THE ROLE OF PLANT FOOD SOURCES IN CONTROLLING VITAMIN A DEFICIENCY IN VIETNAM

Nguyen Cong Khan

PROMOTOREN:

Professor J G A J Hautvast
Hoogleraar Voeding en Gezondheid, Wageningen Universiteit

Professor F J Kok,
Hoogleraar Voeding en Gezondheid, Wageningen Universiteit

CO- PROMOTOREN:

Dr Paul Deurenberg, PhD
Voormalig Universitair Hoofddocent leerstoelgroep Voeding en Gezondheid, Wageningen Universiteit, thans Nutrition Consultant, Singapore

Professor Dr Ha Huy Khoi
Division of Nutrition and Food Safety
President Vietnam Nutrition Association (Vinutas), Hanoi, Vietnam

PROMOTIECOMMISSIE:

Prof. dr. P. Shetty
FAO, Rome

Dr. J.L.A. Hautvast
GGD Regio Nijmegen

Dr. C.M. van Beusekom
Friesland Foods, Leeuwarden

Prof. Dr E.G. Schouten
Wageningen Universiteit

Dit onderzoek is uitgevoerd binnen de onderzoeksschool VLAG

THE ROLE OF PLANT FOOD SOURCES IN CONTROLLING VITAMIN A DEFICIENCY IN VIETNAM

Nguyen Cong Khan

Proefschrift
ter verkrijging van de graad van doctor
op gezag van de rector magnificus van
Wageningen Universiteit,
prof.dr. M.J. Kropff,
in het openbaar te verdedigen
op dinsdag 31 oktober 2006
des namiddags te vier uur in de Aula

Khan Nguyen Cong

The role of plant food sources in controlling vitamin A deficiency in Vietnam

Thesis Wageningen University –with references- with summary in Dutch

ISBN 90-8504-492-8

THE ROLE OF PLANT FOOD SOURCES IN CONTROLLING VITAMIN A DEFICIENCY IN VIETNAM

Nguyen Cong Khan

ABSTRACT

The role of plant food sources in controlling vitamin A deficiency in Vietnam

PhD thesis by Nguyen Cong Khan, Division of Human Nutrition, Wageningen University, Wageningen, the Netherlands.

Elimination of vitamin A deficiency has been high on the agenda of subsequently the Micronutrient Deficiency Meeting held in Montreal, Canada 1991 and the International Conference on Nutrition in Rome, Italy, 1992. During the last decade, the direction of research and approaches towards controlling vitamin A deficiency have changed enormously and has been shaped and advanced largely by public health professionals, policy makers and different organizations.

Although vitamin A deficiency and xerophthalmia is not a public health problem anymore in Vietnam, the prevalence of sub clinical vitamin A deficiency is still high. Main sources of vitamin A in the diet are green leafy vegetables and fruits and only the wealthier part of the population gets a substantial part of their vitamin A from animal sources. To increase the vitamin A intake in the population, several approaches are possible.

For many developing countries a food-based approach using foods naturally rich in vitamin A and other micronutrients is preferable because fruits and vegetables provide 70-80% of the total vitamin A intake due to their high content of provitamin A carotenoids. Thus, an increased consumption of plant provitamin A-rich foods should be encouraged. The question is, however, how much can plant foods contribute to vitamin A supply.

An intervention study in breastfeeding women was carried out, specially designed to provide information about the role of different plant food sources in improving the vitamin A status. The results show that consumption of dark-green leafy vegetable only result in a very small improvement of the vitamin A status, suggesting that the relative bioavailability of β-carotene in dark-green leafy vegetables is lower than previously assumed. Interestingly, the bioavailability of carotenoids differs across different kinds of plant food: β-carotene in yellow/orange fruits is better available than that in dark-green leafy vegetables. The reason of the low bioavailability of carotenoids could be the complex matrix of leaves in addition to absorption inhibitors such as fiber which entraps carotenoids. Parasitic infestation, genetic factors, and dietary factors might play a role as well.

The study shows that approaches beyond the promotion of fruits and vegetables are required to eliminate (sub clinical) vitamin A deficiency. It might be necessary to apply

combination strategies including public health measures, food fortification, “bio-fortification” and other opportunities for targeted supplementation programs. Promotion of consumption of fruits and vegetables should, however, remain part of the holistic approach, not only because of their provitamin A content but also as protective factor in the prevention of chronic diseases.

CONTENTS Page

CHAPTER 1

General introduction

It is estimated that there are about 150 million malnourished children in the world today [1]. The majority of them and their mothers are living in developing countries. It is generally recognized that poverty is the root cause of malnutrition and in turn that malnutrition contributes to poverty [2].

Malnutrition impairs the physical and mental development of young children and with that of the future generation. At the long term this will affect the socio-economic development of a country considerably.

Along with protein energy malnutrition, micronutrient deficiencies like vitamin A deficiency, iodine deficiency and iron deficiency are also important public health problems and together they contribute to half of the ca. 10.4 million children under 5 years of age who die annually in the developing world [3]. At the World Submit for Children in 1990 goals were set to be reached at the turn of the century, goals that were affirmed at the conference ‘Ending Hidden Hunger’ in 1991 and the International Conference on Nutrition in 1992. These goals were as follows:

- virtual elimination of vitamin A deficiency
- virtual elimination of iodine deficiency
- reduction of iron deficiency anaemia in women of reproductive age by one-third compared with 1990 levels.

Although many remarkable achievements have been made during the past decade, malnutrition continues to affect large numbers of people in developing countries, especially in the South-East Asia region [3]. Global coordination for ending malnutrition by the year 2020 has been proposed and comprehensive action should be taken to combat the malnutrition situation [4].

Vitamin A deficiency

Deficiency of vitamin A or retinol is one of the most important nutritional deficiencies in developing countries. Vitamin A deficiency occurs when diets supply insufficient vitamin A and/or carotenoids (provitamin A) required for growth, development and physiological functions, or during periods of illness which cause vitamin A losses [17].

Besides the role of vitamin A in prevention of blindness which is widely recognized, vitamin A is also involved in reproduction, in the maintenance of differentiated epithelia, in the formulation of specific glycoproteins, in mucous secretion, and disease resistance [5-6].

It is estimated that world-wide 2.8 million children have vitamin A deficiency and another 250 million have low serum retinol concentration [7], thus are potentially at risk to develop vitamin A deficiency.

Vitamin A deficiency increases the risk of morbidity and mortality in young children and supplementation has been shown to reduce mortality in children by as much as 23% [8-10]. Recent evidence showed that sub clinical vitamin A deficiency is associated with an increased risk of severe illness and even death, from such common childhood infections as diarrhoea and respiratory infections [11-12].

Vitamin A deficiency not only occurs in children but also young women in their reproductive age are vulnerable. Early reports suggest that vitamin A deficiency is highly prevalent in pregnant and lactating women [13-14]. Vitamin A or beta carotene supplementation beginning prior to and continuing throughout pregnancy reduces maternal mortality related to pregnancy by up to 40% [16].

Vitamin A is present in food in two main forms. The various carotenoids that serve as provitamins are found mainly in plant materials, such as carrots, dark green leafy vegetables, yellow and orange vegetables and fruits. Preformed retinol is found naturally only in foods of animal origin. FAO/WHO recommends an intake of 600 μg retinol equivalent per day, adults need more than children, and pregnant and lactating women usually need more than men [18]. Based on several studies done during the last decade on the bioefficacy and bioavailability of carotenoids, the IVACG adapted the new conversion factor for carotenoids of 1μg retinol equal to 12 μg β-carotene in mixed foods, and of 1 to 24 μg other provitamin A carotenoids in mixed foods [69].

Iron deficiency

Iron is an essential component of hemoglobin, the oxygen transporting protein in blood. Anemia, defined according to age and sex related “cut-off points” of hemoglobin concentration, [19] can result from various nutritional deficiencies including iron, folic acid, cobalamin (vitamin B_{12}), riboflavin (vitamin B_2), copper as well as vitamin A deficiency but can also be due to non-nutritional factors. Iron deficiency is the most common and widespread nutritional disorder in the world. It is estimated that nearly 3 billion people in the world suffer from iron deficiency and/or iron deficiency anemia [20-21].

The pallor of anemia was associated with weakness and tiredness long before its cause was known. Now it is recognized that even without established anemia mild to moderate iron deficiency has adverse functional consequences [22]. Iron deficiency has also been found to have a negative impact on immunity [23], hence making deficient subjects more vulnerable for secondary diseases.

Iron is especially important for infants and children because it is needed for a wide range of metabolic activities and is as such essential for growth. Iron deficiency anemia is associated with growth retardation and increased morbidity in children [24-26]. During infancy and childhood iron deficiency anemia can lead to impaired mental and motor development with possible long term consequences [27-28].

Interactions between vitamin A and iron.

The evidence that vitamin A has a specific relationship with iron comes from both animal and human studies. Early research concluded that vitamin A is essential for normal haematopoiesis as it plays a role in iron metabolism [29]. The mechanisms are poorly understood up to now. It has also been suggested that vitamin A deficiency impairs erythropoiesis and mobilisation of iron from body iron stores into the circulation [30]. In marginal vitamin A deficient rats, supplementation with iron plus vitamin A was more effective in restoring a normal iron status than was iron supplementation alone [31]. These findings in animal studies are confirmed by various studies in children [32-33] and pregnant women [35-36]. A recent study showed that the inhibiting effect of polyphenols and phytates on iron absorption is reduced in the presence of vitamin A in the diet [37].

Prevention and control of vitamin A deficiency

Prevention of vitamin A deficiency may be addressed by appropriate combinations of different approaches:

- supplementation through massive dosing,
- food fortification or enrichment,
- dietary diversification and
- nutrition education.

The most common and traditional strategy has been the massive dosing approach through distribution of high dose vitamin A (in oil) capsules at periodic intervals to ‘at risk’ groups (high dose vitamin A capsules of 200,000 IU (1 IU = 0.3 µg retinol) for children of six months to five years of age, and 100,000 IU for children under one year of age), every four to six months [38-40]. The advantage of this periodical dosing is that it is highly effective and fast but it needs a continuous supply of supplements and a good infra structure and delivery system, so it raises the issues of cost and sustainability. Despite this drawback the vitamin A supplementation coverage has increased significantly in the last decade, spurred on by the linkage of supplementation to immunization which has been a WHO/UNICEF policy since 1994 [41]. Also Asian countries adapted this approach [42].

Vitamin A food fortification or food enrichment is widely applied in industrial countries but it is not common practise in developing countries, including countries in the South-East Asian region. In Guatemala, sugar was the vehicle of choice for vitamin A fortification while in Indonesia, monosodium glutamate fortification with vitamin A proved to be effective on child survival [43] but has not been widely implemented because of its constraints and unsuitability. Oil fortification with vitamin A is legislated throughout most South Asian countries but often it is not enforced [44].

Of the various strategies to reduce vitamin A deficiency, the dietary approach which advocates the use of foods naturally rich in vitamin A and micronutrients is increasingly practised because it seems the most feasible way of providing an adequate vitamin A intake and intake of other (essential) nutrients simultaneously. The most effective foods to improve vitamin A intake are those rich in retinol, but they are also the most expensive. For infants and young children, the promotion of breastfeeding, especially during the first 6 months, is very important in the prevention of vitamin A deficiency in early life [45-46]. In developing countries, fruits and vegetables provide 70-80% of the total vitamin A intake because of their high content of provitamin A carotenoids [47]. Thus increased consumption of plant provitamin A-rich foods and examination of its bioefficacy are encouraged.

Infectious diseases can reduce food intake, reduce intestinal absorption of nutrients and increase urinary losses of nutrients [38, 48]. Thus the prevention of infectious diseases plays also a role in the improvement of the vitamin A status [38].

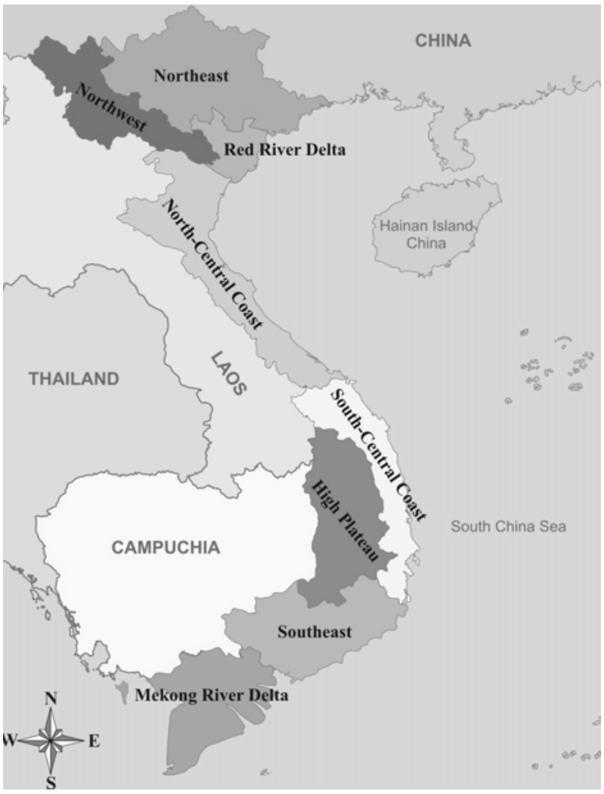
Vietnam

Geographic characteristics of Vietnam

Vietnam has an area of about 33,000 sq km. The country borders with China in the North and with Laos and Cambodia in the West. Vietnam has 3,260 km of coastline which stretches from the North to the South with 8 ecological regions: the Northwest, the Northeast, the Red River Delta, the North-Central Coast, the South-Central Coast, the Southeast, the High Plateau and the Mekong River Delta (Figure 1). Vietnam is divided into 64 provinces, more than 600 districts and about 11,000 communes. The climate is characterized by two distinct seasons: the rainy season (from May to October) and the dry season (from November to April). In the north, the climate is strongly influenced by the Northeast monsoon with many cold periods during the dry season while in the south the climate is typically tropical. The land for agriculture is 6,993,241 ha of which 4,108,855 is used for rice cultivation. Rice is the staple food of Vietnamese and it presents 80 to 85%

of the total food crop production [50]. Water fields (ponds, lakes, rivers, streams) are about 500,000 ha and provide fish.

Figure 1 The ecological regions of Vietnam



Population

The total population is about 82 millions and the annual population growth rate is assessed to be 1.4%. Thirty-five % are children below 15 years of age and 12% is younger than 5 years.

The proportion of women of reproductive age is 28% [51]. The average life expectancy (2003) is 71 years [52]. About 73% of the population lives in the rural areas, and depends mainly on subsistence farming.

Health and nutrition care system

The health care service is provided through a government-controlled network of health facilities and personnel at every level of the administrative structure from the central to communal levels. The preventive health system is represented at all levels. At the central level: the Ministry of Health (Department of Preventive Health and other research institutes, including the National Institute of Nutrition); at the provincial level: the Provincial Centre for Preventive Medicine; at the district level: the Centre for Preventive Medicine and at the commune level: the Commune Health Centres which mainly provide primary health care [53]. There is a section which is responsible for implementation of nutrition programmes and food hygiene activities at provincial and district levels. Community health workers at commune level are responsible for nutrition activities at commune/village level.

Nutritional status.

Protein energy malnutrition (PEM), vitamin A deficiency, iodine deficiency and nutritional anaemia are the main nutritional problems in Vietnam. However, in recent years the prevalence of obesity and associated risk factors is rapidly increasing. In some cities, overweight and obesity has reached high levels in both children (about 12-15%) and adults (about 10-14%), and thus Vietnam is facing a situation of 'double burden' of malnutrition [54, 66].

During the last 15 years the prevalence of underweight among children under 5 years of age reduced from 45% in 1990 to 26.6% in 2004 with an average reduction of 1.3% per year in the period 1990-2000 and 1.8% in the period 2000-2004 [54]. The prevalence of stunting was 56.5% in 1990 and 30.7% in 2004: the average reduction in the period 1990-2000 was 2% per year and in the period 2000-2004 was 1.5%. Although the reduction in child malnutrition over the past years was remarkable, Vietnam remains a country with a high level of malnutrition prevalence which needs continuous concern.

Vitamin A deficiency

The traditional diets consumed in tropical regions as Vietnam are generally low in animal protein and are often based on plant foods [55]. The first nation-wide survey in children under 5 years of age conducted by the National Institute of Nutrition between 1985 and 1988 reported that 0.72% exhibited classical signs of xerophthalmia due to vitamin A deficiency [56]. The prevalence of severe forms of xerophthalmia (0.07% and 0.12% for X2/X3 and XS respectively) was much higher than the WHO criteria for classifying vitamin A deficiency as a public health problem [56]. The prevalence of xerophthalmia was higher after the first year of life and reached a peak in the third year of life. Cultural feeding practices seemed to be an important factor related to vitamin A deficiency. These included low consumption of animal food such as eggs by children, short duration of breast feeding or insufficiency of breast milk and some problems with traditional weaning patterns, and infectious diseases. Not only children, but also women of childbearing age are at high risk of vitamin A deficiency [57, 58]. By the year 2000-

2001, clinical vitamin A deficiency (as xerophthalmia) was no longer existing as public health problem but subclinical vitamin A deficiency (serum retinol <0.70 µmol/l) was reported at 12.0% among children under 5 years of age with significant differences across the regions of Vietnam [59].

Approaches to controlling vitamin A deficiency in Vietnam

The result of the first survey in 1985-1988 has strongly convinced the Vietnamese Government and resulted in the launching of a program to control vitamin A deficiency which started in 1988. The program strategies comprised of nutrition education; universal distribution of high dose vitamin A capsules to children aged 6 to 36 months in combination with immunization and promotion of production and consumption of vitamin A-rich foods at family level [60]. An implementation network was set up based on the existing preventive health structure at all administrative levels. The program has been actively supported by mass organizations such as the Women's Union to mobilize the resources for its implementation. Up to now (2006), the vitamin A supplementation activity is maintained throughout the country twice a year in children from 6 months to 36 months of age with an average coverage of more than 90%.

The home garden for cultivation of vegetables and fruits, a pond for fish culture and a cattle shed for animal husbandry were the common home-based agricultural practice of many Vietnamese families [61]. The association of Vietnam VAC (acronym for Garden (V); Pond (A) and Cattle shed (C) was established in 1986. It focuses on promotion of VAC by giving various forms of technical training and education for its members in order to transfer knowledge and expertise to the farmers [62] and it promotes the cultivation of traditional fruits and vegetables rich in carotenoids [65]. Thus, the VAC might contribute to the variety in people's diet [62, 63]. Home gardening in Vietnam can improve the nutritional vitamin A status of children [64].

Nutrition education activities have been implemented in different ways. Mass education and campaigns were organized twice a year with the involvement of mass media agencies such as TV, radio and newspapers at central and provincial levels. Nutrition education and social mobilization had a positive influence on attitude and practice of different groups involved in micronutrient deficiency control, including community leaders at all levels. This in turn, contributed to the success of vitamin A supplementation programs [66].

In 1995 the Prime Minister ratified a National Plan of Action for Nutrition and in 2001, the Prime Minister ratified the National Nutrition Strategy which specially emphasizes on control of micronutrient malnutrition with the goal of elimination vitamin A deficiency by the year 2010 [67, 68].

Outline of thesis

In the following chapters of this thesis results from various Vietnamese studies in children and lactating women and in households are presented.

Chapter 2 reports the results of a cross-sectional study on sub clinical Vitamin A deficiency and anemia among Vietnamese children less than five years of age in 4 ecological areas of Vietnam.

Chapter 3 reports the results of a cross-sectional study, illustrating the patterns of consumption of retinol and carotenoids by households. Factors related to the consumption of retinol and carotenoids were studied in the Red River Delta population in northern Vietnam.

Chapter 4 describes the results of an intervention study on how plant foods can contribute to the vitamin A supply of lactating women in Pho Yen district, Thai Nguyen province of Vietnam.

Chapter 5 reviews the progress of implementation of Vitamin A Deficiency Control programs in Vietnam.

Chapter 6 discusses the most important findings of the studies described in this thesis and their practical implications.

REFERENCES

1. WHO. Global database on child growth and malnutrition. WHO, Geneva 2004: 75 - 80.
2. Lisa C.Smith and Lawrence Haddad. Overcoming Child Malnutrition in Developing Countries: Past achievements and future choices. International Food Policy Research Institute, Washington DC, 2/2000.
3. WHO. What do we mean by malnutrition? Version 6 Feb 2001; http://www.who.int/nut/nutrition2.htm.
4. Brown P. Coordinated global action could end malnutrition in young children. BMJ 2000; 320: 825.
5. McLaren DS. Global occurrence of vitamin A deficiency. In: Vitamin A deficiency and its control (Bauernfeind JC ed). Orlando: Academic Press Inc, 1986.
6. Sommer A. Vitamin A deficiency and its consequences. A field guide to detection and control. Third edition. WHO, Geneva, 1995.
7. ACC/SCN. Fourth report on the world nutrition situation. Nutrition throughout life cycle.

ACC/SCN in collaboration with IFPRI, Geneva, 2000.

8. Beaton GH, Martorell R, Aronson KJ, Edmonston B, Mccabe AC, Ross AC, Harvey B. 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, 1993.
9. Stephenson LS, Latham MC and Ottesen EA: Global malnutrition. Parasitology 2000;121 (suppl): S5-22.
10. Ramakrisnan U. Prevalence of micronutrient malnutrition worldwide. Nutr Rev 2002; 60: S46-S52.
11. Ahmed FU, Rahman ME & Mahmood CB. Vitamin A deficiency in children with acute diarrhoea: a community-based study in Bangladesh. J Health Popul Nutr 2000; 8: 119-122.
12. Faber M and Spinnler Benade AJ: Factors associated with low serum retinol levels in children aged 6-24 months in a rural South African community. Public Health Nutr 2000; 3: 395-402.
13. Katz J, Khatry SK, West KP, Humphrey JH, LeClerg SC, Kimbrough E, Pohkrel PR and Sommer A. Night blindness is prevalent during pregnancy and lactation in rural Nepal. J Nutr 1995; 125: 2122-27.
14. Suharno D, West CE, Muhilal, Logman MH, de Waart FG, Karyadi D and Hautvast JGAJ. Cross-sectional study on the iron and vitamin A status of pregnant women in West Java, Indonesia. Am J Clin Nutr 1992; 56: 988-993.
15. Christian P, West KP, Khatry SK, LeClerg SC, Kimbrouhg-Pradhan EK, Katz J, Shrestha. Maternal night blindness increases risk of mortality in the first 6 months of life among infants in Nepal. J Nutri 2001; 131:1510-1512.
16. West KP, Katz J, Khatry SK, LeClerg SC, Pradhan EK, Shrestha SR, Connor PB, Dali SM, Christian P, Pohkrel PR and Sommer A. Double blind, cluster randomized trial of low dose supplementation with vitamin A or beta carotene on mortality related to pregnancy in Nepal. BMJ 1999; 318: 570-575.
17. Stephensen CB, Alvarez JO, Kohatsu J, Hardmeier R Kennedy JI and Gammon RB. Vitamin A is excreted in the urine during acute infection. Am J Clin Nutr 1994; 60:388-392.
18. FAO/WHO. Requirement of Vitamin A, iron, folate, and vitamin B_{12} .A joint report of FAO/WHO Expert consultation. FAO Food nutrition series No 23. FAO, Rome 1988.
19. Bothwell TH. Charlton RW, Finch CA, and Cook JD. Iron metabolism in men. Blackwell Scientific Publications, Oxford, 1979.
20. Beard J, Stoltzfus, eds. Iron deficiency anemia: Reexamining the nature and magnitude of the public health problem. Proceedings of the WHO-INACG Conference, USA 2000. J Nutr 2001; supplement 131:2S-11.
21. UNU, UNICEF, WHO, MI. Preventing iron deficiency in women and children. Consensus on key technical issues. Report of UNU, UNICEF, WHO, MI technical workshop, New York 1998, Micronutrient Initiative, 1999.
22. Scrimshaw NS. Functional significance of iron deficiency: an overview. In Enwonwo CO, ed

annual nutrition workshop series, Vol III. Nashville, TN, Meharry Medical College, 1990: 1-13.

23. WHO, UNU, UNICEF. Iron deficiency anemia: Assessment, Prevention, and Control. A guide for programme managers. WHO/NHD/01.3, 2003.
24. Ageles IT, Schultink JW, Matulessi P, Gross R, Sastroamidjojo S. Decreased rate of stunting among anemia Indonesian preschool children through iron supplementation. Am J Clin Nutr 1993; 58:339-342.
25. Allen LH. Nutritional influences on linear growth: a general review. Eur J Clin Nutr 1994; 48: 75S-89S.
26. Lawless JW, Latham MC, Stephenson LS, Kinoti SN, Pertet AM. Iron supplementation improves appetite and growth in anemic Kenyan primary school children. J Nutr 1994; 124: 645-654.
27. Idjradinata P, Pollitt E. Reversal of development delays in iron-deficient anemia infants treated with iron. Lancet 1993; 341:1-4.
28. Lozoff B, Jimenez E, Wolf AW. Long term development outcome of infants with iron deficiency. N Engl J Med 1991; 325: 687-694.
29. Hodges RE, Sauberlich HE, Canham JE, Wallace DL, Rucker RB, Mejia LA, Mohanram M. Hematopoietic studies in vitamin A deficiency. Am J Clin Nutr 1978; 31:876-885.
30. Roodenburg AJ, West CE, Yu S, Beynen AC. Comparison between time-dependent changes in iron metabolism of rats as induced by marginal deficiency of either vitamin A or iron. Br J Nutr 1994; 71: 687-699.
31. Roodenburg AJ, West CE, Hovenier R, Beynen AC. Supplemental vitamin A enhances the recovery from iron deficiency in rats with chronic vitamin A deficiency. Br J Nutr 1996; 75: 623-636.
32. Mejia LA and Chew F. Hematological effect of supplementing anemic children with vitamin A alone and in combination with iron. Am J Clin Nutr 1988; 48: 595-600.
33. Bloem MW, Wedel M, Egger RJ et al. Iron metabolism and vitamin A deficiency in children in Northeast Thailand, Am J Clin Nutr 1989;50: 332-338.
34. Mejia LA and Arroyava G. The effect of vitamin A fortification of sugar on iron metabolism in preschool children in Guatemala. Am J Clin Nutr 1982; 36: 87-93.
35. Panth M, Shatrugna V, Yasodhara P, Sivakumar B. Effect of vitamin A supplementation on haemoglobin and vitamin A levels during pregnancy. Br J Nutr 1990; 64: 351-358.
36. Suharno D, West CE, Muhilal, Karyadi D, Hautvast JGAJ. Supplementation with vitamin A and iron for nutritional anemia in pregnant women in West Java, Indonesia. Lancet 1993; 342: 1325-1328.
37. Garcia-Casal MN, Layrisse M, Solano L, Baron MA, Arguello F, Llovera D, Ramirez J, Leets I, Tropper E. Vitamin A and beta carotene can improve non heme iron absorption from rice, wheat and corn by humans. J Nutr 1998; 128: 646-650.
38. Gillespie S, Mason J. Controlling of vitamin A deficiency. United Nations: ACC/SCN state of the

art series: Nutrition policy discussion paper no 14, 1994.

39. West KP, Sommer A. Periodic large oral doses of vitamin A for prevention of vitamin A deficiency and xerophthalmia: A summary of experiences. IVACG Report, Nutrition Foundation, 1984.

40. DeMaeyer E. Guidelines for use of vitamin A supplementation in the treatment and prevention of vitamin A deficiency and xerophthalmia. Geneva: WHO/UNICEF/IVACG Task force 1987.

41. UNICEF. The State of the World's Children 1998. Oxford University Press.

42. UNICEF East Asia and Pacific Regional Office. Strategy to reduce maternal and child nutrition. UNICEF EAPRO, Bangkok, 2003.

43. Muhilal, Permaesih D, Iunddjradinata YR, Muherdiyantiningsih, Karyadi D. Vitamin A fortified monosodium glutamate and health, growth, and survival of children: a controlled field trial. Am J Clin Nutr 1988; 48: 1271-1276.

44. Gillespie S., Lawrence H. Attacking the double burden of malnutrition in Asia and Pacific. ADB nutrition and development series no.4, 2001: 20-21.

45. Underwood BA. Maternal vitamin A status and its importance in infancy and early childhood. Am J Clin Nutr 1994; 59: 517S-522S.

46. Stoltzfus RJ and Underwood BA. Breast-milk vitamin A as an indicator of the vitamin A status of women and infants. Bull. WHO 1995; 73: 703-711.

47. West CE, Poortvliet EJ. The carotenoid content of foods with special reference to developing countries. Washington, DC: USAID-VITAL, 1993.

48. Tomkins A and Watson F. Malnutrition and infection. ACC/SCN State-of-art nutrition policy discussion paper 1989; no 5, ACC/SCN, Geneva.

49. General Statistics Office of Vietnam (GSO). Administrative unit of Vietnam. GSO, 2000.

50. Ministry of Agriculture and rural development, Vietnam (MARD). The situation of food security in 2004. MARD, Vietnam, 2005.

51. General Statistics Office of Vietnam (GSO). Vietnam General Statistic Office (GSO): Vietnam living standard survey (VLSS). Hanoi, 2000.

52. Vietnam Ministry of Health (MOH): Health statistical year book 2003.

53. Vietnam Ministry of Health (MOH). National Health Survey (NHS) 2001-02 Report. Hanoi, 2003.

54. National Institute of NIN. Trend of nutritional status of mothers and children and effectiveneess of intervention programme in Vietnam in period of 1999-2004. Statistical publishing house Hanoi, 2005.

55. Giay T., Khoi HH., Doan LV., Canh NK. Present daily food intake of Vietnamese peasants of some ecological regions of the country. In Giay T, Dricot JM, Vuysteke J, & Khoi HH (editors) 1986: Applied Nutrition Proceedings of the International Conference on Applied Nutrition. Hanoi 25-29 April 1986, NIN-UNICEF: 294-304.

56. National Institute of Nutrition and National Institute of Ophthalmology, Vietnam. National survey on vitamin A deficiency and xerophthalmia 1985-1988. The research programme 64-D-01

report. NIN, Hanoi, 1990.

57. Bloem MW, Gorstein J. Xerophthalmia free. 1994 National vitamin A deficiency and protein-energy malnutrition prevalence survey. Consultancy reports, NIN Vietnam 1995.
58. Khan NC, Khoi HH, Hien VT, Quang T. Vitamin A and iron status of rural pregnant women. Vietnam J Prac Med, Hanoi 1994; 2: 26-29.
59. Khan NC, Ninh NX , Nhien NV, Khoi HH. Subclinical Vitamin A Deficiency and Anemia among Vietnamese children under five years of age 2000-2001. National Institute of Nutrition. Scientific report of research programs. NIN, 2002.
60. Khan NC, Khoi HH, Giay T, Nhan NT *et al*. Control of vitamin A deficiency in Vietnam : the achievements and future orientation. Food and Nutr Bull 2002; 23: 133-142
61. Tu Giay, Duong Hong Dat. The ecosystem VAC as a mean to solve the food problem in Vietnam: In: Applied nutrition. Proceedings of the international conference on applied nutrition, Hanoi 25-29 April 1986. NIN, UNICEF, Hanoi, 1986.
62. Nguyen Van Man. VAC and Nutrition. In: Applied nutrition. Proceedings of the international conference on applied nutrition, Hanoi 25-29 April 1986. NIN, UNICEF; 1986: 176-84.
63. Phan Van Huan. VAC ecosystem and micronutrient deficiency control in Vietnam. The research thesis. Hanoi college of medicine; 1997. Hanoi, Vietnam.
64. English R, Badcock J. A community nutrition project in Vietnam: effect on child morbidity. Food Nutr Agric 1998; 22:15-21.
65. Le T Vuong. Underutilized β-carotene-rich crops of Vietnam. Food and Nutrition Bulletin, 2000; 21: 173-181.
66. National Institute of Nutrition, Hanoi, Vietnam. Report on research program KH-09 "study on the solution to improve nutritional status and food hygiene practices of people" period 1997-99. NIN, Hanoi, 1999.
67. National Plan of Action for Nutrition 1995-2000. The Government of Vietnam, 1995.
68. National Nutrition Strategy 2001-2010. The Government of Vietnam, 2001.
69. IVACG. Conversion factor for vitamin A and carotenoids. IVACG, ILSI. Washington DC; June 2004.

CHAPTER 2

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

Nguyen Cong Khan, Nguyen Xuan Ninh, Nguyen Van Nhien, Ha Huy Khol, Clive E West (deceased) and Joseph GAJ Hautvast

Submitted for publication

ABSTRACT

Objective: To assess the prevalence of sub clinical vitamin A deficiency and anemia in Vietnamese children.

Design and subjects: 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.

Results: 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 the highest prevalence in the Northern Mountainous areas for vitamin A deficiency and in the Northern Mountainous area and Mekong River Delta for anemia.

Conclusions: 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.

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 was 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 protein energy 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 regions of Vietnam including Northern Mountainous, Red River Delta, South Central Coast and Mekong River Delta.

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. The sample was obtained using a cluster random sampling method. 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 [12] with a hemoglobin meter (HemoCue, Mission Viejo, CA, USA). 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 [15] 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).

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.

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.

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 (1996) 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. The mean (± SD) serum retinol concentration among boys (1.07 ± 0.44 µmol/l) and girls (1.09 ± 0.38 µmol/l) was not significantly different ($p = 0.302$).

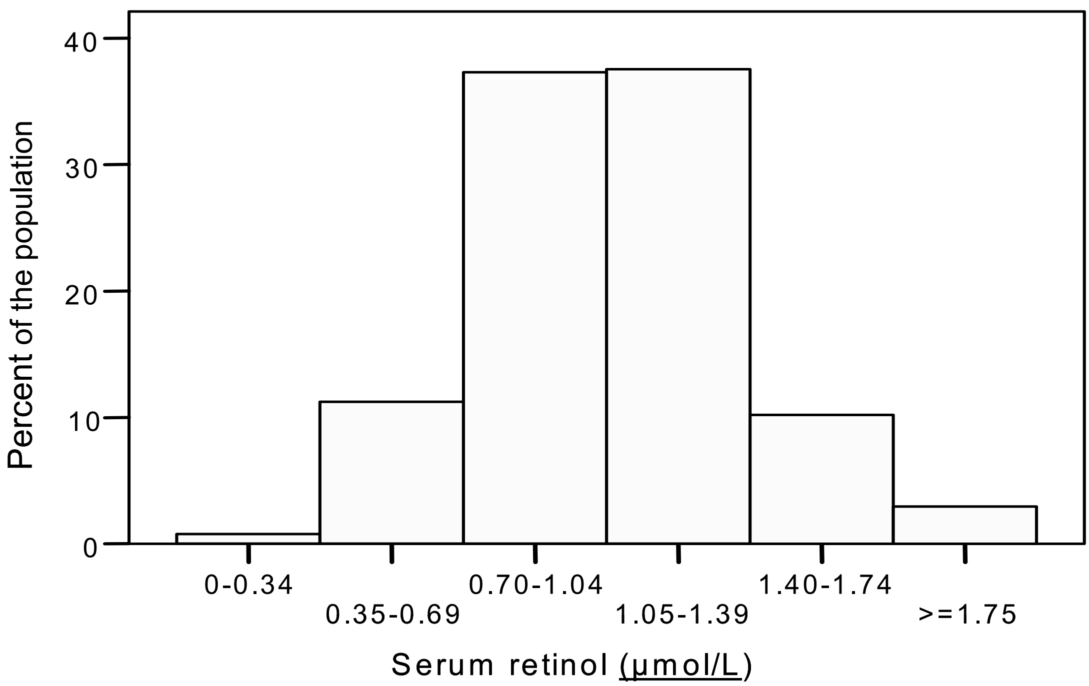
Table 2 Serum retinol (mean ± SD) concentration and prevalence of sub clinical vitamin A deficiency across the regions.

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

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.

Figure 1 Frequency distribution of serum retinol concentrations in 1657 Vietnamese children under 5 years of age.



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).

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

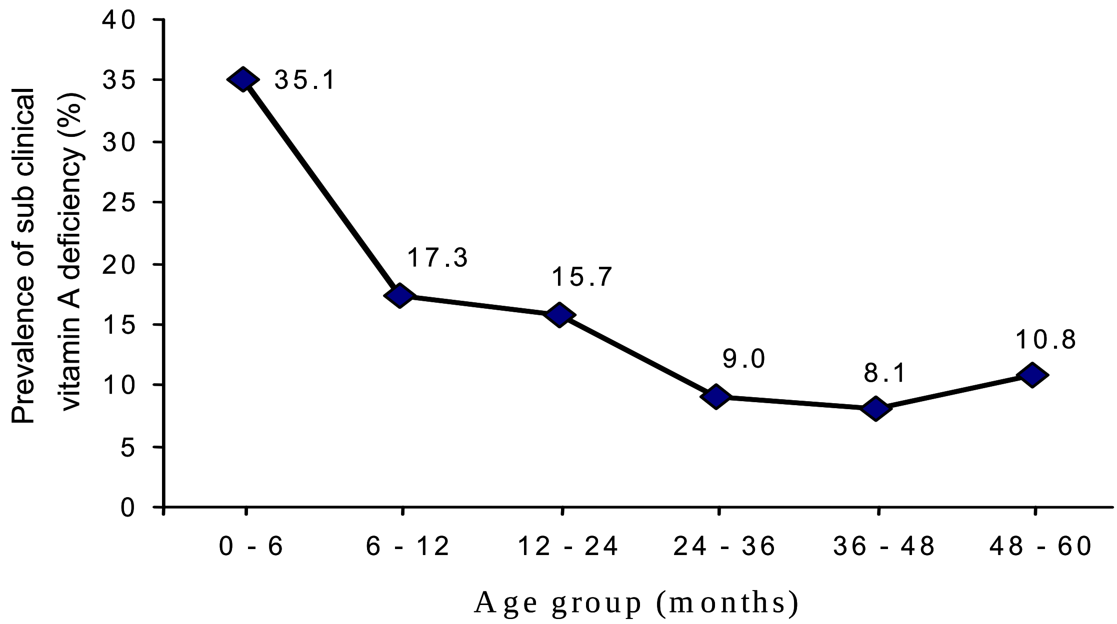
The prevalence of combined vitamin A deficiency and anemia in the children was 6.1% (**Table 4**). A statistically significant relationship was observed between vitamin A deficiency and anemia (Chi-Square $p<0.0001$), and serum retinol and hemoglobin concentration were correlated ($R = 0.16$; $p<0.0001$).

Table 4 Vitamin A Deficiency and anemia†

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

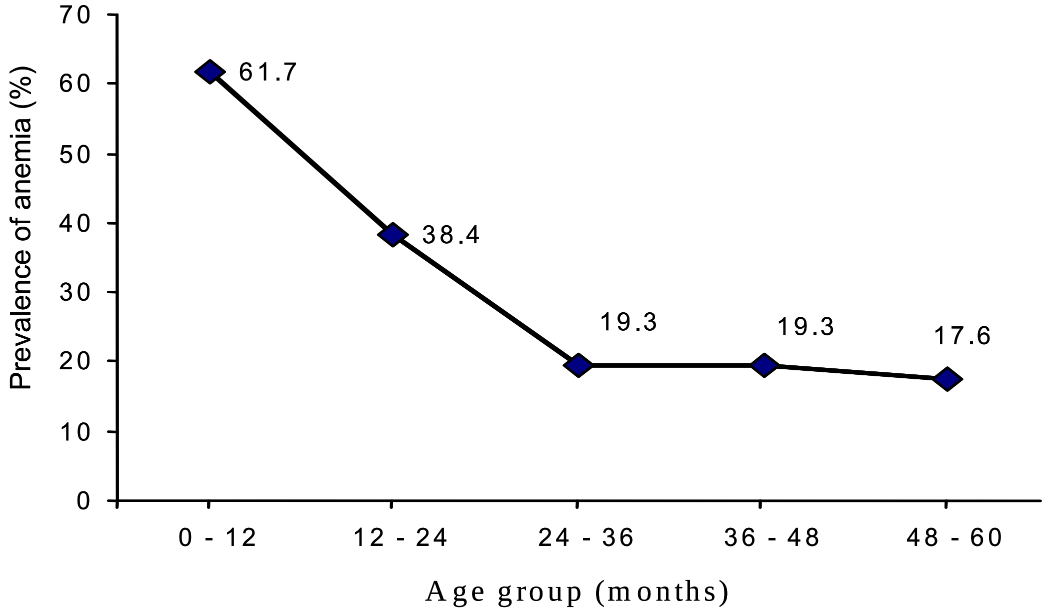
Figure 2 Prevalence (%) of sub clinical vitamin A deficiency by age groups in Vietnamese children



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



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 [6]. 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 health care infrastructure 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 serum retinol 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 [7] and deficiency of vitamin A may occur even during the first months after delivery. 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 [20].

The finding that serum retinol concentrations are positively correlated with hemoglobin concentrations is in agreement with results from previous studies [20, 21, 22, 2]. 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. Heamoglobin levels and iron status responded to vitamin A supplementation [23]. In fact, several intervention studies have shown that vitamin A supplementation improves hemoglobin response such as a study in Malawian infants [24], in school children in Tanzania [25], and in Indonesian pregnant women [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.

ACKNOWLEDGMENTS

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.

REFERENCES

1. Sommer A & West Jr KP. Vitamin A deficiency: Health, Survival, and Vision. New York. 1996. Oxford University Press.
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 K.P 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: Ramakrishnan U, eds. Nutritional Anemias, eds U Ramakrishnan,. Boca Raton, FL. CRC Press. 2001; pp 69-88.
6. Khoi HH, Khan NC, Dung NC., et al. 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, et al Control of vitamin A deficiency in Vietnam: achievements and future orientation. Food Nutr Bull 2002; 23: 133-42.
8. Bloem MW, Johnathan G, Khan NC, Khoi HH et al. 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. National Institute of Nutrition, Vietnam; UNICEF-Vietnam; Centers for Disease Control and Prevention; Program Against Micronutrient Malnutrition, 1995; 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 the assessment of iron status, Washington DC, USA. 1985.
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.
16. National Institute of Nutrition, Vietnam. 2000 National Nutrition Survey. Hanoi, Medical Publishing house. 2002.
17. Khan NC, Mai LB, Minh ND, Do TT, Khoi HH, Clive West (deceased) and Hautvast JGAJ. Intakes of retinol and carotenoids intakes and its determining factors in the Red River Delta population of northern Vietnam. Submitted for publication
18. International Vitamin A Consultative Group. Abstract of XXII IVACG Meeting, Peru, 11/2004.
19. Administrative Committee on Coordination/Sub-Committee on Nutrition. Fourth report on the world nutrition situation. Geneva. 2000.
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. et al. Serum levels of trace elements and iron deficiency anemia in adult Vietnamese. Biol. Trace Elem Res 2006; 110 (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, et al. 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, and 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., et al. 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.E, Muhilal, Karayadi D, Hautvast JAJG. Supplementation with vitamin A and iron for nutritional anemia in pregnant women in West Java, Indonesia. Lancet 1993; 342: 1325–1328.

CHAPTER 3

Intakes of retinol and carotenoids and their determining factors in the Red River Delta population of northern Vietnam

Nguyen Cong Khan, Le Bach Mai, Nguyen Duc Minh, Tran Thanh Do, Ha Huy Khoi, Clive E. West (deceased), Joseph GAJ Hautvast

Submitted for publication

ABSTRACT

Objective: To describe the household intakes of retinol and carotenoids and social economic factors determining their intakes.

Design: Cross-sectional household based survey with 30 randomly selected clusters in the Red River Delta region of northern Vietnam in 2000. Food consumption was assessed using the 24 hours dietary recall method.

Subjects: Data on in total 1,001 households (771 in rural areas and 230 in urban areas) were used in the analyses. Interviewed person was head of household.

Results: Mean (SD) intake of carotenoids was 4178 (3154) µg/capita/day in rural and 4208 (3408) µg/capita/day in urban areas and intake of retinol was 101 (275) µg/capita/day in rural and 201 (470) µg/capita/day in urban areas. Multivariate analyses show that the subjects in households with 4 or more members consume about 700 µg carotenoids less compared to households with less than 3 members. Households with a higher expenditure (4^{th} quartile) consumed about 100 µg retinol /day more than those with a lower expenditure (1^{st} quartile).

Conclusion: Carotenoids from plant food sources is the main source of vitamin A intake of the population and its main determinants are household expenditure and size of household. Food fortification and dietary diversification with special emphasis on promotion of consumption of animal foods should be key strategies for overcoming vitamin A deficiency in Vietnam.

INTRODUCTION

Currently, vitamin A deficiency is a public health nutrition problem in many developing countries around the world, especially in South-East Asia [1]. Vitamin A deficiency increases severity of infection, anemia, poor growth and mortality [2]. Until the year 1995 vitamin A deficiency was regarded as a serious public health problem also in Vietnam, but several years of country-wide vitamin A supplementation programs have improved the situation markedly [3]. However, sub-clinical vitamin A deficiency which is associated with an increasing risk of severe illnesses, even death from diarrhea and respiratory infections, still exists as a public health concern in Vietnam [3].

Dietary modification is an important strategy in the current efforts to improve vitamin A status in vitamin A-deficient populations [4]. In developing countries, people derive 80-85% of vitamin A from plant sources in the form of (pro-vitamin A) carotenoids while pre-formed vitamin A, retinol, exists only in animal foods and accounts for not more than 15-20% of total vitamin A intake [5]. Promotion of consumption of vitamin A-rich foods through home gardening and animal husbandry stimulation programs in Vietnam has been appreciated by the population, especially in rural areas [6]. However, there is lack of information on consumption of vitamin A and/or carotenoids sources by people and factors that are related to intake patterns.

Therefore, the aim of the present study was to find associations between Vitamin A or carotenoids intakes and their determinants, especially socioeconomic factors. The study site was the Red River Delta area in northern Vietnam. The findings of this study provide evidence-based information for food-based approaches to control vitamin A deficiency in Vietnam.

SUBJECTS AND METHODS

Households in the Red River delta of North Vietnam were chosen as the sample sites for this study in 2000. A two stage sampling method was used. Based on a 1999 census [7] which divides this region into clusters including equal number of households (about 100-110 households per cluster), 30 clusters in the Red River Delta were randomly selected. Households within the cluster were randomly selected in the second sampling stage. At each selected cluster (usually a village or sub commune), one third of the households were selected randomly. On average, the number of selected households in each cluster was 33 to 35. The total of 1,041 households in the Red River Delta is representatively for the area. Forty households were excluded from the analyses because data on socio-economic status were not completed. The selected households participated voluntarily in this study and were given compensation for their time and commitment. The study was approved by the Ethical Committee of the Ministry of Health. All information was anonymously coded and could not be traced back to household or individual.

Food consumption in each household was assessed using the 24 hours dietary recall method. The method and the used questionnaire were thoroughly validated in the field in this region in Vietnam. The validity studies were completed by the food consumption study group of the National Institute of Nutrition, Vietnam [8]. Possible bias was eliminated by weighing food items, and showing serving size patterns to the interviewee. Recall bias was limited using a Vietnamese common food album. To prevent subjects from under reporting meals, the commonly used meal pattern was recalled as well. Main respondents were household food preparers, and household members who ate out during the day of investigation and children under the age of 2 were interviewed using proxies. Foods consumed by host and/or guests were estimated and excluded from total household food consumption. Days with special food consumption patterns such as wedding, funeral etc. were changed to another day interview. In addition a food frequency questionnaire was used to investigate the food pattern of the household. Retinol, carotenoids and other nutrients were computed using the Vietnamese Food Composition Table [9] and were then calculated as average intake per capita per day.

Information on socioeconomic factors was obtained from the head of the household, using a structured questionnaire. Economic status was assigned based on household expenditure [10], which include money spent on foods, drinks, health care, education, and some other miscellaneous information. Information on size of household and education of parents were reported by the head of the household, occasionally with assistance from household members, and was cross checked with the “Registration Booklet” of the household. Rural/urban areas are determined by census 1999 [7]. Data on household expenditure were categorized into four levels (quartiles) based on the distribution in the whole study population, and 3 levels of education were assigned: 1. primary school or less; 2. secondary school and high school and 3. higher level than high school.

Data were analyzed using SPSS 11.5 for Windows (SPSS Chicago Inc. Illinois). Data analyzed were considered normally distribution as stated in Central Limited Theory [11]. Independent t test, one way ANOVA, Pearson correlation, and multi-variate analysis were used to compare means and to investigate associations between intakes of retinol and carotenoids and socio-economic factors. Dummy variables were created for socio-economic variables to fit into the multi-variate models. Data are expressed as mean ± SD unless otherwise stated. Significance level is set at $p<0.05$.

RESULTS

The Red River Delta region comprises 9 provinces and/or cities and is an area around the Red River, one of the biggest rivers in Northern Vietnam. The people mainly depend on agricultural production in the rural areas, but the region includes also two big cities (Hanoi and Hai Phong) and 7 smaller cities or towns (urban areas). In this region, people cultivate various kinds of vegetables and fruits throughout the year, while animal food sources such as pig and poultry are mainly produced at household level.

Table 1 Characteristics of studied households

Sub-population	Number of households		
	Rural n (%)	Urban n (%)	Sub-total n (%)
Size of household	771 (100)	230 (100)	1001 (100)
≤ 3 members	120 (15.6)	47 (20.4)	167 (16.8)
4 members	282 (36.6)	105 (45.7)	387 (38.6)
5 members	205 (26.5)	51 (22.2)	256 (25.6)
More than 5 members	164 (21.3)	27 (11.7)	191 (19.0)
Household expenditures	771 (100)	230 (100)	1001
Quartile 1	242 (31.4)	8 (3.5)	250
Quartile 2	233 (30.2)	17 (7.4)	250
Quartile 3	196 (25.4)	55 (23.9)	251
Quartile 4	100 (13.0)	150 (65.2)	250
Education level of mother	629 (100)	167 (100)	796 (100)
Primary school or less	205 (32.6)	31 (18.6)	236 (29.6)
Secondary and high school	411 (65.3)	83 (49.7)	494 (62.1)
Above high school	13 (2.1)	53 (31.7)	66 (8.3)
Education level of father	597 (100)	160 (100)	757 (100)
Primary school or less	190 (31.8)	23 (14.4)	213 (28.1)
Secondary and high school	392 (65.7)	84 (52.5)	476 (62.9)
Above high school	15 (2.5)	53 (33.1)	68 (9.0)

The study sample included 7 clusters in urban areas and 23 clusters in rural areas with a total of 1,041 households. Forty households were excluded from the final analysis due to incomplete socio-economic information. As shown in **Table 1** there were more participating rural households. The rural households generally have more members. In the rural areas the expenditure per household was generally lower and the educational level of both father and mother was higher in the urban areas. The educational level between father and mother was not different in both rural and urban areas.

Table 2 Retinol and carotenoid intakes according to areas and household characteristics.

Sub-populations	Carotenoids and retinol intake (capita per day)			
	Carotenoids (µg)		Retinol (µg)	
Areas	Median (25 - 75%)	Mean (± SD)	Median (25 - 75%)	Mean (± SD)
Rural	3569 (2134 – 5251)	4178 (3154)	22 (8 – 95)	100 (275)**
Urban	3771 (2322 – 5361)	4208 (3407)	81 (11 – 196)	200 (470)**
Size of household				
≤ 3 members	4507 (2725 - 6100)	4966 (3465)	21 (9 – 122)	132 (331)
4 members	3653 (2223 – 5320)	4192 (2963)**	40 (10 – 142)	136 (385)
5 members	3465 (2178 – 5063)	3978 (2842)**	30 (8 – 122)	127 (353)
Above 5 members	2940 (1822 – 4466)	3765 (3791)**	31 (7 – 115)	104 (217)
Household expenditures				
Quartile 1	3383 (2206 – 4916)	4093 (3324)	27 (8 – 65)	87 (309)
Quartile 2	3460 (2019 – 5169)	4049 (3049)	18 (7 – 82)	75 (143)
Quartile 3	3602 (2075 – 5418)	4302 (3098)	30 (10 – 107)	104 (240)
Quartile 4	3902 (2350 – 5540)	4295 (3377)	84 (10 – 205)	218 (498)**
Education levels of mother				
Primary school or less	3454 (2172 – 5155)	4125 (3314)	20 (7 – 105)	119 (370)
Secondary and high school	3510 (2021– 5168)	3955 (2767)	32 (9 – 117)	113 (331)
Above high school	3418 (2149– 5748)	4509 (5123)	84 (18 – 198)	161 (224)
Education levels of father				
Primary school or less	3395 (2030 – 4996)	3964 (3244)	43 (7 – 136)	146 (401)
Secondary and high school	3523(2060– 5211)	4051 (2892)	23 (7 – 100)	104 (332)
Above high school	3188 (2068 - 5732)	4383 (4920)	109 (15 - 222)	172 (222)

* p< 0.05; ** p<0.01

Table 2 shows median, 25 percentile, 75 percentile and mean and SD values of intakes of carotenoids and retinol across subgroups in the study population. Obviously the distribution is skewed in most subgroups. Urban households have significantly higher intakes of retinol but not of carotenoids. Carotenoids intakes are significantly different across household sizes (p<0.01) whereas the difference in retinol intake is not statistically different across household size. There are no differences in carotenoids and retinol intakes across household expenditure levels, except for retinol in the highest expenditure level (p<0.01). The observed highest intake of retinol found in the highest educational level group is not statistically significant.

Table 3 shows that the urban households consume more protein and fat but less carbohydrate than those in rural areas (p<0.01). Households with higher expenditure have higher protein and fat intakes (p<0.01). Total energy (p<0.01), protein and fat intake (p<0.01) was inversely related with household size. The education level of both parents makes no difference in total energy intake but has an impact on protein and fat intakes:

the higher the education level, the higher the intakes of protein and fat (p<0.01). Household expenditure was strongly related to all macro nutrient intakes: households with higher expenditure had higher intakes of energy, protein and lipid.

Table 3 Mean (SD), percentage of energy and macronutrients intakes according to areas and household characteristics.

Sub-populations	Energy and macronutrients intake (capita/day)							
	Energy		Protein		Fat		Carbohydrate	
	(Kcal)	%	(g)	% Kcal	(g)	% Kcal	(g)	% Kcal
Area								
Rural	1895.4 (396.6)**	100	61 (16)**	13.0	25 (156)**	12.0	351 (77)**	75.0
Urban	1762.1 (341.5)**	100	67 (16)**	15.4	35 (18)**	18.1	289 (67)**	66.5
Size of household								
≤ 3 members	1896.3 (392.1)*	100	68 (17)**	14.5	32 (18)**	15.4	329 (76)	70.1
4 members	1888.0 (397.8)*	100	64 (16)**	13.7	30 (17)**	14.5	335 (80)	71.8
5 members	1858.7 (387.4)*	100	61 (16)**	13.2	25 (15)**	12.2	345 (84)	74.6
Above 5 members	1798.4 (361.8)*	100	57 (15)**	12.8	23 (15)**	11.6	337 (75)	75.6
Household expenditures								
Quartile 1	1810.8 (370.1)*	100	57 (16)**	12.6	22 (14)**	11.0	345 (74)**	76.4
Quartile 2	1880.4 (424.5)*	100	60 (16)**	12.8	25 (15)**	12.0	351 (81)**	75.1
Quartile 3	1919.6 (384.9)*	100	65 (15)**	13.7	30 (17)**	14.2	343 (82)**	72.1
Quartile 4	1848.1 (366.0)*	100	69 (17)**	15.2	35 (18)**	17.3	307 (73)**	67.5
Education levels of mother								
Primary school or less	1875.0 (381.2)	100	61 (16)**	13.1	24 (15)**	11.6	350 (75)**	75.3
Secondary and high	1835.5 (387.9)	100	61 (16)**	13.4	27 (16)**	13.4	333 (80)**	73.2
Above high school	1810.7 (362.6)	100	72 (19)**	16.2	38 (18)**	19.3	286 (61)**	64.5
Education levels of father								
Primary school or less	1829.7 (392.8)	100	60 (16)**	13.3	24 (15)**	11.4	338 (79)**	74.8
Secondary and high	1863.0 (386.6)	100	62 (16)**	13.4	27 (16)**	13.1	340 (79)**	73.5
Above high school	1775.7 (298.2)	100	68 (16)**	15.6	37 (19)**	19.1	285 (54)**	65.3

p< 0.05; ** p<0.01 compared to first sub group

There were five variables selected for the multi-variate analysis: area, household expenditure, household size, education of mother and education of father. These factors are known to be related to the intake of pro- and pre-vitamin A [12]. Within the used statistical model, the role of each factor considered on vitamin A intake is adjusted by the rest of variables as presented in Table 4, and vise-versa.

Household size strongly affects the intake of carotenoid intake but not of retinol. Households with 4 members consume about 700 µg of carotenoids less than households with less than 3 members. The carotenoid intake is lower as household size increases ($p<0.05$).

Table 4 The impact of socio economic factors on carotenoids and retinol intakes (mean, 95% CI, µg/capita/day), adjusted for confounders.

	Differences in intake (95%CI)	
Factors	Carotenoids intake	Retinol intake
Areas		
Rural	reference	reference
Urban	-178 (-749 ; 392)	34 (-35 ; 105)
Household expenditure		
Quartile 1	reference	reference
Quartile 2	-12 (-582 ; 557)	-18 (-96 ; 60)
Quartile 3	175 (-402 ; 752)	5 (-71 ; 81)
Quartile 4	56 (-605 ; 717)	102 (16 ; 189)*
Size of household		
≤ 3 members	reference	reference
4 members	-710 (-1305 ; 114)*	10 (-64 ; 84)
5 members	-926 (-1568 ; -283)**	11 (-69 ; - 91)
More than 5 members	-1151 (-1853 ; -448)**	5 (-83 ; 93)
Education levels of mother		
Primary school or less	reference	reference
Secondary and high	-283 (-703; 137)	15 (-35 ; 65)
Above high school	333 (-71; 738)	-8 (-56 ; 41)
Education levels of father		
Primary school or less	reference	reference
Secondary and high	61 (-360; 484)	-23 (-74 ; 28.)
Above high school	-73 (-478 ; 332)	17 (-32 ; 65)

* $p<0.05$; ** $p<0.01$ compared to reference group

There are differences in retinol intake in the various socio-economic groups. However, the differences are small as can be seen in **Table 4**. In the adjusted model, the differences between rural and urban areas in carotenoid and retinol intake are not significant. However, among household expenditure variables, the highest retinol consumption is still observed at the highest expenditure quartile ($p<0.05$). Subjects in the highest expenditure quartile consume about 100 µg retinol /day more than those at the 1th quartile.

DISCUSSION

The present study shows that pro-vitamin A carotenoids are the main source of vitamin A intake of people living in the Red River delta region in northern Vietnam. There is no difference in consumption of carotenoids between rural and urban households after correcting for confounding variables. Among urban households retinol intake derived from animal food sources is about two times higher than in the rural areas.

Because of insufficient data on specific carotenoids in the Vietnamese Food Composition Table [9], specific types of carotenoids in the diet of subjects in this study could not be separately calculated. In the Red River Delta region, dark green leafy vegetables (mean intake 162 g/capita/day) are the main source for plant carotenoids, while fruit intake (52 g/capita/day) is rather low (data not shown). It is recognized that intake of carotenoids from vegetables and fruits are highly seasonal variable [13], and may even changed monthly as observed in Bangladesh [14], making populations that rely on the intake of carotenoids for their vitamin A supply highly vulnerable. Low consumption of vitamin A food sources, especially in rural areas in our study, and recent evidence which indicates low bioavailability of carotenoids [15, 16, 17] from vegetables and fruits compared to the previous assumptions [17] are critical points in looking for possible future approaches to improve the vitamin A status among Vietnamese.

The large standard deviation and the negative skewed distributions in both carotenoid and retinol intake indicates a large variation of vitamin A food resources and illustrates that many individuals in this population consume relative low amounts of both pro- and pre-vitamin A. This may explain the situation of the relative poor vitamin A status in lactating women in this area as observed previously by Khan & Ninh [3]. Unequal distribution of food within the community and household was also documented as a main cause of vitamin A deficiency in other populations [19]. Therefore the rural population in the Red River Delta area of northern Vietnam is still at risk of vitamin A deficiency and this situation is predictable using food consumption information.

Fat plays an important role in absorption and metabolism of carotenoids and retinol in the body. Carotenoids are absorbed by the duodenal mucosal cells through a passive diffusion mechanism which is highly fat-dependent [20, 21]. In addition it is known that in animals with a high fat intake level, liver vitamin A liver concentration is high [22]. The data in this study show that in general, fat intake per capita is low (35 g/d in urban and 25 g/d in rural areas). Fat intake is lower among sub-populations with socioeconomic lower status (Table 3), which can be seen as a risk factor for vitamin A deficiency.

Generally, protein intake shows an improvement compare to an earlier study in this region [23, 24]. Smaller urban households with a higher education level show a significant higher expenditure level and consume significantly higher amounts of protein. However, the correlation between retinol and protein intake among this study population is relatively low (r = 0.23, p<0.001, data not shown). This finding can be explained because the main protein intake among the study population comes from plant food sources and the low retinol intake is due to the low intake of animal food products. Thus, the current policy towards distribution of high dose vitamin A capsules for children from 6-36 months and for lactating mothers is still an important and needed intervention to prevent the disadvantaged in the population from vitamin A deficiency [25].

In this study we used household expenditure as an indicator of socio-economic status: the higher the expenditure, the higher the socio-economic status. This is based on a Vietnam General Statistic Office (GSO) survey according to World Bank recommended indicators [10]. Previous studies showed that families with higher expenditure spend more money on foods, especially animal foods [10, 23]. In the multi-variate analysis model, the carotenoid intake is not different across the various levels of household expenditure. Likewise, quartiles of household expenditure are no different in retinol intake, except for a significant higher retinol intake in the highest quartile (Table 4). This finding is comparable with the findings of a study in Indonesia. In that study, 25% of the subjects whose serum retinol concentration was at the lowest end of the distribution also had the lowest socioeconomic status [26]. This finding may indicate that at the highest expenditure quartile, the difference in retinol intake as a result of high consumption of retinol-rich foods is really a critical point for any food-based strategy to combat vitamin A deficiency. Promotion of animal foods may be a key issue but may at the same time be impossible for populations with medium or low socio-economic status as observed in our study and many others [14, 15, 27].

Education levels of mother and father were not associated with carotenoid and retinol intake. This finding is inconsistent with the results of a study in Bangladesh which reported that vitamin A consumption is higher among those with higher educational levels [28].

In this study the number of family members correlated negatively with carotenoid intake, also after adjustments for confounding variables (Table 4). However, it has to be kept in mind that this survey is based on household data and data were converted as per capita per day, assuming an equal distribution of foods across the household. This assumption is a drawback of this study and limits the interpretation of the data. It is assumed that vegetables and fruits are equally shared between the members in households regardless of age or otherwise dependent needs.

In summary, our study indicates that carotenoids from plant foods are the main source of vitamin A intake among the Red River Delta population in Vietnam. Among socio-economic factors, household expenditure and number of household members are the main determinants for carotenoid and retinol intakes. Promotion of consumption of animal-derived foods and developing vitamin A fortified foods should be the key strategies for Vietnam to deal with vitamin A deficiency in the coming years.

ACKNOWLEDGEMENTS

We thank the staff of the Centers for Preventive Medicine in the provinces Hanoi, Hai Phong, Hatay, Haiduong, Namdinh, Hanam, Thai Binh and Ninhbinh for their support in data collection. We thank Dr Nguyen Thanh Chung from the General Statistic Office of Vietnam who advised on the sampling method and provided relevant documentation. The advice of Dr Paul Deurenberg, Nutrition Consultant in Singapore on the preparation of the paper is highly appreciated.

REFERENCES

1. West Jr KP. Extent of vitamin A deficiency among preschool children and women of reproductive age. J Nutr 2002; 132: 2857S-2866S.
2. Sommer A and West Jr KP. Vitamin A deficiency: Health, Survival and Vision. New York: Oxford University Press. 1996.
3. Khan NC, Ninh NX et al. Sub clinical vitamin A deficiency in children and lactating women in some ecological regions of Vietnam. (Vietnamese). National Institute of Nutrition published, Hanoi. 2003.
4. Ramakrishman U & Darnton-Hill. Assessment and control of vitamin A deficiency disorders. J Nutr 2002; 132: 2947S-2953S.
5. FAO/WHO. Requirements of vitamin A, iron, folate and vitamin B . Report of a joint FAO/WHO expert consultation. FAO Food Nutr 1988; Ser. No. 23.
6. Giay T, Dat DH. The ecosystem VAC as a mean to solve the food problem in Vietnam. In Giay T, Dricot JM, Vuylsteke J, Khoi HH (eds). Applied Nutrition. Proceedings of the international conference on applied nutrition, Hanoi, NIN/UNICEF. 1986.
7. GSO-Vietnam General Statistic Office. Vietnam Living standard Survey, 1998: The Statistical Publishing House, Hanoi. 2000.
8. Dop MC, Mai LB, Laillo A et al. Validation of the 24-hour recall against weighing method at household level. Advantage of comparing methods on the same and separate days: a case study from Vietnam. Poster presentation. Fourth International Conference on Dietary assessment methods, Tucson, USA. 2000.
9. National Institute of Nutrition (NIN) Vietnam. Nutritive composition table of Vietnamese foods. Medical Publishing House, Hanoi. 2000.
10. GSO-Vietnam General Statistic Office. Population and housing census Vietnam 1999: Completed census result. The Statistical Publishing House, Hanoi. 2001.

11. Moore DS and McCabe GP. Introduction to the practice of statistic. 4th Eds. W.H Freeman and company publishing house. New York. 2003.
12. Dung PK, Khan NC, Khoi HH et al. Food consumption with regard to vitamin A intake of children under 5 years of age in rural Vietnam. Proceedings of Seminar on vitamin A deficiency and xerophthalmia, Hanoi, 1986.
13. Sinha DP, Bang FB. Seasonal variation in signs of vitamin A deficiency in rural West Bengak children. Lancet 1973; 2: 228-231.
14. Zeitlin MF, Megawangi R, Kramer EM, Armstrong HC. Mothers' and children's intakes of vitamin A in rural Bangladesh. Am J Clin Nutr 1992; 56:136-47.
15. De Pee S, West CE, Muhilal, Karyadi D, Hautvast JGAJ. Lack of improvement in vitamin A status with increased consumption of dark-green leafy vegetables. Lancet 1995; 346: 75-81.
16. De Pee S, West CE. Dietary carotenoids and their role in combating vitamin A deficiency: a review of literature. Eur J Clin Nutr 1996; 50**:** Suppl: S38-S53.
17. Castenmiller JJM, West CE. Bioavailability and bioconversion of carotenoids. Ann Rev Nutr 1998; 18:19-38.
18. West CE, Eilander A, Van LM. Consequences of revised estimated of carotenoids bioefficacy for dietary control of vitamin A deficiency in developing countries. J Nutr 2003; 133: 2915-2916.
19. United Nations Administrative Committee on Coordination/Subcommittee in Nutrition Second report on the world nutrition situation. Volume **1**. Global and regional results. 1992.
20. Micozzi MS, Brown ED, Ewards BK et al. Plasma carotenoid response to chronic intake of selected foods and β-carotene supplements in men. Am J Clin Nutr 1992; 55: 1020-1025.
21. Parker RS. Absorption, metabolism, and transport of carotenoids. FASEB. Serial reviews. Carotenoids 1996; 4: 542-551.
22. Ribaya-Mecardo JD. Influence of dietary fat on beta-carotene absorbtion and bioconversion into vitamin A. Nutr Rev 2002; 60: 104-10.
23. Ministry of Health (MOH), Vietnam and World Bank. Report on re-analyzing data collected by Vietnam General Nutrition Survey 1987-1989. 1991.
24. Khoi HH. Protein energy nutritional status of rural people in some regions of Vietnam. Prace IZZ 1990; No 53 Warzsava.
25. Khan NC, Khoi HH, Giay T, Nhan NT et al. Control of vitamin A deficiency in Vietnam: The achievements and future orientation. Food and Nutrition Bulletin 2002; 23: 133-142.
26. De Pee S, Bloem MW, Tjiong R, Martini E, Satoto, Gorstein J, Shrimpton R, Muhilal. Who has a high vitamin A intake from plant foods, but a low serum retinol concentration? Data from women in Indonesia. Eur J Clin Nutr 1999; 53: 288-297.
27. West CE, Poortvliet EJ. The carotenoid content of foods with special reference to developing countries. Washington DC: USAID-VITAL. 1993.
28. Ahmed F, Azim A, Akhtaruzzaman M. Vitamin A deficiency in poor, urban, lactating women in Bangladesh: factors influencing vitamin A status. Public Health Nutr 2003; 6: 447-452.

CHAPTER 4

How much plant foods can contribute to the vitamin A supply of lactating women in Vietnam: a randomized controlled trial

Nguyen Cong Khan, Clive E. West (deceased), Saskia de Pee, Diane Bosch, Do Phuong Ha, Paul JM Hulshof, Ha Huy Khoi, Hans Verhoef and Joseph G.A.J. Hautvast

Submitted for publication

ABSTRACT

Background: More information is needed on the efficacy of carotenoids from plant foods for improving vitamin A status.

Objective: To quantify the efficacy of provitamin A-rich vegetables and fruits for improving vitamin A status.

Design: Breastfeeding women in nine rural communes of Thai Nguyen province, Vietnam were randomly allocated to four groups: *1)* 5.6 mg β-carotene/d from green leafy vegetables (vegetable group, n = 73); *2)* 4.8 mg β-carotene/d from orange, yellow fruit (fruit group, n = 69); *3)* 610 μg retinol/d from animal foods and 0.6 mg β-carotene/d (retinol-rich group, n = 70); *4)* 0.4 mg β-carotene/d (control group, n = 68). Meals of groups 1, 2 and 4 contained <30 μg retinol/d. Lunch and dinner were provided per day, 6 d/wk for 10 wk.

Results: Mean (95%CI) changes in serum retinol concentration of the retinol-rich, fruit, vegetable and control groups were 0.25 (0.17; 0.33), 0.13 (0.06-0.18), 0.09 (0.04; 0.27) and 0.00 (-0.06; 0.06) μmol/L respectively. Mean (95%CI) changes in breast milk retinol concentration were 0.49 (0.32; 0.64), 0.14 (0.07; 0.27), 0.15 (0.04; 0.27), -0.07 (-0.21; 0.07) respectively. Based on these findings, the equivalent of 1 μg retinol would be 12 μg β-carotene (95% CI: 8; 22) for fruit and 28 μg β-carotene (17; 84) for green leafy vegetables. Thus apparent mean vitamin A activity of carotenoids in fruit was 50% (95%CI: 25%; 75%) and in leafy vegetables 21% (7%; 35%) of that assumed.

Conclusions: The bioavailability of carotenoids from vegetables and fruit is lower than has been previously assumed.

INTRODUCTION

Deficiency of vitamin A continues to be an important public health problem in many developing countries [1, 2]. Vitamin A deficiency may be prevented by strategies comprising pharmaceutical approaches, dietary approaches (including foods naturally rich in vitamin A or food of which the content has been increased through fortification, breeding or genetic modification), and public health approaches to reduce the need for vitamin A. In developing countries, vegetables and fruit are estimated to provide approximately 70-80% of total vitamin A intake [3, 4]. Consumption of vegetables and fruits is promoted because they contain provitamin A carotenoids and other nutrients. Apart from being precursors of retinol, carotenoids have distinct functions of their own in humans and animals. Because of the negative association of fruit and vegetable consumption with heart disease and cancer, carotenoids have been postulated to play a preventive role [5], although intervention studies with carotenoids have not borne this out [6, 7].

One of the problems of relating dietary intake of carotenoids to health status is that current information on carotenoid bioavailability and bioefficacy as a source of vitamin A, is limited. Until recently it was assumed that consuming 6 μg dietary β-carotene was equivalent to consuming 1 μg of retinol [3], thus a conversion ratio of 6:1. However, a study carried out in breastfeeding women in Indonesia showed no improvement in serum and breastmilk concentration of retinol after feeding dark-green leafy vegetables and carrots, which are rich in β-carotene [8]. A subsequent intervention study carried out in anemic school children found apparent conversion factors of 12:1 for β-carotene in fruits and 26:1 for β-carotene in leafy vegetables [9]. Recently, the US Institute of Medicine (IOM) revised its recommended conversion factors to 12:1 for dietary β-carotene and 24:1 for other carotenoids [10]. The International Vitamin A Consultative Group (IVACG) has adopted these conversion factors, but mentioned that it may be even lower (reflecting lower bioefficacy) in malnourished populations [11]. West and colleagues have argued, that the conversion factor for dietary β-carotene from a mixed diet (ratio of vegetables : fruits = 4:1) might be closer to 21:1 [12].

The study reported in this paper was conducted among breastfeeding women in Vietnam and was designed to measure the difference between bioefficacy of β-carotene provided by either fruits or vegetables. Bioefficacy is defined as the efficiency with which ingested dietary provitamin A carotenoids are absorbed and converted to retinol. We compared this bioefficacy estimated with that obtained from the consumption of retinol in retinol-rich foods. The findings of this study shed further light on what would be the most appropriate conversion factors as well as to factors that affect them.

SUBJECTS AND METHODS

Subjects

The study was carried out in nine rural communes in Pho Yen district, Thai Nguyen Province, Northern Vietnam (~60 km from Hanoi). Communes are the lowest administrative unit and each consists of a few sub-communes or villages. The habitants had a low or middle socio-economic status by national standards. Rice is the staple food and the main constituent of breakfast, lunch and dinner, the three meals that are commonly eaten each day. Green vegetables are consumed frequently, but consumption of ripe yellow or orange fruits is low because such fruits are rather expensive for local people. At the time of the study, there was a local abundance of spring vegetables while mangos were imported. Breastfeeding is universally practiced and the average duration of breastfeeding is 18-20 months. Many women return to physical labor one or two months after delivery.

Using a power calculation, based on the study of breastfeeding women in Indonesia [8], we estimated that 61 women per group would yield a probability of 90% of detecting a difference between experimental groups in a change of serum retinol concentrations of 0.20 µmol/L (α =0.05). We decided to enroll 75 mothers per group, assuming that data on 65 subjects would be left for analysis. Selection criteria for the study were being anemic (Hb <120 g/L), breastfeeding an infant aged 5-15 mo, and no chronic illness. Anemia was a selection criteria because anemic women are more likely to have a low vitamin A status as measured by serum retinol concentration [8, 13, 14]. Breastfeeding an infant aged >4 mo was a criteria because women in this area were eligible to receive a high-dose vitamin A capsule shortly after delivery, and no older than 14 mo because it would be less likely that these women would cease breastfeeding during the 10 week intervention period.

The commune health centers had been asked to provide a list of all breastfeeding women in the commune, including age of the infant. All women breastfeeding an infant aged 5-15 months were invited to have their hemoglobin concentration (Hb) measured by finger-prick (Hemocue, Angelholm, Sweden). All those with an Hb <120 g/L were invited to participate in the study. A total of 9 communes were included in order to obtain the 300 women required. The purpose and procedures of the study were explained to the women and their family members. Almost all women were willing to participate in the study and signed an informed consent form. The study was approved by the Ministry of Health and the Scientific and Medical Ethics Committee of The National Institute of Nutrition, Vietnam.

Assignment of treatment group

At each commune, selected participants were stratified by the age of their breastfed child and then randomly assigned to one of four experimental groups (V=vegetables, F=fruit, R=retinol-rich, and C=control) using alternating sequences (V,F,R,C,V etc for one age group, F,R,C,F,V for the next and so on). In that way, each commune also had nearly equal numbers of subjects in each treatment group. The treatment groups received two meals (lunch and dinner) per day on 6 days/wk for 10 wk that differed in the amount and sources of retinol and provitamin A carotenoids. The vegetable group received provitamin A from leafy vegetables, the fruit group received provitamin A from yellow/orange fruits, the retinol-rich group received retinol-rich foods and the control group received meals low in both provitamin A and retinol. In order to provide a complete meal to all groups, foods with a high vitamin A content were replaced by foods with low vitamin A content. For example, the fruit group received carotene-rich fruits (such as mango, papaya), low-carotene vegetables (such as cabbage) and low-retinol foods (such as pork). Meals contained sufficient fat (minimum required amount is 3 g per meal, see ref 15) to allow maximal absorption of carotenoids and retinol. The size of the side-dishes was fixed, while rice consumption was ad libitum (on average, 450 grams of rice/d per woman was provided). Because the local custom is that lunch and dinner are main meals while a small rice dish with fish sauce is consumed for breakfast, the diet of the participants could be controlled maximally by providing them lunch and dinner.

Interventions

Meal preparation and eating. To standardize meals and supervise consumption, meals were provided from central kitchens, one per subcommune. A total of 29 kitchens were established, each of which served approximately 10 women under the supervision of cooks and a field team. At each kitchen, the meals were prepared by 2-3 collaborators who were members of the Women’s Union. Every six days, these collaborators were provided with recipes and lists with the amount of each food to be purchased, cleaned and cooked per day. Foods not available at the local market, such as mangoes, were provided by the field team. After the foods had been cleaned, the cooks weighted and divided them into two: one half was to be prepared for lunch and one the other half for dinner. Each woman was allocated a seat in the dining room in order to ensure that they received the correct meal. Lunch was served at 12.00 pm and dinner between 5.00-7.00 pm. Participants and family members were informed thoroughly about the importance of consuming all of the side dishes. The cooks kept a record of attendance and recorded foods left over after each meal, excluding rice. Women were asked what they ate for breakfast each day and for their meals on Sunday.

Measurements. On the day before the first meal was given and on the day after the last meal (10 wk after start of the intervention), women were examined medically, a venous blood sample was drawn and a breast milk sample was collected. Blood (6 ml) was collected between 7.30-9.30 am from an antecubital vein, placed on ice, and protected from light. Breast milk was collected between 08:00 and 11:00 am from one breast, which had not been used to feed the child for the previous hour. Milk was collected using a breast milk pump, stored in dark-brown glass bottles and transported on ice to the laboratory, which was located at a distance of 5-6 km from the communities studied. Food consumption data (24 h recalls and double portions) and stool samples were collected, and anthropometric measurements were made. Weight of women was measured in light clothing and to the nearest 0.1 kg using a SECA BEAM scale (Seca Corporation, Hanover, MD) and height was measured to the nearest 0.1 cm using a wall mounted stadiometer. Food consumption data were also collected weekly during the intervention period. On the day after consumption of the last meal, all women also received 30 iron tablets (60 mg Fe/tablet), one of which was to be consumed each day for the next 30 days. Those who were infected by hookworm as assessed by stool examination of stool at baseline were supervised to take a curative course of treatment using albendazole (single dose of 400 mg).

Analysis

Breastmilk analysis. Breast milk was stored immediately upon collection from the field at -20^{o}C for approximately 3 weeks and then sent in dry ice to the laboratory of the Division of Human Nutrition and Epidemiology, Wageningen University where the samples were stored at -80^{o} C until analysis of retinol and carotenoids. The samples were prepared for HPLC analysis under subdued yellow light. To 1000 µL of milk, 125 µL ammonia (25% w/v) and 1000 µL ethanol (96% v/v) was added. The mixture was extracted twice with 4 mL of a mixture of petroleumether (b.p. 40-60 °C) and diethylether (1:1 v/v). The upper layers were removed, pooled, and evaporated under nitrogen at 35 °C until near dryness. The residue was saponified for three hours in the dark with 1.5 mL 5% (w/v) potassium hydroxide in ethanol (96% v/v) and next after addition of 1.5 mL water, extracted twice with 3.0 mL hexane. The hexane layers were pooled and evaporated to dryness under nitrogen and the residue was dissolved in 250 µL methanol/tetrahydrofuran (3:1 v/v) and 25 µL was injected for HPLC analysis. Separations were monitored at 320 nm (retinol) and 450 nm (carotenoids). Within- and between run coefficient of variations were 6.0%

and 1.5% for retinol and 3.8 and 5.4% for β-carotene respectively. Mean recoveries ± SD (n=10) were 101 ± 6% for retinol and 103 ± 4% for β-carotene.

Blood collection and analysis: For baseline and evaluation assessment, hemoglobin concentrations were measured by the cyanmethemoglobin method (International Nutritional Anemia Consultative Group, 1985; Merkotest, Merck, Darmstadt, Germany) and hematocrit by centrifuge method. The remaining blood was centrifuged, and serum was frozen for subsequent shipping in dry ice for analysis of concentrations of retinol and carotenoids [16] at the laboratory of the Division of Human Nutrition and Epidemiology, Wageningen University. To 500 μL of serum, 500 μL sodium chloride (0.9% w/v in water) and 1000 μL ethanol (containing retinyl acetate as an internal standard) was added and next extracted twice with 2.0 mL hexane. The hexane layers were pooled and evaporated to dryness under nitrogen at 35 °C. The residue was dissolved in 250 μL methanol/tetrahydrofuran (3:1 v/v) and 25 μL was injected for HPLC analysis. Separations were monitored at 320 nm (retinol) and 450 nm (carotenoids). All samples preparations were done under subdued yellow light. Within and between-run coefficients of variation were 1.6% and 1.9% for retinol, 3.4% and 8.2% for β-carotene, 4.6% and 7.0% for α-carotene, 3.6% and 11.4% for β-cryptoxanthin, 4.1% and 6.6% for lutein, and 9.6% and 9.3% for zeaxanthin respectively.

Examination of feces. Stool samples were examined by a parasitologist for the presence of worm eggs using the Ridley method, and the load of worm eggs was quantified using the Kato-Katz method [17].

Analysis of duplicate food portions. Duplicate samples of the meals, without rice, were collected at two occasions (the second and ninth week of the intervention). On each occasion, portions were collected for analysis over three consecutive days, corresponding to the three-day menu cycle. Duplicate samples of the meals were pooled per treatment group per three consecutive days, frozen and -20°C and later shipped (in dry ice) to the Division of Human Nutrition and Epidemiology, Wageningen University for analyses of fat, protein, dietary fiber, iron, retinol and carotenoids [18, 19]. Carbohydrate content was calculated by difference. For analysis of retinol and carotenoids, samples were homogenized and extracted with tetrahydrofuran, and the volume of the solvent was reduced to near dryness. The residue was saponified overnight at room temperature with 25 mL 5% (w/v) potassium hydroxide in methanol. Dichloromethane (100 mL) and water (75 mL) were added and after removal of the upper water layer, the lower dichloromethane layer was washed with water until the pH $<$ 9.5. The dichloromethanelayer was then evaporated to dryness and the residue dissolved in methanol: tetrahydrofuran (3:1, v/v) and analyzed by HPLC. The results were averaged per treatment group.

Nutrient intake. Nutrient intake other than from the meals provided was calculated from the 24-h recall data collected once a week using the Vietnamese food composition table [20] except for carotene content. For some fruits and vegetables, the data on carotene content was taken from the results of analysis done in Wageningen [18] and for others from the table with the most recent data on carotene content of food in developing countries [21]. Nutrient intake was then calculated using computer software FoxPro (Cambria, Palo Alto, CA) at the Institute of Nutrition, Hanoi, Vietnam.

Statistical methods

Analysis. Descriptive data are reported as mean and SD for normally distributed parameters and as median and 25 and 75 percentiles for non-normally distributed parameters. Nutrient intake during the intervention period other than derived from foods provided was calculated from the median intake of each woman as assessed by weekly 24-h recall data. The effect of consumption of a diet rich in vegetables, fruits or retinol was assessed by comparing serum and breastmilk indicators of vitamin A and carotenoid status measured at 10 w with values measured at 10 w in women consuming the control diet. Values of serum indicators were normalised by log-transformation before analysis in a multivariate linear regression model. For each indicator, we used multivariate regression to investigate potential confounding effects due to differences in baseline characteristics between groups (serum indicator concentration at baseline, age of the child, community of residence, infection of *Ascaris lumbricoides*, *Trichuris trichiura* or hookworm). Because adjustment did not substantially affect effect estimates, we present effects adjusted for baseline level of the indicator only. When log-transformation did not result in normally distributed variables, we compared groups pair-wise for differences in distributions of serum indicators, with significance testing by the Mann-Whitney U test.

Estimation of conversion factors. The conversion factor (x) for calculating the amount of retinol equivalents provided by provitamin A carotenoids from fruit was derived from the following formula [9]:

$$\left(\frac{\Delta\text{ Serum retinol concentration}}{\text{Retinol intake} + \dfrac{\beta\text{–carotene equivalent intake}}{x}}\right)_{\substack{\text{Retinol-}\\\text{rich group}}} = \left(\frac{\Delta\text{ Serum retinol concentration}}{\text{Retinol intake} + \dfrac{\beta\text{–carotene equivalent intake}}{x}}\right)_{\substack{\text{Fruit}\\\text{group}}}$$

where (Δ serum retinol concentration) was calculated by subtracting the values at the end of follow-up from those at baseline; retinol intake = μg retinol/g food; and β-carotene equivalent intake = (μg *all-trans*-β-carotene + 0.5 × μg α-carotene + 0.5 × μg β-cryptoxanthin + 0.5 × μg *cis*-isomers of β-carotene)/g food. The conversion factor for vegetables was obtained similarly. Upper and lower limits of the 95% CI for conversion factor (*x*) were estimated using the limits of the 95% CIs for the changes in serum concentration of the respective treatment groups.

The computer package SPSS for windows version 11.5.1 (SPSS Inc, Chicago, IL) was used for all statistical calculations. A p-value <0.05 was considered significant.

RESULTS

Subjects

Of the 1512 women screened, 298 met our inclusion criteria. Of the 298 breastfeeding women that started with the intervention, 280 (93.9%) completed it until the end of follow-up (10 wk). One woman refused further participation during the intervention, 2 women moved from the study area, 6 women became pregnant, 2 women were sick when follow-up data were collected, 1 woman's child died, and 6 women refused to give blood at follow-up (for further details see **Figure 1**). At baseline, demographic, anthropometric, biochemical, and parasitological characteristics of the women were similar between the groups (**Table 1)**.

Food consumption and nutrient intake

The record of attendance and leftovers indicated that the proportion of fruit consumed by the fruit group was 96% [CI: 92-100%], the proportion of vegetables consumed by the vegetable group, 94% [CI: 91-97%], and the proportion of retinol-rich foods consumed by the retinol-rich group, 98% [CI: 96-100%]. Food eaten apart from that provided by the intervention was mainly breakfast, which generally contained 1-2 bowls of rice (60-120 grams of rice) with fish sauce, or tofu. Vitamin A content, largely provitamin A carotenoids, of the foods eaten apart from those provided was very small and not different between groups, and was therefore not considered in subsequent analysis. Energy and nutrient intake during the intervention, which included the intake from food provided, is shown in **Table 2**. The meals provided 5.6 mg β-carotene equivalent plus 27 μg retinol for the vegetable group, 4.8 mg β-carotene equivalent plus 15 μg retinol for the fruit group, 0.6 mg β-carotene equivalent plus 610 μg retinol for the retinol-rich group, and 0.4 mg β-carotene equivalent plus 1 μg retinol for the control group. The dietary fiber content in food provided was 10 g in vegetable and fruit groups and 7 g in retinol-rich food group and control group (data not shown). The intake of fat, protein and carbohydrates was similar in the four groups while iron intake was slightly higher in the retinol-rich group. Fat intake contributed more than 16% of energy intake and the intake of approximately 50 g/d would allow for maximum absorption of carotenoids and retinol.

Figure 1 Selection and retention of subjects in the randomized food intervention study in breastfeeding women

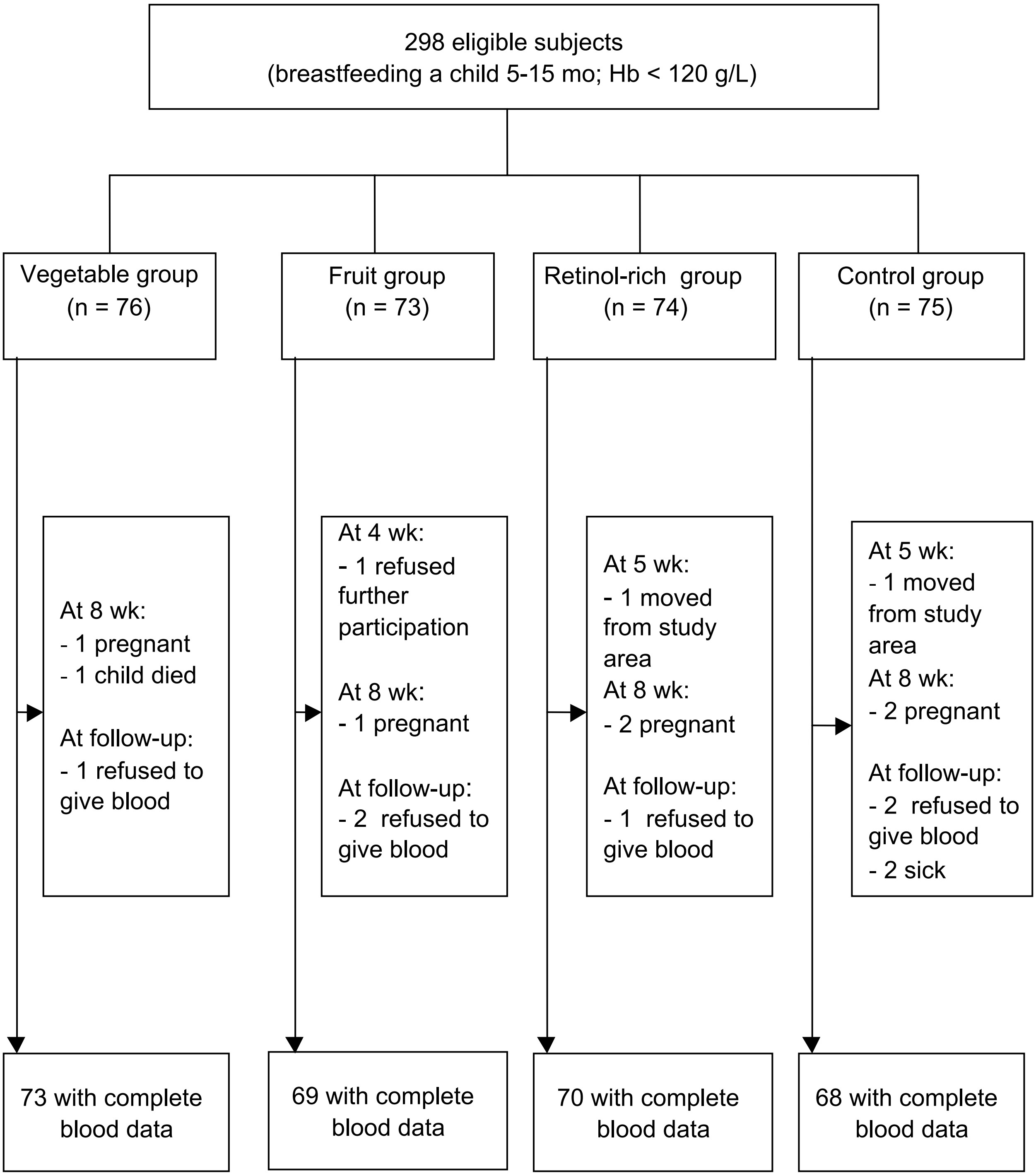


Table 1 Characteristics of breastfeeding women at baseline

	Vegetable (n= 73)	Fruit (n= 69)	Retinol-rich (n= 70)	Control (n= 68)
Demographic and anthropometric data†				
Age of mothers (y)	26.1 ± 4.5	26.0 ± 5.0	25.9 ± 5.3	26.2 ± 5.0
Age of child (mo)	8.6 ± 2.8	8.7 ± 2.6	8.9 ± 2.7	8.9 ± 2.8
Parity	1.8 ± 1.6	1.9 ± 1.4	1.8 ± 1.5	1.8 ± 1.6
Body weight (kg)	44.8 ± 5.4	44.3 ± 4.0	44.2 ± 4.8	44.5 ± 4.4
Height (m)	1.50 ± 0.05	1.50 ± 0.05	1.50 ± 0.06	1.50 ± 0.06
Body mass index (kg/m^2)	19.8 ± 1.9	19.3 ± 2.4	19.7 ± 1.8	19.7 ± 1.8
Middle upper arm circumference (cm)	23.1 ± 1.7	23.0 ± 1.3	22.7 ± 1.5	22.8 ± 1.5
Parasitic infestation Positive stool (%)				
Ascaris lumbricorides	23.1 ± 1.7	62.5	73.8	66.7
Trichuris trichura	34.2	31.3	34.2	37.5
Hookworm	90.0	95.3	93.8	95.3
Negative stool (%)	4.3	3.1	1.5	1.6
Egg loads(epg)‡				
Ascaris lumbricorides	4620 (2478; 13020)	7080 (2538; 16800)	8200 (3420; 23460)	7200 (2800; 1800)
Trichuris trichura	720 (252; 1770)	960 (420; 1680)	660 (240; 1530)	1017 (480; 2364)
Hookworm	3480 (1560; 6720)	4800 (1680; 7800)	3460 (1560; 6000)	4800 (1680; 7800)

† $\bar{x} \pm SD$

‡ Eggs per gram feces for those infected, median (25 and 75 percentiles)

Table 2 Nutrient intake during intervention, including foods provided[¶]

	Amount of provided per group per day			
	Vegetable	Fruit	Retinol-rich	Control
Energy (Kcal)	2817 (2602; 2950)	2781 (2565; 2956)	2745 (2507; 2956)	2755 (2510; 2958)
Fat (g)	49 (48; 52)	52 (51; 56)	50 (49; 54)	50 (48; 53)
Protein (g)	92 (86; 97)	94 (89; 100)	94 (86; 101)	95 (89; 97)
Carbohydrate (g)	485 (438; 513)	465 (421; 501)	467 (426; 508)	475 (438; 507)
Iron (mg)	18 (17; 19) [a]	17 (16; 18) [a]	21 (20; 22) [b]	17 (16; 18) [a]
Vitamin C (mg)	120 (115; 132) [b]	173 (161; 186) [c]	48 (36; 50) [a]	49 (35; 52) [a]
Vitamin A and carotenoids[2]				
Retinol (μg)	27	15	610	1
all-*trans*-β-carotene (μg)	5037	3443	436	239
cis-β-carotene (μg)	777	404	67	35
α-carotene (μg)	437	383	323	194
β-cryptoxanthin (μg)	18	2157	67	3
Lutein (μg)	7590	1661	1022	709
Zeaxanthin (μg)	320	348	103	35
β-carotene equivalent (μg)	5652	4792	644	355

[¶]Values are presented as median (25; 75 percentiles) were summed of nutrients from foods provided (analyzed) and intake of nutrients from foods besides foods provided which were calculated basing on food composition tables. Rice provided was estimated 450 gram per day for all subjects.
[2] From analysis of meal provided, because foods consumed besides food provided had very low retinol and carotenoid content. [3] β-carotene equivalent (μg) = all-*trans*-β-carotene (μg) + 1/2 (*cis*-β-carotene + α-carotene + β-cryptoxanthin)μg .
[a,b] Group not sharing a common superscript are significantly different from one other, $p < 0.05$ (Kruskal-Wallis test).

Food consumption and nutrient intake

The record of attendance and leftovers indicated that the proportion of fruit consumed by the fruit group was 96% [CI: 92-100%], the proportion of vegetables consumed by the vegetable group, 94% [CI: 91-97%], and the proportion of retinol-rich foods consumed by the retinol-rich group, 98% [CI: 96-100%]. Food eaten apart from that provided by the intervention was mainly breakfast, which generally contained 1-2 bowls of rice (60-120 grams of rice) with fish sauce, or tofu. Vitamin A content, largely provitamin A carotenoids, of the foods eaten apart from those provided was very small and not different between groups, and was therefore not considered in subsequent analysis. Energy and nutrient intake during the intervention, which included the intake from food provided, is shown in **Table 2**. The meals provided 5.6 mg β-carotene equivalent plus 27 μg retinol for the vegetable group, 4.8 mg β-carotene equivalent plus 15 μg retinol for the fruit group, 0.6 mg β-carotene equivalent plus 610 μg retinol for the retinol-rich group, and 0.4 mg β-carotene equivalent plus 1 μg retinol for the control group. The dietary fiber content in food provided was 10 g in vegetable and fruit groups and 7 g in retinol-rich food group and control group (data not shown). The intake of fat, protein and carbohydrates was similar in the four groups while iron intake was slightly higher in the retinol-rich group. Fat intake contributed more than 16% of energy intake and the intake of approximately 50 g/d would allow for maximum absorption of carotenoids and retinol.

Effects of interventions on serum indicators of vitamin A status

Serum concentrations of retinol and carotenoids at baseline and after the intervention per treatment group are shown in **Table 3**. There were no significant differences in serum concentrations of retinol and carotenoids at baseline among groups, except all-*trans*-β-carotene which appeared elevated in the vegetable group relative to the control group, albeit non-significant. At the end of follow-up, serum concentrations of retinol were 24% increased in the retinol-rich group compared to the control group, whereas both in the vegetable and fruit group they were increased by 12% (see factor in **Table 3**). Compared to the control group, serum concentrations of β-cryptoxanthin were substantially increased in the fruit group, but not in the vegetable and retinol-rich groups; increased serum concentrations were found for all-*trans*-ß-carotene, *cis*-ß-carotene and α-carotene in the vegetable and fruit groups whereas smaller increases were found in the retinol-rich group; increased serum lutein concentrations were found in the vegetable group and to a lesser degree in the fruit and retinol-rich groups; and marginal or no increases were seen in zeaxanthin concentrations in all four groups.

Table 3 Effects of interventions on serum indicators of vitamin A and carotenoid status

		Intervention groups			
		Vegetable (n= 73)	Fruit (n= 69)	Retinol-rich (n=70)	Control (n= 68)
Retinol concentration (μmol/L)	At baseline	1.15 (1.07-1.24)	1.11 (1.03-1.19)	1.12 (1.03-1.21)	1.12 (1.04-1.21)
	At 10 w	1.26 (1.19-1.33)	1.25 (1.19-1.32)	1.39 (1.31-1.47)	1.12 (1.04-1.21)
	Factor *	1.1 [1.0-1.2]	1.1 [1.0-1.2]	1.2 [1.1-1.4]	1.00
	Change between BL-10w	0.09 [0.04-0.27]	0.13 [0.07-0.19]	0.25 [0.17-0.33]	0.0 [-0.06-0.06]
All-*trans*-β-carotene concentration (μmol/L)	At baseline	0.51 (0.43-0.60)	0.44 (0.37-0.52)	0.46 (0.39-0.53)	0.43 (0.36-0.51)
	At 10 w	0.45 (0.41-0.51)	0.52 (0.46-0.60)	0.29 (0.25-0.32)	0.43 (0.36-0.51)
	Factor *	2.0 [1.9 to 2.1]	2.4 [2.4 to 2.6]	1.3 [1.3 to 1.4]	0.21 (0.18-0.24)
Cis-β-carotene concentration (μmol/L) †	At baseline	0.05 (0.03-0.07)	0.04 (0.03-0.07)	0.04 (0.02-0.06)	1.00
	At 10 w	0.04 (0.03-0.06) (p<0.001)	0.05 (0.03-0.07) (p<0.001)	0.02 (0.01-0.04) (p=0.01)	0.04 (0.02-0.07)
α-Carotene concentration (μmol/L)	At baseline	0.04 (0.03-0.05)	0.05 (0.04-0.06)	0.05 (0.04-0.06)	0.01 (0.01-0.03)
	At 10 w	0.09 (0.08-0.10)	0.08 (0.07-0.09)	0.06 (0.06-0.07)	0.05 (0.04-0.05)
	Factor *	1.7 [1.6 to 1.7]	1.4 [1.4-1.4]	1.1 [1.1-1.1]	0.06 (0.05-0.07)
Lutein concentration (μmol/L)	At baseline	0.95 (0.81-1.12)	0.84 (0.70-1.01)	0.95 (0.85-1.06)	1.00
	At 10 w	0.91 (0.84-0.99)	0.46 (0.41-0.51)	0.53 (0.46-0.60)	0.91 (0.82-1.01)
	Factor *	2.1 [2.0-2.2]	1.1 [1.0-1.2]	1.2 [1.1-1.3]	0.44 (0.39-0.49)
β-Cryptoxanthin concentration (μmol/L) †	At baseline	0.06 (0.04-0.08)	0.03 (0.02-0.05)	0.03 (0.02-0.05)	1.00
	At 10 w	0.03 (0.02-0.06) (p<0.001)	0.40 (0.22-0.70) (p<0.001)	0.04 (0.03-0.05) (p<0.001)	0.03 (0.02-0.05)
Zeaxanthin concentration (μmol/L) †	At baseline	0.04 (0.02-0.06)	0.03 (0.01-0.04)	0.03 (0.02-0.05)	0.02 (0.01-0.03)
	At 10 w	0.02 (0.01-0.03) (p=0.18)	0.03 (0.01-0.04) (p<0.001)	0.03 (0.02-0.04)	0.01 (0.01-0.02)

Geometric mean or † median (25-75 percentiles) [95% CI]. P-values computed by Mann-Whitney U test for differences in distributions at 10 w with the control group.
*Factors indicate the proportional difference in values measured at 10 w in each group relative to values measured at 10 w in the control group, and were derived by exponentiation of effect estimates in a linear regression model with log-transformed values of the serum indicator.

Table 4 Effects of interventions on breastmilk indicators of vitamin A and carotenoid status

		Intervention groups			
		Vegetable (n= 71)	Fruit (n= 65)	Retinol-rich (n=69)	Control (n= 63)
Retinol concentration (μmol/L) *	At baseline	0.74 (0.66-0.83)	0.74 (0.66-0.83)	0.72 (0.63-0.83)	0.69 (0.59-0.80)
	At 10 w	0.86 (0.76-0.97)	0.90 (0.81-0.99)	1.23 (1.12-1.35)	0.63 (0.55-0.73)
	Factor *	1.3 [1.2-1.5]	1.4 [1.3-1.6]	1.9 [1.8-2.2]	1.00
Total β-carotene concentration (μmol/L)	At baseline	0.04 (0.02-0.06)	0.03 (0.02-0.07)	0.03 (0.02-0.06)	0.03 (0.02-0.05)
	At 10 w	0.03 (0.02-0.05)	0.04 (0.00-0.06)	0.02 (0.01-0.04)	0.01 (0.01-0.02)
Lutein concentration (μmol/L	At baseline	0.13 (0.09-0.20)	0.13 (0.10-0.19)	0.14 (0.10-0.20)	0.12 (0.08-0.17)
	At 10 w	0.13 (0.09-0.16)	0.05 (0.04-0.07)	0.06 (0.05-0.11)	0.05 (0.04-0.08)
β-Cryptoxanthin concentration (μmol/L)	At baseline	0.00 (0.00-0.01)	0.00 (0.00-0.01)	0.01 (0.00-0.01)	0.00 (0.00-0.01)
	At 10 w	0.01 (0.00-0.01)	0.07 (0.03-0.14)	0.01 (0.00-0.01)	0.00 (0.00-0.00)
Zeaxanthin concentration (μmol/L)[1]	At baseline	0.01 (0.01-0.02)	0.01 (0.01-0.02)	0.01 (0.01-0.01)	0.01 (0.01-0.02)
	At 10 w	0.01 (0.00-0.01)	0.01 (0.01-0.01)	0.01 (0.00-0.01)	0.00 (0.00-0.01)

Median (25-75 percentiles) or * geometric mean (95% CI)
† See footnote table 3.

Estimation of apparent conversion factors

To estimate the apparent conversion factor, the change in serum retinol concentration (see **Table 3**) and the intake of β-carotene equivalents and of retinol (see **Table 2**) were used. The estimation is based on the assumption that the ratio of the intake of retinol equivalents derived from different sources and the change in serum concentration of retinol is constant. Because the concentration of retinol had not changed over the intervention period in the control group, and because the amount of provitamin A carotenoids and retinol from foods eaten other than foods provided was almost negligible, we could use the formula given above to estimate the conversion factor for β-carotene. Thus we estimated that 28 μg of β-carotene (95% CI: 17; 84) from dark-green leafy vegetables or 12 μg of β-carotene (95% CI: 8; 22) from fruit provide the equivalent of 1 μg of retinol.

Effects of the intervention on breastmilk indicators of vitamin A status

Breastmilk concentrations of retinol and carotenoids at baseline and at 10 w after the start of the interventions are shown per intervention group in **Table 4**. Compared to the control group, the breastmilk retinol concentration increased nearly two-fold in the retinol-rich group, almost 1.5 fold in the fruit group and 1.3 fold in the vegetable group. Concentrations of β-carotene and zeaxanthin remained virtually unchanged in all groups, while lutein concentration increased in the vegetable group and β-cryptoxanthin concentration increased in the fruit group.

Parasitic infestation and hematological indicators

Hemoglobin concentrations at baseline were similar between groups (**Table 1**). When measured by multivariate models, hemoglobin concentrations at 10 w were not or only marginally increased in the vegetable, fruit or retinol-rich groups compared to the control group (not shown). Also, there was no evidence of strong independent associations of hemoglobin or serum retinol concentrations at baseline or at 10 w with infections by either *A. lumbricoides*, *T. trichiura* or hookworm at baseline.

The variations in body weight (pooled mean: -0.4 ± 1.7 kg) were not different between the groups.

DISCUSSION

According to our study, an appropriate estimation would be that 12 μg β-carotene (95% CI: 8μg; 22μg) from fruit and 28 μg β-carotene (95% CI: 17 μg; 84 μg) from dark-green leafy vegetables is equivalent to 1 μg of retinol, rather than the previously assumed ratio of 6:1 for all dietary β-carotene [3]. The results of our study agree highly with those of the Indonesia children's study by de Pee et al who found apparent conversion factors of 12:1 for fruits and 26:1 for vegetables [9], and lend further credence to the conversion factor proposed by West et al for dietary β-carotene from a mixed diet (ratio of vegetables:fruit = 4:1) of 21:1 [12].

The relative changes of retinol concentration in breast milk were much larger than the changes of its concentration in serum, in all three groups as compared to the control group. This result resembles that among breastfeeding women that received a wafer with added β-carotene in the study in Indonesia [8]. The changes of the breast milk retinol concentration in the vegetable group and the fruit group were similar while a larger change was observed in the retinol-rich group. The larger breast milk retinol response suggests an important benefit for the breastfed child, especially when the mother increases her consumption of retinol-rich food. While breast milk concentration of lutein increased in the vegetable group, and that of β-cryptoxanthin in the fruit group, the concentration of β-carotene remained virtually unchanged in both groups despite the increase of its serum concentrations.

The way that we chose to estimate the apparent conversion factors is based on changes in serum retinol concentration in humans after consumption of β-carotene-rich food, which appears appropriate, at least for this study and the one in Indonesia [9]. The main reason is that the largest change in serum retinol concentration occurred in the retinol-rich group, which was the positive control group, indicating that serum retinol concentration at baseline was suboptimal. Therefore, and because it improved less in the fruit and less than that in the vegetable group, it proved to be a good quantitative indicator of improvement of vitamin A status. Another reason is that the conversion factor that was determined for β-carotene from fruit was the same as that found in the study in Indonesia [10] and almost the same as in a recent study among Bangladeshi men (13:1) that used the paired deuterated-retinol-dilution (DRD) technique [22], which estimates body stores of retinol rather than serum retinol concentrations. The conversion factor for vegetables found by this study in Vietnam was also nearly the same as the one found in Indonesia [9], 28:1 vs 26:1. However, it was quite different from the one found among the Bangladeshi men (10:1). That may however be related to the food preparation technique used with more destruction of the matrix in the study in Bangladesh as well as the fact that the men were dewormed prior to the study, which was not the case in either Indonesia or Vietnam [23, 24, 25]. In addition, the rate of dropout was only 6% and >90% of the food provided was consumed, indicating that participation in the study was very good. Suggestions that serum retinol may not adequately reflect functional improvement of vitamin A status, because carotenes can be cleaved not only in the intestinal mucosa but also in other tissues [26], do not appear valid because consumption of β-carotene, whether from foods or synthetic origin, increases serum concentrations of both β-carotene as well as retinol [8, 9, 22, 23]. Thus, while some conversion occurs in the tissue, this is unlikely to be to a different extent depending on the source of β-carotene, and most conversion appears to be in the intestinal mucosa and hence results in changes of serum retinol concentration among individuals with suboptimal vitamin A status.

The relatively wide confidence intervals of the apparent conversion factors, as well as the difference of the conversion factor estimated for β-carotene from leafy vegetables among the Bangladeshi men as compared to the Indonesian children and the Vietnamese breastfeeding women, brings us to factors that affect the bioavailability and bioefficacy of carotenoids. These factors are summarized in the acronym "SLAMENGHI": **S**pecies of carotenoids; molecular **L**inkage; **A**mount of carotenoids consumed in a meal; **M**atrix in which the carotenoid is incorporated; **E**ffectors of absorption and bioconversion; **N**utrient status of the host; **G**enetic factors; **H**ost-related factors and mathematical **I**nteractions between these factors [27]. A quantification of these factors would enable a prediction of bioavailability and bioconversion of carotenoids of certain foods, under specific circumstances, among certain population groups. According to current knowledge, Matrix [24, 28, 29], Effectors of absorption, in particular oil and dietary fibre [15, 30, 31], and may be Host-related factors, in particular parasitic infestation [23, 25], are the most important and modifiable factors affecting bioefficacy of provitamin A carotenoids.

With regard to matrix, more destructive methods are required for freeing β-carotene from chloroplasts within plant cells of dark-green leafy vegetables than from chromoplasts of yellow and orange fruit where β-carotene is dissolved in oil droplets. A study that used destructive methods for freeing β-carotene from chloroplasts within plant cells found that the bioavailability of β-carotene from spinach was improved by the further processing [24], which may also explain much of the difference of the conversion factor determined in Bangladesh as compared to Indonesia and Vietnam [25]. The subsequent incorporation of β-carotene into fat micelles for absorption may also be more difficult for β-carotene from vegetables than from fruits because of the nature of fibres such as pectin and cellulose [31] which may entrap β-carotene before it can be incorporated into micelles.

It has been shown previously that retinol absorption is relatively insensitive to parasitic infection [32]. In this study, the effect of parasitic infestation was not assessed, as deworming was only done after the intervention, but the intensity of *Ascaris* infestation was compared to the changes of biochemical indicators. No relationship was found between *Ascaris* egg count and changes of serum concentrations of retinol or β-carotene. The median number of eggs per gram feces for those infected with *Ascaris* (63-74%) was 5000 to 8000 in different groups. Jalal and co-workers reported a large effect of deworming on the change of serum retinol concentration after consumption of red sweet potato when intensity of *Ascaris* infestation was high but not when it was low [23]. The intensity of infestation in our study population may have been too low to interfere with freeing β-carotene in the intestinal lumen, its subsequent absorption and/or bioconversion. The intensity of parasitic infestation was much higher in the Indonesian study with breastfeeding women [8] that found no impact of dark-green leafy vegetables on vitamin A status than in the one with the children [9], which was used to estimate conversion factors for both the leafy vegetables and the fruits.

One other observation that merits highlighting is the relatively higher bioavailability of lutein than β-carotene from vegetables, which has also been reported as a result from other studies that used food with a higher content of lutein than β-carotene [9, 24, 29]. This difference, as well as the difference observed among the carotenoids from fruit, may be explained by differences in polarity. Carotene bioavailability appears to increase as polarity increases [30].

In conclusion, the apparent conversion factors for β-carotene to retinol found by this study, of 12:1 (95%CI: 8;22) for fruit and 28:1 (95%CI: 17; 84) for green leafy vegetables confirms the findings from the Indonesia children's study and supports the conversion factor proposed by West et al of 21:1 for dietary β-carotene from a mixed diet. Therefore, food based-approaches for combating vitamin A deficiency need to promote consumption of vitamin A from fruit, animal food and fortified food, besides maximizing consumption and bioavailability of carotenoids from dark-green leafy vegetables. Further research should focus on quantifying the impact of parasitic infection and various food matrices on bioefficacy of β-carotene, on inter-individual variation in response to intake of dietary provitamin A carotenoids, on finding good biomarkers of fruit and vegetable intake, and on estimating the absorption of carotenoids with antioxidant activity that may play a role in lowering the risk of cancer and cardiovascular disease.

ACKNOWLEDGEMENT

We thank the health workers, women union members, community leaders of 10 communes and the staff of district health service of Pho Yen district, Thai Nguyen province, Dr Le Bach Mai, Dr Nguyen Kim Canh, Dr Le Danh Tuyen, Dr Nguyen Lan, and other researchers of Institute of Nutrition, Mr Peter van de Bovenkamp and co-workers for laboratory analysis at the Division of Human Nutrition and Epidemiology, Wageningen University. We thank the Nestle Foundation and Wageningen University for funding this study.

REFERENCES

1. WHO. Global prevalence of vitamin A deficiency. MDIS Working paper 2 (WHO/NUT/95.3). Geneva, World Health Organization, 1995.
2. Beaton GH, Martorell R, Aronson KJ, et el. 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 13. Toronto, Canada: University of Toronto, 1993.
3. FAO/WHO. Requirements of vitamin A iron folate and vitamin B12. Report of a joint FAO/WHO. Expert consultation. FAO Food Nutrition Series No 23. Rome: UN Food and Agricultural Organization, 1988: 29-30.
4. National Institute of Nutrition, Hanoi, Vietnam: Report on national food consumption surveys 2000. Hanoi, Vietnam, NIN 2001.
5. Van Poppel G. Epidemiological evidence for β-carotene in prevention of cancer and cardiovascular diseases. Eur J Clin Nutr 1996;50 Suppl 3: S57-S61.
6. Beta Carotene Cancer Prevention Study Group The Alpha-Tocopherol. The Effect of Vitamin E and Beta Carotene on the Incidence of Lung Cancer and Other Cancers in Male Smokers. New Engl J Med 1994;330: 1029-35.
7. Mayne ST. Beta-carotene, carotenoids, and disease prevention in humans. Journal FASEB,1996;10: 690-701.
8. De Pee S, West CE, Muhilal, Karyadi D, Hautvast JGAJ. Lack of improvement in vitamin A status with increased consumption of dark-green leafy vegetables. Lancet 1995; 346: 75-81.
9. De Pee S, West CE, Permaesih D, Martuti S, Muhilal, Hautvast JGAJ. Orange fruit is more effective than are dark-green, leafy vegetables in increasing serum concentrations of retinol and β-carotene in schoolchildren in Indonesia. Am J Clin Nutr 1998; 68: 1058-67.
10. U.S. Institute of Medicine, Food and Nutrition Board, Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. 2000. National Academy Press, Washington, DC.
11. IVACG. Vitamin A conversions to SI, a bookmark. 2002. Available from http://ivacg.ilsi.org/publications/publist.com
12. West CE, Eilander A, Van Lieshout M. Consequences of revised estimates of carotenoid bioefficacy for the dietary control of vitamin A deficiency in developing countries. J Nutr 2002; 132: 2920S-2926S.
13. Suharno D, West CE, Muhilal, Karyadi D, Hautvast JGAJ. Cross-sectional study on the iron and vitamin A status of pregnant women in West Java, Indonesia. Am J Clin Nutr 1992; 56: 988-93.
14. Bloem MW, Wedel M, Egger RJ, Speek AJ, et al. Iron metabolism and vitamin A deficiency in children in Northeast Thailand. Am J Clin Nutr 1989; 50: 332-8.
15. Roodenburg AJ, Leenen R, van het Hof KH, Weststrate JA, Tijburg LB. Amount of fat in the diet affects bioavailability of lutein esters but not alpha-carotene, beta-carotene, and vitamin E in humans. Am J Clin Nutr 2000; 71: 1187-93.

16. Craft NE, Wise SA. Optimization of an isocratic high-performance liquid chromatographic separation of carotenoids. J Chromatogr 1992; 589: 171-76.
17. Polderman AM, Mpamila K, Mashande JP, Bouwhuis-Hoogerwerf M. Methodology and interpretation of parasitological surveillance of intestinal schistosomiasis in Maniema, Kivu Province, Zaire. Ann Soc Belg Med Trop 1985; 65: 243-9.
18. Hulshof PJM, Xu C, van de Bovenkamp P, Muhilal, West CE. Application of a validated method for determination of provitamin A carotenoids in Indonesian foods of different maturity and origin. J Agric Food Chem 1997; 45: 1174-79.
19. Prosky L, Asp NG, Furda J, de Vries JW, Schweizer TF, Harland BF. The determination of total dietary fiber in foods, food products and total diets: interlaboratory study. J Assoc of Anal Chem 1984; 67: 1044-52.
20. National Institute of Nutrition. Food composition and nutritive value of Vietnamese foods. Hanoi, Vietnam. Medical Publisher 1994.
21. West CE, Poortvliet EJ. The carotenoid content of foods with special reference to developing countries. Washington, DC: USAID-VITAL 1993.
22. Haskell MJ, Jamil KM, Hassan F et al. Daily consumption of Indian spinach (*Basella alba*) or sweet potatoes has a positive effect on total-body vitamin A stores in Bangladeshi men. Am J Clin Nutr 2004; 80: 705-14.
23. Jalal F. Effects of deworming, dietary fat and carotenoid rich diets on vitamin A status of preschool children infected with *Ascaris lumbricoides* in West Sumatra Province, Indonesia. PhD dissertation. Ithaca, NY: Cornell University, 1991.
24. Castenmiller JJM, West CE, Linssen JPH, van het Hof KH, Voragen AGJ. The food matrix of spinach is a limiting factor in determining the bioavailability of β-carotene and to a lesser extent of lutein in humans. J Nutr 1999; 129: 349-55.
25. van Lieshout M, de Pee S. Vitamin A equivalency estimates: understanding apparent differences. Letter to the Editor. Am J Clin Nutr 2005; 81: 943-945.
26. Wang X-D. Review: absorption and metabolism of β-carotene. J Am Coll Nutr 1994; 4: 491-96.
27. Castenmiller JJM, West CE. Bioavailability of carotenoids. Pure & Appl. Chem. 1997; 69; 10: 2145-50.
28. Zhou JR, Gugger ET, Erdman JW. The crystalline form of carotenes and the food matrix in carrot root decreases the relative bioavailability of β- and α-carotene in the ferret model. J Am Coll Nutr 1996; 15: 84-91.
29. Van het Hof KH, Brouwer IA, West CE, et al. Bioavailability of lutein from vegetables is five times higher than that of β-carotene. Am J Clin Nutr 1999; 70: 261-268.
30. Borel P, Grolier P, Armand M, et al. Carotenoids in biological emulsions: solubility, surface-to-core distribution and release from lipid droplets. J Lipid Res 1995;37:250-61.
31. Rock CL, Swendseid ME. Plasma β-carotene response in humans after meals supplemented with pectin. Am J Clin Nutr 1992; 55: 96-99.

32. Tanumihardjo SA, Permaesih D, Muherdiyantiningsih, et al. Vitamin A status of Indonesian children infected with *Ascaris lumbricoides* after dosing with vitamin A supplements and albendazole. J Nutr 1996; 126: 451-57.

CHAPTER 5

Control of vitamin A deficiency in Vietnam: the achievements and future orientation

Nguyen Cong Khan, Ha Huy Khoi, Tu Giay, Nguyen Trong Nhan, Nguyen Thu Nhan, Nguyen Chi Dung, Hoang Viet Thang, Dao Ngoc Dien and Hoang Thi Luy

Food and Nutrition Bulletin June 2002; Vol 23, No.2: 133-142

ABSTRACT

Vitamin A deficiency is one of the major nutritional deficiencies in Vietnam. The first survey conducted in 1985-88 showed that the prevalence of severe xerophthalmia was seven times higher than the cut-off point established by the WHO to define vitamin A deficiency as a public health problem. The result of this survey has strongly convinced the Government in launching a program to control vitamin A deficiency, which started in 1988. The program strategies comprised of nutrition education; universal distribution of high dose vitamin A capsules to children aged 6 to 36 months in combination with national immunization days and promotion of production and consumption of vitamin A-rich foods at family level. The implementation network was set up based on existing preventive health structure at all administrative levels. The program has been actively participated by mass organizations such as the women's union and other social sectors. The surveys conducted in 1994 and 1998 showed that prevalence of clinical xerophthalmia is significantly lower than those identified in the baseline survey and below the WHO criteria of public health problem.

The achievements of our program have demonstrated the effective vitamin A supplementation approach that can be done successfully by the preventive health network with the active community participation. In the coming years, developing the approaches other than vitamin A supplementation will be an important choice of our program in order to maintain the past achievements.

INTRODUCTION

Vitamin A deficiency has long been recognized as a serious public health problem in many developing countries. It affects large numbers of preschool children and women of childbearing age. Over 78 million children under five years of age are affected by vitamin A deficiency, putting them at risk in terms of health and survival [1, 2]. Vitamin A deficiency appears to be a major risk factor for both child and maternal mortality [3, 4]. There is strong evidence that vitamin A deficiency increases mortality among children from 6 months to 6 years of age, and that improving vitamin A status of deficient children dramatically increases their chance of survival [4, 5].

The World Summit for Children held in 1990 has set the goal of virtual elimination of vitamin A deficiency and its consequences, including blindness by the year 2000. The World Declaration and Plan of Action for Nutrition of the International Conference on Nutrition (1992) also called for efforts to be made toward eliminating Vitamin A deficiency and xerophthalmia before the end of 90' decade [6].

In Vietnam, problem of vitamin A deficiency among children was recorded in 1958 with hospitalized cases of keratomalacia in northern region [7]. For many years, many cases with keratomalacia were reported in eye hospitals throughout the country [8, 9,10]. However, there was no national data on nature and magnitude of this problem until the first survey conducted in 1985-88. The finding of high rate of blindness due to xerophthalmia from this survey has convinced the Government to launch a program to control vitamin A deficiency, which started in 1988. The program has been implemented by existing preventive health sector. Vitamin A supplementation program was integrated with national immunization days (NIDs). The achievements of our program have demonstrated the effective vitamin A supplementation approach that can be done successfully by the preventive health network with the active community participation.

This paper reviews progress of vitamin A program in Vietnam during the last ten years, its achievements and lessons learnt. The paper also discuss about strategies to eliminate vitamin A deficiency in children and women in Vietnam in the coming years.

PROGRAM DESIGN AND ACTIVITIES

In 1996 and 1997 National institute of nutrition organized two national workshops to address problem of vitamin A deficiency and xerophthalmia and its control. The Government was convinced by the fact that many preschool children in community go blind everyday while the problem can be preventable. With the joint working between National institute of nutrition, National institute of ophthalmology and National institute of pediatrics, the program to control vitamin A deficiency was developed and soon approved by Ministry of Health. The general program objectives were to reduce prevalence of xerophthalmia, especially active forms with corneal lesions leading to blindness and virtually eliminate this disease by the year 2000; to improve dietary intake of vitamin A, fat of people especially of young children and mothers and, to spread awareness among health professionals and people in general about prevention and control of vitamin A deficiency and xerophthalmia. The specific objectives were set up every five years and each year. From beginning, we have received the supports of UNICEF for this program.

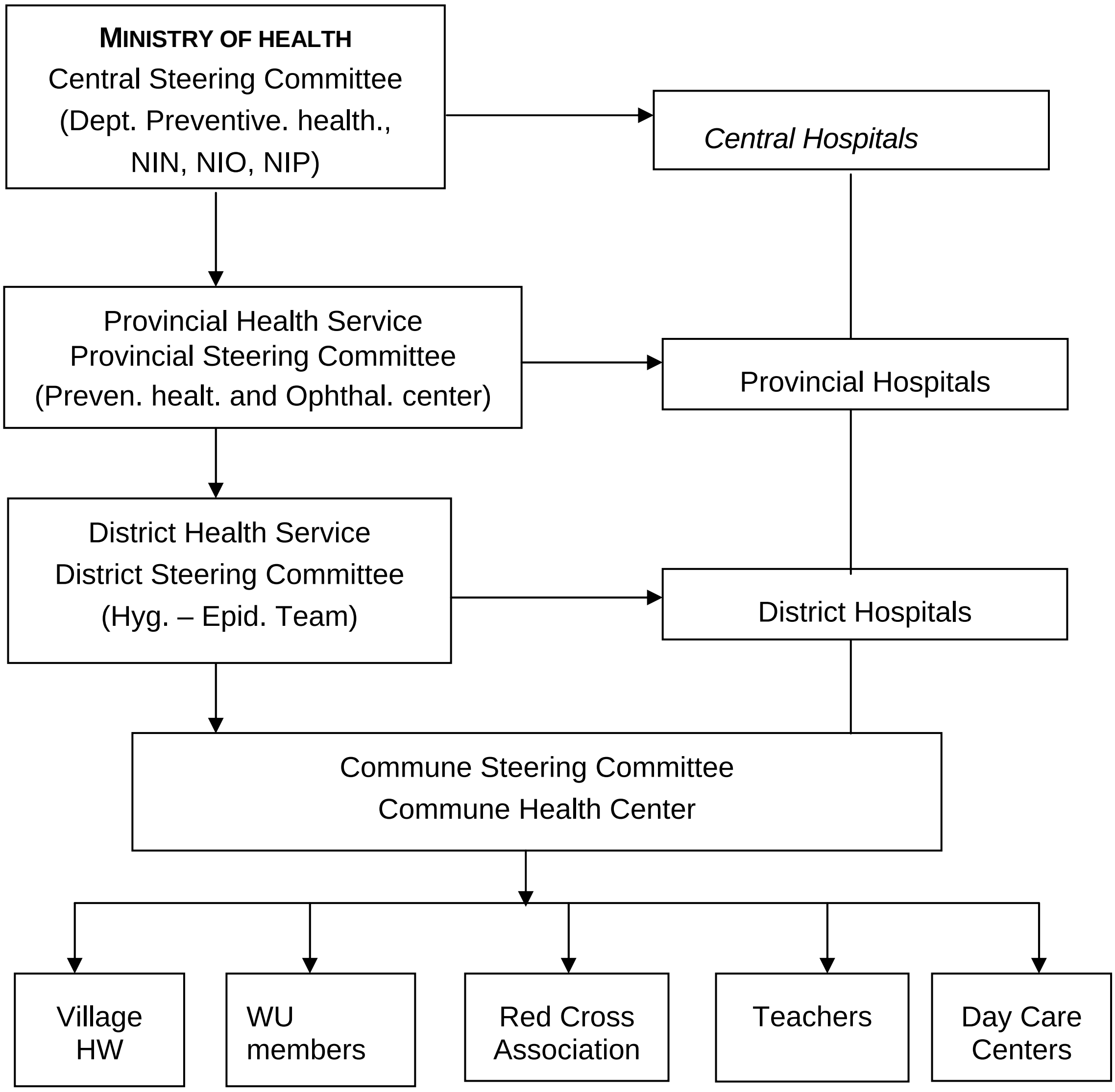
1. Universal Vitamin A supplementation

As shown in **Diagram of program networking**, the program network was established with intensive involvement of both curative and preventive health systems. At the community level, program was implemented by commune health center (CHC) which presents more than 95% of all communes throughout the country. Two distribution campaigns were taken in June (the first and Second) and in December (integrated with National immunization days-NIDs). The administration schedule of vitamin A capsules is shown in **Table 1**. One month before the vitamin A distribution campaigns taken place, CHCs received vitamin A capsules, guidelines, booklets and recording notebooks from district health center which provided by provincial center for preventive medicine. The staff of commune health centers organized training for village collaborators and worked with them on activities prior to campaign. Members of women's union, village health workers or teachers at kindergarten based commune nutrition collaborator network on existing village health collaborator network that participated. The lists of children 6 to 36 months living in each village which were established by village collaborators were available about two weeks before the campaign. At community, the communication, education and propaganda activities began about one week before each vitamin A campaign.

Table 1 Administration schedules of vitamin A capsules (100,000)

Purpose	Target groups	Dose
Universal distribution for prevention	Infants 6-12 months old	1 capsule once a year
	Children 1-3 years old	2 capsules twice a year
	Lactating women	2 capsules within one month after deliverv
Disease-targeted prevention schedule	Children 1-5 years old	2 capsules for each episode of illness
	Infants 6- 12 months	1 capsule for each episode of illness

Diagram of program networking



During the campaign, children were brought by their parents to received vitamin A capsules at the central point in each village. One or two collaborators were responsible for distribution of vitamin A capsules in each point. Children who received the capsule were checked into the list and weighted and then plotted in an individual growth chart. If someone did not come to central point, the village collaborators reached him or her at home to give the capsules. Vitamin A capsules provided by UNICEF and were given free of charge. Just after the campaign, village collaborators reported to community health center. The community health center gathered all records from villages to make a report in the designed form and then sent to district health center about 3-4 days after the campaign completed. However, for communes in mountainous regions or difficulty areas, the vitamin A campaigns took longer than others did, sometimes one week to ten days to complete the campaign. In the days of working for each vitamin A campaign, commune health staff and collaborators received an incentive from commune people committee (local government) or had the lunch or dinner. Vitamin A capsules were also available at community health centers besides the campaigns. When children suffer from measles, diarrhea or acute respiratory infections, they were received a prophylaxis dose at commune health center during health care service. A singer dose of vitamin A 200,000 IU was given to mothers giving birth at commune health center or hospitals.

Vitamin A supplementation also targeted as prophylaxis to high-risk hospitalized children with measles, diarrhea, acute respiratory infections and severe malnutrition. The provision of vitamin A capsules to hospital system was done by provincial station for ophthalmology. Since 1992 vitamin A capsules (100,000 UI) were locally produced with the WHO prescribed "GMP" rules.

At provincial and district levels, the program was implemented in close cooperation with both preventive and curative systems under the guidance of provincial and district health services. For this purpose, one program secretary working at provincial center for preventive medicine was appointed in each province.

The national program was under the direct guidance of the Ministry of health. The National institute of nutrition in Hanoi was appointed as focus point of program and responsible for community-based activities while Institutes of ophthalmology and pediatrics in Hanoi and Eye Center in Ho Chi Minh City were responsible for hospital-based activities. The community-based activities involved also regional institutions including Institute of public health in Ho Chi Minh City, Pasteur institute in Nha Trang and Institute of Epidemiology and hygiene in Tay Nguyen.

In order to test feasibility of program networking and activities, we started first with 7 pilot districts in 1988. One year after the pilot program was tested, we implemented in 27 provinces, and in 1990 this number rose to 31. Since 1993 the program expanded to a national scale and closely integrated with NIDs.

Because most of nutritionists, health workers and medical staff have not been trained in a community nutrition program, training activities for network is important part of our program. National institute of nutrition has organized 286 training courses for 17,100 participants from preventive health sector and members of mass organizations, covering the most health staff working for the program at provincial or district levels. Provincial or district staff was responsible for training the commune health workers. For the curative system, the National institute of ophthalmology conducted various training courses for almost all health staff working at provincial hospitals and provincial ophthalmology stations.

2. Dietary improvement through promotion of food production and consumption at family level.

Horticultural intervention combined with extensive nutrition education is recommended as long-term measure to eliminate micronutrient malnutrition. Adequate production and consumption of vitamin A-rich food play an important role [11]. The garden for growing of vegetables and fruit, pond for fish culture and cattle shed for animal husbandry were the common home-based agricultural practice of many Vietnamese families [12]. However, the term "VAC" was known in Vietnam since early 80's. The VAC stems from Vietnamese that was suggested by Prof. Tu Giay, the founder and the first director of the Vietnam National Institute of Nutrition [12, 13]. It is an acronym for Garden (V); Pond (A) and Cattle shed (C). From the garden different species of plants including vegetables, beans, legumes, roots, tubers and fruits are grown in multi-layered cultivation, mixed cropping and inter-cropping cultivation systems. People may use their pond for cultivating various types of fish, shrimp, and crab. Animal husbandry with poultry and animal, livestock cultivation can link with garden and fishpond culture. Thus, the VAC might contribute to the variety of people's diet [13, 14, 15], and it was considered as a mean to solve problem of household food insecurity in Vietnam [14]. In order to promote nutritional benefits from VAC, a specific guideline for “nutrition square” at family VAC was developed. This encouraged people to focus on growing of vegetables, fruits and cultivating of chicken for eggs for purpose of family consumption.

The association of Vietnam VAC (so-called VACVINA) was established in 1986. In order to promote VAC, the VACVINA has given various technical training and education for its members in order to transfer knowledge and experiences to the farmers. Several projects on vitamin A nutritional improvement through promotion of VAC food production and consumption at family level have been implemented [15]

3. Development of nutrition educational activities for community.

Nutrition education aims at spreading awareness among people about vitamin A deficiency and specifically addressing the problem of feeding patterns related to vitamin A deficiency [16]. The following points were highlighted: promotion of breastfeeding, appropriate weaning practices; educating mothers to feed the child with vegetables, fruits and fat regularly; improving dietary intake of pregnant and lactating mothers with vitamin A-rich foods, introduction of locally available vitamin A-rich foods (combined with VAC activities).

Nutrition education activities have implemented with different ways. Mass education and communication campaigns were organized twice a year with the involvement of mass media agencies such as TV, Radio, and newspapers at central and provincial levels. Within framework of national plan of action for nutrition 1996-2000, Government has funded for such the campaigns. The main emphasis from 1996 onwards is to provide information about all micronutrients (VAD, IDA and IDD) with "micronutrient days campaign" in June. The preventive health sector has provided booklets, posters, and leaflets for communes before each vitamin A distribution campaign. The specific message was given to mobilize the families to bring their children to the distribution point for vitamin A supplementation, weighing and immunization. At the community level, communication activities were done by health workers, nutrition collaborators and information staff of the commune people's committee.

4. Monitoring and evaluation

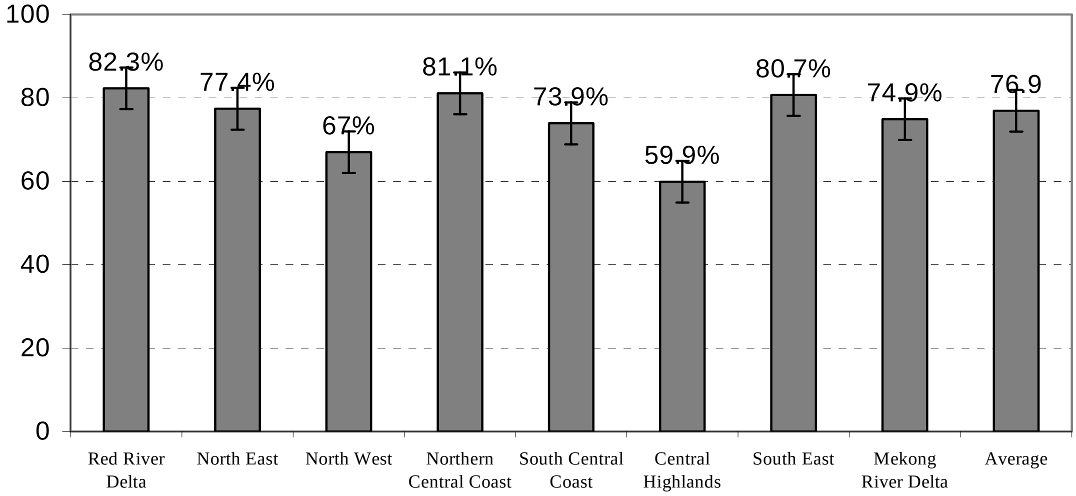
A few days after the vitamin A distribution campaigns, reports in a standard form were sent from communities all the way to central level. Reports computed from hospital system were sent to the Institute of ophthalmology every 6 months, reporting the prophylaxis activities, which were carried out by medical cadres in hospitals and eye stations. Progress was monitored at all levels through the established reporting system and through the post-campaign spot-checking to validate the reported results.

National evaluation was conducted in 1994 and in 1998 with the technical assistance of international experts and financial support of UNICEF.

PROGRAM OUTCOME

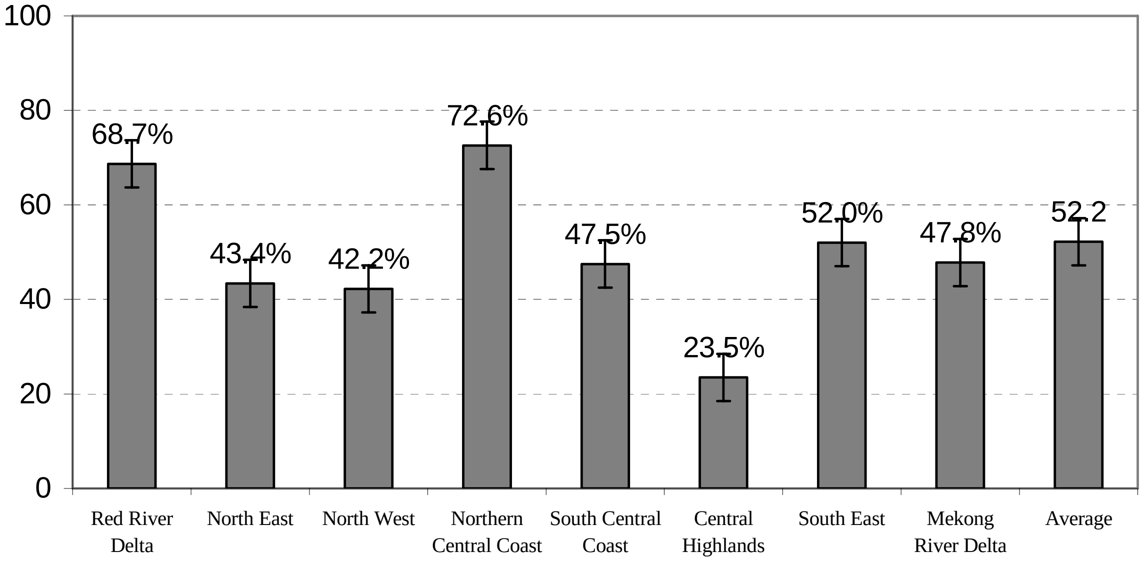
Every 6 month, vitamin A distribution served about 9 millions children under 5 (1993-1996) and about 5 millions children aged from 6 to 36 months (from 1997) in all communes throughout the country. As shown in **Figure 1**, coverage rate of vitamin A supplementation in children were 70 to 80% in almost all regions in the country. However, the coverage rates in some remote regions were lower than that others. Special attention should be given to improve the coverage of such localities. During some initial years, the coverage of vitamin A supplementation for lactating mothers after delivery were quite low. One reason was that capsules are not always available at commune health center. From 1998, vitamin A capsule was packed in the blister form, which can be kept at community health center. The coverage rate in lactating mothers in 1998 was 52.2% for country as the whole but large variation among the ecological zones (**Figure 2**). Since that time, our program addressed the hard-to-reach localities in order to increase coverage rates of vitamin A capsule in children and lactating mothers by integrating with child malnutrition control program.

Figure 1 Vitamin A capsule coverage by region (% children aged 6-36 months) [1]



[1] *During the last 6 months*

Figure 2 Percentage of mothers after delivery receiving vitamin A capsule by regions



The integration vitamin A distribution and EPI in some countries have been reviewed by Unicef [18]. The integration and the close operational cooperation of vitamin A supplementation and EPI/NIDs programs have proven to be a powerful way to enhance and sustain both programs. Micronutrient days has been able to have the involvement of several civil society organizations such as Women's union, Red cross union, education sectors…At every commune, the campaign was organized with actively participation of such civil organizations. The preventive health sector in Vietnam has had experiences in implementing several health care programs and health promotion campaigns. This gave an advantage for implementation of nutrition program. Thus, the program had moved ahead in the integration process of health care activities based on strengthening implementation capacity of the existing preventive health network. The health workers of all communes can manage well with early detection, treatment and prevention of vitamin A deficiency while people in general, also know better how they should do to prevent vitamin A deficiency in children.

Along with supplementation approach, the food production and consumption by family level through the VAC have contributed to vitamin A intake of people. A nutrition improvement project conducted in four communes of Vietnam included 5,588 households with 3,716 young children showed a significant increased production of fruit, vegetables and other food from family garden [15]. Increased intakes of nutrients, including carotene, iron, vitamin C and protein among households with young children was observed. Other evaluations showed that well-developed VAC production by family could contribute between 50 to more than 70 per cent of family income [13, 14, 15]. Promotion of family food production through the VAC Eco-system has been became the Government policy in improving people diet and nutritional status [12].

Table 2 Frequency consumption of vitamin A and carotene rich-foods by children during the last 2 months (*)

Frequency	Never eaten		One/month		One/week		One/day	
	1985-88 survey	in year 2000(**)	1985-88 survey	in year 2000	1985-88 survey	in year 2000	1985-88 survey	in year 2000
Eggs	36.8	14.4	19.0	21.6	33.9	53.9	10.3	10.1
Green vegetable	24.2	8.6	0.5	4.3	12.5	28.8	62.8	58.3
Fats/Oil	27.0	7.2	4.7	8.6	18.0	25.2	50.3	59.0

(*) Children without clinical xerophthalmia. The value is expressed in %

(**) A pilot study in Thanhmien district, Haiduong province – 2000.

Nutrition education and social mobilization have the positive influence on attitude and practice of different groups concerning micronutrient deficiency control, including community leaders at all levels which in turn, contribute greatly to the success of vitamin A supplementation program. The evaluation surveys revealed that 60-70% mothers know about how to prevent nightblindness and the purpose of vitamin A supplementation for their children. Large proportion of mothers knew how to correct the problem of weaning pattern of the child. As shown in **Table 2** there were improvements in feeding practices of young children with more frequent consumption of vitamin A-rich foods and fats are given to children in compared with the past as these foods were commonly restricted because of the habit. [19, 20].

PROGRAM IMPACT

Clinical assessment of vitamin A deficiency and xerophthalmia in the first survey 1985-88 is shown in **Table 3.** Total prevalence of 0.72 per cent in which prevalence of active forms with corneal lesions was 0.07 per cent and of inactive corneal scars 0.12 per cent. Two criteria were exceeded the WHO threshold for public health problem [1]. xerophthalmia with corneal lesions and xerophthalmic scars were prevalent in all ecological regions (**Figure 3**) while nightblindness (XN) and Bitot's spot (X1B) rates were below WHO cut off criteria. Xerophthalmia occurs in the population with very high prevalence of protein-energy malnutrition. Many cases of marasmus or marasmic-kwashiorkor with clinical signs of vitamin A deficiency were found in the field. In these cases, corneal xerosis and ulceration developed quickly after the child suffered from an acute diarrhea, even skip period of nightblindness or Bitot's spot. The rate of blindness consequence in hospitalized children was very high which clearly indicated the severe clinical manifestation of vitamin A deficiency (**Table 4**).

Many countries like Indonesia, India reported high prevalences of XN and X1B [7]. Other study, however, by Cohen N, Rahman H, Mitra M et al. (1985) reported that in rural and very poor urban areas, prevalence of Bitot's spot is 0.09 and 0.16 respectively [21]. Other study done by Pham Duy Tuong et al. in Northern mountainous areas of Vietnam where severe malnutrition in children is very high reported that X1B rate is 0.13 [22].

Table 3 Clinical assessment of vitamin A deficiency and xerophthalmia (The first survey 1985-88, n= 34,214)

Clinical forms	Prevalence (%)	WHO criteria (1981)
Night blindness (XN)	0,37	> 1%
Bitot’s spot (X1B)	0,16	> 0,5%
Corneal ulceration/ Keratomalacia (X2/X3A/X3B)	0,07	> 0,01%
Corneal scars (XS)	0,12	> 0,05%

Figure 3 Distribution of active xerophthalmia with corneal lesions and xerophthalmic scar by ecological regions (the first prevalence survey, 1985-88)

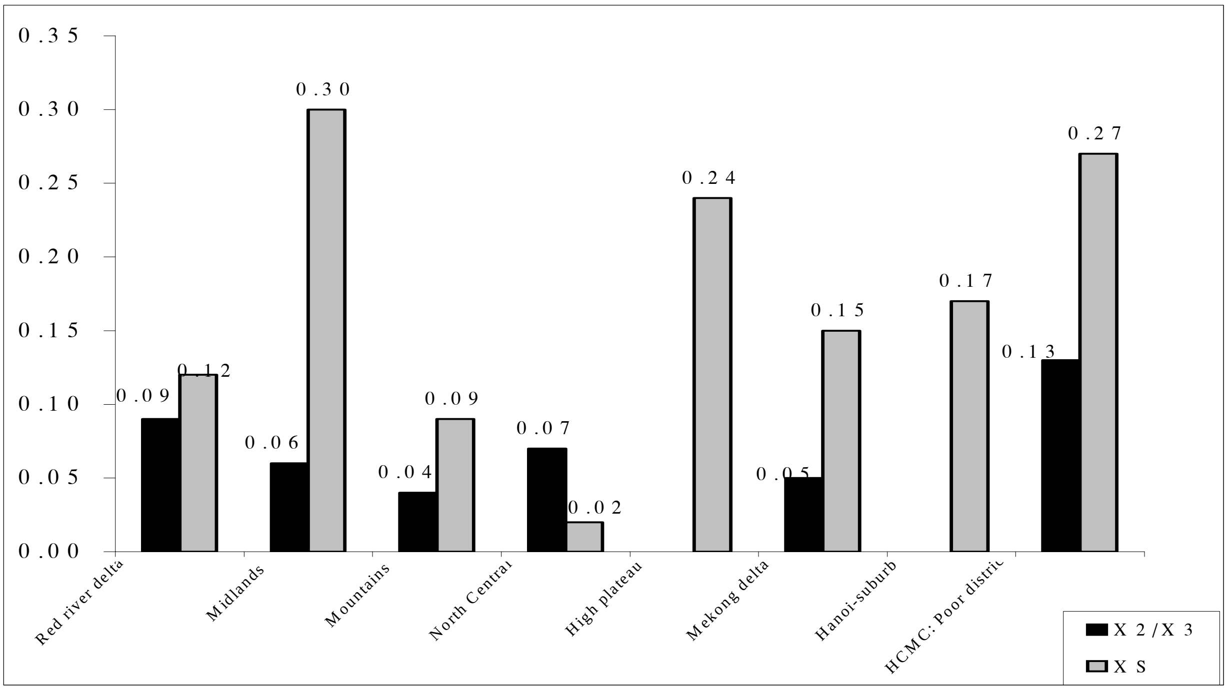


Table 4 Reported cases with xerophthalmia admitted in central hospitals of Vietnam

	At the Institute of Ophthalmology (1979-1983)	At the Institute of Pediatrics (1984-1986)
Number of cases	104	275
Visual impairment (%)	26.9	3.6
Monocular blindness (%)	26.9	8.7
Binocular blindness (%)	13.5	8.0

Children aged from 12 to 36 months had the highest xerophthalmia prevalence and severe clinical forms. The dietary Vitamin A intake of children with xerophthalmia was significant lower than that controls. In many regions, people had belief of avoiding the use of fats, fruit, vegetables, and animal foods for feeding their young children when they suffered from measles, diarrhea and respiratory infections [17, 19].

The 1994 and the 1998 surveys showed that prevalence of clinical xerophthalmia is lower than the WHO criteria for a significant public health problem in preschool and significantly lower than those identified in the baseline survey (**Table 5**). In none of the ecological zone in Vietnam did the prevalence of active cases of xerophthalmia (X3A-

X3B) exceeding any of the WHO cut-off points [26]. The prevalence of nightblindness among vitamin A capsule non-recipients under age 5 was similar to the prevalence noted during the first survey, which indicates the effectiveness of the vitamin A capsule supplementation program (**Table 4**). Prevalence of maternal nightblindness was 0.58% (1994) and 0.90% (1998). Low dietary intake of vitamin A by women might contribute to the low vitamin A status. The survey in 1994 and 1998 pointed out that low vitamin A intake is associated with maternal nightblindness. Mothers with low intake of vitamin A are particularly at risk when they are pregnant and lactation [6]. The fact that the coverage rate of vitamin A supplementation in children was maintaining high in many years, coverage rate of capsule vitamin A in lactating women was rather low (some regions reached about only more than 20%). In controlling of vitamin A deficiency, more effort focussed in children but more attention should be given to mothers too.

Table 5 Clinical assessment of vitamin A deficiency in Vietnam (prevalence, %)

Clinical signs	1988*	1994**			1998***	
	Total sample 34,214¶	Non-VAC recipients 2,953 ¶	Total sample 37,920 ¶	Women 27,803 †	Total sample 12,900 ¶	Women 10,650 †
Night blindness (XN)						
Children under 5	0.37	0.37	0.05		0.20	
Reproductive-age women				0.58		0.90
Bitot's spot (X1B)	0.16	0.23	0.045	ND	ND	ND
X2/X3A/X3B	0.07	ND	0.005	ND	ND	ND
Corneal scars (XS)	0.12	ND	0.048	ND	ND	ND

* National Survey on Vitamin A deficiency, NIN 1988

** National VAD/PEM Survey 1994, NIN/HKI/UNICEF

*** National PEM/VAD Survey 1998. NIN/UNICEF

¶ Sample for children under 5 years of age

† Sample for reproductive-age women (mother of under children 5 examined)

ND: not detectable

Table 6 presents the monitoring data computing number of children with xerophthalmia admitted in main hospitals of Vietnam during ten years (1990-99). The data showed that number of cases with xerophthalmia (corneal xerosis/ulceration forms) admitted in main hospitals throughout the country has dramatically reduced. Although the hospital data is not representative of the community, this figure shows a significant achievement of the program in preventing of nutritional blindness in Vietnam.

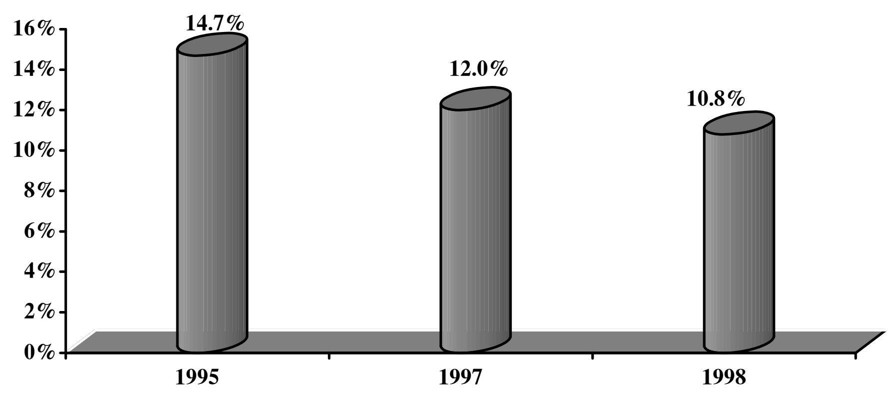
The prevalence of subclinical vitamin A deficiency (serum concentration of retinol $<$ 0.70 μmol/L) in children under 5 was 10.8% (**Figure 4**). In the survey sample, there was no case with very low serum retinol ($<$ 0.35μmol/L) is detected. Subclinical vitamin A deficiency was found to be higher in children below one year of age (**Figure 5**). Prevalence of lactating women with low breastmilk retinol concentration ($< 1.05 \mu mol/L$) was 48.5% in the 1997 (**Figure 6**) and went up in 1998 (58.3). It may reflect a large variation on vitamin A status of women.

Table 6 Number of children with xerophthalmia admitted in main hospitals in Vietnam during 1990 – 1999*

Hospitals/ Year	**90**	**91**	**92**	**93**	**94**	**95**	**96**	**97**	**98**	**99**
In the North										
Hanoi, Inst. of Ophthalmology	6	12	20	18	0	0	1	1	1	0
Hanoi, Inst. of Pediatrics	48	42	48	36	11	6	7	8	4	3
Haiphong, Children's hospital	64	42	38	27	5	0	1	0	0	0
Namha, provincial hospitals	71	51	55	34	21	7	8	1	5	0
Hatay. provincial hospitals	307	36	92	92	51	11	7	2	0	0
In the South										
HCM City, Eye Center	45	41	38	17	9	0	0	0	0	0
Cantho, Children's Hospital	NA	NA	NA	NA	16	3	3	2	1	1
In the Central										
Danang, Provincial hospitals	NA	15	12	10	5	1	1	0	0	0
Hue, Central Hospital	NA	19	13	19	2	4	1	1	0	1
Total	541	258	316	253	120	32	29	15	11	5

* Cases with corneal lesions (X2/X3A/X3B)

Figure 4 Percentage of children with low serum retinol concentration¶



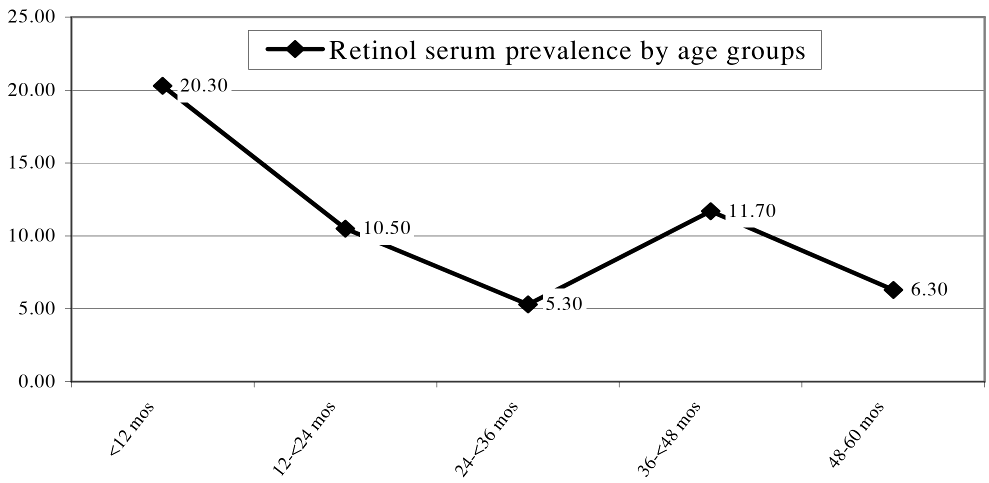
Data 1995 and 1997: a small sample survey

Data 1998: National PEM/VAD survey

¶ Serum retinol concentration $< 0.70 \mu mol/L$

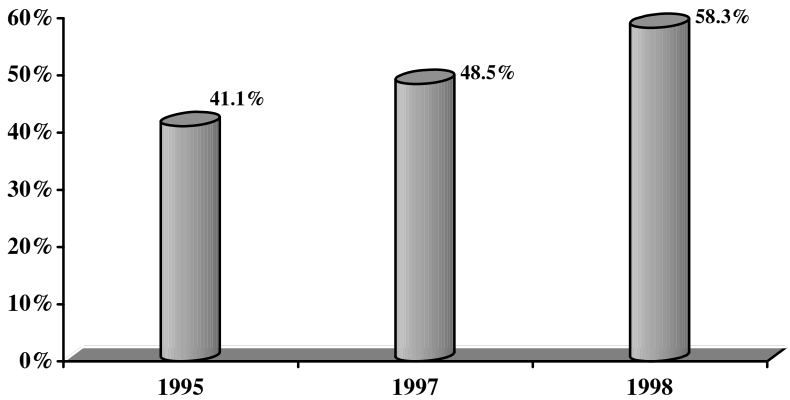
More attention should be given to improving maternal vitamin A nutritional status in the future program. It was suggested that although there were important improvement of people's diet during the last decade in Vietnam, the dietary intakes of micronutrients of Vietnamese are still poor, especially people living in rural and remote area [20]. On the other hands, some food source carotene-rich crops were underutilized for instance Gac fruit in Vietnam (*Momordica cochinchinesis Spreng*) [23]. This is a carotene-rich fruit. The issue is to direct towards identifying local plants foods rich in provitamin A carotenoids, traditional use of plants and methods to improve production, preservation and preparation for family consumption [24, 25].

Figure 5 Prevalence of low serum retinol concentration in children under 5 by age groups (1998 survey)†



† Serum retinol concentration < 0.70 μmol/L

Figure 6 Percentage of breastfeeding mothers with low breastmilk retinoll concentration (*Breastmilk retinol concentration < 1.05 μmol/L)*



FUTURE DIRECTION

In the last decade, supplementation approach played the key role in achieving the program's goal towards elimination of clinical xerophthalmia in children while other approaches are not established yet or are not easy to evaluate in the large-scale. Subclinical vitamin A deficiency is prevalent in Vietnam that may contribute to high mortality and morbidity and growth retardation among young children. The continuing the efforts to achieved further sustainable result in ending micronutrient malnutrition is critical point in our nutrition agenda.

Dietary diversification

Although during the last some years, there is a tendency of diet quality improvement with more protein rich food and less staple food [20], the staple-based diet places Vietnamese population at a risk of micronutrient deficiencies. The epidemiology of vitamin A deficiency associates the problem with diets predominantly consisting of vitamin A-poor staples, such as cereals, grains, tubers, and with little diversity, low and infrequent consumption of animal sources [24]. The main issue here is to address the people of lower economic groups and inhabitants of rural areas because animal products, which can be best, source of vitamin A are not affordable for everyone. More efforts are needed to promote production, preservation, preparation and consumption of micronutrient-rich crops and animal products. The concept of " home-based fortification" which assumes local availability of naturally rich food sources of vitamin A that are underutilized in the diet of high-risk groups may be more practical for Vietnam where centralized fortification is not currently developed [23, 24]. The agricultural strategies may help to alter the content of absorption modifiers in plant-based staple food [25]. The appropriate agricultural technologies may need to apply at large-scale agricultural production and at family scale (family VAC production).

Vitamin A supplementation

This approach provides supplements to the population through the health care system. Because malnutrition in children is high prevalence and other approaches are not adequately developed, the supplementation program is still needed for the years to come. Nevertheless, it requires close supervision by the health-care workers and high compliance by the community to be successful [26]. More attention should be given to supplementation program in remote regions and to lactating mothers after giving birth at the clinics and in community.

Food fortification

Fortifying commonly consumed staple foods with micronutrients is proved the most cost-effective and sustainable solution to eliminate micronutrient malnutrition. The most successful fortification experience with the fortification of salt with iodine has been reported worldwide, including Vietnam. Currently there are 87.5% of the Vietnamese population consume iodized salt. Universal iodized salt was approved by the Government of Vietnam and it is expected to be achieved soon in the coming years. Recently, fortification of other staple foods with other minerals and vitamins for Vietnamese population is also being taken into consideration. Fishsauce fortification with iron is now experimenting by NIN/ILSI [27]. Sugar fortification with vitamin A is in the pilot production stage by Bien Hoa sugar company under the technical support of La Roche [28]. Some researches on biscuit fortification with iron and vitamin A have been carried out [20]. In the last some years, Vietnam has experienced in rapid economic growth including food industry sector. The people can access the good quality of foods not only by production at household level, but also through food distribution via free marketing mechanism. According to current food consumption data, sugar is widely consumed with a daily per capita mean consumption of amount of 15 gram [20]. Cooking oil is also considered as potential vehicle for vitamin A fortification in Vietnam.

However, the challenge for this food fortification approach to be successful is the requirement of a multi-sector partnership between Government sectors, industry (food producers, processors, distributors), international agencies, and other players, which is currently still weak. New communication channels among those partners need to be opened. Promotion of food fortification as a key strategy to overcome micronutrient malnutrition in Vietnam which involves effective partnership of different sectors with supportive legislation environment.

CONCLUSION

The universal vitamin A supplementation to children has been achieved through the strong implementation support structure based on preventive health network. Linking of the vitamin A program with the National immunization days (NIDs) is a good approach and we can make use of this system. This is positive development, indicating that vitamin A program has closely integration with the health care services, effective social mobilization and community participation.

There was a close cooperation between implementing institutions is also a key element of the success. We have paid much attention to promotion of people's dietary intakes of vitamin A through the VAC Eco-system combined with nutrition education. Government at all levels was highly committed to the program. Furthermore, the program has received a great support from international agencies and contributed by all communes in the country.

In the years to come, supplementation program should continue but more target selection oriented. Together with promotion of dietary diversification, food fortification program will begin soon and, is considered as an important strategy in our future program.

ACKNOWLEDGEMENT

We thank UNICEF, MI, Medical committee Netherlands-Vietnam, Division of Human nutrition and Epidemiology, Wageningen University, the Netherlands, CBM and HKI for financial and technical supports for our program implementation, monitoring and evaluation. We thank staff of provincial centers for preventive medicine, Ophthalmology stations, and regional health institutions of Vietnam for their great contribution to the success of this program.

REFERENCES

1. WHO. Global prevalence of vitamin A deficiency. Micronutrient deficiency information system (MDIS). Paper No.2 (WHO/NUT/95.3). Geneva: World Health Organization.
2. MI/UNICEF/Tulane University. Progress in controlling vitamin A deficiency. Ottawa, Canada: Micronutrient Initiative, 1998.
3. Keith P West Jr, Joanne Katz, Subarna K Khatry, Steven C LeClerq, Elizabeth K Pradhan, Sharada R Shrestha, Paul B Connor, Sanu M Parul Christian, Ram P Pokhrel, Afred Sommer. Double blind, cluster randomized trial of low dose supplementation with vitamin A or β-carotene on mortality related to pregnancy in Nepal. BMJ 1999; 318: 570-5.
4. Beaton GH, Martorell R, Aronson KJ et al. Effectiveness of vitamin A supplementation in the control of young child morbidity and mortality in developing countries. United Nations: ACC/SCN state-of-the rat seris: nutrition policy discussion paper no 13, 1993.
5. Gana VAST study team. Vitamin A supplementation in northern Ghana: Effects on clinic attendances, hospital admissions, and child mortality. Lancet 1993; 342:7-12.
6. WHO/FAO Report on International Conference on Nutrition. Roma, 1992.
7. McLaren D. Global occurrence of vitamin A deficiency. In: Bauernfiel JC, ed. Vitamin A and its control. New York: Academic Press 1986:1-18.
8. Nguyen Chi Dung, Ha Huy Tien. Situation of xerophthalmia in hospitalized children from 1979-1983. The Vietnam Practical Medicine Journal. No 6 (254); 1984: 41-42.
9. Chu Van Tuong. Some remarks about xerophthalmia of children at the institute for protection of children's health. The report of the workshop on vitamin A deficiency and xerophthalmia. NIN, Hanoi 1986: 85-87

10. Ngo Nhu Hoa, Hoang Thi Luy. Xerophthalmia and nutritional blidness. The Medical information institute, No 16; 1985.
11. Indira Chakravarty. Food-based strategies to control vitamin A deficiency. Food and Nutrition Bulletin 2000; 21: 135-43
12. Tu Giay, Duong Hong Dat. The ecosystem VAC as a mean to solve the food problem in Vietnam: In: Applied nutrition. Proceedings of the international conference on applied nutrition, Hanoi 25-29 April 1986. NIN, UNICEF, Hanoi, 1986.
13. Nguyen Van Man. VAC and Nutrition. In: Applied nutrition. Proceedings of the international conference on applied nutrition, Hanoi 25-29 April 1986. NIN, UNICEF; 1986:176-84.
14. Phan Van Huan. VAC ecosystem and micronutrient deficiency control in Vietnam. The research thesis. Hanoi college of medicine; 1997. Hanoi, Vietnam.
15. English R, Badcock J. A community nutrition project in Vietnam: effect on child morbidity. Food Nutr Agric 1998; 22:15-21.
16. Ha Huy Khoi. Protein-energy nutritional status of rural people in some regions of Vietnam. Institut zywnosci I zywienia, Warszawa, 1990: 48-60.
17. Ha Huy Khoi, Nguyen Cong Khan. Strategy for controlling micronutrient deficiency in Vietnam. In Proceedings of the scientific symposium held at National institute of nutrition 8-9 October 1996. Hanoi medical publishing house, Hanoi, 1997: 261-268.
18. UNICEF. Integration of vitamin A supplementation with immunization: policy and program implications. Report of a meeting 12-13 Jan 1998. UNICEF, New York, 1998.
19. Ha Huy Khoi, Nguyen Trong Nhan, Nguyen Cong Khan, Nguyen Chi Dung, Pham Thi Khanh Dung, Do Van Phuc. Xerophthalmia and vitamin A deficiency in some northern provinces at present time. The Vietnam medical magazine. 1986; 3: 21-27.
20. National Institute of Nutrition, Hanoi, Vietnam. Report on research program KH-09 "study on the solution to improve nutritional status and food hygiene practices of people" period 1997-99. NIN, Hanoi, 1999.
21. Cohen N, Rahman H, Mitra M et al. Impact of massive doses of vitamin A on nutritional blindness in Bangladesh. Am J Clin Nutr 1987; 45: 970-6.
22. Pham Duy Tuong. Xerophthalmia and vitamin A deficiency in children under 5 in 4 mountainous northern provinces of Vietnam. Practical medicine, Hanoi, 1992.
23. Le T Vuong. Underutilized β-carotene-rich crops of Vietnam. Food and Nutrition Bulletin 2000; 21: 173-181.
24. Underwood BA. Dietary approaches to the control of vitamin A deficiency: An introduction and overview. Food and Nutrition Bulletin 2000; 21: 117-123.
25. Gibson RS, Hotz C, Temple L, Yeudall F, Mtiimuni B, Ferguson E. Dietary strategies to combat deficiencies of iron, zinc, and vitamin A in developing countries: development, implementation, monitoring and evaluation. Food and Nutrition Bulletin 2000; 21: 119 - 231.
26. Martin W Bloem, Jonathan Gorstein. Xerophthalmia free. 1994 National vitamin A deficiency and protein-energy malnutrition prevalence survey. Consultancy reports 1995.

27. Pham Van Thuy, Berger J, Davidson L, Khan NC et al. Regular consumption of NaFeEDTA fortified fish sauce improves iron status in anemic Vietnamese women. Abstract of 2001 INACG meeting Hanoi 17 Feb 2001.
28. National institute of nutrition, Hanoi, Vietnam. National strategy for food fortification in Vietnam. NIN, Hanoi, 2000.

CHAPTER 6

General discussion

The studies presented in this thesis aimed to investigate the vitamin A and iron status in children in Vietnam. In addition, factors related to the consumption of retinol and carotenoids were studied in the population of the Red River delta. The role of plant food sources in the contributing of vitamin A intake was studied in breastfeeding women.

Vitamin A deficiency as a major public health problem in Vietnam

Deficiency of vitamin A is one of the major public health problems in many developing countries in the world [1-3]. Although the prevalence of xerophthalmia (the clinical sign of vitamin A deficiency) has decreased significantly during the last decade, sub clinical vitamin A deficiency, defined as serum retinol concentrations below the threshold of 0.70 µmol/L, is still common. The actual prevalence of sub clinical vitamin A deficiency in Vietnam is, however, uncertain because of a paucity of reliable national data [4].

Vitamin A deficiency increases morbidity and mortality in infants, children and pregnant women and is related to poor growth in children [5, 6]. Moreover, vitamin A deficiency can affect iron metabolism when deficiencies of both nutrients coexist, particularly in an environment that favors frequent infections [7].

As the results of the study described in chapter 2 show, sub clinical vitamin A deficiency and anemia are still important public health problems in Vietnam. The prevalence of low (<0.70 µmol/L) serum retinol in children younger than 5 years was 12.0% and the prevalence of anemia (hemoglobin <110g/L) was 28.4 %. In infants younger than 6 months the prevalence of sub clinical Vitamin A deficiency even reaches 35.1%. Also protein energy malnutrition (PEM) in children is still a nutritional burden in Vietnam [8] and it is known that PEM is often related with deficiencies of micronutrients, especially vitamin A and iron.

Approaches controlling vitamin A deficiency in Vietnam

Different strategies can be used to control vitamin A deficiency. Most countries where vitamin A deficiency is known to be a major public health problem have policies in place for the periodical providing of high dose vitamin A supplements to at risk groups. This approach is known to be very effective [9].

Apart from supplementation a variety of foods can be used to increase the vitamin A intake such as foods naturally rich in retinol, foods naturally rich in provitamin A carotenoids or foods fortified with vitamin A [9, 10].

The national policy in Vietnam is a universal supplementation of a high dose vitamin A capsule twice a year. The supplementation is combined with the national immunization days (NIDs) which started in 1993 (Chapter 5). That this is a successful approach is shown by the fact that the coverage rate of vitamin A supplementation in children has maintained high over the past years but unfortunately the coverage rate in lactating women is rather low; in some regions it reached only about 20% (Chapter 5). In controlling vitamin A deficiency in Vietnam, the supplementation program was a main intervention activity that resulted in the reduction of xerophthalmia and vitamin A deficiency. The discussion is whether the vitamin A supplementation program should continue since it is already implemented for over 15 years. Important issue is whether other approaches including dietary diversification and introduction of foods fortified with vitamin A can replace the pharmaceutical approach.

Is a food-based approach effective in controlling vitamin A deficiency in Vietnam?

Since long people know that animal liver can be used to cure night blindness [11]. In Europe, when retinol fortified margarine was introduced long ago, xerophthalmia is no longer prevalent [12]. Thus, foods naturally rich in retinol, or vitamin A fortified foods can improve vitamin A status. While micronutrient fortified foods are common practice in Europe, also countries like Guatemala and other Central American countries have fortified sugar with vitamin A [13]. Some countries in South Asia have fortified cooking oil with vitamin A [14].

It is well known that fruit and vegetable are important source of provitamin A carotenoids, especially for developing countries. Unfortunately, there is a little evidence for the significant role of carotene-rich fruits and vegetable in improving the vitamin A status of the population [15]. Thus, control of vitamin A deficiency may need to combine different approaches in which food-based intervention needs a critical choice of foods.

Fruits and vegetables in promotion of health and to prevent diseases

It is generally recognised that consumption of fruits and vegetables should be stimulated because of their role in health promotion and prevention of diseases. Besides carotenoids they provide other nutrients and also add variety to the diet. Epidemiological studies strongly suggest that high intake of fruits and vegetables and ascorbic acid, are associated with reduced risk of heart diseases and cancer. A recent study in China showed that increased consumption of vegetables resulted in a significant reduction of ovarian and prostate cancer [16]. A study by Castenmiller et al showed that lutein in vegetables may play a role as an antioxidant while β-carotene may be a surrogate marker for other protective dietary factors [17]. Fruits and vegetables also provide dietary fibre which is regarded as important in the prevention of cancer [18].

Within the framework of the Global Strategy on Diet, Physical Activity and Health, endorsed at the 57th World Health Assembly in May 2004, the WHO actively promotes an increased intake of fruits and vegetables worldwide. Also, increasing the consumption of vegetable and fruit is part of most dietary guidelines targeted at chronic disease prevention [20]. However, promotion of a higher consumption of vegetables and fruits to achieve the international recommendation of micronutrient supply and to help reduce the burden of chronic diseases is not easy. With intensive promotional activities, however, increases in fruit and vegetable intake are possible in both adults and children [19].

The role of dark-green leafy vegetables and yellow/orange fruits in improving the vitamin A status in Vietnam

The most commonly used method to measure the bioavailability of carotenoids is to measure the serum or plasma retinol response following a designed dietary intervention or oral supplementation with carotene in a vitamin A depleted population [21]. In our dietary intervention study, the “treatment” implied “equal amounts of vitamin A, be as vitamin or as provitamin A”. Our study (Chapter 4) showed that at the end of the follow-up, serum concentrations of retinol were 24% increased in the retinol-rich group compared to the control group, whereas the vegetable and fruit group increased by only 12%. This finding does not confirm the generally held assumption that consumption of carotenoids from dark green leafy vegetables and yellow or orange fruits results in an improvement of the vitamin A status compared to equal amount of retinol. The data are in line with breast milk retinol concentrations after 10 weeks of intervention. Compared to the control group, the breast milk retinol concentration increased nearly two-fold in the retinol-rich group, almost 1.5 fold in the fruit group and 1.3 fold in the vegetable group (Chapter 4). These results are in agreement with results from a study done in Indonesia in breastfeeding women [22] and results in a group of school children (serum response of β-carotene from fruits was four times that of vegetable) [23] indicating that dark-green leafy vegetable are less effective in the improvement of the vitamin A status.

Bioconversion and bioavailability of carotenoids

A previous study proposed that bioconversion is the fraction of a bioavailable nutrient (here, absorbed provitamin A, carotenoids) that is converted into the active form of the nutrient (here, retinol) [24]. Thus, bioavailability is the fraction of an ingested nutrient that is available for utilization for normal physiological functions and for storage [25].

The apparent conversion factors for β-carotene to retinol of 12:1 from fruit and of 28:1 from green leafy vegetables (Chapter 4) confirms the findings from the Indonesia children’s study and supports the conversion factor proposed by West et al of 21:1 for dietary β-carotene from a mixed diet.

The SLAMENGHI (**S**pecies of carotenoids; molecular **L**inkage; **A**mount of carotenoids consumed in a meal; **M**atrix in which the carotenoid is incorporated; **E**ffectors of absorption and bioconversion; **N**utrient status of the host; **G**enetic factors; **H**ost-related factors and mathematical **I**nteractions between these factors) factor was used to examine the knowledge and information available on the bioavailability and bioconversion of carotenoids [15]. Each carotenoid appears to have an individual pattern of absorption, plasma transport and metabolism [26]. Data on each SLAMENGHI factor are necessary to fill the gaps in our knowledge about carotenoids. Although the data available are not sufficient to understand all each SLAMENGHI, some conclusion can be drawn from intervention studies.

The relative bioavailability of β-carotene in dark-green leafy vegetables is extremely low compared to previous assumptions [23]. Pure β-carotene is absorbed far more readily than that in foods. For example, the plasma response to pure β-carotene has been found to be about five times higher than a similar amount of β-carotene in carrots [27]. The bioavailability of β-carotene and lutein varied substantially among different vegetables [28]. It is recognized that the availability of carotenoids in dark-green leafy vegetables, root vegetables and fruits partly depends on the matrix in which the carotenoid is located in the unprocessed product. The disruption of the food matrix and loss of cellular structure had an effect on the bioavailability of β-carotene, whereas the bioavailability of lutein was not affected [17]. Effectors of absorption, in particular oil and dietary fiber [29, 30] are the most important and modifiable factors affecting bioefficacy of provitamin A carotenoids.

With regards to host-related factors, we found (Chapter 4) no relationship between parasitic infestation and retinol serum concentrations. This is in contrast with a study in Indonesia in breastfeeding women where such a relationship was evident. However, in a study in school children in Indonesia this was not confirmed [23]. Parasite infestation, which is prevalent in Vietnam as well as many tropical developing countries, may play a role as the host factor in the SLAMENGHI. Further studies are needed to examine this important factor affecting the availability of carotenoids from plant foods sources.

Retinol and carotenoid consumption in Vietnam and its role in the prevention of vitamin A deficiency in Vietnam.

The study described in chapter 3 shows that pro-vitamin A carotenoids are the main source of vitamin A intake of people living in northern region of Vietnam. There is no difference in consumption of carotenoids between rural and urban households. Among urban households retinol intake derived from animal food sources is about two times higher than in the rural areas. Dark-green leafy vegetables (mean intake 162 g/capita/day) are the main source for plant carotenoids, whereas fruit intake (52 g/capita/day) is rather low (Chapter 3). The poorer the household, the lower the intake of retinol.

This raises the question of how to solve micronutrient deficiencies in the low income groups. Follow up of the intake of retinol and carotenoids in various national food consumption surveys has shown that both retinol and provitamin A carotenoid consumption in households are rather low. Mean retinol intake was 20 μg/h/d in 1985 [31], was 30 μg/h/d in 1990 [32] and was as high as 89.3 μg/h/d in 2000 [33]. Mean intake of carotenoids was 2000 μg/h/d in 1985, was 2310 μg/h/d in 1990 [32] and 3109 μg/h/d in 2000 [33]. However, very large variations between households were observed. Another ten year-follow up study [34] showed that while retinol intake in 1995 was significantly higher than that in 1985, the intake of carotenoids remained the same.

A study conducted in the Red River delta region of Vietnam by Ninh *et al* reported a proportion of lactating mother who had low breast milk retinol concentration as high as 56.3% [35]. This suggest a situation were adults, especially women during pregnancy and lactation, have a high risk of vitamin A deficiency due to a low consumption of retinol rich foods (Chapter 3), while supplementation programs mainly target to young children (Chapter 5).

However, also in infants younger than 6 months the prevalence of vitamin A deficiency and anemia is high and it should be a concern in policies for vitamin A supplementation and improving maternal vitamin A and iron status (Chapter 2). In the situation of a low intake of retinol in the population and a high prevalence of childhood malnutrition (like in Vietnam) a universal supplementation with a periodical high dose vitamin A seems to be the best possible approach. There is a need to strengthen the delivery network to attain a high coverage rate of vitamin A distribution in infants and in lactating mothers. Vietnamese women at reproductive age are still at high risk of iron deficiency anemia, chronic energy deficiency and vitamin A deficiency [36-39]. Socioeconomic factors and also cultural factors including feeding habits do influence the nutritional welfare of the household member in the period of economic transition, now happening in Vietnam [40]. That holds especially for women.

The role of plant food sources in the prevention of vitamin A deficiency in Vietnam seems to be modest while achievement in reducing vitamin A deficiency in children is resulted mainly from vitamin A supplementation programs (Chapter 5).

With regard to the promotion of fruit and vegetable consumption which is highly recommended by WHO as the measure of choice to prevent chronic diseases, the low consumption of fruits and vegetables in the studied population in Vietnam is a critical point. As a traditional way of family food production practice in Vietnam, we need to promote the VAC system (home gardening, fish culture and animal husbandry) in rural communities and encouraging the consumption of fruits and vegetables by people, including young children. It needs further strategy to address this problem.

Implication for policies for controlling vitamin A deficiency in Vietnam.

Based on the findings presented and evidences from other studies it can be concluded that approaches other than the promotion of fruits and vegetables are required for eliminating vitamin A deficiency in Vietnam. It is necessary to look for ways of promoting or providing retinol-rich foods, such as eggs, meats, liver, dairy products, processed foods rich in retinol and/or vitamin A fortified foods. Combined approaches are important and include better health care services, immunization and control of infectious diseases, especially control of parasite infestations. For developing countries like Vietnam, to find a solution for vitamin A fortification in foods is of critical consideration. Another approach might be “bio-fortification”, thus the promotion of genetically modified plants such as “Golden Rice” rich in β-carotene and other micronutrients. Although the dark-green leafy vegetables are less effective in improving vitamin A status, it does not mean that increased consumption should not be encouraged. Dark-green leafy vegetables are not only a provitamin A provider, but are an important provider for may other nutrients as well.

For future research, it is necessary to evaluate the effectiveness of food-based programmes to control vitamin A deficiency and to measure the role of different kinds of carotenoid food sources in improving vitamin A status in different population groups. The impact of various parasitic infestations on the bioavailability of carotenoids from ingested foods should be further studied.

REFERENCES

1. Sommer A & West Jr KP. Vitamin A deficiency: Health, Survival, and Vision. New York 1996: Oxford University Press.
2. Semba RD, Bloem MW. The anemia of vitamin A deficiency: epidemiology and pathogenesis. Eur J Clin Nutr 2002; 56: 271-281.
3. West KP. Extent of vitamin A deficiency among preschool children and women of reproductive age. J Nutr 2002; 132: 2857S-2866S.
4. ACC/SCN-IFPRI. Fourth report on world nutrition situation. Geneva, 2000. ACC/SCN in collaboration with IFPRI.
5. West KP, Katz J, Khatry SK, LeClerg SC, Pradhan EK, Shrestha SR, Connor PB, Dali SM, Christian P, Pohkrel PR and Sommer A. Double blind, cluster randomized trial of low dose supplementation with vitamin A or beta carotene on mortality related to pregnancy in Nepal. BMJ 1999; 31: 570-575.

6. Beaton GH, Martorell R, Aronson KJ, Edmonston B, Mccabe AC, Ross AC, Harvey B. 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, 1993.
7. IVACG. Statement on vitamin A and iron interactions. Washington DC, IVACG, ILSI 1998.
8. Nguyen Cong Khan, Le Danh Tuyen, Tran Xuan Ngoc, Phan Hoai Duong, Ha Huy Khoi . Child malnutrition reduction in Vietnam from 1990 to 2004: The trends and factors related. Vietnam Statistical Publishing house, Hanoi, 2005.
9. The Micronutrient Initiative (MI). Progress in controlling vitamin A deficiency. MI/UNICEF/Tulane University; MI 1998.
10. Kus Hardjanti. Special evaluation study of selected ADB interventions on Nutrition and Food fortification. Asian Development Bank, March 2005.
11. Wolf G. A historical note on the mode of administration of vitamin A for the cure of night blindness. Am J Clin Nutr 1978; 31: 290-292.
12. Bloch CE. Further clinical investigation into the diseases arising in consequence of a deficiency in the fat-soluble A factor. Am J Dis Child 1924; 28: 659-667.
13. Arroyave G, Mejia LA, Aguilar JR. The effect of vitamin A fortification of sugar on serum vitamin A levels of preschool Guatemalan children: a longitudinal evaluation. Am J Clin Nutr 1981; 34: 41-29.
14. Gillespie S and Lawrence H. Attacking the double burden of malnutrition in Asia and the Pacific. ADB and IFPRI, 2001.
15. Saskia de Pee and Clive E West. Dietary carotenoids and their role in combating vitamin A deficiency: review of the literature. Eur J Clin Nutr 1996; 50 (suppl 2): S38-S53.
16. Binns CW, Lee AH, Jian L, Zhang M. Vegetable intake and cancer risk in Hangzhou China. Abstract, 18th International Congress of Nutrition, Sep 19-23, 2005, Durban, South Africa, P 49.
17. Jacqueline JM Castenmiller, Clive E West, Jozef PH Linssen, Karin H van het Hof, Alphons GJ Voragen. The food matrix of spinach is a limiting factor in determining the bioavailability of β-carotene and to a lesser extant of lutein in human. J Nutr 1999; 129: 349-355.
18. Suzana Shahar, Azhar Yusoff and Fatimah Arshad. Association between dietary Fibre and Cancer: A case-control study in Malaysia 2004. Malaysia J Nutr 10 (2): 173-182.
19. Pomerleau J, Lock K, Knai C, Mckee M. The effectiveness of interventions and programmes promoting fruit and vegetable intake. Abstract, 18th International Congress of Nutrition, Sep 19-23, 2005, Durban, South Africa, P.50.
20. The Fifty-Seventh World Health Assembly. Global strategy on diet, physical activity and health. Agenda item 12.6; WHA 57.17; 22 May 2004.
21. Nierenberg DW, Dain BJ, Mott LA, Baron JA, Greenberg ER. Effect of 4 y of oral supplementation with carotene on serum concentrations of retinol, tocopherol and five carotenoids. Am J Clin Nutr 1997; 66: 315-319.
22. Saskia de Pee, Clive E West, Muhilal, Darwin Karyadi, Joseph GAJ Hautvast. Lack of improvement in Vitamin A status with increased consumption of dark-green leafy vegetables.

Lancet 1995; 346: 75-81.

23. Saskie de Pee, Clive E West, Permaesih D, Martuti S, Muhilal and Joseph GAJ Hautvast. Orange fruit is more effective than are dark-green, leafy vegetables in increasing serum concentration of retinol and β-carotene in school children in Indonesia. Am J Clin Nutr 1998; 68: 1058-1067.
24 Machteld van Lieshout, Clive E West, Muhilal, Dewi Permaesih, Yan Wang, Xiaoying Xu, Richard B et al. Bioefficacy of β-carotene dissolved in oil studied in children in Indonesia. Am J Clin Nutr 2001; 73: 949-958.
25. Jackson MJ. The assessment of bioavailability of micronutrient: Introduction. Eur J Clin Nutr 1997; 51 (suppl): S1-S2.
26. Jacqueline JM Castenmiller, Clive E West. Bioavailability of carotenoids. Pure Appl Chem 1997; 69: 2145-2150.
27. Brown ED, Micozzi MS, Craft NE, Bieri JG, Beecher G, Edwards BK, Rose A, Taylor PR, Smith JC. Plasma carotenoids in normal men after a single ingestion of vegetables or purified β-carotene. Am J Clin Nutr 1989; 49: 1258-1265.
28. Hof KH van het, Brouwer IA, Clive E West, Haddeman E, Steegers-Theunissen RPM, van Dusseldorp M, Weststrate JA, Eskens TKAB, Hautvast JGAJ. Bioavailability of lutein from vegetables is 5 times higher than that of β-carotene. Am J Clin Nutr 1999a; 70: 261-268.
29. Roodenburg AJ, Leenen R, van het Hof KH, Weststrate JA, Tijburg LB. Amount of fat in the diet affects bioavailability of lutein esters but not alpha-carotene, beta-carotene, and vitamin E in humans. Am J Clin Nutr 2000; 71: 1187-93
30. Rock CL, Swendseid ME. Plasma β-carotene response in humans after meals supplemented with pectin. Am. J Clin Nutr 1992;55:96-99.
31. Ha Huy Khoi. Protein energy nutritional status of rural people in some regions of Vietnam. Thesis. Warszawa, 1990: 30-34.
32. Ministry of Health Vietnam and World Bank. Report on re-analyzing data collected by General Nutrition Survey made in 1987-1989 (by National Institute of Nutrition, Vietnam), Hanoi, 1991.
33. National Institute of Nutrition, Vietnam. 2000 General Nutrition Survey. The Medical Publishing house, Hanoi, 2003: 72.
34. Le Bach Mai. Changing the actual food consumption and nutritional status of households in some areas after ten-year follow-up. National Institute of Nutrition and National Institute of Epidemiology, 2003.
35. Ninh NX, Quyen DT, Thu NN, Hien VT, Nhien NV, Quang T, Khan NC. Subclinical vitamin A deficiency and some related risk factors among children and lactating mothers in the Red river delta provinces in 1988. In “20 years of prevention and control of micronutrient deficiencies in Vietnam: Research and development 1980-2000”. National Institute of Nutrition, Vietnam. Hanoi Medical Publishing House 2001: 113-126.
36. Giay T, Khoi HH, Ninh NX, Nhan BT, Hanh MT. Some epidemiological characteristics of nutritional anaemia in women at procreative age in rural areas and Hanoi city. J Prac Med Hanoi 1990; 3:17-18.

37. Hop LT, Hoa PT, Hau CT, & Khoi HH. Nutritional status of pregnant and breastfeeding women at central Hanoi city and some North rural areas. J Hygiene Epidemiol Hanoi, 1991; 48: 3.
38. Giay T, Khoi HH. Use Body Mass Index in the assessment of adult nutritional status in Vietnam. Eur J Clin Nutr 1994; 48; sppl 3: S124-S130.
39. Khoi HH, Khan NC, Hien VT, Quang T. Preliminary study on relationship between vitamin A deficiency anaemia in pregnant women. Vietnam J Med Hanoi 1994; 7;182: 11-15.
40. David Dollar, Paul Gewwe and Jennie Litvack. Household welfare and Vietnam's transition. World Bank, Washington DC, 1998.

SUMMARY

Vitamin A deficiency is in many developing countries one of the most important nutritional problems. Vitamin A deficiency increases morbidity and mortality of infants, children, and pregnant women, is responsible for poor growth of children and possibly also increases mortality and morbidity of infants infected with HIV. The main cause of vitamin A deficiency is low intake of retinol-rich foods, be it naturally rich in retinol or fortified with the vitamin. In plant foods including dark-green leafy vegetables, yellow and orange fruits, red and orange roots and tubers such as carrots and red sweet potato β-carotene is the main provitamin A. Carotenoids such as β-carotene are the major source of vitamin A in the diet of many people in the developing world. Unfortunately the bioavailability of carotenoids in fruits and vegetables is lower than previously assumed, especially in dark-green leafy vegetables.

To combat vitamin A deficiencies a food-based approach using foods naturally rich in vitamin A is preferable for many developing countries. And with that, factors affecting the bioavailability of carotenoids are important.

The papers in this thesis focus on the prevalence of sub clinical vitamin A deficiency in children, the intake of retinol and carotenoids in the diets of Vietnamese, in the role of plant foods in the contributing of dietary vitamin A intake in breastfeeding women in Vietnam and the policies that have been implemented in Vietnam to combat vitamin A deficiency.

To assess the prevalence of sub clinical vitamin A deficiency and anemia in children, a cross-sectional survey was conducted in 40 villages (clusters) in four ecological regions in Vietnam. In total 1,657 children under 5 years of age were selected for study (Chapter 2). 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 children younger than 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%. Sub clinical vitamin A deficiency and anemia are important public health problems in Vietnam and differ significantly across the regions, with the highest prevalence in the northern mountainous areas.

To investigate the household intakes of retinol and carotenoids and to find social economic factors related to their intakes, a cross-sectional household based survey with 30 randomly selected clusters in the Red river delta region of northern Vietnam was conducted (Chapter 3). Food consumption was assessed using the 24 hours dietary recall method. Data were collected in a total of 1,001 households (771 in rural area and 230 in

urban area). The results show that in the Red River Delta region of Vietnam, dark-green leafy vegetables (mean intake of 162 g/capita/day) are the main source for plant carotenoids, while fruit consumption is rather low (mean intake 52 g/capita/day). Fat and oil consumption were also rather low and this may be a limitating factor in the carotene absorption. The mean (SD) carotenoid intake was 4,178 (3,154) μg/capita/day in rural and 4,208 (3,408) μg/capita/day in urban areas and intake of retinol was 101 (275) μg/capita/day in rural and 201 (470) μg/capita/day in urban areas. A large variation between households was found. Among urban households retinol intake derived from animal food sources was about two times higher than in the rural areas. Households with a higher (household) expenditure (4^{th} quartile) consumed about 100 μg retinol /day more than those with a lower expenditure (1^{st} quartile). This study indicates that carotenoids from plant foods are the main source of vitamin A intake among the Red River delta population in Vietnam. Household expenditure and number of household members are the main determinants for retinol intakes.

Promotion of consumption of animal-based foods and developing vitamin A fortified foods should be a critical point in food-based strategies for controlling vitamin A deficiency.

In order to quantify the efficacy of provitamin A-rich vegetables and fruits for improving vitamin A status, an intervention study was carried out in nine rural communes in Thai Nguyen Province, Northern Vietnam, about 60 km from Hanoi (Chapter 4). Anemic breastfeeding women with an infant aged 5-15 month, and no chronic illness participated in the study. The subjects were randomly allocated to four groups to receive full lunch and full dinner every day for 6 d/wk for a period of 10 wk: Group 1: vegetable group (n = 73) the meals provided 5.6 mg β-carotene/d from green leafy vegetables; Group 2: Fruit group (n = 69) the meals provided 4.8 mg β-carotene/d from orange, yellow fruits; Group 3: Retinol-rich group (n = 70) the meals provided 610 μg retinol/d from animal foods and 0.6 mg β-carotene/d. Group 4: Control group (n = 68) the meals provided 0.4 mg β-carotene/d. Meals of groups 1, 2 and 4 contained <30 μg retinol/d. The rate of dropout was 6% and more than 90% of the food provided was consumed. The results show that there were no significant differences in serum concentrations of retinol and carotenoids at baseline among groups. Mean (95%CI) changes in serum retinol concentration of the retinol-rich, fruit, vegetable and control groups were 0.25 (0.17; 0.33), 0.13 (0.06-0.18), 0.09 (0.04; 0.27) and 0.00 (-0.06; 0.06) μmol/L respectively. Mean (95%CI) changes in breast milk retinol concentration were 0.49 (0.32; 0.64), 0.14 (0.07; 0.27), 0.15 (0.04; 0.27), -0.07 (-0.21; 0.07) respectively. At the end of the follow-up, serum concentrations of retinol were 24% increased in the retinol-rich group compared to the control group, whereas both in the vegetable and fruit group the increase was only 12%.

Based on these findings, the equivalent of 1 μg retinol would be 12 μg β-carotene (95% CI: 8; 22) for fruit and 28 μg β-carotene (17; 84) for green leafy vegetables. Thus, the apparent conversion factors for β-carotene to retinol found in this study are 12:1 for fruit and 28:1 for green leafy vegetables. They confirm the findings from a study in Indonesian children study and support the conversion factor proposed by West et al of 21:1 for dietary β-carotene from a mixed diet.

Therefore, food based-approaches for combating vitamin A deficiency need to promote consumption of vitamin A from fruit, animal food and fortified food, besides maximizing consumption and bioavailability of carotenoids from dark-green leafy vegetables.

Further research should focus on quantifying the impact of parasitic infection and various food matrices on the bioefficacy of β-carotene, on inter-individual variation in response to intake of dietary provitamin A carotenoids, on finding good biomarkers of fruit and vegetable intake, and on estimating the absorption of carotenoids with antioxidant activity that may play a role in lowering the risk of cancer and cardiovascular disease.

The vitamin A deficiency control programs in Vietnam were started in 1992 and comprised nutrition education; universal distribution of high dose vitamin A capsules to children aged 6 to 36 months in combination with national immunization days and promotion of production and consumption of vitamin A-rich foods at family level (Chapter 5). An implementation network was set up based on the existing preventive health structure at all administrative levels. Vitamin A distribution programs have been actively promoted by mass organizations such as the women's union and other social sectors. Two distribution campaigns are held in and December (integrated with National immunization days; NIDs). This approach provides supplements to the targeted population through the health care system. Although the coverage rate of high dose vitamin A supplementation was reported very high among targeted children, sub clinical vitamin A deficiency is still a public health concern (Chapter 2). In addition, the coverage of vitamin A supplementation in breastfeeding women is still low (Chapter 5) and vitamin A intake by households is not adequate (Chapter 3). Vitamin A supplementation policies should continue, but more attention should be given to supplementation in remote regions and to vulnerable groups as lactating mothers after giving birth at the clinics and in community.

In summary, our study showed:

1. Dark-green leafy vegetable and yellow and orange fruits contribute not much in improving vitamin A status of breastfeeding women in Vietnam.

2. Several factors affect the poor bioavailability of carotenoids from plant food source. We confirmed the findings of other studies who found apparent conversion factors of carotenoids to retinol 12:1 for fruits and 26:1 for vegetables.

3. Retinol intake and intake of carotenoids by the population in the Red River Delta region of Vietnam are not adequate. Socioeconomic factors and household size are important determinants of retinol intake in that population.

4. Although a remarkable success have been achieved in vitamin A control programs in Vietnam, sub clinical vitamin A deficiency is still a public health problem. High risk groups for vitamin A deficiency are children under one year of age, especially those under 6 months of age.

These findings suggest that approaches other than the promotion of fruits and vegetables are required for eliminating vitamin A deficiency. It seems necessary to continue the current efforts of mass supplementation and to slowly turn to combination strategies in controlling micronutrient deficiencies.

ALGEMENE SAMENVATTING

In veel ontwikkelingslanden is vitamine A deficiëntie een van de meest voorkomende voedingsproblemen. Als gevolg van vitamine A deficiëntie is ziekte en sterfte onder zuigelingen, jonge kinderen en zwangere vrouwen verhoogd, terwijl ook de groei in kinderen vertraagd is. Recente studies suggereren dat ook de ziekte en sterfte bij kinderen met HIV-infectie verhoogd is.

De belangrijkste oorzaak van vitamine A deficiëntie is een lage opneming van retinol-rijke voedingsmiddelen, zij het voedingsmiddelen die van nature rijk zijn aan retinol of die kunstmatig zijn verrijkt met retinol. In plantaardige voedingsmiddelen zoals groene bladgroente, geel en oranje fruit, rode en oranje wortelen en knollen en de rode zoete aardappel is β-caroteen het belangrijkste provitamine A.

Carotenoïden zoals β-caroteen zijn de belangrijkste bron van vitamine A in de voeding van het merendeel van de mensen in ontwikkelingslanden. Ongelukkigerwijs is de biologische beschikbaarheid van carotenoïden in groente en fruit veel lager dan oorspronkelijk aangenomen. Dit geldt met name voor de carotenoïden uit groene bladgroente.

In ontwikkelingslanden is een op voedingsmiddelen gebaseerde benadering ter bestrijding van endemische vitamine A deficiëntie te preferen boven andere methodes.

Hierdoor is kennis van de biologische beschikbaarheid van retinol en carotenoides belangrijk.

De hoofdstukken in dit proefschrift beschrijven achtereenvolgens de prevalentie van subklinische vitamine A deficiëntie in kinderen van 1 tot 5 jaar, de opneming van retinol en carotenoïden in de Vietnamese voeding en factoren die daarop van invloed zijn, en de rol die plantaardige carotenoïden spelen in de totale opneming van vitamine A met de voeding van vrouwen die borstvoeding geven. In het laatste hoofdstuk worden de verschillende maatregelen die de afgelopen tien jaar in Vietnam zijn genomen ter bestrijding van endemische vitamine A deficiëntie besproken en geëvalueerd.

De prevalentie van subklinische vitamine A deficiëntie en van anemie is bestudeerd in een cross-sectioneel onderzoek in 40 dorpen verspreid over de vier ecologische regio's in Vietnam. In totaal namen 1657 kinderen, in leeftijd variërend van 1 tot 5 jaar, aan het onderzoek deel (hoofdstuk 2). De prevalentie van subklinische vitamine A deficiëntie, gedefiniëerd als een serum retinol waarde beneden 0.70 µmol/l, was 12.0 percent terwijl de prevalentie van anemie (hemoglobine gehalte lager dan 110 g/l) 28.4 percent was. In kinderen jonger dan 6 maanden was de prevalentie van subklinische vitamine A deficiëntie 35.1 percent and de prevalentie van anemie 61.7 percent.

Geconcludeerd kan worden dat zowel subklinische vitamine A deficiëntie als ook anemie nog steeds belangrijke volksgezondheidsproblemen zijn in Vietnam en dat de prevalentie verschilt per regio waarbij de hoogste prevalentie voor beide deficiënties gevonden wordt in de bergachtige gebieden in het noorden van Vietnam

De opneming van retinol en van carotenoïden met de voeding alsmede sociaal-economische factoren die van invloed zijn op de opneming werd onderzocht in een cross-sectionele studie in 30 leefgemeenschappen, willekeurig geselecteerd in de Red River delta regio in het noorden van Vietnam (hoofdstuk 3). Voedselconsumptie werd bepaald met behulp van de 24-uurs opschrijfmethode. In totaal werd de opneming nagevraagd in 1001 huishoudens (771 platteland en 230 stedelijk). De resultaten van de studie laten zien dat groene bladgroente de belangrijkste bron van plantaardige carotenoïden was (gemiddelde opneming 162 g/persoon/day) terwijl de opneming van fruit relatief laag was met 52 g/persoon/dag. Ook de opneming van voedingsvet was relatief laag. Dit kan een beperkende factor zijn bij de absorptie van de carotenoïden. De gemiddelde (SD) opneming van carotenoïden was 4178 (3154) µg/persoon/dag in landelijke gebieden en 4208 (3408) µg/persoon/dag in stedelijke gebieden. De opneming van retinol was 101 (275) µg/persoon/day en 201 (470) µg/persoon/day in respectievelijk landelijk en stedelijk gebied. De huishoudens verschilden onderling zeer sterk in opnemingpatroon. De opneming van retinol in huishoudens met een hoger bestedingspatroon (vierde kwartiel) was ongeveer 100 µg/dag hoger dan in huishoudens met een lager (eerste kwartiel) bestedingspatroon.

De studie laat zien dat carotenoïden uit plantaardige bronnen de belangrijkste bron zijn voor de vitamine A voorziening van de bevolking van de Red River delta in het noorden van Vietnam. Huishoudbestedingspatroon en aantal mensen per huishouden zijn de belangrijkste determinanten voor retinol opneming. Stimulering van consumptie van dierlijke produkten en ontwikkeling van met retinol verrijkte voedinsgmiddelen moeten een belangrijk uitganspunt zijn in op voedingsmiddelen gebaseerde strategieën ter bestrijding van vitamine A deficiëntie.

Om de efficiëntie te bepalen van de verstrekking van provitamine A rijke groentes en fruit in de verbetering van de vitamine A status is een interventie studie uitgevoerd in 9 landelijke dorpen in de provincie Thai Nguyen in het noorden van Vietnam, ongeveer 60 km van Hanoi (hoofdstuk 4). Vrouwen met anemie, die hun kinderen (5 – 15 maanden) borstvoeding gaven, participeerden in de studie. De vrouwen werden willekeurig verdeeld over 4 groepen en kregen elke dag (6 dagen per week) gedurende 10 weken middagmaaltijd en avondmaaltijd verstrekt. Group 1: de groente groep (n = 73), de maaltijden voorzagen in 5.6 mg β-caroteen/d afkomstig uit groene bladgroente; Groep 2: de fruit groep (n = 69), de maaltijden voorzagen in 4.8 mg β-caroteen/d afkomstig uit oranje/geel fruit; Groep 3: de retinol groep (n = 70), de maaltijden voorzagen in 610 µg retinol/d afkomstig uit dierlijke produkten plus 0.6 mg β-caroteen/d. Groep 4: de controle groep (n = 68), de maaltijden voorzagen in 0.4 mg β-caroteen/d. De maaltijden van groep 1, 2 en 4 bevatten minder dan 30 µg retinol/d. Vierennegentig percent van de vrouwen voltooiden de studie en het verstrekte voedsel werd voor meer dan 90 percent geconsumeerd.

Er waren geen significante verschillen in serum retinol en serum carotenoïden tussen de groepen aan het begin van de studie. De gemiddelde verandering (95%CI) in serum retinol in de retinol, de groente, de fruit en de controle groep waren respectievelijk 0.25 (0.17; 0.33), 0.13 (0.06-0.18), 0.09 (0.04; 0.27) en 0.00 (-0.06; 0.06) µmol/l. De gemiddelde veranderingen (95%CI) in retinol waardes in moedermelk waren respectievelijk 0.49 (0.32; 0.64), 0.14 (0.07; 0.27), 0.15 (0.04; 0.27) en -0.07 (-0.21; 0.07). Percentueel nam de serum retinolconcentratie met 24 percent toe in de retinol groep tegen maar 12 percent in de groente en fruit groep. Hieruit kan worden berekend dat de omrekeningsfactor voor retinol uit β-caroteen 1 op 12 is (95%CI: 8, 22) voor fruit en 1 op 28 (95%CI: 17-84) voor groene bladgroente.

Deze gegevens zijn vergelijkbaar met de resultaten van een studie in Indonesische kinderen en bevestigen de omrekeningsfactor van 1 op 21 voor β-caroteen in een gemengde voeding zoals voorgesteld door West. Uit de resultaten kan de conclusie worden getrokken dat programmas ter bestrijding van vitamine A deficiëntie gebaseerd moeten zijn op een aanbeveling van zowel vitamine A opneming uit dierlijke producten als ook van caroteen uit groente en fruit.

Toekomstig onderzoek zou aandacht moeten besteden aan de invloed van parasiet infecties, de invloed van de voedingssamenstelling op de biobeschikbaarheid van β-caroteen met name uit groene bladgroente, en aan inter-individuele variatie. Het zou hulpzaam zijn als er goede indicatoren beschikbaar zouden zijn voor de consumptie van groente en fruit en voor de absorptie van carotenoïden . Ook de rol die anti-oxidanten spelen in de absorptie zou nader bestudeerd moeten worden, mede ook in verband met het risiko voor kanker en voor hart- en vaatziekte.

Programmas ter bestrijding van vitamine A deficiëntie in Vietnam begonnen in 1992 en besteden aandacht aan voedingsvoorlichting naast de verstrekking van vitamine A capsules twee maal per jaar speciaal aan kinderen tussen 6 en 36 maanden. De supplementatie valt samen met de halfjaarlijkse immunisatie programmas (hoofdstuk 5). Speciaal voor dit doel is een netwerk opgezet gebaseerd op de bestaande preventieve gezondheidszorg en het is geïmplementeerd op alle niveaus. De vitamine A distributie programmas worden aktief ondersteund door non-profit organisaties zoals de 'Women's Union' (Vrouwenbeweging). De vitamine A distributie campagnes in juni en december richten zich vooral op de doelgroepen en de dekkingsgraad in kinderen is erg hoog. Ondanks dat is de prevalentie van subklinische vitamine A deficiëntie nog steeds relatief hoog (hoofdstuk 2). Ongelukkigerwijs is de supplementatie ook niet dekkend in zogende vrouwen (hoofdstuk 2) en de opneming van vitamine A in de bevolking is nog steeds niet voldoende of is marginaal (hoofdstuk 3)

De vitamine A supplementatie programmas in Vietnam zouden moeten worden gecontinueerd maar er zou meer aandacht moeten worden besteed aan vitamine A verstrekkingen in afgelegen gebieden en aan kwetsbare groepen zoals vrouwen na de bevalling, zowel in kliniek als thuis, en aan moeders die borstvoeding geven.

Samenvattend kan worden geconcludeerd:

1. In Vietnam, groene bladgroente en geel en oranje fruit dragen onvoldoende bij aan de verbetering van de vitamine A status van moeders die borstvoeding geven
2. Verschillende factoren beinvloeden de biologische beschikbaarheid van carotenoïden uit plantaardige voedselbronnen. De omrekeningsfactoren van carotenoïden naar retinol, (12:1 voor fruit en 26:1 voor groente) zoals gevonden in andere recente studies worden in deze studie bevestigd.
3. Opneming van retinol en carotenoïden in de Red River delta regio in het noorden van Vietnam is niet voldoende. Sociaal-economische factoren en grootte van het huishouden zijn belangrijke determinanten voor de retinol opneming.
4. Ofschoon opmerkelijke successen zijn geboekt in de programmas ter bestrijding van vitamine A deficiëntie in Vietnam, is subklinische vitamine A deficiëntie nog steeds een volksgezondheidsprobleem. Risikogroepen voor vitamine A deficiëntie zijn jonge kinderen, met name kinderen jonger dan 6 maanden.

De gegevens van deze studies suggereren dat benaderingen van de vitamine A problemetiek in Vietnam anders dan alleen de stimulering van groente en fruit consumptie nodig zijn. Een goede aanpak zou kunnen zijn de huidige programmas van massale vitamine A suppementatie voort te zetten en langzaam over te gaan op gecombineerde stategieën.

TÓM TẮT

Thiếu vitamin A là một trong những vấn đề sức khoẻ quan trọng hàng đầu ở các nước đang phát triển. Thiếu vitamin A làm tăng nguy cơ mắc bệnh và tử vong ở trẻ sơ sinh, trẻ nhỏ và bà mẹ có thai, làm giảm tăng trưởng ở trẻ nhỏ, và có thể làm tăng nguy cơ mắc bệnh và tử vong ở trẻ nhiễm HIV. Nguyên nhân quan trọng dẫn tới thiếu vitamin A là do khẩu phần ăn nghèo retinol, do ít tiêu thụ các thực phẩm tự nhiên chứa nhiều retinol hay thực phẩm có tăng cường vitamin A. Thực phẩm nguồn gốc thực vật có nhiều tiền vitamin A là các loại rau lá màu xanh xẫm, các loại quả có màu vàng, các loại củ có màu da cam và đỏ như cà rốt, khoai lang nghệ. Các dạng caroten như β-caroten là nguồn cung cấp vitamin A chính trong bữa ăn ở các nước đang phát triển. Nhưng đáng tiếc là theo các hiểu biết gần đây giá trị sinh học của caroten ở trong quả chín và rau xanh, kể cả rau có lá màu xanh xẫm, thấp hơn so với các tính toán trước đây.

Để phòng chống thiếu vitamin A, giải pháp dựa vào thực phẩm, trong đó việc sử dụng các thực phẩm nguồn gốc tự nhiên giàu vitamin A là giải pháp thích hợp đối với nhiều nước đang phát triển. Chính vì vậy việc quan tâm tới giá trị sinh học của caroten là rất quan trọng.

Các nghiên cứu trình bày trong luận văn gồm tìm hiểu tình trạng thiếu vitamin A tiền lâm sàng ở trẻ nhỏ; tình hình tiêu thụ retinol và caroten trong khẩu phần ăn của người Việt Nam; vai trò của thực phẩm nguồn gốc thực vật trong việc cung cấp vitamin A qua bữa ăn ở phụ nữ đang nuôi con bú và các giải pháp phòng chống thiếu vitamin A đang triển khai ở Việt Nam.

Để đánh giá tỉ lệ thiếu vitamin A tiền lâm sàng và thiếu máu ở trẻ em, một cuộc điều tra cắt ngang được thực hiện ở 40 thôn (cụm) thuộc 4 vùng sinh thái của Việt Nam với tổng số trẻ em dưới 5 tuổi là 1657 trẻ (Chương 2). Tỉ lệ thiếu vitamin A tiền lâm sàng (retinol huyết thanh <0,7µmol/L) là 12,0% và tỉ lệ thiếu máu (hemoglobin <110g/L) là 28,4%. Ở trẻ dưới 6 tháng tuổi, tỉ lệ thiếu vitamin A tiền lâm sàng là 35,1% và tỉ lệ thiếu máu là 61,7%. Thiếu vitamin A tiền lâm sàng và thiếu máu là các vấn đề sức khoẻ cộng đồng quan trọng ở Việt Nam; tỉ lệ thiếu vitamin A tiền lâm sàng và thiếu máu ở mỗi vùng sinh thái dao động khác nhau, vùng có tỉ lệ cao nhất là vùng miền núi phía Bắc Việt Nam.

Để đánh giá lượng retinol và caroten trong khẩu phần ăn vào của hộ gia đình và tìm hiểu các yếu tố kinh tế - xã hội liên quan, một nghiên cứu hộ gia đình được tiến hành ở 30 cụm chọn ngẫu nhiên thuộc vùng đồng bằng sông Hồng (Chương 3). Thông tin về tiêu thụ thực phẩm được thu thập bằng phương pháp hồi cứu hỏi ghi 24 giờ qua. Tổng số hộ gia đình được nghiên cứu là 1001 hộ (771 hộ ở nông thôn và 230 hộ ở thành thị). Kết quả điều tra cho thấy ở vùng đồng bằng sông Hồng, rau có lá màu xanh xẫm là nguồn cung

cấp caroten chính trong bữa ăn (162 g/người/ngày), trong khi đó lượng quả chín tiêu thụ khá thấp (52 g/người/ngày). Tiêu thụ dầu mỡ cũng tương đối thấp, đây có thể là yếu tố làm hạn chế hấp thu caroten. Lượng caroten trung bình là 4178 (± 3154) µg/người/ngày ở nông thôn và 4208 (± 3408) µg/người/ngày ở thành thị; lượng retinol trung bình là 101 (± 275) µg/người/ngày ở nông thôn và 201 (± 470) µg/người/ngày ở thành thị. Có sự khác biệt lớn về mức tiêu thụ retinol ở các hộ gia đình. Ở thành thị, lượng retinol từ nguồn thức ăn động vật cao hơn khoảng 2 lần so với ở nông thôn. Hộ gia đình có mức chi tiêu cao (nhóm chi tiêu 4) tiêu thụ nhiều hơn khoảng 100 µg retinol/ngày so với hộ gia đình có mức chi tiêu thấp hơn (nhóm chi tiêu 1). Nghiên cứu này cho thấy caroten từ rau, quả là nguồn vitamin A chính ở vùng đồng bằng sông Hồng. Chi tiêu hộ gia đình và số thành viên trong hộ là các yếu tố quyết định chính đến lượng retinol tiêu thụ. Nghiên cứu gợi ý rằng trong điều kiện thực tế hiện nay, cần coi việc khuyến khích tiêu thụ thực phẩm có nguồn gốc động vật và các thực phẩm tăng cường vitamin A là một mục tiêu quan trọng trong chiến lược phòng chống thiếu vitamin A dựa vào thực phẩm.

Để lượng hoá hiệu quả của rau quả có chứa nhiều tiền vitamin A đối với việc cải thiện tình trạng thiếu vitamin A, một nghiên cứu can thiệp được tiến hành ở 9 xã nông thôn tỉnh Thái Nguyên, phía Bắc Việt Nam, cách Hà Nội khoảng 60 km (Chương 4). Đối tượng nghiên cứu là bà mẹ đang cho con bú bị thiếu máu, có trẻ từ 5-15 tháng tuổi và không bị mắc bệnh mạn tính. Đối tượng được chia ngẫu nhiên thành 4 nhóm để nhận bữa ăn trưa và ăn tối hàng ngày (6 ngày/tuần trong vòng 10 tuần). Nhóm 1: nhóm Rau (n=73), bữa ăn cung cấp 5,6 mg β-caroten/ngày từ rau có lá màu xanh xẫm; nhóm 2: nhóm Quả chín (n=69), bữa ăn cung cấp 4,8 mg β-caroten/ngày từ quả có màu vàng; nhóm 3: nhóm thực phẩm giàu retinol (n=70), bữa ăn cung cấp 610 µg retinol/ngày từ thực phẩm có nguồn gốc động vật và 0,6 mg β-caroten/ngày; nhóm 4: nhóm chứng (n=68), bữa ăn cung cấp 0,4 mg β-caroten/ngày. Bữa ăn của các nhóm 1, 2 và 4 chứa <30 µg retinol/ngày. Tỉ lệ đối tượng nghiên cứu bỏ cuộc là 6% và tỉ lệ tiêu thụ thực phẩm có trong bữa ăn là hơn 90%. Kết quả nghiên cứu cho thấy không có sự khác biệt về retinol và caroten trong huyết thanh giữa các nhóm nghiên cứu trong điều tra ban đầu. Giá trị trung bình (95%CI) của retinol trong huyết thanh sau 10 tuần can thiệp ở các nhóm thực phẩm giàu retinol, Quả chín, Rau và nhóm chứng lần lượt là 0,25 (0,17; 0,33), 0,13 (0,06-0,18), 0,09 (0,04; 0,27) và 0,00 (-0,06; 0,06) µmol/L. Giá trị trung bình (95%CI) của retinol trong sữa mẹ sau 10 tuần can thiệp ở các nhóm này lần lượt là 0,49 (0,32; 0,64), 0,14 (0,07; 0,27), 0,15 (0,04; 0,27), và -0,07 (-0,21; 0,07) µmol/L. Sau nghiên cứu, lượng retinol huyết thanh tăng 24% ở nhóm thực phẩm giàu retinol so với nhóm chứng, trong khi đó chỉ tăng 12% ở nhóm Rau và Quả chín.

Các kết quả trên cho thấy 1 µg retinol tương đương với 12 µg β-caroten (95% CI: 8; 22) đối với quả chín và tương đương với 28 µg β-caroten (17; 84) đối với rau có lá màu xanh xẫm. Như vậy, tỷ lệ chuyển đổi β-caroten sang retinol trong nghiên cứu này là 12:1 đối với quả chín và 28:1 đối với rau có lá màu xanh xẫm. Các kết quả này nhất quán với kết quả nghiên cứu ở trẻ Inđônêxia của tác giả West và CS với tỷ lệ chuyển đổi là 21:1 đối với β-caroten từ chế độ ăn hỗn hợp.

Như vậy, phương pháp tiếp cận dựa vào thực phẩm để phòng chống thiếu vitamin A nên khuyến khích việc tiêu thụ vitamin A từ quả chín, thực phẩm có nguồn gốc động vật và thực phẩm tăng cường vitamin A, bên cạnh đó cũng cần quan tâm tới giải pháp làm tăng giá trị sinh học của caroten từ rau có lá màu xanh xẫm. Nghiên cứu tiếp theo nên tập trung vào việc lượng hoá ảnh hưởng của nhiễm ký sinh trùng và tương tác của các loại thực phẩm khác nhau đến hiệu quả sinh học của β-caroten và sự khác biệt giữa các cá thể đối với tiêu hoá, hấp thu caroten; tìm hiểu các chỉ điểm sinh học nhạy của tiêu thụ rau quả cũng như vấn đề hấp thu caroten với tư cách là các chất chống ôxy hoá trong việc hạ thấp nguy cơ mắc bệnh ung thư và tim mạch.

Chương trình phòng chống thiếu vitamin A ở Việt Nam được triển khai từ năm 1992, bao gồm giáo dục dinh dưỡng, chương trình phân phối viên nang vitamin A liều cao cho trẻ 6-36 tháng tuổi kết hợp với ngày tiêm chủng toàn quốc, và hoạt động khuyến khích sản xuất và tiêu thụ thực phẩm giàu vitamin A ở cấp hộ gia đình (Chương 5). Mạng lưới triển khai được thành lập dựa trên cơ sở mạng lưới y tế dự phòng ở tất cả các cấp. Nhiều ban ngành đã tham gia tích cực vào chương trình phân phối vitamin A như hội phụ nữ và các tổ chức xã hội khác. Hai chiến dịch uống vitamin A được tổ chức vào tháng 6 và tháng 12 (kết hợp với ngày tiêm chủng toàn quốc) thực hiện việc bổ sung vitamin A liều cao cho các đối tượng đích thông qua hệ thống y tế. Mặc dù tỉ lệ bao phủ viên nang vitamin A liều cao là khá cao ở trẻ em, nhưng thiếu vitamin A tiền lâm sàng vẫn đang là vấn đề sức khoẻ cộng đồng (Chương 2). Ngoài ra, tỉ lệ bao phủ vitamin A ở phụ nữ đang cho con bú vẫn còn thấp (chương 5) và lượng vitamin A trong khẩu phần ăn của đối tượng này cũng còn thấp (Chương 3). Cần tiếp tục triển khai các chương trình bổ sung vitamin A, đặc biệt chú ý hơn vào các vùng khó khăn và nhóm đối tượng có nguy cơ cao như phụ nữ sau sinh ở các bệnh viện và trong cộng đồng.

Tóm lại, nghiên cứu này cho thấy:

1. Rau lá màu xanh xẫm và quả chín màu vàng đóng góp không nhiều vào việc cải thiện tình trạng vitamin A ở phụ nữ đang cho con bú ở Việt Nam.
2. Rất nhiều yếu tố ảnh hưởng đến giá trị sinh học của caroten từ thực phẩm có nguồn gốc thực vật. Nghiên cứu này khẳng định kết quả của các nghiên cứu

khác về tỉ lệ chuyển đổi caroten sang retinol là 12:1 đối với quả chín và 26:1 đối với rau xanh.

3. Lượng retinol và caroten trong khẩu phần ăn của người dân vùng đồng bằng sông Hồng Việt Nam còn thấp. Các yếu tố kinh tế - xã hội và cỡ hộ gia đình có vai trò quan trọng đối với khẩu phần retinol ăn vào.

4. Mặc dù chương trình phòng chống thiếu vitamin A ở Việt Nam đã đạt được những thành công đáng kể, thiếu vitamin A tiền lâm sàng vẫn còn là vấn đề sức khoẻ cộng đồng. Nhóm đối tượng có nguy cơ thiếu vitamin A tiền lâm sàng cao là trẻ dưới 1 tuổi, đặc biệt là trẻ dưới 6 tháng tuổi.

Những kết quả từ nghiên cứu này gợi ý rằng bên cạnh việc khuyến khích tiêu thụ rau xanh quả chín, cần có các tiếp cận khác nhau để giải quyết tình trạng thiếu vitamin A. Cần tiếp tục duy trì các chiến dịch bổ sung vitamin A và dần chuyển sang các chiến lược lồng ghép kết hợp trong hoạt động phòng chống thiếu vi chất dinh dưỡng.

ACKNOWLEDGEMENTS

Professor Hautvast, I am very grateful to you, not only for offering me the possibility to do a PhD in Nutrition, but also because of your constant stimulation, your continuous interest and your support for many years. You are not only the person that did set a milestone for close collaboration in nutrition between Vietnam and The Netherlands, but you personally spent considerable time making arrangements for me to continue my PhD despite my busy schedule. Anytime you visited Vietnam, you were asking me to work out a plan for the completion of my thesis. You created support for me to continue writing the papers. You have made many links and always pushed things ahead. Thanks for your kind, innovative and enthusiastic help and for your strong leadership.

I am also grateful for the help and support I received from the late professor Clive West for his unlimited support in my academic work. Clive had always excellent ideas, wise suggestions and showed in his support friendship and encouragement. I remember, 20 years ago in 1986, that Clive came to Vietnam to give a speech at a national seminar on control of vitamin A deficiency and xerophthalmia at which occasion he gave a strong recommendation to NIN to begin with the implementation of vitamin A deficiency programs and to start research on vitamin A. He then introduced me to the training course on xerophthalmia in Bogor with Dr Muhilal. In 1990 Clive suggested to do a PhD in Wageningen, but it took 5 years to get it started. In 2001 when I was in Wageningen, Clive still gave a very strong support for my research despite his awareness about his disease. In 2004, in the last months of his life, he asked me over the phone to complete my thesis soon so that the defense would happen while he is still alive.

I am also so grateful to Helen, his wife, for her kindness and encouragements and to allow me to work with Clive during his “time off” and his time in Vietnam.

Thanks also to professor Frans Kok and the staff of the Division of Nutrition for their support to have me defend the thesis at the Wageningen University. In May 2002, professor Kok came to Vietnam to visit NIN and discussed with me the progress of the thesis with very encouraging ideas. For your patience that it still took so long since then I am grateful.

I am deeply indebted to professor Ha Huy Khoi, former director of NIN, Vice-president of the Vietnam Nutrition Association and to professor Tu Giay, founding director of NIN and President of the Vietnam Nutrition Association for their systematic support for my study and my work as well. The completion of my thesis would not be possible without the unlimited support and encouragement of Prof Ha Huy Khoi, not only my teacher but also the teacher of many generations of nutrition professionals in Vietnam.

I would like to express my special gratitude to Dr Saskia de Pee for her help and guidance in my studies as well as for her assistance on the first draft of the manuscript of the intervention study. She arranged for me to visit her study site in Bogor, Indonesia back in 1995 and shared her experiences in intervention studies. Later she came to Vietnam to help me organize the field work for my study.

Thanks also to Mr Maarten van Dullemen, former officer of the Medical Committee Vietnam-Netherlands and his wife, Sima. The Dullemen family always made me feel at home with their friendly behavior. Anytime I was in the Netherlands, they made arrangements and it was them who introduced me to Clive West and established the link between NIN and Wageningen with training courses on Vitamin A, food composition tables etc…

Thanks also to Ms Birgit van Benthem and Martine Ritsema from Wageningen for assisting me in pilot field work and for guidance in gathering food consumption data, and to Ms Diane Bosh and Dr Nguyen Thi Kim Canh for their great contribution to the field work during the intervention study. Diane, I thank you for your important support and help in data entering and management as well as sending the sample to Wageningen.

A special word for Dr Le Bach Mai, head, department of community nutrition, NIN for her significant contributions to my study, especially her careful and knowledgeable work on design of food rationing for the intervention study, and to Dr Le Danh Tuyen, my close colleague, and Dr Nguyen Lan and Dr Do Phuong Ha for their time spend in field work and supervising effectively the progress of the intervention study as well as their involvement in data analysis and information gathering.

I would also like to express my gratitude to all staff of the Department of Community Nutrition of NIN; to Dr Nguyen Xuan Ninh, head of the Department of Micronutrient Research and Application of NIN; to Dr Nguyen Thi Kim, NIN staff; to Dr Dang Thanh Son, parasitologist, National Institute of Malariology, Parasitology and Entomology and his staff; Dr Le Thi Huong, Hanoi Medical University; all members of our directorate of NIN; head of departments; and Division of Nutrition in Hanoi School of Public Health for their help and support.

I also want to thank Jan Burema for his statistical guidance and advice and Grietje van der Zee for her help in arranging delivery supplies.

To my “Dutch family” especially Marilou Hautvast, Hans Verhoef, Lous Duym, Gea Brussen, Ingeborg Brouwer, Tina van der Briel, Weinand Klaver, Fre Pepping and his family, Lidwien van der Heyden, Adel den Hartog, Marie Jansen, thanks for all your kind help, companionship and nice words that make me always feel at home during my stays in Wageningen.

Thanks also to Dr Paul Deurenberg, nutrition consultant in Singapore and former staff member of the Division of Human Nutrition, Wageningen University for his practical help in compiling the thesis. His willingness to help me revise the papers and help them submit for publication, and his discussions with professor Hautvast and professor Kok paved the way to defend the thesis at Wageningen University.

Also special thanks to Dr. Ingeborg Brouwer and other staff of Division of Human nutrition, WU for their important help in the preparation for the printing and making other necessary arrangements.

The research would not have been possible without the support and cooperation of Dr Nguyen Van Tan, director, Medical center in Pho Yen district, Thai Nguyen province and his staff, Dr Nguyen Van Vuong, Mr Nguyen Van Chau and other members, as well as the sincere and patient participation of the breastfeeding women in the nine communes in Pho yen district. Thank you so much for your contribution to my research.

It is worthy to thank Nestlé Foundation for the Study of Problems of Nutrition in the World, UNICEF and the Ministry of Planning and Investment of Vietnam for their financial support of all the work under this thesis.

To my teacher, Professor Dao Thi Ngoc Dien from the Pediatric Faculty, Hanoi Medical University, I am deeply indebted for teaching me, for your support, personal concern and attention over time.

Finally, I wish to express my deep appreciation to my beloved wife, mother, father, mother in law, sister, brothers for all your inspiration and moral support.

ABOUT THE AUTHOR

Nguyen Cong Khan was born on 24 July 1956 in Hai toan commune, Hai Hau district, Nam dinh province, Vietnam. In 1974, after graduation of high school in Nam dinh, he was admitted to study in Medicine at Hanoi Medical University. In April 1975, he jointed the Army and served at a unit of military medical team during some last months of Vietnam War and after that he came back Hanoi Medical University to study and graduated with specialization of pediatrics in 1983. From November 1983, he started to work at the National Institute of Nutrition (NIN), Hanoi, Vietnam. In 1986, he participated in a 3 month-training course on vitamin A deficiency and xerophthalmia in Nutrition Research and Development Center, Bogor, Indonesia. From 1988 to 1990, he participated in the course of nutrition in Hanoi Medical University and obtained the diploma of first degree doctor in nutrition (equals Master degree in Nutrution). From January 1990 to June 1990, he participated in a 5 month-training couse on community nutrition held by International Agricultural Center (IAC), Wageningen, the Netherlands and got the honour diploma in community nutrition. In November 1994, he earned the PhD degree in preventive medicine at the National Institute of Epidemiology. From 1995 he started to work on a PhD programme of Human Nutrition Department, Wageningen University, the Netherlands. He visited Wageningen several times for attending courses and analysing data of work done in 1996, 2000 and 2001.

At the same time, he actively participated in research activities of National Institute of Nutrition. In 1995, he was appointed as head of department of community Nutrition, NIN, Vietnam. In May 1998 he was appointed as deputy director of NIN, Vietnam. In February 2002, he was appointed as chair, division of Nutrition and food hygiene, food safety of the Hanoi School of Public Health. In July 2002, he was appointed by Minister of Health, Vietnam as the third director of National Institute of Nutrition, Vietnam. In October 2002, he was promoted as Associate Professor of Hanoi School of Public Health. At present, he is member of Vietnam CODEX committee, member of executive committee of Vietnam preventive medicine association, member of executive committee of Vietnam public health association and General secretary of Vietnam nutrition association.

PUBLICATIONS

1. Nguyen Cong Khan, Clive E. West (deceased), Saskia de Pee, Diane Bosch, Do Phuong Ha, Paul JM Hulshof, Ha Huy Khoi, Hans Verhoef and Joseph G.A.J. Hautvast.
   How much plant foods can contribute to the vitamin A supply of lactating women in Vietnam: a randomized controlled trial.
   Am J Clin Nutr, submitted.

2. Khan Nguyen Cong, Mai Le Bach, Minh Nguyen Duc, Do Tran Thanh, Khoi Ha Huy, Joseph GAJ Hautvast.
   Intakes of retinol and carotenoids intakes and its determining factors in the Red River Delta population of northern Vietnam.
   Eur J Clin Nutr, submitted.

3. Khan NC, Ninh NX, Nhien NV and Ha Huy Khoi and Hautvast JGAJ.
   Sub clinical Vitamin A Deficiency and Anemia among Vietnamese children less than five years of age.
   Asia Pacific J Clin Nutr, submitted.

4. Nguyen Cong Khan, Le Danh Tuyen, Tran Xuan Ngoc, Phan Hoai Duong, Ha Huy Khoi, Joseph GHJ Hautvast.
   Reduction in childhood malnutrition in Vietnam from 1990 to 2004. Asia Pacific J Clin Nutr, Submitted for publication

5. Nguyen Cong Khan. Current health and nutrition status of school children in Vietnam. Vietnam Journal of Medical and Pharmaceutical Information 2006; 1: 2-6.

6. Nguyen Cong Khan, Hoang Thi Kim Thanh, Jaques Berger, Pham Thuy Hoa, Nguyen Dinh Quang, Suttilak Smitasiri and Tomaso Cavalli-Sforza:
   Community mobilization and social marketing to promote weekly iron-folic supplementation: A new approach toward controlling anaemia among women of reproductive age in Vietnam.
   Nutrition Reviews 2005; 63: no12: S87-S93.

7. BT Nhung, Nguyen Cong Khan, LT Hop, DTK Lien, DSNT Le, D Kunii, T Sakai, M Nakamori and S Yamamoto.
   FAO/WHO/UNU equations overestimate resting metabolic rate in Vietnamese adults. Eur J Clin Nutr 2005; 59:1009-1104.

8. Vu Thi T Hien, Nguyen Cong Khan, NT Lam, LB Mai, DSNT Le, BT Nhung, , M Nakamori, D Kunii, T Sakai and S Yamamoto.

Determining the prevalence of osteoporosis and related factors using quantitative ultrasound in Vietnamese adult women.
Am J Epidemiol 2005; Vol. 161, No 9: 824-830.

9. J Berger, NX Ninh, NC Khan, NV Nhien, DK Lien, NQ Trung and HH Khoi. Efficacy of combined iron and zinc supplementation on micronutrient status and growth in Vietnamese infants.
Eur J Clin Nutr 2005; 59, 1009-1104.

10. Pham Van Thuy, Jacques Berger, Yukiko Nakanishi, Nguyen Cong Khan, Sean Lynch and Philip Dixon.
The use of NaFeEDTA-fortified fish sauce is an effective tool for controlling iron deficiency in women of childbearing age in rural Vietnam.
J Nutr 2005; 135: 2596-2601.

11. Jaques Berger, Hoang Thi Kim Thanh, Tomaso Cavalli-Sforza, Suttilak Smitasiri, Nguyen Cong Khan, Silvano Milani, Pham Thuy Hoa, Nguyen Dinh Quang, Fernando Viteri.
Community mobilization and social marketing to promote weekly iron-folic supplementation: Impact on anaemia and iron status.
Nutrition Reviews 2005; 63: No 12: S95-S108.

12. Ha Huy Khoi, Nguyen Cong Khan.
Changes in lipid intake of Vietnamese and related health consequences.
Japanese Journal of Nutrition 2005; 14:15-26

13. Nguyen Cong Khan.
Current health and nutrition status of school children with scope of improving nutrition in National nutrition strategy perspectives.
Vietnam Journal of Medical and Pharmaceutical Information 2005; 1: 6-11.

14. Nguyen Cong Khan, Le Danh Tuyen, Ha Huy Khoi et el.
Trend of nutrition situation of mothers and children in Vietnam period 1994-2004.
Vietnam Statistical Publishing House, 2005: 11-37.

15. Nguyen Cong Khan.
Control of micronutrient deficiency in Vietnam in the years to come: opportunities and challenges.
Vietnam Journal of Medical and Pharmaceutical Information 2004; 6: 5-7.

16. Nguyen Cong Khan.

Nutrition intervention programmes in Vietnam: scaling-up and challenges. SCN News, no 26, July 2003. ISSN 1564-3743.

17. Nguyen Cong Khan, Nguyen Xuan Ninh. Children under one year old is still high risk group of sub-vitamin A deficiency in Vietnam.
    Vietnam Journal of Practical Medicine 2003; 3: 445.

18. Pham Van Thuy, Jacques Berger, Lena Davisson, Nguyen Cong Khan, Nguyen Thi Lam , James D Cook, Richard F Hurrell, Ha Huy Khoi.

    Regular consumption of NaFeEDTA-fortified fish sauce improves iron status and reduces prevalence anaemia in anaemic Vietnamese women.
    Am J Clin Nutr 2003; 78: 284-290.

19. Nguyen Cong Khan, Ha Huy Khoi, Tu Giay, Nguyen Trong Nhan et al. Control of Vitamin A deficiency in Vietnam: Achievement and future orientation. Food and Nutrition Bulletin 2002; 23:133-142.

20. Nguyen Cong Khan, Ha Huy Khoi
    Micronutrient fortification direction in Vitamin A deficiency and Iron anaemia deficiency control.
    Vietnamese Journal of Scientific Activity 2000; 6: 8-9.