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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

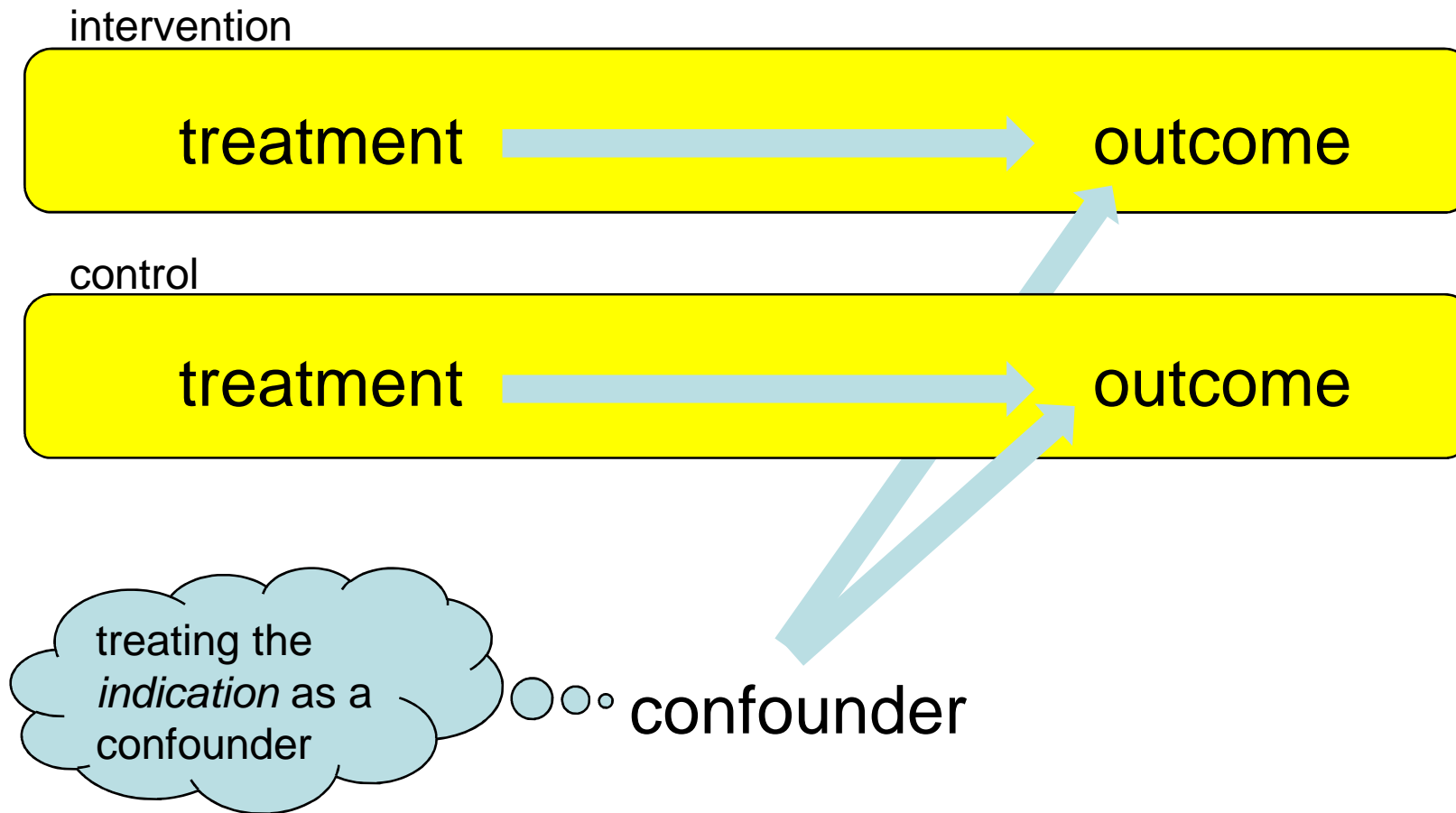
**BUT** rarer events,  
so underpowered

- 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)





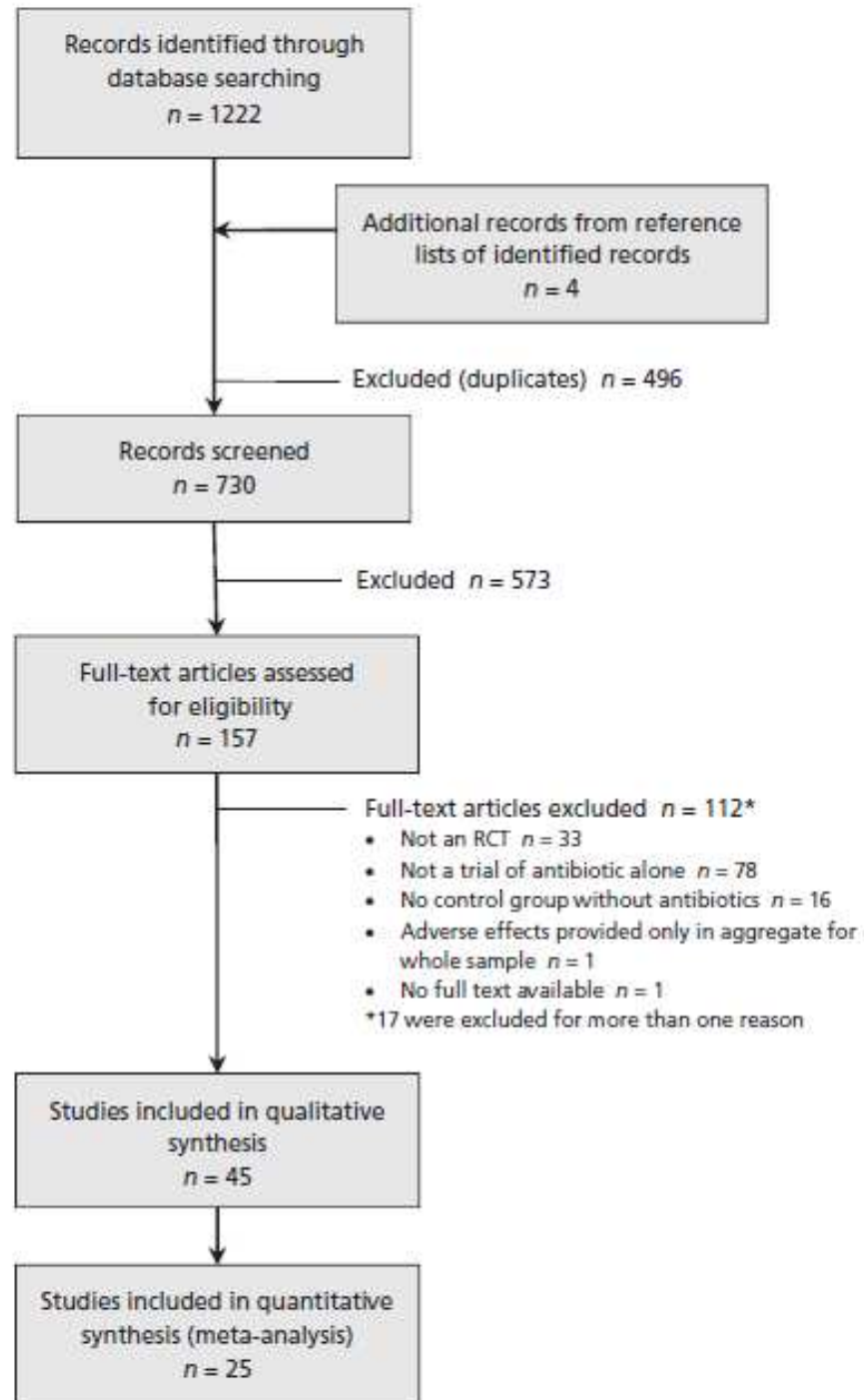
## what we did

### 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

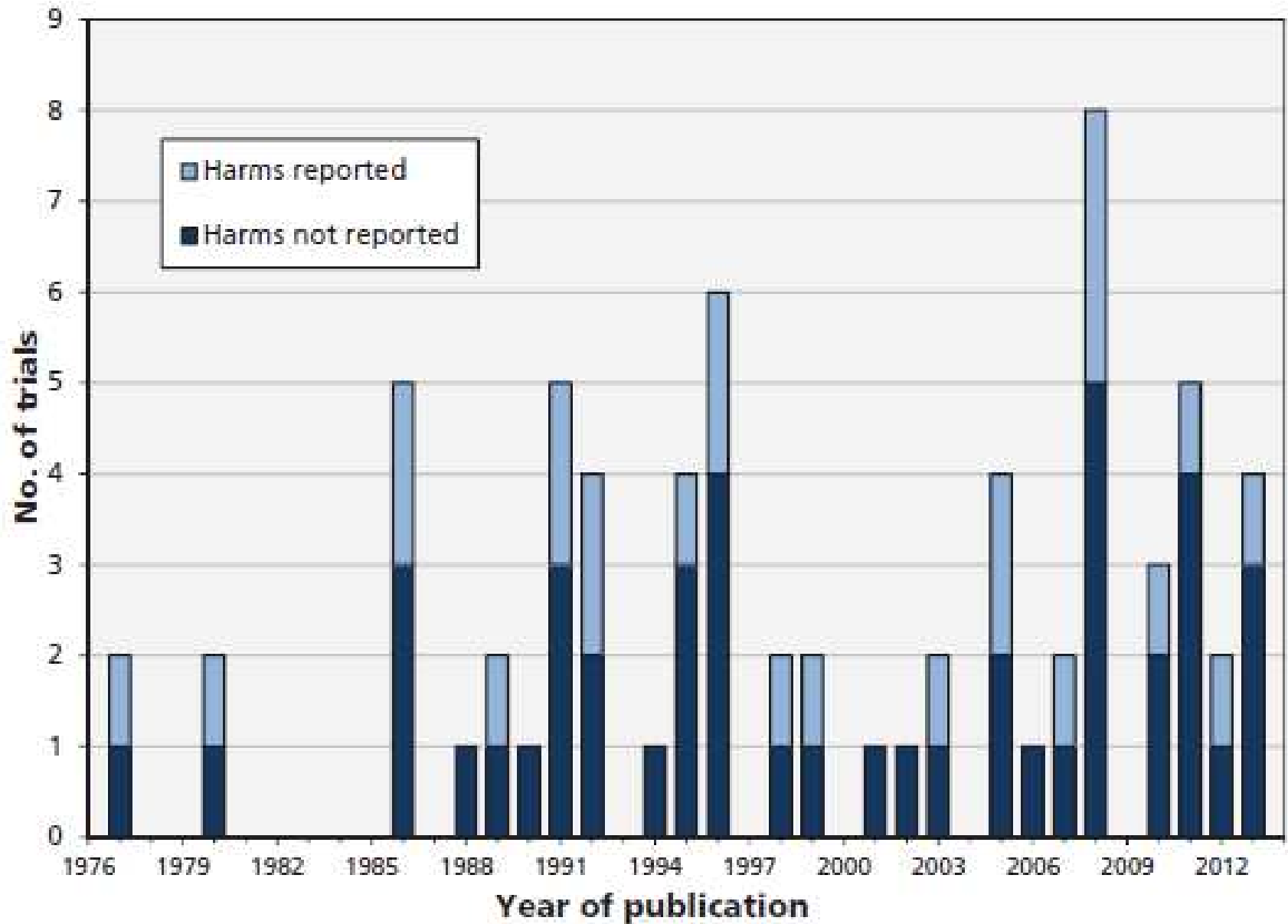
...but

only 25/45 trials → harms data

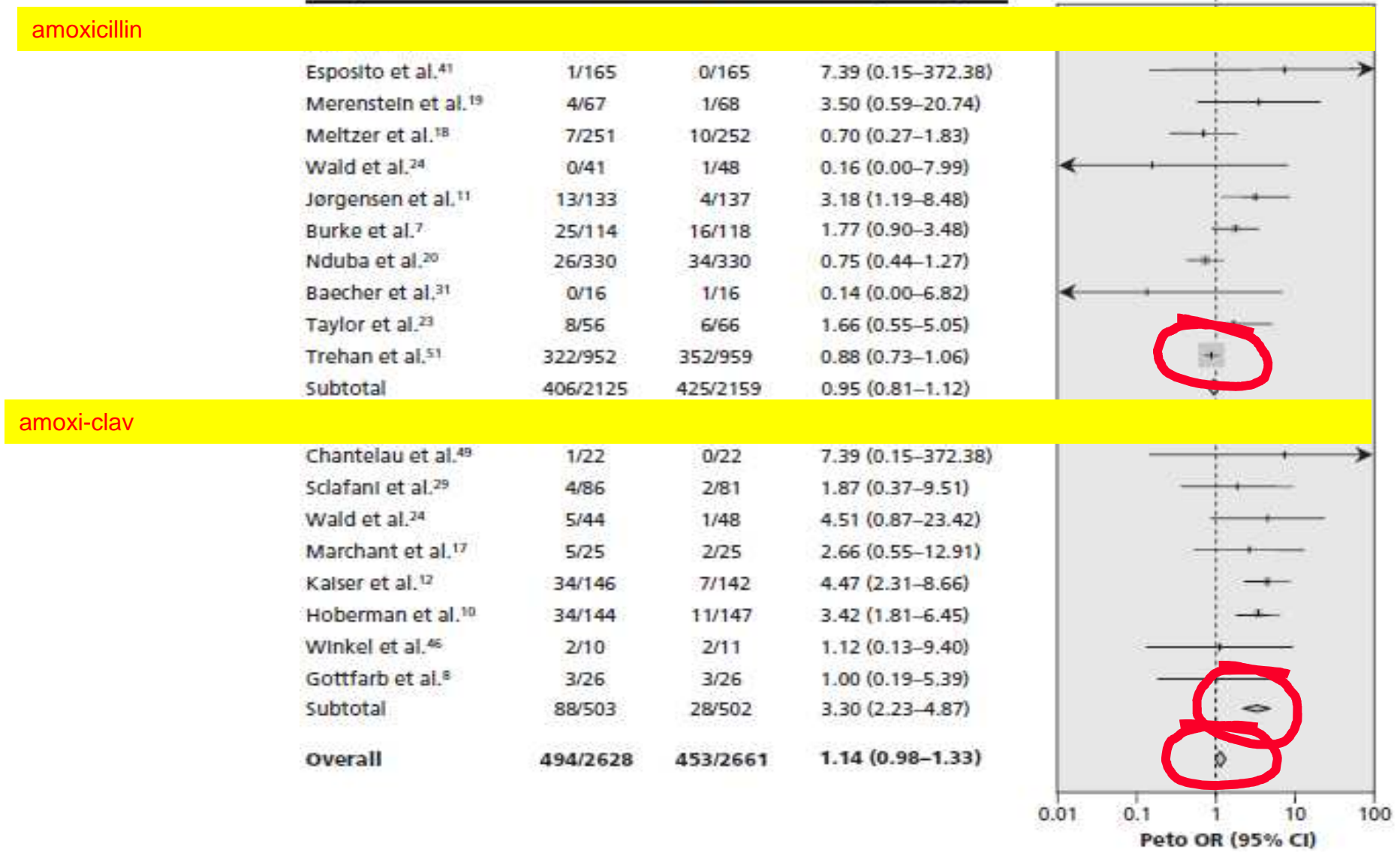
?under-reporting



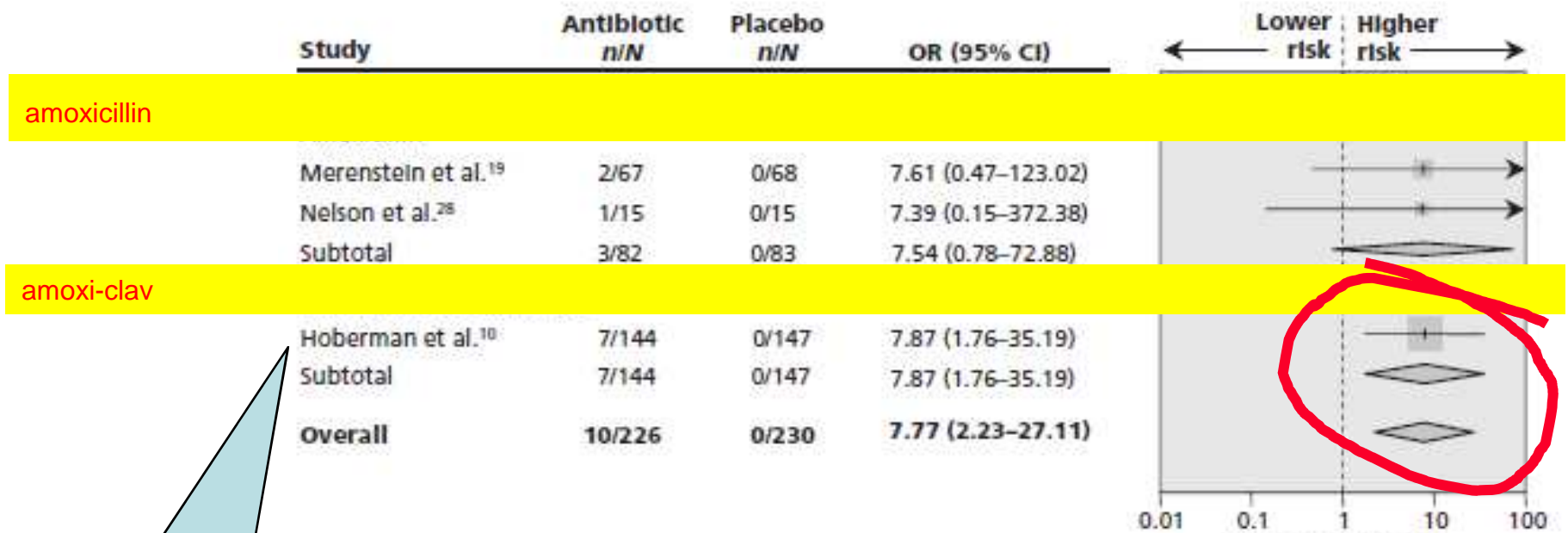
was reporting better with time?



# AE = diarrhoea



AE = thrush



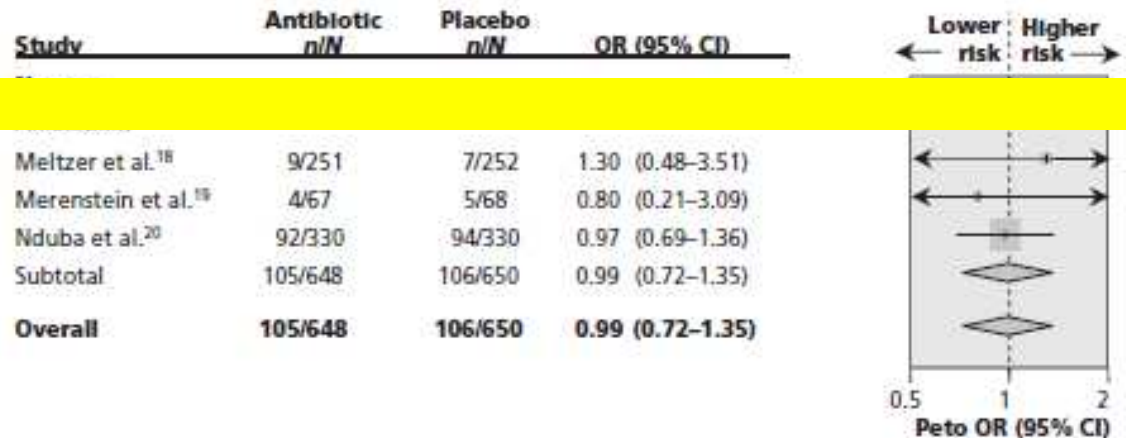
“...diaper-area dermatitis...”



# AE = nausea; vomiting

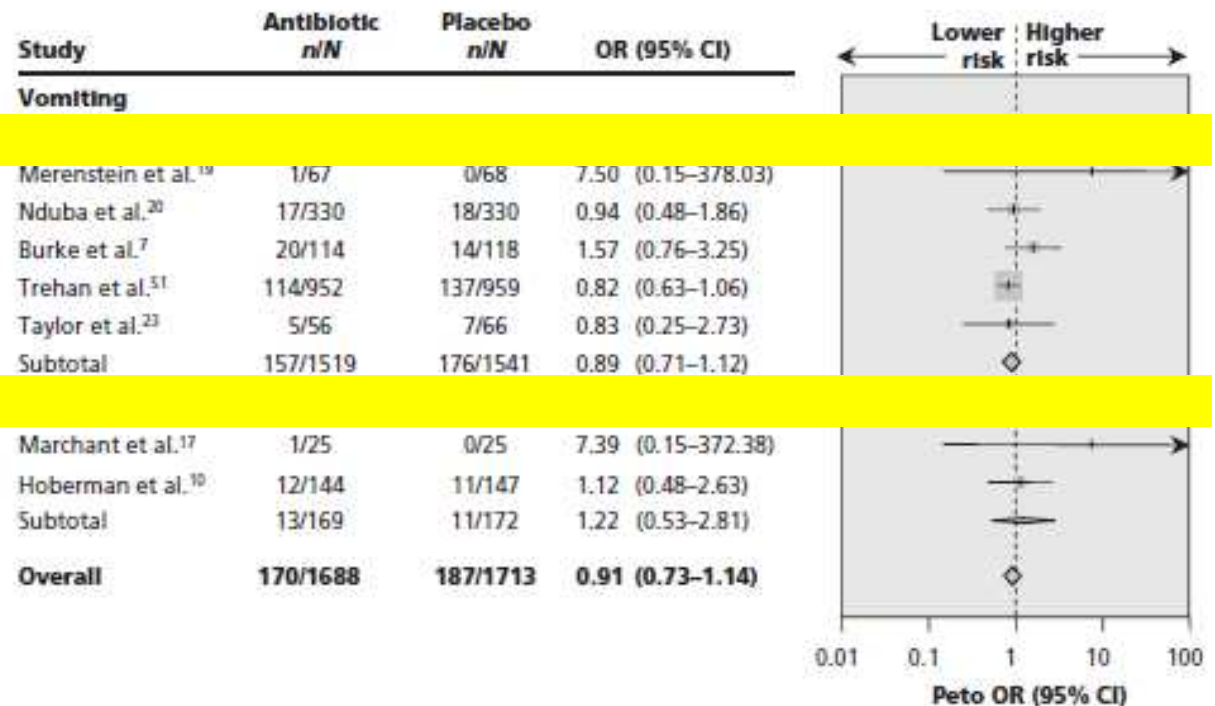
nausea

amoxicillin



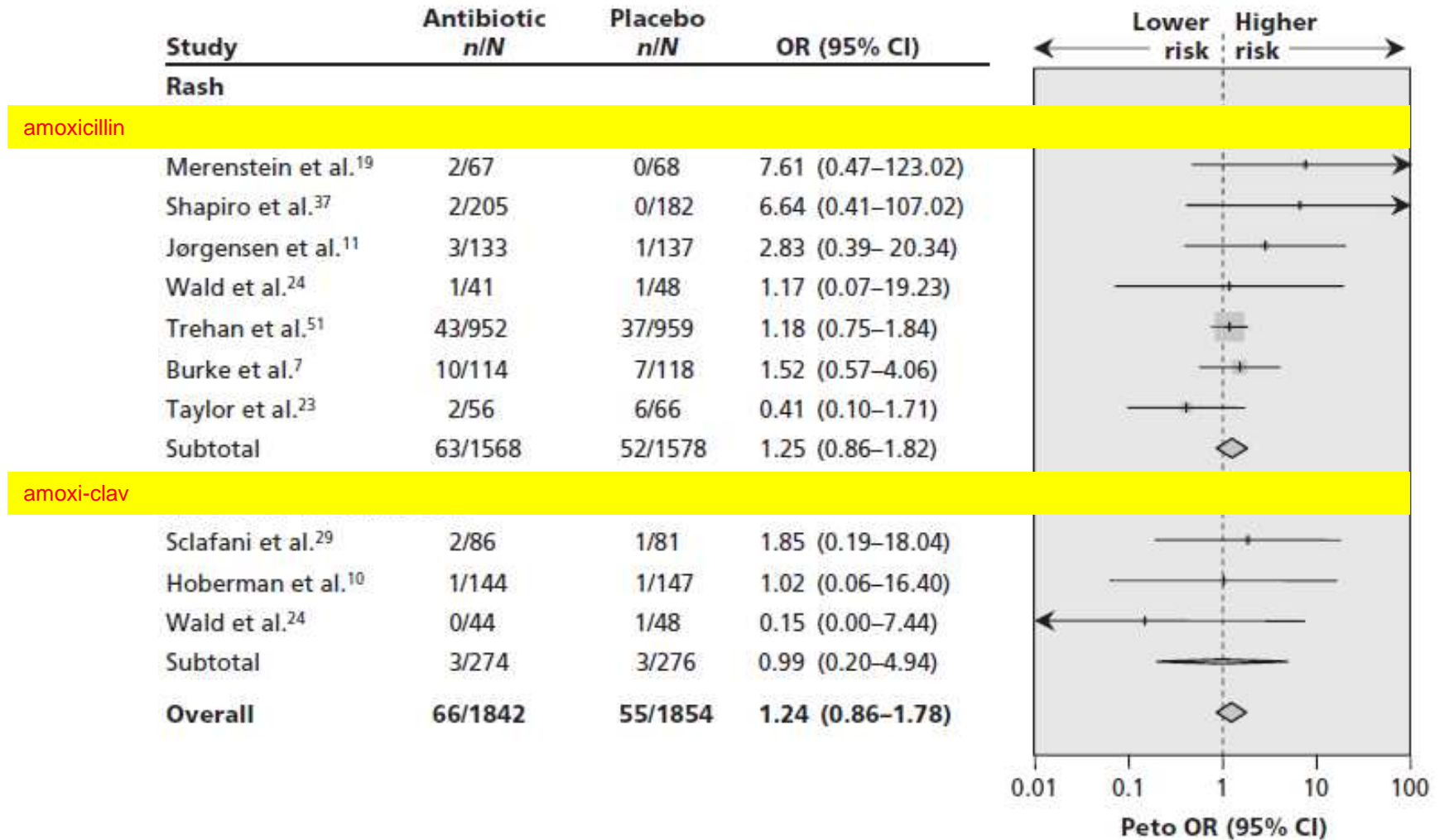
vomiting

amoxicillin





# 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)

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

