Systematic Reviews 101

An introduction to systematic reviews

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About me

• Digital Executive Editor at *The Lancet*, the leading independent general medical journal. Handles peer review and commissioning for *The Lancet* with a special interest in medical technology, health informatics, and surgery.

• Leading the digital transformation of *The Lancet* group, moving to a digital-first approach in all aspects of the business.

• Trained in surgery, specialising in urology and has worked in the United Kingdom, Argentina and Mexico. Studied medicine at Cambridge University and King’s College London.
What is a systematic review?

- A systematic review answers a pre-defined research question by collecting and summarizing all the evidence that fits into a pre-specified eligibility criteria
  - Can be qualitative or quantitative

- A meta-analysis uses statistical methods to summarize the results of the included studies
  - Is quantitative
Why are systematic reviews useful?

• To address unanswered questions without performing a new trial
• Efficient and ethical use of resources
• Can refine large amounts of information
What makes a good SR?

• Adds useful information
• Is registered e.g. with PROSPERO
• Has a clear search strategy
• Quality of evidence is important
• Follows reporting guidelines
• Puts the research into context
Reporting standards - PRISMA

• Guidelines defined by the EQUATOR network

• Preferred Reporting Items for Systematic Reviews and Meta-analyses

• Aims to improve the transparent reporting of systematic reviews and meta-analyses
Cochrane

- Network of international collaborators
- Gather and summarize best health evidence to make informed health decisions
- Publishes systematic reviews, and provides support to authors
- **Handbook** for systematic reviews of Interventions
Meta-analysis

- Combines the results of the included studies to give an overall statistic
- Gives an estimate of the outcome of an intervention based on all the available evidence
- Results are summarized in a Forest plot
Global epidemiology of yaws: a systematic review


Summary

Background To achieve yaws eradication, the use of the new WHO strategy of initial mass treatment with azithromycin and surveillance twice a year needs to be extended everywhere the disease occurs. However, the geographic scope of the disease is unknown. We aimed to synthesise published and unpublished work to update the reported number of people with yaws at national and subnational levels and to estimate at-risk populations.

Methods We searched PubMed and WHO databases to identify published data for prevalence of active and latent yaws from Jan 1, 1990, to Dec 31, 2014. We also searched for ongoing or recently completed unpublished studies from the WHO yaws surveillance network. We estimated yaws prevalence (and 95% CIs). We collected yaws incidence data from official national surveillance programmes at the first administrative level from Jan 1, 2010, to Dec 31, 2013, and we used total population data at the second administrative level to estimate the size of at-risk populations.

Articles

- 59 articles identified by database search
- 4 additional records identified through other sources (e.g., yaws surveillance network)
- 103 records screened
- 48 articles excluded after review of abstracts
- 20 reviews or editorials
- 12 only provided data on yaws
- 6 only provided data on other treponemal diseases
- 3 only provided data on unrelated infectious diseases
- 3 only provided data on unrelated non-infectious diseases
- 4 only provided immunology or genetic data
- 3 on non-human primates
- 28 articles excluded after review of full text
- 5 clinical studies of non-epidemiological factors
- 3 diagnostic studies without epidemiological data
- 3 therapeutic studies without epidemiological data
- 5 did not meet inclusion criteria
- 55 full-text records assessed for eligibility
- 27 studies included in qualitative analyses
- 23 published articles (describing 27 studies)
- 4 unpublished studies (describing 4 studies)
### Example 1

Characteristics and outcomes of the 24 included studies of active and latent yaws prevalence

<table>
<thead>
<tr>
<th>Africa</th>
<th>Year of study</th>
<th>Country</th>
<th>Location</th>
<th>Schoolchildren or community survey</th>
<th>Case ascertainment</th>
<th>Cases (sample size)</th>
<th>Prevalence, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active yaws assessment</td>
<td>2012</td>
<td>Cameroon</td>
<td>Lomié, Zoubalet, Messok</td>
<td>Community</td>
<td>Clinical</td>
<td>97 (1075)</td>
<td>9.02 (7.38-10.90)</td>
</tr>
<tr>
<td>Coldiron et al (2013)</td>
<td>2004</td>
<td>Côte d’Ivoire</td>
<td>Angré</td>
<td>Community</td>
<td></td>
<td></td>
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<tr>
<td>Konan et al (2007)</td>
<td>2005</td>
<td>Democratic Republic of the Congo</td>
<td>Warso</td>
<td>Community</td>
<td>RPR</td>
<td>11 (2182)</td>
<td>0.50 (0.25-0.90)</td>
</tr>
<tr>
<td>Latent yaws assessment</td>
<td>1990</td>
<td>Central African Republic</td>
<td>Lobaye</td>
<td>School children</td>
<td></td>
<td></td>
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<tr>
<td>Ayele et al (2012; Ayele G, personal communication)</td>
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</table>

**Figure 3**  
Cumulative number of yaws cases by subnational regions in the WHO Africa region
Example 2

Atraumatic versus conventional lumbar puncture needles: a systematic review and meta-analysis

Raising the standard of published systematic reviews

A case study from chemical risk research

Paul Whaley
About me

• Researcher at Lancaster University and the Evidence-Based Toxicology Collaboration at Johns Hopkins BSPH
• Background in environmental health advocacy and science communication
• Introduced to systematic reviews as gold-standard approach to evidence synthesis in early 2010
• Associate Editor for Systematic Reviews at Environment International (IF 7.088) – first specialist EH SR editor
• The “frameworks guy”: systematic approaches to evidence surveillance and synthesis; critical appraisal tools; codes of practice; research quality management
Today’s presentation

- Reproducibility issues in chemical risk assessment as a driver of interest in systematic review methods
- Uptake of SR methods
- Challenges we are seeing (poor quality SRs)
- How we are addressing these challenges at *Environment International*
- Implications for you as potential submitting authors and conductors of systematic reviews
A “reproducibility crisis” in primary research
Chemical risk assessment

• Making sense of complex and contradictory evidence about health risks posed by exposure to chemical substances
Reproducibility crisis in chemical risk assessment

Bisphenol-A
Bisphenol-A and impaired fertility

Wisniewski et al. 2015
Lassen et al. 2014
Tiwari & Vanage 2013
Peng et al. 2016
Rahman et al. 2017
Martínez-Peña et al. 2017
Gender dimorphism
Obesity
Premature birth
Breast cancer
Behavioural disorders
Premature puberty
...effects have been demonstrated for BPA [at] levels 10–10,000x lower than the current LOAEL of 50 mg/kg/day Vandenberg et al. 2014

...no health concern for any age group from dietary exposure EFSA 2015

...a potential risk to the unborn children of exposed pregnant women [relating to] a change in the structure of the mammary gland ANSES 2013

...a TDI for BPA has to be 0.7 μg/kg bw/day or lower to be sufficiently protective National Food Institute, Denmark 2015
Same evidence, different conclusions

...no health concern for any age group from dietary exposure

...a TDI for BPA has to be 0.7 μg/kg bw/day or lower to be sufficiently protective

...effects have been demonstrated for BPA [at] levels 10–10,000x lower than the current LOAEL of 50 mg/kg/day

Vandenberg et al. 2014
Solving the problem with systematic review methods

- Accelerating uptake since I started working on this in 2010
Rapid growth in publication of SRs

But we have a problem with quality

- 8989 PubMed records tagged by 2004 as “systematic review” yet actual number of stringently-defined SRs was ~2500 (Moher et al. 2007)
- Most published SRs have major flaws in conduct and reporting (Page et al. 2016)
- ~3% of manuscripts are “decent and clinically useful” (Ioannidis 2016)
- Our own pilot data shows serious omissions in reporting of 19 of 25 SRs published in the top environmental health journals through 2014-2015, before we even look at the validity of the actual methods used
- Fundamental errors mean a lot of effort is being put into projects which are not fit for purpose
My job as an editor

• What can I do at our journal to ensure each SR we publish is fit for purpose?
  – Asks an important question
  – Is truthful
  – Includes all information about methods and results, such that a reader can appraise the validity of the SR’s findings and assess its relevance to their decision-making context

• Gatekeeper and midwife strategies for ensuring we publish high-quality research

• Implications for you as researchers
EDITOR AS GATEKEEPER

Enforcement of reporting standards
Editorial triage
Making best use of peer-review
Enforcement of reporting standards

- Option of PRISMA (Moher et al. 2009) or ROSES (Haddaway et al. 2018)
- Submission of PRISMA or ROSES report as supplemental information is compulsory
- Useful quick check on basic standards
Editorial triage reports

Environment International
Systematic Review Editorial Triage Report

Title of systematic review: systematic review and meta-analysis

Name of lead author: [Name]

Name of handling editor: [Name]

05/16/2018

1. Formulation of objectives

Reviewer satisfaction score (1 = serious concerns; 5 = no concerns)

2

Specific issues raised regarding the research objectives:
[clarity] I see issues with the clarity of the research objectives

Comments:
The objectives are not completely clear. While there is an intent to compare incidence of microbial contamination between bottled vs. mineral water, the importance of this particular comparison is unclear (why not just study prevalence of contamination, period, and see which subgroups of bottled water are at highest risk of contamination), and the significance of the connection to health effects which the authors emphasise is not apparent (is there a threshold level which contaminated bottled water crosses? If so, where? etc.). What counts as "contamination" is also not defined - is this a threshold level of microbota, or mere presence?

2. Search strategy

Reviewer satisfaction score (1 = serious concerns; 5 = no concerns)

2

Specific issues raised regarding the search strategy:
[rep] There are issues with the reporting of the search strategy (e.g. it might not be reproducible), [miss] The search strategy will miss relevant evidence (e.g. issues with search strings, number of databases, etc.)

Comments:
The search strategy could be more clearly reported (e.g. in tables in supplemental information) than it is, as a narrative sequence in a paragraph in the main text. There is no obvious use of exploded search terms, while some seem either restrictive or redundant (e.g. searching "water" AND "bottled water"), which can be an issue in terms of evidence selection (the AND term filters out data). [6/08/2018]
Improved peer-review

- Target of 4 reviewers per submission
  - 2 topic experts
  - 2 methods experts
- Peer-review facilitation tool
  - Testing a Google Forms tool similar to Triage tool
  - Building CREST-SR for full-blooded implementation

Progress so far?

- 46 of 67 submissions rejected since using EVISE (~18 months)
  - 10 in process, 10 sent to production, one declined resubmission
  - 6 SRs, one SM, 2 commentaries, one correspondence
  - Only 3 SRs rejected post peer-review, 43 pre peer-review
- Hopefully that means we are at least filtering out the SRs which are not fit for purpose
Is it really progress?

• We are mainly getting low-quality systematic reviews long after it’s too late for the authors to address major issues (43 of 46 rejections are at desk; 2 years of work rejected in 2 minutes)
  – Objectives lacking research value and/or focus
  – Insensitive search strategies
  – Inappropriate inclusion criteria
  – Inadequate or non-existent risk of bias assessment methods
  – Unstructured, unsystematic interpretation of strength of evidence

• We are making sure readers aren’t receiving misleading research (at least through our own journal) but could do much more to help submitting authors develop high-quality manuscripts
EDITOR AS MIDWIFE

Rethinking the SR workflow and submission process
The solution: accept protocol submissions

- *Environment International* counts protocols as full publications
- First environmental health journal to do this
- Opens up multiple opportunities for editorial interventions
Final piece of the puzzle

- “Recipe-book” for what researchers ought to do, to maximise chance of producing a fit-for-purpose systematic review
- Developing a tool called COSTER – 70 provisions across 8 stages of conducting a systematic review
- Makes explicit the required processes for fulfilling the criteria of e.g. PRISMA or ROSES, and for critical appraisal tools such as CREST

### Step 3: Screening Evidence for Inclusion

<table>
<thead>
<tr>
<th>Proposed Wording</th>
<th>Comments</th>
<th>Notes for explanation / elucidation document</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 Screening of each piece of evidence for inclusion to be conducted by at least two people working independently, with an appropriate process (e.g. third party arbitration) for identifying and settling disputes.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.2 Document decisions in enough detail to allow presentation of the results of the screening process in a PRISMA flow chart.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Implications for submitting authors

- Take advantage of our offer to review and publish protocols
- Follow best-practice standards for conduct of systematic reviews
- Think about the conduct implied by reporting standards
- For internal QC, use the same triage and peer-review tools we do
- Don’t assume that any stage of a systematic review is optional
- It’s good to be boring (results are irrelevant if methods are good)
Thank you.

Questions?
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