FIRST INTERNATIONAL
POST
TUBERCULOSIS
SYMPOSIUM 2019
STELLENBOSCH, SOUTH AFRICA

PROCEEDINGS
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Introduction

The 1st International Post-tuberculosis Symposium was held at the STIAS Institute, Stellenbosch, South Africa on 22 & 23 July 2019. This was a multidisciplinary symposium, the first of its kind, devoted entirely to life and complications arising after tuberculosis, and involved 68 delegates from 13 countries across five continents and representing more than 27 institutions. The delegates all had an expressed interest in the field, and included adult pulmonologists, adult infectious disease specialists, paediatricians, paediatric pulmonologists, public health and family medicine practitioners, epidemiologists, basic science and clinical researchers, radiologists, physiotherapists, psychologists and social-behavioural scientists and patient advocates, including previous patients.

The symposium was conceptualized and implemented by an international steering committee, with the following aims:

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

The Symposium was made possible through financial assistance from The Union Against Tuberculosis and Lung Disease, Stellenbosch University, The IMPALA collaboration and the Desmond Tutu TB Centre.

The Symposium was structured as a working meeting with both state-of-the-art presentations, and workshops (see Appendix 1). Delegates were asked to attend two of eight workshops, which covered a number of different and overlapping aspects of life and illness after tuberculosis, ranging from epidemiology, to basic science and clinical and socio-economic consequences, to advocacy for the field (see Figure 1). Workshops were a forum for experts to interact and discuss in more focused detail the state of knowledge, knowledge gaps and where relevant to try and reach consensus on matters, where none has existed before. Because of the diversity of topics covered, workshop chairs were given freedom to structure their workshops according to the topic needs.

Figure 1.
During the conference a modified Delphi process was employed to achieve consensus, both within the workshops (where applicable) and within the plenary sessions. In many instances the Delphi process was initiated via email with delegates before the Symposium. A Delphi consensus threshold of 66% was set for the plenary sessions, while the workshop chairs were given freedom to set their own consensus thresholds.

**Decision on Terminology**

Due to the variety of terminology used in the literature to date for consequences after tuberculosis, priority was given during the plenary session to achieving consensus in terminology that can be used going forward. Using the Delphi method, initiated before the Symposium, delegates voted with a majority vote of 84% to embrace the term “Post-tuberculosis”, over other terms suggested. The term is proposed as a prefix or adjective, and individual workshops were allow to propose and reach consensus on their own relevant suffixes or nouns. Workshop 1, using the Delphi process described in the proceedings, reached consensus on the term “lung disease”, while workshop 3 embraced the term “economic, social and psychological (ESP) well-being”. Thus the respective terms would be “post-tuberculosis lung disease (PTLD)” and “post-tuberculosis economic, social and psychological well-being” (or Post-TB ESP).

The steering committee and workshop chairs comprised of the following people:

<table>
<thead>
<tr>
<th>Brian Allwood <em>(Chair)</em></th>
<th>Olena Ivanova</th>
<th>Cari Stek</th>
</tr>
</thead>
<tbody>
<tr>
<td>André Amaral <em>(in absentia)</em></td>
<td>Rupert Jones <em>(in absentia)</em></td>
<td>Marieke van der Zalm</td>
</tr>
<tr>
<td>Sumona Datta <em>(in absentia)</em></td>
<td>Florian Marx</td>
<td>Sanne van Kampen</td>
</tr>
<tr>
<td>Uzoh Egere</td>
<td>Jamilah Meghji</td>
<td>Dalene von Delft</td>
</tr>
<tr>
<td>Carlton Evans <em>(in absentia)</em></td>
<td>Kevin Mortimer</td>
<td>Naomi Walker</td>
</tr>
<tr>
<td>Denise Evans</td>
<td>Stellah Mpagama</td>
<td>Robbert Wallis</td>
</tr>
<tr>
<td>Diane Gray</td>
<td>Andrea Rachow</td>
<td></td>
</tr>
<tr>
<td>Graeme Hoddinott</td>
<td>Ingrid Schoeman</td>
<td></td>
</tr>
</tbody>
</table>

The presentations of these proceedings is fulfillment of aim 5, and we would like to thank all the above people and workshop participants for their contributions in compiling this document.
Workshop 1 - Lung complications after pulmonary tuberculosis

Chairs

Jamilah Meghji – Imperial College, London, UK
Brian Allwood – Stellenbosch University, South Africa

Participants

Andrea Rachow – Ludwig-Maximilians-University Munich, Germany
Anthony Byrne – University of Sydney, Australia
Cari Stek – University of Cape Town, South Africa & Institute of Tropical Medicine Antwerp, Belgium
Catherine Tadyanemhandu – University of Zimbabwe, Zimbabwe
Celso Khosa – Instituto Nacional de Saúde (INS), Moçambique
Emily van’t Woud – Leiden University Medical Center, The Netherlands
Eric Bateman – University of Cape Town
Grant Theron – Stellenbosch University, South Africa
Ismail Kalla – University of Witwatersrand, South Africa
Dr James Wagude – Ministry of Health, Siaya County, Kenya
Jan Loot Pretorius – Worcester Academic Hospital, South Africa
Jane Shaw – Stellenbosch University, South Africa
Jantjie Taljaard – Stellenbosch University, South Africa
Jotam Pasipanodya – Texas Tech University Health Sciences Center, USA
Lamla Nqwata – University of Witwatersrand, South Africa
Mohammad Osman – Desmond Tutu TB Centre South Africa
Naomi Walker – Liverpool School of Tropical Medicine, UK
Nyanda Ntingiya – NIMR Mbeya Medical Research Centre, Tanzania
Rebecca Nightingale – Liverpool School of Tropical Medicine, UK
Robbert Wallis – Aurum Institute, South Africa
Rodney Ehrlich – University of Cape Town, South Africa
Stephanie Griffith Richards – Stellenbosch University, South Africa
Sanne van Kampen – Leiden University Medical Center, The Netherlands
Sigrid Schulz – Brewelskloof Hospital, South Africa
Stel lah Mpagama – Kibong’oto Infectious Disease Hospital, Tanzania
Susan Hanekom – Stellenbosch University, South Africa
Obianuju Ozoh – University of Lagos, Nigeria

Background and state of the art

Over the course of the conference, published and unpublished data were presented from Mozambique (Dr Celso Khosa & Dr Andrea Rachow), Peru (Dr Anthony Byrne), USA (Dr Jotam Pasipanodya), South Africa (Professor Rodney Erlich), Malawi (Dr Jamilah Meghji) and South Africa (Dr Brian Allwood), demonstrating the high burden of residual lung damage experienced by adults even after successful treatment for pulmonary tuberculosis.

However, several challenges in the understanding of the global burden and nature of residual post-TB lung disease were highlighted. Firstly, the terminology used to denote residual post-TB lung disease remains varied, such that it is challenging to identify published literature on the subject. Secondly, post-TB lung disease is a heterogenous condition: it can include airway, parenchymal, pleural, and pulmonary vascular abnormalities, which overlap to different degrees in different individuals, and are variably associated with symptoms. This heterogeneity makes measuring and
describing the burden of disease complex. Thirdly, clinical and research groups are currently using a wide range of tools to measure these dimensions of lung pathology, and approaches to quality control and interpretation of data vary widely such that comparison between sites is difficult. Fourthly, patients with post-TB lung damage frequently have multiple respiratory exposures (e.g. smoking, drug abuse, occupational exposures and biomass fuels) and dual respiratory pathology is often seen. Teasing out the component of respiratory impairment that is TB-related can be challenging. Finally, it is important to acknowledge that despite growing interest in this area, there remains a paucity of high quality data: few cross-sectional studies have included control data from non-TB populations, and longitudinal data on the evolution of disease over time and associated long-term patient outcomes remain lacking.

Work is ongoing to enrich the quality of data available on the burden, patterns, and outcomes associated with post-TB lung damage, including studies such as TB Sequel which will include both control and longitudinal data, and other rich longitudinal cohort studies from Malawi, and the USA. Whilst we await these data, this workshop was designed to address some of the other constraints to ongoing research in this area.

The broad aim of this workshop was: “To develop consensus definitions and measurement tools for post-TB lung damage, which can be used for clinical and research purposes, in both low- and high-income settings”. Specific objectives included:

1. **Terminology**
   To develop consensus on a single over-arching term to be used to describe residual lung damage following TB disease, in order to ensure uniformity on how this is referenced / described in the literature.

2. **Minimum case definition**
   To develop consensus on a minimum case definition for post-TB lung damage, for use by those enrolling patients into research studies or clinical cohorts.

3. **Measurement toolbox**
   To outline a set of parameters which would be important to measure in clinical or epidemiological studies investigating the burden, pattern or evolution of post-TB lung damage, and to describe the tools currently being used for this purpose. In addition, to discuss the need for standardisation of tools used to measure these parameters.

4. **Severity score**
   To discuss the utility of developing severity scores for post-TB lung disease, and the approach to deriving these from cohort data / against patient outcomes.

5. **Clinical classification**
   To discuss clinical approaches to disease classification, which might assist patient management in clinical practice.

Of note, the workshop was set up to include both clinical and research practitioners, with different perspectives on how and why post-TB lung disease should be measured and classified. It also included individuals from both resource rich and poor settings, with varying access to measurement tools. Challenges in reaching consensus across these groups were expected, and the aim of this workshop was in part to explore some of the differences of opinion between groups.
Main discussion points

1. Terminology
Agreement was reached by the overall symposium group that the prefix ‘post-TB’ should be used in the literature to describe conditions following on from TB-disease. The suffix to be used to describe respiratory pathology was agreed on as ‘lung disease’. The agreed term to be used to describe residual lung abnormalities is therefore ‘post-TB lung disease’, abbreviated to PTLD.

2. Minimum case definitions
There was broad agreement that a minimal case definition would be useful for clinicians and researchers recruiting patients into cohorts for the management or investigation of PTLD.

Discussions during the workshop highlighted the need for this definition to: be broad and inclusive, with sensitivity prioritised over specificity; be suitable for use in low and high resource settings where different diagnostic tools would be available; allow for dual-pathology with both PTLD and other respiratory pathologies occurring together; allow for patients to have both PTLD from an old episode of TB disease and a recurrent episode of active TB disease. It was acknowledged that lung damage can be asymptomatic, but may still be relevant to patient outcomes. It was also noted that individuals may have had a previously untreated episode of pulmonary TB disease, which was undocumented and untreated, may be left with residual lung damage. Finally, it was noted that dual-pathology is widely seen, and in such cases it can be challenging to identify the primary cause of a patient’s symptoms.

Given these discussions, the minimum case definition for PTLD, agreed after 3 Delphi rounds (Appendix 1), was “Evidence of chronic respiratory abnormality, with or without symptoms, attributable at least in part to previous pulmonary tuberculosis”.

3. Measurement tool-box
There are multiple approaches to measuring the burden, pattern and severity of PTLD. These include measuring physiological impairment using lung function, structural impairment using imaging, recording symptoms as a key manifestation of disease, and functional impairment as a maker of severity. Specific phenotypes of disease which evolve differently over time, with varying rates of disease progression / exacerbations / complications may also exist and recording these behaviours may also be relevant.

To date, clinical and research groups working on PTLD have been measuring different aspects of PTLD, and using different tools to measure these parameters. There was recognition within the workshop that standardisation of approaches and tools would be preferable, but that this is limited by variable access to resources between settings, and the lack of prospective data to determine which ‘core’ aspects of disease / measurements best predict long-term patient outcomes and should be measured. Rather than developing standardised tools for the measurement of PTLD, we instead set out to generate a list of potential approaches, from which those working in this area can choose, according to their available resources. Although it is not possible to standardise measurement tools at present, the need for standardised measurement and quality control approaches was highlighted.

The importance of measuring co-exposures or co-morbidities which may determine the nature of PTLD itself, or patient outcomes once PTLD is in place, was also discussed. A list of core factors which may be effect-modifiers / confounders of PTLD and outcomes has been included. This list is not exhaustive, and researchers may want to collect data on these or other factors.
Table 1: PTLD Measurement toolbox, including aspects of disease, and co-morbidities / co-exposures which may be measured in clinical and research practice, according to available resources.

<table>
<thead>
<tr>
<th>Category</th>
<th>Parameter</th>
<th>Measurement tool / item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-TB lung disease measurement</td>
<td>Self-reported symptoms</td>
<td>Shortness of breath (MRC / mMRC score), cough, sputum, wheeze, chest pain, haemoptysis, fatigue</td>
</tr>
<tr>
<td></td>
<td>Clinical measures</td>
<td>Observations: respiratory rate, oxygen saturation, heart rate, BMI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Investigations: Arterial blood gas</td>
</tr>
<tr>
<td></td>
<td>Lung function</td>
<td>Pre &amp; post bronchodilator spirometry - FEV1, FVC, FEV25-75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lung volumes – RV and TLC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gas transfer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*Measurement, quality control, and interpretation as per international norms strongly recommended</td>
</tr>
<tr>
<td>Radiology</td>
<td>CXR parameters</td>
<td>CT parameters</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*No validated scoring tools as yet available</td>
</tr>
<tr>
<td>Functional capacity</td>
<td>Submaximal tests: 6-minute walk (distance, nadir saturations, time to recovery), sit to stand</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximal tests: Incremental shuttle, cardio-pulmonary exercise testing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*Measurement, quality control, and interpretation as per international norms strongly recommended</td>
<td></td>
</tr>
<tr>
<td>Health-related quality of life</td>
<td>Respiratory focused: St. George’s Respiratory Questionnaire (SGRQ)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>General tools: Short-Form health survey (SF12/SF36), Karnofsky Performance Scale (KPS), COPD asses (CAT)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For economic analyses: Euroqol-5D tools (EQ-5D)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*Local translation, modification and validation strongly recommended</td>
<td></td>
</tr>
<tr>
<td>Disease behaviour</td>
<td>Evidence of cor-pulmonale: pedal oedema, echocardiography (PA pressures)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Evidence of exacerbations: exacerbation rate, hospitalisation rate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Microbiology: colonising / infecting organisms, including bacteria / mycobacteria / viruses / fungi</td>
<td></td>
</tr>
<tr>
<td>Factors influencing disease or outcomes</td>
<td>Co-exposures</td>
<td>Respiratory exposures: Smoking, drugs of abuse, biomass exposure, occupational exposures</td>
</tr>
<tr>
<td></td>
<td>Environmental exposures: Alcohol use, socioeconomic situation</td>
<td></td>
</tr>
<tr>
<td>Co-morbidities</td>
<td>Preceding / concurrent respiratory disease: Silicosis, COPD, Other</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immunosuppression: HIV, Diabetes mellitus, Other</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other comorbidities: Cardiovascular disease, Other</td>
<td></td>
</tr>
</tbody>
</table>

Several methodological challenges were highlighted with some of these measurements:

a) **Spirometry**

We suggest that pre and post-bronchodilator spirometry should be performed according to existing ATS / ERS guidelines, for both clinical and research practice. Rigorous quality control procedures are required, to ensure that only spirometry attempts which are usable and reproducible are used for clinical decision making and research. There is a need for clearer methodological guidelines on how to achieve this.

There still exists much controversy over which reference ranges to use for standardisation of spirometry data obtained from low income settings with populations of different ethnicities, with options including local, regional, GLI-2012, and NHANES III reference standards. Similarly, there is no consensus on whether absolute percentage predicted cut offs, of lower limit of normal (LLN) values should be used to define abnormal measurements. Given the existing controversy, we suggest that PTLD clinicians and researchers continue to use their own approaches, but should specify the approach used clearly in any publications.
b) Imaging
There are currently no reporting tools for post-TB CXR or CT imaging which have been validated against patient outcomes. Some patterns of pathology with are seen following pulmonary tuberculosis disease, such as lung destruction, are not clearly defined in the gold-standard ‘Fleischner guidelines’. The need for validated tools was discussed, but in the absence of these we suggest that researchers and clinicians should continue to use their own approaches, but specify these clearly in any publications.

c) Health related quality of life
There are no HRQoL tools which have been specifically developed for, or validated in post-TB populations. Use of existing tools is encouraged, but the need for local piloting, and adaptation for local use was highlighted.

4. Severity scores
There was unanimous agreement that a data-derived severity scoring system for PTLD, developed and validated against patient outcomes, would be of value in clinical practice and research to stratify patients according to disease severity. Agreement was reached that a single scoring tool should be developed for use in both high and low-resource settings, with flexibility according to the tests available. Finally, the need for any scoring system developed to be simple and easy to use was highlighted.

The outcomes against which this severity score could be derived were discussed, and included: mortality, health related quality of life, rate of lung function decline, and rates of exacerbations / hospitalisations. It remains unclear whether the severity of PTLD is a risk factor for recurrent TB-disease, and it was suggested that recurrent TB disease should also be included as an outcome of interest. There was no consensus around a single outcome which should be prioritised when developing these severity scores – although mortality is likely the most important, all were felt to be meaningful to patient wellbeing. The challenge of deriving a severity score using a composite outcome, including all of these, was however highlighted – it may be that different aspects of PTLD are important in driving each of these different outcomes.

It was agreed that we do not yet have sufficient prospective data to derive PTLD severity scores. However, opportunities to pool cohort data from across studies / settings to derive these scores was highlighted.

5. Clinical patterns
The patterns of PTLD are diverse. The need to develop clinical classification systems to guide management of these patterns was agreed.

A set of clinical disease patterns was developed, based on the expert clinical experience of members of the workshop. A voting system was used to determine what this ‘core’ list should include. It was agreed that each pattern may occur with / without symptoms, and that an individual patient may have multiple patterns. Definitions were not discussed in the workshop, but suggestions have been given here, for future review.

It is anticipated that the management strategies we develop for our patients with PTLD can be targeted towards these core clinical patterns of disease.
Table 2: Suggested PTLD clinical patterns, with preliminary definitions provided. All categories assumed to meet basic PTLD minimum case definition, as described above.

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Clinical patterns</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airways</td>
<td>Tuberculosis associated obstructive lung disease</td>
<td>Airway obstruction (FEV1/FVC ratio &lt;0.7 OR &lt;LLN) thought primarily related to small airway disease.</td>
</tr>
<tr>
<td></td>
<td>Bronchiectasis</td>
<td>CT definition – evidence of airway dilatation &gt; diameter of adjacent vessel, or non-tapering, OR  CXR definition – evidence of ring and tramlines</td>
</tr>
<tr>
<td>Parenchyma</td>
<td>Cavitation</td>
<td>A gas-filled space either within an area of pulmonary consolidation, or surrounded by a thin wall</td>
</tr>
<tr>
<td></td>
<td>Parenchymal destruction</td>
<td>Extensive destruction of lung tissue, with a gas-filled space occupying the volume of ≥1 lobe</td>
</tr>
<tr>
<td></td>
<td>Fibrotic change</td>
<td>Areas of parenchymal scarring, with associated volume loss</td>
</tr>
<tr>
<td></td>
<td>Aspergillus related lung disease</td>
<td>Evidence of aspergilloma on imaging OR chronic pulmonary aspergillosis on imaging and blood testing.</td>
</tr>
<tr>
<td>Pleural</td>
<td>Chronic pleural disease</td>
<td>Evidence of pleural thickening on CXR or CT imaging</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Pulmonary hypertension</td>
<td>Elevated pulmonary artery pressures as estimated using doppler echocardiography or measured at right heart catheterisation.</td>
</tr>
<tr>
<td>vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Other</td>
<td>Other pathology, not meeting the criteria above</td>
</tr>
</tbody>
</table>

6. Clinical management algorithms

Several members of the workshop highlighted a concern that many of the classification systems discussed were relevant for settings with access to investigations or specialist medical knowledge, but that most patients with PTLD likely live in resource poor settings with extremely limited access to diagnostics and medical expertise.

The need for simple, algorithm driven management approaches which could be used by health workers in the primary care setting was highlighted. Rather than developing PTLD specific algorithms, it was suggested that modification of existing tools for the syndromic management of respiratory symptoms in resource poor settings would be preferable. The development of these management algorithms was unfortunately outside the scope of this workshop.

Conclusion and recommendations

1. Research priorities

Workshop participants were asked to specify their priorities for ongoing research on PTLD. Responses varied widely, but included the following themes, building on the content discussed in the workshop:

- Validating +/- standardising the tools used to measure PTLD
- Developing severity or phenotyping scores, which are data derived, and correlate with patient-relevant outcomes
- Moving towards practical management – developing algorithms for the diagnosis and management of PTLD in low-resource settings, which are simple to use and feasible for implementation
- Developing a research agenda which builds on data that is already / will shortly be available
2. Conclusion

A key piece of feedback received during the workshop was that disease classification tools can risk becoming “impractical, costly, and complicated... and more damaging than useful, in clinical practice”. As we develop tools for the measurement and description of PTLD, we are eager to keep this in mind. There is a clear need for both research and clinical tools to be simple, relevant to clinical or research practice, and most importantly relevant to patient outcomes.

We are aware that the approaches outlined here are based largely on expert opinion, rather than clear data on which parameters of disease are most relevant to patient outcomes. They will therefore need to be adopted with caution, and reviewed on a regular basis as data emerge. We anticipate that they will evolve considerably in the coming years, but it is our hope that they will facilitate rather than obstruct clinical care in the long-term.
Workshop 2 - The role of the former TB patient in the context of the End TB strategy

Chairs
Florian Marx – DST-NRF Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA)/ Desmond Tutu TB Centre, South Africa
Dalene von Delft – TB Proof, South Africa

Participants
Busisiwe Beko – MSF Khayelitsha
Anna Coussens – Walter and Eliza Hall Institute of Medical Research, Australia
Johnny Daniels – Médecins Sans Frontières, South Africa
Sumona Datta – Imperial College, UK
Veronique De Jager – TASK Applied Science, South Africa
Elvis Irusen – Stellenbosch University, South Africa
Evelyn Kimani – Kiambu, Kenya
Zama Mahlobo – Stellenbosch University, South Africa
Goodman Makanda – TB Proof, South Africa
Kevin Mortimer – Liverpool School of Tropical Medicine, UK
Stephanus Malherbe – Stellenbosch University, South Africa
Ramonde Patientia – TASK Applied Science, South Africa
Ingrid Schoeman – TB Proof, South Africa

Background and state of the art

The WHO’s End TB Strategy calls for patient-centred care and support. It emphasizes the need for context-specific care of patients, taking their educational, emotional and material needs into consideration. It also calls for an end to stigmatization and discrimination, and for countries to set up mechanisms for former TB patients to provide peer group support, to exchange helpful information and experiences. Lastly, the importance of support for life after TB is emphasized.6

However, few places in the world have been able to implement solutions involving former TB patients to achieve these goals. In those places, research has shown that former TB patients can meaningfully contribute towards the cascade of care of current TB patients and help to reduce TB in communities. Former TB patients and civil society organisations have played an important role in finding missing people with TB7, increasing the uptake of screening for latent TB infection8 and preventive therapy among exposed household contacts, as well as in preventing treatment interruption and improving completion of TB treatment.9

Many TB patients suffer from depression, stigmatization and perceived isolation, during and after therapy.10 The detrimental effect of TB stigma in communities have been well described, especially its impact on diagnostic delays, treatment interruption and non-completion11, however few interventions have been attempted to address stigma in communities.

A fundamental principle of the End TB strategy is to focus prevention and case-finding towards groups at high risk of TB. Former TB patients remain at high risk of TB even after completion of
adequate treatment and therefore require solutions to prevent and promptly detect and treat recurrent TB. Recent research has shown that, in areas where TB is most common, the benefits of such solutions might extend to entire communities as transmission and the burden of TB could be substantially reduced.

**Main discussion points**

There have been repeated calls for more advocacy to increase political will to help mobilize funding for TB, and post TB care. Former TB patients can play a crucial role in improving care of patients through advocacy for better access to new TB innovations, patient-centered research, and the involvement of communities in policy and programmatic decisions if their advocacy work can be sustainably funded.

Peer group support of patients and social awareness campaigns aimed at improving knowledge of TB in communities have shown to reduce internalised and anticipated stigma. Support groups and campaigns led by former patients could have a marked impact on reducing stigma, encouraging health seeking behaviour, early diagnosis, and treatment completion among people living with TB, therefore improving the TB Cascade of Care indicators.

Participants agreed that there is a dire lack of counselling for TB patients in programmes which negatively affects treatment outcomes. On an individual patient level, former patients can provide emotional support, address fears and provide an understanding of side effects of TB therapy to those newly diagnosed in their local language, to improve adherence and awareness. They could also assist with counselling regarding the different TB treatment courses, changes along the way, duration and explain the risk of recurrent TB once treatment has been completed.

As former TB patients are an often neglected high risk group for recurrent TB and post TB lung disease, integrated solutions of post-treatment health-care are needed to address the prevention and management of both recurrent TB and progressive (non-TB) lung disease.

**Conclusion and recommendations**

Workshop participants identified an urgent need for further research and engagement with former TB patients, to identify the most cost-effective and least intrusive or detrimental interventions that improve quality of life after TB and prevent recurrent disease. Yet considering them as valuable to the communities from which they come, while addressing the collective trauma of a TB diagnosis.

For many former TB patients, life after TB is never the same. The lasting physiological, social and psychological effects of the disease continue to shape their lives. Involving and investing in former TB patients to help End TB will empower their lives and improve the lives of others affected by TB.
Workshop 3 - Economic, social and psychological consequences of post-TB impairment

Chairs
Denise Evans – University of the Witwatersrand, South Africa
Olena Ivanova - Klinikum of the University of Munich (KUM), Germany
Graeme Hoddinott – Desmond Tutu TB Centre, South Africa

Participants
Marleen Bakker – Erasmus Medical Center, The Netherlands
Marian Loveday - South African Medical Research Council, South Africa
Alison Lupton Smith – Stellenbosch University, South Africa
Dillon Wademan – Desmond Tutu TB Centre, South Africa

Background and state of the art

“For many persons with tuberculosis, a microbiological cure is the beginning not the end of their illness.”

Physical, psychological, social and economic burden of TB on individuals can be enormous. However, limited data are available on post-TB morbidity and mortality to guide TB elimination strategies and international TB guidelines. People cured of TB often find themselves with long-term socio-psychological consequences of the acute disease episode and post-TB associated lung health complications resulting in ongoing economic, social and psychological distress. The current measures of disease burden (such as disability-adjusted life year) expressed as the cumulative number of years lost due to ill-health, disability or early death, only consider health lost from acute illness and death and do not consider residual disability after treatment completion. Thus, the global TB burden estimates do not fully reflect the consequences of post-TB damage. A holistic approach to prevention and management of acute TB as well as its long-term health, economic, social and psychological consequences is needed.

The main aim of the workshop 3: “Social, economic and psychological consequences of post-TB impairment” was to map an existing evidence and outline main research gaps related to long-term disability and associated risk factors, quality of life, psychological wellbeing, patient cost (i.e. direct out-of-pocket expenses), income loss, social support and protection and social consequences due to long-term TB disease. We also considered the WHO End TB strategy and the impact of long-term disability, and the consequences thereof may have on the third goal (i.e. proportion of TB-affected families facing catastrophic costs due to TB). We also discussed tools and data sources needed to address these research gaps.

Presentations from the participants and chairs

Presentation 1: Life after tuberculosis: some data, some examples, some thoughts and some theory.
Presenter: Dillon T Wademan, Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa
Summary and main points:
Qualitative findings from the Tuberculosis Reduction through Expanded Anti-Retroviral Treatment and Screening (TREATS) project were presented. It aimed at describing TB stigma and popular understanding of TB among community members; the experience of diagnosed TB patients and their households; and the link between TB, depression and anxiety. Study participants reported job loss and inability to find work after TB due to physiological and social injury and persistent stigmatization. They perceived TB as something which one cannot avoid; something that exists in the family and questioned its ‘curability’.

Some questions and points for future discussion based on the presented data were suggested:
- What does it mean for the state, health services and clinicians that patients experience TB as unavoidable, hereditary, or worse, incurable?
- What does it mean for former TB patients that they are unable to continue working or take up new work opportunities after their first or multiple TB episodes?
- What is it about the physiological and social manifestation of TB in South Africa (and probably other LMICs) that leads to greater impact on people’s lives than in the global North?

Presentation 2: Socio-economic consequences of tuberculosis
Presenter: Denise Evans, Health Economics and Epidemiology Research Office, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, South Africa

Summary and main points:
A number of key messages were outlined during the presentation: 1) Post TB lung disease requires more attention and support; 2) Physical, psychological, social and economic burden of TB on the patient before, during and even after TB treatment is significant; 3) Limited evidence on the economic consequences of post-TB disease and proportion of TB patients/households facing catastrophic costs; 4) There is a need to understand mortality and disability after treatment completion (post-TB complications) to better estimate the global burden of disease; and 5) Programmatic interventions to address patients’ needs following TB treatment are lacking and there is a need to consider different service delivery packages. Some tools to measure patient costs, quality of life and health care system costs from the TB Sequel cohort (https://www.tbsequel.org/) were presented and discussed. The need for future research was highlighted including robust epidemiological studies, large multi-country cohort studies, mixed-methods (qualitative and quantitative) studies and implementation science research. The key message from the session was that services should consider the individual, holistically, through all the phases of TB care from the onset of symptoms (pre-treatment), diagnosis and treatment, and even beyond active disease (post-TB disease).

Main discussion points
All agreed that there is a dearth of knowledge about the economic, psychological, and social consequences for patients after a TB disease episode. Based on the two presentations above and the keynote speech during the symposium program, participants discussed the research gaps, available and adapted tools to measure social, economic and psychological long-term consequences and burden of TB.
Conclusion and recommendations

The workshop participants have reflected on the main research gaps in the field and outlined some potential steps and recommendations for future research and management of post-TB consequences at (see Table 1) individual level: to assess clinical symptoms and lung impairment after TB together with other indicators such as depression, quality of life etc.; 2) household and family level: to quantify an economic impact of post-TB morbidity and mortality on households; to describe social impact of TB and post-TB morbidity on family and social networks as well as coping strategies and resilience of TB survivors; 3) health care system level: to ensure continuation and integration of health, social and psychological care; to design and test cost-effective interventions on social, psychological and health care for people who survived TB; to counsel and provide health education and information about “after cure life” during TB treatment. Participants have also suggested an umbrella term to characterize the post-TB consequences - Post-TB economic, social and psychological (ESP) well-being.

Table 1.
Workshop 4 - Paediatric post TB lung disease

Chairs
Diane Gray - University of Cape Town, South Africa
Marieke van der Zalm - Stellenbosch University, South Africa

Participants
Andre Amaral - Imperial College London, UK
Peter Donald - Stellenbosch University, South Africa
Uzoh Egere - Liverpool School of Tropical Medicine, UK
Leah Githinji - University of Cape Town, South Africa
Brigitte Glanzman - Stellenbosch University, South Africa
Pierre Goussard - Stellenbosch University, South Africa
Julie Morrison - Stellenbosch University, South Africa
Ensin Nkereuwem - The MRC Unit the Gambia, Liverpool School of Tropical Medicine, The Gambia
Megan Palmer - Stellenbosch University, South Africa
Richard Pitcher - Stellenbosch University, South Africa
Simon Schaaf - Stellenbosch University, South Africa
Julie Switala - Brooklyn Chest Hospital, Cape Town, South Africa
Lesley Workman - University of Cape Town, South Africa
Heather Zar - University of Cape Town, South Africa

Background and state of the art

Presentations from the participants and chairs
The workshop chair presented during the symposium on what is known about the impact of paediatric pulmonary tuberculosis (PTB). During the workshop we had another 2 presentations of working group members on TB susceptibility genes and what we can learn from TB meningitis mortality as a framework to prevent PTB morbidity and mortality.

Presentation 1 (main symposium): Lung health in children post tuberculosis
Presenter: Diane Gray, Paediatric Pulmonology, University of Cape Town, South Africa

Summary and main points
Tuberculosis in childhood remains an important cause of childhood morbidity and mortality. Ten percent of the estimated global TB cases in 2018 were children, meaning there are over 1 000 000 children newly diagnosed with TB annually, and this is a likely underestimate given the difficulties of diagnosing TB in childhood. In the Drakenstein Child Health Study (DCHS), an African birth cohort study, the TB incidence in the first few years of life was 2900 per 100 000 children annually, a stark reminder of the ongoing transmission within our community and the persistent burden of this potentially devastating disease on children. The majority of children diagnosed and treated for TB will be cured. The WHO estimates of children’s lives saved with treatment in the last 7 years is 5-10 million, many of whom may have long-term respiratory health impacts over and above the many other health, social and financial impacts following TB diagnosis and treatment.

A number of large longitudinal cohort studies have clearly shown the implications of a low lung function trajectory, showing that if you have low lung function in infancy and childhood, this tracks and you are likely to enter adulthood with a low lung function. This has highlighted the importance of optimizing lung health antenatally and in early life; and the need to minimize the impact of early life insults that could set you on a poor trajectory for life.
But does it really matter if you reach adulthood with a lower than average forced expiratory volume in 1 second (FEV₁)? There has been growing evidence that it does and recently published data from the PURE study is compelling. This is an international community-based cohort study which included lung function from nearly 130,000 adults, at baseline and then followed up over 7 years with clinical information of cardiac disease, respiratory events and death. This study showed that starting life with even mild FEV₁ impairment (FEV₁ SD <0 and >1) increased mortality, cardiovascular disease and respiratory events. A finding that was consistent across diverse populations, socioeconomic and risk factors profiles. Hence protecting lung growth during early life is critical, and in the context of TB, this means improving prevention and diagnosis, optimizing treatment to minimize long-term impact of TB on lung health and getting better data to inform management of chronic respiratory consequences. It also highlights the importance of measuring lung function in childhood.

How does TB contribute to lung function decline and chronic respiratory symptoms in childhood? TB is a well-documented cause of bronchiectasis in children, post-infectious causes being the most common and TB, measles and pneumonia being the top offenders. Having been treated for TB has also been associated with low lung function in HIV infected adolescents: adolescents who had TB in childhood had lower lung function than those that did not and this tracked over 2 year follow-up. However, despite the high burden of disease and its association with later chronic lung disease and low lung function there are no data on the spectrum, burden or long term outcomes of lung disease in TB in childhood.

How is paediatric TB different to adults? I think it is useful to briefly look at the various stages of disease after primary TB disease in children (See picture 1). Age is an important factor, with young and/or immunosuppressed children being at high risk for severe and disseminated disease. This is important in how we think about these stages: who is at most risk, what the drivers of poor outcome may be and what the likely spectrum of post-TB illness would be after TB at different ages across childhood.

Picture 1. From Marais et al 2014

Age is a very important factor in determining the type of pulmonary TB. However, even young children can develop severe and disseminated disease, with the very young and HIV infected children at particular risk of this.
What is the spectrum of post TB chronic lung disease and how do we classify it?

- **Structural abnormalities** seen on chest radiograph and/or CT scan: bronchiectasis, parenchymal destruction, fibrosis, cavitation, pleural mass or thickening have all been described in children. These are most commonly described in older children and chronic lung disease post complicated nodal disease is less well followed. In addition, assessing the relative impact from polymicrobial infections, co-morbidities or pre-existing lung disease has not been well studied and needs to be considered in longitudinal studies.

- **Clinical symptoms**: As clinicians, symptoms commonly managed in children after TB include chronic cough, tachypnoea, effort intolerance, wheeze and haemoptysis. However, there is very little, if any, comprehensive data on the prevalence, spectrum or severity of persistent or recurrent respiratory symptoms after TB treatment completion on children. This needs to be collected and assessed in relation to structural and physiological measures. In addition, severity scoring should include social impacts.

- **Lung function impairment**: Lung function should and can be measured in children post-TB, to objectively define impairment, severity, progress and response to treatment. Testing would depend on what the underlying pathology likely is e.g. airflow obstruction, volume restriction, diffusion impairment and/or ventilation inhomogeneity. No studies have tested lung function in children post TB, but studies are underway (e.g. Umoya prospective cohort, Walters/ Van Der Zalm; Diagnostic TB prospective cohort cohort, Zar). These studies, and hopefully more, will provide important information into the burden, severity and spectrum of lung function impairment post TB, in well-defined cohorts who have had robust clinical, microbiological and environmental information collected.

- **Social and developmental consequences**: There is currently no data available on the social and developmental consequences of TB in children. Preliminary work from K. Meyerson showed important findings on attachment after long-term hospital admission for complicated TB (personal communication).

**In conclusion**

- TB in childhood remains a significant problem globally and particularly in priority high burden settings
- TB in childhood can have lifelong consequences for lung health contributing to a growing burden of adult non-communicable disease
- Prevention, case identification and prompt appropriate management of TB in children may improve outcome and reduce the burden of chronic respiratory consequence
- Data defining the true burden, spectrum and progression of post TB lung disease in childhood is urgently needed.
- Consensus on clinical and research definitions and collaborative research efforts would greatly help in speeding up effective work in this area

**Presentation 2**: What we can learn from Tuberculous Meningitis: A Major Cause of Mortality & Long-Term Morbidity Post-treatment in Young Children

**Presenter**: Peter Donald, Department of Paediatrics and Child Health, Stellenbosch University, South Africa

**Summary and main points**

Between 60-80% of deaths as result of tuberculosis in the youngest children, age 2-years or less, are caused by TB meningitis (TBM) and the remainder mainly by miliary TB. Not only are the youngest children at the time of infection more susceptible to disease, but the development of the severest forms of TBM is also more likely. TBM, and miliary TB, will usually develop within 3-9 months after infection, and, the younger the child the more likely it is that a family or household contact may be identified as the source of the child’s infection. An awareness
that TB is often a family disease and a routine enquiry in interviews with adult pulmonary TB patients as to whether there are children in the household could make a significant contribution to the prevention and early diagnosis of this dreaded disease. Our documents and TB posters should all carry the statement that “TB is a family disease!” and a routine question should be: “Are there children in your household?”

Children under 2-years of age with a positive tuberculin skin test (or interferon gamma release assays- IGRA) or in close contact with an adult with pulmonary tuberculosis likely have an active primary infection the course of which is still undetermined and they should receive supervised chemotherapy. These strategies might prevent all forms of long-term TB morbidity, including neurological and lung health outcomes.

**Presentation 3:** Novel candidate susceptibility genes in children with severe, persistent, unusual and recurrent tuberculosis

**Presenter:** Brigitte Glanzmann, Stellenbosch University, South Africa

**Summary and main points**

Understanding why only a subset of infected children develop severe, persistent, unusual and recurrent (SPUR) forms of tuberculosis (TB) is an unresolved question. TB disease development may be as a result of an acquired immunodeficiency, such as that caused by anti-TNF-gamma treatment or HIV, but in patients without an acquired immunodeficiency, TB may be a result of inborn errors of immunity. Resistance or susceptibility to Mycobacterium tuberculosis disease relies on the immune system, which is largely determined by the host’s genetic make-up. Genetic diversity exists between individuals and this may account for the observed differences in susceptibility to clinical TB. To date, there are ten genes that have been identified and have been directly associated with Mendelian Susceptibility to Mycobacterial Disease (MSMD). These MSMD causing genes have all been associated with a disruption in IFN-γ and IL-12 immunity, which has been shown to be essential in the control of mycobacterial infections. Next generation sequencing has been applied to a small cohort of paediatric patients (n=17) with SPUR TB infections and possible disease-associated variants have been identified in all patients. Some of these variants are not in the known MSMD associated genes and therefore warrant further investigation (unpublished data). The identification of variants associated with childhood TB is fundamental to understanding the human immune response to M. tuberculosis and potential differences in post TB respiratory morbidity. The clinical findings of this study may also be significant in terms of diagnosis, treatment and outcomes of individuals.

**Main discussion points**

Before the working group meeting we send out an email with questions around post TB lung disease in children; research priorities and case definitions. These questions were discussed again during the face-to-face meeting and we reached consensus on a couple of them.

Everyone agreed that there is no data available on the impact of paediatric PTB and that there is an urgent need to understand and quantify the problem.

The working group identified the following key research priorities:

- Determining burden and spectrum of pediatric post TB lung disease
- Defining case definitions, standard reporting tools and data definitions
- Investigating determinants of post TB lung disease in children
- Measuring the social and developmental consequences of children and families affected

The chairs send out a Delphi questionnaire on the use of the NIH case definitions, what types of diagnostic tools should be considered to determine post TB lung disease and what could be the minimal case definition.

The NIH 2015 TB case definitions are used in paediatric diagnostic research and categorizes children with suspected Tb into 3 categories: confirmed, unconfirmed and unlikely TB cases. The working group agreed that it is important to not exclude the unconfirmed cases as this would exclude a large group of paediatric TB cases. The group acknowledged the challenges using the unconfirmed TB
cases and separate analyses could be done with the confirmed cases. Important covariates will include the different types of PTB and severity of disease. The working group decided on a minimum case definition for post TB lung disease which will require revisions as more evidence becomes available.

**The proposed minimal case definition for paediatric post TB lung disease:**

“Evidence of chronic respiratory impairment” in a child previously *adequately treated* for pulmonary tuberculosis in whom active TB is excluded, and in whom no other cause of chronic lung disease is the predominant cause. 

* Persistent (> 4 weeks), or recurrent (>2 episodes in 6 months) respiratory symptoms (cough, wheeze, tachypnea, sputum production) AND/ OR persistent radiological changes AND/OR low lung function measurements (<lower limit of normal).

** According to local recommended treatment guidelines and with >80% treatment adherence in South Africa.

Until we have established the impact and burden of paediatric post TB lung disease, we should aim to follow up everyone to define who is at risk for post TB lung disease. There is no capacity in routine care and should initially be done in research settings, including all upcoming treatment trials.

**Next steps and key obstacles**

**What do we need?**

Funding is needed to study the (long-term) impact of TB on the lung health of children as this is currently not supported in the already overburdened routine health services. Estimates of the burden of post TB lung disease are important to get funding allocated to this research.

**What do we have?**

Preliminary data can be attained by retrospectively analyzing data collected in diagnostic, observational and treatment studies. There is data available from several studies with CXR readings at the end of treatment. This could be a first start to measure radiological burden of post TB lung disease. Most multi-drug resistant (MDR) studies follow up after TB treatment, which could be looked at retrospectively. In addition, there are a few studies underway that are determining long-term burden of TB on lung health throughout Africa

**How do we get there?**

It will be important to collaborate and combine data in order to get first estimates of the burden of the problem, it is therefore important to get more insight into the work that is ongoing or planned in this field. Finally, we need to include the community and health care workers early on in the process to get their feedback on experiences after TB and how post TB lung health assessment could be included in routine services.

**Conclusions and recommendations**

The working group identified an urgent need to get data on paediatric post TB lung disease and engage with families and health care workers, to identify key research priorities to improve lung health outcomes in children.
Workshop 5: Pathogenesis/mechanisms of disease & prevention of damage

Chairs
- Cari Stek - University of Cape Town, South Africa & Institute of Tropical Medicine Antwerp, Belgium
- Naomi Walker - Liverpool School of Tropical Medicine, UK
- Robert Wallis - Aurum Institute, South Africa

Participants
- Eric Bateman – University of Cape Town, South Africa
- Anna Coussens - Walter and Eliza Hall Institute of Medical Research, Australia
- Rodney Ehrlich - University of Cape Town, South Africa
- Stephanie Griffith-Richards – Stellenbosch University, South Africa
- Anneke Hesseling - Desmond Tutu TB Centre, South Africa
- Elvis Irusen - Stellenbosch University, South Africa
- Ismail Kalla – University of Witwatersrand, South Africa
- Fanie Malherbe – Stellenbosch University, South Africa
- Florian Marx - DST-NRF Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA), South Africa
- Jotam Pasipanodya – Texas Tech University Health Sciences Centre, USA
- Jantjie Taljaard - Stellenbosch University, South Africa
- Grant Theron - Stellenbosch University, South Africa
- Marieke van der Zalm – Desmond Tutu TB Centre, South Africa
- Gerhard Walzl - Stellenbosch University, South Africa

Background and state of the art

Chronic respiratory symptoms, impaired lung function and persistent radiographic abnormalities (features of post-TB lung disease) are common findings in people with a history of tuberculosis. Current TB treatment regimens aim to promote mycobacterial death by combining a number of antimycobacterial agents. Host-directed therapies (HDT), have started to gain attention in the TB field as possible adjunctive agents to shorten treatment duration, reduce the number of drugs and combat drug resistance. An additional benefit of an HDT added to tuberculosis treatment may be reduced lung damage and prevention of post-TB lung disease. However, an understanding of the pathogenesis of pulmonary damage in TB is fundamental to successfully predicting which interventions could be beneficial.

This workshop examined mechanisms of TB disease from a basic science perspective, focusing on the interaction between host and pathogen in the pathophysiology of tissue damage at a cellular and tissue level and potential host-directed therapies (HDTs).

Key objectives were to:
1) Identify priority target pathophysiological pathways for intervention
2) Review the current landscape of HDT trials: which pathways targeted, agents evaluated, and endpoints used
3) Develop consensus on appropriate endpoints for HDT trials
4) Develop consensus on the research gaps leading to set of recommendations

Presentations from the participants and chairs

**Presentation 1: Mechanisms of TB tissue damage**
**Presenter:** Dr Naomi F Walker, Department of Clinical Sciences, Liverpool School of Tropical Medicine

**Summary and main points:**
This talk highlighted evidence from cellular, ex-vivo, animal and human observational studies indicating a key role for host immune responses in pulmonary tissue damage during active TB. Virulent M. tuberculosis subverts host immune responses promoting mycobacterial survival and transmission. A characteristic (and destructive) feature of pulmonary TB favoring transmission is the formation of a pulmonary cavity. M. tuberculosis-driven, host-derived matrix metalloproteinase activity promotes cavitation. The collagenases, MMP-1 and neutrophil-derived MMP-8 are key MMPs. Neutrophil fate (apoptosis, necrosis or netosis) and the balance of arachidonic acid derivatives influence the release of pro-and anti-inflammatory cytokines, directly and indirectly affecting macrophage fate. Macrophage fate (necrosis) affects M. tuberculosis survival and the extent of the subsequent host inflammatory response that ensues. Host genetic and environmental factors likely play a part in these pathways, but further work is required to understand this fully.

**Presentation 2: Host-directed therapies: What is in the pipeline?**
**Presenter:** Dr Robert Wallis, Aurum Institute, South Africa

**Summary and main points:**
This talked described two general categories of TB host-directed therapy, anti-inflammatory, and anti-microbial (i.e. inducing in phagocytic cells the capacity to kill MTB). Clinical trial of antimicrobial HDTs (metformin, imatinib) will begin shortly. A trial at the Aurum Institute supported by the Gates foundation examined 4 candidate HDTs. Two of these, CC-11050 and everolimus, showed superior recovery of FEV1 at 6 months, 2 months after HDT treatment had ceased, possibly indicating effects on post-inflammatory lung remodeling. If sustained, this effect could recover 2 of the 4 years of life otherwise lost post-TB.

Figure 1.
Presentation 3: Host-directed therapy discovery

Presenter: Dr Anna Coussens, Walter and Eliza Hall Institute of Medical Research, Australia

Summary and main points:
TB pathogenesis centres on the triad of interaction between host, pathogen and environment. TB risk interact, synergistically and in some cases antagonistically, exacerbating the cellular mechanisms of pathogenesis of the infecting bacteria. In order to improve TB patient outcomes we cannot ignore the variability in underlying individual patient risk factors to solely kill the invading pathogen and measure efficacy exclusively on microbiological outcome, we need to develop host-directed therapies which target resolution of the specific pathways of pathogenesis operating in each patient, particularly focusing on preventing and resolving cell death, matrix destruction and fibrosis, the primary mechanisms which lead to long term lung morbidity.

Seasonality in TB presentation has been observed in the Northern and Southern Hemispheres, whilst equatorial countries display a different pattern of seasonality. Vitamin D deficiency has been linked to seasonal TB presentation in these locations of high latitude. Thus, suggesting vitamin D as an HDT globally is likely inappropriate and the reason for considerable inconsistency between trials. There would be no benefit of adjunct vitamin D if the population is not at risk of deficiency. Conversely, vitamin D is likely to benefit those at greatest risk of deficiency. In Cape Town, South Africa, TB notification rates oscillate, with a consistent annual nadir in TB cases in autumn following the summer peak in vitamin D and highest case numbers occurring between winter and spring, the months of lowest vitamin D. Epidemiologists often highlight the winter increase in presentation can be confounded by other contributing factors, such as increased time in doors, and exposure to other respiratory pathogens. However, it is not the peak which is of importance, but the autumn trough; suggesting that environmental conditions leading up to this time of year, improve TB immunity and reduce the risk of TB progression.

We can improve our understanding of the mechanisms of pathogenesis which impact TB risk by studying the cellular contribution to increased risk at these times of reduced or heightened risk. Furthermore, we should also examine the epidemiological factors which exacerbate risk, for example HIV co-infection, other respiratory pathogens and household exposure. Clinical strain variation should not be ignored and researchers need to investigate this diversity, in the context of variation in clinical presentation.

The HDT field therefore has a big task ahead of them. Firstly, we need to determine whether all pathways of pathogenesis can be targeted with the same HDT, or more likely favour an individualized approach, testing HDTs which target specific pathways, selecting the appropriate HDT for the pathogenesis pattern of each patient, based on their underlying risk interactions, and potentially infecting strain. Secondly, we need to assess the efficacy of the HDT, not against microbiological outcome, but reduced markers of pathogenesis in the specific pathways targeted by the HDT. In the same way that a single antimicrobial is an ineffective at killing M. tuberculosis, one single HDT may be ineffective in resolving all pathology.

Presentation 4: Baseline spirometry values in Clinical Tuberculosis Trials

Presenter: Dr Cari Stek, University of Cape Town, South Africa & Institute of Tropical Medicine Antwerp, Belgium
Summary and main points
This talk highlighted the difficulties in performing spirometry in study participants at the beginning of their TB treatment. Participants are often ill and weak, cough or shortness of breath can interfere with the correct performance of spirometry. Especially the need for three reproducible measurements should be reconsidered as an absolute requirement in this setting.

Main discussion points

Participants were self-selected from Symposium attendees. We employed the Delphi method (see Health Technology Assessment 1998; Vol. 2: No. 3 Murphy et al) and open group discussion to arrive at consensus. A Pre-workshop questionnaire included questions to generate agenda items for the workshop and record views of participants on a number of questions selected by the workshop chairs. The responses were recorded anonymously and collated by the chairs for presentation at the workshop. During the workshop, participants were invited to revise their responses following presentations, feedback from the other participants, and open discussion, in further rounds of voting. Options for responses were modified in light of previous rounds of voting.

In the plenary session of the symposium, it was agreed that a consensus would be defined as achieving a majority of 66%.

Pre-workshop Delphi questionnaire
The following summarises the questions and responses obtained from the pre-workshop questionnaire:

Q3 Should all candidate HDTs be tested in animal models?  
(Answered = 5)  
Yes = 1  
No = 2  
Don’t know/Not sure = 2

Q5 Do spirometry criteria need to be revised or adapted to measure function in patients with both acute and chronic disease?  
(Answered = 6)  
Yes = 2  
No = 1  
Don’t know/Not sure = 3

Q6 If only one curve can be obtained due to coughing or shortness of breath, should this be accepted as sufficient?  
(Answered = 6)  
Yes = 3  
No = 0  
Don’t know/Not sure = 3

Q7 Can alternative methods (plethysmography, measurements of tidal breathing, etc) make up for missing information due to coughing or shortness of breath?  
(Answered = 6)  
Yes = 2  
No = 0
Don’t know/Not sure = 4

Q8 Should missing baseline spirometry values be approximated based on other parameters (eg, radiographic extent of disease)?
  (Answered = 6)
  Yes = 0
  No = 4
  Don’t know/Not sure = 2

Q10 What is the minimum period of post-treatment observation necessary?
  (Answered = 6)
  <3 months = 0
  3–12 months = 3
  12–24 months = 2
  >24 months = 1
  Don’t know/Not sure = 0

Q11 Should trials include both HIV + and – patients?
  (Answered = 6)
  Yes = 6
  No = 0
  Don’t know/Not sure = 0
  [NB: Consensus achieved]

Q12 The most suitable endpoint for a HDT trial would be (5 options)?
  Answered = 6 [See results and discussion below]

**Delphi outcomes during the workshop**

During the workshop, we prioritised reaching consensus on was the most suitable end point for a HDT trial (Q12). The majority of trials investigating HDT in pulmonary TB have focused on time to culture conversion as primary endpoint; other endpoints used are mortality, radiological response, and spirometry; one study used a co-primary endpoint of time to culture conversion and symptoms. A co-primary endpoint is defined as the use of two (or more) endpoints for which demonstration of an effect on each in needed for determining that a drug is effective.

The pre-workshop question on this topic was completed by only six respondents, the majority of whom felt a co-primary endpoint would be the most appropriate endpoint for a HDT trial.
During the workshop we repeated the Delphi voting process twice, following further explanation of the issues at hand, in order to get more detail and give more participants an opportunity to share their opinion. We included new suggestions for endpoints. Eleven respondents (out of 14 workshop participants) reached consensus on a co-primary endpoint being the most suitable endpoint for a trial looking at host-directed therapy aiming to reduce lung damage in tuberculosis: 10 of 11 respondents indicated this would be their preferred endpoint. One respondent gave preference to any of the following ‘single parameter endpoints’: tuberculosis relapse, inflammation measured on a PET/CT scan, (six-minute) walk test, or a (still to be determined) biomarker that associates with risk of chronic inflammation. One of the respondents added the following comment: “An endpoint should be based on host improvement, not culture conversion. Rather resolution of inflammation, improved lung function, prevention of relapse etc.”

Although we reached consensus on a co-primary end point, there was no agreement on what the components of this co-primary endpoint should be. Among the 10 respondents, there were six different combinations of parameters suggested as a co-primary endpoint – (see table 1); one respondent did not specify parameters to be included in a co-primary endpoint.

**Table 1.**

```
<table>
<thead>
<tr>
<th></th>
<th>No. of respondents</th>
<th>1st round (number of participants voting for each option)</th>
<th>2nd round (total points for each option)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Co-primary endpoint consisting of</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A Clinical symptoms and radiology</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>B Spirometry and time to sputum culture conversion</td>
<td>2</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>C Walk test and time to sputum culture conversion</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>D Clinical symptoms, radiology and time to sputum culture conversion</td>
<td>1</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>
```
Clinical symptoms, radiology, spirometry and time to sputum culture conversion | 2 | 17
---|---|---
Spirometry, including DLCO, and radiology | 1 | 7
**Single parameter endpoints (as suggested below)** | 1 |
Tuberculosis relapse | | 11
Inflammation measured with PET/CT scan | | 4
Walks test | | 3
Biomarker | | |

[Black out the response if not included in that round of voting]

In an attempt to reach further consensus on the components of a co-primary endpoint, we discussed the various options and asked participants to vote again. This time, they were asked to assign 3 points to their preferred endpoint out of the newly acquired list, 2 points to their second choice and 1 point to their third choice. The outcome of this second round of voting is summarized in the table above.

We were unable to reach further consensus on a preferred end point for a trial looking at host-directed therapy aiming to reduce lung damage in tuberculosis. The main discussion points brought forward are summarized below:

There was a general agreement that microbiological endpoints like time to culture conversion should no longer be the single primary end point of HDT trials in tuberculosis. However, there was no agreement on whether microbiological endpoints should be part of a co-primary end point.

Participants in favour of including a microbiological endpoint argued that this endpoint is important in establishing ‘no harm’ of possible HDTs. Participants against including a microbiological endpoint argued that this outcome in itself should not dictate whether a possible HDT is successful if it does not or negatively affect either the process leading to lung damage (e.g. inflammation) or long-term outcomes that are beneficial for patients treated for tuberculosis, like decreased lung function or tuberculosis relapse.

There was general agreement that with the sparse knowledge about post-tuberculosis lung disease currently available, assessing a wide variety of possible endpoints is needed to gain more knowledge. However, we feel it is impossible to combine all these components into one co-primary endpoint, as this severely reduces the chance of finding any beneficial HDT. We realize we have not sufficiently assessed whether the concept of a co-primary endpoint was known to everyone, and that insufficient knowledge may have affected participants’ choice for a co-primary endpoint with more than two components. Obviously, not including a parameter in the co-primary endpoint does not mean it can or will not be assessed as a secondary end point in the trial.

**Conclusion and recommendations**

Overall, delegates were unable to achieve consensus on many issues, due to lack of evidence and therefore the objectives of the workshop were not realised. However, the following recommendations on clinical trial design and candidate agents for evaluation were agreed:

- Basic science has identified some promising potential candidate HDT for post-TB lung disease. Some HDT clinical trials in progress have evaluated post-TB outcomes and results are expected in the near future. However, the agents evaluated in these trials were not exclusively selected on the grounds of basic science or animal data, and the rationale for
selection was in some cases theoretical or pragmatic. There is a need to develop a pathway from basic science to HDT clinical trials [Objective 1 & 2].

- More clarity is required on post-TB syndrome definitions and outcomes to inform HDT clinical study design: currently clinical trials should collect data on a diverse range of endpoints e.g. syndromic, radiological, physiological, microbiological [Objective 3 – no consensus on a single trial endpoint reached].

- It is not likely that there will be a "one size fits all" preventative or HDT approach. The effect of an HDT is likely to be different at different time course in the illness (including various stages of TB infection). Consensus on sub-groups of post-TB are required to select patients for trials. More research is required to identify potential HDT candidates [Objective 3 & 4].

- HDTs may adversely affect microbiological outcomes (i.e. promote discordant lung health and micro outcomes) and may have the potential to worsen lung damage. All future HDT trials should include post-TB endpoints [Objective 4]

- HDT trials should include people living with HIV infection [Objective 4 – Delphi consensus reached]
Workshop 6: Treatment and holistic management of post-TB

Chairs

Sanne van Kampen, Leiden University Medical Center, The Netherlands
Stellah Mpagama, Kibong’oto Infectious Disease Hospital, Tanzania
Rupert Jones, University of Plymouth, UK (by phone)

Participants

Brian Allwood, Stellenbosch University, South Africa
Anthony Byrne, University of Sydney, Australia
Susan Hanekom, Stellenbosch University, South Africa
Alison Lupton Smith, Stellenbosch University, South Africa
Lamla Nqwata, University of the Witwatersrand, South Africa
Obianuju Ozoh, University of Lagos, Nigeria
Jotam Pasipanodya, Texas Tech University Health Sciences Center, USA
Jane Shaw, Stellenbosch University, South Africa
Catharine Tadyanemhandu, University of Zimbabwe, Zimbabwe

Background and state of the art

Currently, there are no international or national guidelines that advise on how to manage post-TB complications. Current guidelines for TB indicate that after microbiological cure, no follow up is needed. However, from the literature we know that post-TB lung complications are frequent and can lead to considerable morbidity and mortality.

Evidence on the effects of pharmacological and non-pharmacological management of post-TB lung complications are scarce. Except for smoking cessation, there is no evidence to demonstrate whether current therapies actually halt progression of lung destruction or restore lung function. Therefore, practice management focuses primarily on alleviating symptoms. These pharmacological management strategies depend on clinical presentation (either airflow obstruction or restrictive ventilatory defect), and treatment algorithms are derived from the management of other chronic lung diseases such as chronic obstructive pulmonary diseases (COPD), bronchiectasis or restrictive lung diseases. Medicine groups include bronchodilators, anticholinergic, methylxanthines, glucocorticoids, mucolytic and anti-fibrotic agents. Non-pharmacological treatment options include surgery, lung ventilation techniques, pulmonary rehabilitation, patient education for self-management, lung health awareness and training and smoking cessation. Surgical interventions, lung ventilation techniques and newer inhaled bronchodilators/corticosteroids (as single agents or combinations) are not readily available in most low-resource settings. There is some preliminary evidence that pulmonary rehabilitation is effective for post-TB lung complications (e.g. from the Fresh Air studies) but this is not enough for a general recommendation.

Presentations from the participants and chairs

Presentation 1: Systematic review of the literature
Presenter: Dr Sanne van Kampen, Leiden University Medical Center, Netherlands

Summary and main points
A recently published systematic literature review assessed the scope of current evidence on post-TB lung complications. Eight databases were searched for records published between 1 January 1990 and 1 December 2017 using a wide set of search terms. A total of 156 studies addressed post-TB of which 56 were on treatment and management. Most studies assessed surgery, some lung ventilation techniques, and few pulmonary rehabilitation and medication. Most studies were conducted in the US, Europe, Japan and North East Asia, while there was a lack of studies from regions with high burdens of TB (and presumably post-TB), i.e. Eastern Europe/Central Asia, Africa and South East Asia. As surgery and ventilation techniques are not available routinely and may not be available in high burden TB countries, more studies are needed on pulmonary rehabilitation and medication.

**Presentation 2:** Pharmaceutical treatments  
**Presenter:** Dr Stellah Mpagama, Kibong’oto Infectious Disease Hospital, Tanzania  
**Summary and main points**  
Currently, there is no evidence on pharmacological management of post-TB lung complications. Management focuses primarily in alleviating illness; halt progression of lung destruction while restoring lung function. Pharmacological management depending on clinical presentation either airflow obstruction or restrictive ventilatory defect, treatment algorithms are derived from the management of other chronic lung diseases such as chronic obstructive pulmonary diseases (COPD), bronchiectasis or restrictive lung diseases. Medicine groups include bronchodilators, anticholinergic, methylxanthines, glucocorticoids, mucolytic and anti-fibrotic agents. A pilot study including LABA, LAMA and pulmonary rehabilitation estimated the efficacy in post-TB lung diseases. Some of the anti-TB medicines such as fluoroquinolone class protect patients from TB immunopathology, therefore prevents development of post-TB lung diseases. Example minocycline demonstrated dose dependent anti-inflammatory activity and downregulation of extracellular matrix based remodeling pathways and therefore could prevent post-TB lung diseases.

**Presentation 3:** Non-pharmaceutical management  
**Presenter:** Rupert Jones, University of Plymouth (presented by Sanne van Kampen, Leiden University Medical Center, Netherlands)  
**Summary and main points**  
Non-pharmaceutical treatment options for post-TB lung complications are currently also derived from the management of other chronic lung diseases. Like COPD patients, post-TB patients should be offered pulmonary rehabilitation, patient education for self-management, lung health awareness and training, and advice on avoiding tobacco and biomass smoke exposure. Emerging evidence shows the value of pulmonary rehabilitation. Pulmonary rehabilitation usually involves a six-week programme of bi-weekly exercise and education sessions supervised by physiotherapists or nurses. Education for self-management includes strategies to cope with breathlessness and exacerbations. Lung health awareness focuses on the risks of smoke exposure and lifestyle behavior, of which smoking cessation is an important element. Pilot studies of pulmonary rehabilitation in Uganda, Vietnam and Kyrgyzstan confirmed feasibility and acceptability and it only required existing local staff and equipment. Major improvements were seen in exercise capacity and quality of life and unexpected improvements in chest pain. A youtube video of the project was shown: https://www.plymouth.ac.uk/research/primarycare/fresh-air/pulmonary-rehabilitation-in-uganda. Education materials have also been developed for Uganda to train health care workers and inform patients on lung health, self-management and smoking cessation. The current RECHARGE
research programme is conducting 4 fully powered RCTS to assess the efficacy pulmonary rehabilitation in high burden regions.

**Presentation 4:** RCT on bronchodilators for post-TB  
**Presenter:** Anthony Byrne, University of Sydney, Australia  
**Summary and main points**  
A recent Korean study looking at the cost and healthcare utilisation in post-TB patients, showed they have recurrent respiratory events, requiring hospitalisation and other medications, with associated costs. Another Korean retrospective cohort of post TB patients showed improved survival on a LAMA regimen, after adjustment for confounders.

Anthony’s group is now starting a new pilot study in Peru to screen newly diagnosed/early treatment TB patients with lung functions and give treatment (LABA/LAMA and pulmonary rehab) accordingly. At the same time Xpert MTB/RIF is introduced in this setting. His group has also requested funding for an RCT on inhaled bronchodilators for post-TB COPD (LABA/LAMA, not steroid). Discussion points with regards to the RCT were whether patients with eosinophilia and high FENO should be excluded. It was suggested to rather use exclusion of bronchodilator reversibility, since the phenotype of post-TB is not known yet. It was also highlighted that an additional arm with a single LABA (which is easily available and cheap) might add to the usability of the results.

**Presentation 5:** Data on preventing TB lung damage  
**Presenter:** Jotam Pasipanodya  
**Summary and main points**  
Jotam’s group performed a retrospective study suggesting that there was less severe lung function impairments in patients who were on FQ (moxi, not levo) regimens than standard regimen. This brings up the question whether other outcomes should be considered in assessing and prescribing anti-TB treatment than just microbiological cure. Further, minocycline which is known to have potent immunomodulatory activity demonstrated very good bactericidal activity of both log-phase growth and semi-dormant bacilli in the hollow-fiber model. They postulated and presented sequencing data to suggest that minocycline can circumvent and possibly modulate inflammation which drives post-TB lung damage. Question is, should it be prospectively trialled as a possible means of preventing damage when given in addition to routine treatment? It was suggested to consider two categories of interventions for post-TB – those for prevention of damage and those for treatment of established damage.

**Main discussion points**

It will be challenging to develop standardised treatment guidelines for post-TB lung complications, since post-TB has many phenotypes, and these require different treatments and have different treatment outcomes. For example, bronchiectasis and COPD response to bronchodilators is different and can be confounded by fungal infection. In clinical practice as well as research, this means that phenotyping patients before implementing treatment interventions is of great importance. In terms of pharmaceutical treatment options, the participants highlighted the lack of access to medicines in under-resourced settings and the inequity in access even within countries. For example, Nigeria and Tanzania only have access to salbutemol, salmeterol, beclomethasone and aminophylline. South Africa has no SAMA, and only controlled access to LABA/ICS combinations and LAMA. One problem is that there is no data capture of medicine demand and supply that can motivate procurement of
more medicine. The International Multidisciplinary Programme to Address Lung Health and TB in Africa (IMPALA) network is assisting African countries in integrating chronic lung diseases including post-TB in the health systems. Opportunity for getting this data in terms of non-pharmaceutical treatment options, pulmonary rehabilitation seems promising, but there was some discussion on how suitable programmes developed for COPD were for post-TB. The pulmonary rehabilitation programme at Tygerberg was adjusted to suit the local population – e.g. once a week visits because transport is an issue, finding an alternative to walking because of safety issues. In Uganda, the UK programme was amended in terms of the topics of the education sessions - e.g. less on smoking behavior and more on biomass smoke exposure. The is a need for large scale randomized controlled trials (RCTs) on pulmonary rehabilitation as well as implementation studies.

Consensus and Delphi method

This group answered four questions using the Delphi method. All 11 participants (100%) voted for a pre-defined answer (answers were non-exclusive) and then votes were counted and results discussed to see if consensus could be reached.

Question 6.1 Do you think current clinical guidelines for chronic lung diseases are adequate for prevention and treatment of post-TB lung complications?
0% A. Yes
82% B. No
0% C. Unsure
There was consensus about the need for clinical guidelines on post-TB complications as it is likely to be different from many other chronic lung diseases. More evidence is needed on the pathophysiology and outcomes of post-TB before adopting existing guidelines. Key problem is the diversity and spectrum of post-TB complications, which implies that new algorithms might be needed for each clinical phenotype. However, in the meantime patients should already receive the best available care based on expert opinion.

Question 6.2 Which of the following health outcomes should be included to measure success of post-TB treatment in a clinical setting?
73% A. Lung function
73% B. Radiological outcomes (CXR, CT)
91% C. Respiratory symptoms
91% D. Quality of life
82% E. Physical fitness/Clinical measurements
36% Other
Most respondents indicated they would use all the outcomes mentioned. Additionally, outcomes of mortality, exacerbations and hospitalisations, recurrent TB, socioeconomic measures, pulmonary rehabilitation and drug adverse effects were also considered important. These outcomes are not only important to measure success of post-TB treatment, but also to assess people for post-TB lung complications. It was suggested that there should be a minimum package (e.g. lung function testing) for assessing and monitoring post-TB patient.

Question 6.3.1 At what point in time should TB patients be assessed for post-TB?
18% A. During TB treatment
Participants agreed that post-TB should be assessed at least at end of treatment. In addition, some argued that assessment should take place already during and at the start of TB treatment, because some treatment interventions could be run simultaneously with TB treatment and prevent worse lung complications. However, there is no evidence on the effects and test burden on patients. Programmatically and pragmatically it makes sense to screen at the end of TB treatment and refers the patient to the chronic lung disease clinic if a chronic abnormality is found. It should be noted that follow up should be continuous as some lung damage could resolve by itself, while others could only occur months or years after the end of TB treatment.

Question 6.3.2 At what point should TB patients be treated for post-TB?

<table>
<thead>
<tr>
<th>Option</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. During TB treatment</td>
<td>9%</td>
</tr>
<tr>
<td>B. Immediately at the end of TB treatment</td>
<td>9%</td>
</tr>
<tr>
<td>C. ……. Months/years after TB treatment</td>
<td>9%</td>
</tr>
<tr>
<td>D. Every…. months/years for …. Months/years after TB treatment</td>
<td>0%</td>
</tr>
<tr>
<td>E. Not routinely, but only if they present with respiratory symptoms</td>
<td>18%</td>
</tr>
<tr>
<td>Other</td>
<td>18%</td>
</tr>
</tbody>
</table>

No consensus was reached, because too many patient and programme-specifics need to be considered. For example, literature suggests that lung function stabilizes around six months after the end of TB treatment, but this may vary for individual patients. Also, certain host-directed therapies may not be appropriate for all people with post-TB. Timelines for re-assessments and follow up needs research.

Question 6.4 What treatment do you think are most appropriate to offer to post-TB patients at primary care level?

<table>
<thead>
<tr>
<th>Option</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Bronchodilators</td>
<td>55%</td>
</tr>
<tr>
<td>B. Other medicine (please specify)</td>
<td>18%</td>
</tr>
<tr>
<td>C. Pulmonary rehabilitation programme</td>
<td>91%</td>
</tr>
<tr>
<td>D. Education about self-management</td>
<td>82%</td>
</tr>
<tr>
<td>E. Airway clearance</td>
<td>55%</td>
</tr>
<tr>
<td>Other</td>
<td>9%</td>
</tr>
</tbody>
</table>

Almost all participants agreed that pulmonary rehabilitation and education about self-management could be effective for post-TB patients and might be offered at the initial screening. There were varied answers for airway clearance, bronchodilators and other medications, as those should be tailored to the patient phenotype. At present, there is not enough evidence to strongly recommend any of these treatment options for post-TB patients, so (cost-)effectiveness studies are needed. As a start, we can assess current chronic respiratory disease treatment guidelines, since they are already being used now for post-TB. Besides effectiveness, implementation and costs should also be assessed because they will vary per setting. For example, in the UK and the Netherlands, pulmonary rehabilitation programmes are more costly than bronchodilators due to staff costs, while in Uganda and other countries it may be the other way around.
Conclusion and recommendations

The participants agreed that there is a need for specific clinical guidelines for the prevention and treatment of post-TB lung complications. Post-TB complications come in a lot of clinical variations, including COPD, bronchiectasis, fibrosis, etc., which means that there will be a need for targeted treatment options. There is currently not enough evidence on the positive and negative effects of existing treatment for other chronic lung diseases on post-TB patients.

There was consensus on the need to follow up patients after TB treatment and assess for recurrent TB as well as post-TB. Studies are needed to assess the best timepoints to screen and rescreen for post-TB. As a minimum, assessment should occur at TB treatment completion and outcomes should include respiratory symptoms, health related quality of life, exacerbations, lung function, radiological outcomes and mortality. These recommendations can already be included in clinical guidelines.

More research is needed on the (cost-)effectiveness of post-TB treatment options, including pulmonary rehabilitation programmes, education about self-management, airway clearance and bronchodilators (in this order). Existing treatment for chronic respiratory diseases should be assessed for their effectiveness in post-TB. A post-TB clinical trials network could be set up to harmonize study protocols, create a biobank of samples, and create a database of clinical data. Finally, studies should measure the burden of post-TB lung complications and other chronic lung diseases at primary care levels, so that the impact of interventions can be assessed.
Workshop 7 - Health Systems Advocacy

Chairs
Kevin Mortimer, Liverpool School of Tropical Medicine, UK
Uzochukwu Egere, Liverpool School of Tropical Medicine, UK
Ingrid Schoeman, TB Proof, South Africa

Participants
Marleen Bakker – Erasmus Medical Centre Rotterdam, The Netherlands
Busisiwe Beko – Médecins Sans Frontières, South Africa
Olena Invanova – Klinikum of The University of Munich (KUM), Germany
Goodman Makanda – TB Proof, South Africa
Muhammad Osman – Desmond Tutu TB Center, South Africa
Richard Pitcher – Stellenbosch University, South Africa
Phumeza Tisile – TB Proof, South Africa
Dalene von Delft – TB Proof, South Africa
Dillon Wademan – Stellenbosch University, South Africa

Background and state of the art
Tuberculosis care and control are essential elements of the health system. The health system has therefore continued to be at the center of the global efforts to fight Tuberculosis. The realization since the 1990s of the importance of strong health systems for a successful achievement of set TB Control milestones led to several efforts to strengthen health systems in low and middle income countries. TB remains a major public health concern worldwide, with over 10 million incident cases and 1.3 million deaths in 2017. However, ongoing efforts to end TB have resulted in a fall in disease burden and absolute number of TB deaths; TB deaths among HIV negative people has fallen from 1.8 million in 2000 to 1.3 million in 2017. There is therefore now an increasing number of individuals facing ‘life after TB’ challenges including several post-TB lung disorders and irreversible side effects of long-term treatment for drug resistant tuberculosis, like hearing loss.

The Health systems advocacy workshop discussed health systems as a foundation for quality TB care and explored opportunities to impact health systems functioning through advocacy to improve the quality of TB care for all at each step of the TB care cascade, including life after TB. The workshop drew from successful advocacy campaigns that impacted policy and identified priority areas for life after TB advocacy.

Presentations from the participants and chairs

Three presentations were made during the workshop
1. The first presentation was made by Dr Uzochukwu Egere and was an overview of the health system bottle necks in the management of patients with Tuberculosis.
2. Ms Ingrid Schoeman led the 2nd presentation with card decks which used human centred design to illustrate the barriers in TB care cascade.
3. The 3rd presentation was a presentation by Dr Dalene von Delft of an example of advocacy through storytelling and partnership which impact decision making.
**Presentation 1:** Health system bottlenecks in the management of Tuberculosis  
**Presenter:** Dr Uzochukwu Egere, Liverpool School of Tropical Medicine  
**Summary and main points**  
This presentation set the stage for the health systems workshop. It was emphasized that health systems are crucial to realizing the global TB control vision especially as the world embarks on the ambitious elimination milestones. However, health systems remain plagued by several challenges that present formidable bottlenecks in the management of Tuberculosis especially in high burden settings. This presentation identified important health systems bottlenecks which are reflected on the health system building blocks and negatively impact the TB care cascade. Weak health systems were highlighted as a major bottleneck in the TB cascade of care and they characterize most of the health systems of high TB burden countries. Attention was also drawn to lack of effective tools for diagnosis and management of TB. Despite the huge financial investments into global TB control, the funding needs remain largely unmet and most high burden countries continue to depend on external funding support. This negatively impacts several health system building blocks including the health workforce and procurement of medicines and technologies. In addition to these bottlenecks, many other underlying social determinants of TB such as housing, food security and environmental conditions remain unaddressed.

**Presentation 2:** Interactive session using card deck illustrating barriers in TB care cascade  
**Presenter:** Ingrid Schoeman, TB Proof  
**Summary and main points**  
This interactive session focused on identifying priority health system advocacy areas for former TB patients based on their experiences of TB and life after TB. Prior to the symposium, a card deck was developed using principles of human-centred design to illustrate the barriers in the TB care cascade. The process of identifying barriers in the TB care cascade faced by local communities included community health worker TB advocacy training workshops and focus group discussions. Workshop participants included former TB patients and key affected populations, health workers and researchers. Each participant advocated for a barrier in the TB care cascade to be addressed using an illustrated card. Participants debated with one another on the importance of each barrier in the TB care cascade to identify top advocacy priority areas. Former TB patients shared their experiences of life after TB. This discussion was the foundation for engagement on advocacy priority areas post-TB disease. These discussions were particularly enriched by contributions by several former TB patients in the audience of this workshop.

**Presentation 3:** My Patient’s Choice Pledge: an example of advocacy through storytelling and partnerships to improve Drug-Resistant (DR) TB care by changing perceptions of decision makers to accelerate guideline changes.  
**Presenter:** Dr Dalene von Delft, TB Proof  
**Summary and main points**  
In 2017, a coalition of TB survivors, activists and care providers, coordinated by TB Proof, co-launched the Jolene Samuels #MyPatientsChoice Pledge, calling for all people with DR-TB to be offered an informed choice between regimens including a safer and more effective novel drug or a toxic injectable drug. Activists leveraged international advocacy events, collective civil society
organisation (CSO) initiatives and existing relationships with global, national and local healthcare stakeholders, researchers and journalists to gain support. Affected DR-TB survivors led the push for policy change in South Africa (SA) with powerful personal testimonies, supported by a growing body of evidence. Media coverage included 23 online articles and six publications in SA newspapers and magazines. The pledge was signed by 13 organisations and 188 individuals, including the SA DR-TB Director. In June 2018, SA made the landmark announcement that bedaquiline would replace routine injectable use, representing a collective advocacy success for patients, CSOs, academic and healthcare partners. The World Health Organization (WHO) subsequently released new guidelines that also prioritise the use of bedaquiline and linezolid over injectable drugs in DR-TB regimens.

Advocacy campaigns underpinned by strong partnerships between TB affected communities, National TB programme managers, talismanic political TB champions, the media and researchers can improve the quality of TB care for all.

**Main discussion points**

Building on the TB care cascade barriers that were discussed by workshop participants in the debate, six health system barriers in the TB care cascade were presented: fragmented service delivery; poorly trained and supported health workers; poor information recording and reporting (lack of data); a lack of financing in high burden countries to access medical products, vaccines and technologies; and a lack of governance (i.e. policies). Former TB patients shared their experiences of post-TB disease barriers to care: difficulty returning to work (especially if it is physically strenuous); difficulty to follow up for health services when it is not provided for free (financial burden); and a lack of TB counseling services post-TB disease. Health workers shared that gaps in the TB care cascade for post-TB disease included a lack of clinical guidance/ algorithm for health workers treating former TB patients; and a lack of funding for implementation trials to measure costs and collect data.

The workshop participants emphasized that solutions to post-TB disease challenges should be cost effective. For instance, embedding TB follow-up within health services that former TB patients are already using could overcome the financial burden for patients to return to a clinic incurring transport fees and possible loss of income for the date of visit to the healthcare facility. Recognizing that partnerships are key to influencing decision makers, several potential partners were suggested for engagement including the WHO, Pharmaceutical companies, Ministers of health, National TB Programs, Clinicians, Researchers and the Media. The importance of engaging high-level government officials and appointing champions for post TB advocacy was also emphasized.

**Conclusion and recommendations**

The Health Systems advocacy workshop was interactive and presented an opportunity for passionate discussions. The Health System was clearly shown to be the foundation for quality TB care and the basis for developing advocacy strategies for life after TB. The workshop noted two priority areas on which health systems advocacy should be focussed at this stage:

1. Evidence gaps in Post TB health and wellbeing

The paucity of data and evidence-based information in this relatively new area was noted. To provide the much-needed evidence base for successful advocacy, the workshop identified the urgent need for increased funding for research specifically to identify the most cost-effective interventions that improve quality of life during and after TB.
2. Lack of clinical guidelines and algorithms for management of post TB lung disease and counselling of TB patients

There are no guidelines currently within the health systems to support health workers to manage patients after they have been treated for TB. The workshop identified this as an urgent priority. It was recommended that, in collaboration with The International Union Against Tuberculosis and Lung Disease (‘Union’), a guideline should be developed drawing on any current evidence base and expert opinion where necessary and made available for clinicians. This could be in the form of The Union’s ‘orange-book’ in the first instance and subsequently reviewed as more evidence becomes available. This was considered a low hanging fruit that could be achieved relatively soon.
Workshop 8 - Epidemiology of PTLD: burden of disease, mortality and risk factors

Chairs
Andrea Rachow – Ludwig-Maximilians-University Munich, Germany
André Amaral – Imperial College London, UK

Participants
Khosa Celso – Instituto Nacional de Saúde (INS), Moçambique
Rodney Ehrlich – University of Cape Town, South Africa
Denise Evans – Health Economics and Epidemiology Research Office, South Africa
Graeme Hoddinott – Desmond Tutu TB centre, South Africa
Olena Ivanova — Klinikum of The University of Munich (KUM), Germany
Marian Loveday – South African Medical Research Council, South Africa
Jamilah Meghji – South African Medical Research Council, South Africa
Ensinqwane Nkereuwem – Liverpool School of Tropical Medicine, The MRC Unit the Gambia
Nyanda Ntinginya – NIMR Mbeya Medical Research Centre, Tanzania
Lesley Workman – University of Cape Town, South Africa

Background and state of the art

There is accumulating evidence that a large number of tuberculosis (TB) survivors suffer from chronic post TB lung disease (PTLD), which seems to include a number of pathologic pulmonary conditions and symptoms\(^ {47,48}\) and may partly explain observed excess mortality in this group of people.\(^ {47,48}\) In the absence of a general case definition for PTLD and state of the art assessment guidelines, the conditions and clinical outcomes described as PTLD by different authors\(^ 1\) as well as the methodologies used to measure, analyse and report pathology are extremely diverse. This has resulted in a huge variation in the reported post TB outcomes (i.e. prevalence and characteristics of PTLD) making it very difficult to compare across studies. Further, risk factors for PTLD are largely unknown and only few co-variates such as sex, age, and HIV-status have been assessed in a small number of studies.\(^ {49}\)

Presentations from the participants

**Presentation 1:** “Post TB lung impairment in spirometry at six months after end of TB treatment, and associated risk factors, in pulmonary TB patients from Maputo, Mozambique”

**Presenter:** Celso Khosa, Instituto Nacional de Saúde (INS), Maputo, Mozambique; Andrea Rachow, Ludwig-Maximilians-University Munich, Division of Infectious Diseases and Tropical Medicine, Munich, Germany.

**Summary and main results:** More than 60% of enrolled pulmonary TB patients had chronic abnormal lung function measured by spirometry half a year after end of anti-TB therapy, and more than 50% of them were classified as having at least moderate or severe impairment by spirometry. Female sex, a low haemoglobin and a high amount of smoked cigarettes during life time were associated with lung impairment after TB.
Main discussion points

The workshop was characterized by a discussion of examples of currently available data on the burden and characteristics of PTLD, with a special focus on the limitations of existing evidence (e.g. due to the type of outcome assessed, the measurement tools or the approach to data analysis). The recent findings of the abovementioned Mozambican TB cohort study provided further material for this discussion, especially on the methodological challenges of PTLD research. The main discussion points were: a) the confirmation of previous TB disease in the context of different study settings; b) the main adverse post TB lung outcomes to be studied; c) how they should be measured; d) the limitations of potential measurement tools; and e) the ascertainment of death due to PTLD. Going from there, strategies for PTLD research were discussed for different research settings and questions. In the second half of the workshop, challenges and strategies on data collection for the analysis of potential risk factors and effect modifiers were discussed with a focus on identification of potentially relevant covariates, timing from active pulmonary TB disease, selection of measurement tools and data collection strategies and labelling issues.

Due to the limited amount and the heterogeneous type of available data on PTLD, the absence of concrete definitions for PTLD and how it is diagnosed and the diversity in the professional backgrounds of workshop participants, no formal process for reaching consensus among participants was deployed. Rather, the attempt was made to identify research gaps and to discuss a way forward to overcome current limitations in the research field. Initially, the workshop participants agreed that there is sufficient evidence for the existence of PTLD, however, the relevant, main adverse clinical phenotypes and outcomes are so far unknown. And although, several studies have assessed the association of a history of TB or other “measure” of TB with certain clinical outcomes, such as airflow abnormalities on spirometry, estimates of the burden of PTLD are scarce. Further, apart from studying purely clinical or lung-specific outcomes of PTLD, it was agreed that outcomes such as quality of life, social network, financial costs, side effects of treatment and mental disorders should also be addressed as relevant aspects of PTLD. In general, it was acknowledged, that there are no agreed or common tools or methods to measure, analyse and publish data on PTLD. This is associated with the lack of a consensual definition, no agreed methods to assess pulmonary disorders in post TB patients, different research settings and, moreover, no relevant treatment guidelines published that are aiming at the prevention, diagnosis and treatment of PTLD. It was found that the most common tools to assess PTLD are radiology, spirometry, 6-minute walking test, symptom screening and specific questionnaires (e.g. Saint George Respiratory Questionnaire). It was stated that most of these tools were not adapted for use in TB patients or specific patient groups, such as children, and also not adapted to developing settings of low-income countries. The majority of participants agreed that adaptation to local settings should occur. However, if a standardized tool exists, which could be used to compare findings from various settings, that would be preferable. The use of affordable, robust and portable devices outside clinics was also discussed. Further, due to the skills and knowledge deficit in many developing settings, proper and continuous training is still necessary.

Concerning risk factors for PTLD, there was a consensus that it is unknown how far risk factors, which are commonly known to be associated with poor lung health (cigarette smoking, coal mining, etc.) contribute to the development of chronic lung disease among people with a history of TB. Pre-existing lung damage might be an important risk factor for TB, however, there is not enough data on that. Likewise, pre-existing lung damage might be also relevant for the grade of post-TB lung
damage, but this is difficult to analyse in a clinical trial, as lung function data before TB are usually not available from TB patients in developing settings. Other relevant risk factor for PTLD could be indoor and outdoor air pollution, passive smoking during childhood, alcohol consumption and TB medication. Finally, HIV-coinfection, delay in TB diagnosis and treatment initiation, mental health and other comorbidities should be assessed as co-factors that may play a role in the development of PTLD.

**Conclusion and recommendations**

Although PTLD was neglected in the past, there is suggesting evidence to make us believe in a large disease burden and thus relevance for post TB morbidity and mortality. In order to enable future research on PTLD, first, consensus on disease definition is needed. Based on that, a methodological framework needs to be set up and described for both the diagnosis of the different PTLD phenotypes and the conduct of research studies of PTLD that are also addressing limited settings in high incidence countries. Until PTLD-specific validated research tools are available, existing guidelines and pulmonary assessment tool kits should be used. Among the first questions that need to be addressed by research studies are the burden of PTLD in terms of prevalence, observed clinical phenotypes and disease severity. Furthermore, the relevant clinical outcomes that are defining long-term morbidity and mortality after TB need to be defined in order to prioritize clinical and therapeutic interventions.
References


43. Kim J, Keshavjee S, Atun R. Health systems performance in managing tuberculosis: analysis of


# Appendix 1. Final program symposium

## POST-TUBERCULOSIS SYMPOSIUM 2019 – FINAL PROGRAMME

### DAY ONE
**MONDAY 22 JULY**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Topic</th>
<th>Speaker(s)</th>
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<tr>
<td>08.00 - 08.30</td>
<td>Registration</td>
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<tr>
<td>08.30 - 09.00</td>
<td>Session 1</td>
<td>Welcome, Introductions and Expectations</td>
<td>Brian Allwood / Kevin Mortimer</td>
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<tr>
<td>09.00 - 09.10</td>
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<td>Message from Rector of Stellenbosch University</td>
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<td>09.10 - 09.30</td>
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<td>Opening Address</td>
<td>Eric Bateman</td>
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<tr>
<td>09.30 - 09.50</td>
<td></td>
<td>Lecture #1: Patient perspectives</td>
<td>Ingrid Schoeman</td>
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<td>09.50 - 10.10</td>
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<td>Lecture #2: Pulmonary TB outcomes</td>
<td>Andrea Rachow</td>
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<td>10.10 - 10.30</td>
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<td>Lecture #3: Phenotyping in post-TB disease</td>
<td>Brian Allwood</td>
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<td>10.30 - 11.00</td>
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<tr>
<td>11.00 - 11.20</td>
<td>Session 2</td>
<td>Lecture #4: Children after TB</td>
<td>Diane Gray</td>
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<td>11.20 - 11.40</td>
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<td>Lecture #5: Socio-economic consequences &amp; QALY</td>
<td>Denise Evans</td>
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<td>11.40 - 12.00</td>
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<td>Lecture #6: Targeting TB control to former TB patients</td>
<td>Florian Marx</td>
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<tr>
<td>12.00 - 13.00</td>
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<td>GROUP PHOTOGRAPH &amp; LUNCH</td>
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<tr>
<td>13.00 - 15.00</td>
<td>WORKSHOPS</td>
<td>Workshop 1: Lung complications after TB</td>
<td>Brian Allwood / Jamila Meghji</td>
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<tr>
<td>13.00 - 15.00</td>
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<td>Workshop 2: Former TB patients in the context of the End TB Strategy</td>
<td>Florian Marx / Dalene von Delft / Sumona Datta</td>
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<td>13.00 - 15.00</td>
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<td>Workshop 3: Socio-economic and psychological Impact</td>
<td>Olena Ivanova / Denise Evans / Graeme Hodinott</td>
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<td>13.00 - 15.00</td>
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<td>Workshop 4: Paediatric complications of TB</td>
<td>Marieke van der Zalm / Diane Gray</td>
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<td>15.00 - 15.30</td>
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<tr>
<td>15.30 - 16.30</td>
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<td>Workshops 1-4 (continue)</td>
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<td>16.30 - 17.30</td>
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<td>Plenary Workshop Feedback</td>
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### DAY TWO
**TUESDAY 23 JULY**

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<td>08.30 - 08.40</td>
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<td>Logistics Update</td>
<td>Naomi Walker</td>
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<td>08.40 - 09.00</td>
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<td>Lecture #7: Mechanisms of TB destruction</td>
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<td>Lecture #8: Host directed therapy to improve TB outcomes</td>
<td>Rob Wallis</td>
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<td>09.20 - 09.40</td>
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<td>Lecture #9: Pulmonary rehabilitation</td>
<td>William Worodnia</td>
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<td>Lecture #10: Therapies for treatment post TB</td>
<td>Steleah Mpagama</td>
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<td>Lecture #11: Malawi cohort</td>
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<td>11.00 - 11.20</td>
<td>Session 4</td>
<td>Lecture #12: Advocacy for Post-TB disease</td>
<td>Kevin Mortimer</td>
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<td>Lecture #13: Diagnosing recurrent TB among former TB patients</td>
<td>Grant Theron</td>
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<td>Lecture #14: Mortality after TB</td>
<td>Mohammed Osman</td>
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<td>13.00 - 15.00</td>
<td>WORKSHOPS</td>
<td>Workshop 5: Pathogenesis /mechanisms of disease &amp; prevention of damage</td>
<td>Naomi Walker / Car Stok / Rob Wallis</td>
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<td>13.00 - 15.00</td>
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<td>Workshop 6: Treatment &amp; holistic management</td>
<td>Sanne van Kampen / Rupert Jones / Steleah Mpagama</td>
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<td>13.00 - 15.00</td>
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<td>Workshop 7: Health systems advocacy</td>
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<td>Workshop 8: Burden of disease / risk factors / mortality (Epidemiology)</td>
<td>Andrea Rachow / Andre Amaral</td>
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<td>Discussion: Focus of Definitions</td>
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