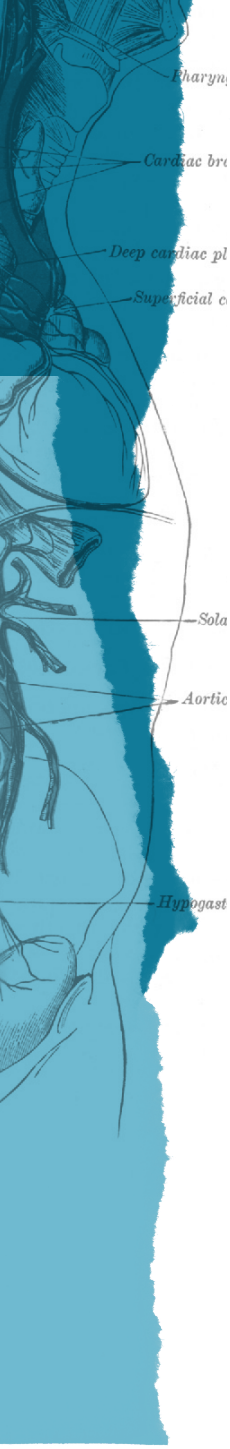

Fecha de recepción: 17 de octubre de 2023
Fecha de aceptación: 15 de febrero de 2024

REVISIÓN SISTEMÁTICA

https://dx.doi.org/10.14482/sun.40.03.070.484

Long-term Effect of Laryngeal Tuberculosis on the Voice: A Systematic Review

Efecto a largo plazo de la tuberculosis laríngea en la voz: Una revisión sistemática

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ABSTRACT

Objective: This systematic review aims to describe the long-term effects of laryngeal tuberculosis on the adult voice.

Materials and methods: The review followed the PRISMA statement guidelines and utilized the PIO model for database selection. The quality of evidence was assessed, and recommendations were graded using the GRADE system.

Results: The review identified 36 articles meeting the inclusion criteria through keyword searches in the DECS and MESH databases. Laryngeal tuberculosis (LTB) was found to have significant long-term effects on the voice, as the larynx plays a crucial role in sound production and vocal quality. Even after the disease has been treated and cured, voice changes and alterations may persist. The vocal folds were the most affected and frequently mentioned structure leading to changes in voice quality and functionality. Dysphonia emerged as the primary effect of LTB, attributed to alterations in the flexibility and oscillatory function of the vocal folds for voice production.

Conclusions: Laryngeal tuberculosis has a lasting impact on the adult voice, primarily affecting the vocal folds and resulting in dysphonia. These findings underscore the importance of early diagnosis and appropriate management to mitigate long-term voice-related consequences in individuals with LTB.

Keywords: Laryngeal tuberculosis, long-term effect, voice, voice disorders, dysphonia.

RESUMEN

Objetivo: Esta revisión sistemática tiene como objetivo describir los efectos a largo plazo de la tuberculosis laríngea en la voz de los adultos.

Materiales y métodos: Esta revisión se realizó siguiendo la declaración PRISMA, identificando las bases de datos con los criterios de inclusión. Se utilizó el modelo PIO y la clasificación de la calidad de la evidencia y la graduación de la fuerza de la recomendación se realizó mediante el sistema GRADE.

Resultados: La búsqueda se realizó en las bases de datos, según los cruces de variables construidos a partir de las palabras clave DECS y MESH. Seguidamente, se aplicaron los filtros, para la obtención de 36 artículos como muestra final, los cuales se utilizaron en esta investigación. La LTB puede tener efectos significativos a largo plazo, ya que la laringe es una herramienta fundamental para la producción del sonido y la calidad vocal, y si se llega ver afectada por la TB, puede haber cambios y alteraciones en la voz que perduran incluso después de que la enfermedad haya sido tratada y curada.

Conclusiones: La estructura más afectada y más mencionada son las cuerdas vocales, que puede provocar alteraciones en la calidad y funcionalidad de la voz. La disfonía es el principal efecto des-

encadenado por el LTB, ya que los pliegues vocales presentan alteraciones en su flexibilidad y en su función oscilatoria para la producción de la voz.

Palabras clave: Tuberculosis laríngea, efecto a largo plazo, voz, trastornos de la voz, disfonía.

INTRODUCTION

Tuberculosis (TB) is a chronic infectious disease, caused by a mycobacterium, mainly affecting the lungs and consequent extrapulmonary involvement, such as the larynx (1) (2). Incidentally, laryngeal tuberculosis (LTB) can become the first clinical manifestation of pulmonary tuberculosis (1) (2) (3). At present, LTB is an uncommon manifestation of TB, being the most frequent disease that affects the larynx, which represents 1% of the cases (4) (5) (6), due to the fact that there are no concrete characteristics of this disease (7), since the clinical models are constantly changing (8) (9) (10) because this disease can be located both in the posterior larynx (arytenoid cartilage) and, more frequently, in the anterior part of the larynx (vocal folds and epiglottis), therefore, making it difficult to diagnose and even to the point of being confused with other diseases, such as fungal laryngitis, syphilis, Wegener's granulomatisis, and sarcoidosis (8) (9) (11) (12) (13).

All cases of LTB can have major epidemiological consequences (14), if not detected in time, as it is considered a highly contagious disease (15). According to WHO, TB has been declared a global epidemiological emergency, since a large part of the world's population is exposed to contact with the mycobacterium, where 1 in 10 people may develop this disease at some point in their lives (16) (17). LTB has been one of the most common and prevalent health problems, although, in recent years, (18) the number of TB cases has been reduced, however, the decrease has not been as significant (19). According to WHO, by mid-2021, 1.6 million people died from this disease (20) (8). TB in China averages 0.0036%, equivalent to 4.5 million patients with active pulmonary TB and 1.5 million new infections per year (21) (22), followed by Russia, with an average of 0.3-1.4% (23) (24) (25). According to studies, men are four times more likely to be affected than women (21) (26), with the vocal folds being the main site with the greatest lesion, as they are the oscillatory mechanism for producing the voice (22).

LTB involvement (27) can develop most frequently through bronchogenic (28), hematogenous or lymphatic spread of lung disease, on the other hand, it can also develop through direct invasion

of the larynx by inhalation (9) (22) (29). LTB infection (30) can cause irreversible changes in the vocal folds, together with alterations in the epiglottis, anterior and posterior commissure, vestibular and aryepiglottic folds, causing dysphonia as the main effect (4) (31). On the other hand, effects such as hoarseness, cough, dysphagia, and odynophagia and weight loss are also reflected (1) (2) (26) (20). Furthermore, LTB is divided into four categories of videolaryngoscopic appearances (32), being mainly the granulomatous lesion, followed by ulcerative, erosive, and non-specific inflammatory lesions (6) (33) (34). LTB can be difficult to treat, especially in advanced cases, and may require surgery or prolonged drug treatment (20) (35). If the person is misdiagnosed (36), LTB can have serious consequences for the patient and the person with whom he or she is in contact (9) (37).

In addition, LTB (38) can have a significant impact on a person's quality of life, as it can cause dysphonia, difficulty swallowing and breathing (39), and LTB can leave long-term sequelae, negatively affecting the process of restoring voice quality (31). Considering the arguments and findings previously revealed the following research question arises: What is the long-term effect of laryngeal tuberculosis on the adult voice?

METHOD

The research methodology is descriptive in which the inquiry, collection, organization, and analysis of the scientific information established in a time window of 10 years, where it is developed taking into account the parameters of the PRISMA statement supported by the authors Brian Huttona, Ferrán Catalá-Lópeza, David Moher (40), a tool that allowed the systematic review of the scientific literature from the identification of databases, search, and selection of research articles on LTB and its long-term effects on the voice (41). The studies were selected based on inclusion and exclusion criteria that facilitate the evaluation of the quality and reliability of the studies and eventually allow answering the research question (42) (43).

The PIO model was used to construct the research question; however, the comparison section was not applied (44) (45). This tool is used because it serves to improve the specificity and conceptual clarity of the clinical problems to be studied, as well as to perform searches with greater quality and precision, which allows for the collection of pertinent and precise data to answer the problem question (46) (47).

The classification of the quality of evidence and grading of the strength of recommendation was performed through the GRADE pro GDT system (48).

Research Question

According to the thematic established for the research, the components of the PIO model shown in table 1 were used, resulting in the following research question: What is the long-term effect of laryngeal tuberculosis on voice quality in adults?

Table 1. Research Question

Component	Description
P: Patient or problem of interest (Population)	Adults with laryngeal tuberculosis
I: Intervention	Voice disorders
C: Comparison	-
O: Result	Long-term effects, time.

Source: own elaboration.

Inclusion and Exclusion Criteria

Table 2. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Subject: Articles focused on laryngeal tuberculosis. Population: Studies in adult humans. Design: Observational studies (cohort, case-control, cross-sectional) or clinical trials. Objective: To evaluate the long-term effect (more than 5 years) of laryngeal tuberculosis on voice. Language: English or Spanish. Date of publication: Articles published in the last 10 years (2013 - 2023). Type of publication: Original scientific articles.	Subject: Articles focused on pulmonary tuberculosis, extrapulmonary (except laryngeal) or without specification of location. Population: Studies in animals, children or adolescents. Design: Review studies, meta-analyses, case studies, case series, editorials, letters to the editor. Objective: Studies that do not evaluate the effect of laryngeal tuberculosis on the voice. Language: Languages other than English or Spanish. Publication date: Articles published before 2013 or after 2023. Type of publication: Books, blogs, websites, conference abstracts, theses.

Source: own elaboration.

The present systematic review employed a comprehensive search strategy that combined key terms from the Descriptors in the Health Sciences (DECS) and Medical Subject Headings (MESH). This strategy made it possible to identify and select literature relevant to the study topic, as detailed in table 3.

Tabla 3. Descriptores DECS y MESH

Source	Keyword	Related Terms
DECS MESH	Time	Effects, Long-Term, Long-Term Effects
DECS MESH	Tuberculosis, Laryngeal	No records found
DECS MESH	Vocal Cords	Vocal Fold, Vocal Ligament
DECS MESH	Laryngeal mucosa	Laryngeal Epithelium
DECS MESH	Larynx	No records found
DECS MESH	Voz Voice	Phonation, Speech
DECS MESH	Phonation	Speech, Voice, Voice Quality
DECS MESH	Voice Disorders	Voice Disorder, Neurologic, Voice Disturbance, Voice Fatigue
DECS MESH	Dysphonia	Phonation Disorders, Vocal Cord Dysfunction

Source: Information obtained from DECS and MESH.

Search Strategies

To carry out an exhaustive and precise search, a search strategy was designed using equations formed by key terms. These equations were constructed with the help of logical operators such as AND/OR and symbols such as "" and (). This search strategy was applied in several scientific and academic journal databases as well as open access repositories, all in English. For more details (see table 4).

Sources of Information

The information sources used in this systematic review were classified into two categories:

- Scientific and academic journal databases: PubMed, Springer Link, Taylor & Francis, Scopus, and ScienceDirect.
- Open access repositories: Scielo, Redalyc and Dialnet.

Table 4. Search for equations

Source	Search Algorithm
Scientific and Academic Journal Databases: PubMed, Springer Link, Taylor & Francis, Scopus and ScienceDirect. Open access repositories: Scielo, Redalyc and Dialnet.	Primary search: ("Laryngeal tuberculosis" OR "Tuberculosis" AND "Larynx") AND ("Voice disorders" OR "Dysphonia" OR "Phonation"). Secondary searches: ("Laryngeal tuberculosis" OR "Tuberculosis" AND "Larynx") AND ("Long term effect" OR "Time") 3. 3. ("Laryngeal tuberculosis" OR "Tuberculosis" AND "Larynx") AND "Vocal cords" AND "Vocal cords". 4. ("Laryngeal Tuberculosis" OR "Tuberculosis" AND "Larynx") AND "Laryngeal Mucosa" AND "Laryngeal Mucosa" AND "Laryngeal Mucosa". ("Tuberculosis" OR "Tisis") AND ("Larynx") AND ("Laryngeal")

Source: own elaboration.

Characteristics of the Studies

In the initial phase, studies were classified considering inclusion and exclusion criteria. Priority was given to those studies that focused on laryngeal tuberculosis and its effects on the voice, as reflected in their titles. Subsequently, selected studies were reviewed to ensure that they aligned with the target population of this review, i.e., adults with laryngeal tuberculosis. Studies involving children and adolescents were excluded to maintain focus on the research topic.

Selection and Analysis

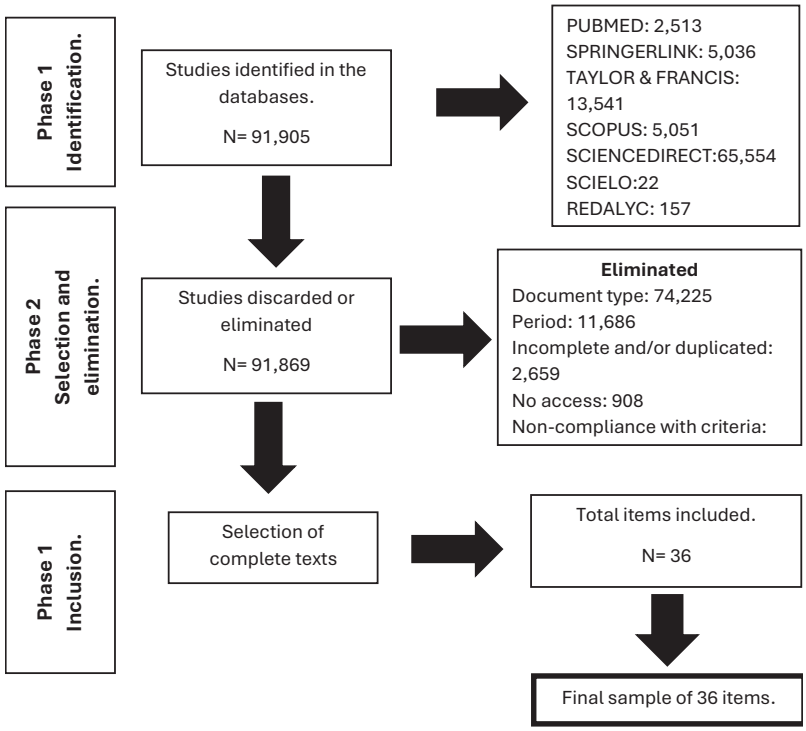
A preliminary selection of studies was made based on review of inclusion criteria, population characteristics, study type, and year of publication. An Excel registration table, designed

by the authors, was then completed independently, detailing the key elements of each of the selected studies.

The process of identification, screening, eligibility assessment, and inclusion of the articles was carried out following the structure proposed by the PRISMA statement. For the analysis, the GRADE system was used, which made it possible to evaluate aspects such as the number of studies, study design, risk of bias, inconsistency, indirect evidence, imprecision, and degree of certainty of the study (48).

RESULTS

The eligibility criteria were determined following the order established in the methodology by developing each of the phases of the PRISMA flowchart (Figure 1).



Source: own elaboration.

Figure 1. PRISMA Diagram

Identification Phase

A search was carried out in eight databases: five scientific and academic journal databases (PubMed, Springer Link, Taylor & Francis, Scopus, and ScienceDirect), and three open access repositories (Scielo, Redalyc, and Dialnet). This search was based on the cross-referencing of variables constructed from the keywords DECS and MESH in English. A total of 91905 articles were obtained. Subsequently, filters were applied for type of document, period, incomplete or duplicate texts, articles without access and non-compliance with the criteria. Finally, a final sample of thirty-six (36) articles was obtained and used in this review (see table 5).

Table 5. Filters Applied

Data Banks	Nº of found texts						
	Total, of items	Filtered					
		Type of Document	Period	Incomplete and/or Duplicated Texts	No Access	Non-compliance with Criteria	Selected Articles
Pubmed	2513	2305	122	18	13	43	12
Springer link	5036	3503	929	3	0	600	1
Taylor & francis	13541	12104	1111	8	21	295	2
Scopus	5051	617	3370	100	352	593	17
Sciencedirect	65554	55622	6084	2520	521	806	1
Scielo	22	0	15	3	0	3	1
Redalyc	157	74	45	0	0	38	0
Dialnet	31	0	10	6	0	13	2
Total	91905	74225	11686	2659	908	2391	36

Source: own elaboration.

Selection and Elimination Phase

The final selection of the research articles was made by preliminary reading of the titles, abstracts and then the introduction. This allowed the identification of the most relevant articles with respect to the topic under investigation, selecting 36 articles. The results for each variable crossing in English are listed below (see table 6) for the eight databases.

Table 6. Results of Cross-referencing Variables in English in the Databases

Crosses	Source						
	Pubmed	Springer Link	Taylor & Francis	Scopus	Sciencedirect	Scielo	Dialnet
Tuberculosis + larynx	2	0	0	12	0	0	0
Tuberculosis + larynx + Dysphonia	8	0	1	0	1	0	0
Tuberculosis laryngeal + voice disordes + dysphonia	1	0	0	0	0	0	0
Tuberculosis + Larynx + Laryngeal mucosa	1	0	1	1	0	0	0
Tuberculosis + Laryngeal Mucosa	0	1	0	0	0	0	0
Tuberculosis larynx + Vocal Cords	0	0	0	1	0	0	0
Tuberculosis + Tisis + Larynx	0	0	0	3	0	0	1
Tuberculosis + Voice + Dysphonia	0	0	0	0	0	1	0
Tuberculosis + Voice + Phonation + Dysphonia	0	0	0	0	0	0	1
Total	12	1	2	17	1	1	2

Source: own elaboration.

Within the search for the selection of articles, 9 crossings of variables in English between the different variables were used, resulting in 12 articles in PubMed, 1 article in Springer Link, 2 articles in Taylor & Francis, 17 articles in Scopus, 1 article in ScienceDirect, 1 article in Scielo and 2 articles in Dialnet, giving a total of 36 articles.

Inclusion Phase

The selection was made after reading the titles and abstracts of the articles, being analyzed in their entirety with a complete reading, applying criteria that allowed a selection, which gave an answer to the question posed. The selection corresponded to a final sample of 36 articles (see table 7).

Table 7. Selection of studies

N	Source	Title	Author	Year	URL	Contribution
1	PubMed	Laryngeal tubercolosis: a case report with focus on voice assessment and review of the literature	Andrea Migliorelli, Tomas Mazzocco, Ana Bonsembiante, Daniele Bugada, Marco Fantini, fabricarlos, Marco Stacchini	2022	(1) (accessed April 19, 2023)	Research based on a systematic review and case study, which provides information on LTB and its main symptoms in the voice and its effects in a certain period of time.
2	PubMed	Primary tuberculosis of the larynx	F el Ayoubi, yo chariba, A El Ayoubi, S Chariba, L'Essakalli	2014	(2) (accessed April 19, 2023)	Research based on a case study, providing information on the findings found by the primary LTB.
3	PubMed	Appearance and morphologic features of laryngeal tuberculosis using laryngoscopy: A retrospective cross-sectional study	jian zang, ying tian, Xuejun Jiang, Xu Yong Lin	2020	(3) (accessed April 20, 2023)	Research that provides information on the locations and morphological characteristics of LTB, for a correct diagnosis.
4	PubMed	Laryngeal and Voice Disorders in Patients with Pulmonary Tuberculosis	Gamal Yousef, Bassam Hasan Mahboub, Safinaz-Nagib Azab.	2021	(4) (accessed April 19, 2023)	Research that provides information on LTB, its main symptoms and structures affected at a given time.
5	PubMed	Head and neck tuberculosis: Literature review and meta-analysis.	Xu Qian, Andreas E Albers, Duc T M Nguyen, Yue Dong, Yuping Zhang, Frank Schreiber, Branko Sinikovic, Xiaohong Bi, Edward A Graviss	2019	(5) (accessed May 7, 2023)	Research provides information on the manifestation of extrapulmonary TB, with epidemiological and clinical characteristics.
6	PubMed	Laryngeal Tuberculosis in Pregnant Women: A Case Report and Review of the Literature	Jorge Luis Hurtado Alegre, Anita Trigoso Gutiérrez, Eduardo Matos Prado, Jorge Huaringa Marcelo	2018	(6) (accessed May 1, 2023)	Research that provides information on the case study of a pregnant woman with chronic dysphonia, and her main symptoms in the larynx, with a positive result for bacilli test.
7	Scopus	Extranodal tuberculosis of the head and neck: Our experiences at a tertiary care teaching hospital of East India	Swain, S., Mohanty, J., Sahu, M.	2020	(8) (accessed May 17, 2023)	Research that provides information on TB in the head and neck area, where it affects the larynx.

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8	Scopus	Dysphonia-the single symptom of rifampicin resistant laryngeal tuberculosis	Paulauskiene, I; Mickeviciene, V.	2016	(9) (accessed May 26, 2023)	Research that provides information on the most frequent symptoms in the larynx due to TB.
9	Scopus	Tuberculosis in the Head and Neck: Changing Trends and Age-Related Patterns	Gehrke, Thomas; Hackenberg, Stephan; Tecle, Nyat; Hagen, Rudolf; Scherzad, Agmal	2021	(10) (accessed May 15, 2023)	Research that provides information on head and neck diagnoses of the alterations caused by TB.
10	Scopus	A clinic-epidemiological study of head and neck tuberculosis — A single-center experience	Pajor, AM; Józefowicz-Korczyńska, M; Korzeniewska-Koseła, M;Kwiatkowska, S.	2016	(11) (accessed May 26, 2023)	Research that provides information on the prevalence of LTB in countries and with respect to gender.
11	Scopus	Otolaryngological Manifestations of Tuberculosis: A Clinical Study	Bokare, B., Mehta, K	2022	(12) (accessed May 26, 2023)	Research that reinforces the knowledge on TB and its different presentations and manifestations in the larynx.
12	Taylor & Francis	Interferon-γ release assay in the diagnosis of laryngeal tuberculosis	Bing Fei, Zheng Wu, Kehua Min, Jingbo Zhang, Chuanlian Ding, Hao Wu	2014	(13) (accessed May 14, 2023)	Research that provides information on the early diagnosis of LTB and its manifestations.
13	PubMed	Laryngeal tuberculosis in the United States of America: A forgotten disease	Jeana L Benwill,Juan C. Sarriá	2014	(15) (accessed May 7, 2023)	Research that provides information on the most frequent manifestations and the structures involved with LTB.
14	Dialnet	Tuberculosis laríngea sin afectacion pulmonar en un paciente joven inmonucompetente	Lucas Cristóbal Reyes Meza, Nataly Matamoros Portillo, Dorysela Reyes Meza, Doris Lastenia Enamoradochoa, Jorge Luis Guevara Barrientos	2016	(16) (accessed May 29, 2023)	Research that provides information about LTB, showing a case study with the main symptoms it can cause in the larynx and the lesions it can cause in the laryngeal structures.
15	Dialnet	Laryngeal TBC: a rare localization of tuberculosis	Joanna Veruschka Santeliz Casavilca	2021	(17) (accessed May 29, 2023)	Research that provides information about TB and the symptoms it can cause in the person and the structures it can alter.

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16	PubMed	Factors Associated with Clinical and Topographical Features of Laryngeal Tuberculosis	João Gustavo Corrêa Reis, Clarissa Souza Mota Reis, Daniel César Silva da Costa, Márcia Mendonça Lucena, Armando de Oliveira Schubach, Raquel de Vasconcellos Carvalhaes Oliveira, Valeria Cavalcanti Rolla, Fátima Conceição-Silva, Claudia María Valete Rosalino	2016	(20) (accessed on April 20, 2023)	Research based on a cross-sectional study, which identifies the factors associated with the clinical characteristics of LTB, and the main symptoms presented in patients.
17	Scopus	Primary Laryngeal Tuberculosis: A Series of 15 Cases	Agarval, R.; Gupta, L.; Singh, M.; Khurana, N.; Chaudhary, D.	2019	(21) (accessed May 23, 2023)	Research that provides information on TB with laryngeal involvement and the organs that can be affected shows the clinicopathological characteristics and the alterations that occur in the voice.
18		Secondary laryngeal tuberculosis in Tibet China: A report of six cases	Huaidong Du a 1, Guoyu Cai b 1, Sang Ge b, Wang Ci b, Liang Zhou	2017	(22) (accessed May 27, 2023)	Research that provides information on the clinical characteristics of LTB, in order to help in the detection of an accurate and timely diagnosis.
19	Scopus	Clinical case of destructive pulmonary tuberculosis combined with laryngeal tuberculosis	Naumov AG; Bokova KV; Zherebyat'eva NS; Zhukova EV; Konygina KS; Sujova OA	2019	(23) (accessed May 27, 2023)	Research that provides information on the timely detection of LTB, through the assessment of symptoms.
20	PubMed	A Case of Laryngeal Tuberculosis, Endobronchial Tuberculosis and Pulmonary Tuberculosis Coexistent in an Immunocompetent Host	Akshay Avula, Sam Ngu, Wissam Mansour, Dhineshreddy Gurala, Rabih Maroun	2020	(26) (accessed May 1, 2023)	Research that provides information on LTB in general, its main effects on the voice.
21	Scopus	Laryngeal tuberculosis mimicking malignancy: A case report	Eltilib, M., Boyd, W., Saramago, I., Asking, F., Zamora, c.	2020	(29) (accessed May 15, 2023)	Research that provides information on the symptoms caused by TB in the larynx.

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22	PubMed	Evaluation of voice disorders in patients with active laryngeal tuberculosis	Marcia Mendonça Lucena, Fernanda Dos Santos da Silva, Ananda Dutra da Costa, Gabriela Rodrigues Guimaraes, Ana Cristina Nunes Ruas, Federico Pereira Bom Braga, Mateus Pereira Bom Braga, João Gustavo Corrêa Reis, Daniel César Silva da Costa, Mariana Reuter Palmeiro, Valeria Cavalcanti Rolla, Claudia María Valete Rosalino	2015	(31) (accessed May 1, 2023)	Research that provides information on the lesions observed by LTB and its process in the voice, describing the anatomical characteristics and voice quality in patients with LTB.
23	Taylor & Francis	Case report of a laryngeal tuberculosis during pregnancy – challenges in diagnosis and management	Julian Pfäffli, Amina Nemmour, Philipp Kohler & Sandro J. Stoeckli	2023	(33) (accessed May 14, 2023)	Research that provides the laryngeal manifestations of TB, along with its treatment.
24	Springer Link	Association of laryngeal and nasopharyngeal tuberculosis: a case report	Youssef Darouassi ,Mehdi Chihani ,Abderrahim Elktaibi ,Mohamed Mliha Touati ,Karim Nadaur ,Amine Benjelloun ,Brahim Bouaity &haddu ammar	2015	(34) (accessed May 7, 2023)	Research that provides information on LTB, by means of a case report.
25	Scopus	Comparative analysis of clinical features of primary and secondary laryngeal tuberculosis	Yufeng Ai, Hongbing Liu, hong xu, Yuehui Liu, lihua li	2021	(35) (accessed May 26, 2023)	Research that provides information on a clinical picture, with its diagnosis and treatment of primary and secondary LTB.
26	Scopus	Laryngeal tuberculosis: A rare cause of critical airway obstruction	Cole, AE; Heaton, D; Chekairi, A.	2018	(39) (accessed May 24, 2023)	Research that provides information on LTB, from the means of spread, what area is affected and what symptoms occur in the voice.

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27	PubMed	Clinical study of tuberculosis in the head and neck region-11 years' experience and a review of the literature	Pai pang,Weiyi Duan,shuchun liu,Shuangbai,Yanan Ma,ruiwu li,fayu liu&Sol de Changfu	2018	(50) (accessed April 19, 2023)	Research based on a systematic review and case study, providing information on the main symptoms and the most common site of LTB.
28	PubMed	Isolated laryngeal tuberculosis as an uncommon manifestation of extrapulmonary tuberculosis in adults: a case report	Imen Mariem Abbassi, Mounira El Euch, Fatima Jaziri, Asma Kefi, Fethi Ben Hamida, Sami Turki, Khaoula Ben Abdelghani, Taieb Ben Abdallah	2022	(51) (accessed May 1, 2023)	Case study research, providing information on the most frequent cause of laryngeal and TB, and effect on the voice with its duration time.
29	Scopus	Tuberculous Abscesses in the Head and Neck Region	Landegger, Lukas D	2022	(52) (accessed May 14, 2023)	Research that provides information on the conditions caused by TB in the head and neck region.
30	Scopus	Laryngeal tuberculosis: A report of two cases	Alzafer, S., Üstun, C.	2020	(53) (accessed May 23, 2023)	Research that provides information on LTB and its treatment and diagnosis.
31	Scopus	Hoarseness of voice as a rare presentation of tuberculosis: A case report study	Felemban, Taher; Ashi, Abdalá; Sindi, Abdalá; Rayab, Mohannad; Al Jehani, Zuhair.	2019	(54) (accessed May 23, 2023)	Research that provides case study information on a case with LTB and the symptoms presented by the person and findings.
32	Scopus	Laryngeal tuberculosis mimicking laryngeal carcinoma on F-FDG PET/CT imaging	Cengiz, A; Göksel, S; Başal, Y; Döğer, F; Yürekli, Y.	2018	(55) (accessed May 24, 2023)	Research providing information on a presentation of TB in the larynx.
33	Scopus	Laryngeal tuberculosis diagnosed by stool sample cultures: A case report	Yin, N; Delord, M; Giovanni, A; Brouqui, P; Lagier, J.-C.	2015	(56) (accessed May 26, 2023)	Case study research providing information on LTB and its detection for accurate diagnosis.
34	Scopus	Diagnosis of laryngeal tuberculosis in a high TB burden area	Matimba, A. , Moncho, M. , Musoke, J. , Seedat, RY	2020	(57) (accessed May 27, 2023)	Research providing information on extrapulmonary TB with laryngeal involvement, on the lesions caused by LTB in the structures of the larynx.

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35	Scopus	Primary Laryngeal Tuberculosis: Our Experiences at a Tertiary Care Teaching Hospital in Eastern India	Swain, S.K., Behera, I.C., Sahu, M.C.	2019	(58) (accessed May 27, 2023)	Research that provides information on primary LTB, such as the structures it affects, and what symptoms are triggered and their treatment.
36	Scielo	Diagnóstico patológico y molecular de un caso de tuberculosis laríngea primaria en un médico	Jurado, Leonardo F; Palacios, Diana M; Álvarez, Johanna; Baldión, Margarita; Campos, Guillermo	2014	(59) (accessed May 28, 2023)	Research that provides information on primary LTB and its clinical manifestations, discussing diagnoses and associated risk factors.

Source: own elaboration.

Table 8. Characterization of Laryngeal Tuberculosis according to Lesion Type

Injury	Structure	Duration
Lesion in the vocal folds (31) (8) (22)	Larynx	No specification
Lesion in the vestibular folds (31) (8) (22)		No specification
Epiglottis injury (31) (8)		No specification
Lesion in the arytenoid folds (31)		No specification
Lesion in the interarytenoid region (31) (22)		No specification
Lesion in the arytenoid region (31) (8)		No specification
Multiple injuries (50)		10 months (50)
Epithelioid cell granulomas (21)		Ranges from 1 to 18 months (21)
Chronic granulomatous inflammation (3)		No specification
Pale edema (13)	Vocal folds	No specification
Superficial ulcers (13)		No specification
Ulceroproliferative lesion (21)	Right vocal fold	1 a 2 months (21)
Exophytic lesion (21)		
Moderate Reinke's edema (1)		No specification
Mild inflammatory nonspecific exophytic lesions (4) (3)	Left vocal fold	15 days to 8 months (4)
Epithelial lesion (59)		No specification
Similar appearance of a hyperplastic tumor. (1)		No specification
Ulcerative lesion (56)		3 months (56)
Ulceroproliferative lesion (21) (3)	Vestibular folds (2) (21) (3) (57)	12 months (21)
Granuloma (2) (57) (20)		No specification

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Granular tumors (2)	Anterior commissure (2) (21)	No specification
Exophytic lesion (21)		1 month (21)
Exophytic lesion (21)	Epiglottis (21) (3) (26) (54)	8 a 18 months (21)
Ulceroproliferative lesion (21) (3)		8 months (21)
Edematous mucosa (26)		No specification (26)
Glottic mass (54)		4 months (54)
Pale edema (3)	Arytenoid region (3) (54)	No specification
Glottic mass (54)		4 months (54)
Ulcerous mass (15)	Left arytenoepiglottic folds (15)	1 month (15)

Source: own elaboration.

Table 9. Characterization of laryngeal tuberculosis according to function

Effect	Function	Duration
Dysphonia (26)	Tense, asthenic, raspy and cracked voice (4)	1 a 8 months (4) (26)
Hoarseness (26)	Voice change (21)	1 a 18 months (21)
Cough (26) (11)	No specification	1 month (15)
Stiffness	Alteration in flexibility, loss of voice (4)	1 a 8 months (4)
Pain	No specification	Present more than 3 months (29)

Source: own elaboration.

We analyzed the outcomes of the effects of LTB on the voice (see table 10), such as dysphonia, in which 7 studies were included with low certainty, 3 studies of hoarseness were included with low certainty, 5 studies of granulomas were included with low certainty, 3 studies of ulcerative lesions were included with low certainty, 3 studies of exophytic lesions were included with low certainty, 2 studies of sore throat were included with low certainty, 1 study of exophytic lesions was included with low certainty, 3 studies with ulcerative lesions with low certainty, 3 studies with exophytic lesions with low certainty, 2 studies with sore throat with low certainty, 1 study with glottic mass with low certainty, and, finally, 1 study with cough with low certainty.

Table 10. Rating of the quality of the evidence

Certainty assessment							N° of patients		Effect		Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations		Laryngeal tuberculosis	Relative (95% CI)	Absolute (95% CI)		
Dysphonia (follow-up: median 12 months; evaluated with: Jitter and Shimmer) (1)												
1	observational studies	not serious	not serious	not serious	not serious	None	1/1 (100.0%)	-	-	-	⊕⊕◯◯ Very Low	
Dysphonia (follow-up: median 18 months; evaluated with: Jitter y Shimmer) (4)												
35	observational studies	not serious	not serious	not serious	not serious	None	35/35 (100.0%)	-	-	-	⊕⊕◯◯ Very Low	
Epithelioid cell granulomas (follow-up: median 9 months; evaluated by histopathological examination) (21)												
15	observational studies	not serious	not serious	not serious	not serious	None	9/15 (60.0%)	-	-	-	⊕⊕◯◯ Very Low	
Ulceroproliferative lesion (follow-up: median 2 months; evaluated with: laryngoscopy) (21)												
15	observational studies	not serious	not serious	not serious	not serious	None	10/15 (66.7%)	-	-	-	⊕⊕◯◯ Very Low	
Exophytic growth (follow-up: median 9 months; evaluated with: Laryngoscopy) (21)												
15	observational studies	not serious	not serious	not serious	not serious	None	5/10 (50.0%)	-	-	-	⊕⊕◯◯ Very Low	
Granulomatous tumor lesions (follow-up: median 8 months; evaluated with: Laryngoscopy) (4)												
35	observational studies	not serious	not serious	not serious	not serious	None	7/35 (20.0%)	-	-	-	⊕⊕◯◯ Very Low	
Nonspecific mild inflammatory exophytic lesions (follow-up: median 8 months; evaluated with: Laryngoscopy) (4)												
35	observational studies	not serious	not serious	not serious	not serious	None	4/35 (11.4%)	-	-	-	⊕⊕◯◯ Very Low	
Ulcerated lesion (follow-up: median 3 months; evaluated with: Laryngoscopy) (56)												
1	observational studies	not serious	not serious	not serious	not serious	None	1/1 (100.0%)	-	-	-	⊕⊕◯◯ Very Low	
Glottic mass (follow-up: median 4 months; evaluated with: Laryngoscopy) (54)												
1	observational studies	not serious	not serious	not serious	not serious	None	1/1 (100.0%)	-	-	-	⊕⊕◯◯ Very Low	
Exophytic lesion (follow-up: median 1 months; evaluated with: Laryngoscopy) (15)												
127	observational studies	not serious	not serious	not serious	not serious	None	88/127 (69.3%)	-	-	-	⊕⊕◯◯ Very Low	
Hoarseness (follow-up: median 1 month) (34)												
1	observational studies	not serious	not serious	not serious	not serious	none	1/1 (100.0%)	-	-	-	⊕⊕◯◯ Very Low	
Cough (follow-up: median 5 months) (33)												
1	observational studies	not serious	not serious	not serious	not serious	None	1/1 (100.0%)	-	-	-	⊕⊕◯◯ Very Low	
Granulomas (evaluated with : Laryngoscopy) (57)												
80	observational studies	not serious	not serious	not serious	not serious	None	80/80 (100.0%)	-	-	-	⊕⊕◯◯ Very Low	
Dysphonia (follow-up: median 6 months) (59)												
1	observational studies	not serious	not serious	not serious	not serious	None	1/1 (100.0%)	-	-	-	⊕⊕◯◯ Very Low	

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Dysphonia (follow-up: median 12 months) (9)												
1	observational studies	not serious	not serious	not serious	not serious	None	1/1 (100.0%)	-	-	-	⊕⊕◯◯ Very Low	
Dysphonia (evaluated with: Jitter and Shimmer) (31)												
24	observational studies	not serious	not serious	not serious	not serious	None	24/24 (100.0%)	-	-	-	⊕⊕◯◯ Very Low	
Ulcers (evaluated with : Laryngoscopy) (8)												
11	observational studies	not serious	not serious	not serious	not serious	None	11/11 (100.0%)	-	-	-	⊕⊕◯◯ Very Low	
Pain (13)												
83	observational studies	not serious	not serious	not serious	not serious	None	38/83 (45.8%)	-	-	-	⊕⊕◯◯ Very Low	
Dysphonia (51)												
1	observational studies	not serious	not serious	not serious	not serious	None	1/1 (100.0%)	-	-	-	⊕⊕◯◯ Very Low	
Granuloma (follow-up: median 1 months; evaluated with: Nasofibroscopy) (58)												
1	observational studies	not serious	not serious	not serious	not serious	None	1/1 (100.0%)	-	-	-	⊕⊕◯◯ Very Low	
Hoarseness (follow-up: median 5 months) (16)												
1	observational studies	not serious	not serious	not serious	not serious	None	1/1 (100.0%)	-	-	-	⊕⊕◯◯ Very Low	
Hoarseness (follow-up: median 3 months) (53)												
1	observational studies	not serious	not serious	not serious	not serious	None	1/1 (100.0%)	-	-	-	⊕⊕◯◯ Very Low	
Hoarseness (29)												
1	observational studies	not serious	not serious	not serious	not serious	None	1/1 (100.0%)	-	-	-	⊕⊕◯◯ Very Low	
Hoarseness (follow-up: median 12 months) (55)												
6	observational studies	not serious	not serious	not serious	not serious	None	6/6 (100.0%)	-	-	-	⊕⊕◯◯ Very Low	
Granular tumors (evaluated with: Laryngoscopy) (22)												
10	observational studies	not serious	not serious	not serious	not serious	None	10/10 (100.0%)	-	-	-	⊕⊕◯◯ Very Low	
Pany (2)												
1	observational studies	not serious	not serious	not serious	not serious	None	1/1 (100.0%)	-	-	-	⊕⊕◯◯ Very Low	
Granulomatous lesion (evaluated with: Laryngoscopy) (23)												
1	observational studies	not serious	not serious	not serious	not serious	None	1/1 (100.0%)	-	-	-	⊕⊕◯◯ Very Low	
Dysphonia (follow-up: median 5 months) (20)												
57	observational studies	not serious	not serious	not serious	not serious	None	57/57 (100.0%)	-	-	-	⊕⊕◯◯ Very Low	

Source: own elaboration.

ANALYSIS AND DISCUSSION

TBL is a specific form of TB that affects the upper respiratory tract, specifically the larynx; it is an infectious disease caused by the bacterium Mycobacterium tuberculosis, which is transmitted mainly through the air when an infected person coughs, sneezes, or speaks (1) (3) (12). Normally, this disease can be seen in people without the Bacillus Calmette-Guerin vaccine, who are malnourished, or in patients with AIDS, low immunity or chronic smoking (8). The main factors of LTB are alcohol abuse and smoking (8). Previously, LTB had a great decrease of cases, favoring the quality of people's voice, thanks to ant tuberculosis drugs and prevention programs worldwide (9). On the other hand, this disease used to affect young adults between 20 and 30 years of age and without distinction of gender, but, currently, according to studies, its prevalence lies in people between 40 and 60 years of age and can affect four times more middle-aged men than women (21) (26) (57).

However, in spite of everything, LTB is still considered an uncommon manifestation of TB, as it is rarely taken into account, since the clinical signs of LTB have changed in the last decades (5) (9). This condition is equivalent to 1% of TB cases, since there are no established characteristics of this disease, due to the fact that the clinical models are constantly changing, to the point of simulating another disease or covering the main disease, as in this case, LTB by diseases such as: fungal laryngitis, syphilis, Wegener's granulomatisis, and sarcoidosis (8) (9), which delays the correct diagnosis (11). It is important to take into account that this condition still occurs and continues to be one of the most frequent diseases of the larynx, affecting vocal function and the quality of life of people with TB (26) (55). According to WHO, this disease has been declared a global epidemiological emergency, since a large part of the world population is exposed to contact with the mycobacterium, where 1 out of every 10 people may develop this disease at some time in their lives (16) (17). On the other hand, it is reported that, by mid-2021, 1.6 million people died from this disease (20) (8) (60).

LTB can be primary, which is caused by direct invasion of inhaled substances by bacilli (26) (29) (59), and on the other hand, it can be secondary, being produced by coughing and expectoration from the tracheobronchial tree or through the bloodstream from places other than the lungs (8) (61) (39) (35). The main means of transmission is the direct contamination of pulmonary secretions with high bacillary load from contaminated sputum, passing through the posterior

commissure, affecting the arytenoids, the interarytenoid space, the ventricular folds and vocal folds, and, to a lesser degree, the laryngeal surface of the epiglottis, since they are exposed to the greatest impact of sputum at the moment of coughing, characterized by the formation of granulomas (16).

Although LTB is usually a clinical manifestation of pulmonary TB, supported by the most widely accepted and most prevalent bronchogenic theory (1) (2) (3), there is also a theory called hematogenic, which is uncommon and has a lower incidence, in which cases of LTB occur without pulmonary involvement, where the bacillus is transmitted through the blood (16).

Among the findings of laryngeal biopsies, the main lesion of LTB most frequently mentioned are granulomas, followed by ulcerative lesions and nonspecific lesions (2) (6) (13). However, variability is reported, exophytic lesions, edema and glottic masses can also be found (1) (3) (21), and in turn, these lesions are reflected in certain structures such as: the glottic region (true vocal folds, vestibular folds, anterior and posterior commissures) which is usually the most affected, followed by the supraglottic region (epiglottis, aryepiglottic folds) (3) (20) (6) (8) (15), affecting the quality of the voice, preventing its adequate production and causing great alterations (2) (9) (8) (13) (57).

Thus, the vocal folds are the most affected site, since the glottis is the entrance to the respiratory tract, being directly exposed to the bacilli, whether they are expelled from the lungs or inhaled from the air droplets (51) (55). In addition, sound production depends on the flexibility of the vocal folds, the correct function of the muscles involved in the production and integrity of the vocal tract tissues and the formation of waves in the mucosal layer (31).

These can present lesions caused by chronic cough or excessive vocalization, which causes an increased probability of bacterial invasion (3) (21) (61). Vocal folds present a direct relationship with voice quality, since they are the oscillatory component for voice production, therefore, they are the main site affected by LTB (20) (5). Therefore, dysphonia is the main clinical effect of LTB infection (3) (5) (53), which is a disorder characterized by altered vocal quality, pitch and loudness, being one of the most common laryngological effects, and the first of many laryngeal diseases (9) (50).

Due to LTB, in the sub epithelial space, there are usually areas of scarring and fibrosis, which alter the movement of the vocal folds to close and open the glottis, altering its vibration for phonatory production, manifesting rapidly progressive dysphonia, to the point of causing aphonia in the patient (2) (6). Other effects are hoarseness, cough, sore throat, stiffness, voice change, and even paralysis of the vocal folds (55) (35) (58). In the case of those who present cough; this can be variable depending on the lesions, since in certain cases the patient experiences dry laryngeal cough with a foreign body impression associated with hemoptysis (2). LTB can have significant long-term effects, since the larynx is a fundamental tool for sound production and vocal quality, and if TB affects it, there can be changes and alterations in the voice that last even after the disease has been treated and cured (1).

According to studies, voice effects such as dysphonia, hoarseness, cough, pain, and stiffness, which are caused by LTB, can begin from 1 to 3 months after the pulmonary symptoms and can last from 1 to 8 months or even in the greatest of cases up to 18 months (4), leaving large marks and negatively affecting voice adjustments (31) (21).

The long-term effects vary according to the individual, since the susceptibility of the host depends on the state of its specific and non-specific resistance mechanisms (62). This will depend on the degree of lesion that the person has in the laryngeal structures and the response they have to the antituberculosis drug, whether positive or negative (57). In most cases, the lesions and effects produced by LTB on the voice improve, thanks to a timely and effective pharmacological and therapeutic treatment (1), achieving a total cure of LTB, without leaving sequelae (2).

However, in other cases, after the antituberculosis treatment, LTB can leave certain marks or sequelae, affecting the quality and functionality of the voice, as is the case of dysphonia, mainly because, according to the literature, dysphonia is the only effect of LTB that is resistant to rifampicin, a drug used for the treatment against TB (9), therefore, its prevalence is much higher, compared to the other effects (3). Next, we find hoarseness as one of the most prolonged effects, even after treatment (53). In the case of the vocal folds, they may be left with diffuse scars and may be slightly swollen, but their mobility was no longer affected (1). Normally, residual adhesions may remain after treatment, so that the voice function will not be adequate (35). Usually, after starting therapy or treatment against LTB, week's later improvements in symptoms and appearances

in the larynx appear, making it return to normal in several months, however, if the effects are very large and because large scars, permanent functional laryngeal damage may occur (3).

CONCLUSIONS

The most affected and most frequently mentioned structure is the vocal folds, which causes alterations in the quality and functionality of the voice. On the other hand, dysphonia is the main effect that triggers LTB, since the vocal folds present alterations in their flexibility and oscillatory function for voice production, and although there is an effective pharmacological and therapeutic treatment, which manages to eliminate 100% of the TB bacteria, and to avoid the appearance of long-term sequelae, it also often only manages to reduce the effects left by LTB, such as dysphonia and hoarseness, which are some of the main effects on the voice that can continue to remain and affect the functionality of the voice, in the case of dysphonia since it is resistant to rifampicin.

Funding: None.

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