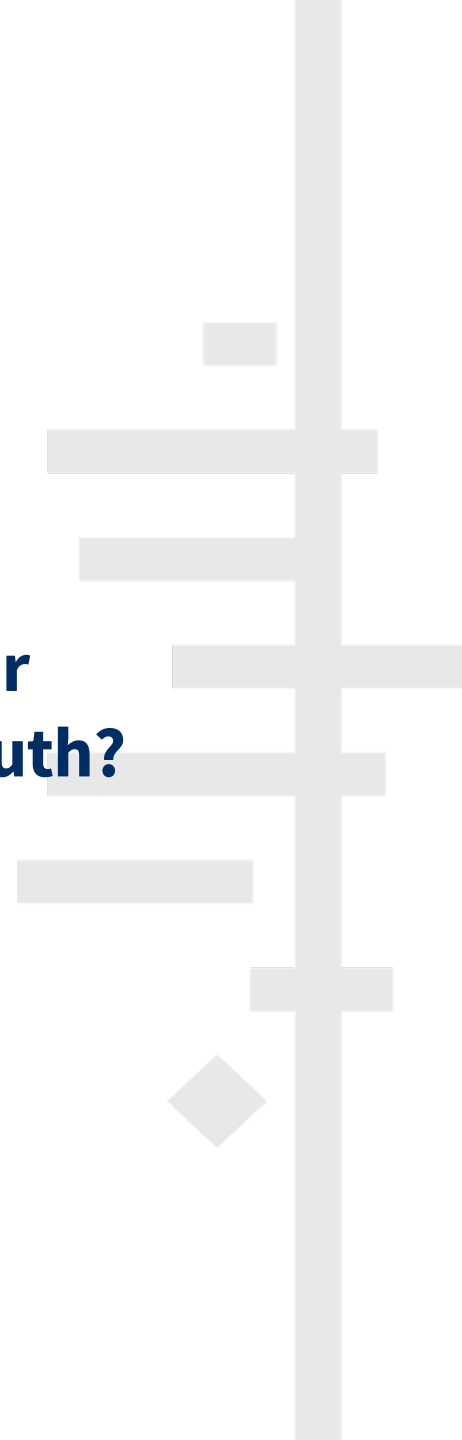# Overview

- Recap of imprecision

- What's changed?

- Application of new guidance

Imprecision

Would your clinical action change if either the upper or lower boundary of the 95% confidence interval represented the truth?
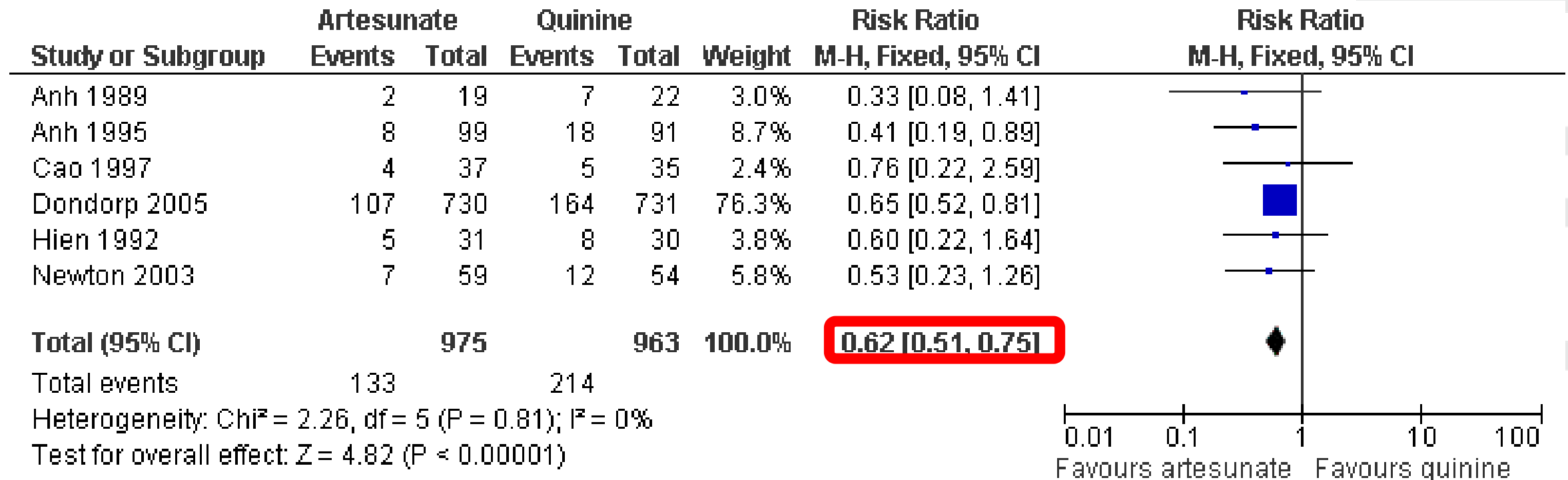
Things to consider

- Width of 95% confidence intervals

- Clinically important differences
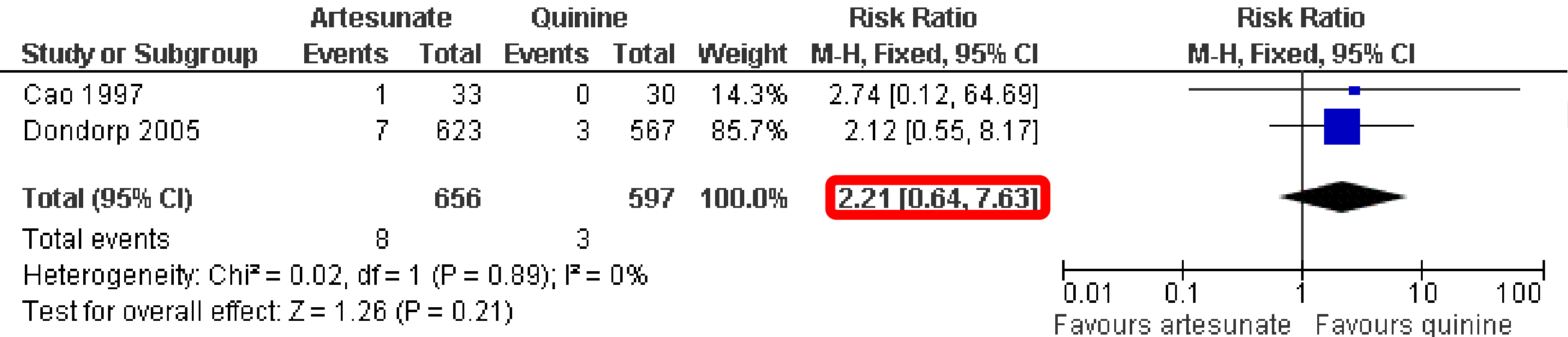
- Optimal information size

- Anticipated absolute effects

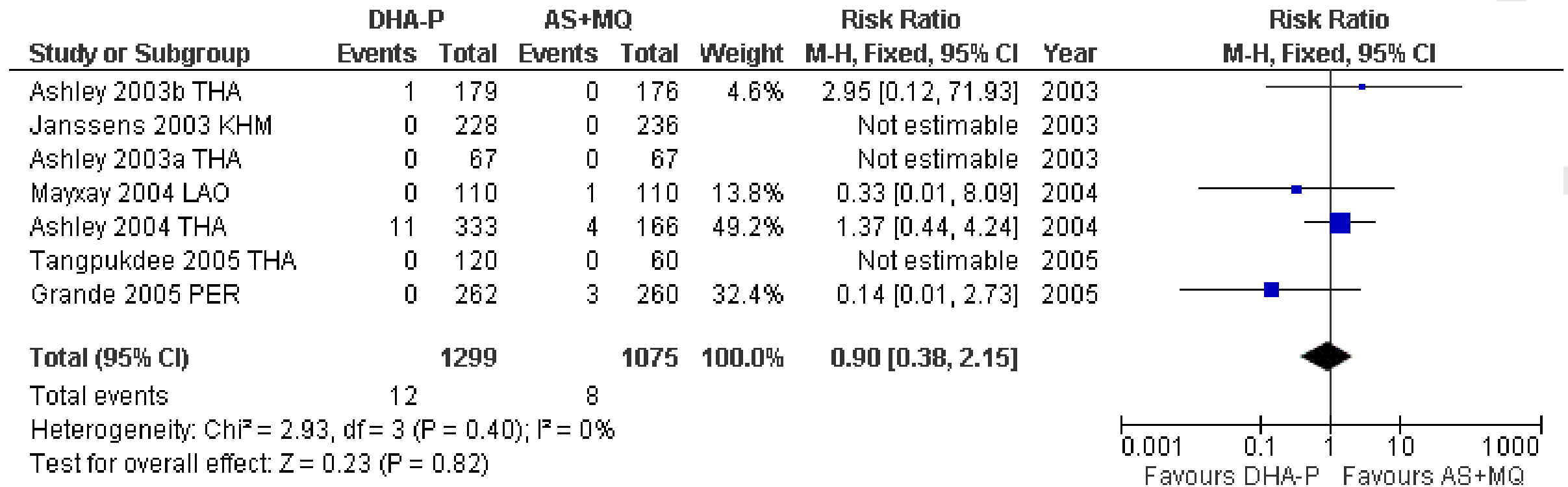# Artesunate vs quinine in severe malaria

Outcome: Death

Study or Subgroup	Artesunate Events	Total	Quinine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Anh 1989	2	19	7	22	3.0%	0.33 [0.08, 1.41]	
Anh 1995	8	99	18	91	8.7%	0.41 [0.19, 0.89]	
Cao 1997	4	37	5	35	2.4%	0.76 [0.22, 2.59]	
Dondorp 2005	107	730	164	731	76.3%	0.65 [0.52, 0.81]	
Hien 1992	5	31	8	30	3.8%	0.60 [0.22, 1.64]	
Newton 2003	7	59	12	54	5.8%	0.53 [0.23, 1.26]	
Total (95% CI)		975		963	100.0%	0.62 [0.51, 0.75]	
Total events	133		214				

Heterogeneity: Chi² = 2.26, df = 5 (P = 0.81); I² = 0%
Test for overall effect: Z = 4.82 (P < 0.00001)

0.01 0.1 1 10 100
Favours artesunate Favours quinine

Artesunate vs quinine in severe malaria

Outcome: Neurological disability at discharge

Study or Subgroup	Artesunate Events	Total	Quinine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Cao 1997	1	33	0	30	14.3%	2.74 [0.12, 64.69]	
Dondorp 2005	7	623	3	567	85.7%	2.12 [0.55, 8.17]	
Total (95% CI)		656		597	100.0%	2.21 [0.64, 7.63]	
Total events	8		3				

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 1.26 (P = 0.21)

Favours artesunate   Favours quinine

DHA-P vs AS+MQ in uncomplicated malaria

Outcome: Serious adverse events

Study or Subgroup	DHA-P Events	DHA-P Total	AS+MQ Events	AS+MQ Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Ashley 2003b THA	1	179	0	176	4.6%	2.95 [0.12, 71.93]	2003
Janssens 2003 KHM	0	228	0	236		Not estimable	2003
Ashley 2003a THA	0	67	0	67		Not estimable	2003
Mayxay 2004 LAO	0	110	1	110	13.8%	0.33 [0.01, 8.09]	2004
Ashley 2004 THA	11	333	4	166	49.2%	1.37 [0.44, 4.24]	2004
Tangpukdee 2005 THA	0	120	0	60		Not estimable	2005
Grande 2005 PER	0	262	3	260	32.4%	0.14 [0.01, 2.73]	2005
Total (95% CI)		1299		1075	100.0%	0.90 [0.38, 2.15]	
Total events	12		8				

Heterogeneity: Chi² = 2.93, df = 3 (P = 0.40); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)

GRADE GUIDANCE SERIES

GRADE Guidance 34: update on rating imprecision using a minimally contextualized approach

Linan Zeng[a,b,*], Romina Brignardello-Petersen[b], Monica Hultcrantz[c], Reem A. Mustafa[d], Mohammad H. Murad[e], Alfonso Iorio[b,f], Gregory Traversy[g], Elie A. Akl[h], Martin Mayer[i,j,k], Holger J. Schünemann[b,f], Gordon H. Guyatt[b,f]

[a]Pharmacy Department/Evidence-based Pharmacy Centre, West China Second University Hospital, Sichuan University and Key Laboratory of Birth Defects and Related Disease of Women and Children, Ministry of Education, No. 20, Section 3, South Renmin Road, Chengdu 610041, China
[b]Department of Health Research Methods, Evidence and Impact, McMaster University, 1280 Main Street West, Hamilton, L8S 4L8 Ontario, Canada
[c]Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU), S:t Eriksgatan 117, Stockholm 102 33, Sweden
[d]Division of Nephrology and Hypertension, Department of Internal Medicine, University of Kansas Medical Centre, 3901 Rainbow Blvd, MS3002, Kansas City, KS 61160, USA
[e]Evidence-based Practice Center, Mayo Clinic, 200 1st ST. SW, Rochester, MN 55905, USA
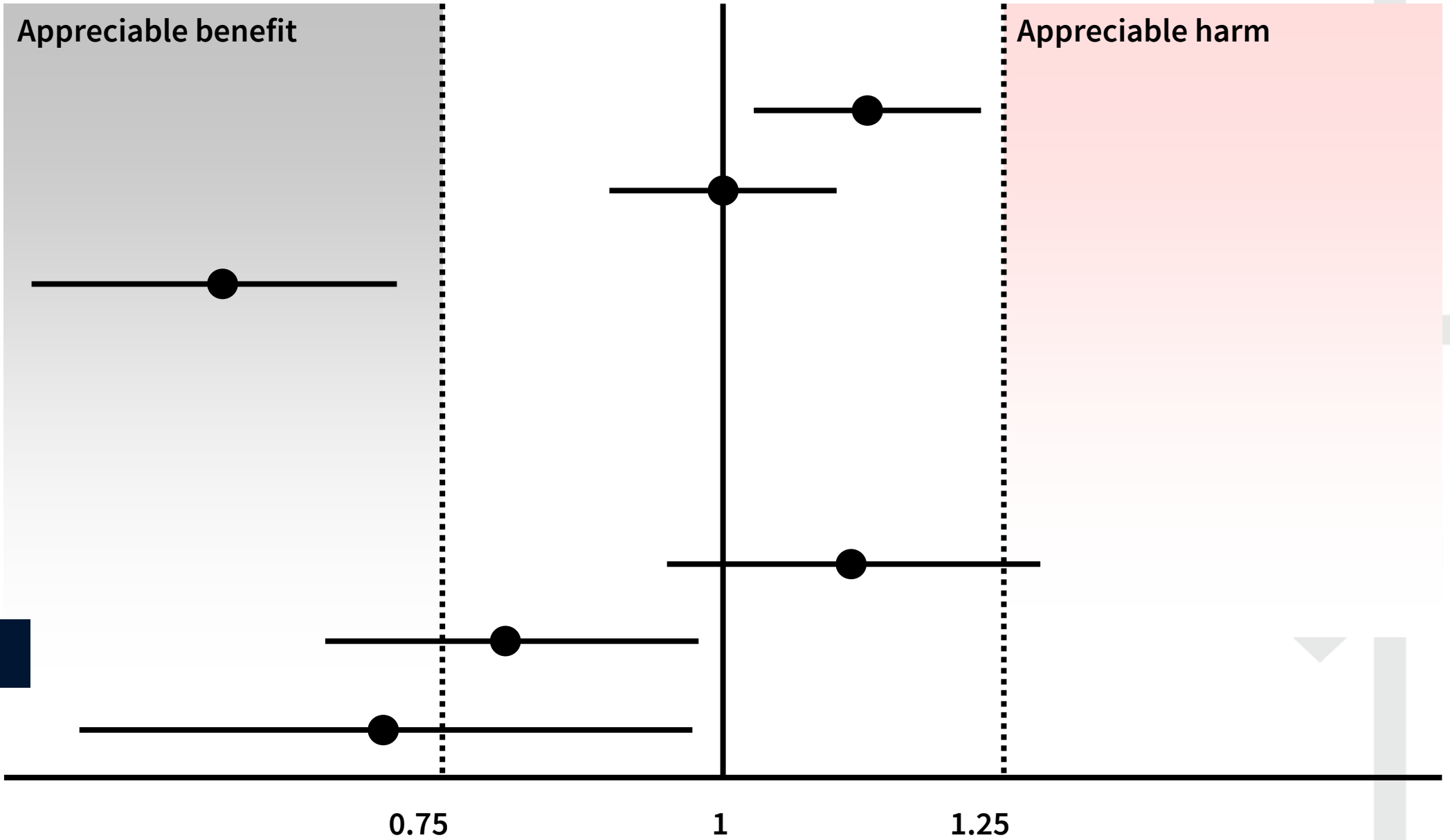[f]Department of Medicine, McMaster University, 1280 Main Street West, Hamilton, L8S 4L8 Ontario, Canada
[g]Public Health Agency of Canada, 785 Carling Avenue, Ottawa, K1A 0K9 Ontario, Canada

Things to consider

- Width of 95% confidence intervals
- **Clinically important differences**
- Optimal information size
- **Anticipated absolute effects**
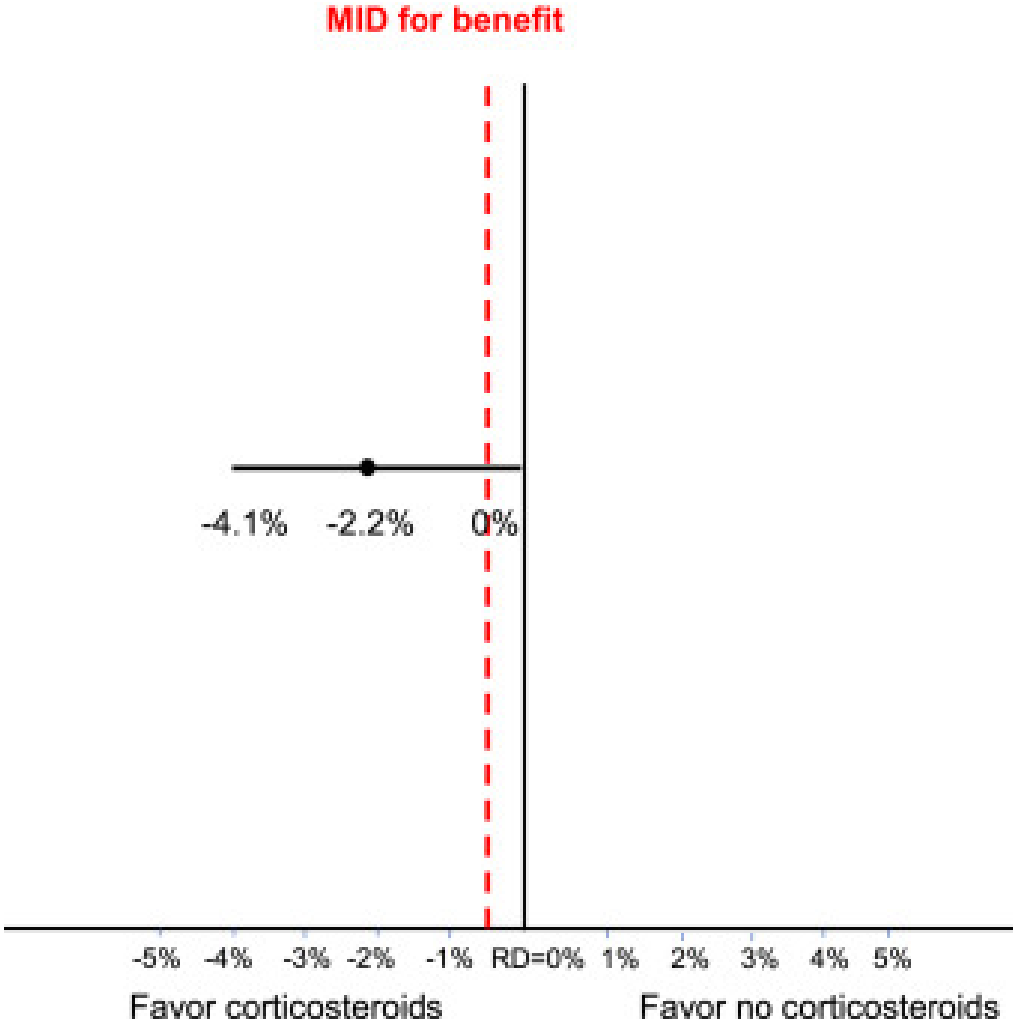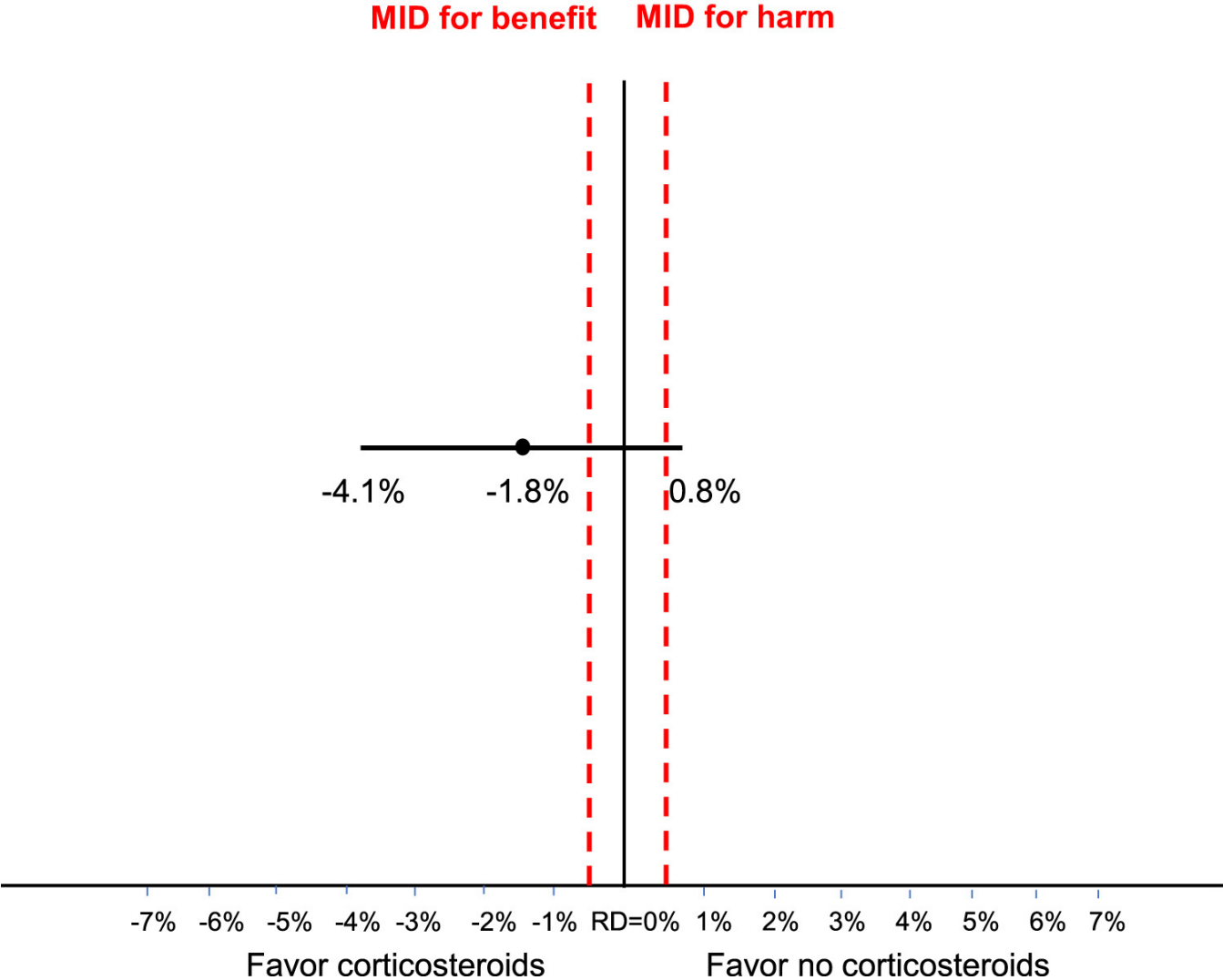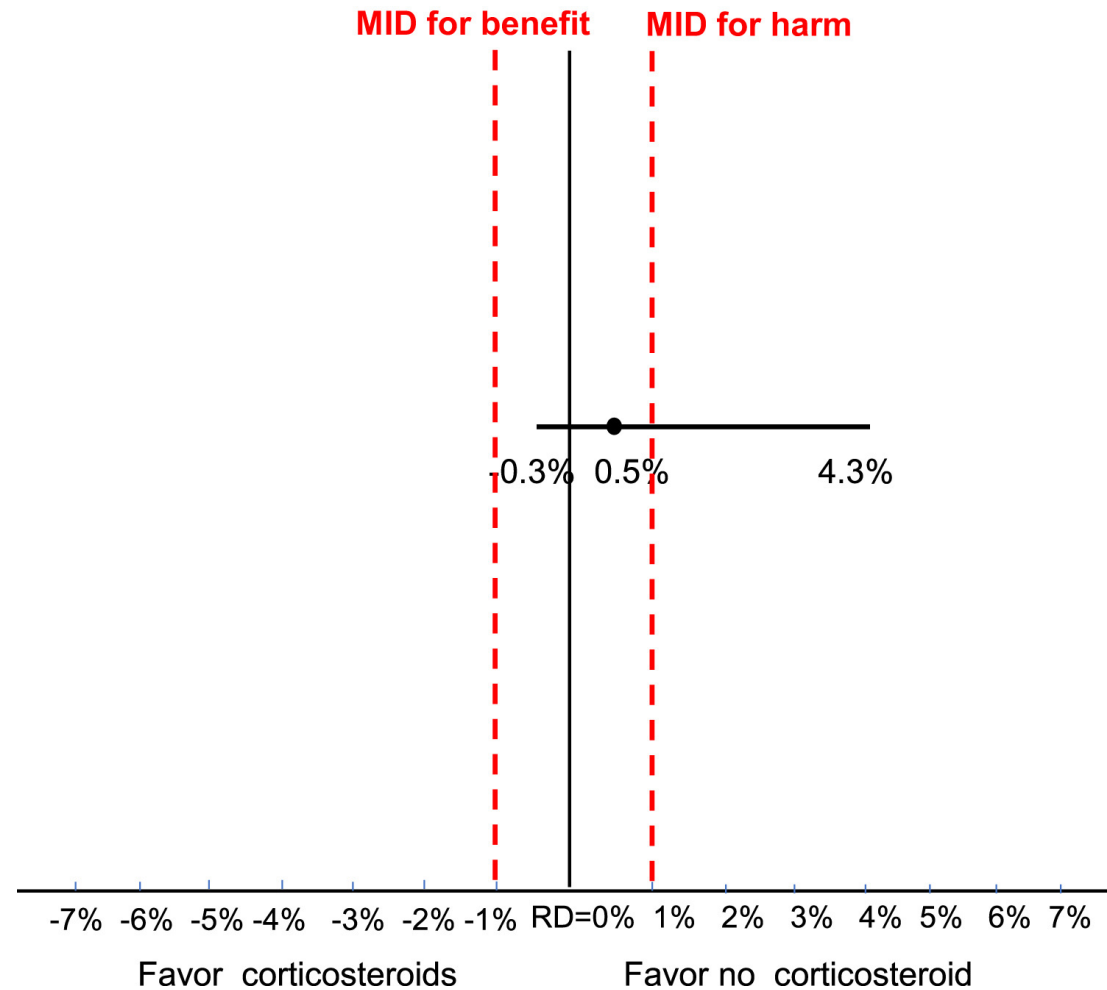- **Also can downgrade by 3!**

Corticosteroids vs. no corticosteroids for patients with sepsis

Outcome: Death

Corticosteroids vs. no corticosteroids for patients with sepsis

Outcome: Death

Corticosteroids vs. no corticosteroids for patients with sepsis

Outcome: No. of strokes

OIS

- When the confidence interval does not cross threshold(s) of interest and the relative effect is large

- Always downgrade by 2 if…

  - For dichotomous outcomes, when the ratio of the upper to the lower boundary of the CI is more than 2.5 for odds ratio or three for risk ratio

  - For continuous outcomes, when the total sample size of a meta-analysis is smaller than 30–50% of the OIS

Cochrane GRADE Levels of Certainty

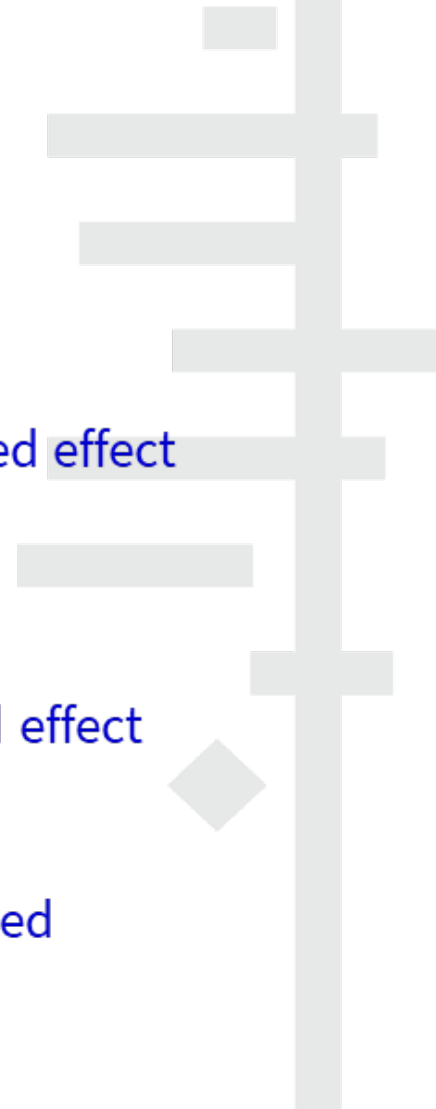| Level	What it means
⊕⊕⊕⊕ HIGH	We have a lot of confidence that the true effect is similar to the estimated effect
⊕⊕⊕⊖ MODERATE	We believe that the true effect is probably close to the estimated effect
⊕⊕⊖⊖ LOW	The true effect might be markedly different from the estimated effect
⊕⊖⊖⊖ VERY LOW	The true effect is probably markedly different from the estimated effect

Cochrane

Levels of Certainty: Plain language

Level	What it means *Compared to quinine…*
⊕⊕⊕⊕ HIGH	Artesunate reduces mortality
⊕⊕⊕⊖ MODERATE	Artesunate probably reduces mortality
⊕⊕⊖⊖ LOW	Artesunate may reduce mortality
⊕⊖⊖⊖ VERY LOW	We *don't know* if artesunate reduces mortality

Impact

- More downgrades by 2 for imprecision

- Flexibility to downgrade by 3 leading to 'We don't know…'

Summary

- Imprecision grading using a minimally contextualized approach

- Focus on anticipated absolute effects rather than relative effects

- OIS should only be considered when relative effects are large and CIs don't cross thresholds of interest

- Can downgrade by 3 for imprecision