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Quantifying common adverse effects of a drug used *for any indication* from RCTs: the example of amoxicillin

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why we did the review

- antibiotic resistance crisis
- primary care focus
- need to reduce antibiotics for common ARIs
apart from resistance, antibiotic...
 - ...minimal benefit
 - ...have common harms
-- but poorly quantified

amoxicillin +/- clavulinate

antibiotic resistance

- tonnage antibiotics → $\frac{3}{4}$ in primary care
- opportunity for *shared decision making*
- need common harms data



how AEs are usually measured

- secondary outcomes of RCTs

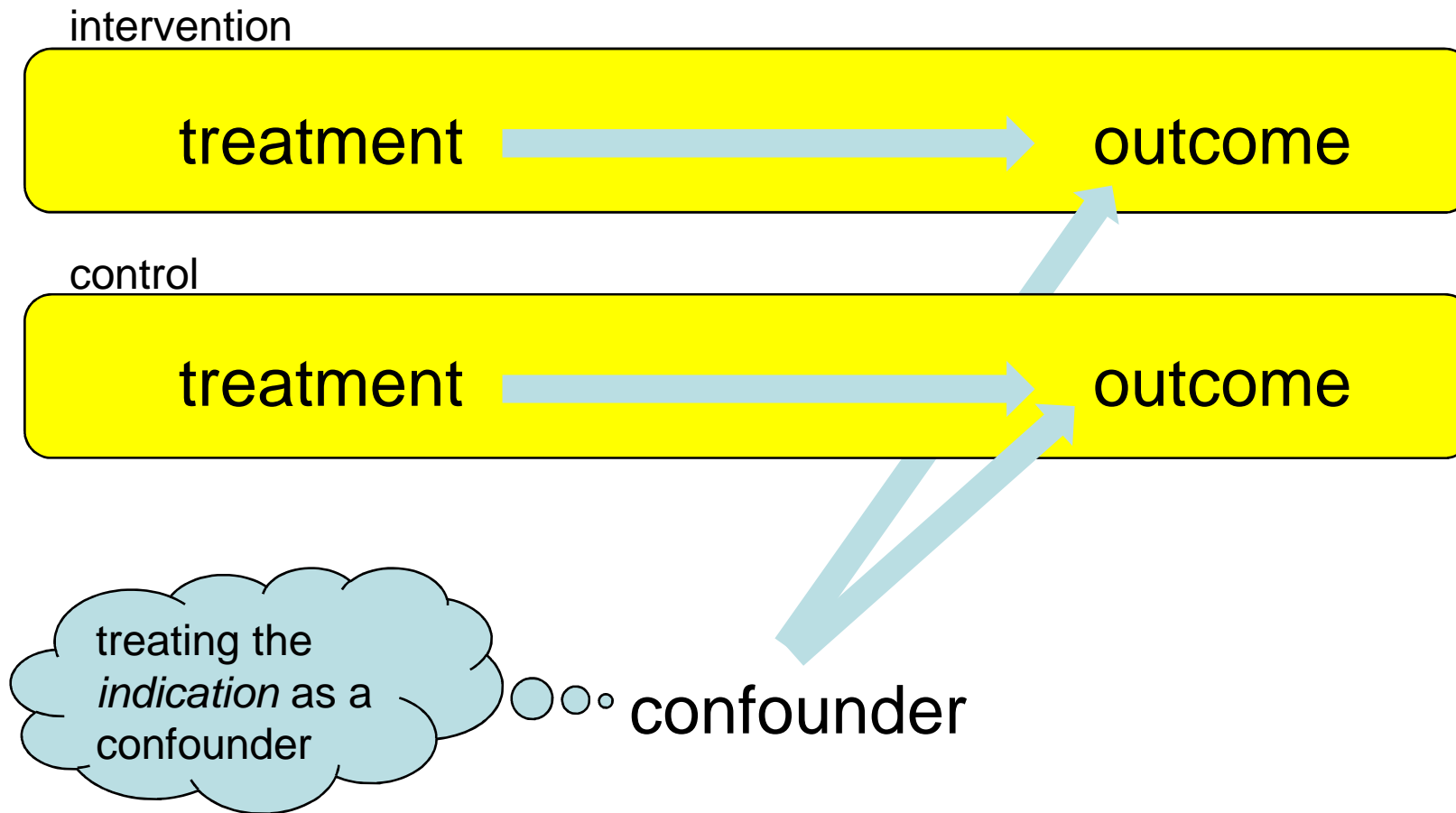
BUT rarer events,
so underpowered

- observational studies
 - post-marketing surveillance
 - national AEs voluntary reporting
 - other observational studies

BUT
confounders...

dealing with confounding

randomisation



what we did

PICO

P – *any* patients for *any* indication

I – amoxicillin / co-amoxiclav

C – placebo

O – *any* adverse events (AEs)



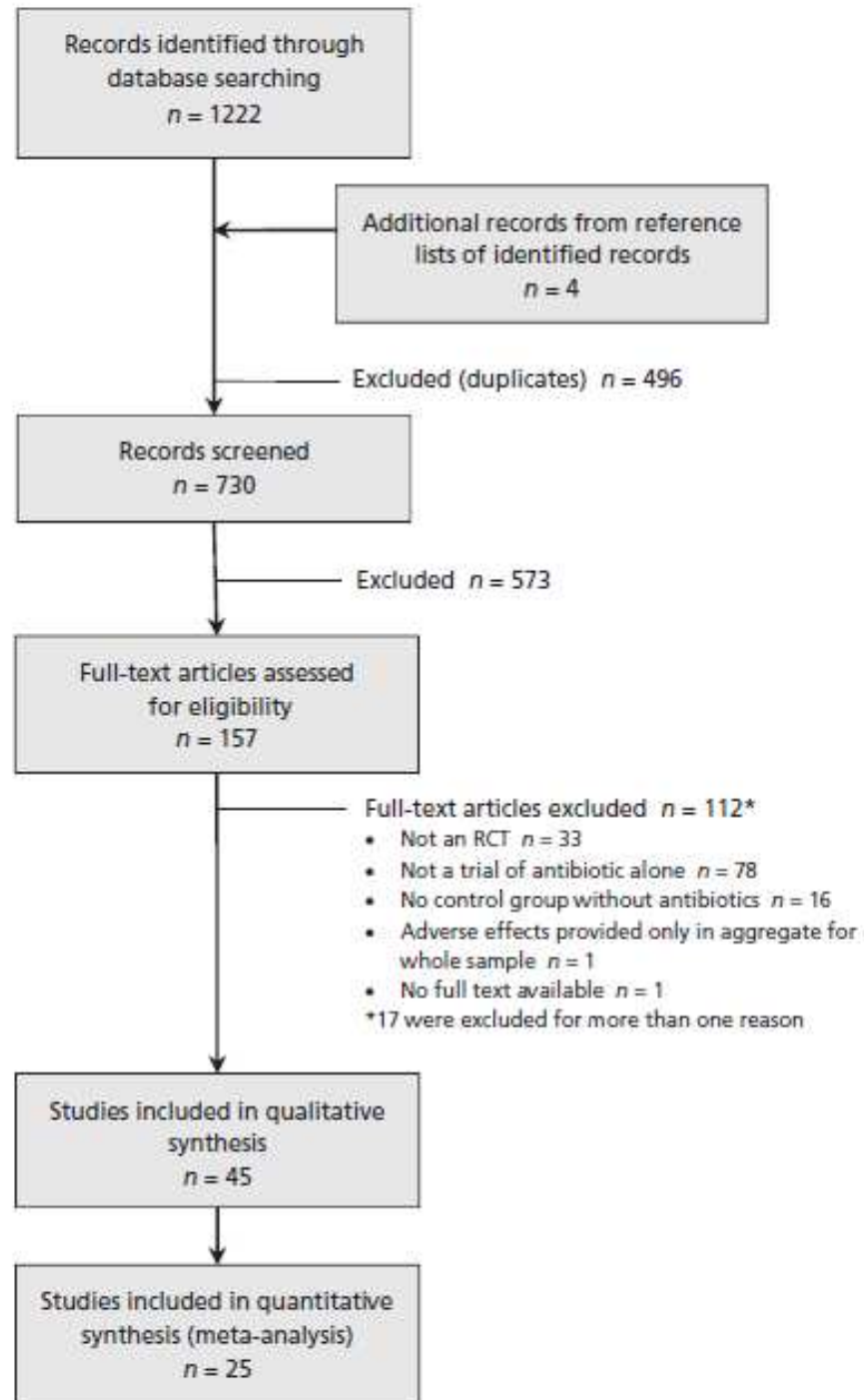
what we did

search

- RCT for *any* indication
- MEDLINE; Embase; Cochrane CENTRAL
- placebo



search



- we discarded all but 45 (27 of amoxicillin and 17 co-amoxiclav)
- 1 trial had both in a 3-arm trial



what we found

risk of bias... low

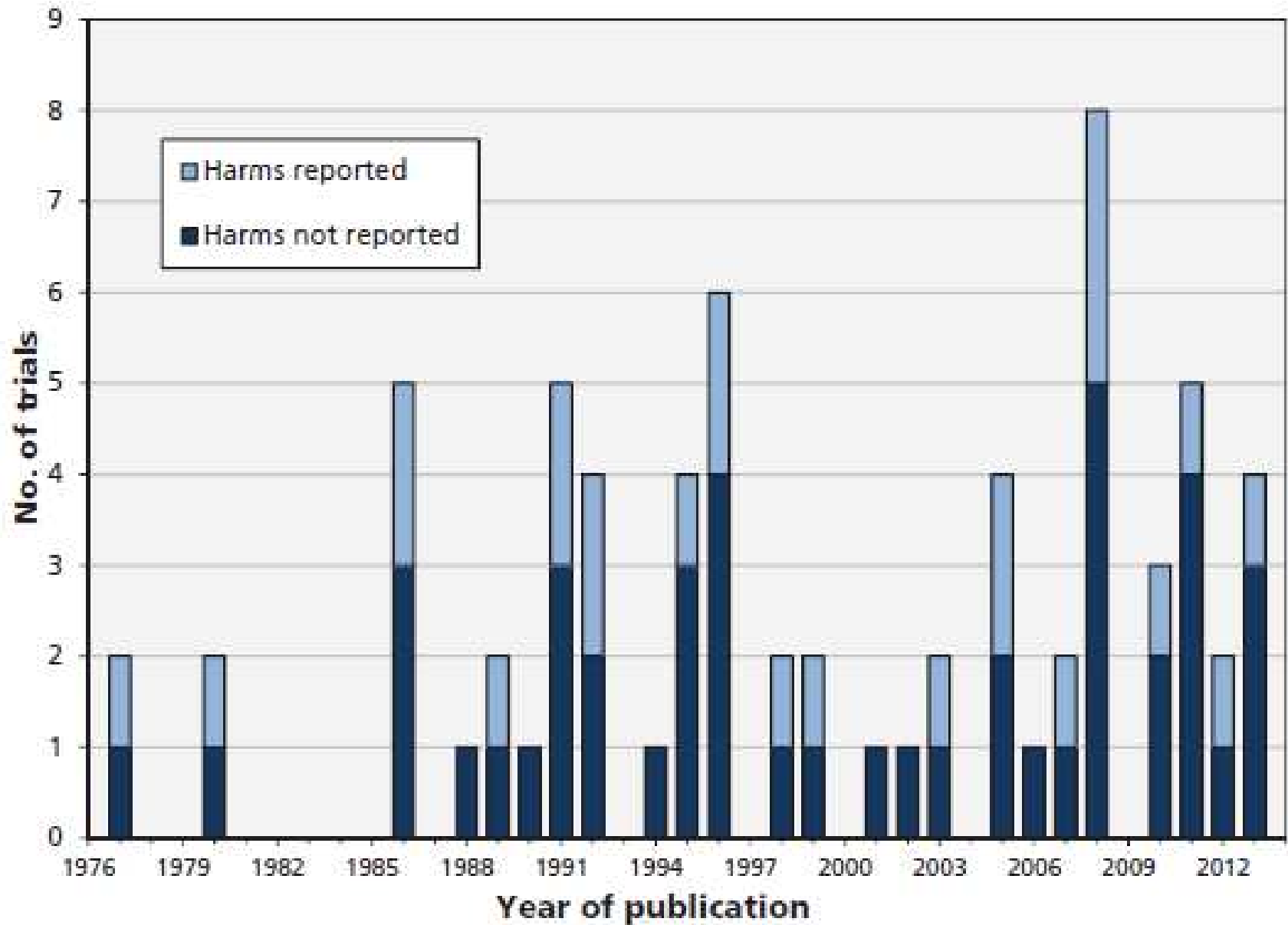
...but

only 25/45 trials → harms data

?under-reporting

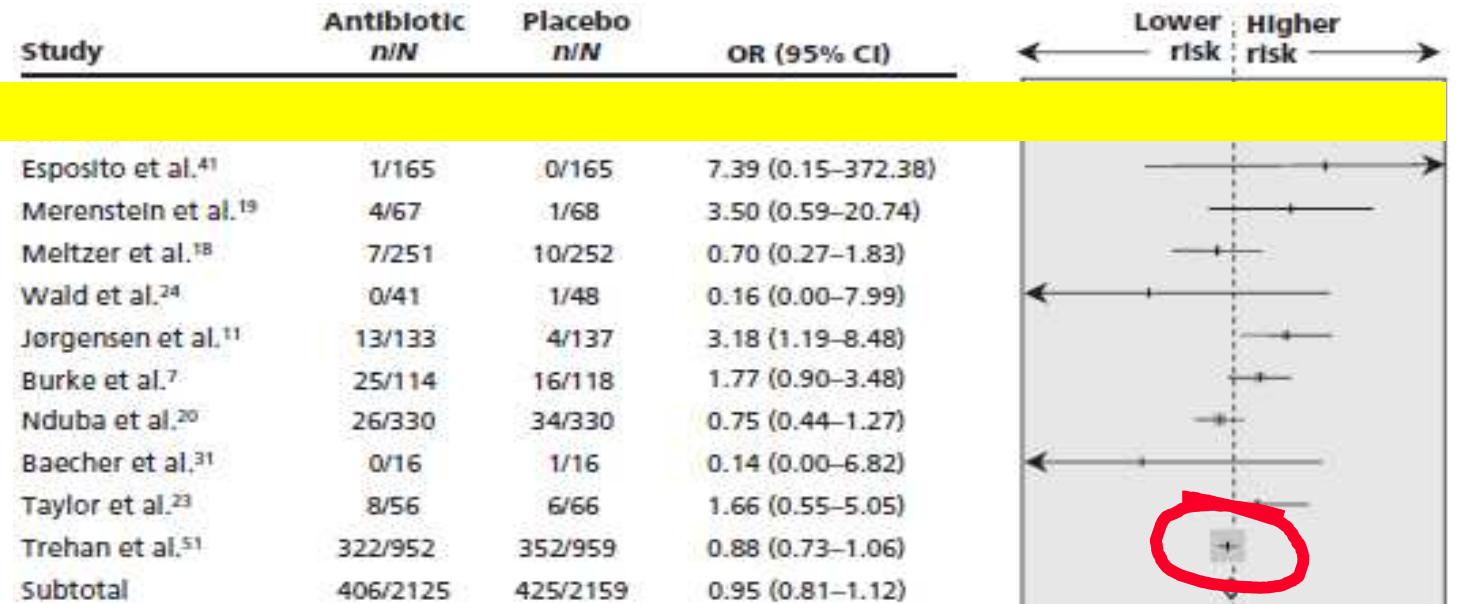


was reporting better with time?

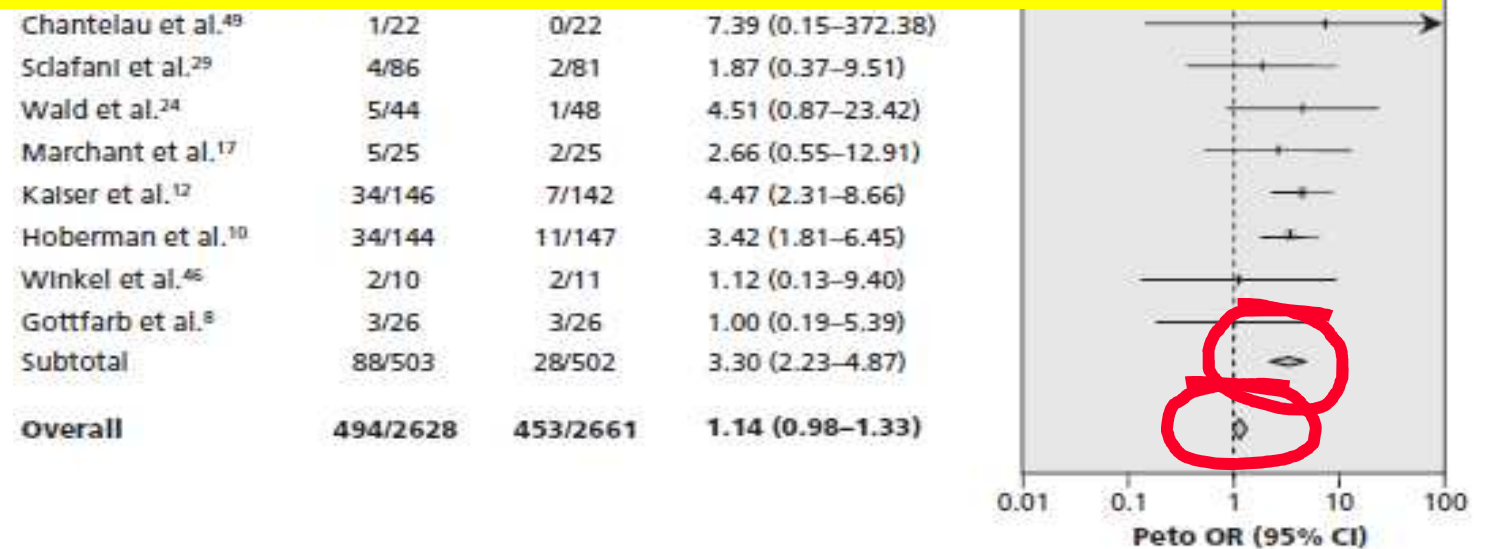


AE = diarrhoea

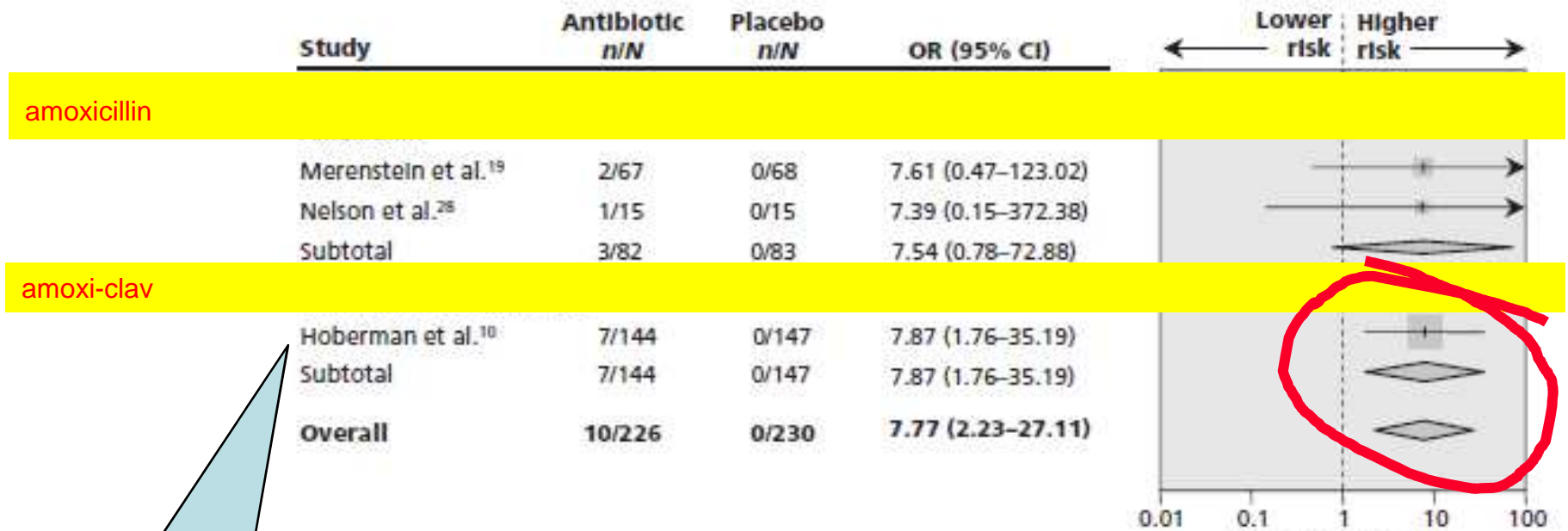
amoxicillin



amoxi-clav



AE = thrush



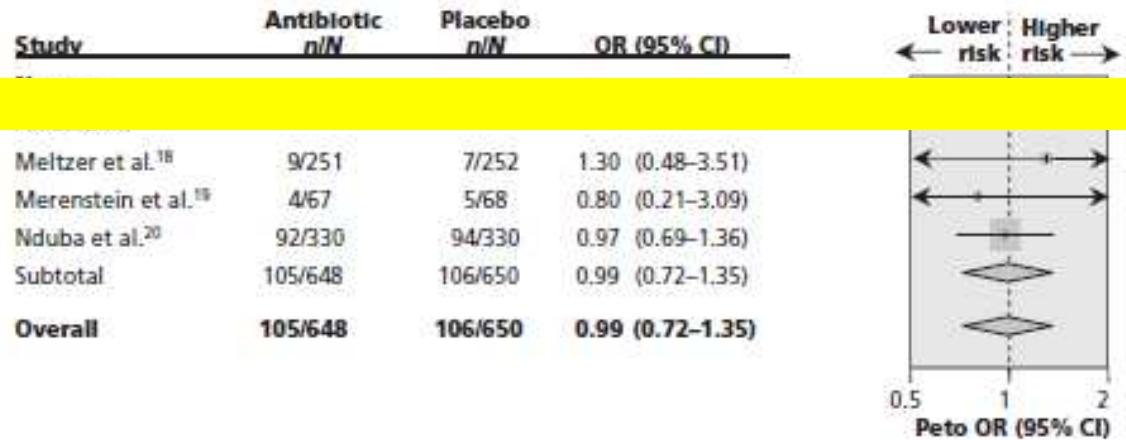
“...diaper-area dermatitis...”



AE = nausea; vomiting

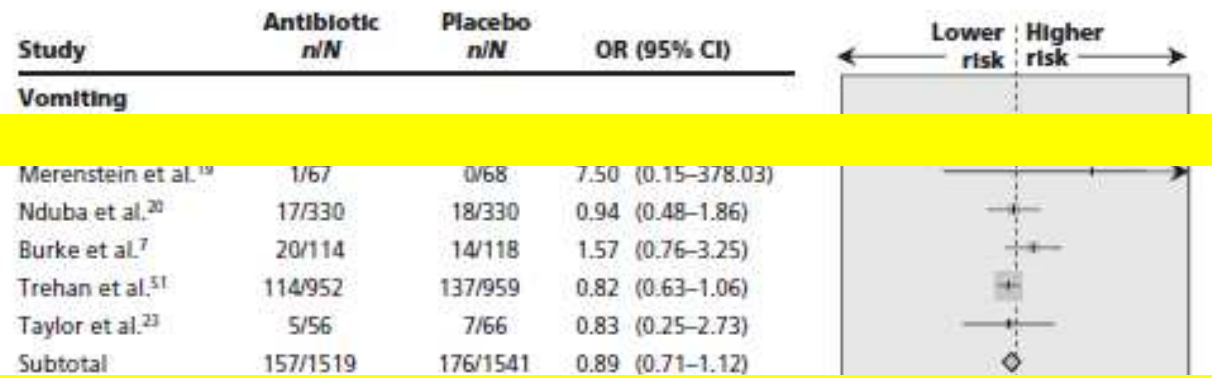
nausea

amoxicillin



vomiting

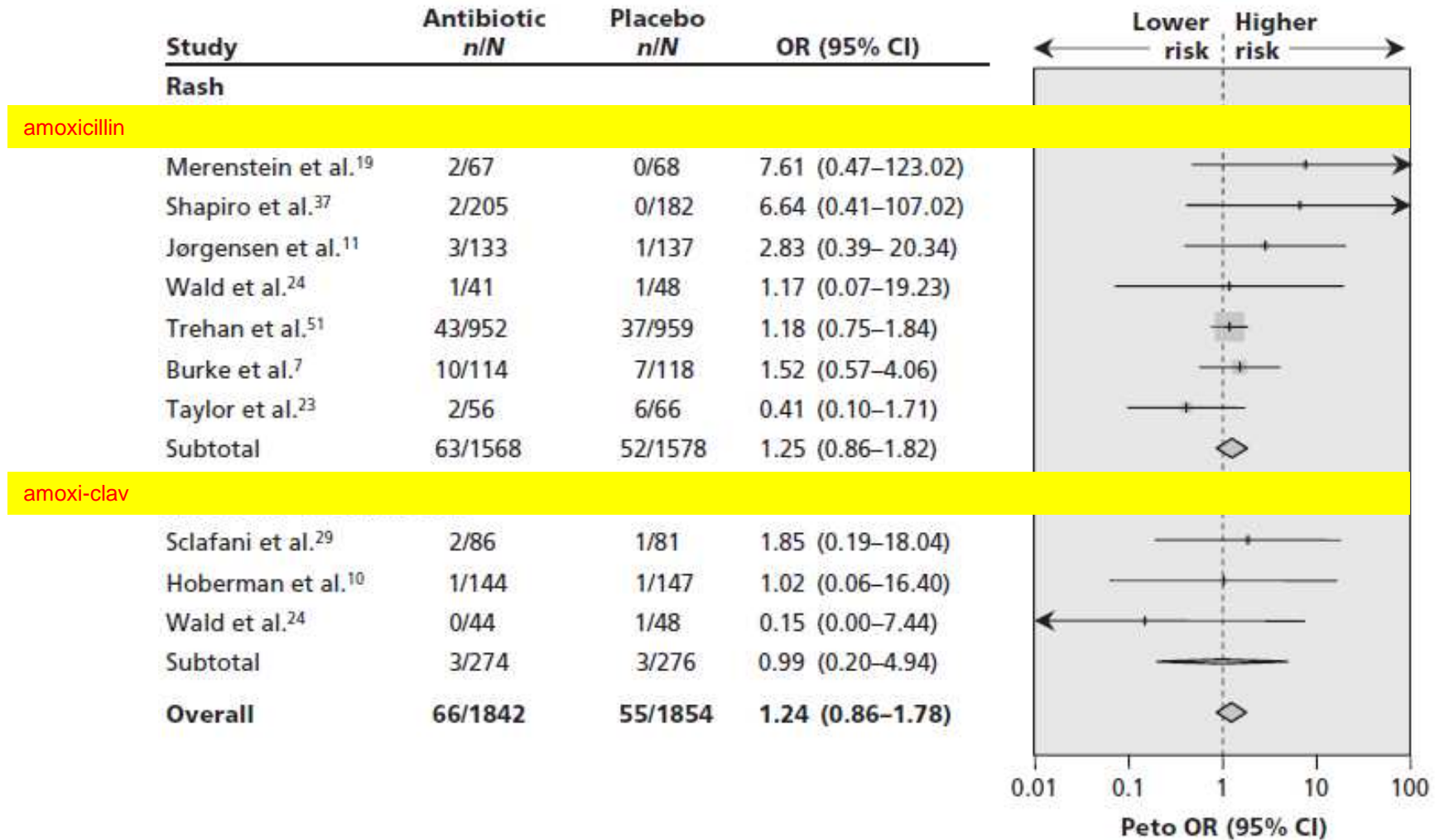
amoxicillin



amoxi-clav



AE = rash



conclusions 1

search

- RCTs poorly report AEs
- evidence of common AEs for amoxicillin (+/- clavulanate)
 - co-amoxiclav → diarrhoea ~ NNT = 10, [95%CI 6-17]
 - Amoxicillin + co-amoxiclav → candida NNT = 27 [95%CI 24-42]
- if poor reporting, then gross under-estimate

Gillies M, Ranakusuma A, Hoffmann T, Thorning S, McGuire T, Glasziou P, Del Mar C. Common harms from amoxicillin: a systematic review and meta-analysis of randomized placebo-controlled trials for any indication. Can Med Assoc J. 2014



conclusions 2

search

- this method of quantifying AEs depends on proper reporting in RCTs
- AEs reporting in RCTs must be improved
- data used in Decision Aids
- we are currently reviewing a new set of antibiotics (macrolides and cephalosporins)

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