Hollm-Delgado MG, Piel FB, Weiss DJ, et al. **Vitamin A supplements, routine immunization, and the subsequent risk of Plasmodium infection among children under 5 years in sub-Saharan Africa.** eLife. 2014;3:e03925.

Introduction

Despite substantial evidence from animal and in vitro studies that vitamin A, through its retinoic-acid metabolite, may confer protection against malaria morbidity and mortality[1-4], evidence from human trials is scarce and inconclusive[5,6]. In addition, there are concerns that vitamin A supplementation (VAS), when combined with routine vaccination, particularly diphtheria-tetanus-pertussis vaccine (DTP) [7,8], may impose detrimental effects on malaria outcomes, which could undermine support for existing VAS programs in malaria endemic regions. In sub-Saharan Africa, where VAD overlaps with malaria and other infections, research into the interactions between vitamin A and malaria may inform the development of better integrated control strategies.

This issue of NNA summarizes an article by Hollm-Delgado[9] recently published in *eLIFE* reporting on the association between routine high-dose VAS and childhood malaria risk, in the context of high vaccine coverage.

Methods

Data available in the Macro International Demographic and Health Surveys (DHS) database were screened for nationally representative surveys during which children were tested for *P. falciparum* parasites using conventional microscopy. Of 20 national surveys reviewed, data from four countries, namely Burkina Faso, Mozambique, Rwanda and Senegal, were available on the children's vaccination history and exposure to VAS. The child's date of vaccination (BCG, DTP, measles and polio) was collected from the child's health card. For VAS, consumption of VAS during the previous 6 months and the date of the last dose were recorded. All surveys were conducted between May 2010 and September 2011. Analyses were restricted to children 6-59 months of age.

Malaria was defined as either the presence of *P. falciparum* parasitemia, as assessed by light microscopy at the time of the survey, or the presence of *P. falciparum* antegenemia, as determined by the histidine-rich protein 2 (HRP-2)-based rapid diagnostic test (RDT). The primary exposure of interest was VAS in the past 6 months.

Multivariate logistic regression models were used to assess the association between receipt of VAS in the past 6 months and presence of malaria according to the two different methods of diagnosis. Supplemented and non-supplemented groups were compared with respect to potential confounders, such as age, breastfeeding practices, maternal education and wealth index. In addition, separate models were constructed to assess potential effect modifiers such as birth weight, age at the time of malaria screening and routine vaccinations, including DTP.

Results and Conclusions

The final sample for the models based on microscopic diagnosis of malaria included 8390 children (n=2821 from Burkina Faso, n=2260 from Mozambique; n=2085 from Rwanda and n=1218 from Senegal). Of these children, 6098 children from Burkina Faso, Rwanda and Senegal who also provided test results for RDT, were included in the RDT models. The Mozambican survey did not include a malaria RDT component, so was excluded from the RDT models. The prevalence of *P. falciparum* parasitemia according to the microscopic exams was 28% (2312/8390), whereas the prevalence of *P. falciparu*m antigenemia, as assessed by RDT, was 35% (2113/6098). Overall, 62% of children received a VAS in the previous 6 months, with substantial disparities across the four countries (9% in Burkina Faso, 87% in Mozambique, 72% in Rwanda and 59% in Senegal).

High-dose VAS in the previous 6 months was associated with nearly 57% reduction in risk for *P. falciparum* parasitemia (relative risk (RR) =0.43 [0.36-0.52]) and a 78% reduction in risk for *P. falciparum* antigenemia (RR=0.22 [0.16-0.29]). The protective effect of VAS appeared to be more pronounced among children 36 months and older (P of interaction = 0.01), and among children with a birth weight of 2500 g or more (P of interaction = 0.02). There was no evidence that the effect of VAS on malaria was modified, in either direction, by routine vaccinations, including DTP.

Policy Implication

Evidence from this large pooled analysis of four nationally representative surveys supports the hypothesis that VAS may prevent or ameliorate malaria outcomes. The lack of association between routine vaccinations, VAS and risk of malaria are particularly relevant in light of emerging concerns that concurrent VAS and DTP administration may exacerbate adverse malaria outcomes[7,8]. Thus, this study provides further justification for continuing VAS programs in malaria-endemic settings, even in the context of high coverage of routine vaccines.

NNA Editor's Comments*

The present analyses used data derived from four national DHS that included information on VAS, malaria infection and vaccination records. It is important to recognize that information on VAS coverage obtained from DHS may not be as reliable as data from post-event coverage surveys because of the long recall period and the possibility that the interviewee may not be the same person who attended the VAS distribution. To obtain reliable VAS coverage information, it is recommended to implement post-event coverage surveys within 4-6 weeks of the VAS campaign to ensure accurate recall by the caretaker[10].

Regardless of this limitation, demonstrating that there was no evidence of adverse effects of VAS on malaria infection may provide yet another reason in support of continuing high-dose VAS programming in Sub-Saharan Africa and may change the dynamics of ongoing discussions regarding the scaling-back of existing high-dose VAS programs[11,12]. It is interesting that the magnitude of the protective effect reported here (up to 78% reduction in malaria risk) exceeds the ~ 30% efficacy reported by the only two trials specifically designed to evaluate the effects of high-dose VAS on malaria[5,6]. This disparity in effect sizes calls for additional research into the mechanisms through which VAS modulates malaria outcomes. In particular, evidence is needed

regarding the optimal duration of VAS needed to achieve desired malaria-specific effects, the specific aspects of malaria pathology-hepatic stage replication, blood-stage replication, or malaria-related inflammation- affected by VAS, and the context-specific effect modifiers of the VAS-malaria interaction.

*These comments have been added by the editorial team and are not part of the cited publication.

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