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Response to: 'Serious danger signals', response to: 'The effect of neonatal vitamin A supplementation on morbidity and mortality at 12 months: a randomized trial'

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Christine Benn and colleagues suggest that maternal vitamin A supplementation (MVAS) cannot explain the heterogeneity of results shown across neonatal vitamin A supplementation (NVAS) trials. We agree that maternal vitamin A status may not explain the entirety of the heterogeneity of effect across trials. However, we found significant effect modification by MVAS in our cohort, and also illustrated that maternal vitamin A status (defined by both MVAS and dietary intake) shows a similar trend; the biggest reduction in mortality with NVAS was found among the subgroup of infants whose mothers had not received supplemental vitamin A and also had inadequate vitamin A in their diets. The published body of evidence also lends support to this hypothesis. To date, there have been 11 randomized trials conducted in eight countries. Three of the four studies that found benefit of NVAS were conducted in populations classified as having moderate to severe vitamin A deficiency.[1–3] Given our results, the larger body of evidence, and biological plausibility, we argue that maternal vitamin A status is at least one of the reasonable explanations for the heterogeneity of effect of NVAS on infant mortality.

Benn and colleagues also propose that over time there is an increasingly negative effect of NVAS in female infants. We tested this hypothesis using a Cox proportional hazard model; we included a term for the interaction between sex, NVAS, and time categorized into 0–5 and 6–12 months. Using the likelihood ratio test (to compare the full and reduced model) we do not find strong evidence of a NVAS, sex, and 6-month time interaction ($P = 0.14$). In Tanzania, the effect of NVAS on mortality among females appears to be somewhat consistent from 1 to 12 months. However, Benn *et al.* propose an interesting hypothesis regarding vitamin and vaccination interaction, and our group is currently conducting a more thorough analysis to investigate this hypothesis.

Whereas our study generated evidence that maternal vitamin A status might be a source of heterogeneity of the effect of NVAS on infant mortality in Tanzania, additional efforts to investigate potential effect modification within and across all NVAS trials could provide the highest quality evidence to inform local and global policy. Our team is contributing to ongoing pooling efforts aimed at examining sources of heterogeneity across completed NVAS studies.

References

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