Interpretation of large-scale randomised evidence

Need for reliable assessment of MODERATE effects on mortality

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This lecture was originally given in the London School of Hygiene, and can be watched on YouTube:
http://www.youtube.com/watch?v=v-yb60PzZ7I&list=PL_jbyPdyg6uqm1ps-aElRSa_SxThzMLh

The ideas in it are described conversationally in our chapter on trials in the fifth edition of the Oxford Textbook of Medicine; this chapter is available electronically in Bangkok from: Ammarin Thakkinstian or Stephen Pinder

Single copies for use in Thailand can be obtained on request from: Rpeto@ctsu.ox.ac.uk
Need for reliable assessment of MODERATE effects on mortality

ISIS-2: aspirin for acute MI
Requirements for reliable assessment of MODERATE effects: NEGLIGIBLE biases, and SMALL random errors

GUARANTEED AVOIDANCE OF MODERATE BIASES:
- Proper randomization
  (non-randomised methods might suffer moderate biases)
- Analysis by allocated treatment
  (including all randomised patients: ‘intention to treat’ analysis)
- Chief emphasis on overall results
  (no unduly data-dependent emphasis on particular subgroups)
- Systematic overview of all relevant randomised trials
  (no unduly data-dependent emphasis on particular studies)

SMALL RANDOM ERRORS:
- Large numbers in any new trials
  (to be really large, trials should be “streamlined”)
- Systematic overview of all relevant randomised trials
  (which yields the largest possible total numbers)

Assessment of MODERATE differences in survival

• Need all the main trial results, to avoid undue emphasis on particular studies
• Likewise, avoid unduly data-dependent emphasis on particular subgroups
False-negative mortality effect in a subgroup defined only by the medieval astrological birth sign: the ISIS-2 trial of aspirin among > 17 000 patients with acute MI. (Lancet 1988; 332: 349)

<table>
<thead>
<tr>
<th>Astrological birth sign</th>
<th>No. of 1-month deaths (aspirin vs placebo)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Libra or Gemini</td>
<td>150 vs 147</td>
<td>NS</td>
</tr>
<tr>
<td>All other signs</td>
<td>654 vs 869</td>
<td>2p&lt;0.000 001</td>
</tr>
<tr>
<td>Any birth sign*</td>
<td>804 vs 1016 (9.4%)</td>
<td>2p&lt;0.000 001</td>
</tr>
</tbody>
</table>
Magnesium infusion in acute myocardial infarction (MI): meta-analysis of small trials CONTRADICTED by big trial

<table>
<thead>
<tr>
<th>Randomised comparison</th>
<th>Deaths/patients (% dead)</th>
<th>Odds ratio &amp; CI</th>
<th>Control better</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>9 small trials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>42/ 754 (5.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>86/ 740 (11.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LIMIT-2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>90/ 1159 (7.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>110/ 1157 (10.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ISIS-4</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>2216/29011 (7.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>2103/29039 (7.2%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ALL TRIALS**

<table>
<thead>
<tr>
<th>Deaths/patients (% dead)</th>
<th>Odds ratio &amp; CI</th>
<th>Control better</th>
</tr>
</thead>
<tbody>
<tr>
<td>2348/30924 (7.59%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2307/30936 (7.46%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.4 (SD 2.1) extra deaths per 1000 treated

Test for heterogeneity:
- between 9 small trials & 2 larger trials: $\chi^2 = 18.6; p<0.0001$
- between LIMIT-2 & ISIS-4: $\chi^2 = 5.7; p<0.02$

**Figure:**
- Trial name: Nitroxin, Magnesium, Deth, Abidion, Fardisil, Schonander, Candesartan, Transdermal
- Deaths/patients: Magnesium, Control
- Data of death rate: Magnesium, Control

- Subtotal (9 small trials, identical to LIMIT-2): 0.44 (0.38-0.51)
- Subtotal (12 small trials): 0.43 (0.35-0.51)
- Subtotal (9 small trials, identical to LIMIT-2): 0.44 (0.38-0.51)
- Subtotal (12 small trials): 0.43 (0.35-0.51)
- LIMIT-2: 0.74 (0.60-0.90)
- ISIS-4: 0.57 (0.48-0.68)
- Total: 0.63 (0.54-0.73)
Fibrinolytic treatment in acute myocardial infarction:

meta-analysis of small trials CONFIRMED by big trials
Vitamin A supplementation and child mortality:

meta-analysis of small trials estimated treatment effect HALVED by big trial
Six-monthly vitamin A from 1 to 6 years of age
DEVTA: cluster-randomised trial in 1 million children in North India

Shally AWASTHI (KG Medical Univ, Lucknow, UP),
Richard PETO & Simon READ (CTSU, Univ Oxford, UK),
Donald BUNDY (World Bank, Washington, DC) et al.
Lancet 27 April 2013 (online 14 March)

DEVTA covers more than half (72/118) of the administrative blocks in 7 districts near Lucknow, the state capital of Uttar Pradesh, North India

7 DEVTA districts in Uttar Pradesh
1 Lucknow
2 Raibarelli
3 Unnao
4 Kanpur
5 Hardoi
6 Lakhimpur
7 Sitapur

NB Delhi to Kathmandu is 800 km (8 degrees of longitude); shaded area is 30,000 km²
Pre-school rural North India

- Vit A deficiency common
- 2-3% die at ages 1-6 (mainly acute infection)
- DEVTA: can 6-monthly vit A reduce this mortality?
DEVTA: cluster-randomised trial
8000+ villages in 72 clusters

36 blocks
6-monthly
VITAMIN A

36 blocks
allocated open
CONTROL

Also, visit all villages 6 monthly to get mortality (25,000 child deaths recorded)
DEVTA vit A schedule, 1999-2004

200,000 IU vit A given on six-monthly mass-treatment days to all age 6-72m

Compliance:
Vitamin A group got ~9.5 of 11 doses
controls got ~1 non-trial vit A dose

DEVTA: biomedical monitoring

Annually, 1 village per block randomly chosen & children examined

Bitot’s spots 1.4% vs 3.5%, 2p<0.01 (comparing 36 vit A vs 36 control clusters)

Plasma retinol < 0.35 μM/L (10 μg/dL), ie, severe deficiency: 6% vs 13%, 2p<0.00001
DEVTA: mortality results (ages 1-6)

Mean probability that a 1.0-year-old would die by age 6.0 years, 36 vit A vs 36 control blocks:

2.5% vs 2.6%

2p = 0.22, not significant (comparing 36 vs 36 blocks)

DEVTA: 72 cluster-specific death risks at ages 1-6
36 control blocks vs 36 vitamin A blocks

Deaths per 1000 1-year-olds

Control (mean 26.0)  Vitamin A (mean 24.9)
DEVTA: Cause-specific mortality (per 1000 aged 1.0), vit A vs control

<table>
<thead>
<tr>
<th>Cause of death (at ages 1-6)</th>
<th>36 vitamin A vs 36 control blocks</th>
<th>Difference ± se *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>6.9 vs 7.3</td>
<td>0.4 ± 0.4</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3.7 vs 3.6</td>
<td>-0.1 ± 0.3</td>
</tr>
<tr>
<td>Measles</td>
<td>1.6 vs 1.7</td>
<td>0.1 ± 0.2</td>
</tr>
<tr>
<td>Other infection**</td>
<td>8.2 vs 8.8</td>
<td>0.6 ± 0.6</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>2.0 vs 2.0</td>
<td>0.0 ± 0.2</td>
</tr>
<tr>
<td>Other ***</td>
<td>2.5 vs 2.6</td>
<td>0.1 ± 0.2</td>
</tr>
<tr>
<td>All causes</td>
<td>24.9 vs 26.0</td>
<td>1.1 ± 0.9</td>
</tr>
</tbody>
</table>

* 36 vit A vs 36 control cluster-specific values
** Mostly fever; also includes the few wholly unspecified causes
*** 60% accident or homicide, 40% non-infective disease

DEVTA: subgroup analyses

No significant heterogeneity between proportional mortality reductions produced by vit A among:

- Male and female
- De-wormed regularly and not de-wormed
- Younger and older (ages 1-2 and 3-6)
DEVTA: vit A vs control mortality ratio, $R = 0.96$ (99% CI 0.87-1.05)

DEVTA on its own is consistent **both** with little effect on mortality **and** with prevention of >10% of all mortality

So, DEVTA must be considered not on its own but with the other relevant trials (which collectively show definite benefit)

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**DEVTA and 8 previous trials**

DEVTA: $R = 0.96$, $2p = 0.22$

(99%CI 0.87-1.05)

8 others: $R \approx 0.77$, $2p < 0.00001$

(99%CI 0.68-0.89)

Total: $R \approx 0.89$, $2p < 0.0001$

(95%CI 0.84-0.95)

Difference between $R$ in DEVTA & in the 8 other trials: $2p = 0.001$. Extreme play of chance????
Community vit A supplementation: change produced by DEVTA in the totality of the trial evidence

Mortality reduction still highly significant (2p <0.0001) in DEVTA + the 8 other trials

But, much more likely to be about 5-15% than, as previously estimated, about 20-30% (ie, a quarter or half of previous estimate)
Figure 4: Ghanaian children with moderately severe malaria: only 10% parasite reduction 4 hours after just one rectal AS suppository, but about fourfold parasite reduction by hr 12.
Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial


Summary
Background Most malaria deaths occur in rural areas. Rapid progression from illness to death can be interrupted by prompt, effective medication. Antimalarial treatment cannot rescue terminally ill patients but could be effective if given earlier. If patients who cannot be treated orally are several hours from facilities for injections, rectal artesunate can be given before referral and acts rapidly on parasites. We investigated whether this intervention reduced mortality and permanent disability.

Methods In Bangladesh, Ghana, and Tanzania, patients with suspected severe malaria who could not be treated orally were allocated randomly to a single artesunate (n=4554) or placebo (n=4572) suppository by taking the next numbered box, then referred to clinics at which injections could be given. Those with antimalarial injections or negative blood smears before randomisation were excluded, leaving 12068 patients (6072 artesunate; 5996 placebo) for analysis. Primary endpoints were mortality, assessed 7–30 days later, and permanent disability, reassessed periodically. All investigators were masked to group assignment. Analysis was by intention to treat. This study is registered in all three countries, numbers ISRCTN83097018, 46434637, and 70957026.

Results Mortality was 154 of 6072 artesunate versus 177 of 5996 placebo (2.5% vs 3.0%, p=0.1). Two versus 13 (0.3% vs 2.2%, p=0.002) were permanently disabled; total dead or disabled: 56 versus 198 (2.6% vs 3.3%, p=0.0484). There was no reduction in early mortality (56 vs 53 deaths within 6 h, median 2 h). In patients reaching clinic within 6 h (median 3 h), pre-referral artesunate had no significant effect on death after 6 h or permanent disability (71/1450 [5.0%] vs 82/1426 [5.7%], risk ratio 0.86 [95% CI 0.53–1.38], p=0.35). In patients still not in clinic after more than 6 h, however, half were still not there after more than 15 h, and pre-referral rectal artesunate significantly reduced death or permanent disability (29/1566 [1.9%] vs 57/1559 [3.7%], risk ratio 0.49 [95% CI 0.32–0.77], p=0.0013).

Interpretation If patients with severe malaria cannot be treated orally and access to injections will take several hours, a single inexpensive artesunate suppository at the time of referral substantially reduces the risk of death or permanent disability.

Main result: numbers died or permanently disabled, subdivided by time (hours, h) since rectal insertion

<table>
<thead>
<tr>
<th>Time to arrive at an antimalarial injection facility (or to death)</th>
<th>Died / permanently disabled</th>
<th>Artesunate</th>
<th>Placebo</th>
<th>Binomial p-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died quickly (0-6h, median 2h)</td>
<td>56</td>
<td>51</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Arrived at injection facility quickly (0-6h, median 3h)</td>
<td>71</td>
<td>82</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Still not at injection facility after &gt;6h (median time to death / arrival 15h)</td>
<td>29</td>
<td>57</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

MITT analyses  * Binomial p-value and risk ratio calculations do not require reliable knowledge of denominators
<table>
<thead>
<tr>
<th>Year trial published, author or trial name, country [reference]</th>
<th>Mortality rate ratio, RR (&amp; 95% CI*)</th>
<th>Equivalent numbers of deaths†</th>
<th>Mortality rate ratio, RR Vitamin A : Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986, Sommer, Indonesia [1]</td>
<td>0.66 (0.44-0.97)</td>
<td>41 vs 62</td>
<td>0.66 (95% CI 0.46-0.97)</td>
</tr>
<tr>
<td>1990, Vijayaraghavan, India [2]</td>
<td>1.00 (0.65-1.55)</td>
<td>40 vs 40</td>
<td>1.00 (95% CI 0.65-1.55)</td>
</tr>
<tr>
<td>1990, Rahmathullah, India [3]</td>
<td>0.46 (0.30-0.71)</td>
<td>30 vs 66</td>
<td>0.46 (95% CI 0.30-0.71)</td>
</tr>
<tr>
<td>1990, West, Nepal [4]</td>
<td>0.70 (0.56-0.88)</td>
<td>128 vs 183</td>
<td>0.70 (95% CI 0.56-0.88)</td>
</tr>
<tr>
<td>1992, Daulaire, Nepal [5]</td>
<td>0.74 (0.55-0.99)</td>
<td>77 vs 105</td>
<td>0.74 (95% CI 0.55-0.99)</td>
</tr>
<tr>
<td>1992, Herrera, Sudan [6]</td>
<td>1.06 (0.82-1.37)</td>
<td>120 vs 113</td>
<td>1.06 (95% CI 0.82-1.37)</td>
</tr>
<tr>
<td>1992, Arthur, Ghana [7]</td>
<td>0.30 (0.12-0.75)</td>
<td>6 vs 20</td>
<td>0.30 (95% CI 0.12-0.75)</td>
</tr>
<tr>
<td>1993, VAST, Ghana [8]</td>
<td>0.81 (0.68-0.98)</td>
<td>208 vs 257</td>
<td>0.81 (95% CI 0.68-0.98)</td>
</tr>
<tr>
<td><strong>1986-93, subtotal (8 trials)‡</strong></td>
<td><strong>650 vs 846</strong></td>
<td></td>
<td><strong>0.77 (99% CI 0.68-0.89)</strong></td>
</tr>
<tr>
<td><strong>2011, DEVTA, India</strong></td>
<td><strong>1472 vs 1540</strong></td>
<td></td>
<td><strong>0.96 (99% CI 0.87-1.05)</strong></td>
</tr>
<tr>
<td><strong>Total (DEVTA + 8 others)‡</strong></td>
<td><strong>2122 vs 2386</strong></td>
<td></td>
<td><strong>0.89 (95% CI 0.84-0.95)</strong></td>
</tr>
</tbody>
</table>

8 previous trials of regular vitamin A supplementation & child mortality, DEVTA (Lancet, 27 April 2013) and weighted averages of results from 8 or from 9 trials.

Het. between 8 trials p=0.01; between DEVTA and subtotal of 8 trials p=0.001. ‡Weighted average does NOT assume RRs in all studies are the same. Trials excluded if <20 deaths, started with disease, or only single-dose.
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