Vitamin A Supplementation, Infectious Disease and Child Mortality: A Summary of the Evidence

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Abstract

This manuscript reviews the evidence related to the effects of vitamin A (VA) supplementation of women and children on child health and mortality. VA supplementation of children aged 6–59 months has been well studied, and meta-analyses have consistently demonstrated effects on all-cause mortality, yet its mechanisms and the reasons for heterogeneous effects on mortality across trials continue to be debated. Recent meta-analysis of cause-specific mortality suggests beneficial effects on diarrheal mortality, with null but potentially beneficial effects also present for mortality from measles, lower respiratory infection, and meningitis. Some evidence suggests that pneumonia severity may increase with VA supplementation in this age group, particularly among well-nourished children. Maternal supplementation with VA during pregnancy has not shown benefits on neonatal mortality in large trials. A recent meta-analysis suggested that high-dose supplementation of lactating women immediately following delivery did not affect child survival. There is still uncertainty around the benefits of neonatal VA supplementation that should be resolved once the findings of ongoing trials are reported.

Introduction

Next year will mark the 100th anniversary of the isolation of ‘fat soluble A’ by McCollum and Davis [1]. Although interest in vitamin A (VA) waned over much of the subsequent century, a renewal of interest in the 1980s led to numerous randomized trials testing the efficacy of VA supplementation on adverse outcomes among preschool age children, infants and neonates, and pregnant and lactating women. In this chapter, we provide an overview of the epidemiological
evidence on routine preventive VA supplementation of neonates, infants, and children and child health outcomes. It is important to note that VA supplementation has long been demonstrated as efficacious in the treatment of measles and both treatment and prevention of xerophthalmia, and in the interest of brevity we have not extensively reviewed that evidence here [2].

**Epidemiology and Causes of Vitamin A Deficiency during Childhood**

VA deficiency is a problem of greatest public health concern among children less than 5 years of age and pregnant and lactating women. It has been estimated that 190 million preschool children and 19.1 million pregnant women have low serum retinol concentrations (<0.70 μmol/l) in countries at risk [3]. Night blindness, the first stage of clinical VA deficiency, affects 5.2 million preschool age children and 9.75 million pregnant women in countries at risk. Among the WHO regions, South East Asia and Africa have the highest prevalence of preschool subclinical VA deficiency (at 49 and 44%, respectively), although the absolute number of children at risk is much higher in South East Asia (91 vs. 56 million children) [3].

The mean requirement for VA during early childhood ranges from 180 μg retinol equivalents (RE)/day for neonates and infants to 200 μg RE/day up to age 6 years, with recommended safe intake set at 375 and 450 μg RE/day, respectively [4]. In children, clinical symptoms of VA deficiency include night blindness as the first physical manifestation, proceeding to conjunctival and corneal involvement which then leads to corneal ulceration and scarring resulting in blindness if uncorrected [2]. It is well accepted that the immune-compromising effects of VA deficiency manifest long before the physical appearance of deficiency [2].

VA deficiency during infancy and early childhood is caused by multiple factors including maternal VA deficiency (and low concentrations of retinol in breast milk), suboptimal breastfeeding, complementary foods low in VA, and severe or repeated episodes of infectious disease [5]. Sources of performed VA include liver, eggs, milk, and fortified foods, all of which are consumed infrequently in developing countries. Generally, foods containing provitamin A carotenoids such as green leafy vegetables and yellow-orange fruits such as mango and papaya are thought to provide the majority of dietary VA in such countries. Following the downward adjustment of conversion factors for provitamin A carotenoids for estimating intake of VA from plant foods, it has been generally assumed that such foods contribute relatively little towards meeting VA requirements [6–8]. While plant sources of food are unlikely by themselves to fully meet requirements when consumed in the quantities typical of many developing country diets, there is some evidence that their consumption may still offer protection against xerophthalmia, mortality, and growth faltering, particularly among children not supplemented with VA [9–12].
Supplementation during Pregnancy

Early work by Mellanby and Green reported in 1929 suggested the potential for VA to reduce puerperal septicemia, although little follow-up research on the potential for VA to reduce mortality or morbidity among pregnant women occurred over the next 60 years [13]. More recently, a large randomized controlled trial in Nepal reported a 44% reduction in maternal mortality associated with daily supplementation with VA or β-carotene throughout pregnancy [14]. Based on these promising findings, large confirmatory trials were launched in Bangladesh and Ghana, neither of which reported significant decreases in pregnancy-related mortality up to 6 weeks [15, 16]. Pooled analysis of these three trials suggests no overall effect of supplementation on maternal mortality, though heterogeneous findings have spurred debate over whether the differences are attributable to chance or context [17]. One consistent observation across all of these large studies was the lack of an effect on neonatal mortality, effectively putting to rest the suggestion that VA supplementation during pregnancy could be an effective child survival initiative although other potential benefits are being explored [17].

Postpartum Vitamin A Supplementation

Postpartum VA supplementation was originally devised as a strategy to improve VA status of the mother/infant dyad, and was once implemented as a program in many countries. A recent meta-analysis examined the effect of maternal postpartum VA supplementation on infant mortality and morbidity [18]. The analysis reported no significant effect on mortality (RR = 1.05, 95% CI: 0.92–1.20) or risk of diarrhea or acute respiratory infection [18]. Based on a review of the evidence, WHO recently issued guidelines stating that VA supplementation of postpartum women is not recommended for the prevention of maternal and infant morbidity or mortality (table 1) [19].

Maternal Vitamin A Supplementation and HIV Transmission

Observational studies in the 1990s suggested that low maternal VA status was associated with greater risk of HIV transmission from mother to child as well as higher rates of infant mortality [20–22]. Accordingly, four randomized placebo-controlled trials exploring various combinations of VA and/or β-carotene supplementation to women and infants were launched in Tanzania, Malawi, South Africa, and Zimbabwe [23–26]. The design and results of these trials are presented in table 2. In a pooled analysis of these trials, antenatal or postpartum maternal supplementation with VA or VA/BC was found to have no effect on HIV transmission (RR = 1.04, 95% CI: 0.87–1.24) [27].
It is important to note heterogeneity in the content of supplements and timing of supplementation across these trials. Findings from two of the trials suggest that VA supplementation may increase the risk of HIV transmission. The Tanzania trial, which tested the effects of supplementation with VA/BC during pregnancy and postpartum reported a 38% increase in HIV transmission or death compared to the control group (RR = 1.38, 95% CI: 1.09–1.76, p = 0.009) [23]. In the Zimbabwe trial, risk of either HIV transmission or mortality was higher among infants whose mothers received a one-time 400,000 IU dose or who directly received a 50,000 IU dose as neonates [26]. Paradoxically, the group that had received both maternal and child supplementation showed no difference in risk compared with the control group. Yet, among those infants who were PCR negative at 6 weeks, all three groups including either maternal postnatal and/or neonatal VA supplementation had approximately double the mortality risk compared with the placebo group (table 2).

There is some evidence from in vitro and other epidemiological studies supporting the hypothesis that VA could increase transmission [28]. An in vitro study suggested that VA could increase the expression of CCR5 receptors leading to increased replication of HIV-1 and increased susceptibility of monocytes and macrophages to HIV [29]. Evidence from a prospective cohort study in the

<table>
<thead>
<tr>
<th>Population subgroup</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td>Pregnant women [53]</td>
<td>Not recommended for the prevention of maternal and infant morbidity and mortality, but in areas where VA deficiency is a severe public health problem, VA supplementation is recommended for prevention of night blindness. Quality of evidence: high for maternal mortality, moderate for other outcomes.</td>
</tr>
<tr>
<td>Early infants (1–5 months) [54]</td>
<td>Not recommended as a public health intervention for the reduction of morbidity and mortality. Quality of evidence: moderate for infant mortality, low for other outcomes.</td>
</tr>
<tr>
<td>Older infants and young children 6–59 months of age (including HIV+) [49]</td>
<td>Infants 6–11 months of age: 100,000 IU once. Children 12–59 months of age: 200,000 IU every 4–6 months. Quality of evidence: high for all-cause mortality, moderate to very low for other outcomes.</td>
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<tr>
<td>First author and year</td>
<td>Setting</td>
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<td>Coutsoudis, 1999 [25]</td>
<td>South Africa</td>
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<td>Fawzi, 2002 [23]</td>
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<td>Kumwenda, 2002 [24]</td>
<td>Malawi</td>
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<td>Humphrey, 2006 [26]</td>
<td>Zimbabwe</td>
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United States suggested a U-shaped relationship between dietary intake of VA and HIV disease progression and mortality [30, 31]. Further analysis of breast milk samples from the Tanzanian trial revealed that VA/β-carotene supplementation was associated with increased risk of subclinical mastitis as well as increased HIV viral load in breast milk, suggesting a potential mechanism for increased transmission [32, 33].

**Neonatal Vitamin A Supplementation**

Two recent meta-analyses have consolidated the findings of studies of VA supplementation within the first 30 days of life, but reached different conclusions [34, 35]. The first reported no significant effect on mortality risk during a 12-month follow-up period (6 studies, RR = 0.92, 95% CI: 0.75–1.12) [36]. The second study presented findings disaggregated by time to follow-up, and found a significant reduction of mortality risk among all infants at 6 months (5 studies, RR = 0.86; 95% CI: 0.77–0.97) but not at 12 months (4 studies, RR = 1.02; 95% CI: 0.87–1.20) [35]. The latter paper argued that routine programmatic VA supplementation reached many children above 6 months in most of the included study countries, potentially leading to an attenuation of findings when using a follow-up period exceeding the first 6 months of life. A WHO technical consultation on neonatal VA supplementation also noted disparate findings in effects of supplementation by region; studies from Asian contexts appeared more suggestive of benefit than studies in Africa, although such differences were not statistically significant in meta-regression [37]. A separate meta-regression has also suggested that a protective effect appears to be more evident among neonates supplemented in the first 48 h of life living in areas of prevalent VA deficiency [38].

At this time, the WHO does not recommend neonatal VA supplementation [39]. In response to recommendations from a WHO technical consultation on neonatal supplementation research priorities, trials are currently underway in Tanzania, Ghana, India, and Pakistan to better understand the potential contextual differences noted above and improve estimates of the efficacy of neonatal supplementation [37]. More work is also needed to understand potential mechanisms through which neonatal supplementation might affect mortality risk; it has been hypothesized that it may do so through effects on the immune system or organ maturation [37].

**Vitamin A Supplementation among Infants 1–6 Months of Age**

In contrast to older (or younger) age groups, there is little evidence that VA supplementation of infants 1–6 months of age is protective against mortality.
Several studies in Asia, one in Africa, and a multicenter study have been undertaken, and none showed statistically significant benefit; a recent pooled estimate was also null (5 studies, RR = 1.05, 95% CI: 0.88–1.26) [40].

**Vitamin A Supplementation for 6- to 59-Month-Olds**

*All-Cause Mortality*

The most recent and comprehensive meta-analysis of published studies reported that VA supplementation of children 6–59 months of age led to a 24% reduction in all-cause mortality (RR = 0.76, 95% CI: 0.69–0.83), an estimate that remained largely the same as previous analyses [41, 42]. Heterogeneity in the findings of included studies was also apparent (I² = 48%, p = 0.02). Many explanations have been proposed for heterogeneity across trials including coexisting micronutrient deficiencies or differences in dietary fat intake (which may influence absorption or utilization of VA), differences in dosing frequency or amount, and differences in the incidence/prevalence of infectious disease. In the most recent review, significant beneficial effects were apparent in both Africa and Asia, among both boys and girls, and among multiple age strata (6–12 and 12–60 months) [41].

An interesting nuance is that more frequent dosing than the currently recommended WHO frequency of 4–6 months was associated with a 54% reduction in all-cause mortality (compared with a 19% reduction among those supplemented every 4–6 months). This suggests the possibility that at least in some settings, a more frequent dosing schedule than is currently implemented could increase the efficacy of the intervention (provided that it could be implemented with similar coverage rates). Paradoxically, the analysis also found that those who received less frequent dosing appeared to have greater mortality benefit than those who received supplementation every 4–6 months, an observation that cannot be easily explained [41].

Another important recent development in the evidence base related to supplementation of this age group was the presentation of preliminary findings of the **DEVTA** trial, the largest randomized controlled trial of VA supplementation to date (conducted in India and involving over 1 million participants), a trial that remains unpublished at the time of this publication (2012). Findings available online suggested that supplementation every 6 months with 200,000 IU had only a small (RR = 0.96, 99% CI: 0.88–1.05) statistically non-significant benefit on all-cause mortality [8]. In sensitivity analysis of all trials conducted to date including these findings, the overall effect estimate of the meta-analysis remained statistically significant, but the benefit was cut in half (from 24 to 12%) [41]. Some have used these findings to support arguments questioning the efficacy of VA [43]. Others have argued that the continued presence of VA deficiency in the VA arm of the trial (2.2% had Bitot’s spots and 11% had plasma retinol <0.35 μmol/l) is evidence that the dose may not have been adequate to achieve maximal efficacy [8, 44].
VA has a number of important roles in immunity including maintenance of epithelial integrity, regulating differentiation and function of monocytes, and influencing differential Th1/Th2 responses [45]. Early research in the 1930s generated interest around the ‘anti-infective’ properties of VA, and an early trial by Ellison demonstrated that VA dramatically lowered mortality rates of children with measles [1, 46, 47]. Since that time, a number of hospital-based trials have firmly established the efficacy of VA in the treatment of measles [45, 48].

In the most recent meta-analysis of epidemiological studies, VA supplementation significantly reduced the risk of mortality due to diarrhea by 28% (RR = 0.72, 95% CI: 0.57–0.91) as well as incidence of diarrhea by 15% (13 studies, RR = 0.85 (95% CI: 0.82–0.87), but no effect on prevalence of diarrhea was observed (2 studies, RR = 1.08, 95% CI: 1.05–1.12). Based on the relationship between supplementation and mortality, it has been posited that VA may help to protect against severe diarrhea, but might not affect more mild forms, although recent meta-analyses have not disaggregated by severity of the outcome [2]. The mechanism through which VA affects incidence or severity of diarrhea is uncertain, although the vitamin plays an important role in maintenance of epithelial integrity and in mucus secretion, both of which may help to protect against diarrhea [48].

It is well documented that measles is a precipitating factor of a great deal of child xerophthalmia and that supplementation with VA as treatment during a measles episode strongly reduces the risk of mortality [2]. Recent meta-analysis of trials of routine preventive supplementation also suggests reductions in measles-related mortality, although this finding was not statistically significant (5 trials, RR = 0.80, 95% CI: 0.51–1.24).

In contrast to diarrhea and measles, evidence for an effect of VA supplementation on lower respiratory tract infections including pneumonia has been greatly inconsistent. The most recent review of the effects of supplementation on cause-specific morality attributable to lower respiratory tract infections indicated a non-significant trend toward benefit (7 studies, RR = 0.78, 95% CI: 0.54–1.14), while finding a non-significant increase in incidence of lower respiratory tract infections (7 studies, RR = 1.14, 95% CI: 0.95–1.37). Another recent meta-analysis of the effects of VA on mortality specifically attributable to pneumonia also reported null effects, though the risk estimate was significantly attenuated compared with the above analysis, and some of the included studies differed (7 studies, RR = 0.94, 95% CI: 0.67–1.30) [40].

There is evidence from both hospital-based studies and community-based trials that VA supplements may increase the risk of acute lower respiratory tract infections among well-nourished children [48]. It has been speculated that high-dose VA might cause dysregulation of the immune system or a proinflammatory immune response, although this is uncertain [45, 48].
Programmatic Considerations

WHO recently issued guidance recommending high-dose VA supplementation for infants and children 6–59 months of age in settings where VA deficiency is a public health problem (table 1) [49]. Economic analyses have repeatedly ranked VA supplementation of children 12–59 months of age as one of the most cost-effective health interventions available, it was recently ranked at the top of the list along with zinc supplementation of interventions chosen by the Copenhagen consensus. Biannual distribution of capsules to children 6–59 months containing 200,000 IU VA is a relatively inexpensive intervention to implement and requires little additional human resource mobilization. Initially coupled in many countries with National Immunization Days for polio (for at least one round per year), in recent years efforts have been made to distribute VA through child health days along as part of a package often including insecticide-treated bednets, anti-helminth medication, and other core child health interventions. Critics of VA capsule supplementation programs have expressed concern that capsule supplementation, originally considered to be a short-term solution to controlling the deficiency has been implemented in many countries for decades, and that it might be holding back funding of other approaches to controlling VA deficiency [43].

There are also programmatic uncertainties and issues requiring further research. Two-round coverage rates are often quite high, nearing 80% in many countries, but children who are missed by one or both rounds are often socio-economically worse off than those reached, and could therefore be at greatest risk of deficiency [50]. It is difficult to quantify how many lives are saved each year from such programs, as few effectiveness evaluations have been undertaken. It is possible that more frequent supplementation could be more efficacious, particularly since it is known that serum retinol declines 4 months after supplementation [2], yet more frequent supplementation also requires more resources and risks donor and community fatigue. There is some evidence suggesting that the effect of VA supplementation on risk of all-cause mortality may differ by vaccination status of children [51, 52]. These findings are of potential concern to programs given that vaccination is a convenient potential health contact for the administration of VA. Lastly, the rapid expansion of other strategies for addressing VA deficiency including home fortification with micronutrient powders, fortification, and homestead food production, suggests the need for more work to develop strategies to balance or target different approaches including consideration of the potential adverse effects of VA fortification in areas of high HIV prevalence.

Conclusions

The basis for VA supplementation of 6- to 59-month-old infants and young children is well established through many trials. More work is needed to
understand the mechanisms through which VA reduces all-cause and cause-specific mortality and to more firmly establish the evidence related to supplementation of other groups, particularly neonates.

References

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