Data Extraction and Quality Assessment

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Berlin, 12 November 2010
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The medical literature can be compared to a jungle. It is fast growing, full of deadwood, sprinkled with hidden treasure and infested with spiders and snakes. Morgan. Can Med Assoc J, 134, Jan 15, 1986
Disclosure

• I serve as co-chair of the Evidence Synthesis subgroup of Stop TB Partnership’s New Diagnostics Working Group

• I am a member of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group

Objectives

• Describe tips for data extraction (developing the form, extracting data, entering data)
• Discuss risk of bias
• Describe quality assessment of randomized controlled trials
• Describe quality assessment of diagnostic accuracy studies
What are data?
Data are any information about (or deriving from) a study, including
- Methods
- Participants
- Setting
- Interventions
- Outcomes
- Results
- Publications
- Investigators

Check list of data elements
- **Source**
  - Study ID
  - Citation/author email
- **Eligibility**
  - Confirm eligibility
  - Reason for exclusion
- **Methods**
  - Study design
  - Sequence generation
  - Allocation sequence concealment
  - Blinding
- **Participants**
  - Total number
  - Setting
  - Diagnostic criteria
  - Age
  - Sex
- **Results**
  - Sample size
  - Missing participants
  - Summary data for each intervention group (e.g. 2×2 table for dichotomous data)

Cochrane handbook 2008, Chapter 7
Why use a data extraction form?

- Links what is reported by investigators in papers and reports and the systematic reviewers
- Links the review question and the criteria for study selection
- Records the many decisions that occur
- Provides the data for inclusion in an analysis

Meade MO, Richardson WS. Selecting and appraising studies for a systematic review. Annals of Internal Medicine 1997; 127: 531-537

It’s your choice - paper or electronic

<table>
<thead>
<tr>
<th>Paper</th>
<th>Electronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convenience or preference</td>
<td>Convenience or preference</td>
</tr>
<tr>
<td>Extraction can be done almost anywhere</td>
<td>Combines data extraction and data entry into one step</td>
</tr>
<tr>
<td>Easy to create and implement (no need for programming or specialist software)</td>
<td>Data from reviews involving large numbers of studies are easily stored, sorted, and retrieved</td>
</tr>
<tr>
<td>Easy to compare among different reviewers</td>
<td>May program the form to ‘lead’ the reviewer through the data collection process (in Access, can pose questions that depend on answers to previous questions)</td>
</tr>
<tr>
<td>Provides record of all changes</td>
<td>Environmental friendly</td>
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</tbody>
</table>
Tips for designing data extraction form

- Include review title
- Record name / initials of person completing form
- Include unique study ID (and unique report ID)
- Use tick boxes or coded responses
- Include ‘yes’; ‘no’; not reported’ or ‘unclear’
- Always collect sample sizes when collecting outcome data, in addition to collecting initial (e.g. randomized) numbers
- Leave plenty of space for notes

Commercial serological tests for the diagnosis of tuberculosis: an updated systematic review and meta-analysis, Steingart et al unpublished
Does Bleach Processing Increase the Accuracy of Sputum Smear Microscopy for Diagnosing Pulmonary Tuberculosis?
IGRAs for LTBI screening in contact and outbreak investigations in low and middle income countries: a systematic review, Zwerling and Pai unpublished

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
</tr>
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<tbody>
<tr>
<td>1</td>
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<tr>
<td>Adel, 2010 EMJG Gambia Low income Household contacts 704 21 yrs (19-44)</td>
<td>286</td>
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<tr>
<td>Adel, 2007 EMJG Gambia Low income Household contacts (children) 206</td>
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<td>Balcells, 2011 JID Chile Upper middle income HIV positive outpatients (source track contacts) 116</td>
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<tr>
<td>Hansted, 2009 BMC Pulmonary Upper middle income High risk for TB group (contacts of active TB) 46 14 yrs</td>
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<tr>
<td>Hansing, 2010 JID Thailand South Africa Upper middle income Household Contacts, children 0-6 and adults 22 8 yrs (29 children, 53 adults)</td>
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<tr>
<td>Kamphuis, 2005 JID Istan Lower middle income High Risk of Exposure????</td>
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<td>Lenn, 2007 Scand J Infect Dis Taiwan Children (0-12 yrs) exp to smear positive cases 30 26 yrs (27-44)</td>
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<td>Makishita, 2011 JID Brazil Household contacts 30 3 yrs (6-15 yrs)</td>
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<td>Nakao, 2007 JID Nigeria Lower middle income Household contacts 415 yrs 207 5 yrs</td>
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<tr>
<td>Nicol, 2008 JID South Africa Upper middle income Household contacts (0-2 yrs) 95 23 yrs (0-5 yrs)</td>
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<tr>
<td>Okada, 2007 JID Cambodia Low income Household contacts 35 yrs 217 2 yrs (0-6)</td>
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<tr>
<td>Ozekinci, 2007 JID Turkey Upper middle income Household Contacts 36 3 yrs (18-59)</td>
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<td>Pan, 2009 JID India Lower middle income Household contacts (Minor Testing) 200 25 yrs (median 6-8)</td>
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<td>Perri, 2010 JID India Lower middle income Household contacts 200 5 yrs (median 6-8)</td>
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<tr>
<td>Patel, 2001 JID India Lower middle income Household contacts 150 5 yrs (median 6-8)</td>
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<tr>
<td>Rakhshand, 2001 JID Nigeria Lower middle income Contacts of BBs, BB + community contacts 268 14 yrs (median 6-8)</td>
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</tbody>
</table>

**Tips for performing data extraction**

- Provide detailed instructions; process is subjective!
- Best done by two independent reviewers
  - If done by one reviewer, the second reviewer can cross-check % of forms
- Pilot test the data extraction form
- Resolve disagreements between reviewers by discussion or third reviewer
Tips for data entry

• Once data extraction is complete, enter data into database manager such as Access, Excel
• Enter only consensus data
• Request missing data by emailing authors
  - Ask specific, pointed questions
  - Do not overwhelm authors with too many questions!

Quality Assessment
What is quality?

• “In the context of systematic reviews, the quality of evidence reflects the extent of confidence that an estimate of effect is correct.” Gordon Guyatt BMJ 2008

What is quality?

• “In the context of making recommendations, the quality of evidence reflects the extent to which our confidence in an estimate of the effect is adequate to support a particular recommendation.” Gordon Guyatt BMJ 2008

• With GRADE (The Grading of Recommendations Assessment, Development and Evaluation) approach, evidence is graded as high, moderate, low, very low

www.gradeworkinggroup.org
Bias and variability – definitions

• “Bias is any process at any stage of inference tending to produce results that differ systematically from the true values.” Murphy EA. *The Logic of Medicine.* Baltimore: Johns Hopkins University Press, 1976.

• Variability arises from differences among studies, such as population, setting, different definitions of target disorders.

![Image](image-url)
Hierarchy of evidence based on study quality

**STUDY DESIGN**
- Randomized Controlled Trials
- Cohort Studies and Case Control Studies
- Case Reports and Case Series, Non-systematic observations
- Expert Opinion

Holger Schünemann, 2010 TEACH, NY Acad Med, August 2010

“Everything should be made as simple as possible but not simpler.”

**Can you explain the following?**

- Generation of allocation sequence
- Concealment of allocation sequence
Relative risk reduction: > 99.9 %

1/100,000) U.S. Parachute Association reported 821 injuries and 18 deaths out of 2.2 million jumps in 2007
Simple hierarchies are (too) simplistic

**STUDY DESIGN**

- Randomized Controlled Trials
- Cohort Studies and Case Control Studies
- Case Reports and Case Series, Non-systematic observations
- Expert Opinion

**BIAS**

- Randomized Controlled Trials
- Cohort Studies and Case Control Studies
- Case Reports and Case Series, Non-systematic observations
- Expert Opinion

Holger Schünemann, 2010 TEACH, NY Acad Med, August 2010

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**The Hazards of Scoring the Quality of Clinical Trials for Meta-analysis**

Peter Jüni, MD
Ana-Maria Witschi, MD
Ralph Blüth, MD, PhD
Mathias Egger, MD, MPH

**Context**

Although it is widely recommended that clinical trials undergo some type of quality review, the number and variety of quality assessment scales that exist make it unclear how to achieve the best assessment.

**Objective**

To determine whether the type of quality assessment scale used affects the conclusions of meta-analytic studies.

**Methods**

A **systematic** meta-analysis of 17 trials comparing low-molecular weight heparin (LMWH) with standard heparin in high-quality vs low-quality trials as determined by 22 quality scales.

**Main Outcome Measures**

Pooled relative risks of deep vein thrombosis with LMWH vs standard heparin in high-quality vs low-quality trials as determined by 22 quality scales.

**Results**

Pooled relative risks from high-quality trials ranged from 0.82 (95% confidence interval [CI], 0.69-0.99) to 0.99 (95% CI, 0.67-1.42) in 22 different scales. Although the association between treatment effect and scoring was significant, the association with each quality domain was not significant. This may reflect the size of the effect of small differences in treatment effect, the need for more robust quality criteria, the need for more detailed treatment effect, the need for more specific quality domains, and the need for more detailed analysis of quality domains.

**Conclusions**

We conclude that the use of summary scores to identify trials of high impact is problematic. Relevant methodological aspects should be assessed individually and their influence on effect size explored.

JAMA 2010;303:920-926
rejection was particularly ironic in view of the fact that it had published
one of the earliest and most important systematic reviews ever done.18
It was because of the widespread and incautious use of the term
“meta-analysis” that the term “systematic reviews” was chosen as the
title for the first edition of this book.16 Although meta-analysis may
reduce statistical imprecision and may sometimes hint at biases in
reviews (for example through tests of homogeneity, or funnel plots), it
can never prevent biases. As in many forms of research, even elegant
statistical manipulations, when performed on biased rubble, are inca-
pable of generating unbiased precious stones. As Matthias Egger has put
it – the diamond used to represent a summary statistic cannot be
assumed to be the jewel in the crown!

Iain Chalmers

Quality assessment for systematic
reviews of interventions
Randomized controlled trials

- **Sequence generation**
  - Adequate: referring to a random number table; using a computer random number generator; coin tossing; shuffling cards or envelopes
  - Inadequate: sequence generated by odd/even date of birth, date of admission, clinic record number

- **Allocation concealment**
  - Adequate: numbered/coded drug containers of identical appearance; central randomization; sequentially numbered, sealed, opaque envelopes, etc
  - Inadequate: using a list of random numbers, using unsealed or non-opaque envelopes, etc

<table>
<thead>
<tr>
<th>Domain</th>
<th>Description</th>
<th>Review authors’ judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence generation</td>
<td>Describe the method used</td>
<td>Was allocation sequence adequately generated?</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Describe the method used</td>
<td>Was allocation adequately concealed?</td>
</tr>
<tr>
<td>Blinding of participants, personnel and outcome assessors</td>
<td>Describe all measures used to blind study participants and personnel about intervention</td>
<td>Was knowledge of the allocated intervention adequately prevented during the study?</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Describe the completeness of outcome data for each main outcome</td>
<td>Were incomplete outcome data adequately addressed?</td>
</tr>
<tr>
<td>Selective outcome reporting</td>
<td>State how the possibility of selective outcome reporting was examined</td>
<td>Are reports of the study free of selective outcome reporting?</td>
</tr>
<tr>
<td>Other sources of bias</td>
<td>State any important concerns about bias</td>
<td>Was the study apparently free of other problems that could put it at a high risk of bias?</td>
</tr>
</tbody>
</table>

http://www.cochrane.org/training/cochrane-handbook, Chapter 8
Higher-dose rifampin for the treatment of pulmonary tuberculosis: a systematic review

Steingart et al, accepted paper, IJTLD, 2010

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomization</th>
<th>Allocation</th>
<th>Blinding</th>
<th>Reporting</th>
<th>Comparability at baseline*</th>
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<td>Decoux 1974</td>
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<tr>
<td>Hong Kong II 1075</td>
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<td>Yes</td>
<td>Yes</td>
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<td>Keit 1976</td>
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<td>Singapore 1075</td>
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<td>Long 1979</td>
<td>Yes</td>
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<td>Rusnami 2007</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Comparability at baseline for at least age and sex; majority of studies were also comparable for extent of disease

- Selection
  - Representativeness of exposed cohort
  - Selection of non exposed cohort
  - Ascertainment of exposure
  - Demonstration that outcome of interest was not present at start of study

- Comparability
  - Comparability of cohorts on basis of design or analysis

- Outcome
  - Assessment of outcome
  - Was follow-up long enough for outcomes to occur
  - Adequacy of follow up of cohorts

Newcastle-Ottawa Scale: cohort studies
http://www.cochrane.org/training/cochrane-handbook
Predictive value of interferon-gamma release assays for incident active tuberculosis disease in low, middle and high-income countries: A systematic review, Rangaka et al, unpublished

Modified Newcastle-Ottawa Quality Assessment Scale for Cohort Studies

Selection
For the cohort or subgroup that was intended (e.g. contacts), did the study include a representative sample?
Yes (●)
No
Unclear or not reported
1. Were the exposed and non-exposed (IGRA+ vs. IGRA-) individuals drawn from the same source population?
   a) Yes (●)
   b) No
   c) Unclear or not reported
2. Determination of the index test
   a) Index test is clearly defined and test is described in detail to permit its replication (●)
   b) Index test performed in whole cohort or random sample
   c) Written self-report
   d) No description
3. There is demonstration that active TB was not present at the start of the study (baseline)
   a) Yes (●)
   b) No
   c) No description

Newcastle-Ottawa Scale: case-control studies

Selection
- Is the case definition adequate?
- Representativeness of the cases
- Selection of controls
- Definition of controls

Comparability
- Comparability of cases and controls

Exposure
- Ascertainment of exposure
- Same method ascertainment for cases & controls
- Non-response rate
Quality assessment for systematic reviews of diagnostic accuracy studies

Bias in diagnostic studies

- centripetal
- clinical review
- co-intervention
- comparator review
- diagnostic access
- diagnostic review
- diagnostic safety
- diagnostic suspicion
- differential verification
- disease progression
- extrinsic interobserver variability
- inappropriate reference standard
- Incorporation
- indeterminate results
- intraobserver variability
- intrinsic interobserver variability
- loss to follow-up
- observer variability
- partial verification
- patient cohort
- patient filtering
- popularity
- population
- referral
- sampling
- spectrum
- temporal effects
- test review
- withdrawal
- work-up bias
- yet-another-bias
What is the most important type of bias in diagnostic accuracy studies?

Evidence of bias and variation in diagnostic accuracy studies. Rutjes. CMAJ.2006

RDOR = relative diagnostic odds ratio
Quality and Reporting of Diagnostic Accuracy Studies in TB, HIV and Malaria: Evaluation Using QUADAS and STARD Standards

Patricia Scolari Fontela¹, Nitika Pant Pai¹, Ian Schiller¹, Nandini Dendukuri², Andrew Ramsay³, Madhukar Pai¹**

¹Department of Immunology, Epidemiology and Microbiology, McGill University, Montreal, Canada. ²Epidemiology Programme for Research and Training in Tropical Diseases, World Health Organization, Geneva, Switzerland. ³Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, Montreal, Canada.

Abstract

Background Poor methodological quality and reporting are known concerns with diagnostic accuracy studies. In 2000, the QUADAS tool and the STARD standards were published for evaluating the quality and improving the reporting of diagnostic studies, respectively. However, it is unclear whether these tools have been applied to diagnostic studies of infectious diseases. We performed a systematic review on the methodological and reporting quality of diagnostic studies in TB, malaria, and HIV.

Methods We identified diagnostic accuracy studies of commercial tests for TB, malaria, and HIV through a systematic search of the literature using PubMed and EMBASE (2004–2006). Original studies that reported sensitivity and specificity data were included. Two reviewers independently extracted data on study characteristics and diagnostic accuracy, and used QUADAS and STARD to evaluate the quality of methods and reporting, respectively.

Results Ninety (18%) of 538 articles met inclusion criteria. All studies had design deficiencies. Study quality indicators that were met in less than 25% of the studies included adequate description of withdrawals (9%), reference test execution (10%), absence of index test review bias (19%), and reference test review bias (22%). In terms of quality of reporting, 9 STARD indicators were reported in less than 25% of the studies: methods for calculation and estimates of reproducibility (8%), adverse effects of the index test (2%), estimates of diagnostic accuracy between subgroups (18%), distribution of severity of disease for diagnoses (18%), number of eligible patients who did not participate in the study (16%), labeling of the test readers (16%), and description of the team assessing the test and management of interobserver results (21%). The use of STARD was not explicitly mentioned in any study. Only 27% of the journals that published the studies included in this review required authors to use STARD.

Conclusions Recently published diagnostic accuracy studies on commercial tests for TB, malaria, and HIV have modest to low quality and are poorly reported. The more frequent use of tools such as QUADAS and STARD may be necessary to improve the methodological and reporting quality of future diagnostic accuracy studies in infectious diseases.

Quality of TB accuracy studies using QUADAS

<table>
<thead>
<tr>
<th>Quality item</th>
<th>45 studies n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate spectrum composition</td>
<td>26 (58)</td>
</tr>
<tr>
<td>Adequate reference standard</td>
<td>44 (98)</td>
</tr>
<tr>
<td>Absence of disease progression bias</td>
<td>42 (93)</td>
</tr>
<tr>
<td>Absence of partial verification bias</td>
<td>44 (98)</td>
</tr>
<tr>
<td>Absence of differential verification bias</td>
<td>42 (93)</td>
</tr>
<tr>
<td>Absence of incorporation bias</td>
<td>45 (100)</td>
</tr>
<tr>
<td>Absence of index test review bias</td>
<td>6 (13)</td>
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<tr>
<td>Absence of reference test review bias</td>
<td>7 (16)</td>
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<tr>
<td>Absence of clinical review bias</td>
<td>14 (31)</td>
</tr>
<tr>
<td>Report of uninterpretable results</td>
<td>9 (20)</td>
</tr>
<tr>
<td>Description of withdrawals</td>
<td>3 (7)</td>
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</tbody>
</table>

### QUADAS items scored as Yes, No, or Unclear

<table>
<thead>
<tr>
<th>Representative spectrum</th>
<th>Index test described</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection criteria described</td>
<td>Reference test described</td>
</tr>
<tr>
<td>Acceptable reference std</td>
<td>Index test result blinded</td>
</tr>
<tr>
<td>Acceptable delay between tests</td>
<td>Reference test result blinded</td>
</tr>
<tr>
<td>Partial verification avoided</td>
<td>Relevant clinical information</td>
</tr>
<tr>
<td>Differential verification avoided</td>
<td>Indeterminate results</td>
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<tr>
<td>Incorporation bias avoided</td>
<td>Study withdrawals</td>
</tr>
</tbody>
</table>

Methodological quality summary: review authors’ judgments about each methodological quality item for each included study, created in RevMan

Initiatives to improve quality and reporting

- **STARD**: reporting of diagnostic studies
- **PRISMA**: reporting of systematic reviews/meta-analyses of RCTs
- **STROBE**: reporting of observational studies
- **MOOSE**: reporting of meta-analyses of observational studies
- **AMSTAR**: assessing quality of systematic reviews

[Equator Network](www.equator-network.org/).
1. Was an 'a priori' design provided?

2. Was there duplicate study selection and data extraction?

3. Was a comprehensive literature search performed?

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?

5. Was a list of studies (included and excluded) provided?

6. Were the characteristics of the included studies provided?

7. Was the scientific quality of the included studies assessed and documented?

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?

9. Were the methods used to combine the findings of studies appropriate?

10. Was the likelihood of publication bias assessed?

11. Was the conflict of interest included?
References and tools

- The EQUATOR Network website - the resource centre for good reporting of health research studies www.equator-network.org/

With special thanks to

- Madhu Pai
- Holger Schünemann
- Penny Whiting