

# Sight and Life

SPECIAL  
VITAMIN A  
ISSUE

**18** NEW TEST KIT'S POTENTIAL FOR THE ANALYSIS OF VITAMIN A

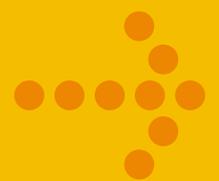
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7 “This year we welcome the 7 billionth person into the world. We don’t know where. We don’t know when. Nearly 1 billion people in the world go to bed hungry each night. The good news is that there are 2 billion online. You are one of them. Just think what we could achieve if all 2 billion of us did something small to end hunger.”

*Source: United Nations World Food Programme, [www.wfp.org](http://www.wfp.org), November 2011*

**Welcoming  
the 7 billionth  
person**



# Welcome

## Crisis – A Time for Decisions

As I write this editorial, a significant milestone in the development of mankind has been reached: a world of 7 billion people. At a time when our understanding of food production, health and nutrition is more sophisticated than ever, the growth of the world’s population places unprecedented pressure on the planet’s resources. More than any previous generation, we live in one world with a shared economy, communication system and logistics infrastructure. Yet this world is divided between those who are in an economically favorable situation and those who cannot cover their most basic needs, not to mention their nutritional needs; nearly a billion people go hungry to bed each night.

### The food crisis

The food crisis which has been developing for years has found poignant expression in the current sufferings of the people in the Horn of Africa. While the world has learned how to provide humanitarian support in such instances, we are still gaining new insights into the ramifications of such crises. Events such as the famine in Somalia have knock-on effects far beyond their own borders and time, creating a downward spiral with incalculable consequences. What happens in the Horn of Africa affects the whole of Africa; and what affects Africa affects the whole world.

## “What affects Africa affects the whole world”

At the same time, the problem of hidden hunger continues unabated, with more than 2 billion people in both the developing and the developed worlds subsisting on a diet whose caloric intake is not matched by its nutritional value. Such individuals, even if obese, are literally starving from the inside. The food crisis, therefore, has more than one dimension. It is not just that the price of commodities has risen dramatically, forcing the poorest of the poor to expend an ever greater proportion of their income on feeding themselves and their families, and buying more staples at the expense of micronutrient-rich animal food

.....  
“The people who are crazy enough to think they can change the world are the ones who do”  
*Apple’s “Think Different” commercial, 1997*  
.....

and vegetables; it is that many who have the capacity to fill their bellies are – whether by choice or by ignorance – filling them with the wrong sort of food.

The food crisis has another dimension, however. In the developed world, those on adequate incomes are faced with unprecedented choice in the supermarkets. Encouraged by the availability of attractively packaged and presented food, consumers are habitually buying more than they require – and throwing away a significant portion of it. This tendency has been reinforced by the use of ‘best before’ and ‘sell by’ dates, which have encouraged not only consumers but also supermarkets to throw away vast quantities of perfectly edible and nutritious food. This issue has recently been highlighted by a German movie entitled ‘Taste the Waste’, and the Feeding the 5,000 Campaign that provided a free lunch in London’s Trafalgar Square for 5,000 people on 18 November, all made from fresh food that would otherwise have been wasted. This is especially ironic, because we could feed many more people on this planet, particularly in the developing world, if we used better food storage and conservation techniques.



### The economic crisis

The global food crisis is occurring in parallel with a global economic crisis. Symbolized by the 2008 collapse of the seemingly all-powerful global financial services firm Lehman Brothers, it continues to send out shock waves. At the time of going to press, the future of Greece as a member of the European Union is in doubt on account of its escalating public debts, Italy's economic viability is also under the microscope, the governments of the European Union are joining forces to prevent the euro from collapsing, and specters of the Great Depression of 1929 are being invoked by worried onlookers. So significant is the loss of faith in the euro zone that even the massive US economy – traditionally inward – rather than outward-focused – is becoming increasingly concerned by it.

The high-growth economies of the world, however – Brazil, India and China especially – still have significant numbers of citizens who are not adequately nourished. And in the rush to catch up with the industrialized world, natural resources are being used up at an unparalleled rate as these economies invest in the technology and infrastructure to create sought-after consumer goods.

### From crisis to decision

Ironically, given the current state of Greece's economy, the word crisis is of Greek origin. It comes from the Greek *krisis*, literally, decision. A crisis is a moment of decision, a turning point for better or worse. It can also be a moment of opportunity – when fresh thinking leads to ideas, and action leads to change. Living in one world, we have more than the technology and infrastructure to bring us together. We have, if we choose to listen to them, the visionaries, and the scientists, and the inventors, and the business leaders. I personally have been inspired by the passion, creativity and leadership of the late Steve Jobs, founder and CEO of Apple. He has indeed changed our world.

.....  
 “We have the power  
 to shape our future”  
 .....

We have – each of us in our own way – the power to shape our future. How much more evidence do we need that the present system is failing not just the very poor but even the very rich? The time for change has come. We at *Sight and Life* are committed to working for changes that will improve the nutritional status of the world's poorest populations. We believe in a world where no-one should suffer from an inadequate or unhealthy diet, and no-one should have to be born to that destiny.

With best regards,



## A growing population ...

Even though the world population growth rate has slowed from 2.1 percent per year in the late 1960s to 1.2 percent today, the size of the world's population has continued to increase – from 5 billion in 1987 to 6 billion in 1999, and to 7 billion in 2011.

## ... in the world's ...

The sixth billion and seventh billion were each added in record time – only 12 years. If the 2.1 percent growth rate from the 1960s had held steady, world population would be 8.7 billion today. It is entirely possible that the eighth billion will be added in 12 years as well, placing us squarely in the middle of history's most rapid population expansion.

This prospect seems to run counter to the prevailing belief that concern over population growth is a thing of the past, and that today's 'population problem' is that birth rates are too low, not too high. In fact, there is some truth to that notion, depending on the region or country one is talking about. Today, most population growth is concentrated in the world's poorest countries – and within the poorest regions of those countries.

*Source: Population Reference Bureau, [www.prb.org](http://www.prb.org), November 2011*

## ... poorest countries

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# *Sight and Life* Turns 25

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## **We commemorate our 25<sup>th</sup> anniversary with a book, a mission statement and a logo**

The year 2011 sees the 25<sup>th</sup> anniversary of the foundation of *Sight and Life*. With this in mind, we are delighted to share our new mission statement:

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We care about the world's most vulnerable populations and exist to help improve their nutritional status. Acting as their advocates, we guide original nutrition research, disseminate its findings and facilitate dialog to bring about positive change.

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## **New logo, new layout**

We have also created a brand new *Sight and Life* logo. Looking back over 25 years of commitment to changing the lives of the most vulnerable in the world, and changing our focus from vitamin A to multiple micronutrients, our principal aim was for a logo to reflect this progress. In addition to the need to echo our scientific progress, we wanted to adapt as well to the changes in the design and readability of our magazine – to get science across in an easily comprehensible language. The feedback we have received to date on our new logo and layout from individuals, universities and organizations around the world has been very warm and encouraging. In this issue, we are sharing just a few of the many positive messages we have been sent.

## **The 25<sup>th</sup> anniversary book**

Chiming with the upcoming anniversary of the foundation of *Sight and Life*, the organization is soon to publish its 25<sup>th</sup> anniversary book. Exploring the history, work and mission of our organization over the years, the book also shines a light on our vision going forward.

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The new look of this magazine is indeed worth appreciating. I must acknowledge the fact that you and your team have worked hard to achieve this. All the articles are well written, however the biofortification summary along with the newer researches in carotenoid was of great interest to me as I am currently working with HarvestPlus on the Pearl millet project in India and carotenoids have been my research area since a decade. Congratulations once again.

*Dr Vanisha S Nambiar | Maharaja Sayajirao University of Baroda | Gujarat, India*

Thanks for this magazine.

*Mr Dominic M Mogere,  
CEO | CHRCC | Kericho, Kenya*

*f Tissandier Fred Tissandier*

Congrats! #FF RT @Sightandlife:  
New *Sight and Life* from  
[www.sightandlife.org](http://www.sightandlife.org). Enjoy its new  
look & feel we launch 4 25th anniversary.  
13 May

*micronutrient MI*

Congratulations! RT @Sightandlife:  
New *Sight and Life* now available from  
[www.sightandlife.org](http://www.sightandlife.org). 13 May

Dear Sir

I want to congratulate you for your 25th Anniversary and also to thank you for the good services you render to the poor in the society. I join you in the celebration of the anniversary while in Ghana.

*Esther Pegree Bayuo | Northern School of Business  
| Tamale, Ghana*

Congratulations on all that you achieved. Information and knowledge disseminated through *Sight and Life* magazine to us have guided us in our policy decisions on the fight to eradicate malnutrition. Experiences shared were very useful to us. Keep up the Good Work. *Ms Margaret Eshiett | Standards Organization of Nigeria*

*HarvestPlus*

Latest edition of @SightandLife is out with a great new look AND an article on the #biofortconf. <http://bit.ly/lyf21v>. 22 Jun

# The “*Sight and Life* in My Life” Essay Competition

In the last issue of *Sight and Life* Magazine, we revealed the results of our essay competition and shared Abubakar Bulako and Prince Abugri’s winning entries with our readers. However, given that we received many other fascinating stories on how *Sight and Life* has influenced our readers, we are now pleased to share some of the highlights with you, in the form of abridged extracts from the many wonderful entries we received. Some entries touched on entrants’ personal experiences, some examined *Sight and Life’s* impact on their community, while others defined *Sight and Life* in ways that were simple, accessible and memorable.

## Appreciating the value of nutrition

Mauline Akumu, for example, who is from Nairobi, Kenya, had never heard of *Sight and Life* until five years ago, at High School, when she experienced headaches, and pain and numbness in her feet, and was diagnosed with a multi-vitamin deficiency and mineral imbalance. A simple eye irritation then worsened, so she found herself losing her vision. An ophthalmologist told her about *Sight and Life’s* research into vitamins, and suggested that her diminished visual perception was the result of vitamin and mineral deficiency. She explains what happened next:

“Through *Sight and Life*, I learned a lot of things about nutrition, such as the nutritional benefits of orange-fleshed sweet potatoes. But for *Sight and Life*, I would probably not be telling this story, as I would have lost my vision and would be hospitalized somewhere with diverse nutritional diseases. Although I ended up with myopia, it’s better than living in complete darkness. I’ve been able to improve my diet and I try to educate others around me through my own personal experience. Most people now appreciate the value of investing in their health by adopting proper dietary plans, and paying more attention to the nutritional value of what they put into their mouths. More importantly, the role of nutritionists is being appreciated now more than ever.”

Meanwhile, Muditha Vitharana, a secondary school science teacher from Ratnapura, Sri Lanka, came into contact with *Sight and Life* through an art competition. Her Eighth Grade students took part, and one was a prize-winner. *Sight and Life* is now part of her life, and that of her students. Muditha has taught them to think about nutrition, as well as how to grow vegetables, fruit and green leaves. She has also initiated the use of a traditional Sri Lankan drink called Kola Kanda, which is enriched with vitamin A. “I have changed my students’ attitudes, and I hope to use them to spread this wisdom throughout the community,” she writes.



Raising awareness of vitamin A capsules at Chaitanya Mahila Mandhali school

### A dream come true

Dr Okey Egboluche, from the Department of Ophthalmology, Federal Medical Centre, in Ebonyi State, Nigeria, first encountered *Sight and Life* as a student optometrist. Throughout his career, Dr Egboluche has benefited from its support, both in Nigeria and abroad, and has aimed to use this to help his fellow man in numerous projects. His work culminated in a *Sight and Life* grant to proceed with his master's degree in

health sciences (public health) at the University of Teeside, UK. "It was a dream come true – my family still talk about it," he writes. Although he was denied a visa to study because the course start date was too close, he will always cherish *Sight and Life's* support. "I still believe there will be other opportunities to partner with *Sight and Life* in improving the lot of mankind," he says.

## Essay competition extracts

"As a nurse, midwife and health educator, *Sight and Life* has widened the scope of my nutrition knowledge. I have shared this with family, friends, mothers, expectant and nursing mothers, school children, teachers, colleagues, other health worker-nutritionists, nursing students, and midwifery and community health officers in training, etc. It has a 'multiplier effect.'" *Asomugha Virginia, Institute of Child Health, Unth Enugu, Nigeria*

"I decided to arrange a health education program, updating my knowledge with the help of *Sight and Life* Magazine. I started up health education programs for pregnant mothers in antenatal clinics, where I have been teaching them about micronutrients, including vitamin A. As a result, most of them have changed their food habits. I've also trained our field midwives and health workers to teach primary school children about nutrition. *Sight and Life* Magazine has been a handbook for our health education program."

*Dr OVS Vitarana, Blood Bank, Provincial General Hospital, Ratnapura, Sri Lanka*



People in Ekondo Titi, Ndian Division, South West Cameroon learn about the importance of receiving vitamin A capsules

"Our involvement with *Sight and Life* can be expressed in terms of receiving and dispatching nutritional knowledge. This automatically and directly affects the lives of the people who might otherwise die within the next week. Saving life is the greatest love *Sight and Life* owes to humanity."

*Didier Kheambo, Executive Director, Solidarity Health and Development Effort (Sohdecam), Republic of Cameroon*



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## Partners in success

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"In 2000, a friend introduced me to *Sight and Life* Magazine, which had a drawing competition on Nutrition for Health. I received a congratulatory letter, and was awarded a wristwatch and Swiss pencils. I decided to get involved with vitamin A elimination, and to make people in my village aware of it. Focusing on mothers, we provided information, skills and materials and began a project to grow and distribute free vitamin A source seedlings ... I followed up with the provision of locally available sources such as carrots, pumpkins, paw-paw and dark green leafy vegetables, among others. Good results were seen. To this day, I continue to receive support from *Sight and Life* and consider them my partners in success."

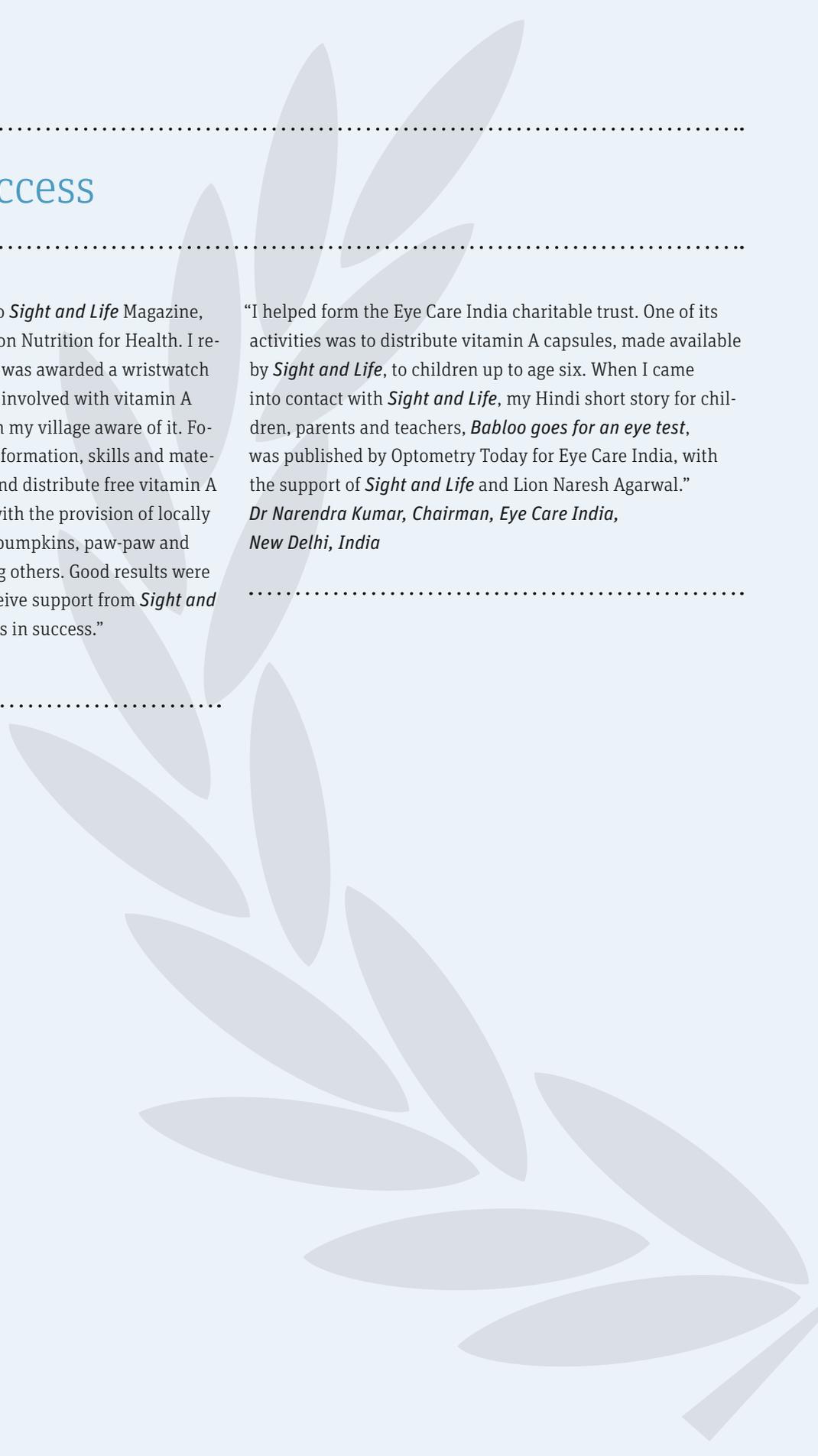
*Edwin Momanyi, Nyamira, Kenya*

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"I helped form the Eye Care India charitable trust. One of its activities was to distribute vitamin A capsules, made available by *Sight and Life*, to children up to age six. When I came into contact with *Sight and Life*, my Hindi short story for children, parents and teachers, *Babloo goes for an eye test*, was published by Optometry Today for Eye Care India, with the support of *Sight and Life* and Lion Naresh Agarwal."

*Dr Narendra Kumar, Chairman, Eye Care India,  
New Delhi, India*

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# Micronutrients, Macro Impact: The story of vitamins and a hungry world



To mark the 25<sup>th</sup> anniversary of its creation, *Sight and Life* is publishing a book entitled ***Micronutrients, Macro Impact: The story of vitamins and a hungry world***. This unique publication tells the story of the organization's evolution in the context of the world's growing understanding of the complexity of micronutrients and their interaction within the human body. It draws on documentary evidence, as well as recent interviews with leading thinkers in the micronutrient area, to tell a complicated story in simple, robust, and compelling terms.

The extensively illustrated book is divided into the following chapters:

- > The Battle Against Vitamin A Deficiency
- > From Vitamin A to Micronutrients
- > Micronutrient Deficiency
- > Micronutrient Deficiency in the Developed World
- > Taking a Strategic Approach
- > The Role of Policy-Making and Advocacy
- > Science Leads the Way: New approaches to making change
- > From Research to the Field
- > Local Versus Global

## Sustainable Solutions

In 2012, the Centenary of Vitamins, we will be just three years away from the target set for the achievement of the Millennium Development Goals, one of which is to halve, between 1990 and 2015, the proportion of people who suffer from hunger. ***Micronutrients, Macro Impact: The story of vitamins and a hungry world*** is essential reading for anyone interested in the relation between nutrition, health, and economics. Told in layman's language but packed with scientific fact, it explains the vital importance of micronutrients, and makes a powerful plea for using these vital substances to help build healthier, more prosperous, and more sustainable societies.

# Gender Inequality Gap

The Global Gender Gap Report's index assesses 134 countries on how well they divide resources and opportunities amongst male and female populations, regardless of the overall levels of these resources. The report measures the size of the gender inequality gap in four areas:



**ECONOMIC PARTICIPATION AND OPPORTUNITY**  
Outcomes on salaries, participation levels and access to high-skilled employment



**EDUCATIONAL ATTAINMENT**  
Outcomes on access to basic and higher level education



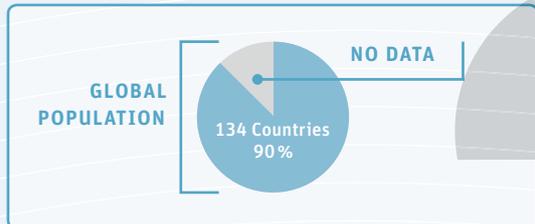
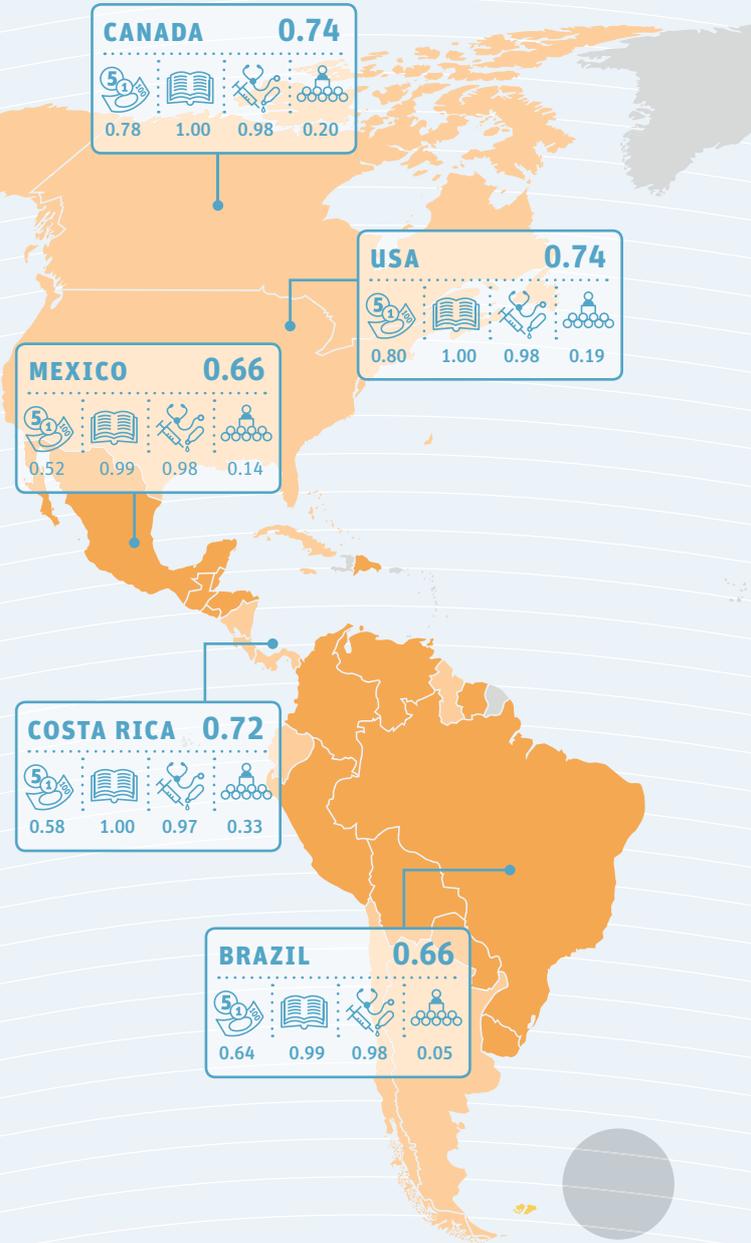
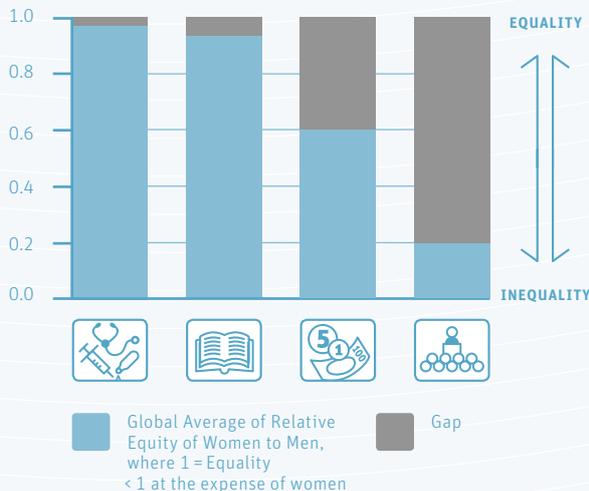
**HEALTH AND SURVIVAL**  
Outcomes on life expectancy and sex ratio

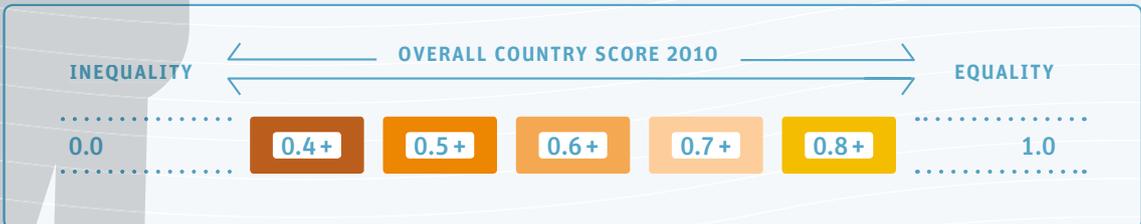
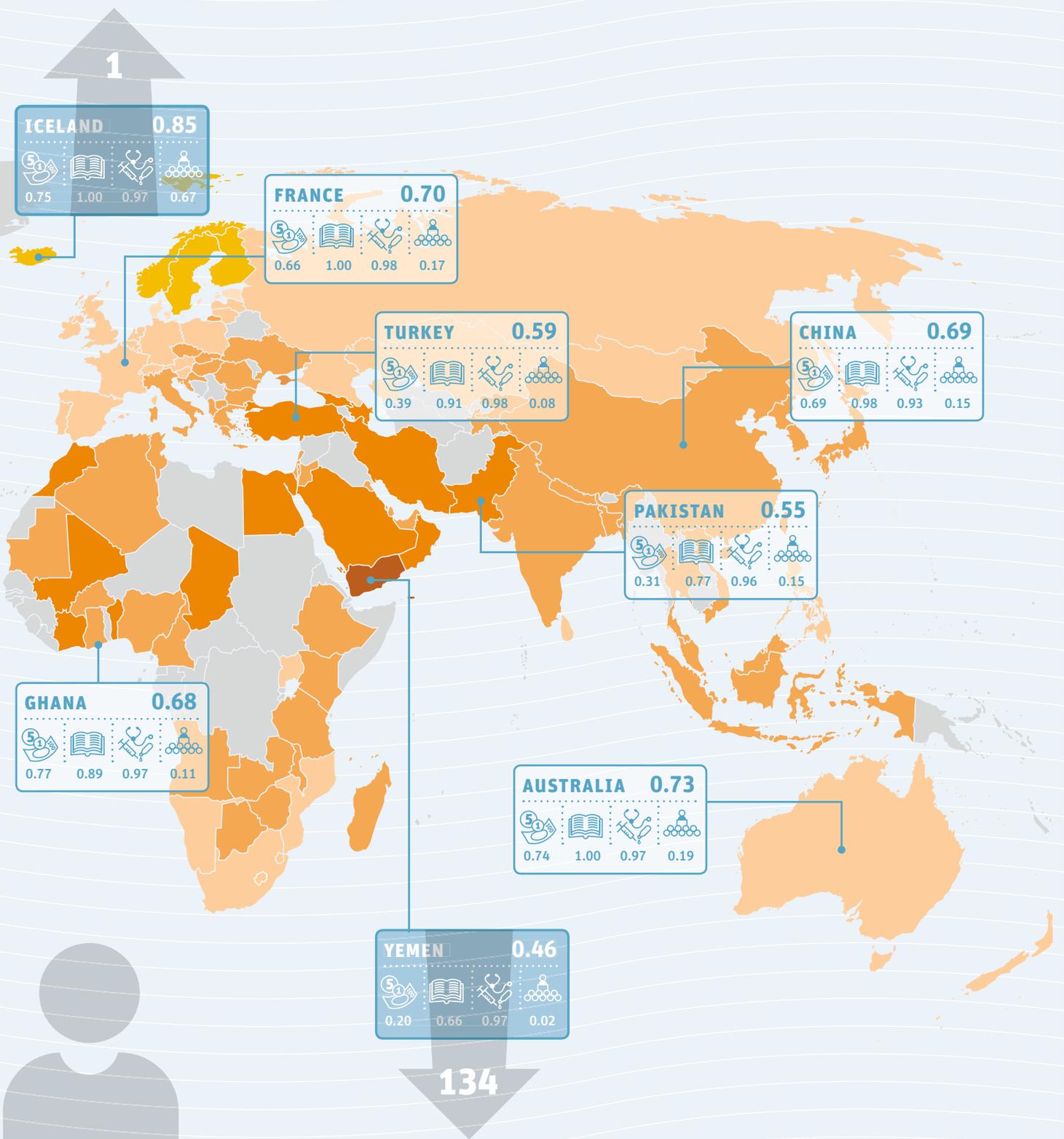


**POLITICAL EMPOWERMENT**  
Outcomes on representation in decision-making structures

## WHERE IS THE GAP?

2010 Global snapshot of the gender gap in four areas:





# A New Test Kit's Potential for the Rapid Analysis of Vitamin A in Human and Cow Milk

## Florian J Schweigert

University of Potsdam, Potsdam, Germany

## Simone K Frey, Ralf Mothes

BioAnalyt, Teltow, Germany

## Omar Dary

A2Z, The USAID Micronutrient Project, Washington, DC

## Paola Juarez, Viviana Lascano

Institution of Nutrition of Central America and Panama (INCAP), Guatemala City, Guatemala

## Summary

Breast milk is the most important source of vitamin A for infants and young children, and its content depends on the nutritional status of this vitamin in the mother. Therefore, the determination of vitamin A in breast milk constitutes an important parameter, not only for estimating the supply of this essential nutrient during the first years of human life, but also for approximating this vitamin's status in populations. On the other hand, the dairy industry is generally required to ensure the appropriate concentration of this vitamin in milk and its derivatives. The analysis of vitamin A in milk is time-consuming and cost-intensive, and requires sophisticated equipment and well-trained technicians. All these limitations could be overcome with a new rapid test kit – iEx™ MILA – with a portable fluorophotometer, the iCheck™ FLUORO. A comparison of vitamin A determinations of human breast milk and cow milk samples using this novel method and two different HPLC methods correlated well, and showed close agreement. Within only five minutes, using very simple labora-

tory equipment, vitamin A can be directly determined in milk without saponification or any other treatment steps. Preliminary results suggest that this method works acceptably well in liquid and unfrozen samples of milk. Additional experiments are ongoing, with the goal of finding procedures to improve the performance of the simple fluorometric method for other sample types, and for milk after freezing or drying.

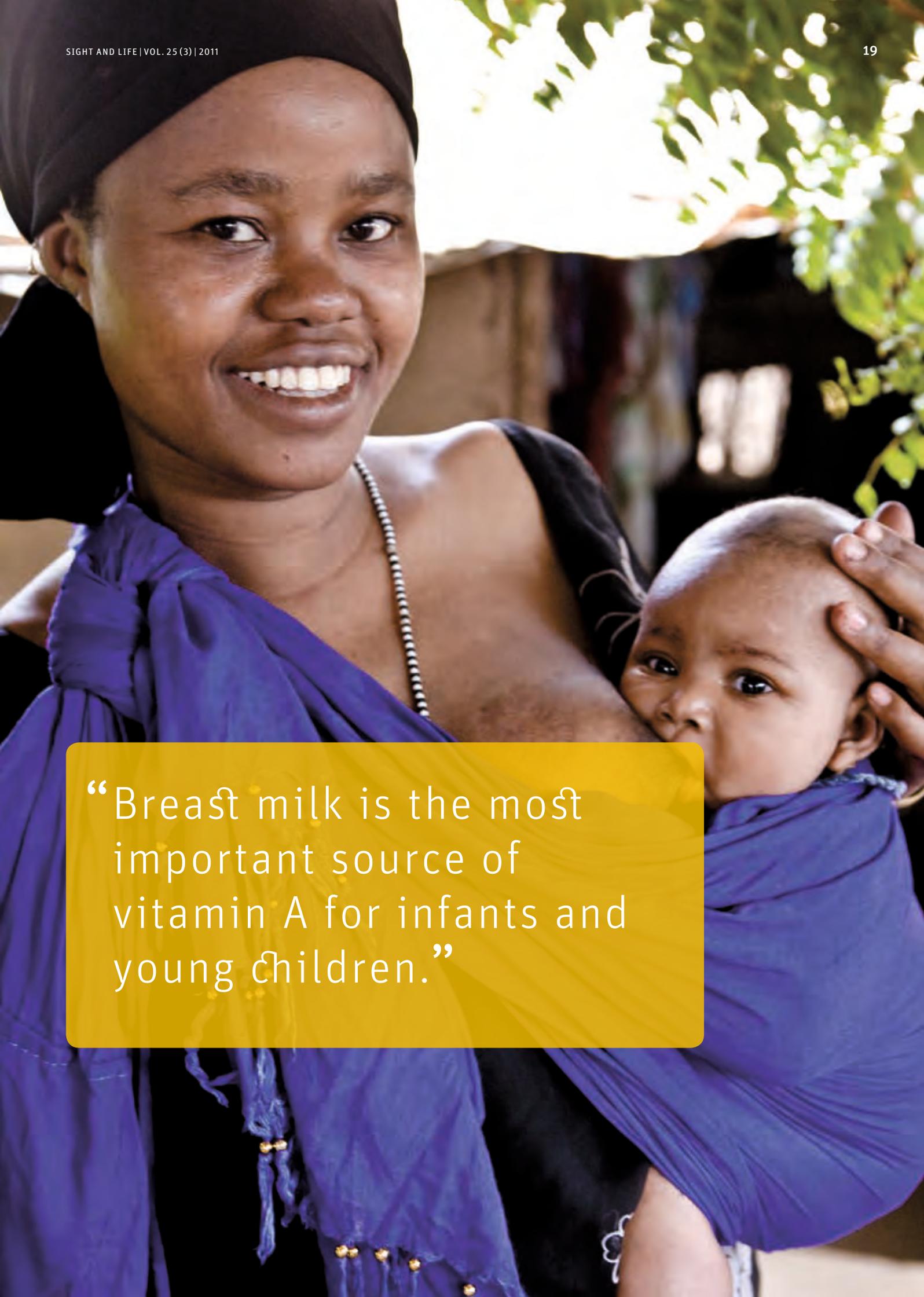
## Background

Milk is one of the most nutritious foods available. It not only contributes essential amino acids and fatty acids and calcium, but also – when the mother has the appropriate nutrition status – important amounts of iodine and vitamins B<sub>2</sub>, B<sub>12</sub>, D and A.

Human milk should supply a sufficient amount of vitamin A to cover the needs of newborns and infants. Vitamin A content is highest in the colostrum shortly after birth and continuously decreases thereafter.<sup>1</sup> Vitamin A content is highly dependent on the mother's vitamin A status. Thus, in general, mothers in developing countries have lower levels of vitamin A in their milk; this is regarded as important as a biomarker of vitamin A status and for monitoring vitamin A interventions.<sup>2</sup>

In cow's milk, due to seasonal variations in the carotene content of the diet, the content of vitamin A is highly variable.<sup>3</sup>

“During cow milk processing, all or part of the fat is removed: the vitamin A content is therefore reduced, prompting the mandatory fortification of liquid cow milk with vitamin A in many countries”



“Breast milk is the most important source of vitamin A for infants and young children.”



FIGURE 1: Rapid test kit system consisting of a portable fluorometer, disposable extraction and measuring vials and applicators

During cow milk processing, all or part of the fat is removed, and the vitamin A content is therefore reduced. This situation has prompted the mandatory fortification of liquid cow milk with vitamin A in many countries, such as Argentina, Brazil, Guatemala, Honduras, Malaysia, Mexico, the Philippines, the USA and Venezuela.<sup>4</sup> It is advisable to regularly check the vitamin A content to optimize the product-appropriate composition. Current methods to quantify vitamin A in milk and milk products are mainly based on the use of high-performance liquid chromatography (HPLC), which is relatively time-consuming and expensive, and requires well-trained personnel in a sophisticated laboratory environment. To overcome these analytical limitations, a new device has been developed that enables the precise analysis of vitamin A based on fluorometric detection of the vitamin.

The aim of this study was to make an initial comparison of results with this portable test kit, as compared with results ob-

tained via the HPLC reference method. The comparison was carried out at two different laboratories, using two different HPLC methods with different milk samples.

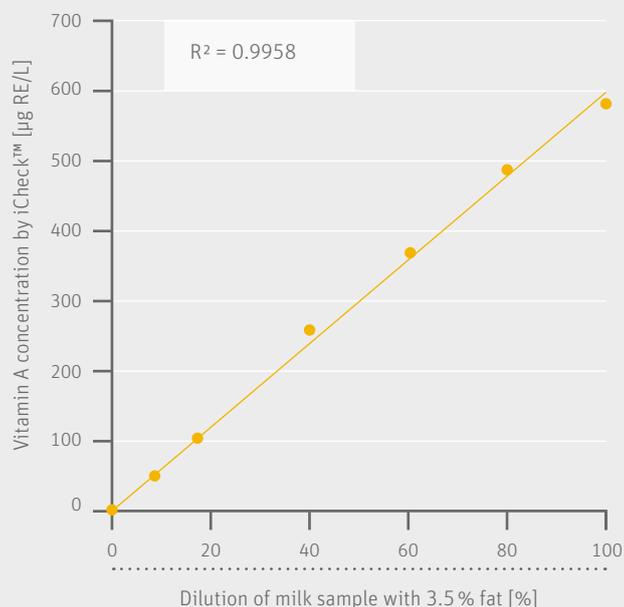
#### Methods

The test kit consists of disposable reagent vials (iEx™ MILA) and a portable photometer – the iCheck™ FLUORO (Figure 1). Using the applicators supplied, 0.5 mL of milk is directly injected into the vial. The sample is thoroughly shaken for 10 seconds to get a homogeneous mixture and a good extraction of vitamin A into the organic phase. After this step, the sample is allowed to settle for five minutes to allow good separation of the organic phase and the water-soluble phase. The vial is then directly inserted into the photometer, which is calibrated to register readings through the organic phase. After 30 seconds, the results are read as  $\mu\text{g}$  retinol equivalents (RE)/L.

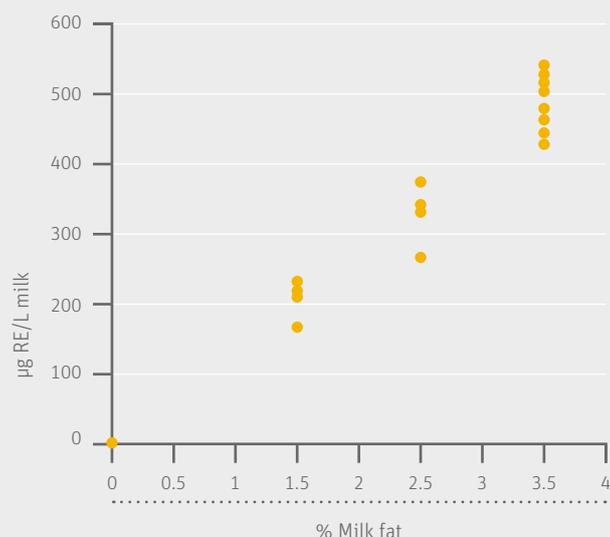
TABLE 1: Comparison of vitamin A levels in human breast milk and in cow milk assessed with the iCheck FLUORO kit and HPLC method at the University of Potsdam

Type of samples	Number of samples	HPLC – Vitamin A (Range, $\mu\text{g}$ RE/L)	% Difference HPLC/iCheck (Mean $\pm$ SD)
Human breast milk	16	251 – 1450	103 $\pm$ 13
Cow milk	21	21 – 731	105 $\pm$ 9

**FIGURE 2:** Positive correlation with serial dilutions of a milk sample measured with the rapid test kit



**FIGURE 3:** Content of vitamin A in commercial homogenized cow milk, thoroughly mixed before analysis, determined using iCheck™ FLUORO against the fat content of the same samples



If the amount of milk is limited, less than 0.5 mL of milk can be used and the amount made up to 0.5 mL with water, in which case the dilution factor should be considered in the calculation of the final result. For example, if 0.25 mL of milk is injected and then 0.25 mL of H<sub>2</sub>O added, the results should be multiplied by 2 (final volume/milk volume = 0.5/0.25).

HPLC standard methods<sup>1</sup> were used to determine vitamin A in the same samples and on the same day as the determination carried out using iCheck™ FLUORO.

Thirty liquid cow milk samples (21 from the University of Potsdam, 9 from INCAP) and five milk powder samples (INCAP) were obtained from local stores. Sixteen human breast milk samples were collected from a single woman over a lactation period of four months.

### The results

The assay was characterized using a series of dilutions made with cow milk, fortified cow milk, and human breast milk. **Figure 2** shows this linearity for the serial dilution of a cow milk sample. Linearity ( $r^2 = 0.99$ ) was observed between 100 and 2500 µg RE/L. Precision was tested over a range of 60 to 600 µg RE/L. The coefficient of variation (CV) was < 3.5%. The quantification limit (LoQ) was established at 50 µg RE/L. At this level, the CV was still below 20%, which is usually regarded as indicative of the LoQ.

The results for the different sample groups of liquid milk in both institutions were highly positively correlated ( $r^2 > 0.94$ ) between the HPLC method and that of iCheck. **Table 1** shows the comparative results of the two methods in the University of Potsdam, and **Table 2** presents the results by INCAP. At the University of Potsdam, HPLC reported 5% higher values for both cow milk and human breast milk. As regards INCAP, the HPLC method reported values that differed by -5% to +18% from the iCheck method, but were still within the variance of the method. As expected, there was a close relationship between the vitamin A content in cow milk and the fat content (**Figure 3**), with the highest values in milk with a fat content of 3.8%, and levels below the detection limit in fat-free milk.

Although the accuracy and precision of the iCheck method may be lower than that of the HPLC method, the former's simplicity and speed make it very attractive for routine analysis, and for determination of vitamin A in the field. It is now important to validate it in epidemiological surveys that determine the vitamin A content in breast milk, which to date has been very difficult to carry out. If it can be proved that the method produces reliable results, this will make breast milk retinol an important indicator for establishing populations' vitamin A status.

INCAP's results with powdered milks (**Table 2**) show that the extraction procedure for vitamin A was not good enough; hence, the HPLC reported 45% higher values than the iCheck.



**TABLE 2:** Comparison of vitamin A levels in cow milk assessed with the iCheck FLUORO kit and HPLC method at INCAP

Type of samples	Number of samples	HPLC – Vitamin A (Range, µg RE/L)	% Difference HPLC/iCheck (Mean ± SD)
Cow milk reconstituted from milk powder	5	1182–1504	144 ± 15
Whole cow milk in liquid form	5	1119–1455	118 ± 13
Skim cow milk in liquid form	4	280–511	95 ± 10

### Conclusion

In summary, the iCheck method assesses vitamin A levels in fluid milk with a simplicity and speed superior to that of current HPLC methods. Milk samples need no pre-treatment, such as centrifugation or saponification, before use. The method allows analysis of 45 milk samples in one hour, as compared to at least one day when HPLC is used. These characteristics make the iCheck method an attractive procedure, both for use in epidemiological surveys focusing on measuring the retinol content of breast milk samples, and for the dairy industry. Samples can be transported under refrigeration to a simple laboratory, or determination can be carried out on the spot.

### Acknowledgement

The kind support of *Sight and Life* is gratefully acknowledged.

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# Liver as a Vitamin A Source

## Adequate vitamin A status in a poor South African community despite high levels of stunting and underweight

**Lize van Stuijvenberg, Serina Schoeman**

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**Ali Dhansay**

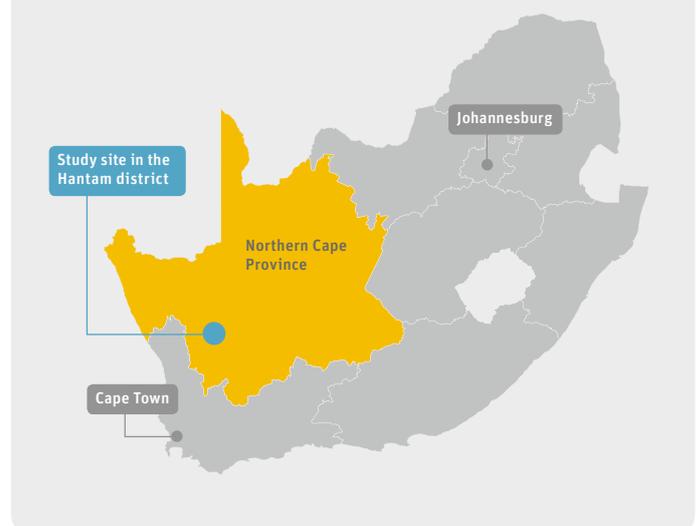
Currently from the Executive Research Directorate, Medical Research Council, Cape Town, South Africa

### Introduction

Vitamin A deficiency is estimated to affect 190 million preschool children globally,<sup>1</sup> and is usually associated with low socio-economic conditions and poor anthropometric status.<sup>1–3</sup> The Nutritional Intervention Research Unit of the South African Medical Research Council (MRC) recently undertook a study on the vitamin A status of preschool children in the Hantam district of the Northern Cape, one of South Africa's nine provinces (**Figure 1**). The results showed that, despite poverty and high levels of stunting and underweight, vitamin A deficiency was virtually absent in this community.<sup>4</sup>

This study,<sup>4</sup> supported by the MRC, Cape Town, South Africa, as well as a grant from *Sight and Life*, comprised 243 preschool children attending the local primary health care facility in the area. Only children that had not received a vitamin A supplement during the six months preceding the study were included for assessment. Non-pregnant female caregivers below the age of 50 years (89.3% biological mothers; 10.7% caregivers) were also assessed. Serum was analyzed for levels of retinol and C-reactive protein (CRP). Height and weight were measured and expressed as height-for-age, weight-for-age and weight-for-height z-scores, using World Health Organization (WHO) growth standards. Information on socio-economic status, liver intake and breastfeeding history was obtained by questionnaire, and the history of vitamin A supplementation from the child's Road to Health card.

**FIGURE 1:** Map indicating the study site



### Adequate vitamin A status

The prevalence of stunting, underweight and wasting among the children was 40.5%, 23.1% and 8.4%, respectively. This was approximately double the South African national prevalence and can, according to WHO criteria, be respectively classified as “very high”, “high” and “medium to high” (**Figure 2**). Surprisingly, only 5.8% of the children had serum retinol levels below 20 µg/dL (mean 31.3 µg/dL) (**Figure 3**). When children with raised CRP concentrations were excluded from the dataset, the prevalence was below 5%. This virtual absence of vitamin A deficiency is in sharp contrast to the national prevalence of 63.6% (**Figure 4**).<sup>5</sup> None of the children were clinically deficient (serum retinol concentrations < 10 µg/dL). In the mothers or caregivers, mean serum retinol was 55.1 µg/dL, with none having levels below 20 µg/dL. However, 19 mothers/caregivers (9%) presented with serum retinol concentrations in excess of 75 µg/dL (**Figure 5**).



Dry and arid conditions typical of the Northern Cape area; people from the local abattoir often gather here after work to sell surplus liver.

It is unlikely that the adequate vitamin A status in this population was the result of the vitamin A supplementation program, as children that received a vitamin A supplement during the preceding six months were not included in the study. Furthermore, 77% of the participants had not received a vitamin A supplement during the 18-month period prior to the study, and as many as 39.5% had never been exposed to vitamin A supplementation at all.

#### An affordable source of vitamin A

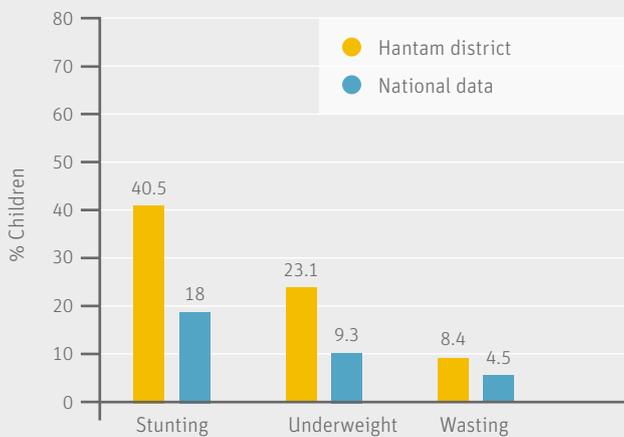
The study area is characterized by arid conditions, and yellow or green leafy vegetables are not cultivated or frequently consumed. Sheep farming is the main industry, and abattoir activities take place on a daily basis. There is thus a regular surplus of organ meat, which results in liver being available to this community at low cost (US\$ < 0.5 per kg liver), and often being distributed via informal trading. Liver was found to be eaten in 98.2% of households, and by as many as 89.2% of the preschool children. The majority of households (87.1%) ate liver at least once a month, while 30% reported eating liver once a week or more (Figure 6).

Liver was introduced into the diet of the child at a median age of 18 months, while 44.8% have been eating liver from the age of 12 months or even younger.

.....  
**“Liver was found to be eaten in 98.2% of households, and by as many as 89.2% of the preschool children”**  
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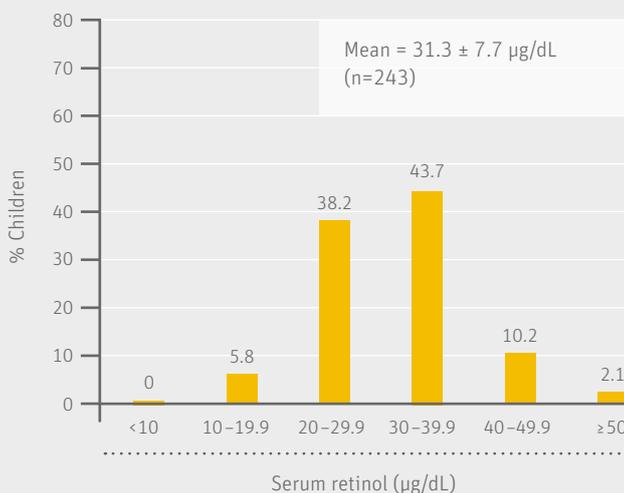
Liver is a highly concentrated, but an often under-valued source of preformed vitamin A. Sheep liver contains approximately 7,800 µg retinol equivalents (RE) per 100 g.<sup>6</sup> The estimated average daily requirement (EAR) for children aged one to three years and four to eight years is only 210 and 275 µg RE, respectively.<sup>7</sup> This means that liver does not have to be eaten in great amounts or even every day. Only 20–25 g of liver once a week or one 40–50 g portion twice a month would be sufficient to meet the vitamin A requirement of the preschool child. Figure 7 illustrates the number of days that a child’s EAR would

**FIGURE 2:** Anthropometric status of the preschool children from the Hantam district compared to national data



theoretically be met by a specific amount of liver consumed. Liver is also a good source of other nutrients, such as iron, zinc and B-vitamins.<sup>6</sup> However, in relation to its vitamin A content, liver contains considerably less of these micronutrients, and to meet the EAR for iron and zinc, for example, liver would have to be consumed on a near daily basis. This is not only impractical, but liver, if eaten every day, could result in an excessive intake of vitamin A. Cases of vitamin A toxicity have been documented in young children<sup>8,9</sup> and adults<sup>10</sup> in situations where liver had been eaten several times a week for extended periods.

**FIGURE 3:** Distribution of serum retinol in the preschool children attending the Hantam primary health care facility and eligible for vitamin A supplementation



“Only 20 – 25 g of liver once a week or one 40 – 50 g portion twice a month is sufficient to meet the vitamin A requirement of the preschool child”

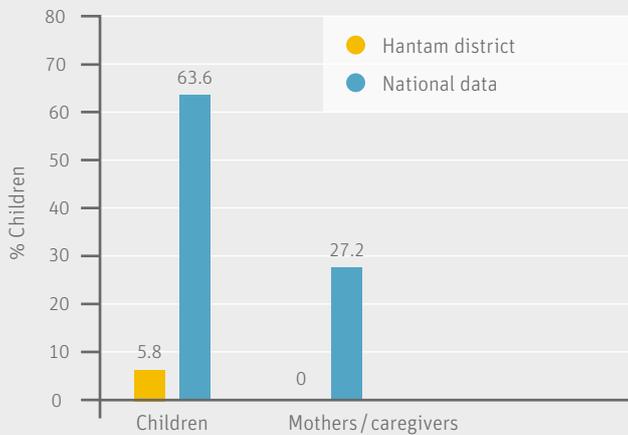
Periodic high-dose vitamin A supplementation is widely employed to control vitamin A deficiency.<sup>11</sup> The food-based approach, however, remains the ultimate goal<sup>12</sup> and, although it may take years to show the desired effect, is the solution that should be strived for. In this community, liver is an affordable source of meat and a favorite food among the poor, and a sustainable food-based vitamin A “intervention” is therefore already in place. A significant negative correlation was found between the educational level of the mother and the frequency of liver consumption. This suggests that it is the poorer or more vulnerable people who eat liver most, and thus unknowingly engage in practices that naturally protect them against vitamin A deficiency. The benefits of this community’s liver consumption habits are further amplified by a high breastfeeding initiation rate (93%), and a long median duration of breastfeeding (18 months), with the result that the children also indirectly benefit from their mothers’ liver intake.

“In this community, liver is an affordable source of meat and a favorite food among the poor, and a sustainable food-based vitamin A “intervention” is therefore already in place”

#### Implications and concerns

The results of this study have implications for the South African national vitamin A supplementation program, in that the prophylactic approach may not be necessary in areas where liver is frequently eaten – even though the community may be socio-economically deprived and seemingly undernourished. With its exceptionally high vitamin A content, liver acts as a vitamin A supplement. Additional vitamin A in the form of high-dose supplements would be superfluous and may create unnecessary strain on the health budget and already limited human resources.

**FIGURE 4:** Prevalence of serum retinol <20 µg/dL in the Hantam district compared to national data



While vitamin A supplementation undoubtedly has benefits in vitamin A deficient populations,<sup>13</sup> its effect in vitamin A sufficient populations is not known. Concerns regarding the universal application of vitamin A supplementation have been expressed by several authors in the past,<sup>14–16</sup> and more recently in a commentary by Latham,<sup>17</sup> in which he challenges the wisdom and validity of regularly providing high-doses of vitamin A to children, especially those that are not vitamin A deficient. There are, for example, indications that high-dose vitamin A supplementation may actually increase respiratory-related morbidity in children that are *not* vitamin A deficient.<sup>18</sup> The long-term effect of periodic high-dose vitamin A supplements

on the bone health of young children that are vitamin A sufficient but compromised in terms of other micronutrients is also not known. In adults, long-term intake of preformed vitamin A of only twice the RDA has been associated with osteoporosis and hip fractures.<sup>19–21</sup>

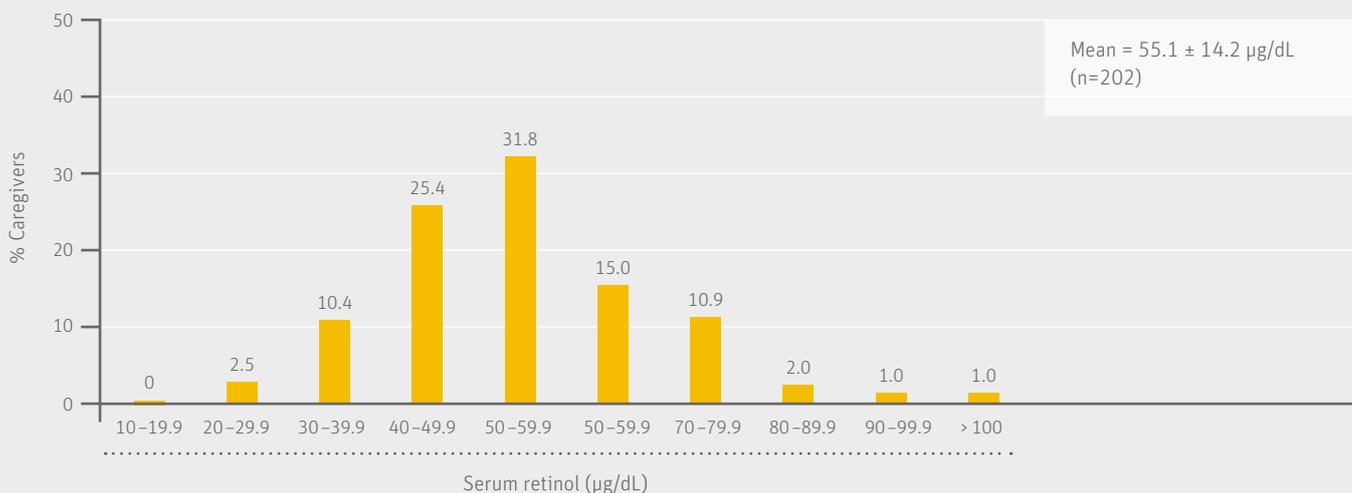
“The high levels of stunting and underweight in this particular community is a concern, and suggests that the children are likely to be deficient in nutrients other than vitamin A”

The high levels of stunting and underweight in this particular community is a concern, and suggests that the children are likely to be deficient in nutrients other than vitamin A. Providing these children with high-dose vitamin A capsules – which they do not need – may create a false perception amongst health authorities that the children’s nutritional needs are being attended to, and that other interventions are less important.

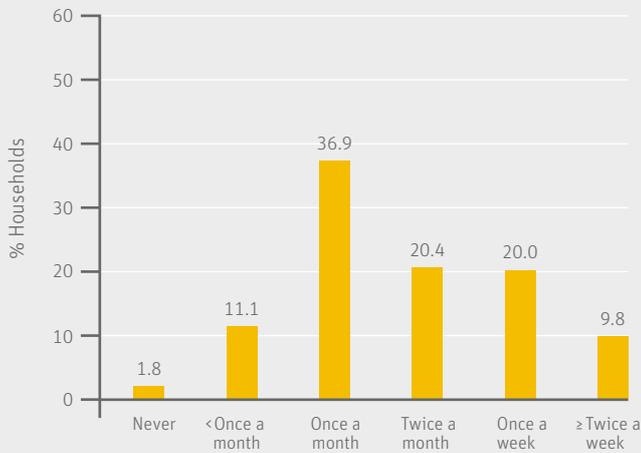
### Conclusion

The virtual absence of vitamin A deficiency in the study population highlights the fact that, although national data from a country indicate a public health problem, there may be pockets within that country that are different due to unique eating

**FIGURE 5:** Distribution of serum retinol in mothers/caregivers of preschool children attending the Hantam primary health care facility



**FIGURE 6:** Distribution of the frequency of liver consumption at household level



habits and local circumstances. South Africa is a country that is diverse in terms of culture, geography and socio-economic status, and this diversity also influences the eating habits of its people. This underscores the complexity of formulating a single policy that would address the diverging needs of the South African population.

“South Africa is a country that is diverse in terms of culture, geography and socio-economic status, and this diversity also influences the eating habits of its people”

The frequent intake of liver is probably not restricted to the study area, as sheep farming is the predominant activity in most of the dry and outstretched Northern Cape province. An extensive survey, covering the whole of this province, and which will establish how many and where these liver eating pockets exist, is currently under way.

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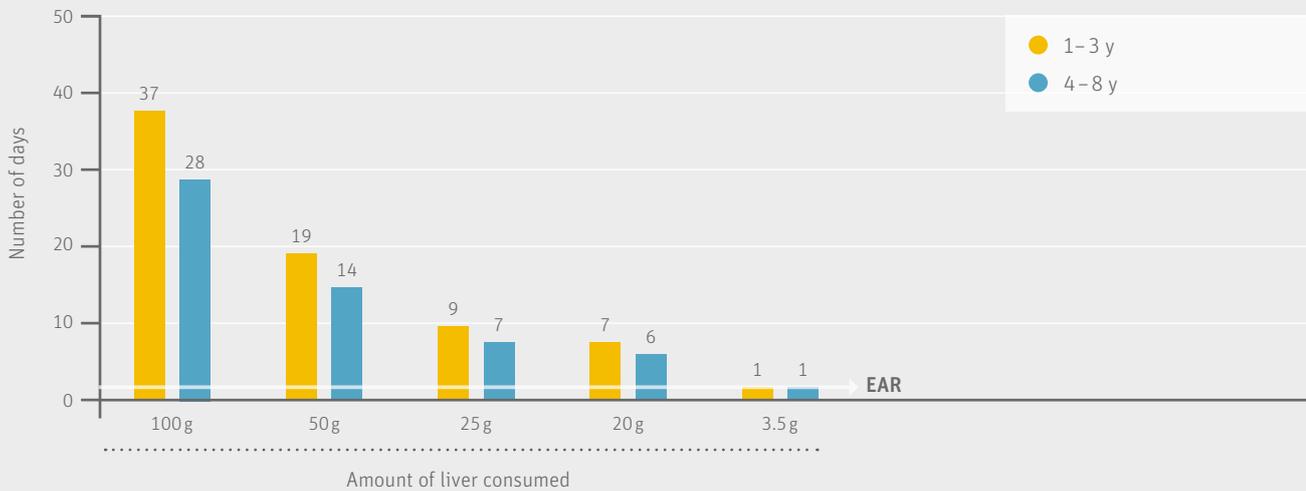


Informal liver trading.

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**FIGURE 7:** Number of days that a child's Estimated Average Requirement (EAR) would theoretically be met by an amount of liver consumed



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# The Importance of Early Nutritional Intervention

## How maternal and child undernutrition in early life can affect health in later years

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### Introduction

As early as the 1960s, animal studies demonstrated the adverse effects of undernourishment during critical periods in development, and the potential for early dietary manipulations to “program” physiologic responses later in life.<sup>1,2</sup> In 1991, Barker and colleagues began a series of epidemiologic studies to investigate the potential link between early childhood undernutrition and disease outcomes later in life.<sup>3,4</sup> Recently, scientific evidence linking undernutrition in the infant and child to increased risks of childhood mortality and poor cognition early in life<sup>5</sup> and the higher risks of non-communicable diseases (NCDs) and obesity during adulthood<sup>5-8</sup> has emerged.

The strong association between maternal malnutrition and poor infant nutrition reinforces the need to consider the mother-infant dyad when assessing the risk for developing NCDs later in life (**Figure 1**). While maternal undernutrition and micronutrient deficiencies have been linked to adverse outcomes in the child, it is also important to consider the risks associated with imbalanced nutrition and obesity in the mother. Overweight in adult women has been linked to an increased risk of developing NCDs, including cancer, diabetes, hypertension and cardiovascular disease.<sup>9,10</sup> Imbalanced maternal nutrition has also been shown to affect the development of NCDs in the offspring, and to lead to the development of maladaptive responses in the child as a way to compensate for poor nutrition.<sup>11,12</sup>

This article explains the role of maternal and child nutrition in the development of NCDs later in life. Evidence from animal studies and epidemiologic studies in humans provides the basis for understanding the idea of programming and for the

### Key messages

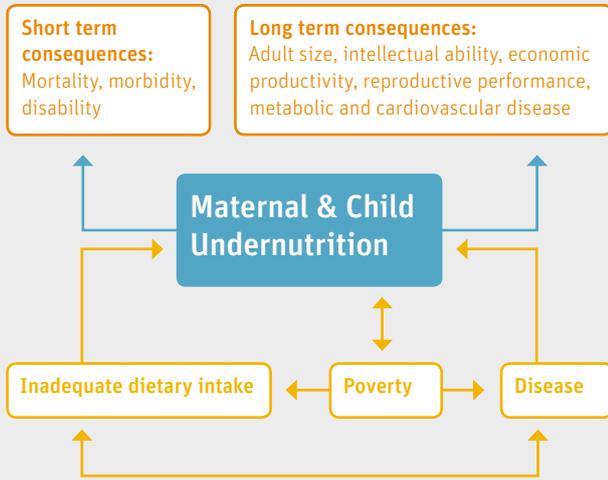
- > Undernourishment during critical periods in development can lead to adverse health outcomes and has been shown to increase the risk of developing non-communicable diseases (NCDs) later in life.
- > Long-term negative health consequences are thought to be due to “programming,” a process by which adverse stimuli can either impair the development of a somatic structure or alter a physiological setting.
- > The “thrifty phenotype” hypothesis proposed that poor fetal and infant nutrition can subsequently lead to the development of non-insulin-dependent diabetes and the metabolic syndrome later in life by initiating permanent changes in glucose-insulin metabolism.
- > Unbalanced nutrition in adult women has been associated with increased risks of cancer, hypertension, diabetes, and cardiovascular disease in the mother, as well as with poor long-term health outcomes in the child.
- > The adverse health outcomes associated with NCDs and their association with imbalanced maternal and childhood nutrition strongly supports the use of the life-cycle approach as a tool for monitoring and prevention.



“The strong association between maternal malnutrition and poor infant nutrition reinforces the need to consider the mother-infant dyad.”

An excellent example of the effects of stunting taken in South Africa. The girl on the left, who suffers from this condition, is aged seven, as is the girl on the right.

**FIGURE 1:** Consequences of impaired maternal and child nutrition as related to poor diet, poverty, and disease



development of the “thrifty phenotype” hypothesis, respectively. Using these concepts as a basis for linking imbalanced nutrition and the development of NCDs later in life, it reviews the current scientific evidence on the long-term effects of poor maternal and child nutrition, and reinforces the need for an adequate diet in both mother and child to prevent the subsequent development of NCDs.

### The “thrifty phenotype” hypothesis

In 1991, Barker and colleagues began a series of epidemiological studies to investigate the relationship between poor fetal and infant growth and the development of glucose intolerance,<sup>3</sup> the metabolic syndrome,<sup>4</sup> cardiovascular disease,<sup>13</sup> and other associated risk factors<sup>14</sup> later in life. In the original study, 93 of 468 male participants were found to have impaired glucose tolerance or undiagnosed diabetes, with a higher proportion of men with impaired glucose tolerance having lower mean birth weight and lower weight at one year.<sup>3</sup> Increasing weight at one year was inversely associated with concentrations of 32–33 split proinsulin, an indicator used to demonstrate  $\beta$ -cell dysfunction.<sup>3</sup> These results suggested that permanent changes in glucose-insulin metabolism occurred in response to poor nutrition in early life, and led to the development of impaired glucose tolerance and non-insulin-dependent diabetes.

Follow-up studies by Barker and colleagues further demonstrated the association between lower birth weight and adverse health outcomes later in life. Increasing birth weight was inversely associated with the occurrence of syndrome X, defined by the presence of non-insulin-dependent diabetes mellitus, hypertension, and hyperlipidemia.<sup>4</sup> Similarly, higher rates of

coronary heart disease were observed in individuals with a history of low birth weight<sup>15</sup> and men who were small at birth due to a failure to grow were at an increased risk of cardiovascular disease compared to men whose small size at birth was due to prematurity.<sup>16</sup>

The conclusions of these studies led to the development of the “thrifty phenotype” hypothesis, which proposed that poor fetal and infant nutrition initiate permanent changes in glucose-insulin metabolism, and can subsequently lead to the development of non-insulin-dependent diabetes and the metabolic syndrome later in life.<sup>17</sup> The theory suggested that a “fetal nutritional thrift” occurs in an effort to selectively protect brain growth in conditions of undernutrition, and results in a differential impact on the growth and function of different organs.<sup>17</sup> The co-occurrence of undernutrition early in life and overnutrition in childhood and adulthood was hypothesized to impair glucose tolerance, due to increased insulin resistance and reduced capacity to secrete insulin because of poor pancreatic  $\beta$ -cell development (Figure 2),<sup>17</sup> demonstrating the ability of postnatal events to modify the risks associated with low birth weight.<sup>18</sup>

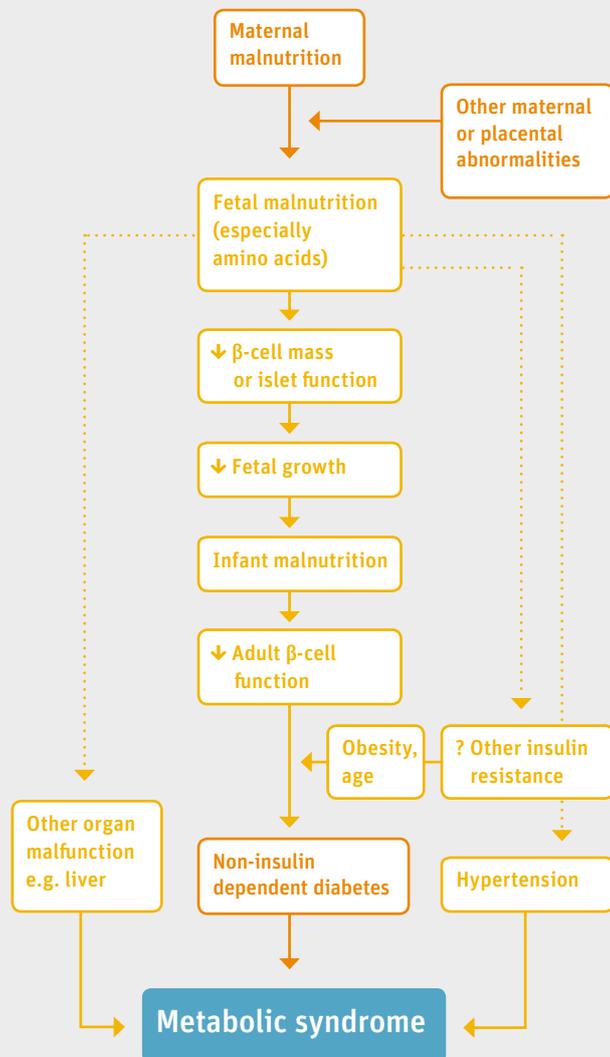
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**“Numerous studies in diverse populations worldwide have confirmed the link between poor fetal and infant growth and the development of NCDs or associated risk factors”**  
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### Beyond the “thrifty phenotype” hypothesis

Since the initial proposal of the “thrifty phenotype” hypothesis, numerous studies in diverse populations worldwide have confirmed the link between poor fetal and infant growth and the development of NCDs or associated risk factors.<sup>19</sup> While the strength of the association has varied across studies, the development of insulin resistance has been consistent across all age groups studied.<sup>17</sup> Recent studies have also demonstrated an increased susceptibility to non-insulin-dependent diabetes in children who caught up in weight and body mass index following undernutrition in early life.<sup>20</sup> These results are particularly significant for countries undergoing a transition from more traditional lifestyles to urbanization, and populations shifting from a high prevalence of infectious disease morbidity to an increased prevalence of diseases such as diabetes, cardiovascular disease and cancer.<sup>21</sup>

The ability to program a later susceptibility to non-insulin-dependent diabetes has also been investigated in studies as-

**FIGURE 2:** The proposed mechanism for the “Thrifty Phenotype” hypothesis



(Adapted from Hales<sup>17</sup>)

sessing prenatal overnutrition. In studies of Pima Indians, newborns weighing less than 2.5 kg or more than 4.5 kg exhibited an increased prevalence of non-insulin-dependent diabetes, compared to infants who weighed 2.5 to 4.5 kg at birth.<sup>22</sup> The U-shaped association between birth weight and the occurrence of non-insulin-dependent diabetes reinforced the conclusions from the Barker studies, and provided evidence for a new association with overnutrition. Although rat studies have demonstrated fetal insulin resistance,<sup>23</sup> abnormal cholesterol metabolism,<sup>24</sup> and raised adult blood pressure<sup>25</sup> in the offspring of rats who were fed high saturated fats during pregnancy, McCance and colleagues provided an alternative explanation. They proposed that the increased risk associated with higher birth weight could

instead be due to the high prevalence of non-insulin-dependent diabetes in the population, and could potentially signify a genetic predisposition to insulin resistance.<sup>22</sup>

Finally, recent studies have addressed some of the criticisms of Barker and colleagues' original studies, such as their reliance on birth weight as the primary measure of prenatal etiologic pathways.<sup>26</sup> There has also been an increasing focus on the role of genetic and environmental factors in the subsequent development of adult onset NCDs, and the effects of suboptimal maternal nutrition, as detailed below.

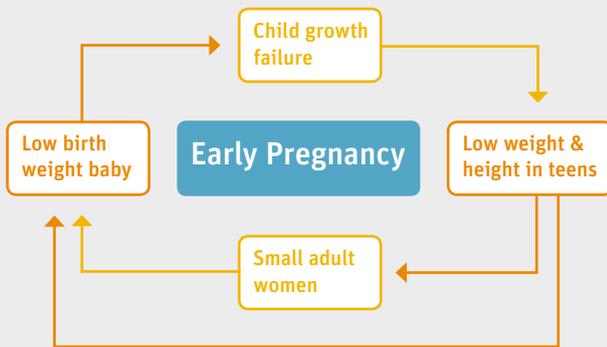
### The role of imbalanced maternal nutrition

Fetal undernutrition, which occurs when fetal nutrient demand exceeds placental supply, is influenced by a variety of factors, including maternal body composition and maternal dietary intake.<sup>27</sup> Adaptations by the fetus to undernutrition, including altered hormone production, metabolic changes, and the redistribution of blood flow,<sup>28</sup> demonstrate the potential role of the mother in fetal programming.<sup>27</sup> Decreased maternal food intake, for example, can lower the concentrations of insulin, insulin-like growth factor-1 and glucose in the fetus, reducing the transfer of amino acids and glucose from mother to fetus and adversely affecting fetal growth.<sup>29</sup> Because underweight women have been shown to have a higher incidence of low birth weight infants,<sup>30</sup> it is increasingly more important to monitor the prevalence of maternal undernutrition and the effects it can have on a child's risk of developing NCDs.

Maternal short stature, thought to reflect malnutrition early in life, has been linked to a number of adverse outcomes in the mother-infant dyad, including an increased risk of stunting and cephalopelvic disproportion in the child.<sup>31,32</sup> Because child stunting has been associated with an increased risk of obesity and chronic diseases later in life, the effects of imbalanced nutrition in both the mother and the child may have the capacity to compound from generation to generation.<sup>32</sup> In 2005, Garrett and Ruel investigated the prevalence of stunted child-overweight mother pairs worldwide, and found a higher frequency of this phenomenon in countries undergoing a nutrition transition.<sup>33</sup> The authors proposed that, even in the midst of economic development, countries with historically high rates of childhood stunting may continue to experience childhood stunting, whereas increased household availability of food and energy may promote growing rates of obesity among stunted mothers.<sup>33</sup>

.....  
**“Maternal overweight can have significant health consequences for both the mother and the child”**  
 .....

**FIGURE 3:** The use of the life-cycle approach in assessing the consequences of imbalanced nutrition in the mother and child



Maternal overweight can have significant health consequences for both the mother and the child. Direct links to cancer, diabetes, hypertension, and cardiovascular disease in women who are overweight have been well-established.<sup>9,10</sup> Similarly, children exposed to diabetes or maternal obesity *in utero* have been shown to be at increased risk of developing non-insulin-dependent diabetes,<sup>34,35</sup> cardiovascular risk factors,<sup>36</sup> and the metabolic syndrome.<sup>37</sup> As the prevalence of overweight and obesity increases, the effects of maternal overnutrition are becoming increasingly more relevant, and demonstrate the need to maintain a balanced diet throughout the life cycle. Fluctuations in either direction, namely through undernutrition or overnutrition, can result in adverse health consequences for both mother and child. These findings also reveal the detrimental effects that can occur if there is a perpetuating cycle of obesity, insulin resistance, and their associated disease outcomes, without intermittent nutritional interventions.

### The role of genetics

A genetic link between low birth weight and later diabetes was initially proposed by Hattersley and colleagues<sup>38</sup> as an alternative explanation to the environmental influences described above. A mutation known to cause maturity onset diabetes of the young (MODY), a syndrome of early onset non-insulin-dependent diabetes with an autosomal dominant inheritance pattern,<sup>39</sup> has been associated with lower birth weight and later diabetes when present in the fetus.<sup>40</sup> The mutation's low frequency, however, makes it an unlikely explanation for the associations described by Barker and colleagues. Instead, insulin's role as a growth promoter *in utero* may explain why mutations altering insulin secretion or resistance could also affect fetal growth and the development of diabetes.<sup>38</sup>

Additional associations between low birth weight and the subsequent development of diabetes have been investigated with regard to genetics. The offspring of diabetic fathers were found to have a lower birth weight and an increased risk of later developing diabetes.<sup>41</sup> Furthermore, low birth weight in the child was predictive of diabetes if paternal diabetes was present; the same association was not observed for maternal diabetes, which had previously been associated with increased birth weight.<sup>41</sup> Twin studies, on the other hand, have shown that the increased risk of developing non-insulin-dependent diabetes is independent of genetic constitution.<sup>42</sup> Although genetic polymorphisms may ultimately play a role in birth weight and the resultant changes in glucose metabolism,<sup>43</sup> the effects are much weaker than those of decreased birth weight.<sup>44</sup>

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**“The adverse health outcomes associated with NCDs strongly support the use of the life-cycle approach”**

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### Conclusions

The adverse health outcomes associated with NCDs and their link to imbalanced maternal and childhood nutrition strongly support the use of the life-cycle approach as a tool for monitoring and prevention (Figure 3). Monitoring should be performed throughout all decades of life, extending from gestation to adult life, as well as across generations.<sup>45</sup> While insulin resistance has been used as the prototypical example of a “thrifty” characteristic, more recent evidence has expanded the time in which “thrifty”-like characteristics can manifest themselves, ranging from changes in development to phenotypic changes seen well after birth.<sup>46-49</sup> This further reinforces the need to take on a life-cycle approach when considering NCDs.

As the co-occurrence of undernourishment in the child and overweight in the mother becomes increasingly more prevalent,<sup>33</sup> future policies and nutritional interventions must be developed to combat the adverse effects associated with imbalanced nutrition during critical periods, and the capacity for postnatal events to modify the risks associated with low birth weight. Ultimately, the goal of reducing the prevalence rates of glucose intolerance, non-insulin-dependent diabetes, cardiovascular disease, and the metabolic syndrome is dependent upon further scientific investigation, and the integration of knowledge regarding all associated risk factors and subsequent adverse health outcomes.

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# Vitamin A Supplementation

## Beneficial effects on mortality and morbidity in children aged six months to five years

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#### Key messages

- The most recent meta-analysis of 16 published vitamin A supplementation trials confirmed a 24% reduction in risk of all-cause mortality in children aged six months to five years in response to vitamin A.
- The effects of vitamin A were not significantly different in Africa and Asia, infants and preschool children, or boys and girls.
- There was a 28% reduction in cause-specific mortality associated with diarrhea, and the incidence of diarrhea (15%) and measles (50%) in vitamin A treated children were both significantly reduced.
- One large, unpublished vitamin A supplementation trial in India did not individually demonstrate significant effects on mortality, but its inclusion in the meta-analysis (n=17) still revealed a clinically significant 12% reduction in the risk of death in vitamin A treated children.
- Cultural, economic, environmental, and social factors in India may make vitamin A status especially poor, and two vitamin A trials have failed to produce significant benefits. It is probable that 200,000 IU every six months may not rectify the situation for more than a few months in the year, and WHO recommendations of

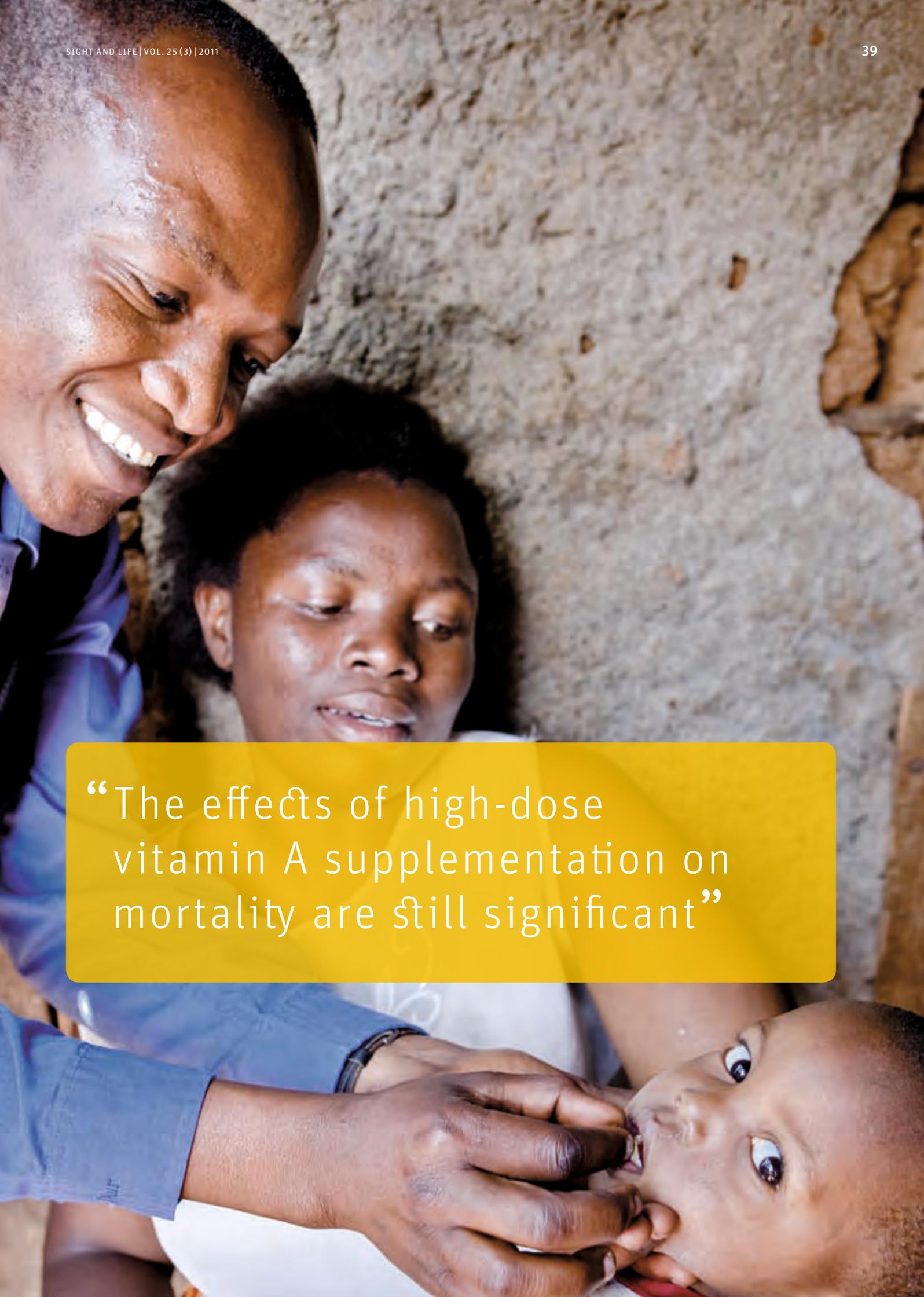
supplementation every three to four months should be instituted wherever and whenever possible.

- WHO-recommended universal vitamin A supplementation in India fails to reach 50% or more of children under five years old.
- Food fortification with vitamin A, possibly in addition to vitamin A supplements, may be the only way to rectify the clinical and biochemical vitamin A deficiencies in Indian children.

#### Introduction

In 1993, three meta-analyses reported that high-dose vitamin A supplementation (VAS) provided an up to 30% reduction in child mortality, especially deaths from diarrhea and measles in low- and middle-income countries.<sup>1–3</sup> Since that time, VAS has been widely advocated and is provided in many of these countries to children aged six months to five years, with an average coverage rate of 86%.<sup>4</sup> In this commentary, I describe the results of a new systematic review and meta-analyses, which include all VAS trials up to 2010, and reconfirm the association of lower mortality following high-dose supplementation with vitamin A.<sup>5,6</sup> The authors also confirm that the effects of VAS on mortality are still significant – even when they include the largely unpublished Deworming and Vitamin A (DEVTA) trial; this is despite the fact that this trial alone found that vitamin A did not significantly reduce the risk of mortality.<sup>7</sup> The DEVTA trial raises issues concerning the effectiveness of VAS. I discuss these, and also the related question of whether there is still a need for VAS if adequate food fortification with vitamin A is in place.

The results of the new meta-analyses were published in the *British Medical Journal* in 2011.<sup>5</sup> In addition, the complete protocol was peer reviewed and published by the Cochrane Collaboration in 2010.<sup>6</sup> The review contributed significantly to the

A photograph showing a man in a blue shirt smiling and feeding a baby. A woman is looking on. The background is a textured wall.

“The effects of high-dose vitamin A supplementation on mortality are still significant”

preparation of recent WHO guidelines for VAS in children aged six to 59 months (Box).<sup>8</sup> The new analysis of all-cause mortality included eight VAS trials in addition to those that had been available for the earlier meta-analyses, adding a further 30% of apparently-healthy children to those previously analyzed. The authors also expanded on the previous reviews by investigating the effects on illnesses that led to death. The authors scoured the literature from 1950 to 2010, without restriction in terms of language or publication status, and examined all randomized trials of oral VAS in children aged six months to five years. Studies of children with current illnesses, of children in hospital, or of food or  $\beta$ -carotene fortification were excluded.

The new analysis included 43 trials involving approximately 215,636 children for the final evaluation. However, not all trials could be evaluated for all outcomes. There were 16 trials that included mortality data; the meta-analyses found a 24% reduction in all-cause mortality. There was a 28% reduction in deaths associated with diarrhea in seven trials, and the incidence of diarrhea and measles in association with VAS was reduced by 15 and 50% in 12 and six trials respectively. A reduced prevalence of vision problems, including night blindness (68%) and xerophthalmia (69%), was found in two trials. In three trials, there was an increased risk of vomiting within the first 48 hours of supplementation.

### Criteria for the meta-analyses

The authors undertook a review to include all available evidence for VAS in children aged six months to five years, and added to previous reviews by investigating the effects on morbidity and the illnesses that lead to death. By investigating all effects in the same review, current estimates were provided of treatment effects, and potential pathways were identified through which VAS might reduce mortality. In addition to examining the prophylactic effects of vitamin A on mortality, **the authors also conducted five subgroup analyses:**

1. Comparisons of WHO-recommended vitamin A dose (100,000 international units, or IU, between six and 12 months; 200,000 IU every four to six months) versus lower or higher doses;
2. Frequency of dosing – high (doses within six months) versus low (one dose only or at > 6 months interval);
3. Effectiveness of VAS by continent;
4. Age – six to 12 months versus one to five years; and
5. Gender – boys versus girls.

There were primary and secondary outcome measures. The primary measure was all-cause mortality at the longest follow-up, but the authors also compared outcomes within the first year and in more than one year after VAS. Secondary outcome

measures included cause-specific mortality from diarrhea, lower respiratory tract infection (LRTI), measles, and meningitis. In addition, the authors compared the incidence and prevalence of the same morbidities, plus Bitôt's spots, night blindness, and xerophthalmia. Adverse events (vomiting and bulging fontanel) were noted and analyzed when possible, and serum retinol concentrations, as a measure of vitamin A status, were examined as continuous or dichotomous outcomes.

In concordance with the objectives of the Cochrane Collaboration, the authors assessed potential bias with respect to methods of treatment allocation, blinding of participants, assessors and providers, and completeness of a trial report. Risk of bias was assessed as high (seriously weakens confidence in the results), low (unlikely to seriously alter results), or unclear. All outcomes were reported with 95% confidence intervals, and overall effects were weighted by the inverse of the variance with a fixed effect model to obtain an average effect size. Other details of the search strategy and statistical analysis can be read in the report.<sup>5</sup>

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**“The meta-analyses found a 24% reduction in all-cause mortality”**  
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### VAS trials extracted for analysis

From several thousand reports, the authors extracted 43 trials used for qualitative analysis, of which 39 were used in the quantitative analyses. In addition, there was one large completed (but largely unpublished) trial that was examined separately; namely, the De-worming and Vitamin A (DEVTA) trial.<sup>7</sup> The authors commented that the trial was likely to meet the eligibility criteria and could be included if there were future updates of the current review.<sup>5</sup> The 39 trials that were analyzed included 215,043 participants, or 99.8% of the children in the review. Of the 43 included trials, 37 compared VAS with a placebo and four used factorial designs comparing vitamin A with other treatments, such as zinc or de-worming. In the other trials, raw data were not available in one, and different doses of vitamin A were combined for the main analysis of the other. The median of the mean ages was 30.5 months, and most trials assigned equal numbers of boys and girls.

### All-cause mortality

All-cause mortality was examined in 17 of the 43 trials, although one reported no mortality<sup>9</sup> so was not included in the analysis. Nevertheless, the 16 trials included 90% of the children in the 43 trials in the review. The data are shown in **Table 1**, together with sub group analyses to investigate specific associations with location, dose, age, and sex all-cause mortality. The table shows

**BOX:** Suggested vitamin A supplementation for infants, children and pregnant women (Data from WHO Guidelines 2011)<sup>8</sup>

Target group	Dose <sup>a</sup>	Frequency	Suitable conditions for intervention
Neonates	At the present time, VAS as a public health intervention is not recommended for neonates within the first 28 days after birth		
Infants 1–5 months	or infants within the first five months after birth (strong recommendations)		
Infants 6–11 months (including HIV+)	100,000 IU (30 mg RE) vitamin A	Once	Populations where the prevalence of night blindness is > 1% in children 24–59 months of age OR where the prevalence of plasma retinol concentrations $\leq$ 0.70 $\mu\text{mol/L}$ is
Children 12–59 months (including HIV+)	200,000 IU (60 mg RE) vitamin A	Every 4–6 months	20% or higher in infants and children 6–59 months of age
Pregnancy	Up to 10,000 IU (daily) OR up to 20,000 IU (weekly)	Daily or weekly for a min. of 12 weeks until delivery	Populations where night blindness $\geq$ 5% in pregnant women or children 24–59 months

VAS, vitamin A supplementation; IU, international units; RE, retinol equivalents; HIV+, human immunodeficiency virus positive

a. Vitamin A can be delivered using soft gelatine capsules, single dose dispenser or graduated spoon. Manufacturers have adopted red capsules for 200,000 IU and blue capsules for 100,000 IU, by consensus.

This information can be found on the WHO eLENA website: <http://www.who.int/elena/en/index.html>

the rate ratio and the heterogeneity of the meta-analysis. The rate ratios for all studies indicate that there were fewer deaths in the groups receiving vitamin A; that is, the overall ratio for the meta-analyses was less than 1.0, with the exception of one study in Latin America.<sup>10</sup> Heterogeneity is a test to determine whether there are genuine differences underlying the results of the studies, or whether the studies were generally homogeneous. The greater the  $I^2$  statistic, the greater the heterogeneity or inconsistency between the studies.<sup>11</sup> In general,  $I^2$  values of 25, 50 and 75% can be taken to mean low, moderate and high inconsistency between studies.

Vitamin A was associated with a 24% reduction in all-cause mortality, and there was moderate inconsistency in the results ( $I^2 = 48\%$ ) (Table 1). Most trials reported results within 13 months; however, five trials measured mortality after 13 months, when the rate ratio was 0.75 (95% CI, 0.64, 0.88). The 25% reduction in all-cause mortality in the longer trials did not differ from the shorter studies, but there was substantially more inconsistency ( $I^2 = 57\%$ ) (data not shown). There was no influence of location, age and sex on all-cause mortality. That is, there were no significant differences in the reductions in all-cause mortality between Africa (15%) and Asia (31%;  $P=0.12$ ); children aged six to 12 (41%) and 12 to 60 months (32%;  $P=0.46$ ) and between males (20%) and females (20%;  $P=0.89$ ). There were smaller numbers of trials within the subgroups, so any differences in the mortality rates from the main study should be interpreted with caution.

Dosing frequency produced some anomalous results. In four trials, a single dose of vitamin A produced a consistent 34%

reduction in all-cause mortality ( $I^2=0\%$ ). More frequent doses every four to six months in 11 trials found an only 19% reduction in mortality and moderate inconsistency ( $I^2=48\%$ ). In addition, in a single trial that dosed more frequently than every four to six months, there was 54% reduction in mortality, which was biologically plausible.<sup>12</sup> The difference between these results was significant ( $P=0.02$ ), but the larger reductions in mortality associated with the smaller group numbers should, again, be interpreted cautiously.

Finally, the authors examined the effects of adding the unpublished DEVTA study to the 16 trials examined above (Table 2). The study was large, including over a million subjects, and when analyzed alone found only a small, non-significant benefit from vitamin A on all-cause mortality. However, when the study was examined with the other 16 studies, although the reduction in all-cause mortality fell from 24 to 12%, it remained significant. However, there was substantial and significant heterogeneity ( $I^2=64\%$ ). The large size of the DEVTA study meant that it contributed 65.2% of the combined effect to all-cause mortality and, although individually it did not reveal any significant benefit for vitamin A supplements, when included in the meta-analysis the combined result still remained clinically significant.<sup>5</sup>



**TABLE 1:** Analyses for all-cause mortality in studies of the effect of vitamin A supplementation in children under five years and the influence of location, dose, age and sex<sup>a,b</sup>

Subgroup (test for difference)	All trials <sup>c</sup>	Trials in primary analysis (%) <sup>d</sup>	Fixed effect rate ratio (95% CI)	Heterogeneity <sup>e</sup> I <sup>2</sup> (%); Q (P)
All studies	43	16 (37)	0.76 (0.69 – 0.83)	48; 29.10 (P=0.02)
<b>Location (P=0.12)</b>				
Africa	6	5 (12)	0.85 (0.73 – 0.98)	59; 9.8; (P=0.04)
Australia	2	0	–	–
Asia	28	10 (23)	0.69 (0.61 – 0.79)	40; 15.00 (P = 0.09)
Latin America	7	1 (2)	1.00 (0.14 – 7.08)	–
<b>Dose (P=0.02)</b>				
WHO single dose	15	4 (9)	0.66 (0.52 – 0.83)	0; 2.15 (P=0.54)
WHO dose (every 4 – 6 months)	18	11 (26)	0.81 (0.72 – 0.90)	48; 19.17 (P=0.04)
More frequent	10	1 (2)	0.46 (0.3 – 0.71)	–
<b>Age (P=0.46)</b>				
6 – 12 months	32	4 (9)	0.59 (0.43 – 0.82)	0; 3.51 (P=0.45)
12 – 60 months	37	4 (9)	0.68 (0.57 – 0.81)	15; 2.72 (P=0.32)
<b>Sex (P=0.89)</b>				
Males	43	5 (12)	0.80 (0.66 – 0.91)	62; 7.79 (P=0.05)
Females	43	5 (12)	0.80 (0.65 – 0.95)	0.0; 2.87 (P=0.41)

a. All-cause mortality measured in 16 trials at the longest follow-up in all studies; data from reference.<sup>5</sup> The summary effect is shown as a rate ratio (95% confidence intervals). Rate ratios less than one indicate a benefit from vitamin A which was significant if both CI were also < 1.

b. Mortality outcome was reported in 17 trials but one of these reported no events<sup>9</sup> so only 16 trials were available for the primary meta-analysis.

c. All trials in subgroup.

d. All trials in subgroups with data available for analysis. Significances for differences between subgroups are shown in column 1 above the relevant section.

e. Tests for heterogeneity examined the null hypothesis that all studies are examining the same effect. Cochrane's 'Q' (P) (= 'risk of bias' tool) is one measure but has certain disadvantages. I<sup>2</sup> statistic was introduced to overcome the problems in 'Q'.<sup>11</sup> See text for interpretation of I<sup>2</sup>

“Where incidence data were available, analyses showed that numbers of cases of diarrhea (15%) and measles (50%) were both significantly depressed by vitamin A”

#### Cause-specific mortality and morbidity

The authors examined their data to determine whether vitamin A reduced mortality from diarrhea, measles, meningitis, and lower respiratory tract infections (LRTI) (Table 3). LRTI and pneumonia outcomes were combined *post hoc*, as they have similar pathology and many studies did not have complete diagnostic information. The results indicated that only diarrhea mortality was significantly reduced by vitamin A (27%). The rate ratios for

the other three diseases were all less than 1.0, i.e., a reduction in mortality following vitamin A, but were not significant.

The trials were also examined to determine the effects of vitamin A supplementation on the incidence and prevalence of diarrhea, malaria, measles, and LRTI (Table 4). Incidence is the figure expressing the number of new cases within a defined time period, such as the duration of the trial, while the prevalence is the number of cases at a fixed point in time. Where incidence data were available, analyses showed that numbers of cases of diarrhea (15%) and measles (50%) were both significantly depressed by vitamin A. Prevalence data for diarrhea suggested that the number of cases were increased following vitamin A (8%), but there were only two trials. No trial looked at the prevalence of measles.

One trial reported that the incidence of malaria was significantly lower in the VAS group (27%), but there were no prevalence studies. Seven trials contained incidence data on LRTI, and the rate ratio suggested that respiratory problems increased

**TABLE 2:** The effect of including the DEVTA trial in the meta-analysis on all-cause mortality<sup>a</sup>

Trials available for study	Trials in analysis of all-cause mortality (%)	Fixed effect rate ratio (95% CI)	Heterogeneity I <sup>2</sup> (%)
43	16 (37)	0.76 (0.69 – 0.83)	48
44 <sup>b</sup>	17 (39)	0.88 (0.84 – 0.94)	64

a. All-cause mortality measured at the longest follow-up in all studies. See **Table 1** for further explanation of data.

b. Trials available for meta-analysis including the Deworming and Vitamin A Trial (DEVTA)<sup>7</sup>

following vitamin A treatment (14%). However, they were small studies, and although the results were consistent (I<sup>2</sup>=22%), they only included 8% of the participants and the results were not significant. There was only one prevalence study on LRTI, which reported that respiratory disease was non-significantly lower in the VAS group.

“Evidence suggested that vitamin A produced a large reduction in the incidence and prevalence of night blindness and a large reduction in the prevalence of xerophthalmia”

#### Vision outcomes, serum retinol concentrations and adverse events following high-dose vitamin A

Only a small number of studies in the review examined vision outcomes (n=1–4) (**Table 5**). The evidence suggested that vitamin A produced a large reduction in the incidence and prevalence of night blindness (15%), and a large reduction in the

prevalence of xerophthalmia (68%). Effects on Bitôt’s spots and the incidence of xerophthalmia were not significant.

Three trials reported that high-doses of vitamin A tripled the risk of vomiting within 24 hours. A bulging fontanel was also examined in three trials, but the results were inconclusive.

A number of trials examined serum retinol concentrations (n=13), and some used serum retinol to assess vitamin A deficiency (< 0.70 µmol/L; n=4). These analyses suggested that VAS reduced the proportion of children with deficiency (29%), and increased serum retinol concentrations. However, heterogeneity was substantial and the analyses included no more than 3% of the children under review (**Table 4**). Furthermore, it is most unlikely that any of these trials will have corrected serum retinol concentrations for the influence of inflammation, since only one of the trials included<sup>13</sup> was published since the introduction of a method of correction in 2003.<sup>14</sup> Therefore, some serum retinol concentrations will have been depressed by inflammation, and vitamin A deficiency will have been over-estimated.

#### The (unpublished) DEVTA trial

The DEVTA study was a cluster-randomized trial of 1 million children of one to six years of age in North India.<sup>7</sup> In the state of Uttar Pradesh, 72 administrative blocks were randomly allocated

**TABLE 3:** Cause-specific mortalities in vitamin A trials in children 6 month to 5 years<sup>a</sup>

Outcome	Number (%) of trials <sup>a</sup>	Participants %	Rate ratio (95% CI), fixed effect	Heterogeneity I <sup>2</sup> (%)	Follow-up weeks
Diarrhea	7 (16)	42	0.72 (0.57, 0.91)	2	48–104
Measles	5 (12)	41	0.80 (0.51, 1.24)	0	52–104
Meningitis	3 (7)	19	0.57 (0.17, 1.88)	0	48–108
LRTI <sup>b</sup>	7 (16)	42	0.78 (0.54, 1.14)	14	48–104

a. Subgroups of trials where cause-specific mortalities were available were extracted from 43 trials containing 215,633 participants. For further details on analyses see legend for **Table 1**.

b. LRTI is lower respiratory tract infection.

**TABLE 4:** Incidence and prevalence of morbidities in children aged six months to five years, following vitamin A supplementation studies<sup>a</sup>

Illnesses	Number (%) of trials <sup>b</sup>	Participants % of number in all studies	Rate ratio (95% CI), fixed effect	Heterogeneity I <sup>2</sup> (%)	Follow-up weeks
<b>Diarrhea</b>					
Incidence	13 (30)	17	0.85 (0.82, 0.87)	95	24–60
Prevalence	2 (5)	7	1.08 (1.05, 1.12)	87	48
<b>Malaria</b>					
Incidence	1 (2)	<1	0.73 (0.60, 0.88)	NA	52
Prevalence	2 (5)	11	0.72 (0.41, 1.28)	0	48
<b>Measles</b>					
Incidence	6 (14)	9	0.50 (0.37, 0.67)	0	16–78
Prevalence	0	0	NA	NA	NA
<b>LRTI<sup>c</sup></b>					
Incidence	7 (16)	8	1.14 (0.95, 1.37)	22	24–60
Prevalence	1 (2)	<1	0.46 (0.21, 1.03)	NA	48

a. Incidence expresses the number of new cases within a defined time period e.g., the duration of a trial, while prevalence is the number of cases at a fixed point in time.

b. Subgroups of trials where cause-specific mortalities were available were extracted from 43 trials containing 215,633 participants. For further details on analyses see legend to **Table 1**.

c. LRTI is lower respiratory tract infection.

to vitamin A (200,000 IU every six months) or control. Dosing was given on mass treatment days by existing health workers (at Anganwadi centers) to all children aged between six months and six years. Separately, all villages were visited every six months to monitor any child deaths. Annually, one village per block was randomly chosen and visited to collect blood samples and record illnesses in the past three weeks, and eye conditions.

Over a five year period (1999–2004), the treatment group had, on average, 10 of the 11 VAS and the control group had on average one non-trial dose of vitamin A. Twenty-five thousand child deaths were recorded. In the VAS blocks the probability of death before six years was 24.9 per 1,000, as against 26.0 per 1,000 in the controls, a risk ratio of 0.96 (95% CI 0.89, 1.03). That is, a non-significantly lower risk of 4% was associated with vitamin A treatment. VAS did significantly reduce the prevalence of Bitôt's spots (2.2% vs 4.3%;  $P < 0.03$ ) and low plasma retinol concentrations  $< 0.35 \mu\text{mol/L}$  (11% vs 22%;  $P < 0.00001$ ) (**Table 6**). In addition, VAS was associated with a lower prevalence of pneumonia (2.6% vs 4.1%;  $P < 0.03$ ), but there was no effect on measles. The cut-off for Bitôt's spots recommended by the WHO for satisfactory vitamin A status is  $\leq 0.5\%$ ;<sup>15</sup> thus, vitamin A deficiency remained in both groups during the trial. Likewise, the presence of more than 10% with retinol concentrations  $< 0.35 \mu\text{mol/L}$  is an indication of severe vitamin A deficiency, and even if the authors had corrected plasma retinol for the presence

of inflammation, it is likely that much evidence of low serum retinol concentrations would have remained.

### “Children who are deficient in vitamin A are unlikely to be deficient in that nutrient alone”

Several factors may explain the lower effect of VAS on all-cause mortality in the DEVTA trial. There may be design or other limitations in the trial which will not be revealed until the trial has been published in a peer-reviewed journal. In addition, VAS may have been inadequate to correct the vitamin A deficiency present in the community. It has been shown by others that a high-dose of vitamin A given to vitamin A deficient patients is not sufficient to increase serum retinol concentrations for more than two to three months.<sup>16,17</sup> That is, children, even in the vitamin A villages, may still have been vitamin A deficient for more than half of the year. Evidence for the continuing presence of vitamin A deficiency was found in the DEVTA study (**Table 6**) and has already been discussed. Furthermore, children who are deficient in vitamin A are unlikely to be deficient in that nutrient alone. Vitamin A is present in eggs, milk and flesh foods and green leafy vegetables. These foods are important sources of

**TABLE 5:** Effect of high-dose vitamin A on vision, serum retinol concentrations and adverse events<sup>a,b</sup>

Outcome	Number (%) of trials	Participants – % of number in all studies	Rate ratio (95% CI)	Heterogeneity I <sup>2</sup> (%)	Follow-up weeks
<b>Bitôt' Spots</b>					
Incidence	1 (2)	13	0.93 (0.76, 1.14)	NA	72
Prevalence	4 (9)	29	0.45 (0.33, 0.61)	64	36–96
<b>Night blindness</b>					
Incidence	1 (2)	13	0.53 (0.28, 0.99)	NA	72
Prevalence	2 (5)	11	0.32 (0.21, 0.50)	0	52–68
<b>Xerophthalmia</b>					
Incidence	3 (7)	27	0.85 (0.7, 1.13)	63	48–72
Prevalence	2 (5)	27	0.31 (0.22, 0.45)	0	36–84
<b>Serum retinol concentr.</b>					
No. deficient (<0.7 μmol/L)	4 (9)	1	0.71 (0.65, 0.78)	78	24–96
Serum retinol concentr.	13 (30)	3	0.31 (0.26, 0.36)	95	4–96
<b>Adverse events</b>					
Vomiting	3 (7)	1	2.75 (1.81, 4.19)	21	48 hours
Bulging fontanel	3 (7)	<1	5.00 (0.24, 103.72)	NA	48 hours

a. Trials were selected from 43 trials containing 215,633 participants. For further details on analyses see legend to **Table 1**.

b. NA = not available.

many other nutrients: energy, protein, fat, micronutrients and minerals. Just providing vitamin A is not going to correct other deficiencies or reduce exposure to infections.

It will be argued that most of the other trials with vitamin A did have an impact on all-cause mortality. However, communities differ in their culture, cooking habits, and social attitudes – not to mention the level of poverty. Hence, nutritional status differs. In a previous article in *Sight and Life* on the differences between Asian and African infants in their response to neonatal dosing with vitamin A, it was noted that withholding colostrum from newborn infants was far commoner in the Indian sub-continent than in Africa.<sup>18</sup> In a review of the literature, Ross and Harvey suggested that the potential amount of vitamin A from colostrum over the six days from a mother living in a poor environment was ~3.6 mg (12.5 μmol RE or 12,000 IU).<sup>19</sup> A deficit of this amount could have a long-term effect on the vitamin A status of the infant from which, in a poor environment, it might be difficult to recover. Thus, vitamin A deficiencies in India may be more severe than in those other countries where VAS has reduced mortality. In another high-dose vitamin A intervention trial in Central India, there was also no effect on all-cause mortality,<sup>20</sup> yet a recent study the same region found continuing evidence of vitamin A deficiency in the form of Bitôt's spots, night blindness and conjunctival xerosis in excess of WHO criteria.<sup>21</sup> Likewise, other recent studies in West Bengal (NE India)<sup>22</sup> and

Maharashtra (Western Central India)<sup>23</sup> reported Bitôt's spots above acceptable limits and high numbers of subclinical deficiency based on serum retinol.

Thus, it would seem that there is no lack of evidence of vitamin A deficiency in many parts of India but, in spite of this, two large intervention trials failed to significantly influence all-cause mortality.<sup>7,20</sup> This means either that vitamin A is not responsible for reducing infection and mortality, or that the amount of vitamin A needed to overcome deficiency is insufficient, and that more frequent treatment is needed. In support of the latter suggestion, Rahmathullah and colleagues, in a randomized controlled trial in Southern India, gave small weekly doses of vitamin A (8,333 IU) or 20 mg vitamin E to the controls. This involved 15,417 preschool children; all-cause mortality was reduced by 54% (relative risk 0.46 [95% CI 0.30, 0.71]).<sup>12</sup> Weekly dosing with vitamin A is impractical as a national program, but the success of this trial suggests that alternative measures are needed to provide a regular supply of vitamin A to preschool children. Food fortification with vitamin A could provide a regular basic intake to supplement other dietary sources, and there are plans to begin fortification of milk and cooking oil with vitamin A in Rajasthan (personal communication, Dr C Clewes, Global Alliance for Improved Nutrition, or GAIN). In addition, rice is being considered as a possible vehicle, since it is widely consumed throughout India. A product combining natural rice with a fortified,

**TABLE 6:** Bitôt's spots, plasma retinol, measles and pneumonia in children in the DEVTA study<sup>a</sup>

Variable measured	Vitamin A group	Control group	Significance
Bitôt's spots	2.2%	4.3%	P = 0.003
Plasma retinol <0.35 µmol/L	11%	22%	P = 0.00001
Measles (past three weeks)	1.4%	0.8%	P = 0.20
Pneumonia (past three weeks)	2.6%	4.1%	P = 0.03

a. Data from reference<sup>7</sup> was collected annually from one randomly chosen village per block.

reconstituted grain was successfully field-tested as long ago as 1995 in Indonesia,<sup>24</sup> and it is timely for something similar to be introduced to India. A trial with multiple micronutrient fortified rice, also containing vitamin A, has just been completed in the south of India and the results are being published shortly (personal communication Dr K Kraemer, *Sight and Life*). Universal vitamin A supplementation should only be a short-term mitigation strategy, and additional measures are needed.

## “Food quality could be improved via fortification with vitamin A – cooking oil and rice are potential vehicles”

### Conclusions

Most vitamin A supplementation trials have been shown to reduce the risk of all-cause mortality in preschool children, and the most recent meta-analysis has confirmed this. The meta-analysis also showed a significant effect on mortality – even when the very large and unpublished non-significant Indian trial was included. In fact, two large VAS trials in India found no significant effect of vitamin A treatment on mortality, but it is possible that vitamin A status was only partially restored. In any case, the lack of an impact on all-cause mortality in those areas where vitamin A intervention appears to be unsuccessful does not mean that there have been no benefits, or that universal vitamin A supplementation should be stopped.<sup>25</sup> There has been a reduction in clinical vitamin A deficiency in India in the last 20–30 years,<sup>26</sup> and halting the program before the dietary intake is improved may reverse this progress – allowing the re-emergence of blinding xerophthalmia. VAS needs to continue to prevent this happening, but coverage needs to improve. The National Nutrition Monitoring Bureau reported in 2003 that only 23% of rural preschool children obtain the full dose of vitamin A recommended by the WHO,<sup>26</sup> and that in West Bengal the figure was only 4%.<sup>22</sup> In addition, the supply and quality of the

food needs to be improved, especially for people in the poorest sections of the community. Food quality could be improved via fortification with vitamin A, and cooking oil and rice are potential vehicles for this. The meta-analysis showed that vitamin A protected against diarrhea and measles. These illnesses are major causes of morbidity and death, and fortification, together with universal vitamin A supplementation, should make greater inroads into the problem of vitamin A deficiency in India.

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## Opinion 1: Operations Research Could Help to Fine-Tune Vitamin-A-Related Interventions

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We agree with Dr Thurnham's suggestion that there is a need for more research into whether increasing the frequency of dosage could be a way of boosting the effectiveness of vitamin A supplementation in the context of highly prevalent vitamin A deficiency.<sup>1</sup> Nearly all vitamin A supplementation programs worldwide supplement children every six months, despite evidence that more frequent dosing might increase efficacy.<sup>2,3</sup> The need for more frequent dosing in certain contexts is also supported by surveillance data from rural Bangladesh, which shows that childhood night blindness routinely exhibited seasonal peaks during the months leading up to supplementation, despite the very high coverage of the bi-annual National Vitamin A Program.<sup>4</sup>

Program implementers might view the suggestion of adding an additional round of vitamin A capsule distribution to

programs as an example of the “perfect being the enemy of the good,” since mobilizing successful distribution campaigns requires significant community outreach activities by health workers. While this is an important concern, one could also argue that low-hanging fruit could be left on the tree during the final push to reach the MDGs, if new approaches to addressing vitamin A deficiency are not explored. Effectiveness studies comparing different dosage frequencies could be integrated into existing programs and might bring a more definitive answer to this question.

Of course, food-based strategies are also an important option for improving the vitamin A status of populations. Fortification of staple foods is a time-proven strategy for controlling micronutrient deficiencies, and has distinct advantages. While fortification programs in South Asia have historically been challenged by the lack of a suitable delivery vehicle, newer technologies such as rice fortification, home-based fortification with Sprinkles™ and MixMe™, and biofortification (Golden Rice™) are increasingly accepted as viable strategies for improving vitamin A status. Each of these options could be used to improve the vitamin A status of an entire population, in addition to specific population groups such as young children. However, it is also important to consider the potential unintended consequences of universal fortification with vitamin A. For example, there is some evidence that vitamin A may increase mother-to-child transmission of HIV, though the dosage and form of vitamin A that may lead to such effects is uncertain.<sup>5</sup> For HIV prevalent areas, targeted delivery of vitamin A to children (through supplementation or home-based fortification) might therefore have advantages as a strategy, since vitamin A supplementation has been shown to reduce mortality among both HIV+ and HIV- preschool-aged children.<sup>6</sup>

Policy-makers will increasingly be called upon to make decisions about when to target or even phase out universal vitamin A

supplementation programs, as fortification programs are expanded or as improvements in vitamin A status take place. Such decisions should not be taken lightly, as children’s lives (and sight) hang in the balance. Careful monitoring of the adequacy of interventions to control deficiency, particularly among hard-to-reach populations, will be of critical importance during such transitions. The development of more field-friendly methods to accurately assess vitamin A status would be a welcome tool to facilitate such decision-making.

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## Opinion 2: Mechanistic Research Could Help to Fine-Tune Vitamin-A-Related Interventions

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The new meta-analysis on the health and survival benefits of vitamin A supplementation (VAS) by Mayo-Wilson and colleagues<sup>1</sup> confirms and extends what we already knew with a comforting degree of certainty; namely, that intermittent high-dose VAS given to children aged six to 59 months in low-income countries saves about one quarter of them from dying in childhood. Alfred Sommer and his colleagues at the Johns Hopkins Bloomberg School of Public Health – whose institutional motto is

“Protecting Health, Saving Lives – Millions at a Time” – can take much of the original credit for this. They recognized the value of a serendipitous finding, replicated it, and then pressed its case as a translatable intervention that has since, indeed, saved uncountable lives. The comments that follow should in no way be interpreted as undermining the enormity of this success.

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## “The accelerating march of modern science provides us with the tools to illuminate the way forward”

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Empiricism has had many successes in medicine. After all, it took more than 2,200 years after Hippocrates described the use of willow extracts for pain relief until the first chemical synthesis of salicylic-acetic anhydride, and a further 40 years before Bayer marketed Aspirin. Another 60 years or so passed before the mechanism of action was uncovered, and before clinical trials documented its anti-clotting efficacy. These discoveries have now armed physicians with the knowledge of when, in whom, and how much to prescribe, a knowledge of the drug’s contraindications, and an armory of alternative non-steroidal anti-inflammatory agents. With vitamin A, we are in an analogous position to the Hippocratic era; we know it works, but we have no idea why, and we don’t know to whom, when, and in what quantities it would be most efficaciously given. In short, we are still looking through a glass darkly.

### Many questions remain

A stern critic might observe nutritionists to be dangerously complacent. There is much still to be learnt about vitamin A, even at the epidemiological level. The accompanying commentary by Thorne-Lyman and Fawzi lists some of the questions around dosing frequency, and supplementation versus fortification. Many additional questions can be listed: Could neo-natal administration of vitamin A save additional lives? If not, why not? Why do the very large studies of vitamin A in pregnancy and maternal deaths show such disparate results? Is it true that maternal vitamin A supplementation increases mother-to-child-transmission of HIV? And if so, how? Is it true that lower doses of vitamin A might actually be more efficacious, as has been suggested (and note the large discrepancy in lives saved in the Mayo-Wilson analysis with different dosing regimes)? Is it true that vitamin A administration may have a malign interaction with inactivated vaccines such as DTP, especially in girls? Is it true that neo-natal VAS obliterates the apparent later benefit of early measles vaccination in reducing all-cause mortality? Is it true that the benefits of VAS are waning with time, and that some of the possible downsides

might start to compete with the upsides before too long? Each of these questions has its champion.

Neither the Mayo-Wilson meta-analysis nor David Thurnham’s summary shed any light on the mechanism of action of VAS. There is an underlying assumption that it results simply from a reversal of deficiency, but the epidemiological evidence does not support this, and there are other possible mechanisms involving a re-setting of the adaptive immune system that urgently require to be investigated if we are to maximize the potential benefits of VAS and ensure that we do no harm. The accelerating march of modern science provides us with the tools to illuminate the way forward, if we have the wisdom to stop peering through that glass darkly and to come face to face with the underlying pathways and mechanisms.

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# Dr Donald S McLaren

# The Legacy of a Life

The distinguished scientist Dr Donald S McLaren is one of the great pioneers of the study of vitamin A deficiency disorders. Throughout his extraordinary life, he has been at the forefront of research in this field, and has published many groundbreaking books, papers and other key texts. Although Dr McLaren has been in retirement for the past two decades, he has generously played a significant role in the work of *Sight and Life* during this period.

Dr McLaren recently spared some time to reflect with *Sight and Life* Magazine on his unique career.

**Sight and Life Magazine (SAL):** Dr McLaren, you have had a long and distinguished career and are still extremely active in the field of vitamin A studies. What is the main focus of your working life today?

**Donald McLaren (DM):** I've been retired since 1998, although I have been involved in a number of activities for *Sight and Life* over the years, acting in a consultancy capacity for the organization – mainly writing a number of monographs. In particular, I wrote the *Sight and Life Manual on Vitamin A Deficiency and Disorders*, which has already gone through two editions, with a third likely.

**SAL:** Why has vitamin A been such a main point of focus in your life?

**DM:** As is explained in my autobiography – *Towards the Conquest of Vitamin A Deficiency Disorders*, which is published by *Sight and Life* – when considering my career, you have to remember that it took place in a totally different era from today. Everything was entirely different; there's no chance that anybody else would follow the same path today. The world is a different place.

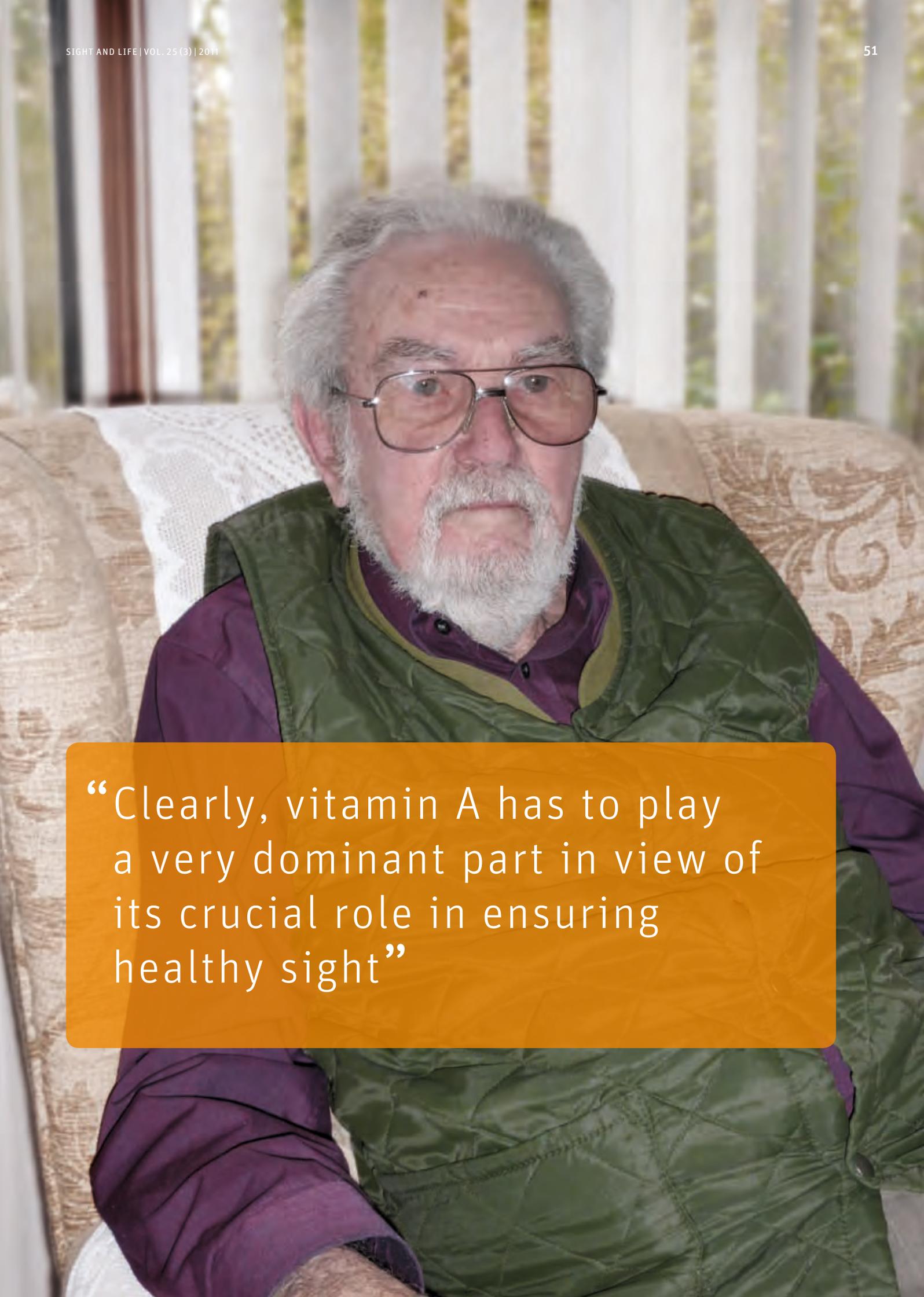
Born in 1924, I was brought up in the Protestant Church, which had an important influence on my development. As a

child at Sunday School at The Metropolitan Tabernacle, a very large Baptist Church in Newington Butts in south east London, I was influenced by a missionary from China, Owen Warren, who talked about his work there. I wanted to become a missionary myself, but China was out of bounds by the time I was old enough to consider such a path for myself. I opted for Medicine instead, thanks to a brush with pain and disease as a child. I was also much influenced by the life of the great missionary from the Alsace – Albert Schweitzer, the author of *On the Edge of the Primeval Forest* and a Nobel prizewinner.

I went to study Medicine at Edinburgh and, soon after I arrived, I met the lady who graciously agreed to be my wife. We left for India after I qualified in 1949 with an MB ChB degree, and I ended up in a hospital there in a tribal area in Orissa, south of Kolkata, on the east coast of India. Through that, I felt directed towards scientific work, rather than continuing in missionary work. I submitted my research to Edinburgh University and was awarded a Clinical Doctor of Medicine degree. Most of my work had to do with xerophthalmia, which was the most common blinding disease prevalent in young children in the world at that time.

After five years, I joined the London School of Hygiene and Tropical Medicine, to start my PhD in nutrition. I did laboratory research at the Human Nutrition Research Unit (HNRU), which investigated blindness in animals caused by vitamin A deficiency. As my PhD studies came to a close, another opportunity presented itself via my professor, who was advising the World Health Organization (WHO) in Geneva. One day, he told me there was an opportunity to work for WHO as consultant in Indonesia. I went there and was able to write a report on the situation as I





“Clearly, vitamin A has to play a very dominant part in view of its crucial role in ensuring healthy sight”

encountered it. I found that very severe blinding – occasioned by vitamin A deficiency – was prevalent in number of big cities in Indonesia. This was the first report that WHO had ever issued on the disease.

I also did one or two other “first things” thanks to my consultancy work in Indonesia. After a year, I was invited to attend the very first international meeting on xerophthalmia – my paper was only one of two that were given on findings in young children. The other one was given to the meeting by an older doctor, HAPC Oomen, who had also been a missionary in a Catholic hospital in Indonesia.

Another “first” was that, in the early 1960s, WHO had become much more interested in my work. They commissioned a scientific research program, including a survey of the whole world. Three of us did this – Dr Oomen travelled in Asia, I travelled in Africa and the Middle East, and a Latin American eye doctor covered that hemisphere. This was the very first time, scientifically, that understanding of VADD and xerophthalmia was put together and published. Part of this research, funded by the National Institutes of Health in the US, was the first ever trial in the field, under experimental conditions, of vitamin A capsules aimed at preventing the disease. I was responsible for carrying out that work, along with another colleague from WHO. I wrote the very first book on the subject, *Malnutrition and the Eye*, which was published in 1963. I was able to pioneer research into that phase of vitamin A deficiency during the early days of the conquest of xerophthalmia.

**SAL:** *Looking back at your achievements, is there one that you think is most important to the wider world?*

**DM:** That’s very difficult to say. In the case of vitamin A deficiency, it wasn’t so much a matter of discovering the cause. This had long been known, especially since the vitamin itself was discovered in about 1912. The area that I was able to contribute to was, largely, communicating what was known in the laboratory and the hospital to governments, to international organizations, to the public – and to broadcast it, and bring people to understand how serious it was and what a terrible disease it was. I could help people understand that only few units of vitamin A in the diet could prevent everything going wrong. So my work was very influential in that regard.

**SAL:** *You have acted as an advocate for those who didn’t necessarily have a voice themselves. Are there lessons you have learned from taking on this role?*

**DM:** That’s a very difficult question to answer. In 1974, I published an article in *The Lancet* entitled *The Great Protein Fiasco*. In my opinion, the belief in the “Protein Gap” is one of the

greatest errors committed in the name of nutrition science in the past half-century. But the lesson has been learned. In the world as a whole, and especially in India, Africa and the Middle East, the problem was broader than one of protein deficiency alone. It was more about the deficiency of energy sources in general. The children under review were pure skin and bone, just like the ones in the Horn of Africa at the present time. This is not just protein deficiency; it’s a failure of all food energy sources, or starvation, as with adults in prisoner-of-war camps.

There is the same failure to recognize obesity. Its real causes are still not known; it’s very complex and, of course, is out of control – even in developed countries.

Thirdly, it’s only really in the last year or two that there has been a recognition that nutrition, or malnutrition, *in utero*, during the first year of life, has a lifelong influence on the individual as far as the increased occurrence and severity of a whole range of chronic degenerative disorders is concerned. Recent research suggests that disorders of a whole new area known as epigenetics may be responsible.

Finally, there is a lack of nutrition teaching in medical schools. I’ve published research supported by the Wellcome Trust which shows how – not only in Europe but also in the UK and North America – the teaching of nutrition in general is grossly neglected, even today.

**SAL:** *You suggest a major failing of the medical and healthcare systems in the broadest sense. Is there a reason why the subject of nutrition is not taught more broadly and deeply?*

**DM:** I have followed the subject of nutrition in Germany, the UK and the US. In each case, the relevant medical school failed to separate out nutrition as a full subject. It hid it under Biochemistry and sometimes Agriculture. Many dietitians are non-medical and have inadequate teaching in Medicine as a background. But that’s what is needed. In addition, pretty much without exception, medical schools do not examine nutrition – because of its low status. You’ll never get medical students to prepare for exams unless they’re going to gain something for their pains. I’ve tried to change this, as have others on the inside, but without success. I wrote a paper in the *American Journal of Clinical Nutrition* that raises these points and argues that the subject of nutrition carries less and less value within medical schools.

In my time, this work with xerophthalmia was dominated by medical doctors and eye doctors, in particular ophthalmologists and biochemists. Today, the study of nutrition has moved away from vitamin A. International bodies don’t record the incidence of xerophthalmia, as for all intents and purposes, this is seen as a disease which is no longer a public health problem. More recently many of the adverse effects of vitamin A deficiency of only relatively minor degree on the effects of infection have been

controlled, by vitamin A intervention. Much of this successful work is due to the efforts of Al Sommer and his team at Johns Hopkins University; many countries have supplementation programs; and of course *Sight and Life* has played a prominent part in spreading the word.

*Sight and Life* has had to shift its focus and responded to the changing situation, turning away from xerophthalmia and introducing the concept of micronutrient malnutrition. Today, the “Sight” element in the whole ethos of *Sight and Life* has changed. The focus has moved from xerophthalmia and now focuses on nutrition security.

**SAL:** *You’ve contributed to many publications, and have played a significant role as a writer and communicator. Which of these publications has been most important to you?*

**DM:** I published the first ever book on malnutrition and the eye. However, I also published the first nutrition textbook to be written primarily for teaching medical students in medical school – *Nutrition and its Disorders* – which went to four editions. Similarly, I published a pediatric nutrition textbook, which went to three editions and was the first in its field. Other publications include *Nutrition in the Community* and a color atlas which showed all the clinical signs of diet-related disorders. But I’ve also written over 50 articles in other people’s books and, of course, over 200 scientific papers, many but not all of which were on vitamin A. In the long term, though, one has to rate one’s original publication, even if it is not now readily accessible.

**SAL:** *2012 is the 100<sup>th</sup> Year of Vitamins. How do you think this should be celebrated?*

**DM:** Clearly, vitamin A has to play a very dominant part in view of its crucial role in ensuring healthy sight. But there are many other nutrients that merit attention, including trace elements – minerals such as iron or zinc that are beneficial in the diet. I see little value in celebrating vitamins without referring to these nutrients as well.

**SAL:** *You have talked of your early influences – the passion and conviction that inspire your work. Do you have a particular saying or philosophy that you refer to when you’re in difficult situations, or struggling with a scientific problem? Is there something specific that gives you strength?*

**DM:** I did coin a term which appeared in my book, but a scientific paper or medical textbook is not the place for this kind of thing, I’m afraid! It’s quite short: “Poverty in the Midst of Plenty.” This describes the phenomenon of vitamin A deficiency, especially in the cities of Asia. People in that part of the world have an

almost mystical belief in the nutritional value of rice, and see it as a complete diet. This is far from the case, however, because rice does not contain vitamin A. Ironically, that part of the world abounds in dark green, leafy vegetables, but these are not consumed as part of the traditional diet. This factor was unfortunately neglected by IVACG for a long time. Dr Ooman, however, was a botanist as well as a medical doctor, and he understood this issue. He realized that high levels of chlorophyll – which are present in green, leafy vegetables – are associated with high levels of β-carotene, which is synthesized in the body to form vitamin A.

**SAL:** *Is there anything outside your work that inspires you?*

**DM:** I am still a practicing Christian. In addition, once I had the leisure of retirement, I was able to look into the chemistry of carotenoids, and all the related compounds. They are one of most important groups of substances in the whole world. Carotenoids in microorganisms are to be found in the very beginning of the evolution of life. From them come ultimately all energy sources in photosynthesis, the vitamin A-related photoreceptors of all eyes, and in nearly all cells they serve in nuclear receptors in such processes as gene expression, growth and development. Today knowledge advances at an unprecedented rate. To me this affirms that such a resulting Creation demands a corresponding Creator.

*Interview by Jonathan Steffen*

# Fifteen Years of Fortifying With Folic Acid: Birth Defects are Reduced and Healthcare Expenses are Averted

**Sarah Zimmerman**

Flour Fortification Initiative, Atlanta, Georgia, USA

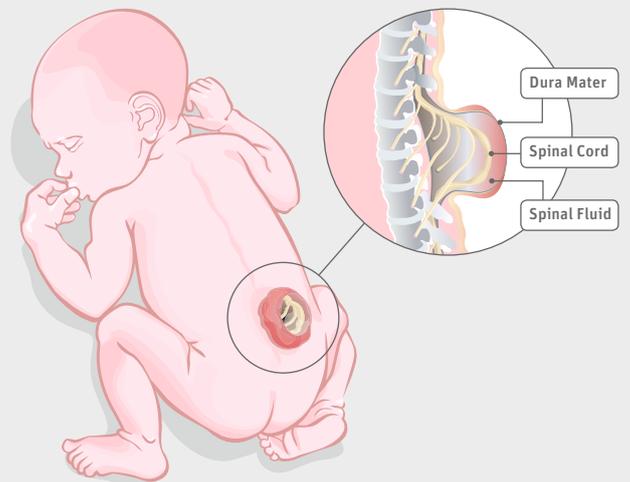
## Introduction

Fifteen years of experience has shown that fortifying flour with folic acid is a reliable method of significantly reducing the incidence of neural tube defects (NTDs) such as spina bifida, anencephaly, and encephalocele (Figure 1). In 1996, Oman was the first country to achieve national-scale fortification of flour with folic acid to prevent these permanently disabling or fatal birth defects. Also in 1996, the United States and Canada were beginning to add folic acid to flour, but these larger countries did not achieve nationwide coverage until the end of 1997. By 2008, an estimated 22,000 birth defects were prevented due to this intervention,<sup>1</sup> and by 2011 this vitamin was required to be added to flour in 57 countries (Table 1).

Oman experienced exceptional results, as its incidence of spina bifida dropped from an average of 3.17 per 1,000 births before fortification to an average of 0.96 per 1,000 births after fortification for a 70% reduction.<sup>2</sup> Other studies show a 30 to 60% reduction in NTD rates due to fortification (Table 2). In ad-

“All people need folic acid to produce and maintain new cells and decrease the risk of folate deficiency anemia”

**FIGURE 1:** Spina bifida (open defect)



© Robert Pfeiler

dition, fortifying flour with folic acid saves millions of healthcare dollars annually, because the cost is minimal compared to the cost of providing surgeries, physical therapy and rehabilitation for children with spina bifida.

All people need folic acid to produce and maintain new cells and decrease the risk of folate deficiency anemia. Women, in particular, need folic acid at least a month before conception and in the early days of pregnancy, because the neural tube, which ultimately develops the child’s brain and spinal cord,

**TABLE 1:** Countries with mandatory regulation to add folic acid to flour, their population and number of births

Country <sup>1</sup>	Population (2010) <sup>2</sup>	Annual births (2009) <sup>3</sup>	Country <sup>1</sup>	Population (2010) <sup>2</sup>	Annual births (2009) <sup>3</sup>
Argentina	40,412,000	691,000	Puerto Rico	3,749,000	52,000
Australia	22,268,000	270,000	Qatar	1,759,000	16,000
Bahrain	1,262,000	14,000	Saint Vincent	109,000	2,000
Barbados	273,000	3,000	Saudi Arabia	27,448,000	593,000
Belize	312,000	7,000	Senegal	12,434,000	476,000
Bolivia	9,930,000	262,000	South Africa	50,133,000	1,085,000
Brazil	194,946,000	3,026,000	Tanzania	44,841,000	1,812,000
Canada	34,017,000	358,000	Turkmenistan	5,042,000	111,000
Cameroon	19,599,000	711,000	United States	310,384,000	4,413,000
Chile	17,114,000	252,000	Uruguay	3,369,000	50,000
Colombia	46,295,000	917,000	Uzbekistan	27,445,000	558,000
Costa Rica	4,659,000	76,000	Yemen	24,053,000	861,000
Cote d'Ivoire	19,738,000	729,000	<b>Total</b>	<b>1,722,085,000</b>	<b>34,149,000*</b>
Cuba	11,258,000	116,000			
Dominican Republic	9,927,000	224,000			
Ecuador	14,465,000	279,000			
Egypt	81,121,000	2,029,000			
El Salvador	6,193,000	125,000			
Fiji	861,000	18,000			
Ghana	24,392,000	766,000			
Grenada	104,000	2,000			
Guadeloupe	461,000	6,000			
Guatemala	14,389,000	456,000			
Guinea	9,982,000	397,000			
Guyana	754,000	13,000			
Haiti	9,993,000	274,000			
Honduras	7,601,000	202,000			
Indonesia	239,871,000	4,174,000			
Iran	73,974,000	1,390,000			
Iraq	31,672,000	949,000			
Jamaica	2,741,000	52,000			
Jordan	6,187,000	158,000			
Kazakhstan	16,026,000	308,000			
Kyrgyz Republic	2,737,000	122,000			
Kuwait	5,334,000	52,000			
Mauritania	3,460,000	109,000			
Mexico	113,423,000	2,021,000			
Morocco	31,951,000	651,000			
Nepal	29,959,000	730,000			
Nicaragua	5,788,000	140,000			
Oman	2,782,000	62,000			
Palestine	4,039,000	150,000			
Panama	3,517,000	70,000			
Paraguay	6,455,000	154,000			
Peru	29,077,000	605,000			

<sup>1</sup> Flour Fortification Initiative database. Countries are at different stages of implementation.

<sup>2</sup> [http://esa.un.org/unpd/wpp/Sorting-Tables/tab-sorting\\_population.htm](http://esa.un.org/unpd/wpp/Sorting-Tables/tab-sorting_population.htm).

<sup>3</sup> UNICEF (2009).

\* How many of these births might have been affected by a neural tube defect without the flour fortification program is difficult to calculate precisely.

forms within 28 days of conception. Fortified flour adds to the dietary intake of folic acid through staple foods such as bread, tortillas, noodles and pasta.

### Adding folic acid to flour

Flour has been fortified with iron and some B vitamins since the 1940s, but adding folic acid to flour did not begin until 50 years later. In 1991, The Lancet published a study showing unequivocally that folic acid can prevent NTDs.<sup>3</sup> The study, prepared by Sir Nicholas Wald, professor of environmental and preventive medicine at the Wolfson Institute of Preventive Medicine in London, was a randomized double blind prevention trial conducted at 33 centers in seven countries. One conclusion was that, "public health measures should be taken to ensure that the diet of all women who may bear children contains an adequate amount of folic acid."<sup>3</sup>



**TABLE 2:** Decrease in neural tube defects (NTDs) due to fortifying flour with folic acid

Country	NTD prevalence pre-fortification per 1,000 births	NTD prevalence post-fortification per 1,000 births	Percentage decrease in NTD prevalence
<b>Argentina<sup>8</sup></b>			
Spina bifida	1.27	0.66	48
Anencephaly	0.86	0.37	57
<b>Brazil<sup>8</sup></b>			
Spina bifida	1.45	1.42	2*
Anencephaly	1.12	0.69	38
<b>Canada<sup>9</sup></b>			
Spina bifida	0.86	0.40	53
Anencephaly	0.52	0.32	38
<b>Chile<sup>8</sup></b>			
Spina bifida	1.02	0.46	55
Anencephaly	0.63	0.37	41
<b>Costa Rica<sup>10</sup></b>			
Spina bifida	0.73	0.29	60
Anencephaly	0.37	0.12	68
<b>Iran<sup>11</sup> (all NTDs)</b>	3.16	2.19	31
<b>Oman<sup>2</sup></b>	0.73	0.73	0.73
Spina bifida	Average 1991 – 1996	Average 1997 – 2006	–
<b>Saudi Arabia<sup>12</sup></b>			
King Abdul-Aziz University Hospital in Jeddah (all NTDs)	1.9	0.76	60
<b>South Africa<sup>13</sup></b>			
Spina bifida	0.93	0.54	42
Anencephaly	0.41	0.37	10
<b>United States<sup>14</sup></b>			
Spina bifida	0.50	0.35	30
Anencephaly	0.26	0.18	31

\*The study in Brazil was for three months; the authors concluded that a longer period of time was needed to assess fortification's effects.

Some countries report spina bifida and anencephaly separately; others report all NTDs together, including encephalocele.

Spina bifida is malformation of the spine; anencephaly is a malformation of the brain (which is always fatal); encephalocele causes sac-like protrusions of the brain and its membranes that are visible through openings in the skull. The severity of encephalocele varies, depending on its location.

Dr Godfrey Oakley, then the director of the US Centers for Disease Control Division of Birth Defects and Developmental Disabilities, had been leading his team to investigate the cause of NTDs. When Wald's research was published, Oakley and the March of Dimes Foundation began advocating for folic acid to be added to the US standard for enriched flour. The United States issued this regulation in March 1996, and full implementation was required by January 1998.<sup>4</sup> Oakley is now a research professor of epidemiology at the Rollins School of Public Health at Emory University in Atlanta, USA.

Also in 1996, countries in the Middle East considered several public health strategies to improve general nutrition. With encouragement from international organizations such as the World Health Organization (WHO), the United Nations Children's Fund (UNICEF), and the Micronutrient Initiative (MI), fortifying flour with iron and folic acid was one of the interventions under consideration.<sup>5</sup> To test the feasibility of flour fortification, Oman Flour Mills began fortifying flour on a trial basis. Oman Flour Mills covered 75% of the market in Oman; the mill was well-equipped to begin fortification without a major investment.<sup>5</sup>



Dietary fortification with folic acid during pregnancy can have significant health benefits for new born babies.

By October 1996, when a regional workshop was held in Oman to consider multiple health interventions, the mill was fortifying flour successfully – and it continues to do so.<sup>5</sup>

“Globally recognized recommendations for adding folic acid to wheat flour were published in 2009”

Deciding how much folic acid to add to flour to prevent NTDs was a challenge in the early 1990s. Guatemala and El Salvador added folic acid to flour in 1992 to replace the naturally occurring vitamin that was lost in the milling process; however, the

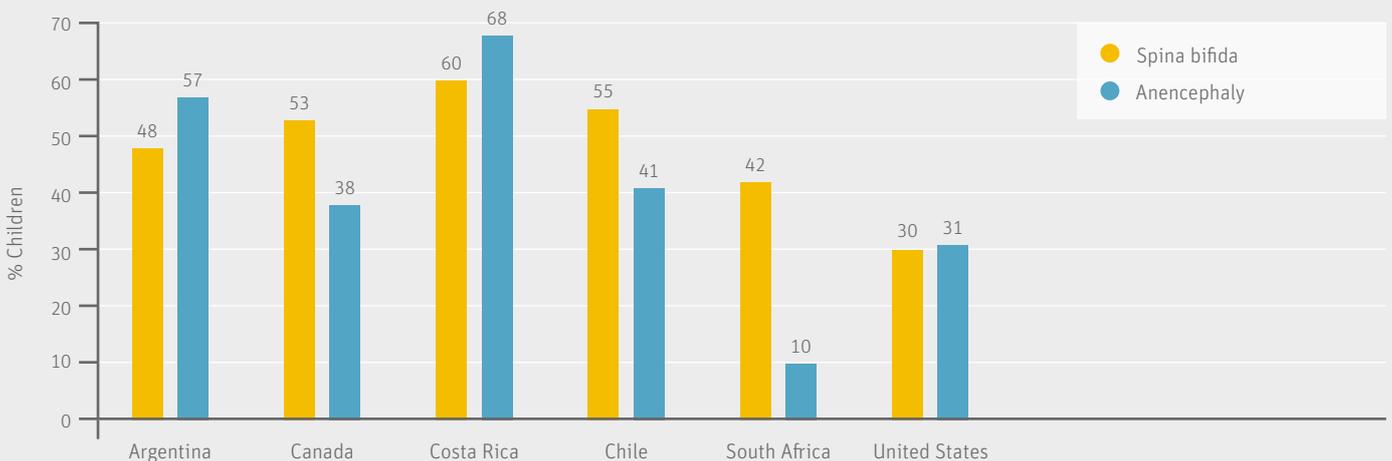
amounts were not high enough to significantly impact the incidence of NTDs.<sup>6</sup> A key result of the 1996 workshop in Oman was the country’s decision to update its wheat flour standard to require folic acid at a minimum of 1.5 mg/kg, according to the meeting’s consensus statement. At a follow-up workshop in Beirut in 1998, this became the accepted regional level. The United States and Canada agreed to fortify flour at 1.4 and 1.5 mg/kg, respectively. Central American countries agreed to fortify with folic acid at a rate of 1.8 mg/kg in 2002.<sup>6</sup> Globally recognized recommendations for adding folic acid to wheat flour were published in 2009, with levels ranging from 1 to 5 mg/kg, based on a country’s consumption patterns.<sup>7</sup>

Decrease in neural tube defects

The decrease in the incidence of NTDs attributable to flour fortification varies, depending on the amount of folic acid added to flour and the NTD rate prior to fortification. Figure 2 provides examples of flour fortification’s impact in a variety of settings.

The March of Dimes estimates that more than 300,000 infants worldwide are affected by an NTD annually.<sup>15</sup> With the consumption of 400 µg folic acid daily at least one month prior to conception, and in the early days of pregnancy, 50 to 70% of NTDs may be prevented.<sup>16</sup> Some researchers call these “folic acid preventable spina bifida and anencephaly.” A 2008 study estimated that about 22,000 neural tube birth defects were prevented globally due to flour fortification.<sup>1</sup> That figure represented 9% of the estimated folic acid preventable cases of spina bifida and anencephaly.<sup>1</sup> By 2010, more countries were fortifying flour, and an estimated 28,066 birth defects were prevented, for a total of 13.8% of the total number of folic acid preventable spina bifida and anencephaly.<sup>17</sup>

FIGURE 2: Percentage decline in Spina bifida and Anencephaly after fortification



## “Currently, 63 countries require flour fortification”

Currently, 63 countries require flour fortification; 57 of those countries include folic acid in the fortification standard. These 57 countries reported 34.2 million births in 2009 (Table 1).

Precisely how many NTDs can be prevented due to flour fortification is difficult to measure, because many countries do not have a surveillance system for birth defects. In addition, a minimal number of NTDs will occur even when the mother consumes the recommended amount of folic acid at the appropriate time. Also, the number of pregnancies terminated due to an NTD diagnosis is often not available or is not taken into consideration by researchers. However, a few studies have estimated the number of NTDs prevented as a result of flour fortification. **These include:**

- › Costa Rica, where the National Children’s Hospital treated 105 children with spina bifida in 1995. The country began fortifying wheat and maize flour with folic acid in 1998. The hospital treated 26 children with spina bifida in 2001; fortification was the only intervention conducted during that time period.<sup>18</sup>
- › Chile, where fortification is associated with preventing 175 NTDs per annum.<sup>19</sup>
- › South Africa, where approximately 406 cases of spina bifida are prevented annually through fortification.<sup>13</sup>
- › The United States, where fortification of flour and breakfast cereals is credited with preventing 1,000 NTDs a year.<sup>20</sup>

### The economic impact

The most common NTD is spina bifida, which occurs when the spinal cord does not form correctly. In mild cases, the permanent loss of some sensation or movement occurs. Severe cases include paralysis and varying degrees of loss of bowel and bladder control. Some spina bifida symptoms can be treated with surgeries and therapy, but spina bifida cannot be cured.

Caring for children with spina bifida can require multi-disciplinary medical treatment, including surgeries, physical therapy and continence care. Wellington Hospital in New Zealand found that a newborn with spina bifida had undergone surgeries costing NZ\$680,000 (US\$569,000) before his second birthday.<sup>21</sup> The hospital’s study also found the direct surgery and hospital costs for six teenagers, from their birth, was NZ\$944,000 (US\$790,000) per individual.<sup>21</sup> More than 20 years ago, in-hospital care for 1,500 patients with one type of spina bifida in Spain was US\$2.9 million per annum.<sup>22</sup> The data collected between 1986 and 1988 did not include prostheses, orthoses and incontinence devices.<sup>22</sup>

The on-going cost of fortifying flour with iron, folic acid and other B vitamins is between US\$2 and US\$3 per metric ton of flour. Three countries have compared the costs of fortification with the cost of spina bifida treatment, and found that fortifying flour is far more economical, **as follows:**

- › Chile’s costs for fortification, compared with the savings in surgical treatment and rehabilitative services for children with spina bifida, represented a cost:benefit ratio of 1:12.<sup>19</sup>
- › South Africa saved 30 Rand for every one Rand spent on fortification, when it calculated the cost of treating a child with spina bifida during the first three years of life.<sup>13</sup>
- › The USA reports annual fortification costs of approximately \$3 million (US). Direct medical costs averted are \$145 million per annum; consequently, \$48 are saved annually for every dollar spent on fortification.<sup>23</sup>

## “It is cost effective to fortify flour with other nutrients in addition to folic acid”

The cost:benefit ratio varies, based on the expenses incurred by the country’s health care system and the estimated number of NTDs prevented. Anencephaly cases are typically not included in the cost:benefit analysis, because this NTD causes the baby to be born without parts of the brain and skull. These children do not live long enough to receive extensive medical care. The value of the caregiver’s time is also not included in most economic analyses.

Once the milling infrastructure is in place to fortify flour, it is cost effective to fortify flour with other nutrients, in addition to folic acid. Flour is also routinely fortified with iron, thiamine, riboflavin and niacin. Some countries add vitamin D, vitamin B<sub>12</sub>, vitamin A and zinc to flour. The economic implications of fortifying with these additional nutrients are not included in the folic acid cost:benefit studies.

### Conclusion

When the study showing folic acid’s role in preventing NTDs was published 20 years ago, women who might become pregnant were encouraged to consume at least 400 µg of this vitamin daily. Fortifying flour provides folic acid through commonly consumed staple foods. The 15-year record of this practice shows that it is a reliable method of reducing the prevalence of births affected by neural tube defects. The cost of adding folic acid to flour is minimal, especially when compared to the cost of treating children with spina bifida and the immeasurable impact on their families.

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# Global Food Price Volatility

## Helen Keller International's response and renewed urgency to act

Founded in 1915 by Helen Keller and George Kessler, Helen Keller International (HKI) is among the oldest international non-governmental organizations (NGOs) devoted to preventing blindness and reducing malnutrition in the world. It currently works in 22 countries: 13 in Africa, eight in Asia-Pacific, and the United States.

### A dire situation

HKI's position paper was originally issued in June 2008, at a time when global food price volatility, and the subsequent social unrest, resulted in an increased number of people suffering from hunger and increased household food insecurity. Price volatility is devastating for poor people, and market instability can adversely affect rural farm livelihoods. In 2011, global food price volatility is once again undermining food security; the dire situation for poor households is being exacerbated by the global financial crisis, which has led to a decline in foreign development aid.

Wealthy economies must put in place both short- and long-term measures to address food price volatility. HKI supports efforts to diversify and boost the yields of small-scale producers, to reduce the work burden on women, and to improve household nutrition. Sustainable agriculture practices, which decrease dependence on oil-based agriculture through increased local, diversified food production, provide a viable pathway forward to improve household food security, rural livelihoods and the resilience of national food production to climate and market perturbations. HKI believes it is imperative that nutrition interventions are scaled up urgently to respond to ongoing food insecurity.

### One billion undernourished

Price volatility in 2008 resulted in 100 million additional people joining the ranks of those who are chronically hungry. There are now nearly one billion undernourished people worldwide (Food and Agriculture Organization of the United Nations, 2010). Chil-

dren under the age of five and pregnant and lactating women are at the highest risk of the grave consequences of vitamin and mineral deficiencies – hidden hunger. Typically, poor households respond to higher food prices by purchasing more staple foods and fewer fruits, vegetables and animal-source foods. Staple foods tend to be poorer sources of the vitamins and minerals that are essential for optimal health. Deficiencies in vitamin A, iron, zinc and folic acid cause increased mortality and undermine human development, well-being, and economic productivity. Food price volatility will further slow progress toward eradicating extreme hunger and poverty, and reducing child mortality.

**“Deficiencies in vitamin A, iron, zinc and folic acid cause increased mortality and undermine human development, well-being, and economic productivity”**

UNICEF (2011) cites weather shocks, exchange rate fluctuations – particularly the weakening of the US dollar – and financial investment and speculation in commodities as drivers of current global food price volatility. As climate change intensifies and weather patterns become more unpredictable with more extreme temperature and precipitation events, food insecurity will be exacerbated in most regions of the developing world. Some have cited increased food demand as a factor, but the total global consumption of food grains has increased only marginally (2%) over the past year, while for some crops, consumption has actually decreased. Note that a large increase has occurred in the global price of maize due to USA subsidies for biofuels; this has led to price increases in maize substitutes for livestock feed. There are other structural factors as well, *inter alia* trade regimes, corporate concentration, and lack of rural infrastructure. A fix for all of these ills, at least in part, lies in strengthening local

**TABLE 1: HKI programs****> Preventing malnutrition through Essential Nutrition**

**Actions:** HKI promotes Essential Nutrition Actions (ENA), using Behavior Change Communications (BCC) to focus on the critical 1,000 day window between conception and the first two years of life.

**> Promoting household food production (HFP) to improve food security and nutrition:**

HKI promotes household production of nutrient-rich foods: fruits, vegetables, poultry and small livestock.

**> Reaching the “Hard to Reach” with Vitamin A**

**supplements:** Since the 1970s, one of HKI’s signature programs has been vitamin A supplementation (VAS), which is also a component of ENA. In populations with vitamin A deficiency (VAD), twice-yearly VAS of children 6–59 months can reduce under-five mortality by over twenty percent.

**> Supporting industrial food fortification:** HKI works with governments to establish appropriate policies and regulations, advocates and works with private sector millers and cooking oil producers to promote fortification of the product, and develops communications strategies to generate consumer demand for the products.

**> Addressing malnutrition:** HKI has expertise in enhancing national and local capacity for the community-based management of acute malnutrition (CMAM) in collaboration with health personnel and community volunteers in a number of African countries.

**> Nutritional surveillance for timely warning, planning and advocacy:** HKI believes that national nutritional surveillance systems (NNSS) are important for collecting and robustly monitoring data on relevant indicators. NNSS can provide timely warning of crises, monitor their progression and the impact of nutrition interventions, and guide policy and program design.

Abridged from HKI statement issued 24 June 2011

communities’ agricultural resilience through crop diversification, better natural resource management, and improved rural and regional market infrastructure. It is imperative that there is a renewed global strategy to increase and diversify local production for climate and market resilient food security.

**HKI’s response**

Many global groups have noted that the response must include immediate actions, such as comprehensive social protection programs and food and nutrition support. The response must also include longer-term initiatives to improve the terms of trade and to boost local, diverse production, especially of nutrient-dense food crops.

“The response must include longer-term initiatives to improve the terms of trade and to boost local, diverse production, especially of nutrient-dense food crops”

Many of HKI’s programs seek to improve food security and nutritional status among vulnerable families (Table 1). These approaches can be contextualized for inclusion in the basket of strategies supported by governments and development agencies to reduce the negative nutritional consequences of the current global financial and food price crises.

*(Abridged)*

for more information, please visit:

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# Perspectives on Regulation of Food Supplements

## Simon Pettman

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The International Alliance of Dietary/Food Supplement Associations (IADSA) is the leading international expert association regarding the globalization of food supplement markets and increasing regulatory challenges. Bringing together food supplement associations from five continents, the IADSA aims to build an international platform for debate, and a sound legislative and political environment for the development of the food supplement sector worldwide.

There are few areas of regulation undergoing as much change at present as those impacting food supplements. Food supplements come in many shapes, sizes and packaging, but are essentially products provided in unit dose form to maintain and improve nutrition and health. How food supplements are defined varies according to the traditions and legal frameworks across the world.

### Extending regulatory focus

With the global market for food supplements estimated to be in the region of US\$80 billion with market growth, particularly in Asia and Latin America, reaching more than 10% in some countries, it is no surprise that so many regulatory bodies are extending their focus to supplements.

“Many regulatory bodies are extending their focus to supplements”

Traditionally, the food supplement has been seen to be the multi- or single vitamin and mineral product, often sold at levels lower than 100% of the recommended daily amount. However, in many markets, vitamin and mineral supplements are gradually moving to a less than 50% share of the total ingredients sold. These ingredients now include fish oils, botanicals and botanical extracts and many other substances such as coenzyme Q<sub>10</sub>,

glucosamine and amino acids. As the market has grown and diversified, regulatory bodies have recognized that either new regulation needs to be developed or existing regulation should be modified. Many governments are still completing this regulatory process, ensuring that all elements are covered – from the manufacturing requirements to the labeling of products.

While national and regional actions are important, the global *Guidelines on Vitamin and Mineral Supplements* developed by the international food standards setting body, Codex Alimentarius, is a key reference point for all governments engaged in this area. Codex completed its *Guidelines* in 2005. While it has its limitations, it is a very important document.

Within all of these discussions, similar issues are on the table: maximum levels of vitamins and minerals; the use of botanical and other ingredients; the claims that can be made for products; and the manufacturing quality of products.

### Guaranteed quality

Quality is the basis for all products brought to the market and this should be primarily guaranteed through Good Manufacturing Practices (GMPs). The issue faced at present is that the approach to GMPs has diverged across the world. This year, the IADSA published the first global Guide to Good Manufacturing Practices. Developed by an international working group of experts from five continents, it is a hugely valuable piece of work for both governments and industry. It will still take time to ensure that all aspects of this guide are implemented in all regions of the world, but it is a huge step forward.

“The shift towards a safety-based approach is of great importance worldwide”

### Vitamins and minerals

The maximum level of vitamins and minerals permitted is historically the most discussed issue in the regulatory world of food supplements. In some jurisdictions, no limits are established in law and the manufacturer is required to ensure products brought to market are safe. In others, limits are based on a nutrient-

**TABLE 1:** Overview of the main food supplement issues currently under discussion/revision in key global markets

	ASEAN in process	China	EU	Japan	Korea	Russia	USA
<b>Category Name</b>	Health Supplement	Health Food	Food Supplement	Food	Health Functional Food	Biological Active Substance	Dietary Supplement
<b>Categorization</b>	National Law	Food	Food	Food	Food	Food	Food
<b>Vitamin &amp; Minerals</b>	√	√	√	√	√	√	√
<b>Botanicals in definition</b>	√	√	√	√	√	√	√
<b>Other Substances in definition (i.e. fish oil, pro- biotics)</b>	√	√	√	√	√	√	√

The table above shows the different existing categorisations of food supplements in key markets across the globe and highlights the similar issues currently under discussion or being revised within these markets.

appropriate risk assessment methodology. In a few countries, the outdated system of using the recommended daily allowance to define the maximum level still continues. The trend of governments over the past decade has very much been towards the second option – ensuring that, where levels are established, they are in line with a global approach to risk assessment. This process was helped first by the agreement of such an approach in Codex, and secondly by the publication of a World Health Organization report in this area, also in 2005. We may not see the same maximum levels in place across world in the near future, but the shift towards a safety-based approach has nonetheless been of great importance worldwide.

### Botanicals

Few countries contest the use of botanicals in supplements. However, there is debate in many regions around which botanicals can be permitted, and the extent to which botanical ingredients used in traditional medicines may also be sold in food supplements. However, it is important to be clear that medicines are primarily developed to treat or cure a condition, while the primary purpose of supplements is to maintain and protect health. Many regulatory bodies are increasingly accepting this dual usage.

Claims often form the key element which distinguishes a food supplement from a medicine. There is no doubt that in some parts of the world – and particularly on the internet – outrageous claims are made for supplements, which should immediately disappear from the market. The challenge for regulators is to ensure coherent and effective enforcement action to deal with

these claims and those who bring them to market. The mistake is to not permit any claims, or to permit only a very small selection of claims for products. The IADSA considers that a balanced system for claims is essential: one that provides guarantees for all involved in the process, from those who wish to invest in the science of ingredients or bring the claims to market, to the regulators who enforce and the consumers who use the products.

The world of food supplement regulation is highly diverse and dynamic. But, while regional and national influences play a significant role, the central themes dominating the minds of regulatory bodies remain the same.

*(Abridged)*

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# Reflections on Differences in Impact of Vitamin A on Maternal Mortality: The Role of Context

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## Introduction

We recently reported<sup>1</sup> that maternal provision of a weekly equivalent of a recommended dietary allowance (RDA) of vitamin A, either preformed (7,000 µg retinol equivalents, RE) or as β-carotene (42 mg, or ~7,000 µg RE), failed to reduce mortality related to pregnancy in a rural population in northern Bangladesh. This finding from the nearly seven year, ~60,000 pregnancy JiVitA-1 Trial was unexpected, given endemic vitamin A deficiency,<sup>2</sup> corroborated by reports of frequent night blindness during pregnancy,<sup>3</sup> variable and seasonally low vitamin A intakes among rural women,<sup>4</sup> and a high maternal mortality risk of ~575 per 100,000 live births.<sup>5,6</sup> We expected these conditioning factors to lead to a result similar to that observed in the southern plains in Nepal in the mid-late 1990s, where continuous weekly supplementation with the same dosages of vitamin A or β-carotene, compared to a placebo (the NNIPS-2 trial), led among ~20,100 pregnancies to a reduction of 44% in mortality related to pregnancy<sup>6</sup> (Table 1). Other than (an unlikely) chance occurrence, what contextual factors might explain this difference in vital response to a comparable nutritional intervention within the same region, and what generic interpretive guidelines might we derive from these joint findings?

With respect to the original trial in the southeastern district of Sarlahi, an area typical of the rural plains (*terai*) of Nepal, there was little doubt that maternal vitamin A deficiency existed. Twenty percent of women of reproductive age were vitamin A deficient,<sup>7,8</sup> and night blindness affected 10–15% of mothers during pregnancy.<sup>9,10</sup> This condition was observed to be associated with infrequent provitamin A carotenoid and vitamin A food intake, and higher risks of hyporetinolemia, morbidity, anemia, wasting malnutrition,<sup>11</sup> and mortality.<sup>12</sup> The maternal mortality risk was high in the population – reflected by an all-cause pregnancy-related mortality rate of 704 per 100,000 pregnancies, and a maternal mortality ratio of 600 per 100,000 live births

in the placebo group<sup>6</sup> – and comparable to indirect estimates reported for Bangladesh in the late 1990s.<sup>5,6</sup> The impact of vitamin A supplementation was biologically coherent, in that there were concurrent reductions in both maternal hyporetinolemia<sup>6,13</sup> and night blindness.<sup>10</sup> There was some evidence of a reduction in the maternal morbidity burden.<sup>14</sup> Mortality risk reduction was particularly striking among women prone to night blindness.<sup>12</sup> All-cause infant mortality through six months of age was unaffected,<sup>15</sup> although there was evidence of improved survival among infants born to mothers prone to night blindness.<sup>16</sup> Elicited by trained lay interviewers, these studies revealed night blindness to be a sensitive and specific indicator of maternal vitamin A deficiency, and a health risk for mother and infant.<sup>17</sup> Notwithstanding its stronger effect on maternal mortality,<sup>6</sup> possibly related to additional antioxidant effects,<sup>13</sup> β-carotene supplementation had an expectedly lesser impact in raising low serum retinol and preventing night blindness.<sup>6,10</sup> In line with emerging theories on developmental nutritional exposure, the spectrum of vitamin A impact appeared to extend to offspring far beyond infancy.

## A spectrum of plausible nutritional effects

Maternal vitamin A supplementation may have affected the long-term health of the fetus and infant. Opportunities to follow the “randomized controlled trial cohort” in Nepal have begun to reveal the extended effects of preconception through early postnatal vitamin A supplementation on aspects of offspring health in preadolescence (i.e., between nine and 13 years old). For example, lung size and function,<sup>18</sup> as observed in animal experiments<sup>19,20</sup> and for which plausible mechanisms exist,<sup>21,22</sup> as well as natural antibody mediated immunity (Palmer *et al*, submitted 2011), were significantly enhanced in children born to mothers randomized to receive a dietary supplement of vitamin A versus a placebo. On the other hand, no effects were observed at this age on early indicators of cardiovascular disease,<sup>23</sup> cognition (Buckley *et al*, submitted, 2011) or asthma.<sup>24</sup> Together, our findings to date suggest that, within this marginally nourished, high health risk and low resource setting of rural Nepal, maternal vitamin A supplementation repleted a deficient population and, in so doing, exerted a spectrum of plausible nutritional effects on short- and longer-acting mechanisms of health.

**TABLE 1:** Impact of maternal vitamin A or  $\beta$ -carotene supplementation on mortality related to pregnancy

	Placebo	Vitamin A	$\beta$ -carotene
<b>Nepal (NNIPS-2)<sup>6</sup></b>			
No. of pregnancies	7,241	7,747	7,201
No. of deaths	51	33	26
Mortality rate per 100,000 live births	704	426	361
Relative risk, RR	1.00	0.60	0.51
95% confidence interval	–	(0.37 – 0.97)	(0.30 – 0.86)
P-value	–	<0.04	<0.01
<b>Bangladesh (JiVitA-1)<sup>1</sup></b>			
No. of pregnancies	19,862	19,806	19,998
No. of deaths	41	47	50
Mortality rate per 100,000 live births	206	237	250
Relative risk, RR	1.00	1.15	1.21
95% confidence interval	–	(0.75 – 1.76)	(0.81 – 1.81)
P-value	–	0.52	0.35
<b>Ghana (Obaapa Vit A)<sup>26</sup></b>			
No. of pregnancies	39,234	39,601	–
No. of deaths	148	138	–
Mortality rate per 100,000 live births	377	348	–
Odds ratio, OR	1.00	0.92	–
95% confidence interval	–	(0.73 – 1.17)	–
P-value	–	0.51	–

### “Analyses reflecting the nutritional coherence of supplementation are less advanced for the trial population in Bangladesh”

Analyses reflecting the nutritional coherence of supplementation are less advanced for the trial population in Bangladesh. There was clearly no impact on mortality related to pregnancy,<sup>1</sup> which is likely due to there being virtually no mortality fraction remaining that could be attributable to vitamin A deficiency. However, there appear to have been effects on other aspects of health: There was a lower risk of bacterial vaginosis in both vitamin A and  $\beta$ -carotene supplemented women,<sup>25</sup> and vitamin A supplementation appeared to alter the relationship between maternal body composition and birth size – a novel finding, implicating the role of vitamin A nutriture in altering materno-fetal protein and energy metabolism (Shaik *et al*, unpublished, 2011).

Other relationships are still being explored, but findings to date suggest that, while maternal mortality was not affected, less obvious biological mechanisms were – some of potential public health importance in what may be considered a marginally vitamin A nourished population.

#### Many questions

Still, when different trials reveal diverse responses to outcomes, many questions arise: Do the neutral (versus negative, which are adverse) effects of vitamin A on maternal mortality, as recently reported from large trials in Bangladesh<sup>1</sup> and, more distantly, Ghana<sup>26</sup> (Table 1) negate the coherent outcomes of maternal vitamin A supplementation in Nepal, as some would suggest?<sup>27</sup> If studies with diverse effects pass muster with respect to design,



**TABLE 2:** Dietary intake, nutritional status and mortality risk among pregnant women participating in community-based randomized vitamin A or  $\beta$ -carotene supplementation trials, representing context, in Nepal (NNIPS-2)<sup>1</sup> and Bangladesh (JiVitA-1)<sup>2</sup>

	Nepal NNIPS-2 N~20,000	Bangladesh JiVitA-1 N~60,000	Rate Ratio <sup>3</sup>
<b>Diet frequency <math>\geq 3</math> times in past 7 days, %</b>			
Meat and liver	3.0	12.0	4.0
Eggs	0.7	18.5	26.4
Milk	39.0	30.0	0.76
Fish	6.0	56.0	9.0
Yellow fruits and vegetables	14.5	32.0	2.2
Dark green leafy vegetables	16.5	23.0	1.4
<b>Nutritional status and mortality</b>			
Serum retinol <0.70 $\mu\text{mol/L}$ , %	19	7.7	0.40
Night blind during previous pregnancy, %	11.0	8.7	0.79
MUAC <21.5 cm, %	55.0	25.0	0.45
Pregnancy mortality rate (placebo) per 100,000 pregnancies <sup>4</sup>	704	206	0.29
Education > 6 years, %	8.7	31.3	3.6
Attendance at birth by provider, %	29.8	42.2	1.4

<sup>1</sup>The second major trial of the Nepal Nutrition Intervention Project, Sarlahi (NNIPS), a research activity in collaboration with the National Society for the Prevention of Blindness (Nepal Netra Jyoti Sangh), Kathmandu, Nepal, supported by the Office of Nutrition, US Agency for International Development (USAID), Washington, DC, with additional assistance from *Sight and Life*, Basel, Switzerland.

<sup>2</sup>The first major field trial of the JiVitA Project, a maternal and child health and nutrition research project that was conducted under the National Family Health and Population Project of the Governments of the People's Republic of Bangladesh and the United States, supported by USAID, Washington, DC and the Bill and Melinda Gates Foundation, Seattle, WA, USA, with additional assistance from *Sight and Life*, Basel, Switzerland.

<sup>3</sup>Rate ratio is a simple ratio of proportions reported for Bangladesh to Nepal for all variables.

<sup>4</sup>Rates are drawn from the placebo-assigned group in each trial population.

adequacy of sample size to provide sufficient statistical power, rigor of implementation, appropriateness of analysis and evidence-justified interpretation, and if the populations are suitably resonant with a broader population of interest,<sup>28</sup> to what degree does one nutrition intervention trial “confirm” or “refute” findings from another of similar nutrient content and delivery? Should findings from one study meeting the above criteria indeed be seen as confirming, or trumping, the findings from another? And, if trials are to be trumped, why is it popular to disregard plausible evidence from hypothesis-driven trials with positive impact, in favor of studies showing no benefit, even when the trials may be of comparable quality, but conducted in different ecologies of risk? In populations where varying levels of nutrition and health risks are likely to alter the health impact of a comparable intervention, should trials seek to confirm or negate those of others? Or is the challenge necessarily more complex, of seeking to either extend or delimit the geographic or phenotypic bounds of positive effects which have been observed in a particular setting?

## “Questions related to differences in context can be qualitatively addressed”

### A qualitative approach

For these two rural South Asian populations in northern Bangladesh and southeastern Nepal, questions related to differences in context can be qualitatively addressed by examining some differences in maternal nutritional status, vitamin A deficiency, mortality risk, dietary intake, socioeconomic status, and the availability of (minimal) care at birth. The district research site of Gaibandha, with a population of over 600,000 people, typifies rural Bangladesh<sup>24</sup> and, by means of varied data from the past two decades, the district research site of Sarlahi, with its population of ~200,000 people, has long reflected life in the *terai* of

Nepal. So, in their day (nearly a decade apart), the sites appeared to resonate with larger populations of interest across Gangetic South Asia. But were these populations comparable? The answer appears to be no, at least at levels of factors that may influence maternal mortality. Despite evidence through the 1990s that maternal vitamin A deficiency and mortality were entrenched public health problems across rural Bangladesh, change in nutritional well-being has also become part of the country's rural dynamic, a trend less apparent in the *terai* of Nepal through the 1990s. These population differences have become apparent in indicators of gender, social, economic, health and nutritional disparity. Specifically (drawing from collected data), among enrolled participants in each trial the following characteristics distinguished Bangladeshi mothers from Nepalese mothers (Table 2):

- > Pregnancy-related mortality in the control group was ~30% of the rate observed in Nepal (~206 vs 700 per 100,000 pregnancies), a change that can also expect to shift the mix of causes of death amenable to a nutritional supplement;
- > Wasting malnutrition, reflected by a low arm circumference (< 21.5 cm), was less than half as prevalent as in Nepal (25% vs 54%), indicating better protein and energy status, which favors survival;
- > Approximately two to 20 times more mothers reported regularly consuming (i.e., three or more times per week) various preformed vitamin A rich foods – meat and liver, eggs and fish – a pattern that would have been expected to reduce maternal vitamin A deficiency;
- > Maternal vitamin A deficiency during early to mid pregnancy (i.e., low plasma retinol under 0.70  $\mu\text{mol/L}$ ) was 40% of the level seen in Nepal (7.7% vs 19%);
- > Attendance at birth by a semi-skilled or traditional birth attendant was 40% more frequent than in Nepal, suggestive of more immediate availability of potentially life-saving care;
- > A sixth grade or higher education was 3.6 times more common than among women in Nepal (31% vs 9%, respectively), reflecting possibly greater access to resources; and,
- > Infrastructure, including paved roads, tube wells and other facilities, were constantly being improved in Gaibandha over the seven year period of the trial, a trajectory that had been impossible in Nepal during more than a decade of political turmoil and insurrection during the 1990s.

#### Hiding hidden hunger

Viewing these comparisons, we see a population of women in Bangladesh who, in relation to women in the *terai* of Nepal, were at a far lower risk of death associated with pregnancy, were eating a better diet (including sources of preformed vitamin A), and were generally better nourished, educated and, likely, cared for around the time of delivery. Although both populations occupy

rural flanks of the greater Gangetic floodplain, the Bangladeshi context was different (i.e., relatively more healthful) and the risk of maternal mortality lower. It can, thus, be argued that the fraction of mortality reduction achievable with a vitamin A or  $\beta$ -carotene supplement, as seen in Nepal in the mid-1990s, may have gradually occurred in Bangladesh during the following decade through improvements in diet and nutritional status, especially vitamin A and protein energy status. Pregnancy-related mortality in Bangladesh was, however, also markedly lower than that achieved even with efficacious, supplemental vitamin A or  $\beta$ -carotene in Nepal, likely reflecting an additional decrement in risk due to improved access to other life-saving resources and services in Bangladesh. Although we considered all available, nationally and locally relevant vital statistics and indicator data on health, diet, micronutrient status, and took care to identify a research site in Bangladesh that would reflect a typical rural Bangla population setting, it would have been extremely valuable to have had broader, more current data to guide the design and conduct of the latter trial. In general, inadequate and often outdated data on micronutrient deficiencies remains a vexing public health problem, keeping “hidden hunger hidden” in guiding research and programs in this new decade as well.

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**“For nutrition, context matters, because populations may vary widely in many nutritional aspects resulting from differences in life stage, diet, disease patterns, environment and (epi)genetic predisposition”**

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#### Varying populations

For nutrition, context matters.<sup>29</sup> This is because populations may vary widely in many nutritional aspects, resulting from differences in life stage, diet, disease patterns, environment and (epi)genetic predisposition. They also may vary in terms of risks of health outcomes that we anticipate will respond to nutrition interventions. Time is an additional dimension. Populations can change in nutritional need across seasons and years, depending on access to food, development opportunity, environmental demand, and dominant diseases. Beyond contributions to knowledge,



including systematic overviews as appropriate, we have come to view the conduct of equally rigorous nutrition trials in different settings more as attempts to extend and delimit the bounds of impact, rather than confirm or negate effects elsewhere, and to generate findings that can guide context-considered policies and program decisions. An operative context for a particular public health effect may be broad (e.g., across regions), as seen with the ability of vitamin A to reduce preschool child mortality and, likely, nutritional blindness in many diverse settings where undernutrition, vitamin A deficiency, and high child mortality nonetheless prevail.<sup>30</sup> Or it may be more circumscribed, as seems to be occurring with maternal vitamin A supplement use.

Under extant conditions in rural Nepal, a vitamin A intervention that reaches women of reproductive age can be expected to reduce maternal night blindness and mortality, and may help strengthen offspring resilience against some forms of chronic disease later in life. In Bangladesh, it will not reduce maternal mortality, though other health effects may accrue. Perhaps we should be more willing to admit into evidence, and act on, differences in impact across varying nutritional landscapes. Importantly, locally relevant evidence can inform local, national, and regional program options and allocations of resources. This argument would seem to question a conclusion appearing in an article that summarized findings from a major trial in Ghana, West Africa, where maternal vitamin A also clearly had no effect on mortality related to pregnancy: “The results of this trial in Ghana vindicate the decision not to change Safe Motherhood policy immediately after the Nepal trial.”<sup>31</sup> Assuming that the comment is intended to convey a global perspective, perhaps a more appropriate inference would be that there is no need to deliver antenatal vitamin A to reduce maternal mortality in Ghana, and possibly other comparable areas in West Africa. But I would argue that the mortality findings in Ghana have little relevance to Nepal. Surprisingly, perhaps, neither do the findings in Bangladesh.

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# *Sight and Life* and Vitamin Angels Partnership for Vitamin A Capsule Distribution is Extended Worldwide

As *Sight and Life* commemorates 25 years of service to science and humanity, it is time to reflect on what has been achieved and to plan for the future. The mid 1980s witnessed a crisis of epidemic food hunger in Eastern Africa, unprecedented in modern times. In the wake of this crisis, *Sight and Life* was launched to disseminate information needed to combat malnutrition, and to take direct action, focusing on the provision of vitamin A capsules. In the 25 years since its founding, *Sight and Life's* mission has expanded to include advocacy for program intervention, based upon pioneering efforts to identify and disseminate scientific understanding of the impact of micronutrients on human health.

## Strengthening, fostering and improving

Working on many fronts to alleviate malnutrition is central to the successes of *Sight and Life*, and forming strategic partnerships with other organizations is how we are able to contribute to achieving better nutrition for all. One such partnership that evolved in recent years is with Vitamin Angels ([vitaminangels.org](http://vitaminangels.org)), a leading independent humanitarian organization dedicated to combating malnutrition by connecting at-risk populations in need with essential micronutrients. As *Sight and Life* Director Klaus Kraemer recently noted, "By partnering with Vitamin Angels, *Sight and Life* strengthens local supply and distribution capacity, mobilizes communities and governments, fosters the creation of public-private partnerships to combat, in particular, vitamin A deficiency (VAD), and improves the lives of millions of children and women."

VAD is a major contributing cause to poor health among young children and, according to the World Health Organization, it affects an estimated 190 million children. VAD leads to xerophthalmia, an eye disorder that can progress to blindness in children. As a vital micronutrient, vitamin A is essential to the body's immune system and controls the maintenance of body cells. Thus, VAD weakens the body's defenses, and increases the risk of infectious diseases that can lead to otherwise preventable child deaths.

## Catalyzing supply and distribution systems

While *Sight and Life* continues to address the issue of VAD, its mandate is again expanding and now includes other nutritional topics of importance. With this broadening of our mandate, *Sight and Life* is transferring the management of direct distribution of vitamin A, along with responsibilities to catalyze locally sustainable vitamin A supply and distribution systems, to Vitamin Angels. Vitamin Angels specializes in working with local non-governmental organizations (NGOs). From next year, all enquires regarding vitamin A capsules will go through our partner, Vitamin Angels, as *Sight and Life* will end the direct supply and distribution of vitamin A capsules at the close of 2011. Through this partnership, *Sight and Life* seeks to further consolidate and strengthen the capacity of local NGOs to distribute vitamin A capsules. According to Howard Schiffer, President and Founder of Vitamin Angels, "The collaboration with *Sight and Life* will also strengthen our collective ability to reach especially those individuals experiencing VAD who reside in families at the bottom 30% of the income pyramid, by more formally aligning and drawing upon the respective core strengths of each organization."

*Sight and Life* continues to care about the world's most vulnerable populations, to help improve their nutritional status, and to advocate to alleviate micronutrient deficiency globally.

For more information on Vitamin Angels,

please visit: <http://www.vitaminangels.org/starting-your-micronutrient-project>

For more information on *Sight and Life*, please visit:

<http://www.sightandlife.org>



Administering vitamin A to a child.

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“The collaboration with *Sight and Life* strengthens our collective ability to reach especially those individuals experiencing VAD who reside in families in the bottom 30% of the income pyramid”

*Howard Schiffer, President and Founder, Vitamin Angels*

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# Highlights of the 16<sup>th</sup> International Symposium on Carotenoids

Krakow, 17 July 2011

## George Britton

The University of Liverpool (retired),  
Liverpool, UK

### An event in Krakow

The International Symposia on Carotenoids are held every three years. The 16<sup>th</sup> Symposium in the series was held in the fine UNESCO Cultural Heritage city of Krakow, Poland. It was hosted by the Jagiellonian University, one of the oldest universities in Europe, which was founded in the 14<sup>th</sup> century and numbers the astronomer Copernicus among its famous scholars. The conference was ably planned and organized by Kazimierz Strzałka (Chair), aided by Anna Wisniewska (Secretary) and an active local organizing committee, with administration in the hands of the Targi w Krakowie team, who worked tirelessly and efficiently to ensure that everything went smoothly. The modern facilities of the Auditorium Maximum gave an immediate good impression as soon as we arrived on Sunday for Registration and a Welcome Reception, at which we were greeted by Kazimierz Strzałka, and treated to trays of local delicacies served by young people in colorful traditional costume. This provided a perfect opportunity to catch up with old friends and begin new friendships, and for young scientists and students to experience the warm and friendly atmosphere of the “carotenoid family”,

“The conference was ably planned and organized by Kazimierz Strzałka”



Krakow city centre with the Mariacki Church.

putting faces and personalities to names that they knew well from the literature.

At 9 a.m. on Monday, July 17, a traditional Krakow trumpet fanfare signaled the opening of the Symposium by Kazimierz Strzałka and Fred Khachik, president of The International Carotenoid Society (ICS), with some words of greeting from the Chair of the Krakow City Council. Part of the attraction of the carotenoid field is its diversity and interdisciplinary nature, which was clear from the full program of plenary and invited lectures, selected oral communications and poster presentations. ICS Awards for a lifetime of achievement in their research field were presented to John W Erdman (University of Illinois, USA; first Norman Krinsky Award for Human Nutrition), Johan Lugtenburg



ICS President Fred Khachik wearing the red hat, a Krakow tradition for honoured guests.

(Leiden University, The Netherlands; Otto Isler Award for Chemistry), and Joseph Hirschberg (Hebrew University of Jerusalem, Israel; Trevor Goodwin Award for Biochemistry and Biology). They all presented plenary lectures, as did Yasushi Koyama (Kwansei Gakuin University, Japan); Joseph Levy (Ben-Gurion University of the Negev, Israel); Wilhelm Stahl (University of Düsseldorf, Germany); Paul Bernstein (University of Utah, USA); and Karol Subczynski (Medical College of Wisconsin, USA). The bulk of the program consisted of eight sessions, some dedicated to the memory of Norman Krinsky, Trevor Goodwin, Hans-Dieter Martin, and Rodney Ausich, all of whom died in the three years following the previous symposium.

### Presentations on vitamin A deficiency

A number of presentations were relevant to vitamin A deficiency. In his plenary lecture, Johan Lugtenburg described the synthesis of carotenoids with isotopic labeling (especially  $^{13}\text{C}$ ) at any specified position or combination of positions, which has made labeled carotenoids available for biological studies. Samples of labeled  $\beta$ -carotene and retinol were used by Guangwen Tang to show that the conversion of  $\beta$ -carotene into vitamin A in carotene-rich maize and Golden Rice is very efficient (3.2:1 and 2.3:1, respectively, compared to 7.7:1 for spinach and 2.1:1 for  $\beta$ -carotene in oil), so that these staple foods, biofortified with  $\beta$ -carotene, can provide a good dietary source of vitamin A. Georg Lietz used similar labeling methods to show that single nuclear polymorphisms (SNPs) within and upstream of the  $\beta$ -carotene 15,15'-monooxygenase (BCMO1) can influence the effectiveness of using provitamin A carotenoids to increase vitamin A status. Igor Shmarakov reported that BCMO1 is highly expressed in hepatic stellate cells; the liver can thus be a significant site of  $\beta$ -carotene conversion. Other reports showed that the scavenger receptors SR-BI and CD36 are involved in the ab-

sorption of  $\beta$ -carotene,  $\beta$ -cryptoxanthin and  $\alpha$ -carotene, but not with the uptake of retinol, and that divalent cations may inhibit micelle formation and carotenoid uptake.

Much work on carotenoid biosynthesis was aimed at modifying the carotenoid content and composition of various food crop plants. A review of general progress was given in the plenary lecture by Joseph Hirschberg. Also particularly relevant were talks by Elli Wurtzel on increasing the carotene content in the endosperm of maize and other cereal crops, with the long-term target of a sustainable solution to vitamin A deficiency, and by Ralf Welsch on phytoene synthase as a target for increasing carotene content in cassava and other roots. Other talks and posters presented studies with a variety of food crop plants, including potato, carrot, rice and oranges. The effects of processing on carotenoid stability in vegetables were reviewed by Reinhold Carle.

### The role of xanthophylls lutein and zeaxanthin

The role of the xanthophylls lutein and zeaxanthin in the human macula, and their importance for protecting against age-related macular degeneration (AMD) were emphasized. The identification of two key xanthophyll-binding proteins responsible for the uptake and stabilization of the macular carotenoids, namely GSTP1 (for dietary zeaxanthin and non-dietary *meso*-zeaxanthin) and StARD3 (for dietary lutein) was described in the plenary lecture by Paul Bernstein. The transgenic expression of human GSTP1 in mouse retina, reported in a poster by Binxing Li, could provide a valuable experimental model. Plenary lecturer Karol Subczynski showed that, in membranes, lutein and zeaxanthin are excluded from domains with a high cholesterol concentration (rafts), and are concentrated in domains that contain mainly unsaturated lipids, including the polyunsaturated DHA, as found in the macula. Johanna Seddon discussed how genetic, nutritional and behavioral factors, including smoking and high BMI, predict increased risk of AMD. Aspects of dietary supplementation with lutein or zeaxanthin were evaluated by Richard Bone and John Landrum, and by Wolfgang Schalch. Other speakers described the abnormal distribution of macular pigment in some retinal disorders, macular pigment changes after cataract surgery with intraocular lens implantation, a role for the macular xanthophylls in reducing effects of glare, improving recovery times after photostress and improving chromatic contrast, and the antioxidant and photoprotective properties of macular xanthophylls in cultured



retinal pigment epithelium. A description of the orientation and dynamics of lutein in a lipid bilayer, derived from computational studies, and experimental demonstrations of antioxidant activity of lutein in models of photoreceptor membranes were also relevant to the functioning of the xanthophylls in the macula.

A position statement by The Science and Nutrition Advisory Board on the *Macular Xanthophylls* and *DHA* highlighted the importance of lutein and zeaxanthin for normal retinal development and retinal health throughout life, and also for maintaining cognitive function. In this potentially exciting new area, Elizabeth Johnson discussed the association of lutein (and zeaxanthin) with the maintenance and improvement of cognitive function in the aging brain and in old people. Adrian Wyss showed that supplementation with lutein supports neuron survival, through protection against oxidative and other stress, and significantly promotes several aspects of mental performance in aged mice. Related to this, Györgyi Horvath reported that administration of a water-soluble lutein-RAMEB complex to rat primary sensory neurons resulted in inhibition of a transient receptor potential ion channel.

Rohini Vishwanathan reported that lutein is the predominant carotenoid in the infant brain, suggesting that the fortification of infant formula milk with lutein may be advantageous for brain development. Matthew Kuchan showed that the inclusion of lutein in infant formula milk, at a level needed to achieve the same plasma lutein levels as in infants fed human milk, is safe and well tolerated.

### Biological activity of carotenoids

A major recurring theme – that the biological activity of carotenoids in relation to cancer and other serious diseases and disorders may be due to modulation of the ligand-activated nuclear receptor family and other transcription systems by carotenoid metabolites – was developed by plenary lecturers Joseph Levy and John Erdman. The latter dealt primarily with metabolites of non-provitamin A carotenoids, especially lycopene. Yoav Sharoni showed that carotenoids and oxidation products inhibit estrogenic activity in cancer cells, but stimulate the expression of estrogen-induced genes in osteoblast bone cells. The effects of  $\beta$ -carotene on the growth of prostate cancer cells were shown by Joanna Dulinska-Litewka to involve androgen-regulated processes. Earl Harrison described the ability of naturally occurring  $\beta$ -apo-carotenoids to function as retinoid receptor antagonists.

The effects of  $\beta$ -cryptoxanthin and its metabolites on cellular receptors and signaling molecules in relation to protection against lung cancer were reported by Xiang-Dong Wang, and Hoyoku Nishino reviewed the anti-cancer health-promoting actions of lycopene. Work from the LYCOCARD project on lycopene and atherosclerosis was reported.

## “This was a typically stimulating and enjoyable meeting”

### Oxidative stress and reactive oxygen species

The interaction of carotenoids with oxidative stress and reactive oxygen species (ROS) remains of interest. Paola Palozza suggested that carotenoids, at low concentration, may be responsible for the regulation of ROS-mediated cellular functions. Werner Siems attributed the harmful side effects of high-dose  $\beta$ -carotene supplementation to a pro-oxidative mechanism under heavy oxidative stress, leading to rapid formation of toxic breakdown products. The accumulation of carotenoids in mitochondria leads to oxidative stress, dysfunction and impaired respiration, but Johannes von Lintig showed that mammalian cells express a mitochondrial carotenoid oxygenase, BCDO2, that degrades carotenoids to protect these vital organelles. Plenary speaker Wilhelm Stahl discussed the mechanisms by which carotenoids and metabolites may protect skin against photo-oxidative damage.

The hypothesis that storage and mobilization of retinoids and carotenoid accumulation in hepatic stellate cells may be important for the prevention of the development of liver injury was addressed by William Blaner. In posters, a deficiency of BCMO1 in knock-out mice was shown to induce non-alcoholic steatohepatitis and supplementation of obese mice with 10-apolycopene-10-oic acid to decrease steatosis in liver by upregulating a key factor in lipid homeostasis. The influence of retinoids and carotenoids on lipid metabolism in adipose tissue, and mechanisms by which fucoxanthin exerts anti-obesity effects and fucoxanthin and astaxanthin have preventive effects on inflammatory bowel disease were also described.

Major contributions on photosynthesis and photochemistry, including the plenary lecture by Yasushi Koyama, reported detailed work on spectroscopic studies and energy transfer, and several presentations on the xanthophyll cycle, reflecting the interests of the hosts. Although few new carotenoid structures were reported, chemistry coverage included new sources of  $\kappa$ -ring carotenoids, preparation of selected carotenoids by synthesis, and new developments in analysis by HPLC. Of increasing interest in biosynthesis are isomerization and cleavage reactions. Fundamental spectroscopic studies of membranes, aggregation, surface properties and adhesion are relevant to the functioning and application of carotenoids in many contexts.

### The closing ceremony

For the Symposium Excursion and Banquet, we made a short journey to the famous and hugely impressive Wieliczka Salt Mine. After descending almost 400 steps, we had a guided tour

of the 1% of the mine that is open to the public, marveling at several caverns, including chapels and a “cathedral”, all carved in salt, before arriving in a large chamber for the Symposium Banquet. After the meal, Kazimierz Strzałka and Fred Khachik thanked the organizing team for all their hard work and efforts. They presented ICS President’s Outstanding Service Awards to Maria Stackiewicz-Sapuntzakis, “in appreciation for editing, authoring and publishing the *Carotenoids Newsletter* and a lifetime of dedicated service to the Carotenoid Society,” and to Synnøve Liaaen-Jensen, Hanspeter Pfander, and the author of this article, “in appreciation for editing, authoring and publishing the *Carotenoid* book series and a lifetime of dedicated service to the carotenoid field.”

In the closing ceremony, prizes and certificates were presented to Susanne Baldermann (Japan); Alexander Betke (Germany); Jayong Chung and Xiang-Dong Wang (Korea and USA); Milan Durchan (Czech Republic); Binxing Li (USA); Sarah Wagener (Germany;) and Muhammad Zeeshan (Norway), the authors of the best poster presentations, as selected by an evaluation committee. After a few final words, Kazimierz Strzałka handed the Symposium banner over to the new ICS President, Hideki Hashimoto, to be passed on to the organizer of the next Symposium.

Abstracts of all lectures, oral and poster presentations are published in a special issue of *Acta Biologica Cracoviensia* (Vol 53, Suppl 1, 2011). All contributors have been invited to submit work presented for publication in 2012 in a special issue of *Acta Biochimica Polonica*.

After a typically stimulating and enjoyable meeting, attended by 259 participants from 37 countries, we now look forward to the 17<sup>th</sup> International Symposium on Carotenoids. This will be held in 2014 at the Park City Resort, Salt Lake City, Utah, USA, with Paul Bernstein of the University of Utah as organizer. Regular attendees know that this is an event not to be missed, and have already highlighted it in their diaries. Anyone who is interested in carotenoids, but has not experienced the special atmosphere and scientific level of these meetings, is strongly encouraged to try to attend, and to visit the website of the International Carotenoid Society ([www.carotenoidsociety.org](http://www.carotenoidsociety.org)) for detailed information as this becomes available.

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“The 17th International Symposium on Carotenoids will be held in 2014 in Salt Lake City, Utah, USA”

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# *Sight and Life* Luncheon Forum on Contributions of Micronutrients to Achieve the MDGs

## Noel W Solomons

CeSSIAM, Guatemala City,  
Guatemala

### A call for awareness

*Sight and Life* sponsored a lunchtime forum on micronutrients' contribution to achieving the Millennium Development Goals (MDGs) at the Asian Conference of Nutrition, Singapore, July 13–16. The forum combined a call for better awareness among different sectors of society about the micronutrient problems worldwide, with a network of topical issues in international nutrition. *Sight and Life* Director Klaus Kraemer opened the session with a talk entitled "Contributions of micronutrients to achieve the Millennium Development Goals – status of the *Hidden Hunger Atlas*." Beginning with an inventory of these goals' progress towards the deadline of 2015, Dr Kraemer found that either insufficient progress or no progress at all had been made in the regions of Sub-Saharan Africa and South and Western Asia. Annually, over a million children under five years of age die due to vitamin A and zinc deficiencies, while over 600,000 stillbirths or neonatal deaths are caused by iron deficiency anemia, and over 100,000 succumb during pregnancy due to iron deficiency anemia (IDA). In addition, 350,000 children become blind due to vitamin A deficiency. Almost 20 million babies are mentally impaired due to maternal iodine deficiency, and neural tube defects due to inadequate maternal folate intakes affect 150,000

**"Insufficient or no progress at all  
towards achieving the MDGs has been  
made in the regions of Sub-Saharan  
Africa and South and Western Asia"**

infants each year. This compilation of preventable adverse statistics of death and disability led in 2009 to the United Call to Action on Vitamin and Mineral Deficiencies.

Dr Kraemer used the term "hidden hunger" to differentiate between food and nutrition security. Hidden hunger was defined, on the basis of an Expert Panel deliberation in Bangkok in 2009, as "a lack or loss of dietary quality that leaves individuals or populations with deficiencies in essential micronutrients (vitamins & minerals), which negatively impact on health, cognition, function, survival, and economic potential." He asserted that the condition was "hidden," because only the tip of the iceberg, clinical manifestations of micronutrient deficiencies, is visible – for example as xerophthalmia, cretinism, or anemia, etc. Most of the deficits of vitamins and minerals fall into the subclinical domain of functional impairment (such as cognitive deficits and immune defects), altered biomarkers, or even chronic inadequate intake from a low quality diet.

It was noted that the Copenhagen Consensus 2008 classified micronutrient supplements for children (vitamin A, zinc) as the leading cost-effective measure for the investment of a finite quantity of public health funding. The annual cost of supplementation initiatives would be less than US\$2 per beneficiary in Africa and Asia. Fortification measures such as salt iodization and flour fortification with multiple micronutrients could be provided for a few cents of each dollar.

Dr Kraemer presented the outline of a *Hidden Hunger Atlas* – a map of the world highlighting, first, the severity of multiple micronutrient deficiencies across a continuum of grades, and second, the number of disability-adjusted life years (DALYs) lost per 100,000. The concentration of hidden hunger sites was in Western and Central Africa, South Asia and Afghanistan.

The talk concluded with a description of the 1,000 days window of opportunity for preventing irreversible damage due to under- and overnutrition. This extends from conception to the child's second birthday. As the micronutrient deficiencies of the

**TABLE 1:** The Millennium Development Goals related to micronutrient nutrition

**GOAL 1: Eradicate extreme poverty**

- > Halve the proportion of people whose income is less than US\$1 a day
- > Halve the proportion of people who suffer from hunger

**GOAL 4: Reduce child mortality**

- > Reduce by two thirds the under-five mortality rate

**GOAL 5: Improve maternal health**

- > Reduce by three quarters the maternal mortality rate

mother and the offspring over these 1,000 days can produce death, disability and reduced physical growth and performance capacity, Dr Kraemer called upon stakeholders in government, academia, and the private sector to commit to delivering micronutrients at scale, saying that the achievement of the MDGs depended, in part, on this commitment (Table 1).

**Traditional vegetarianism produces specific nutrient imbalances**

CS Yajnik of the Kamalnayan Bajaj Diabetes Research Centre in Pune, India, gave a presentation entitled “Maternal one-carbon fetal programming and adiposity and insulin resistance (IR).” India has a double burden, with one of the world’s highest incidences of low birth weight infants, and one of the greatest rates of diabetes mellitus. Moreover, it is increasingly the young and the poor who are experiencing the development of diabetes. The public health implications are imposing, but it remains to be determined whether there might be a link between *in utero* fetal events and the glucose intolerance and metabolic disruptions that lead to diabetes mellitus over the course of a life.

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**“It is increasingly the young and the poor who are experiencing the development of diabetes in India”**

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Insights into this and other more complex relationships derive from the Pune Maternal Nutrition Study, which began in 1993 with the enrollment of 2,675 women, and measured their hemoglobin and body size. Over the next three years, 814 became pregnant. Birth weights were measured and body fat phenotype was recorded in 770 newborns. Growth was recorded at six-monthly intervals through the early years of life. When

members of the cohort reached six years of age, they and their parents were examined for size, body composition, insulin resistance and cardiovascular disease (CVD) risk factors. When the cohort reached 12 years of age, the parental and child variables were repeated, with the addition of cognitive assessment of the child.

The typical mother entered the study as a non-smoker and non-drinker, weighing 42.1 kg, with a height of 1.52 m and a body mass index (BMI) of 18.1 kg/m<sup>2</sup>. They consumed an average of 1,700 kcal daily, 73% of which was carbohydrate. Incidences of gestational diabetes and pregnancy-induced hypertension were exceedingly low. Infants were born with a median gestational age of 39.5 weeks, weighing 2.65 kg. The perinatal mortality rate was <sup>21</sup>/1,000 and infants were exclusively breastfed. Neither the customary energy nor the fat intake of the mothers was associated with birth weight. However, the frequency of the consumption of green leafy vegetables (GLV) was directly related to birth weight, from a mean of 2,584 g for those who never consumed GLV, to 2,735 g for those who consumed them more frequently than every other day.

Looking at the relationship the other way, the risk of low birth weight (small for gestational age) was directly associated with increased circulating levels of homocysteine in the background context of high rates of maternal vitamin B<sub>12</sub> and folate deficiencies. At six years of age in the cohort, there was a direct relationship of the child’s fat mass with perinatal maternal folate status and an inverse relationship of child BMI with maternal perinatal vitamin B<sub>12</sub> status. There was an even stronger interactive relationship between high folate status and low vitamin B<sub>12</sub> status, in terms of the insulin resistance measure of the six year olds. Vegetarian dietary practices are responsible for this relationship of folate adequacy (due to plant sources such as herbs and legumes) and low levels of vitamin B<sub>12</sub> (which is uniquely abundant in foods of animal origin). The findings were interpreted as indicating that maternal micronutrient status had guided fetal programming, which in turn determined adiposity and glucose tolerance six years into life. This also pointed the Pune investigators towards the common intersection of the metabolic functions of folate and vitamin B<sub>12</sub> in one-carbon reactions in intermediary metabolism.

To support the notion of a causal relationship, Dr Yajnik cited studies in experimental animals, in which methyl-donor nutrients were supplemented to Agouti mice or methyl-donor nutrients were restricted to ewes in the periconceptual period. The offspring showed an excess or depletion of methylation of DNA sequences, respectively, and the corresponding epigenetic regulation of genes. The phenotypic changes in the offspring mice and offspring lambs had clinical abnormalities. This supports the feasibility of altered intakes of one-carbon-related nutrients as a mechanism for fetal programming.

### Multiple micronutrient supplementation to pregnant women

Parul Christian, from the Center for Human Nutrition, Bloomberg School of Public Health in Baltimore, Maryland, USA, spoke on the topic of “Antenatal micronutrient supplementation: short- and long-term consequences.” It is widely recognized that vast numbers of underprivileged women in low-income societies not only have iron deficiency, but also have multiple additional mineral and vitamin deficiencies. In a study of pregnant women in Nepal, biomarker indicators of nutrient insufficiency were present in more than 30% of subjects for zinc, iron, vitamin A, vitamin E, vitamin K, riboflavin, and vitamin B<sub>6</sub>. Less than 30% of individuals showed deficits for folate, vitamin B<sub>12</sub>, vitamin D, and copper. Micronutrient deficiencies, moreover, are associated with adverse pregnancy outcomes for both elements of the dyad. There are maternal outcomes related to anemia, body composition and mortality. There are short-term infant outcomes in the same domains, as well as prematurity, birth weight and resistance to infections, and longer-term outcomes in childhood related to growth, body composition, and various aspects of metabolic function and physical performance. These realities gave rise to interest in assessing the benefits, and occasionally the risks, to the mother and offspring.

After setting these conceptual bases of interest, Dr Christian provided lessons from the published literature. The in-depth comparisons that followed started with the simple matter of gestational supplementation with iron-folate tablets or placebos in two USA sites and in lowland Nepal. Birth weights were significantly higher with nutrient supplementation than with no treatment; however, the intervention only reduced low birth weight infants in two studies, and in only one was prematurity significantly curtailed. Iron as part of a multiple-micronutrient (MMN) supplement was no better or worse than iron and folic acid supplements in supporting hemoglobin and ferritin concentrations in pregnant women in a dozen trials across the developed world.

Dr Christian then focused on a meta-analysis, involving 12 randomized-controlled field trials with MMN supplements in pregnancy in Asian and African sites and one Latin American site. MMN had a significant protective effect on the number of low birth weight infants. However, when 10 of the studies monitoring perinatal and early neonatal mortality were analyzed, the MMN increased infant loss, but not to a degree that reached statistical significance. To examine the heterogeneity of effects on survival, however, the speaker focused on the Summit Trial in Indonesia, in which iron-folic acid supplementation was associated with greater cumulative mortality than MMN after three months. She also focused on a study in China, in which survival with both iron and folic acid and iron-containing MMN was much lower than that of the reference group over 30 postpartum days.

Carrying out the examination of survival to seven years of age in the Nepal study, the provision of iron-folic acid to Nepalese mothers was associated with better survival than vitamin A alone. This was also true in comparison with the multiple-micronutrient combination of vitamin A and 11 additional nutrients.

The final consideration was longer-term growth after differential maternal supplementation during gestation in two trials in Nepal. In one experience, at two years of age, the offspring of mothers who received MMN had significantly greater growth in height, weight and head circumference than those receiving only iron, folic acid and vitamin A. In the other Nepalese study, carried out to seven years, there were few distinctions in anthropometry among the five maternal-gestational supplementation regimens, with the exception of iron-zinc-vitamin A. This group was consistently shorter in stature and had lower body fat than the control group of vitamin A alone. These children also underwent comparisons for metabolic indicators between six and eight years of age. No differences were found in relation to the regimen of gestational supplementation of the mother, blood pressure, insulin resistance or glycosylated hemoglobin. However, when a combined pediatric profile of metabolic syndrome (MS) was composed, the offspring of mothers supplemented with folic acid and vitamin A were 37% less likely to have MS than the controls.

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**“The glaring reality in MMN supplementation to pregnant women is the inconsistency and heterogeneity seen between geographic sites, and among different combinations of micronutrients”**  
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The glaring reality in MMN supplementation to pregnant women is the inconsistency and heterogeneity seen between geographic sites, and among different combinations of micronutrients. These are mixed blessings for policy makers, and mixed messages from the experience of mixing micronutrients in antenatal supplementation. Guidance can only be *situational*, and is not universal across the globe.

### Micronutrient-fortified rice

Jee Hyun Rah, Nutrition Manager of the DSM-World Food Programme (WFP) partnership in Basel, Switzerland, concluded the lunchtime session with a presentation on “Scientific evidence on micronutrient-fortified rice: Where do we stand?” Dr Rah began by noting that rice was the major staple food for millions of indi-

**TABLE 2:** Multiple options for the fortification of rice

Fortification format	Advantages	Disadvantages
<b>Dusting</b>		
Dusting the polished rice grains with powder form of MN premix	-> Simple -> Low cost	-> Very high losses with washing and cooking
<b>Coating</b>		
MN premix and ingredients (e.g. waxes, gums) sprayed on to the surface of rice grain kernels	-> Water proof	-> Discolored kernels
<b>Cold extrusion</b>		
Produces simulated kernels by passing a dough made of rice flour, fortificant mix and water through a simple pasta press	-> Wash proof -> No limits to types of nutrients	-> Expensive -> Organoleptic properties could be improved
<b>Hot extrusion</b>		
Produces simulated kernels by using broken grains, milled to rice flour to make a dough, with fortificant mix, extruded at high temperature and shaped into kernels	-> Similar to original rice in size, shape, color and taste -> Excellent nutrient retention	-> Technologically elaborate

viduals, providing one fifth of the world's food calories – mostly in Asia. The average consumption of milled rice per person per annum in Asia is 150 kg. Over the next decade, another 1.2 billion new rice consumers will be added to the Asian population. All these features point to the need to increase rice production in the region, by at least 33% above current levels.

Whereas crude rice is a rich source of micronutrients, over half of their content of thiamine, niacin, folate and iron is lost in the process of milling and polishing white rice. A rice fortification process would allow for the restoration of the original micronutrient content lost in milling and additional amounts of micronutrients specifically deficient in the target population could be added. There are multiple options for this rice fortification, each with their advantages and disadvantages (Table 2).

The retention of the added micronutrients through the process of hot extrusion to make NutriRice™ ranges from over 90% for vitamin A, folate and niacin, to 84% for thiamine, and 75% for vitamin B<sub>12</sub>. One or two grains of NutriRice™ are added to 100 kernels of milled white rice to establish the desired micronutrient intake from the staple.

With respect to the biological and nutritional impact of fortified rice, Dr Rah admitted that data from controlled trials in humans are scarce at the moment, but cited three published trials of iron-fortified rice in anemic and iron-deficient populations in India, Mexico, and Brazil. Target daily intakes of iron were 20 mg

or more, and established that, in each experience, a significant reduction in both anemia prevalence and rates of iron deficiency was observed with the iron-fortified variety.

Two trials with NutriRice™ have been conducted in school-children; one an uncontrolled one-year intervention in China, and the other a six-month controlled intervention in Bangalore, India. The NutriRice™ contained additional amounts of vitamin A, and assorted B vitamins, iron and zinc. In China, there was a significant improvement in all nutrient biomarkers for iron, zinc, vitamin A, thiamine, and riboflavin over the year, and academic and cognitive performance improved. The latter indices improved more in previously anemic subjects, although they only constituted 14% of the original sample. In India, a control group with normal rice was compared with a group consuming high-iron or low-iron NutriRice™ containing additional micronutrients, including vitamin B<sub>12</sub>. Hemoglobin concentrations improved equally in six months over the initial levels with both iron additions to the rice. NutriRice™ increased vitamin B<sub>12</sub>



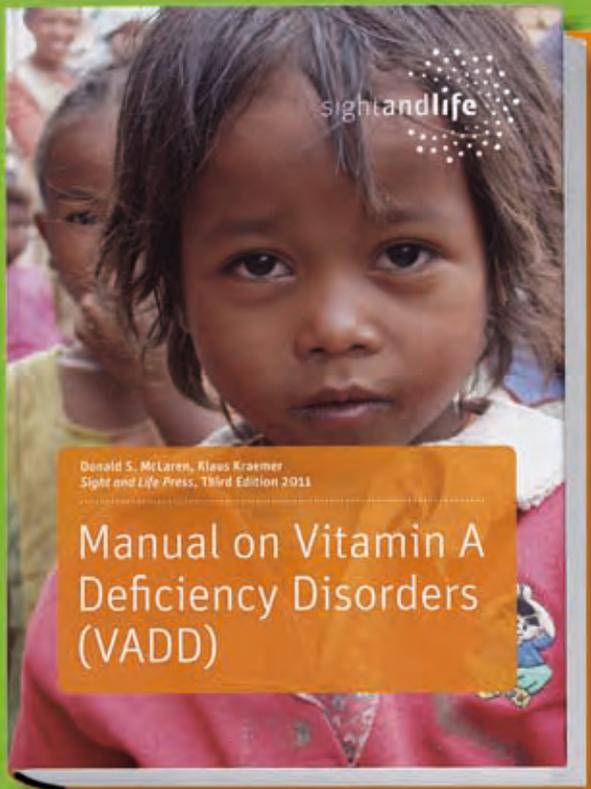
nutrition at the end of the intervention, as compared to the unfortified rice group. Physical endurance was better in the high-iron group than in the other two arms of the trial after six months.

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“Rice fortification is an effective, affordable way to improve the nutritional status of whole populations”  
.....

Cost estimates for a product with vitamin A, four B vitamins, iron and zinc have been generated for two scenarios: In one, an adult consumes half of the daily calories (1,100 kcal) from fortified rice; in the other, the energy contribution is one third (720 kcal). The additional cost of fortification is 0.6 cents (US) for the former and 0.4 cents for the latter. The experience to date led the speaker to conclude that rice fortification is an effective, affordable way to improve the nutritional status of whole populations.

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# Updating Vitamin D Issues Relevant to the Asian Region

## Noel W Solomons

CeSSIAM, Guatemala City, Guatemala

DSM sponsored a symposium entitled “Vitamin D: New Insights and Call to Action”, chaired by Manfred Eggersdorfer of DSM Nutrition Science and Advocacy in Basel, Switzerland, and co-chaired by Kalpana Bhaskaran, of the Singapore Nutrition and Dietetic Association during the 11<sup>th</sup> Asian Congress of Nutrition in Singapore. Its goal was to demonstrate the importance of vitamin D nutrition for the Asian continent.

### Basic biology and nutritional roles

Amrishi Mithal, an endocrinologist at Medanta Medicity, India gave an overview of vitamin D, focusing on its metabolism, bio-availability, sources, and intake recommendations. He reviewed the basic metabolism of the dermal synthesis of the vitamin by ultraviolet “B” (UVB) radiation, converting 7-dehydro-cholesterol in the skin into cholecalciferol. This is metabolized to the 25-hydroxylated form on passage through the liver; later, in the renal tissue, it becomes the active hormone 1,25-hydroxy-vitamin D<sub>3</sub>. The latter hormone is active at the level of calcium metabolism in the intestine and in bone, but the most reliable diagnostic biomarker of nutritional status is the circulating concentration of 25-OH-vitamin D (25(OH)D).

“There are two chemical forms of vitamin D, which are derived from different origins and sources”

There are two chemical forms of vitamin D, which are derived from different origins and sources. The variety derived from skin synthesis in animals is vitamin D<sub>3</sub> (cholecalciferol); its richest sources are salmon, mackerel, tuna and liver oil. The other – less relevant – variety is vitamin D<sub>2</sub> (ergosterol), which is abundant in sun-exposed Shitake mushrooms and, to a lesser extent, egg

yolk, and is produced commercially from the UV irradiation of yeast. Vitamin D is added to fortified dairy items such as margarine, butter, milk, yoghurt, and cheese, and to certain juice and breakfast cereal products. The speaker commented that “dietary sources are not major contributors to circulating vitamin D, as it is rarely present in foods that are commonly consumed, unless they have been fortified.”

### Influential factors

A number of factors influence individuals’ effective exposure to the solar ultraviolet radiation that drives synthesis in the skin. These include the latitude (greater distance from the equator) in interaction with the season (in the winter months at high northern or southern latitudes, the angle of sunlight through the atmosphere abolishes UVB exposure), and the time of day. (Even in summer, UVB intensity is only sufficient for vitamin D synthesis from 10:30 am to 2:30 pm.) Individual characteristics and behaviors also intercede. People with white skin are more efficient at skin synthesis than those with darker pigmentation. Synthesis efficiency decreases as the skin ages, falling by two to threefold from 25 years to 75 years. Sunscreen, when used effectively, blocks all vitamin D formation, as does the use of clothing to cover normally sun-exposed areas of skin. Higher ozone levels in the upper atmosphere impede the flow of appropriate radiation to the surface.

Vitamin D’s classic function is considered to be the endocrine function, related to calcium binding protein, both in the intestine with consequences for skeletal bones. Studies in Europe and the USA reveal that supplementation with vitamin D decreases the risk of falls and bone fractures. The latter effect is attributed to conserving bone mineralization. However, the mechanism for the reduced falls is not clear; it could be related to an independent effect on the strength of skeletal muscle quality and function.

### Autocrine cell signaling

In the past decade, newer actions of the vitamin in “autocrine” cell signaling have been uncovered. This constitutes a chemi-

**TABLE 1:** Guidelines – RDI for vitamin D (Endocrine Society, June 2011)

	For skeletal health	For extraskeletal health	To maintain 25(OH)D > 30 ng/mL
0–1 year	400 IU/day	?	–
1–18 years	600 IU/day	?	1000 IU/day
19–50 years	600 IU/day	?	1500–2000 IU/day
50–70 years	600 IU/day	?	1500–2000 IU/day
>70 years	800 IU/day	?	1500–2000 IU/day
Pregnant women	600 IU/day	?	1500–2000 IU/day
Lactating women	600 IU/day	?	1500–2000 IU/day
Obese, on anticonvulsants, antifungal, AIDS Rx	2-3 X RDI –	– –	– –

cal messenger hormone being secreted within a cell, to bind to receptors within the same cell. With respect to carcinogenesis, vitamin D can be shown to exert a control of cell proliferation, in part due to the suppression of the growth of new blood vessels and, in part, due to the programmed death of previously dividing cells. The role of vitamin D as an autocrine hormone, which is participating in signaling pathways *within* body cells, is a possible explanation. This mechanism is similarly suspected to be the basis of the antibacterial action of vitamin D, and of its anti-inflammatory effects and actions to reduce the process of autoimmunity.

Michael Holick, in a review for the *Endocrine Society*, suggested a set of cut-offs for circulating concentrations of 25-OH-vitamin D: For “deficient,” <20 ng/mL (<50 nmol/L, reduced bone density and greatly elevated parathyroid hormone {PTH} secretion); for “inadequate,” < 20–30 ng/mL (50 nmol/L to 75 nmol/L, PTH remains elevated); and for “adequate,” >30 ng/L (>75 nmol/L, improved efficiency of calcium absorption and PTH levels flatten out). The presenter provided his own survey, collecting blood samples from physicians in all parts of India, from north to south. There was no real axial gradient, but an astonishingly high rate of frankly deficient levels was encountered, ranging from 75% of participants in Kolkata to 90% in Mumbai.

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**“In some regions, such as South Asia and the Middle East, frank vitamin D deficiency is common in all age groups, from neonates to the elderly”**  
 .....

In 2009, the International Osteoporosis Foundation produced a statement which drives the criterion for frank vitamin D deficiency even lower. It states: “While 25(OH)D levels below 30 ng/mL are common in most populations, levels below 10 ng/L, that constitute frank vitamin D deficiency, are most commonly seen in populations at risk, in particular the elderly. In some regions, such as South Asia and the Middle East, frank vitamin D deficiency is common in all age groups, from neonates to the elderly.” It follows this epidemiological information with a conclusion about its therapeutic consequences: “Given the proposed definitions of vitamin D sufficiency, it is possible that populations at high risk will have to resort to supplementation to achieve desired 25(OH)D levels.”

#### Dynamic flux

Recommendations for daily dietary intakes of vitamin D have been in dynamic flux. Throughout the first decade of the new millennium, both the Recommended Nutrient Intake (RNI) of the United Nations, and the Recommended Dietary Allowance (RDA) of the US and Canada for the vitamin through most of the lifespan was 200 IU daily. In 2010, this tripled to 600 IU for the RDA. The Endocrine Society has produced its RDI for the vitamin (**Table 1**). The Society guidelines have two levels. The first tier is identical to that of the current RDA, but is only considered valid for optimizing skeletal health. The second tier (**the third column of Table 1**) is aimed at maintaining a circulating concentration of 25(OH)D considered to be adequate. The experts do not have enough empirical evidence as yet for a consensus on intakes that supports the vitamin’s extraskeletal functions (**the middle column, Table 1**).

The Endocrine Society has also considered whether there is an upper limit of vitamin D dose. The estimation of an upper tol-

**TABLE 2:** Food and Nutrition Board considerations for high-dose exposure to vitamin D

	Dose	Higher doses for correction of vitamin D deficiency
<6 months	1000 IU/day	2000 IU/day
6 months – 1 year	1500 IU/day	2000 IU/day
1 – 3 years	2500 IU/day	4000 IU/day
4 – 8 years	3000 IU/day	4000 IU/day
8 – 18 years	4000 IU/day	4000 IU/day
>18	4000 IU/day	10,000 IU/day

erable intake level (UL) from the *Dietary Reference Intakes* process in the US-Canada, undertaken by the Food and Nutrition Board, is illustrated by age (Table 2). What the Society considers to be tolerable amounts when used for the correction of an existing vitamin deficiency are set out in parallel in the right-hand column. In its opinion, in the younger and older ends of the lifespan, it is safe to correct a deficiency with daily dosages above the UL.

#### Geographical aspects

Dr Sreeram Ramagopalan, a researcher at the University of Oxford, UK, has actively investigated South Asians in India and their compatriots living as expatriates in England. He spoke of some of the geographic aspects of the theme, in a discussion of vitamin D-gene interactions in multiple sclerosis (MS). MS is an inflammatory, demyelinating disease of the central nervous system, probably autoimmune in origin. It is clinically variable, with a female predominance of 3:1. MS is the most commonly acquired neurological disease in young adults.

### “The major clues to the origin of multiple sclerosis are genetic and geographic”

The major clues to the origin of multiple sclerosis are genetic and geographic. MS occurs in family clusters, which argues for a hereditary basis. Moreover, modern genetics and genomics have identified a family of MS genes, associated with the class II major histocompatibility complex on human chromosome 6. With respect to geography, MS is increasingly common beyond 40° North and South. The highest risks for the affliction are to be found in the USA, Iceland, Scandinavia, and Northern Europe in the northern latitudes, and in New Zealand in the southern latitudes. For example, MS has an occurrence frequency of ~1/1000 in

Canada and ~1/400 in Scotland. By contrast, it is far less common in South Africa and Australia, the homes of European descendants located nearer to the Equator. Also, within the US, UK and France, MS prevalence can be mapped over the UVB intensity patterns. Additional solar-related evidence comes from the excess prevalence of MS in the Northern Hemisphere in persons born in May, after a period of low UVB intensity in the previous nine months, compared to those in November, after a pregnancy covering the entire summer months. The pattern is reversed in the Southern Hemisphere. This geographic distribution evokes the potential of solar exposure to be a factor in the etiology.

The direct relationships of MS to vitamin D status itself come from a longitudinal study of US nurses, in which there was a 32% lower incidence of new MS in women taking supplements with vitamin D – below 400 IU per day – and a 41% lower incidence when the daily dose exceeded 400 IU. A case-control study among US military personnel with banked serum samples found a 51% reduction in risk of MS if their historical 25-OH-vitamin D concentration was greater than 100 nmol/L.

### “There is potential for an interaction of genetics and vitamin D status, mediated by oral intake or solar exposure”

The genetic aspects of MS have been examined. There is a genetic component: The more closely related you are to an MS patient, the higher your risk of getting the disease. About 30 other genes show a more modest effect. A specific human leukocyte antigen (HLA) class II region (*HLA-DRB1*) exerts the strongest effect on MS risk. A domain for a vitamin D response element has been related to the promoter in the region, and polymorphism variation has been shown. This finding gives rise to the potential for an interaction of genetics and vitamin D status, mediated by oral intake or solar exposure. This is summarized by Dr Ramagopalan as follows:

- > Vitamin D (acting via the vitamin D receptor, VDR) binds the HLA-DRB1 promoter;
- > VDR binding influences the expression of HLA-DRB1;
- > The timing of when this interaction is important for MS is yet to be understood.

In the question and answer period after the presentation, it was disclosed that the same barriers of skin pigmentation to solar penetration of persons in South Asia, near the Equator, are even more problematic for compatriots living in the latitudes of the UK.

**TABLE 3:** Cut-off criteria with a pediatric perspective

Vitamin D status	25(OH)-D level	
	nmol/L	(ng/mL)
Severe deficiency	≤ 12.5	5
Deficiency	≤ 37.5	15
Insufficiency	> 37.5 – 50.0	> 15 – 20
Sufficiency	> 50 – 250	> 20 – 100
Excess	> 250	> 100
Intoxication	> 375	> 150

Data from Misra M, Pacaud D, Petryk A, et al; Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society (2008). Vitamin D deficiency in children and its management: review of current knowledge and recommendations. *Pediatrics* 122: 398–417

### Epidemiology of vitamin D deficiency and its consequences

With respect to the epidemiology of the Asian region, Geok Lin Khor of the International Medical University of Malaysia spoke on vitamin D deficiency and its consequences. She noted that UVB radiation is most intense in zones between latitudes 23.5°N and 23.5°S of the equator. In terms of diagnosis, she recognized the same cut-off criteria, established by Holick, which had been cited by Dr Mithal. As Prof. Khor focused on Asia, where rickets is a valid concern, she alerted the audience to an alternative set of 25(OH)D criteria focused on the pediatric population (Table 3).

Prof. Khor contributed a systematic review of literature on the epidemiology of vitamin D status in populations of all ages in Asian countries. Articles and reports selected for this review were based on these eligibility criteria:

- Studies conducted in countries in Asia
- Subjects not institutionalized in homes needing special care
- Articles/reports in English published after 2000
- Preferably, sample size above 100 subjects
- Classification of vitamin D status includes cut-off levels of 25 nmol/L (10 ng/mL) and 50 nmol/L (20 ng/mL) serum 25(OH)D for comparability of data.

In this latter classification for nutritional status, she divided the deficiency category into two classes: very deficient and deficient.

In her review, studies were included from Malaysia (4° N), three areas in India (between 19° and 26° N) and from two age groups, both in Beijing (at 40° N). Prof. Khor pointed out that the expected gradient of decreasing circulating 25(OH)D levels and latitude were not observed in her review. In fact, across dif-

ferent child groups within Beijing in the northern climate, there is the same range as is seen among the other Asian sites.

### Major implications

In a review of published results in pregnant or non-pregnant women from Asia, results were somewhat more congruent with the expected inverse relationship between distance from the Equator and circulating vitamin D levels. The sites in ascending distance from the Equator were: Kuala Lumpur; Jakarta; Mysore; Tirupati; Hong Kong; Lucknow; Dhaka; Delhi; and Beijing. However, in Lucknow, in northern India, there was a twofold difference between average 25(OH)D in summer (~56 nmol/L) and winter (~28 nmol/L). This could also have major implications for fetal exposure and long-term health. Similarly, in Tirupati in south-central India, at 13° N, middle-aged women had a mean circulating vitamin D concentration of ~15 nmol/L in an urban zone and ~20 nmol/L in a rural area.

Finally, Prof. Khor presented a review of the summary findings of a diverse array of published reviews by other authors on important and poorly resolved questions relating to circulating vitamin D levels and a series of outcomes. These included those changes in bone mineral density (BMD) during pregnancy, associations with background BMD, the association with fracture risk, and thresholds for vitamin D concentration and clinical rickets (Table 4).

## “Infants born of undernourished mothers are at risk of hypovitaminosis D”

### Conclusions

Prof. Khor closed with a series of conclusions, which she synthesized from her own intensive examination of vitamin D levels in Asian populations, and from reviews that included populations from across the globe. She concluded that infants born of undernourished mothers are at risk of hypovitaminosis D, as human milk is usually low in vitamin D. Policies are needed for the supplementation of pregnant women and infants with vitamin D. Children and adolescents require adequate vitamin D to meet optimal growth and development. Since diet can only provide a limited amount of the daily requirements for vitamin D, sun exposure – 15 minutes daily – should be encouraged for all. Monitoring the circulating levels of 25(OH)D of vulnerable population groups may be necessary to improve vitamin D status.

Maternal vitamin D deficiency is widespread in Indian women, which raises concerns about the vitamin status of the fetus,

**TABLE 4:** Conclusions from systematic reviews of relevant questions of associations with circulating 25 (OH) vitamin D concentrations**Is there an association between circulating vitamin D and changes in bone mineral density (BMD) during pregnancy?**

- > "There was insufficient evidence for an association between 25(OH)D and changes in bone density during pregnancy.
- > One good prospective cohort did not find an association between serum 25(OH)D and the changes in BMD that occur during lactation.
- > Limitations in the study design and sources of bias highlight the need for additional research on vitamin D status in pregnancy and lactation, and the association with bone health outcomes."

**Is there an association between circulating vitamin D and bone mineral density (BMD)?**

- > "There was discordance between the results from RCTs and the majority of observational studies that may be due to the inability of observational studies to control for all relevant confounders.
- > Based on results of the observational studies, there is fair evidence to support an association between serum 25(OH)D and BMD or changes in BMD at the femoral neck."

**Is there an association between circulating vitamin D and fracture risk?**

- > "One of three cohorts reported an inverse association between serum 25(OH)D and fractures, and nine of twelve case-control studies found lower 25(OH)D concentrations in cases versus controls.
- > Based on the above studies, the level of evidence for an association between serum 25(OH)D and fractures is inconsistent."

**What is the relationship between circulating vitamin D and rickets?**

- > "There is fair evidence for an association between low serum 25(OH)D and established rickets, regardless of assay type (RIA, CPBA, HPLC).
- > There is inconsistent evidence to determine if there is a threshold concentration of serum 25(OH)D above which rickets does not occur."

given that maternal-to-fetal transfer is the primary route for nourishing the offspring *in utero*.

Geeta Triok Kumar of Delhi University, India spoke on the health implication of vitamin D in infancy. She is the lead investigator in the only randomized clinical trial (RCT) to date to examine the mortality and morbidity of infants in relation to vitamin D supplementation. She is also interested in the long-term consequences of vitamin D status in fetal life and early life.

She demonstrated that most of the research on the relationship of maternal vitamin D status and pregnancy and infant outcomes is based on cross-sectional associations. Interpretation of results from supplementation trials during pregnancy is complicated by the type, dose and duration of supplement. Direct supplementation of infants with the vitamin is another approach. Low birth weight (LBW) term infants would be a target group for the benefits of assuring an adequate vitamin status. The Delhi Infant Vitamin D Supplementation (DIViDS) study, an individually randomized, double-blind, placebo-controlled trial of weekly vitamin D<sub>3</sub> supplementation of Indian infants for

the first 6 months of life, represents the first study of its kind addressing the LBW issue.

A sample was comprised of 2,000 singleton births of infants with at least 37 weeks of gestational age, but weighing between 1.8 and 2.5 kg, captured for enrollment within 48 hours of birth. To facilitate the follow-up, they had to live within a 15 km radius of the base hospital. Severe congenital abnormalities or death within the first week were the exclusion criteria. Field workers supervised the weekly supplementation of 1,400 IU of vitamin D, mixed with expressed breast milk for the first six months. The primary outcome variable was the rate of all inpatient hospital admissions or death in the first six months of infancy. The secondary outcome was growth. At six months, the supplemented infants had significantly higher circulating 25(OH)D concentrations and lower rates of severe vitamin D deficiency, but half of the infants receiving the weekly supplementation had concentrations <50 nmol/L. Nevertheless, arm circumference and length were significantly greater at six months in the vitamin D group. The 10% combined hospitalization or death incidence by six months showed no difference from treatment status.

**RCT designs**

With respect to the failure to find any reduction in mortality, it was concluded in the question-and-answer period that followed the presentations that the sample size of the Delhi RCT did not have statistical power to detect effects on mortality, given that the demise of children, even in such deprived circumstances, is rare. The speaker's conclusion, however, was that more RCT designs with vitamin D supplementation for mothers, infants and both elements of the dyad are pertinent to the resolution of how best to address vitamin D deficiency on a public health basis in Asia.

An association between low UVB solar radiation and high incidence rates of type 1 (early onset) diabetes mellitus has been noted in geographic mapping. Incidence rates of type 1 diabetes approached zero in regions worldwide with high UVB exposure. Some data on the protective effect of vitamin D supplementation in early childhood on development of type 1 diabetes has been gathered in recent years. In one study cited, the use of cod liver oil in the first year of life was associated with a significantly (26%) lower risk of type 1 diabetes. In another experience cited,

consumption of the recommended daily amount of vitamin D in infants born close to the Arctic Circle in northern Finland, of 2,000 IU, regularly had a 78% lower incidence of type 1 diabetes than those taking less than the recommended dose. Finally, in a meta-analysis on the risk of diabetes with vitamin D supplementation in five studies involving children from different locations in Europe – one cohort and four case-control designs – found an aggregate 29% lower risk for type 1 diabetes.

Four Asian investigators who carried out a personal investigation of vitamin D demonstrated the theoretical risk of impaired vitamin D in Asian populations and documented its short- and long-term consequences. Most importantly, they outlined outstanding questions, and suggested directions in which research in vitamin D should go in the coming years.

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# Intervention Programs Tackling Micronutrient Deficiencies in Asia

**Noel W Solomons**

CeSSIAM, Guatemala City,  
Guatemala

The Global Alliance for Improved Nutrition (GAIN) sponsored a symposium entitled “Intervention Programs Tackling Micronutrient Deficiencies” at the Asian Congress of Nutrition in Singapore, July 13 – 16. Participants came from one country in East Asia and five countries in Southeast Asia. However, those nations represented can be grouped separately. The first group included China and its contiguous neighbors, Vietnam and Thailand, along with Cambodia, which sits between them. The remaining sites are two sprawling archipelago nations, Indonesia and the Philippines, in the Indian and Pacific Oceans. Regina Moench-Pfanner of GAIN’s Nutrition Unit chaired the session, with Nyugen Cong Khan serving as co-chair. Martin Bloem of the World Food Programme (WFP) was the moderator for the interactive panel and audience discussion at the conclusion of the individual presentations. The panel of speakers, with their individual national reports and perspectives, were well selected, given their major projections in the area of micronutrients and food fortification. The panel included Junshi Chen of China, Li Thi Hop of Vietnam, Emorn Wasantwisut of Thailand, Chan Theory of Cambodia, Juan Antonio Solon of the Philippines, and Soekirman of Indonesia. The session auditorium remained filled with a rapt and interested audience throughout the two hours of presentations and discussion.

“This is a region with nations of diverse sizes, ethnic make-up and economic development”

For a region with nations of such diverse sizes, ethnic make-up and economic development, it was interesting and informative to examine an overview of the commonalities and contrasts across

the settings. A number of features were common to many or all of the country sites represented in the symposium. For instance, several talks tried to base their strategies for action on an assessment of the nutrient deficits in the population, and focus them on the segments of the societies most in need. Micronutrients of interests most often mentioned by the speakers and addressed by the presentations were iodine, iron and vitamin A; zinc and folate were also prominent in some discourses. Although “intervention programs” can have a number of meanings, fortification, and not dietary diversification or supplementation, was the focus of most speakers. Moreover, the scale of the actions in the various nations ranged from pilot and exploratory to mandatory by law, and from scaled-up to national level.

## A panorama of nutrient deficiencies

The usual departure point for development and implementation of nutritional interventions is an assessment of the nutritional needs and status of a population. As shown in **Table 1**, the presenters for all but one country provided a contemporary survey or intervention-study data to manifest the continuing extent of malnutrition in their nations. Interestingly, given the detail of intervention strategy development presented no justifying nutrient-status data was presented for the remaining site.

In terms of nutrient intake, a GAIN-sponsored Vietnamese national survey for two macronutrients (energy and protein), four vitamins and three minerals, revealed less than 100% of reference intake for all nutrients in both urban and rural settings, with the exceptions of vitamin C and thiamine. Prof. Hop illustrated critically low (<60% of recommended levels) intakes of vitamin A, calcium and zinc. The results from laboratory biomarkers paint a varied picture from a survey of 1,500 households containing 1,526 women and 586 children aged six to 59 months. There was profound and widespread deficiency in circulating zinc levels, with relatively minor abnormalities of vitamin A and iron status in Vietnam (**Table 1**).

From general data from unspecified surveys covering the past decade in Thailand, a higher rate of maternal anemia and lower rates of zinc deficiency have been recorded. The problematic

**TABLE 1:** Survey findings on nutrient vulnerability of specific populations by country

Nation	Nutrient/condition	Population sectors
China	Anemic	-> Older women >60%
	Iron-deficiency anemic	-> Schoolchildren 10–35% Fertile women 17–46%
Vietnam	Anemic	-> Adult women 21% Under-5 children 15%
	Iron deficient	-> Adult women 13% Under-5 children 13%
	Marginal vitamin A	-> Adult women 5%
	Zinc deficient	-> Adult women 67% Under-5 children 52%
	Marginal/deficient folate	-> Adult women 28% Under-5 children 8%
Thailand	Anemic	-> Not specified 20%
	Vitamin A deficient	-> Lactating mothers <1% Schoolchildren 3%
	Zinc deficient	-> Schoolchildren 30–50%
	Low urinary iodine status	-> Pregnant women >60%
Cambodia	Anemic	-> Pregnant women 58% Reproductive-age 44% Under-5 children 41%
	Vitamin A deficient	-> Under-5 children 22%
	Night blindness	-> Pregnant women 8%
Indonesia	Vitamin A deficient	-> Schoolchildren 53–58% Pregnant & lactating women 10–17%
Philippines	No data provided	

With the exception of China, the reported prevalence values derive from survey or literature data. For China, pooled prevalence data for baseline rates in intervention studies have been cited.

situation is with iodine; less than 40% of pregnant women in one survey experience had urinary iodine concentrations in excess of the deficiency-threshold concentration of 150 µg/L. In Cambodia, rates of anemia in women and children are much higher than in its two neighbors, and vitamin A deficiency is a major public health problem (Table 1).

“Fortification and fortified staple foods or commercialized products were the singular focus of the narratives from five nations”

China is a diverse country, in which no country-wide generalization can easily be made with respect to micronutrient status. In selected populations, chosen for intervention trials for their conditions of being able to see an effect of iron intervention (and which presumably will be the beneficiaries of the interventions), however, one can see the extremes that exist in that nation. Thus, a range of rates for all anemia or for specifically iron deficiency anemia, ranging above 30% and much higher, are illustrated in specific population sectors in the efficacy trials cited by Prof. Chen.

#### Fortification innovation and interventions across Asia

As mentioned, fortification and fortified staple foods or commercialized products were the focus of the presentations from five nations. Across this quintet, 15 specific fortification interven-

**TABLE 2:** Specific micronutrient intervention programs mentioned in the presentations by country

China	Thailand	Cambodia	Indonesia	Philippines
-> Salt iodization	-> Salt iodization	-> Salt iodization	-> Vitamin A fortification of oil	-> Multi-nutrient
-> Vitamin A fortification of oil	-> Triple-fortified (Fe, vitamin A, iodine) instant noodle	-> Vitamin A fortification of oil		fortifying powder for
-> Fe fortification of soy sauce	iodine) instant noodle	-> Multi-nutrient fortified		complementary foods
-> Multi-nutrient fortified	seasoning mix	corn soy blend		
wheat flour	-> Double-fortified	-> Multi-nutrient fortified rice		
-> Multi-nutrient fortified rice	(Fe, iodine) fish sauce			
-> Fortified complementary				
food				

tions were mentioned in detail, as outlined in **Table 2**. Heading the list were standard staple-food fortification programs, consisting of iodine in salt in three countries, and vitamin A in edible cooking oils in two countries. Powdered nutrient mixes are featured in two settings, one explicitly as a seasoning condiment and the other a tasteless complement. Iron alone, or with one other nutrient, in popular condiment sauces stood as examples of programs directed at iron deficiency and iron deficiency anemia. The final six examples were multiple micronutrient interventions, with from five to 16 different micronutrients incorporated into the product.

### China

China's inhabitants represents a third of the world's population, dwarfing the cumulative population of the five ASEAN nations in the symposium. China has six types of fortification. Only one, the fortification of salt with iodine, is mandatory. The other five are case studies and do not reach the entire population of the nation. These include iron fortification of soy sauce, vitamin A fortification of cooking oil, and multiple micronutrients in fortified rice and in wheat flour. Finally, a multimicronutrient fortified complementary food supplement is part of the innovative mix in the Republic of China. In a comprehensive presentation, Prof. Chen examined the efficacy or effectiveness studies carried out in various target populations with the various interventions.

The iodization of salt only became mandatory in China in 1994; currently, 96% of households have iodized salt, and endemic goiter rates have fallen from 20% before fortification to the current less than 5%. For elimination of iron deficiency anemia, soy sauce fortification has been the option. It is consumed daily by 80% of the national population, with an average of 13 mL/day. NaFeEDTA, a highly bioavailable form of iron, has

been chosen, and 23 to 26 mg of elemental iron are added per 100 mL, providing an average of 3 mg per consumer per day. In field studies, fortified soy sauce dramatically reduced rates of anemia and iron deficiency anemia. It also improved growth among recipients in the three to six years age group. No specific details were given on the extent of vitamin A deficiency in parts of China, nor on the particulars of fortified oil distribution.

Interesting approaches in the multiple micronutrient domain were exemplified in the regional trials and programs with multi-nutrient fortified cereal products in poor rural populations. The archetype wheat flour had seven nutrients: vitamin A, thiamine; riboflavin, niacin, folic acid, iron, and zinc; Fe was added at 25 mg and folic acid at 1 mg per kg of flour. A five-nutrient variant, without vitamin A or niacin but with 30 mg of Fe and 2 mg of folic acid per kg, was used in an area with a specifically high incidence of neural tube defects (NTDs). With implementation of the archetype flour, micronutrient status for the indicators measured improved and NTD rates declined. Later, with respect to the simplified and folic acid enriched variant, a study of consumption patterns for wheat flour after its introduction at a subsidized price found the rate of NTDs per 1,000 live births differs from over 80 to less than three between women who consumed less than a kg of fortified flour per month, and those consuming over 7 kg. A typical Chinese person consumes more rice than wheat, 238 g per day on average with only little variation between rural and urban dwellers, and across social classes. Current studies



have found high acceptability of a DSM rice with fortified reconstituted rice kernels, although no efficacy studies have yet been published. Finally, a pilot study with a vitamin A-free, 5-micronutrient (vitamin D, riboflavin, calcium, iron and zinc), soy-based complementary food supplement, supplying 44 kcal and 3.9 g of protein daily to 1,000 infants in the second half of infancy in Gansu Province, has shown significant reductions in anemia rates and improvements in gross and fine motor performance and development quotients at 12 months of age.

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## “Micronutrient malnutrition has not been self-correcting to date through Thailand’s economic transition”

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### *Thailand*

Prof. Wasantwisut prefaced her remarks on Thailand by pointing out that, from before the 1960s, this was a low-income country with problems of undernutrition, showing gradually declining rates of protein-energy malnutrition up to 1990. Over the past three decades, it has transitioned to rapid economic growth rates, with a rise in overweight and obesity. As her presentation illustrated, however, micronutrient malnutrition has not been self-correcting to date through the economic transition. Thailand has programs of periodic vitamin A capsule supplementation, weekly or daily iron supplementation depending on the age group, and iodized salt. The variability in urinary iodine alluded to above is a source of consternation over a dilemma. Despite mandated iodine addition, it appears that poor quality control among small salt producers leads to an inadequately iodized product, and only 50% of households recently surveyed had adequate iodine concentrations in their salt. In addition to improved inspection and monitoring, Thai officials have mandated the use of iodized salt in soy and fish sauces, and in animal feeds.

Fortification of commercial foods is voluntary. Two products, triple-fortified and double-fortified seasoning-powder for instant noodles, have been developed, tested and marketed to deal with both iodine issues and residual iron deficiency anemia. The iron used is NaFeEDTA. In efficacy studies of the seasoned noodles in schoolchildren in North East Thailand, a variant of the marked brand – quadruple fortified with zinc, as well as the standard trio of micronutrients – showed efficacy in three domains: **1.** it lowered the prevalence of low urinary iodine excretion, and of deficient circulating zinc levels; **2.** it reduced the incidence of respiratory infections; and **3.** it improved performance in a battery of cognitive tests. Earlier studies had shown that both noodles and fish sauce reduced rates of anemia in anemic populations.

### *Cambodia*

The major achievement of fortification in Cambodia has been with the iodization of salt. In 2000, before the enactment of a mandatory iodization decree in 2003 in Cambodia, 14% of households had adequately iodized salt in samples taken in a national household survey. By the next survey, in 2005, this had surged to 72%, and then advanced to 83% in the most recent survey, in 2010. No mention was made of its impact on urinary iodine, or whether any “overshoot” in biological effects was to be observed. The World Food Programme is active in Cambodia, with major programs for the distribution of multiple micronutrient fortified corn-soy blend and vitamin A fortified cooking oil. Rice is the major staple cereal in the country, and the WFP is also conducting acceptability trials with a multimicronutrient fortified variety of rice, similar to that in various stages of advancement in other Asian countries at this time.

Mention was also made of some current pilot and occasional fortification activities on a lesser scale. On the horizon for future scaling up, to address the major anemia problem (**Table 1**), are two condiments, fish and soy sauces, which have been tested in a pilot fashion. Both supply 400 mg of iron per liter of sauce. Studies have shown them to be acceptable in the Cambodian population. Mrs Theary noted commercial specialty products with a minor impact on the national market, including fortified wheat flour (for household baking) and a fortified instant porridge (designed for children aged six to 23 months). Both products are imported into Cambodia, and sustainable and predictable intake by the low-income populations is an unlikely eventuality.

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## “The focus in Indonesia was on vitamin A fortification of oil.”

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### *Indonesia*

The focus in Indonesia was on vitamin A fortification of oil. No other nutrient was considered. The context was exclusively on palm oil as the vehicle, given the growing extent of palm fruit cultivation in Indonesia. Native palm oil is red due to a rich content of provitamin A carotenes. The consuming public, however, prefers clear oil for household use. Refined cooking oil with added retinyl palmitate is the intervention under consideration. Only 6% of the vitamin is lost in the first frying, and over 50% is still retained after three uses of the same oil. Duly fortified with vitamin A, 21 g of oil per day, providing 190 kcal, would increase average intakes above 100% of the RDA. Four commercial brands of cooking oil on the Indonesian market are vitamin A fortified, but the majority of the population – those of low income – consumes unbranded (generic) oil from open communal markets. These are produced by six large, and multiple

small, production mills across the archipelago. Prof. Soekirman outlined a process, spearheaded by the Indonesian Fortification Coalition, to empower and enable these produced in a public-private partnership, to add the requisite retinyl palmitate to produce a clear cooking oil, based on palm oil, to combat the residual vitamin A deficiency (Table 1).

### The Philippines

The report by Dr Solon from the Philippines was something of a departure in the series. The narrative of the presentation was dedicated to the development and social marketing of micronutrient powders in the Philippines; it concerned a nationwide – if not actually “national” – action across the archipelago from the particular vantage point of the Nutrition Center of the Philippines. The presentation highlighted the development, partial efficacy and acceptability testing, social marketing and distribution plans for a 16-micronutrient powder aimed at home-fortification of complementary foods. The presenter provided detailed information on the consumption patterns of complementary foods, among them porridge, noodles and cereal; 91% of all children receive solid or semi-solid foods by six to eight months of age in the Philippines, but only 49% of partially breast-fed children from six to 23 months met the national criterion of a minimum acceptable diet. Modeling has been conducted on buying power across the socioeconomic classes of the nation to determine the potential penetration of a tasteless, colorless (white) sachet-based powder to enhance micronutrient intake with meals of the common complementary foods consumed.

As noted, there was no data presented from an evaluation of nutritional deficiencies throughout the country, or the specific micronutrient needs to be corrected. Moreover, the specific enumeration and dosages of micronutrients in the packet, and details of iron bioavailability and nutrient stability in storage and in mixing were omitted. Some members of the audience were no doubt left with the sensation of getting the cart before the horse: i.e., developing and creating the demand for a home-fortification product without establishing the contributions needed – if any – to assure adequate intakes of the 16 nutrients of interest.

### Summary and conclusions

The presentations ranged from the broadly comprehensive to the narrowly particular, and from a unique focus on the nutritional situation (without discussion of interventions) to the converse, i.e., a discussion of interventions, with little or no context of nutritional needs. A number of additional issues stand out. Some were addressed in the audience participation in the question-and-answer period. Others were not touched upon, perhaps due to lack of time. The contrasting extent of serum-zinc-based zinc deficiency between the moderate rates in Thailand and the high rates in neighboring Vietnam was a point of inquiry. This also

led to the question of how stunting rates can be, relatively, so modest in both countries, if zinc deficiency is a substantial background public health problem.

The linking of micronutrient interventions to foods with intrinsic health consequences was an issue raised in discussion. This applies to refined palm oil, in the Indonesian experience, as its profile of saturated fatty acids has been associated in some studies with a higher disposition to coronary artery atherosclerosis. More emphatic, however, were the questions regarding the high sodium content of fish and soy sauces and instant noodles, variously, in the Thai, Cambodian and Chinese intervention contexts. Efficacy and effectiveness trials were strong in China, but weak or absent across much of the rest of the region.

In sum, Asia is a gigantic region of the world in terms of its extent and population. It is in no way being ignored by the major facilitators of micronutrient enhancement for diets, including GAIN, *Sight and Life*, and WFP, among others. As heterogeneous as the nutritional status indices across the region are the efforts to provide effective, safe, affordable and sustainable security for micronutrients. This session provided a kaleidoscopic view of the scope, strengths and weaknesses of current efforts to inform an interested public at the Asian Congress of Nutrition.

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# Travel Grant Report

## Asian Congress of Nutrition 2011, Singapore

### RMLR Thilakarathne

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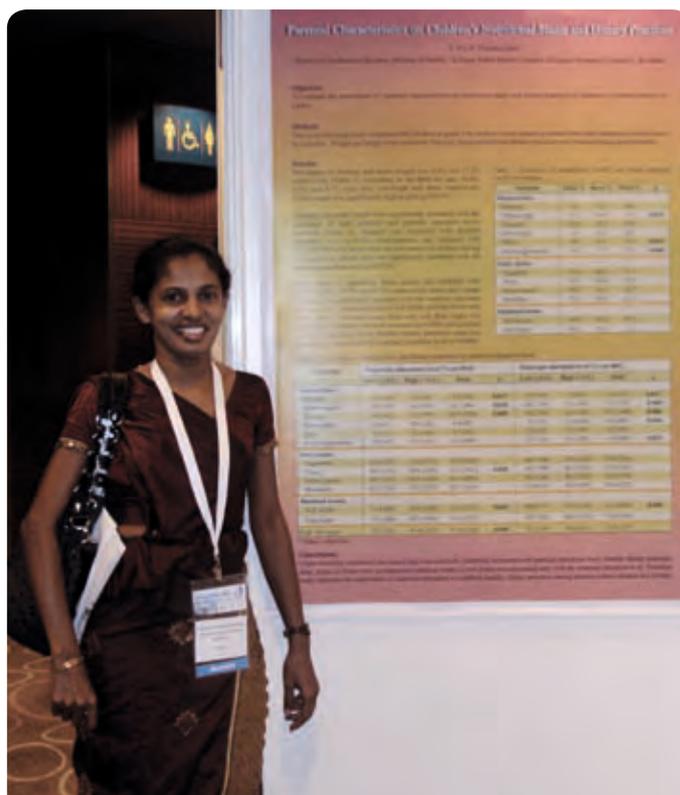
The Asian Congress of Nutrition (ACN) is a gathering of many internationally and regionally renowned experts, scientists, nutrition professionals, industry stakeholders and practitioners in nutrition, dietetics and related fields, which is held every four years under the Federation of Asian Nutrition Societies.

The 11<sup>th</sup> ACN took place at the Suntec Singapore International Convention and Exhibition Center, Singapore on 13–16 July 2011, on the theme of “Nutritional Well-Being for a Progressive Asia – Challenges and Opportunities.” It provided a venue for sharing new knowledge from research, development and best practices in the advancement of nutrition. It allowed participants to discuss their experiences, ideas and viewpoints on current nutrition issues. It served as an excellent platform for nutritionists to strengthen their professional network, as it attracted a large Asian and international audience.

### Nutrition innovation

*Sight and Life* provided the necessary funds for me to attend the ACN. I gained fresh knowledge and updates on many controversial areas, such as the health effects of fat and DHA, among other topics. I gained much knowledge of different methods and tools that other countries use for dietary assessment with different modifications to overcome their limitations. Other benefits included exposure to recent nutrition innovations and to different people from a vast cultural diversity. I also had the chance to present the results of my research work at a prestigious congress, and saw my poster on pages 179 and 180 of the congress book.

“I would like to thank *Sight and Life* for supporting a young scientist in South Asia, where both ends of the malnutrition spectrum exist”



RMLR Thilakarathne in front of her poster at the Asian Congress of Nutrition, held in Singapore on 13–16 July 2011.

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# Food Fortification During “The First 1,000 Days” for a Good Start in Life

## Meeting at the International Atomic Energy Agency, Vienna

### Ines Egli

Institute of Food, Nutrition and Health,  
ETH Zurich, Switzerland

### Lena Davidsson

Division of Human Health, International Atomic  
Energy Agency, Vienna, Austria

### Background and purpose

Adequate nutrition during the first 1,000 days of a child’s life from conception through fetal development to early childhood is essential for optimum mental and physical development of the child, and helps ensure his or her passage into becoming a healthy adult. During this time period, however, many wom-

en and children, in both the developing and developed world, suffer from malnutrition. This can lead to a range of negative health effects, including poor pregnancy outcome, decreased immune defense, and poor mental and physical development in children. Providing good nutrition during the first 1,000 days of life presents a window of opportunity to improve health and well-being throughout the whole life cycle.

Food-based strategies to improve micronutrient nutrition that target “the first 1,000 days”, such as food fortification, typically focus on infants and young children from six months to two years of age. They include packaged nutrient mixtures to be added to home prepared meals at the time of consumption, as well as centrally produced complementary foods. Both types of strategy have been shown to be efficacious in well-controlled intervention studies. The current challenge is to scale up these intervention strategies to be included in nationwide nutrition programs. Experience with mass fortification of staples and condiments, and a few interventions targeted at infants and young children, has highlighted major difficulties in moving from small-scale efficacy studies to effective large-scale intervention programs. Potential barriers to successful food fortification include technical barriers to improve the bioavailability and stability of fortification compounds; safety issues; and monitoring and evaluation. The cost of the fortification mixture or fortified food to the consumer is obviously an issue that needs careful evaluation. Experience of mass fortification programs can be used to



The end result of scaling up nutrition: a little girl in Uganda eating a hearty meal.





The meeting was organised by the Division of Human Health at the International Atomic Energy Agency, Vienna.

identify obstacles that may hinder the successful implementation of food fortification strategies that are targeted specifically at infants, young children, and pregnant women.

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**“The overall purpose of the meeting was to identify potential obstacles and to suggest solutions for the effective scaling up of food fortification strategies for the first 1,000 days”**

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The overall purpose of the meeting, organized by the Division of Human Health at the International Atomic Energy Agency, Vienna, Austria on 7–9 September 2011, was to identify potential obstacles, and to suggest solutions for the effective scaling up of food fortification strategies designed to improve the nutritional status and health of the young child during the first 1,000 days of life to achieve optimum growth and development. About 30 participants from academic institutions, governmental and non-governmental organizations, and the food industry gathered in Vienna to share experience from national and regional mass and targeted fortification programs in Africa, Asia, Latin America, and the Middle East, and to discuss up-scaling of the programs and the way forward.

#### Sessions I to V

The meeting was structured into five half-day sessions:

**Session I:** Session I set the scene with key lectures by Alan Jackson, Jamaica, and Richard Hurrell, Switzerland. In his lecture entitled “Nutrition during the critical 1,000 day window

of opportunity,” Alan Jackson pointed out the importance of the nutritional status of mothers at conception and during pregnancy, and its impact on the health status, as well as the risk of morbidity and mortality of the infant during later life. Richard Hurrell presented an overview of current fortification strategies and recommendations, and addressed the challenges of providing fortified foods to women and young children to improve nutrition during the 1,000 days in his lecture, “Food fortification: an overview.”

**Session II:** Country representatives presented their experiences of mass fortification of the following: wheat and corn flour in South Africa; wheat flour in Kuwait; wheat flour in Chile; wheat flour and cooking oil in Morocco; and fish sauce in Thailand. The session was closed by Lynnette Neufeld from the Micronutrient Initiative (MI), Canada, presenting the MI’s framework for achieving improved micronutrient nutrition through food fortification.

**Session III:** Session III shared experiences of the targeted fortification of milk in Chile; Incaparina and Vitacereal in Guatemala; Progresia in Mexico; and various interventions with fortified foods in Peru.

**Session IV:** Stan Zlotkin, Canada, presented his experience of targeted fortification using lipid-based spreads and micronutrient powders. Experiences with wheat flour and vegetable oil fortification in Ghana; current fortification strategies in Burkina Faso; and wheat flour, rice and salt fortification in India were also highlighted during the meeting.

**Session V:** “Moving the agenda forward” included a presentation on operational issues by Omar Dary, USA. He highlighted the various influencing factors between the scientific evidence of efficacy studies and the effectiveness of food fortification programs, as well as the need for close collaboration between the different sectors involved in the programs. In his talk “Scaling up: GAIN experience”, Dominic Schofield, Switzerland, presented lessons learned based on Global Alliance for Improved Nutrition (GAIN) experience and identified the crucial issues for successful up-scaling of fortification programs. The final discussion, entitled “Moving the agenda forward”, by Richard Hurrell and Dominic Schofield, Switzerland, highlighted the need for the development of guidelines to scale up food fortification strategies to target the 1,000 days window of opportunity. It stressed the importance of moving away from a focus on product development to the integration of food fortification in nutrition and health programs.

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# Promoting partnerships and capacity building.

## Report from Kenya

### Progress at the Kwale District Eye Centre

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#### Helen E Roberts

Kwale District Eye Centre, Kwale District, Kenya

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The Kwale District Eye Centre charity relies on donations and we have had to drastically cut staff numbers, field activities, training and vehicle numbers. We have been forced to redefine our targets, expecting to achieve fewer cataract operations, less integration of low-vision and blind children into society and schools, and fewer patients treated. Some improvement occurred towards the end of 2010, but adequate funding remains the key issue as to how much we can help those in need. We work with all manner of people, both locally and internationally.

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“We continue to identify children with low vision, who face stigma and discrimination”

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Professor Shuette taking students and staff through an examination.

**Low vision and education**

Each year, we continue to identify more children with low vision, who still face stigma and discrimination. Currently, we support 469 children with severe visual impairment, 130 of whom have albinism. We are happy to report that we received some support from the Verkaart Development Team. This enabled us to expand the team; we recruited a vision therapist to help with the increasing number of children who are being identified as suffering from incurable poor vision. We hope that many more individuals and organizations will continue to give support.

**Skills development**

In order to provide quality care, we keep our staff abreast of new skills and technology. Our Nurse-In-Charge attended a Training of Trainers course to enable her to transfer skills. We sent two nurses for a three-month ophthalmology skills up-

grading course. They topped their class with an excellent performance. Two staff from Low Vision attended two weeks of training in Moshi, Tanzania.

**Rehabilitation of the irreversibly blind**

This program was worst affected by the cuts in funding. Children and young adults who are irreversibly blind need training to realize their full potential. If this does not happen, they revert to their old lives, where they are discriminated against and stand almost no chance of realizing their basic human rights to an education, employment and a normal life. Despite being totally blind, they attend a normal school. They need teachers trained in special needs; both low vision and Braille. The children and young people in the program were lucky enough to have a teacher, but still needed Braille machines and paper. Luck was on their side, as funding was received for Braille machines and paper.

**Eye camps**

In remote areas without static eye services, we work closely with the community and local authorities to ensure that the socioeconomic burden of avoidable blindness is reduced. At Wundanyi Camp, in response to a request from the local Constituency Development Fund and the area MP, 55 people received sight-restoring cataract surgery. In response to a request by the local community through The Sayyid Abass Foundation, we travelled 1,200 km to Rhamu, a village not far from the border with Somalia and Ethiopia. Patients turned up in huge numbers. Most were blinded by cataract. In this hot, dusty area, with only solar power available, the team saw over 1,200 people and performed 234 cataract operations in only six days.

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Children taking part in a school awareness session, to help reach disabled children in the community.

# 01

## The SUN movement gains momentum

The good news is that the SUN movement continues to gain momentum under the strong leadership of David Nabarro, Special Advisor to the UN Secretary General

on Food and Nutrition Security. Some 21 countries have now signed on as Early Risers, with a few others waiting in the shadows.

## Civil Society states that the moment is now

SUN has gained increased support from Civil Society. Following the SUN follow-up meeting earlier this year in Washington, a number of Civil Society groupings launched a statement in support of SUN, where they stress: "The 1,000 days between pregnancy and a child's second birthday is the critical window of opportunity, and it is closing for thousands more children every day. It does not have to be this way. We know the most effective ways to reduce maternal and child undernutrition, as well as when to intervene. With this knowledge comes the responsibility to act – decisively and with unwavering commitment. With world hunger surging, the moment is now."

**The statement highlights five key areas that cannot be neglected, going forward:**

1. National governments must lead the way: We urge national governments, especially in high burden countries, to commit domestic resources that are clearly identifiable and tracked, to improve maternal and child nutrition and to strengthen and coordinate multi-sector nutrition plans in national development strategies and in humanitarian crises. This should be done in consultation with a broad spectrum of Civil Society and other stakeholders.
2. Scale-up is imperative: We call on the international community, including bilateral and multilateral development partners, to provide the resources needed to scale up direct nutrition interventions and nutrition-sensitive development. The cost of scaling up is estimated to be about \$12 billion per year. Households and national governments will provide a significant share of this but donor assistance must be ramped up to support country-led plans.

3. International leadership is needed: We urge high level political leadership nationally and globally to rally around a specific goal. This is critical for garnering public attention. At the global level, we urge the international community to move quickly to agree to a strong leadership structure for nutrition.
4. Human capacity must be built: Acknowledging the primacy of action at the national, sub-national and local level, we encourage development partners to support the building of capacity at all these levels, to develop human resources, improve management systems, strengthen institutions and support inter-agency and inter-sectoral coordinating committees.
5. Accountability is paramount: Our work must be guided by a shared set of principles and guidelines that actions by all stakeholders do no harm and that there are mechanisms in place to ensure that all stakeholders uphold their commitments.

The full unabridged statement is available on the SUN website at [www.unscn.org](http://www.unscn.org).

Of the SUN Early Riser countries, 76% are from Africa. This is important as, based on current trends, Sub-Saharan Africa will be unable to meet the MDG hunger-reduction target by 2015.

## SUN keeps on growing and glowing

SUN enjoyed prominence in New York at the September United Nations General Assembly. A high-level SUN meeting was held at the UN, followed the next day by a full-day SUN meeting to discuss the link between malnutrition and non-communicable diseases later in life, to share the first year of SUN's progress, and to strengthen action in taking the movement forward.

Dr Margaret Chan, Secretary General of the WHO, recognized that the "critical importance of nutrition has been badly neglected in recent decades." She said that, "opportunities have been missed and many of the lost opportunities have had life-long consequences, so we need to give impetus to act with urgency." This urgency was clearly and vividly spelt out by Anthony Lake, Executive Director of UNICEF, when he stated, "Some 20 million children around the world have severe acute malnutrition. If all these children were from one region, it would be the world's greatest catastrophe. This provides 20 million reasons why we have to address malnutrition as a matter of urgency."

It was clear from many of the speakers that investing in nutrition in the first 1,000 days pays handsome dividends later in life, and that multi-stakeholder movements are undoubtedly the way forward. President Kikwete of Tanzania stressed how malnutrition impedes economic development. He said that it is a good investment now and in the future, but requires political will, and multi-stakeholder efforts and investments. He confirmed Tanzania's determination to overcome the challenges that it faces in addressing malnutrition, and to ensure the co-ordination of activities. This commitment, and the need for scaling-up interventions, was expressed by other country spokespeople and donor countries. Donors again pledged their support. US Secretary of State Hilary Clinton informed the meeting that their funding for nutrition had been increased, "because the US sees these investments as vital and having a high impact." The private sector also showed its support for SUN. Stephan Tanda of Royal DSM stated that it is a committed partner. He said, "Public-private partnerships are critical to implement the wisdom of policymakers in order to make real changes at the local country and community level. Only by working together can we impact the lives of those who need it most."

There were also some sage words of advice, including the need for more leadership at a country level. Carolyn Miles, the newly appointed President and CEO of Save the Children, urged for more timely and regular data. She said that it is necessary to keep everyone accountable to those we aim to serve, that we must increase the funding for nutrition, and that we must work together more effectively and efficiently.

Finally, SUN once again received the highest ongoing support and praise from Ban Ki-moon, the Secretary General of the United Nations. "I welcome SUN's intent to focus on interventions that directly empower women and their households, and to encourage government policies – in particular those for agriculture, health, education, employment and social protection – to be sensitive to nutritional needs. The UN system is committed to the SUN Movement and our shared work to support national efforts, promote multi-stakeholder action, help integrate the policies of different sectors, and advocate for nutrition internationally. Nutrition is strongly embedded in the work of my High Level Task Force for Food Security and the efforts of the Every Woman Every Child effort. Many individuals, networks, governments, organizations, businesses and international bodies have worked hard to ensure the necessary synergy for the Movement to work, and I applaud those individual and collective contributions. For my part, I will continue to stay closely engaged in the SUN Movement and look forward to the impact it will have on our quest to achieve the Millennium Development Goals and truly sustainable development."

Visit [www.scalingupnutrition.org](http://www.scalingupnutrition.org), not only to watch the webcast, but also to view the excellent SUN video launched in New York. This is a valuable resource for anyone wanting an advocacy tool to support SUN efforts. The site also features the SUN One-Year Progress Report, with updates from SUN countries.



## The SUN shines at the FANUS congress



From left to right: Dr Paul Amuna (SUN Task Team C), Prof. Anna Lartey (SUN Task Team C), Dr Klaus Kraemer (*Sight and Life*), Jane Badham (*Sight and Life*), Joseph Mugyabuso (Save the Children), Sandra Mutuma (Action Against Hunger).

*Sight and Life* sponsored a session at the Federation of African Nutrition Societies (FANUS) meeting in Abuja, Nigeria, September 12 – 15, to introduce nutritionists to SUN, and to highlight the need to harness the power and potential of scaling-up nutrition in Africa. The session also allowed for discussion time with members of the SUN Task Teams for Advocacy and Communication and Civil Society. The five speakers shared various key components of the SUN movement, including its genesis (presented by Jane Badham); the vital role of ensuring early multi-stakeholder engagement including civil society (presented by Dr Paul Amuna); and the private sector (presented by Dr Klaus Kraemer). Joseph Mugyabuso of Save the Children then shared Tanzania's

experience to date as an Early Riser country. Finally Prof. Anna Lartey, President-Elect of the International Union of Nutritional Sciences, showed how African countries are sadly lagging behind in reaching the MDG targets – now only three years away. She stressed that Africa should fully engage with SUN; embrace the opportunity it presents to place nutrition at the center of development plans and policies; and grasp the lifeline that it potentially offers. Engaging, however, is just the start – Africa also has to deliver.

**To see all presentations, visit**

[www.sightandlife.org](http://www.sightandlife.org) and click on “Scaling Up Nutrition SUN at FANUS Conference” on the home page.

**Did you know?** Dadaab refugee camp in Kenya is the world's biggest refugee camp. Dadaab, with capacity for 90,000, is expected to have to cope with over 500,000 refugees by the end of 2011.

## The Second FANUS Congress



Olaide Aderibigbe (second from left), an African Nutrition Leadership Programme Alumna, with other ANLP Alumni at the FANUS congress.

The Second Federation of African Nutrition Societies (FANUS) conference was held in Abuja, Nigeria from 12 to 15 September 2011, on the theme of “Accelerating Nutrition Action for Africa’s Development.” *Sight and Life* sponsored Olaide Aderibigbe to attend and she submitted this report:

“Although, there were some hitches faced by the conference organizers, the conference was successful, and I personally benefited a great deal from the seminars, symposiums, scientific presentations, and poster sessions. I was afforded the opportunity to give a presentation on my research, *Iron status and adiposity in women from developing countries: A review* and appreciated the audience’s feedback. Dr Allan Jackson, from Southampton University in the UK, gave me valuable links, websites, and names of others doing similar work that I could collaborate with in the future. This was most welcome, and met my objective of using the conference to grow my network.

I enjoyed many of the sessions, but will share with you the presentation by Tom Schaezel, Technical Director of the Infant and Young Child Nutrition Project of the Manhoff Group. This was entitled “Maximizing the Nutritional Benefits of Agricultural Interventions.” The presentation reviewed the nutritional impact of agricultural interventions over the last 30 years. This was an eye-opener for me. He highlighted the common factors (involvement of women, focus on food crops instead of cash crops, income generation, etc.) in agricultural

interventions that had a positive impact on nutritional status. I learnt about a tool that can be used to measure the nutritional impact of any intervention, which I believe will be useful for promoting nutrition, and for the monitoring and evaluation of interventions in my country, Nigeria.

It was also exciting to meet up with a former colleague who has been working in a similar field in Uganda. We agreed to write a joint proposal on how to improve nutritional education in our countries, as this congress made it clear to me that, despite the existence of a nutritional food base with enriched diversity in Africa, there is a lack of nutrition education amongst the people.

Looking back at the FANUS meeting, all of my objectives for attending the conference were met: I was able to present my research work, and I received input into it; I formed useful links for future collaborations; and I was able to learn from the successes in nutritional research made by colleagues in other parts of Africa. My thanks are due to *Sight and Life* for sponsoring me to attend this meeting.

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## United States Secretary of State speaks up and out on the Horn of Africa crisis and the need for innovative partnerships into the future



Secretary Clinton and the IFPRI Director General, Shenggen Fan.

Speaking at an International Food Policy Research Institute (IFPRI) meeting in Washington in August to discuss solutions for ending hunger and poverty, US Secretary of State Hillary Rodham Clinton stated that, like never before, hunger and undernutrition is on our minds every day. This is as a result of the crisis raging in the Horn of Africa where, she said, “A severe drought has put more than 12 million people in Ethiopia, Kenya, Djibouti, and Somalia in danger of starvation. It is also a refugee crisis, because at this point, hundreds of thousands of people have left their homes in search of food and safety. Some are walking more than 100 miles with their children in their arms to reach refugee camps, which are so overcrowded that thousands wait outside the fences, and more arrive every minute, many close to death.”

Clinton made it clear that, while dealing with the crisis, it was critical for the world to also maintain its focus on the future by continuing to invest in long-term food and nutrition security in countries that are susceptible to drought and food shortages. She outlined the US joint initiative of setting up the 1,000 Days Campaign to improve nutrition during the critical period from the start of pregnancy through a child’s second birthday. “Nutritional deficits during those 1,000 days lead to permanent stunting, reduced cognitive function, and a greater susceptibility to disease that cannot be reversed by improved nutrition later in life,” she said.

Clinton reiterated that we have the know-how and the tools to do this. “We do have the know-how. We have the tools. We have the resources. And increasingly, we have the will to make chronic food shortages and undernutrition a memory for the millions worldwide who are now vulnerable,” she said. She highlighted the fact that, in order to create a food-secure future, the private sector has to be engaged to come up with innovative ideas, and shared two examples of public-private projects in which the United States is involved with Africa. The first is with Souktel, a technology company that aims to text life-saving information to people so that, in a crisis, they know where relief can be found nearby. The second supports a partnership with DSM, General Mills and Cargill, helping food processors in Kenya and other countries to improve their ability to produce high-quality, nutritious, safe food that, said Clinton, “will benefit local consumers, and prepare local food producers to compete in regional markets.”

The full speech can be viewed at the IFPRI website, please visit: <http://www.ifpri.org/pressroom/briefing/ifpri-welcomes-us-secretary-state-hillary-clinton>

**Did you know?** By 2050, there will be two to three billion more people on Earth, of whom some 70% will live in cities – more than are alive today.

## 04 BOND – Biomarkers of Nutrition for Development

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH)/US Department of Health and Human Services, in collaboration with partners representing the breadth of the global food and nutrition enterprise, created the Biomarkers of Nutrition for Development (BOND) Program to meet the growing need for discovery, development, and implementation of reliable and valid biomarkers to assess nutrient exposure, status, function, and effect. One of the primary goals of the BOND project is to harmonize the processes for making decisions about what biomarkers are best for use in support of research, program development and evaluation, and generation of evidence-based policy.

This initiative responds to the need to examine the scientific basis for choosing appropriate methodologies to assess the role and impact of diet and nutrition in health promotion and disease prevention in populations and individuals; and support the development and evaluation of programs and policies to improve diet and nutrition.

### The BOND approach

The program will have two separate but complementary tracks. First, the Translational Track will develop processes to inform various user groups about appropriate biomarker selection and use. The development and use of the translational materials will then generate a research agenda that will support the next track. The first phase of this process

will include the development of an interactive web-based resource and “query-based system” (QBS) to provide evidence-based advice to users about specific nutrients of interest. The eventual goal will be to include all essential nutrients, high-priority bioactive components of food, and relevant markers of health. The first set of nutrients to be posted on the QBS will be iodine, vitamin A, iron, zinc, folate, and vitamin B<sub>12</sub>. The Research Track will support the discovery of biomarkers and development of their use. Both tracks ultimately lead to evidence-based guidance specific to the needs of specific users, communities, and contexts.

### BOND users

The information generated by the BOND process is intended to support activities represented by the food and nutrition community, including (but not limited to) users who conduct nutrition surveys; make policies related to nutrition and/or nutritional status; implement food/nutrient programs; intend to include nutritional components in their research projects or clinical protocols; seek careers in nutrition, dietetics, or medicine or in education fields focused on these topics; and fund research on or programs related to food/nutrition.

### More information about the BOND Program

is available at [http://www.nichd.nih.gov/global\\_nutrition/programs/bond/](http://www.nichd.nih.gov/global_nutrition/programs/bond/)

## 05 London School of Hygiene and Tropical Medicine Reports on Europe's Nutrition Advocacy Landscape

This report, funded by the Gates Foundation, investigates how European stakeholders are engaged in addressing under-nutrition, in order to inform the nutrition advocacy agenda and identify opportunities for scaled up investments. The key findings are categorized into five themes.

First, multilateral organizations are making nutrition a strategic priority with a growing emphasis on integration and understanding how food security and rural development initiatives can best support nutrition outcomes. The European

Commission is a significant funder, but it is suggested that the investments they make need to be protected within institutional policy. The research also highlights the need for stronger leadership and coordination within and between these organizations.

Secondly, nutrition is becoming a more prominent focus amongst the bilateral donors (France, Ireland, Spain and the United Kingdom are taking the lead); they are integrating nutrition across programs and placing a high priority on

results-based frameworks. The challenge in this sector is how to establish financial flows, as nutrition funding commonly sits within and across several development sectors. NGOs are also increasingly engaging in nutrition advocacy and are bringing valuable technical expertise and field knowledge to inform evidence-based policies, but are commonly constrained by funding parameters.

Private sector interest in undernutrition is also recognized through market-based approaches and public-private partnerships. The challenge they face is establishing a sustainable business model in order to deliver a return on investment. The report points out that there is still a level of distrust between the public and private sector; as a result, the private sector is often not considered part of the response to undernutrition.

Finally, it seems that in Europe private funders for nutrition are limited. This is, generally, a result of their perception that the nutrition problem is too complex. They are also unsure how their funds can achieve an impact. There is thus some potential to increase this source of funding.

In conclusion, the report highlights that there are several interrelated themes across the sectors, which can be translated into a real opportunity for nutrition-direct and nutrition-sensitive interventions. There is, however, a need for the nutrition agenda to ensure stronger messaging and goals.

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**The full report is available at**

[www.lshtm.ac.uk/eph/nphir/research/nutritionadvocacy/](http://www.lshtm.ac.uk/eph/nphir/research/nutritionadvocacy/)

## 06 Nature Article: Freeze Food's Footprint



A vegetable market.

In its 21 July edition, Nature journal published an excellent article by Dr Jason Clay, Vice President of Market Transformation for the World Wildlife Fund. He addressed the bold question of “How do we feed a rapidly growing population while also protecting our planet?” He stressed that we need to do more with less, meaning more production with less impact on land, water, and other natural resources. He outlined eight strategies that could be applied globally and simultaneously to reform the global food system – thereby increasing food production, and protecting the planet:

1. **Genetics:** Use the potential of genetics in traditional plant breeding, as well as new modern technologies.
2. **Better practices:** Improve the poorest-performing producers to enhance food production, increase income, and reduce environmental impacts.

3. **Efficiency through technology:** Double the efficiency of every agricultural input, including water, fertilizer, pesticides, energy, and infrastructure.
4. **Degraded land:** Rehabilitate abandoned or underperforming lands.
5. **Waste:** Reduce post-harvest losses and improve infrastructure.
6. **Consumption:** Use traditional crop leaves and other “famine foods” in urban areas.
7. **Carbon:** Plant tree crops and deep-rooted grasses to prevent topsoil erosion that reduces soil carbon and fertility.
8. **Property rights:** Increase the number of Africans who hold a title to their land, so that they will be more likely to invest in it.

According to Clay, “To freeze the footprint of food, we need smart policies, innovative ideas, and new technologies. We must intensify food production rather than expand it.” Feeding an additional two billion people without expanding resources will require the unprecedented global collaboration of governments, NGOs, and the private sector. If we are to freeze the food footprint, the time to act is now.

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**Taken from** [www.globalharvestinitiative.org/index.php/2011/08/freezing-the-footprint-of-food-2/](http://www.globalharvestinitiative.org/index.php/2011/08/freezing-the-footprint-of-food-2/)  
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Advocating  
better nutrition  
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**Editor's note:** *Sight and Life* reviews recent publications which may be of particular interest to our readers. However, no publications other than *Sight and Life* publications are available from us, nor do we have any privileged access to them.

## Getting Better

### Why global development is succeeding – and how we can improve the world even more

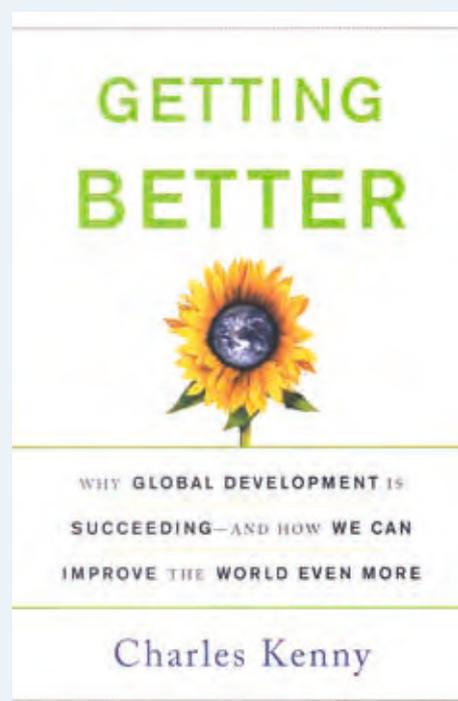
The global economy is nearly eight times larger than in 1950, and the world's population has increased from 2.5 billion to 6.5 billion people. The conventional wisdom remains that development has failed. *Getting Better* reports the good news. Economist Charles Kenny argues against the naysayers, demonstrating that the story of the modern world is one of widespread and historically unprecedented progress. Even people today who remain as poor as their parents or grandparents have seen massive quality of life improvements. The evidence for any country being caught in a Malthusian nightmare, where the population exceeds the country's "carrying capacity," is threadbare. No country is stuck in a technological dark age without hope of exit – indeed; technologies of increased production have spread worldwide. *Getting Better* offers a fresh, hopeful new look at our global economy. That's not to say that life is grand for everyone, or that we don't have a long way to go. But improvements have spread far, and can spread even further.

This book is about progress in Africa and around the world, what has caused it, and how we can keep it going. It says that, despite counterclaims and hand wringing, things are getting better, everywhere. Those countries with the lowest quality of life are making the fastest progress in improving it – across measures including health, education, and civil and political liberties. The progress results from the global spread of technologies and ideas, in which Third World governments,

alongside aid agencies and non-profits, have played a vital role. This is not to deny continued deprivation and suffering worldwide, alongside considerable waste, incompetence, and corruption in government and assistance programs. But, he writes, progress is a sign that things can get better, and that we have some considerable capacity to make them better – the best motivation to try even harder to overcome deprivation and suffering.

For more information, please visit

[http://www.perseusbooksgroup.com/basic/book\\_detail.jsp?isbn=0465020151](http://www.perseusbooksgroup.com/basic/book_detail.jsp?isbn=0465020151)

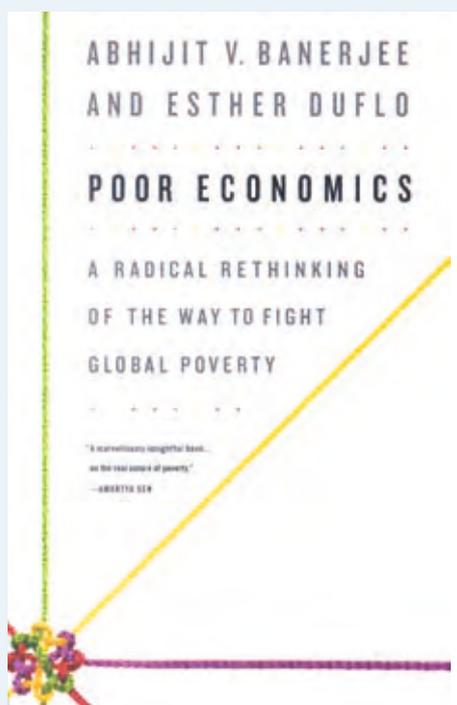


## Poor Economics: A radical rethinking of the way to fight global poverty

Poor Economics is about the very rich economics that emerge from understanding the economic lives of the poor. It examines the theories that help make sense of what the poor can achieve, and where and why they need a push. Each chapter describes a search for these sticking points, and how to overcome them. The book opens with the essential aspects of people's family lives, such as what they buy; how many children they choose to have; and so on. It then describes how markets and institutions work for the poor: Can they borrow, save, and insure themselves against the risks they face? Throughout, it returns to the same basic questions: Are there ways for the poor to improve their lives? What is preventing them from being able to do these things? Is it the cost of getting started, or is it easy to get started but harder to continue? What

makes it costly? Do people sense the nature of the benefits? If not, what makes it hard for them to learn them?

Poor Economics is ultimately about what the lives and choices of the poor tell us about how to fight global poverty. It helps us understand, for example, why microfinance is useful without being the miracle some hoped for; why children of the poor can go to school year after year and not learn anything; and why the poor don't want health insurance. It also tells much about where hope lies: why token subsidies might have more than token effects; how to better market insurance; why less may be more in education; and why good jobs matter for growth. Above all, it makes clear why hope is vital and knowledge critical, and why we have to keep on trying – even when the challenge looks overwhelming. Success isn't always as far away as it looks.



For more information, please visit

<http://www.pooreconomics.com/>

# The IAEA Human Health Series

The International Atomic Energy Agency (IAEA) is the world's center of cooperation in the nuclear field. It was set up as the world's "Atoms for Peace" organization in 1957 within the United Nations family. The Agency works with its Member States and multiple partners worldwide to promote safe, secure and peaceful nuclear technologies.

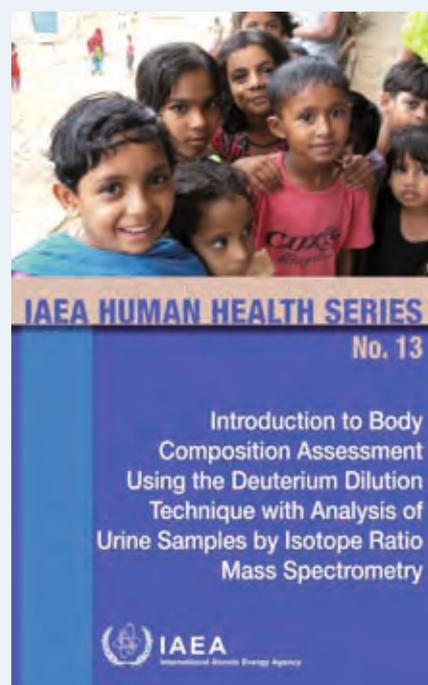
Topics covered by the 16 publications in this series include, among others, *Assessment of Body Composition and Total Energy Expenditure in Humans Using Stable Isotope Techniques*, published in 2009. This publication was developed as part of the IAEA's efforts to contribute to the transfer of technology and knowledge in the use of stable isotope techniques as research tools in nutrition among nutritionists, analytical chemists and other professionals. It provides information on the theoretical background as well as the practical application of state of the art methodologies to monitor changes in body composition and total energy expenditure, and reflects recent advances in analytical techniques.

The publication *Introduction to Body Composition Assessment Using the Deuterium Dilution Technique with Analysis of Urine Samples by Isotope Ratio Mass Spectrometry* (published 2011) complements the above IAEA title, providing practical guidance on the use of the stable isotope technique to assess body composition in settings where biological samples can be analyzed by isotope ratio mass spectrometry (IRMS).

**Other new titles for 2011 include:** *Quality Assurance Programme for Digital Mammography; Atlas of Bone Scintigraphy in the Developing Paediatric Skeleton: The Normal Skeleton Variants and Pitfalls; Planning National Radiotherapy Services: A Practical Tool; Dual Energy X Ray Absorptiometry for Bone Mineral Density and Body Composition Assessment; and Introduction to Body Composition Assessment Using the Deuterium Dilution Technique with Analysis of Saliva Samples by Fourier Transform Infrared Spectrometry.*

**For more information, please visit**

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# Food and Nutrition Bulletin

## (Volume 32, Number 3, September 2011)

### Special Section

This special section of the Food and Nutrition Bulletin, “Assessing the Impact of Micronutrient Interventions under Special Circumstances Such as Refugee Camps and Emergency Operations”, is timely. Monitoring and evaluation of the implementation and impact of interventions is critical, but is less easy to effect in programmatic settings – especially in emergency and refugee populations. The World Food Programme and United Nations High Commissioner for Refugees held a one-day meeting to discuss challenges and possible solutions. This shares their important deliberations, practical experiences and lessons learnt. Topics include the choice of impact indicators, and adherence to taking the product/supplement as intended. Numerous possible evaluation designs are discussed, with pros and cons and recommendations. Three specific home fortification experiences and outcome studies in different refugee settings are included as papers.

The authors’ honesty about the limitations and difficulty of drawing firm conclusions about their success is refreshing, making this a must-read for anyone working in planning, implementing, and evaluating programs being moved to scale.

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***Assessing the impact of micronutrient intervention programs implemented under special circumstances – Meeting report.***

**Authors:** de Pee S, Spiegel P, Kraemer K, Wilkinson C, Bilukha O, Seal A, Macias K, Oman A, Fall AB, Yip R, West K, Zlotkin Sk, Bloem MW

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***Effects of multimicronutrient home fortification on anemia and growth in Bhutanese refugee children.***

**Authors:** Bilukha O, Howard C, Wilkinson C, Bamrah S, Husain F

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***Provision of micronutrient powder in response to the Cyclone Sidr emergency in Bangladesh: Cross-sectional assessment at the end of the intervention.***

**Authors:** Rah JH, de Pee S, Halati S, Parveen M, Mehjabeen SS, Steiger G, Bloem MW, Kraemer K

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***Relationship of the availability of micronutrient powder with iron status and hemoglobin among women and children in the Kakuma Refugee Camp, Kenya.***

**Authors:** Ndemwa P, Klotz CL, Mwaniki D, Sun K, Muniu E, Andango P, Owigar J, Rah JH, Kraemer K, Spiegel PB, Bloem MW, de Pee S, Semba RD

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***Understanding low usage of micronutrient powder in the Kakuma Refugee Camp, Kenya: Findings from a qualitative study***

**Authors:** Kodish S, Rah JH, Kraemer K, de Pee S, Gittelsohn J

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