Original Article

Sub clinical vitamin A deficiency and anemia among Vietnamese children less than five years of age

Nguyen Cong Khan MD, PhD[1,2], Nguyen Xuan Ninh MD, PhD[1], Nguyen Van Nhien MD[1], Ha Huy Khoi PhD, DSc[1], Clive E West PhD[3,4] (deceased) and Joseph GAJ Hautvast MD, PhD[3]

[1]*National Institute of Nutrition, Hanoi, Vietnam*
[2]*Division of Nutrition, Hanoi School of Public Health, Vietnam*
[3]*Division of Human Nutrition, Wageningen University, Wageningen, The Netherlands*
[4]*Department of Gastroenterology, University Medical Center, Nijmegen, The Netherlands*

The objective of the study was to assess the prevalence of sub clinical vitamin A deficiency and anemia in Vietnamese children. For this, a cross-sectional survey was conducted in 40 villages (clusters) of four ecological regions in Vietnam during Apr-May 2001. In total 1657 children less than 5 years old were included by a cluster random sampling method. The prevalence of sub clinical vitamin A deficiency (serum retinol <0.70 µmol/L) was 12.0% and the prevalence of anemia (hemoglobin <110g/L) was 28.4 %. In the children under 6 months the prevalence of sub clinical vitamin A deficiency was 35.1 % whereas the prevalence of anemia in this group was as high as 61.7%. The prevalence of children with both sub clinical vitamin A deficiency and anemia was 6.1%. Sub clinical vitamin A deficiency and anemia prevalence differed significantly across the regions, with highest prevalence in the Northern Mountainous areas for vitamin A deficiency and in the Northern Mountainous area and Mekong River Delta for anemia. It is concluded that sub clinical vitamin A deficiency and anemia are still important public health problems in Vietnam. Sustainable strategies for combating vitamin A deficiency and nutritional anemia are needed and should concentrate on target groups, especially infants and malnourished children in high risk regions.

Key Words: vitamin A deficiency, anemia, children urban, rural prevalence, Vietnam

Introduction

Vitamin A deficiency and iron deficiency anemia can have important health consequences for preschool children. These include growth failure, depressed immune responses, higher risk of xerophthalmia and blindness and increased morbidity and mortality.[1,2] Globally, it is estimated that about 127 million preschool children under 5 years of age are vitamin A deficient, of whom 4.4 million have xerophthalmia.[3] Iron deficiency, not only the main cause of anemia in Vietnam, but also a major problem among preschool children worldwide, has been associated with retarded psychomotor development and growth retardation. [4,5]

During the 1980's vitamin A deficiency and xerophthalmia in children younger than 5 years was a serious nutritional problem in Vietnam.[6,7] A country-wide survey done in 1994 showed that the prevalence of clinical forms of vitamin A deficiency were lower than the threshold of being a public health problem set by WHO (7, 8). A small sample survey reported that the prevalence of sub-clinical vitamin A deficiency (serum retinol <0.7 µmol/L) ranged from 14.7% in 1995 to 12% in 1997.[6] There is lack of information on the prevalence of sub-clinical vitamin A deficiency in the various ecological regions in Vietnam and it can be assumed that the prevalence varies with age, poverty and prevalence of malnutrition.

There is also lack of data on the prevalence of anemia in children in Vietnam. A survey on anemia and nutritional risk factors conducted in 1995 showed a high prevalence of anemia in preschool children and in adult women.[9]

Therefore, the aims of the present study were to assess the prevalence of sub-clinical Vitamin A deficiency and anemia among children less than five years of age in 4 different ecological region of Vietnam including Northern Mountainous, Red River Delta, South Central Coast and Mekong River Delta.

Subjects and methods

A cross-sectional survey was conducted in 4 out of the in total 8 ecological regions of Vietnam, including Northern Mountainous, Red River Delta, South Central Coast and Mekong River Delta.

Corresponding Author: Dr Nguyen Cong Khan, National Institute of Nutrition, 48B Tang Bat Ho, Hanoi, Vietnam.
Tel: + 84 4 9716058/ + 84 4 9717090; Fax: + 84 4 9717885
Email: nckhan@hn.vnn.vn
Manuscript received 8 March 2006. Accepted 11 May 2006.

In total forty clusters (villages) were selected from the four mentioned regions. At each cluster all children under 5 year of age (about 30 to 40) were selected for the study. Ethical approval of the study protocol was obtained from the Ethical Committee of the National Institute of Nutrition and the Ministry of Health, Hanoi. Informed consent was obtained from the parents of the children.

Weight was measured to the nearest 0.1 kg with a pediatric scale (SECA beam balance, Hamburg, Germany) with the children minimally clothed. Length of children under 24 months and height of children over 24 month was measured to the nearest 0.1 cm using a WHO-model length measuring board [10] provided by UNICEF. Z-scores of the indicators weight-for-age (W/A), height-for-age (H/A), and weight-for-height (W/H) were calculated with EPI-INFO Version 6.04 (CDC, Atlanta) by using the National Center for Health Statistics data as a reference.[11]

Blood samples were collected in the morning (8-11 am). Two mL of venous blood were drawn into polypropylene tubes. The tubes were kept in darkness in a cool box (4^{o}C). Hemoglobin (Hb) concentration in whole blood was measured with a hemoglobin meter (HemoCue, Mission Viejo, CA, USA).[12] Anemia was defined as a hemoglobin concentration less than 110 g/L.[13] Hemoglobin was measured only in the districts Northern Mountainous, South Central Coast and Mekong River Delta. At the time of the measurements in the Red River Delta area the instrumentation was not available. Within 4 hours of blood collection serum was obtained by centrifugation at 3000 rpm for 10 min at room temperature in a local laboratory. Samples were immediately frozen in dry-ice for transportation to the Micronutrient Laboratory of the National Institute of Nutrition in Hanoi and were kept at –70^{o}C until laboratory analyses.

High performance liquid chromatography (HPLC) was used to measure serum retinol.[14] All-trans retinol (purity: 98%) and retinyl acetate (purity: 95%) from Sigma-Aldrich Corporation (Steinheim, Germany) were used as external and internal standards. Chemicals used in analysis were purchased from Merck (Darmstadt, Germany). All extraction and HPLC procedures were carried out under reduced light and under nitrogen in order to prevent oxidation of the compounds. Lower limits of detection for retinol and retinyl acetate in serum are 4 ng/mL and 6 ng/mL, respectively. Sub-clinical vitamin A deficiency was defined as serum retinol less than 0.7 μmol/L. The World Health Organization regards vitamin A deficiency as an important public health problem if the prevalence ranges from 2-10% (mild), 10–20 % (moderate) or more than 20% (severe). [14]

Pooled human serum was used to measure intra- and inter-assay coefficients of variation (CV) in laboratory analyses. The within- and between-assay CV were 4% and 8.5% respectively.

The data were statistically analyzed using SPSS for WINDOWS, version 12.0; SPSS, Chicago, IL). Data were checked for normal distribution by using the Kolomogrov-Smirnov test. Differences in variables across groups of subjects were tested with ANOVA or with Chi-Square test. Correlations are Pearson's correlations. Results are expressed as mean ± SD unless otherwise indicated. Significance is set at $p<0.05$.

Results

A total of 1657 children, 858 boys and 799 girls, from 40 communes of four ecological regions were included in this study. Physical and anthropometry characteristics are presented in Table 1. The mean (± SD) age of children in the study was 32.3 ± 15.5 months. Nine of the children had hemoglobin concentration lower than 80g/L and were referred to the commune health center for treatment. Mean W/A Z-score was -1.70 ± 0.99, mean H/A Z-score was -1.59 ± 1.36 and mean W/H Z-score was -0.94 ± 0.84. About 40.2 % of the children had W/A Z scores ≤ than -2, 35.7% of the children had H/A Z-scores ≤ -2 and 8.8% of the children had W/H Z-scores ≤ -2. No significant differences were observed in Z-scores across ages and between boys and girls. As shown in Table 2, the mean serum retinol concentration of the studied children was 1.08 ± 0.42 μmol/L, resulting in an overall prevalence of sub clinical vitamin A deficiency of 12%. However, the prevalence was highly different across ecological regions ($p<0.0001$). Using the WHO cut-offs, only the Red River Delta region has mild sub clinical vitamin A deficiency, the South Central Coast and the Mekong River Delta had moderate vitamin A deficiency and the prevalence of vitamin A deficiency in the Northern Mountainous area should be classified as severe.[15] The mean (± SD) of serum retinol concentration among boys (1.07 ± 0.44 μmol/L) and girls (1.09 ± 0.38 μmol/L) were not significantly different (p= 0.302).

Table 1. Physical characteristics (mean ± SD) of children under 5 years of age in the various regions

Regions	n (% female)	Age (month)	W/A Z-score	H/A Z-score	W/H Z-score
North Mountainous	294 (50.3)	26.4 ±16.2	-1.61 ± 1.04	-1.46 ± 1.36	-0.89 ± 0.91
Red River Delta	464 (51.3)	32.8 ± 14.8	-1.46 ± 1.06	-1.33 ± 1.37	-0.82 ± 0.83
South Central Coast	462 (45.9)	34.3 ± 14.2	-1.81 ± 0.85	-1.75 ± 1.10	-0.99 ± 0.70
Mekong River Delta	437 (46.2)	33.5 ± 16.2	-1.89 ± 0.96	-1.79 ± 1.54	-1.06 ± 0.91
Total	1657 (48.2)	32.3 ± 15.5	-1.70 ± 0.99	-1.59 ± 1.36	-0.94 ± 0.84

W/A: weight for age; H/A: height for age; W/H: weight for height. Z-scores are based on the NCHS data (1977) as reference.

Table 2. Serum retinol (mean ± SD) concentration and prevalence of sub clinical vitamin A deficiency across the regions.

Regions	N	Retinol (μmol/L) Mean ± SD	Sub clinical Vitamin A deficiency* (%)
North Mountainous	294	0.93 ± 0.39	24.5
Red river Delta	464	1.18 ± 0.49	4.3
South Central Coast	462	1.11 ± 0.38	11.0
Mekong River Delta	437	1.05 ± 0.34	12.8
Total	1 657	1.08 ± 0.42	12.0

* Defined as serum retinol <0.70 μmol/L

Table 3. Mean ± SD hemoglobin levels and prevalence of anemia among Vietnamese children less than five years of age in three different regions.

Regions	N	Hb (g/L) Mean ± SD	Prevalence of anemia, % *
North Mountainous	293	114.9 ± 11.6	30.0
South Central Coast	460	116.3 ± 12.1	24.3
Mekong River delta	388	113.1 ± 12.1	32.0
Total	1,141	114.8 ± 12.1	28.4

* defined as hemoglobin <110g/L

Table 4. Vitamin A Deficiency and anemia†

Anemia**	Vitamin A Deficiency* Yes (n=168)	Vitamin A Deficiency* No (n=973)	Total
Yes (n=254)	70 (6.1%)	254 (22.3%)	324 (28.4%)
No (n=719)	98 (8.6%)	719 (63%)	817 (71.6%)
Total (n=973)	168 (14.7%)	973 (85.3%)	1141 (100%)

† OR (CI 95%): 2.02 (1.44-2.83), Chi-Square, $p<0.0001$;
* defined as serum retinol <0.70 μmol/L; ** defined as hemoglobin <110g/L

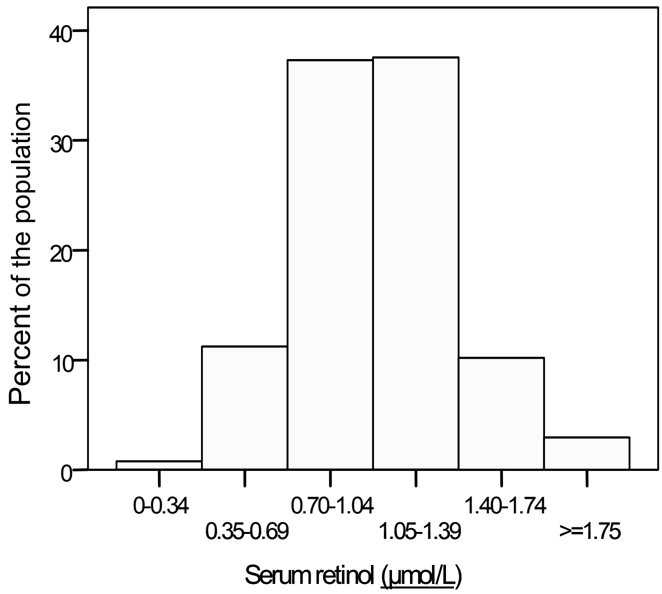

Figure 1. Frequency distribution of serum retinol concentrations in 1657 Vietnamese children under five years of age

Figure 1 shows the frequency distribution of serum retinol concentrations in the study population. A large proportion of the children (37.3%) had serum retinol values in the range of 0.70 to 1.04 μmol/L, thus just above the cut-off level for sub clinical vitamin A deficiency.

The mean (± SD) hemoglobin concentration in the children was 114.8 ± 12.1g/L. Hemoglobin levels among boys (n = 605) and girls (n = 536) were 114.6 ± 12.3 and 115.1 ± 11.8 g/L respectively and were not statistically different (p= 0.498). In the total population 28.4 % of the children were anemic (Table 3). The mean (± SD) ages of children with and without anemia were 25.2 ± 15.9 and 34.6 ± 14.9 months, respectively ($p<0.0001$).

The prevalence of combined vitamin A deficiency and anemia in the children was 6.1% (Table 4). A statistically significant relationship was observed between vitamin A deficiency and anemia (Chi-Square $p<0.0001$), and serum retinol and hemoglobin concentration were correlated (R = 0.16; $p<0.0001$).

In addition, a significant negative correlation was found between levels of vitamin A deficiency and age of children (R = -0.10; $p<0.0001$), and anemia and age of children (R = - 0.27; $p<0.0001$). Figure 2 and Figure 3 show the decrease with age in the prevalence of sub clinical vitamin A deficiency and anemia respectively.

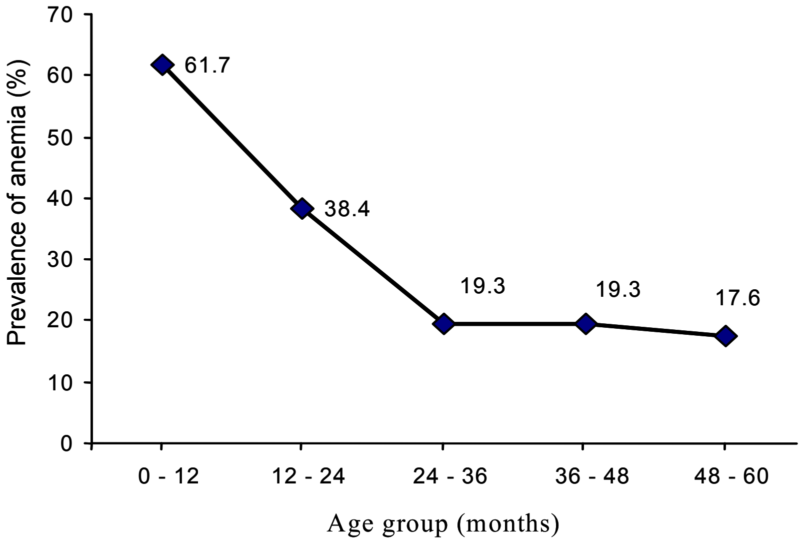

Figure 3. Prevalence (%) of anemia by age group in Vietnamese children

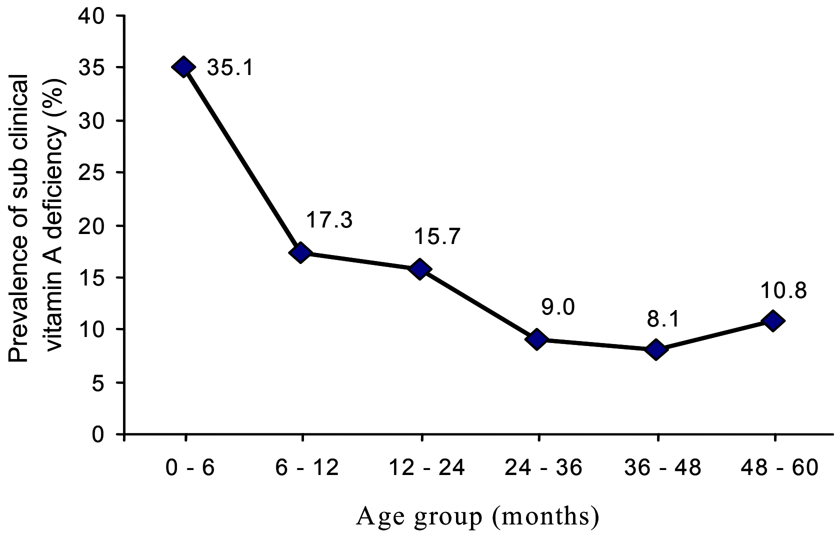

Figure 2. Prevalence (%) of sub clinical vitamin A deficiency by age groups in Vietnamese children

Discussion

Combating vitamin A deficiency and nutritional anemia are amongst the major challenges to all public health and nutrition programs in developing countries. In Vietnam vitamin A deficiency has been a great public health problem.[11] Universal supplementation of vitamin A to children in Vietnam started in 1992 with support of UNICEF. An annual coverage rate of 70 – 90 % of high dose vitamin A supplementation capsules is reported through the effective network of existing preventive healthcare infra structure at all administrative levels.[7] However, at the present time, there is lack of data on sub clinical vitamin A deficiency based on serum retinol levels. Recently we have developed the technique for serum retinol analysis, using HPLC, at the National Institute of Nutrition in Hanoi and the technique is periodically validated by the biochemical laboratory of the Division of Human Nutrition of the Wageningen University, The Netherlands. The serumretinol analyses in this survey are the first obtained data on retinol levels in 4 ecological regions.

The overall prevalence of sub clinical vitamin A deficiency was found to be 12% in the present children population. This indicates that sub clinical vitamin A deficiency is still a public health problem in Vietnam. The prevalence was highest in Northern Mountainous region where the coverage of high dose vitamin A capsules is known to be lowest compared to other regions (vitamin A capsule coverage at two nearest distribution campaigns was 61.3%, 92.0%, 79.1%, 85.4% for North Mountainous, Red River Delta, South Central Coast and Mekong River Delta regions respectively, data not shown). Low consumption of vitamin A-rich food has been reported in several areas in Vietnam.[16,17] So, improving of vitamin A status of children in Vietnam will still depend on supplementation programs. Other measures such as fortification, complementary food and improving feeding pattern should also be addressed in the years to come.

It is worthwhile noting that the prevalence of vitamin A deficiency in this study is extremely high (see Figure 2) in children under 6 months (35%) and in children from 6 to 12 months of age (17%). This probably reflects the fact that the coverage of high dose vitamin A supplementation capsules to mothers after delivery is not very high; covering rate only about 50% of mothers and deficiency of vitamin A may occur even during the first months after delivery.[7] Several studies in other countries confirm a high prevalence of vitamin A deficiency in children in the first six months of life.[18] Moreover, a high proportion of children has low concentrations of serum retinol (0.70 - 1.04 μmol/L) and is thus very vulnerable to deficiency (Figure 1). Special intervention programs to improve the vitamin A status of children less than one year of age are therefore needed.

Besides sub clinical vitamin A deficiency, anemia was highly prevalent (28.4%) among children under 5 years of age. Although we did not measure the iron status (ferritin, transferrin) directly we may assume that the main cause of anemia in these children is iron deficiency. The prevalence of anemia in this study is lower than global estimates for preschool children (42%) in developing countries.[19] However, the prevalence of anemia was very high in infants under 12 months of age (61.7%, see Figure 3). This may be the consequence of a poor iron store of children due to a poor iron status of the mother.[9]

The finding that serum retinol concentrations are positively correlated with hemoglobin concentrations is in agreement with results from previous studies.[2, 20, 21, 22] Vitamin A deficiency definitely impairs hemoglobin synthesis[23]. This was most clearly demonstrated in a clinical experiment involving anemic adults who were depleted of vitamin A. Supplementation of vitamin A was responsive to hemoglobin levels or iron status.[23] In fact, several intervention studies have shown that vitamin A supplementation improves hemoglobin response such as a study in Malawian infants, in school children in Tanzania, and in Indonesian pregnant women [24, 25, 26, 27].

A limitation of the present study is that no information on dietary intakes and socio- economic status were available. Such data may provide useful information to explain the situation of vitamin A deficiency and anemia in the studied population.

In conclusion, our data show that sub clinical vitamin A deficiency and anemia are important public health problems in Vietnamese children under the age of 5 years. Sustainable strategies for combating vitamin A deficiency and nutritional anemia are needed and should concentrate on target groups, especially infants, malnourished children and especially in high risk regions.

Acknowledgements
We thank the children and families who participated in this survey and the staff of the National Institute of Nutrition for their excellent laboratory work. We are grateful to all the staff of the Preventive Medicine Centers of Provinces, District Health Centers and Communes where the surveys were conducted. The advice of Dr Paul Deurenberg, Nutrition Consultant in Singapore on the preparation of the paper is highly appreciated.
Sponsorship: The Government of Vietnam and UNICEF Hanoi financially supported this study.

References

1. Sommer A, West Jr KP. Vitamin A deficiency: Health, Survival, and Vision. New York: Oxford University Press, 1996: 19-21.
2. Semba RD, Bloem MW. The anemia of vitamin A deficiency: epidemiology and pathogenesis. Eur J Clin Nutr 2002; 56: 271-281.
3. West Jr KP. Extent of vitamin A deficiency among preschool children and women of reproductive age. J Nutr 2002; 132: 2857S-2866S.
4. Yip R. Iron deficiency and anemia. In: Semba RD, Bloem MW, eds. Nutrition and health in developing countries. Totowa, NJ: Humana Press, 2001; p 327.
5. Lozoff B, Wachs TD. Functional correlates of nutritional anemias in infancy and early childhood-child development and behavior. In: Nutritional Anemias, eds U Ramakrishnan, CRC Press 2001; pp 69-88.
6. Khoi HH, Khan NC, Dung NC. Progress of vitamin A deficiency control program in Vietnam. In 20 Years Prevention and Control of Micronutrient Deficiency in Vietnam. Medical Publishing House, 2001; pp 4-23.
7. Khan NC, Khoi HH. Control of vitamin A deficiency in Vietnam: achievements and future orientation. Food Nutr Bull 2002; 23: 133-142.
8. Bloem MW, Johnathan G, Khan NC, Khoi HH. Vietnam Xerophthalmia Fee: A report of National survey on xerophthalmia 1994, NIN/UNICEF/HKI. Hanoi, Vietnam, 1995.
9. NIN/UNICEF/CDC/PAMM. Report of the National Anemia and Nutrition Risk Factor Survey, Vietnam 1995. National Institute of Nutrition, Vietnam; UNICEF-Vietnam; Centers for Disease Control and Prevention; Program Against Micronutrient Malnutrition, 1995; pp 13–30.
10. World Health Organization. Measuring Change in Nutritional Status, Geneva, 1983
11. National Center for Health Statistics. NCHS growth curves for children, birth–18 years, United States. Washington, DC: US Department of Health, Education and Welfare, 1977.
12. International Nutritional Anemia Consultative Group. Measurements of iron status. A report of INACG, 1985: 4-8
13. Hodges RE, Sauberlich HE, and Mohanram M. Hematopoietic studies in vitamin A deficiency. Am J Clin Nutr 1978; 31: 876–885.
14. International Vitamin A Consultative Group. Biochemical methodology for assessment of vitamin A status, The Nutrition Foundation, Washington DC, USA, 1982.
15. World Health Organization. Indicators for assessing vitamin A deficiency and their application in monitoring and evaluating intervention programs. WHO/NUT/96.10. WHO, Geneva, 1996: 7-9.
16. Khan NC, Mai LB, Minh ND, Do TT, Khoi HH and Hautvast JGAJ. Intakes of retinol and carotenoids intakes and its determining factors in the Red River Delta population of northern Vietnam. Submitted Eur J Clin Nutr. for publication.
17. National Institute of Nutrition, Vietnam. 2000 National Nutrition Survey. Hanoi, Medical Publishing House, 2002.
18. Wieringa FT, Dijkhuizen MA and West CE. Estimation of vitamin A deficiency in infants. International Vitamin A Consultative Group. Abstract of XXII IVACG Meeting, Peru, 2004: 47.

19. Administrative Committee on Coordination/Sub-Committee on Nutrition. Fourth Report on the World Nutrition Situation. Geneva, 2000: 24.
20. Gamble MV, Palafox NA, Dancheck B, Ricks MO, Briand K, and Semba RD. Relationship of vitamin A deficiency, iron deficiency, and inflammation to anemia among preschool children in the Republic of the Marshall Islands. Eur J Clin Nutr 2004; 58: 1396-1401.
21. Palafox NA, Gamble MV, Dancheck B, Ricks MO, Briand K, and Semba RD Vitamin A deficiency, iron deficiency, and anemia among preschool children in the Republic of the Marshall Islands. Nutrition 2003; 19: 405-408.
22. Nhien NV, Khan NC. Serum levels of trace elements and iron deficiency anemia in adult Vietnamese. Biol Trace Elem Res (in press).
23. Allen Linsay H. Iron supplements: Scientific issue concerning efficacy and implications for research and programs. J Nutr 2002; 132: 831S-819S.
24. Kumwenda N, Miotti PG, Taha TE. Antenatal vitamin A supplementation increases birth weight and decreases anemia among infants born to human immunodeficiency virus–infected women in Malawi. Clin Infect Dis 2002; 35: 618-624.
25. Mwanri L, Worsley A, Ryan P, Masika J. Supplemental vitamin A improves anemia and growth in anemic school children in Tanzania. J Nutr 2000; 130: 2691-2696.
26. Muslimatun S, Schmidt MK, Schultink W. Weekly supplementation with iron and vitamin A during pregnancy increases hemoglobin concentration but decreases serum ferritin concentration in Indonesian pregnant women. J Nutr 2001; 131: 85-90.
27. Suharno D, West C, Hautvast JAJG. Supplementation with vitamin A and iron for nutritional anemia in pregnant women in West Java, Indonesia. Lancet 1993; 2: 1325–1328.

Original Article

Sub clinical vitamin A deficiency and anemia among Vietnamese children less than five years of age

Nguyen Cong Khan MD, PhD[1,2], Nguyen Xuan Ninh MD, PhD[1], Nguyen Van Nhien MD[1], Ha Huy Khoi PhD, DSc[1], Clive E West PhD[3,4] (deceased) and Joseph GAJ Hautvast MD, PhD[3]

[1]*National Institute of Nutrition, Hanoi, Vietnam*
[2]*Division of Nutrition, Hanoi School of Public Health, Vietnam*
[3]*Division of Human Nutrition, Wageningen University, Wageningen, The Netherlands*
[4]*Department of Gastroenterology, University Medical Center, Nijmegen, The Netherlands*

五歲以下越南兒童之亞臨床維生素 A 缺乏及貧血

本研究的目的為評估越南兒童亞臨床維生素 A 缺乏及貧血的盛行率。為此，在 2001 年 4 月到 5 月，越南 4 個生態區的 40 個村落(聚集)執行了一個橫斷性調查。以集束隨機抽樣法，選入 1657 名五歲以下兒童。亞臨床維生素 A 缺乏(血清視網醇<0.70 μmol/L)的盛行率為 12%，貧血的盛行率為 28.4%(血紅素<110g/L)。六個月以下嬰兒之亞臨床維生素 A 缺乏盛行率為 35.1%，這個族群之貧血盛行率高達 61.7%。兒童亞臨床維生素 A 缺乏及貧血兩者都有的盛行率為 6.1%。亞臨床維生素 A 缺乏及貧血的盛行率在不同的地區有顯著差異，北部山區維生素 A 缺乏盛行率較高，而北部山區及湄公河三角洲貧血盛行率較高。總結，亞臨床維生素 A 缺乏及貧血在越南仍然是重要的公共衛生問題。我們需要永續的政策，並集中在目標族群來解決維生素 A 缺乏及營養性貧血，尤其是處在高危險地區的嬰兒及營養不良的兒童。

關鍵字：維生素 A 缺乏、貧血、兒童市區鄉村盛行率、越南。