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

Dr. Karen du Preez

MBChB, MSc (Epi)

Desmond Tutu TB Centre, Stellenbosch University

DESMOND TUTU TB CENTRE | STELLENBOSCH | UNIVERSITEIT · SENTRUM · IZIKO
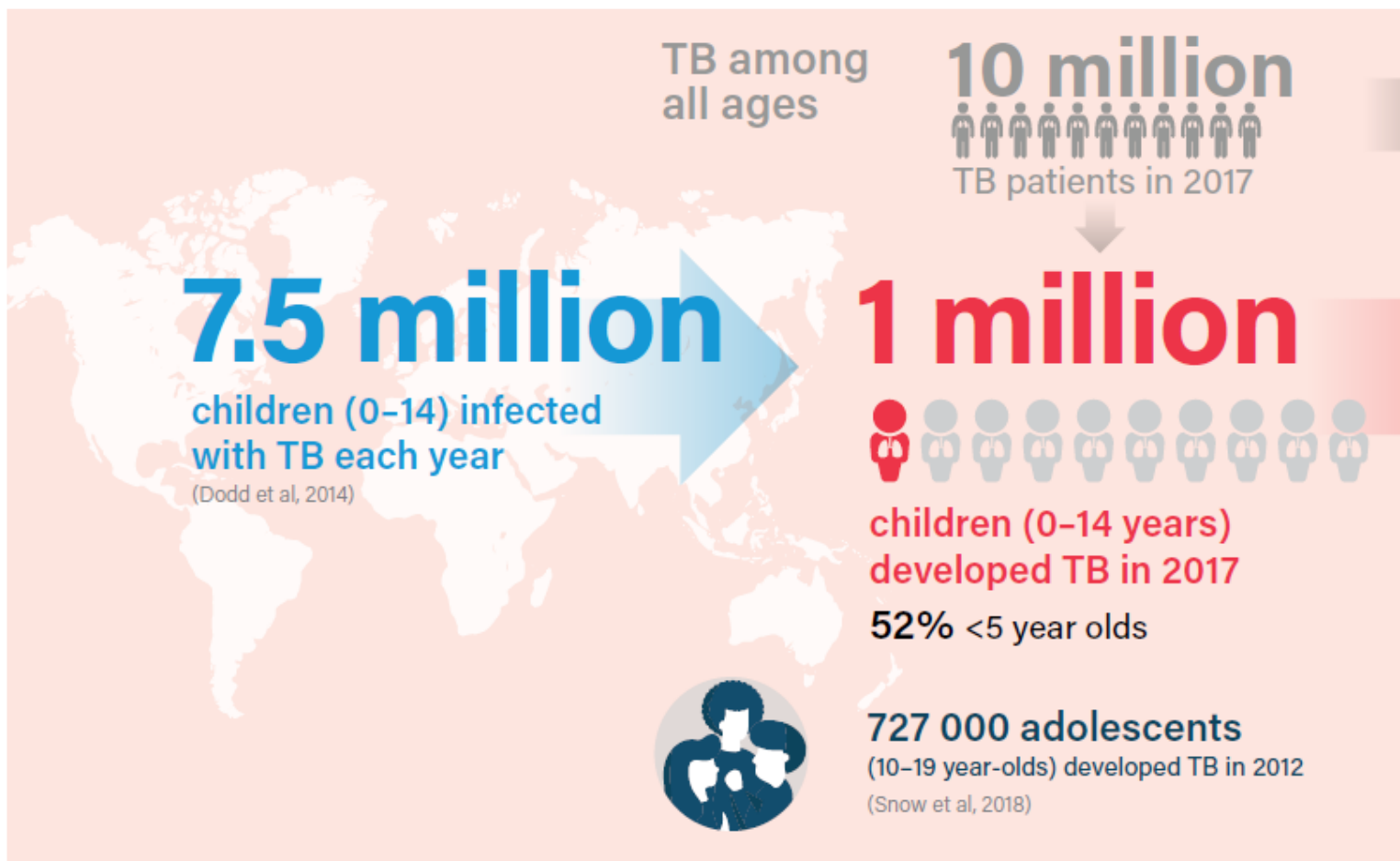*Every breath counts*

UNIVERSITEIT iYUNIVESITHI STELLENBOSCH UNIVERSITY

100 1918·2018

forward together · saam vorentoe · masiye phambili

THE BURDEN OF TUBERCULOSIS IN CHILDREN

TB among all ages

10 million

TB patients in 2017

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

52% <5 year olds

727 000 adolescents

(10–19 year-olds) developed TB in 2012

(Snow et al, 2018)

World Health Organization. Roadmap towards ending TB in children and adolescents (2018)

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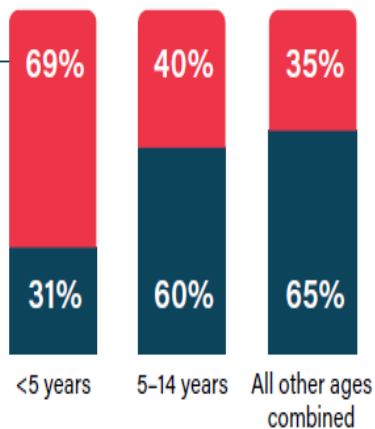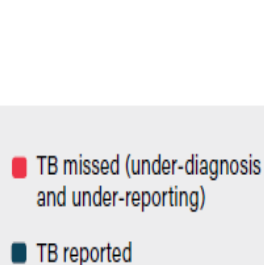(Dodd et al, 2014)

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

	<5 years	5–14 years	All other ages combined
TB missed	69%	40%	35%
TB reported	31%	60%	65%

- TB missed (under-diagnosis and under-reporting)
- TB reported

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

World Health Organization. Roadmap towards ending TB in children and adolescents (2018)

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

STUDY AIM

To determine the <u>burden and outcomes</u> of paediatric TBM at a <u>global</u> level, and at a national and sub-national level in <u>South Africa</u>, identifying opportunities for <u>prevention, earlier diagnosis and treatment.</u>

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

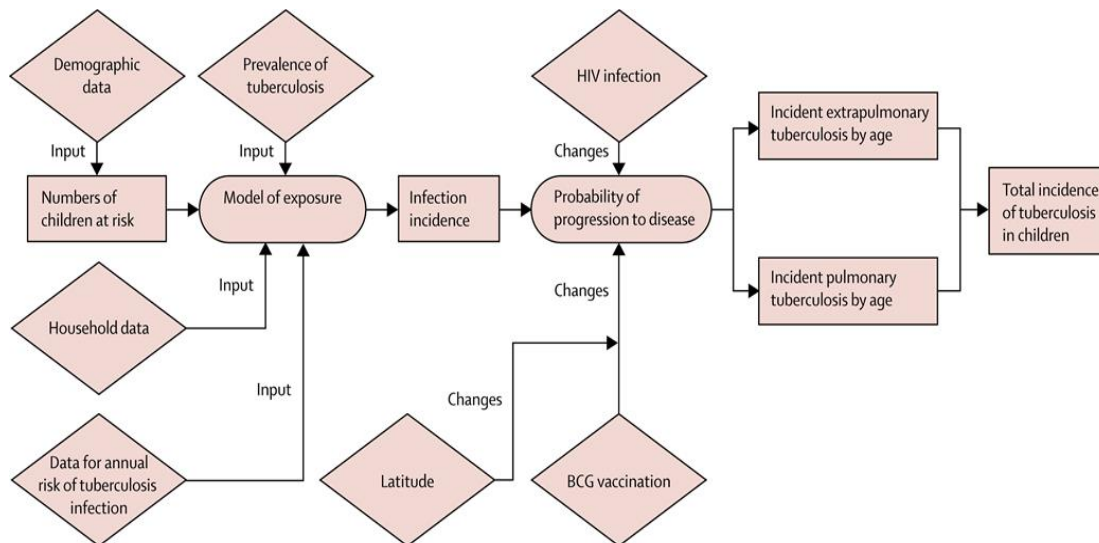**Specific Aim 3:** Prospective childhood TBM cohort study at a *sub-national* level

Integration of results of specific aims to inform national and global programme evaluation and policy development

OVERVIEW OF THE STUDY TEAM

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
PI	**Karen du Preez**			
Overarching mentors	Primary SA-based mentor: **Anneke Hesseling**		Primary US-based mentor: **Jeffrey Starke**	
Co-mentors	**James Seddon**	**Helen Jenkins**	**Simon Schaaf**	**Stephen Graham**
National and international collaborations	**Juliet Pulliam**, SU-SACEMA; **Pete Dodd,** University of Sheffield, UK	**Zahn Munch**, SU-Department of Geography & Environmental Sciences; **Kelly Dooley**, JHU	**R Solomons & R van Toorn,** SU-Pediatric neurology; **Andrew Boulle**, Western Cape Provincial DOH	**WHO Child and Adolescent TB working group**; International Union Against Tuberculosis and Lung Disease

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

Figure 1. Overview of the existing model that will be built on to estimate the burden of TBM in children

Dodd, et al., Lancet Infect Dis. 2016

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 1/2nd 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

Marais, et al., CID, 2016.

AIM 3:   PROSPECTIVE CHILDHOOD TBM COHORT STUDY AT A SUB-NATIONAL LEVEL

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.

Contact details:

Dr Karen du Preez

Desmond Tutu TB Centre,
Stellenbosch University

karen_dupreez@sun.ac.za