Systematic reviews and meta-analyses

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What is a systematic review?

In a systematic review data from original research (research already done and, in most cases, already published) is assembled in its entirety and critically appraised according to a pre-defined protocol; and sometimes combined through meta-analysis, to answer a clear clinical question.

Leibovici L, Falagas M. Systematic reviews and meta-analyses in infectious diseases: how are they done and what are their strengths and limitations. Infect Dis Clinics North Am 2009; in press.

Systematic reviews start with a (clinical) question that contains definitions for:

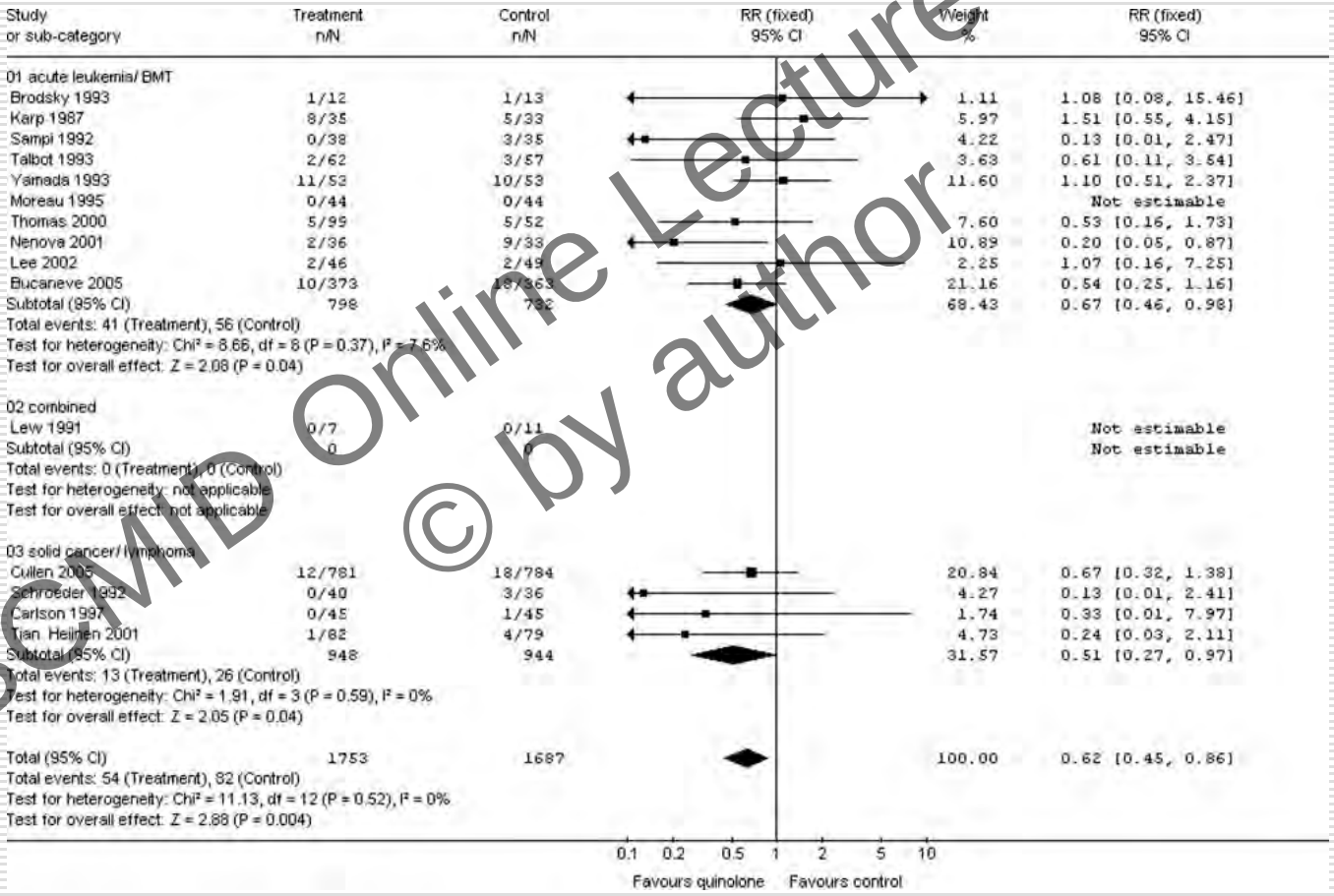
- Patients
- Intervention/s
- Comparison
- Outcome

Example (i): Clinical question:

Does antibiotic prophylaxis reduce mortality in neutropenic patients?

- Patients: Pts with neutropenia
- Intervention/s: Antibiotic prophylaxis
- Comparison: Placebo or no treatment
- Outcome: All-cause mortality

Example (i): Does antibiotic prophylaxis reduce mortality in neutropenic patients?



Gafter-Gvili A et al. Annals Intern Med 2005; 142:979; Leibovici L et al. Cancer 2006;107:1743

Example (i): Does antibiotic prophylaxis with fluoroquinolones reduce mortality in neutropenic patients with acute leukemia or BMT?

Gafter-Gvili A et al. Annals Intern Med 2005; 142:979; Leibovici L et al. Cancer 2006;107:1743

Example (iii): Explanative question:

Does combination treatment (β-lactam + aminoglycoside) improve outcomes in patients with Gram (-) infections?

- Patients: Pts with severe Gram (-) infections
- Intervention/s: β-lactam + aminoglycoside
- Comparison: β-lactam
- Outcome: All-cause mortality

Outcomes that matter to patients (and clinicians)

- In systematic reviews we choose outcomes (and especially the main outcome) that matter to patients
- In trials the choice of outcomes is sometimes (many times?) influenced by other considerations:
  - The need for a manageable sample size
  - Outcomes that can be manipulated with ease

What matters to a patient with febrile neutropenia?

- Alive at 30 days
- No major complications
- Back to normal activity as soon as possible

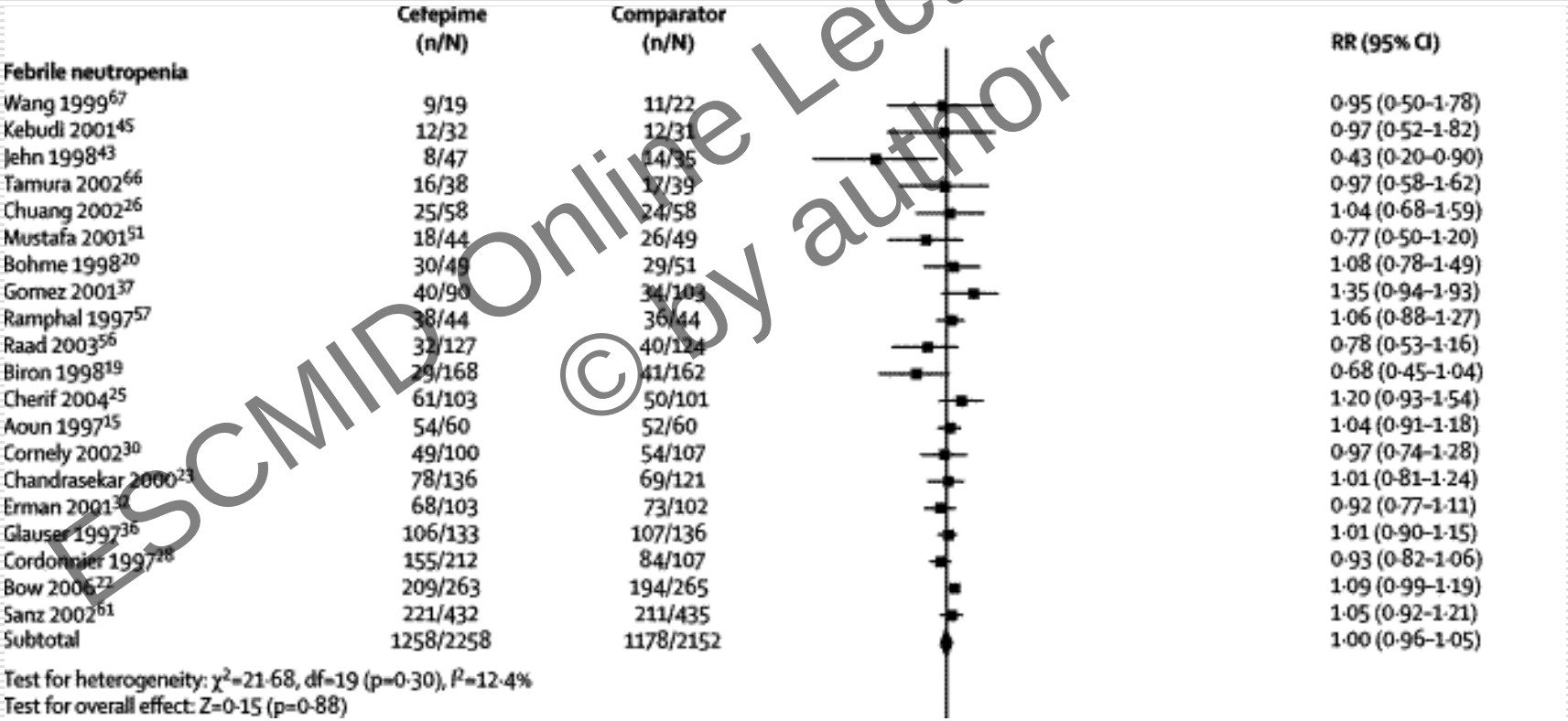
The outcome chosen in all clinical trials on antibiotic treatment of febrile neutropenia:

Treatment failure: A composite outcome:

- Febrile, demise, complications
  - **(~30% of counts)**
- Antibiotic treatment was changed
  - **(~70% of counts)**

Cefepime for treatment of febrile neutropenia: failure

Yahav D et al. Lancet Infect Dis. 2007; 7:338-48.

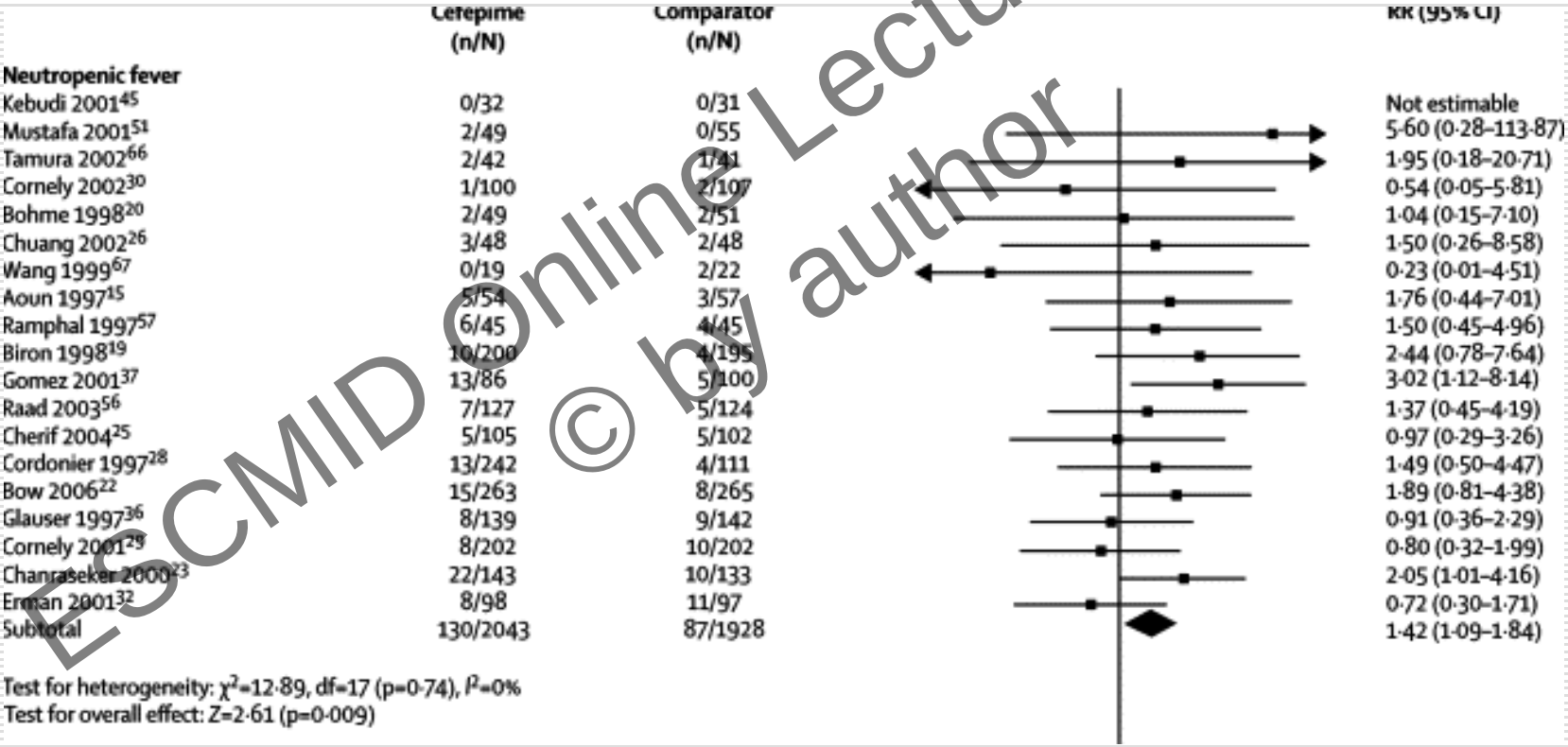


	Cefepime (n/N)	Comparator (n/N)	RR (95% CI)
Febrile neutropenia			
Wang 1999[67]	9/19	11/22	0·95 (0·50–1·78)
Kebudi 2001[45]	12/32	12/31	0·97 (0·52–1·82)
Jehn 1998[43]	8/47	14/35	0·43 (0·20–0·90)
Tamura 2002[66]	16/38	17/39	0·97 (0·58–1·62)
Chuang 2002[26]	25/58	24/58	1·04 (0·68–1·59)
Mustafa 2001[51]	18/44	26/49	0·77 (0·50–1·20)
Bohme 1998[20]	30/49	29/51	1·08 (0·78–1·49)
Gomez 2001[37]	40/90	34/103	1·35 (0·94–1·93)
Ramphal 1997[57]	38/44	36/44	1·06 (0·88–1·27)
Raad 2003[56]	32/127	40/124	0·78 (0·53–1·16)
Biron 1998[19]	29/168	41/162	0·68 (0·45–1·04)
Cherif 2004[25]	61/103	50/101	1·20 (0·93–1·54)
Aoun 1997[15]	54/60	52/60	1·04 (0·91–1·18)
Cornely 2002[30]	49/100	54/107	0·97 (0·74–1·28)
Chandrasekar 2000[23]	78/136	69/121	1·01 (0·81–1·24)
Erman 2001[32]	68/103	73/102	0·92 (0·77–1·11)
Glauser 1997[36]	106/133	107/136	1·01 (0·90–1·15)
Cordonnier 1997[28]	155/212	84/107	0·93 (0·82–1·06)
Bow 2006[22]	209/263	194/265	1·09 (0·99–1·19)
Sanz 2002[61]	221/432	211/435	1·05 (0·92–1·21)
Subtotal	1258/2258	1178/2152	1·00 (0·96–1·05)

Test for heterogeneity: χ^2=21·68, df=19 (p=0·30), I^2=12·4%
Test for overall effect: Z=0·15 (p=0·88)

Cefepime for treatment of febrile neutropenia: mortality

Yahav D et al. Lancet Infect Dis. 2007; 7:338.



	Cefepime (n/N)	Comparator (n/N)	RR (95% CI)
Neutropenic fever			
Kebudi 2001[45]	0/32	0/31	Not estimable
Mustafa 2001[51]	2/49	0/55	5·60 (0·28–113·87)
Tamura 2002[66]	2/42	1/41	1·95 (0·18–20·71)
Cornely 2002[30]	1/100	2/107	0·54 (0·05–5·81)
Bohme 1998[20]	2/49	2/51	1·04 (0·15–7·10)
Chuang 2002[26]	3/48	2/48	1·50 (0·26–8·58)
Wang 1999[67]	0/19	2/22	0·23 (0·01–4·51)
Aoun 1997[15]	5/54	3/57	1·76 (0·44–7·01)
Ramphal 1997[57]	6/45	4/45	1·50 (0·45–4·96)
Biron 1998[19]	10/200	4/195	2·44 (0·78–7·64)
Gomez 2001[37]	13/86	5/100	3·02 (1·12–8·14)
Raad 2003[56]	7/127	5/124	1·37 (0·45–4·19)
Cherif 2004[25]	5/105	5/102	0·97 (0·29–3·26)
Cordonier 1997[28]	13/242	4/111	1·49 (0·50–4·47)
Bow 2006[22]	15/263	8/265	1·89 (0·81–4·38)
Glauser 1997[36]	8/139	9/142	0·91 (0·36–2·29)
Cornely 2001[29]	8/202	10/202	0·80 (0·32–1·99)
Chanraseker 2000[23]	22/143	10/133	2·05 (1·01–4·16)
Erman 2001[32]	8/98	11/97	0·72 (0·30–1·71)
Subtotal	130/2043	87/1928	1·42 (1·09–1·84)

Test for heterogeneity: χ^2=12·89, df=17 (p=0·74), I^2=0%
Test for overall effect: Z=2·61 (p=0·009)

Problems with choosing all-cause mortality as the primary outcome:

- Not the primary outcome in the original trials: thus not reported in all of them
- Probably only a (small?) portion attributable to infection

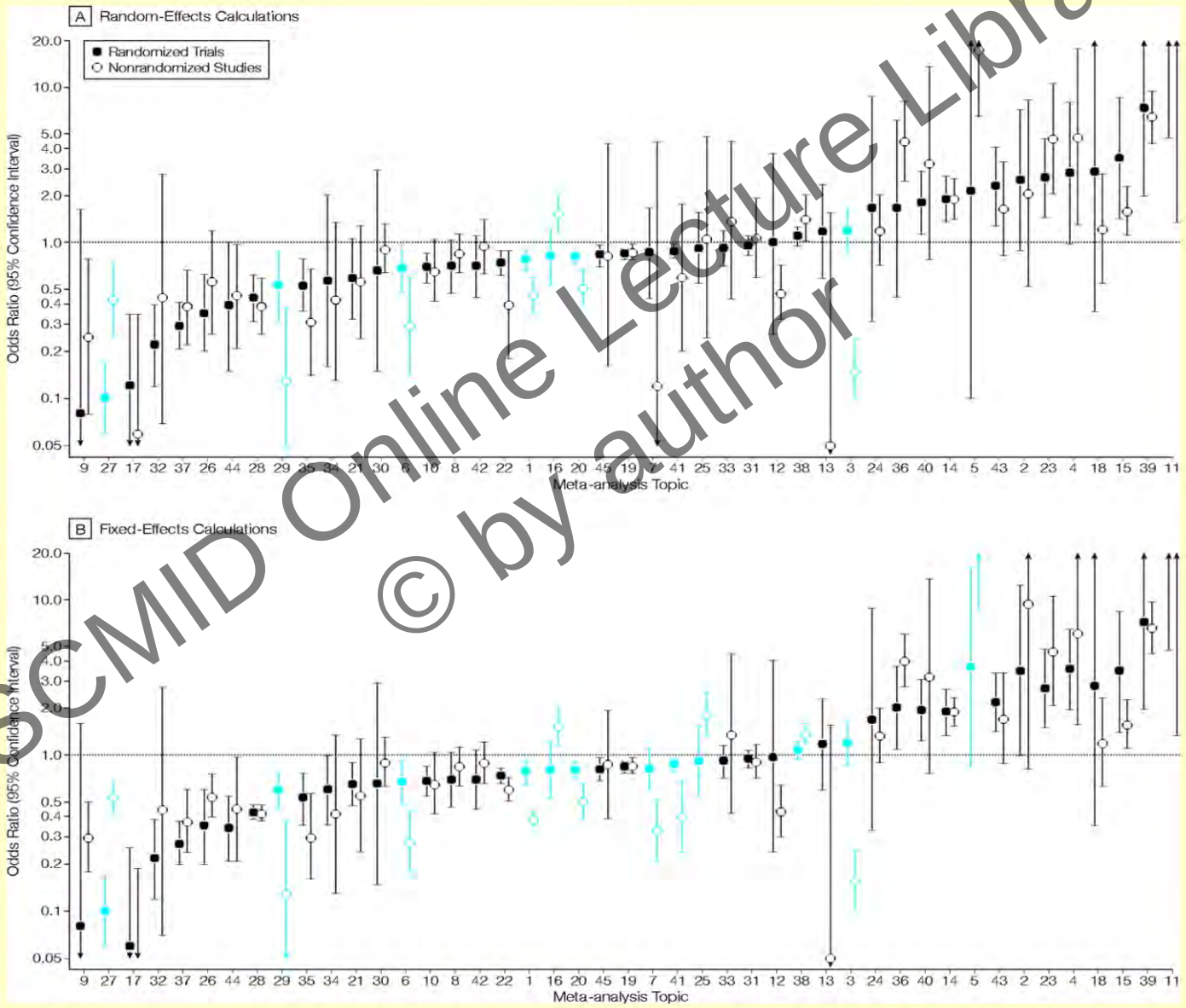
Efforts to avoid bias in the workings of the review:

- Write a protocol at the beginning of the review and stick to it
- Collect all the original research that was done (according to the protocol's definitions): include all languages of publication and all data, whether published or not
- Two researchers, independently, make the important decisions and abstract data

Efforts to circumvent bias inherent in the original research:

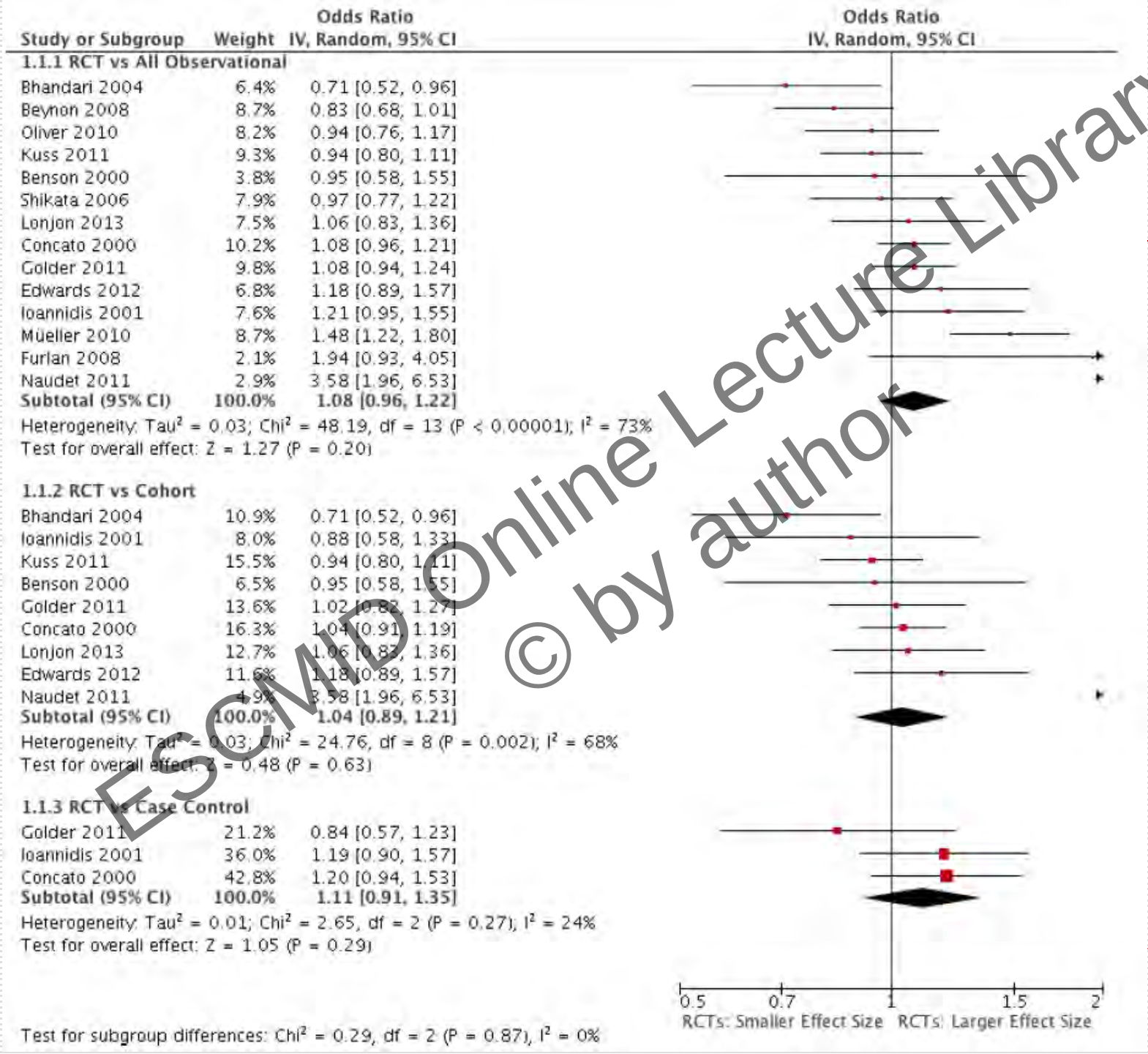
- Start with your own question (PICO) and not with what was done in the original studies
- Include studies with designs that are most likely to prevent bias: i.e. in most cases only randomized controlled trials
- Asses the methodological rigor of the original trials (studies) and test whether it influences the outcome measure

Comparison of the Summary Odds Ratio and 95% Confidence Interval in Randomized Trials vs Nonrandomized Studies for the 45 Topics



Ioannidis, J. P. A. et al. JAMA 2001;286:821-830.

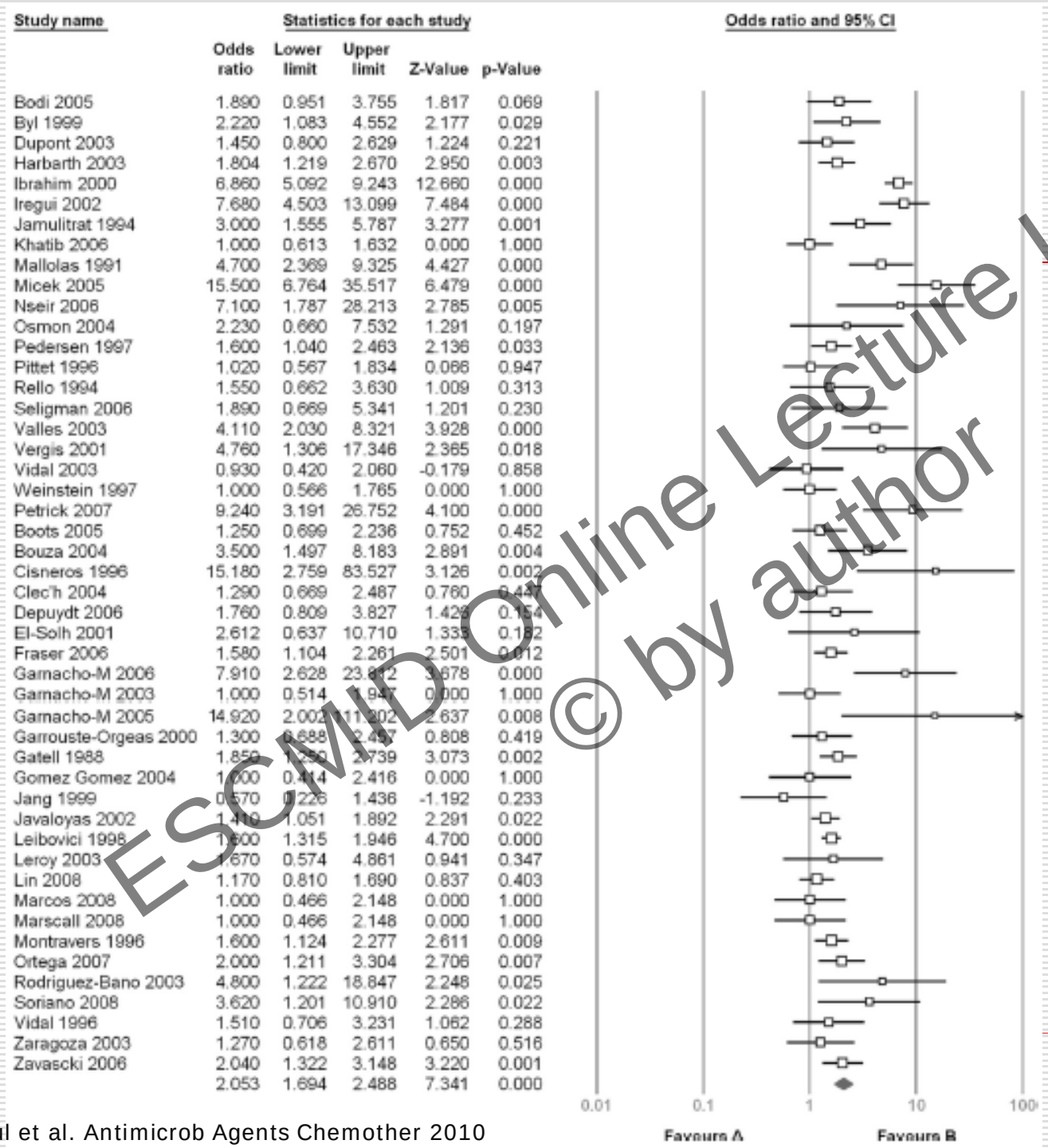
JAMA



Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials

Anglemyer et al. Cochrane Database of Systematic reviews 2014

Association of appropriate empirical antibiotic treatment and all-cause mortality



Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Bodi 2005	1.890	0.951	3.755	1.817	0.069
Byl 1999	2.220	1.083	4.552	2.177	0.029
Dupont 2003	1.450	0.800	2.629	1.224	0.221
Harbarth 2003	1.804	1.219	2.670	2.950	0.003
Ibrahim 2000	6.860	5.092	9.243	12.660	0.000
Iregui 2002	7.680	4.503	13.099	7.484	0.000
Jamulitrat 1994	3.000	1.555	5.787	3.277	0.001
Khatib 2006	1.000	0.613	1.632	0.000	1.000
Mallolas 1991	4.700	2.369	9.325	4.427	0.000
Micek 2005	15.500	6.764	35.517	6.479	0.000
Nseir 2006	7.100	1.787	28.213	2.785	0.005
Osmon 2004	2.230	0.660	7.532	1.291	0.197
Pedersen 1997	1.600	1.040	2.463	2.136	0.033
Pittet 1996	1.020	0.567	1.834	0.066	0.947
Rello 1994	1.550	0.662	3.630	1.009	0.313
Seligman 2006	1.890	0.669	5.341	1.201	0.230
Valles 2003	4.110	2.030	8.321	3.928	0.000
Vergis 2001	4.760	1.306	17.346	2.365	0.018
Vidal 2003	0.930	0.420	2.060	-0.179	0.858
Weinstein 1997	1.000	0.566	1.765	0.000	1.000
Petrick 2007	9.240	3.191	26.752	4.100	0.000
Boots 2005	1.250	0.699	2.236	0.752	0.452
Bouza 2004	3.500	1.497	8.183	2.891	0.004
Cisneros 1996	15.180	2.759	83.527	3.126	0.002
Clec'h 2004	1.290	0.689	2.487	0.760	0.447
Depuydt 2006	1.760	0.809	3.827	1.428	0.153
El-Solh 2001	2.612	0.637	10.710	1.333	0.182
Fraser 2006	1.580	1.104	2.261	2.501	0.012
Garnacho-M 2006	7.910	2.628	23.812	3.678	0.000
Garnacho-M 2003	1.000	0.514	1.947	0.000	1.000
Garnacho-M 2005	14.920	2.002	111.202	2.637	0.008
Garrouste-Orgeas 2000	1.300	0.688	2.457	0.808	0.419
Gatell 1988	1.850	1.250	2.739	3.073	0.002
Gomez Gomez 2004	1.000	0.414	2.416	0.000	1.000
Jang 1999	0.570	0.226	1.436	-1.192	0.233
Javaloyas 2002	1.410	1.051	1.892	2.291	0.022
Leibovici 1998	1.600	1.315	1.946	4.700	0.000
Leroy 2003	1.670	0.574	4.861	0.941	0.347
Lin 2008	1.170	0.810	1.690	0.837	0.403
Marcos 2008	1.000	0.466	2.148	0.000	1.000
Marscall 2008	1.000	0.466	2.148	0.000	1.000
Montravers 1996	1.600	1.124	2.277	2.611	0.009
Ortega 2007	2.000	1.211	3.304	2.706	0.007
Rodriguez-Bano 2003	4.800	1.222	18.847	2.248	0.025
Soriano 2008	3.620	1.201	10.910	2.286	0.022
Vidal 1996	1.510	0.706	3.231	1.062	0.288
Zaragoza 2003	1.270	0.618	2.611	0.650	0.516
Zavascki 2006	2.040	1.322	3.148	3.220	0.001
	2.053	1.694	2.488	7.341	0.000

OR of inappropriate empirical treatment for mortality 2.05 (95% CI 1.69-2.49)

ul et al. Antimicrob Agents Chemother 2010

Systematic review and meta-analysis of observational studies:

- Publication bias
- Bias by indication
- For meta-analysis:
  - Use raw data? (with all the inherent bias?)
  - Use multivariable adjusted ORs? (what about missing information?)
- Patient-data meta-analysis.

Methodological rigor of the original trials (studies?):

- Asses the methodological rigor of the original trials.
- Use each component for sensitivity analysis.

- For observational studies, the Newcastle-Ottawa scale.

Asses the methodological rigor of the original trials:

- Allocation generation (truly randomized)
- Allocation concealment
- Blinding(x1,x2,x3,x4)
- Number of drop-outs and intent to treat analysis

Adequate allocation concealment:

Before enrolling the participant, the researcher had no way of knowing the arm of the treatment the participant would be allocated to:

- Opaque closed envelopes, to be opened after the participant (who fits inclusion criteria) signed the informed consent
- Central randomization (idem)

Questions about dimensions of methodological rigor:

- Do they really matter? Do they matter the same for all outcomes, all interventions?
- Use a scale? (Jadad scale?)
- Does ‘described’ or ‘not described’ = ‘done’ or ‘not done’?

Wood L, Egger M, Gluud LL, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: metaepidemiological study. BMJ 2008;336(7644):601–5.

Sensitivity analysis according to methodological rigor: Quinolone vs beta-lactam for CAP: Shefet D et al. Arch Intern Med 2006;165:1992.

Table 2. Sensitivity Analyses for Individual Methodological Quality Components*

Variable	Adequate	Unclear or Inadequate
Allocation concealment		
Overall mortality		
RR (95% CI)	1.06 (0.66-1.69)	1.18 (0.77-1.80)
No. of studies/patients	6/1390	17/3456
Clinical failure		
RR (95% CI)	0.98 (0.81-1.19)	0.89 (0.77-1.02)
No. of studies/patients	6/1390	18/3292
Bacteriological failure		
RR (95% CI)	0.96 (0.61-1.52)	0.68 (0.53-0.86)
No. of studies/patients	5/469	13/1499
Allocation generation		
Overall mortality		
RR (95% CI)	1.09 (0.69-1.73)	1.16 (0.76-1.77)
No. of studies/patients	9/1753	14/3093
Clinical failure		
RR (95% CI)	0.99 (0.82-1.19)	0.87 (0.77-1.01)
No. of studies/patients	9/1685	15/2997
Bacteriological failure		
RR (95% CI)	0.89 (0.60-1.30)	0.67 (0.52-0.87)
No. of studies/patients	7/602	11/1366

Abbreviations: CI, confidence interval; RR, relative risk.
*Combined effect estimates for each comparison are shown for studies reporting adequate vs unclear or inadequate methodological quality criteria.

Intent to treat analysis

- All patients are counted in the group to which they were randomized.
- Please pay attention that in superiority studies with a high percentage of drop-outs intent to treat analysis is conservative
- …but in equivalence studies per-protocol analysis is more conservative

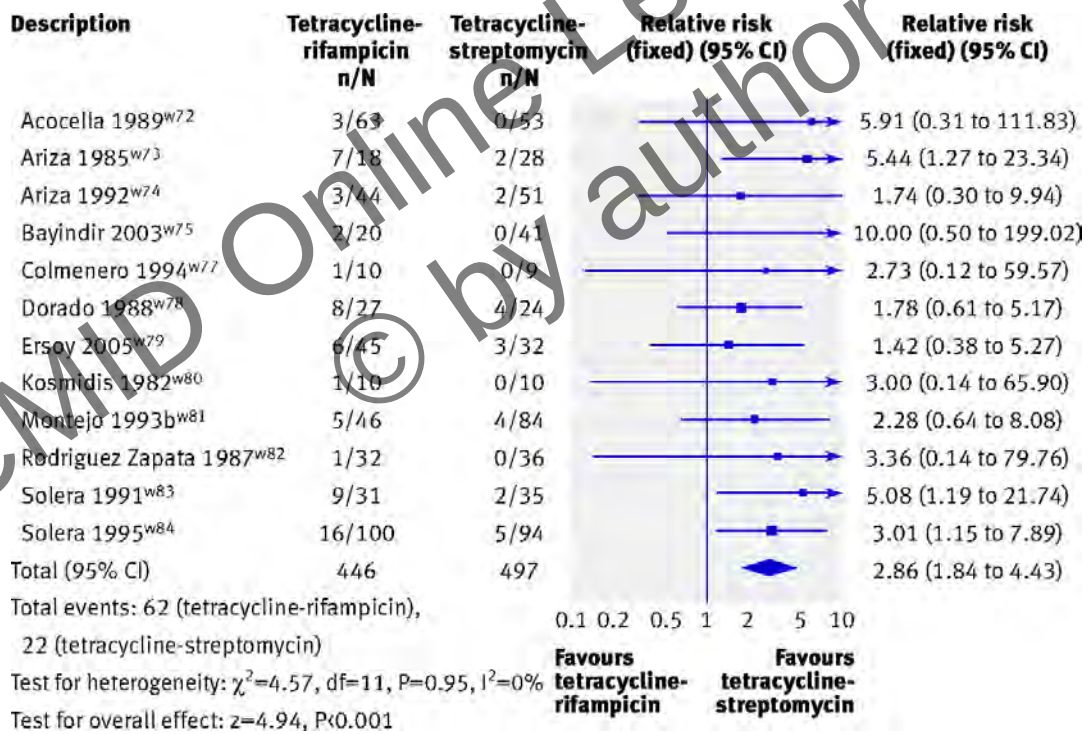
Measuring heterogeneity (i):

- Cochran's Q is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies.
- Q is distributed as a chi-square statistic with k (numer of studies) minus 1 degrees of freedom.
- Q has low power as a comprehensive test of heterogeneity.
- Q has too much power as a test of heterogeneity if the number of studies is large.

Measuring heterogeneity (ii):

- The I^2 statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance.
- $I^2 = 100\% \times (Q\text{-}df)/Q$.
- It does not inherently depend upon the number of studies.

A few examples:
Antibiotic treatment for brucellosis to avoid recurrence:



Description	Tetracycline-rifampicin n/N	Tetracycline-streptomycin n/N	Relative risk (fixed) (95% CI)	Relative risk (fixed) (95% CI)
Acocella 1989[w72]	3/63	0/53		5.91 (0.31 to 111.83)
Ariza 1985[w73]	7/18	2/28		5.44 (1.27 to 23.34)
Ariza 1992[w74]	3/44	2/51		1.74 (0.30 to 9.94)
Bayindir 2003[w75]	2/20	0/41		10.00 (0.50 to 199.02)
Colmenero 1994[w77]	1/10	0/9		2.73 (0.12 to 59.57)
Dorado 1988[w78]	8/27	4/24		1.78 (0.61 to 5.17)
Ersoy 2005[w79]	6/45	3/32		1.42 (0.38 to 5.27)
Kosmidis 1982[w80]	1/10	0/10		3.00 (0.14 to 65.90)
Montejo 1993b[w81]	5/46	4/84		2.28 (0.64 to 8.08)
Rodriguez Zapata 1987[w82]	1/32	0/36		3.36 (0.14 to 79.76)
Solera 1991[w83]	9/31	2/35		5.08 (1.19 to 21.74)
Solera 1995[w84]	16/100	5/94		3.01 (1.15 to 7.89)
Total (95% CI)	446	497		2.86 (1.84 to 4.43)

Total events: 62 (tetracycline-rifampicin), 22 (tetracycline-streptomycin)

Test for heterogeneity: $\chi^2=4.57$, df=11, P=0.95, $I^2=0\%$

Test for overall effect: z=4.94, P<0.001

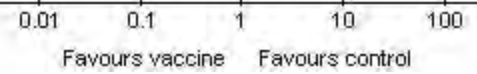
Skalsky, K. et al. BMJ 2008;336:701-704

A few examples:

Influenza vaccine vs placebo for flu-like illness:

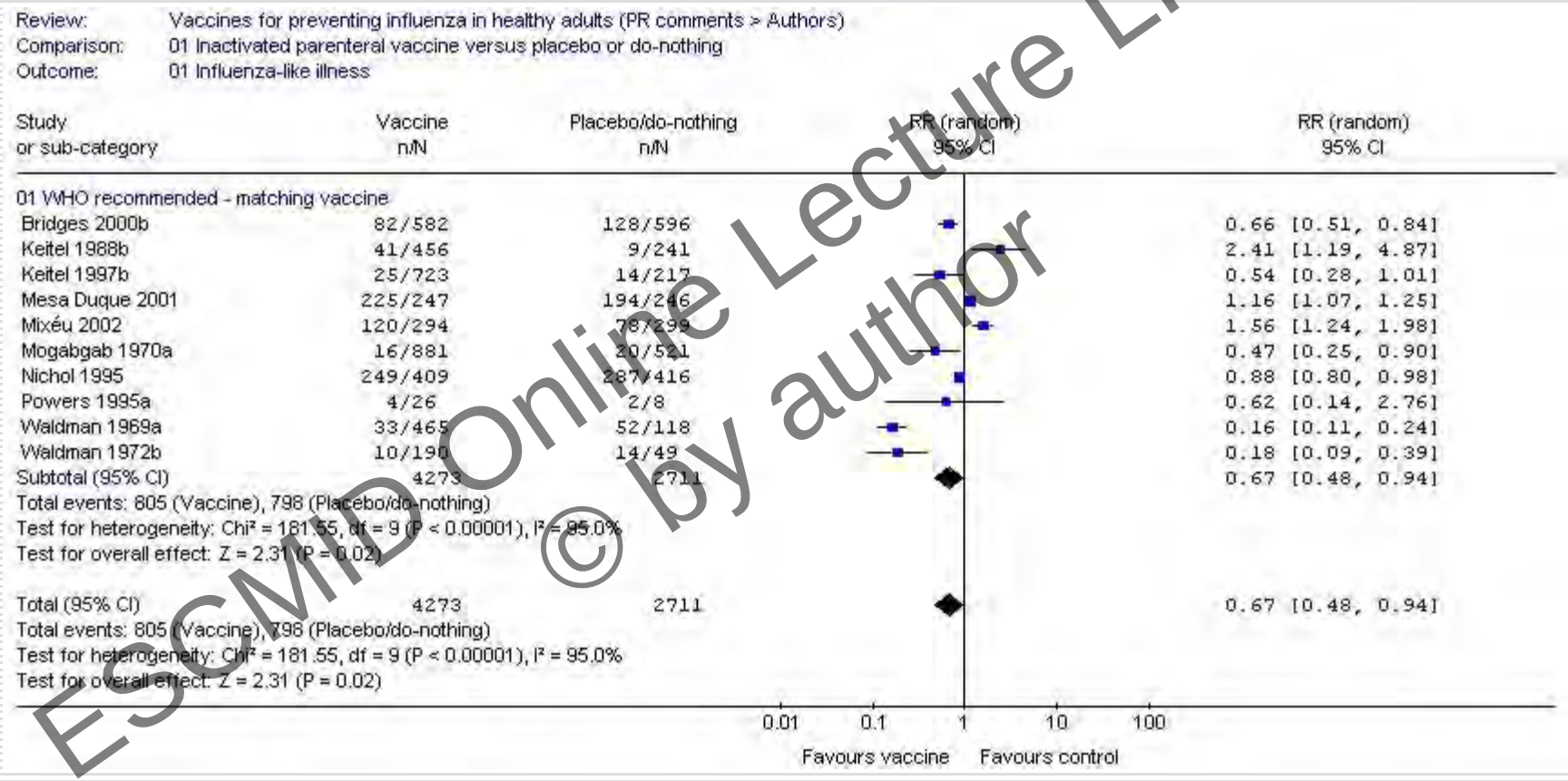
Review: Vaccines for preventing influenza in healthy adults (PR comments > Authors)
Comparison: 01 Inactivated parenteral vaccine versus placebo or do-nothing
Outcome: 01 Influenza-like illness

Study or sub-category	Vaccine n/N	Placebo/do-nothing n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Quality
01 WHO recommended - matching vaccine						
Bridges 2000b	82/582	128/596		14.61	0.66 [0.51, 0.84]	A
Keitel 1988b	13/456	9/241		3.39	0.76 [0.33, 1.76]	B
Keitel 1997b	25/723	14/217		5.25	0.54 [0.28, 1.01]	B
Mesa Duque 2001	194/247	225/246		20.96	0.86 [0.80, 0.93]	A
Mixéu 2002	86/294	98/299		15.07	0.89 [0.70, 1.14]	B
Mogabgab 1970a	16/881	20/521		5.11	0.47 [0.25, 0.90]	B
Nichol 1995	249/409	287/416		20.28	0.88 [0.80, 0.98]	A
Powers 1995a	4/26	2/8		1.18	0.62 [0.14, 2.76]	B
Waldman 1969a	52/465	33/118		10.09	0.40 [0.27, 0.59]	B
Waldman 1972b	14/190	10/49		4.07	0.36 [0.17, 0.76]	A
Subtotal (95% CI)	4273	2711		100.00	0.70 [0.59, 0.83]	
Total events: 735 (Vaccine), 826 (Placebo/do-nothing)						
Test for heterogeneity: Chi² = 33.82, df = 9 (P < 0.0001), I² = 73.4%						
Test for overall effect: Z = 4.17 (P < 0.0001)						
Total (95% CI)	4273	2711		100.00	0.70 [0.59, 0.83]	
Total events: 735 (Vaccine), 826 (Placebo/do-nothing)						
Test for heterogeneity: Chi² = 33.82, df = 9 (P < 0.0001), I² = 73.4%						
Test for overall effect: Z = 4.17 (P < 0.0001)						



A few examples:

Influenza vaccine vs placebo for flu-like illness (simulation):



Exploring heterogeneity: Looking for differences between studies that abolish (within each group) heterogeneity

- Methodological rigor
- Factors pre-defined in the protocol
- Then, factors selected post-hoc
- Fixed effect meta-analysis if heterogeneity non-significant.
- Random effect if significant?

Why do we need them?

Move away from eminence-based medicine:

Encourage (young) clinicians to do patient-oriented research

I have not touched upon:

- Systematic reviews of diagnostics
- Network meta-analysis or indirect comparions.

To do a systematic review and meta-analysis (i):

- Use the Cochrane handbook
- Consider doing a Cochrane review
- Involve person/s versed in the domain (clinician/s) and person/s in methods
- Start with a clinical question:
  - Patients
  - Intervention/s
  - Comparison
  - Outcome
- Main outcome that matters to patients
- Write a protocol

To do a systematic review and meta-analysis (ii):

- Avoid bias in the workings of the systematic review (double extraction of data)
- Deal with heterogeneity
- Deal with possible bias in the original studies

To do a systematic review and meta-analysis (iii):

- Help readers interpreting the data:
  - Describe the patients and interventions in the included trials
  - Translate your results into an absolute measure (e.g., numbers needed to treat)
  - Weigh benefits against harm

But… the oseltamivir story

- First peer reviewed pooled analysis of 10 randomised trials of oseltamivir published in the *Archives of Internal Medicine* by Kaiser and colleagues.
- Cochrane reviewers gained access to unpublished data and included a total of 20 trials.

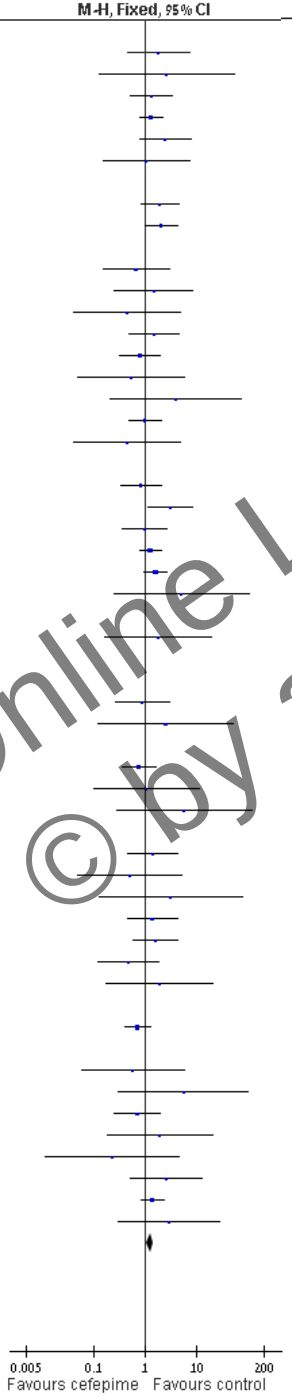
The cefepime story

- We performed a systematic review and meta-analysis of 54 RCTs comparing cefepime to other beta-lactams.
- Mortality was significantly increased in the cefepime arms.
- A company representative wrote to us that there are no more data to share with us.
- The FDA issued a warning and asked for additional data from the company.
- The company unearthed 30 (!) unpublished RCTs. Only 6 pieces of information were given to the FDA for each trial.

Study or Subgroup	Cefepime Events	Cefepime Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Included in systematic review						
Aoun 1997	5	53	3	58	1.0%	1.82 [0.46, 7.26]
Aufiero 1997	2	57	0	29	0.2%	2.59 [0.13, 52.16]
Barckow 1993	13	53	5	27	2.4%	1.32 [0.53, 3.33]
Beaucaire 1999	29	141	21	134	7.7%	1.31 [0.79, 2.18]
Biron 1998	10	202	4	198	1.4%	2.45 [0.78, 7.68]
Bohme 1998	2	49	2	51	0.7%	1.04 [0.15, 7.10]
Bonfitto 1999	0	77	0	71		Not estimable
Bow 2006	15	263	8	265	2.8%	1.89 [0.81, 4.38]
Chandrasekar 2000	22	143	10	133	3.7%	2.05 [1.01, 4.16]
Chang 1998	0	20	0	16		Not estimable
Cherif 2004	3	95	4	85	1.5%	0.67 [0.15, 2.91]
Chuang 2002	3	47	2	46	0.7%	1.47 [0.26, 8.38]
Cordero 2001	1	84	2	76	0.8%	0.45 [0.04, 4.89]
Cordonnier 1997	13	242	4	111	2.0%	1.49 [0.50, 4.47]
Cornely 2001	8	202	10	202	3.6%	0.80 [0.32, 1.99]
Cornely 2002	1	100	2	107	0.7%	0.54 [0.05, 5.81]
Edelstein 1991	3	40	0	22	0.2%	3.93 [0.21, 72.73]
Erman 2001	13	98	13	97	4.7%	0.99 [0.48, 2.02]
Gentry 1991	1	59	2	53	0.8%	0.45 [0.04, 4.81]
Gentry 1992	0	23	0	10		Not estimable
Glauser 1997	8	139	10	142	3.5%	0.82 [0.33, 2.01]
Gomez 2001	13	86	5	100	1.7%	3.02 [1.12, 8.14]
Grossman 1999	7	76	7	75	2.5%	0.99 [0.36, 2.68]
Hoepelman 1993	32	173	26	175	9.2%	1.24 [0.78, 2.00]
Holloway 1996	35	421	22	419	7.9%	1.58 [0.95, 2.65]
Huang 2002	2	26	0	26	0.2%	5.00 [0.25, 99.34]
Huang 2005	0	50	0	50		Not estimable
Jehn 1998	2	58	1	52	0.4%	1.79 [0.17, 19.20]
Jiang 2003	0	30	0	30		Not estimable
Kebudi 2001	0	32	0	31		Not estimable
Leophonte 1993	7	87	4	44	1.9%	0.89 [0.27, 2.86]
Lin 2001	2	41	0	20	0.2%	2.50 [0.13, 49.76]
Mallet 1997	0	31	0	26		Not estimable
McCabe 1996a	17	225	11	111	5.3%	0.76 [0.37, 1.57]
McCabe 1996b	2	64	1	34	0.5%	1.06 [0.10, 11.30]
Mustafa 2001	2	49	0	55	0.2%	5.60 [0.28, 113.87]
Newton 1993	0	159	0	72		Not estimable
Oryan 1996	7	105	5	105	1.8%	1.40 [0.46, 4.27]
Ponce 1999	1	25	2	25	0.7%	0.50 [0.05, 5.17]
Preheim 1995	1	39	0	41	0.2%	3.15 [0.13, 75.08]
Raad 2003	7	127	5	124	1.8%	1.37 [0.45, 4.19]
Ramphal 1997	9	94	6	100	2.1%	1.60 [0.59, 4.31]
Saez-Llorens 1995	3	69	6	66	2.2%	0.48 [0.12, 1.83]
Saito 1992a	2	94	1	89	0.4%	1.89 [0.17, 20.52]
saito 1992b	0	83	0	87		Not estimable
Sanz 2002	19	432	27	435	9.6%	0.71 [0.40, 1.25]
Schaad 1998	0	149	0	150		Not estimable
Schrank 1995	1	13	2	15	0.7%	0.58 [0.06, 5.66]
Schwartz 1996	5	231	0	115	0.2%	5.50 [0.31, 98.61]
Sharifi 1996	8	305	6	161	2.8%	0.70 [0.25, 1.99]
Tamura 2002	2	42	1	41	0.4%	1.95 [0.18, 20.71]
Wang 1999	0	19	2	22	0.8%	0.23 [0.01, 4.51]
Willis 1998	5	54	2	55	0.7%	2.55 [0.52, 12.56]
Zanetti 2003	28	108	19	101	7.0%	1.38 [0.82, 2.31]
Zervos 1998	3	59	1	56	0.4%	2.85 [0.31, 26.57]
Subtotal (95% CI)		5843		5041	100.0%	**1.26 [1.08, 1.46]**
Total events	374		264			

Heterogeneity: Chi² = 31.04, df = 44 (P = 0.93); I² = 0%

Test for overall effect: Z = 3.01 (P = 0.003)



Study or Subgroup	Cefepime Events	Cefepime Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Published in journal, excluded from systematic review						
Al411118 Yamamura 1997	5	59	4	57	14.9%	1.21 [0.34, 4.27]
Al411221 Barie 1997	3	164	11	159	41.0%	0.26 [0.08, 0.93]
Al411245 Badaro 2002	17	159	10	158	36.8%	1.69 [0.80, 3.57]
CPM4495001 Shahid 2008	2	15	2	15	7.3%	1.00 [0.16, 6.20]
Subtotal (95% CI)		397		389	100.0%	0.98 [0.59, 1.64]
Total events	27		27			

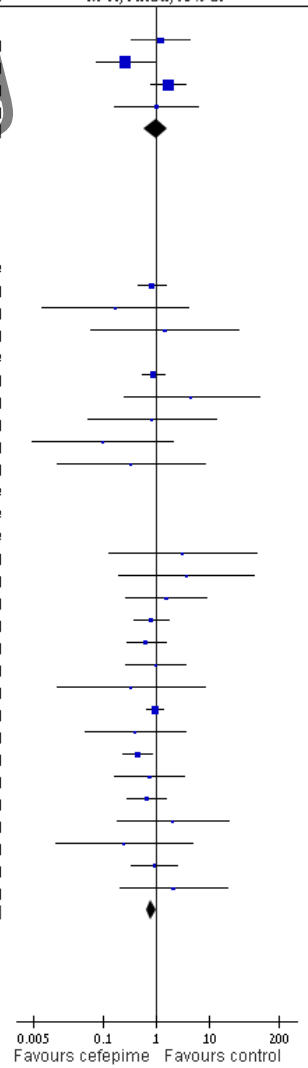
Heterogeneity: Chi² = 6.29, df = 3 (P = 0.10); I² = 52%

Test for overall effect: Z = 0.06 (P = 0.95)

1.5.2 Unpublished supplied by sponsor						
Al411056	0	37	0	37		Not estimable
Al411070	26	387	16	194	10.8%	0.81 [0.45, 1.48]
Al411071	0	32	1	16	1.0%	0.17 [0.01, 3.99]
Al411075	1	104	0	50	0.3%	1.46 [0.06, 35.15]
Al411079	0	20	0	20		Not estimable
Al411097	30	627	34	622	17.3%	0.88 [0.54, 1.41]
Al411113	4	114	0	57	0.3%	4.54 [0.25, 82.88]
Al411119	1	114	1	93	0.6%	0.82 [0.05, 12.87]
Al411120	0	241	2	121	1.7%	0.10 [0.00, 2.08]
Al411137	0	35	1	36	0.8%	0.34 [0.01, 8.14]
Al411149	0	50	0	24		Not estimable
Al411154	0	16	0	16		Not estimable
Al411157	0	22	0	12		Not estimable
Al411169	1	119	0	123	0.2%	3.10 [0.13, 75.35]
Al411179	3	34	0	17	0.3%	3.60 [0.20, 65.96]
Al411184	3	35	2	36	1.0%	1.54 [0.27, 8.68]
Al411196	10	59	13	61	6.5%	0.80 [0.38, 1.67]
Al411205	8	85	12	82	6.2%	0.64 [0.28, 1.49]
Al411206	4	32	4	31	2.1%	0.97 [0.27, 3.54]
Al411218	0	181	1	181	0.8%	0.33 [0.01, 8.13]
Al411219	41	181	44	185	22.1%	0.95 [0.66, 1.38]
Al411222	1	16	3	19	1.4%	0.40 [0.05, 3.44]
Al411228	12	82	25	76	13.2%	0.44 [0.24, 0.82]
Al411230	3	307	4	308	2.0%	0.75 [0.17, 3.33]
Al411242	8	76	11	68	5.9%	0.65 [0.28, 1.52]
Al411247	2	218	1	225	0.5%	2.06 [0.19, 22.60]
CPM0896003	0	14	2	18	1.1%	0.25 [0.01, 4.89]
CPM4497002	6	29	7	31	3.4%	0.92 [0.35, 2.41]
CPM6796007	2	22	1	23	0.5%	2.09 [0.20, 21.45]
Subtotal (95% CI)		3289		2782	100.0%	**0.80 [0.66, 0.97]**
Total events	166		185			

Heterogeneity: Chi² = 14.45, df = 23 (P = 0.91); I² = 0%

Test for overall effect: Z = 2.22 (P = 0.03)



To do a systematic review and meta-analysis (iv):

- Are all the trials available?

Thank you