

When are randomized trials unnecessary?

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CBC 2004

Isn't it obvious?

Would it be unethical to:

- Withhold surgery for acute appendicitis?
- Rapid fluid resuscitation in septic shock?
- Withhold monitoring in type II diabetes?

Randomized trials showing unnecessary or harmful

Some types of “obvious” effect

1. Mechanically obvious
2. Rapid effects (in stable condition)
3. Very large relative risk (compared with historical controls)
4. N-of-1 reversible effect

I. Mechanically obvious



2. Rapid effects in stable conditions

The “Mother’s Kiss”

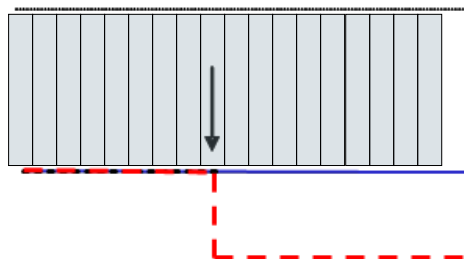
Child with nasal foreign body

- Dislodged with Parent Kiss method
- Case series of success 15/19
 - Botma J Laryngol Otol 2000



* Glasziou, Chalmers, Rawlins, McCulloch BMJ 2007

Detecting signal in noise



a) stable + sudden change

The size of effect with the parent kiss technique

- less than 10 seconds to see the effect compared to
- hours before (for 2 hours this is 720 periods of 10 seconds)
- So Rate Ratio
= $(1/1)/(0.5/720) = 1,440$



* Glasziou, Chalmers, Rawlins, McCulloch BMJ 2007

Examples of dramatic effects

Some historical examples of treatments with dramatic effects

- Insulin for diabetes^{w1}
- Blood transfusion for severe haemorrhagic shock^{w2}
- Sulphanilimide for puerperal sepsis^{w3}
- Streptomycin for tuberculous meningitis^{w4}
- Defibrillation for ventricular fibrillation^{w5}
- Closed reduction and splinting for fracture of long bones with displacement
- Salicin for acute rheumatism^{w6}
- Neostigmine for myasthenia gravis^{w7}
- Tracheostomy for tracheal obstruction^{w8}
- Suturing for repairing large wounds
- Drainage for pain associated with abscesses
- Pressure or suturing for arresting haemorrhage
- Ether for anaesthesia
- One way valve or underwater seal drainage for pneumothorax and haemothorax^{w9}
- Phototherapy for skin tuberculosis^{w10}
- Combination chemotherapy with cisplatin, vinblastine, and bleomycin for disseminated testicular cancer

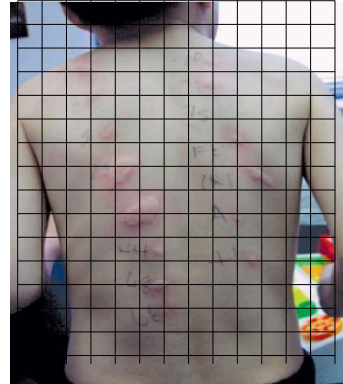
Location matches exposure
= large effect



Nickel watch band

Did the skin prick cause the reaction?

- Choose 1 of the 100 grid cells at random for injection
- Is there a local reaction in the chosen cell?
- $P < 0.01$



Anecdotes as Evidence. Aronson BMJ 2006

3. Large relative risk (reduction) Pellagra & Diet

- Experimental orphanages
 - “MJ” had 79 cases; 1 year after diet no recurrences, no new cases
 - “BJ” 130 cases; 1 year after diet 1 recurrence, no new cases
 - Recurrence = 1/209 cases
- Other similar institutions
 - Recurrence rates between 58% and 75%.



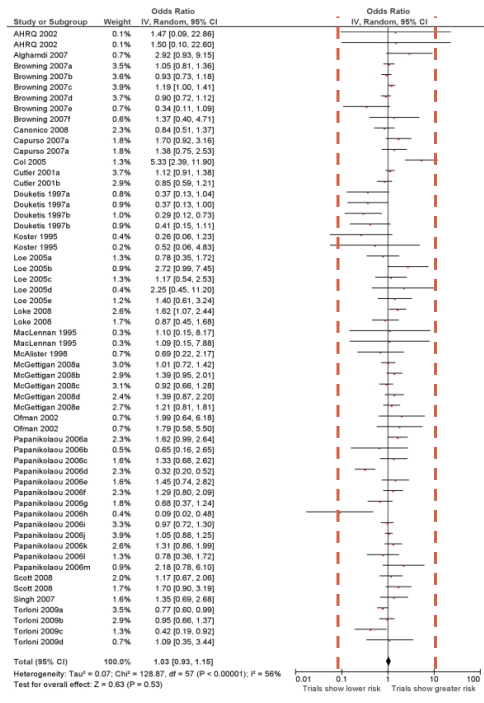
Joseph Goldberger

Goldberger J (1907). Typhoid "bacillus carriers". In: Rosenau MJ, Lumsden LL, Kastle JH. Report on the origin and prevalence of typhoid fever in the District of Columbia. Hygienic Laboratory, Bulletin No 35, pp 167-174.

Bias:
Unpredictable direction
but limited in size

- Review ADRs in observational studies versus randomized trials

Golder, Plos, 2008



4. Single patient trial of prostigmine Myasthenia Gravis: fast & reversible



Tensilon (prostigmine) test:
Before (left); After (right)

<http://www.neuro.wustl.edu/neuromuscular/mtime/mgdx.html>

Deep Brain Stimulation (DBS)

- Parkinson's tremor
- Switch symptoms on and off with DBS



Factors that may increase the quality of evidence

↑ if large magnitude of effect

“Modeling studies suggest that confounding alone is unlikely to explain associations with a relative risk greater than 2 (or less than 0.5), and very unlikely to explain associations with a relative risk greater than 5 (or less than 0.2)”

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Some conclusions

- RCTs are necessary for small effects
- RCTs are unnecessary to demonstrate **dramatic** effects of treatments
- Is the observed effect greater than plausible biases?