Designing a MDR-TB Injectable Sparing Regimen in Children: Research Priorities, Design Considerations and Discussion

Tuberculosis Scientific Committee Meeting

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Outline

- Background
- Who to include
- Composition of control arm
- Composition of intervention arm
- Other questions and challenges

Considerations for study

- **Entry points**
  - how to diagnose TB disease
  - how to diagnose “MDR-TB”
  - disease severity (deciding treatment regimen and treatment duration)
- **End points/Treatment response (Outcomes)**
  - Culture-confirmed or not (bacteriological cure vs. Rx completion)
  - Favourable vs. unfavourable outcomes
- **Safety/tolerability**
  - Adverse effects of drugs - monitoring
- **Microbiology**
  - Which lab bacteriology to use and how/when (e.g. Xpert only initial diagnosis)

Entry points – who should be included (1a)

Certainty of diagnosis and DST-patterns

- DR-TB disease: Clinical, radiological, or microbiological pathology, in combination with diagnosis of confirmed, probable, (or possible) DR-TB disease (Seddon et al JPIDS 2013)
- Not TB infection only, which should include children with positive bacteriology who have no clinical or radiological disease

Entry points – who should be included (1b)

Certainty of diagnosis and DST-patterns

- For research into paediatric DR-TB, it is important to describe the precise drug susceptibility test (DST) result:
  - **Confirmed** DR-TB: DST pattern of child's isolate
  - **Presumed (probable)** DR-TB: DST pattern of the likely source case(s)
  - Therefore not only the "category" (MDR/Pre-XDR/XDR) but full available DST result
  - Should possible DR-TB be included? (no DST result of child or source)
- Only MDR-TB and more, or also RIF-mono-resistant? What about incomplete results (GXP only)

Entry points – who should be included (2)

Age: 0-17 years

- Important to include adolescents – different types of pulmonary disease, rarely studied
- Important to include infants – immune system developing and different pharmacokinetics

HIV status

- Both HIV-uninfected and HIV-infected children should be included

Entry points – who should be included (3)

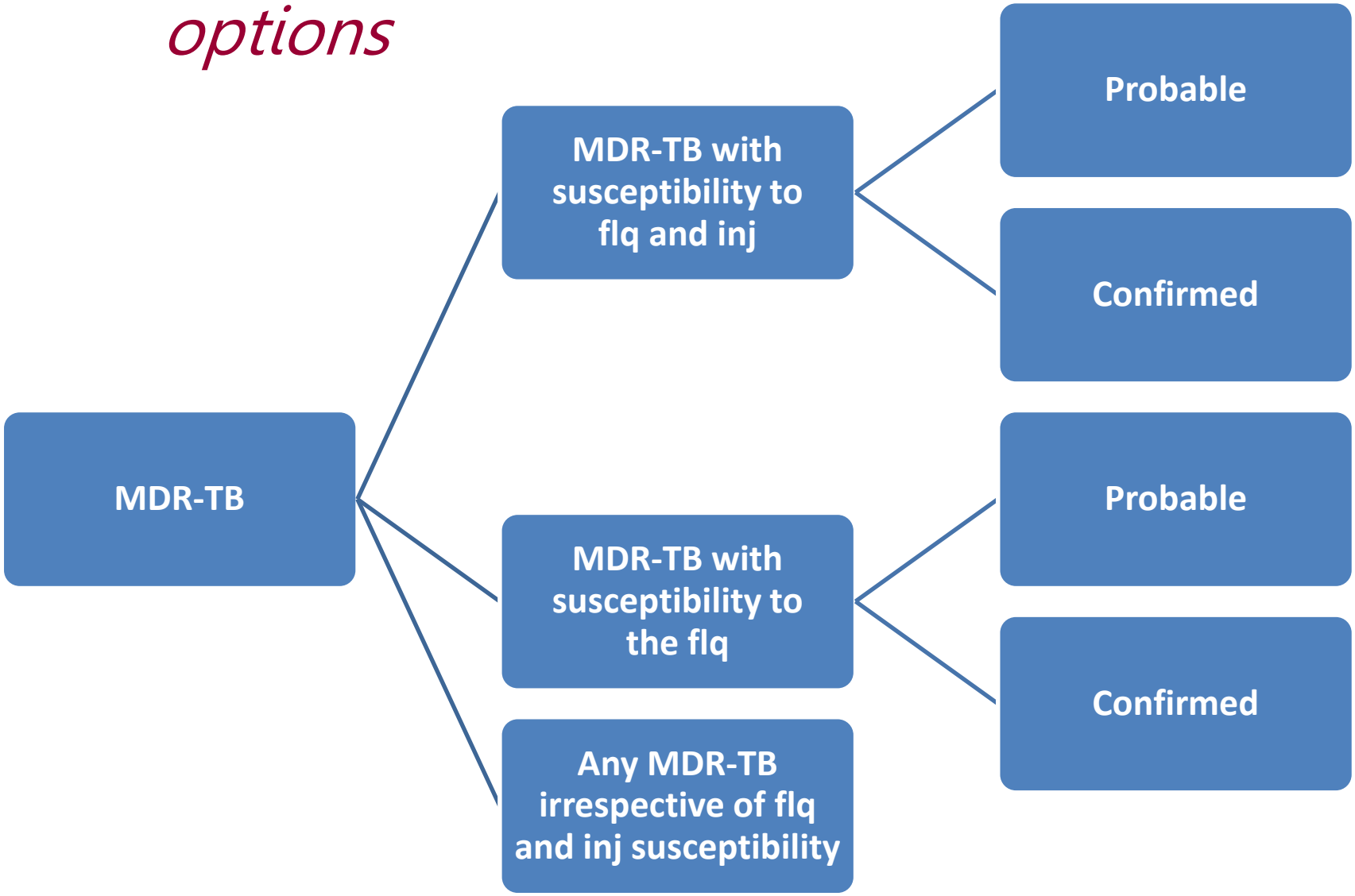
Types of TB

- Pulmonary TB – yes
- Extrapulmonary TB – yes, but not TB meningitis / miliary TB (?) unless certainty about regimen's drugs penetrating CSF?

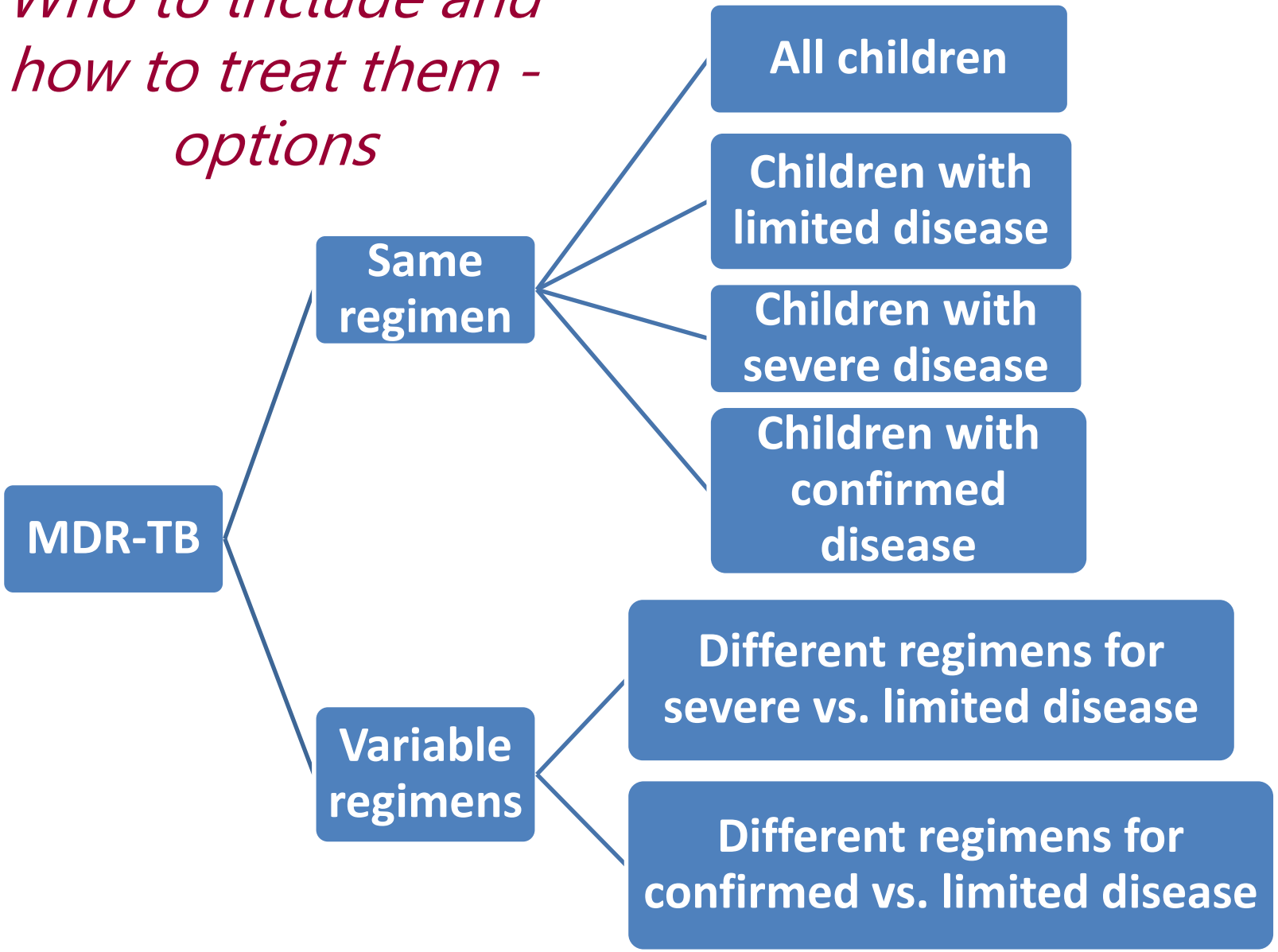
Disease severity

- Very important consideration:
  severe and non-severe TB disease – could definitely influence treatment duration and treatment outcome
- Classification by Wiseman et al. (PIDJ 2013) or Shine-trial classification for non-severe disease

Who to include - options



Who to include and how to treat them - options



Control Arm – options

- Standard traditional 18 month 'WHO' regimen where every child receives the same regimen for the same duration
  - 6Am/Mfx or Lfx/Cyc orTzd/Eth/Z/H 12Mfx/Cyc/Eth/Z/H
  - ?Lnz ?Clof ?PAS (>MDR-TB)
- Clinician designed regimen based on WHO principles (4 active drugs plus Z) – variable regimens for
  - Variable types of resistance
  - Variable types of severity
  - Treatment response
- 9-12 month regimen
  - 4-6Am/H/Eth/Clof/Mfx/E/Z +5-6Clof/Mfx/E/Z

Intervention arm principles

- In designing a regimen we need to consider the following when thinking about which drugs to include
  - Different mechanisms of action
  - Different mechanisms of resistance
  - Toxicity (also similar toxicity other drugs, e.g. mitochondrial tox with LNZ, BDQ, ARVs)
  - Distribution (penetration)
  - Interaction (other drugs)
  - Ease of use (children and healthcare programs)

Intervention arm thoughts (no injectable)

E / Z / H

Mfx / Lfx

Eth / Cyc

Lnz / Cfz

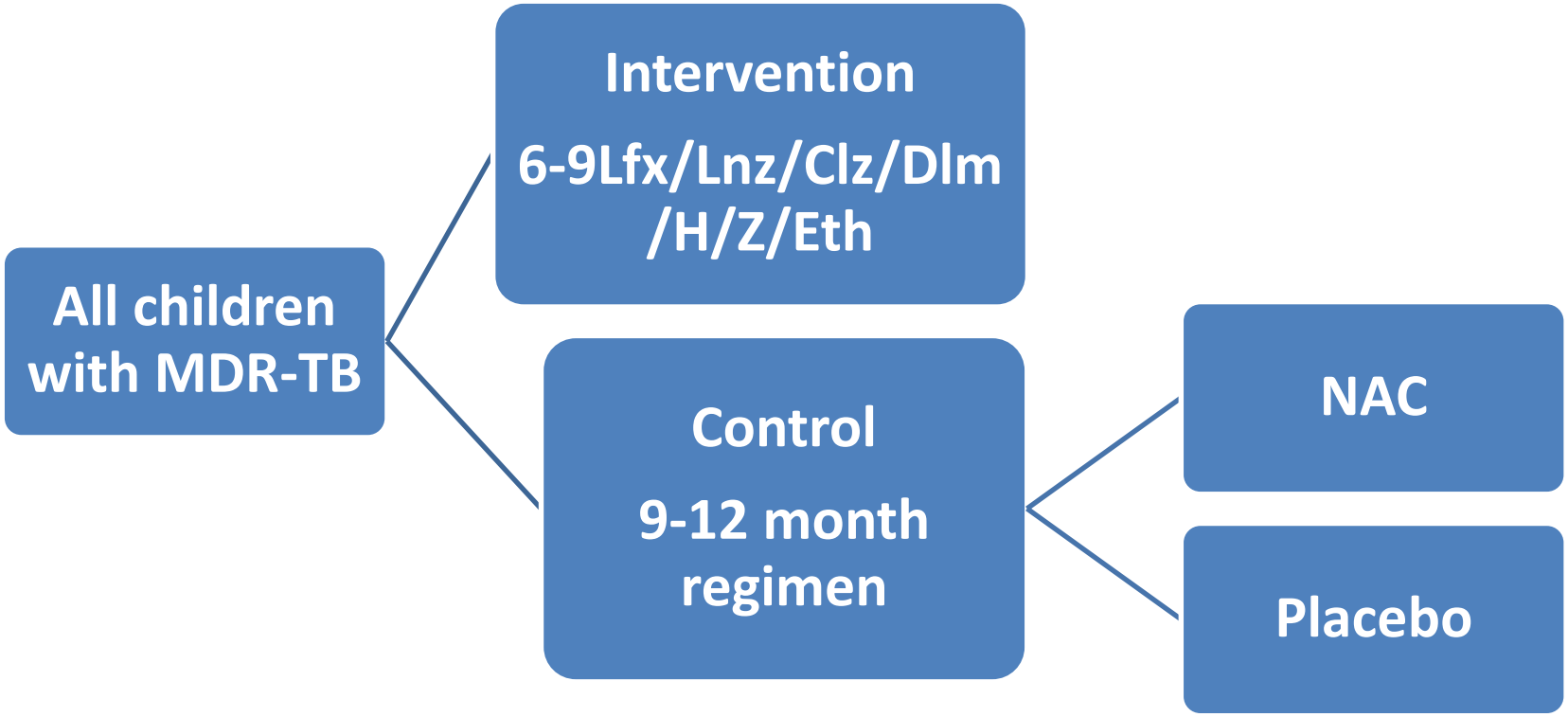
Dlm

Duration?

Other Questions (to get more out of study)

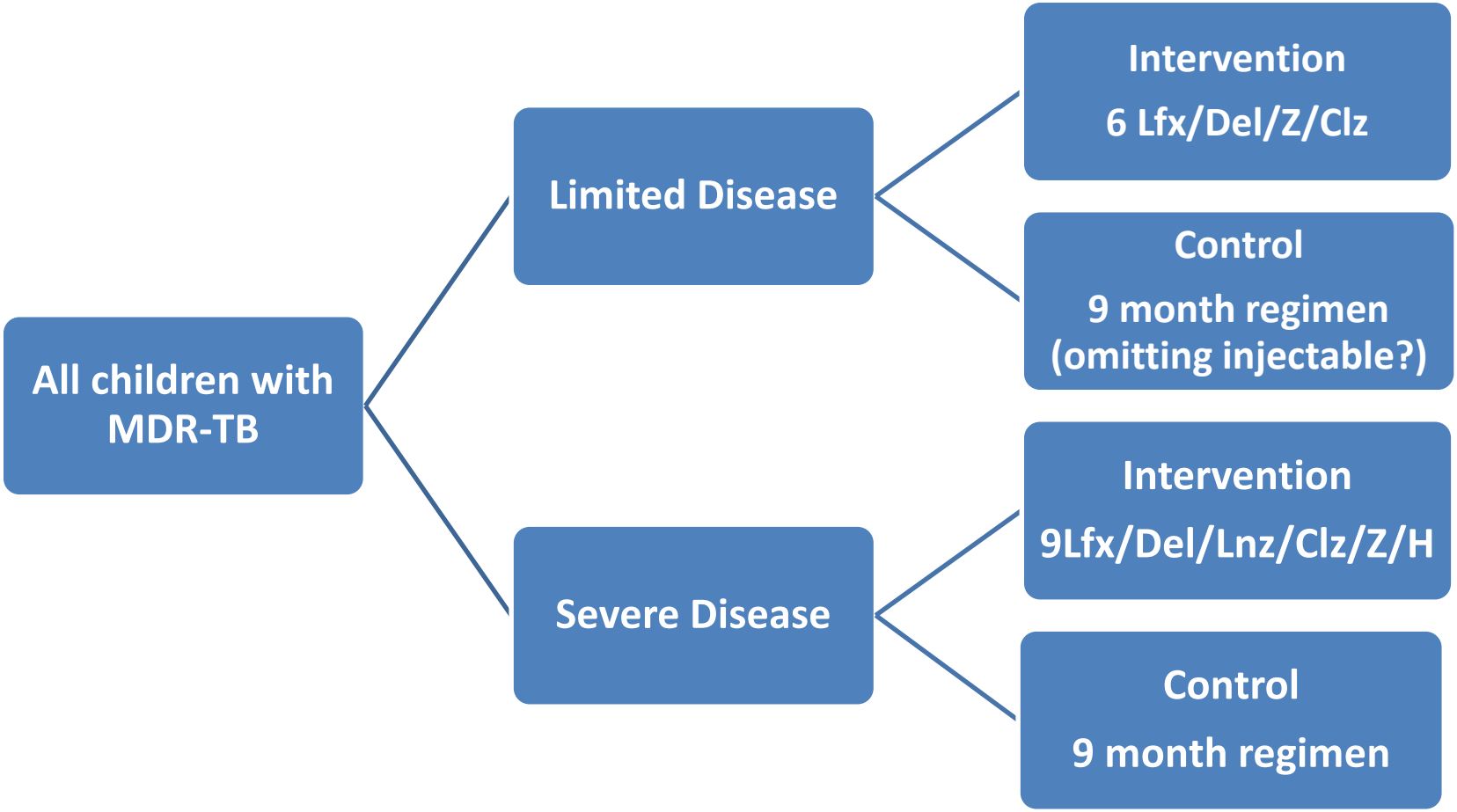
- Drugs
  - Aspirin
  - Steroids
  - NAC (N-acetyl-cysteine)
  - Ibuprofen
  - Efflux pump inhibitors
  - Vitamin D
- Delivery
  - Inhaled therapy
- Other
  - Nutritional support
  - Psychosocial support

Possible Trial 1



Opt out for individual children; Lnz or Lfx change to PAS or BDQ if intolerable/resistance?

Possible Trial 2



Role of BDQ if becomes available for children?

Trial implementation and uptake considerations

- Effective
- Safe
- Child friendly and program friendly (once daily dosing)
- Simplicity of regimen
- Monitoring for AE

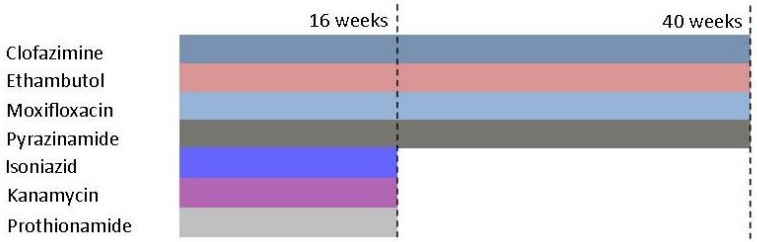
STREAM: Regimens for Stage 2

Regimen A

Locally used WHO-approved MDR-TB regimen

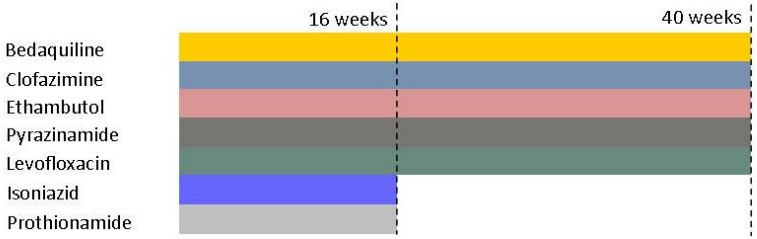
Regimen B

(Stage 1 study regimen)



Regimen C

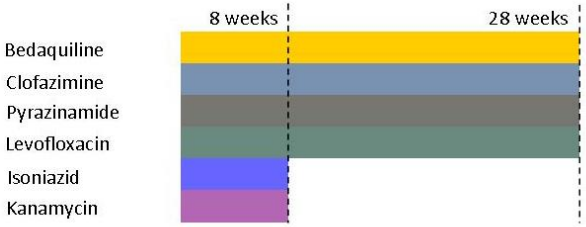
(modified Stage 1 study regimen, all oral)



- **Bedaquiline added**
- **Moxifloxacin replaced by levofloxacin**
- **Kanamycin dropped**

Regimen D

(modified Stage 1 study regimen, shortened)



- **Bedaquiline added**
- **Moxifloxacin replaced by levofloxacin**
- **Prothionamide dropped**
- **Ethambutol dropped**

Table 1. Planned or ongoing Phase 2 or 3 trials of MDR-TB treatment or preventive therapy

MDR-TB Treatment trials		*MDR-TB Preventive therapy trials*	
Trial	**Components of intervention arm**	**Trial**	**Components of intervention arm**
NC005	PZA, BDQ, PTA	VQUIN	**LFX**
Opti-Q	**LFX** + standard of care	TB-CHAMP	**LFX**
STREAM II	BDQ, CFZ, EMB, PZA, **LFX**, INH, PTO	PHOENIx	DLM
NIX-TB	**LZD**, BDQ, PTA		
STAND	PZA, MFX, PTA		
NEXT-TB	PZA, **LFX**, ETO/hdINH, **LZD**, BDQ		
C208	BDQ + standard of care		
Trial 213	DLM + standard of care		
endTB	Combinations including **LZD**, BDQ, CFZ		

PZA-pyrazinamide; BDQ-bedaquiline; PTA-pretomanid; LFX-levofloxacin; EMB-ethambutol; MFX-moxifloxacin; PTO-prothionamide; CFZ-clofazimine; hdINH-high dose isoniazid; LZD-linezolid; ETO-ethionamide; DLM-delamanid

Slide: courtesy Anthony Garcia-Prats

Data gaps/Challenges

- Optimal and safe use of FQNs across age spectrum – PK studies in progress: LFX and MFX (0-8 yrs)
- Optimal and safe use of LNZ (PK data pending) – toxicity concerns – full duration of treatment (replace if AEs)
- Clofazimine PK and safety (planned IMPAACT capsule) Role of BDQ? (P1108 and Janssen study) – as data available to replace other drugs for resistance/toxicity?
- Role of BDQ/DLM co-treatment (planned IMPAACT capsule)
- Changing landscape: MDR-TB treatment guidelines, access programs
- Timing of inclusion wrt adult trials (adolescents)
- Formulations - including clofazimine (gelcaps), FQNs

Questions?