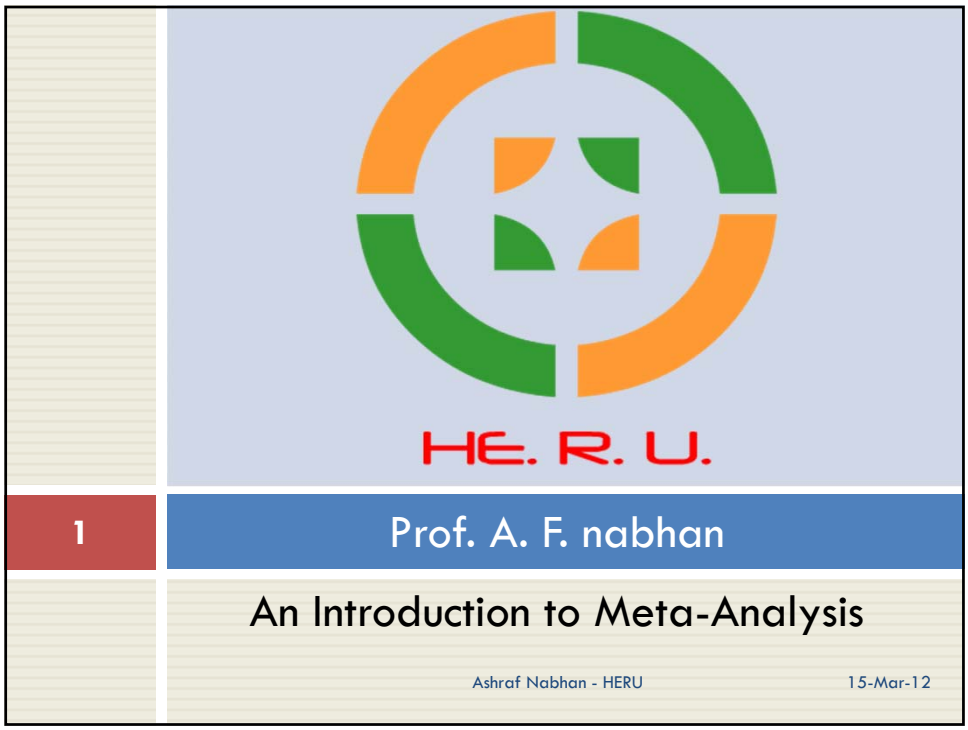

Workshop Learning Objectives

2

- To Define the review question
- To develop criteria for including studies
- To Assess risk of bias in included studies
- To Analyze data and undertake meta-analyses
- To Interpret results and draw conclusions

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3

Systematic Review

HERU SRG Workshop Session 1

Rationale

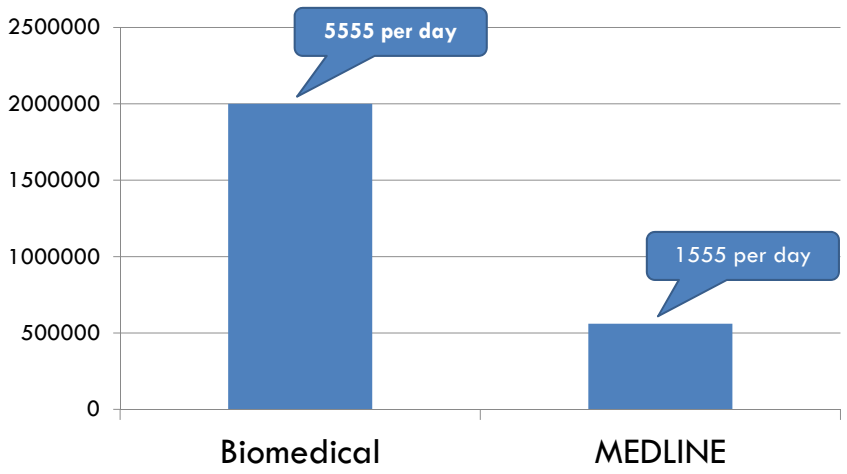
4

- People making decisions about health care interventions, need reliable info
- Too much information, too little time

$$\text{Usefulness} = \frac{\text{Relevance x Validity}}{\text{Work}}$$

Review the World Literature

5



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6

Oppppsssssss

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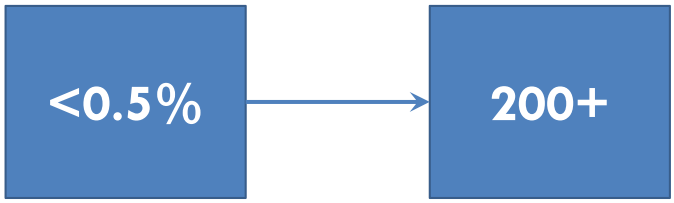
How much is valid & relevant?

7

- What is the **Number Needed to Read** ☺ to select Both valid and relevant info ?



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RESQUE

8

RE	S	QU	E
Review question defined	Search for and Select studies	Quality assessment (RoB)	Evidence Assimilation

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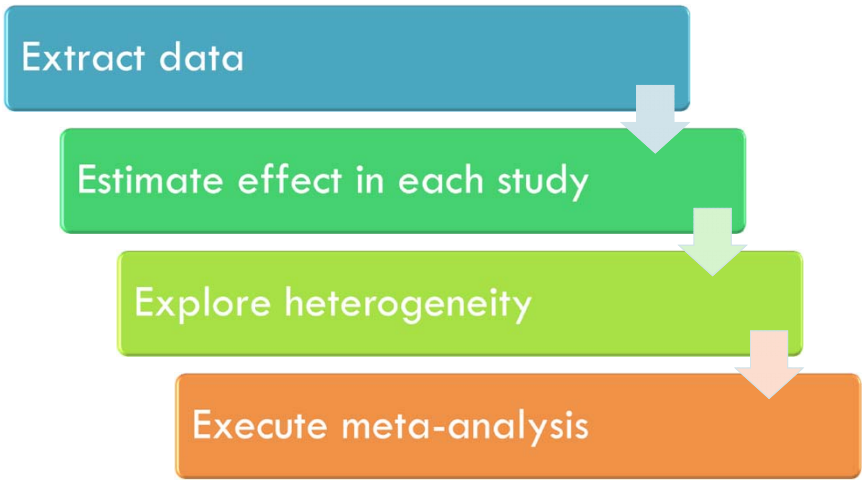
Evidence Assimilation

9



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10

SR of intervention trials

Relevance

Validity

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The Relevant question in SR

11

- Broad versus Narrow questions
  - Debate ….
- Ask the ***relevant*** question - PICO
  - Population/Patients
  - Intervention
  - Comparison
  - Outcome
    - Primary: Main ***outcomes*** measures for the SoF table
    - Secondary

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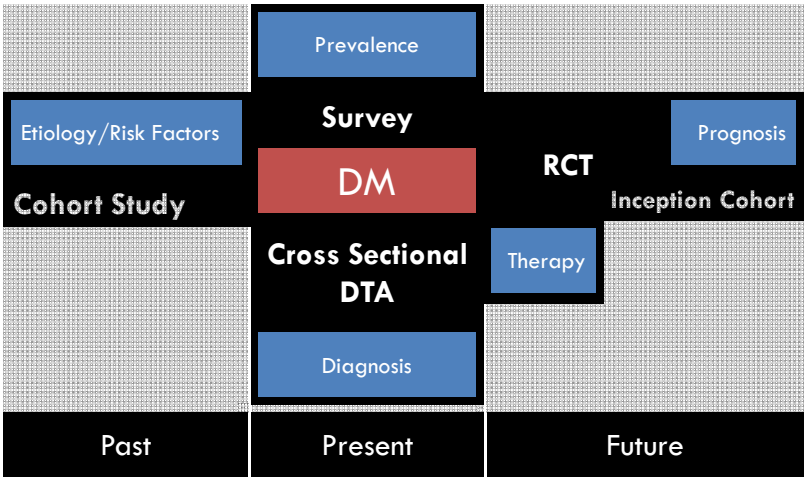
Find the *valid* design

12



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Eligible studies

13

- RCTs
- Quasi-RCTs

Important to Remember

14

- **Our decisions about which studies to include is based on the Design of Studies, and not the results.**

What if?

15

Comprehensive search →

No studies

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The other side is always green

16

identified a gap in knowledge

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17

Risk of Bias

Session 2: RoB tool

RoB in SR of intervention trials

18

Trash In, Trash Out

- a meta-analysis of invalid studies may produce a misleading result, yielding a narrow confidence interval around the wrong intervention effect estimate

Validity

19

external

- whether the study asks an appropriate RQ

internal

- whether the study answers its research question 'correctly'

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Bias

20

- is a systematic (Methodical) error, or deviation from the truth, in results or inferences.
- can lead to underestimation or overestimation of the true intervention effect.

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Bias and Imprecision

21

Bias	Imprecision
• systematic error • replications of the study would reach the wrong answer on average	• random error • replications of the study will produce different estimates because of sampling variation even if they would give the right answer on average

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Types of bias

22

Selection	differences in baseline characteristics
Performance	differences in the care that is provided
Detection	differences in how outcomes are determined
Attrition	differences in withdrawals from a study
Reporting	differences in reported & unreported findings

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Domains in RoB assessment

23

Selection	Sequence generation Allocation concealment
Performance	Blinding of participants & personnel
Detection	Blinding of outcome assessment.
Attrition	Incomplete outcome data
Reporting	Selective outcome reporting

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Random Sequence generation

24

'Low risk' of bias	'High risk' of bias
• random number table • computer random number generator • Coin tossing • Shuffling envelopes • Throwing dice • Drawing of lots	• Alternation • date of admission; • hospital record number. • judgment of clinician • preference of participant • availability of intervention

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Allocation Concealment

25

'Low risk' of bias

- Central allocation (including telephone, web-based, pharmacy-controlled)
- Sequentially numbered identical drug containers
- Sequentially numbered, opaque, sealed envelopes

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Blinding (Masking)

26

Effective blinding of

Participants/Personnel

Similar care

To avoid performance bias

Effective blinding of

Outcome assessors

Similar measurement

To avoid detection bias

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Performance & Detection bias

27

'Low risk' of bias.

- No blinding but the outcome or the outcome measurement is not likely to be influenced by lack of blinding
- Effective Blinding of participants & key study personnel ensured

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Attrition bias

28

- two reasons for withdrawals or incomplete outcome data
  - Exclusions: some participants are omitted from reports of analyses, despite outcome data being available to the trialist.
  - Attrition: outcome data are not available.

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Attrition bias

29

'Low risk' of bias

- No missing outcome data
- Missing outcome data balanced in numbers and with similar reasons across groups

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Reporting bias

30

- Outcomes/studies with significant results are more likely to be reported
- selective reporting bias may be one of the most substantial biases affecting results from individual studies

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Selective outcome reporting

31

'Low risk' of bias.	The protocol is available and all of the study's pre-specified (primary and secondary) outcomes have been reported in the pre-specified way

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Other biases

32

- In addition there are other sources of bias that are relevant only in certain circumstances.
- e.g. carry-over in cross-over trials

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Exercise …

33

- Assess the RoB in
- Each team works on a single subgroup
- Use Revman 5

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34

Undertaking Meta-Analysis

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Mathematics, rightly viewed, possesses not only truth, but supreme beauty - a beauty cold and austere, like that of sculpture

The couch potato approach

- Vote-counting Methods
  - Count the studies with positive results.
  - If the proportion (+) is significantly greater than ½, then we conclude an overall positive effect.
- Disadvantage:
  - Does not consider sample size or precision.
  - Does not yield an effect estimate.

What is meta-analysis?

37

- To Estimate an 'average' or 'common' effect
- To Improve the precision of an estimate by using all available data

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When can we do a meta-analysis?

38

- When more than one study has estimated an effect
- When the data are available

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Two stage process

39

- A point estimate of the effect of intervention for each study
- A pooled estimate of the effect of intervention as a **weighted average** of the treatment effects estimated in the individual studies.

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Weighted average

40

$$Weighted\ \ average = \frac{sum\ of\ (effect \times weight)}{sum\ of\ weights} = \frac{\Sigma TiWi}{\Sigma Wi}$$

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Weighting studies

41

- ***Weighting*** means ***adjusting***
- Lower ***variance*** = More weight
  - The weight given to each study is *the inverse of the variance* of the effect estimate
- **More information** = More weight
  - More participants (Larger studies have smaller SE)
  - More events
- **More precision** (narrow CI) = More weight

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We do not do a simple average

42

- A simple average gives each study equal weight
- This seems intuitively wrong
- Some studies are more likely to give an answer closer to the 'true' effect than others

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Could we just ADD the data?

43

- One approach to combining trials would be to add all the treatment groups together, add all the control groups together, and compare the totals
- This is wrong for several reasons and it can give the wrong answer

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Problems with simple addition

44

- breaks the power of randomization
- imbalances within trials introduce bias
- it can give the wrong answer

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We Do **NOT** add numbers

45

Experimental		Control		RR	ARR
Event	Total	Event	Total		
20	36	13	19	0.81	-12.9%
5	58	7	65	0.80	-2.1%

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We Do **NOT** add numbers

46

Experimental		Control		RR	ARR
Event	Total	Event	Total		
20	36	13	19	0.81	-12.9%
5	58	7	65	0.80	-2.1%
25	94	20	84	**1.12**	**2.8%**

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47

The forest plot

Displaying results graphically

The Forest Plot

48

- there's a label to tell you
- what the comparison is
- what the outcome of interest is

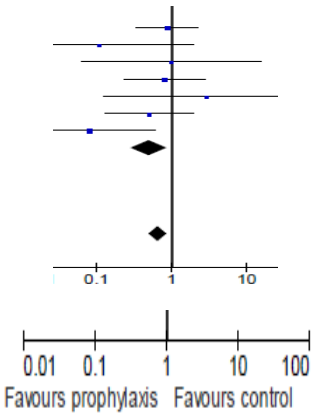
1 Antibiotic prophylaxis vs Placebo

1.1 Wound infection

The Forest Plot

49

- The vertical line in the middle is where the treatment and control have the same effect – there is no difference between the two
- At the bottom there's a horizontal line. This is the scale measuring the treatment effect



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The Forest Plot

50

Study or Subgroup	Prophylaxis Events	Prophylaxis Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Herniorraphies						
Andersen 1980	5	137	6	150	4.8%	0.91 [0.28, 2.92]

Risk Ratio M-H, Fixed, 95% CI

For each study there is an id

The data for each trial are here, divided into the experimental and control groups

This is the % weight given to this study in the pooled analysis

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The Forest Plot

51

Study or Subgroup	Prophylaxis Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Herniorraphies							
Andersen 1980	5	137	6	150	4.8%	0.91 [0.28, 2.92]	

The data shown in the graph are also given numerically

•Each study is given a blob, placed where the data measure the effect. The size of the blob is proportional to the % weight
•The horizontal line is the CI (The wider the horizontal line is, the less confident we are of the observed effect)

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The Forest Plot

52

The label above the graph tells you what effect measure has been used

Study or Subgroup	Prophylaxis Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Herniorraphies							
Andersen 1980	5	137	6	150	4.8%	0.91 [0.28, 2.92]	

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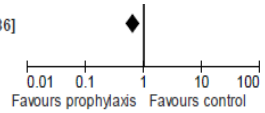
The Forest Plot

53

The pooled estimate is given a diamond shape where the widest bit in the middle is located at the calculated pooled estimate, and the horizontal width is the CI

Total (95% CI) 4188 2637 100.0% 0.65 [0.50, 0.86]
Total events 121 104
Heterogeneity: Chi² = 12.34, df = 12 (P = 0.42); I² = 3%
Test for overall effect: Z = 3.04 (P = 0.002)
Test for subgroup differences: Chi² = 1.35, df = 1 (P = 0.25), I² = 25.7%



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54

Heterogeneity

What is heterogeneity?

What are the causes of heterogeneity?

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Heterogeneity

55

- Heterogeneity is variation between the studies' due to Differences between studies with respect to:
  - Patients: diagnosis, in- and exclusion criteria, etc.
  - Interventions: type, dose, duration, etc.
  - Outcomes: cut-off points, duration of follow-up, etc.
  - Quality and methodology: randomised or not, allocation concealment, blinding, etc.

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Reasons: in plain language

56

- Unknown characteristics of the design & conduct of studies
- Known differences in treatment regimen across studies
- Variation in patient compliance with treatment
- Variation in definition of the outcome measure
- Differences in known patient characteristics
- Differences in unknown patient characteristics
- Differing lengths of follow-up
- Differences due to chance, or spurious effects

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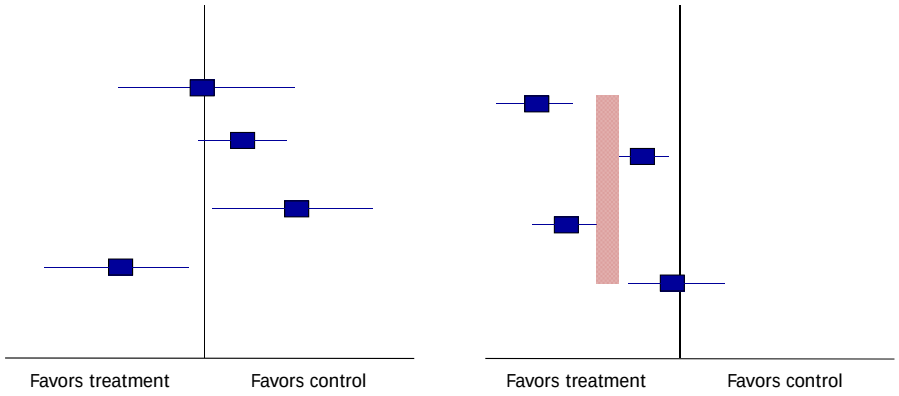
Heterogeneity

57



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Dealing with heterogeneity

58

- Explore heterogeneity
  - Subgroup Analysis
  - Sensitivity Analysis
- ignore heterogeneity: use fixed effect model
- Allow heterogeneity: use random effect model
- Do not pool at all

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Random vs fixed effect model

59

- The formulas for both analyses are identical, *the only difference being the definition of the* ***variance***
- For the ***fixed*** effect analysis: ***intra-studies*** *variance*
- For the ***random*** effects analysis: ***intra-studies*** *variance* ***plus*** *the* ***inter-studies*** *variance*

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Random (vs fixed) effect model

60

- Random effects yield larger variances. Thus, CI for the combined effect increases in width.
- The weights are more balanced.
  - If variance between studies is large, it will dominate the weights and all studies will be weighted more equally
  - weight for large studies less in random effects model
- Exercise: within-study 1 var .1, within-study 2 var .4
  - Scenario 1: between-studies var 0
  - Scenario 2: between-studies var 1

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Exercise for random effect model

61

		Scenario 1	Scenario 2
Study 1	IV	10	0.91
Study 2	IV	2.5	0.71
	Σ IV	12.5	1.62
Study 1	Weight	0.8	0.56
Study 2	Weight	0.2	0.44

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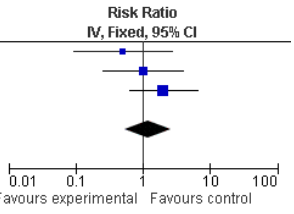
Heterogeneity

62

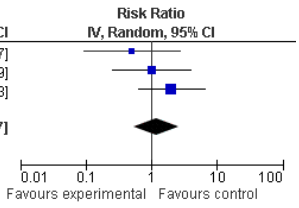
Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
S1	2	100	4	100	21.8%	0.50 [0.09, 2.67]
S2	4	100	4	100	33.2%	1.00 [0.26, 3.89]
S3	8	100	4	100	44.9%	2.00 [0.62, 6.43]
Total (95% CI)		**300**		**300**	**100.0%**	**1.17 [0.54, 2.57]**
Total events	14		12			

Heterogeneity: Chi² = 1.85, df = 2 (P = 0.40); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)



Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
S1	2	100	4	100	21.8%	0.50 [0.09, 2.67]
S2	4	100	4	100	33.2%	1.00 [0.26, 3.89]
S3	8	100	4	100	44.9%	2.00 [0.62, 6.43]
Total (95% CI)		**300**		**300**	**100.0%**	**1.17 [0.54, 2.57]**
Total events	14		12			

Heterogeneity: Tau² = 0.00; Chi² = 1.85, df = 2 (P = 0.40); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)



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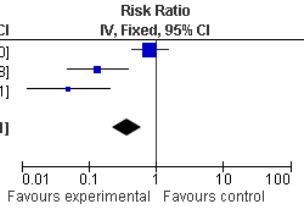
Heterogeneity

63

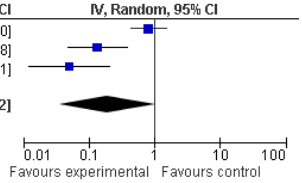
Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
S1	16	200	20	200	63.9%	0.80 [0.43, 1.50]
S2	4	500	30	500	23.5%	0.13 [0.05, 0.38]
S3	2	400	40	400	12.6%	0.05 [0.01, 0.21]
Total (95% CI)		**1100**		**1100**	**100.0%**	**0.37 [0.22, 0.61]**
Total events	22		90			

Heterogeneity: Chi² = 17.23, df = 2 (P = 0.0002); I² = 88%
Test for overall effect: Z = 3.88 (P = 0.0001)



Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
S1	16	200	20	200	36.4%	0.80 [0.43, 1.50]
S2	4	500	30	500	33.5%	0.13 [0.05, 0.38]
S3	2	400	40	400	30.2%	0.05 [0.01, 0.21]
Total (95% CI)		**1100**		**1100**	**100.0%**	**0.19 [0.04, 1.02]**
Total events	22		90			

Heterogeneity: Tau² = 1.92; Chi² = 17.23, df = 2 (P = 0.0002); I² = 88%
Test for overall effect: Z = 1.93 (P = 0.05)



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64

Interpretation

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Interpretation

65

- "Evidence of absence" vs "Absence of evidence"
- In the example below, as more data is included, the overall odds ratio remains the same but the confidence interval decreases.
- It is not true that there is 'no difference' shown in the first rows of the plot – there just isn't enough data to show a statistically significant result.

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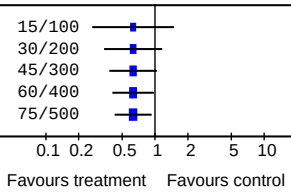
Interpretation

66

Review: Steff
Comparison: 01 Absence of evidence and Evidence of absence
Outcome: 01 Increasing the amount of data...

Study or sub-category	Treatment n/N	Control n/N	OR (fixed) 95% CI	OR (fixed) 95% CI
1 study	10/100	15/100		0.63 [0.27, 1.48]
2 studies	20/200	30/200		0.63 [0.34, 1.15]
3 studies	30/300	45/300		0.63 [0.38, 1.03]
4 studies	40/400	60/400		0.63 [0.41, 0.96]
5 studies	50/500	75/500		0.63 [0.43, 0.92]



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Interpretation

67

- Weighing up benefit and harm
- When interpreting results, don't just emphasise the positive results.
- A treatment might cure hirsutism in PCOS, but kill one person in 10,000 (very important as hirsutism is not life threatening).

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Interpretation - Quality

68

- Rubbish studies = unbelievable results
- If all the trials in a meta-analysis were of very low quality, then you should be less certain of your conclusions.
  - Instead of "Treatment X cures depression", try "*There is some evidence that Treatment X cures depression, but the data should be interpreted with caution due to a high risk of bias in the included trials.*"

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RESQUE yourself and your patient

69

- Relevant Review question
- Search and Select trials by DESIGN not by results
- Quality assessment by RoB tool
- Evidence Assimilation
  - Extract data
  - Estimate effect of intervention in each study
  - Explore heterogeneity
  - Execute meta-analysis
  - Examine results carefully to draw conclusions

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Now what?

70

- Have a large cup of Cappuccino
- Let us Do it

All the best

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