

# Vitamin A supplementation and neonatal mortality in the developing world: a meta-regression of cluster-randomized trials

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**Objective** 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.

**Methods** Studies of neonatal supplementation with vitamin A have yielded contradictory findings with regard to its effect on the risk of infant death, possibly owing to heterogeneity between studies. One source of that heterogeneity is the prevalence of vitamin A deficiency among pregnant women, which we examined using meta-regression techniques on eligible individual and cluster-randomized trials. Adapting standard techniques to control for the inclusion of a cluster-randomized trial, we modelled the logarithm of the relative risk of infant death comparing vitamin A supplementation at birth to a standard treatment, as a linear function of the prevalence of vitamin A deficiency in pregnant women.

**Findings** Meta-regression analysis revealed a statistically significant linear relationship between the prevalence of vitamin A deficiency in pregnant women and the observed effectiveness of vitamin A supplementation at birth. In regions where at least 22% of pregnant women have vitamin A deficiency, giving neonates vitamin A supplements will have a protective effect against infant death.

**Conclusion** A meta-regression analysis is observational in nature and may suffer from confounding bias. Nevertheless, our study suggests that vitamin A supplementation can reduce infant mortality in regions where this micronutrient deficiency is common. Thus, neonatal supplementation programmes may prove most beneficial in regions where the prevalence of vitamin A deficiency among pregnant women is high.

*Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español. الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.*

## Introduction

Vitamin A deficiency is a public health concern in more than half of all countries, and most of the countries affected are in Africa or south-eastern Asia.<sup>1</sup> This deficiency, which is the main cause of blindness in undernourished children,<sup>2,3</sup> contributes to morbidity and mortality from severe infections, including those common in childhood, such as diarrhoeal diseases and measles.<sup>4,5</sup> Currently, an estimated 250 million preschool children in the world have vitamin A deficiency, and 250 000 to 500 000 of such children go blind every year. Of the children who go blind, half die within one year of losing their eyesight.<sup>1</sup> International awareness of the role of vitamin A in improving and maintaining health has led to decades of supplementation being provided to preschool children.<sup>4</sup>

In children over 6 months of age, vitamin A supplementation has been shown to decrease all-cause mortality.<sup>6–10</sup> However, the benefits in children under 6 months of age are still unclear, even though young infants are especially vulnerable to vitamin A deficiency. In general, all infants are born with low stores of vitamin A and depend on external sources, including breast milk, to build body stores.<sup>11,12</sup> The milk of lactating women in developing countries typically has lower concentrations of vitamin A than that of women in developed countries,<sup>12</sup> which means that neonates may not obtain their daily requirements.<sup>11</sup> Direct supplementation of neonates and infants younger than 6 months has shown promising results in terms of survival, yet findings have been contradictory. Studies conducted in Bangla-

desh,<sup>13</sup> India<sup>11</sup> and Indonesia<sup>12</sup> have shown reductions in all-cause mortality (15%, 22% and 63%, respectively) in infants who received vitamin A supplementation relative to controls. Giving neonates vitamin A has also been found to significantly reduce diarrhoea case-fatality rates and the incidence of fever.<sup>14</sup> In contrast, trials in Guinea-Bissau,<sup>15</sup> Nepal<sup>16</sup> and Zimbabwe<sup>17</sup> suggest a lack of benefit from vitamin A supplementation. The positive findings have led to different recommendations, but these are controversial<sup>15,18</sup> and there is much disagreement throughout the world on the appropriate policy surrounding neonatal vitamin A supplementation.<sup>19,20</sup> Clearly, further controlled trials with infants and neonates are needed.

To examine some of the systematic differences in the findings of conflicting studies, we performed a meta-regression analysis in which the logarithm of the relative risk (logRR) of infant death (measured at either 6 or 12 months of age) was modelled as a function of the prevalence of vitamin A deficiency among pregnant women in the general population. Unlike a simple meta-analysis, a meta-regression model attempts to explain the variation among studies in terms of a study-level characteristic. A meta-regression analysis is observational in nature and is thus not likely to put an end to the controversy surrounding neonatal supplementation, but it may provide some insight into effectiveness in subsequent trials, based on the prevalence of vitamin A deficiency. The inclusion of a cluster-randomized trial<sup>13</sup> in the meta-regression analysis entails a unique application of the proposed method, as discussed later in this paper.

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Table 1. **Studies included in meta-regression in which the logarithm of the relative risk of infant death in infants given vitamin A supplements was modelled as a function of the prevalence of vitamin A deficiency in pregnant women:**

$$\log(\text{RR}_i) = \beta_0 + \beta_1 \text{VAD}_i + \varepsilon_i$$

Study location	Randomization unit	Sample size (no.)	Follow-up (months)	Prevalence of VAD <sup>a</sup> (%)	RR <sup>b</sup>	95% CI
Bangladesh <sup>13</sup>	"Sectors" <sup>c</sup>	15 937	6 <sup>d</sup>	22.5	0.85	0.73–1.00
Guinea-Bissau <sup>15</sup>	Infant	4 345	12	20.4	1.06	0.80–1.42
India <sup>11</sup>	Infant	11 619	6	22.8	0.78	0.63–0.97
Indonesia <sup>12</sup>	Infant	2 067	12	34.2	0.37	0.16–0.87

CI, confidence interval; RR, relative risk; VAD, vitamin A deficiency.

<sup>a</sup> The prevalence of VAD as obtained from global VAD tables.<sup>22</sup>

<sup>b</sup> Relative risks and confidence intervals are based on mortality rates as calculated at the end of study follow-up.

<sup>c</sup> The study randomized 596 sectors in a cluster randomized strategy.

<sup>d</sup> Follow-up until 24 weeks of age, regardless of initial supplementation date.

## Methods

### Inclusion criteria

The fundamental question of interest was whether the log(RR) of death among infants who received vitamin A supplements at birth versus placebo or a standard treatment such as vaccination was related to the level of vitamin A deficiency among pregnant women in the general population. To reconcile the conflicting evidence from different studies, we developed inclusion criteria that took into account extraneous sources of heterogeneity, such as varying target populations and differences in the time when vitamin A supplementation was administered. The a priori inclusion criteria were that trials: (i) be randomized; (ii) have an appropriate control group that did not receive any vitamin A supplements; (iii) be administered at the population level (i.e. no supplements provided to specific subgroups of interest, such as infants or mothers, with or without specific health concerns); and (iv) have the vitamin A supplements administered within the first two days of life. These criteria were designed to allow for a focused and comprehensive analysis of the efficacy of giving neonates vitamin A supplements in the general population. In addition, the criteria were set to ensure that the effect of vitamin A supplementation could be extrapolated to the general population by excluding subjects who may have received vitamin A supplements after the first two days of life or who may have belonged to specific groups treated with vitamin A. This is of primary concern, given the significant variability in vitamin A supplementation trials.

Two studies in Zimbabwe were excluded because their participants were either HIV– or HIV+ mothers only.<sup>17,21</sup>

A study in Nepal was excluded because it provided vitamin A supplements every four months and hence was not designed to dose neonates.<sup>16</sup> A fourth trial was excluded because it was designed to measure the efficacy of a smaller dose of vitamin A, rather than the standard dose.<sup>8</sup> Characteristics of the included studies are presented in Table 1.

### Statistical analysis

A traditional meta-analysis combines all estimates of an observed treatment effect into a single overall estimate of the efficacy of a particular intervention. In general, the observed treatment effects are obtained from individually-randomized clinical trials, which ensures that, on average, each estimate of the treatment effect is not confounded by other factors. Nonetheless, observed treatment effects may lead to differing conclusions stemming from varying inclusion criteria and study populations, variations in the study protocols (e.g. dose or length of follow-up) and random error. Differences in the observed treatment effects are often the result of between-study heterogeneity, or simply heterogeneity. While attempts to explore the impact of heterogeneity on a meta-analysis are important, a meta-analysis tacitly accepts heterogeneity by combining different studies in the search for a single underlying treatment effect.<sup>23</sup>

The use of cluster-randomized design is becoming more common, and a meta-analysis may be influenced by the inclusion of one or more cluster-randomized trials.<sup>24</sup> The greatest threat to statistical validity is the failure to incorporate the appropriate design effect in variance calculations.<sup>25</sup> Failing to account for clustering in a meta-analysis will contribute to an underestimation of the within-study variance, resulting in an unrealistically

high weight for that particular treatment effect. Furthermore, care must be taken when combining results from cluster-randomized and individually-randomized trials, because the intervention itself may interact with the unit of randomization.<sup>26</sup>

As explained above, meta-regression analysis attempts to relate the effect size to study-level characteristics. This approach not only acknowledges between-study heterogeneity but also attempts to explain it at the study level. Similar to a classical meta-analysis, a meta-regression employs weights (typically random effects<sup>27</sup>) to account for larger or more accurate studies. Because meta-regression analysis is observational in nature, rigorous causal associations cannot be directly ascertained.<sup>27</sup>

The prevalence of vitamin A deficiency among pregnant women was the main explanatory variable in this meta-regression analysis. While different proxies for vitamin A deficiency<sup>22</sup> exist in the target infant populations, this measure was deemed the most appropriate because it was obtained by weighting the combined prevalences of low serum retinol and xerophthalmia reported by studies from the countries of interest. This approach to estimating national prevalences of vitamin A deficiency avoids potential bias resulting from restriction to women who are diagnosed with xerophthalmia, given that maternal vitamin A deficiency that is less than severe may also have a detrimental effect on infant survival. Estimates of the prevalence of vitamin A deficiency are subject to uncertainty because of the difficulty of obtaining accurate measurements.<sup>2</sup> As such, prevalence estimates used for our analysis differ from those in other published reports.<sup>28</sup> However, 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, while remaining consistent with the literature.<sup>28</sup>

Infant mortality was the endpoint of interest; thus, RRs < 1 demonstrate the protective effect of vitamin A supplementation on infant mortality. Although vitamin A supplementation was administered to neonates, mortality was measured at either 6 or 12 months of age. In an attempt to reduce the skewness of the distribution of the RRs, we used the log(RR) as the dependent variable of interest. That is, we fitted the following weighted linear regression:

$$\log(\text{RR}_i) = \beta_0 + \beta_1 \text{VAD}_i + \varepsilon_i$$

where  $\text{VAD}_i$  corresponds to the prevalence of vitamin A deficiency among pregnant women in study  $i$  ( $i = 1, 2, 3, 4$ ) and  $\varepsilon_i$  is an independently and identically distributed normal random variable with zero mean and fixed variance. Within the range of our explanatory variable,  $\beta_1$  represents the change in the log(RR) for each percentage increase in the prevalence of vitamin A deficiency among pregnant women and  $\beta_0$  represents the intercept.

The study weights used in a random effects meta-regression analysis are obtained as the inverse of the sum of the within-trial variance and the residual between-trial variance. By contrast, the fixed effects meta-regression analysis would simply weight each study by the inverse of its within-study variance. The fixed effects model is a special case of the random effects model in which the between-trial variance is estimated as zero. Throughout the analysis, we applied the random effects model because it acknowledges the presence of residual heterogeneity.<sup>27</sup> Regardless of the model of choice, the appropriate weights in a meta-regression analysis should include an adjustment for the effect of clustering. This adjustment is easily incorporated into the within-trial variance by multiplying the standard estimate of the variance by the design effect, as correctly applied in the Bangladesh trial.<sup>13</sup> In general, failing to adjust for the effect of clustering would result in the use of inaccurate weights, possibly leading to biases in the estimated covariates and standard errors.

Although unnecessary for the meta-regression analysis, a minor variation of Cochran's  $Q$  statistic for heterogeneity, as well as the  $I^2$  statistic,<sup>29</sup> are required to adjust for the inclusion of a cluster-

randomized trial. Both of these statistics account for the clustering effect in the estimation of the within-study variance for any included cluster-randomized trials.

All statistical analyses were performed using the *R* software package, with appropriate modifications to account for the incorporation of cluster-randomized trials.<sup>30</sup> The between-study heterogeneity was estimated using restricted maximum likelihood and empirical Bayes techniques;<sup>27</sup> the residual heterogeneity component was estimated as zero, and this reduced the random effects model to a fixed effects meta-regression.

## Results

As a precursory analysis, a fixed effects meta-analysis model (adjusted for clustering) demonstrated an overall protective effect of vitamin A supplementation with respect to infant death using the generalized inverse method.<sup>25</sup> The fixed effects RR was 0.85 (95% confidence interval, CI: 0.75–0.95), which indicates a statistically significant overall reduction in mortality. To assess the impact of study heterogeneity on the meta-analysis, the  $Q$  statistic is often used as a basis for deciding between the fixed or random effects meta-analysis model.<sup>29</sup> With this method, the null hypothesis of study homogeneity is rejected (i.e. the studies are found to be heterogeneous and the fixed effects model is invalidated) if the observed value of  $Q$  exceeds the 95% critical value of a  $\chi^2$  distribution with degrees of freedom equal to the number of included studies minus one. This value is obtained from statistical tables or software. Within this framework, the  $Q$  statistic is calculated as 6.55, a value that does not exceed the 95% critical value of 7.81 (on three degrees of freedom). A simple method to quantify the between-study heterogeneity is through the  $I^2$  statistic. Using this method, the  $I^2$  value (adjusted for clustering) of 0.54 suggests the presence of moderate heterogeneity, despite the lack of statistical significance of the  $Q$  statistic. For the sake of completeness, the random effects meta-analysis estimates a RR of 0.84 (95% CI: 0.69–1.03), which does not suggest a statistically significant reduction of infant mortality as a result of neonatal vitamin A supplementation.

The results of the meta-regression analysis are presented graphically in Fig. 1, as well as the fitted meta-regression line and expected 95% confidence bands. Specifically, the intercept ( $\beta_0$ ) is estimated

as 1.66 (95% CI: 0.20–3.13) and  $\beta_1$  is estimated as  $-0.08$  (95% CI:  $-0.15$  to  $-0.02$ ). These findings suggest a statistically significant linear relationship between the prevalence of vitamin A deficiency among pregnant women in the study population and the observed effectiveness of neonatal vitamin A supplementation in preventing infant death in a given study. The findings suggest that a study taking place in an area where the prevalence of vitamin A deficiency among pregnant woman is at least 22% would be likely to show a statistically significant, protective effect of vitamin A supplementation against infant death.

## Discussion

Meta-regression analysis aims to relate the size of an effect to one or more characteristics of the studies involved.<sup>27</sup> More specifically, it investigates whether a covariate (potential "effect modifier") explains the heterogeneity of treatment effects between studies.<sup>27</sup> In our analysis, the study-level covariate of interest was the prevalence of vitamin A deficiency among pregnant women, and the outcome variable – overall infant mortality – represented the efficacy of neonatal vitamin A supplementation in developing countries. We found a statistically significant relationship between the covariate and infant mortality, which suggests that vitamin A supplementation to neonates within the first two days of life confers a benefit in regions where vitamin A deficiency is common. This is an important finding given the current debate as to whether giving neonates vitamin A supplements helps reduce infant mortality in populations where endemic vitamin A deficiency and high infant mortality exist.<sup>18,31</sup>

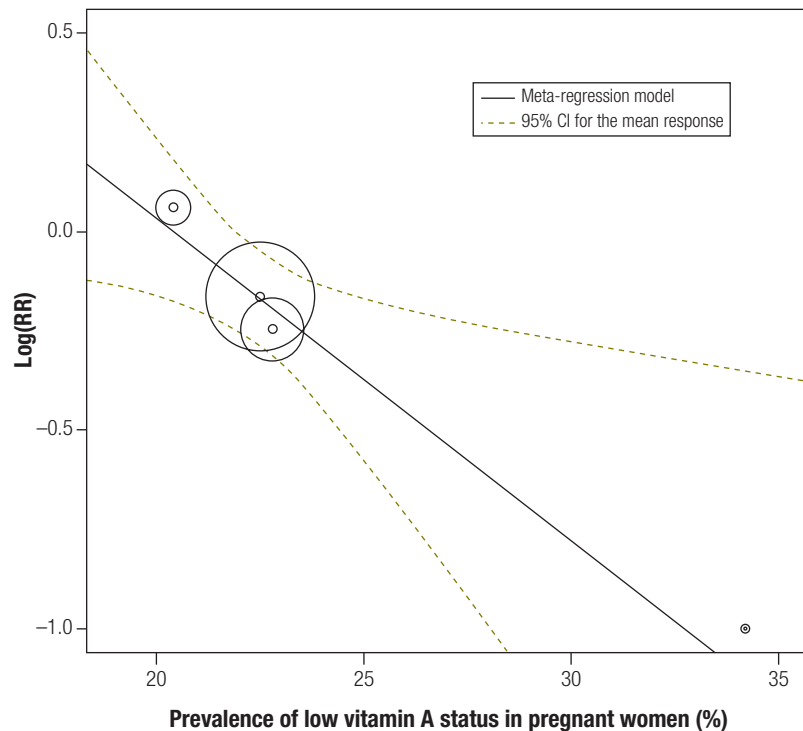
A recent meta-analysis suggests that there is insufficient evidence to support neonatal supplementation with vitamin A.<sup>32</sup> Although the study is methodologically sound and appropriate, its application of more general inclusion criteria may limit its ability to ascertain the role of the prevalence of vitamin A deficiency on infant mortality. Furthermore, to calculate the prevalence of vitamin A deficiency the study employed maternal night blindness as a proxy, but the latter is associated only with the most severe cases of vitamin A deficiency. Also, the prevalence of maternal night blindness was dichotomized ( $\geq 5\%$  versus  $< 5\%$ ) and this may have reduced its statistical power.<sup>33</sup> This problem is avoided in the

current study through the use of a continuous covariate.

The results of our analyses will be useful in predicting the benefits of providing neonates with vitamin A supplements in certain trials; that is, in trials conducted in regions with a prevalence of vitamin A deficiency of 22% or more among pregnant women. Some authors have advocated implementation of neonatal vitamin A supplementation in Asia but not in Africa until further trials are carried out.<sup>18</sup> However, our findings point to another plausible approach to the global problem of nutritional deficiency. In general, vitamin A supplementation may prove beneficial in regions where the prevalence of vitamin A deficiency among pregnant women is high. Therefore, both Asian and African countries experiencing nutritional deficiencies may benefit from vitamin A supplementation programmes for infants.

In our meta-regression analysis, we controlled for a significant source of variation between studies (background prevalence of vitamin A deficiency); nevertheless, there is a possibility of residual heterogeneity.<sup>27</sup> For example, studies may differ with regard to the vitamin A content of supplementary foods, the rate of infant growth and the burden of infectious diseases, all of which may translate into different requirements or losses of vitamin A.<sup>12,31</sup> In addition, we made no distinction between trials employing a single large dose of vitamin A or vitamin A supplements in regular but smaller amounts – a potentially valuable insight given that a higher-dose regimen has been shown safe but not more efficacious than a lower-dose regimen provided to infants.<sup>34,35</sup> Differences in vaccination coverage among trials may further explain study heterogeneity. The protective effect of neonatal vitamin A supplementation may depend not only on the prevention of vitamin A deficiency, but also on a synergistic (positive) interaction with routine vaccinations.<sup>5</sup> Vitamin A supplementation may strengthen ongoing immune reactions induced by vaccines; for example, when given with a live vaccine, vitamin A may further enhance the capacity of the antigen-presenting cells to deliver polarizing signals from helper to non-helper T-cells, an essential component of

Fig. 1. Meta-regression<sup>a</sup> plot of log relative risk (RR) of infant death in infants given vitamin A supplements as a function of the prevalence of vitamin A deficiency (VAD) in pregnant women:  $\log(\text{RR}_i) = \beta_0 + \beta_1 \text{VAD}_i + \varepsilon_i$



CI, confidence interval; RR, relative risk; VAD, vitamin A deficiency.

<sup>a</sup> Circles are proportionate to study weights in the meta-regression.

cell-mediated immunity.<sup>5</sup> The beneficial effects of vitamin A supplements when given with the vaccines against tuberculosis (bacille Calmette-Guérin or BCG vaccine) and measles can be attributed to this mechanism. In addition, vitamin A deficiency has been linked to iron and other micronutrient deficiencies.<sup>36,37</sup> Thus, there may be a positive interaction between vitamin A supplementation and overall infant nutritional status.

The Indonesian study<sup>12</sup> was a leverage point in the meta-regression analysis (Fig. 1). Although meta-regression appropriately accounts for the lower precision of this study in comparison to the others, a sensitivity analysis conducted after removing the Indonesian trial yielded an estimate of  $\beta_1 = -0.12$  with a two-sided *P*-value of 0.09. While statistical significance is lost with the omission of this study, estimates of  $\beta_1$  remain consistent.

Our study had limitations, particularly owing to the use of meta-regression methods. A meta-regression describes an observational association across trials,

even though the original studies may be randomized.<sup>27</sup> Thus, meta-regression does not have the benefit of randomization to make causal inferences and may introduce bias by confounding. Also, there is the possibility of residual heterogeneity, as mentioned earlier. However, the prevalence of vitamin A deficiency explains much of the observed heterogeneity (supported by the estimate of zero for the between-study variance).

The observational analysis employed in this paper is unlikely to put an end to the controversy on the effectiveness of neonatal supplementation with vitamin A. However, we hope that it will contribute to continued debate in the literature and help to focus attention on the role of vitamin A supplementation, micronutrient deficiencies and nutrition in general on infant mortality. ■

**Competing interests:** None declared.

## ملخص

**إضافات فيتامين (أ) ووفيات الولدان في البلدان النامية: تحوف تلوي لتجربة عنقودية معشاة**

الغرض قياس العلاقة بين انتشار عوز فيتامين (أ) بين الحوامل وتأثير إضافة فيتامين (أ) للولدان الجدد على وفيات الرضع. الطريقة أدت دراسات إضافة فيتامين (أ) للولدان الجدد إلى نتائج متضاربة حول تأثيره على خطر وفاة الرضيع، ومن المحتمل أن ذلك يعود إلى التباين بين الدراسات. وأحد مصادر هذا التباين هو انتشار عوز فيتامين (أ) بين الحوامل، والذي فحصه الباحثون باستخدام تقنيات التحوف التلوي على الأفراد المؤهلين والتجارب العنقودية المعشاة. وبتطبيق معايير تقنية للسيطرة على إدراج التجربة العنقودية المعشاة، أعد الباحثون نموذجاً لوغاريتمياً للخطر النسبي لوفيات الرضع بمقارنة بإضافة فيتامين (أ) عند الولادة مع علاج معياري، كدالة خطية لانتشار عوز فيتامين (أ) بين الحوامل.

الموجودات أظهر تحليل التحوف التلوي علاقة خطية يعتد بها إحصائياً بين انتشار عوز فيتامين (أ) بين الحوامل والفعالية الملحوظة لإضافة فيتامين (أ) عند الولادة. ففي المناطق التي تعاني فيها الحوامل من عوز فيتامين (أ) بنسبة لا تقل عن 22% فإن إضافة فيتامين (أ) للولدان الجدد سيكون له تأثير واق ضد وفاة الرضع. الاستنتاج إن تحليل التحوف التلوي في طبيعته يعتمد على الملاحظة وقد يعاني من التحيز والالتباس. إلا أن هذه الدراسة تشير إلى أن إضافة فيتامين (أ) يمكن أن يحد من وفيات الرضع في المناطق التي يشيع فيها حدوث عوز هذا المغذي الزهيد المقدار. وبالتالي فإن برامج تكملة غذاء الولدان الجدد بفيتامين (أ) يمكن أن تبرهن على جدوى قصوى في المناطق التي ينتشر فيها عوز فيتامين (أ) بين النساء الحوامل.

## Résumé

### Apport complémentaire en vitamine A et mortalité néonatale dans le monde en voie de développement : une méta régression des essais randomisés en cluster

**Objectif** Évaluer la relation entre la prévalence de la carence en vitamine A chez les femmes enceintes et l'effet d'un apport complémentaire néo-natal en vitamine A sur la mortalité infantile.

**Méthodes** Des études portant sur l'apport complémentaire néo-natal en vitamine A ont donné des résultats contradictoires quant à l'effet sur le risque de mortalité infantile, possiblement à cause de l'hétérogénéité entre les études. Une des sources de cette hétérogénéité est la prévalence de la carence en vitamine A parmi les femmes enceintes ; ce que nous avons étudié au moyen de techniques de méta-régression sur des individus admissibles et d'essais randomisés par grappes. Par une adaptation des techniques standards permettant de contrôler l'inclusion d'un essai randomisé par grappes, nous avons modélisé le logarithme du risque relatif de mort infantile en comparant l'apport complémentaire en vitamine A à la naissance à un traitement standard, en fonction linéaire de la prévalence de la carence de vitamine A chez les femmes enceintes.

**Résultats** L'analyse de méta-régression a révélé une relation linéaire statistiquement significative entre la prévalence de la carence en vitamine A chez les femmes enceintes et l'efficacité observée d'un apport complémentaire en vitamine A à la naissance. Dans les régions où 22% au moins des femmes enceintes manquent de vitamine A, les compléments en vitamine A donnés aux nouveau-nés ont un effet protecteur contre la mortalité infantile.

**Conclusion** Une analyse de méta-régression est, par nature, une analyse d'observation et elle peut souffrir d'influences combinées. Néanmoins, notre étude suggère que les apports complémentaires en vitamine A sont susceptibles de réduire la mortalité infantile dans les régions où la carence de ce micronutriment est commune. Les programmes de complémentation néo-natale peuvent par conséquent se montrer plus bénéfiques dans les régions où la prévalence du manque de vitamine A chez les femmes enceintes est élevée.

## Resumen

### Suplementos de vitamina A y mortalidad neonatal en los países en desarrollo: metarregresión con ensayos aleatorizados por grupos

**Objetivos** Evaluar la relación existente entre la prevalencia de una deficiencia de vitamina A en embarazadas y el efecto de la administración neonatal de vitamina A en la mortalidad de menores de un año.

**Métodos** Los estudios sobre administración neonatal de suplementos de vitamina A han arrojado resultados contradictorios en lo que respecta a su efecto sobre el riesgo de muerte en menores de un año, posiblemente a causa de la heterogeneidad interensayo. Una de las causantes de dicha heterogeneidad es la prevalencia de una deficiencia de vitamina A entre las embarazadas, la cual hemos analizado con métodos de metarregresión en personas aptas para los mismos y con ensayos aleatorizados por grupos. Se determinó el logaritmo del riesgo relativo de mortalidad en menores de un año mediante la adaptación de los métodos habituales para controlar la inclusión de un ensayo aleatorizado por grupos. Dicho logaritmo se calculó comparando la administración de vitamina A en el momento del nacimiento con un tratamiento típico, como función lineal de la prevalencia de una deficiencia de vitamina A en mujeres embarazadas.

**Resultados** El análisis de metarregresión mostró una relación lineal estadísticamente significativa entre la prevalencia de una deficiencia de vitamina A en mujeres embarazadas y la eficacia observada en la administración de vitamina A en el nacimiento. En aquellas regiones en las que al menos el 22% de las mujeres embarazadas presenta una deficiencia de vitamina A, la administración neonatal de vitamina A tendrá un efecto protector contra la mortalidad en los menores de un año.

**Conclusión** El análisis de metarregresión es observacional y puede sufrir sesgo de confusión. No obstante, nuestro estudio sugiere que la administración de vitamina A puede reducir la mortalidad en los menores de un año en aquellas regiones en las que suele observarse una carencia de este micronutriente. Por ello, los programas de administración neonatal pueden resultar muy beneficiosos en las regiones donde se observa una prevalencia elevada de mujeres embarazadas con carencia de vitamina A.

## References

- World Health Organization. *Micronutrient deficiencies*. Geneva: WHO; 2008. Available from: <http://www.who.int/nutrition/topics/vad/en> [accessed 2 April 2010].
- Brown E, Akre J, editors. *Indicators for assessing vitamin A deficiency and their application in monitoring and evaluating intervention programmes*. Geneva: World Health Organization; 1996 (WHO/NUT/96.10).
- Sommer A. *Vitamin A deficiency and its consequences: a field guide to their detection and control*. Geneva: World Health Organization; 1995.
- Bates CJ. Vitamin A. *Lancet* 1995;345:31–5. doi:10.1016/S0140-6736(95)91157-X PMID:7799706
- Benn CS, Balé C, Sommerfelt H, Friis H, Aaby P. Hypothesis: Vitamin A supplementation and childhood mortality: amplification of the non-specific effects of vaccines? *Int J Epidemiol* 2003;32:822–8. doi:10.1093/ije/dyg208 PMID:14559758
- Fawzi WW, Chalmers TC, Herrera MG, Mosteller F. Vitamin A supplementation and child mortality. A meta-analysis. *JAMA* 1993;269:898–903. doi:10.1001/jama.269.7.898 PMID:8426449
- Beaton GH, Martorell R, Aronson K, Edmonston B, McCabe G, Ross A, et al. *Effectiveness of vitamin A supplementation in the control of young child morbidity and mortality in developing countries* (ACC/SCN State-of-the-Art Series Nutrition Policy Discussion Paper No. 13). Geneva: United Nations, Administrative Committee on Coordination, Subcommittee on Nutrition; 1993. Available from: <http://www.unu.edu/unupress/food/8f154e/8F154E04.htm> [accessed 2 April 2010].
- Benn CS, Martins C, Rodrigues A, Jensen H, Lisse IM, Aaby P. Randomised study of effect of different doses of vitamin A on childhood morbidity and mortality. *BMJ* 2005;331:1428–32. doi:10.1136/bmj.38670.639340.55 PMID:16306060
- Rahmathullah L, Underwood BA, Thulasiraj RD, Milton RC, Ramaswamy K, Rahmathullah R et al. Reduced mortality among children in southern India receiving a small weekly dose of vitamin A. *N Engl J Med* 1990;323:929–35. PMID:2205798
- West KP Jr, Pokhrel RP, Katz J, LeClerq SC, Khatri SK, Shrestha SR et al. Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet* 1991;338:67–71. doi:10.1016/0140-6736(91)90070-6 PMID:1676467
- Rahmathullah L, Tielsch JM, Thulasiraj RD, Katz J, Coles C, Devi S et al. Impact of supplementing newborn infants with vitamin A on early infant mortality: community based randomised trial in southern India. *BMJ* 2003;327:254. doi:10.1136/bmj.327.7409.254 PMID:12896935
- Humphrey JH, Agoestina T, Wu L, Usman A, Nurachim M, Subardja D et al. Impact of neonatal vitamin A supplementation on infant morbidity and mortality. *J Pediatr* 1996;128:489–96. doi:10.1016/S0022-3476(96)70359-1 PMID:8618182
- Klemm RD, Labrique AB, Christian P, Rashid M, Shamim AA, Katz J et al. Newborn vitamin A supplementation reduced infant mortality in rural Bangladesh. *Pediatrics* 2008;122:e242–50. doi:10.1542/peds.2007-3448 PMID:18595969
- Tielsch JM, Rahmathullah L, Thulasiraj RD, Katz J, Coles C, Sheeladevi S et al. Newborn vitamin A dosing reduces the case fatality but not incidence of common childhood morbidities in South India. *J Nutr* 2007;137:2470–4. PMID:17951487
- Benn CS, Diness BR, Roth A, Nante E, Fisker AB, Lisse IM et al. Effect of 50,000 IU vitamin A given with BCG vaccine on mortality in infants in Guinea-Bissau: randomised placebo controlled trial. *BMJ* 2008;336:1416–20. doi:10.1136/bmj.39542.509444.AE PMID:18558641
- West KP Jr, Katz J, Shrestha SR, LeClerq SC, Khatri SK, Pradhan EK et al. Mortality of infants < 6 mo of age supplemented with vitamin A: a randomized, double-masked trial in Nepal. *Am J Clin Nutr* 1995;62:143–8. PMID:7598058
- Malaba LC, Iliff PJ, Nathoo KJ, Marinda E, Moulton LH, Zijenah LS et al.; ZVITAMBO Study Group. Effect of postpartum maternal or neonatal vitamin A supplementation on infant mortality among infants born to HIV-negative mothers in Zimbabwe. *Am J Clin Nutr* 2005;81:454–60. PMID:15699235
- Tielsch JM. Vitamin A supplements in newborns and child survival. *BMJ* 2008;336:1385–6. doi:10.1136/bmj.39575.486609.80 PMID:18558638
- Benn CS, Fisker AB, Jørgensen MJ, Aaby P. Conflicting evidence for neonatal vitamin A supplementation. *Vaccine* 2008;26:4111–2. doi:10.1016/j.vaccine.2008.04.021 PMID:18486284
- Bhutta ZA, Haider BA, Cousens S, Black RE. Response to "Conflicting evidence for neonatal vitamin A supplementation (letter)" by Benn et al. [*Vaccine*, 2008]. *Vaccine* 2008;26:4304–5. doi:10.1016/j.vaccine.2008.06.007 PMID:18573293
- Humphrey JH, Iliff PJ, Marinda ET, Mutasa K, Moulton LH, Chidawanyika H et al.; ZVITAMBO Study Group. Effects of a single large dose of vitamin A, given during the postpartum period to HIV-positive women and their infants, on child HIV infection, HIV-free survival, and mortality. *J Infect Dis* 2006;193:860–71. doi:10.1086/500366 PMID:16479521
- West KP Jr, Rice A, Sugimoto J. *Tables on the global burden of vitamin A deficiency and xerophthalmia among preschool aged children and low vitamin A status, vitamin A deficiency and maternal night blindness among pregnant women by WHO region*. Geneva: World Health Organization; 2002. Available from: <http://www.jhsph.edu/CHN/GlobalVAD.pdf> [accessed 2 April 2010].
- Lau J, Ioannidis JP, Schmid CH. Summing up evidence: one answer is not always enough. *Lancet* 1998;351:123–7. doi:10.1016/S0140-6736(97)08468-7 PMID:9439507
- Laopaiboon M. Meta-analyses involving cluster randomization trials: a review of published literature in health care. *Stat Methods Med Res* 2003;12:515–30. doi:10.1191/0962280203sm3470a PMID:14653354
- Darlington GA, Donner A. Meta-analysis of community-based cluster randomization trials with binary outcomes. *Clin Trials* 2007;4:491–8. doi:10.1177/1740774507083389 PMID:17942465
- Donner A, Klar N. Issues in the meta-analysis of cluster randomized trials. *Stat Med* 2002;21:2971–80. doi:10.1002/sim.1301 PMID:12325113
- Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? *Stat Med* 2002;21:1559–73. doi:10.1002/sim.1187 PMID:12111920
- World Health Organization. *Global prevalence of vitamin A deficiency in populations at risk 1995–2005: WHO global database on vitamin A deficiency*. Geneva: World Health Organization; 2009.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58. doi:10.1002/sim.1186 PMID:12111919
- R Development Core Team. *R: a language and environment for statistical computing*. Vienna: R Foundation for Statistical Computing; 2007.
- Villamor E, Fawzi WW. Vitamin A supplementation: implications for morbidity and mortality in children. *J Infect Dis* 2000;182(Suppl 1):S122–33. doi:10.1086/315921 PMID:10944494
- Gogia S, Sachdev HS. Neonatal vitamin A supplementation for prevention of mortality and morbidity in infancy: systematic review of randomised controlled trials. *BMJ* 2009;338:b919. doi:10.1136/bmj.b919 PMID:19329516
- Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. *Stat Med* 2006;25:127–41. doi:10.1002/sim.2331 PMID:16217841
- Benn CS, Martins C, Rodrigues A, Jensen H, Lisse IM, Aaby P. Randomised study of effect of different doses of vitamin A on childhood morbidity and mortality. *BMJ* 2005;331:1428–32. doi:10.1136/bmj.38670.639340.55 PMID:16306060
- Idindili B, Masanja H, Urassa H, Bunini W, van Jaarsveld P, Aponte JJ et al. Randomized controlled safety and efficacy trial of 2 vitamin A supplementation schedules in Tanzanian infants. *Am J Clin Nutr* 2007;85:1312–9. PMID:17490968
- Wieringa FT, Dijkhuizen MA, West CE, Thurnham DJ, Muhilal, Van der Meer JW. Redistribution of vitamin A after iron supplementation in Indonesian infants. *Am J Clin Nutr* 2003;77:651–7. PMID:12600856
- Schmidt MK, Musimatun S, West CE, Schultink W, Hautvast JGAJ. Vitamin A and iron supplementation of Indonesian pregnant women benefits vitamin A status of their infants. *Br J Nutr* 2001;86:607–15. doi:10.1079/BJN2001444 PMID:11737959