DIAGNOSTIC RCTS
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VERY FEW DIAGNOSTIC RCTS IN TB

- A few on active case detection
- A trial on same-day smear diagnosis (TDR)
- A trial on Xpert MTB/RIF in South Africa
- Ongoing trials on Xpert MTB/RIF
- Cluster-randomized stepped wedge designs for phased implementation
Comparison of two active case-finding strategies for community-based diagnosis of symptomatic smear-positive tuberculosis and control of infectious tuberculosis in Harare, Zimbabwe (DETECTB): a cluster-randomised trial

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Summary

Background: Control of tuberculosis in settings with high HIV prevalence is a pressing public health priority. We tested two active case-finding strategies to surge high periods of infectiousness before diagnosis, which is typical of HIV-positive tuberculosis and is a key driver of transmission.

Methods: Clusters of households in the high-density residential suburbs of Harare, Zimbabwe, were randomly assigned to receive six rounds of active case finding at monthly intervals in either mobile van or door-to-door visits. Randomization was done in blocks of six clusters, with one in four blocks for each intervention group. The 25 intervention clusters were randomly assigned to intervention groups, with clusters assigned to each intervention group in a balanced fashion in each month. In both groups, adult residents of the cluster who were identified as likely to have tuberculosis were interviewed, and those who had symptoms of active tuberculosis were referred for further evaluation. The primary outcome was the cumulative yield of smear-positive tuberculosis per 1000 adult residents, computed between intervention groups, adjusted for intervention group. The secondary outcome was change in prevalence of smear-positive tuberculosis from before intervention to before round of intervention in 25% of randomly selected households from the two intervention groups combined. Analysis was based on participants who provided sputum in the two surveys. This trial is registered, number D3799455542.

Findings: 46 clusters were identified and randomly allocated equally between intervention groups. A total of 15 341 adults in the mobile van group and 14 514 in the door-to-door group at baseline. HIV prevalence was 20% (95% CI 0.19% to 0.21%) and in the 3 months before intervention, the smear-positive case notification rate was 2.6 per 1000 adults per year. The trial was completed as planned with no adverse events. The mobile van delivered 251 outreach visits, which were conducted by 150 participants providing a total of 157 437 visits (adjusted risk ratio 1.45% CI 1.51% to 1.49%); the overall prevalence of smear-positive tuberculosis declined from 6.5 per 1000 adults (95% CI 3.5% to 9.5%) to 3.7 per 1000 adults (95% CI 2.9% to 4.6%) (adjusted risk ratio 0.49% CI 0.45% to 0.53%).

Interpretation: Wide implementation of active case finding, particularly with a mobile van approach, could have major effect on tuberculosis transmission and disease.

Figure 1: Trial profile

*Analysis based on mean population from the two household enumeration surveys.

Lancet 2010
Twelve-monthly versus six-monthly radiological screening for active case-finding of tuberculosis: a randomised controlled trial

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ABSTRACT
Background: The incidence of tuberculosis has increased among South African mineworkers despite comprehensive control programmes, including a radiological screening programme. We aimed to assess the impact of a six-monthly versus a twelve-monthly radiological screening strategy for active tuberculosis case-finding.

Methods: Eligible workers at a gold mining company were randomly assigned to the control arm screening at baseline, 12 and 24 months or the intervention arm (additional intervention) at 12 and 18 months after baseline. Study outcomes included proportion of tuberculosis cases detected by screening, proportion with severe symptoms, cohort of disease and mortality.

Results: 30,615 miners were screened. Compared with 12-monthly screening, 6-monthly screening detected more tuberculosis cases, but also more cases, partly due to greater attention to screening and further investigation after “interval” compared with usual radiographs. Tuberculosis cases detected by 6-monthly versus 12-monthly screening were less symptomatic (p = 0.39) and a lower proportion of tuberculosis-specific mortality (8.4% versus 9.3%, p = 0.44) which was not significant in the first 2 months of treatment (0.6% versus 2.2%, p = 0.04) when death from tuberculosis was most likely.

Discussion: In settings with a high prevalence of HIV and tuberculosis, despite standard tuberculosis control measures, frequent case finding may reduce the burden of tuberculosis, prevent transmission through earlier detection of active tuberculosis cases, and increase awareness of tuberculosis cases identified through screening may lead to earlier diagnosis.

Thorax 2010

Figure 1: Study flow chart. "On tuberculosis (TB) treatment for multidrug-resistant tuberculosis for the entire study period."

Thorax 2010
**NON-INFERIORITY RCT ON SAME-DAY MICROSCOPY**

**Same-day ZN**
- Non-inferiority trial
- Adults with cough > 2 weeks
- Schemes randomised by week

![Schematic diagram of same-day ZN test with spot and morning samples on Day 1 and Day 2.]

Cuevas L et al. TDR/WHO

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**The NEW ENGLAND JOURNAL of MEDICINE**

Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

Catharina C. Boehme, M.D., Pamela Nabeta, M.D., Dora Hilleman, Ph.D., Mark P. Nicol, Ph.D., Shubhada Shenai, Ph.D., Fiona Knapp, M.D., Jerry Allen, B. Tech., Rasim Tahalili, M.D., Robert Blakemore, B.S., Rosana Stammjee, M.D., Ph.D., Ana Miltonic, M.S., Martin Jones, Ph.D., Sean M. O'Brien, Ph.D., David H. Persing, M.D., Ph.D., Sabine Ruesch-Gerdes, M.D., Eduardo Guiruz, M.D., Camilla Rodrigues, M.D., David Alland, M.D., and Mark D. Perlman, M.D.
Cape Town Xpert MTB/RIF Demo Study Design: Phase I

Find-Supported Demonstration Study

Cape Town Demo Study: Summary

TB suspect / MDR suspect
Two sites

Nicol M et al. Union Conference, Berlin 2010
A RANDOMISED CONTROLLED TRIAL OF POINT-OF-TREATMENT GENEXPERT MTB/RIF ASSAY FOR THE DIAGNOSIS OF TB AT PRIMARY CARE CLINICS IN HIGH HIV PREVALENCE RESOURCE LIMITED SETTINGS

Inclusion criteria:
- TB symptoms (WHO algorithm)
- X-ray and HIV testing
- >16 years old
- Mobile numbers collected (GPS)
- Informed consent

Randomization:
- Parallel randomized to control or cluster study period
- Intervention
- Direct comparison of clusters, which can be matched

Cross-over:
- Randomized order of control and intervention
- Requires fewer clusters but longer time
- Wash-out between periods

Van den Hof, S
### Stepped Wedge Design

- Unidirectional cross-over
- All transfer from control to intervention, but at different times
- Randomization of order of transfer
  - More than one cluster may transfer at once
  - Restrained in case of small number of clusters
- Need even more time than in regular cross-over design

![Stepped Wedge Design Diagram]

Van den Hof, S

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### Example Stepped Wedge Design

- Roll-out of GeneXpert in Brazil
  - Rio de Janeiro and Manaus
- 14 clusters = defined areas in which all health care units send in samples to same laboratory for diagnosis of TB
- GeneXpert used instead of smear microscopy (and culture)
- Transfer from smear to GeneXpert in 7 steps
- Main effects studied:
  - Diagnosis and treatment registration of bacteriologically confirmed pulmonary TB, overall and for HIV+ individuals
  - Proportion of TB patients diagnosed with MDR
  - Time to appropriate treatment after diagnosis for (MDR) TB patients
  - Cost-effectiveness
  - (Treatment outcomes)

Van den Hof, S
Using the Principles of Randomized Controlled Trial Design to Guide Test Evaluation

Sarah J. Lord, MBBS, MS, Les Irwig, MBCh, PhD, Patrick M. M. Bossuyt, PhD

The decision to use a new test should be based on evidence that it will improve patient outcomes or produce other benefits without adversely affecting patients. In principle, long-term randomized controlled trials (RCTs) of test-plus-treatment strategies offer ideal evidence of the benefits of introducing a new test relative to current best practice. However, long-term RCTs may not always be necessary. The authors advocate using the hypothetical RCT as a conceptual framework to identify what types of comparative evidence are needed for test evaluation. Evaluation begins by stating the major claim for the new test and determining whether it will be used as a replacement, add-on, or stage test to achieve these claims. A flow diagram of this hypothetical RCT is constructed to show the essential design elements, including population, prior tests, new test and existing test strategies, and primary and secondary outcomes. Critical steps in the pathway between testing and patient outcomes, such as differences in test accuracy, changes in treatment, or avoidance of other tests, are displayed for each test strategy. All differences between the tests at these critical steps are identified and prioritized to determine the most important questions for evaluation. Long-term RCTs will not be necessary if it is valid to use other sources of evidence to answer these questions. Validity will depend on issues such as the spectrum of patients identified by the old and new test strategies. Key words: diagnostic techniques and procedures/standards; sensitivity and specificity; randomized controlled trials as topic; outcome assessment (health care) (Med Decis Making 2009;29:1-13)
b. The add-on test
Difference in test-treatment pathway using add-on test shown in black

TP = true positive, FN = false negative
Pathway A includes patients testing positive on the add-on test but negative on the existing test who would not have been assigned to treatment A using the existing test strategy.

c. The triage test
Difference in test-treatment pathway using triage test shown in black
Does rapid test A differentiate between diseased and non-diseased better than rapid test B?

Is survival in patient who do receive rapid test A better than in those who do receive rapid test B?
DIAGNOSTIC RCT: IS IT REALLY DIAGNOSTIC?

When performing a randomized trial to determine the impact of a diagnostic test or strategy on patient outcome, an initially diagnostic research question is transformed into therapeutic research question (with the goal of establishing causality) with corresponding consequences for the design of the study. A disadvantage of a randomized approach to directly quantify the contribution of a diagnostic test and treatment on patient outcome is that it often addresses diagnosis and treatment as a single combined strategy, a "package deal." This makes it impossible to determine afterwards whether a positive effect on patient outcome was attributed solely to the improved diagnosis by using the test under study or to the chosen (new) treatment strategies.

Some drawbacks:

- Tests must be sufficiently accurate
- Actions after each possible test results must follow a clear unambiguous protocol
- Sample sizes may be large
- Diversity and complexity of diagnostic process leads to infinite number of possible trials
- Ethical questions
  - OK to randomize to an experimental test?
  - Once a test is WHO-approved, OK to deny to half of trial participants?
1. Randomization
   a. Valid randomization
   b. Concealment of allocation

2. Blinding

3. Sufficiently long follow-up

4. Analyses