TB ASSOCIATED MORBIDITY IN CHILDREN AND ADOLESCENTS - FEEDBACK FROM THE 2ND INTERNATIONAL POST TB SYMPOSIUM

WHO child and adolescent TB working group meeting
Tuesday 14-11-2023 Paris
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Paediatrician and associate professor
Desmond Tutu TB centre,
Stellenbosch University, South Africa
TB associated morbidity in children and adolescents

- Brief overview literature & feedback from 2\textsuperscript{nd} post TB symposium
- Post TB lung disease
- Post TBM disease
- Socio-economic and HRQoL

Child & Adolescent TB Working Group
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Quantifying the global number of tuberculosis survivors: a modelling study

Peter J Dodd, Courtney M Yuen, Shanthini M Jayasooriya, Marieke M van der Zalm, James A Seddon

• 155 million TB survivors (1980-2019) were alive in 2020
  • ~ 6-18 million were <15 years
  • ~ 15.5 million were adolescents

• A total of 3480 million life-years were lived “after TB”
  • Children <15 years contribute 12% to these life-years

Dodd et al. Lancet ID 2021
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- A total of 3480 million life-years were lived “after TB”
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→ These children and adolescents are potentially at risk for TB-associated morbidity

Dodd et al. Lancet ID 2021
TB associated morbidity - the concept

Figure: Illustration of post-tuberculosis DALY loss for a typical survivor of pulmonary tuberculosis treatment in India without HIV infection

Quaife et al. Lancet 2020
TB associated morbidity - the concept

Children & adolescents?

*Figure: Illustration of post-tuberculosis DALY loss for a typical survivor of pulmonary tuberculosis treatment in India without HIV infection*

Quaife et al. Lancet 2020
Early life insults can affect trajectory of lung function

Timing and severity of insult might impact on trajectory

Catch up growth vs accelerated decline

Ref: Gabrielle Y et al. CHEST 2021; 160(3):879-889
The impact of LRTIs on lung function

Impact LRTI on tracking
What happens after PTB?

Ref: Chan et al Paediatrics 2015
Post TB lung disease in children and adolescents

Magnitude and factors associated with post-tuberculosis lung disease in low- and middle-income countries: A systematic review and meta-analysis

Elizabeth Maleche-Obimbo, Mercy Atieno Odhiambo, Lynette Njeri, Moses Mburu, Walter Jaoko, Fredrick Were, Stephen M. Graham

- N=1 with radiological outcomes in children
- N= 8 studies with adolescents included, but no disaggregated data
- N=6 with symptoms & radiological outcomes
- 7-49% abnormal radiology
Reduced lung function and health-related quality of life after treatment for pulmonary tuberculosis in Gambian children: a cross-sectional comparative study

Esin Nkereuwem 1,2, Schadrac Agbla 3,4, Azeezat Sallahdeen 1, Olumuyiwa Owolabi 1, Abdou K Sillah 1, Monica Genekah 1, Abdouli Tunkara 1, Sheriff Kande 1, Maryama Jawara 1, Lamin Saidy 5, Andrew Bush 6,7, Toyin Togun 1,2,8, Beate Kampmann 1,2,9

185 children treated for PTB, 2014-2019

77 children not contacted
• 66 unreachable
• 11 died

108 children contacted

40 children excluded
• 28 below 5 years
• 6 unwilling to participate
• 4 relocated from the study area
• 2 with recurrent tuberculosis

68 post-tuberculosis cases enrolled

91 age-matched children enrolled

<table>
<thead>
<tr>
<th>Spirometry</th>
<th>Post-tuberculosis cases</th>
<th>Comparison group</th>
<th>P value</th>
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<tbody>
<tr>
<td>FEV1 z-score, mean (SD)</td>
<td>-1.52 (-0.99)</td>
<td>-0.83 (-0.84)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>FVC z-score, mean (SD)</td>
<td>-1.32 (1.02)</td>
<td>-0.87 (0.89)</td>
<td>0.014†</td>
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<tr>
<td>FEV1/FVC ratio z-score, mean (SD)</td>
<td>-0.54 (0.91)</td>
<td>-0.03 (0.81)</td>
<td>0.001†</td>
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<td>Abnormal spirometry, n (%)</td>
<td>20 (38.5)</td>
<td>15 (17.4)</td>
<td>0.009†</td>
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<td>Pattern of spirometry</td>
<td></td>
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<td>Normal, n (%)</td>
<td>32 (61.5)</td>
<td>71 (82.6)</td>
<td>0.0295</td>
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<tr>
<td>Obstructive, n (%)</td>
<td>1 (1.9)</td>
<td>2 (2.3)</td>
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<tr>
<td>Restrictive, n (%)</td>
<td>19 (36.4)</td>
<td>13 (15.1)</td>
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- Children with PTB (0-5y) →
  - ↓Anthropometry at age of 5 years
  - Greater risk of subsequent wheezing
  - Lower lung function at age of 5 years
- Premorbid lung function was not associated with PTB
Teen TB study, Cape Town South Africa

Baseline clinical assessment N=100

- DS-tuberculosis N=40
- MDR-tuberculosis N=10
- Tuberculosis exposed N=50

Exclusion:
N=5; 1 tuberculosis disease diagnosed

4 did not meet quality criteria for repeatability and acceptability

Analysis N=45

Month 2 assessment

- Lung function measurement N=48
- Analysis N=42

Exclusion:
N=8; 1 screen failure, 1 lost to follow-up

6 did not meet quality criteria for repeatability and acceptability

Assessment following treatment completion

- Lung function measurement N=41
- Analysis N=37

Exclusion:
N=11; 1 died, 6 lost to follow-up

4 did not meet quality criteria for repeatability and acceptability
Teen TB study, Cape Town South Africa

- Adolescents with TB had
  - Restrictive disease was most common
  - Lower spirometry and plethysmography indices even after treatment completion

- Overall lung health was poor in both groups

vd Zalm/ Seddon preprint 2023
PTLD: More data is needed

The data says we need more data.
TB meningitis in children and adolescents

• Most severe form of extrapulmonary TB, especially among young children

• Deadliest, most debilitating form of TB
  • Deaths: 19.3% (14.0 – 26.1)
  • Neurological sequelae among survivors: 53.9% (42.6 – 64.9)
  • Probability of survival without sequelae: 36.7% (27.9 – 46.4)

• TBM modelling study by Du Preez/ Dodd/ Seddon. in progress → Presentation @ Union tomorrow
  • Estimated burden: ~24,000 children each year
  • Estimated mortality: ~16,100 children each year
  • Estimated morbidity: 70% of all TBM survivors each year
Substantial between-study heterogeneity in assessment of neurological sequelae measures

<table>
<thead>
<tr>
<th>Sequelae Patients</th>
<th>Risk (95% CI)</th>
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<tbody>
<tr>
<td>Sumaya et al (1975)</td>
<td>24 45</td>
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<tr>
<td>Sunakorn et al (1978)</td>
<td>7 20</td>
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<td>Visudhiphan et al (1979)</td>
<td>17 44</td>
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<td>Sunakorn et al (1980)</td>
<td>9 15</td>
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<td>Frontera et al (1981)</td>
<td>16 29</td>
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<td>Visudhiphan et al (1989)</td>
<td>13 44</td>
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<td>Jacobs et al (1992)</td>
<td>15 42</td>
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<td>Shian et al (1993)</td>
<td>8 12</td>
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<td>Yaramis et al (1998)</td>
<td>79 165</td>
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<td>Degehe et al (2003)</td>
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<td>Karande et al (2005)</td>
<td>70 95</td>
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<td>Kumar et al (2005)</td>
<td>107 123</td>
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<td>VanWell et al (2009)</td>
<td>294 359</td>
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<td>Tinsa et al (2010)</td>
<td>3 6</td>
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<td>Pooled</td>
<td>718 1127</td>
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Heterogeneity 0.6 (95% CI 0.3-1.5)

Evaluation and Management of TBM Sequelae

• Lack of uniform approach to evaluate sequelae
  • Functional
  • Neurodevelopmental
  • Neurocognitive
  • Neurobehavioural
• Paucity of appropriate rehabilitation and other therapies
• No standard measure of impact on quality of life or socio-economic burden

Economic and psycho-social consequences following TB

• For children – mostly spinal TB and TBM are described
  • Rapid review of post-TB literature to gain an understanding of the available evidence on the economic, psychological, and social impacts of TB (Nightingale et al, 2023)
    → lack of studies on children and adolescents
  • Scoping review on the long-term socio-economic effect of TB among children and adolescents (Atkins et al, 2022)
    → lack of studies on children and adolescents
  • Scoping review of interventions to address TB-associated respiratory disability
    → lack of studies on children and adolescents
Scoping review to identify HRQoL measures

No disease-specific measure for children and adolescents affected by TB available

- No disease specific measure available
- Lacks a holistic understanding of HRQoL
  - Impact on family
  - Impact on development of child
- Most measures developed in high-income countries
  - Lack of socio-economic context

Anthony et al, submitted 2023
Definition 2019 Post TB symposium PTLD paediatrics:
“Evidence of chronic respiratory impairment in an individual previously adequately treated for pulmonary tuberculosis in whom active tuberculosis is excluded, and in whom no other cause of chronic lung disease is the predominant cause.”

With the consideration of toolbox to add layers to further define

New post TBM?
“Evidence of chronic neurological, cognitive, behavioural and developmental impairment in an individual previously adequately treated for tuberculosis meningitis in whom active tuberculosis is excluded, and in whom no other cause of neurological impairment is the predominant cause.”

With the consideration of toolbox to add layers to further define

Proceedings 1st and 2nd post TB symposium, Stellenbosch
Consensus research definition

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With the consideration of toolbox to add layers to further define.
Toolbox development and standardization

**Self-reported symptoms**

**Clinical measures**

**Functional testing**

**Imaging**

**Other tests incl HRQoL**

Proceedings 1st and 2nd post TB symposium, Stellenbosch
5. Post-TB in paediatric and adolescents

Post-TB lung disease
Quantification of the burden of and risk factors for PTLD in children and adolescents; and the characterisation of the spectrum of PTLD disease

Determining the most appropriate assessment and tools for PTLD in children and adolescents

Evaluating the impact and role of possible interventions in children and adolescents with PTLD

Determining the impact and role of possible interventions in children and adolescents with PTLD

Evaluating interventions to prevent PTLD in children and adolescents

Post-TBM sequelae
Establish validated and culturally appropriate tools to assess neurodevelopment and function in children with TBM

Standardisation of patient follow up and strengthened surveillance to include physical, neurocognitive, and neurodevelopmental assessments

Evaluation of whether optimised anti-TB therapy and host-directed therapy could improve long-term neurodevelopmental and neurocognitive outcomes across various paediatric age ranges

Evaluation and characterisation of early intervention and targeted neurorehabilitation services to improve outcomes

Post TB well-being/HRQoL
Development a disease-specific HRQoL measure, basic descriptive data on adolescent experiences and comorbidities, and improved understanding of the burden of care on caregivers and to understand what impact this burden has on the child’s QoL

Data on long-term outcomes of children and adolescents with osteo-articular TB and more optimal rehabilitation methods are needed
“Post tuberculosis”: the urgent need for inclusion of lung health outcomes in tuberculosis treatment trials

• Prevention is key!
• TB-associated morbidity measures need to be included in treatment studies
• Consensus on standardization of measurements/ tools and outcomes is needed

Byrne at al ERJ- from post TB steering committee
Acknowledgments

Workshop participants and academic working group

This project is part of the EDCTP2 programme supported by the European Union.