Early neonatal vitamin A supplementation and infant mortality: two alternative hypotheses

Christine Stabell Benn, MD, PhD, DMSc
Professor, University of Southern Denmark

In 2008, WHO hosted a technical consultation on neonatal vitamin A supplementation (NVAS)(1). The investigators of the existing NVAS trials participated. At that time, six NVAS trials had been conducted, yielding conflicting results. Some investigators supported the prevailing "NVAS-prevents-vitamin-A-deficiency" hypothesis; they proposed that the variability of effects was seen because there were differences in the prevalence of vitamin A deficiency (VAD) in different settings. Based on our NVAS trials in Guinea-Bissau, we put forward an alternative hypothesis; that NVAS interacted negatively with subsequent diphtheria-tetanus-pertussis (DTP) vaccine in females, the "Negative interaction between NVAS and DTP in females" hypothesis (2-5). If true this would lead to negative effects of NVAS in females in areas with high DTP coverage. We proposed to test the hypothesis in the other NVAS trials.

WHO conducted three new large NVAS trials. In the initial proposal, the NVAS and placebo recipients were only followed to age 6 months. Since much of a potential negative interaction between NVAS and DTP vaccine in females would only occur after 6 months, when most children would have received DTP vaccine, we suggested that the trials collect vaccination information and follow children to age 12 months. This was accepted in the final protocol(6).

In 2014, the three trials were published(7-9). The Indian trial found a marginal 10% (95% CI 0 to 19%) mortality reduction by 6 months, which was offset by 12 months(9). None of the trials found beneficial effect of NVAS by 12 months.

The hypothesis of a negative interaction between NVAS and DTP in females was not tested. However, the age-sex-mortality pattern showed that the effect of NVAS became increasingly negative in females with increasing age (10). From 6-11 months of age NVAS tended to be associated with reduced mortality in males (RR 0.89, 95% CI 0.73 to 1.08) while it was associated with an increased mortality in females (1.20 (1.02 to 1.42))(10).

Immunological studies have shown that by 4-6 months of age, following three doses of DTP vaccine, NVAS vs. placebo was associated with consistently higher TNF-alpha:IL-10 ratio and lower IL-17 responses to unrelated antigens in females; the opposite effect of NVAS was seen in males(11). These effects of NVAS may be mediated via epigenetic changes; retinoids may initiate stable epigenetic changes which regulate stem cell differentiation (12), and have been shown to induce histone modifications at promoter locations of several cytokines(13). While the link between these immunological markers and subsequent mortality remains to be understood, the results support long-lasting interaction between NVAS, DTP and sex with respect to immune function.

The table summarises the key observations from the now 11 NVAS trials(5, 7-9, 14-21) (excluding a small trial from Nepal, which did not include children immediately after birth(22)).

A new meta-analysis of these NVAS trials was recently published(23), including a meta-regression of the trials and a meta-analysis of individual level data.

The meta-regression showed that NVAS was associated with reduced 6-month mortality in the trials conducted in Southern Asia, in contexts with moderate or severe maternal VAD, where early infant
mortality was >30/1000 live births, >75% of infant mortality occurred in the first 6 months or >32% mothers had no schooling. These associations had disappeared by 12 months(23).

In the meta-analysis of individual level data there was no association of NVAS with reduced mortality in children of mothers who had not received vitamin A (RR at 12 months 1.05 (95% CI 0.95 to 1.16) vs. 1.00 (0.92-1.09) in women who had received vitamin A), or in women who suffered from night blindness (RR 0.94 (0.64 to 1.37) vs. 0.88 (0.78-1.00) in women who did not suffer from night blindness) (23). Furthermore, there was no association of NVAS with reduced mortality in low birth weight or preterm newborns, who would be likely to suffer from VAD(24). If NVAS worked by preventing VAD, one would have expected that the effect was more beneficial in the subgroups that were more likely to suffer from VAD than in the subgroups that were less likely to suffer from VAD.

The authors mention that the meta-analysis of individual-level data showed that the effect of NVAS may differ by baseline maternal retinol levels. However, even without correction for multiple comparisons, there was no strong association between NVAS and mortality among children of mothers with serum retinol<1.05 umol/L(23), the RR at 12 months being 0.82 (95% CI 0.60-1.13), and inclusion of maternal retinol levels from the Tanzania trial ((23), web appendix C) would have further attenuated the association. With conflicting results between a meta-regression of 11 data points and a meta-analysis of individual level data, the analysis based on individual level data should weigh more(25). Nonetheless, the paper is likely to be interpreted as support of the prevailing hypothesis that NVAS prevents vitamin A deficiency.

In a situation with two alternative hypotheses, it is important to compare their ability to explain the totality of observations. As seen in the table, the hypothesis of a negative interaction between NVAS and DTP in females explains a substantial part of the observations.

The authors of the meta-analysis briefly mention that the difference between Asia and Africa may be due to NVAS having harmful effects in females after they receive DTP vaccine and the coverage of DTP being higher in Africa. The hypothesis can be tested in several of the NVAS trials. A full analysis plan for this is available online(26).

Some are advocating that NVAS be made policy in Southern Asia(27). However, the meta-analysis suggests no benefit of NVAS by 12 months, even in Asia. Hence, if there were benefit by 6 months, it was offset by negative effects from 6-12 months. Importantly, there was indication of harm in some subgroups. The hypothesis that NVAS prevents VAD could possibly explain why NVAS had no effect in children who were severely vitamin A deficient (because the dose was too small to correct the VAD) or in areas where there was no VAD to correct. However, it cannot explain how NVAS may be harmful in certain subgroups. Before we understand these effects, we should not move to widespread NVAS distribution. It is therefore important to test the alternative hypothesis in the existing datasets.
Table: The observations regarding NVAS and the explanatory power of two competing hypotheses

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NVAS associated with reduced mortality up to 6 (but not 12) months of age in Asian studies (23)</td>
<td>Maternal VAD more prevalent in the Asian studies</td>
<td>DTP vaccine was given late and with lower coverage in the rural Asian studies(28), and negative effects were not yet apparent by 6 months of age</td>
</tr>
<tr>
<td>NVAS associated with increased mortality up to 12 months of age in African studies (23)</td>
<td>Several of the African studies were conducted in low-birth weight infants(15), and in children with low vitamin A stores(18, 29); yet no beneficial effect was found. Maternal VAD cannot explain why the effect would be negative in Africa</td>
<td>DTP vaccine was given early and with high coverage in the urban African studies(28)</td>
</tr>
<tr>
<td>Sex-differential NVAS effects from 6-12 months; negative effect in females from 6-12 months (10)</td>
<td>The hypothesis cannot explain sex-differential effects and negative effects in females from 6-12 months</td>
<td>A negative effect interaction between NVAS and DTP in females would become visible after children started receiving DTP, i.e. it would be more prominent from 6-12 months</td>
</tr>
<tr>
<td>NVAS harmful in females after DTP in the three studies which analysed it (4, 5, 15)</td>
<td>The hypothesis cannot explain negative effects in females</td>
<td>Completely compatible</td>
</tr>
<tr>
<td>Meta-regression: NVAS associated with reduced mortality up to 6 (but not 12) months of age in areas where maternal VAD common (23)</td>
<td>Compatible - but association with mortality only to 6 months of age, and only in meta-regression and not individual-level data</td>
<td>Compatible since DTP was given later and with lower coverage in the trials with maternal VAD(9, 28)</td>
</tr>
<tr>
<td>Meta-regression: NVAS associated with reduced mortality up to 6 and 12 months of age in areas with high early infant mortality(23)</td>
<td>Compatible if high early infant mortality is a proxy for VAD</td>
<td>In areas with high early infant mortality, most deaths would occur before DTP</td>
</tr>
<tr>
<td>Meta-regression: NVAS associated with reduced mortality up to 6 (but not 12) months of age in areas with low maternal schooling(23)</td>
<td>Compatible if low maternal schooling is a proxy for VAD</td>
<td>Compatible if low maternal schooling is a proxy for later DTP and lower coverage of DTP</td>
</tr>
</tbody>
</table>

Green colour: Observation consistent with hypothesis. Red colour: Observation is not consistent with hypothesis. Yellow: ambiguity. DTP=diphtheria-tetanus-pertussis vaccine; NVAS=neonatal vitamin A supplementation ; VAD=vitamin A deficiency
References


