

# Newborn Vitamin A Dosing and Early Infant Survival:

## Current Evidence and Controversy

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### Introduction

The recommendation that vitamin A supplementation to newborn infants be included as a strategy for reducing early infant mortality in Asian populations in the recent “What Works?” article in the Lancet series on maternal and child undernutrition has generated significant controversy regarding the strength of evidence to support this approach.<sup>1</sup> Both sides of this controversy have been voiced in letters to the editor, including one by an author of the Lancet paper, and editorials in leading journals accompanying the most recent results from trials.<sup>2–7</sup> The World Health Organization is currently conducting a meta-analysis of the effects of vitamin A supplementation in the first six months of life, but these results have yet to be published in the peer-reviewed literature and are inaccessible to the scientific and program communities.<sup>2</sup> Here, we provide a context for these discussions in the scientific literature and a summary of the available, peer-reviewed evidence.

### Context for newborn vitamin A supplementation

It is well accepted that vitamin A supplementation to children 6–59 months of age in settings with both endemic vitamin A deficiency and high mortality can improve child survival.<sup>1, 8</sup> Conversely, the available evidence shows that vitamin A supplementation to infants 1–5 months of age in similar settings has no effect on mortality<sup>9, 10</sup> nor does supplementation of women during pregnancy with vitamin A have an overall impact on mortality in their infants<sup>11, 12</sup>. In addition to these already acknowledged differences in the effect of vitamin A by age, it is reasonable to assume that there is unlikely to be a mortality benefit in any population without endemic vitamin A deficiency or where child mortality rates are low. This is because infectious causes of death that are most likely to be reduced by vitamin A will already be low in such populations.

It appears that infants are born with low body stores of vitamin A irre-

spective of where they are born, especially among those born prematurely or with low birthweight.<sup>13, 14</sup> For this reason, the risk of significant vitamin A deficiency in a population of newborns may best be determined by assessing the status of their mothers. Vitamin A deficiency in mothers likely affects the amount of retinol transferred from the mother to fetus in late pregnancy and the concentration in her breast milk.<sup>15–17</sup>

### The current evidence

In the early 1990s, our group at Johns Hopkins was exploring opportunities for the distribution of vitamin A within other community-based programs and wanted to ensure that supplementation was safe for even the youngest infants. This led to a safety trial of vitamin A supplementation around the time of birth at a hospital in Bandung, Indonesia, that demonstrated the safety of this approach.<sup>18</sup> Infants of mothers who chose to deliver in this hospital setting were enrolled. To our surprise, follow-up of the infants in that trial demon-

strated a large and statistically significant 64% reduction in infant mortality in the vitamin A group compared with placebo (**Table 1**).<sup>19</sup> Given this unexpected finding and the relatively small size of the Indonesian trial, a larger and representative, community-based, randomized trial of vitamin A supplementation at birth was conducted in south India, an area with endemic vitamin A deficiency. This trial also demonstrated a significant 22% reduction in early infant mortality (**Table 1**).<sup>20, 21</sup>

Concurrently, a factorial trial of both maternal postpartum and newborn vitamin A supplementation was conducted in urban Harare, Zimbabwe, that demonstrated no impact of either intervention on early infant mortality among infants of HIV-negative mothers (**Table 1**).<sup>22</sup> Results among infants whose mothers were HIV-positive were also negative overall, but there was significant effect modification by the timing of infant HIV infection.<sup>23</sup>

Most recently, two trials have been reported, one from Guinea-Bissau and one from Bangladesh; both trials supplemented infants at birth or within the first few days of life.<sup>24, 25</sup> The Guinea-Bissau trial showed no impact on early infant mortality but the Bangladesh trial showed a significant 15% reduction in early infant mortality (**Table 1**).

For some, especially those looking to make global policy statements, the answer to the variation in the results from these trials would be to conduct a pooled, or meta-analyses in order to estimate an average effect of vitamin A supplementation across all studies. This technique combines the results of studies together using a variation of a weighted-averaging approach. Critical, however, to the effective and appropriate use of meta-analysis is to be sure you are pooling studies with similar designs and characteristics. This is true in both pooling of results from trials of treatments for specific illness and in community-based prevention trials. For example, it would be inappropriate to pool results of trials evaluating lipid-lowering drugs on cardiovascular outcomes in patients with and without diabetes. One would expect *a priori* the results of trials of an effective drug for treatment of hyperlipidemia to show different

impacts on adverse outcomes in those with and without a complicating co-morbidity. Therefore, prior to moving to a meta-analytic approach to summarize the available evidence on newborn vitamin A supplementation, it is critical to determine if the characteristics of the study populations are similar and, as a result, whether one should expect to see a common 'average' effect on mortality.

We have already framed one aspect of this assessment with the expectation that vitamin A supplementation is likely to have an impact only in populations with significant vitamin A deficiency and high mortality. Which of the study populations in trials reported in the peer-reviewed literature meet these criteria? Based

on data in **Table 1**, only the community-based trials in south India and Bangladesh show both these characteristics. Both of these trials were conducted in populations with high infant mortality and had rates of maternal night blindness in pregnancy that met the criteria for defining vitamin A deficiency as a problem of public health importance. However, both African studies were con-



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ducted in populations with little vitamin A deficiency and mortality rates that were very low (Zimbabwe), or where the highest risk infants were excluded (low birthweight infants) and free care and drugs were provided to sick children (Guinea-Bissau). One would then expect vitamin A supplementation in these two African study populations to have little to no effect on mortality, an expectation consistent with their results. Therefore, combining these four trials in a meta-analysis would violate the principle assumptions of this analytic strategy and be inappropriate. The 'weighted average' effect of combining all these trials in a meta-analysis would have no relevance to any real population.

The study that is most inconsistent with expectation among the randomized trials conducted to date is the one from Indonesia. This study was the first and smallest of the trials, conducted in a hospital-based setting, showed little evidence of vitamin A deficiency among the participating mothers, and the baseline infant mortality was low. Despite these characteristics, there was a large and statistically significant reduction in early infant mortality. There are two

**Table 1:** Summary of randomized trials of newborn vitamin A supplementation and child survival in primarily HIV-negative populations

Study	Vitamin A status
Indonesia <sup>19</sup>	Maternal serum retinol: Vitamin A: Mean = 1.79 µmol/L Control: Mean = 1.75 µmol/L <b>Interpretation:</b> Distribution of serum retinol suggests little vitamin A deficiency.
India <sup>20-21</sup>	Maternal night blindness during pregnancy index = 5.2%. <b>Interpretation:</b> Meets the criteria to define vitamin A deficiency as a public health problem.
Zimbabwe <sup>22</sup> HIV Negative Mothers	Baseline serum retinol: - Total: 37.1% <1.05 µmol/L 6 weeks post-partum serum retinol: - Control: 6.0% <1.05 µmol/L <b>Interpretation:</b> 6 week post-partum serum retinol distribution suggests little vitamin A deficiency. Baseline values subject to significant hemodilution due to late pregnancy plasma volume expansion.
Guinea-Bissau <sup>24</sup>	Maternal retinol binding protein 0.3% <1.11 µmol/L* *equivalent to serum retinol <1.05 µmol/L. <b>Interpretation:</b> Distribution of retinol binding protein suggests little vitamin A deficiency.
Bangladesh <sup>25</sup>	Maternal night blindness in last pregnancy = 9.7% <b>Interpretation:</b> Meets the criteria to define vitamin A deficiency as a public health problem.

potential explanations for this inconsistency. It is well known that vitamin A deficiency is highly prevalent in both women and children in much of Indonesia.<sup>15</sup> Given the tight homeostatic control of serum retinol levels, liver reserves may have been low in these women despite their serum retinol levels seeming adequate. Another explanation is that the findings were due to chance.

In summary, except for one of the five randomized trials that have been done, the data are consistent with a beneficial impact of newborn vitamin A supplementation on early infant mortality in populations with both endemic vitamin A deficiency and high mortality. In populations without these two attributes, there was no observed survival benefit to newborn supplementation.



Village in rural Bangladesh

Study population	Sample size for analysis	Primary results # deaths/rate
<ul style="list-style-type: none"> <li>- Infants born at single hospital.</li> <li>- Exclusions:               <ul style="list-style-type: none"> <li>• BW&lt;1500 g</li> <li>• Life threatening illness</li> </ul> </li> <li>- Followed through 12 months</li> </ul>	Vitamin A: 1034 Control: 1033	Vitamin A: 7 (7.2/1000 person-years) Control: 19 (19.8/1000 person-years) RR=0.36 (95% CI: 0.16, 0.87) <b>Interpretation:</b> Control group mortality rates low
<ul style="list-style-type: none"> <li>- Population-based in two rural districts in Tamil Nadu</li> <li>- Exclusions:               <ul style="list-style-type: none"> <li>• Born &gt;20 km outside study area</li> <li>• Infant died prior to first post-delivery visit</li> </ul> </li> <li>- Followed through 6 months</li> </ul>	Vitamin A: 5786 Control: 5833	Vitamin A: 146 (53.8/1000 person-years) Control: 188 (69.1/1000 person-years) RR=0.78 (95% CI: 0.63, 0.96) <b>Interpretation:</b> Control group mortality rates high
<ul style="list-style-type: none"> <li>- Hospital and maternity clinic in urban Harare.</li> <li>- Exclusions:               <ul style="list-style-type: none"> <li>• Life threatening illness</li> <li>• Multiple birth</li> <li>• BW &lt;1500 g</li> <li>• HIV + mother</li> </ul> </li> <li>Followed through 12 months</li> </ul>	Vitamin A: 4592 Control: 4601	Vitamin A: 88 (21.0/1000 person-years) Control: 82 (19.3/1000 person-years) RR=1.08 (95% CI: 0.80, 1.46) <b>Interpretation:</b> Control group mortality rates low
<ul style="list-style-type: none"> <li>- Followed through 24 months; results shown here only through 12 months for consistency with other studies.</li> </ul>	Vitamin A: 2106 Control: 2169	Vitamin A: 88 (49.0/1000 person-years) Control: 86 (45.6/1000 person-years) RR=1.07 (95% CI: 0.79, 1.44) <b>Interpretation:</b> Control group mortality rates high
<ul style="list-style-type: none"> <li>- Population-based in two rural districts of northwest Bangladesh</li> <li>- Exclusions:               <ul style="list-style-type: none"> <li>• Born outside study area</li> <li>• Died prior to first post-delivery visit</li> </ul> </li> <li>- Followed through 6 months</li> </ul>	Vitamin A: 7956 Control: 7992	Vitamin A: 306 (38.5/1000 live births) Control: 360 (45.1/1000 live births) RR=0.85 (95% CI: 0.73, 1.00) <b>Interpretation:</b> Control group mortality rates high

### Mechanisms for age-specific effects of vitamin A supplementation

The reasons for the differences in observed effect of vitamin A supplementation by age are unclear but some combination of the following mechanisms are likely to play a role:

- It is clear that the benefits of vitamin A supplementation on survival are mediated in newborns and for children aged 6–72 months through an effect on case fatality, not on the incidence of infection.<sup>21</sup> It may be that the mechanism by which this occurs is different in these two age groups. For newborns, this benefit may be mediated through an accelerated maturation of gut and respiratory tissue similar to that seen with corticosteroid treatment of pregnant women

who are expected to deliver prematurely, to accelerate lung maturation in the infant; or through an effect on innate immune system function. For older children, the mechanism is thought to be related to maintenance of epithelial barriers and improvements in antigen-specific immune response.<sup>26</sup>

- The lack of beneficial impact in the 1–5 months age range has been attributed to the protective effects of nearly exclusive breast feeding in the first half of infancy whereas poor quality complementary foods may reduce vitamin A intake in older infants whose breast milk vitamin A intake is decreased and who experience more frequent episodes of gastroenteritis.

While these hypothetical mechanisms have been proposed, there is little strong evidence with which to

understand these age-specific effects of vitamin A supplementation on child survival.

## Conclusion

While mechanistic explanations remain theoretical, there is compelling evidence that newborn vitamin A supplementation can reduce the risk of infant death in Southern Asia by about 20%.<sup>1</sup> At current levels of infant mortality, high coverage of supplementation could reduce the numbers of infants dying each year by some 200,000 in Asia. This represents a worthwhile pursuit toward achieving the Millennium Development Goals while research continues to reveal mechanisms to strengthen biological plausibility. Further, there appears to be a strong indication for field intervention trials that can provide decisive evidence of public health impact of newborn vitamin A delivery in African populations with vitamin A deficiency and high infant mortality.

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