Vitamin A Supplementation Contradicting single effect interventions

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Vitamin A supplementation

WHO’s vitamin A policy – implemented for more than 20 years – after studies showed 23-30% reduction in overall mortality

| Suggested vitamin A supplementation scheme for infants children 6–59 months of age |
|---|---|
| **Target group** | Infants 6–11 months of age (including HIV+) | Children 12–59 months of age (including HIV+) |
| **Dose** | 100 000 IU (30 mg RE) vitamin A | 200 000 IU (60 mg RE) vitamin A |
| **Frequency** | Once | Every 4–6 months |
| **Route of administration** | Oral liquid, oil-based preparation of retinyl palmitate or retinyl acetate | |
| **Settings** | Populations where the prevalence of night blindness is 1% or higher in children 24–59 months of age or where the prevalence of vitamin A deficiency (serum retinol 0.70 μmol/l or lower) is 20% or higher in infants and children 6–59 months of age |
Neonatal vitamin A supplementation
2008: Status neonatal vitamin A supplementation

[Graph showing mortality ratio with 95% CI for various countries, with Asia having 18% lower mortality and Africa having 15% higher mortality.]
Guinea-Bissau: Neonatal vitamin A in the DTP window

Vita I: Normal-birth-weight

- 10% lower mortality
- 120% higher mortality

Vita II: Low-birth-weight

- 30% lower mortality
- 40% higher mortality

Benn et al, Vaccine 2009, BMJ 2010
Guinea-Bissau: Neonatal vitamin A in the DTP window

**Vita III: Normal-birth-weight**

**Boys**

- 20% lower mortality

**Girls**

- 30% higher mortality

**Combined analysis of 3 studies from Guinea-Bissau**

- **Males**: 0.80 (0.52, 1.25)
- **Females**: 1.59 (1.07, 2.37)
- **Overall (I-squared = 80.4%, p = 0.024)**

**Girls: 59% (7-137%) higher mortality,**

The effect in girls very different from the effect in boys (**p=0.02**)

Benn et al, J Nutr 2014
Three new neonatal vitamin A trials initiated by the WHO and funded by BMGF: India, Ghana, Tanzania including >100,000

Hypothesis: 15% mortality reduction within each trial
2015: Status neonatal vitamin A supplementation

Results of new metaanalysis
Combined estimate: No effect (1% increase in mortality)
WHO’s vitamin A policy – implemented for more than 20 years – after studies showed 23-30% reduction in all cause mortality

**Suggested vitamin A supplementation scheme for infants children 6–59 months of age**

<table>
<thead>
<tr>
<th>Target group</th>
<th>Infants 6–11 months of age (including HIV+)</th>
<th>Children 12–59 months of age (including HIV+)</th>
</tr>
</thead>
<tbody>
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<td>200 000 IU (60 mg RE) vitamin A</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
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<td>Every 4–6 months</td>
</tr>
<tr>
<td><strong>Route of administration</strong></td>
<td>Oral liquid, oil-based preparation of retinyl palmitate or retinyl acetate⁹</td>
<td></td>
</tr>
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<td>Populations where the prevalence of night blindness is 1% or higher in children 24–59 months of age or where the prevalence of vitamin A deficiency (serum retinol 0.70 μmol/l or lower) is 20% or higher in infants and children 6–59 months of age</td>
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</tr>
</tbody>
</table>

Evaluated in single-intervention studies – prior to the implementation of the vaccination program

I.e. interactions with vaccines were not investigated
Vitamin A and vaccines

- We have proposed that vitamin A interacts with vaccines, amplifying the non-specific effects of vaccines (Benn et al, Int J Epidemiol 2003)
- Supported by a number of observations, among others a reanalysis of one of the old vitamin A trials from Navrongo, Ghana (Benn et al, Am J Clin Nutr 2009)

Ghana VAST conducted in 1989-91; 19% (2-32%) reduction in mortality

<table>
<thead>
<tr>
<th></th>
<th>Vitamin A</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated</td>
<td>18% (-16-67%)</td>
<td>higher mortality</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>40% (8-60%)</td>
<td>lower mortality</td>
</tr>
<tr>
<td>Some but not all DTP</td>
<td>160% (41-380%)</td>
<td>higher mortality</td>
</tr>
</tbody>
</table>

Interpretation: Negative interaction btw VAS and subsequent DTP in girls
Randomized trial testing the effect of vitamin A to children > 6 months
Enrolling 7587 children in urban and rural Guinea-Bissau between 2007-2010

Overall effect: 9% (-41-41%) lower mortality

P for same effect in boys and girls = 0.003

Ane Fisker, Pediatrics 2014
Overview – vitamin A supplementation to children > 6 months

Old studies: 24% lower mortality

DEVTA

Our trial
The effect of campaigns: OPV and Vitamin A

In Bandim and Navrongo

<table>
<thead>
<tr>
<th>Studies</th>
<th>Period</th>
<th>OPV: reduction in mortality</th>
<th>Vitamin A: increase in mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age of children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bandim</td>
<td>2002-2014</td>
<td>25% (15-33%)</td>
<td>42% (24-63%)</td>
</tr>
<tr>
<td></td>
<td>0-3 years</td>
<td></td>
<td></td>
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<tr>
<td>Navrongo</td>
<td>1996-2015</td>
<td>12% (4-19%)</td>
<td>1 campaign: no effect</td>
</tr>
<tr>
<td></td>
<td>0-3 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined Bandim and Navrongo</td>
<td></td>
<td>18% (4-30%) reduction</td>
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</tbody>
</table>

Preliminary unpublished data
CONCLUSION
No such thing as a single effect of vitamin A supplementation
It is all about context:
Vitamin A in Asia...
Vitamin A with DTP vaccine...
Vitamin A to girls...

IGNORE OR EXPLORE?