The analysis of tuberculosis prevalence surveys

Babis Sismanidis with acknowledgements to Sian Floyd

Harare, 30 November 2010
Background

Prevalence = TB cases / Number of eligible participants (95% CI of a proportion)
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Prevalence = TB cases / Number of eligible participants (95% CI of a proportion) - *NO*

- Only correct if participants randomly sampled individually from general population

- Cluster sampling used instead to simplify logistics and reduce cost

- Cluster sampling needs to be accounted for in analysis
Overview

(New) key issues covered:

A. Analysis at cluster level (classical approach)

B. Analysis at individual level – allowing for correlation among individuals in the same cluster

C. Accounting for missing data
A) Cluster level analysis

Method used:

1. Calculate point prevalence in each cluster

2. Calculate the overall point prevalence
   (with each cluster weighted according to its size)

3. Estimate design effect
   (observed between-cluster variation to the variation predicted if individuals independent)

4. Calculate 95% confidence interval for overall TB point prevalence estimate, corrected for the design effect
B) Individual level analysis

- Individuals within the same cluster are likely to be more similar to each other than they are to individuals in other clusters:
  - infectious disease tends to cluster in time and space
  - shared risk factors for infection, and for progression from infection to disease (genetic, environmental, socio-economic)
  - TB cases vary in their infectiousness (may be more infectious, and/or more or closer contact with non-cases, in some clusters than others)

- Between-cluster variation = within-cluster correlation (how similar individuals from the same cluster are)
Implication for statistical analysis

• Each individual provides less information than they would if their response was independent of other individuals in the same cluster.

• If we ignore correlation among individuals in the same cluster / between-cluster variation, then the main problem is:

  – estimated standard errors are too small

  – so confidence intervals are too narrow

  – and p-values are too small
  (if we make comparisons between groups)
2 recommended methods to account for cluster sampling

(1) “Robust” standard errors

(2) Random-effects (multi-level) model

= "hierarchical" logistic model in the case of the analysis of a cluster sample survey of TB prevalence
Method (1) – “robust” standard errors

• Ordinary logistic regression model

• but with “robust” standard errors that are calculated based on the observed variability in TB prevalence among clusters

So:

• gives the same estimate of TB prevalence as a logistic model assuming statistical independence of individuals

• But standard errors, CIs and p-values are corrected for clustering
Method (1) – “robust” standard errors (cont)

Advantages
- Straightforward and intuitive - uses standard logistic regression method to obtain point estimate of TB prevalence, giving equal weight to each individual in the sample

- **Always works** – i.e. can always fit this model to the data

Disadvantages
- Does not take account of clustering in the point estimate of TB prevalence

- However, this is relatively less important when the size of each cluster is similar (as in the design of TB prevalence surveys)
Sample weights, or self-weighting sample?

- No need for “sample weights”, if the sample size in each cluster is the same or similar, and the clusters are selected with probability proportional to size.

- Recommended that sample size in each cluster is the same or at least similar because this makes the analysis both more straightforward and more intuitive.
Method (2) – “random-effects” model

- In an ordinary logistic regression model, the estimation ignores the clustering.

- In a random-effects model, the estimation allows explicitly for the clustering.

- This makes the model look at individuals in the same cluster similar to each other to some extent (within-cluster correlation) and different to individuals in other clusters to some extent (between-cluster variation).
Method (2) – “random-effects” model (cont)

Disadvantages

• May not be able to fit the model satisfactorily

• The equations that need to be solved to fit this model are very complicated. Numerical approximations are required to solve them, and sometimes they do not work well

• Approximations are sometimes not reliable. If so, results of the model should not be accepted, and instead use the simpler, more pragmatic method (1) robust standard errors
Method (2) – “random-effects” model (cont)

Advantages

• Clustering is taken into account in the point estimate of TB prevalence, as well as in the standard errors, CIs, and p-values

• We also obtain an estimate of the between-cluster variation, and within-cluster correlation

• Method can now be implemented in combination with correcting for missing values (STATA, since early 2008)

So:

This is the method of choice
Individual-level analysis for correlated data; key messages

• **Method 1** – easy to understand, always works, expected to provide unbiased estimate of TB prevalence

• **Method 2** – mathematically / statistically “satisfying”, because it is based on a full probability model for the data including the within-cluster correlation – *but it does not always work*

• Recommend starting with Method 1, and then trying 2

• Report both – results are more convincing if they are similar for the different methods

• Individual-level preferred over cluster-level analysis because they allow for investigating association between TB prevalence and risk factors **AND** correcting for missing data (*more to follow*)
C) (There is always) missing data

Missing outcome data
- Individuals do not participate in the screening survey
- Individuals do not attend for chest X-ray screening
- Individuals with an X-ray suggestive of TB, and/or TB symptoms, do not provide sputum
- Individuals provide sputum but it is lost, or contaminated

Missing data on “explanatory” variables
- Should be possible to collect virtually complete data on age, sex, stratum, and cluster

Missing data could provide biased estimates of prevalence and associations with explanatory variables. How to handle missing data in the analysis depends on what we believe is the reason for the missingness
3 types of missing data

1) Missing completely at random (MCAR): no adjustment required, ignore missing data

2) Missing at random (MAR): missing value imputation required. Compare the point estimate of TB prevalence with and without imputation of missing values, to assess if an analysis ignoring the missing data introduces bias

3) Missing not at random (MNAR): sensitivity analysis required to study the extend of bias
Missing data; key messages

• Must describe the percentage of individuals with missing data, for each key variable
e.g. symptom screening questionnaire, chest X-ray, smear and culture results

• Must describe (and tabulate) how the percentage of individuals with missing data on key outcome variables varies according to characteristics known to be associated with TB (e.g. age, sex, stratum, cluster)

• Unless data are “missing completely at random”, an analysis restricted to individuals with complete data may introduce bias

• Very important to keep missing data on outcome variables (X-ray, smear and culture results), and key explanatory variables (individual characteristics known to be associated with TB) to a minimum
Missing data; key messages

• There will always be some missing data

• With a rare disease, such as TB, it can be important to use imputation even when the percentage of individuals with missing data is low

• To address potential bias impute data (based on patterns in the observed data) if missing at random

• Can calculate a confidence interval for TB prevalence that allows for BOTH the clustering in the survey design AND the uncertainty introduced by the imputation
Example; prevalence of bacteriologically confirmed TB, Philippines TB prevalence survey 2007

<table>
<thead>
<tr>
<th>% (95% CI)</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall point prevalence</td>
<td>0.66 (0.52-0.81)</td>
<td><strong>0.66 (0.53-0.80)</strong></td>
<td>0.60 (0.46-0.73), $P^0=0.004$</td>
</tr>
<tr>
<td>Point prevalence by stratum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metro Manila</td>
<td>0.67 (0.10-1.24)</td>
<td>0.64 (0.16-1.12)</td>
<td>0.58 (0.20-1.10)</td>
</tr>
<tr>
<td>Other urban</td>
<td>0.66 (0.47-0.86)</td>
<td>0.68 (0.50-0.86)</td>
<td>0.61 (0.39-0.83), $P^0=0.004$</td>
</tr>
<tr>
<td>Rural</td>
<td>0.66 (0.45-0.87)</td>
<td><strong>0.65 (0.46-0.85)</strong></td>
<td>0.59 (0.40-0.77)</td>
</tr>
</tbody>
</table>

Overall crude prevalence

**136/20,544** (0.66, 0.56-0.78)

Stratum crude prevalence

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<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metro Manila</td>
<td>15/2,253 (0.67, 0.37-1.10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other urban</td>
<td>50/7,519 (0.66, 0.49-0.88)</td>
<td></td>
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</tr>
<tr>
<td>Rural</td>
<td>71/10,772 (0.66, 0.52-0.83)</td>
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</tbody>
</table>

Model 1: CI corrected for clustering
Model 2: CI corrected for clustering, plus missing data imputed
Model 3: Point prevalence and CI corrected for clustering
A couple of parting thoughts

• The clustered sampling design must be accounted for in the analysis

• Even well designed and conducted surveys, need to investigate the potential bias of missing data

• The analysis of TB prevalence surveys is not simple, proper care should be taken

• Different approaches should be used and their results reported; consistency of results across different methods makes for convincing conclusions