

# MSc Programme in International Health Epidemiology and Statistics

Why was the advert for Actimel  
banned by the ASA?

Lecture 9

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## Before lecture exercise

- Select 10 red tiles and 10 blue tiles at random from baskets.
- These represent 10 patients allocated to two different treatments.
- You need to decide which treatment is most successful and by how much
- Count number of red and blue happy faces.
- Which treatment is more successful?
- How sure are you of the result?
- Look up the p-value on the handout.

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## Aims of the lecture

- To distinguish a systematic review from other studies
- To formulate a question using the PICO (Population, Intervention, Comparator, Outcome) principle
- To explain sources of bias in systematic reviews
- Explain what is meant by external validity of randomised trial

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## Reviewing the literature

- Expert view
  - Editorial or commentary
- Narrative (non-systematic reviews)
  - Often broad in scope
  - Methods and approach not always specified
  - Variable reliability
- Systematic review

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## Systematic review

A review of the evidence on a **clearly formulated question** that uses **systematic and explicit methods** to **identify, select** and **critically appraise** relevant primary research, and to **extract and analyse data** from the studies that included in the review. Statistical methods (meta analysis) may or may not be used”

NHS Centre for Reviews and Dissemination (CRD)  
[http://www.york.ac.uk/inst/crd/pdf/crdreport4\\_complete.pdf](http://www.york.ac.uk/inst/crd/pdf/crdreport4_complete.pdf)

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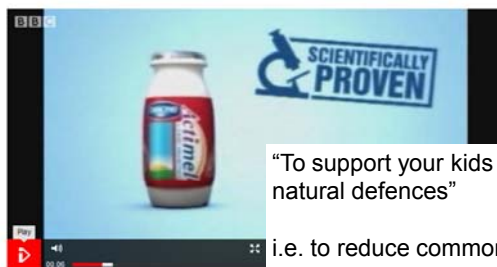
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### 'Healthy' yogurt TV advert banned



“To support your kids natural defences”

i.e. to reduce common, every-day childhood infections.

A TV advert which asserted that Actimel yogu  
<http://news.bbc.co.uk/1/hi/uk/8306116.stm>

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## Clearly formulated question

- PICO (S)
- Population
- Intervention
- Comparator
- Outcomes
- Study Design

Sally Kerry  
Lecture 8

Physician Assistant Studies  
Evidence Based Practice in  
Healthcare

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### Population

Healthy school children

### Actimel trials

Younger children in day care  
Children taking antibiotics  
Children with diarrhoea  
Children in developing countries with diarrhoea  
Hospitalised children

 Barts and The London  
School of Medicine and Dentistry

[www.smd.qmul.ac.uk](http://www.smd.qmul.ac.uk)

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## Population

### General issues

- Children, adults or older adults
- Primary care v secondary care
- Health system

 Barts and The London  
School of Medicine and Dentistry

[www.smd.qmul.ac.uk](http://www.smd.qmul.ac.uk)

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**Intervention**

One bottle a day

**Actimel trials**

Two bottles a day

 [www.smd.qmul.ac.uk](http://www.smd.qmul.ac.uk)

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**Intervention  
or  
Indicator (risk factor)**

- Different dosages
- Different route of administration
- Specific drug or drug class
- Concomitant interventions

 [www.smd.qmul.ac.uk](http://www.smd.qmul.ac.uk)

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**Control or comparator**

Not taking Actimel

**Actimel trials**

Often a 'control' product

 [www.smd.qmul.ac.uk](http://www.smd.qmul.ac.uk)

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## Control or Comparator

- Placebo
- Usual care
- Standard treatment
- Alternative therapy

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### Outcome

Common, every-day childhood infections.  
e.g. colds, diarrhoea and vomiting

### Actimel trials

Number of Common infectious diseases  
Number of colds  
Duration of symptoms  
Absence from school  
Inconsistency in between outcomes

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## Outcomes

- Patient orientated outcomes vs clinical
- Intermediate e.g. blood pressure or events
- Disease specific vs all cause
- Short term v long term effects

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## Systematic and explicit methods to select studies

- Use PICO to define search terms
- Balance wide v narrow search
- Use more than one database
- Grey literature
- Trials registers
- References, citations and expert advice

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## Systematic and explicit methods to select studies

After obtaining references from each search

- Identify unique set of articles
- Check titles and abstracts
- Read papers
- Define eligible studies; clear inclusion criteria
- Inclusion decision ideally made by more than one assessor

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## Assessment of study quality

- Record key quality criteria e.g. blind assessment
- Scoring system may be used
- Poor quality studies may be excluded
- Sensitivity analysis investigating effect of study quality

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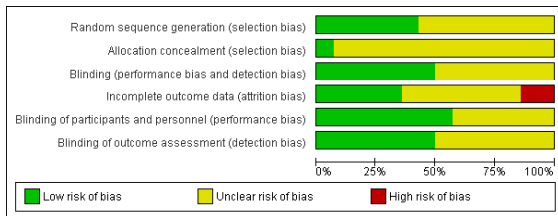
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## Assessment of study quality: figures



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## Data extraction and analysis

- Independent extraction
- Summarise descriptions of each study and key findings
- Ideally combine quantitatively
  - Meta analysis
  - Forest plots
  - Statistical assessment of publication bias

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## Meta analysis

- Subset of systematic reviews will provide data suitable for meta analysis
- Need to have same outcomes
- Increases precision of any estimate of effect
- Identifies whether variability observed is between studies is greater than expected from natural variation

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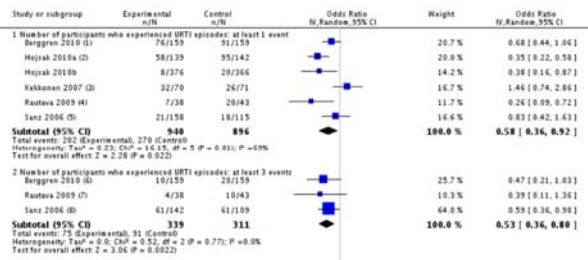
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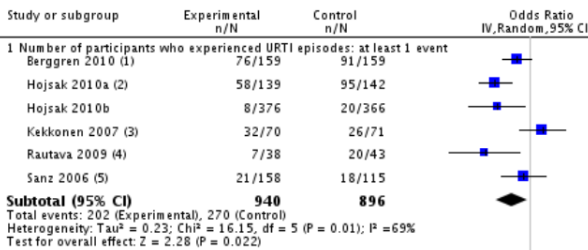
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## Meta analysis: probiotics for respiratory tract infections

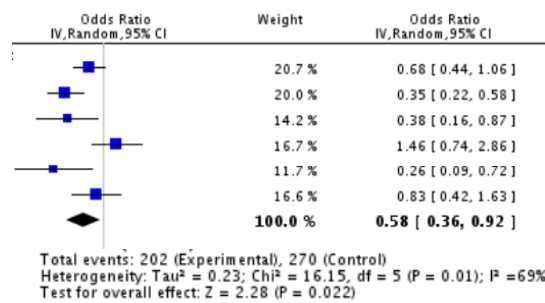


Hao Q, Lu Z, Dong BR, Huang CQ, Wu T. Probiotics for preventing acute upper respiratory tract infections. *Cochrane Database of Systematic Reviews* 2011, Issue 9.

## Meta analysis outcome: >=1 infection



## Meta analysis





## Meta analysis

Overall effect

Odds ratio 0.58 (0.36 to 0.92)

P=0.022

Taking a probiotic reduces the odds of getting a cold by 0.58

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## Heterogeneity

Heterogeneity – tendency for studies to be more variable than expected due to random variability

Total events: 202 (Experimental), 270 (Control)  
Heterogeneity:  $\tau^2 = 0.23$ ;  $\text{Chi}^2 = 16.15$ ,  $df = 5$  ( $P = 0.01$ );  $I^2 = 69\%$   
Test for overall effect:  $Z = 2.28$  ( $P = 0.022$ )

P=0.01 means significant heterogeneity

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## Heterogeneity

Tendency for studies to be different

Qualitative assessment

- Are outcomes/interventions similar enough

Quantitative assessment

- Do study results vary more than would be expected just through random sampling
- Are there patterns which indicate publication bias

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## Exercise

Which is better red or blue?

How certain are you?

6 red successes  $\rightarrow$  probability = 0.6

4 blue successes  $\rightarrow$  probability = 0.4

Risk difference =  $0.6 - 0.4 = 0.2$

95% confidence interval -0.21 to 0.53

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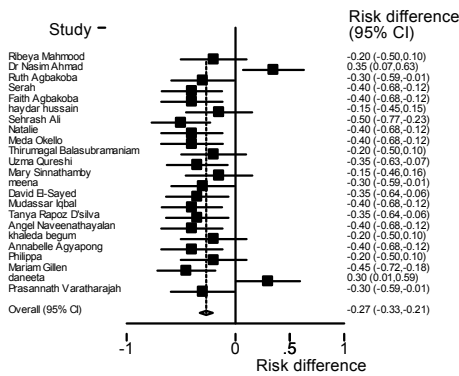
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## Random samples of size 20




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## Variability between study results

- Different populations
- Different interventions
- Study quality
- Difference in measuring outcomes
- Random variability

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## Publication (reporting) bias

The tendency for negative/uninteresting findings to be

- Unpublished
  - study
  - outcome
- Published in obscure journals
- Have their publication delayed

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## Detecting publication bias

- Funnel plot
  - Plots effect size against measure of study size
  - Look out for large studies with smaller effect than overall effect
- Sensitivity methods
  - Trim and fill; use funnel plot to estimate what studies would be needed to make it symmetrical and then see what effect adding these studies would have on the estimate

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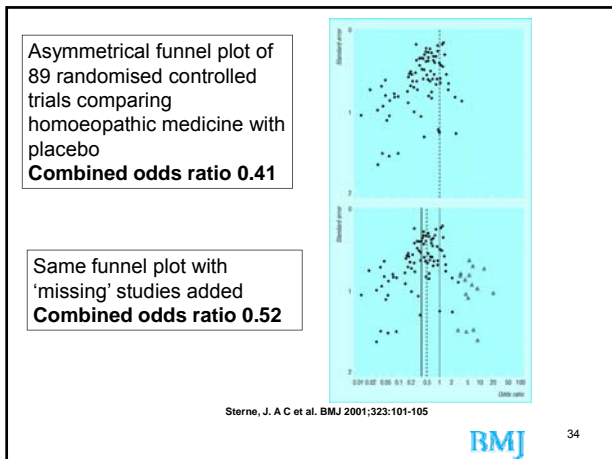
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### Difference between proportions

Does tamiflu (oseltamivir) prevent respiratory tract infections requiring antibiotics in children with confirmed influenza

28% in those given placebo  
17% in those given tamiflu  
Difference 11 (4 to 19)

Barts and The London School of Medicine and Dentistry www.smd.qmul.ac.uk

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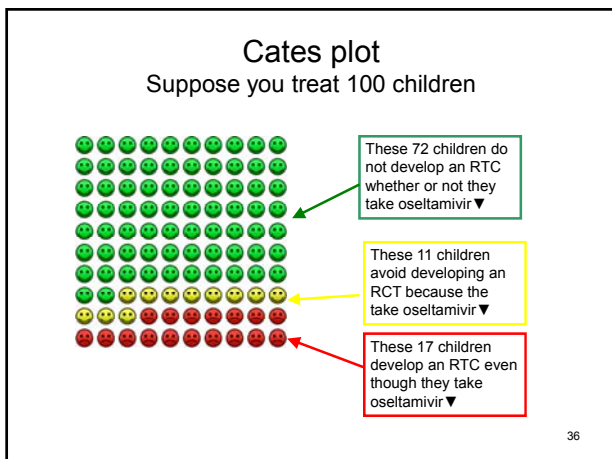
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### Number needed to treat

Number of people you need to treat to avoid one adverse event

$$\text{NNT} = 1/\text{Risk difference}$$

For tamiflu

Risk difference = 0.11

Number needed to treat =  $1/0.11=9$

95% confidence interval (5 to 29)

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### Continuous outcomes

Mean duration of symptoms

One study by Vrese

Control mean(SD) = 8.9 (1.0) days

Probiotics mean(SD) = 7.0 (0.5) days

Difference = 1.9

95% confidence interval 1.75 to 2.05;  $P < 0.05$

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### Continuous outcomes

Simple comparison of two groups

Use a t-test

Gives confidence interval for difference

Adjusting for confounders

Use regression model

Present results as "adjusted difference"

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## Summary

- Systematic reviews require a clear precise protocol for selecting, extracting and analysing data
- Meta analysis is the pooling of quantifiable results
- Less risk of bias when
  - Large number of studies
  - No evidence of heterogeneity
  - No evidence of publication bias

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