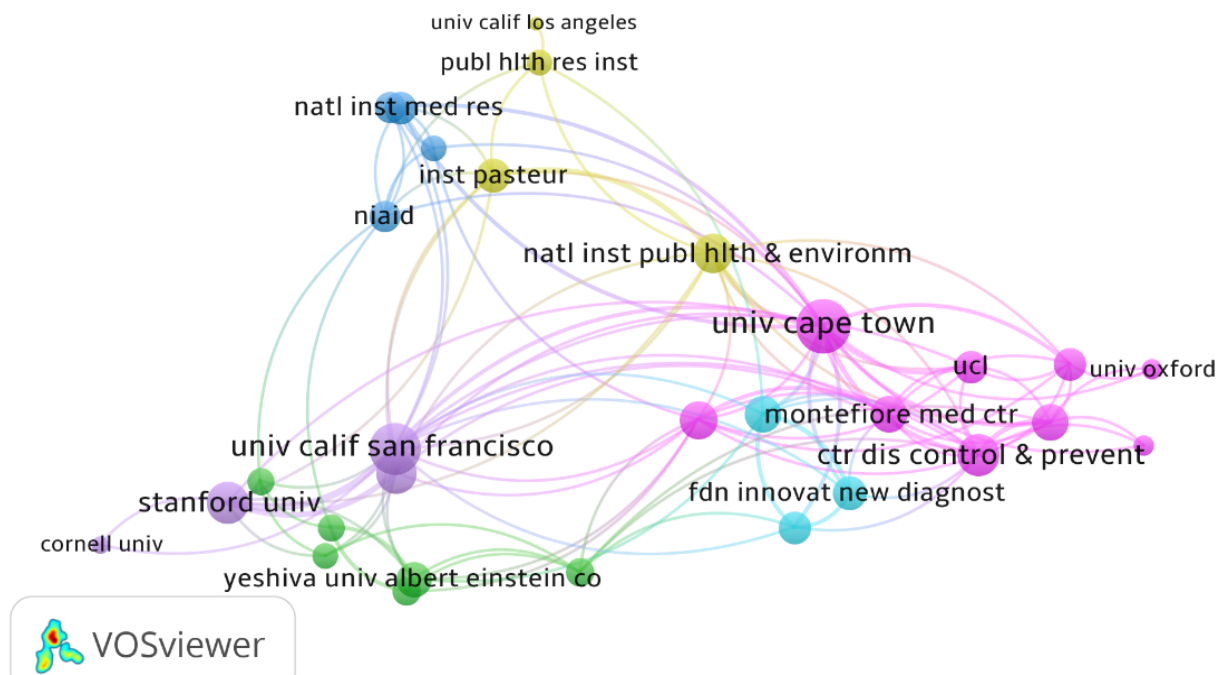
The VOSviewer program was used to map and visualize bibliometric collaboration networks between authors and organizations reported and how those social structures of knowledge link



or relate to each other to verify the most influential authors and Organizations'. A minimum of 2 instances of authors was required to meet the search criteria. In the analysis, only 22 presented in 4 clusters with Links (L=91, TLS=132) times. Alland D was first based on the (TLS=23) times, followed by Allen, J (TLS=15) times, and Nicol, MP (TLS=19) times, among others (Figure 3.A). A minimum number of 3 instances of authorship per organization were selected to meet the search criteria. Among 219 organizations only 32 met the threshold. Only 30 presented in 6 clusters with Links (L=115, TLS=155) times. University of Cape Town (L=20, TLS=32) times, followed by University of California San Francisco (L=18, TLS=28) times, World Health Organization (L=10, TLS=13) times, and Stanford University (L=9, TLS=18) times, among others (Figure 3.B).



(A)



(B)

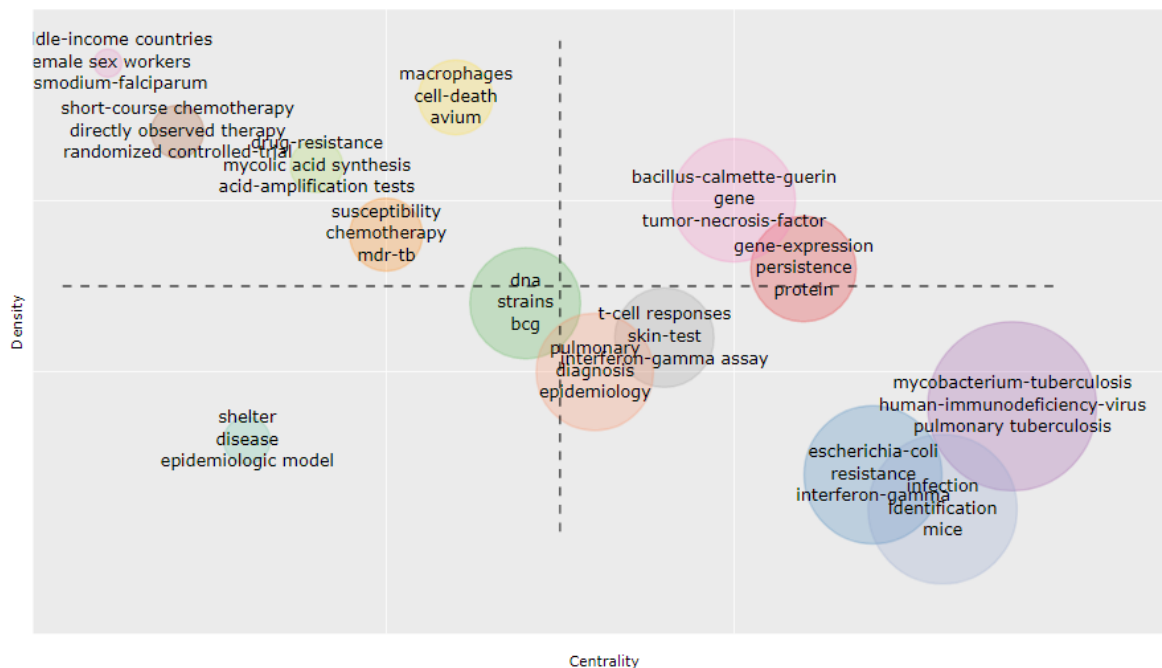
**Figure 3:** Mapping analysis of co-authorship analyses of authors (A) and Organizations (B) based on the length (L) and Total length strength (TLS).

### Thematic Analysis of Tuberculosis related publications

The analysis of the thematic map analysis of the key research themes based on scientific publications on the subject of TB among the top 100 most cited papers is shown in Figure 4. Four themes quadrant is presented going by their centrality and density rank values along with vertical-axis and horizontal-axis density, and to analyze the thematic evolution of given research in TB field. Themes in the upper-right quadrant are called the motor-themes or represent the hot topics, as they present high density and strong centrality. The figure shows that the spheres (circles) are proportional to the number of documents equivalent to each Keyword in each quadrant indexed in the top 100 most cited TB articles. Themes located in the lower-right

quadrant are called the general and transversal or basic themes. The quadrant specifies keywords that are vital in the TB research field but are not developed.

Additionally, the themes located in the lower-left quadrant are called either disappearing or emerging themes of research on TB. The quadrant specifies research studies that are weakly developed and marginal with low centrality and low density. Themes in the upper-left quadrant are very focused and peripheral. They possess well-developed internal ties but insignificant external ties, and thus they are only of marginal relevance to TB research. Consequently, the scientific publications given in the above figure, we notice that the studies include (bacillus-calmette-querin, gene, and tumor-necrosis-factor studies beside the gene-expression, persistence, and protein) high density and strong centrality, indicating that they are related visibly to other themes that are conceptually closely related to the TB research.



**Figure 4:** Thematic progression of TB-related publications (1965-2018)

## Research area on TB research

The source journals were assigned to one or more subject categories defined by WoS to investigate the influences of TB-related publications in various research areas. The TB source journals were categorized into 21 research areas or subjects, among which 34 documents were published under General and Internal Medicine, and 21 of the documents on TB were published in the area of Science & Technology. Other Topics and ten documents were published in the area of microbiology. Other research areas are illustrated in **Table 6**.

**Table 6:** The reported research area indexed in web of science

Research area (N=21)	TC	NP
General & Internal Medicine	31594	34
Science & Technology - Other Topics	22293	21
Microbiology	8643	10
Immunology	5609	6
Immunology; Research & Experimental Medicine	4442	6
General & Internal Medicine; Respiratory System	2593	2
Infectious Diseases	2295	3
Biochemistry & Molecular Biology; Cell Biology	2183	2
Microbiology; Pharmacology & Pharmacy	2097	2
Public, Environmental & Occupational Health	1325	2
Respiratory System	1225	2
Biochemistry & Molecular Biology; Microbiology	982	1
Immunology; Infectious Diseases	801	1
Veterinary Sciences	787	1
Rheumatology	730	1
Immunology; Infectious Diseases; Microbiology	605	1
Mathematical & Computational Biology	605	1
Biochemistry & Molecular Biology; Cell Biology; Research & Experimental Medicine	560	1
Biotechnology & Applied Microbiology; Pharmacology & Pharmacy	553	1
Cell Biology	546	1
Genetics & Heredity	539	1

TC: Total citation reported, NP: Number of publications reported in each research area

## Factors Influencing Citations Scores

The correlation analysis of possible factors influencing citations in TB research articles is presented in Table 7. The significant correlations were found between the number of citations and number of documents per year ( $r=0.9579$ ,  $p<0.0001$ ), number of countries ( $r=0.9570$ ,  $p<0.0001$ ), number of articles per journal ( $r=0.8721$ ,  $p<0.0001$ ), number of authors ( $r=0.4601$ ,  $p<0.0001$ ), and number of documents per [Institution](#) ( $r=0.6159$ ,  $p<0.0001$ ).

**Table 7:** Association between factors that are affecting the No. of citations and study variables.

Variables	Spearman (r)	P_value
No. Citations & number documents per year	0.9579	<0.0001
No. Citations & Number of authors	0.4811	<0.0001
No. Citations & Number of documents	0.4326	<0.0001
No. Citations & number of article per journal	0.8721	<0.0001
No. Citations & Number of documents per Institution	0.6159	<0.0001
No. Citations & Institution with Subdivision	0.6627	<0.0001
No. Citations & number of countries	0.9570	<0.0001

## 4. DISCUSSION

The In this study, a comprehensive analysis of the global top 100 most cited TB articles was implemented to assess the trends and track TB research development[58,60–64]. However, no review studies combining bibliometric analysis of the scientific research productivity on top 100 articles on TB have been summarized. We expanded this topic in terms of top-cited articles based on the number of times cited or shows the most productive authorships, countries, journals, and organization enhanced the research production in the world [49,50,65]. The [main advantage](#) of carrying out review research following traditional methods is using a limited number of publications to offer the reader insight into the scientific topic. In contrast, bibliometric analysis

tools are considered techniques used by many researchers to overcome the subjective factors in the traditional review process. It avoids missing central literature while exploring the intellectual structures, research hotspots, active authors, and offers empirical new insight into specific scientific fields to evaluate publication characteristics, support the policymakers to take timely scientific responses, and identify the gap over time frame [66].

Determining the prominent journals contributed during the study period in TB's field provides the most top research indicators. Through the analysis, our findings provide vital information for authors to select high-quality journals and other bibliometric research [49,50,67]. Our study further uses the Thematic progression to detect better, monitor, and visualize the evolution of the TB research field and those reported in other previous studies [68][58,69]. Our analysis shows the most influential authors' contributions from different institutions and countries that have published the most significant TB-related publications in various journals. This information also becomes indicators of their research skills and degree of influence for each author in the TB field. The most active authors and their affiliated institutes must acknowledge their contribution to the top 100 most cited articles during the study period which were generally from the United State (US).

Finally, this study provides comprehensive information as it shows additional evidence regarding TB Epidemiology, Diagnosis, Management with further analysis of the topmost 100 cited publications, which would be particularly valuable to the health officer, decision maker in dealing with the problem regarding TB in the world.

To the best of our knowledge, this is the narrative review followed by the top 100 cited publications using bibliometric analysis to assess the growth trend by using a scientometric method and identifying the hot topic besides the factors that influence the citations. Compared

with traditional reviews, the net social work visualized analysis based on VOSviewer software, and R-Studio can help scientific readers to better understand the evolution of research and assess the trends of publication and hotspots in the TB fields.

Furthermore, the present study has focused on Metadata obtained from the Web of Science (WoS) database only through the relevant keywords, and only full research articles and review papers published in English were included. On the other hand, a comprehensive analysis of the research status and trends of the top 100 articles only with the most cited times could guide beginners and researchers in the TB field. However, some limitations should be noted in this study. Firstly, all publications were derived only from one literature source: the WoS, without including other databases such as Scopus, PubMed, and Google scholar. Secondly, we only included publications published in English, where our study does not include publications published by others. Therefore, some selection biases may be presented besides the limitation of document types during the search of the top 100 articles..

## 5. Conclusion

In conclusion, the present study has provided comprehensive information on the top 100 articles on TB produced by over a thousand research contributed from 12 countries in the world. They highlighted that TB is still the current global health problem, which require adequate preventive and control measures at the inter-state level between countries.

The current study examines the global prevalence of TB that takes the life of one in four adults in developing countries and significantly threatens children's lives. The burden of TB is similarly prevalent among people infected with HIV, making it a potential co-infection disease. We further expanded on the etiology, diagnosis, and potentiality of treatment resistance among infected



people, making it even more worrisome. The enormous preponderance of the disease calls for urgent intervention given the current evidence. The evidence from developing countries warrants the need to scale up clinical research on Tuberculosis to create more options for further treatments. The national government in developing countries should scale up investment to improve healthcare infrastructure in the country, especially in regions that are most vulnerable to the disease. The importance of health education cannot be overstretched. So, the government and other NGOs should educate people on the risk of avoiding TB.

**Funding:** No funding was received for this study.

**Conflicts of Interest Statement:** The authors declare no conflict of interest.

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