Operational challenges to conduct LTBI studies

Gavin J. Churchyard
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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
Overview

- Operational challenges with respect to
  - General considerations
  - study design
  - special populations
- Conclusion
Operational challenges: general considerations
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
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)
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
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.
Operational challenges: study design
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
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
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
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
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
Operational challenges: special populations
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
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
Conclusion
Conclusion

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