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A global trend on tuberculosis co-infection with microorganism over the past 29 years

Afifah Khairunnisa[1], Rosantia Sarassari[2], Sri Darmawati[1,3*]

[1]Clinical Laboratory Science, Universitas Muhammadiyah Semarang, Semarang, Indonesia.
[2]Eijkman Research Center for Molecular Biology, National Research and Innovation Agency (BRIN), Cibinong, Indonesia.
[3]Department of Medical Laboratory Technology, Faculty of Health and Nursing Science, Universitas Muhammadiyah Semarang, Semarang, Indonesia.

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ABSTRACT

Tuberculosis is a global disease problem that is still difficult to overcome. WHO reports that TB cases are increasing from year to year. This is directly proportional to the mortality rate due to TB, which has increased significantly, reaching 1.6 million by 2022. High mortality rates can result from immunosuppression and co-infection by other microorganisms such as bacteria, fungi, and viruses. This can prolong symptoms and worsen the patient's condition. This article presents a bibliometric study of research articles on tuberculosis co-infection with microorganisms indexed in the Scopus journal database from 1966 to 2024. An accumulating total of 422 documents were disseminated globally, averaging 14 documents annually. The US produced the most documents (94), followed by India (73), the UK and South Africa (40), and China (33). Since 2002, global publishing numbers have continually increased. Co-infections, microbiology of co-infection, clinical articles, and case reports are popular trends these days. This study provides a comprehensive overview of global research on tuberculosis co-infections with microorganisms, spanning from 1966 to 2024.

INTRODUCTION

Tuberculosis is a global illness that remains difficult to control. The World Health Organization estimates the number of individuals diagnosed with tuberculosis will reach 10.6 million by 2021, an increase of 600,000 from 2020. The number of deaths caused by TB has also increased significantly from 1.3 million in 2020 to 1.6 million in 2021 [1]. India (28%), Indonesia (9.2%), China (7.4%), the Philippines (7.0%), Pakistan (5.8%), Nigeria (4.4%), Bangladesh (3.6%), and the Democratic Republic of the Congo (2.9%) are the countries with the most tuberculosis cases worldwide [2]. *Mycobacterium tuberculosis* infection has become a serious concern because it can cause death by a single infectious pathogen. This is worsened by the occurrence of mixed infections, commonly referred to as co-infections [3]. TB co-infection can be caused by bacteria, fungi, or viruses (Fig. 1) [3,4].

Based on research conducted in Cambodia, the most common bacteria found in the sputum of tuberculosis patients are *Klebsiella* and *Pseudomonas* [5]. This is similar to research of pathogenic bacteria co-infection in tuberculosis patients in Nigeria, which found that *Klebsiella* and *Pseudomonas* we not the most dominant Gram-negative bacteria, while *Staphylococcus aureus* was the most common Gram-positive bacteria [6]. Other studies have shown the co-infection of tuberculosis with yeasts and molds. The study showed that TB-infected patients were able to be infected with the yeast *Candida* sp. In the samples, several candida species were even found such as *Candida tropicalis, Candida krusei*, and *Candida parapsilosis* [7]. Previous studies have also shown that about 15%–32% of TB-HIV infected patients are also positive for *Candida* [8]. Besides *Candida*, *Aspergilus* has also been reported as the most common co-infecting agent in TB patients. A study conducted in Ghaemshahr City, Iran, in 2018 reported

*Corresponding Author
Sri Darmawati, Department of Medical Laboratory Technology, Faculty of Health and Nursing, Universitas Muhammadiyah Semarang, Semarang, Indonesia. E-mail: ciciekdarma @ unimus.ac.id

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that *Aspergillus fumigatus* was the dominant fungal species present in TB co-infections [9,10].

At this point, a lack of study has been conducted on the co-infection mechanisms between tuberculosis and other microorganisms. TB is a disease that can induce immune dysfunction. Consequently, enabling more infections induced by bacteria or fungi. Another case was identified in Bangladesh, where a tuberculosis patient co-infected with *K. pneumoniae* exhibited immunological dysfunction exacerbated by comorbidities such as diabetes mellitus, potentially worsening the patient's condition (Fig. 2) [11].

The most common bacterial co-infection of concern to the WHO is TB-HIV. The probability of developing active tuberculosis is 20–30 times greater in those with HIV compared to those without HIV. Co-infection with TB and HIV increases mortality rates and makes managing both illnesses increasingly challenging [12].

Mycobacterium tuberculosis is transmitted via airborne particles when an infected individual coughs, sneezes, speaks, laughs, or sings, dispersing little droplets containing pathogens into the environment. These droplets may be inhaled by individuals in nearby locations, resulting in tuberculosis infection [13]. *Mycobacterium tuberculosis* enters into the lungs and is detected by immune cells. It is mainly encountered by alveolar macrophages, the initial line of defense [14]. HIV infection significantly modifies the immunological environment, increasing risk to tuberculosis. The virus predominantly attacks CD4+ T cells, essential for initiating an efficient immunological

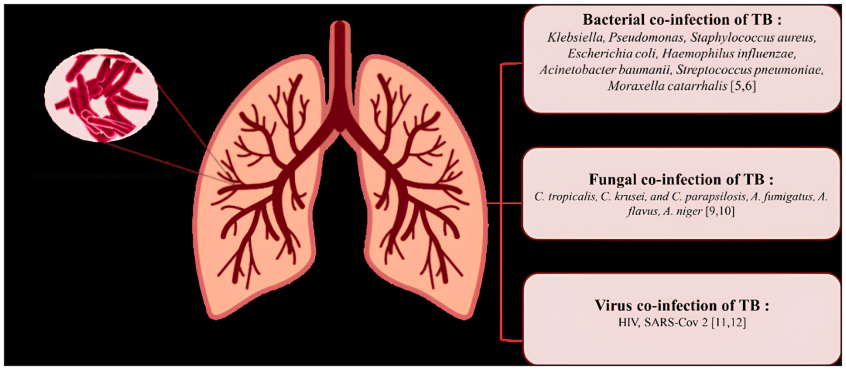

Figure 1. Tuberculosis co-infection with pathogen microorganism.

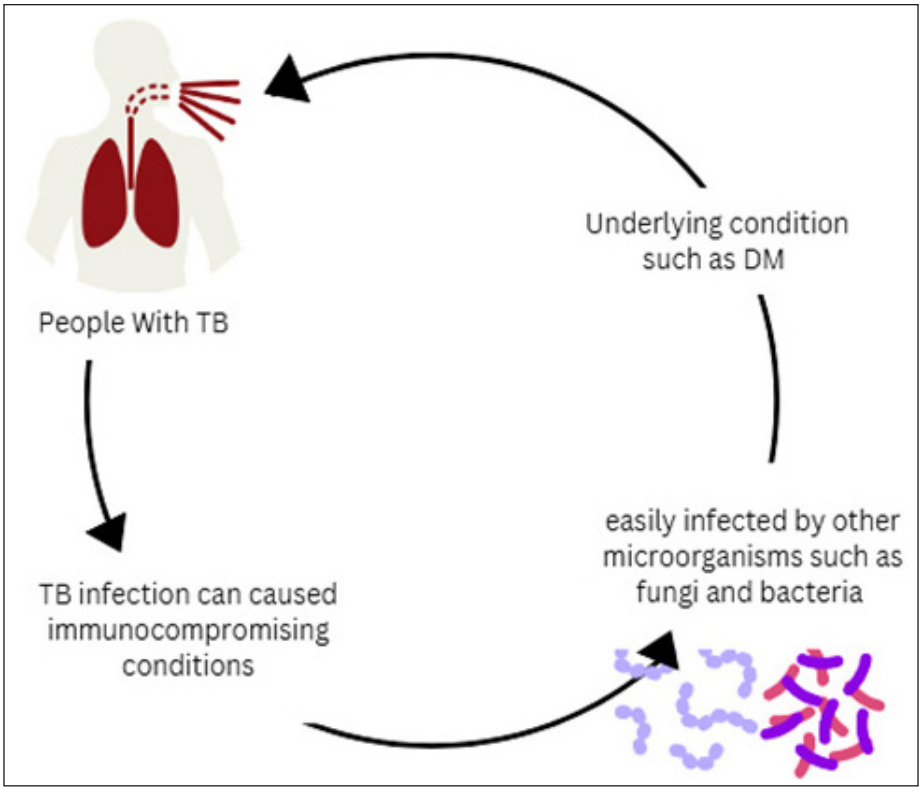

Figure 2. TB co-infection with microorganism.

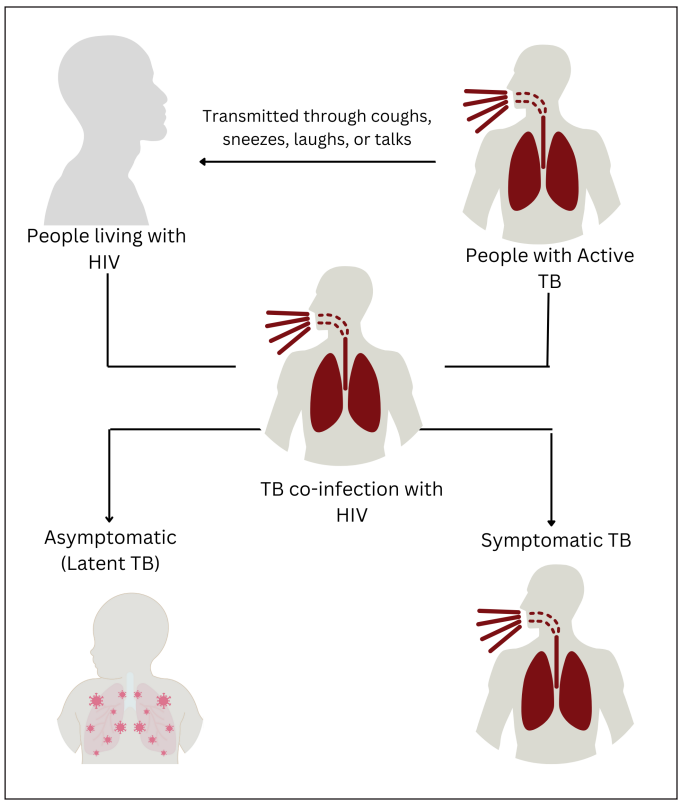

Figure 3. The transmission of TB into TB co-infection with HIV.

response against *M. tuberculosis*. The decrease of these cells results in compromised macrophage activity, diminishing their capacity to phagocytose and eliminate bacteria effectively [15]. In addition, tuberculosis and HIV provoke persistent immunological activation, potentially resulting in further depletion of CD4+ T cells and other immune dysfunctions. This persistent stimulation may lead to heightened viral replication within granulomas, promoting a negative loop in which each infection worsens the impact of the other (Fig. 3) [16].

Another viral infection that can cause death in TB patients is co-infection with SARS CoV-2. Research shows that TB patients with co-infection with SARS CoV-2 cause the potential latent TB to develop into TB infection [17]. These co-infections may result in longer treatment times and more serious lung damage and increase mortality rate.

Research related to TB co-infection microorganisms has not been studied in detail. To our knowledge, there are currently no bibliometric studies available on such research. Furthermore, it is essential to assess the global study overview of the scientific literature about TB co-infection microorganisms. The present investigation focused to deliver a thorough review of the published work on microorganism co-infection with tuberculosis over the past 29 years by visualizing international collaborations, evaluating the performance of prominent universities, examining the output of leading journals, analyzing the characteristics of frequently cited articles, and identifying promising research topics. The findings of this investigation enable academics and practitioners to evaluate the influence of their work through an illustrated evaluation of the research conditions in the field.

MATERIAL AND METHOD

The Scopus database was used to obtain all publications published over a 29-year period (1966–2024) on tuberculosis co-infection with microorganisms. In numerous domains, Scopus is considered as the primary resource for bibliometric analysis [18–20]. A bibliometric filter was extracted on July 12, 2024. To obtain papers on TB co-infection bacteria from the Scopus database, input the key phrases [“Tuberculosis” and “bacteria” and “co-infection”] in the “title” and “abstract” fields. The database maintained by Scopus identified 422 articles regarding TB co-infection. The data retrieved include document type, publication year, institutions, nations, journal titles, citations, and keywords. The acquired data were assessed utilizing VOSviewer [21].

RESULTS AND DISCUSSION

From 1966 to 2024, an overall of 422 articles concerning tuberculosis co-infection with microorganisms were published globally, averaging 14 documents annually. The literature on TB co-infection microorganisms from all around the world was thoroughly reviewed for this study. Our findings demonstrate that over the previous 29 years, researchers from all around the world have demonstrated a strong interest in TB microorganism co-infection. Research on co-infection began in 1966 (Fig. 3). This is because the 1960s also marked the onset of the HIV/AIDS epidemic. As the impact of HIV/AIDS became more apparent, researchers began to investigate the relationship between HIV and TB, which led to a significant increase in the study of co-infection with TB [22]. Research on TB co-infection microorganisms peaked in 2011 (Fig. 3). This was due to a number of factors, including an increase in TB-HIV case notifications and a high mortality rate from TB co-infection. For example, cases increased by 25.6% in Latin America and the Caribbean in 2011 [23,24]. In addition, the development of diagnostic technology has also influenced the high research interest in this sector. Diagnostic developments, such as interferon-gamma release assays and nucleic acid amplification tests, are needed to improve the accuracy of diagnosis in coinfected patients [25,26]. Research related to tuberculosis co-infection with microorganisms has also seen a significant increase by 2021. This is due to the COVID-19 pandemic that has significantly disrupted TB treatment services, including a decrease in the number of TB cases tested. This results in fewer TB cases identified, which in turn leads to an increase in undiagnosed and untreated TB cases, which ultimately contributes to higher TB-related deaths and more TB transmission in the community. Therefore, many researchers are interested in knowing the impact of COVID-19 on TB transmission and its clinical impact [27–29].

The leading category is research articles (n = 342; 81.04%), succeeded by reviews (n = 59; 13.9%), letters (n = 7; 1.6%), short surveys (n = 1; 0.2%), conference papers (n = 4; 0.9%), book chapters (n = 3; 0.7%), and errata (n = 2; 0.5%). English comprised the majority of the documents (n = 387; 91.7%), followed by Portuguese, German, and French (n = 6;

1.4%), and then Spanish and Chinese (n = 5; 1.2%), Turkish (n = 3; 0.7%), and Russian, Hungarian, and Czech (n = 2; 0.5%), with Japanese (n = 1; 0.2%) trailing in popularity. In contrast, the United States is the nation with the most publications (n = 94; 22.2%), followed by India (n = 73; 17.2%), the United Kingdom and South Africa (n = 40; 9.4%), and China (n = 33; 7.8%). Table 1 and Figure 4 indicate that the USA (n = 23) had the highest number of international collaborations, succeeded by the UK (n = 17), South Africa (n = 14), and Brazil (n = 12). The United States is a nation that takes a leading role in the case of global health. The United States has significant funds and resources dedicated to TB research, including organizations such as the National Institutes of Health and the Centers for Disease Control and Prevention. This resource supports extensive research on co-infection with TB [30].

India and China are also active in making publications related to TB co-infection, which has also triggered high cases of TB in India and China, and even India is the country with the highest TB cases in the world, followed by Indonesia and China [2]. UK and South Africa are also countries that are actively publicizing in the field of TB co-infection. Two of the ten universities with the most publications on TB co-infection are located in the United Kingdom. Similarly, South Africa is home to 4 of the 10 universities with the most publications related to TB co-infection (Table 2). This is because South Africa has one of the highest rates of TB coinfection in the world, with

Table 1. The involvement and collaboration of the 10 leading nations globally in the publication of tuberculosis co-infection with microorganisms from 1996 to 2024.

SCR[a]	Country	Number of doc	Number of collaboration[b]
1	United States	94	23
2	India	73	9
3	United Kingdom	40	17
4	South Africa	40	14
5	China	33	6
6	Brazil	23	12
7	Germany	17	8
8	France	16	8
9	Iran	13	1
10	Uganda	12	5

[a]SCR = Standard competition ranking. [b]Number of collaborating countries with a minimum threshold of 20 documents.

Table 2. The most productive institutions in publications related to Tb co-infection with microorganism.

No	Affiliation	Number
1	University of KwaZulu-Natal	12 (2,8%)
2	South African Medical Research Council	10 (2,4%)
3	London School of Hygiene &Tropical Medicine	10 (2,4%)
4	Makerere University	9 (2,1%)
5	Makerere University College of Health Sciences	9 (2,1%)
6	University of Cape Town	8 (1,9%)
7	Fudan University	8 (1,9%)
8	University of the Witwatersrand, Johannesburg	8 (1,9%)
9	University of Pretoria	8 (1,9%)
10	University College London	8 (1,9%)

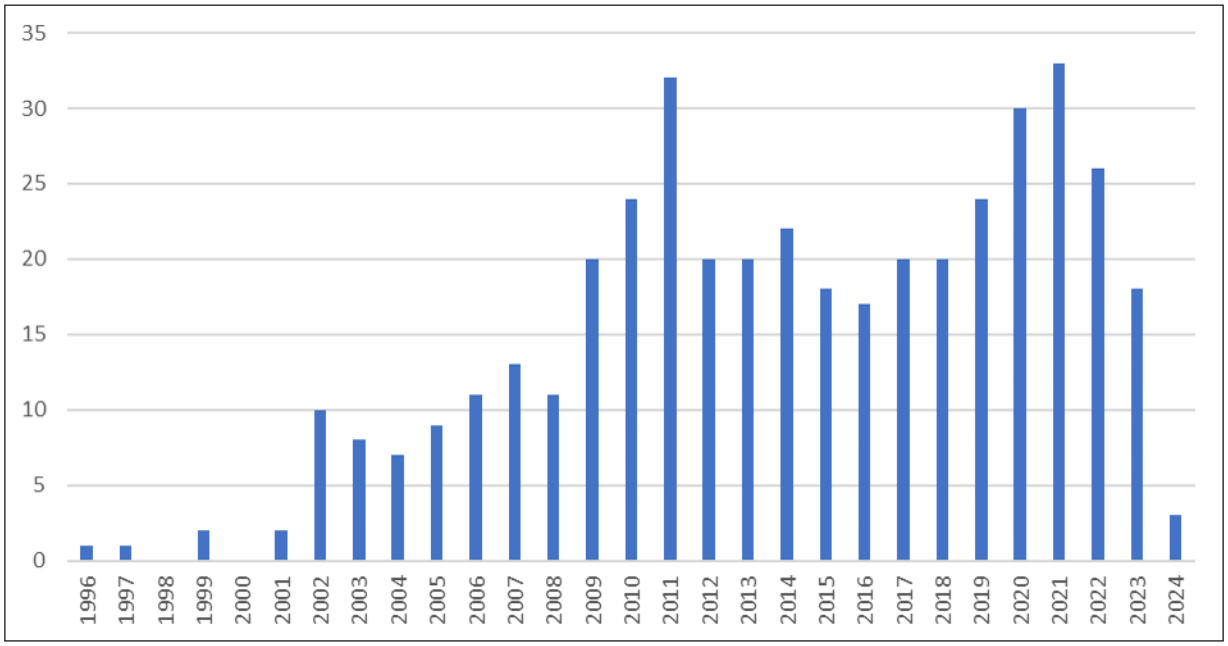

Figure 4. A summary of research articles regarding TB co-infection with microorganisms from 1996 to 2024. A total of 422 papers were retrieved from the Scopus database. Since 2002, research on tuberculosis co-infection with microorganisms has become increasingly prolific, with the highest volume of publications occurring between 2011 and 2021.

Table 3. The highest article citation on TB co-infection.

No	Doc title	Authors	Source	Year	Citation	Doc type
1	Tuberculosis and COVID-19 Interaction: a review of biological, clinical, and public health effects	Visca, D., Ong, C.W.M., Tiberi, S., Migliori, G.B., Goletti, D.	Pulmonology, 27 (2), pp. 151-165	2021	181	review
2	Impact of HIV-1 co-infection on presentation and hospital-related	Jeena, P.M, Pillay, P., pillay, T., Coovadia, H.M	International Journal of Tuberculosis and Lung Disease, 6 (8), pp. 672-678	2002	129	article
3	Novel isatinyl thiosemicarbazones derivatives as potential molecule to combat HIV-TB co-infection	Banerjee, D., Yogeeswari, P., Bhat, P., Srividya, M., Sriram, D.	European Journal of Medicinal Chemistry, 46(1), pp. 106–121	2011	120	article
4	Tuberculosis and HIV co-infection in children	Venturini, E., Turkova, A., Chiappini, E., de Martino, M., Thorne, C.	BMC Infectious Diseases, 14, S5	2014	119	review
5	Dynamics of co-infection with *M. tuberculosis* and HIV-1	Kirschner, D.	Theoretical Population Biology, 55(1), pp. 94–109	1999	94	article

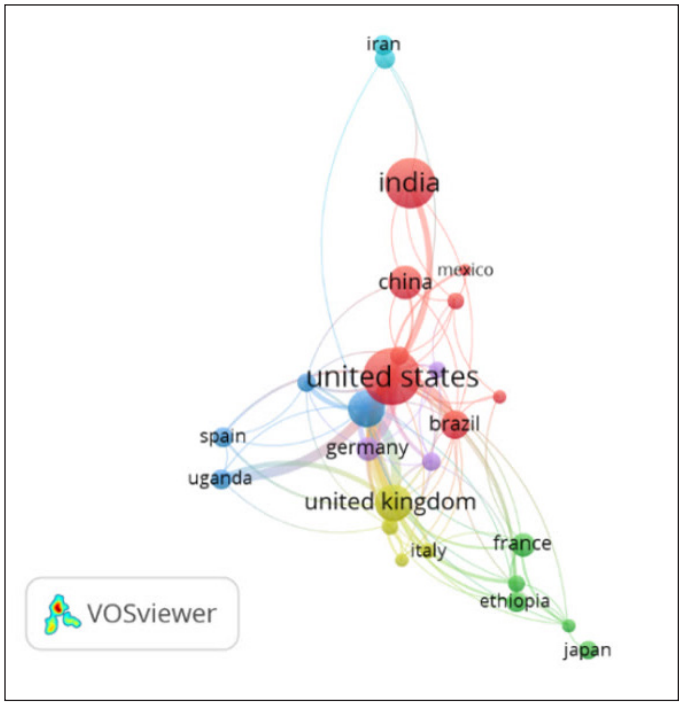

Figure 5. Collaboration in mapping countries. Among the 27 countries, 6 published a minimum of 20 papers. The circle's dimensions correlate with the number of foreign partnerships.

approximately 60% of HIV patients being co-infected with TB. The South African Tuberculosis Vaccine Initiative and the Centre for the AIDS Programme of Research in South Africa are two examples of the country's well-established research infrastructure. These organizations produce a significant amount of papers and carry out in-depth research on the co-infection of HIV and TB (Table 1, Fig. 5) [31].

Using VOSviewer, the phrases are extracted and then categorized into color gradients ranging from blue to yellow, which correspond to the publishing year (Fig. 6). Early publications on TB co-infection were made by the US, Brazil, Belgium, and Mexico. Other nations, including India, Japan, and Canada then followed after. South Africa, the United Kingdom, Uganda, and Germany followed next. Recently, the latest research has been published by the following countries: China, Ethiopia, Italy, and Spain. China is a country with a fairly high burden of TB cases. For example, in the province of Hubei, TB outbreaks during the pandemic, highlighting the challenge of managing TB cases in the midst of COVID-19 responses. This obviously increases researchers' interest in co-infecting TB with COVID-19. The study includes studies related to the clinical impact, detection, and characteristics of tuberculosis patients coinfected with COVID-19 [32–35]. Higher rates of mortality are linked to co-infections with SARS-CoV-2 and tuberculosis. In patients who tested positive for both TB and COVID-19, a global investigation found an 11% mortality rate, which is substantially higher than the anticipated mortality rates for COVID-19 without others. Additionally, according to reports from South Africa, patients with co-infections have a twice as great chance for fatalities in comparison to those with *M. tuberculosis* mono-infections [17]. A retrospective study conducted in Indonesia found that co-infection with SARS-CoV-2 and tuberculosis was linked to increased clinical severity and mortality. Serum hemoglobin levels and the number of co-morbidities were related to severity; 54 (0.7%) of 7,786 suspected TB patients had co-infection between TB and SARS-CoV-2, with 35 having rifampicin-sensitive TB and 19 having rifampicin-resistant TB, according to the study [36].

Table 3 presents the articles with the most citations for TB co-infection, together with the five most often cited articles in the Scopus database. The paper with the most citations has been published in Pulmonology, with a citation count of 181. A large number of studies define the clinical characteristics of TB-HIV co-infection and the dynamics associated with this co-infection. Additionally, it provides a resource and showcases significant improvements in the field of TB co-infection research (Table 3).

Four distinct clusters, represented by the colors red, blue, yellow, and green (Fig. 7a). Cluster 1 (red color) includes

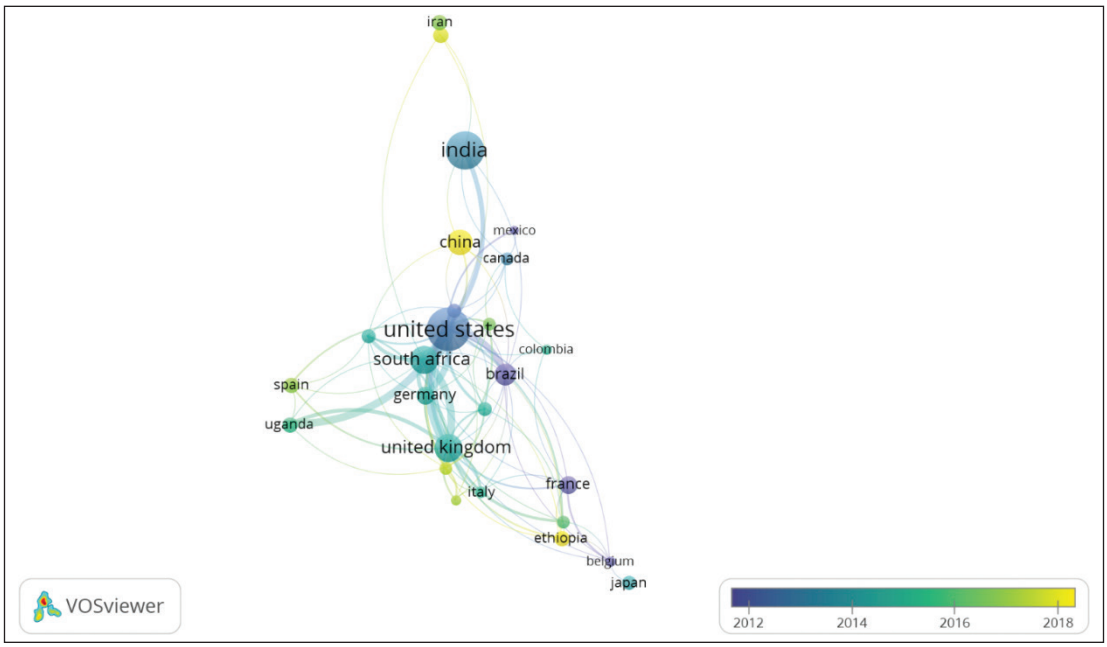

Figure 6. Mapping of nations having ongoing publications regarding tuberculosis co-infection pathogens. Blue signifies older publications, whereas yellow denotes more current ones.

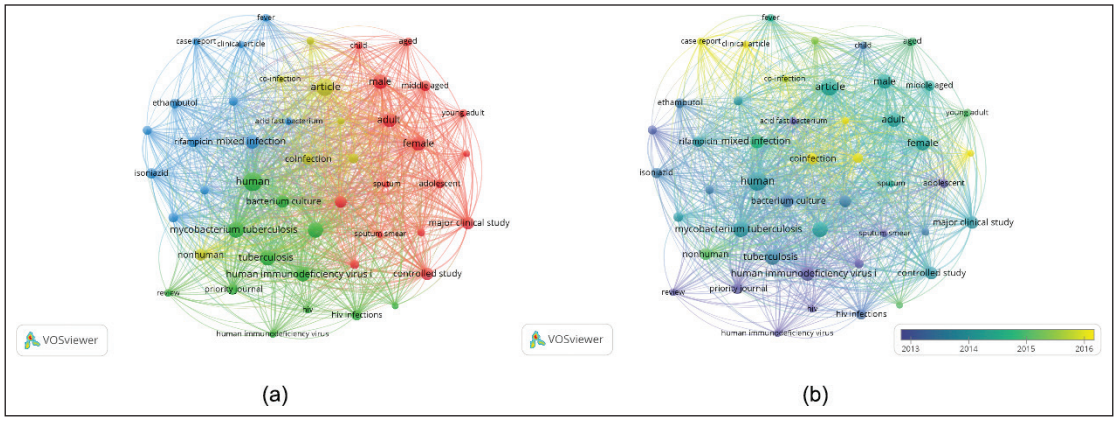

Figure 7. Clustering of occurrence terms from VOSviewer derived from the abstracts and titles of research publications on tuberculosis co-infection with microorganisms. (a) Network visualization. (b) Overlay visualization.

terms such as child, adult, male, female, and sputum smear; cluster 2 (green color) includes human, bacterium culture, *M. tuberculosis,* tuberculosis, HIV, and HIV infection; cluster 3 (yellow color) includes article and co-infection; and cluster 4 (blue color) includes mycobacterium, enthambutol, isoniazid, and mixed infection classification. VOSviewer classifies the extracted phrases using a color gradient from blue to yellow, indicating publication years from old to new. The initial investigations on TB co-infection with microorganisms elucidated several crucial words, including sputum smear, HIV, acid fast bacterium, bacterium culture, and tuberculosis. Lately, emerging issues include co-infection and multiple infections (Fig. 7b). Initiation research related to TB co-infection is loaded with TB outbreak, TB identification, diagnosis, treatment, as well as clinical characteristics of patients [2,32,37–42]. Identification of tuberculosis co-infection microorganisms is important to support appropriate treatment for the patient, due to the mixed infection impact that can increase the severity of the patient's disease [3,5,6–8,12,17,24,28,29,31,43,44]. Future research developments can focus on epidemiological studies and advanced diagnostic technologies and also focus on therapeutic management of combined infections due to exposure to bacteria and viruses, for example, in co-infections with HIV and SARS-CoV-2 is critical, given the increased severity and complexity of these infections [45–48].

CONCLUSION

This bibliometric analysis examines boundaries and identifies emerging trends in the field of tuberculosis co-infection with microorganisms over the previous 29 years. The analysis demonstrates that in terms of publications, citations, funding sources, and international collaborations, the United States is at the leading edge of this field of study. The university that contributes the most to this field and has produced the most

articles is KwaZulu-Natal University. It was evident from the network of co-cited reference clusters and keywords that co-infection is a popular issue in studies. It also suggests that the co-infection of tuberculosis with microorganisms will be a crucial topic in establishing the precise diagnosis so that patients are provided effective treatment. However, bibliometric evaluation is generally more objective than conventional evaluations, and it nevertheless possesses many unavoidable limits. Initially, we exclusively incorporated the articles from the Scopus database. In addition, some new research will emerge as this study was taken until June 2024.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

CONFLICT OF INTEREST

The authors reports no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

PUBLISHER'S NOTE

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USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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