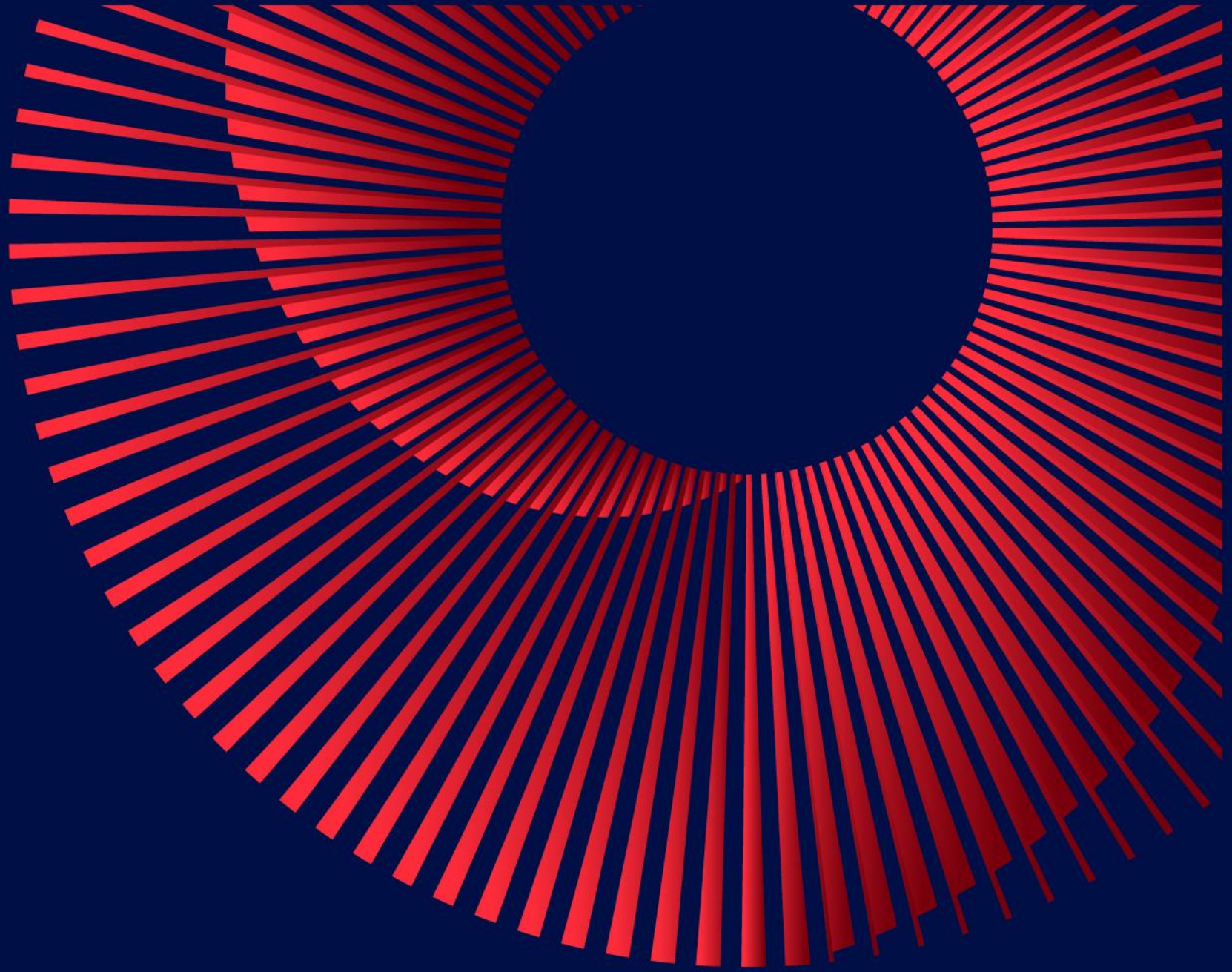
THE UNIVERSITY OF MELBOURNE

Faculty of Medicine, Dentistry and Health Sciences

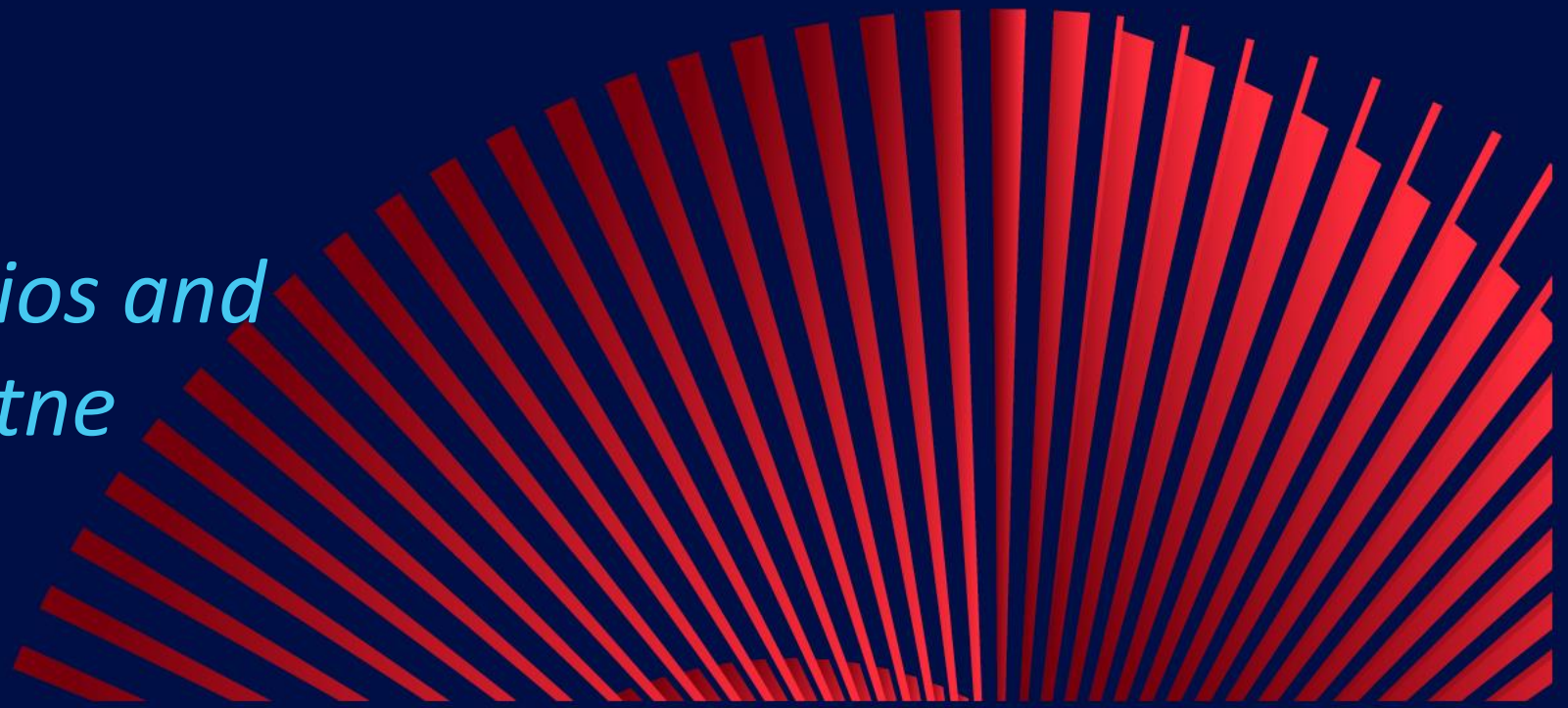
MISCH *Hub*

Methods and Implementation Support for Clinical and Health Research



Systematic reviews and meta-analysis

A/Prof Emily Karahalios and
Ms Rukshala Gunaratne



The University of Melbourne acknowledges the Traditional Owners of the unceded land on which we work, learn and live: the Wurundjeri Woi-wurrung and Bunurong peoples (Burnley, Fishermans Bend, Parkville, Southbank and Werribee campuses), the Yorta Yorta Nation (Dookie and Shepparton campuses), and the Dja Dja Wurrung people (Creswick campus).

The University also acknowledges and is grateful to the Traditional Owners, Elders and Knowledge Holders of all Indigenous nations and clans who have been instrumental in our reconciliation journey.

We recognise the unique place held by Aboriginal and Torres Strait Islander peoples as the original owners and custodians of the lands and waterways across the Australian continent, with histories of continuous connection dating back more than 60,000 years. We also acknowledge their enduring cultural practices of caring for Country.

We pay respect to Elders past, present and future, and acknowledge the importance of Indigenous knowledge in the Academy. As a community of researchers, teachers, professional staff and students we are privileged to work and learn every day with Indigenous colleagues and partners.



Acknowledgements

Professor Joanne McKenzie, Monash University

Professor Dallas English, Cancer Council Victoria and University of Melbourne

Professor Julie Simpson, University of Melbourne

Objectives

- Explain the key concepts of a systematic review
- Identify the steps involved in conducting a systematic review
- Understand the principles of meta-analysis
- Explain the differences between fixed-effect and random-effects meta-analysis
- Introduce the concept of heterogeneity

Narrative literature reviews

- Reported in the background section of most papers
- Summarise studies relating to a research question
- Criticisms
  - Not necessarily comprehensive
  - Methods not replicable
  - Rarely use quantitative synthesis
  - Included studies up to the discretion of the reviewer
  - Findings reported and their interpretation can reflect personal opinion of the reviewer

Mulrow CD: The medical review article: state of the science. Annals of internal medicine 1987, 106(3):485-488.
Thompson SG: Meta-analysis of clinical trials. In: Encyclopedia of biostatistics. 2nd ed. Edited by Armitage P, Colton T. Hoboken, N.J.: John Wiley & Sons; 2005.

Systematic reviews

- Collate all the empirical evidence to answer a specific research question.
- Use explicit, systematic methods to minimize bias
- Includes transparent, complete, and accurate account of:
  - why the review was done;
  - what was done;
  - and what was found.

Lasserson TJ, Thomas J, Higgins JPT. Chapter 1: Starting a review. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.
Page M J, McKenzie J E, Bossuyt P M, Boutron I, Hoffmann T C, Mulrow C D et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews *BMJ* 2021; 372 :n71 doi:10.1136/bmj.n71

Why undertake a systematic review?

Evidence-based research:

- Public health decisions based on epidemiologic evidence
- Single studies rarely provide definitive results
- Unbiased selection of relevant information
- Increased power and decreased bias

Ethical and scientific integrity:

- Know what research has been done
- Base new research on evidence from existing research

Steps and key features of a systematic review

Steps:

1. Define the research question - PICOTs
2. Plan the methods
3. Register with PROSPERO

Key features:

Clearly stated research question

Pre-defined eligibility criteria

Explicit, reproducible methodology

Khan KS, Kunz R, KleijnenJ, Antes G: Five steps to conducting a systematic review. Journal of the Royal Society of Medicine 2003, 96(3):118-121.

Steps and key features of a systematic review

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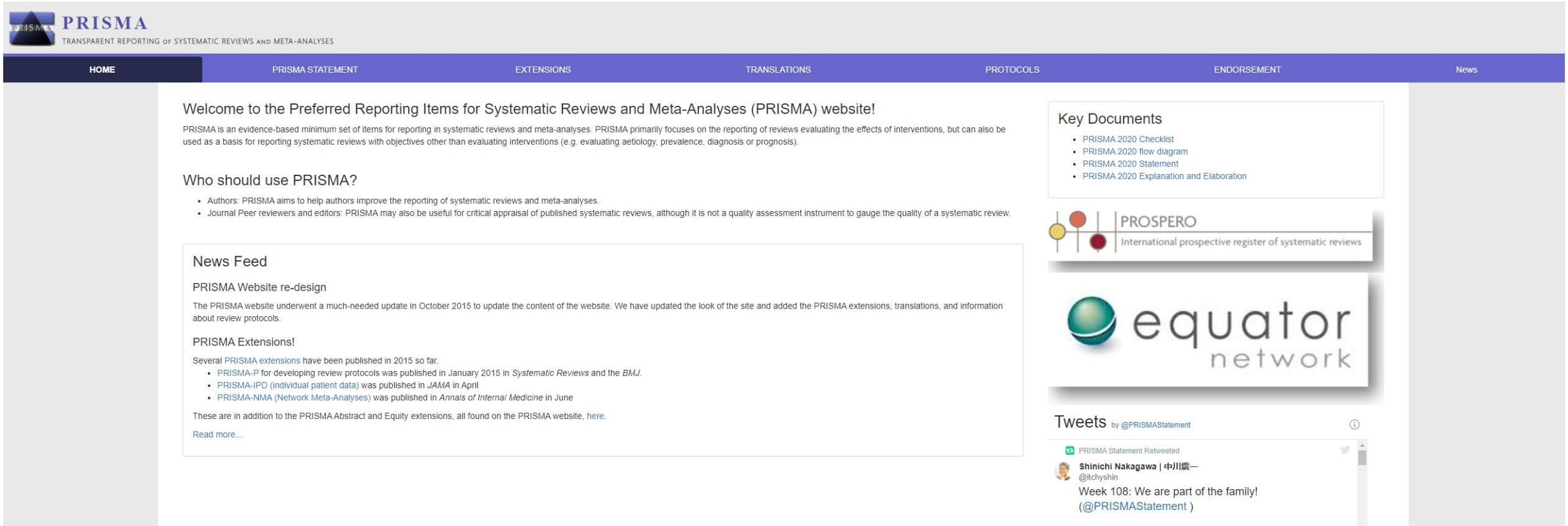
Khan KS, Kunz R, KleijnenJ, Antes G: Five steps to conducting a systematic review. Journal of the Royal Society of Medicine 2003, 96(3):118-121.

Steps and key features of a systematic review

- Methods:
  - Eligibility criteria – PICOTs
  - Information sources
  - Search strategy
  - Study selection
  - Data collection and management
  - Risk of bias – Risk of Bias 2 (RoB 2), ROBINS-I
  - Data synthesis

Sterne JA, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials BMJ 2019; 366: I4898
Sterne JA, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions BMJ 2016; 355 :i4919
Lasserson TJ, Thomas J, Higgins JPT. Chapter 1: Starting a review. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook

PRISMA



http://www.prisma-statement.org/

Steps and key features of a systematic review

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PROSPERO


NIHR | National Institute for Health Research
PROSPERO
International prospective register of systematic reviews
Home | About PROSPERO | How to register | Service information
Search | Log in | Join
Welcome to PROSPERO
International prospective register of systematic reviews
PROSPERO is fast-tracking registration of protocols related to COVID-19
PROSPERO accepts registrations for systematic reviews, rapid reviews and umbrella reviews. PROSPERO does not accept scoping reviews or literature scans. Sibling PROSPERO sites registers systematic reviews of human studies and systematic reviews of animal studies.
Before registering a new systematic review, check PROSPERO and the resources on COVID-END to see whether a similar review already exists. If so, please do not duplicate without good reason. Your efforts may be much more useful if switched to a different topic. This will avoid research waste and contribute more effectively to tackling the pandemic.
Shortcut for already registered reviews of human and animal studies relevant to Covid-19, tagged by research area

Steps and key features of a systematic review

Steps:

1. Define the research question - PICOTs
2. Plan the methods
3. Register with PROSPERO
4. Search for relevant studies
5. Apply eligibility criteria to select studies for inclusion and data extraction
6. Collect data
7. Assess studies for risk of bias
8. Synthesise the findings
9. Interpret results and draw conclusions
10. Improve and update the review

Key features:

A priori specified research question

Pre-defined eligibility criteria

Explicit, reproducible methodology

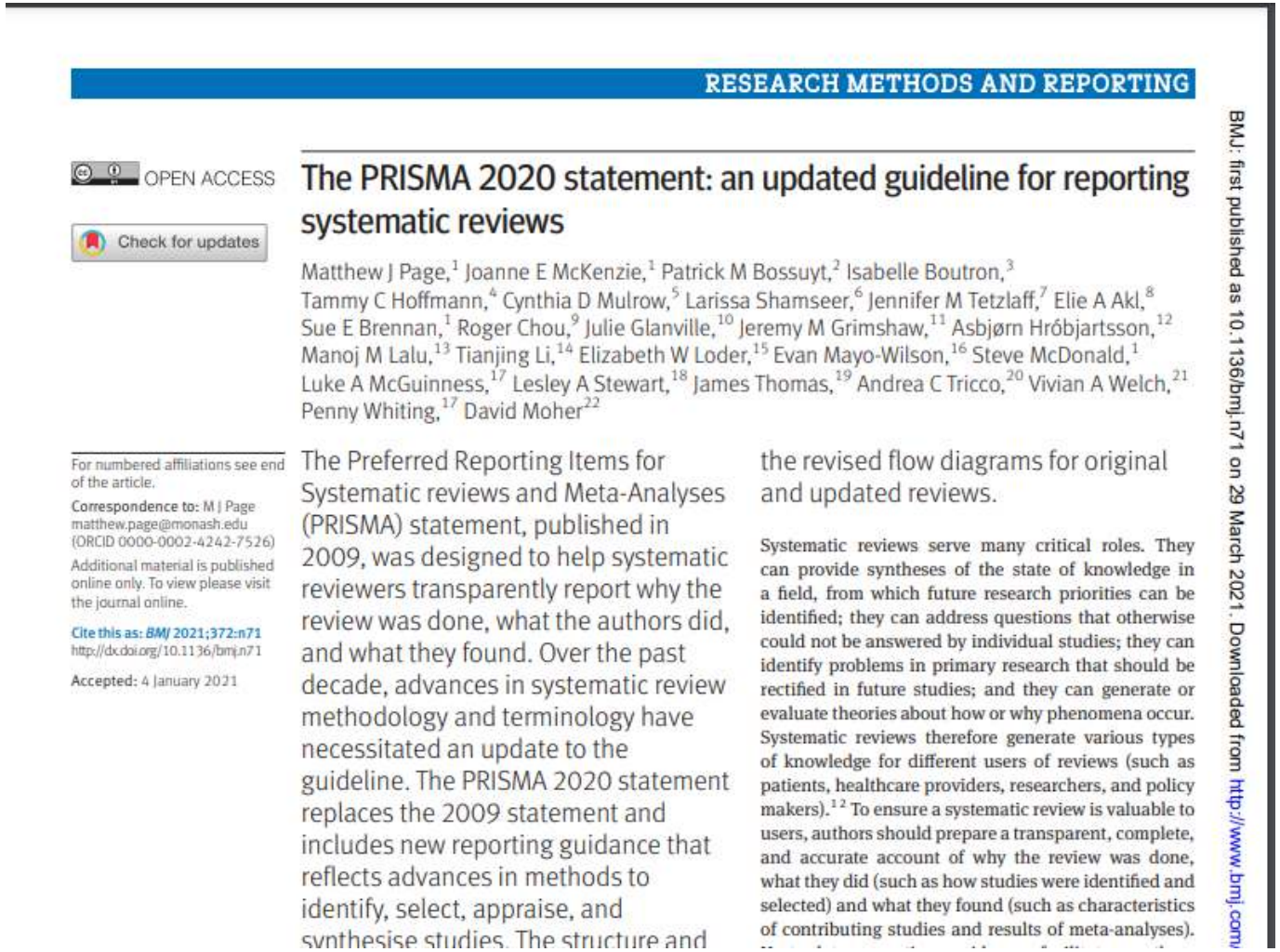
Systematic search to find all relevant research

Assessment of validity of the included studies

Systematic synthesis and presentation of findings

Khan KS, Kunz R, KleijnenJ, Antes G: Five steps to conducting a systematic review. Journal of the Royal Society of Medicine 2003, 96(3):118-121.

PRISMA-2020



OPEN ACCESS

Check for updates

The PRISMA 2020 statement: an updated guideline for reporting systematic reviews

Matthew J Page,[1] Joanne E McKenzie,[1] Patrick M Bossuyt,[2] Isabelle Boutron,[3] Tammy C Hoffmann,[4] Cynthia D Mulrow,[5] Larissa Shamseer,[6] Jennifer M Tetzlaff,[7] Elie A Akl,[8] Sue E Brennan,[1] Roger Chou,[9] Julie Glanville,[10] Jeremy M Grimshaw,[11] Asbjørn Hróbjartsson,[12] Manoj M Lalu,[13] Tianjing Li,[14] Elizabeth W Loder,[15] Evan Mayo-Wilson,[16] Steve McDonald,[1] Luke A McGuinness,[17] Lesley A Stewart,[18] James Thomas,[19] Andrea C Tricco,[20] Vivian A Welch,[21] Penny Whiting,[17] David Moher[22]

For numbered affiliations see end of the article.

Correspondence to: M J Page matthew.page@monash.edu (ORCID 0000-0002-4242-7526)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2021;372:n71 http://dx.doi.org/10.1136/bmj.n71

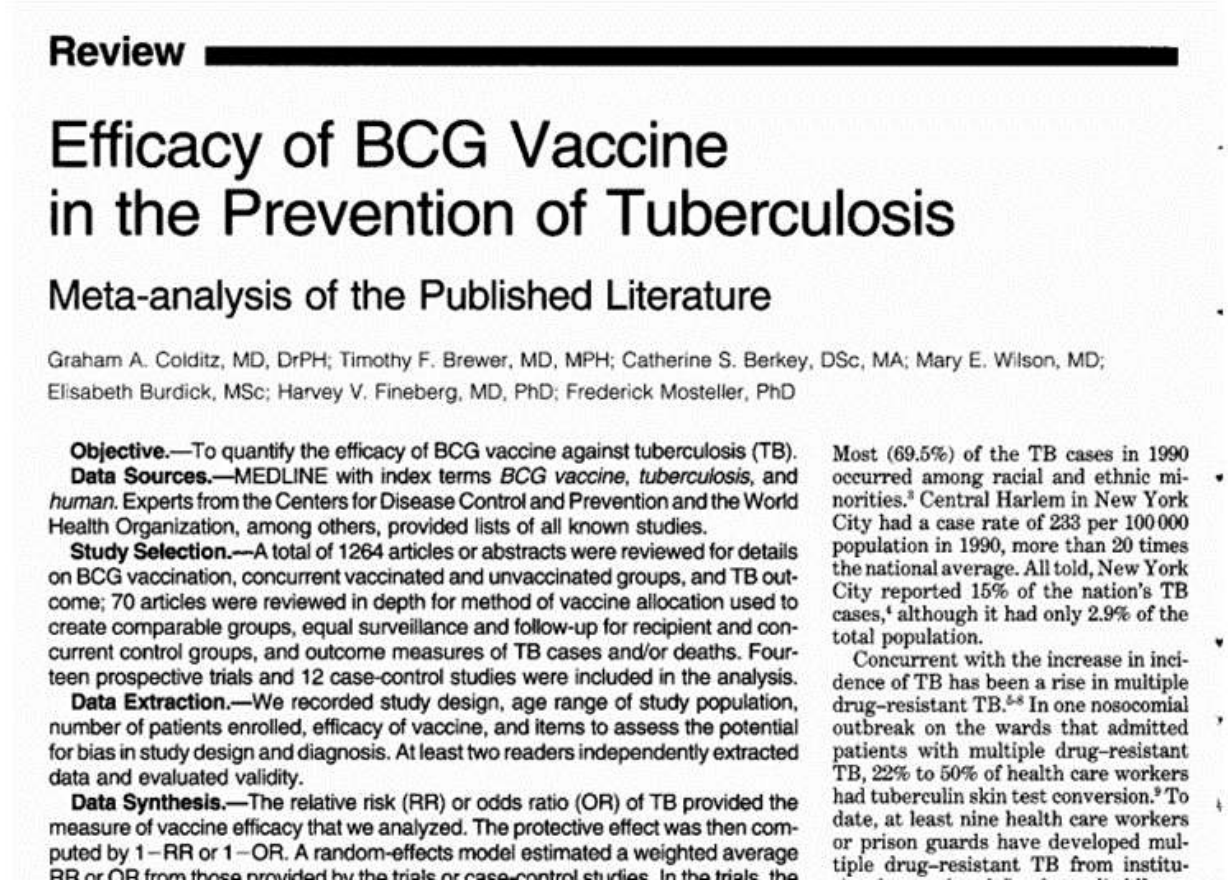
Accepted: 4 January 2021

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement, published in 2009, was designed to help systematic reviewers transparently report why the review was done, what the authors did, and what they found. Over the past decade, advances in systematic review methodology and terminology have necessitated an update to the guideline. The PRISMA 2020 statement replaces the 2009 statement and includes new reporting guidance that reflects advances in methods to identify, select, appraise, and synthesise studies. The structure and the revised flow diagrams for original and updated reviews.

Systematic reviews serve many critical roles. They can provide syntheses of the state of knowledge in a field, from which future research priorities can be identified; they can address questions that otherwise could not be answered by individual studies; they can identify problems in primary research that should be rectified in future studies; and they can generate or evaluate theories about how or why phenomena occur. Systematic reviews therefore generate various types of knowledge for different users of reviews (such as patients, healthcare providers, researchers, and policy makers).[1 2] To ensure a systematic review is valuable to users, authors should prepare a transparent, complete, and accurate account of why the review was done, what they did (such as how studies were identified and selected) and what they found (such as characteristics of contributing studies and results of meta-analyses).

BMJ: first published as 10.1136/bmj.n71 on 29 March 2021. Downloaded from http://www.bmj.com/

Example – Efficacy of BCG vaccine against tuberculosis



Review

Efficacy of BCG Vaccine in the Prevention of Tuberculosis

Meta-analysis of the Published Literature

Graham A. Colditz, MD, DrPH; Timothy F. Brewer, MD, MPH; Catherine S. Berkey, DSc, MA; Mary E. Wilson, MD; Elisabeth Burdick, MSc; Harvey V. Fineberg, MD, PhD; Frederick Mosteller, PhD

Objective.—To quantify the efficacy of BCG vaccine against tuberculosis (TB).

Data Sources.—MEDLINE with index terms *BCG vaccine*, *tuberculosis*, and *human*. Experts from the Centers for Disease Control and Prevention and the World Health Organization, among others, provided lists of all known studies.

Study Selection.—A total of 1264 articles or abstracts were reviewed for details on BCG vaccination, concurrent vaccinated and unvaccinated groups, and TB outcome; 70 articles were reviewed in depth for method of vaccine allocation used to create comparable groups, equal surveillance and follow-up for recipient and concurrent control groups, and outcome measures of TB cases and/or deaths. Fourteen prospective trials and 12 case-control studies were included in the analysis.

Data Extraction.—We recorded study design, age range of study population, number of patients enrolled, efficacy of vaccine, and items to assess the potential for bias in study design and diagnosis. At least two readers independently extracted data and evaluated validity.

Data Synthesis.—The relative risk (RR) or odds ratio (OR) of TB provided the measure of vaccine efficacy that we analyzed. The protective effect was then computed by 1−RR or 1−OR. A random-effects model estimated a weighted average RR or OR from those provided by the trials or case-control studies. In the trials, the

Most (69.5%) of the TB cases in 1990 occurred among racial and ethnic minorities.[3] Central Harlem in New York City had a case rate of 233 per 100 000 population in 1990, more than 20 times the national average. All told, New York City reported 15% of the nation's TB cases,[4] although it had only 2.9% of the total population.

Concurrent with the increase in incidence of TB has been a rise in multiple drug-resistant TB.[5-8] In one nosocomial outbreak on the wards that admitted patients with multiple drug-resistant TB, 22% to 50% of health care workers had tuberculin skin test conversion.[9] To date, at least nine health care workers or prison guards have developed multiple drug-resistant TB from institu-

Colditz, et al. 1994. *Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature*. Journal of the American Medical Association 271: 698–702.

Example – Efficacy of BCG vaccine against tuberculosis

Aim: To quantify the efficacy of the BCG vaccine against tuberculosis.

P – Humans

I – BCG vaccine

C – Control

O – Tuberculosis incidence

S – Randomised trials and case-control studies

Databases searched: MEDLINE

Search strategy: BCG vaccine, tuberculosis, and human

Other search methods:

- Scanning references of retrieved articles
- Reviewing previously compiled list and review articles of BCG studies
- Contacting experts on BCG vaccination

Eligibility criteria:

- Studies that measured the efficacy of BCG vaccination in preventing TB cases
- Studies of TB prevalence, control programs and reviews were excluded
- Included trials had to randomly establish concurrent comparison groups
- Both intervention and control groups of included studies had to have equivalent surveillance procedures and similar lengths of follow-up.

Data extraction items (selected): year of publication, year that vaccination began, study design, age range, study location, BCG dose, etc

Data extraction methods: At least 2 people independently extracted the data, with adjudication by a third reader when needed.

Risk of bias/methodological quality: Developed scoring systems to assess potential for bias.

Colditz, et al. 1994. *Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature*. Journal of the American Medical Association 271: 698–702.

Example – Efficacy of BCG vaccine against tuberculosis

Aim: To quantify the efficacy of the BCG vaccine against tuberculosis.

P – Humans

I – BCG vaccine

C – Control

O – Tuberculosis incidence

S – Randomised trials and case-control studies

Databases searched: MEDLINE Search more than 1 database

Search strategy: BCG vaccine, tuberculosis, and human Give full search strategy for all databases searched

Other search methods:

- Scanning references of retrieved articles
- Reviewing previously compiled list and review articles of BCG studies
- Contacting experts on BCG vaccination

Selection process: Provide further details for the selection process

Eligibility criteria:

- Studies that measured the efficacy of BCG vaccination in preventing TB cases
- Studies of TB prevalence, control programs and reviews were excluded
- Included trials had to randomly establish concurrent comparison groups
- Both intervention and control groups of included studies had to have equivalent surveillance procedures and similar lengths of follow-up.

Data extraction items (selected): year of publication, year that vaccination began, study design, age range, study location, BCG dose, etc List and define all variables for which data were sought and all

Data extraction methods: At least 2 people independently extracted the data, with adjudication by a third reader when needed. Any processes for obtaining or confirming data from study investigators

Risk of bias/methodological quality: Developed scoring systems to assess potential for bias. Present details of the tool(s) used, how many reviewers assessed each study and whether they worked independently.

Register with PROSPERO

Colditz, et al. 1994. *Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature*. Journal of the American Medical Association 271: 698–702.

Objectives

- Explain the key concepts of a systematic review
- Identify the steps involved in conducting a systematic review
- Understand the principles of meta-analysis
- Explain the differences between fixed-effect and random-effects meta-analysis

What is a meta-analysis?

A meta-analysis is a statistical analysis which combines the results of several independent studies considered by the analyst to be ‘combinable’.

Two stage process to pool estimates across studies

- Extract/calculate suitable summary statistics for each study
- Calculate a weighted average of these values

Huque MF: Experiences with meta-analysis in NDA submissions. Proc Biopharmaceutical Section Am Statist Assoc1988, 2:28-33.
Page MJ et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews *BMJ* 2021; 372 :n71 doi:10.1136/bmj.n71
Stroup DF et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000 Apr 19;283(15):2008-12. doi: 10.1001/jama.283.15.2008. PMID: 10789670.

Advantages of meta-analysis

- Allows interpretation of the effectiveness of an intervention across a large number of studies
- Increases the precision of the estimated intervention effect
- Allows examination of the consistency of the effects
  - Can settle controversies arising from conflicting studies
- Answer questions not posed/answered by individual studies
- Provides the opportunity to explore which factors are associated with the variability in the magnitude and direction of intervention effects

When shouldn't you use a meta-analysis?

- Different exposures/interventions/treatments are being measured
- Diverse outcomes
- Meta-analysis of studies that are at risk of bias might be seriously misleading
- Meta-analyses in the presence of serious publication and/or reporting bias are likely to produce an inappropriate summary

Caveats about meta-analysis

- Presence of biases in the included studies, and reporting biases, threatens the validity of meta-analysis results
- Decision over what is ‘combinable’ is subjective, and has been a major reason for criticism of the method
- Systematic reviews (meta-analyses) take a broader perspective than in a single study

Deeks JJ, Higgins JPT, Altman DG: Analysing data and undertaking meta-analyses. In: Cochrane Handbook for Systematic Reviews of Interventions. edn. Edited by Higgins JPT, Green SE. Chichester (UK): Wiley & Sons; 2008.

Steps and decisions in undertaking a meta-analysis

1. Calculate an effect estimate (summary statistic) for each study
2. Combine the effects using a weighted average



DO NOT START HERE!

1. Effect measure
2. Meta-analysis model
   - Fixed (common) effect
   - Random effects
     - Methods to estimate between study variance (heterogeneity)
3. Meta-analysis methods
   - Inverse-variance
   - Mantel-Haenszel
   - Peto Odds Ratio
4. Approach to calculating the confidence interval for the pooled effect

Steps in undertaking a meta-analysis

1. Calculate an effect estimate for each study

Type of outcome data	Effect measure	Information needed
Binary	Odds ratio Risk ratio Risk difference	# cases and # non cases in each treatment arm
Continuous	Mean difference Standardised mean difference	Mean difference and standard error (SE)
Counts and rates	Rate ratio	RR and 95% CI
Time-to-event (survival)	Hazard ratio	HR and 95% CI

Example – BCG vaccine & tuberculosis

Meta-analysis of 11 randomised trials

Aim: to quantify the efficacy of the BCG vaccine against tuberculosis.

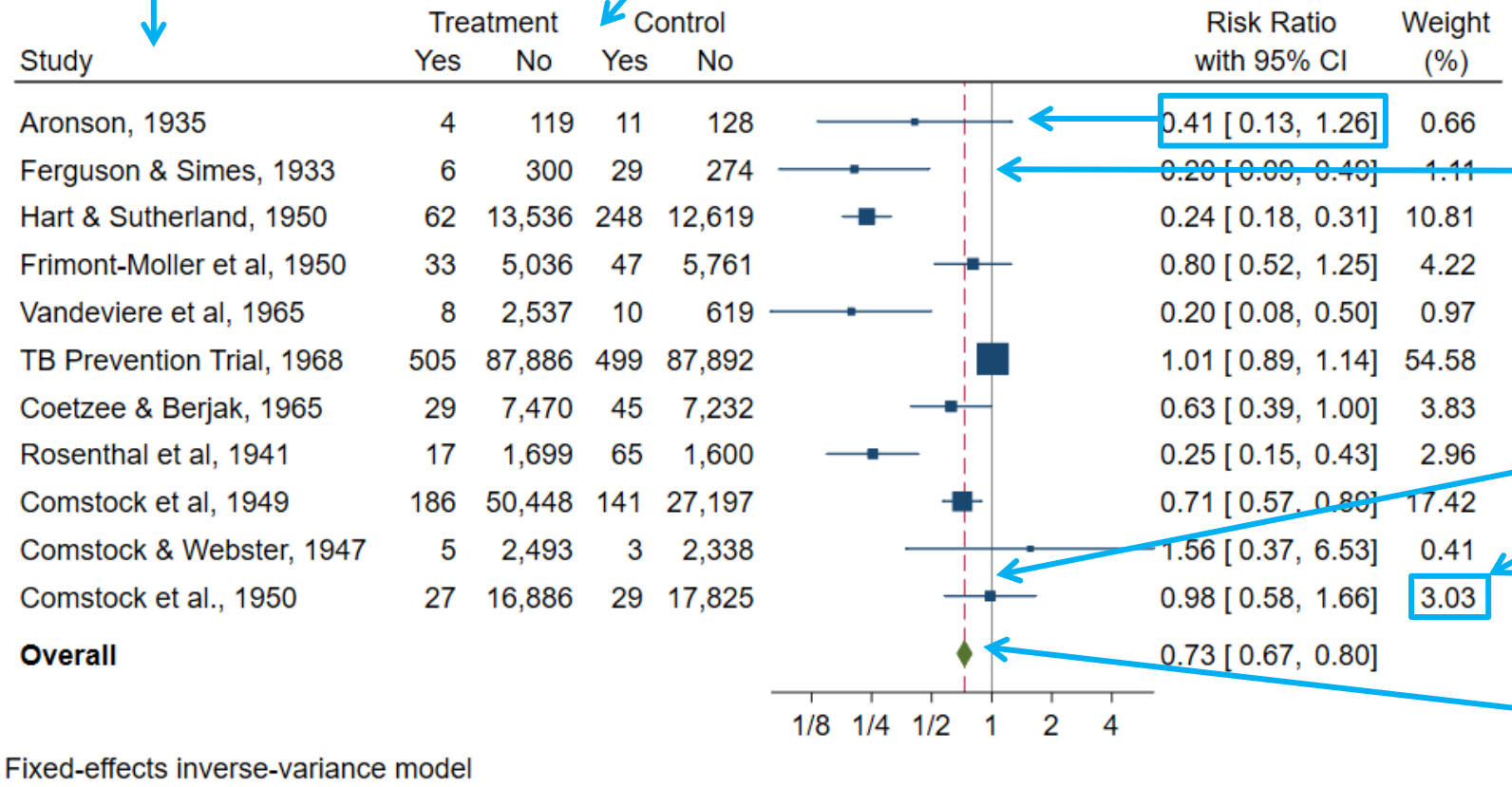
Author (Trial name)	Vaccine group		Control group			
	# cases	# non-cases	# cases	# non-cases	Risk ratio (RR)	95% Confidence interval (CI)
Aronson (Northern USA)	4	119	11	128	0.41	0.13, 1.26
Ferguson & Simes (Canada)	6	300	29	274	0.21	0.09, 0.49
Hart & Sutherland (UK)	62	13,536	248	12,619	0.24	0.18, 0.31
Frimont-Moller (Madanapalle)	33	5,036	47	5,761	0.80	0.52, 1.25
Vandeviere (Haiti)	8	2,537	10	619	0.20	0.08, 0.50
TB Prevention trial (Madras)	505	87,886	499	87,892	1.01	0.90, 1.15
Coetzee & Berjak (South Africa)	29	7,470	45	7,232	0.63	0.39, 1.00
Rosenthal (Chicago)	17	1,699	65	1,600	0.25	0.15, 0.43
Comstock (Puerto Rico)	186	50,448	141	27,197	0.71	0.57, 0.89
Comstock & Webster (Georgia School)	5	2,4933	3	2,338	1.56	0.37, 6.53
Comstock (Georgia Community)	27	16,886	29	17,825	0.98	0.58, 1.66

Colditz, et al. 1994. *Efficacy of BCG vaccine in the prevention of tuberculosis. Meta-analysis of the published literature*. Journal of the American Medical Association 271: 698–702.

Example – BCG vaccine & tuberculosis

List of included studies

Data for each study



Study	Treatment Yes	Treatment No	Control Yes	Control No	Risk Ratio with 95% CI	Weight (%)
Aronson, 1935	4	119	11	128	0.41 [0.13, 1.26]	0.66
Ferguson & Simes, 1933	6	300	29	274	0.20 [0.09, 0.49]	1.11
Hart & Sutherland, 1950	62	13,536	248	12,619	0.24 [0.18, 0.31]	10.81
Frimont-Moller et al, 1950	33	5,036	47	5,761	0.80 [0.52, 1.25]	4.22
Vandeviere et al, 1965	8	2,537	10	619	0.20 [0.08, 0.50]	0.97
TB Prevention Trial, 1968	505	87,886	499	87,892	1.01 [0.89, 1.14]	54.58
Coetzee & Berjak, 1965	29	7,470	45	7,232	0.63 [0.39, 1.00]	3.83
Rosenthal et al, 1941	17	1,699	65	1,600	0.25 [0.15, 0.43]	2.96
Comstock et al, 1949	186	50,448	141	27,197	0.71 [0.57, 0.89]	17.42
Comstock & Webster, 1947	5	2,493	3	2,338	1.56 [0.37, 6.53]	0.41
Comstock et al., 1950	27	16,886	29	17,825	0.98 [0.58, 1.66]	3.03
Overall					0.73 [0.67, 0.80]	

Fixed-effects inverse-variance model

Estimate and CI for each study

Null value (no effect)

Box area proportional to the weight for individual study

Meta-analysis estimate and CI

Decisions when undertaking meta-analysis

1. Effect measure – risk ratio
2. Meta-analysis model
   - Fixed (common) effect
   - Random effects
     - Methods to estimate between study variance (heterogeneity)
3. Meta-analysis methods
   - Inverse-variance
   - Mantel-Haenszel
   - Peto Odds Ratio
4. Approach to calculating the confidence interval for the pooled effect

Meta-analysis review

Fixed-effect

- Studies weighted according only to amount of information they contain
- Assumes there is one true intervention effect
- Assumes that the observed variation in the effect estimates of the different studies is due to sampling variation and the true relative risk is the same in all the study populations
  - If each study had a very large sample size then each study would yield an estimate very close to the common/true effect

$$\widehat{RR}_{FE} = \frac{\sum_{i=1}^{n}\left[w_i \times \widehat{RR}_i\right]}{\sum_{i=1}^{n} w_i}$$

Where,

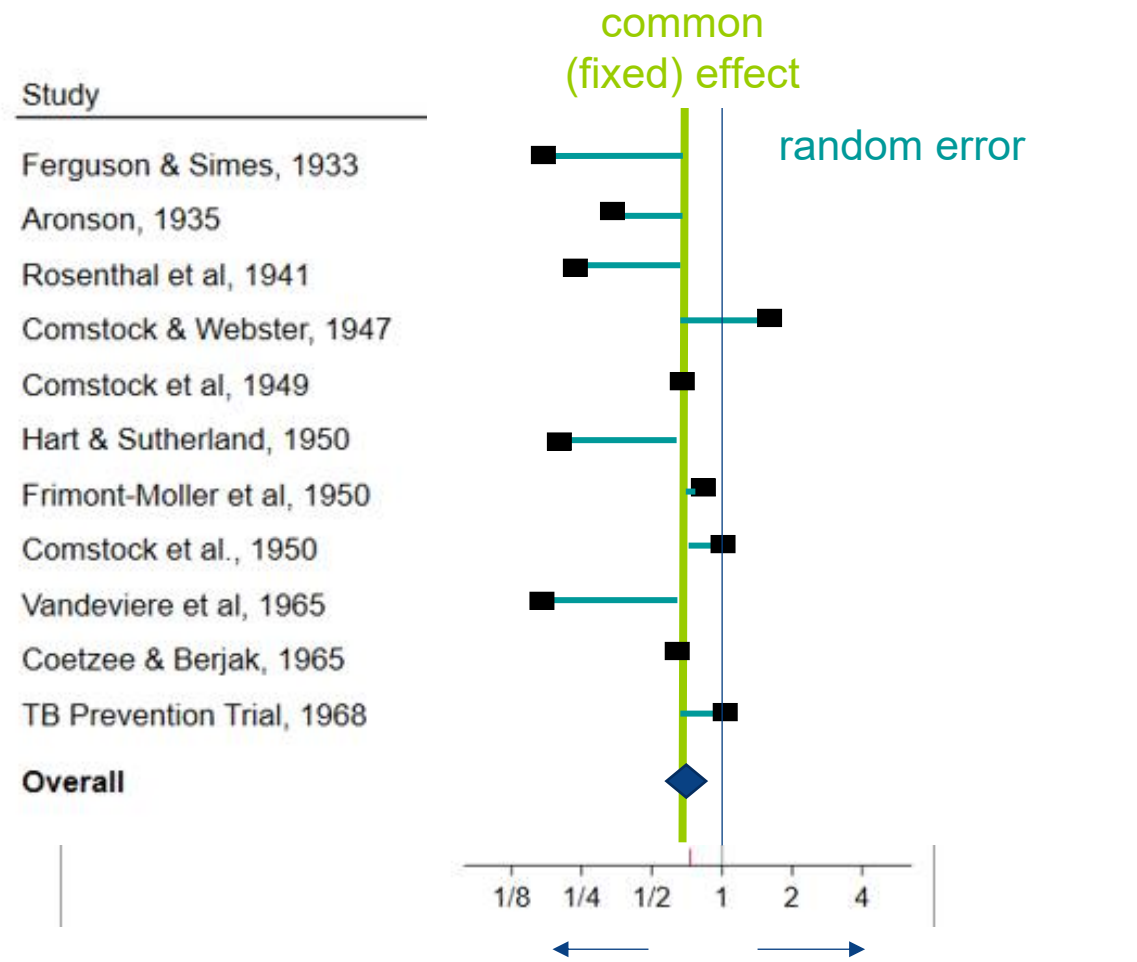
n is the number of studies;

$\widehat{RR}_i$ is the effect estimate (risk ratio) for each study;

$w_i = \frac{1}{\widehat{SE}_i}$ is the weight for each study;

$\widehat{SE}_i$ is the variance for each study

Meta-analysis – fixed-effect



Decisions when undertaking meta-analysis

1. Effect measure – risk ratio
2. Meta-analysis model
   - Fixed (common) effect
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4. Approach to calculating the confidence interval for the pooled effect

Meta-analysis review

Fixed-effect

- Studies weighted according only to amount of information they contain
- Assumes the observed variation in the effect estimates of the different studies is due to sampling variation and the true relative risk is the same in all the study populations

Random-effects

- Weight incorporates amount of heterogeneity between studies
- Assume that the true effect estimates differ across studies

$$\widehat{RR}_{RE} = \frac{\sum_{i=1}^{n}\left[w_i^* \times \widehat{RR}_i\right]}{\sum_{i=1}^{n} w_i^*}$$

Where,

n is the number of studies;

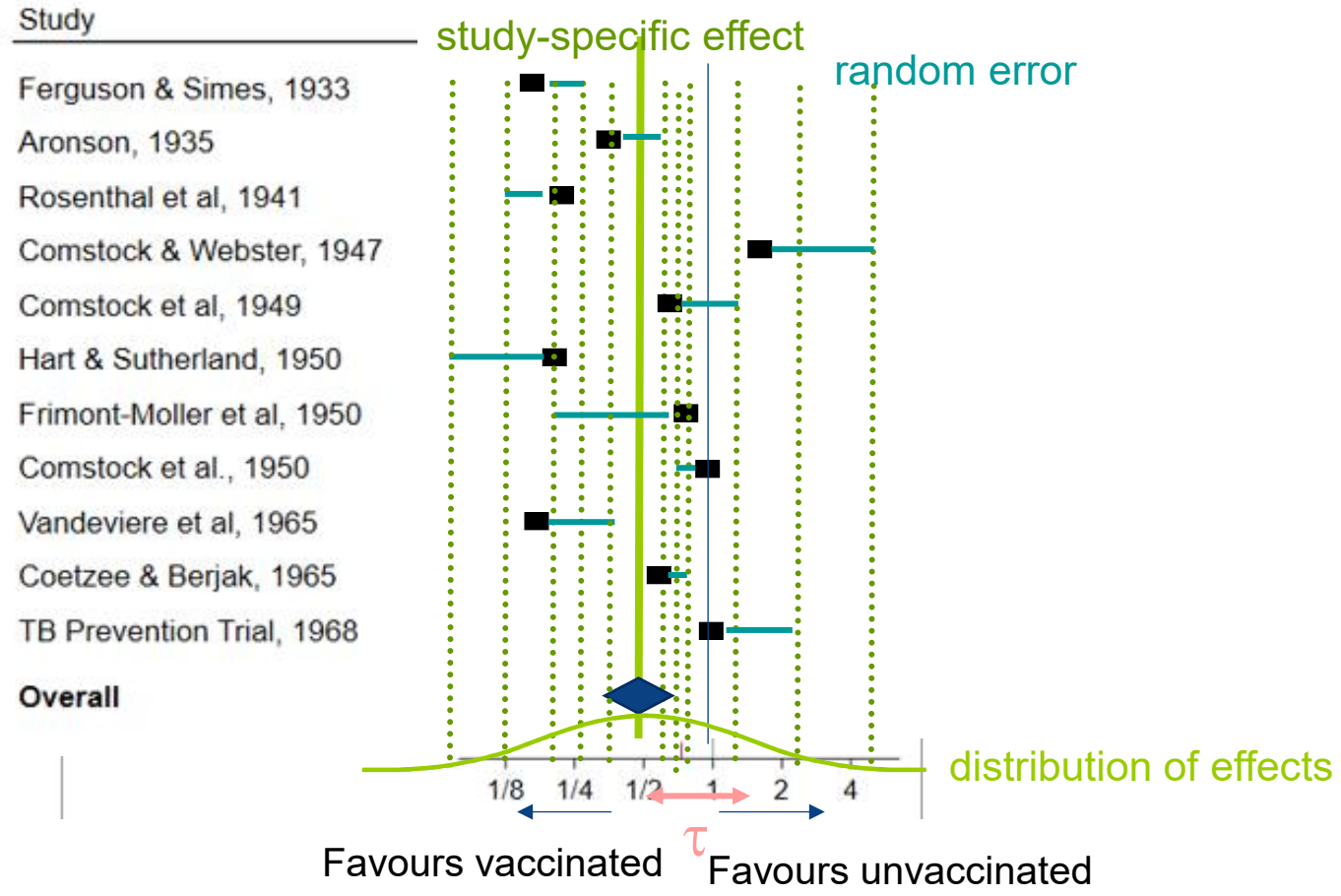
$\widehat{RR}_i$ is the Risk Ratio for each study;

$w_i^* = \frac{1}{\widehat{SE}_i + \hat{\tau}^2}$ is the weight for each study;

$\widehat{SE}_i$ is the standard error (variance) for each study;

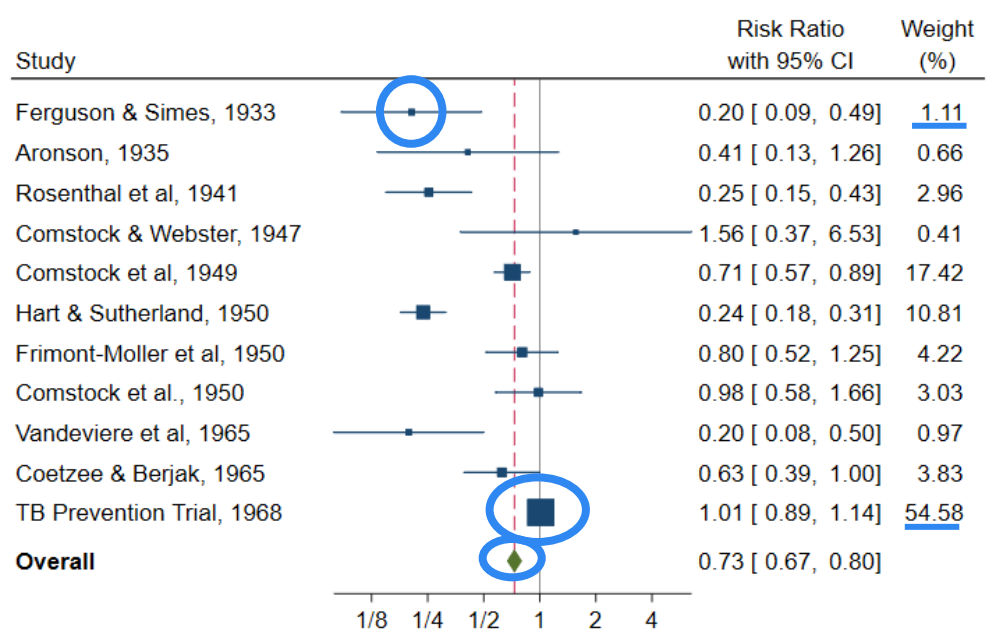
$\hat{\tau}^2$ is the between−study variance

Meta-analysis – random-effects



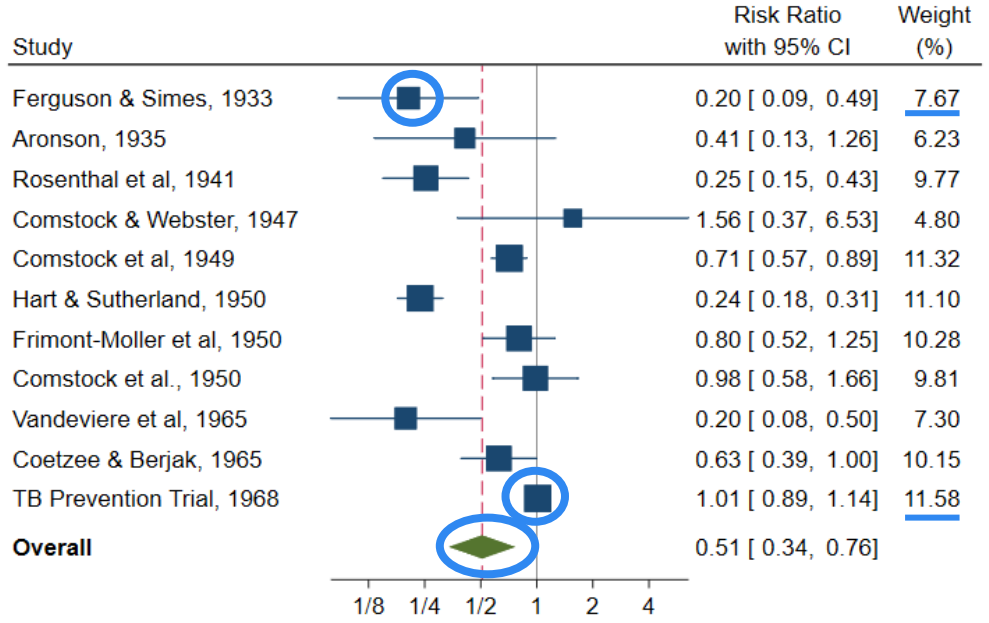
Fixed-effect and random-effects meta-analysis

Fixed-effect meta-analysis



Fixed-effects inverse-variance model
Sorted by: startyr

Random-effects meta-analysis



Random-effects REML model
Sorted by: startyr

Wider confidence intervals for the effect estimate and larger p-values

Weights from random-effects model are smaller.

Fixed-effect and random-effects meta-analysis

Fixed-effect meta-analysis

- Assumes no important heterogeneity contributing to the effect estimates of your studies.
- Will give a more precise effect estimate, with a narrower 95% CI.
- Might be unrealistic because it ignores heterogeneity that might be present.
- Pooled effect estimate might not be applicable to all populations, contexts, and variations on the intervention.

Random-effects meta-analysis

- Takes into account any heterogeneity.
- Makes assumptions about the distribution of the study effects, which might not be accurate.
- Pooled effect estimate does not resolve or explain causes of heterogeneity.

Decisions when undertaking meta-analysis

1. Effect measure – risk ratio
2. Meta-analysis model
   - Fixed (common) effect
   - Random effects
     - Methods to estimate between study variance (heterogeneity)
3. Meta-analysis methods
   - Inverse-variance
   - Mantel-Haenszel
   - Peto Odds Ratio
4. Approach to calculating the confidence interval for the pooled effect

Objectives

- Explain the key concepts of a systematic review
- Identify the steps involved in conducting a systematic review
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- Explain the differences between fixed-effect and random-effects meta-analysis
- Introduce the concept of heterogeneity

Meta-analysis review

Fixed-effect

- Studies weighted according only to amount of information they contain
- Assumes the observed variation in the effect estimates of the different studies is due to sampling variation and the true relative risk is the same in all the study populations

Random-effects

- Weight incorporates amount of heterogeneity between studies
- Assume that the true effect estimates differ across studies

$$\widehat{RR}_{RE} = \frac{\sum_{i=1}^{n}\left[w_i^* \times \widehat{RR}_i\right]}{\sum_{i=1}^{n} w_i^*}$$

Where,

n is the number of studies;

$\widehat{RR}_i$ is the Risk Ratio for each study;

$w_i^* = \frac{1}{\widehat{SE}_i + \hat{\tau}^2}$ is the weight for each study;

$\widehat{SE}_i$ is the standard error (variance) for each study;

$\hat{\tau}^2$ is the between−study variance

Heterogeneity

- Observed differences between studies included in a systematic review
- Types of heterogeneity:
  - Clinical
  - Methodological
  - Statistical

Heterogeneity - clinical

Participants

- For example, conditions under investigation, eligibility criteria for trials, geographical variation

Interventions

- For example, intensity/dose/duration, sub-type of drug, mode of administration, experience of practitioners, nature of the control (placebo/non/standard care)

Outcomes

- For example, definition of an event, follow-up duration, ways of measuring outcomes, cut-off points on scales

Heterogeneity - methodological

Study design

- For example, randomised vs non-randomised studies, crossover vs parallel group vs cluster randomised

Conduct of the study

- For example, allocation concealment, blinding etc.

Outcomes

- For example, way of measuring, definition of events, choice of cut-off points and time points for measurement

Statistical analysis

- For example, approach used to analyse the data, imputation methods for missing data

Heterogeneity - statistical

What people think it is:

- There is more observed variation than that expected by chance alone

What it actually is:

- Variation in true effects underlying the studies
  - Measured by the between study variance τ^2
- Might be due to diversity (different treatment effects) or bias (different problems)

Objectives

- Explain the key concepts of a systematic review
- Identify the steps involved in conducting a systematic review
- Understand the principles of meta-analysis
- Explain the differences between fixed-effect and random-effects meta-analysis
- Introduce the concept of heterogeneity

What we didn't cover…

- Explain the key concepts of a systematic review
- Identify the steps involved in conducting a systematic review
- Understand the principles of meta-analysis
- Explain the differences between fixed-effect and random-effects meta-analysis
- Introduce the concept of heterogeneity
- Explain how to quantify heterogeneity
- Synthesis Without Meta-analysis (SWiM guidelines)
- Network meta-analysis
- How to minimize, assess and deal with reporting biases
- Quantifying the certainty of evidence
- Other types of revies: scoping reviews, rapid reviews, umbrella reviews…

Key references

- Cochrane Handbook for Systematic Reviews of Interventions:
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Thank you

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