Overview of post-TB lung Disease (PTLD)

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GTN (Global Tuberculosis Network)

Conflict of interest disclosure

❑X I have no real or perceived conflicts of interest that relate to this presentation.

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Learning Objectives

- Question: have we finished our work when the patient is cured from TB (and from COVID-19?)
- The history:
- the JBP Review: the beginning
- the Stellenbosh Symposium: the standardisation
- the Lancet GH paper: the measurement
- The IJTLD clinical document: the summary
- Evidence on PTLD and on the need to manage it
- Evidence on post-COVID-19 disease and on the need to manage it

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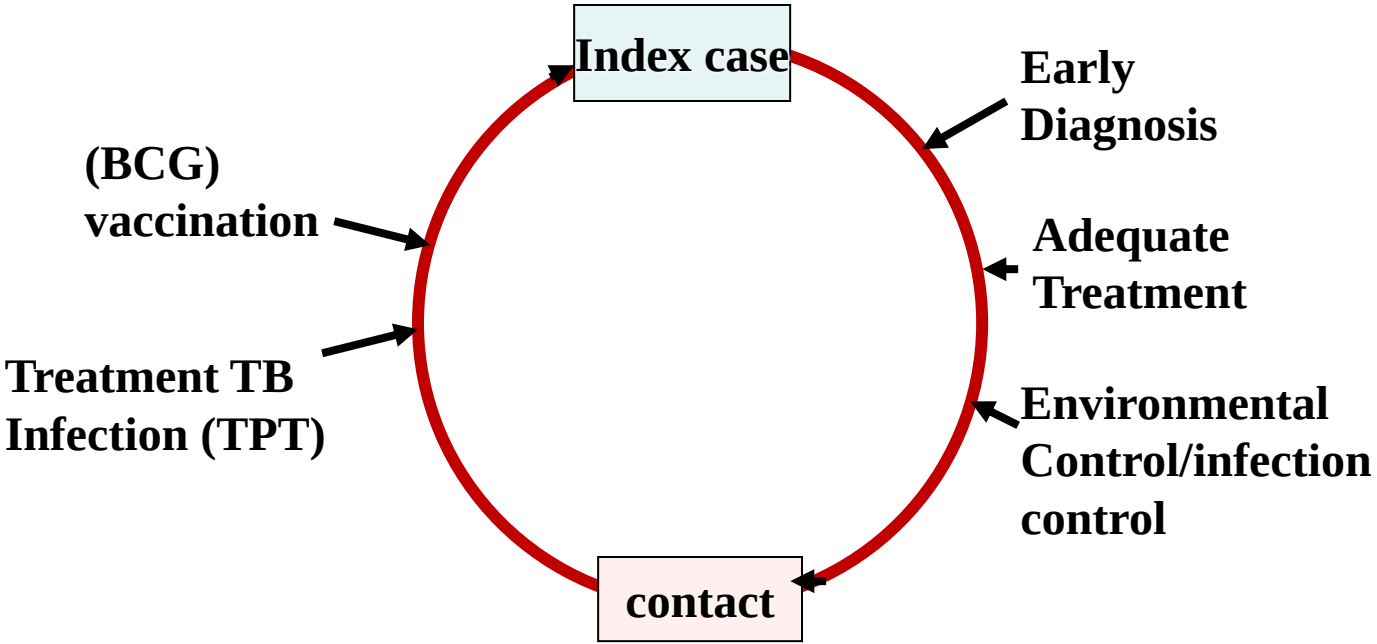
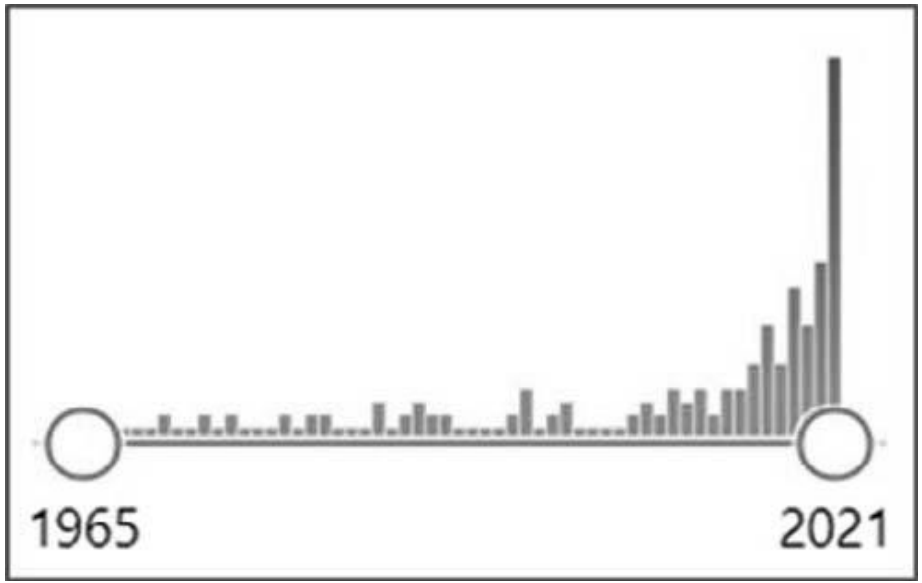
Programmatic approach to TB: we diagnose, treat and prevent infection and disease, and we are happy when the patient is cured



Are we happy with this in 2023?

Let’s start from some scientific evidence



PTLD publications 1965-2021

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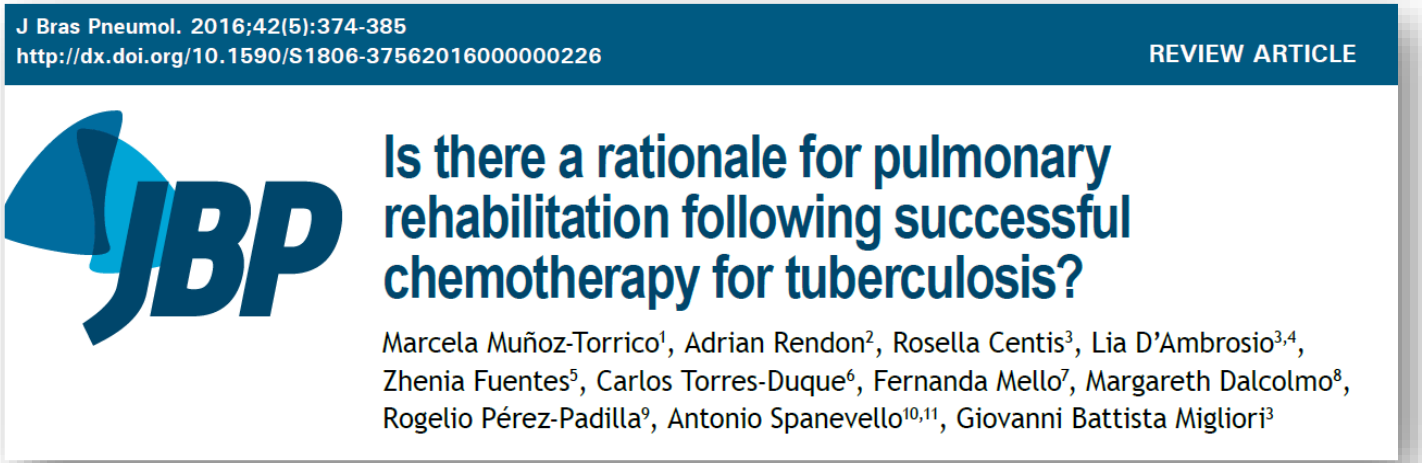
The history of PTLD (1): First review on the topic (2016)



J Bras Pneumol. 2016;42(5):374-385
http://dx.doi.org/10.1590/S1806-37562016000000226

REVIEW ARTICLE

JBP

Is there a rationale for pulmonary rehabilitation following successful chemotherapy for tuberculosis?

Marcela Muñoz-Torrico[1], Adrian Rendon[2], Rosella Centis[3], Lia D'Ambrosio[3,4], Zhenia Fuentes[5], Carlos Torres-Duque[6], Fernanda Mello[7], Margareth Dalcolmo[8], Rogelio Pérez-Padilla[9], Antonio Spanevello[10,11], Giovanni Battista Migliori[3]

Post-treatment sequelae
Detroyed lung
Functional evaluation of sequelae (DS-TB; MDR-TB)
Pulmonary rehabilitation (PR) interventions (physiotherapy, LTOT, ventilation)

The story of a patient

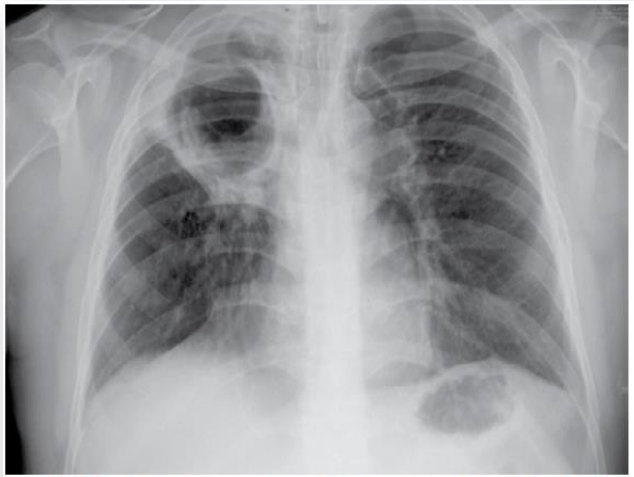
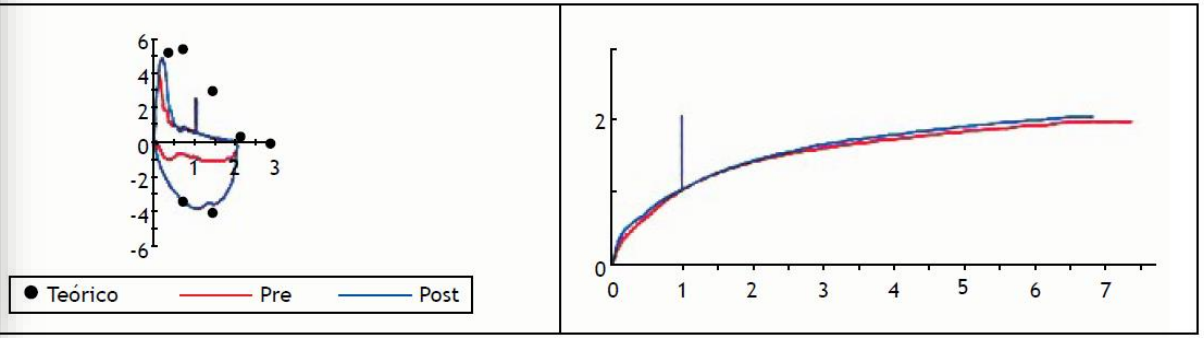


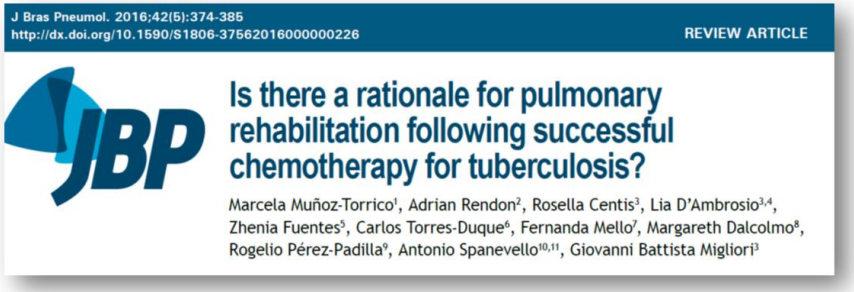
Figure 1. Chest X-ray of a 39-year-old male patient with a history of pan-susceptible tuberculosis treated for six months in 2007. The patient was considered cured. Later in time, he reported a six-month history of cough, mild dyspnea, but no fever. Tuberculosis relapse was ruled out; sputum smear microscopy and culture were negative. The image shows a giant cavity in the right upper lobe and some fibrotic changes.



	Pre-Bronch			Post-Bronch		
	Real	Teórico	%Teórico	Real	%Teórico	%Cambio
--ESPIROMETRÍA--						
FVC (L)	1.99	2.85	69	2.04	71	+2
FEV1 (L)	1.05	1.63	64	1.06	65	+1
FEV1/FVC (%)	53	71	74	52	73	-1

Figure 2. Spirometry of the same patient shown in Figure 1. FEV_1/FVC ratio was below 70%. FEV_1 was decreased and unresponsive to bronchodilator. FVC was also diminished. Fixed airway obstruction was detected, and mild restriction was considered. The final diagnosis was pulmonary sequelae of tuberculosis. Espirometría: spirometry; teórico: predicted; pre/post bronch: pre-/post-bronchodilator; real: observed; and cambio: change.

The evidence
Allowed to recommend…


J Bras Pneumol. 2016;42(5):374-385
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REVIEW ARTICLE

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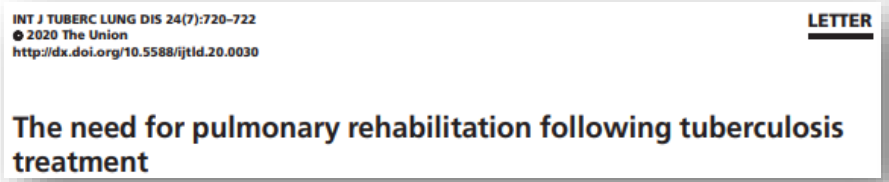
It is recommended that any future evaluation of tuberculosis and MDR-TB sequelae include complete information on

a) The characteristics of the patients (age, sex, ethnicity, etc.)
b) A complete description of the disease, including history of previous treatments, bacteriological status, pattern of drug resistance, and history of current treatment (drugs and regimen) with an emphasis on adverse events and their management
c) A complete description of the physiopathological status of the patients, including spirometry (and bronchodilator response), assessment of lung volumes (plethysmography or others), determination of DLCO, arterial blood gas analysis, 6MWT, radiological evaluation (ideally including CXR), and QoL evaluated with a general instrument and a specific respiratory instrument (SGRQ or others)
d) Rationale and consistence of the proposed PR plan, with clear pre- and post-test comparisons and evaluation of costs
e) Ideally, further studies should include the number of patients who need PR, since this will help to estimate the need for PR planning

Post-TB Lung Disease (PTLD) and post-COVID-19 sequelae: have we finished our work at the end of TB and/or COVID-19?

- TB disease can lead to chronic lung functional impairment resulting in **decline of pulmonary function**
- Pulmonary sequelae can be obstructive or restrictive in nature and **can hamper exercise capacity as well as quality of life (QoL)**
- Prevalence of functional impairment at the end of anti-TB treatment: **13% - 68%** in new TB cases and **75% - 96%** in MDR-TB cases
- **Mortality rates** for TB survivors may be up to **three times higher** than that of the general population
- **Pulmonary rehabilitation is effective in PTLD. Research** is undergoing to understand the relevance of post-COVID-19 sequelae and need for rehabilitation



INT J TUBERC LUNG DIS 24(7):720–722
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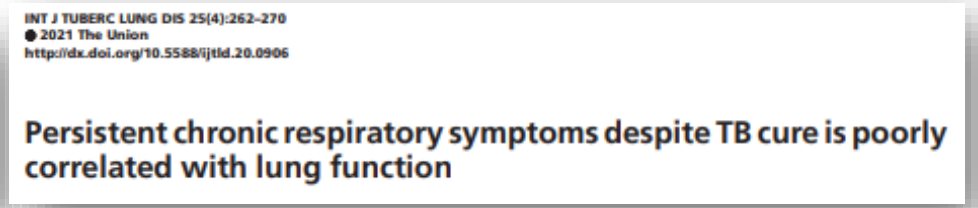
LETTER

The need for pulmonary rehabilitation following tuberculosis treatment



INT J TUBERC LUNG DIS 25(4):262–270
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http://dx.doi.org/10.5588/ijtld.20.0906

Persistent chronic respiratory symptoms despite TB cure is poorly correlated with lung function

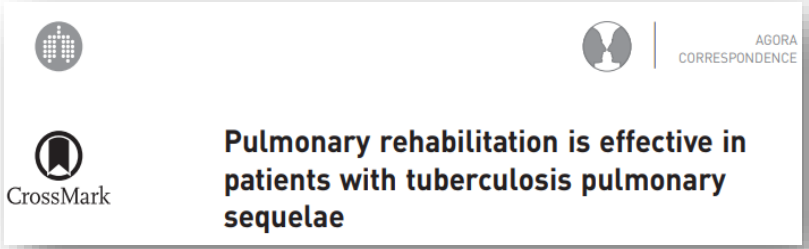
Visca D, et al. The need for pulmonary rehabilitation following tuberculosis treatment. Int J Tuberc Lung Dis. 2020;24:720-722

Allwood BW, et al. Persistent chronic respiratory symptoms despite cure from tuberculosis correlated poorly with lung function. Int J Tuberc Lung Dis 2021; 25: 262–270

Mini-review of the literature:
- a high proportion suffer from limited capacity to perform exercise and have poor QoL;
- patients in low-income countries are mainly younger;
- PR is effective in improving walking distance and core spirometry parameters
- PR programmes ranging from 3 to 32 weeks

Assessment of 145 patients who successfully completed TB treatment:
- 38% had an obstructive pattern and 54% a restrictive pattern
- 19% had chronic cough
- 42% had wheezing
- 25% a dyspnoea score of 3 or 4 (MRC)

Some evidence for TB - 1.



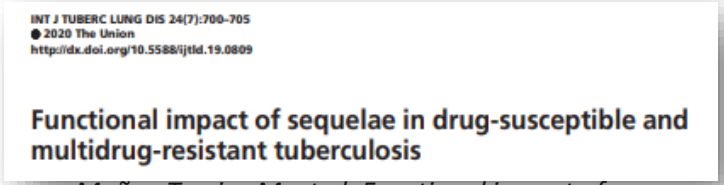
AGORA
CORRESPONDENCE

CrossMark

Pulmonary rehabilitation is effective in patients with tuberculosis pulmonary sequelae

Visca D, et al. Pulmonary rehabilitation is effective in patients with tuberculosis pulmonary sequelae. Eur Respir J. 2019 Mar 14;53(3):1802184.

Retrospective study on 43 post-TB patients. After 3 week PR programme subjects with impaired lung function showed a significant improvement in:
6-MWT, final Borg dyspnea, fatigue scores, FEV1, FVC, mean partial pressure of arterial oxygen and median oxygen saturation in arterial blood



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Functional impact of sequelae in drug-susceptible and multidrug-resistant tuberculosis

Muñoz-Torrico M, et al. Functional impact of sequelae in drug-susceptible and multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2020 Jul 1;24(7):700-705.

61 patients (34 DS-TB and 27 MDR-TB) assessed after TB treatment:
- 66% had functional impairment
- 49% had DLCO
- 16% hypoxemia at rest
- 74% with persistent respiratory symptoms (cough, phlegm, or wheezing)
- 40.4% dyspnea
- Functional damage is more apparent in DR-TB

Some evidence for TB - 2.

Some evidence for TB - 3.

INT J TUBERC LUNG DIS 24(8):820–828
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http://dx.doi.org/10.5588/ijtld.20.0067

VIEWPOINT

Post-tuberculosis lung health: perspectives from the First International Symposium

Allwood BW, et al. Post-tuberculosis lung health: perspectives from the First International Symposium. Int J Tuberc Lung Dis. 2020 Aug 1;24(8):820-828

First meeting dedicated to life and well-being after TB. Delegates from 13 countries across five continents, representing more than 27 different institutions. Consensus reached on a toolkit for future PTLD measurement and on PTLD patterns to be considered

J Bras Pneumol. 2022;48(2):e20210515
https://dx.doi.org/10.36416/1806-3756/e20210515

ORIGINAL ARTICLE

Post-tuberculosis lung disease: a comparison of Brazilian, Italian, and Mexican cohorts

Denise Rossato Silva[1,2], Alana Ambos Freitas[1], Amanda Reis Guimarães[2], Lia D'Ambrosio[3], Rosella Centis[4], Marcela Muñoz-Torrico[5], Dina Visca[6,7], Giovanni Battista Migliori[4]

1. Faculdade de Medicina, Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.
2. Programa de Pós-Graduação em Ciências Pneumológicas, Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.
3. Public Health Consulting Group, Lugano, Switzerland.
4. Servizio di Epidemiologia Clinica delle Malattie Respiratorie, Istituti Clinici Scientifici Maugeri – IRCCS – Tradate, Italia.
5. Clínica de Tuberculosis, Instituto Nacional de Enfermedades Respiratorias Ismael Cosio Villegas – INER – Ciudad de México, México.
6. Divisione di Riabilitazione Polmonare, Istituti Clinici Scientifici Maugeri – IRCCS – Tradate, Italia.
7. Dipartimento di Medicina e Chirurgia, Malattie dell'Apparato Respiratorio, Scuola di Medicina, Università degli Studi dell'Insubria, Tradate, Italia.

Submitted: 22 December 2021.
Accepted: 24 January 2022.

Study carried out at the Faculdade de Medicina da Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.

ABSTRACT

Objective: To evaluate lung function in a cohort of patients with a history of pulmonary tuberculosis in Brazil, as well as to evaluate the decline in lung function over time and compare it with that observed in similar cohorts in Mexico and Italy. **Methods:** The three cohorts were compared in terms of age, smoking status, pulmonary function test results, six-minute walk test results, and arterial blood gas results. In the Brazilian cohort, pulmonary function test results, six-minute walk test results, and arterial blood gas results right after the end of tuberculosis treatment were compared with those obtained at the end of the follow-up period. **Results:** The three cohorts were very different regarding pulmonary function test results. The most common ventilatory patterns in the Brazilian, Italian, and Mexican cohorts were an obstructive pattern, a mixed pattern, and a normal pattern (in 58 patients [50.9%], in 18 patients [41.9%], and in 26 patients [44.1%], respectively). Only 2 multidrug-resistant tuberculosis cases were included in the Brazilian cohort, whereas, in the Mexican cohort, 27 cases were included (45.8%). Mean PaO_2 and mean SaO_2 were lower in the Mexican cohort than in the Brazilian cohort ($p < 0.0001$ and $p < 0.002$ for PaO_2 and SaO_2, respectively). In the Brazilian cohort, almost all functional parameters deteriorated over time. **Conclusions:** This study reinforces the importance of early and effective treatment of drug-susceptible tuberculosis patients, because multidrug-resistant tuberculosis increases lung damage. When patients complete their tuberculosis treatment, they should be evaluated as early as possible, and, if post-tuberculosis lung disease is diagnosed, they should be managed and offered pulmonary rehabilitation because there is evidence that it is effective in these patients.

Keywords: Tuberculosis; Tuberculosis, multidrug-resistant; Spirometry; Rehabilitation.

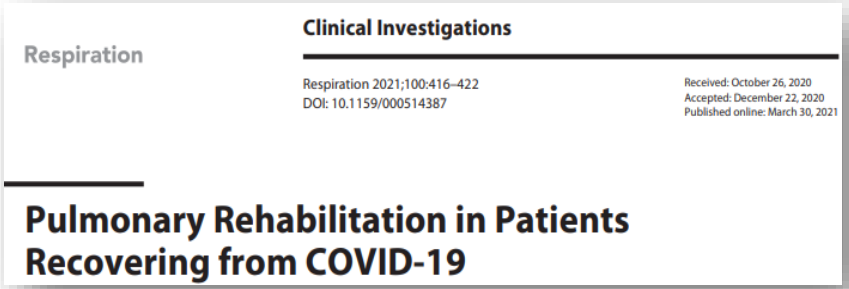
- Some variability
- Most common pattern:

- BRA: Obstructive: (50.9%)
- ITA: Mixed (41.9%)
- MEX: Normal (44.1%)

- PaO_2 and Sat HB% worse in MEX
- Funbctional parameters deteriorating over time when assessed (BRA)

Need for Post-COVID-19 rehabilitation?

- Still uncertain what is the proportion of COVID-19 survivors with persistent symptoms for months after recovering from the initial infection
- Long-term consequences vary from mild symptoms to severe conditions, often affecting multiple organs.
- Symptoms may primarily be breathlessness but also include fatigue, sleeping difficulties, low grade fever, depression, anxiety, impacting cardiac, pulmonary and renal systems
- Patients' QoL may be improved with individual and tailored rehabilitation programmes



Respiration

Clinical Investigations

Respiration 2021;100:416–422
DOI: 10.1159/000514387

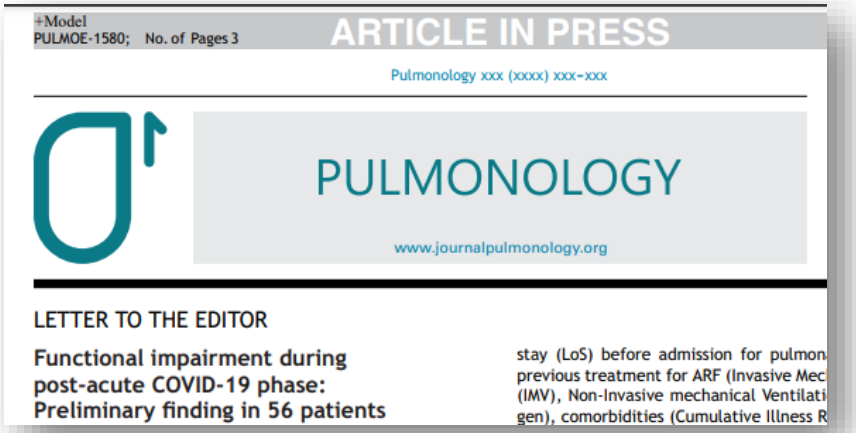
Received: October 26, 2020
Accepted: December 22, 2020
Published online: March 30, 2021

Pulmonary Rehabilitation in Patients Recovering from COVID-19

Zampogna E, et al. Pulmonary Rehabilitation in Patients Recovering from COVID-19. Respiration. 2021;100(5):416-422.

Retrospective study on 140 patients:
- After rehabilitation (median 24 days) improvements in Short Physical Performance Battery (SPPB), Barthel Index (BI) and 6MWT

Some evidence on COVID-19 – 1.



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Pulmonology xxx (xxxx) xxx–xxx

PULMONOLOGY

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LETTER TO THE EDITOR

Functional impairment during post-acute COVID-19 phase: Preliminary finding in 56 patients

stay (LoS) before admission for pulmon
previous treatment for ARF (Invasive Mec
(IMV), Non-Invasive mechanical Ventilati
gen), comorbidities (Cumulative Illness R

Zampogna E, et al. Functional impairment during post-acute COVID-19 phase: Preliminary finding in 56 patients. Pulmonology. 2021 Jan 6:S2531-0437(20)30268-3

Assessment of clinical and functional presentation of 56 post-acute COVID-19 before rehabilitation:
All 56 patients showed a reduced Barthel Index and Euro Quality of Life and increased Barthel Dyspnea Index. Total Short Physical Performance Battery score of 0 in 48% of pts.

Some evidence on COVID-19- 2.

Journal Pre-proof

The role of blood gas analysis in the post- acute phase of COVID-19 pneumonia

Dina Visca Giovanni Battista Migliori Anh Tuan Dinh-Xuan Rosella Centis Stefano Belli Michele Vitacca Maria Aliani Elisabetta Zampogna Davide Feci Patrizia Pignatti Martina Zappa Laura Saderi Giovanni Sotgiu Antonio Spanevello

Visca et al. The role of blood gas analysis in the post- acute phase of COVID-19 pneumonia. Arch Bronconeumol. 2021, doi: https://doi.org/10.1016/j.arbres.2021.06.003

Assessment of the role of alveolar-to-arterial oxygen ($AaDO_2$) gradient and P/F in 145 COVID-19 survivors (P: PaO_2; F: O_2 inhaled Fraction)

$AaDO_2$ is more sensitive than P/F in COVID-19 post-acute phase to monitor lung damage in patients not admitted to the intensive care unit

Need for rehab in post-acute COVID-19 patients

- We have seen in the clinical presentation that patients with TB and COVID-19 may have a cumulative effect of the respective sequelae, thus making them as a group potentially in need of further attention
- In terms of programmatic activities, this means to consider evaluating patients at the end of TB/COVID-19 (at least those with ‘problems’) and their rehabilitation, with impact on health services.
- The UNION has just completed a first document on the Clinical Standards for evaluation and rehabilitation of PTLD patients and is working at the post-COVID-19 document

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The history of PTLD (2): Stellenbosh (2020)

INT J TUBERC LUNG DIS 24(8):820–828

http://dx.doi.org/10.5588/ijtld.20.0067

VIEWPOINT

Post-tuberculosis lung health: perspectives from the First International Symposium

B. W. Allwood,[1] M. M. van der Zalm,[2] A. F. S. Amaral,[3] A. Byrne,[4] S. Datta,[5,6,7] U. Egere,[8] C. A. Evans,[5,6,7] D. Evans,[9] D. M Gray,[10] G. Hoddinott,[2] O. Ivanova,[11] R. Jones,[12] G. Makanda,[13] F. M. Marx,[2,14] J. Meghji,[15] S. Mpagama,[16] J. G. Pasipanodya,[17] A. Rachow,[11,18] I. Schoeman,[13] J. Shaw,[1] C. Stek,[19,20] S. van Kampen,[21] D. von Delft,[13] N. F. Walker,[15,22] R. S. Wallis,[23] K. Mortimer[24,25]

Table 1 Aims of the 1st Post-Tuberculosis Symposium

Aim 1	To advocate for patients suffering with post-TB complications
Aim 2	To facilitate face-to-face networking between leaders in the field
Aim 3	To define the current state of knowledge surrounding post-TB diseases
Aim 4	To discuss and achieve consensus on important aspects of post-TB lung diseases
Aim 5	To produce a reference document for researchers and workers in the field

TB = tuberculosis.

A consensus was reached on a toolkit for future PTLD measurement and on PTLD patterns to be considered. The importance of extra-pulmonary consequences and progressive impairment throughout the life-course was identified, including TB recurrence and increased mortality. Patient advocates emphasised the need to address the psychological and social impacts post TB and called for clinical guidance. More generally, there is an urgent need for increased awareness and research into post-TB complications.

Table 2 Post-TB lung disease measurement toolbox, including aspects of disease and comorbidities/co-exposures which may be measured in clinical and research practice, according to available resources

Category	Parameter	Measurement tool/item
Post-TB lung disease measurement	Self-reported symptoms	Shortness of breath (MRC/mMRC score), cough, sputum, wheeze, chest pain, haemoptysis, fatigue
	Clinical measures	Observations: respiratory rate, oxygen saturation, heart rate, BMI Investigations: arterial blood gas
	Lung function	Pre- and post-bronchodilator spirometry: FEV_1, FVC, FEV_{25-75} Lung volumes: RV and TLC Gas transfer *Measurement, quality control and interpretation as per international norms strongly recommended
	Radiology	CXR parameters CT parameters *No validated scoring tools as yet available
	Functional capacity	Submaximal tests: 6-minute walk (distance, nadir saturations, time to recovery), sit to stand Maximal tests: incremental shuttle, cardiopulmonary exercise testing *Measurement, quality control and interpretation as per international norms strongly recommended
	Health-related quality of life	Respiratory focused: St George's Respiratory Questionnaire General tools: Short-Form Health Survey (SF12/SF36), Karnofsky Performance Scale, COPD Assessment Test For economic analyses: WHO TB patient cost surveys *Local translation, modification and validation strongly recommended
	Disease behaviour	Evidence of cor pulmonale: pedal oedema, echocardiography (pulmonary artery pressures) Evidence of exacerbations: exacerbation rate, hospitalisation rate Microbiology: colonising/infecting organisms, including bacteria/mycobacteria/viruses/fungi
	Socio-economic consequences	Mental health symptom screen (WHO self-reporting questionnaire-20 or Kessler psychological distress scale); TB-related stigma (Stigma Scale for Chronic Illness or Van Rie TB-related stigma tool); self-reported disability related to TB (Sheehan Disability Scale) Socio-economic information and patient costs (direct and indirect): WHO TB patient cost surveys

Table 4 Post-TB priority areas and research priorities

Topic	Priority areas and research priorities
Epidemiology of PTLD	Common methodological framework across studies Follow-up studies defining meaningful clinical outcomes Investigation of factors affecting development of PTLD (e.g., environmental, occupation, clinical and behavioural factors)
Lung complications after TB	Validation of tools used in PTLD Evaluation of clinically meaningful phenotypes and predictors of morbidity and mortality Development of validated severity scoring system
Pathogenesis and prevention	Development of pathways from basic science to HDT trials Assessment of most meaningful endpoints in HDT trials Clinical trials of HDTs
Pulmonary consequences of TB in children	Obtain disease estimates of burden of disease Obtain estimates of spectrum of disease Retrospective analysis of existing diagnostic, observational and treatment data
Social, economic and psychological impact	For the individual: report disability (e.g., quality of health, mental health, pain, TB-related stigma), economic consequences and proportion facing catastrophic total costs For the community: quantify the economic and social impact of social and family networks For the health system: determine the cost of residual disability to the health system
Treatment and holistic management	Optimal timing of assessment for post-TB complications Non-pharmacological studies: pulmonary rehabilitation, education on self-management, airway clearance techniques Pharmacological studies: bronchodilators (e.g., long-acting beta-agonists, long-acting anti-muscarinic agents)
Health care systems	Prioritisation of advocacy for research funding to generate needed evidence Development of guidelines for clinicians using available evidence and expert opinion Engagement of international organisations, professional bodies and pharmaceutical industries
Role of people affected by TB	Peer group support and community interventions to reduce stigma Sustainable funding for affected community-driven advocacy and support for their involvement in research, policy and programmatic decisions Former patient engagement to address recurrent TB

TB = tuberculosis; PTLD = post-TB lung disease; HDT = host-directed therapy

- **Important idea**
- **Pulmonary Rehab not discussed**

Learning Objectives

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The history of PTLD (3): The measurement of health effects (Lancet GH 2021)

Lifetime burden of disease due to incident tuberculosis: a global reappraisal including post-tuberculosis sequelae

Nicolas A Menzies, Matthew Quaife, Brian W Allwood, Anthony L Byrne, Anna K Coussens, Anthony D Harries, Florian M Marx, Jamilah Meghji, Debora Pedrazzoli, Joshua A Salomon, Sedona Sweeney, Sanne C van Kampen, Robert S Wallis, Rein M G J Houben, Ted Cohen

122 million DALYs due to incident tuberculosis disease estimated in 2019, with 58 million DALYs attributed to post-tuberculosis sequelae, representing 47% of the total burden estimate.
The study shows that human suffering for PTLD exists in all ages and in young age groups exceeds that for TB disease

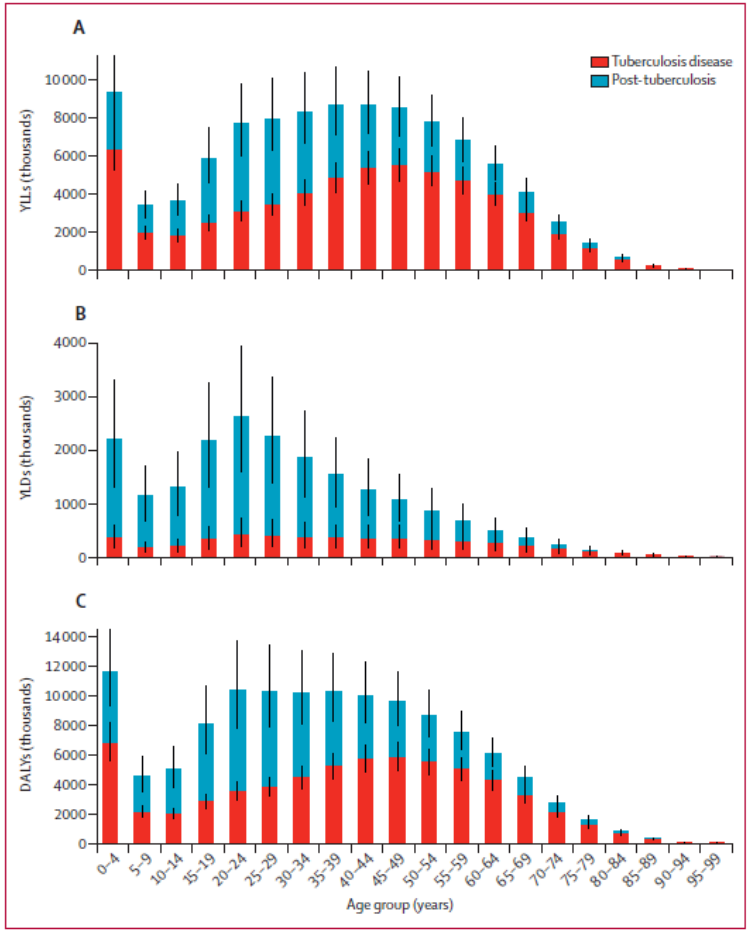

Figure 1: **Estimates of YLLs (A), YLDs (B), and DALYs (C) attributable to tuberculosis disease in 2019, stratified by age group of disease incidence, and disease period***

YLL=years of life lost. YLD=years lived with disability. DALYs=disability-adjusted life-years. *Black bars represent 95% uncertainty intervals.

The impact of PTLD is dramatic

YLLs: years of life lost

>TB in intermediate age groups; >years lost by young pts

YLDs: years lived with disability

>years lived with disability by young pts

DALYs: disability-adjusted life years

DALYs (1 incident case) from PTLD (0.45+5.95= 6.4, green areas) are higher than to those from TB disease (1.57+4.23= 5.8, azur areas)

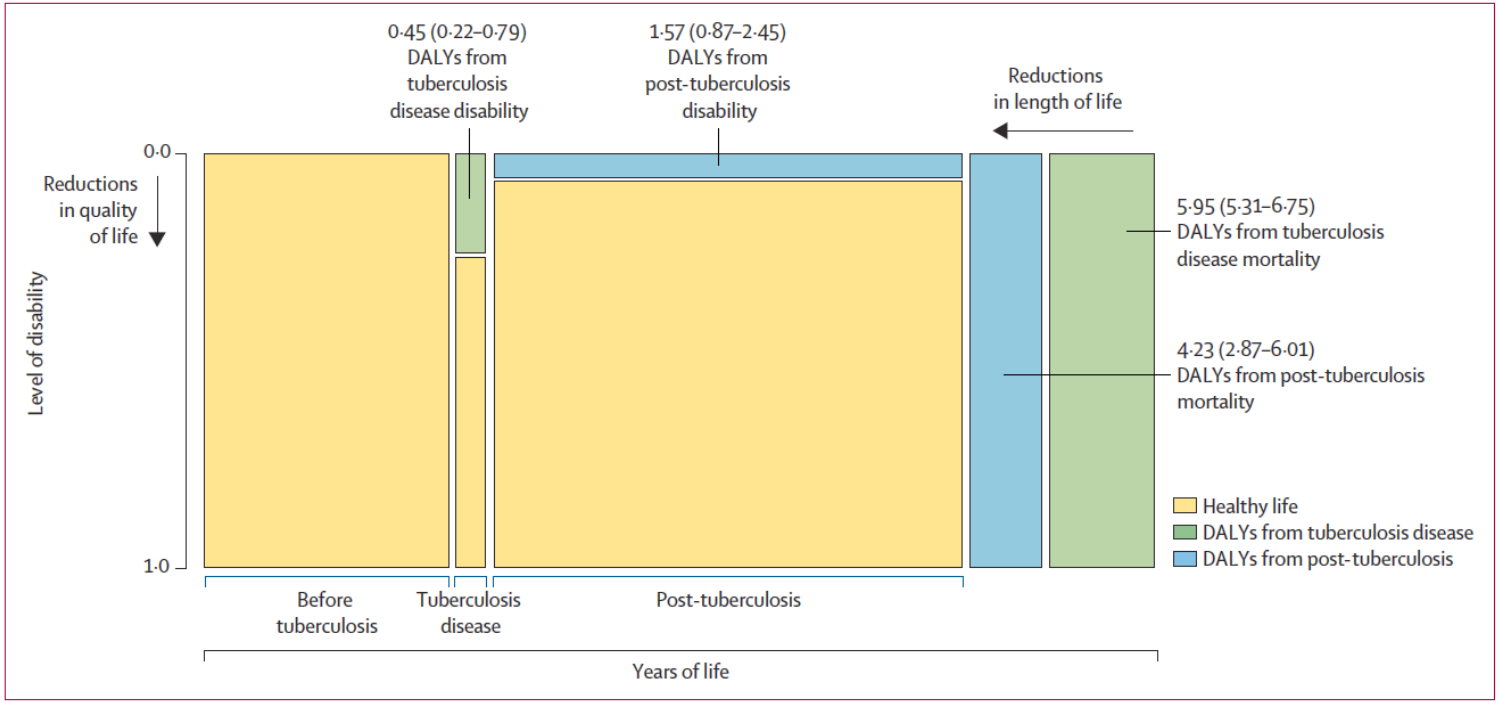

Figure 2: **Average DALYs per incident tuberculosis case from increased disability and mortality rates attributable to tuberculosis, stratified by tuberculosis disease and post-tuberculosis period***

Area of each green and blue rectangle is proportional to the number of DALYs indicated, other dimensions not to scale. Values in parentheses represent 95% uncertainty intervals. DALYs=disability-adjusted life-years. *Total DALYs per incident tuberculosis case are equal to the sum of these values.

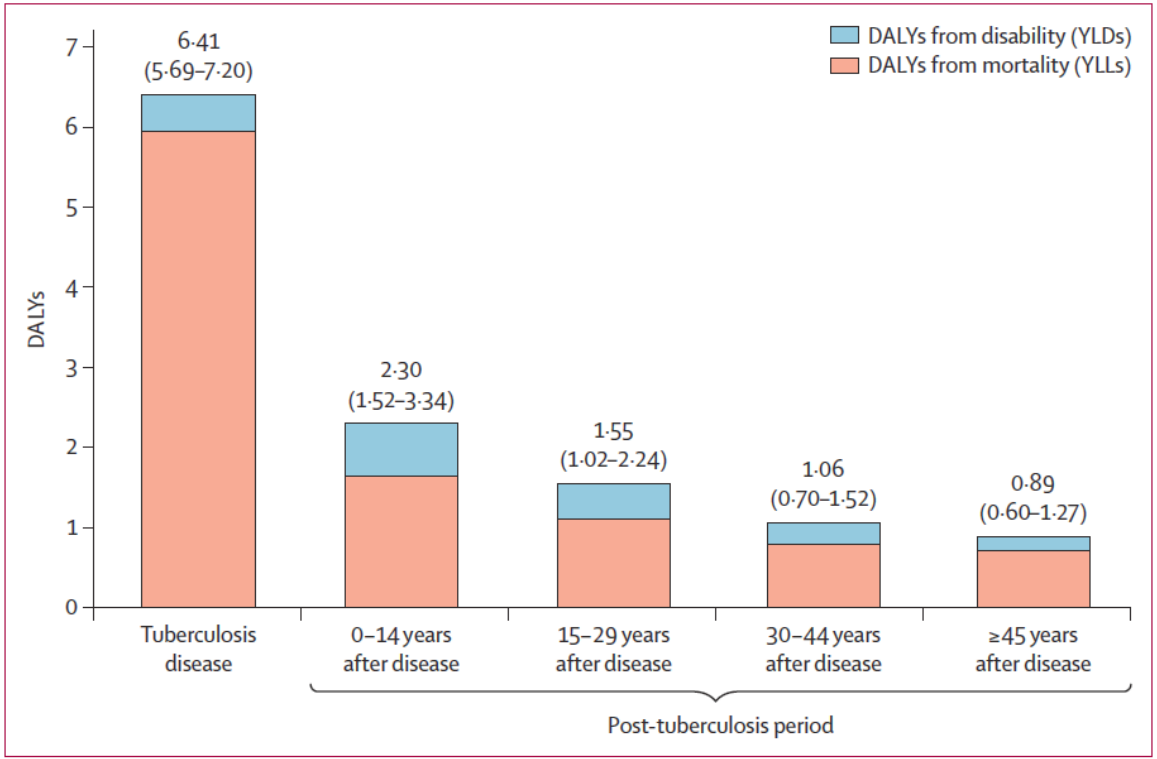

Figure 3*: DALYs per incident tuberculosis case, stratified by tuberculosis disease and post-tuberculosis period
YLL=years of life lost. YLD=years lived with disability. DALYs=disability-adjusted life-years. *Total DALYs per incident tuberculosis case equal to the sum of these values. Values in parentheses represent 95% uncertainty intervals.

DALYs (1 incident case) for disability and mortality per age groups.

All ages affected, younger groups have higher DALYs as longer life expectancy

Learning Objectives

- Question: have we finished our work when the patient is cured from TB (and from COVID-19?)
- The history:
- the JBP Review: the beginning
- the Stellenbosh Symposium: the standardisation
- the Lancet GH paper: the measurement
- **the IJTLD clinical document: the summary**
- Evidence on PTLD and on the need to manage it
- Evidence on post-COVID-19 disease and on the need to manage it

The history of PTLD (4): Clinical statement (2023)

INT J TUBERC LUNG DIS 27(4):248–283

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CLINICAL STATEMENT

Post-TB health and wellbeing

SUMMARY

TB affects around 10.6 million people each year and there are now around 155 million TB survivors. TB and its treatments can lead to permanently impaired health and wellbeing. In 2019, representatives of TB affected communities attending the '1st International Post-Tuberculosis Symposium' called for the development of clinical guidance on these issues. This clinical statement on post-TB health and wellbeing responds to this call and builds on the work of the symposium, which brought together TB survivors, healthcare professionals and researchers. Our document offers expert opinion and, where possible, evidence-based guidance to aid clinicians in the diagnosis and management of post-TB conditions and research in this field. It covers all aspects of post-TB, including economic, social and psychological wellbeing, post TB lung disease (PTLD), cardiovascular and pericardial disease, neurological disability, effects in adolescents and children, and future research needs.

KEY WORDS: quality of life; post-tuberculosis lung disease; tuberculous neuropathy; tuberculous pericarditis; post-TB socio-economic burden

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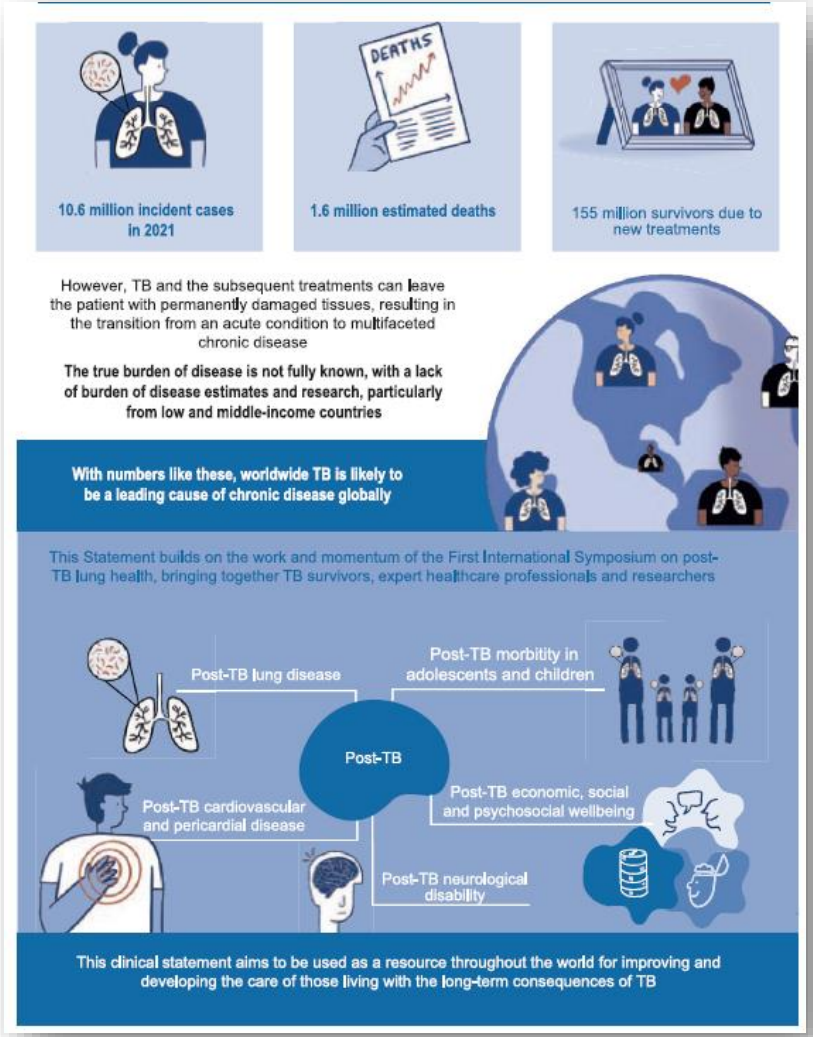


- 155 M TB survivors
- Post TB includes
- Morbidity in children and adolescents
- Post TB neurological disability
- Post-TB cardiovascular disability
- PTLD

- Rehabilitation not discussed much

Measuring post-TB wellbeing

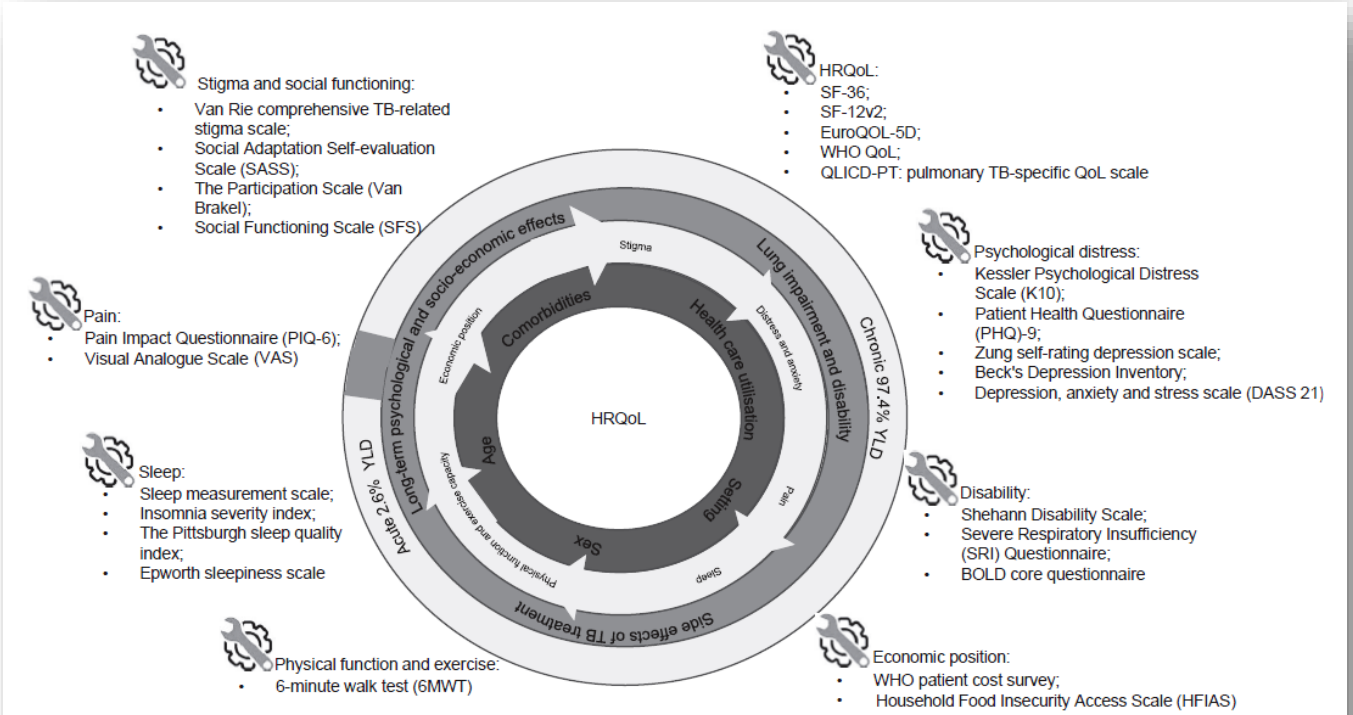


Figure 4 Modelling and measuring post-TB wellbeing: schematic showing some of the psychological and socio-economic consequences that lead to a poor perception of HRQoL and the tools used to measure these. HRQoL = health-related quality of life; SF = Short Form (Health Survey); YLD = years lived with a disability.

Classification of PTLD (severity)

Table 1 Proposed severity classification of PTLD*

Category	Description	Prognosis*
Not detected	Does not meet the definition of PTLD	Effects on future lung health, symptoms and survival not well defined
	No detectable abnormality on lung function testing or chest imaging	Normal future lung health and survival can be expected
Mild	No or minimal symptoms	Possibility of accelerated decline in lung function and increased risk of future lung pathology and exacerbations
	Normal lung function Normal or minimal structural lung disease detected on chest imaging	
Moderate	Variable symptoms	Increased risk of accelerated decline in lung function, future lung pathology, exacerbations
	Abnormal lung function (obstructive, mixed, restrictive, reduced DL_{CO}) Detectable abnormalities on chest imaging such as bronchiectasis, fibronodular scarring	
Severe	Significant and debilitating symptoms that reduce a person's quality of life and may also affect ability to carry out daily tasks	High risk of future complications such as recurrent chest infections, chronic fungal infection (including aspergillosis) and haemoptysis
	Lung function testing typically shows abnormalities	Increased mortality risk
	Chest imaging typically demonstrates significant structural lung disease such as parenchymal lung destruction, bronchial wall thickening, bronchiectasis and cavitation	

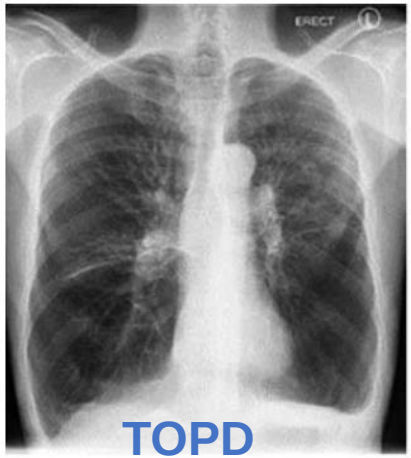
* Based on limited and/or low-quality evidence.
PTLD = post-TB lung disease; DL_{CO} = diffusion capacity of lungs for carbon monoxide.

Proposed classification of PTLD clinical patterns

Table 2 Suggested classification of PTLD clinical patterns*

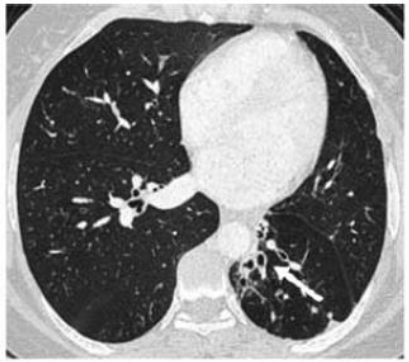
Compartment	Clinical patterns	Definition
Airways	TB-associated obstructive lung disease	Airway obstruction (FEV_1/FVC ratio <0.7 or <LLN) thought to be primarily related to small airway disease (Figure 5A)
	Tracheobronchial stenosis	Narrowing of the trachea and/or airways, which can increase airway resistance
	Bronchiectasis	CT definition: thickening of airway wall, evidence of airway dilatation > diameter of adjacent vessel, or non-tapering; *OR* CXR definition: evidence of ring shadows and tramlines (Figure 5B)
Parenchyma	Cavitation	A gas-filled space either within an area of pulmonary consolidation, mass or nodule (Figure 5E)
	Parenchymal destruction	Extensive destruction of lung tissue, with a gas-filled space occupying the volume of ≥1 lobe (Figure 5C)
	Fibrotic change	Areas of parenchymal scarring, with associated volume loss (Figure 5D)
	Aspergillus-related lung disease	Evidence of radiological change associated with chronic pulmonary aspergillosis, including pleural thickening, aspergilloma, thin/thick-walled cavities, associated with positive cultures and/or immune assays (Figure 5E)
Pleural	Chronic pleural disease	Evidence of pleural thickening on CXR or CT imaging.
Pulmonary vascular	Pulmonary hypertension	Elevated pulmonary artery pressures as estimated using doppler echocardiography or measured at right heart catheterisation (Figure 5F)
Other	Other	Other pathology, not meeting criteria above

* Adapted from [5].
PTLD = post-TB lung disease; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; LLN = lower limit of normal; CT = computed tomography; CXR = chest X-ray.



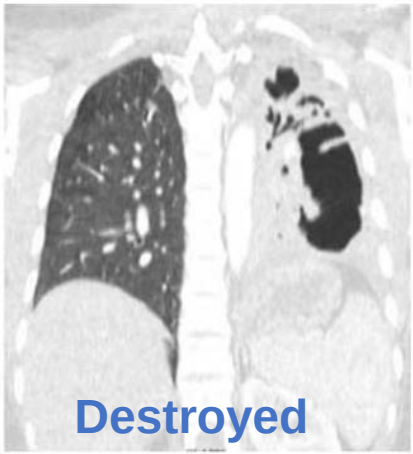
A

TOPD



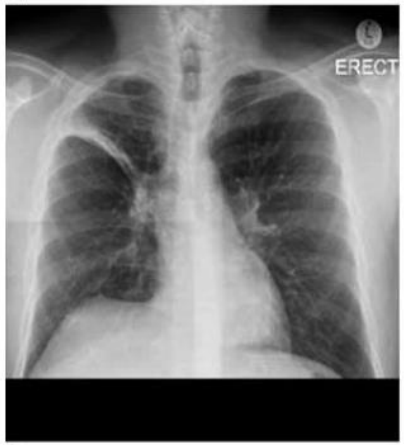
B

Focal bronchiectasis



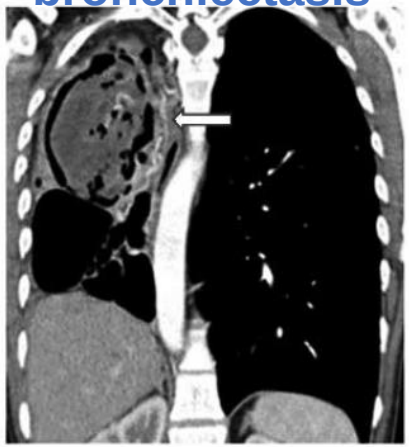
C

Destroyed left lung



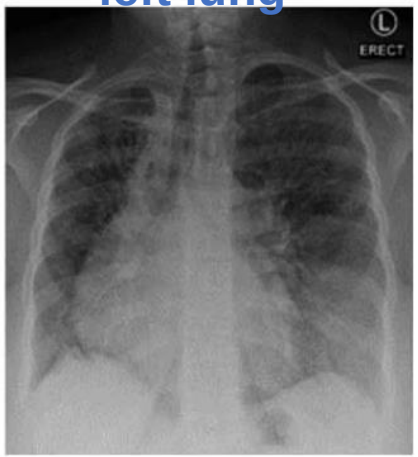
D

TOPD



E

Cavity



F

TOPD, bronchiectases & pulmonary hypertension

TOPD:
TB-related
Ostructive
Pulmonary
Disease

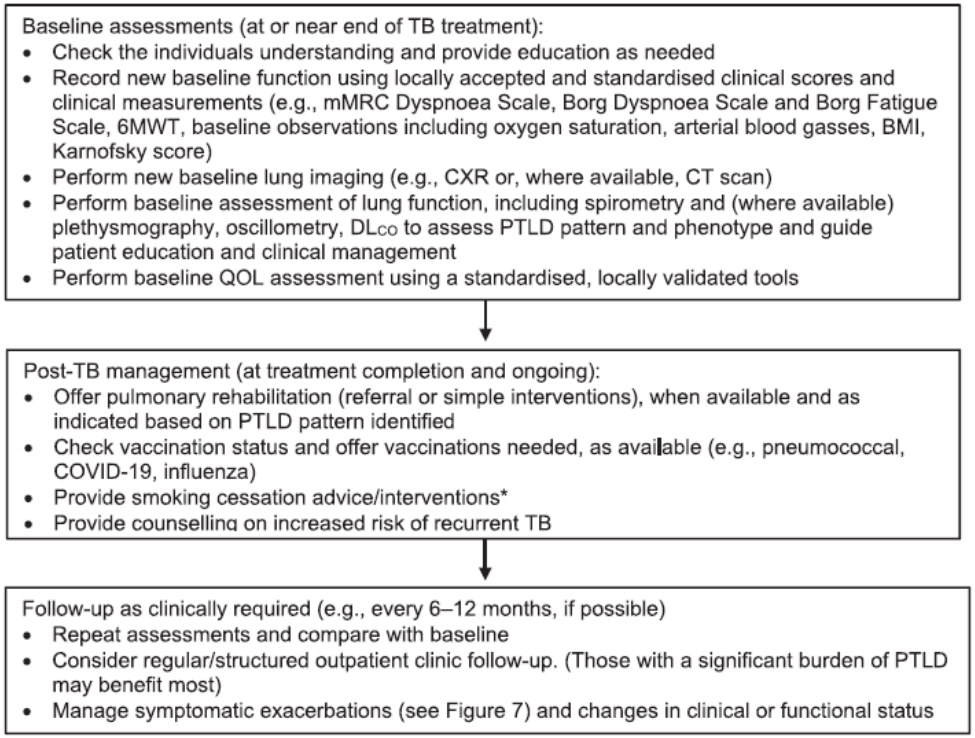


Figure 6 Recommendations for assessment and care planning for TB treatment. A systematic approach to post-TB follow-up is recommended, including a baseline assessment (ideally recorded at, or just before, the end of TB treatment) to allow objective comparison of change over time. *Can be initiated at any time during or after TB treatment. mMRC = Modified Medical Research Council Dyspnoea Scale; 6MWT = 6-minute walk test; BMI = body mass index; CXR = chest X-ray; CPExT = cardiopulmonary exercise test; CT = computed tomography; DL_{CO} = diffusion capacity of lungs for carbon monoxide measurement; PTLD = post-TB lung disease; QoL = quality of life.

PTLD

- ❑ **Assessment**
- ❑ **Management**
- ❑ **Follow-up**

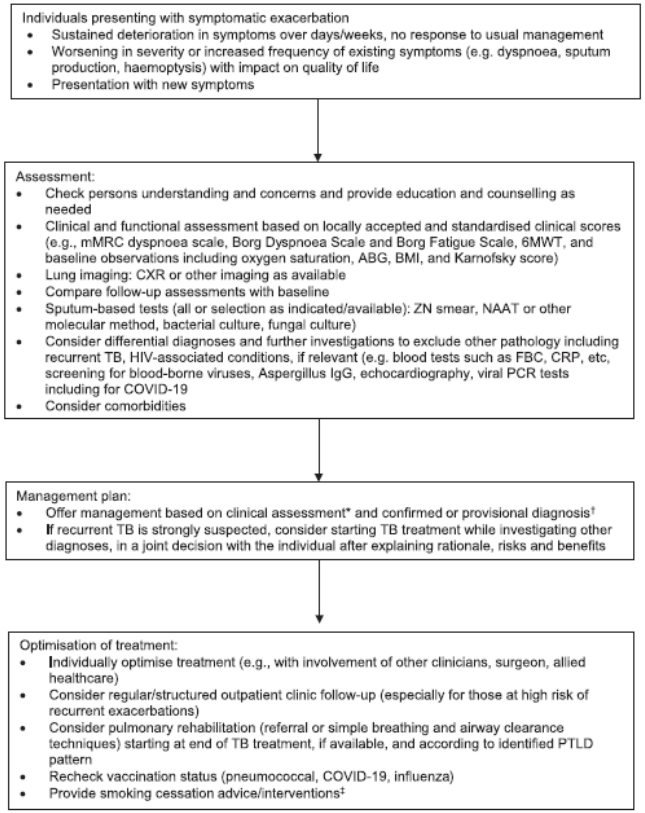


Figure 7 Proposed approach to clinical assessment of symptomatic exacerbations of PTLD. *Lung function tests are generally not required at every clinical assessment or during an acute exacerbation but should be used as a diagnostic investigation and repeated to compare with baseline values when clinical deterioration is observed. †Based on a comparison of assessment findings with baseline assessment at end of TB treatment, and on results of current investigations. ‡Can be initiated at any time during treatment or follow-up. mMRC = Modified Medical Research Council; 6MWT = 6-min walk test; ABG = arterial blood gas; BMI = body mass index; CXR = chest X-ray; ZN = Ziehl-Neelsen; NAAT = nucleic acid amplification test; FBC = full blood count; CRP = C-reactive protein; IgG = immunoglobulin G; PCR = polymerase chain reaction; PTLD = post-TB lung disease.

PTLD: individuals with symptomatic exacerbation, worsening/increased frequency or new symptoms, no response to uisual treatment, impaired QoL

Assessment: councelling/education, clinical, functional, imaging, microbiology, co-morbidities

Management plan: approach to PTLD or TB if necessary

Optimization of treatment: medical, rehab, vaccinations, smoking cessation

Table 4 Potentially comorbid or alternative diagnoses among individuals with PTLD

- Chronic pulmonary aspergillosis
- NTM infections
- Chronic colonisation and disease with non-Aspergillus species (e.g., *Pseudomonas*, *Haemophilus*, *Staphylococcus aureus*, *Nocardia*, NTM)
- Occupational lung disease (e.g., silicosis)
- Mycoses (e.g., histoplasmosis, cryptosporidiosis, pneumocystis): geographic distribution and epidemiology varies
- Smoking-related diseases including those associated with exposure to indoor smoke (e.g., emphysema, bronchiectasis)
- HIV and its complications
- Pulmonary hypertension
- Thoracic malignancy
- COPD
- Asthma
- COVID-19 and post-COVID-related lung disease

NTM = non-tuberculous mycobacteria; COPD = chronic obstructive pulmonary disease.

Conditions to consider for differential diagnosis and/or as co-morbidities

Table 7 End-of-treatment assessment for post-TB lung disease in children and adolescents*

	Non-severe PTB†	Severe PTB
Clinical assessment and symptom/signs screening	X‡	X
Imaging (CXR)		X
Lung function test (spirometry)		X
6MWT		X
HRQoL		X

* Source: Migliori G, et al.[46]

† Applicable only to acid-fast bacilli smear-negative case; defined as PTB confined to one lobe with no cavities (<1 lobe), no signs of miliary TB and no complex pleural effusion, intrathoracic lymph node TB with no significant airway obstruction and no bilateral airway narrowing and peripheral lymph node TB.[227]

‡ Further investigations should be performed if there are any residual symptoms.

PTB = pulmonary TB; CXR = chest X-ray; 6MWT = 6-min walk test; HRQoL = health-related quality of life.

End- treatment assessment in children and adolescents

Functional impact of sequelae in drug susceptible and multidrug-resistant tuberculosis cases

Marcela Muñoz Torrico[1], Silvia Cid-Juárez[2], Laura Gochicoa-Rangel[2], Luis Torre-Bouscolet[3], Miguel Angel Salazar-Lezama[4], Hector Villarreal-Velarde[1], Rogelio Pérez-Padilla[5], Dina Visca[6,7], Rosella Centis[8], Lia D'Ambrosio[9], Antonio Spanevello[6,7], Laura Saderi[10], Giovanni Sotgiu[10], Migliori GB[8,11]

Table 2 Functional details of 34 DS- and 27 DR-TB cases at the end of anti-tuberculosis treatment*

	DS-TB (n = 34) mean ± SD	MDR/RR/XDR-TB (n = 27) mean ± SD	P value
FEV_1 pre-BD, median [IQR]	2.4 [1.7–2.9]	1.9 [1.6–2.2]	0.03†
FEV_1 pre-BD, %predicted	83.4 ± 22.3	67.4 ± 22.7	0.008†
FEV_1 post-BD, median [IQR]	2.6 [1.9–3.0]	2.0 [1.5–2.4]	0.02†
FEV_1 post-BD, %predicted	87.2 ± 22.5	70.9 ± 21.9	0.007†
FVC pre-BD, median [IQR]	3.1 [2.6–3.8]	2.5 [2.2–3.6]	0.11
FVC pre-BD, %predicted‡	92.3 ± 19.7	81.1 ± 24.2	0.05
FVC post-BD, median [IQR]	3.1 [2.7–3.7]	2.5 [2.1–3.7]	0.13
FVC post-BD, %predicted	93.2 ± 20.5	82.2 ± 25.1	0.07
FEV_1/FVC pre-BD	75.8 ± 11.3	69.7 ± 10.9	0.04†
FEV_1/FVC post-BD	79.2 ± 10.9	72.4 ± 9.3	0.02†
TLC	5.1 ± 1.2	4.8 ± 1.4	0.31
TLC, %predicted	98.5 ± 14.1	87.0 ± 21.4	0.02†
RV, median [IQR]	1.8 [1.5–2.2]	1.8 [1.5–2.1]	0.92
RV, %predicted, median [IQR]	105 [89–126]	99 [84–123]	0.37
RV/TLC, median [IQR]	104 [95–140]	122 [100–139]	0.16
DLCO, %predicted	83.5 ± 20.1	69.0 ± 19.6	0.006†
PaO_2	67.0 ± 9.9	64.5 ± 7.8	0.29
SaO_2	92.5 ± 2.7	91.6 ± 3.4	0.26
Haemoglobin, g/dL	14.0 ± 2.1	14.9 ± 2.5	0.18
Distance at 6-MWT, m	547.2 ± 81.6	512.3 ± 108.3	0.18
Lowest SaO_2 during 6MWT, median [IQR]	86 [85–91]	87.5 [84–88]	0.40
Final SaO_2, median [IQR]	89 [85.5–92.0]	88 [84.5–90.0]	0.31

* GSA was obtained in 57 patients (31 DS/26 DR-TB).
† Statistically significant.
DS-TB = drug-susceptible tuberculosis; DR-TB = drug-resistant TB; MDR = multidrug-resistant; RR = rifampicin-resistant; XDR = extensively drug-resistant; FEV_1 = forced expiratory volume in 1 sec; BD = bronchodilator; IQR = interquartile range; FVC = forced vital capacity; TLC = total lung capacity; RV = residual volume; DLCO = carbon monoxide diffusion capacity of the lung; PaO_2 = partial pressure of oxygen in the arterial blood; SaO_2 = oxygen saturation in arterial blood; 6-MWT = 6-min walking test; GSA = genomic signal analysis.

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Functional impact of sequelae in drug-susceptible and multidrug-resistant tuberculosis

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SUMMARY

BACKGROUND: Evidence on the impact of tuberculosis (TB) treatment on lung function is scarce. The aim of this study was to evaluate post-treatment sequelae in drug-susceptible and drug-resistant-TB (DR-TB) cases in Mexico and Italy.
METHODS: At the end of TB treatment the patients underwent complete clinical assessment, functional evaluation of respiratory mechanics, gas exchange and a 6-minute walking test. Treatment regimens (and definitions) recommended by the World Health Organization were used throughout.
RESULTS: Of 61 patients, 65.6% had functional impairment, with obstruction in 24/61 patients (39.4%), and 78% with no bronchodilator response. These effects were more prevalent among DR-TB cases (forced expiratory volume in 1 s/forced vital capacity [FEV_1/FVC] < lower limit of normality, 14/24 vs. 10/34; P = 0.075). DR-TB patients showed moderately severe (FEV_1 < 60%) and severe obstruction (FEV_1 < 50%) (P = 0.008). Pre- and post-bronchodilator FEV_1 and FEV_1/FVC (% of predicted) were significantly lower among DR-TB cases. Plethysmography abnormalities (restriction, hyperinflation and/or air trapping) were more frequent among DR-TB cases (P = 0.001), along with abnormal carbon monoxide diffusing capacity (DLCO) (P = 0.003).
CONCLUSION: The majority of TB patients suffer the consequences of post-treatment sequelae (of differing levels), which compromise quality of life, exercise tolerance and long-term prognosis. It is therefore important that lung function is comprehensively evaluated post-treatment to identify patient needs for future medication and pulmonary rehabilitation.
KEY WORDS: TB; MDR-TB; functional evaluation; post-treatment; sequelae; rehabilitation

DRUG-SUSCEPTIBLE (DS-TB) AND multidrug-resistant tuberculosis (MDR-TB) are a clinical and public health priority worldwide. According to the World Health Organization (WHO), the overall number of estimated TB cases was 10 million in 2018, with approximately half a million rifampicin-resistant TB (RR-TB) cases, 78% of which were diagnosed as MDR-TB.[1] The management of DS-TB is standardised, requiring 6 months of treatment with a regimen of four anti-TB drugs in the intensive phase, followed by a further two anti-TB drugs during the continuation phase.[2,3] More than 80% of patients managed in quality-assured TB programmes achieved successful outcomes.[1]

The management of MDR-TB and extensively drug-resistant TB (XDR-TB) is much more difficult, requiring at least 4–5 second-line anti-TB drugs (which are expensive and toxic) for a period of 18–24 months.[4–7] Even with shorter MDR-TB regimens (9–12 months), patients can face drug toxicity issues. Unfortunately, the proportion of successful outcomes among MDR-TB cases is only approximately 55%,[1] although the inclusion of new drugs (e.g., bedaquiline and delamanid) might increase the treatment success rate.[8–10]

Given the high TB burden in economically disadvantaged countries,[1] the major focus of national TB programmes has historically been the adequate therapeutic management of patients to break the chain of transmission.[1,9,11] However, TB is a chronic

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Lung function trajectories in South African children with pulmonary TB: A prospective study

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Results

152 children with at least one successful spirometry test from September 2015-August 2022 were included: 62 (41%) confirmed PTB, 61 (40%) unconfirmed PTB and 29 (19%) with non-PTB-LRTI. Median (IQR) age was 10.1 (7.5, 11.5) years; 51% were male and 10% were living with HIV. At enrolment, 76% had abnormal spirometry, with restrictive disease most common. Spirometry [forced expiratory volume in 1 sec z-score (z-FEV_1); forced vital capacity z-score (z-FVC)] improved in all groups over time. However, in confirmed PTB, z-FEV_1/z-FVC decreased by three months [from 0.2 (-0.5, 1.4) to -0.4 (-1.1, 0.5)], and remained low through 12 months. In contrast to children with confirmed PTB, those with unconfirmed disease had steady improvements in z-FEV_1 and z-FVC to 12 months. Risk factors for lower lung function included older age, female and nutritional impairment.

Conclusions

Children with confirmed PTB had reduced lung function over 12 months. Childhood PTB may set a developmental pathway of lung impairment through life.

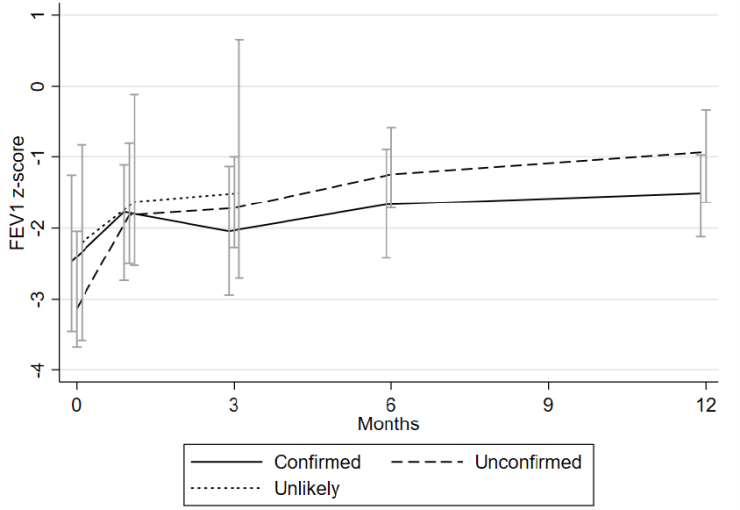

Figure 2a. Median FEV1 z-scores over time, among children with confirmed pulmonary TB (PTB), unconfirmed PTB, and non-PTB lower respiratory tract illness (LRTI)

Confirmed children (continuous line) with TB have lower FEV1 (upper left) and FVC (lower right) than unconfirmed and children unlikely to have TB (dotted lines)

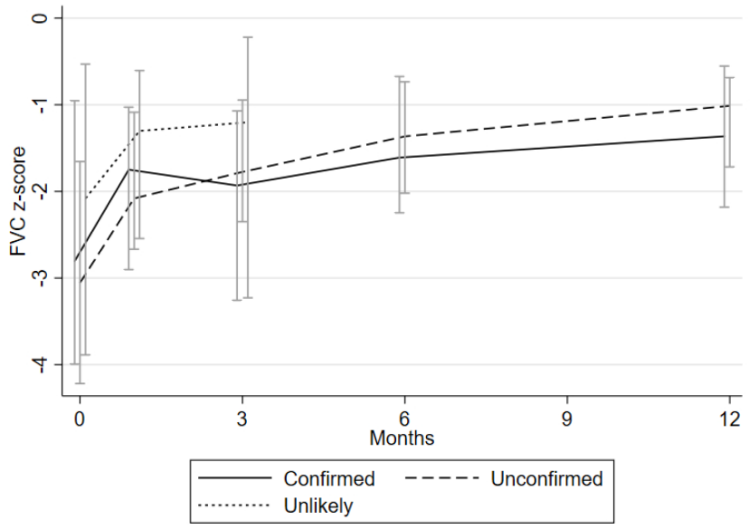

Figure 2b. Median FVC z-scores over time, among children with confirmed pulmonary TB (PTB), unconfirmed PTB, and non-PTB lower respiratory tract illness (LRTI)

Suggested reading to re-order ideas and keep the essentials

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https://dx.doi.org/10.36416/1806-3756/e20230055

EDITORIAL

Diagnosis and management of post-tuberculosis lung disease

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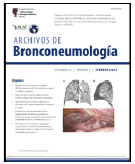

Review Article

Breathing Back Better! A State of the Art on the Benefits of Functional Evaluation and Rehabilitation of Post-Tuberculosis and Post-COVID Lungs

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Conclusions

- Increasing attention on PTLD
- First Review Published in 2016
- Growing evidence also from low– income countries
- The Stellenbosh UNION initiative allowed to standardise basic definitions
- The IJTLD International Standards (2021) describe the clinical steps to evaluate and manage PTLD in patients completeing anti-TB treatment
- A follow-up conference in Stellenbosh, WHICH FOLLOWED the Clinical Standards, allowed to present a detailed clinical statement of post-TB disease, including PTLD
- Rehabilitation has been recognized as a major element of PTLD management and the core information is included in the Clinical Standards document

First we do what is necessary,

then we do what is possible

and, finally,

we work to make the impossible, possible…

Thank you