Interdisciplinary and multi-level approach to estimate the disease burden and outcomes of childhood tuberculous meningitis

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THE BURDEN OF TUBERCULOSIS IN CHILDREN

7.5 million children (0–14) infected with TB each year (Dodd et al, 2014)

10 million TB patients in 2017

1 million children (0–14 years) developed TB in 2017
52% <5 year olds

727,000 adolescents (10–19 year-olds) developed TB in 2012 (Snow et al, 2018)

7.5 million children (0–14) infected with TB each year (Dodd et al, 2014)

1 million children (0–14 years) developed TB in 2017

CASE DETECTION GAP

% of TB patients that are missed in different age groups

- TB reporting gap is biggest among younger children

- 69% <5 years
- 40% 5-14 years
- 35% All other ages combined

Overall 55% of estimated children with TB (0–14 years) are not reported to national TB programmes

PAEDIATRIC TB SURVEILLANCE

- TB surveillance should capture the full spectrum of disease
- Young children – high risk of disseminated forms of TB, such as TB meningitis (TBM)
- Paediatric TBM - high morbidity and mortality and often permanent neurological disability
- Substantial economic and social burden on families and public health services

Marais, et al., Int J Tuberc Lung Dis, 2004
Chiang, et al., Lancet Infect Dis, 2014
Schoeman, et al., Dev Med Child Neurol, 2002
SURVEILLANCE OF PAEDIATRIC TB MENINGITIS

- Non-distinct symptoms → diagnostic delays, advanced presentation and severe morbidity.
- Early diagnosis and treatment are critical to improve TBM outcomes.
- Routine TB surveillance data does not distinguish TBM from other forms of TB.

Chiang, et al., Lancet Infect Dis, 2014
Lincoln, et al., J Pediatr, 1960
Van Toorn, et al., Int J Tuberc Lung Dis, 2012
To determine the burden and outcomes of paediatric TBM at a global level, and at a national and sub-national level in South Africa, identifying opportunities for prevention, earlier diagnosis and treatment.
### OVERVIEW OF SPECIFIC RESEARCH AIMS

| Research | Specific Aim 1: Modelling the *global* disease burden of childhood TBM | Specific Aim 2: Spatiotemporal analyses of reported childhood TBM at *national* level | Specific Aim 3: Prospective childhood TBM cohort study at a *sub-national* level | Integration of results of specific aims to inform national and global programme evaluation and policy development |
# OVERVIEW OF THE STUDY TEAM

<table>
<thead>
<tr>
<th>Research</th>
<th>Specific Aim 1: Modelling the <em>global</em> disease burden of childhood TBM</th>
<th>Specific Aim 2: Spatiotemporal analyses of reported childhood TBM at <em>national</em> level</th>
<th>Specific Aim 3: Prospective childhood TBM cohort study at a <em>sub-national</em> level</th>
<th>Integration of results of specific aims to inform national and global programme evaluation and policy development</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
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<tr>
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<td>Co-mentors</td>
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<td>R Solomons &amp; R van Toorn, SU-Pediatric neurology; Andrew Boulle, Western Cape Provincial DOH</td>
<td>WHO Child and Adolescent TB working group; International Union Against Tuberculosis and Lung Disease</td>
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AIM 1 - MODELLING THE GLOBAL DISEASE BURDEN AND ATTRIBUTABLE MORTALITY OF CHILDHOOD TBM

- Lit review to determine parameters of the age-related risk of disease progression to TBM following *M. tb* infection
- Existing mathematical model
- Considering the impact of HIV, BCG and TB preventive therapy

Anticipated outcomes:
First estimates of the global burden of childhood TBM and the attributable paediatric TB mortality
(Expected results: 2021)
AIM 2 - SPATIOTEMPORAL ANALYSES OF REPORTED CHILDHOOD TBM AT NATIONAL LEVEL

- Routine TB surveillance data in SA captures ICD10 diagnostic information
- Cleaned, de-duplicated electronic TB register dataset: 2004 - 2017
- ~750,000 children and adolescents; ~8,500 with a 1/2\textsuperscript{nd} ICD 10 TBM code
- Only include diagnosed and reported cases

Planned analyses:

- Ecological analyses to evaluate geographic (district-level) and temporal variation of paediatric TBM using the following indicators:
  - case notification/100,000 population,
  - percentage of all childhood TB cases attributed to TBM,
  - successful TBM treatment outcomes, and
  - all-cause mortality during TBM treatment.

Anticipated outcome:

To determine population-level drivers of high burden locations and unfavourable outcomes
(Expected results: 2021/2022)
AIM 3: PROSPECTIVE CHILDHOOD TBM COHORT STUDY AT A SUB-NATIONAL LEVEL

Anticipated outcome:
To determine the incidence and case fatality rate of childhood TBM in Cape Town
(Expected results: 2023/2024)

- Prospective, observational cohort study (24 months enrolment, 12 months follow-up)
- All children with TBM living in the City of Cape Town health district will be included
- Expected sample size: 160 – 240 (80-120 children per year)
- Clinical classification using consensus TBM research case definitions
Case identification of all diagnosed cases:
- Increase awareness of paediatric TBM at primary healthcare facilities
- SOP + training to standardise diagnostic practices at hospitals
- Provincial Health Data Centre (algorithm in development – ICD10 code at any public health facility / NHLS – all CSF + TB bacteriology / suggestive biochemistry)
- Concurrent clinical hospital surveillance (dedicated study nurse)

Case identification of all undiagnosed cases:
- Post-mortem data from sudden unexpected childhood deaths (forensic pathology)
- Hospital surveillance of all paediatric meningitis-related deaths (medical record review)
- Routine mortality data (vital statistics data for all deaths listing meningitis of unknown cause – to calculate proportion of children in each SD)
AIM 3: PROSPECTIVE CHILDHOOD TBM COHORT STUDY AT A SUB-NATIONAL LEVEL

Data collection:

- Diagnostic certainty, disease severity, comorbidities, outcomes and missed opportunities for prevention and earlier diagnosis
- Baseline, month 6 and month 12

Analytical approach:

- Childhood TBM incidence rates (overall and stratified by age, SD and HIV status)
- Case fatality rates (overall and stratified by age, disease stage and SD)
- Exploratory: development of a diagnostic checklist to facilitate earlier diagnosis
- GIS and spatial methods to produce maps detailing missed opportunities for prevention, TBM stage at presentation (proxy for late dx) and the number of related HC visits to identify geographic clusters where intervention are needed (principal component analysis)
STUDY SUMMARY

*Provide critical information on the global and national (SA) burden, incidence and related mortality of TBM in children whilst identifying opportunities to improve prevention and care through in-depth prospective surveillance.*

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