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Effects of Vitamin A supplementation on child morbidity: A twenty-year time series analysis in the northeastern region of Brazil

Hermano Alexandre Lima Rocha · Anamaria Cavalcante e Silva · Luciano Lima Correia · Jocileide Sales Campos · Márcia Maria Tavares Machado · Álvaro Jorge Madeiro Leite · Antonio Jose Ledo Alves da Cunha

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Abstract The present study aimed to determine the prevalence of supplementation between 1987 and 2007, and to measure the impact of this on morbidity. Five sequential cross-sectional studies in a 20-year time span were analyzed. Each had a sample of 8,000 domiciles representative of Ceará, in northeastern Brazil. Data were analyzed with descriptive statistics, followed by bivariate and multivariate analyses. Increases in coverage, ranging from 9.6 to 65.8 % were verified, and the study found that the impact of supplementation in reducing morbidity may not be significant. The study also found that supplementation may be associated with higher frequency of certain morbidities (OR 1.8, CI 95 % 1.20–2.95). When the supplementation variable was adjusted for socioeconomic factors, the risk was higher for diarrhea (OR 5.56, CI 95 % 2.63–11.75). The study concluded that in Brazil, vitamin A supplementation may have little benefit in reducing morbidity.

Keywords Vitamin A · State Health Care Coverage · Child morbidity

Introduction

Vitamin A deficiency continues to be a global public health problem, affecting about 15 % of Brazilian children [1]. Recent studies show no statistical significance for the correlation between vitamin A deficiency and increased morbidity, with some indicating an increased risk of developing morbidities in supplemented children [2–4]. This means that the association between vitamin A deficiency and increased morbidity is no longer widely accepted. However, the benefits of vitamin A supplementation on children have been the focus of some recent research [2, 3, 5].

In the 1980s, researchers found a direct relationship between vitamin A supplementation and reduced child morbidity and mortality, particularly diarrhea, respiratory tract infection (RTI), and measles [6]. Clinical studies of

H. A. L. Rocha (✉) · L. L. Correia · M. M. T. Machado
Department of Public Health, Universidade Federal do Ceará, Rua Prof Costa Mendes, 1609, Fortaleza, CE 60430-130, Brazil
e-mail: hermano@ufc.br

L. L. Correia
e-mail: correialuciano@hotmail.com

M. M. T. Machado
e-mail: marciamachadoufc@gmail.com

A. C. eSilva · J. S. Campos
Centro Universitário Christus - Unichristus, Rua Rua João Adolfo Gurgel 133, Fortaleza, CE, Brazil
e-mail: anamariacasil@yahoo.com.br

J. S. Campos
e-mail: jocileide23@gmail.com

Á. J. M. Leite
Department of Pediatrics, Universidade Federal do Ceará, Rua Prof. Costa Mendes, 1609, Fortaleza, CE 60.430-130, Brazil
e-mail: marciamachadoufc@gmail.com

A. J. L. A. da Cunha
Department of Pediatrics, Universidade Federal do Rio de Janeiro UFRJ, Av Pedro Calmon, 550, Cidade Universitaria, Rio de Janeiro, RJ 21941901, Brazil
e-mail: antonioledo@yahoo.com.br

severe cases of measles provided the basis for investigating the impact of vitamin A supplementation in reducing infant mortality [7]. However, more recent studies have questioned the effectiveness of vitamin A supplementation in reducing morbidity. For example, a placebo-controlled double-blind trial in Indonesia noted an increase of 39 % in the incidence of lower airway infection in supplemented children and observed benefits only in malnourished children [2]. Conversely, recent meta-analyses have documented the effectiveness of supplementation [5], with the Devta study showing a reduction in child morbidities with vitamin A supplementation [5]. While there is a paucity of recent research in Brazil, a study published in 1994 showed reduction in mortality following vitamin A supplementation for children suffering from severe diarrhea [8].

The Survey of Maternal and Child Health of Ceará (PESMIC), reported here, was initially carried out in 1987 with the aim of describing the health status and health service coverage in the maternal and child population in the state of Ceará, in northeastern Brazil. Key indicators measured in this population were socio-economic, anthropometric, nutritional, other morbidities and mortality, as well as access to health services, including supplemental vitamin A.

The present study aimed to investigate the prevalence of vitamin A supplementation in five distinct moments over a 20-year period in this semiarid region of Brazil, observing the potential effects on morbidity in children.

Materials and methods

The PESMIC studies used as the basis for the present analysis were cross-sectional population-based statewide surveys of a representative sample of women of reproductive age and preschool children in Ceará. Characterized as one of Brazil's poorest states, Ceará, with 8.5 million inhabitants, is recognized as the state most successful in proportionally reducing the infant mortality rate. The PESMIC study comprised women of childbearing age, (10–49 years), and children aged 0–35 months, all of whom were residents of Ceará [9, 10].

The cluster sampling used census tracts and stratification between the capital city, Fortaleza, and the rural municipalities. The sample size was calculated at 8,000 households and represented approximately 35,000 people, including 11,000 women and 2,000 children of the target age groups. The sample size was originally established in 1987 to estimate the state infant mortality rate and was maintained throughout the project, collecting data in 1987, 1990, 1994, 2001, and 2007 [10].

Data on supplementation were collected through a standardized questionnaire administered to the mothers by interview, with a recall period of 12 months before the interview. Morbidity data such as prevalence of diarrhea and RTI were collected by direct inquiry about watery evacuations, fever, and dyspnea in both the previous 24 h and the previous 15 days. Information about child hospitalizations in the previous 12 months was also collected. Following administration of the questionnaires, mothers and children had their anthropometric measures taken.

The present study analyzed PESMIC data from 1987 to 2007. Most variables were dichotomized. Bivariate analysis was performed between variables considered determined by vitamin A supplementation, such as morbidities and hospitalizations, using Chi square and Kendall Tau B tests.

To adjust for the crude risk found in the bivariate analysis for the morbidities caused by the vitamin A supplementation, logistic regressions were conducted for morbidities in 1987 and 2007, using morbidities related to socioeconomic status, maternal educational level, and health service coverage as confounders. One regression model was constructed for each of the morbidities.

In this cross-sectional study, the outcome measure used was the odds ratio (OR) and was estimated using non-conditional logistic regression.

The data analysis was performed using EpiInfo v. 7 for Windows, CDC and SPSS® v. 17. In all PESMIC studies, informed consent was obtained from the women and mothers of the children. Consent was obtained from parents or guardians for adolescents under 18 years of age. Following the introduction of Research Ethics Committees into Brazil, formal approval was sought for the study protocols for the fourth and subsequent surveys.

Results

The present study found that the impact of supplementation on morbidity was not always in the direction of reduction. The bivariate analysis for 1987 and 2007 showed little evidence of a positive effect, with most OR not statistically significant. In 1987, only one of the morbidities was significantly affected by vitamin A supplementation; specifically, increased hospitalizations due to pneumonia. In 1994, supplementation did not affect any of the studied morbidities. In 2001, lower RTI showed a higher incidence in supplemented children (OR 1.65, CI 95 % 1.0–2.7). In 2007, upper RTI was little impacted by vitamin A supplementation, with an OR of 1.34 (CI 95 % 1.0–1.6). Vitamin A supplementation did not have a protective effect for any of the analyzed morbidities in any of the years investigated (Table 1).

Table 1 Association between vitamin A supplementation and upper RTI, lower RTI, Diarrhea, and hospitalization in children aged 0–35 months

Year	Morbidity	Supplementation with Vitamin A		Crude odds ratio	CI 95 %	*P* value
		Yes No (%)	No No (%)			
1987	Upper RTI[a]	204 (47.3)	1,876 (46.2)	1.04	0.8–1.2	0.350
	Lower RTI[a]	103 (23.9)	915 (22.5)	1.07	0.8–1.3	0.280
	Diarrhea[b]	116 (26.9)	1,053 (26.0)	1.04	0.8–1.3	0.366
	Hospitalization due to Diarrhea[c]	18 (4.2)	177 (4.4)	0.95	0.5–1.5	0.490
	Hospitalization due to Pneumonia[c]	24 (5.6)	123 (3)	1.88	1.2–2.9	0.006
1994	Upper RTI	832 (54.5)	481 (51.6)	1.12	0.9–1.3	0.089
	Lower RTI	294 (19.2)	204 (21.9)	0.85	0.6–1.0	0.062
	Diarrhea[b]	215 (15.4)	124 (14.6)	1.06	0.8–1.3	0.318
	Hospitalization due to Diarrhea[c]	120 (43.5)	44 (43.6)	0.99	0.6–1.5	0.540
	Hospitalization due to Pneumonia[c]	73 (26.4)	19 (18.8)	1.54	0.8–2.7	0.083
2001	Upper RTI	404 (51)	333 (46.8)	1.18	0.6–1.2	0.056
	Lower RTI	45 (5.7)	25 (3.5)	1.65	1.0–2.7	0.030
	Diarrhea[b]	84 (12.1)	75 (12.0)	1.01	0.7–1.1	0.507
	Hospitalization due to Diarrhea[c]	48 (40.0)	24 (32.0)	1.41	0.7–2.6	0.165
	Hospitalization due to Pneumonia[c]	29 (24.2)	16 (21.6)	1.15	0.5–2.3	0.411
2007	Upper RTI	432 (50.9)	194 (43.6)	1.34	1.0–1.6	0.007
	Lower RTI	275 (31.0)	132 (28.6)	1.11	0.8–1.4	0.205
	Diarrhea[d]	124 (14.67)	54 (12.4)	1.20	0.8–1.6	0.165
	Hospitalization due to Diarrhea[c]	16 (1.8)	8 (1.7)	1.03	0.4–2.4	0.560
	Hospitalization due to Pneumonia[c]	38 (4.3)	12 (2.6)	1.67	0.8–3.2	0.079

[a] In life time

[b] In the previous 7 days

[c] In the previous 3 months

[d] In the previous 15 days

In the logistic regression, the supplementation impact was adjusted for the socioeconomic and healthcare variables, comparing 1987–2007. In 1987, there was no statistically significant adjusted OR for any of the morbidity outcomes, with all risk ratios around the null value. In 2007, however, when the program coverage was above the national average (65 % of the target children were supplemented) [11], a statistically significant increased risk for all morbidities in vitamin A supplemented children was found. For hospitalization due to diarrhea and pneumonia, the adjusted OR for supplemented children were 4–5 times higher than for non-supplemented children (Table 2).

Discussion

The present study demonstrates a limited statistical relationship between the occurrence of vitamin A supplementation and frequency of morbidity. It also highlights that for some variables, the measure of association tended to risk rather than to protection, as in the hospitalization for pneumonia (adjusted OR 4.62, CI 95 % 2.49–8.55).

The profile of morbidity and mortality in Ceará has experienced drastic changes in the past 20 years, as can be seen in the PESMIC series [9] and in the official data from the National Mortality Information System. Of particular note is the substantial decrease in infant mortality from diarrhea and pneumonia, causes of death that were more likely to be benefited by vitamin A supplementation [6, 7].

Although there is some consensus in terms of the medical benefits of vitamin A for immunity [5, 12], and some population studies that show the positive influence of supplementation on child mortality and morbidity [5, 6], doubts about the benefit of vitamin A supplementation remain. The Indonesian placebo-controlled double blind trial showed a 39 % increase in the incidence of infection of the lower airways in supplemented children [2], and a placebo-controlled study conducted in Ghana showed similar findings [3]. While some research has found a protective relationship between supplementation and the

Table 2 Adjusted association between vitamin A supplementation and upper RTI, lower RTI, Diarrhea, and hospitalization in children aged 0–35 months for 1987 and 2007

Year	Morbidity	Supplementation with Vitamin A		Crude odds ratio	Adjusted[e] odds ratio	95 % CI for adjusted odds ratio
		Yes No (%)	No No (%)			
1987	Upper RTI[a]	204 (47.3)	1,876 (46.2)	1.04	0.99	0.76–1.28
	Lower RTI[a]	103 (23.9)	915 (22.5)	1.07	1.13	0.83–1.54
	Diarrhea[b]	116 (26.9)	1,053 (26.0)	1.04	1.03	0.76–1.38
	Hospitalization due to Diarrhea[d]	18 (4.2)	177 (4.4)	0.95	0.80	0.44–1.42
	Hospitalization due to Pneumonia[d]	24 (5.6)	123 (3)	1.88	1.33	0.76–2.35
2007	Upper RTI	432 (50.9)	194 (43.6)	1.34	1.28	1.02–1.61
	Lower RTI	275 (31.0)	132 (28.6)	1.11	1.37	1.07–1.74
	Diarrhea[c]	124 (14.67)	54 (12.4)	1.20	1.90	1.37–2.64
	Hospitalization due to Diarrhea[d]	16 (1.8)	8 (1.7)	1.03	5.56	2.63–11.75
	Hospitalization due to Pneumonia[d]	38 (4.3)	12 (2.6)	1.67	4.62	2.49–8.55

[a] In life time

[b] In the previous 7 days

[c] In the previous 15 days

[d] In the previous 3 months

[e] Variables used as covariates in regression: Father living at home; Illiterate mother; Mother's age; Access to piped water; Family wage/income; Birth weight; Distance to the nearest basic health unit (in 1987); Appointment with a physician (2007)

development of morbidity or mortality, these tend to be for specific diseases, such as measles [13].

The present study found that vitamin A supplementation tended to show no statistically significant relationship with the infant morbidities analyzed (RTI, diarrhea, and related hospital admissions), and furthermore, if a significant relationship was observed, it was in an increased prevalence of morbidities in children who had received supplementation. This finding, though counterintuitive, could be hypothetically explained by the way in which children who have more access to vitamin A supplementation tend to be those who have better access to health services, possibly because they have a heavier burden of disease [14]. Another possible explanation is that the current pattern of childhood disease is no longer affected by supplementation with megadoses of vitamin A. In addition, the findings suggest that this may be because that group of children has higher social and health resource needs and is therefore more likely to be sick.

It is known that vitamin A deficiency affects innate immunity by impeding normal regeneration of mucosal barriers damaged by infection and reduces the function of neutrophils, macrophages, and natural killer T cells [15]. However, studies in animal models have shown that excess vitamin A is just as damaging to immune function as deficiency, indicating that vitamin A has a complex regulatory role of the immune system [16]. It could therefore be assumed that higher doses of vitamin A may cause some damage to the immune system, resulting in a higher incidence of morbidity in supplemented children.

The present study supports the findings of studies published elsewhere [2, 3], that there is little evidence of benefit from supplemental vitamin A. Considering the above, the present authors recommend that the program of supplemental vitamin A in Brazil should be submitted to a more comprehensive assessment.

The cost of vitamin A supplementation should also be evaluated to determine whether public interventions such as this are cost-effective. Although there is no cost analysis of the program in Brazil, an Indian study estimated that each applied dose would cost US$0.65 [17]. Given the number of doses applied in 2010 in Brazil, the annual cost of the program would be approximately 5 million US dollars. This corresponds to the annual maintenance cost for four secondary level hospitals [18].

Finally, the present study concludes that the vitamin A supplementation program requires further investigation and evaluation, both in terms of cost-effectiveness and of impact on morbidity and morbidity. This is particularly relevant given the national context of relatively low program coverage and a decreasing burden of morbidity and mortality from infectious diseases. In this case, it is recommended that at least two types of studies are undertaken: (1) An evaluation study of the operational aspects of the program, using specific evaluation methodology such as observing the process under which the program operates, program results, impact on the target population and cost-effectiveness [19, 20]; and, (2) A longitudinal study, ideally a cohort study, which follows supplemented and non-

supplemented children to directly measure the association between the administration of vitamin A and the incidence of a number of diseases.

The limitations of the present study include the fact that it uses data collected without the specific purpose of evaluating the vitamin A supplementation program. This meant that there was a lack of control of the number of megadoses each child received and at what age they received them; information that would be needed to evaluate the real supplemented level of vitamin A. Data were further limited in that they were based upon self-report by mothers.

Moreover, the study did not use analytical methodology to specifically evaluate the program. Finally, it is noteworthy that the supplementation program of vitamin A has a satisfactory operation in Ceará, even above the national average, which gives the results rather more significance than if the program were operationally deficient.

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References

1. ADA, Paiva, Rondó, P. H. D. C., Gonçalves-Carvalho, C. M. R., Illison, V. K., Pereira, J. A., Vaz-de-Lima, L. R. A., et al. (2006). Prevalência de deficiência de vitamina A e fatores associados em pré-escolares de Teresina, Piauí. Brasil. *Cad saúde pública, 22*(9), 1979–1987.
2. Dibley, M. J., Sadjimin, T., Kjolhede, C. L., & Moulton, L. H. (1996). Vitamin A supplementation fails to reduce incidence of acute respiratory illness and diarrhea in preschool-age Indonesian children. *The Journal of nutrition, 126*(2), 434–442.
3. Ross, D. A., Dollimore, N., Smith, P., Kirkwood, B., Arthur, P., Morris, S., et al. (1993). Vitamin A supplementation in northern Ghana: Effects on clinic attendances, hospital admissions, and child mortality. *The Lancet, 342*(8862), 7–12.
4. Rotondi, M. A., & Khobzi, N. (2010). Vitamin A supplementation and neonatal mortality in the developing world: A meta-regression of cluster-randomized trials. *Bulletin of the World Health Organization, 88*(9), 697–702.
5. Awasthi, S., Peto, R., Read, S., Clark, S., Pande, V., & Bundy, D. (2013). Vitamin A supplementation every 6 months with retinol in 1 million pre-school children in north India: DEVTA, a cluster-randomised trial. *The Lancet, 381*(9876), 1469–1477.
6. Sommer, A., Djunaedi, E., Loeden, A., Tarwotjo, I., West, J., Tilden, R., et al. (1986). Impact of vitamin A supplementation on childhood mortality: A randomised controlled community trial. *The Lancet, 327*(8491), 1169–1173.
7. Ellison, J. (1932). Intensive vitamin therapy in measles. *British Medical Journal, 2*(3745), 708.
8. Barreto, M. L., Farenzena, G., Fiaccone, R., Santos, L., Assis, A., Araújo, M., et al. (1994). Effect of vitamin A supplementation on diarrhoea and acute lower-respiratory-tract infections in young children in Brazil. *The Lancet, 344*(8917), 228–231.
9. e Silva, A. C., Correia, L. L., Campos, J. S., de Oliveira Andrade, F. M., da Silveira, D. M., Madeiro Leite, A. J., et al. (2014). Reducing child mortality: The contribution of Ceará State, Northeast of Brazil, on Achieving the Millennium Development Goal 4 in Brazil. *Maternal and Child Health Journal*. doi:10.1007/s10995-014-1566-0.
10. Victora, C. G., Barros, F. C., Tomasi, E., Ferreira, F. S., MacAuliffe, J., Silva, A. C., et al. (1991). A saúde das crianças dos estados do Ceará, Rio Grande do Norte e Sergipe, Brasil: Descrição de uma metodologia para diagnósticos comunitários. *Rev Saúde Pública, 25*, 218–225.
11. Souza, W Ad, & VilasBoas, O M Gd C. (2002). A deficiência de vitamina A no Brasil: Um panorama. *Rev panam salud pública, 12*(3), 173–179.
12. da Silva, R., Lopes, E, Jr, Sarni, R., & Taddei, J. (2005). Níveis plasmáticos de vitamina A em crianças carentes com pneumonia na fase aguda e após recuperação. *Journal of Pediatrics, 81*(2), 162–168.
13. Fawzi, W. W., Chalmers, T. C., Herrera, M. G., & Mosteller, F. (1993). Vitamin A supplementation and child mortality: A meta-analysis. *JAMA, 269*(7), 898–903.
14. Nair, H., Nokes, D. J., Gessner, B. D., Dherani, M., Madhi, S. A., Singleton, R. J., et al. (2010). Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: A systematic review and meta-analysis. *The Lancet, 375*(9725), 1545–1555.
15. Stephensen, C. B. (2001). Vitamin A Infection, and Immune Function*. *Annual Review of Nutrition, 21*(1), 167–192.
16. Friedman, A., & Sklan, D. (1989). Antigen-specific immune response impairment in the chick as influenced by dietary vitamin A. *The Journal of nutrition, 119*(5), 790–795.
17. Chow, J., Klein, E. Y., & Laxminarayan, R. (2010). Cost-effectiveness of "golden mustard" for treating vitamin A deficiency in India. *PLoS One, 5*(8), e12046.
18. Zanchet, A., Belini, G., Kinzler, J. (2007). Estrutura de custos de um hospital público e seu resultado econômico: um estudo de caso. *Ciências Sociais Aplicadas em Revista, 7*(13), 29–42.
19. Donabedian, A. (1988). The quality of care: How can it be assessed? *JAMA, 260*(12), 1743–1748.
20. Donabedian, A. (1990). The seven pillars of quality. *Archives of Pathology and Laboratory Medicine, 114*(11), 1115–1118.