

Systematic Review and Meta-Analysis... Tools, Termites and Tricks of the Trade...

Larry Young Sheri Keitz

Teaching Objectives

- To shun fear and learn to love forest plots
- To review principles of when it is appropriate to combine studies
- Interpret the results of a meta-analysis including forest plots
- Understand what systematic reviews can and cannot do for you
- Demonstrate teaching techniques and identify resources to assist

Extra-Special Teaching Objective

• CERTIFIED to be JARGON FREE

Need a volunteer



Are Systematic Reviews Scary? Raise your hand if you...

- Always skip the methods section on Systematic Reviews because it sounds like gobbledy-gook
- Make your colleagues teach the systematic review session so you don't look like an idiot
- Think a "Forest Plot" might be a good buy given the current housing market.

How to decrease fear

 What strategies have you seen this week (small or large group) to decrease fear in the learning environment?

Teaching Time Out

- Simplify concepts
- Avoid numbers and Jargon
- There are tools to assist your teaching — TIPS Series

Sj

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Tips for teachers of evidence-based medicine: 4. Assessing heterogeneity of primary studies in systematic reviews and whether to combine their results

Rose Hatala, Sheri Keitz, Peter C. Wyer, Gordon Guyatt, for the Evidence-Based Medic Teaching Tips Working Group

💽 2 Microsoft Offi... 🕞 🛅 Systematic Review

🔮 Meta-analysis ses...

linicians wishing to quickly answer a clinical question may look for a systematic review rather than searching for primary articles. Such a review is also called a meta-analysis when the investigators have tatistical techniques to combine results across Google Chrome , 🌆 2 Microsoft Offi... , 🔂 4 Heterogeneity ...

are geared to learners who are familiar with ho tors should present the magnitude³⁻⁵ and pr treatment effects in a study with binary outcon ratio or relative risk reduction) and who hav accored a for tharapy articlas

Gleeful to Grief-stricken Scale

 Validated instrument for assessing levels of comfort (glee) or fear (grief) in EBM workshop participants



Reactions of people on hearing that they need to look at a meta-analysis:





Words that start with the letter "F"!

Ridicularia Exemplarum...

The best way to understand just about anything in medicine is to reflect on a patient...or other life dilemmas.

The following tale is one such dilemma...

Disclaimer

- All characters and events in this presentation are fictional.
- Any use of names (or initials) is purely unintentional and any similarities to actual persons, in this room or elsewhere, are purely coincidence.
- We cannot emphasize enough how coincidental similarities of our fictional entities to any real life individual, entity, or character are.

Meet Our Heroine...

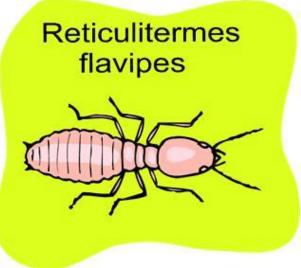
- A "young" faculty member (SK) had just moved to Miami from Durham NC.
- She bought a house.



Things were going well...

- She had a great job (Some days)
- Worked with the most supportive bosses you could ask for (Some bosses)
- Nothing bad ever happened (Almost nothing)
- There were never any crises for her to manage (Definitely not written by SK)

Until one Tuesday at X 3 AM while lounging at the side of her pool...





She won't lose that kitchen to termites!

- Call to her best friend, a librarian... we'll call her "Connie".
- I need to know what I can do to get rid of these termites before they destroy my kitchen island... and I want the best evidence there is.



Two minutes later, Connie calls back...

- I found 4 studies on this brand new product!
- But I know you wanted the *best* evidence.



THE TRUTH IS OUT THERE



Somewhere in those 4 studies.

The Evidence Pyramid (Of Truth)

Systematic Review/Meta-analysis

RC

Observational Studies

(Cohort)

Case-Control

Case Series

Unsystematic Clinical Experience

Says Connie...

- I know you are super busy.
- As it happens we have a faculty member here at Duke who needs to publish more (we'll call him "Tom").
- I think with some help he can put this together in a meta-analysis for you.

Let's help Tom summarize each study.

	Ρ	С	0	F/U
Cearras				
Villasboas				
Symes				
Brown				

First Authors Are Here If You Need Help!

	Р		С	Ο	F/U
Cearras et al	Miami termites	Termicillin on walls	Placebo	Dead termites	30

	Ρ		С	0	F/U
Cearras et al	Miami termites	Termicillin on walls	Placebo	Dead termites	30
Villasboas et al	Rochester termites	Termicillin on walls	Placebo	Dead termites	30

	Ρ		С	Ο	F/U
Cearras et al	Miami termites	Termicillin on walls	Placebo	Dead termites	30
Villasboas et al	Rochester termites	Termicillin on walls	Placebo	Dead termites	30
Symes et al	Miami termites	Termicillin on walls	Termaban	Dead termites	30

	Ρ		С	Ο	F/U
Cearras et al	Miami termites	Termicillin on walls	Placebo	Dead termites	30
Villasboas et al	Rochester termites	Termicillin on walls	Placebo	Dead termites	30
Symes et al	Miami termites	Termicillin on walls	Termaban	Dead termites	30
Brown et al	Miami termites	Termicillin aerosolized	Placebo	Termites whose wings fell off	30

Next Exercise

Instructions to be given by a visiting celebrity scholar....

 Go to video and then do what the video tells you to do.... (use discretion in your interpretation)

Celebrity Scholar.



	Ρ		С	Ο	F/U
Cearras et al	Miami termites	Termicillin on walls	Placebo	Dead termites	30
Villasboas et al	Rochester termites	Termicillin on walls	Placebo	Dead termites	30
Symes et al	Miami termites	Termicillin on walls	Termaban	Dead termites	30
Brown et al	Miami termites	Termicillin aerosolized	Placebo	Termites whose wings fell off	30

	Р		С	Ο	F/U
Cearras et al	Miami termites	Termicillin on walls	Placebo	Dead termites	30
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Symes et al	Miami termites	Termicillin on walls	Termaban	Dead termites	30
Brown et al	Miami termites	Termicillin aerosolized	Placebo	Termites whose wings fell off	30

	Р		С	0	F/U
Cearras et al	Miami termites	Termicillin on walls	Placebo	Dead termites	30
Villasboas et al	Rochester termites	Termicillin on walls	Placebo	Dead termites	30
Symes et al	Miami termites	Termicillin on walls	Termaban	Dead termites	30
Brown et al	Miami termites	Termicillin aerosolized	Placebo	Termites whose wings fell off	30

	Р		С	0	F/U
Cearras et al	Miami termites	Termicillin on walls	Placebo	Dead termites	30
Villasboas et al	Rochester termites	Termicillin on walls	Placebo	Dead termites	30
Symes et al	Miami termites	Termicillin on walls	Termaban	Dead termites	30
Brown et al	Miami termites	Termicillin aerosolized	Placebo	Termites whose wings fell off	30

	Р		С	0	F/U
Cearras et al	Miami termites	Termicillin on walls	Placebo	Dead termites	30
Villasboas et al	Rochester termites	Termicillin on walls	Placebo	Dead termites	30
Symes et al	Miami termites	Termicillin on walls	Termaban	Dead termites	30
Brown et al	Miami termites	Termicillin aerosolized	Placebo	Termites whose wings fell off	30

One of these things is not like the others...



Is pooling sensible?

• A priori determination of whether it makes sense to combine on a principled basis.

• You have not looked at the data yet...

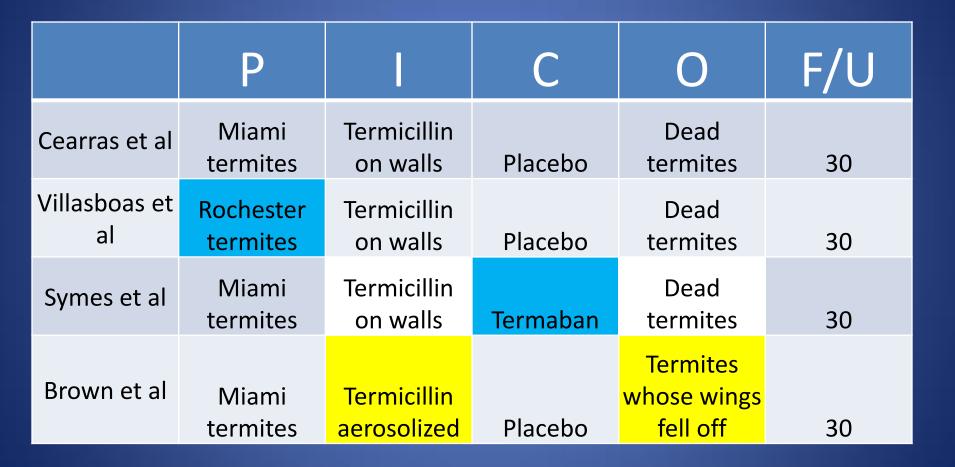
The Common Sense Test

Is pooling sensible?

MA of all kinds of treatments for all cancers?

• MA of steroid treatments for COPD?

 MA of studies looking at CT-angiogram for diagnosis of pulmonary embolism?

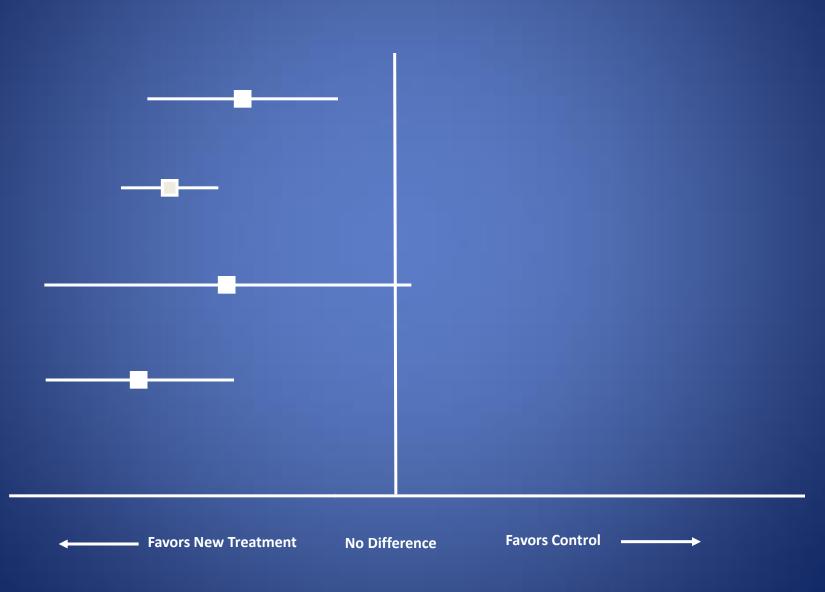


Does combining RESULTS make sense?

Comes from a review of dots and lines

What are the dots and lines in a MA?

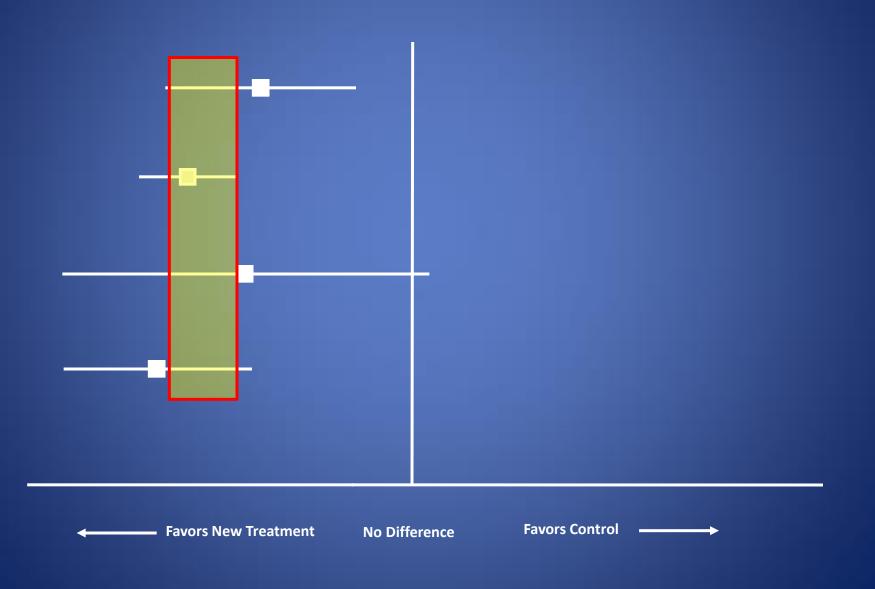




Eye-ball test



Can we combine?

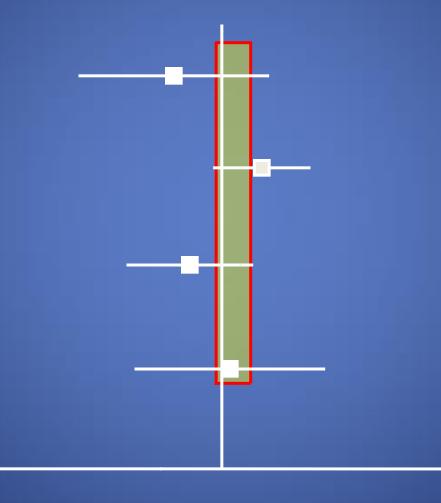




Eye-ball test



Can we combine?



------ Favors New Treatment

No Difference

Favors Control

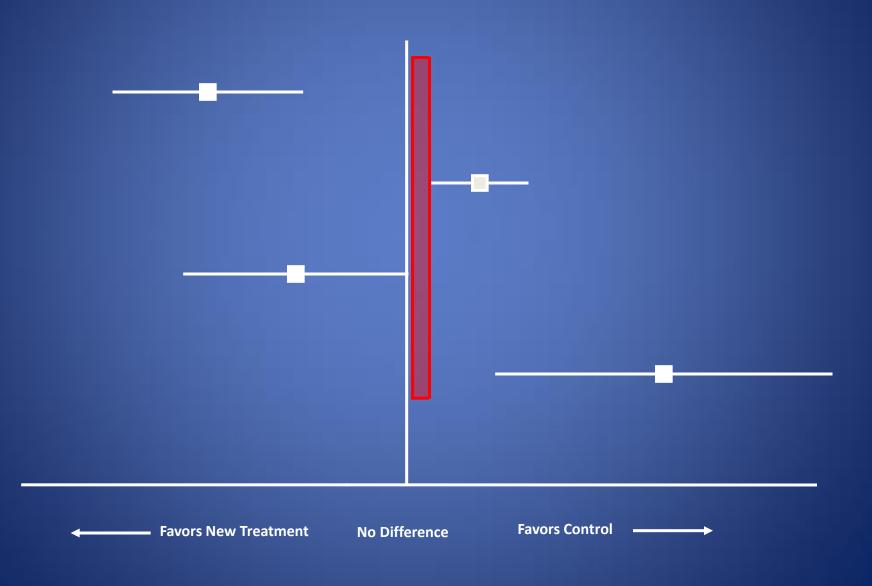




Eye-ball test



Can we combine?



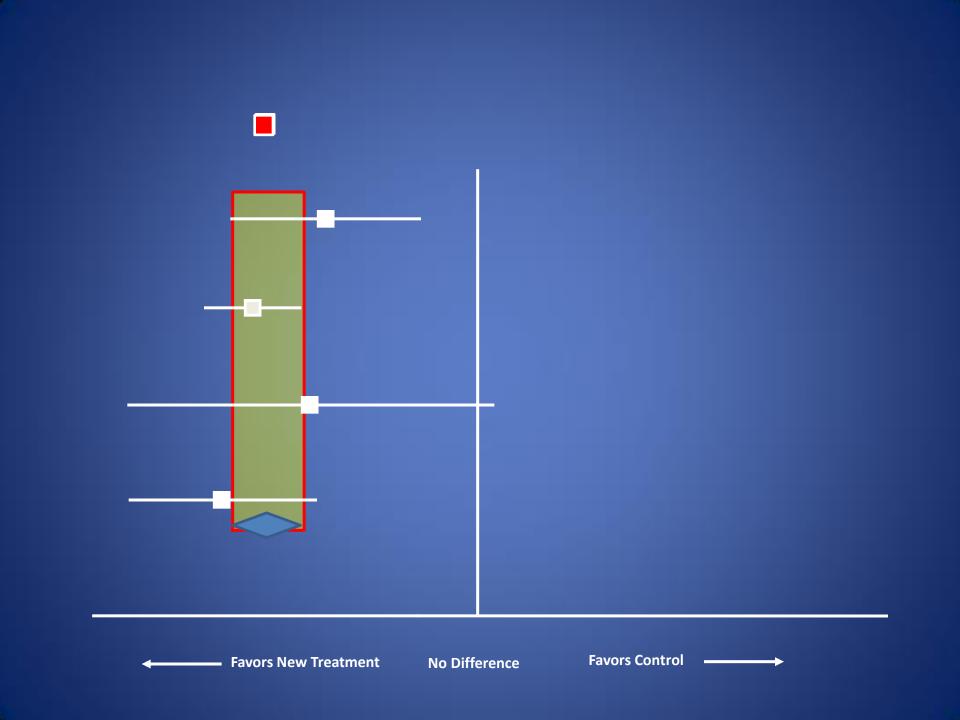
Okay: What is the "Eye-ball test"?



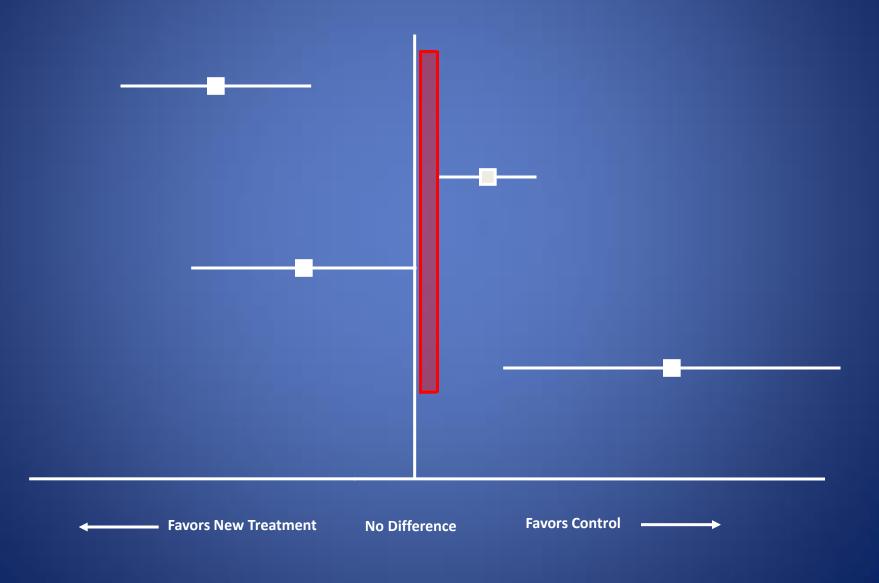
Eye-ball test

 Visual impression of degree of overlap of each study's results (find a common neighborhood of truth)

 Visual impression of where the estimates of study "effects" themselves lie (where are the dots)



Back to result 3: if not, why not?



Why might things be different

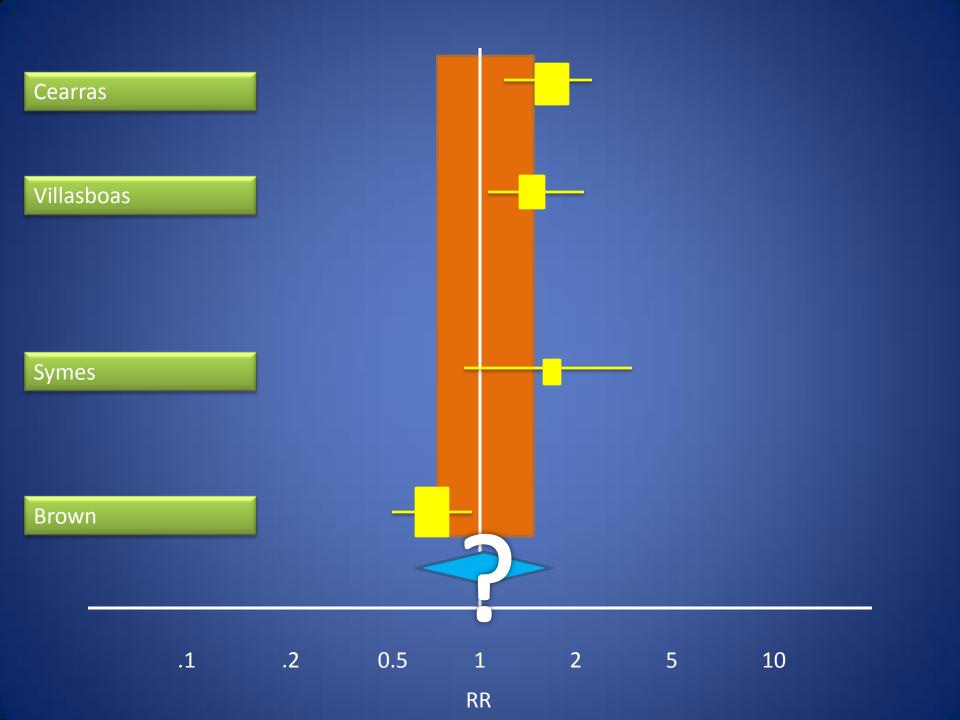
- P: Termites born in different climates
- I: Preparations of brand new drug
- C: Active control / placebo
- O: dead termites vs. lost wings
- T: Treatment Question
- T: RCT or Meta-analysis of well done RCTs

Should We Combine?

						Dee	ulte			
							ults. nites/larvae			
						Intervention Comparison Group Group		RR	95% CI	
	Population	Intervention	Comparison	Outcome	Follow Up (days)				Lower	Upper
Cearras et al	Miami termites	Termicillin on walls	Placebo	Dead termites	30	87	50	1.74	1.2	2.6
Villasboas et al	Rochester termites	Termicillin on walls	Placebo	Dead termites	30	85	57	1.491228	1.04	2.4
Symes et al	Miami termites	Termicillin on walls	Termaban	Dead termites	30	80	45	1.777778	0.9	3.97
Brown et al	Miami termites	Termicillin aerosolized	Placebo	Termites whose wings fell off	30	40	50	0.8	0.5	0.9
Summary								1.70	0.98	3.2

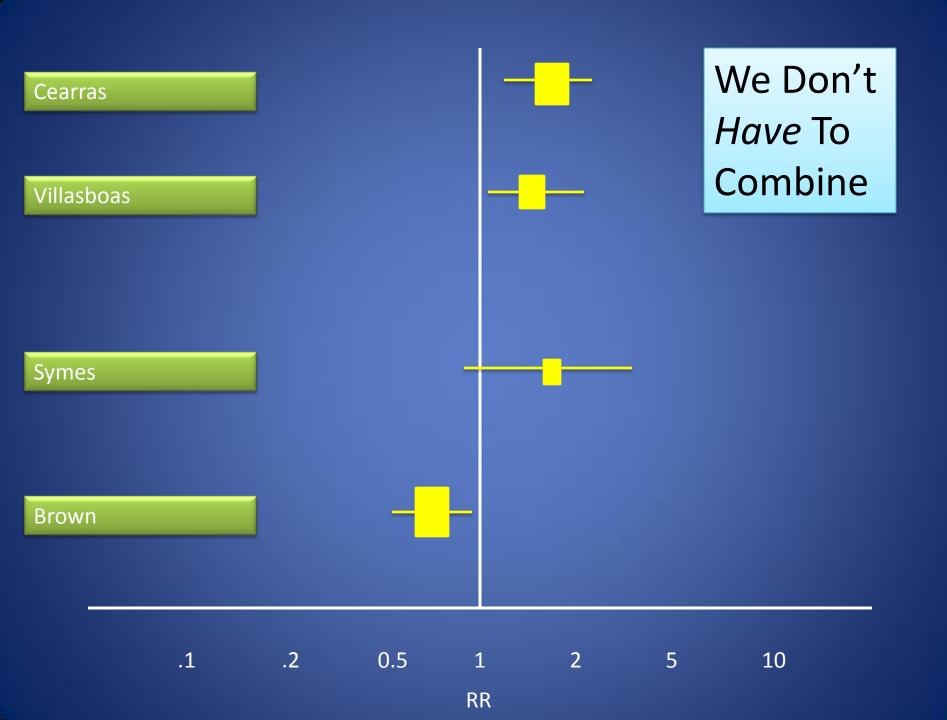
Let's help Tom build a Forest plot.

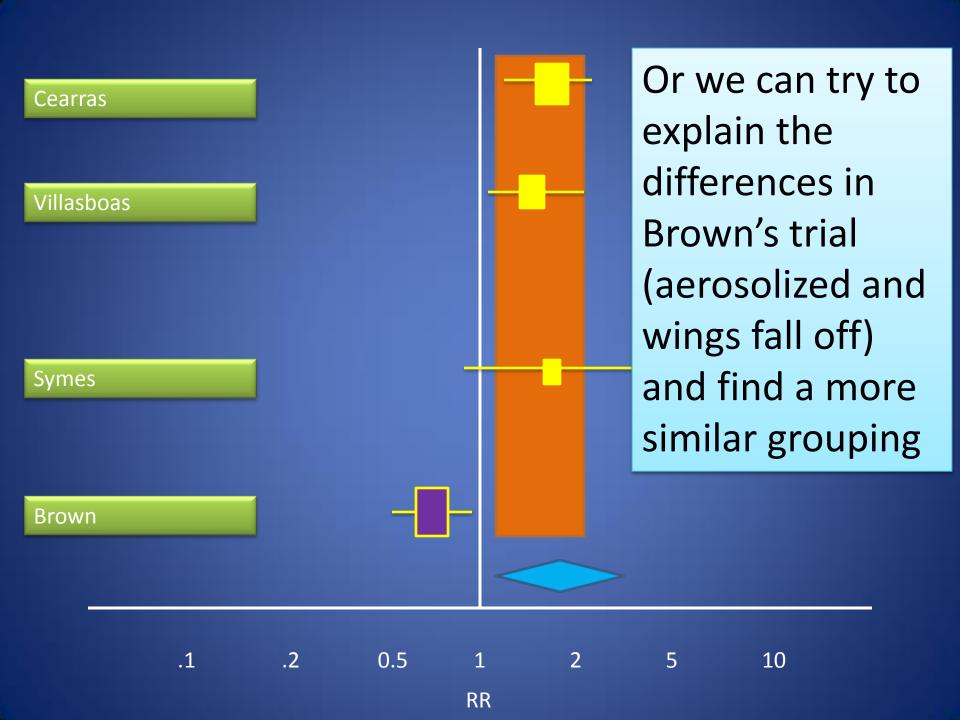




To Combine Or Not To Combine?

- Systematic review vs. meta-analysis
- Disbelievers be comforted...





Back To Our Heroine.

C

- I guess it works!
- Where do I get some?

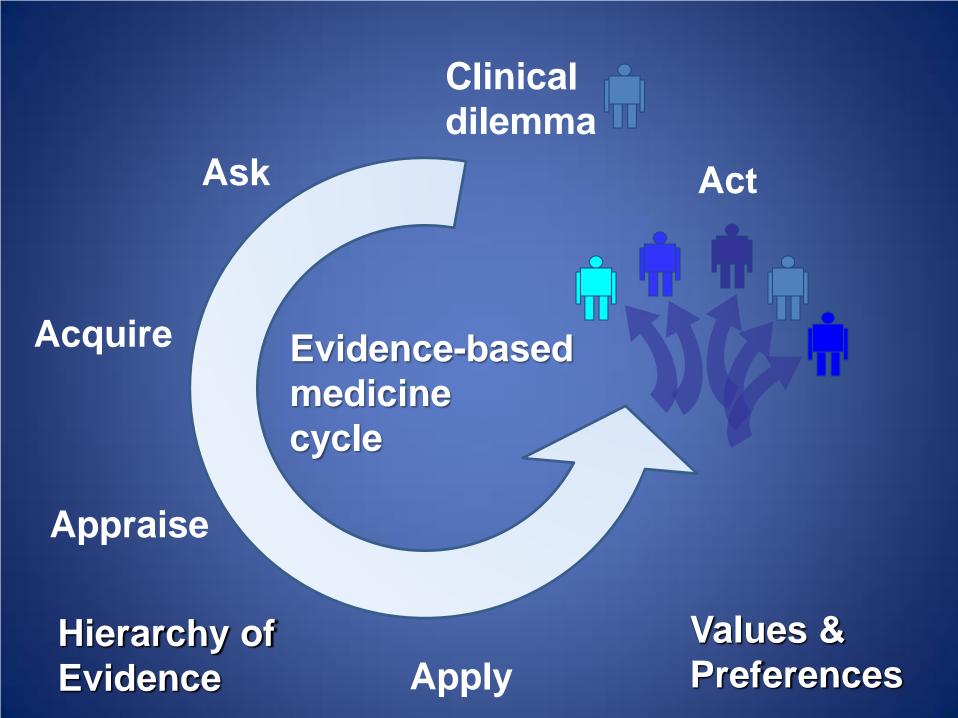
Tips for minimizing learner fear

Use non-medical examples

Use common sense approach explanations rather than statistical ones

Back to case scenario

Right after this commercial message (bathroom break)



Case Scenario: "My Husband Has What!"

- It's Friday night and you have finally returned from work at 9:37 PM.
- On your answering machine is a frantic message from your best friend from college.
- Her husband has just returned from his annual physical. He had complained about epigastric pain.
- The doctor ran some tests, and...

"My Husband Has A Bacteria!"

- He was found to have *H. pylori*.
- After much time reassuring her that this was not the end of the world (not as if her house had termites, after all), she tells you that he has been given 3 different medications to take for 14 days.
- But he's worse than the 9 month old and gets diarrhea and "belly pain" when he takes any medication.

The Question.

- She asks if there is anything that they can do to prevent him (and her) from suffering for the next 2 weeks.
- She has heard that *probiotics* might work.
- Being the EBM expert that you are, you reply, "I'll find out and get back to you!"
- What's our first step?

Those 6 Letters Again.

- Patients with H. pylori receiving triple therapy for eradication.
- I: probiotics (micro-organisms that have beneficial effects for the host).
- C: placebo or no additional treatment.
- O: cure rate, diarrhea, abdominal pain.
- T: therapy/prevention.
- T: RCT or MA of well done RCTs.

Success!

Connie

THERAPEUTICS

Review: Eradication therapy supplemented by probiotics increased eradication rates and reduced side effects in *H. pylori* infection

Tong JL, Ran ZH, Shen J, Zhang CX, Xiao SD. Meta-analysis: the effect of supplementation with probiotics on eradication rates and adverse events during *Helicobacter pylori* eradication therapy. Aliment Pharmacol Ther. 2007;25:155-68.

Clinical impact ratings: Gastroenterology ★★★★★☆ Infectious Disease ★★★★☆☆

QUESTION In patients with *Helicobacter pylori* infection, do probiotics improve eradication rates and reduce side effects of anti-*H. pylori* treatment? Outcomes: *H. pylori* eradication rates and side effects.

toms of diarrhea, epigastric pain, nausea, and taste disturbance (Table).

MAIN RESULTS

CONCLUSION

Let's appraise the article together... in 5 minutes?



Words that start with the letter "F".

• FRAME IT

– Did the authors define (frame) a sensible clinical question using PICO framework?

FIND IT

 Did the authors do a detailed and exhaustive search (find) that is unlikely to systematically miss important relevant studies?

"F"our-step plan for teaching

FILTER AND FETCH

 Did authors select studies based on inclusion criteria, assess risk of bias, collect data from individual studies in a reproducible manner?

FINDINGS AND FOREST PLOTS

 Review findings of a systematic review and the forest plots or summary statistics if graphs are not provided for meta-analysis.

Success (2)... Appraisal

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		^						
	Alimentary Pharmacology & Therapeutics							
Meta-analysis: the	effect of supplementation with probiotics on							
	eradication rates and adverse events during Helicobacter pylori							
eradication therapy	eradication therapy							
J. L. TONG*, Z. H. RAN*, J. SH	J. L. TONG*, Z. H. RAN*, J. SHEN*, C. X. ZHANG† & S. D. XIAO*							
*Department of Gastroenterology,	SUMMARY							
Shanghai Institute of Digestive Dis- ease, Renji Hospital, Shanghai Jiao	Background							
Tong University, School of Medicine, Shanghai, China; †Department of	Recent evidence found probiotics could inhibit Helicobacter pylori col-							
Pharmacy, Jiangni Hospital, Nanjing,	onization from both in vitro and in vivo studies.							
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What are the results

• Everyone: look at Figure 2 (page 162).

Describe the dots and lines

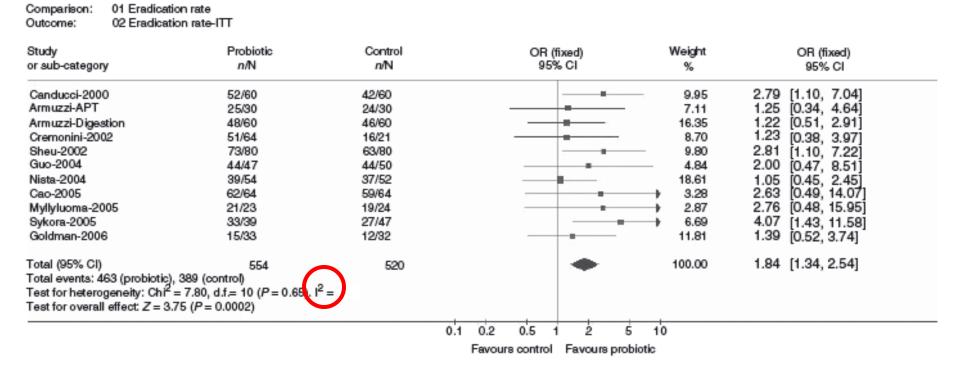


Figure 2. The effect of probiotics supplementation vs. without probiotics on eradication rates by intention-to-treat analysis. (n = number of successful eradication; N = number of participants).

I² what?

- What is the range of possible values for I²
- Explain in a sentence?
- Is the variability between studies due ONLY to chance?
- Is the variability between studies due ONLY to a real difference in treatment?

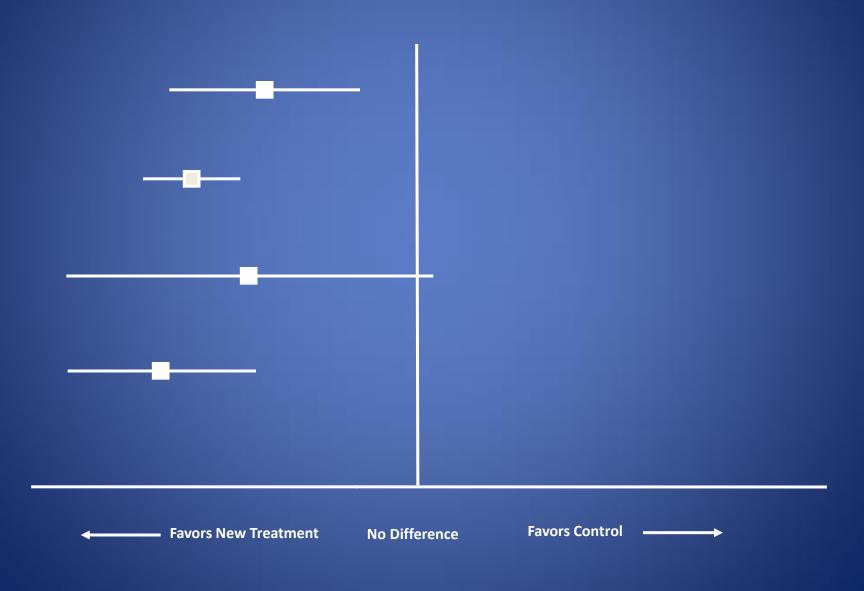
• From 0 to 100

 The variability that is due to a real difference

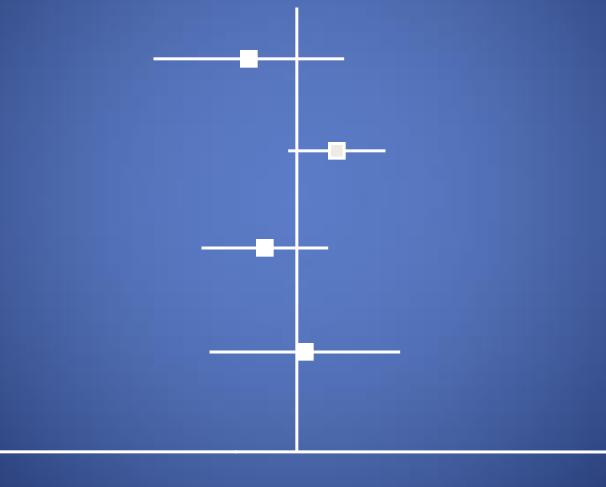
$$I^2 = 0$$

•
$$I^2 = 100$$

Result 1: what is I²



Result 2: what is I²



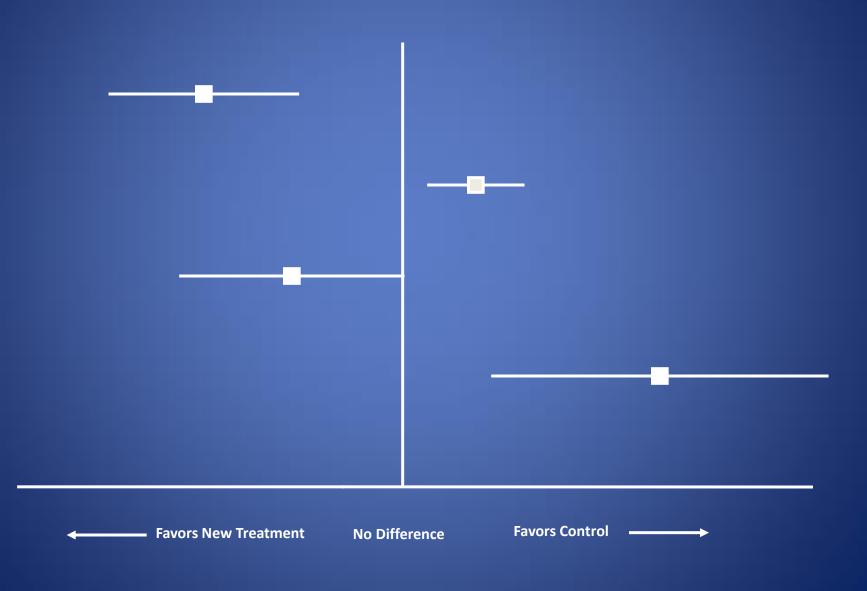
—— Favors New Treatment

No Difference

Favors Control



Result 3: what is I²



Eradication Rate

Comparison: 01 Eradication rate Outcome: 02 Eradication rate-ITT

Study or sub-category	Probiotic <i>n/</i> N	Control n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% Cl
Canducci-2000	52/60	42/60		9.95	2.79 [1.10, 7.04]
Armuzzi-APT	25/30	24/30		7.11	1.25 [0.34, 4.64]
Armuzzi-Digestion	48/60	46/60		16.35	1.22 [0.51, 2.91]
remonini-2002	51/64	16/21		8.70	1.23 [0.38, 3.97]
3heu-2002	73/80	63/80		9.80	2.81 [1.10, 7.22]
3uo-2004	44/47	44/50		4.84	2.00 [0.47, 8.51]
lista-2004	39/54	37/52		18.61	1.05 [0.45, 2.45]
ao-2005	62/64	59/64		3.28	2.63 [0.49, 14.07]
lyllyluoma-2005	21/23	19/24		2.87	2.76 0.48, 15.95
ykora-2005	33/39	27/47		6.69	4.07 [1.43, 11.58]
oldman-2006	15/33	12/32		11.81	1.39 [0.52, 3.74]
otal (95% CI)	554	520	•	100.00	1.84 [1.34, 2.54]
otal events: 463 (probiotic),	389 (control)		-		. / .
est for heterogeneity: Chi ²	= 7.80, d.f.= 10 (P = 0.65).	l ² =			
est for overall effect: $Z = 3$.					
			0.1 0.2 0.5 1 2 5	10	
			Favours control Favours prot	biotic	

Figure 2. The effect of probiotics supplementation vs. without probiotics on eradication rates by intention-to-treat analysis. (n = number of successful eradication; N = number of participants).

 $^{2} = 0\%$

Side Effect - Overall

Comparison:

02 Side-effect

Study or sub-category	Probiotic n/N	Control n/N	OR (fi 95%		OR (fixed) 95% Cl
Canducci-2000 Armuzzi-Digestion	6/60 26/60	6/60 37/60		7.23	1.00 [0.30, 3.30] 0.48 [0.23, 0.99]
Cremonini-2002	11/64	12/21	← ∎	20.04	0.16 [0.05, 0.46]
Guo-2004 Tursi-2004	6/47 5/35	15/50 13/35		16.98 14.92	0.34 [0.12, 0.97] 0.28 [0.09, 0.91]
Myllyluoma-2005 Sykora-2005	20/23 7/39	22/24 9/47	+ <u> </u>	3.76 8.97	0.61 [0.09, 4.01] 0.92 [0.31, 2.76]
					. , ,
Fotal (95% CI) Fotal events: 81 (probiotic) _, 1	328 14 (control)	297	-	100.00	0.44 [0.30, 0.66]
Test for heterogeneity: Chi ² = Test for overall effect: Z = 4.0	: 8.07, d.f.= 6 (P = 0.23). I ² =				
			0.1 0.2 0.5 1	2 5 10	
		e Effects in p	us bistis	More Side Effects	

Figure 4. The effect of probiotics supplementation vs. without probiotics on the incidence of total side effects. (n = number of side effects; N = number of participants).

$|^2 = 25\%$

Diarrhea

Comparison: 02 Side-effect							
Outcome: 02 diarrhoea							
Study	Probiotic	Control	OR (fixed)	Weight	OR (fixed)		
or sub-category	n/N	n/N	95% CI	%	95% CI		
Canducci-2000	3/60	5/60		6.35	0.58 [0.13, 2.54]		
Armuzzi-APT	1/30	8/30		10.35	0.09 [0.01, 0.82]		
Armuzzi-Digestion	4/60	14/60		17.48	0.23 [0.07, 0.76]		
Cremonini-2002	3/64	6/21		11.52	0.12 [0.03, 0.55]		
Nista-2004	5/54	16/52		19.79	0.23 [0.08, 0.68]		
Tursi-2004	0/35	3/35	4	4.62	0.13 [0.01, 2.63]		
Duman-2005	12/204	21/185		27.73	0.49 [0.23, 1.02]		
Myllyluoma-2005	4/23	2/24		2.16	2.32 [0.38, 14.08]		
		EL-					
Total (95% CI)	530	467	•	100.00	0.34 [0.22, 0.52]		
Total events: 32 (probiotic), 75 (co			Ť				
Test for heterogeneity: Chi ² = 10.1	15. d.f.= 7 (P = 0.18). I ² =						
Test for overall effect: Z = 4.90 (P							
			0.01 0.1 1 10	100			
		· · · · · · · · · · · · · · · · · · ·					
	Fewer Side Ef	Tects in pr	obiotic Iviore	Side Effects			

Figure 5. The effect of probiotics supplementation vs. without probiotics on the incidence of diarrhoea. (n = number of diarrhoea; N = number of participants).

$|^2 = 31\%$

Epigastric Pain

Comparison: 02 Side-effect Outcome: 03 epiga.stric p						
Study or sub-category	Probiotic n/N	Control n/N	OR (fixed) 95% Cl	Weight %		OR (fixed) 95% CI
Canducci-2000 Armuzzi-APT Armuzzi-Digestion Cremonini-2002 Nista-2004 Tursi-2004 Myllyluoma-2005	4/60 10/30 4/60 7/64 24/54 0/35 4/23	2/60 9/30 6/60 3/21 34/52 4/35 7/24			2.07 1.17 0.64 0.74 0.42 0.10 0.51	[0.36, 11.76] [0.39, 3.47] [0.17, 2.40] [0.17, 3.15] [0.19, 0.93] [0.01, 1.90] [0.13, 2.06]
Total (95% Cl) Total events: 53 (probiotic), 65 (Test for heterogeneity: Chi ² = 5. Test for overall effect: Z = 2.07 (.67, d.f = 6 (P = 0.46). I ² = (P = 0.04)	282 Effects in pro	obiotic More	100.00 Side Effects	0.62	[0.39, 0.97]

Figure 6. The effect of probiotics supplementation vs. without probiotics on the incidence of epigastic pain. (n = number of epigastic pain; N = number of participants).



Nausea

Comparison: Outcome:	02 Side-effect 04 nausea					
Study or sub-category		Probiotic n/N	Control n/N	OR (fi 95%		OR (fixed) 95% Cl
Test for heterog	2 5 (probiotic), 71 (cont	d.f.= 6 (P = 0.22). I ² =	9/60 11/30 14/60 3/21 26/52 3/35 5/24 282		13.02 16.84 17.47 7.09 33.39 4.96 7.24 100.00	1.00 [0.37, 2.72] 0.19 [0.05, 0.78] 1.19 [0.52, 2.73] 0.51 [0.11, 2.34] 0.35 [0.15, 0.79] 0.31 [0.03, 3.17] 0.57 [0.12, 2.72] 0.58 [0.38, 0.88]
		Fewer Side	Effects in pr	obiotic	More Side Effects	;

Figure 7. The effect of probiotics supplementation vs. without probiotics on the incidence of nausea. (n = number of nausea; N = number of participants).



Taste Disturbance

Comparison: 02 Side-effect Outcome: 05 taste disturbance

Study	Probiotic	Control	OR (fixed)	Weight	OR (fixed)
or sub-category	n/N	n/N	95% CI	%	95% CI
Armuzzi-APT	7/30	15/30		20.10	0.30 [0.10, 0.92]
Armuzzi-Digestion	4/60	16/60		19.35	0.20 [0.06, 0.63]
Cremonini-2002	4/64	8/21		17.12	0.11 [0.03, 0.41]
Nista-2004	29/54	31/52		24.92	0.79 [0.36, 1.70]
Myllyluoma-2005	16/23	16/24		18.52	1.14 [0.33, 3.90]
Total (95% CI)	231	187	-	100.00	0.38 [0.17, 0.85]
Total events: 60 (probiotic), 86	(control)		-		
Test for heterogeneity: Chi ² = 1	0.95 , $d.f. = 4$ ($P = 0.03$). $I^2 =$				
Test for overall effect: Z = 2.34					
	Fewer Side Eff	ects in nroh	iotic More	Side Effects	

Figure 8. The effect of probiotics supplementation vs. without probiotics on the incidence of taste disturbance. (n =number of taste disturbance; N = number of participants).



Back to your best friend...

 In patients with H. pylori infection, probiotic supplementation improves eradication rates and reduces side effects of anti-H. pylori treatment.

What Systematic Reviews Can Do for You

- Save time
- Increase power to detect rare events

 Obviate need for large, expensive trials
 Detect harm
- Increase the precision of the estimate of effect
- Enhance generalizability of the results if samples from different populations are included

What Systematic Reviews Can't Do for You

- Allow you to determine "equivalency" of different interventions
- "Get rid of" bias from individual studies

Teaching Objectives

- To shun fear and learn to love forest plots
- Understand what systematic reviews can and cannot do for you
- To review principles of when it is appropriate to combine studies
- Interpret the results of a meta-analysis including forest plots
- Demonstrate teaching techniques and identify resources to assist

Extra-Special Teaching Objective

- JARGON FREE (at least for the first half...)
- Avoided words
 - Point Estimate
 - Confidence Interval
 - -Summary Statistic
 - -Heterogeneity
 - **—** |²

Take Home Points.

- A well done meta-analysis seeks to get us closer to the truth by combining results of well done individual trials.
- Sometimes it's okay to combine the results of different trials... sometimes it's not.
- Differences between trials can be assessed using different methods.
- $I^2 = 0$ is EXCELLENT.
- $I^2 = 100$ is AWFUL.
- We can all still learn a lot from Cookie Monster.

Gleeful to Grief-stricken Scale

 Validated instrument for assessing levels of comfort (glee) or fear (grief) in EBM workshop participants



We Hope It Wasn't So Scary After All.



Thank You.