Neonatal vitamin A supplementation and infant mortality

The recent publication in the Bulletin on this subject presents a study whose findings lead to an erroneous conclusion that will misinform global health policymakers regarding the benefits of neonatal vitamin A supplementation. The authors’ stated objective was “to assess the relationship between the prevalence of vitamin A deficiency among pregnant women and the effect of neonatal vitamin A supplementation on infant mortality”. However, they excluded relevant studies, used inappropriate data on the prevalence of vitamin A deficiency in pregnant women and drew unsubstantiated conclusions.

To begin with, three relevant trials were not included in the analysis. One such trial was published in March 2010, before the authors submitted their paper. Another was excluded because it was conducted in infants born to HIV-negative mothers, but the authors do not explain why they viewed these participants as not belonging to the “general population”. A third trial was excluded because the vitamin A supplements were administered within the first month of life (i.e. in the neonatal period, as officially defined) rather than within the first 48 hours. However, the alleged differential effect of administering vitamin A in the first 48 hours of life as opposed to later in the neonatal period is not supported by any existing data.

The authors have obtained prevalence figures for maternal vitamin A deficiency from a table that is no longer accessible at the site for which a link was provided. We fortunately had access to the data in paper format. The authors claim that “the included values represent the best estimates of the prevalence of vitamin A deficiency in pregnant women at the time individual subjects were enrolled in each study”. However, this is not correct. The prevalence figures for maternal vitamin A deficiency that were used are largely based on studies conducted in different time periods or on “guesstimates”, as witnessed by an unlikely prevalence of precisely 20.4% in several countries. Extrapolation of such national-level prevalence data to individual study subjects is prone to serious error. For example, in the Indonesian trial the imputed prevalence of vitamin A deficiency was 34.2%, higher than in any of the other included trials. However, the women who participated in the trial had mean serum retinol levels very similar to those observed in a reference population of white women of reproductive age in the United States. Thus, the true prevalence of vitamin A deficiency among study subjects in the Indonesian trial, where the largest treatment effect was observed, was probably lower than in any of the other included trials.

Conclusions emanating from a meta-regression of the results of four trials are fragile. The Cochrane guideline states that “meta-regression should generally not be considered when there are fewer than 10 studies in a meta-analysis”. It further warns that even this will be too few when the covariates are unevenly distributed.

Based on their analysis, the authors conclude that neonatal vitamin A supplementation may prove most beneficial for reducing infant mortality in settings where the prevalence of vitamin A deficiency among pregnant women is at least 22%. This cut-off is just below the prevalences of 22.5% and 22.8% used for two countries where trials showed a positive impact, yet barely above the 20.4% prevalence in Guinea-Bissau, where no benefit was found. Furthermore, the cut-off is not supported by Rotondi et al.’s figure, in which the relative risk (RR) of 1 (log(RR) of 0) corresponds to a prevalence of approximately 20.5% instead of 22%. Irrespective, it is biologically implausible that the effect of vitamin A supplementation should depend on such marginal differences in maternal vitamin A deficiency.

Finally, the title of the manuscript is inaccurate, since the outcome of interest in the included trials was infant mortality, not neonatal mortality, and three of the four included trials were individually randomized.

Although we consider the use of national-level vitamin A data of questionable relevance, we performed meta-regression using the “metareg” command in Stata version 9.2 software (StataCorp. L.P., College Station, United States of America) with the restricted maximum likelihood option, and we included all relevant trials to determine whether this analysis would have changed the authors’ conclusions. The national prevalence of maternal vitamin A deficiency turned out not to be a significant predictor of the effect of vitamin A supplementation on infant mortality, as expressed by the log(β) (β: 0.003; 95% confidence interval: −0.022 to 0.029; P = 0.76) in this meta-regression (details available upon request).

The tendency to influence global policy on the basis of selective and inappropriate analysis of available data needs to be strongly discouraged. None of the evidence available at present provides grounds for determining where neonatal vitamin A supplementation is likely to reduce infant mortality based on the population prevalence of this micronutrient deficiency. Global policy formulation must await further input from the four ongoing trials evaluating this intervention, as well as documentation of consistent trends in these and previous trials.

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Author reply

We would like to thank the editorial team of the *Bulletin* for the opportunity to respond to the comments by Sachdev et al. regarding our recently published manuscript. While we understand their concerns related to the potential overgeneralization of our results, we would like to emphasize that the manuscript was produced within a hypothesis-generating context. Clearly, any attempts to rigorously establish the modifying effect of the prevalence of low vitamin A status in pregnant women (or neonates) on the observed effectiveness of neonatal vitamin A supplementation would require access to individual-level measurements (e.g., the observed serum retinol levels for each mother or neonate) from all available trials. This is so because no single study is large enough to detect potential interactions at the individual level; however, individual-level data, while ideal, are unlikely to be available in practice. For this reason, we investigated the *a priori* hypothesis that the prevalence of vitamin A deficiency among pregnant women was a potential modifier. Prior to publication of the manuscript, the aforementioned prevalence values were available in an online report. However, as Sachdev et al. have brought to our attention, this report is no longer available from the specified online resource. Should other investigators wish to view the report, please feel free to contact the corresponding author (Michael Rotondi) via e-mail.

While there are limitations to using the prevalence of low vitamin A status among pregnant women in a meta-regression model, Sachdev et al.’s suggestion that the mean serum retinol levels observed in a study of Indonesian women were similar to those found in a reference population in the United States is potentially subject to ecological bias. In fact, it is possible that neonates exhibiting lower serum levels may have derived greater benefit from supplementation than those with higher serum levels. The key point is that any metric (with the exception of individual-level data) is subject to ecological bias, and there is no way to know with certainty which measure yields correct results. Finally, the authors’ claim that it is “biologically implausible that the effect of vitamin A supplementation would depend on such marginal differences in maternal VAD” may be unfounded. For example, if a randomized trial were to enroll 10,000 neonates, an increase of a single percentage point in the prevalence of vitamin A deficiency among pregnant women would result in the birth of an additional 100 neonates to mothers deficient in vitamin A. The inclusion of these additional children could change the log relative risk by potentially altering the mortality rates in the treatment and/or control group. Thus it is plausible for marginal differences in the prevalence of maternal vitamin A deficiency to have an impact on effectiveness in vitamin A supplementation trials.

Although the conclusions from a meta-regression analysis become more robust as the number of included studies increases, Cochrane Collaboration guidelines are designed to be used by a broad audience under ordinary circumstances. In particular, simulation studies have shown that the described hypothesis test performs at the appropriate significance level, even in a fixed-effects meta-regression incorporating only a small number of studies. Note that this assumes that the use of the fixed-effects meta-regression model is appropriate, as demonstrated by an estimate of zero for the residual heterogeneity. This assertion was replicated in Rotondi’s methodological work in the context of the meta-regression of cluster-randomized trials and it continues to be the subject of current research.

In addition, the recently completed trial in Guinea-Bissau further supports our hypothesis of a potential modifying role for the prevalence of vitamin A deficiency. That is, repeating the meta-regression analysis (including this newly-completed study) provided an estimate of $\beta_1 = -0.09$ (95% confidence interval, CI: $-0.15$ to $-0.03$), which is consistent with our earlier estimate of $-0.08$ (95% CI: $-0.15$ to $-0.02$). However, based on the inclusion criteria used in the original paper, the new study would not have been included in the meta-regression analysis, since the trial only targeted low-birthweight neonates and thus represented a specific subgroup. The use of restricted inclusion criteria provides a reasonable approach to controlling for additional effects.
sources of heterogeneity between trials. For example, although Sachdev et al.¹ state that “there are no data to support a differential effect of vitamin A in the first 48 hours and later in the neonatal period,” a non-significant hypothesis test for differences in effect resulting from the timing of the supplementation does not indicate that the effects are in fact equivalent. In particular, given the relatively small number of studies that were included in this test,⁴ a non-significant result is more likely to be observed unless a very large difference exists. For this reason, we considered it best to focus our attention on a single covariate while controlling for other possible, if unproven, sources of heterogeneity through establishing strict inclusion criteria. This decision was made at the start of the project given the considerable heterogeneity in the vitamin A trial literature. Finally, Sachdev et al.¹ indicate that the title is incorrect. Our original title was “Neonatal vitamin A supplementation and newborn mortality: an application of meta-regression of cluster randomized trials.” While our study included only a single cluster randomized trial, the latter part of the title refers to the general methodological approach, which can accommodate more than one cluster trial. Furthermore, the term “newborn” was changed to “neonatal” at the editor’s request. Nonetheless, we accept responsibility for the potentially misleading title and apologize for any confusion this may have caused.

While our research is the first to have used a continuous measure for the prevalence of vitamin A deficiency, the limitations of our approach must be understood. Specifically, the results of our meta-regression analysis should not be interpreted as proof of a causal association, as a meta-regression model is both observational and ecological in nature. In addition, the strict inclusion criteria may limit the generalizability of the findings. As Sachdev et al.¹ correctly point out, when all completed neonatal vitamin A supplementation trials are included in the analysis, our hypothesis is not supported. However, our approach is consistent with the fact that the literature, being extremely heterogeneous, makes combining all trials quite impossible unless appropriate adjustments are made to account for the known discrepancies in study protocol and inclusion criteria. While we are not in favour of searching for unreasonable sources of heterogeneity, we feel that our pre-specified hypothesis is indeed plausible and should be explored in the future, particularly with individual-level data. Until then, we anxiously await the results of future trials that may or may not lend further support to our hypothesis and that may generate other potential explanations for the vast discrepancies found in the literature on the effects of neonatal vitamin A supplementation.

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References