

## **Module 16: Strength and relevance of the evidence.**

**CAUTION!! This module is not up-to-date.**

**Authors MUST refer to ‘Chapter 12: Interpreting results and drawing conclusions’ in the *Cochrane Handbook for Systematic Reviews of Interventions* for current information.**

This module will cover how to discuss your results both in terms of how effective (or ineffective) an intervention may be and how the results of your review may be applied to individual health care situations. We will discuss interpretation of the results of your review as it applies to writing your results and discussion section, not with respect to using the review to making an actual decision about health care.

### **Learning objectives**

- Be able to recognize the components of evidence in health care interventions and understand their relative contributions to the strength of evidence of a systematic review (study design, number of studies, study quality, statistical significance, clinical importance, biological plausibility, and consistency of results)
- Be able to interpret the available evidence as strong, weak or inconclusive and be able to justify these ratings
- Judge whether a particular systematic review is likely to be of limited or wide applicability
- Recognize the features of a particular systematic review that may limit or widen its applicability (considering degree of mismatch between trial characteristics and settings to which the results may be applied)
- Understand the purpose, calculation and application of NNTs to assist assessment of appropriate application

### **Relevant sections of the *Cochrane Handbook for Systematic Reviews of Interventions***

- Chapter 12: Interpreting results and drawing conclusions

### **Where does this go in a Cochrane review?**

- The information in this Module relates to the Results and Discussion section of your review.

The forest plots and summary statistics you generate in RevMan form the results of your review, but it is essential that you summarize them in the Results section. Make sure you include all the important results, not just those that are statistically significant.

The purpose of the Discussion and Reviewers' Conclusions section of your review is for you to help the reader interpret your results. There are three main things you need to cover:

- Any limitations of your review and the assumptions you have made
- The strength of the evidence
- The relevance of the evidence

### **Limitations and assumptions of the review**

From all the previous modules you have seen that when preparing a systematic review we make many choices, most based on assumptions. All the choices you made that may have affected the results of your review should be outlined in the Methods section of your review, and preferably tested with sensitivity analyses. There may be some aspects of your review (for example that most included trials had methodological flaws, or were small; or that you haven't been able to get the data for some of the included trials, or there is funnel plot asymmetry) that you want to highlight in your Discussion section, along with some thoughts about how these issues may have affected the results of your review.

### **Strength of evidence**



Read Section [12.2](#) of the *Cochrane Handbook for Systematic Reviews of Interventions*

Section 12.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* discusses some things you may like to consider when discussing the strength of evidence in your review and you should read it now.

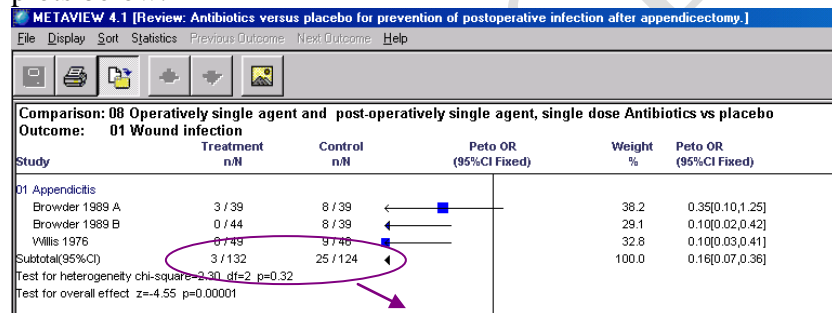
The phrase 'strength of evidence' applies to more than just the results of your review, although your review will obviously contribute greatly to the overall body of knowledge on its topic. It is how strong the overall case for the use or cessation of use for the intervention is. The strength of evidence relating to your review question is determined by factors both within your review and external to your review.

### Internal factors

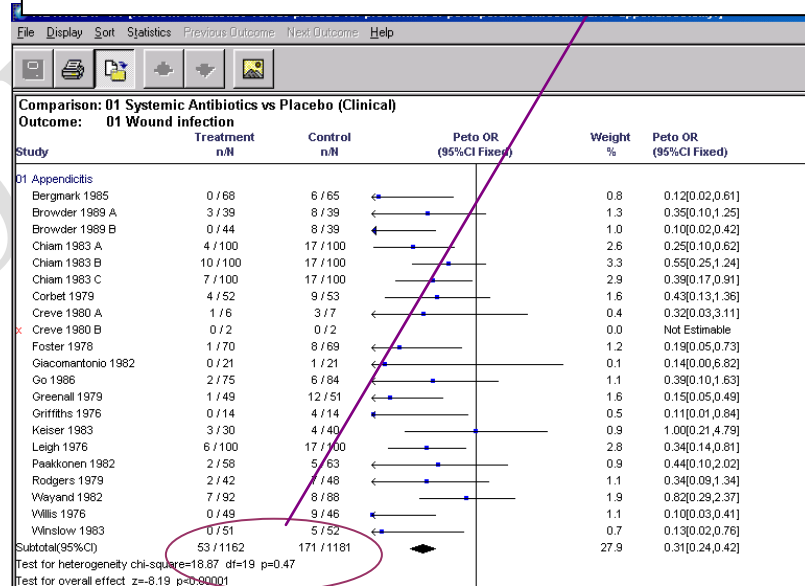
Some factors internal to your review which you may want to consider when drawing conclusions about the strength of evidence are

- Methodological issues relating to both the review and the included trials as outlined in earlier modules. If most included trials were methodologically sound, with adequate allocation concealment, careful control for confounding and little missing data you may be more confident regarding the strength of your conclusions.
- The number of studies in your review and the number of participants in the studies. If your data are sparse, the evidence is less strong and you should be careful about what you conclude.

For example, compare the strength of evidence from the forest plots below.

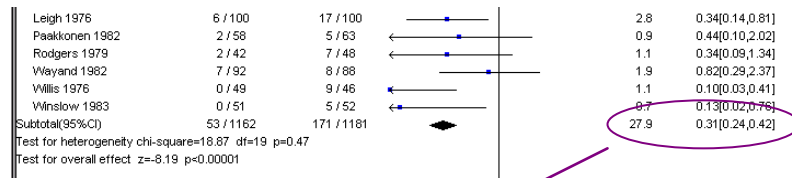


3 trials with total of 256 participants versus 21 trials with total of 2343 participants, the strength of evidence in the second example is greater

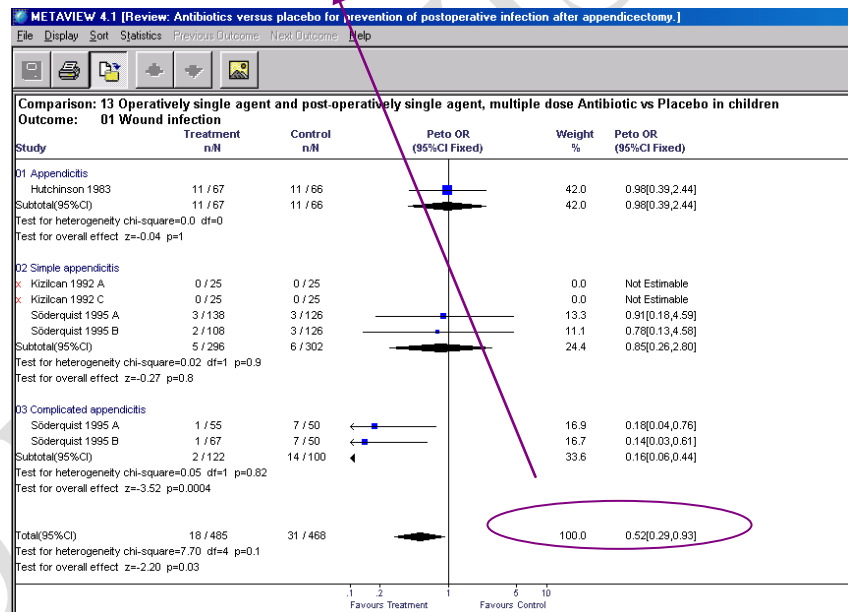


- The size of the treatment effect. If your summary treatment effect is large, and the confidence intervals fall within a range that would be considered clinically significant, the strength of evidence is greater.

For example, compare the strength of evidence from the forest plots below.

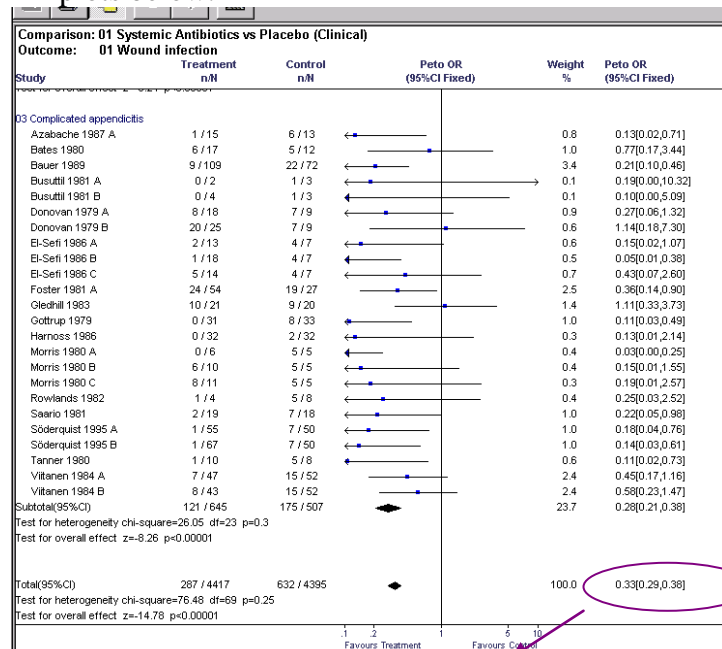


OR of 0.31 with upper confidence interval of 0.42 indicates confidence intervals fall within a clinically significant range compared to OR of 0.52 with upper CI of 0.93, upper confidence interval may not be clinically significant. The first example is stronger evidence for an important effect.

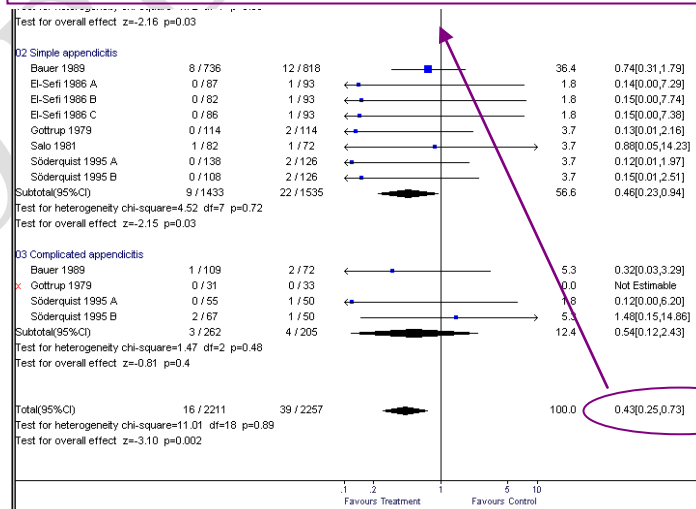


- The precision of the treatment effect. If the confidence intervals around your summary estimate are narrow and so you are more sure that the 'true' result lies within the range bordered by the upper and lower confidence interval (and is clinically significant) you can be more confident about the strength of evidence.

For example, compare the strength of evidence from the forest plots below.

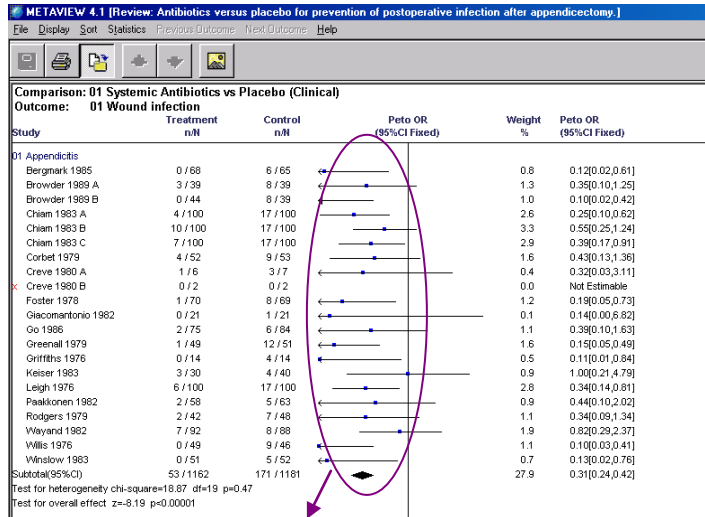


CIs of 0.29 to 0.38 compared to 0.25 to 0.73  
 The first example is more precise, hence greater strength of evidence

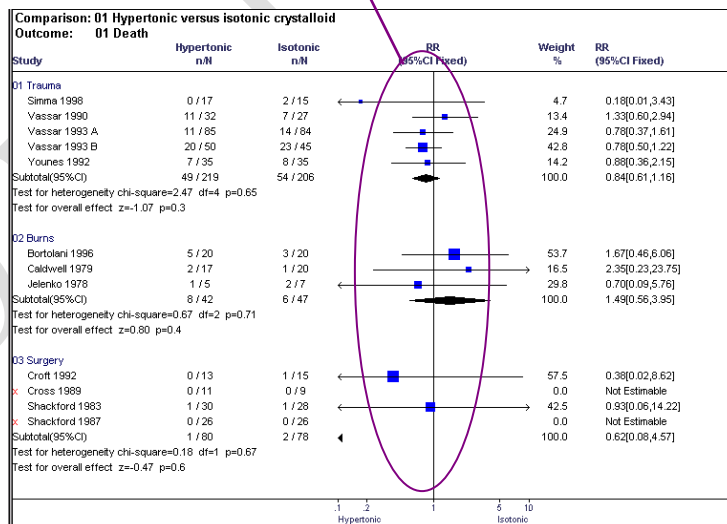


- The consistency of the results. If the results of all or most of the trials in your review are in the same direction (i.e. demonstrating an effect) the evidence is stronger (although ensure you also discuss the possibility of publication bias).

For example, compare the strength of evidence from the forest plots below.



Consistency of effect versus disagreement between trials (i.e. all effect estimates in example 1 to the left of the line, example 2 differs in direction). The first example offers greater strength of evidence



- The consistency of outcomes. If the intervention is showing similar effects on all related outcomes (for example if an exercise program both significantly reduces pain and increases function) you may be more confident to conclude it is effective.

For example, compare the strength of evidence from the forest plots below.

**METAVIEW 4.1 [Review: Antibiotics versus placebo for prevention of postoperative infection after appendectomy.]**

File Display Sort Statistics Previous Outcome Next Outcome Help

Comparison/Outcome	No. of Studies	No. of Participants	Statistical Method	Effect Size
<b>Total number of included studies: 58</b>				
<b>01 Systemic Antibiotics vs Placebo (Clinical)</b>				
01 Wound infection	71	8812	Peto OR [95% CI]	0.33 [0.29,0.38]
02 Postoperative intra abdominal abs...	20	4468	Peto OR [95% CI]	0.43 [0.25,0.73]
03 Length of stay in hospital	8	1200	WMD [Fixed] [95% CI]	-1.69 [-1.78,-1.61]

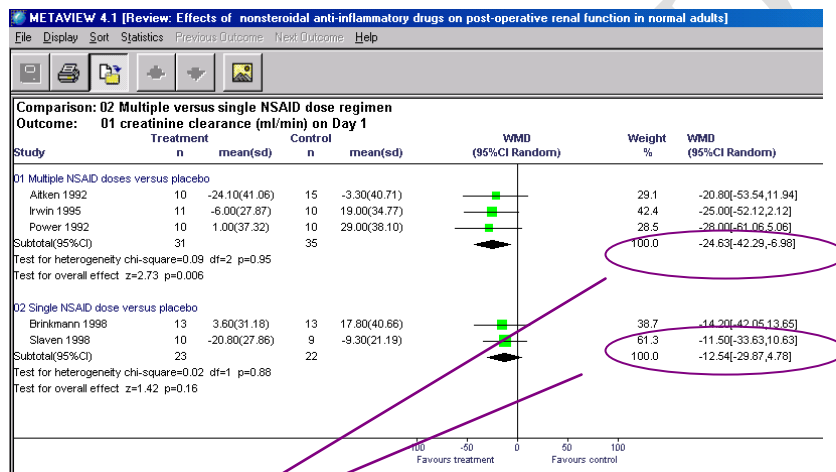
Consistent effect across all measured outcomes (example 1) versus beneficial effect for some outcomes and not others (example 2)

**METAVIEW 4.1 [Review: Antihypertensive drug therapy for mild to moderate hypertension during pregnancy]**

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Comparison/Outcome	No. of Studies	No. of Participants	Statistical Method	Effect Size
<b>Total number of included studies: 39</b>				
<b>01 Any antihypertensive drug versus none (subgrouped by class of drug)</b>				
01 Maternal death	3	306	Relative Risk [Fixed] [95% CI]	2.85 [0.30,27.00]
02 Eclampsia	4	508	Relative Risk [Fixed] [95% CI]	0.34 [0.01,8.15]
03 Severe hypertension	17	2155	Relative Risk [Fixed] [95% CI]	0.52 [0.41,0.64]
04 Proteinuria/pre-eclampsia	19	2402	Relative Risk [Fixed] [95% CI]	0.99 [0.84,1.18]
05 HELLP syndrome	1	197	Relative Risk [Fixed] [95% CI]	2.02 [0.38,10.78]
06 Pulmonary oedema	1	176	Relative Risk [Fixed] [95% CI]	5.23 [0.25,107.40]
07 Additional antihypertensive	10	1285	Relative Risk [Fixed] [95% CI]	0.42 [0.30,0.58]
08 Changed/stopped drugs due to m...	13	1202	Relative Risk [Fixed] [95% CI]	1.88 [0.89,3.95]
09 Maternal side effects	8	633	Relative Risk [Fixed] [95% CI]	1.74 [1.04,2.91]
10 Antenatal hospital admission	3	306	Relative Risk [Fixed] [95% CI]	0.94 [0.78,1.12]
11 Induction of labour	5	563	Relative Risk [Fixed] [95% CI]	0.91 [0.77,1.07]
12 Elective delivery (induction of labo...	5	710	Relative Risk [Fixed] [95% CI]	0.91 [0.83,1.00]
13 Caesarean section	17	2221	Relative Risk [Fixed] [95% CI]	0.96 [0.85,1.08]
14 Placental abruption	9	1214	Relative Risk [Fixed] [95% CI]	1.83 [0.77,4.37]
15 Total reported fetal or neonatal de...	23	2727	Relative Risk [Fixed] [95% CI]	0.71 [0.46,1.09]
16 Fetal or neonatal death (subgroup...			Relative Risk [Fixed] [95% CI]	Totals not selected
17 Preterm birth (< 37 weeks)	12	1738	Relative Risk [Fixed] [95% CI]	1.00 [0.87,1.15]
18 Preterm birth (subgrouped by gest...			Relative Risk [Fixed] [95% CI]	Totals not selected
19 Small for gestational age	17	2159	Relative Risk [Fixed] [95% CI]	1.13 [0.91,1.42]
20 Small for gestational age (subgrou...			Relative Risk [Fixed] [95% CI]	Totals not selected
21 Admission to special care baby unit	7	1251	Relative Risk [Fixed] [95% CI]	1.08 [0.90,1.30]
22 Respiratory distress syndrome	5	825	Relative Risk [Fixed] [95% CI]	0.28 [0.12,0.63]
23 Neonatal hypoglycaemia	4	679	Relative Risk [Fixed] [95% CI]	0.87 [0.46,1.63]
24 Neonatal bradycardia	3	418	Relative Risk [Fixed] [95% CI]	1.93 [1.05,3.53]
25 Neonatal jaundice	2	346	Relative Risk [Fixed] [95% CI]	0.89 [0.59,1.35]
26 Follow-up of the children at 1 year...	1	110	Relative Risk [Fixed] [95% CI]	0.33 [0.01,8.01]
27 Follow-up of the children at 7 1/2 ...			Relative Risk [Fixed] [95% CI]	Totals not selected

- Apparent dose response relationship. It may be that if an intervention is significantly beneficial (or harmful), the more of the intervention you have, the better (or worse) you will do. This is known as a dose-response relationship and, in studies of causation, the presence of a dose-response relationship (i.e. the more of a harmful agent you are exposed to the greater your chance of developing the outcome), the stronger the evidence of association. In some reviews however dose-response association may not be important, for example if there is no threshold dose.



Multiple doses appear to have a greater effect than single doses, which may strengthen the evidence.

*External factors*

- Biological plausibility. Your conclusion will be strengthened if the effect makes sense. There may well be laboratory based research to explain the effect demonstrated by your results, for example studies analyzing the biomechanics of hemiplegic gait may help explain evidence for the effect of a physiotherapy intervention following stroke. Similarly, the effect on intermediate outcomes, such as physiological markers, may help to explain and so strengthen the effect demonstrated by your review.

- Other evidence. There may be non-randomised studies, such as cohort studies or case series which are not included in your review but support your conclusions. This may strengthen the evidence. It is important to bear in mind however that these studies were excluded from your review for a reason (probably methodological) and so not too much weight should be given to their conclusions. In addition, you are unlikely to have systematically searched for these non-randomised studies and so you may not have all available information.
- Concordance with related reviews. If your review results are similar to other related reviews and the intervention appears effective (or not effective) in other comparable situations, this will strengthen your conclusions. For example, if an analgesic medication demonstrated similar pain relieving properties in a review of populations with acute pain and a review of populations with chronic pain, the strength of evidence for the intervention could be interpreted as stronger.

All of the above points need to be considered when helping the reader interpret the results of your review. Your conclusions about the effect of the intervention should reflect the strength of evidence as determined by these internal and external factors.

### **Applicability and Relevance of the evidence**

Even if the evidence is strong, with significant, precise, consistent and plausible results, it may not be useful to all those reading your review. Clinicians and consumers, looking for evidence about the best way to deal with an individual health care situation, will not only need evidence which is strong, they will need to know if it applies to them and is relevant to their clinical need.



Read Section [12.3](#) of the *Cochrane Handbook for Systematic Reviews of Interventions*

Section 12.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* discusses Applicability, or Relevance, and you should read it now.

Don't forget that the results of your review may be used in many different populations and settings around the world. Care needs to be taken not to interpret your review only as it applies to your own setting. Reviewers should try to help the reader in applying the results of their review to individual settings.

A useful way of doing this is to ask yourself if there are any reasons why the results of your review may be different if the intervention was used in a different setting. Some examples may be:

- **Biologic and cultural variation**

There may be genetic reasons why an intervention may have varying effects in different populations with varying risks and co-morbidities. There may be gender or age differences in response to the treatment, or the intervention may simply not be feasible or acceptable in a given setting.

- **Variation in baseline risk**

If all the trials in your review include populations with a similar baseline risk of the outcome (i.e. control event rate), while this may strengthen the evidence for the effect of the intervention in such populations, it may limit the applicability of the results. In asking whether the review is *relevant*, the issue is whether or not the evidence matters. In some cases interventions are assessed only by their effect on outcomes that are not important to the people with the disorder. Take the example of antiviral regimes for people living with HIV. If a review were only to report the effect of the regime on CD-4 count, and not include relevant outcomes such as health related quality of life, adverse drug effects or survival, the review may not be relevant to people living with HIV, although it may be helpful to their physician.

A relevant review is one that asks a sensible question. A review, or indeed a trial, that assesses the effect of an intervention compared to placebo when there is a proven effective treatment which can be used is clinically irrelevant. What we need to know is whether the new intervention is better than the existing proven intervention. You may choose to include trials comparing the new intervention to placebo in your review in order to draw an indirect comparison (as discussed in Module 14, Further Considerations In Meta-Analysis), however the primary question of your review should be to determine effect compared to the existing intervention.

### **Summary**

In conclusion, when writing the Discussion section of your review you need to consider not only how convincing the evidence is in terms of the effect of the intervention, but also how this evidence will help in the many clinical settings in which people will wish to apply it.

The following Modules will discuss making conclusions from your review with respect to trade-offs between benefit and harm, and ways of expressing uncertainty.