Systematic Reviews 101

An introduction to systematic reviews

Naomi Lee & Paul Whaley

23 May 2018

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 prespecified 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 Metaanalyses
- Aims to improve the transparent reporting of systematic reviews and meta-analyses





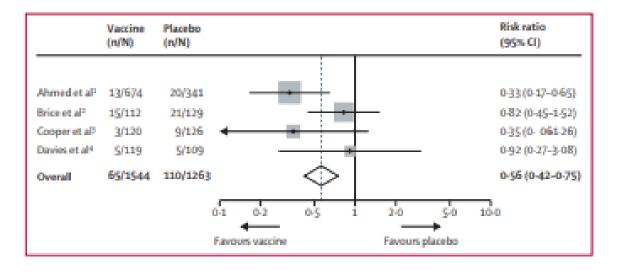
Cochrane

- 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



Articles

Global epidemiology of yaws: a systematic review



Oriol Mitjà, Michael Marks, Diby J P Konan, Gilbert Ayelo, Camila Gonzalez-Beiras, Bernard Boua, Wendy Houinei, Yiragnima Kobara, Earnest N Tabah, Agana Nsiire, Damas Obvala, Fasiah Taleo, Rita Djupuri, Zhang Zaixing, Jürg Utzinger, Lasse S Vestergaard, Quique Bassat, Kingsley Asiedu

oa

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.

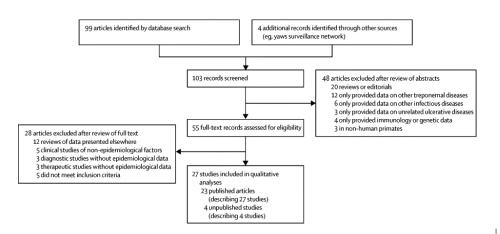
Methods We searched PubMed and WHO databases to identify published data for prevalence of active and latent yaws from Jan 1, 1990, to Dec 31, 2014. We also searched for ongoing or recently completed unpublished studies from the WHO yaws surveillance network. We estimated yaws prevalence (and 95% CIs). 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.

Lancet Glob Health 2015;

This online publication has been corrected. The corrected version first appeared at thelancet.com on June 8, 2015

See Comment page e300

Barcelona Institute for Global Health, Barcelona Centre for International Health Research, Hospital Clinic, University of Barcelona, Barcelona, Spain (O Mitjà PhD,



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

	Year of study	Country	Location	Schoolchildren or community survey	Case ascertainment	Cases (sample size)	Prevalence, % (95% CI)
Africa							
Active yaws assessment							
Tabah et al (2012; Tabah EN, personal communication)	2012	Cameroon	Lomié, Zoubalot, Messok	Community	Clinical	97 (1075)	9.02 (7.38–10.90)
Herve et al (1992) ⁹	1990	Central African Republic	Lobaye	School children	VDRL and TPHA	12 (213)	5-63 (2-94-9-63)
Boua et al (2012; Boua B, personal communication)	2012	Central African Republic	Lobaye, Sangha- Mbaeré	School children	Clinical	230 (2030)	11-33 (9-98-12-79)
Coldiron et al (2013)10	2012	Republic of Congo	Bétou, Ebyellé	Community	RDT	183 (6215)	2.94 (2.54-3.40)
Konan et al (2007) ¹³	2004	Côte d'Ivoire	Adzopé	Community	RPR	11 (2182)	0.50 (0.25-0.90)
Gerstl et al (2009) [™]	2005	Democratic Republic of the Congo	Wasolo	Community	RPR and TPHA	56 (1176)	4-76 (3-62-6-14)
Nsiire et al (2011; Nsiire A, personal communication)	2011	Ghana	Volta Region	School d		~	Niger
Akogun (1999) ¹⁶	1998	Nigeria	Garkida	Commu	Mali 📈	, ,	
Latent yaws assessment				قي.	3 B	urkina Faso	
Ayelo et al (2012; Ayelo G, personal communication)	2012	Benin	Toffo, Zé, Allada	School d	Front -	Benin	}
Herve et al (1992) ⁹	1990	Central African Republic	Lobaye	School d	uinea	099	Nigeria

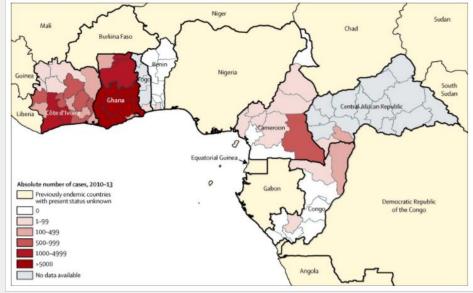


Figure 3

Cumulative number of yaws cases by subnational regions in the WHO Africa region

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



Siddharth Nath, Alex Koziarz, Jetan H Badhiwala, Waleed Alhazzani, Roman Jaeschke, Sunjay Sharma, Laura Banfield, Ashkan Shoamanesh, Sheila Singh, Farshad Nassiri, Wieslaw Oczkowski, Emilie Belley-Côté, Ray Truant, Kesava Reddy, Maureen O Meade, Forough Farrokhyar, Malgorzata M Bala, Fayez Alshamsi, Mette Krag, Itziar Etxeandia-Ikobaltzeta, Regina Kunz, Osamu Nishida, Charles Matouk, Magdy Selim, Andrew Rhodes, Gregory Hawryluk, Saleh A Almenawer

Background Atraumatic needles have been proposed to lower complication rates after lumbar puncture. However, Lancet 2018; 391: 1197-204 several surveys indicate that clinical adoption of these needles remains poor. We did a systematic review and metaanalysis to compare patient outcomes after lumbar puncture with atraumatic needles and conventional needles.

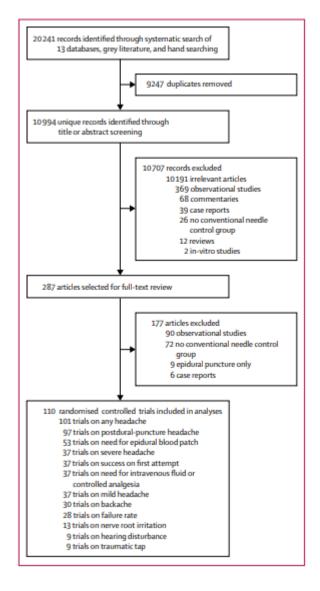
Methods In this systematic review and meta-analysis, we independently searched 13 databases with no language restrictions from inception to Aug 15, 2017, for randomised controlled trials comparing the use of atraumatic needles and conventional needles for any lumbar puncture indication. Randomised trials comparing atraumatic and conventional needles in which no dural puncture was done (epidural injections) or without a conventional needle control group were excluded. We screened studies and extracted data from published reports independently. The primary outcome of postdural-puncture headache incidence and additional safety and efficacy outcomes were assessed by random-effects and fixed-effects meta-analysis. This study is registered with the International Prospective Register of Systematic Reviews, number CRD42016047546.

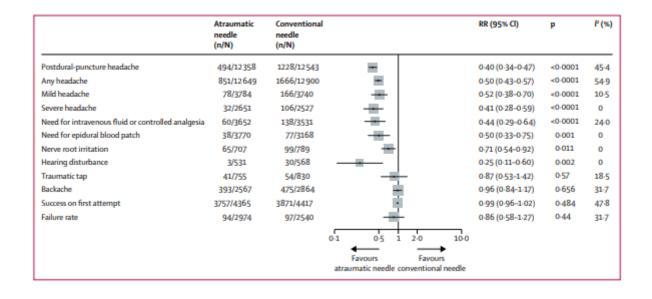
December 6, 2017 http://dx.doi.org/10.1016/ 60140-6736(17)32451-0 Division of Neurosurgery (S Nath BSc. A Koziarz BSc. S Sharma MD, S Singh MD,

Prof K Reddy MBBS, S A Almenawer MD), Division of Critical Care (W Alhazzani MD. Prof R Jaeschke MD. E Belley-Côté MD,









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

The Proposal to Lower P Value Thresholds to .005

John P. A. loannidis. MD, DSc Research Center, Meta-Research Innovation Center at of Medicine, Health Research and Policy. Biomedical Data Science, and Statistics, Stanford University, Stanford, California.

nificance testing are creating challenges in biomedical science and other disciplines. The vast majority (96%) of articles that report P values in the abstract, full text, or both include some values of .05 or less.1 However, many of the claims that these reports highlight are likely false.2 Recognizing the major importance of the statistical significance conundrum, the American Statistical Association (ASA) published³ a statement on P values in 2016. The status quo is widely believed to be problematic, but how exactly to fix the problem is far more be cogently arrived at. contentious. The contributors to the ASA statement also wrote 20 independent, accompanying commentaries folutions. Another large coalition of 72 methodologists reposal met with strong endorsement in some circles and P values are misinterpreted, overtrusted, and mis-

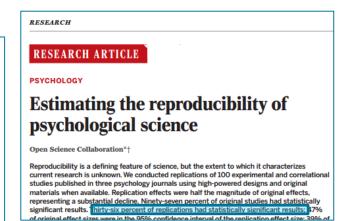
section of these 3 problems. Multiple misinterpretations of P values exist, but the most common one is that they represent the "probability that the studied hypothesis is true."3 A P value of .02 (2%) is wrongly considered to mean that the null hypothesis (eg, the drug is as effective as placebo) is 2% likely to be true and the al- of various biases affecting the results increases. ternative (eg. the drug is more effective than placebo) and transparency."3 Better-looking (smaller) P values alone do not guarantee full reporting and transpar- (perhaps crudely) in black and white, significant or nonency. In fact, smaller P values may hint to selective reporting and nontransparency. The most common misuse of the P value is to make "scientific conclusions and business or policy decisions" based on "whether a P value statistical significance, does not measure the size of an the proposed reduction in the level for declaring statisti-

P values and accompanying methods of statistical sig-fully considered how low a P value should be for a research finding to have a sufficiently high chance of being true. For example, adoption of genome-wide significance thresholds (P < 5 × 10⁻⁸) in population genomics has made discovered associations highly replicable and these associations also appear consistently when tested in new populations. The human genome is very complex, but the extent of multiplicity of significance testing involved is known, the analyses are systematic and transparent, and a requirement for $P < 5 \times 10^{-8}$ can

However for most other types of biomedical research, the multiplicity involved is unclear and the analycusing on different aspects and prioritizing different soservational exploratory research that lacks preregistered cently proposed⁴ a specific, simple move: lowering the protocols and analysis plans, it is unclear how many routine P value threshold for claiming statistical signifiantly analyses were performed and what various analytic cance from .05 to .005 for new discoveries. The propaths were explored. Hidden multiplicity, nonsystematic exploration, and selective reporting may affect even experimental research and randomized trials. Even though it is now more common to have a preexisting pro used. The language of the ASA statement enables the disthe trial posted on a public database, there are still sub stantial degrees of freedom regarding how to analyze data and outcomes and what exactly to present. In addition, many studies in contemporary clinical investiga tion focus on smaller benefits or risks; therefore, the risk

Moving the P value threshold from .05 to .005 will is 98% likely to be correct. Overtrust ensues when it is shift about one-third of the statistically significant reforgotten that "proper inference requires full reporting" sults of past biomedical literature to the category of just "suggestive." This shift is essential for those who believe significant categorizations. For the vast majority of past observational research, this recategorization would be welcome. For example, mendelian randomization studies show that only few past claims from observational passes a specific threshold" even though "a P value, or studies with P < .05 represent causal relationships.5 Thus, effect or the importance of a result," and "by itself, cal significance may dismiss mostly noise with relatively







Chemical risk assessment

 Making sense of complex and contradictory evidence about health risks posed by exposure to chemical substances







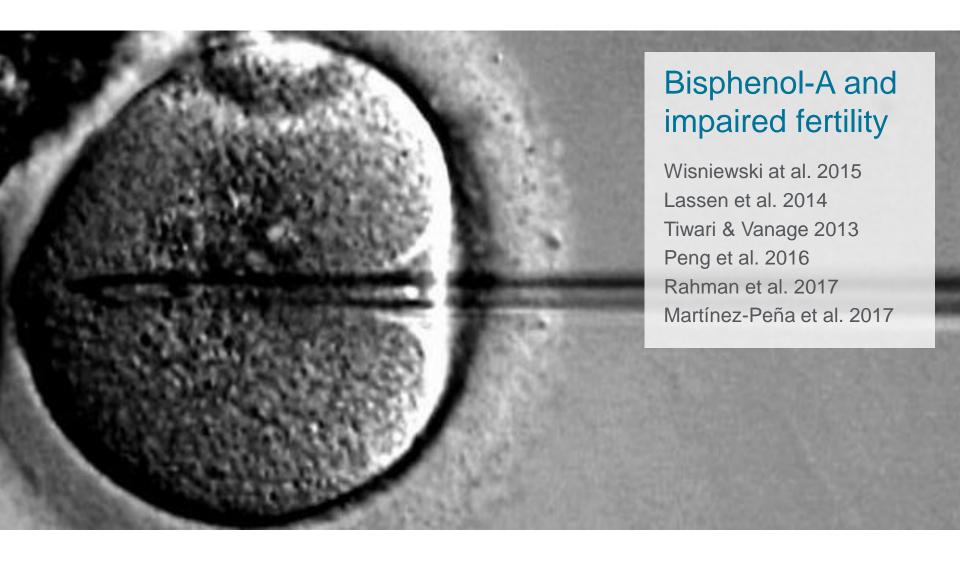
Reproducibility crisis in chemical risk assessment

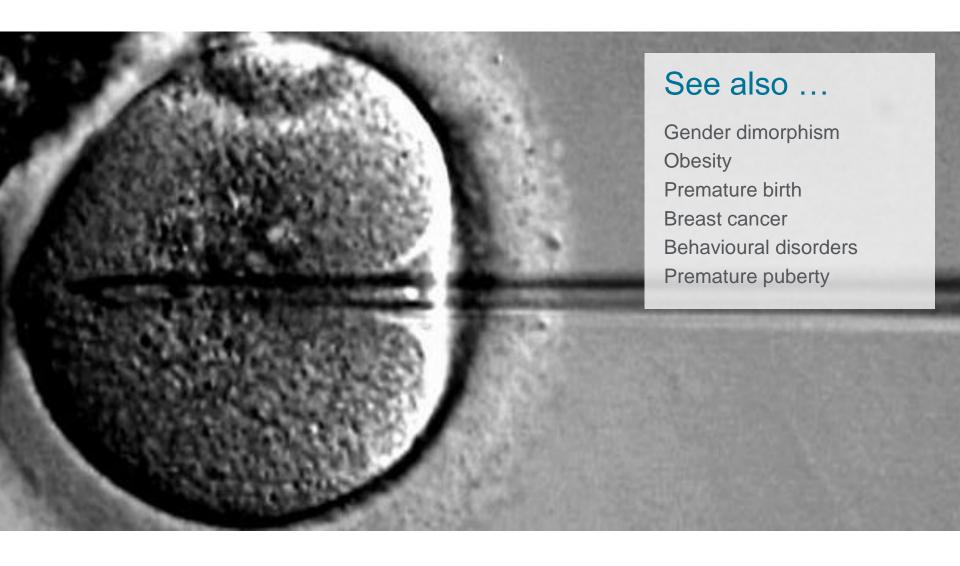
Bisphenol-A





















International Agency Research on Cancer





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

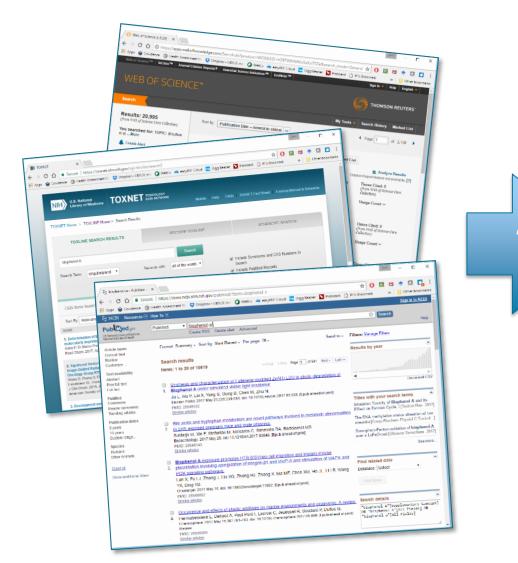
...a TDI for BPA has to be **0.7**µg/kg bw/day or lower to be

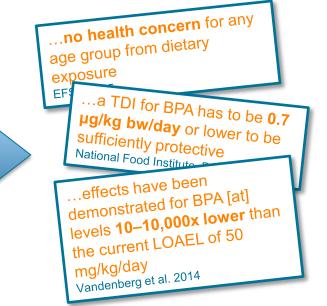
sufficiently protective

National Food Institute, Denmark 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

Same evidence, different conclusions





Solving the problem with systematic review methods

Accelerating uptake since I started working on this in 2010











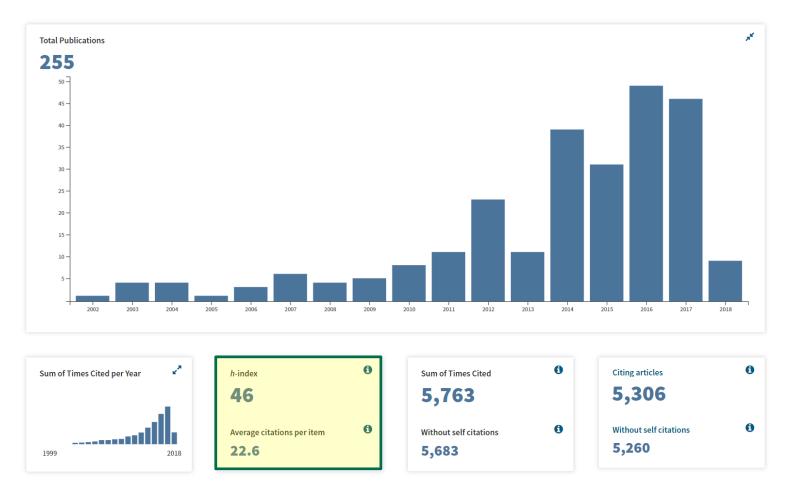




Program on Reproductive Health and the Environment



Rapid growth in publication of SRs



TITLE: ("systematic review"); Refined by: WEB OF SCIENCE CATEGORIES: (TOXICOLOGY) AND [excluding] WEB OF SCIENCE CATEGORIES: (PHARMACOLOGY PHARMACY); Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI, IC.

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" (loannidis 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

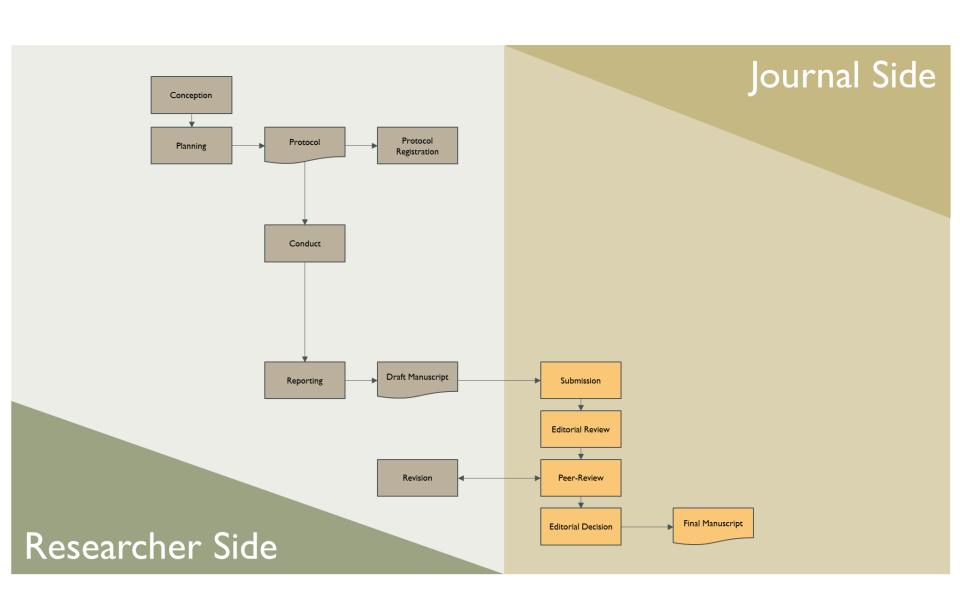
- What can I do at our journal to ensure each SR we publish is fit for purpose?
 - Asks an important question
 - Is truthful
 - Includes all information about methods and results, such that a reader can appraise the validity of the SR's findings and assess its relevance to their decision-making context
- Gatekeeper and midwife strategies for ensuring we publish high-quality research
- Implications for you as researchers

EDITOR AS GATEKEEPER

Enforcement of reporting standards

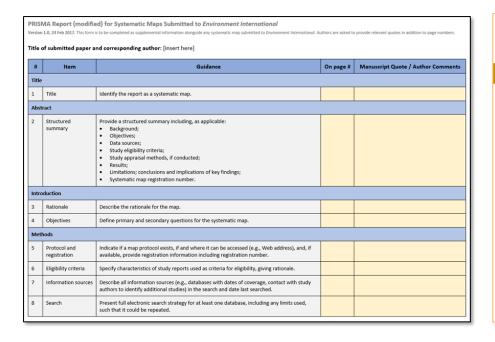
Editorial triage

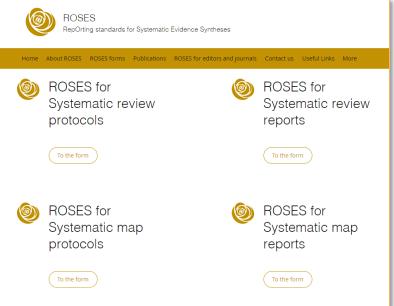
Making best use of peer-review



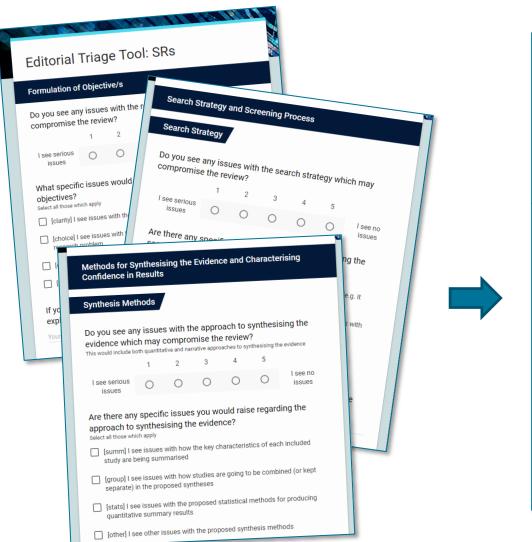
Enforcement of reporting standards

- 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 of handling editor. Paul Whaley 05/16/2018 1. Formulation of objectives Reviewer satisfaction score (1 = serious concerns; 5 = no concerns) Specific issues raised regarding the research objectives: [clarity] I see issues with the clarity of the research objectives 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 microbiota, or mere presence? 2. Search strategy Reviewer satisfaction score (1 = serious concerns; 5 = no concerns) 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,

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 are a hit strange in terms of Boolean operator (why AND2) and redundancy ("water" should can't

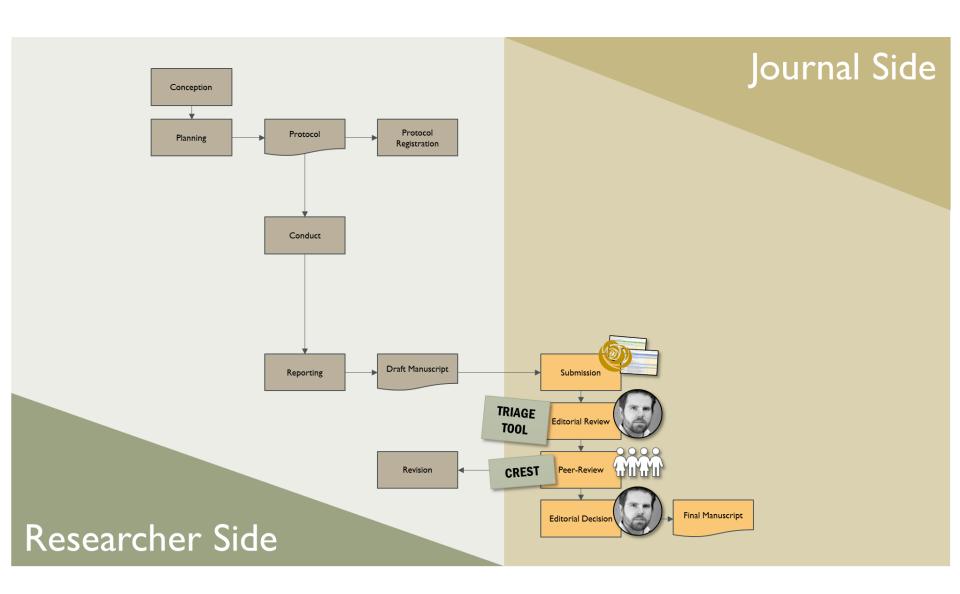
Comments

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 fullblooded implementation

Whaley et al. "A Tool for Critical Appraisal of Evidence Syntheses in Toxicology: Systematic Reviews (CREST-SR)" Under development

mportance	-	ating whethe ne conduct of		-	sed by the res	searchers is o	of sufficie
1.1.1 Ratio	onale. Has th	ne decision to	conduct ar	nd publish a r	eview been a	dequately ju	ıstified?
Level of concern:	□ None	None-Minor	☐ Minor	Minor-Mod	☐ Moderate	☐ Mod-Major	☐ Major
						 uncertainty Important t decisions? Important t stakeholder 	o policy o
Recomme	ndations fo	r manuscript	in relation 1	to justificatio	on of conduct		
Can the cor	ncerns with th	r manuscript ne review as id e manuscript?		-	on of conduct		



Progress so far?

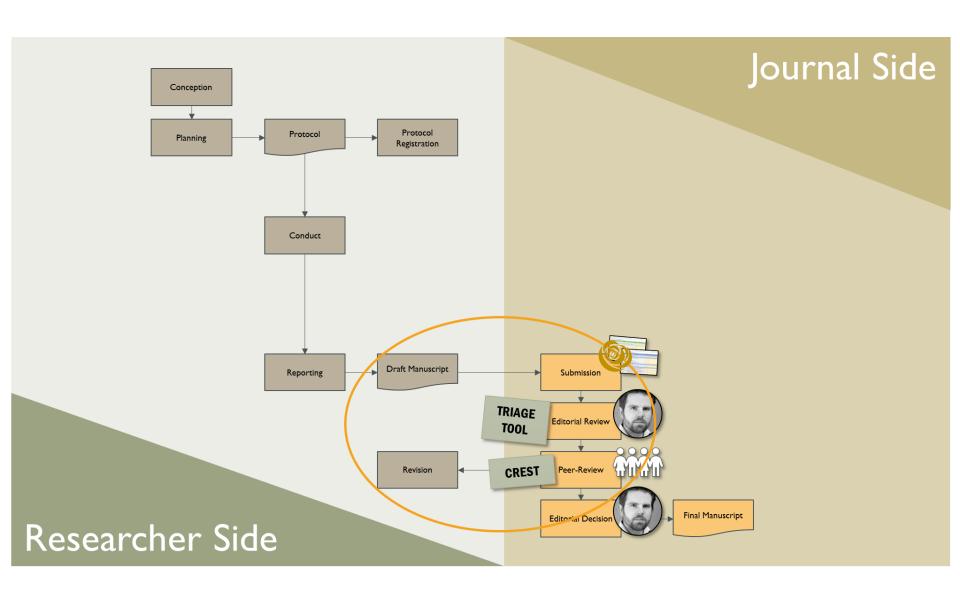
- 46 of 67 submissions rejected since using EVISE (~18 months)
 - 10 in process, 10 sent to production, one declined resubmission
 - 6 SRs, one SM, 2 commentaries, one correspondence
 - Only 3 SRs rejected post peer-review, 43 pre peer-review
- Hopefully that means we are at least filtering out the SRs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

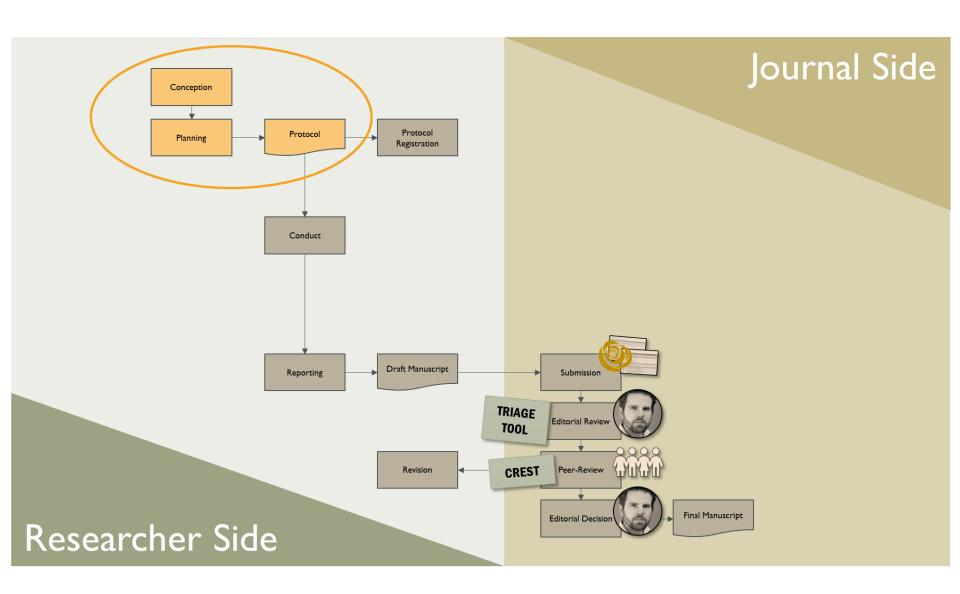
Is it really progress?

- 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

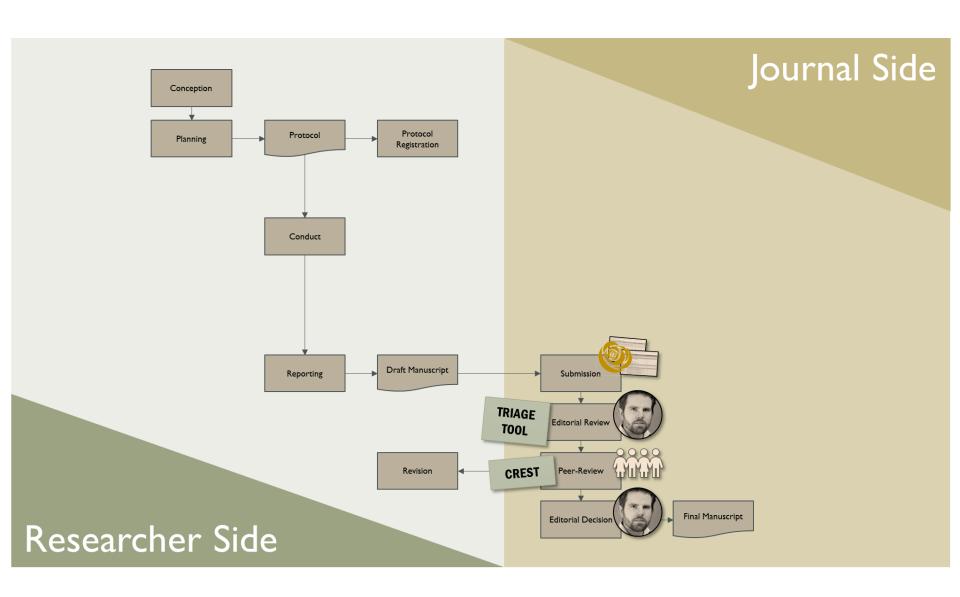
Rethinking the SR workflow and submission process

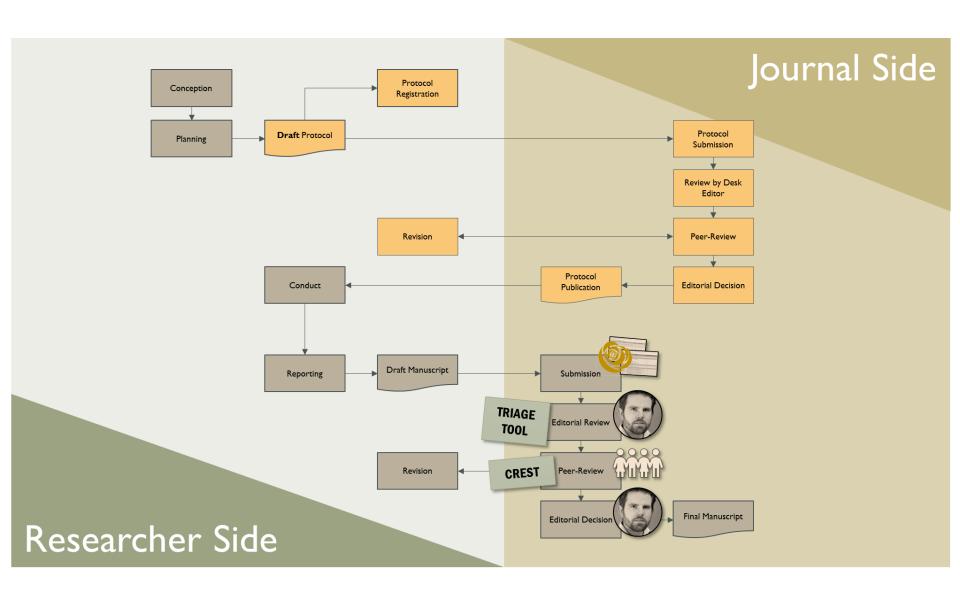


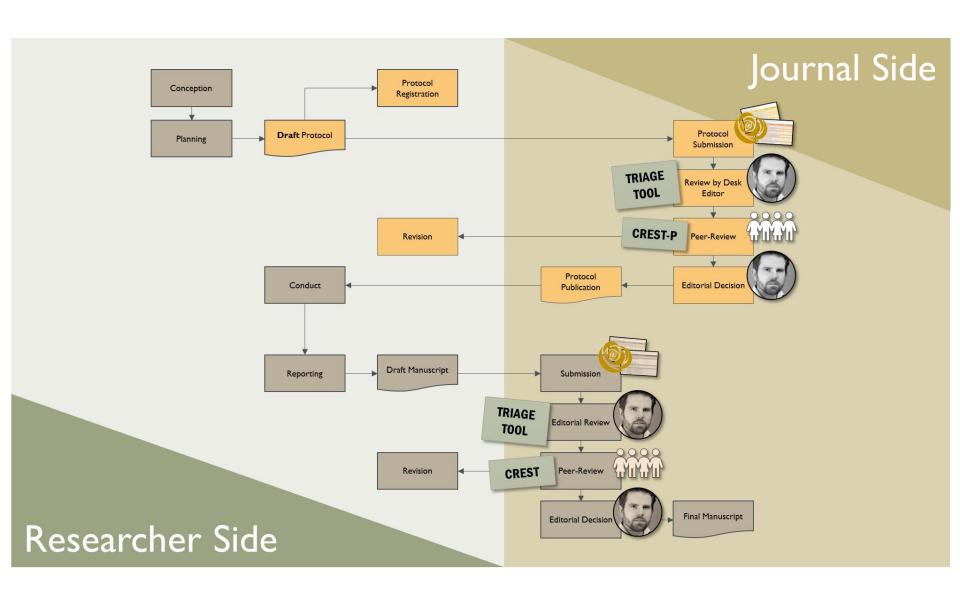


The solution: accept protocol submissions

- Environment International counts protocols as full publications
- First environmental health journal to do this
- Opens up multiple opportunities for editorial interventions



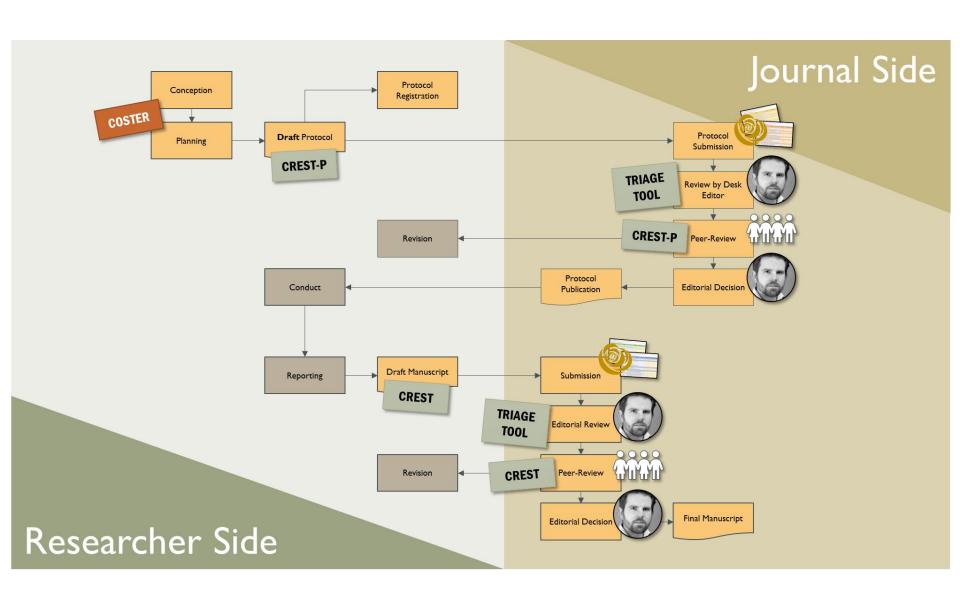




Final piece of the puzzle

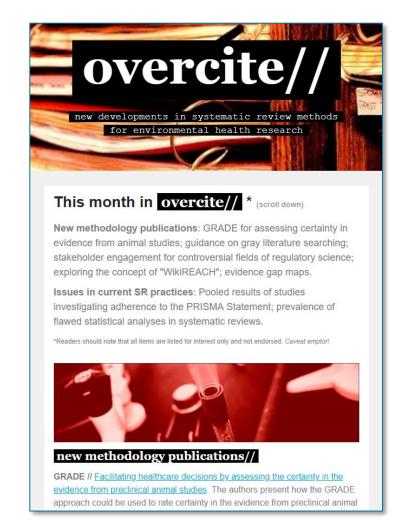
- "Recipe-book" for what researchers ought to do, to maximise chance of producing a fit-for-purpose systematic review
- Developing a tool called COSTER 70 provisions across 8 stages of conducting a systematic review
- Makes explicit the required processes for fulfilling the criteria of e.g. PRISMA or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

Step 3: Screening Evi	dence for inclusion	
Proposed Wording	Comments	Notes for explanation / elucidation document
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.		
3.2 Document decisions in enough detail to allow presentation of the results of the screening process in a PRISMA flow chart.		



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)
- Find out more? Subscribe to our newsletter: http://bit.ly/overcite



Thank you.

Questions?

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