RESEARCH PAPER

Association of Vitamin A Status With Under-Five Mortality in India

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Objective: To re-estimate the survival benefit from Vitamin A supplementation (VAS) in India using meta-analysis and to correlate mortality and vitamin A deficiency (VAD) in children aged 6 month to 5 year. **Methods:** Pooled risk ratio (fixed effects model) for mortality reduction with VAS was calculated from available Indian studies. Computed mortality rates in 6 months to 5 years children in Indian states were regressed on VAD prevalence estimates of the states. **Results:** There was no reduction in risk of all-cause mortality with VAS (RR=0.96; 95% CI: 0.89, 1.03). When regressing mortality on VAD in high or low VAD prevalence states, the regression coefficients were discordant. **Conclusion:** No survival benefit was observed for VAS in India from the available literature. The targeting of VAS programs should be given serious consideration.

Keywords: *Deficiency, Policy, Prevalence, Universal supplementation.*

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The World Health Organization's (WHO) recommendation for high-dose vitamin A supplementation (VAS) in children aged 6 months to 5 years, is for settings where vitamin A deficiency (VAD) is a public health problem, with ≥20% VAD prevalence as evaluated by a low serum retinol concentration [1]. This was assumed to be national condition in India, where universal VAS has been implemented for many years now. An additional and important consideration for implementing universal VAS was a Cochrane analysis [2] that showed a 12% reduction in 6 months to 5 year mortality with VAS [RR (95% CI) 0.88 (0.83, 0.93)]. This survival benefit was assumed to be relevant for India as well.

The recent Comprehensive National Nutrition Survey (CNNS) showed that the serum retinol levels based national VAD prevalence in children was 15.7% (95% CI: 15.2%, 16.3%); which was significantly less than the cut off for identifying VAD as a public health problem [3]. Secondly, the potential survival benefit of VAS would be more relevant to India if it was calculated from Indian studies. The purported survival benefit [2] also merits re-evaluation based on contemporary data, given the impressive decline in child mortality in recent years. Here, we evaluate the potential reduction in under-five mortality attributable to VAS from Indian data, and examine current estimates of 6 months to 5 years mortality (which is the age range of the survival benefit attributed to VAS), in different Indian states in relation to their VAD prevalence [3].

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METHODS

Meta-analysis of Indian studies: For the meta-analysis, we identified VAS studies conducted in India from the included trials in the Cochrane review [2]. Studies evaluating fortification or weekly low dose supplemen-tation were excluded. Raw data from the identified studies was extracted from the original publications and confirmed from the Cochrane review input [2]. We performed meta-analysis using Review Manager (RevMan) version 5.4.1 software [4]. The pooled effect size of risk ratio (RR) was estimated by inverse variance weighted average, as in the Cochrane review [2]. All study details regarding context, participants and quality are available in the original Cochrane review [2]. A sensitivity analysis was performed with a random effects model.

Association of child mortality with VAD: Infant mortality rate (IMR) estimates for 2018, the last year (2016-2018) of the CNNS that provided the state-based VAD prevalence values [3], were obtained from the Sample Registration System bulletin [5]. IMR data were complete for all States and Union Territories of India. Neonatal mortality rate (NMR) and under 5 years mortality rate (U5MR) data for 2018, for 22 of 30 states (including Jammu and Kashmir), were shared by the Ministry of Health and Family Welfare,

Government of India. Missing state values for NMR and U5MR were imputed from a linear regression of each on the IMR. Mortality in children aged 6 months to 5 years was computed using the following equations (all mortality estimates are per 1000 live births): 6 months to 5 years mortality = U5MR - 0 to 6 month mortality; 0 to 6 month mortality = NMR + [0.5 × (IMR-NMR)], conservatively assuming that 50% mortality in the 1 -12 month age group occurred before 6 months of age.

VAD prevalence estimates in different states were obtained from the CNNS [3], conducted in 30 states and Union Territories of India from 2016 to 2018, using a multistage stratified probability proportion to size sampling design. Serum retinol measurements were made on 9563 children aged 1-5 years. Serum retinol levels were adjusted for C-reactive protein (CRP), as a marker of inflammation using a new probability method [6]. Linear regression analysis of 6 month to 5 year mortality on VAD prevalence was performed for all states, and separately for states with prevalence <20% (upper limit of 95% CI<20%) and for the remaining states.

The potential reduction in under-five mortality that could accrue was estimated by applying attributable fraction derived from the meta-analyzed RR estimates of 6 months to 5 years children to U5MR.

RESULTS

Meta-analysis of Indian studies: Five trials were included in the meta-analysis [7–11]. One study was excluded, as the intervention comprised a small weekly dose of vitamin A [12]. There was no beneficial effect of VAS on mortality with the fixed effects model (**Fig. 1**; RR=0.96; 95% CI: 0.89, 1.03; *P*=0.23; I^2=56%; Heterogeneity *P*=0.06). The findings were similar with the random effects model (RR=0.84; 95% CI: 0.56, 1.26; *P*=0.40).

Association of child mortality with VAD: The R^2 for the regression of NMR against IMR was 93% and for the regression of U5MR against IMR was 98.4%; both regressions had good fits. Missing NMR and U5MR values in 8 states were predicted from these regressions. The calculated national 6 month to 5-year mortality rate was 8.5/1000 births, and for states ranged from 6 to 41/1000 live births (Kerala and Madhya Pradesh, respectively). VAD ranged from 0.7% to 40.8% [3].

Mortality was not associated with VAD prevalence when all states were considered [β= 0.08 (95% CI:-0.04, 0.20)]. However, mortality was negatively associated (**Fig. 2**) with VAD in states with VAD prevalence not <20% β (95% CI) = -0.27 (-0.49, -0.05)]. At the national level, there was no predicted mortality gain that would accrue from VAS, using the pooled RR from the Indian studies of survival benefit with VAS.

DISCUSSION

In present day India, the motivation for continuing the universal high-dose VAS is suspect, particularly when based on a purported survival benefit. Globally, the effect of VAS on reducing child mortality has attenuated [13], and the drop in child mortality rates and the incidence of morbidities associated with VAD [14] all point in this direction.

The present meta-analysis of Indian studies also showed no evidence of survival benefit of VAS. Even if the survival benefit from global studies that were conducted when VAD was rife [2] were used, the absolute risk reduction for 6 months to 5-years national mortality would be 1/1000 live births (95% CI: 0.6, 1.4), translating to a reduction of U5MR (per 1000 live births) from 36 to 35 (95% CI: 34.6, 35.4). The absolute U5MR reduction with this assumption ranged from 0.3 to 1.9/1000 live births across states. Under real life programmatic settings, it is unlikely that any survival benefit will accrue, even with this optimistic assumption.

There are several reasons to conclude that the relation

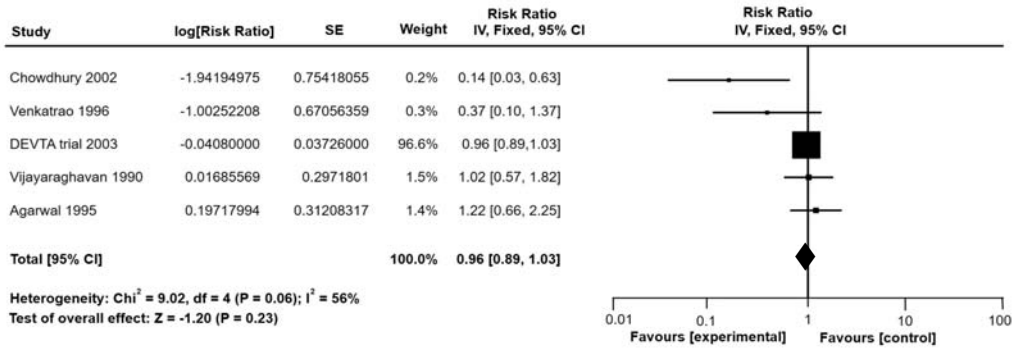
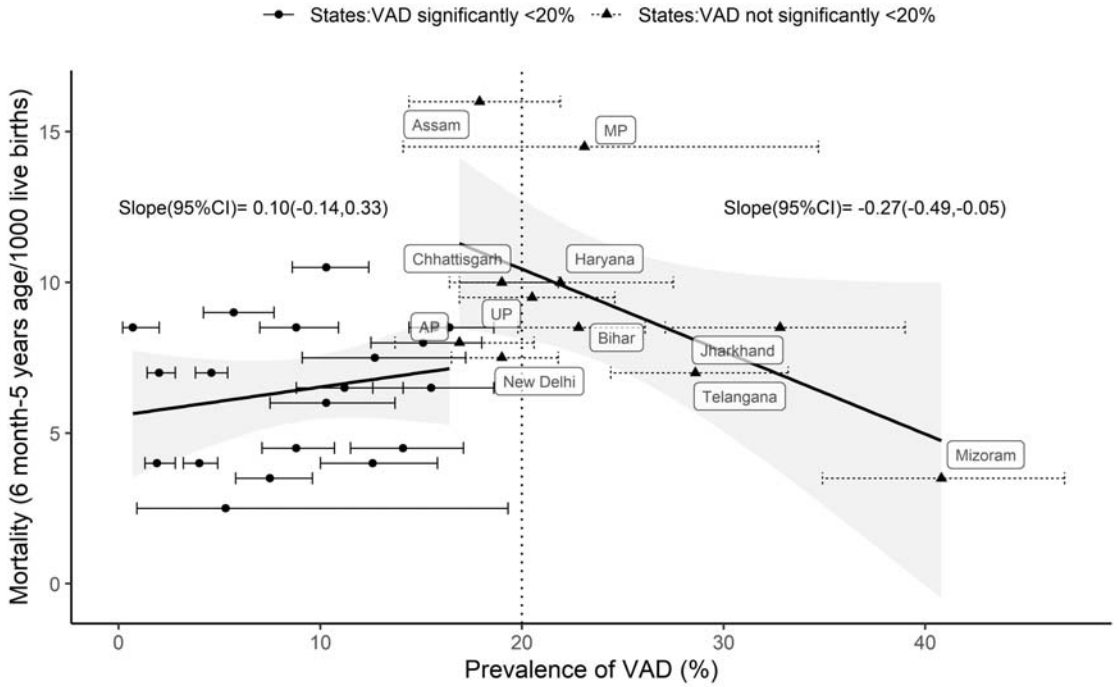


Fig. 1 Fixed effects model meta-analysis of the effect of mega dose vitamin A supplementation on mortality in under-five children in studies conducted in India.

between mortality and VAD does not exist in the present context. Overall, there was an absence of any association between mortality and VAD, when all states were considered. Next, there was discordance in the sign of the regression coefficient of mortality on VAD prevalence, when VAD prevalence was either high or low. Finally, the association of mortality with VAD was counter-intuitively negative in states with higher VAD prevalence. Limitation of this analysis is the use of state level estimates with the likelihood of the ecologically inference fallacy, if individual effects are interpreted based on these aggregate data.

The next step then, is to consider the roll back of the national VAS program, into a targeted program for defined states [3]. The definition of these states could be first, based on the >20% prevalence of VAD cut-off, or for those with higher mortality. A state-based analysis of VAD by Reddy, et al. [3] showed that only three states (Mizoram, Telangana and Jharkhand) had significantly >20% VAD prevalence (based on the lower 95% CI limit being >20%). There were 19 states with VAD prevalence significantly <20% (upper 95% CI limit being <20%). Therefore, in the most rigorous sense, only Mizoram, Telengana and Jharkhand qualify for continuation of VAS, as their VAD prevalence was significantly greater than 20%. Second, one could consider those states whose VAD prevalence was not significantly lower than 20% (where their 95% CI included 20%) in addition to higher (greater than national value) mortality rates. This occurred in the states of Assam, Bihar, Chhattisgarh, Haryana, Madhya Pradesh and Uttar Pradesh (**Fig. 2**). A targeted VAS approach could be considered in these nine states, with surveillance in the other states where VAS can be rolled back.

A similar roll-back approach has been suggested in a recent re-assessment of the need for national VAS programs across different countries [15]. This analysis suggested the cessation of VAS programs based on VAD and mortality data as the first step, which would help targeting limited resources, and then ensuring VAS coverage where required. Further, the decline in child mortality from diarrhea and measles (the morbidities that significantly contribute to VAD-related mortality) is probably because of improvements in nutritional status, water and sanitation, and vaccinations, and the explicit role of VAS in this decline is not clear [16]. In agreement and in conclusion, the Indian national VAS program cannot be justified on the basis of recent estimates of national VAD prevalence, nor based on a survival benefit. There is now a need for serious consideration of a targeted approach to



AP: Andhra Pradesh; UP: Uttar Pradesh; MP: Madhya Pradesh; VAD: vitamin A deficiency. Circles: States with VAD prevalence significantly <20% (data points represented by circles, upper limit of 95% CI<20%). Triangles: States with VAD prevalence not significantly <20% (data points represented by triangles, upper limit of 95% CI not less than 20%). Error bars indicate 95% CI of VAD prevalence. Dashed vertical line corresponds to the 20% prevalence mark of VAD.

Fig. 2 Prevalence of vitamin A deficiency and 6 month to 5 year mortality in Indian states.

VAS in India, and a potential basis for the targeting of this program has been suggested.

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Ethics clearance: This study was conducted with publicly available secondary data. The details of ethics clearance for data collection are reported elsewhere.
Contributors: HPS,UK: were involved in the data acquisition, analysis, drafting the work; SG: involved in analysis and interpretation of data, revising the manuscript critically for important intellectual content; TT,AVK: involved in conception of the work, analysis and interpretation of data, revising the manuscript critically for important intellectual content and final approval of the version to be published.
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