Operational challenges to conduct LTBI studies

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Background

- Scaling up TB PT is a priority to meet the End TB targets
- Need studies of TB preventive therapy to inform new regimens and novel delivery strategies to maximise scale up of LTBI management

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Overview

- Operational challenges with respect to
  - General considerations
  - study design
  - special populations
- Conclusion

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Operational challenges: general considerations

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Research priorities & funding

- Most HBCs have no National TB research plans
- LTBI research has been seen as a low priority
- Limited funding for LTBI studies
  - particularly for implementation research studies
- Most research funding comes from resource rich countries, which is difficult to access
- Funds to support programmatic scale up of interventions, such as Global Fund and PEPFAR, typically preclude research

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Regulatory & ethical aspects

- Regulatory approval may take a long time, particularly if unlicensed drugs are being evaluated
  - Requires a clinical trial design
- Standard of care may pose a challenge (policy and practice differ)

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Stakeholders

- Obtaining stakeholder support may be challenging due to concerns of toxicity and resistance, particularly if there is a strong anti TB preventive therapy lobby

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Participant recruitment & retention

- Uptake of health prevention strategies is typically poor, particularly among men, which makes recruitment challenging
- Rumours abound regarding side effects
  - Impotence & fertility
  - Making one weak
  - Death
- Retention in study challenging
  - Greatest loss occurs in first month (due to minor SEs)
- To ensure good adherence to study medication requires measures to support & monitor adherence

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Operational challenges: study design

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Individually randomised controlled trials

- RCTs done to evaluate safety & efficacy of new regimen or delivery strategy
- RCTs are conducted by research staff at dedicated clinical trial sites to maximise recruitment, retention and ascertainment of endpoints
- Requires partnership with routine health service
  - Participant recruitment
  - Referral of participants for management of AEs
- RCTs take a long time to complete and are expensive

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Pragmatic & cluster randomised trials

- Pragmatic & cluster randomized trials done to evaluate effectiveness of LTBI regimens and delivery strategies in as close to real world settings as possible
- Conducted in routine clinics
  - Space, electricity, telephones, internet connectivity may be constrained
- Requires both routine health care workers and research staff
  - Need to be clear on who does what
- Integration with routine care
  - Eg, HIV treatment and antenatal care

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Pragmatic & cluster randomised trials

Data collection & entry

- Clinic registers collect minimal information
- ? adapt registers or supplement data collection with study specific case report forms
- Clinic staff busy and find it challenging to collect additional data
- Use of study specific data collection tools, such as electronic data capture, is challenging for routine staff

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Pragmatic & cluster randomised trials

- Drug procurement, storage, distribution, dispensing and drug accountability
  - Typically research staff responsible but requires integration with routine pharmacy system
- Adherence monitoring and support
  - Who is responsible?
    - Study treatment vs chronic medication (eg HIV treatment)
- Ascertainment of study outcomes
  - Research staff typically responsible for ascertaining study outcomes

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Demonstration studies

- Demonstration projects done to show feasibility prior to scale up
- Implemented by routine health services
- No additional research processes required
- Ascertainment of study outcomes by the routine health service may be incomplete
- Routine data used for the study
  - Data collection may therefore be incomplete and less accurate

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Operational challenges: special populations

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Children

- Children require parental consent
- Need referral links into paediatric services
- Diagnosis of TB detected by active case finding in children challenging
  - International case definitions recently published
- Paediatric formulations may not be available

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Prisoners

- Prisoners are considered vulnerable populations & require careful consideration of ethical principles
- May have higher prevalence of risk factors for developing hepatitis
- Screening for TB
  - High prevalence of symptoms
  - CXR may be more sensitive

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Conclusion

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- There are many operational challenges for doing LTBI studies
- Most challenges can be overcome with careful planning