Meningitis sequelae, their impact, and follow-up care in low income countries – how much do we know?

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Overview

- Global burden of disability and WHO Roadmap
- Meningitis sequelae – what do we know
- Joseph's journey through care
- Follow-up care in the low income setting
- Evaluating neurodisability – the challenges

Childhood neurodisability

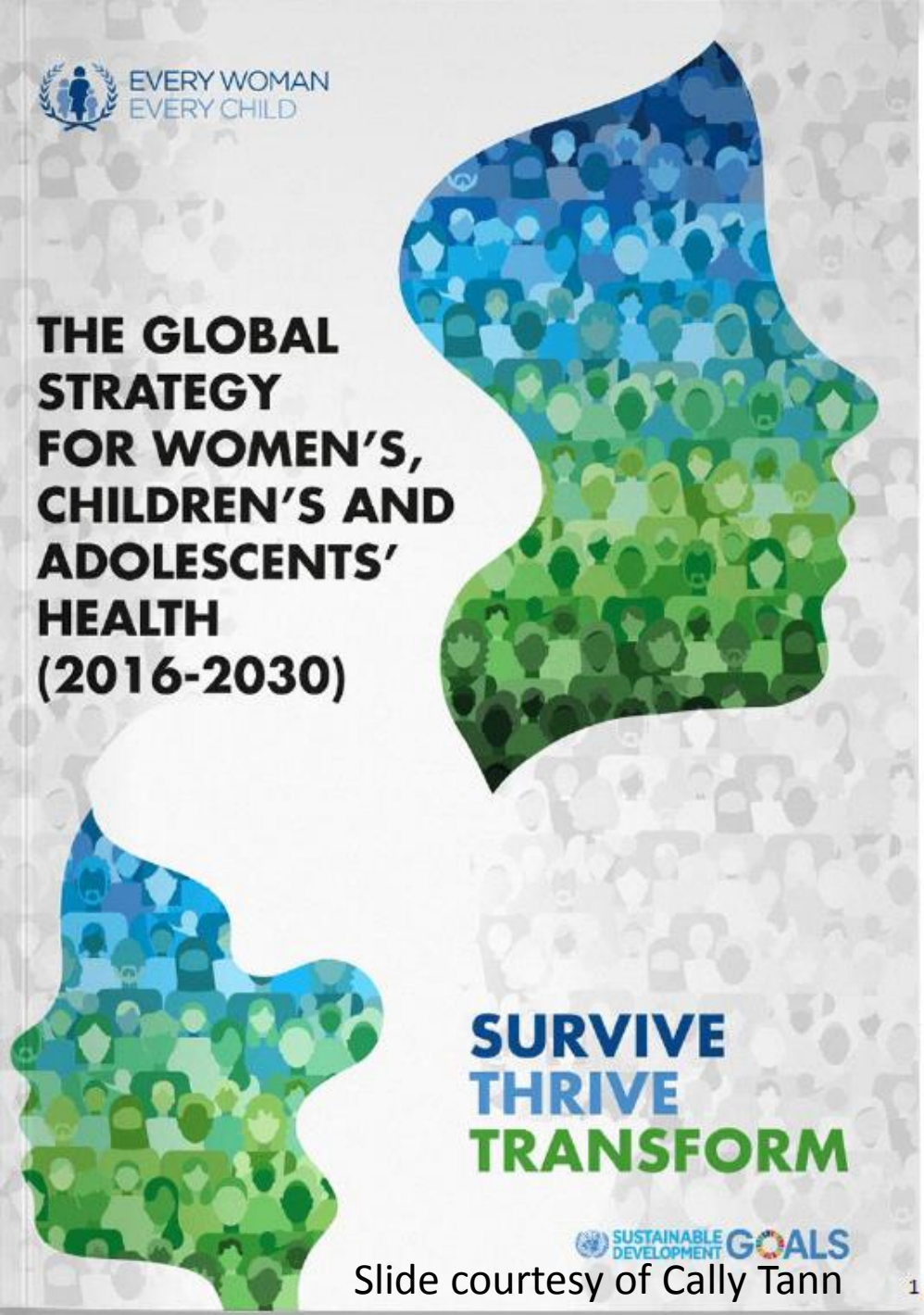
One of the most important precursors of:

- psychopathology,
- poor adaptive functioning
- educational disadvantage

Later life

- less likely to be living independently
- be in paid employment or
- have cohabiting relationships

Moffitt, T.E., et al., *A gradient of childhood self-control predicts health, wealth, and public safety.* Proc Natl Acad Sci U S A, 2011



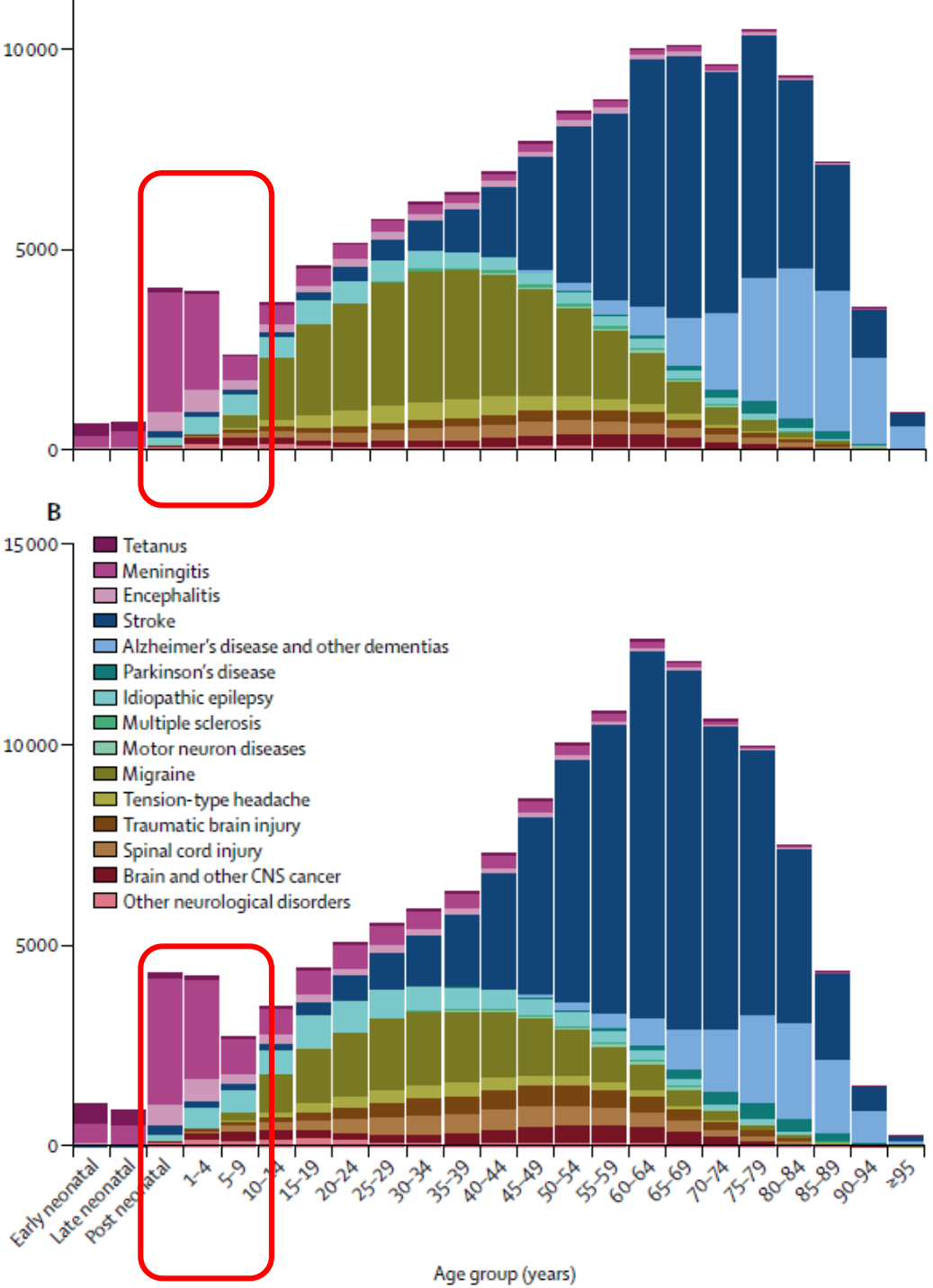
Slide courtesy of Cally Tann

- In era of Sustainable Development Goals there is a renewed emphasis on **early child development to maximise the developmental potential for all children**

- The Global Strategy supports the need for all children to **SURVIVE and THRIVE**

- Estimated **53 million children with developmental disability**[1]

[1] Global Research on Developmental Disabilities Collaborators *Lancet Glob Health* 2018; 6: e1100–21



Global, regional, and national burden of neurological disorders, 1990–2016

Lancet Neurol 2019; 18: 459–80

- Meningitis one of the 4 leading contributors of neurological DALYs
- Burden greatest in s-Saharan African region and S Asia

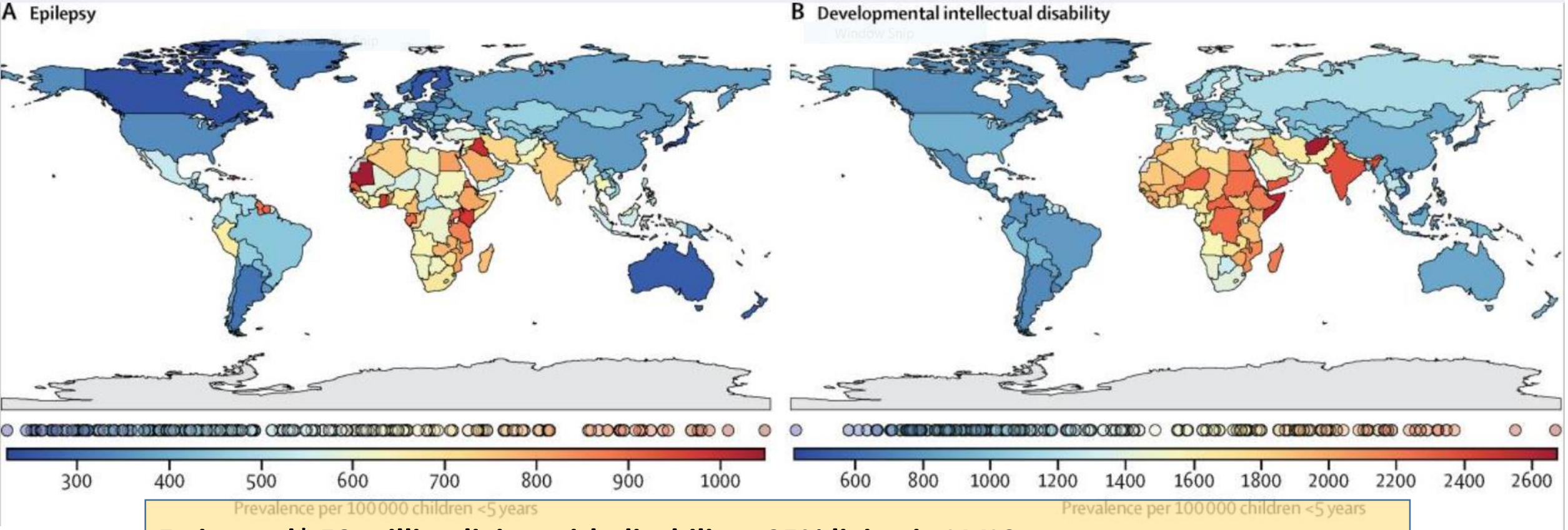
Paediatric Bacterial Meningitis Surveillance in WHO African Region, 2011-2016

CID 2019

- 49,844 reported meningitis cases
- 1670 (3.3%) lab confirmed

Developmental Disabilities among children < 5 years…, 1990-2016. GBD study

Lancet Global Health 2018



Estimated* 53 million living with disability - 95% living in LMICs
Highest numbers in sub-Saharan Africa (71.3%)
South Asia has highest prevalence of children with developmental disabilities in 2016

***Limited data especially from LMICs & therefore reliance on statistical estimates of trends**

Defeating meningitis by 2030

World Health Organization

- A global strategy to tackle main causes of acute bacterial meningitis

The Global Roadmap is based on **five pillars**:

Pillar 1: Prevention and epidemic control
Pillar 2: Diagnosis and treatment
Pillar 3: Disease surveillance
Pillar 4: Support and aftercare for families and survivors
Pillar 5: Advocacy and information

- Recognition of lack of follow-up post infection and treatment
- Many sequelae not apparent on discharge
- Are risks same for each causal agent?
- How is risk decreased with prompt treatment?
- Role of adjunctive therapies in prevention of sequelae?

Pillar 4 - to build and strengthen health systems to provide the necessary care and programmatic support.

SG11: Strengthen recognition of sequelae both in hospital and by follow up after discharge

SG12: Increase availability and access to appropriate care for survivors with sequelae

SG13: Empower survivors and their families to maximize their health and quality of life

Challenges of assessing outcome post bacterial meningitis

Image – Anna Vines World Hope

- Lack of methodologically sound studies - heterogeneity
- Follow-up time post infection
  - Exclude transient impairments
  - Include later developmental sequelae
- Verification of infection
  - Use of appropriate, clearly described diagnostic methods
- Use of standardised tests in assessment of neurodevelopment

Carter J, Newton CR Brain Res Reviews 2003

Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis

Karen Edmond, Andrew Clark, Viola S Korczak, Colin Sanderson, Ulla K Griffiths, Igor Rudan

***Lancet Infect Dis* 2010**

Systematic review and meta analysis:

- Jan 1980 to Mar 2008
- Overall risk of disabling sequelae in survivors: 20%
- Proportion with sequelae varied by infecting organism:

Organism	Median (%)	IQR (%)
S. pneumonia	24.7	16.2 – 35.3
H. influenza type b	9.5	7.1 – 15.3
Meningococcus	7.2	4.3 – 11.3

Most common types of sequelae:

- Hearing loss – 33.6%
- Seizures 12.6%
- Motor deficit: 11.6%
- Cognitive impairment: 9.1%
- Vision impairments: 6.3%
- Behavioural…… ?
- 20% impairments involved multiple domains

Carter J

Neurocognitive impairment post CNS infection

- Cognitive, motor and hearing impairments
- Prevalence of epilepsy increasing over time
- Impact of bacterial aetiology

Brain Res Rev 2003

Molyneux E

Edmond K

- Disabling sequelae impacted by:
- HIV co-infection
- Younger age

ADC 2003; Lancet ID 2010

Grimwood K

School age survivors of ABM

- Verbal performance
- IQ
- reading accuracy
- visuo-motor integration
- All lower cf controls

Paediatrics 1995

Hearing loss post ABM – a Silent Crisis?

- High prevalence of SNHL post ABM (but not TBM)
  - ~6% of all acquired SNHL in children
- Studies of incidence and cause of HL post ABM are limited
  - Quality of audiometry variable
  - Severity and timing of HL inconsistently reported
- Early referral needed for Optimum outcome

Lack of sufficient or quality hearing input during early childhood
- poor speech and language
- poor academic development

Hearing Outcomes in Children with Meningitis at RCWMCH
Kuschke et al SAMJ

- Retrospective review Jan 15-Jun 16
- 68 cases (12 confirmed)
- Only 16 (23.5%) referred
- Overall prevalence of HL: 42.8%
- 23.5% severe to profound
- Late referrals/lack of awareness amongst health professionals

Pathophysiology and developmental outcome of TB meningitis

- Arterial ischaemic stroke likely main cause of irreversible neurological damage
- Infarction commonly occurs in the basal ganglia and associated with:
  - language delay, spatial neglect, executive dysfunction, autism and attention deficit hyperactivity disorder (ADHD). *Riva 2019*
- The most common impairments at follow-up are in
  - cognition, learning, emotion and behaviour
- Poor neurodevelopmental outcome is associated with:
  - younger age
  - delayed presentation and treatment initiation
  - multiple, bilateral and large infarctions
  - clinical severity
  - hydrocephalus.
    Schoeman 2002; van Well 2009; Humphries 1990
- Persistent visual and hearing deficits uncommon *Schoeman 2002*

Impact of bacterial meningitis on families and communities:

- Survivors – at risk of long-term disabling sequelae
  - Hidden from view in many societies
  - Subjected to stigma and neglect (*Nakayama & Tann, 2013*
  - Undercounted in national and international statistics
- Few data sources on risk of disability
  - severity and distribution of sequelae
- Financial burden on families – often not calculated or underestimated

Image courtesy of Anna Vines, World Hope

Joseph’s story

- Previously thriving and active toddler
- ABM at 2 years
- Treated IV antibiotics for 5 days
- Discharged to home - no follow-up
- Abandoned by mother - cared for by elderly grandmother
- Presented at 10 years of age with:
  - Severe dysphagia and failing to thrive
  - Four limb Cerebral palsy
  - Epilepsy – biting through bottom lip
  - Non-verbal and ? hearing

Joseph's story

- Assessed by visiting Speech and language therapist
  - Positioning/feed thickeners
- Admitted to local hospital for NGT feeding
  - Gastrostomy inserted using catheter tubing
- Followed up Cheshire Homes
- 'Rehabilitation' and donated wheelchair
- Epilepsy - Phenobarbitone
- Travel to clinic costly – loss to follow-up

Follow-up care in low income settings (LICs)

- Limited resources and facilities for children and adults with disabilities
- Fragmented
- Provision often by NGOs, charitable and civil society organisations
- Expensive!
  - Average life time cost for meningitis sequelae in Dakar, Senegal:
  - Est $35,000 – 98% for childcare and productivity; *Edmonds PIDJ 2012*

Therapy Services

Public Sector Services

- Very limited resources
- Enormous workload – stroke and trauma rehab
- Often serving very large geographical areas
- No/limited outreach services
- Costly private provision

	Kalawati Saran Children's Hospital	PGIMER	Edward Frances Small Teaching Hospital
	New Delhi	Chandigarh	Banjul, Gambia
Population served	~2 million	60-80 million	1.6 million
Annual admissions	25 000	30 000	?
Neurology neurorehab Drs	4	8	0
Physiotherapists	4	6	2
Occupational therapists	2	4	0
Speech and language	1	3	0
Wheelchair services	Nil	Nil	Nil

What hearing/ENT services are there in sub-Saharan Africa?

Gambia:
Population
NO qualified audiologists
No native ENT surgeons
2 schools for the deaf

Cameroon:
Population:~16.38 million
NO qualified audiologists
37 ENT surgeons
Several schools for the deaf – none Government funded

Sierra Leone:
Population:~5.25 million
NO qualified audiologists
No native ENT surgeons
2 schools for the deaf

Zambia:
Population:~17 million
1 audiologist
2 ENT surgeons
6 schools for the deaf

Malawi:
Population:~18 million
3 audiologists
2 ENT surgeons
6 schools for the deaf

Sound Seekers
Helping people with hearing loss in Africa

- **Train local health professionals to deliver ear and hearing health services**
- **x3 Malawi graduate students in MSc audiology programme in UK**
- **Train school teachers in hearing loss awareness**
- **Support inclusion of children with HL in schools**
- **Rights and advocacy**

Hearing aids improve communication in up to 90%
In LMICs, <1:40 who need a hearing aid have one

Physiotherapy Services in Freetown Sierra Leone

- Rehabilitation Centre
  - World Hope International
- Provision of equipment:
  - Splints, chairs, standing frames

BUT

- Few children brought to centre
- Local staff afraid to work with disabled children

Challenges identified

- Limited knowledge of disability
- Stigmatisation
  - Local belief system that child possessed by demons/cursed
  - Seizures *'witched'*
  - Encouraged by local Chiefs, religious leaders
- Parents refusing to complete therapy – fear of demons
- The disabled child blamed by community for any mishap

Overcoming challenges to providing therapy in Sierra Leone

- Outreach care – home-based therapy across Freetown
- School visits – supply of seating/tables
- Basic feeding
- Empowerment and peer support to carers
  - Reducing self-stigmatisation
  - Improving confidence
- Healthcare worker support and training
- Support from high profile citizens

- Therapy **training programme**
- 2 year certificate training for rehabilitation assistant
- Basic competencies assessed to become a Rehabilitation Therapist
- Now a large team
  - Therapists/assistants and trainees
  - Support workers
  - Pastoral and educational support workers
- Electronic records!
- Ongoing **M&E**

Evaluating neurodisability

To understand and characterise impairment requires:

- Appropriately developed neurodevelopmental assessment tools
  - early identification and treatment of disability
  - improve opportunities for developmental change and rehabilitation

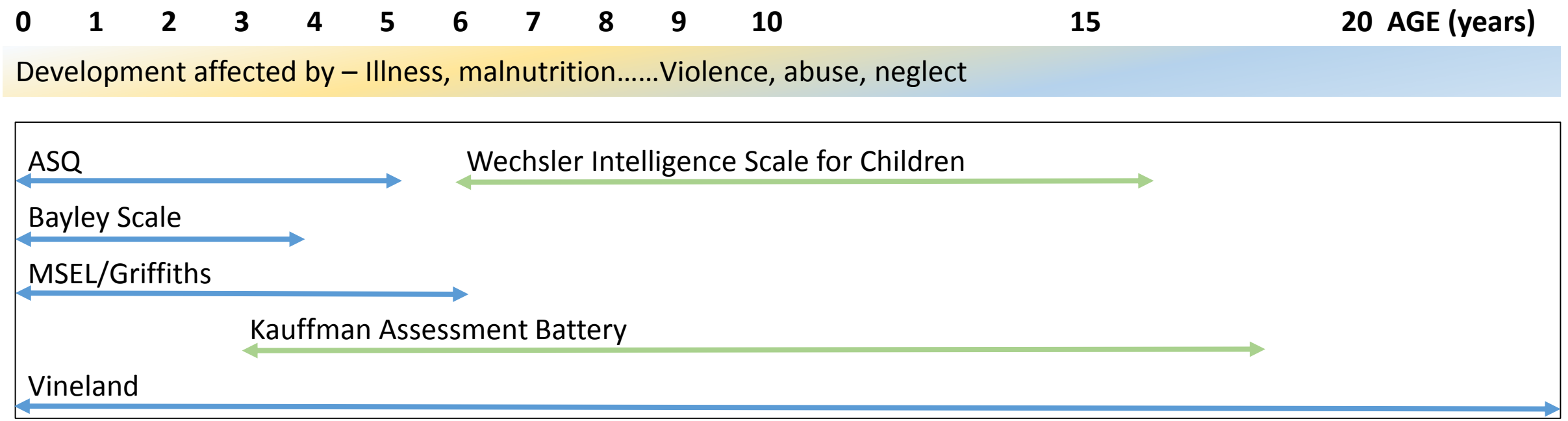
Challenges:

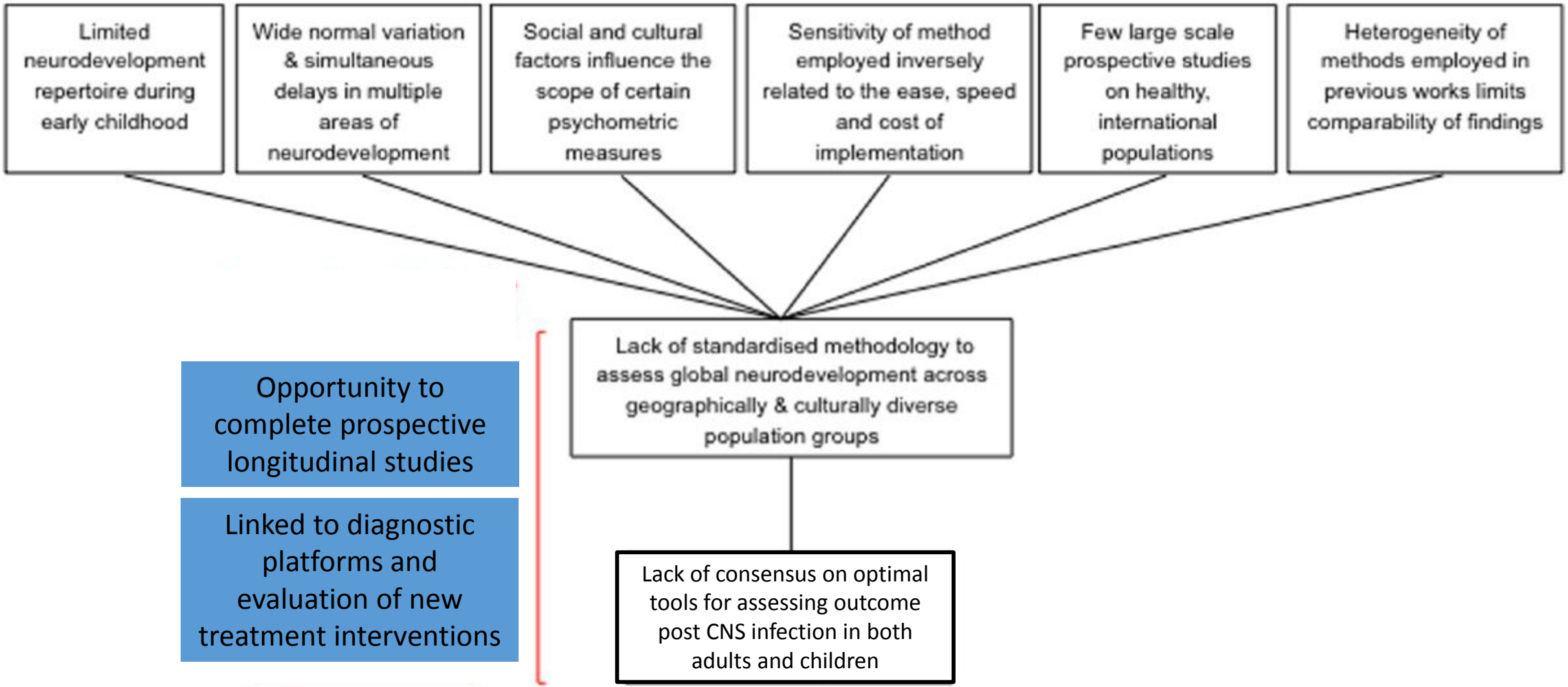
- Lack of robust, standardised assessment tools
- Developed for and normed across geographical and cultural settings

- Most NDATs developed in High Income Settings
- Tools often ‘adapted’ for LICs
  - May not evaluate same construct across

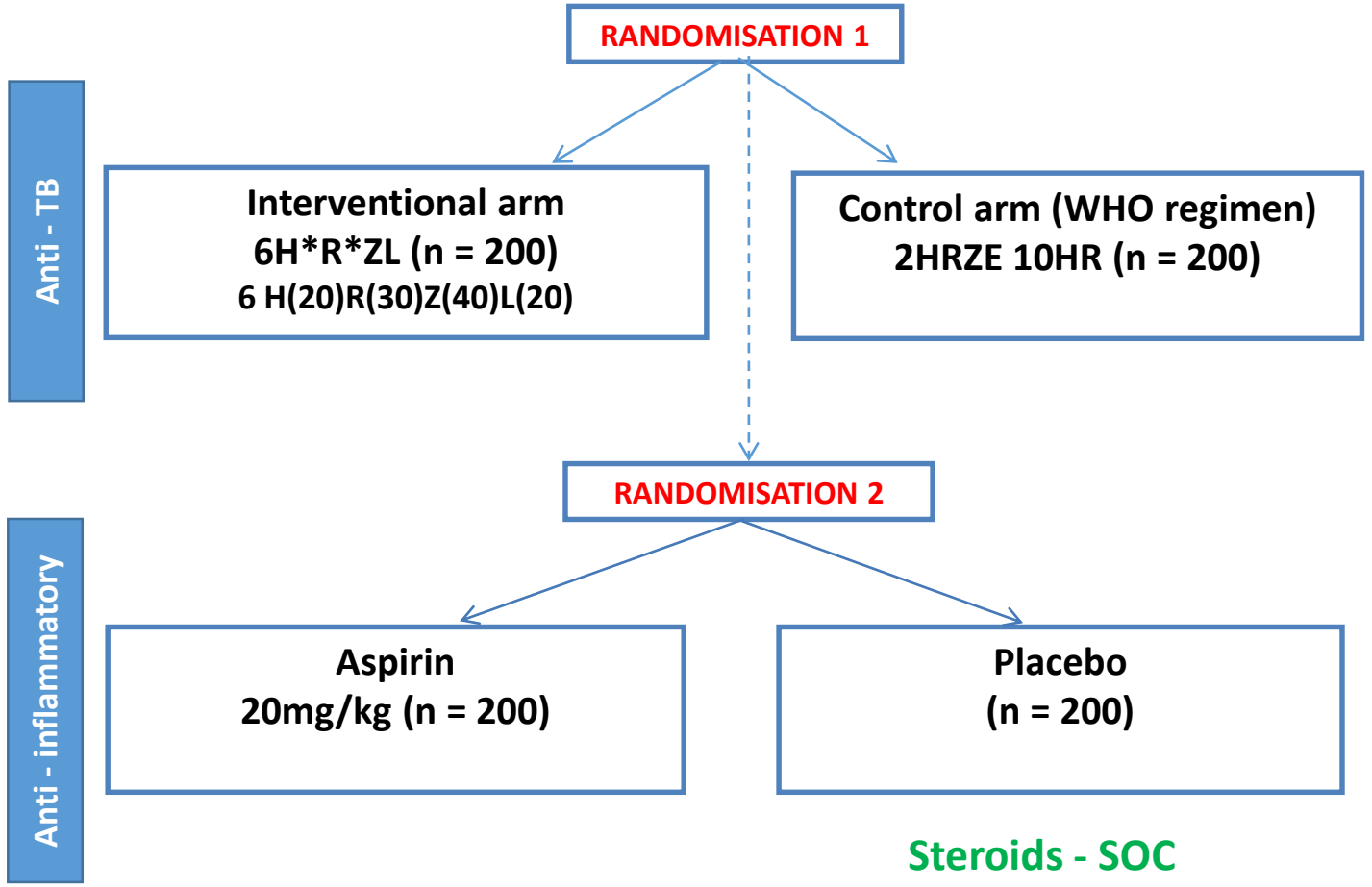
0-5 YEARS
EARLY DEVELOPMENTAL SKILLS
Language, Motor
Visual-receptive

6 YEARS AND BEYOND
DOMAIN SPECIFIC
Emerging executive function, attention
Emotional and behavioural function





Adapted from Fernandes et al PlosOne 2014



THE SURE TB MENINGITIS TRIAL

Multi-site, partially blinded RCT of WHO standard of care

vs

Short intensive 4 drug regimen

Factorial "2 for 1" design

Primary Outcome – ATT arm

All cause mortality at 48 weeks

Primary outcome – Aspirin arm

Motor outcome at 48 weeks

Substudy:

Longitudinal neurodevelopmental outcome

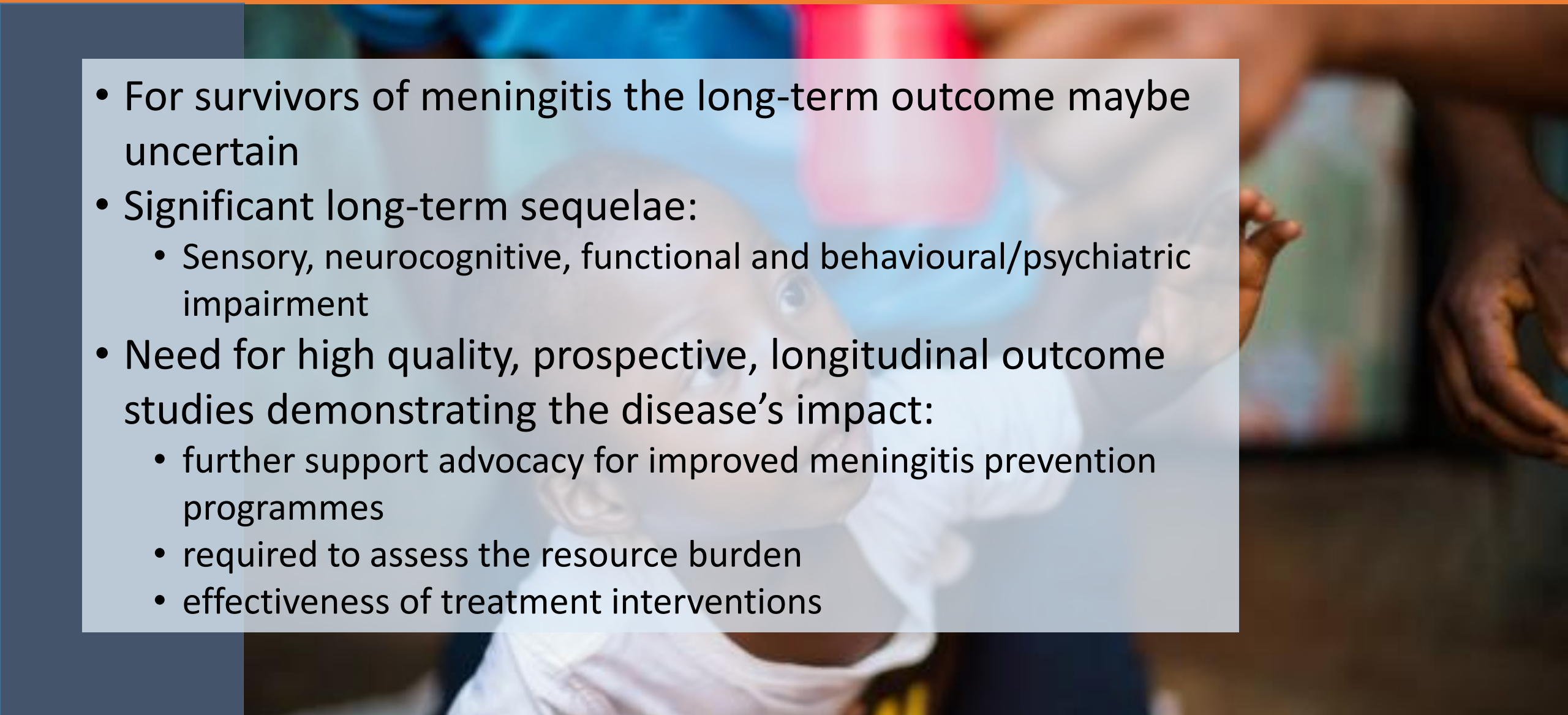
$6H^{HD}R^{HD}ZL$ = INH 20mg/kg, *High Dose RMP 30-35mg/kg*, PZA 40mg/kg and **LFX 20mg/kg**; (+PK)

Asssessing Neurodevelopmental outcome requires:

- Standardised, locally normed, functional and neurocognitive assessments
- That vary by age targeting:
  <5 years - early developmental skills
- ≥5 years – cognitive, functional, behaviour and attention
- No requirement for costly or extensive staff training
- Uniform methods for adapting existing NDATs
  - Translation/back translation
  - Adjustment of stimuli for cultural variables
  - Healthy control group

See: Davis A, Anderson ST and Chung F et al Neurocognitive and functional impairment in adult and paediatric Tuberculous Meningitis Wellcome Open Research Oct 2019

Summary



- For survivors of meningitis the long-term outcome maybe uncertain
- Significant long-term sequelae:
  - Sensory, neurocognitive, functional and behavioural/psychiatric impairment
- Need for high quality, prospective, longitudinal outcome studies demonstrating the disease's impact:
  - further support advocacy for improved meningitis prevention programmes
  - required to assess the resource burden
  - effectiveness of treatment interventions

Acknowledgements

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- https://www.youtube.com/watch?v=y6L_91xtbjw