Prevalence surveys post-2015
Why, How, Where

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Outline

How?
1. Use rapid tests that are more convenient than culture but may perform less well
2. Strengthened governance/oversight
3. Good Clinical Data Management Practices
4. Report production and use of results

Where?
Summary of survey challenges

1. **Culture** under-performs in 58% of surveys

Low culture confirmation among smear-positive cases
Summary of survey challenges (con’t)

2. Substandard data management
   - Inadequate plan, 32%
   - Major errors left unfixed during investigations, 26%
   - >1 year to get a clean dataset, 26%

3. Suboptimal use of results
   - >1 year to publish the survey report, 44%
   - >1 year to get results accepted by authorities, 21%
1- Replace smear/culture with Xpert

- Molecular tests more convenient than gold standard based on culture
- Culture difficult to implement with high and consistent quality
Survey designs using rapid tests

**Design 1**
- Xray & symptom screen -> Xpert in screen+

**Design 2**
- Xray & symptom screen -> Xpert in screen+
- Confirmation of Xpert+ using a different test

**Design 3** (where X-ray is very problematic)
- Xpert in all survey participants
- Confirmation of Xpert+ using a different test
Xpert performance (against culture)

$se = 0.67$  
($0.62 - 0.71$)

$sp = 0.98$  
($0.97 - 0.99$)

Walusimbi et al. BMC Infectious Diseases 2013, 13:507
http://www.biomedcentral.com/1471-2334/13/507
Apparent vs bias-corrected prevalence

\[ n = 5000 \text{ screen + }, \ m = 150 \text{ Xpert +} \]
\[ se = 67\% \text{ (exact)}, \ sp = 98\% \text{ (exact)} \]

Apparent prevalence:

\[ \Theta = \frac{m}{n} = 3(2.5 - 3.5)\% \]

Bias-corrected:

\[ \Phi = \frac{\Theta + sp - 1}{se + sp - 1} \]
\[ \Phi = 1.5(0.86 - 2.3)\% \]

Sensitivity and specificity uncertain

\[ n = 5000 \text{ screen+}, \ m = 150 \ Xpert + \]
\[ se = 67\%, \ (\text{Standard Deviation} \ 2.25\%) \]
\[ sp = 98\% \ (\text{SD} \ 0.5\%) \]

1. Setup MCMC model in Stan or Jags
2. Generate posterior distribution of \( \Phi \)
Model description (Design 1)

$n$ samples, $m$ Xpert+

$m \sim \text{Binomial}(n, \Theta)$

$\Theta = se\Phi + (1 - sp)(1 - \Phi)$

$\Phi \sim \text{Uniform}(0, 1)$

$se \sim \text{Beta}(291.9, 143.8)$

$sp \sim \text{Beta}(767.34, 15.66)$

data

likelihood distribution

probability of Xpert+

prior on $p(\text{disease})$

sensitivity distribution

specificity distribution
Propagate uncertainty

\[ n = 5000 \text{ screen+}, \ m = 150 \text{ Xpert+} \]
\[ se = 67\%, \ (SD \ 2.25\%) \]
\[ sp = 98\% \ (SD \ 0.5\%) \]

**apparent prevalence**: \( \theta = 3 \ (2.5 - 3.5)\% \)

**bias-corrected**: \( \Phi = 1.7 \ (1.1 - 3.1)\% \)
What about sampling design effects (deff)?

1. Calculate effective sample size 
   \[ n' = \frac{n}{\text{deff}} \]

2. Adjust the number of Xpert+ cases for effective sample size \( n' \) such that 
   \[ \frac{m'}{n'} = \frac{m}{n} \]

3. Run MCMC model using adjusted values \( m' \) and \( n' \) in place of \( m \) and \( n \)
2 - Governance - Good Clinical Practice

• Established ethical and scientific quality standards for the design, conduct, recording and reporting of clinical research

• Rights, safety, and well-being of subjects are protected, consistent with principles in the Declaration of Helsinki

• Ensures the integrity of clinical research data.

GCP equation

GCP = Quality Data + Ethics
Formula for successful compliance

- Procedures and responsibilities are defined
  - Learn/understand them
  - Refer to them often
  - Respect them
- Train on GCP / Practice GCP
- Follow the protocol
- Keep accurate records
Addressing non compliance

If findings of non-compliance,
  • Institute and document corrective actions
  • Retrain as necessary
  • Establish a re-assessment
  • Carefully review data queries requested
  • Promptly execute follow-up for actions identified during monitoring
GCP - shared responsibilities

1. Sponsor
2. Principal investigator
   - represents investigators, leads report writing
3. Investigators
   - qualified, responsible for onsite implementation
4. Survey Monitor(s)
   - posted onsite, represents the sponsor
   - ensures data quality and integrity
5. Independent Data Monitoring Committee
   - reports to the sponsor
3 - Good Clinical Data Management Practices

- Validation of database (integrity, safety, confidentiality, backup, audit trail, checks, automated reports)
- **Audit-trail** for corrections (CRF correction practice, record changes)
- Copies of records (CRFs, db tables)
- Record retention (source docs, record repository)
Effective Quality Control in all surveys

- Ongoing and concurrent review (100% CRFs)
- Data correctly* entered onto CRFs
- Data can be found in source documents

*Data quality: accurate, legible, complete, contemporaneous, attributable, changes documented and explained
Quality Assurance: internal audits and monitoring

• Planned, systematic
• Retrospective sampling of records
  – Pulls the pieces together to measure accuracy
•Ensures that staff are compliant with guidelines
4 - Invest more in report production and communication

• Budget and staffing for report production
• Anticipate possible results and discuss implications with public health authorities
  – survey results are reliable
  – policy changes based on findings
  – engaging with the media, an opportunity
## Where a survey is needed

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Prev B+ ≥2.5 per 1000 (from previous survey)</td>
<td>Sample size &lt; 70,000</td>
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<tr>
<td>&gt;5 years since last survey</td>
<td>Meaningful comparison</td>
</tr>
<tr>
<td>Incidence ≥ 1.5 per 1000/yr</td>
<td>Sample size &lt; 70,000</td>
</tr>
<tr>
<td>No VR</td>
<td>No reliable measure of TB burden</td>
</tr>
<tr>
<td>U5MR &gt; 10/1000</td>
<td>Indicator of low access to quality health services</td>
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Group 1 - survey 2007-2015
Group 2 - no survey 2007-2015
Future surveys, in conclusion

1. Rapid molecular tests in replacement of culture, post-hoc adjustments for suboptimal test performance
2. Strengthen oversight and monitoring
3. Adopt GCP and GCDMP
4. Prioritize surveys in endemic countries
   – with a survey done in 2007-2015, to assess trends
   – with poor measurements of TB burden
Questions

1. Do you recommend that more national surveys should be done? If yes,

2. Do you agree with the 4 suggested updates to survey methods: Xpert instead of smear/culture; strengthened governance/oversight; GCDMP; invest more on reporting and communication?

3. Do you have any other suggestions to improve methods?

4. Do you agree with proposed criteria to identify which country should consider a survey?

5. Should there be prioritization of countries from a global/regional perspective? (e.g. %burden by country)
Suggestions

1. Do you recommend that national prevalence surveys should be conducted post-2015?

YES

If yes:
Do you agree with the suggested updates to survey methods, in particular:
Suggestions

2. Do you agree with the suggested updates to survey methods, in particular:

2.1 Use of Xpert® MTB/RIF (hereafter Xpert) instead of smear microscopy and culture, with adjustments to survey results until Xpert has equivalent performance to culture

YES but:

• Await results from Bangladesh, Kenya and Philippines
• Need research in the general population to check the sensitivity and specificity e.g. may be different in the general population due to earlier stage of disease (or do we need this if Xpert Ultra has equivalent performance to culture)
• Update to Xpert Ultra when it becomes available

Ken’s note requirements ....method 3 DRC example

2016/2017 prevalence surveys to use both culture and Xpert, with post-2017 surveys likely being able to use Xpert Ultra following completion of field evaluation studies assessing equivalence to culture.
Suggestions

2.2 Strengthening of overall governance/oversight mechanisms including more formal arrangements for survey monitoring and related actions by implementers and sponsors;

2.3 Ensuring Good Clinical Data Management Practices, including quality control at each stage of data handling to ensure that all data are reliable and have been processed correctly;

YES
• Two groups expressed concern about impeding surveys if GCP too demanding
• One group expressed surprise at the amount already invested in this scientific research without Sponsor requiring GCP e.g. onsite monitor, Independent Data Monitoring Committee

Commission work on how GCP principles should be implemented in the context of prevalence surveys, some work already underway from USAID
Suggestions

2.4 Investment of more resources in the work required once results are finalized, especially to ensure the timely production of survey reports and effective communication of findings and their implications.

YES

• Funding should be in the budget from the beginning
• Standard template to help with the writing
• Standard database, standard figures/tables
3. Do you have any suggestions for other improvements to survey methods?

No major suggestion

Points noted were: look at CAD (to be reviewed), add HIV testing (has been done in 6 countries in Africa already)
Suggestions

4. Do you agree with the proposed criteria for identifying which countries should consider a national survey post-2015, or would you propose modifications to these criteria?

Group 1 countries:
• 5 years is too short a timeframe, although longer time periods risk institutional memory
• Is 250 per 100,000 too high? (Exclude: China, Gambia, Rwanda, Sudan, Thailand)

Group 2 countries:
• Cut-off using number of cases?
• The “access to health indicator” is indirect.
Suggestions

5. Should there be any country prioritisation within groups 1 and 2, from a regional and/or global perspective?

• For both groups, risk countries in list may think they need to do a survey
• The language should not discourage countries from doing a survey
• Countries should meet 10 prerequisites for conducting a survey listed in the Lime book as well as meeting epidemiological criteria

These are defined as: 1) strong commitment and leadership from the NTP, Ministry of Health and a core group of professionals; 2) identification of a suitable institute, organization or agency to lead and manage the survey; 3) adequate laboratory capacity, especially for culture; 4) compliance with the regulations of the national regulatory authority; 5) reliable and timely procurement and logistics; 6) funding; 7) assurance of security in the field for survey teams and participants; 8) data management; 9) community participation; 10) external support and technical assistance.

Also important to note that there are four countries in group 2 that stand out in terms of their contribution to global TB burden: India (22%), South Africa (5%), DRC(3%), Mozambique (2%). The rest are all less than 1%