sightandlife

FRONTIERS IN NUTRITION

VOL. 29 (1) | 2015

Sight and Life

Contents

"The *Sight and Life* magazine is a valued resource and it keeps me and my colleagues updated on both developments and news that ensures we remain in touch even though we live and work in Africa."
Susan Tswane, South Africa

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

Thanks for this magazine.
Mr Dominic M Mogere,
CEO | CHRCC | Kericho, Kenya

> **Frontier:** "A border between two countries", "a distant area where few people live", or "the limits of knowledge in a particular field"
> *Merriam Webster*

Nutrition Advocacy: Key Milestones

1990 > World Summit for Children

1991 > 1st Hidden Hunger Conference, Montreal, Canada

1992 > International Conference on Nutrition I, Rome, Italy

1992 > Micronutrient Initiative formed

2000 > United Nations establish Millennium Development Goals

2000 > Bill & Melinda Gates Foundation founded

2002 > Global Alliance for Improved Nutrition (GAIN) created

2004|08|12 > Copenhagen Consensus

2006 > Repositioning Nutrition as Central to Development, World Bank

2008|13 > The Lancet series on Maternal and Child Nutrition

2010 > Scaling Up Nutrition (SUN) formed

2013 > Nutrition for Growth global summit, London, UK

2014 > 1st revitalized Micronutrient Forum

2014 > International Conference on Nutrition II, Rome, Italy

2014 > Global Nutrition Report

2015 > Sustainable Development Goals

Welcome

When do We Reach the Frontiers of Nutrition?

I am glad that *Frontiers in Nutrition* is not a protected topic. Typing it into the well-known search engine reveals 26,000 hits. The theme has been widely used for conferences, book titles, and postgraduate courses, and most recently, *Frontiers in Nutrition* was added to the "Frontiers in" journal series of the Nature Publishing Group with the mission: *"No subject pertains more to human life than nutrition. The aim of Frontiers in Nutrition is to integrate major scientific disciplines in this vast field in order to address the most relevant and pertinent questions and developments."*

What are the most pertinent questions and developments in nutrition, however? The last edition of this magazine was dedicated to implementation science, which we at *Sight and Life* believe is the new *Frontier in Nutrition* if we are to successfully apply in programs the vast body of reliable evidence that already exists and build new evidence further downstream during the implementation process.

From MDGS to SDGs

At the dusk of the Millennium Development Goals (MDGs) and the dawn of the Sustainable Development Goals (SDGs) – the final edition of *Sight and Life* in 2015 will be dedicated to the MDGs and SDGs – we wanted to give leading thinkers in nutrition science the opportunity to share with our readers where they think the *Frontiers* are located. You will find the products of their thought in this edition of the magazine, in whose pages you can explore a wide variety of topics including multiple micronutrients in pregnancy, epigenetics, biomarkers and bio-indicators, benefit-risk assessment, inflammation, nutrigenetics and nutrigenomics, proteomics and metabolomics, mobile health, systems nutrition, and food systems, as well as early life nutrition and the developmental origins of adult disease.

Why these topics are so dominated by basic sciences will become evident in the thought-provoking commentary by Andrew Prentice entitled "Discovery Science for Global Health." Being a nutrition think tank and, as such, engaging a wide range of thinkers, carries with it the risk that the editor may not fully agree with all the opinions these contributors express. The very fact that they promote thinking and dialogue is in itself, however, positive.

In Andrew's piece, I struggle with his opinion that with regard to the recommendation for the use of prenatal multiple micronutrient supplements, the glass is half-empty rather than half-full. I concur rather with the opinion of many in the field that the evidence is compelling enough to change policies and guidelines regarding prenatal multiple micronutrient supplements. I fully agree with Andrew, however, that the nutrition community has to re-invent itself in some way and make better use of trials and programs to advance the science. Understanding the biology of malnutrition and growth, for instance, will help us to design more effective interventions. It is not enough to continually state that more research is warranted when we have another inconclusive study result. I have seen too many underpowered RCTs based on incorrect assumptions as to the malnutrition problem. Ideally, basic and applied scientists and programmers will work together to ask the right questions and find the right answers to (unexpected) results. As a minimum requirement, let's agree to gather sufficient information on the magnitude of the malnutrition problem before initiating research and/or programs; this will give adequate room for response to the intervention.

> "It is not enough to continually state that more research is warranted when we have another inconclusive study result"

Bridging the nutrient gap

At the recent Asian Congress on Nutrition (ACN) in Yokohama, Japan, Regina Moench-Pfanner and I organized a symposium entitled "Bridging the nutrient gap – which delivery channels can effectively provide the missing nutrients?" This symposium emphasized the need for quality data in order to make informed decisions. Junsheng Huo presented implementation experience with iron-fortified soy sauce in China, and Van Khanh Tran shared the Vietnamese micronutrient deficiency control program. Both China and Vietnam based their micronutrient control programs

on thorough efficacy testing linked to available national nutrition data. Both countries also monitor the progress of their mitigation strategies. However, countries should place more emphasis on the elucidation of the etiology of anemia when anemia is a key public health concern, particularly when it is no longer a severe or moderate problem. Alternative strategies, such as targeted multiple micronutrient interventions for populations at risk (for example, micronutrient powder for infants and young children and/or inflammation control through improved water, sanitation and hygiene) should be sought. Here again, we can expect major gains from discovery science.

Giving nutrition the voice it deserves

Frontiers in the Nutrition Sciences was also the topic of the annual symposium of the US Food and Nutrition Board (FNB) of the Institute of Medicine almost 30 years ago in 1987. In the proceedings, the Chairman and Director of the FNB stated: *"It [the topic] symbolizes the Board's concern about declining attention to nutrition … but more importantly it expresses the Board's conviction that nutrition research has a bright and challenging future. Realization of this potential, however, requires cognizance of advances in molecular biology and related biological and physical sciences …"* The symposium provided insights into basic and applied sciences for nutrition in the US and internationally as well as research and training in nutrition sciences. The volume included a commentary by Joan D Gussow with a remarkable statement on how impotent the nutrition community felt at that time to influence nutrition messages and policy: *"We nutrition educators have seen ourselves as a relatively powerless voice shouting into the wind of information that sells … information that may or may not have consequences for eaters' nutritional status."* Some might say that this is US-specific and does not apply to the nutrition context in low- and middle-income countries. I would argue, however, that the global nutrition community didn't have a real voice until recently. Thankfully, nutrition has a bright and challenging future and has gained a voice.

Scaling up effective nutrition programs

Significant milestones in nutrition advocacy have been achieved in the past 25 years (please see table), but it is perhaps the 2008 Lancet series on Maternal and Child Nutrition and the subsequent formation of the Scaling Up Nutrition (SUN) Movement that have been most instrumental in giving nutrition the voice it deserves. The SUN has been outstandingly successful in advocacy and political mobilization, raising the profile of nutrition at the global level: 55 countries have signed up to the movement. However, according to the Independent Comprehensive Evaluation (ICE) report of the SUN, there has been only limited translation of this raised awareness into action at country level. For the scaling-up of effective nutrition programs, it will be essential to increase capacity at country level, particularly leadership development and support in program design and delivery, as well as monitoring & evaluation through implementation research.

At *Sight and Life*, we are concerned about capacity building, leadership development and implementation science in nutrition. In March 2014, the World Food Programme, the Institute of Human Nutrition of Columbia University and *Sight and Life* convened thought leaders from multiple sectors on capacity development. This initiative will lead to a publication entitled "Educating and training a workforce for nutrition in a post-2015 world." Other important initiatives of *Sight and Life* include the long-term partnership with the African Nutrition Leadership Programme, and, last but not least, our support for the creation of a new society fostering implementation science in nutrition. In February of this year, we hosted a planning workshop with key individuals from leading organizations with a stake in implementation science; a report is forthcoming.

> "At *Sight and Life*, we are concerned about capacity building, leadership development and implementation science in nutrition"

Encouraging smarter and more effective interventions

But when do we reach the frontiers of nutrition? This is largely context-specific. In low-income countries and fragile states, with limited individual and institutional capacity, the frontier may be reached when dietary intakes are assessed and the results have to be converted into programs. In other, more sophisticated, contexts, the frontier may only be reached when 5,000–10,000 proteins are classified in proteomics. The instrumentation is here not the limit: the interpretation is the frontier, using bioinformatics. And the frontiers are not static. As the German scientist Georg Christoph Lichtenberg stated in the last quarter of the 18th century, *"Where the frontier of science once was is now the center."* Therefore it is up to us, the nutrition community, to define the *Frontiers in Nutrition* based on context and need, working in partnership across sectors and disciplines, considering the whole continuum of evidence and gathering more evidence downstream in programs so as to give discovery science a role for smarter and more efficacious interventions.

With warm regards,

Klaus Kraemer

> "Where the frontier of science once was is now the center"
> *Georg Christoph Lichtenberg (1742–1799)*

Share your thoughts with us – and with the world!

Sight and Life encourages scientific discourse. We therefore invite you to share with us your views on what are the real frontiers in nutrition.

Social Media

Social media such as blogs, Facebook or LinkedIn have enabled the nutrition community to share its voice far beyond peer-reviewed publications and presentations at conferences and workshops. This has provided more opportunity to engage with policy-makers, media and the public at large.

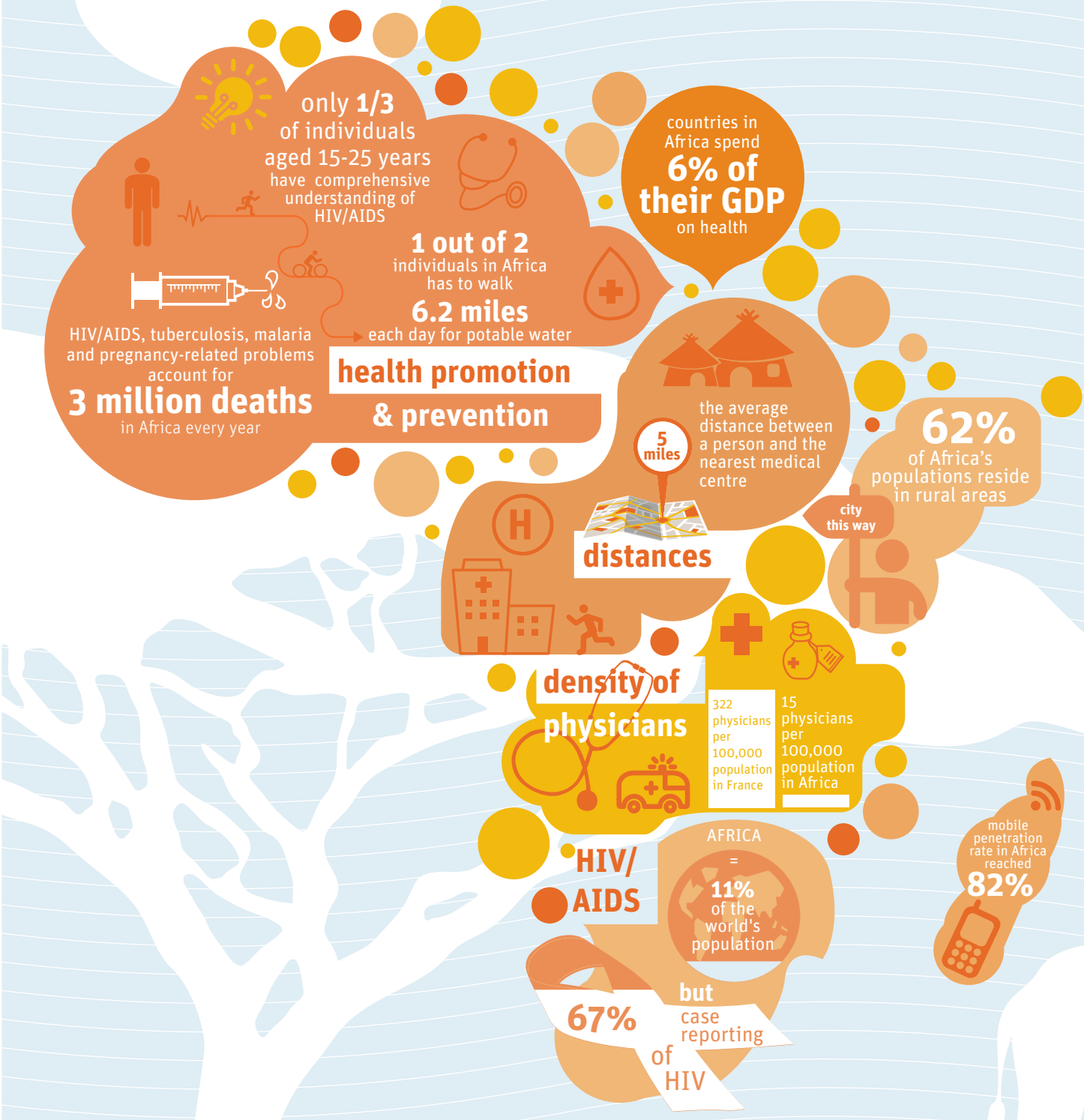
These new possibilities come with risks and benefits. Risks, as more anecdotal evidence and myths can be circulated. Benefits, because the voice of nutrition can be better heard, and can exert a greater positive influence. For the benefits to outweigh the risks requires a much greater level of responsibility from those of us nutrition professionals who are active on social media.

This development has, however, ensured that we are no longer "*a relatively powerless voice shouting into the wind*." We have the tools to share messages about what works and what doesn't. At the same time, the level of "noise" in the online environment has increased tremendously, and the recipient may be hopelessly overwhelmed in the attempt to identify reliable information.

Monthly Blog

We at *Sight and Life* are excited to announce the launch of a new monthly blog on nutrition and health-related topics. Please visit our website to read it: we hope it will prove interesting, and that it will stimulate your own nutrition advocacy efforts. We will continue to disseminate impartial information using this new platform, and we look forward to receiving your feedback on it.

Mobile Healthcare in Africa:
SERVING POPULATIONS, SAVING LIVES



mHealth could save over 1 million lives in Sub-Saharan Africa over the next five years.

The mobile health market in Africa is expected to rise to **US $1.2 billion** by 2017.

PREVENTION

My Healthline is an SMS based information service in Cameroon providing advice on contraception, sexuality, HIV/AIDS and STDs.

Delivering prevention and awareness information via text messages to pregnant and young mothers in Mali has helped reduce perinatal and maternal mortality **by 30%.**

DIAGNOSIS

With mHealth, **twice as many patients** in rural areas can have access to basic care.

In Botswana, a mobile telemedicine program with the Ministry of Health using mobile devices enables the collection of clinical data and images. They are sent to a remote specialist for diagnosis.

TREATMENT

In Kenya, mHealth helped to improve antiretroviral medication compliance **by 11%.**

Botswana has successfully deployed a mobile-enabled program that reduced government response times to malaria outbreaks from four weeks to three minutes.

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Sources: www.statistiques-mondiales.com | WHO | Eds Kinney MV, Lawn JE, Kerber KJ, Science in Action – Saving the lives of Africa's mothers, newborns and children, ASADI, 2009 | PwC | AMREF | The Lancet

"First 1,000 Days of Life" Competition: Results

In issue 3 | 2013 of this magazine, we invited our readers to participate in our "First 1,000 Days of Life" Competition. This was in response to your requests, communicated to us in our 2013 Readership Survey, for opportunities to get more directly involved with *Sight and Life*.

We are delighted to announce the winners in the categories Photographs, Infographics and Drawings. Winners of third prizes will receive a book, winners of second prizes, a digital camera, and winners of first prizes, an iPad. No entries were received in the category Video.

A big thank-you goes to everyone who submitted entries. We have very much enjoyed reviewing them, and the final selection was not an easy one. Whether or not you participated in this particular competition, please do stay in touch with us. We always welcome your suggestions!

Photographs

1st Prize

Vittorio Oppizzi, consultant at GAIN
"This photo was taken in Ankober, Ethiopia, outside a health clinic supported by IPO (Increasing People Opportunities), an Italian organization of which I am a trustee."

2nd Prize

James Mbarie, Communication Officer, Macheo Children's Center, Kenya
"I would like to meet new people and learn more about photography."

3rd Prize

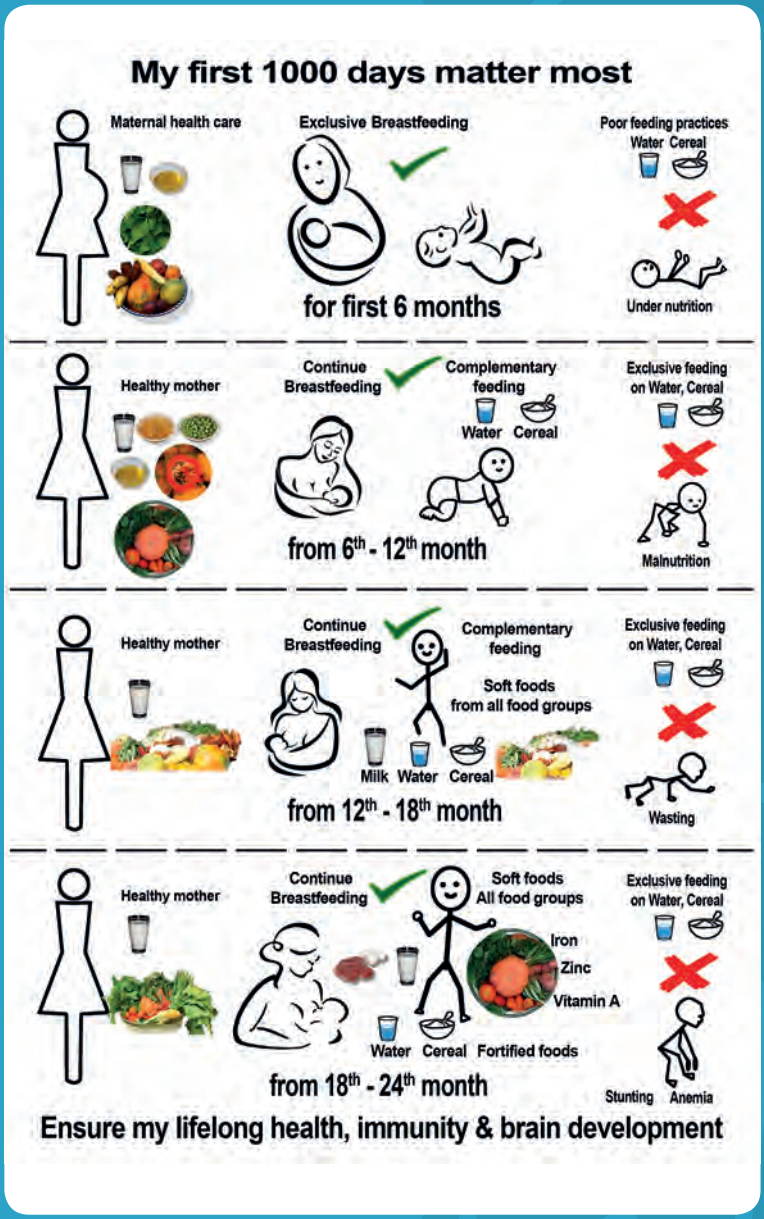
Anna-Marie Ball, Manager for Partnerships and Strategic Alliances (Africa), HarvestPlus
"All our work at HarvestPlus is about ensuring that mothers and children can get off to the right nutritional start – and in this photo, young Lydia is enjoying orange sweet potato with beans that are high in iron. A fabulous combination for her growing body!"

Infographics

1st Prize

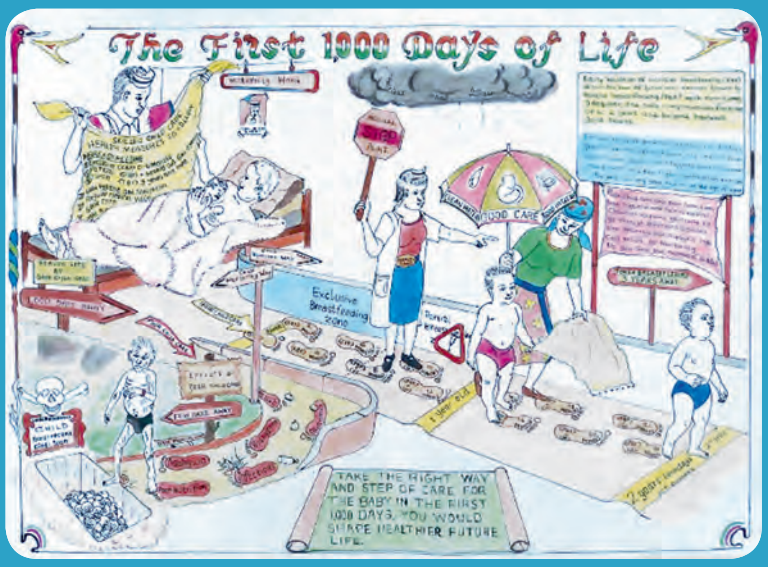
Shobha Mocherla, Audio-Visual Producer, Central Audio-Visual Unit (CAVU). LV Prasad Eye Institute, Hyderabad, India

"I believe that a turnaround in child health is possible by making nutrition channels available, accessible, affordable and acceptable primarily to women from the time they begin making decisions for the family. The importance of providing nutritive care to the girl child – the future child-bearer and breast-milk provider – needs to be sufficiently highlighted in any nutrition strategy, particularly one addressed to the Indian populace, which now exceeds one billion people."



Drawings

1st Prize



Edwin Momanyi, P1 Teacher and Vitamin Products Farmer, Nyamira, Kenya

"My main aim in entering this competition is to create awareness that the 1,000 days between a woman's pregnancy and her child's second birthday offer a unique window of opportunity to shape healthier and more prosperous futures. Good care during this period can have a profound impact on a child's ability to grow, learn, and rise out of poverty. It can also shape a society's long-term health, stability and prosperity."

2nd Prize

Disanayaka Chamathka Wimansi, Grade Six student, R/Sivali Central College, Hidellana, Rathnapura, Sri Lanka

"Our teacher taught us about the human life cycle from embryo to adulthood. She talked about the value of nutrition, immunization, sanitation, growth monitoring, and milestones. I was encouraged to enter this competition by my aunt."

FOOD... for Thought

Discovery Science for Global Health

A bright new dawn – or a case of the Emperor's New Clothes?

Andrew M Prentice
MRC International Nutrition Group, The Gambia

This is an unusual issue of *Sight and Life*, and some readers might be surprised by the complexity and detail of the content that Klaus Kraemer and his editorial team present here.

We can read about the wonders of the microbiome – the myriad organisms that travel through life with us and affect our health and well-being. We can read of genetics and epigenetics and metastable epialleles, of genomics and epigenomics, and of nutrigenetics and nutrigenomics; and why not nutriepigenetics? We can read of the proteome and the deep proteome, the metabolome and every other type of –ome, even including the nutriome (a new one for me, I confess). We can read of systems nutrition and flexible phenotypes and metabolic-inflammatory health, some of which can be analyzed by a next-generation *"sequential windowed data independent acquisition of the total high resolution mass spectra (SWATH-MS) on triple time-of-flight mass spectrometer"* (page 72). Who would have thought we would read about such wonders in the pages of *Sight and Life*?

Some of you will be quite reasonably challenging the presence of such basic science in a journal known for its core mission of eradicating malnutrition worldwide. Others will be daunted by the complexity of the topics addressed. Please bear with us, nevertheless, because the manner in which we navigate these scientific swamps and harness these new technologies has very important implications for future global health, and it lies squarely within *Sight and Life's* vision of *"a world free from malnutrition"*.

And for those of you who do wish to challenge the relevance of basic research, this is precisely what I propose to do on your behalf in this contribution. I myself strongly believe that discovery science in nutrition will paradoxically lead us more quickly to effective interventions than continuing to feel our way in the dark with trial after trial that yield results that disappoint and perplex us. This conviction needs to be stress-tested, however, if we are not to promise a false dawn.

> "I strongly believe that discovery science will lead us more quickly to effective interventions than continuing to feel our way in the dark with trial after trial"

Trials and tribulations: Interpreting unexpected outcomes from micronutrient interventions

Some years ago, I used this title for my EV McCollum lectures and made the argument that nutritional science lacked both the discipline and the method to make the quantum leaps in progress that are required to eliminate malnutrition. We are seduced by the possibility of a silver bullet that will provide a quick fix.

This tendency has been encouraged by the fact that decades – or even centuries – ago, single-nutrient interventions enjoyed some remarkable results. Lemons cured scurvy in seafarers, beriberi is a thing of the past, iodine fortification has saved countless children from cretinism, folic acid has prevented neural tube defects, and mass administration of vitamin A has saved lives. But these were the low-hanging fruit, and a greater number of attempted interventions have either failed or else have caused adverse outcomes, iron supplementation being the most prominent example of late. When our favorite supplement doesn't work, we argue that we should have given more of it

Andrew Prentice with co-pilot in his microlight

(or perhaps less), or that we should have given it to a different age group, or in a different population, or in combination with something else; for surely it must work!

We can use the example of iron to illustrate how basic science has transformed our understanding of this micronutrient's biology and how this might lead to fresh intervention approaches within the near future. Our former view was that humans were very poorly designed to absorb dietary iron and therefore needed all the help they can get. We worried about phytates blocking absorption, and gave mothers and children large non-physiological bolus doses of readily absorbable iron taken without food to avoid the phytates. With the discovery of hepcidin (the hormone that acts as the master regulator of iron) and the mapping of the molecular pathways involved in iron absorption and distribution, we now know that our former views, and the attempted therapeutic interventions that arose from them, were shamefully misguided.

"We can use the example of iron to illustrate how basic science has transformed our understanding of this micronutrient's biology and how this might lead to fresh intervention approaches within the near future"

The new biology informs us that children in infectious environments are working hard to keep iron out of their systems because it will feed the pathogens that threaten them. With the benefit of hindsight, we can see that we were mistaken in our ignorant attempts to batter down the gut epithelial barrier and swamp the chaperone systems (transferrin) that nature has taken eons to evolve. The hepcidin blockade explains why supplemental iron has limited efficacy in poor populations and why, when properly studied, supplementation has been shown to do harm.

But how can we use this new knowledge to eliminate iron deficiency? There are at least three clear messages:

- First, elimination of infections and inflammation will be the most powerful route to eliminating iron deficiency. Instead of battering down the exquisitely evolved hepcidin blockade, we must find the right key, politely open the door, and pass the iron respectfully to the waiting chaperones.
- Second, because hepcidin cleverly integrates information about iron need and threat of infection, it has exciting potential to be developed into a point-of-care diagnostic that may inform health workers that a person is "safe and ready to receive iron," thus allowing targeted approaches that should be both safer and more effective. In conjunction with the National Nutrition Agency (NaNA) of The Gambia, and supported by the Bill & Melinda Gates Foundation through our HIGH Consortium (Hepcidin & Iron in Global Health), we are currently trialing this concept in young children and pregnant mothers.
- Third, we now know that unabsorbed iron from our previously used mega doses alters the gut microbiota, favoring enteric pathogens. Therefore we need to develop new formulations where any unabsorbed iron will not be accessible to those pathogens. Novel nano-particulate formulations are showing great promise in this regard.

These are examples of how basic molecular sciences can point to a pathway to impact and can completely reroute the direction of endeavor.

"Basic molecular sciences can completely reroute the direction of endeavor"

Facing up to our disappointments and starting out on a new path

Let's consider now the issue of how nutrition interventions could improve reproductive outcomes. Naturally we are all believers in the concept that optimizing a mother's diet must be good for her baby, but we are faced by multiple frustrations. There are numerous meta-analyses of the effects of multiple micronutrient (MMN) supplementation on birth outcomes, and we can interpret the results with either a "glass-half-full" or a "glass-half-empty" mindset. The optimist in us all points out that there is unequivocal evidence for benefit, and we cling to such hopes because our entire field, and many whole organizations within it, are dependent upon such success, and – *inter alia* – we have spent tens of millions of research dollars studying over 74,000 pregnancies to reach these conclusions.

But let's put ourselves in the shoes of the brutally incisive health minister of Ugangambwe to whom we are pitching for the funds to implement a country-wide MMN intervention in pregnant women. He could rightfully point out that the 43 g increase in birth weight is less than one tenth of a standard deviation, and that gestation has been lengthened by just 18 hours (and with confidence intervals including zero). The 12% reduction in low birth weight equates to a number needed to treat (NNT) of around 30 in SE Asia and around 100 in Africa, and, statistically speaking, most of this effect will occur by moving babies who were a few grams under the cut-off to a

few grams over the cut-off. The same is true for pre term birth, except that the NNT will be close to 100 in most populations and the majority of the effect will be achieved by shifting a few babies a day beyond the 37 weeks threshold used to define preterm. And the minister will go on to point out that we have had no effect on stillbirths or neonatal deaths. At this stage, we make a rapid retreat from the minister's office with our nutritional tails between our legs.

Such nihilism can be crushing, and it risks diverting funding away from nutrition – but such a trend is already evident, and we need to reverse it by providing some shining examples of success. To counteract the nihilism, we can point out that the effects of MMNs might be additive to those of iron and folate, which is almost always used as the control group. This might well be true, but the meta-analyzed effects of iron are also disappointing. This in turn might be because we generally exclude iron-deficient and anemic women from such trials at recruitment, thus diminishing our ability to show benefit. The bottom line is that we can use our rose-tinted glasses to speculate and can hope that the benefits of MMNs are better than they appear, but after all this investment, we still do not know whether or not that is true. There are trial designs and settings where a placebo can be legitimately used (especially in view of concerns about the safety of iron) and where exclusions can be minimized. I am aware of one such trial that will shortly report interesting and encouraging results.

Where do we go from here? Do we admit defeat? Do we carry on regardless with more of the same? Or do we regroup and design a fresh approach? Surely it must be the latter.

To those of you who are still unconvinced that we need discovery science, let me set you a quiz:

1. What is the cause of pregnancy-induced hypertension and pre-eclampsia?
2. What causes fetal growth retardation in poor mothers?
3. What causes stillbirths and fetal malformations?
4. Why are babies so vulnerable to neonatal sepsis?
5. What causes stunting?

I could go on, but I think you will have got the point by now. Anybody who can answer anything other than "We don't really know" can come and have my job as a professor.

> "We must believe, together with Bill Gates, that the intelligent application of innovation will get us out of the swamps"

Against this background, we can share Bill Gates's frustration that the diet-related health deficits in poor populations are proving so intractable, but we must also share his vision that the intelligent application of innovation will get us out of the swamps.

Discovery research: Science fact or science fiction?

So how do we distinguish science fact from science fiction? How do we cut through the hype and focus on the most promising avenues to pursue? This is a significant issue for scientists and funders alike, and it is becoming ever more challenging as the plethora of methodologies expands.

One can't help but recall Hans Christian Andersen's tale of *The Emperor's New Clothes*. Most readers will know the plot, but for those who don't, a vain and wealthy emperor is promised a new suit of clothes by two swindling tailors. He is told that the cloth will be so fine that it is invisible to anyone unfit for their position or hopelessly stupid. The tailors pretend to dress him, and he walks among his subjects, who applaud the fine new robes for fear of being thought unfit or stupid, until a child – too young to follow the pompous deceit – cries out that the king is naked. Are we discovery scientists pulling off a pompous deceit? Are we persuading our funding bodies to fund an illusion?

My answer is a firm "no", yet I believe that if we want to get a proportion of funding redirected from "suck it and see" empirical trials towards high-class science that will re-write the therapeutic manual in global health, we have an obligation to show some clear examples of success. To use a very useful phrase coined, I believe, by Chris Wilson at the Gates Foundation, we must show that we can move "from nice-to-know to need-to-know."

The development of powered flight: An analogy for our endeavor

On the windowsill of my office is a picture of Dr Dave Hilmers – a collaborator from Houston who helped us with our stable-isotope iron absorption studies. He is smiling out from beneath a flying helmet at the controls of my microlight in The Gambia (an ultralight to US readers).

His picture brings to mind a powerful analogy for our current endeavors in discovery science for global health nutrition: the invention of heavier-than-air flight. This is credited to the Wright brothers in 1903. They were not alone in their endeavors – in fact, it was a highly competitive field. Most proponents were taking the empirical approach, jumping from mountainsides with flimsy and uncontrollable wings strapped to their backs. There were many failures, and many people died trying. Despite their lack of formal education, the Wright brothers applied a much more back-to-basics, analytical approach founded on hypothesis, experimentation and progressive refinement. They made a small, home-made wind-tunnel and thereby devised

completely new methods for pilot control. Success did not come overnight, but once they had achieved the key breakthrough (three-axis-controls), their progress was astonishing and led to the most versatile and reliable means of human transport invented to date.

But let's return to Dave Hilmers to extend the analogy with reference to global health. Before training as a pediatrician and scientist, Dave was a Shuttle astronaut, and flew four extra-terrestrial missions. He had therefore flown in the most advanced aircraft ever invented. My microlight is the antithesis of the Shuttle: basic in the extreme, it has been simplified so that – without aileron, elevator or rudder – it can be flown with precision. In other words, a stroke of innovative genius of the type that Bill Gates seeks (involving in this case the design of flexible wings) allowed a great invention capable of space flight to be reverse-engineered so as to give a very low-cost basic equivalent.

A suggested road map for discovery science in global health

Although I have been (self-) challenging in this article, I remain totally convinced that intelligently applied discovery science will provide us with the next-generation interventions that we so urgently need. I would suggest the following as some of the components of a roadmap to success:

1. We need to attract the very best brains to nutritional science and to collaborate with the world's brightest minds in diverse related fields in order to achieve quantum progress in the new world of "big science". Many of these minds will need to be mathematicians in order to be able to cope with the complex challenges laid out elsewhere in this issue.
2. We must educate funding bodies to the fact that there are no quick fixes, and we must assist them to make complex decisions as to which domains of discovery science are likely to yield most benefit. Metaphorically speaking, we must help the Emperor (funding bodies) to detect the scoundrels, and we must educate his courtiers to tell him the truth. Sometimes these decisions are surprisingly simple – for example, the human genome is (largely) immutable, whereas the epigenome is modifiable by diet (see article on pages 35–38), therefore investments in epigenetics are likely to be more fruitful than investments in genetics.
3. We must be more critical of methods applied in empirical research; and at the same time, we must advocate for clearly thought out, cleverly designed, well implemented and robust trials containing sufficient measures of intermediate markers to allow insights into why the trial has failed if it does.
4. Blue-sky investigators should be forced to apply the "pathway to impact" test. Even if the impact may be quite far over the horizon, they should at least be able to articulate a cogent plan for their pathway to impact.
5. As the visionaries in our field push the boundaries of potential medical interventions (such as bacteriophage manipulation of the microbiota to eliminate enteric dysfunction in low-income settings, or CRISPR-Cas9 editing of CCR5 to eliminate HIV), we will need to greatly enhance our systems for safety testing and high-level ethics oversight.

> "I remain convinced that intelligently applied discovery science will provide us with the next-generation interventions we so urgently need"

As a scientist working at the coalface, you would expect me to argue that we also need more funding. We do, but perhaps a greater challenge is to invest the research dollars that are available more wisely than we have done in the past. The millions of dollars that have been spent on some large empirical trials predicated upon a poor initial reasoning and producing zero results would keep whole institutes in Africa going for many years. Such precious research dollars could perhaps be spent more wisely. And if we are to advocate greater investment in discovery science, we need to strengthen institutions in low-income settings so that they can participate as respected partners in the methodological renaissance.

The future *will* be bright – for mothers and children worldwide – if we can wisely harness the spectacular power of these new technologies in discovery science.

I am most grateful to the following colleagues for their very helpful feedback: Amat Bah, Carla Cerami, Hal Drakesmith, Phil James, Sophie Moore, Martin Mwangi, Sant-Rayn Pasricha, Dan Raiten, Matt Silver and Rita Wegmuller.

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Balancing Discovery and Delivery

The role of nutrition research in achieving sustainable development

Lindsey Lenters
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Key messages

- We are at a pivotal point in time with reference to global nutrition priorities.
- We have sufficient knowledge of maternal, fetal/newborn and child nutrition to prioritize the scaling up of evidence-based interventions.
- There is, however, a continued need for enhanced understanding of knowledge gaps and investment in research.
- There is also the need for continued development of data systems and metrics for tracking progress, especially for emerging areas of focus.
- The Sustainable Development Goals (SDGs) offer an important opportunity to build on progress to date, and to reconsider existing elements of our approach to improving nutrition, health and human capital worldwide.

Though nutrition has increasingly moved into the global policy spotlight as a stand-alone issue, with national governments and civil society alike taking up the call to invest in nutrition programming, the world is currently not on track to meet nutrition targets set out by the World Health Assembly.[1]

With continued focus and efforts to both invest in proven interventions and enhance data systems, progress can be accelerated. The existing body of evidence points towards key interventions that can have a marked impact on reducing malnutrition-related morbidity and mortality in mothers and children; however, clear gaps remain in the evidence base, a selection of which are highlighted here.

With the launch of the Sustainable Development Goals (SDGs) comes a challenge to rethink our approach to taking action on nutrition issues – a push to think more concretely about the crucial importance of the social determinants of health, as well as the complex political, social and ecological systems that influence an individual's nutritional status. Within the SDGs, which frame our collective development agenda in an aspirational and holistic manner, it will be important to maintain a clear focus on nutrition, so as not to lose momentum towards a world where everyone is able to meet their growth and development potential, supported by a strong nutritional foundation.

> "Within the SDGs it will be important to maintain a clear focus on nutrition"

Much progress has been made towards building the case for investment in nutrition. In 2008, the first Lancet Series on Maternal and Child Undernutrition highlighted the importance of nutrition during pregnancy and the first 24 months in a child's life as a critical window for growth and development over the life-course.[2] Since 2008, the global nutrition agenda has gained increasing momentum with national governments, civil society, and the private sector establishing policies and targeting funds towards evidence-based nutrition interventions to reduce stunting, wasting and micronutrient deficiencies in children, and likewise to enhance the nutritional status of women of childbearing age. Much of the momentum for the nutrition movement

can be attributed to initiatives such as the Scaling Up Nutrition (SUN) Movement: these initiatives galvanize efforts towards actualizing targets through engaging and supporting national governments and civil society to integrate nutrition policy and programming into their existing structures.[3]

Despite the advocacy and acceptance of global initiatives in this direction, progress remains slow. Rates of undernutrition remain unacceptably high, as elucidated in the updated analysis of the Lancet Series on Maternal and Child Nutrition in 2013[2] and the most recent Global Nutrition Report.[1] Globally, 165 million children are still stunted, resulting in truncated cognitive and physical development, ultimately limiting productivity over the lifespan. Progress made towards reducing undernutrition has not yet been able to break the cycle of poverty in most countries where the burdens of stunting, wasting and micronutrient deficiencies are highest. Yet, if the 10 evidence-based nutrition interventions put forth in the Lancet Series were scaled up to 90% coverage, an estimated 900,000 lives could be saved in high nutrition-burden countries, the prevalence of stunting could be reduced by 20%, and that of severe wasting by 60%.[4]

> "Rates of undernutrition remain unacceptably high"

Exclusive breastfeeding is one of the recommended evidence-based interventions where rates have remained woefully low.[4] Recent data from long-term follow-up of a population-based cohort in Pelotas indicates that duration of breastfeeding is associated with higher intelligence quotient (IQ) scores: participants who were breastfed for 12 or more months scored higher on IQ exams (3.76-point difference, 95% CI 2.20–5.33) compared to participants breastfed for less than one month. This analysis also demonstrates that IQ is responsible for 72% of the effect of breastfeeding practices on income later in life using mediation analysis techniques.[2] Yet evidence alone is not enough to successfully promote behavior change. Household practices and individual attitudes are significant determinants of exclusive breastfeeding; these in turn are intrinsically linked to the broader social, economic and cultural context. To successfully increase exclusive breastfeeding rates means establishing an enabling context where it is a viable and valued choice for mothers.

The importance of maternal nutritional status during preconception and pregnancy

Emerging evidence highlights the importance of maternal nutritional status during the preconception period and during pregnancy for long-term health of the child. Inadequate nutrition in the periconception period is linked to small-for-gestational-age (SGA) births, and SGA has been shown to increase mortality risks for infants, to increase risks of stunting at 24 months, and has also been linked to the development of certain non-communicable diseases in adulthood. Black et al[2] estimate that 20% of stunting in children (height-for-age z-score <-2) originates in the fetal period, as shown by being born SGA. Again, the determinants of maternal nutritional status are a complex array of individual, household and community factors.

The importance of nutritional status among adolescents

Adolescent health is another emerging area of focus, requiring a systems-based approach. Adolescence and young adulthood represent key points in the lifespan where preventive and early clinical interventions can promote health gains in later life. It is well recognized that much of the at-risk behaviors that affect adult health and outcomes begin in adolescence. Additionally, health and nutritional status in the preconception period have important impacts on pregnancy outcomes and on the subsequent growth and development of children. For example, low maternal BMI puts infants at risk of being SGA.[2] Micronutrient status has similarly important impacts on the developing fetus. For example, low maternal vitamin D status is associated with a higher risk of perinatal morbidity and mortality due to an increased risk of severe pre-eclampsia.[5]

A focus on nutritional status in adolescents is an imperative, given that 19% of young women in developing countries, and more in some contexts, will have given birth before they turn 18 (equivalent to 20,000 young women giving birth every day).[6] While adolescence has long been recognized as an important intervention point, development of health information systems focused on tracking adolescent health lags behind information systems for early childhood and adulthood. This is slowly shifting, as adolescence rises on the global action agenda.[6] School-based interventions represent one approach to making progress; however, much work remains to be done to find optimal delivery platforms and to develop targeted programming.

The Double Burden and the need for an integrated approach

There is also rapidly expanding evidence and momentum on the strategies needed to address the growing obesity epidemic. The prevalence of combined overweight and obesity rose by 27.5% for adults and 47.1% for children worldwide from 1980 to 2013.[7] The prevalence of obesity is highest in high-income countries, yet 76% of affected children actually reside in low- and middle income countries (LMICs).[2] Obesity in childhood increases the child's risk of cardiovascular disease and diabetes (and their associated comorbidities) and increases risk of gastro-intestinal complications and psychological effects.[7] Furthermore, LMICs are increasingly experiencing the Double Burden of disease: concurrent challenges of undernutrition and overnutrition. There is

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a clear window of opportunity to intervene and to curtail the rising rates of overweight and obesity, along with the associated chronic diseases; however, an integrated strategy is needed, as is a more robust evidence base for effective interventions to prevent overweight and obesity.

"An integrated strategy is needed to tackle overweight and obesity"

Given the recognition of the need for strategies that match the complexity of nutrition issues, the most recent Lancet Maternal and Child Nutrition Series put forth an enhanced conceptual framework for nutrition interventions, including both nutrition-sensitive and nutrition-specific interventions, as well as contextual factors that determine nutrition outcomes.[4] Nutrition-sensitive approaches include interventions or programs addressing underlying determinants of fetal and child nutrition and development. For example, approaches to address poverty and food insecurity; maternal empowerment and education, household and community resources for care-giving; access to family planning, health services and a hygienic environment. Maternal depression, low parental schooling, and precarious social safety nets have also all been recognized as key determinants of children's nutritional status, and efforts are under way to scale up implementation and integration of nutrition-sensitive interventions to impact health and nutrition of women and children. There is a critical need to link these interventions with nutrition-specific interventions and to clearly demonstrate impact on nutritional outcomes (reduced stunting, wasting and micronutrient deficiencies).

There is also increasing information around understanding the biology and effects of malnutrition, both undernutrition and overweight/obesity, in relation to functional outcomes and potential mechanisms. The effects of nutritional vulnerability around critical periods of brain development and fetal growth are increasingly coming to light through epigenetic studies. For example, DNA methylation on specific chromosome regions (metastable epialleles) occurs in the early embryonic phases and appears to be susceptible to characteristics of the maternal environment, including maternal nutritional status.[8]

Advances in technology

Our deepening understanding of the importance of the preconception environment on metastable epialleles and DNA methylation has been possible due to rapidly advancing technology. Improvements in biochemical tests and laboratory methods are needed to continue enhancing our understanding of the biological processes behind malnutrition. New biomarkers are needed to more easily and accurately capture nutritional status. Greater collaboration is also needed between public health and basic science researchers: amid growing recognition of the roles the microbiome plays in modulating host health, there is a need to be able to accurately detect, classify and understand the function of the constituents of the microbiome, and their complex interactions with each other and the host. The emerging link between the development of acute malnutrition and disturbed gut microbiome is a key example of how collaborative research can enhance our understanding of disease processes with the view towards improving treatment options.[9] Furthermore, developmental outcomes, not just survival outcomes, are increasingly being recognized as key indicators of effective interventions. Within this, developmental plasticity (changes in neurons and synapses seen as a result of developmental processes) is a priority research area, looking at the long-term effects of the early-life environment and prompting a more careful consideration of what the benchmarks ought to be for "effective interventions".[10]

Measuring nutritional outcomes

An important issue lies in our ability to measure nutritional outcomes and to track progress in real time. Credible, timely and easily digestible nutrition data is essential for policy-makers and program implementers to make informed decisions and track progress towards targets (see **Table 1** for current status of data on intervention coverage from the 2014 Global Nutrition Report). Further work to identify new biomarkers would assist with more easily and accurately characterizing malnutrition.

Nutrition is a prime example of an issue that is best addressed through a systems approach – it cannot be adequately conceptualized through a biomedical lens alone, given that food and the associated behaviors are intrinsically linked to culture and social norms. Since nutritional status is affected by a complex range of factors, it can be easily lost in the fray. We have seen nutrition rise into the realm of high politics, in part through building a focused base of biomedical and epidemiological research, as well as through cost-effectiveness analyses and the establishment of focused targets and priority interventions. However, this approach may have promoted an overly medicalized view of nutrition, prompting a disproportionate investment in interventions addressing the proximal determinants of nutrition rather than investments in addressing the social determinants of health and other structural issues that ultimately lead to poor nutritional status.

"Nutrition challenges are best addressed through a systems approach"

TABLE 1: Data on intervention coverage (IFPRI, 2014)

Time period	Intervention	Status of data on coverage
Preconception	Folic acid supplementation/fortification	Data are only available on coverage of iron–folic acid supplementation during pregnancy (not for all women of reproductive age or during periconceptual period, as modeled in Bhutta et al (2013).
Pregnancy	Balanced energy-protein supplementation	No program data exist as far as we know.
	Calcium supplementation	Few programs exist as far as we know.
	Multiple micronutrient supplementation	There are no national programs for multiple micronutrient supplementation in pregnancy.
Breastfeeding	Promotion of breastfeeding (including early initiation)	Data are available on exclusive breastfeeding, early breastfeeding initiation, and continued breastfeeding. Note that these are practices, not program coverage.
Preventive	Complementary feeding for food-secure and -insecure population	Data are available on practices, minimum acceptable diet (MAD), minimum diet diversity (MDD). There are no data on program coverage.
	Vitamin A supplementation for children 6–59 months old	Coverage data exist for many countries.
	Preventive zinc supplementation	There are no preventive zinc supplementation programs globally, and so currently coverage is zero.
Curative	Zinc for treatment of diarrhea	Data are available for 58 countries; for 50 countries the coverage rate is < 5 percent.
	Feeding for children with moderate acute malnutrition	No programs for moderate acute malnutrition exist presently at scale.
	Therapeutic feeding for severe wasting	Geographic data are available but are not very meaningful. Direct coverage data are not national.
All	Universal salt iodization	Coverage data exist for many countries.

The global community has also seen increased emphasis on accountability and measuring impact. The collective eagerness to make progress towards nutrition targets is admirable at its core; yet care must be taken to avoid the focus becoming on the metrics themselves, rather than the human state that the metrics are meant to represent. If we narrowly focus on attaining targets, it becomes easy to rationalize any means of reaching those numbers. Unsustainable interventions may end up being prioritized if they are easiest to measure and show the largest changes in the short run.

The SDGs and the nutritional status of populations worldwide

The launch of the SDGs represents an important push to reconsider our approach to improving the nutritional status of populations worldwide. The SDGs highlight the need for a systems approach to tackling the most pressing issues facing our planet: extreme poverty, climate change, and strained natural resources. The SDGs provoke policy-makers and leaders to think about development in a new light. They represent a shift away from thinking about "lifting up" low-income countries to benchmarks set by high-income countries. Rather, the SDGs challenge all nations to change their approach to economic growth.

> "The SDGs are what a vision ought to be: lofty and ambitious"

The SDGs are what a vision ought to be: lofty and ambitious. They are a challenge to strive for excellence and to grapple with complexity. Yet, within this framing, do we risk losing momentum towards achieving nutrition targets? If the MDGs (Millennium Development Goals) were too narrow and overly reductionist, the SDGs by contrast may be overly open-ended, risking once again losing nutrition in the fray. We cannot assume that optimal nutrition and food security will naturally follow from improved

TABLE 2: Embedding nutrition targets within the SDG targets[1]

Nutrition target	Where nutrition target can be embedded within the SDG targets
Reduce low birth weight (WHA target)	**Target 3.2:** "by 2030 end preventable deaths of newborns and under-5 children"
Reduce anemia in women of reproductive age (WHA target)	
Increase rate of exclusive breastfeeding (WHA target)	
Prevent increase in under-five overweight (WHA target)	**Target 3.4:** "by 2030 reduce by one third premature mortality from NCDs through prevention and treatment"
Increase coverage of nutrition-specific interventions	**Target 3.8:** "achieve universal health coverage"
Increase coverage of nutrition-sensitive interventions	**Target 1.3:** "implement nationally appropriate social protection measures for all and by 2030 achieve substantial coverage of the poor and the vulnerable"
	Target 6.1: "by 2030 achieve universal and equitable access to safe and affordable drinking water for all"
	Target 6.2: "by 2030 achieve access to adequate and equitable sanitation and hygiene for all and end open defecation"
Improve the enabling environment	**Target 5.5:** "ensure women's full and effective participation and equal opportunity for leadership at all levels of decision making in political, economic, and public life"
	Target 10.3: "ensure equal opportunity and reduce inequalities in outcome such as stunting by wealth quintile"

economic development, as evidenced by the emergence of the obesity epidemic in high-income countries. Clearly there is a need for a concerted focus on nutrition and food policy, within the context of a more holistic set of development goals.

Of the 17 SDGs, several relate to nutrition-specific and nutrition-sensitive topics, namely:

Goal 1: End poverty in all its forms everywhere
Goal 2: End hunger, achieve food security and improved nutrition and promote sustainable agriculture
Goal 3: Ensure healthy lives and promote well-being for all at all ages
Goal 6: Ensure availability and sustainable management of water and sanitation for all
Goal 10: Reduce inequality within and among countries

Table 2 outlines proposed nutrition targets that could be embedded within the SDG targets. A clear, focused approach to tracking our progress towards nutrition targets will build on the groundswell of work done to date, while drawing upon the strengths of the SDGs in promoting an approach to development that addresses root causes in a manner sensitive to the needs of humans as well as those of the planet.

The importance of implementation research

There is a need for continued research across the spectrum of description, discovery, development and delivery. Given the key importance of delivering evidence-based interventions to populations in need, greater emphasis should be placed on implementation research and innovative strategies for the integration of nutrition into existing and emerging platforms for delivery, including those that to date have largely focused on delivering MNCH and child survival interventions.

The need to tackle nutrition challenges with a systems lens is paramount. Equally paramount is the need for enhanced investment in training nutrition experts, integrating nutrition into the curricula for healthcare providers broadly, and for augmenting nutrition literacy levels within the general public. Dedicated nutrition specialists are in demand, but fundamental change will be seen only when nutrition is understood and valued across every sector.

In summary, we are at a pivotal point in time in relation to global nutrition priorities. We know enough about the relationships of maternal, fetal/newborn and child nutrition, and their association with short- and long-term outcomes, to prioritize evidence-based interventions. Simultaneously, there is a continued need for enhanced understanding of knowledge gaps that can be addressed with a concerted research agenda. There is also a need for continued development of data systems and metrics for accurately tracking progress towards targets. The SDGs offer an important opportunity to build on the progress to date, and to reconsider existing elements of our approach to improving nutrition and health status worldwide.

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Views Perspectives in Nutrition Science

Evidence of Multiple Micronutrient Supplementation (MMS) in Pregnancy

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Key messages

- Maternal multiple micronutrient (MM) deficiencies are common in many resource-poor settings, and although routine iron supplementation is recommended, prenatal MM supplement use is uncommon.
- Evidence gathered over the past decade or so indicates that a one-a-day MM supplement enhances birth outcomes, including improvement in birth weight and reduction in low birth weight and preterm birth, although not survival.
- New guidelines for recommending prenatal MM supplementation should be urgently considered, followed by planning of policies and program implementation in LMIC.

Background and history

There is sufficient evidence that micronutrient deficiencies are common, co-exist, are exacerbated during pregnancy, and are likely to influence maternal, fetal, and newborn health. Inadequate and poor-quality diets, cultural food beliefs, limited access and seasonal availability, gender bias, and illness all contribute to the chronic deficiency experienced by women of reproductive age in low and middle income countries (LMIC), where adverse birth outcomes – including high rates of fetal growth restriction, preterm birth, and neonatal and infant mortality – continue to be high.

> "Micronutrient deficiencies are exacerbated during pregnancy and are likely to influence maternal, fetal, and newborn health"

In the past, attention in these settings has been focused on adequate food (balanced energy-protein) supplementation and iron-folic acid use during pregnancy. Multiple micronutrient supplementation (MMS) as a strategy to enhance birth outcomes only began to receive attention recently. In contrast to this, in many high income countries, prenatal multivitamin-mineral supplement use is common and recommended, although not universal. Currently, as it has done in the past, the WHO recommends daily iron and folic acid supplement use as part of antenatal care for reducing the risk of low birth weight and maternal anemia and iron deficiency.[1]

In 1998, UNICEF/WHO and the UN University convened a technical meeting to discuss, and propose a formulation for, a prenatal micronutrient supplement intended for widespread use in developing countries.[2] The supplement was designed and called UNIMMAP (United Nations Multiple Micronutrient

Birth measurement in the JiVitA-3 trial, Bangladesh

Antenatal Preparation): it contained 15 micronutrients at dosages that approximated the recommended dietary allowances (RDA) for pregnancy (Table 1). The use of this supplement took place in subsequent research undertaken to substantiate its efficacy and safety, in part guided by WHO/UNICEF, who coordinated several studies. Daily prenatal supplementation was examined for its ability to enhance fetal growth and increase birth weight in various regions of the world. Several investigators also tested micronutrient supplements with formulations similar to, but not identical to, the UNIMMAP. Thus in the past decade and more, an impressive number of randomized controlled trials have been completed providing evidence of the impact of daily MMS during pregnancy on birth outcomes in diverse LMIC settings. Numerous systematic reviews, along with pooled and meta-analyses, have also been undertaken recently to evaluate the effects of "multiple" micronutrients, although supplements have contained anything from 8 to 29 different vitamins and minerals. This article aims to provide a summary of the findings of these trials and the current state of knowledge regarding evidence for an impact of this intervention strategy on pregnancy outcomes and implications for policy and programs for LMIC.

Efficacy trials of MMS: Study design and outcomes

Randomized controlled trials of antenatal multiple micronutrient supplementation (MMS) were conducted in most settings, using iron-folic acid as the control, although some included a placebo with iron-folic acid being provided to all pregnant women as a service. The MM supplement also contained the same amount of iron as found in the controls (30 mg) in most cases, although not all (Table 2). In some instances, the recommended 60 mg of iron was compared against 30 mg found in the UNIMMAP supplement, while in two instances the MM supplement was modified to contain the higher amount of iron to match the control. All except one trial did not include food supplementation, in which the MMS effect was compared within categories

TABLE 1: The UNIMMAP formulation

	IOM RDAs for Pregnancy|Lactation	UNIMMAP Formulation
Vitamin A (µg RE)	750/770	800
Vitamin D (µg)	5 (200 IU)	5
Vitamin E (mg)	15	10
Folic Acid (µg DFE)	600	400
Thiamin (mg)	1.4	1.4
Riboflavin (mg)	1.4	1.4
Niacin (mg)	18	18
Vitamin B_{12} (µg)	2.6	2.6
Vitamin B_6 (mg)	1.9	1.9
Vitamin C (mg)	80/85	70
Iron (mg)	27	30
Zinc (mg)	12/11	15
Iodine (µg)	220	150
Copper (µg)	1000	2000
Selenium (µg)	60	65

IOM: Institute of Medicine
RDA: Recommended Dietary Allowances
RE: Retinol Equivalents
DFE: Dietary Folate Equivalents

of early or late food supplementation.[19] In one trial, vitamin A was included in the control group receiving iron-folic acid.[4] The primary outcomes examined in the studies included birth weight, and other dimensions of birth size, rates of low birth weight, preterm birth, small-for-gestational-age, stillbirth, and neonatal mortality. Some studies followed infants through the first year of life or into childhood. Maternal anemia was an outcome in a majority of trials. Except for two trials, the majority of trials were not powered to find differences in neonatal or infant mortality as an outcome, but were designed to show significant effects on birth weight and reduction in the prevalence of low birth weight. Heterogeneity was high with respect to prevalence of low birth weight and levels of maternal undernutrition (low BMI and height) in populations, and beyond one trial in Nepal,[20] few examined prevalence of multiple micronutrient deficiencies during pregnancy.

> "The majority of trials were designed to show significant effects on birth weight and reduction in the prevalence of low birth weight"

Summary of findings: Update

Since the last meta-analysis,[21] which included 16 trials, and the Cochrane systematic review, which included 21 trials,[22] a large MMS trial was completed in Bangladesh examining impact on infant mortality.[16] Another trial in China was also completed,[10] and provides additional data, although prevalence of low birth weight in this study was low. An update of the Cochrane systematic review is currently under way. However, we conducted a meta-analysis to include the new studies to the previous group of trials, which were all designed to test prenatal MMS of the UNIMMAP or a similar formulation. We excluded three trials originally that were previously included in the meta-analysis conducted by Ramakrishnan et al:[21] one that was done among HIV-infected mothers, one small clinic-based trial among undernourished women that contained an unusual supplement with 29 vitamins/minerals, and one small trial conducted in France. All three trials were deemed inappropriate for inclusion for the stated reasons. Thus in a total of 15 trials, we examined continuous outcomes of birth weight and gestational age, and dichotomous outcomes of low birth weight, preterm birth, small-for-gestational-age (SGA), stillbirth, and neonatal mortality (**Table 2**). Reported outcomes varied by study. We used either fixed or random effects models to generate effect size estimates depending on significant heterogeneity and I^2 of > 50%. Meta-analyses results and estimates

TABLE 2: Details of studies included in the meta-analysis

Country	Intervention	Control	Sample Size	Study | Reference
Pakistan	UNIMMAP (30 mg iron)	Iron (60 mg)-folic acid	2,378	Bhutta et al 2009 [3]
Nepal	MM (60 mg iron)	Iron (60 mg)-folic acid and vitamin A	1,340	Christian et al 2003 [4,5]
Bangladesh	UNIMMAP (30 mg iron)	Iron (30 mg)-folic acid	705	Eneroth et al 2010 [6]
Tanzania*	MM (no iron)	Placebo	7,866	Fawzi et al 2007 [7]
Zimbabwe*	MM (no iron)	Placebo	1,106	Friis et al 2004 [8]
Guinea-Bissau	MM (30 mg iron)	Iron (60 mg)-folic acid	740	Kaestel et al 2005 [9]
China	MM (30 mg iron)	Iron (60 mg)-folic acid	11,835	Liu et al 2013 [10]
Nepal	UNIMMAP (30 mg iron)	Iron (60 mg)-folic acid	1,052	Osrin et al 2005 [11]
Mexico	MM (60 mg iron)	Iron (60 mg)	633	Ramakrishnan et al 2003 [12]
Burkina Faso	UNIMMAP (30 mg iron)	Iron (60 mg)-folic acid	1,052	Roberfroid et al 2008 [13]
Indonesia	UNIMMAP (30 mg iron)	Iron (30 mg)-folic acid	11,101	Shankar et al 2008 [14]
Indonesia	UNIMMAP (30 mg iron)	Iron (30 mg)-folic acid	725	Sunawang et al 2009 [15]
Bangladesh	UNIMMAP (27 mg iron)	Iron (27 mg)-folic acid	26,808	West et al 2014 [16]
Niger	UNIMMAP (30 mg iron)	Iron (60 mg)-folic acid	2,550	Zagre et al 2007 [17]
China	UNIMMAP (30 mg iron)	Iron (30 mg)-folic acid	2,876	Zeng et al 2008 [18]

*Iron-folic acid was provided through antenatal care

of treatment effects are presented in the **Table 3** and **Figure 1** (for low birth weight) and **Figure 2** (for SGA).

There was an overall modest but significant increase in mean birth weight of 43.2 g with MMS and a resulting significant reduction in low birth weight of 12%. MMS influenced both preterm birth (10% reduction) and small-for-gestational-age (9% reduction) – two underlying causes of low birth weight, although the reduction in SGA was only marginally significant. Neither stillbirth nor neonatal mortality was significantly reduced with supplementation. Although these treatment effects appear somewhat more conservative than previously shown, they are derived from a more cohesive group of trials that were designed and executed to demonstrate the efficacy of a UNIMMAP or a similar MM formulation.

> "There was an overall increase in mean birth weight of 43.2 g with MMS and a resulting significant reduction in low birth weight of 12%"

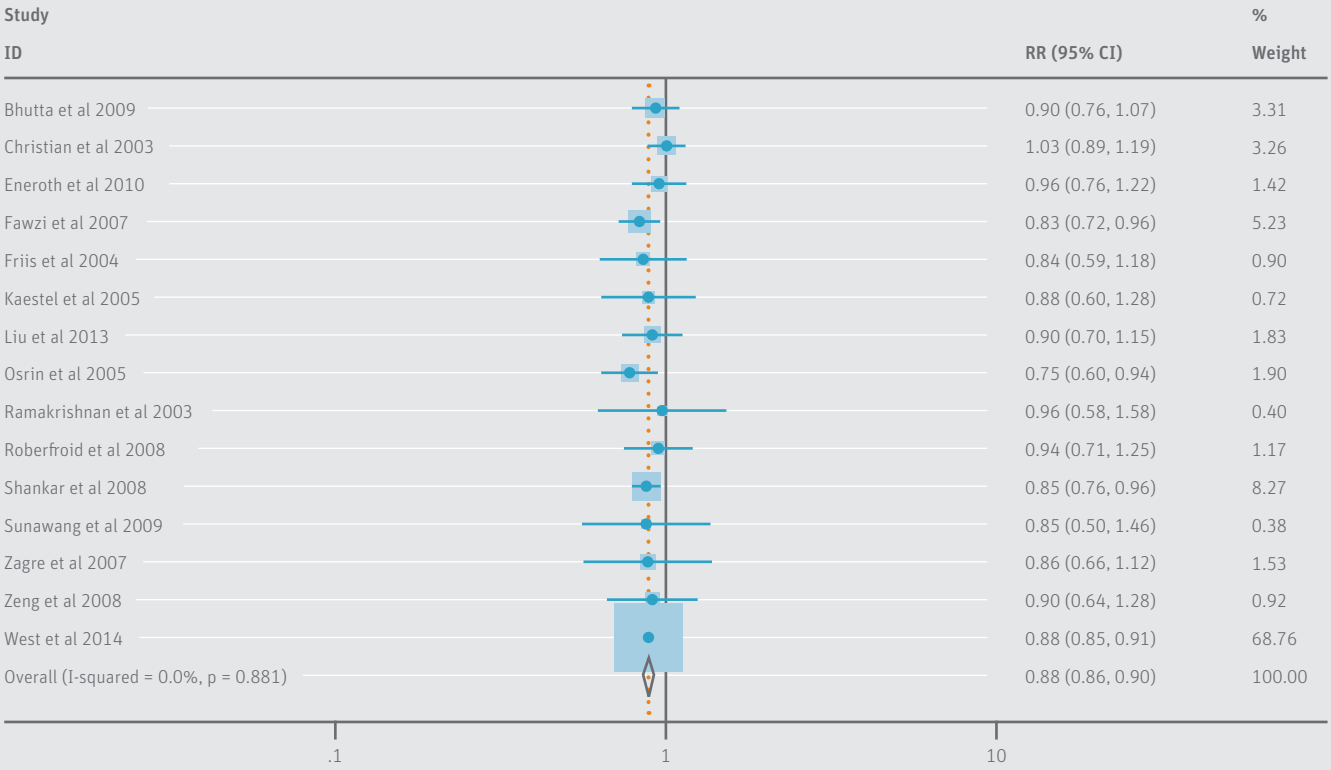
Effect modification

The meta-analysis by Ramakrishnan et al[21] identified several effect modifiers that merit discussion. One was a sub group analysis of five trials in which starting supplementation after

TABLE 3: Meta-analysis of multiple micronutrient supplementation effects using 15 trials conducted in LMIC settings

Outcomes	No. of trials	Treatment effects	95% CI
Birth weight, g	15	43.2	36.8–49.6
Gestational age, wk	10	0.11	0.00–0.21
Low birth weight (< 2.5 kg)	15	0.88	0.86–0.90
Preterm birth (< 37 wk)	10	0.90	0.84, 0.96
SGA (< 10th percentile)	7	0.91	0.84, 1.00
Stillbirth	12	0.94	0.87, 1.01
Neonatal mortality rate	12	0.98	0.91, 1.05

FIGURE 1: Treatment effects of multiple micronutrient supplementation on low birth weight (n=15)



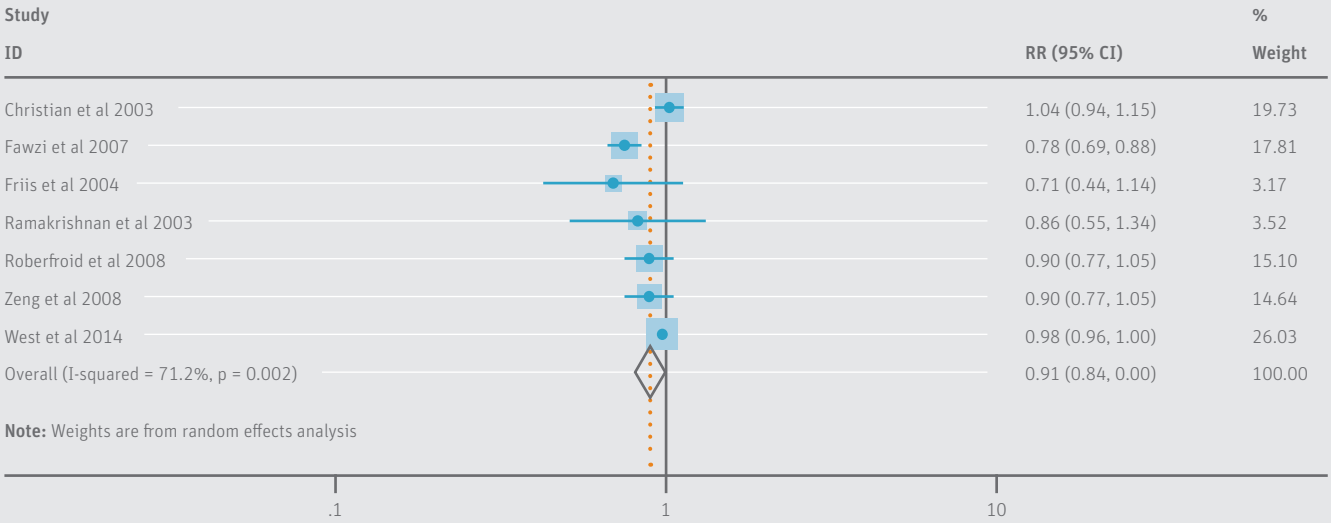
12 weeks of gestation vs. beginning earlier in the first trimester was found to be associated with an increased risk of neonatal mortality related to MMS (RR=1.38, 95%CI: 1.05–1.81). A previous pooled analysis,[23] when not all studies had been completed, also showed overall neonatal and perinatal mortality relative risks of > 1.0 associated with supplementation, although these were not statistically significant. Additionally, subgroup analyses indicated that MMS enhanced birth weight more in women with higher BMI, and an increased risk of large-for-gestational-age was also noted.

These findings raised concerns related to providing multiple micronutrients in settings where home deliveries were still common and both antenatal and obstetric care was poor. The increased risk of neonatal mortality in women who began supplementation later was not clearly understood and Ramakrishnan et al[21] noted that "findings from ongoing large trials in Bangladesh and China are awaited and may help clarify this issue." Both these trials are now included in the meta-analyses that were conducted (**Table 3**).

The recent findings from the Bangladesh trial[16] should be examined more closely. This RCT was called JiVitA-3. It was conducted between 2008 and 2013, and was designed and powered to show the effect of MMS on 6-month infant mortality as the primary outcome. The trial enrolled and supplemented over 44,000 pregnant women and included a total of 28,516 singleton live births. Maternal undernutrition was high in this rural Bangladeshi context, where 90% of women gave birth at home, 40% had early pregnancy BMI of < 18.5 and 50% had height < 150 cm. Low birth weight and SGA prevalence in the control group was 46% and 64%, and preterm birth rate was high at 22%. MMS had no impact on 6-month infant mortality (RR=0.95, 95% CI: 0.86–1.06), although there were significant interactions by sex and level of adherence. There was no mortality reduction in boys, but a statistically significant 17% reduction in mortality among girls. Significant increases in gestational age resulted in higher birth weight, length and other dimensions of size as well as significant reductions in rates of preterm birth, low birth weight, and a non-significant reduction in stillbirth.

Thus, in this undernourished setting there appeared to be beneficial effects of MMS on fetal and birth outcomes, without evidence of harm. In a post-hoc analysis, boys in the MM group were more likely to have a verbal-autopsy-based, physician-assigned, cause of death of birth asphyxia compared to those in the control. In contrast, girls did not experience this higher risk with supplementation, but had a lower risk of sepsis-related deaths if they were in the MM group. The strength of evidence from these analyses should be interpreted with caution, as verbal autopsy data are prone to misclassification and the study was not powered to examine cause-specific mortality differences by group. Overall, the JiVitA-3 trial results showed no reduction, but

FIGURE 2: Treatment effects of multiple micronutrient supplementation on small-for-gestational-age (n=7)



also no increase, in neonatal or infant mortality. This may alleviate previous concerns about potential harm, although it is likely that in environments where maternal short stature and constraint exist, there may be a risk of cephalopelvic disproportion and increased newborn morbidity with interventions targeted to achieve increased fetal growth and birth size. Countries will need to continue striving to improve facility-based delivery and skilled birth attendance in such settings, as everywhere else.

One should note that in all trials, the MM supplement (which included iron-folic acid) was compared to the current standard care of iron-folic acid, which itself is known to benefit birth outcomes. Haider et al,[24] in a systematic review of iron-folic acid supplementation trials (with 60 mg of iron), showed significant effects of the intervention relative to placebo on the outcome of birth weight (41.2 g, 95% CI: 1.2–81.2 g) and reduction in low birth weight (RR: 0.81, 95% CI: 0.71–0.93), although effects on preterm birth (RR: 0.84, 95% CI: 0.68–1.03) and SGA (RR: 0.85,95% CI: 0.67–1.08) were not significant. Folic acid included in the supplement is not considered to contribute to improvement in outcomes, which are probably attributable to iron, based on evidence from trials comparing prenatal folic acid alone vs. a placebo that have not shown a benefit.[4,10] In summary, it is important to recognize that the effects of MMS are over and above those achieved with iron-folic acid and are therefore likely to be larger (perhaps additive) if compared with no supplementation or a true placebo.

Policy implications and way forward

In conclusion, a strong body of research now appears to provide a solid evidence-base to support the widespread use of prenatal multiple micronutrient supplements. The two large trials completed recently may help address some of the uncertainties that existed for adopting a single multiple micronutrient supplement for global use, and the sum total of evidence is probably sufficient to show the public health value of prenatal micronutrient supplement use.

> "A strong body of research now appears to provide a solid evidence-base to support the widespread use of prenatal multiple micronutrient supplements"

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Epigenetics, Nutrition and Human Health

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Imagine yourself at the scene of a crime where you need to determine the age of a victim or perpetrator. If you are lucky, you will have access to skin or dental tissue, or perhaps anthropometry measures, all of which may help determine an approximate age. However, recent research suggests that you could instead obtain an astonishingly accurate measure of chronological age with an "epigenetic clock" that uses a very small number of epigenetic marks in the genome.[1] This would allow you to pin down a sample's age to within a few months, irrespective of the tissue from which it was obtained.

The field of epigenetics is currently attracting a lot of attention from scientists and the wider public. Epigenetic processes describe changes to the genome that can alter gene expression without changing the underlying DNA sequence[2] (**Figure 1**). One such mechanism is DNA methylation of cytosine bases at CpG dinucleotide sites, and there is strong evidence that this can be influenced by a diverse array of intrinsic and environmental factors, including age, disease, stress, exposure to pollutants, and nutrition. Furthermore, epigenetic marks have been associated with a range of diseases affecting health throughout the life course, including cancers, and neurological and metabolic disorders.[3] Together, these observations suggest that our epigenomes carry a "cellular memory" of environmental insults, with the potential for lasting effects on health and disease. Epigenetic changes at certain locations are also believed to be heritable, raising the possibility of trans-generational effects that cannot be explained by standard Mendelian genetics.[4]

Diet and epigenetics in The Gambia

Our group is exploring human diet-epigenome interactions by exploiting an "experiment of nature" in rural Gambia whereby

FIGURE 1: Epigenetic mechanisms of DNA modification. Reproduced with permission from Yan MS-C, Matouk CC, Marsden PA.[5]

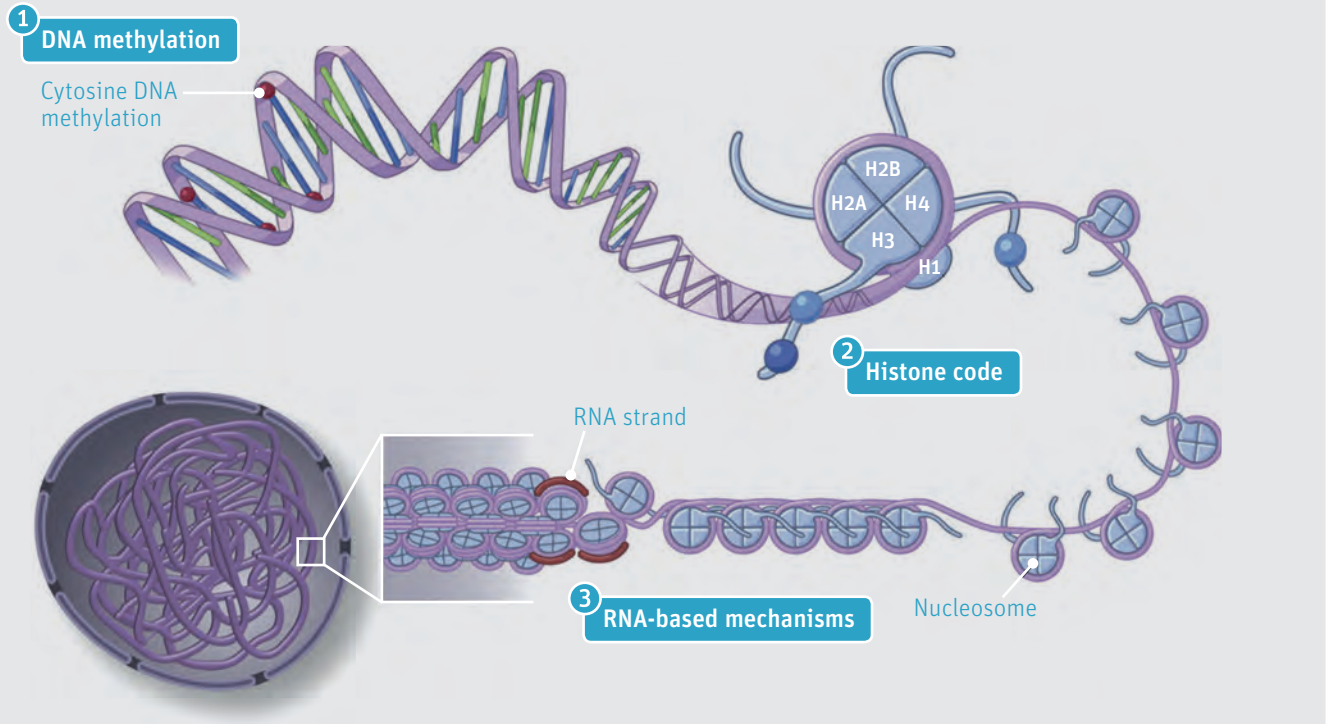


FIGURE 2: Keneba in the rainy and dry seasons

fluctuations in energy balance and maternal nutrition show a distinct bimodal seasonal pattern (**Figure 2**). Our study population experiences a rainy ("hungry") season from July to September, with increased energy expenditure through agricultural work, depleted food stores, and peaks of malarial and diarrheal diseases. The dry ("harvest") season occurs from February to April, when harvesting takes place, leading to improved food security.

> "Epigenomes carry a 'cellular memory' of environmental insults, with the potential for lasting effects on health and disease"

Almost 20 years ago, we uncovered strong evidence that the season when a child is born has a profound effect on lifelong health. Gambian children born during the rainy season are up to 10 times more likely to die prematurely in young adulthood.[6] Since then, pieces of the puzzle are starting to fall into place, with nutrition-related epigenetic regulation in the early embryo emerging as a highly plausible candidate mechanism.

Five years ago, in partnership with Rob Waterland at Baylor College of Medicine in Houston, we demonstrated that season of conception predicts DNA methylation at certain genomic loci known as metastable epialleles (MEs). These are CpG sites whose methylation state varies between individuals, but where variation is correlated across tissues originating from all germ layers in a single individual[7] – indicating that the marks must have been laid down in the first few hours after conception before cell types start to specialize. This period in the very early embryo is when the methylome is globally reprogrammed – a period crucial to development.[8] We therefore use MEs as a device to study the influence of a mother's nutrition on the epigenome of the baby at the time of conception.

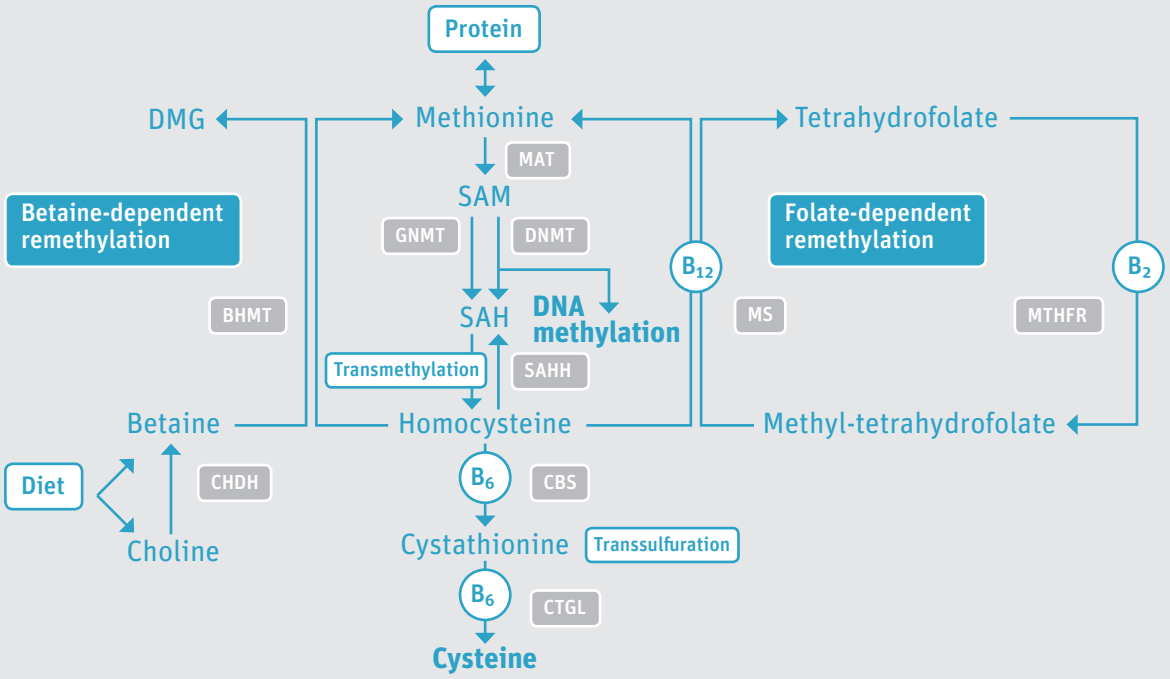
> "We use metastable epialleles as a device to study the influence of a mother's nutrition on the epigenome of the baby at the time of conception"

We have since shown that a mother's levels of several key nutrients vary by season and predict DNA methylation at six MEs in their offspring.[9] These nutrients play a role in 1-carbon metabolism, a biological pathway crucial for the provision of methyl (CH3) groups required for DNA methylation (**Figure 3**). The two main carriers that activate, transport and transfer these methyl groups are tetrahydrofolate (THF) and S-adenosylmethionine (SAM). While 1-carbon units are used as substrates for a whole range of intricate biochemical processes (including cellular biosynthesis, redox status regulation and genome maintenance through the regulation of nucleotide pools), it is their role in cytosine and histone methylation that is central to the interplay between diet and the epigenome.

Linking diet, epigenetics and health

Our latest research has identified another ME that is sensitive to the periconceptional environment in Gambian infants.[11] The associated gene has been implicated in the regulation of immune function and is a putative tumor suppressor, suggesting a potential epigenetic pathway linking a nutritional insult affecting the very early embryo to some serious outcomes in later life. This requires rigorous testing, but work in animal models has already demon-

FIGURE 3: An overview of 1-carbon metabolism. Reproduced with permission from Dominguez-Salas P, Moore SE, Cole D et al.[10]



BHMT, betaine-homocysteine methyltransferase; B_2, vitamin B_2; B_6, vitamin B_6; B_{12}, vitamin B_{12}; CBS, cystathionine-β-synthase; CHDH, choline dehydrogenase; CTGL, cystathionine-γ-lyase; DMG, dimethylglycine; DNMT, DNA methyltransferases; GNMT, glycine N-methyltransferase; MAT, methionine adenosyltransferase; MTHFR, methylenetetrahydrofolate reductase; MS, methionine synthase; SAH, S-adenosylhomocysteine; SAHH, S-adenosylhomocysteine hydrolase; SAM, S-adenosylmethionine

strated that maternal diet can influence the offspring epigenome, with subsequent dramatic effects on phenotype. In the case of the Agouti mouse, pregnant dams fed a diet rich in methyl donor micronutrients (vitamin B_{12}, folic acid, betaine and choline) produced offspring with increased methylation at the agouti locus, leading to fewer obese yellow offspring and more lean brown offspring (**Figure 4**) – characteristics that persisted into adult life, with associated differences in appetite, adiposity and glucose tolerance.[12,13]

Implications for the future

Our Gambian studies offer the first-in-human evidence that periconceptional nutrition can affect the epigenome of the fetus. Just as the epigenetic clock shows that our genome carries an epigenetic signature of the ageing process, it seems that it also bears the hallmark of nutritional exposures at the very start of life.

> "Our Gambian studies offer the first-in-human evidence that periconceptional nutrition can affect the epigenome of the fetus"

The next task is to characterize more clearly how this affects phenotype. To what extent does disrupted methylation affect gene expression? How might these effects influence lifelong risk of morbidity and mortality? Most importantly, from a translational perspective, can epigenetic errors be corrected by optimizing the maternal metabolome through periconceptional nutritional supplementation?

The best known periconceptional nutrition supplement to prevent neural tube defects is folic acid. While the mechanism in this particular example has not yet been conclusively described, epigenetics is a strong contender. Given current research, we believe it is possible to speculate that other forms of periconceptional supplementation might positively influence the epigenome of the unborn child, leading to lifelong health gains across a whole variety of phenotypes.

Clearly the process of validating key findings, further delineating the mechanisms involved, and translating the science into practical public health policy requires a large collaborative effort, along with advances in technology and access to funding. While it is not possible to predict the precise direction research will take in this rapidly evolving field, it seems likely that nutritional considerations will remain paramount in the development of epigenetic therapies to improve health over the life course.

FIGURE 4: The effect of maternal diet on offspring phenotype of the Agouti mouse. Coat color corresponds to methylation levels at the agouti locus. Reproduced with permission from the American Society for Microbiology, Waterland et al.[12]

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Directions in Nutritional Assessment

Biomarkers and bio-indicators: providing clarity in the face of complexity

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Introduction

Among the greatest challenges facing the nutrition community is integrating nutrition into all aspects of global efforts in health promotion and disease prevention. Despite compelling evidence of its importance to human development,[1–3] a full appreciation of how nutrition affects health is still lacking throughout the continuum of health care providers, programmers and policymakers. In large part, this disconnect is the result of relying on evidence that is often not directly or specifically linked to the biology of nutrition in a meaningful manner.

Over the years, attempts have been made to put the differential responses due to inadequacy of individual nutrients into a classification scheme based on specificity of response. The classification of Type 1 and Type 2 nutrients offered by Golden et al is a widely accepted application of this approach.[4] Type 1 nutrients (e.g., vitamin A) are directly and inextricably linked to explicitly defined outcomes, e.g., xerophthalmia, by a well described biological relationship.

By contrast, Type 2 nutrients, such as zinc, are not directly linked to particular outcomes. In fact, the categorization of nutrients by this paradigm is dependent on context. For example, vitamin A is clearly a Type 1 nutrient with respect to its role in preventing xerophthalmia, but it appears to be a Type 2 nutrient with respect to its activity in reducing risk of infection. This is more than a semantic issue, as addressing such physiological impacts calls for an understanding of the actual root causes. That challenge requires tools capable of identifying relationships between nutrients and specific outcomes. It necessitates a clear appreciation of the functions of nutrients within relevant biological systems (e.g., immune, neurological). Further, it requires evidence that changes in nutrient status will, in fact, have functional consequences. These are the domains of nutritional assessment.

Objectives of nutritional assessment

Our ability to understand the role of nutrition in health is driven by our capacity to address three fundamental questions:

1. Where do normal nutrient requirements end and specific health /physiological condition-related needs begin?
2. What is the role of diet /nutrition in those conditions that would require special consideration above and beyond provision of a balanced diet providing all essential nutrients needed for growth, development and health?
3. What are the best types and amounts of evidence to support the establishment of standards of care and the development of programs to address the role of nutrition in health promotion and disease prevention?

These questions are based on the premise that nutrition is involved in all aspects of human biology. Nutrition status is achieved as a result of a series of behavioral, physiological and metabolic processes involved in the taking in, and utilization of, dietary substances /nutrients that must be present to support growth, repair and maintenance of the body as a whole or in any of its parts. This definition illustrates the complexity of nutrition, as well as the need to be integrative in assessing nutritional status. It shows the necessity for a variety of tools capable of probing this complexity at key points – not just in the ingestion/exposure of nutrients, but also in their metabolism/utilization and their function under conditions of both health and disease/stress. Accordingly, interpreting such results calls for an appreciation of the various direct and indirect interactions of nutritional status in affecting, and being affected by, these processes or conditions. These various factors must be considered in determining nutritional needs and standards of care or the roles of diet/nutrition in health and/or disease.

"Nutrition requires a variety of tools capable of probing complexity at key points"

Historically, four approaches have been used to assess nutritional impacts on given health conditions. These are:

- measurement of dietary intake;
- inferences from anthropometry;
- assessment of biochemical indices / biomarkers of nutrient status; and
- responses to direct nutritional intervention.

Because context matters, it can be difficult to draw conclusions or generalize upon specific results based on only one of these approaches. **Textbox 1** contains some of the reasons why this is a challenge.

Textbox 1: Reasons for using an integrated approach to nutritional assessment

- In the absence of biochemical indices / biomarkers, intake data alone are insufficient to determine functional status or the effect of nutrients on an individual's health.
- In the current global context, the dual burden of overnutrition (overweight and obesity) and undernutrition (underweight and nutrient deficiency) co-exist at both population and individual levels. Thus we cannot rely on anthropometry alone to make a judgment about nutrition and health.
- With regard to nutrition and health relationships, it is difficult to make any inferences about biochemical indices without knowing an individual's intake.
- Physiology vs. Exposure: Abnormal circulating levels of a particular nutrient may be due to many factors, e.g., inadequate intake, inflammation, inherent biochemical abnormalities, pathologies, or problems associated directly or indirectly (via interactions with therapeutics / interventions) with a given condition.
- Without knowing the pre-intervention status of an individual, it is difficult to distinguish between the effects of correcting a primary nutrient deficiency and those of correcting a secondary nutritional anomaly associated with disease, medicines, etc.
- The ability to determine optimal nutrient doses for interventions is contingent on an appreciation of dietary intake, physiological need, nutritional status, and the impact of the condition on the processes of nutrition.

A response to the challenge: BOND

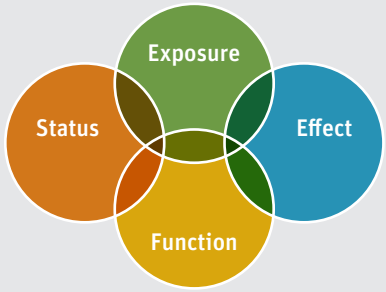
The Biomarkers of Nutrition for Development (BOND) program began in 2010 as a collaboration between the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) of the US National Institutes of Health and the Bill & Melinda Gates Foundation (BMGF).[5] The goal is to provide information and services to support the entire food / nutrition research and global health community. Specifically, BOND is designed to develop consensus on accurate assessment methodologies that are applicable and relevant to users domestically and internationally in both the public and private sectors. BOND intends to serve the breadth of the food and nutrition user community, including: researchers (lab / clinical / surveillance), clinicians, program (planners / implementers / evaluators), and policy-makers (data consumers). Support to the global health community's efforts to address the increasingly complex food, nutrition and health context is provided through the discovery, development and implementation of new tools to evaluate these relationships.

In its first phase, the BOND project adopted a classification scheme to provide some clarity to these issues. The scheme was based on the assumption that the ability to answer the questions above is contingent on the tools needed to address: **1)** exposure (what has been consumed, including bioavailability); **2)** status (where an individual or population stands relative to an accepted cut-off, e.g., adequate, marginal, deficient); **3)** function (reflecting the role of a nutrient **within** a relevant biological system); and **4)** effect (the impact of a given status or intervention **on** nutrient status and function). **Figure 1** reflects the relationships of these categories.

Different perspectives: biomarkers vs indicators vs bio-indicators

From the outset, the focus of the BOND has been on tools that reflect the need for the discovery, development and deployment of biomarkers in these categories. However, there has always been a conundrum regarding the relevance of these categories to the needs of individual user groups, e.g., clinicians, researchers and program directors. More specifically, what are the roles

FIGURE 1: Relationships between exposure, status, function and effect



of: **a)** those outcomes that might be used to reflect some aspect of function or effect, but independently are not sensitive or specific measures of unique nutrient relationships; and **b)** those measures traditionally used for program development and evaluation, but again, not sensitive or specific to nutrition. **Textbox 2** provides definitions of three categories that again overlap, but clearly serve different roles depending on the user's needs.

"BOND focuses on tools that reflect the need for the discovery, development and deployment of biomarkers in selected categories"

Textbox 2: Types of measures

Biomarkers: "A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." [6]

Bio-indicator: "[These] include biological processes, species, or communities and are used to assess the quality of the environment and how it changes over time."[7]

Public Health Indicators: "A measure used to express the behavior of a system or part of a system." [8]

The tension between types and utility of these measures has implications for the BOND user communities. For example, a user involved in public health program development or evaluation might rely on what are traditionally referred to as "indicators," reflecting a response of a system to a given intervention. In the field of nutrition, examples run the gamut from growth through changes in population status of a targeted nutrient and certain measures of neuro-development/capacity to universally accepted clinical parameters such as anemia. Indicators also include such broad, non-specific measures as mortality or disability-adjusted life year (DALY).

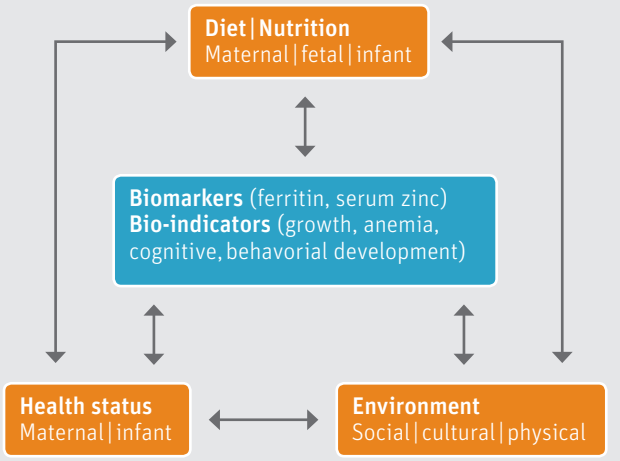
These are often used as triggers for implementing or stopping population-based programs. However, they tell us little about the specific nature of the relationships within diet, nutrition and health. The distinction between an *indicator* and a *biomarker* is not a simple matter of semantics; it reflects expectations about what that information means and how it should be used. For example, a DALY has meaning in the context of population trends and responses, but it lacks specificity with regard to causal factors and, particularly, the effects of nutrition. Moreover, the leap from a biomarker to an indicator is huge, and covers a large spectrum of potential biological relationships. That chasm requires an intermediary step to make a more logical connection.

In exploring this conundrum, it is useful to look outside the *nutrition* field to see how other disciplines might be thinking about this common challenge. An illuminating example is to be found in the environmental sciences, where a quick search of the literature reveals that the term "bio-indicator" is an important part of that vernacular. In the context of an ecological system, the distinction between *biomarkers* and *bio-indicators* represents a hierarchy from the molecular level (toxin levels, sensitive and specific markers of an impacted biological system) to the macro-level (changes in population levels of sensitive species). An example of a bio-indicator in environmental science might be a sentinel species used to assess perturbations of a system. The population might be reduced but without specific biomarkers, and the reasons for that disappearance would be unknown. So biomarkers provide essential context to allow a more meaningful interpretation of bio-indicators and thereby inform interventions to remedy the problem. Thus bio-indicators seem to offer exactly the kind of transitional tool needed to fill that gap in nutrition between biomarkers and indicators.

"Bio-indicators seem to offer exactly the kind of transitional tool needed to fill that gap in nutrition between biomarkers and indicators"

A recent example of this interpretive challenge can be seen in the controversy surrounding the utility of intermittent, high-dose vitamin A supplements.[9,10] In simple terms, the argument

FIGURE 2: Interpreting biomarkers/bio-indicators in a complex environment



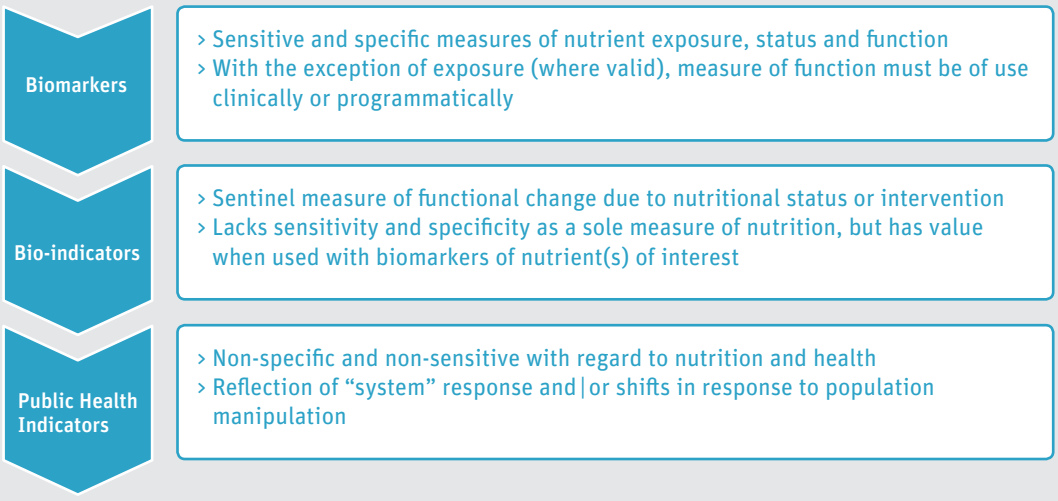
stems from trends in reduced mortality rates that suggest a diminished impact of vitamin A supplementation programs. Additional fuel for this controversy is offered from the paradoxical lack of sustained responsiveness of serum retinol to high-dose vitamin A supplements. Of course, there is no discourse about the essentiality of vitamin A or the need to be vigilant about ensuring its dietary adequacy. The biological conundrum is the link between the biomarker (serum retinol) and the public health indicator (mortality), without which it is difficult to make a case for either risk or benefit.

The decisions made by the *nutrition* community about such controversies are used by public health officials who need clear guidance as to why a change is needed and what are its implications. Thus the debate should be about risk and efficacy. Our ability to attribute trends in non-specific outcomes such as mortality to any specific factor depends on the extent of our knowledge of relevant causal pathways reflected by the relationship between nutrient biomarkers and bio-indicators reflecting functional effect(s). The difference among the three measures (biomarkers, bio-indicators and public health indicators) will be reflected in our ability to assess such pathways. The absence of the intermediary benefits of bio-indicators as indices of function highlights the dichotomy between such public health indicators as mortality and biomarkers. It also emphasizes the need to develop strategies that integrate the role of nutrition within biological systems in a manner that can be translated most effectively to standards of care and evidence-informed programs and policies.

The use of both biomarkers and bio-indicators would facilitate more discrete descriptions of the roles of nutrients in vulnerable individuals/populations, and enable more informative assessments of the responses to dietary/nutritional interventions. In many ways, this distinction speaks to expectation. A biomarker should yield information specific to a given physiological condition, whereas a bio-indicator should yield a relevant, albeit non-specific, reflection of the net effects of several factors. The impact of various factors on use and interpretation of biomarkers and bio-indictors is reflected in **Figure 2**.

There are traps to be avoided in using biomarkers and bio-indicators in nutrition. Without the contextual information pro-

FIGURE 3: Interrelationships among biomarkers, bio-indicators and public health indicators



The nature of the intersections between biomarkers, bio-indicators and public health indicators in making nutrition/health links.

vided by biomarkers, including information about nutrient exposure, a bio-indicator can be misinterpreted and therefore trigger actions that will not achieve the desired goal. For example, using anemia as a public health trigger without the necessary contextual information from biomarkers of inflammation, iron status, hemoglobinopathies etc. could result in an intervention of no benefit, and indeed potential harm, to at least half of a targeted population.[11,12] At the clinical level, this issue can affect the ability to make a differential diagnosis; at the population level, it can affect the ability to address a large-scale problem without increasing concerns of safety or inefficient use of limited resources. **Figure 3** shows the relationships of biomarkers and bio-indicators used in making nutrition/health decisions.

Future directions and conclusions

The value of biomarkers and bio-indicators to clinical and population-based nutritional assessment is clear in terms of both diet/nutrition and health links. It also provides clarity with regard to the effect of either nutritional status or interventions. A need exists, however, to understand the relative value of these terms as well as the relevant tools and operative contexts of each. Both terms are essential in the vernacular of nutritional assessment. As both terms emerged to facilitate communications about multifunctional outcomes of complex systems, their use should assist *nutrition* researchers in such emerging areas as the microbiome and its role in human health and development. That area calls for bio-indicators reflecting function implications of changes in the gut ecology and biomarkers reflecting specificity of these effects as well as precipitating factors (e.g., dietary changes).[12]

> "The value of biomarkers and bio-indicators to nutritional assessment is clear in terms of both diet | nutrition and health links"

The goal of the BOND project is to add value to efforts to address nutrition in health through an open and inclusive deliberative process. The first phase of BOND focused on the traditional approach to nutritional assessment with emphases on single nutrients (iron, zinc, iodine, folate, vitamin A, vitamin B_{12}) and biomarkers of exposure, status, and function. The project's second phase will take a systems approach that will address the roles of multiple nutrients in various health and developmental contexts. The targets will include the neurological system (central and peripheral), growth (linear and body composition),[8] and specific nutrient clusters within each. In each case, the focus will be on the linkage between specific biomarkers and bio-indicators that reflect the roles of nutrients within these systems. For example, for neuro-development, nutrient clusters might include aromatic amino acid precursors of neuro-transmitters, vitamins (pyridoxine, riboflavin, thiamin) that serve as cofactors in those metabolic pathways, and bio-indicators of function (e.g., evoked potentials, measures of cognitive function, measures of behavioral development).

In addition, an ongoing focus must be on the implementation of available biomarkers and bio-indicators to meet the clinical and programmatic needs of low-/middle-resource settings. As was evident during Phase I of BOND, there are numerous platforms available for deployment of biomarker methodologies (e.g., dried blood spot/paper-based,[10] multiplex platforms,[11] "lab-on-a-chip"[12]). The real challenges will be in matching particular biomarkers to particular purposes, and in determining which biomarkers can be deployed in cost-effective ways to provide the necessary contextual information for the interpretation of useful bio-indicators.

Finally, while the goal might be to have a battery of sensitive and specific tests to allow for a meaningful diagnosis or assessment of need at scale, vigilance will be needed to ensure the recognition that an integrated approach to effective implementation must include input from the continuum of expertise and delivery systems (health, food, agriculture, etc.) that will enable a coordinated and effective solution to what will be a complex situation.

Useful nutritional assessment is a complex undertaking that must take into consideration a myriad of factors related to diets, food habits, nutrient utilization, physiological status and health status. As we learn more about human biology, we must look for tools capable of probing this complexity at various points, and for ways of integrating the information those tools can provide. While such tools have traditionally been referred to as biomarkers, in nutrition that term has become elastic through use both in situations of specific relevance to certain nutrients and in non-specific evaluation of context. Therefore, a new paradigm is proposed to facilitate communication about, and implementation of, nutritional assessment. This paradigm distinguishes the term "biomarker" as a specific measure of the amount, activity or function of a given nutrient, and adds the term "bio-indicator" as a measure of the net effects of contextual factors, including nutrition and non-specific outcomes.

The evidence generated from the study of these relationships must be translatable to a broad community of potential users with varying degrees of technical expertise. The continuum represented by biomarkers, bio-indicators and public health indicators reflects the nature of the needs across the food, nutrition, and health enterprise. The appreciation of the relative strengths and weaknesses of these measures can help to ensure that these

tools are used most effectively and that they reflect the goals of full integration of food and nutrition in all aspects of the efforts to improve the health of individuals and populations.

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Prioritizing Nutrition Interventions: Modeling Impact on Health

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Key messages

- Understanding the potential public health impact of different nutrition program scenarios and related cost investments (cost-effectiveness) can help inform decision-making.
- Modeling tools assist in prioritizing implementation of nutrition programs by simulating their effect related to their investment costs. Effects can be modeled on population proportions with adequate intakes, reduced mortality, or overall health impact.
- Composite metrics such as the disability-adjusted life year (DALY) contain multiple dimensions of disease / health, which makes them particularly suitable for comparing risks against benefits and health impacts of alternative nutrition programs.
- The public health impact of nutrition programs can be substantial compared to the costs of these programs, and data collection and analysis to evaluate cost-effectiveness is a valuable investment.

The need for approaches that model the health impact of nutrition interventions

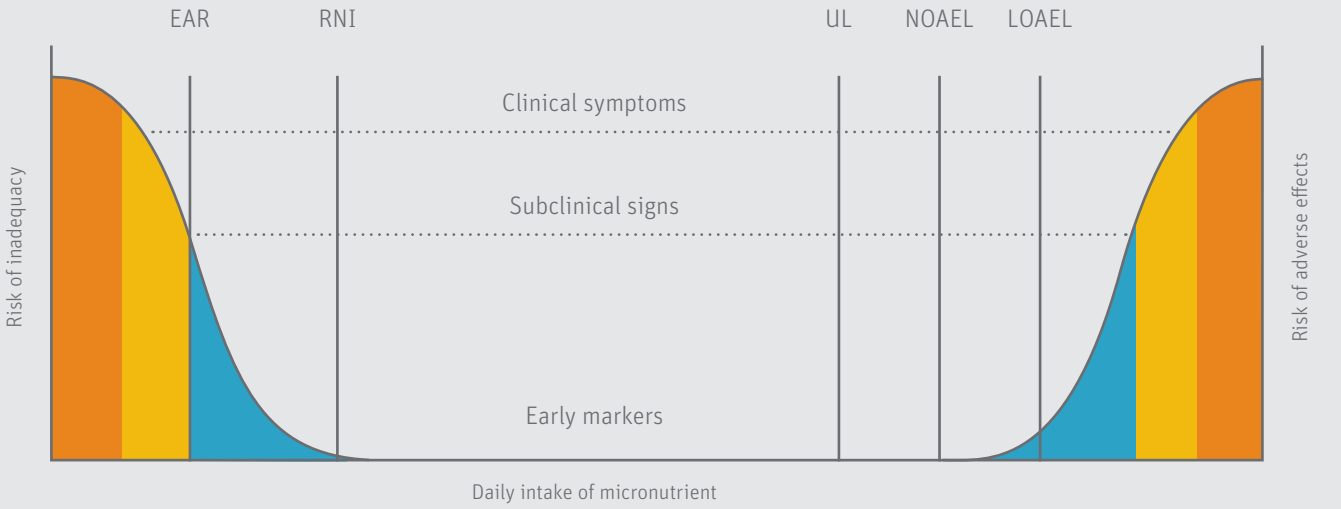
Significant research over the past decade has advanced our understanding of the impact and cost-effectiveness of nutrition interventions aimed at reducing maternal and child morbidity and mortality in developing countries. Substantial evidence exists to indicate that by addressing micronutrient deficiencies, countries can make significant progress towards achieving the Millennium Development Goals.[1]

Several guides for program planners exist that assist in nutrition program design by guiding the approach so as to improve the design, delivery, and effectiveness of nutrition interventions. However, few tools currently exist that can be used by policymakers to translate available scientific knowledge into concrete and strategically prioritized investment decisions. For example, supplementation, fortification, and biofortification are all approaches that can potentially reduce micronutrient deficiency. However, the choice of the appropriate cost-effective nutrition intervention strategies for national control programs is difficult. Cost-effectiveness of programs depends on distribution of micronutrient inadequacy, potential for effective coverage, and program delivery costs. There is the risk of providing insufficient or excessive amounts, missing those at risk, or else of redundant coverage, and with it, unnecessary costs. Such decisions require an understanding of the micronutrient intake distributions in the various population groups and geographic regions, the related magnitude of the nutritional problem, and the population groups and regions affected. Moreover, it requires the ability to estimate the health impact that can be achieved by different intervention portfolios designed to address the same problem but directed at targeted population segments or subgroups.

> "There is growing need for tools that can help decision-makers to select nutrition intervention strategies that achieve optimal health impact with the fewest risks, and the lowest costs"

According to the definition by WHO, health impact assessment is a means of assessing the health impacts of policies, plans and projects in diverse economic sectors using quantitative, qualitative and participatory techniques.[2] A health impact

FIGURE 1: Dose-response relationship between micronutrient intake and adverse effect risk in terms of incidence and severity (based on Renwick, 2004 and 2008[6,19])



EAR: Estimated Average Requirement **RNI:** Reference Nutrient Intake **UL:** Upper Tolerable Intake Level
NOAEL: No Observed Adverse Effect Level **LOAEL:** Lowest Observed Adverse Effect Level

assessment can help decision-makers to make choices about alternatives to, and improvements to, programs to prevent disease/injury and to actively promote health. There is growing need for tools that can help decision-makers to select nutrition intervention strategies that achieve optimal health impact with the fewest risks, and the lowest costs, while targeting vulnerable but underserved populations.

A tool that estimates lives saved by health interventions

The Lives Saved Tool (LiST) is a tool recently developed with the aim of informing program managers and public health policy-makers about the possible impact of different health intervention packages.[3,4] The tool helps estimate the impact of introducing or scaling up a variety of existing child health interventions (e.g., newborn resuscitation, oral rehydration therapy, hand washing, measles vaccine, antimalarials) within countries and given local conditions. The output provided by the LiST tool is the number of mortalities averted plus costing results for feasible increases in coverage. The tool was recently used to estimate mortalities averted at estimated costs of different selected high-impact maternal, newborn, and child health interventions in different Sub-Saharan African countries.[5] This computer-based tool allows users to set up and run multiple scenarios to look at the estimated impact on mortality of different health intervention packages and coverage levels for their countries, states or districts.

There is, however, still need for a tool that helps to prioritize investments in different nutrition programs based on their estimated health impact in relation to costs of their implementation. Such a tool could help decision-makers to select nutrition intervention strategies that achieve optimal health impact with the least risks, using available resources while targeting critical but underserved populations.

> "There is still need for a tool that helps to prioritize investments in different nutrition programs based on their estimated health impact"

A method that estimates the impact of increasing nutrient intakes on the population fraction with inadequate intakes

At intakes below the estimated average requirement (EAR), the risk of inadequacy is estimated to be 50% or more;[6,7] at intakes between the EAR and reference nutrient intake (RNI), the risk of inadequacy is still between 50% and 2–3%[6,7] (Figure 1). The risk of adverse effects due to excessive intake may start to increase with intakes above the no observed adverse effect level (NOAEL) or the lowest observed adverse effect level (LOAEL), although the true risk function is not known for most nutrients (Figure 1). To establish a maximum safe intake level that is unlikely to pose a risk of adverse health effects, an upper tolerable intake level (UL) is developed. This is set an uncertainty factor

(ranging from 1 to 10) lower than the NOAEL or LOAEL in order to account for uncertainty of the data.[8]

To estimate the effect of food fortification on population numbers with adequate nutrient intakes, the EAR cut-point method can be used. As its starting-points, the EAR cut-point method assumes that the proportion of a population with intakes below the EAR and above the UL for a given nutrient corresponds to, respectively, the proportion having inadequate and the proportion having excessive intake of that nutrient.[9–11] The effect of different fortification scenarios on population intakes below the EAR and above the UL can be simulated using IMAPP, an Intake Monitoring, Assessment and Planning Program.[12] Population fractions with intakes below the EAR and above the UL provide, however, little information on the magnitude of the health risk.[6] In some cases, more in-depth understanding may be required. For example, the UL for niacin for adults is 35 mg/d, an uncertainty factor (UF) 1.5 (indicating a good level of confidence in the data) lower than the LOAEL for niacin of 50 mg/d. The adverse effect noted is a relatively benign vasodilatation causing flushing of the skin, an effect that is reversible by reducing intake. The UL for vitamin B_6 is 100 mg/d for adults, an uncertainty factor 2 lower than the NOAEL of 200 mg/d. The adverse effect observed – sensory neuropathy – is a serious and irreversible condition. Therefore, public health concern over a segment of the population routinely consuming niacin in excess of the UL would not be as great as if a segment of the population were routinely consuming vitamin B_6 in excess of the UL.

Assessing the impact of nutrient deficiency control programs on nutrient adequacy and costs

Recently, a useful model has been developed that aims to optimize the "impact" of nutrient deficiency control programs within specified budget and specified coverage, or to minimize cost at specified impact and coverage.[13] The model requires estimates of the number of individuals in a population group with inadequate intakes, reflected by intakes below the EAR. The model requires, in addition, an estimate of the program coverage, i.e., the proportion of the population at risk of inadequacy annually exposed to the program. The model simulates the "impact" of alternative interventions by modeling the number of individuals converted from inadequate to adequate intakes, represented by individuals with intakes meeting their EAR.[12] The effective coverage is estimated as the target population at risk of inadequacy exposed to the program and converted to adequacy. The costs of delivering the intervention per individual effectively covered can be used as an indicator of cost-effectiveness. In Cameroon, this prioritization model was used to predict the effects of alternative nutrition intervention strategies on the averted number of children with inadequate vitamin A intake and absorption.[13]

The different strategies that were simulated included micronutrient powders, high-dose vitamin A supplements, fortified and biofortified foods, and deworming. The effect of high-dose vitamin A supplements on the number of individuals with adequate intakes was estimated from a kinetic model of liver vitamin A stores by determining the additional dietary intake needed to maintain adequate liver stores.[14] National surveys to determine the spatial distribution of micronutrient deficiencies among population subgroups at greatest risk, regional data on food intake, and estimated costs of the different interventions served as inputs for the model. The method identified large spatial differences in micronutrient inadequacies in Cameroon. Currently efforts are ongoing to link this impact and cost optimization model with the Lives Saved output of the LiST tool.

"The costs of delivering the intervention per individual effectively covered can be used as an indicator of cost-effectiveness"

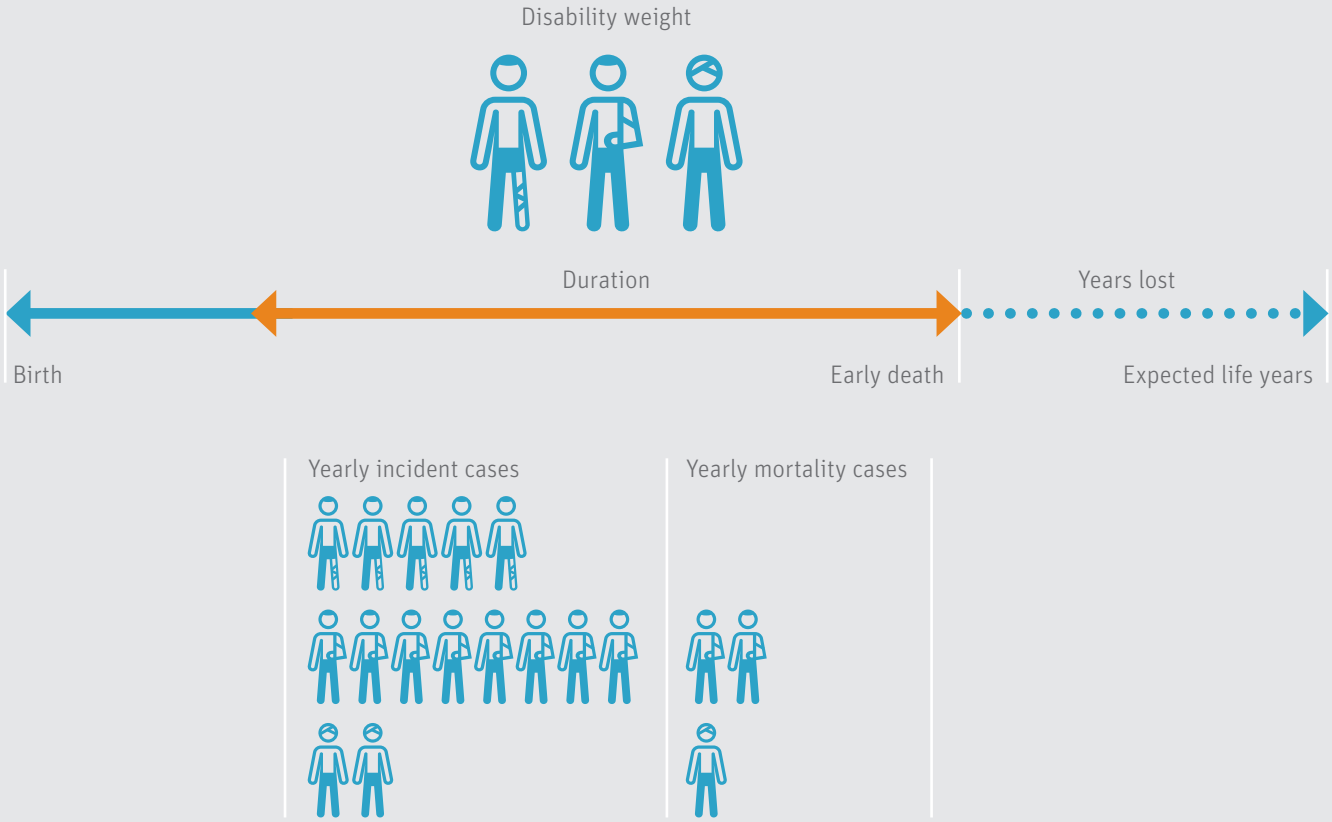
In some cases, inadequate intakes in the population may provide insufficient information for decision-making, as it does not pertain to the full range of relevant health dimensions associated with a certain public health problem. The morbidities of different nutrient inadequacies vary widely, from growth retardation through impaired immune function, blindness, skin disorders, hypogonadism and anorexia, to cognitive dysfunction. The health consequences of these morbidities not only depend on the number of people affected, but also on the severity and the time lived with the disorder, and related mortality. In these cases, incorporating various relevant health attributes in a composite health metric may improve the decision-making process.

Assessing the health impact of nutrition programs using composite metrics

Many health impact metrics present limitations for priority setting: they do not permit comparisons across different interventions or health areas. However, health metrics that capture different dimensions of disease or health are useful tools to estimate the existing disease burden or health impact of a public health intervention. Evaluation of the existing potential "health impact" of a nutrition intervention is an important basis to help decision-makers reach informed decisions in prioritizing cost-effective public health solutions.

An example of a widely accepted effectiveness indicator is the disability-adjusted life year (DALY). The DALY is a compos-

FIGURE 2: The Disability-Adjusted Life Year (DALY) is a quantitative composite measure of disease burden and comprises different aspects of disease burden, such as years of life lost due to adverse effects as well as the incidence, duration and severity of the adverse effects. The health impact of a (nutrient or health) intervention can be expressed as DALYs averted.



ite health metric and combines the incidence rates of mortality and adverse health effects due to a disease or nutrient deficiency, as well as the severity, duration, and frequency of the adverse effects (**Figure 2**). The DALYs averted can be used to assess and compare cost-effectiveness of diverse country programs by relating their cost savings and investments to their health impact. Moreover, DALYs averted can be used to compare the health impact of addressing different types of nutrient inadequacies.

For example, the magnitude of disease burden may differ substantially between different types of nutrient inadequacies: deficiencies of vitamin A and zinc were estimated to be responsible for a combined 9% of global childhood DALYs, and iron and iodine deficiencies combined for 0.2%.[15] This difference in disease burden is largely attributable to the large number of deaths resulting from vitamin A and zinc deficiency. DALYs can be used in risk-benefit modeling by comparing the public health gain from reducing nutrient inadequacy to possible health loss from excessive intakes. A tool[16] and software[17] have been made available by WHO that can assist policy-makers in estimating the public health burden in terms of DALYs. Risk-benefit software tools are also available.[18]

"DALYs can be used in risk-benefit modeling by comparing the public health gain from reducing nutrient inadequacy to possible health loss from excessive intakes"

Limitations and opportunities

Data collection is a first important step in understanding the current distribution of prevalence of food and nutrient consumption by region and population group. This can be used to provide an indication of the nutrient inadequacies that require policy attention. A next step in prioritizing possible nutrition interventions is to qualitatively or quantitatively estimate their impact. The most straightforward method merely considers a single determinant

TABLE 1: Metrics of program effectiveness due to a nutrition intervention

Metric	Impact assessment
Inadequate intakes	↓ number of people with intake < EAR
Mortality	↓ number of people dying from nutrient inadequacy
Disease burden	↓ number of people dying from nutrient inadequacy
	↓ number of disabled life years (incidence, duration, and severity of adverse effects)

of program impact in terms of increased prevalence or incidence of the population with adequate intakes. The advantage of this method is that it is relatively straightforward, requiring mostly estimates of shifts in nutrient adequacies and program coverage in the population. An advanced impact-cost prioritization tool has recently been developed that facilitates the prioritization of different programs based on their expenditures and their effect on number of the target population with adequate intakes (Table 1). This prioritization tool considers whether program expenditures are used efficiently to reach those in need without exposing others to possible risk of excessive intakes. LiST is another tool that prioritizes programs based on their impact on mortality (Table 1), which is a reasonable proxy of disease burden at young ages, since mortality at young ages contributes substantially to disease burden. However, the benefit of nutrient or health interventions may not be limited to lives saved; it may also extend to benefits for health (e.g., reduced disease severity or duration).

> "The benefit of nutrient or health interventions may not be limited to lives saved; it may also extend to benefits for health"

When addressing a single nutrient inadequacy, the number of individuals converted to adequate intakes may provide an adequate indication of program impact that may serve as a basis for program prioritization. However, when prioritizing the impact of addressing different types of nutrient inadequacies with different health burdens, this may require a different approach that considers multiple health dimensions. Composite metrics constitute a valuable tool by incorporating different morbidity aspects and mortality in one measure (Table 1). They will demonstrate that the biggest impacts are achieved by investing in the mitigation of those nutrient inadequacies that involve chronic disabilities, and the highest death toll. The use of composite metrics has the advantage that the health impact of different nutrition and health interventions can be equally compared, relating them to program investments. Composite metrics also allow for equal comparison of health risks related to inadequate against excessive nutrient intakes. The method of estimating composite metrics is, however, more complicated, requires morbidity and mortality data, and can be subject to uncertainties when based on too many assumptions.

The main limitation in assessing health impact is that, in poor-resource settings, the data available are often limited. Representative quality population data on dietary intake are scarce, data on micronutrient-inadequacy-related adverse effect incidence and mortality are even scarcer, and frequently little is known about the anticipated program costs. Another limitation is the difficulty of estimating the proportion of the population at risk who will be effectively covered by the program. Meaningful modeling requires adequate data inputs. However, the savings from better planned and implemented programs can be much greater than the costs of data collection and analysis. Optimization modeling and application of quantitative metrics is promising, as it enables policy-makers to take informed decisions, and countries to choose vital, cost-effective nutrition interventions.

> "Optimization modeling and application of quantitative metrics enables policy-makers to take informed decisions, and countries to choose vital, cost-effective nutrition interventions"

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Inflammation and Biomarkers of Nutrition

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Key messages

- Inflammation is a physiological response to an injury or pathogen.
- The response is proportional to the insult.
- The response is a protective mechanism initiation by release of cytokines from monocytes and macrophages.
- A typical response is 7 to 10 days and is self-limiting.
- As part of the inflammatory response, a number of important nutritional biomarkers decline both rapidly and markedly, leading to an apparent increase in the prevalence of nutritional deficiencies, e.g., vitamin A, iron and zinc.
- Other nutritional biomarkers associated with the uptake, binding and transfer of serum iron increase during inflammation, e.g., ferritin, ceruloplasmin and lactoferrin.
- In an apparently healthy population, some of the biomarker changes can be adjusted using APP to correct the apparent nutritional status, e.g., ferritin and retinol can be adjusted to normalize iron and vitamin A status.
- In some diseases, the depression in nutrient concentration may be particularly severe and can have adverse health consequences. For example, in measles, supplements of vitamin A are recommended to overcome the metabolic depression and improve speed of recovery from the disease.
- In other disease situations, nutritional intervention is potentially harmful, e.g., iron in malaria-endemic areas and β-carotene supplements to smokers.
- In general, the changes in nutritional biomarkers associated with inflammation are transient, and concentrations will return to the pre-disease situation without nutritional intervention as the inflammation disappears.
- Chronic inflammation in response to systemic tissue damage is a feature present in apparently healthy elderly persons.
- Ways of influencing chronic inflammation through diet and / or lifestyle is an active area of research.

Introduction

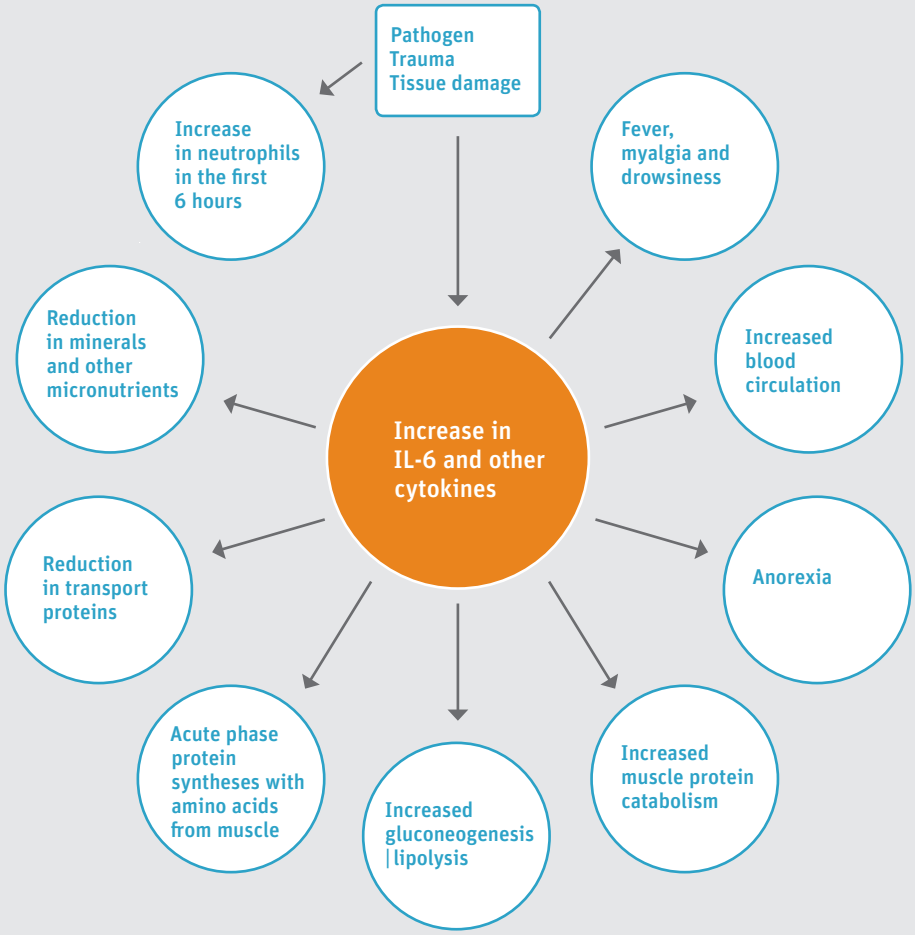
"Feed a cold, starve a fever"

Proverbs typically date back many generations, but "feed a cold, starve a fever" may beat them all. This saying has been traced to a 1574 dictionary by John Withals, which noted that "fasting is a great remedy of fever." The belief was that eating food may help the body generate warmth during a "cold" and that avoiding food may help it cool down when overheated.[1] However, others have suggested the maxim dates back to the 14th century and that the proper phrasing should have been "Feed a cold and stave off a fever".[2] However, this is not the interpretation which has persisted in folklore into the 21st century, and it is interesting to ponder why!

Fever, of course, is a sign of acute inflammation, and the inflammatory response is a mechanism whereby the body protects itself to a greater or lesser degree from any form of trauma, whether this arises from a small cut, major surgery, bacterial, viral or parasitic infections.

> "Fever is a sign of acute inflammation, and the inflammatory response is a mechanism whereby the body protects itself from any form of trauma"

FIGURE 1: Some of the changes associated with inflammation following infection or trauma



We are born with an innate immune system which is exquisitely sensitive to disturbance within the body and can orchestrate an inflammatory response which is appropriate to the magnitude of a given trauma. A common feature of this response is a rapid fall in the blood concentration of several micronutrients, including iron,[3,4] zinc[4] and retinol (vitamin A).[5] The withdrawal of food from a patient would prevent any possible antagonism between food intake and the reduction in blood nutrients associated with inflammation, since any input from the diet would be minimized. Whether the metabolic role of these nutrient reductions is to conserve precious nutrients or to withhold them from pathogens, starving during fever may have unwittingly assisted recovery, and might have perpetuated belief in the proverb.

The inflammatory response

The biochemical and physical changes in a body that are initiated in response to tissue damage or a foreign organism are termed the inflammatory or acute phase response (APR). The interaction between the body and the invader is responsible for the clinical signs and symptoms of disease: the responses begin the moment the foreign material is detected, and they expand exponentially to meet the perceived threat.[6] So fever with raised body temperature, increased blood flow through the body, anorexia, headache, cough, vomiting and diarrhea are classic symptoms of acute disease and are accompanied by a number of metabolic changes designed to assist the body to fight the invader (**Figure 1**).

The inflammatory response is typically initiated by tissue macrophages or blood monocytes.[7] Activated macrophages release a broad spectrum of protein mediators of which cytokines of the interleukin 1 (IL-1) and tumor necrosis factor (TNF) families play a unique role in triggering the next series of reactions both locally and distally. Locally, stroma cells, e.g., fibroblasts and endothelial cells, are activated to produce a second wave of cytokines that include IL-6 as well as more IL-1 and TNF. The cytokines magnify the inflammatory stimulus and potentially

TABLE 1: Characteristics of some well-known acute phase proteins

Type	Acute Phase Protein	Normal serum concentration g|L	Characteristics and response to inflammation and important properties	Time to maximum
1. Enhanced by	C-reactive protein	0.001	Increase 20–1000 fold	24–48 hours
IL-1 and TNF[7]	Serum amyloid A (SAA)	~0.01	Increase 20–1000 fold	24–48 hours
	α_1-acid glycoprotein (AGP)	0.6–1.0	Increase 2–5 fold	4–5 days
2. Enhanced	α_1-anti-chymotrypsin (ACT)	0.2–0.6	Anti-proteinase, increase 2–5 fold	24–48 hours
by IL-6[7]	Fibrinogen	1.9–3.3	Coagulation of blood cells and clumping	3 days
			of bacteria. Increase 30–60%	
	Ceruloplasmin	0.3–0.4	Transport of copper and ferroxidase activity.	4–5 days
			Increase 30–60%	
	Haptoglobin	0.4–1.74[5]	Binds free hemoglobin; concentration may	4–5 days
			appear to fall in hemolytic illness	
	Hemopexin		Binds heme; only moderate increases in APR	
	Hepcidin:	Urine:	6–8 fold in response to	2 hours
	NB Increased by iron	Median 2.96 (IQR 0.95–6.72)	inflammation (IL-6)[46]	
	loading & inflammation	nmol / mmol Cr [47]	5 fold at 24 hr in response to	24 hours
	or reduced by anemia		iron loading[46]	
	and hypoxia[46]			

Data obtained from references[7,13,14] except where indicated otherwise. Abbreviations used interleukin (IL), tumor necrosis factor (TNF), creatinine (Cr).

prime all cells in the body with the potential to initiate and propagate the inflammatory response.

The endothelium plays a critical role in communicating between the site of trauma or infection and circulating leukocytes. IL-1 and TNF induce major changes in gene regulation and endothelial surface expression of adhesion and integrin molecules, including intracellular adhesion molecules (ICAM). These molecules interact specifically with circulating leukocytes and neutrophils, slow their flow, and initiate trans-endothelial migration into the tissue. Serum protease activity will activate the complement system which is a part of the innate immune response and helps antibodies and phagocytic cells to clear pathogens from an organism by attacking their membranes.[8] Alterations in vascular tone are early features of the APR. Dilation and leakage from blood vessels occur particularly in post-capillary venules, resulting in tissue edema and redness or increased micro-vascular permeability.[7]

Inflammatory cytokines, especially IL-6, have particularly important effects on the hypothalamus and the liver. Within the hypothalamus, the temperature set-point may be altered, generating a fever and, in the liver, there are alterations in most metabolic pathways and gene regulation to control levels of essential metabolites for defense, damage limitation and the repair of tissues following recovery. In particular the liver response is characterized by coordination and stimulation of the acute phase proteins (APP). Muscle protein catabolism is a source of amino-acids for APP synthesis and gluconeogenesis, while lipolysis of body fat supplies fatty acids to meet demands for extra energy.[9] (**Figure 1**)

Fever is one of the most common manifestations of infection.[10] It enhances host defenses and increases requirements for energy. Moderate increases in body temperature can exert a beneficial effect by increasing metabolism and the production of cells and soluble molecules needed to combat infection, since all biological and biochemical processes are speeded up by raising body temperature. Some infectious agents can even be killed by increasing temperature. However a 1°C rise in body temperature can increase basal metabolism by 10–13%[10,11] and potentially impose a major demand on body energy stores. Thus there is at the very least a transient malnutrition involving energy, protein, fat and micronutrients. The severity and the length of the infection will determine the time needed for nutritional catch-up. It is suggested that correction to nutrient stores may take four times as long to repair and increase energy and protein requirements by 30–100%.[10]

"Fever is one of the most common manifestations of infection"

The metabolic changes which occur during inflammation are short-term, catabolic, and designed to inhibit and destroy the invading organisms. However, the APR cannot be allowed to continue for more than 8 to 10 days, otherwise tissue reserves will be depleted and the body will become too weak to recover. Hence the APR comprises a sequence of self-limiting components which change from *"bullets to bandages"* as one stimulus declines and is replaced by another; or to put it another way, as the pathogens are removed and rebuilding and repair commences.

The acute phase proteins (APP)

Since the discovery in 1930[12] of C-reactive protein (CRP) in patients with pneumonia, there has been an ever-expanding interest in the APP. The APP are a highly heterogeneous group of plasma proteins (**Table 1**) both in respect of their physicochemical properties and of their biological actions. Biological actions can include anti-proteinase activity, coagulation properties, transport functions, immune response modulation, and/or miscellaneous enzymatic activity. However, the one feature they all have in common is a role in the function of restoring the delicate homeostatic balance disturbed by injury, tissue necrosis or infection.[13]

The production of APPs is induced and regulated by the cytokines. In general, IL-6 enhances production of all APP, but CRP, serum amyloid A (SAA) and α_1-acid glycoprotein (AGP) are specifically enhanced by IL-1 and TNF. IL-6 can also synergistically enhance their production.[7] The time course of the APPs is related to their functions: those with a role in removal of the invader are raised first, while those more involved with repair follow (**Table 1**). The pattern of the APR after elective surgery (not preceded by infection) is a rise in cortisol at 6 hours, followed by a rise in blood leukocytes which peaks at 10 hours. There appears to be a delay of about 6 hours before any rise in the APP occurs. CRP, SAA and α_1-antichymotrypsin (ACT) activity increase rapidly and peak around 48 hours, while most of the others peak later (**Table 1**).[14] Most APP increase in concentration in response to trauma or infection but there are four negative APP where concentrations fall following trauma: retinol-binding protein (RBP), transthyretin, transferrin and albumin (**Table 2**). As these are also nutritional biomarkers, they are dealt with in the next section.

Biomarkers of nutrition

Infection and nutrition are intimately linked.[10] The demands on energy to fuel the inflammation and provide amino acids for the *de novo* synthesis of the many APPs are described above. In addition, rapid and large changes in the serum concentrations of a number of nutrients that are used as nutritional biomarkers occur. The speed and amount of change are more likely to indicate direct effects of the APR on metabolism rather than indirect effects such as hemodilution and vascular changes induced by the inflammation. Serum retinol,[15,16] iron,[3,4] ferritin,[17] zinc[4] and 25-hyroxycholecalciferol (vitamin D)[18] concentrations change by 40% or more in the 48 hours following infection or trauma. The concentrations of most nutritional biomarkers decrease, and where changes in concentration are small, e.g. 10%, then the increase in microvascular permeability is probably mainly responsible. The increased leakiness of the vasculature is probably responsible for most, if not all, of the fall in transferrin and albumin concentrations,[14] and possibly also transthyretin. The liver RBP production, however, is definitely depressed by endotoxin,[19] and the serum concentration falls in a similar way to that of retinol.[14–16] Ferritin, ceruloplasmin and lactoferrin are the exceptions to the other nutritional biomarkers since concentrations increase. The rate of increase in ferritin is comparable with that of CRP, SAA and ACT (**Table 3**).

> "Infection and nutrition are intimately linked"

Interpretation of nutritional status in the presence of inflammation and infection

Covert inflammation

Inflammation can be present both in apparently healthy and in sick people. In the absence of overt disease, inflammation is usually mild, but nutritional biomarkers are still altered (**Table 3**)

TABLE 2: Negative acute phase proteins

Acute phase protein	Abbreviation, other names	Normal serum concentration g/L	Characteristics	Time to maximum effect
Albumin	Alb	35–45		
Transferrin	Tf	2–3	All proteins:	
Thyroxin-binding protein	Pre-albumin, transthyretin	0.3–0.4	Decrease 30–60%	24–48 hours
Retinol-binding protein	RBP	39–45 mg/L		

TABLE 3: Nutritional biomarkers influenced by inflammation

Serum biomarkers: unless otherwise indicated	Direction of change[#]	Acute response (24 to 48 hours) %	Chronic or long-term response (3 to 10 days) %	Reference
Retinol	–	40–70	10–15	15, 16, 20, 48
Retinol-binding protein	–	40–70	10–15	15, 16, 20, 48
Carotenoids	–	20–50	40–60	33, 49-51
Zinc	–	70	10–15	4
Iron	–	50		4
Ferritin	+	100% or more	100% or more	17
Transferrin receptor	(–) +	Small fall	~50 increase	52
25-Hydroxy-cholecalciferol	–	40	20–30	18
Pyridoxine	–	No information	Negative association with inflammation	53, 54
Selenium	–	No information	40–60	55
Leukocyte ascorbic acid	–	~40	Normalized in 5 days	56
Vitamin C	–	Little effect	Variable fall	55
Hemoglobin	–	Little effect	5–10	52
Albumin	–	10–15	10–15	14
Transferrin	–	10–15	10–15	14

[#]Signs indicate the direction of change '–' fall and '+' increase.

and do not reflect true nutritional status. Hence we developed methods using CRP and AGP concentrations to characterize the type of inflammation and adjust serum retinol and ferritin concentrations with correction factors to improve the assessment of vitamin A and iron status.[20,21] In the absence of overt disease, people with inflammation are generally in convalescence[22] and require nutritional supplements to restore the body's nutritional reserves.

Overt inflammation

In people who are sick, it is more difficult to generalize. It is important to understand the reasons for the changes in the biomarkers produced by the trauma in order to interpret nutritional status and know whether it is appropriate to supplement with nutrients or not. The reasons for the changes may differ as illustrated by vitamin A and iron. In some cases, interpretation and intervention may depend heavily on nutritional status prior to infection.

In the case of vitamin A, we previously showed that the depression in plasma retinol concentrations by malaria in urban and rural Thai adults was similar – a difference of approximately 0.6 µmol/L between the means of the controls and respective patient groups.[23] However, concentrations of retinol in the control subjects in the rural community were significantly lower than those in the urban adults, so depression of retinol by malaria in the rural adults produced many more patients with dangerously low retinol concentrations than in the urban group. However, there is no evidence that the risk of vitamin A deficiency is increased in people with malaria, therefore there would seem to be no case for supplementation with vitamin A. The depression in serum retinol produced by malaria is transient and reversible on recovery and, as far as we know, it does not affect recovery from the disease.

In the case of measles, however, there are reports from Africa, India and SE Asia that measles was associated with a high risk of xerophthalmia and blindness.[24,25] Measles is a viral disease which strongly depresses retinol concentrations and damages epithelial tissues.[24,26] Several groups showed that vitamin A supplements provided enormous benefits for the treatment of, and recovery from, severe measles.[27,28] Hussey and Klein[28] also showed that the benefits of vitamin A in measles prevailed in spite of the fact that vitamin A deficiency almost never occurred in the region served by their hospital. Thus in measles cases it is possible that the damage caused to epithelial tissues exceeds any potentially protective effects from the reduction in plasma retinol. Vitamin A supplements are now recommended as part of the treatment of measles even in developed countries.[29]

> "Vitamin A supplements provide enormous benefits for the treatment of severe measles"

Sick boy at Kakuma refugee camp, Kenya

However, vitamin A supplements in the form of β-carotene are not always without harm. Smokers have an increased risk of lung cancer, and several prospective studies have shown them to have low plasma β-carotene concentrations.[30] However, two β-carotene supplementation studies in smokers in Finland and the USA were associated with increased rates of lung cancer.[31] There is evidence that smokers have mildly elevated CRP concentrations[32,33] but we do not know what advantages low β-carotene concentrations confer, and supplements did not reduce human cancer rates as had been expected.[34] Did the antioxidant β-carotene supplements accelerate development of pre-existing cancers?[35]

Although there is a very obvious difference in the demography of the measles and lung cancer scenarios, it does not follow that nutritional supplements in poor communities will always be beneficial and those in developed countries potentially harmful. Low iron status is associated with impaired cognition and poor growth, but in the presence of inflammation it may be protective, particularly in countries where malaria is endemic. Malaria is caused by a parasite which destroys red cells, causing severe anemia and death. However, attempts to correct the anemia and improve iron status with iron supplements have worsened the situation. Oppenheimer showed that iron dextran given *i.p.* to improve iron status in 2-month old infants in Papua New Guinea was associated with more severe malaria,[36] and a trial giving iron supplements to children in Pemba[37] had to be stopped, as there was an increase in hospital admissions in those children receiving the iron. The adverse effects of iron may be because hemoglobin released from lysed red cells will potentially oxidize and damage tissues. The APP haptoglobin will scavenge hemoglobin, but in malaria-endemic communities, production of haptoglobin is often insufficient. Providing more iron from supplements increases this potential damage.

Diseases, epidemics and fevers have been a scourge of mankind over the last 500 years and doctors were generally impotent to intervene. The only treatments available were dietary, leeches to increase anemia, and other remedies that made the human body less attractive to the invading pathogen. *"Starving the fever"* may have increased the chance of recovery.

Ageing and chronic inflammation in apparently healthy elderly people

One of the research areas which has perhaps received too little attention is the etiology of chronic inflammation in the elderly and how to minimize, delay or prevent the increased risk of disease that accompanies inflammation. There is evidence that the lifestyle is an important factor in determining the risk of chronic inflammation and disease. Diet is a significant part of lifestyle, and dietary factors have been implicated in the risk of coronary heart disease (CHD), cancers, age-related macular disease (AMD), and others. Dietary excesses are implicated in obesity and alcoholism, and these increase the risk of non-communicable diseases such as diabetes, cancers and cardiovascular disease.

Our innate immune system is designed to detect foreign material entering the body, but it will also respond to damaged cellular and tissue components generated endogenously. Oxygen is essential for life but oxidation will generate free radicals, potentially causing tissue damage. Endogenously sited antioxidant enzymes and antioxidant nutrients repair and minimize the effects of oxidation, but these protective mechanisms may be overwhelmed by external factors. Smoking and obesity are two such external factors that increase oxidative stress and potentially overwhelm the body's antioxidant defenses. Inflammatory changes initiated from endogenously generated damage may need to be considered differently to the typical acute phase response.

"Our immune system is designed to detect foreign material entering the body, but it will also respond to damaged cellular and tissue components generated endogenously"

Age-related macular degeneration (AMD) is a leading cause of blindness in all populations of European origin.[38] The pathogenesis of AMD is not well understood, but a hallmark of early disease is the appearance of drusen deposits, which accumulate in the space between the retinal pigment epithelium and Bruch's membrane in the eye. Studies on the molecular composition of drusen have implicated inflammation and particularly the local activation of the alternative pathway of the complement cascade in the retina.[39] The complement system plays an important role in the defense against microbial pathogens by the classical stimulation route by external factors,[40] but there is also a mechanism whereby systemic activation through the alternative pathway can occur and is implicated in the pathology of AMD.[40,41] Raised concentrations of pathogenic complement end-products in the blood of patients with early AMD is further evidence of acute activation of the alternative pathway. The macula contains a high concentration of the xanthophyll carotenoids, lutein and zeaxanthin, which should reduce the risk of oxidative damage, but efficiency of this system may be compromised as people age for a number of reasons, including poor diet, smoking and obesity.[42] Interestingly, lutein supplements have recently been shown to markedly decrease circulating concentrations of complement end-products in the blood of patients with early AMD, and the authors suggest that such supplements may provide a simple method to control the inflammatory pathway of the innate immune system.[41,43]

Changes to biomarkers of the complement cascade have also been shown to accompany Alzheimer's disease[44] and may be a component in other neurological diseases, e.g., Parkinson's and multiple sclerosis. Inflammatory changes initiated systemically, especially in the brain, may be difficult to detect by blood biomarkers, and reversing or alleviating the effects of the disease may be even more difficult to achieve by dietary supplements. Inflammatory changes may, however, be early biomarkers of systemic damage in the tissues. Such changes may be reversible in the early stages by alterations to lifestyle and diet, but more research is needed to better understand the impact of inflammation on the etiology of the non-communicable diseases and how lifestyle may influence them.

> "More research is needed to better understand the impact of inflammation on the etiology of the non-communicable diseases"

Conclusions

Inflammation is an innate protective response to assist the human body to overcome an infection or repair tissue damage. The response is initiated by the release of cytokines from stimulated macrophages and is proportional to the level of the disturbance. The response often includes a rise in body temperature, increased blood flow, anorexia, and catabolism of muscle protein and body fat. The latter provide the amino acids and fatty acids for extra energy and the synthesis of APP. Transient reductions in the serum concentrations of many nutritional biomarkers accompany the many metabolic changes and make assessment of nutritional status difficult, but if there is no overt evidence of disease, changes in the concentrations of CRP and AGP can be used to improve the assessment of vitamin A and iron status. However, in the presence of disease, status cannot be easily assessed. Furthermore, the nutrient reductions can be harmful, as in the case of measles, where the disease increases the risk of xerophthalmia and vitamin A supplements have proven benefit in treatment. Yet nutrient supplements in people with inflammation can increase disease risk, as in the case of β-carotene and iron. Chronic inflammation in response to systemic damage is a particular feature in the elderly and increases the risk of non-communicable diseases such as cancer, heart and neurological diseases. Methods to reduce chronic inflammation in apparently healthy elderly people is an active area of research.

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How Nutrigenetics Can Help Prove that Nutrient-Based Interventions Reduce Disease Risk

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Key messages

- Current designs for nutrition intervention studies often yield inconsistent results because they aggregate nutrient-sensitive and nutrient-insensitive people, creating "noisy" data that can obscure the effects of the intervention.
- The reasons why people are metabolically different are only just being elucidated, and underlying mechanisms include genetic and epigenetic variation and microbiome differences.
- The tools for measuring genetic variation are the most developed, and they can help reduce some of the variance in data that makes it hard to prove that nutrient-based interventions reduce disease risk.

Why is it so hard to prove that nutrient-based interventions reduce risk for disease?

All too often, a report that a nutritional intervention reduced disease risk is followed shortly thereafter by another publication observing that, in a different population, the effect of the nutritional treatment could not be replicated. For example, a meta-analysis of clinical trials concluded that vitamin D_3 decreased mortality in elderly women who are in institutions and dependent care.[1] Subsequently, other investigators observed that, in critically ill patients with vitamin D deficiency, administration of high-dose vitamin D_3 compared with placebo did not reduce mortality.[2] Inconsistent results fueled confusion about whether vitamins A or E lower the risk for developing lung cancer. Some clinical trials produced results suggesting efficacy, but other large randomized trials reported that these vitamins increased lung cancer risk.[3–6] There are many other examples of what appear to be nutritional contradictions.

Why is it so hard to prove that nutrient-based interventions reduce risk for disease?

Understanding nutrition and metabolism requires complicated systems biology, and it is always possible that inconsistent results from clinical trials are due to confounding variables that were not properly controlled for. For example, many studies do not provide a sufficiently low intake of the nutrient for the control group, or they do not provide adequate intake of other essential nutrients needed for the test nutrient to manifest its effect. A more common reason for inconsistent effects of a nutrition intervention is that nutrition studies are inherently "noisy", having relatively large variance in measurements compared to the magnitude of the effect size of the nutrient intervention. This noise makes it difficult to detect significant effects. Some of this noise derives from measurement error (e.g., assessment of dietary intake is challenging and prone to measurement error),[7] but a good deal of this noise is due to metabolic variation between people.

> "A good deal of the 'noise' in nutrition studies is due to metabolic variation between people"

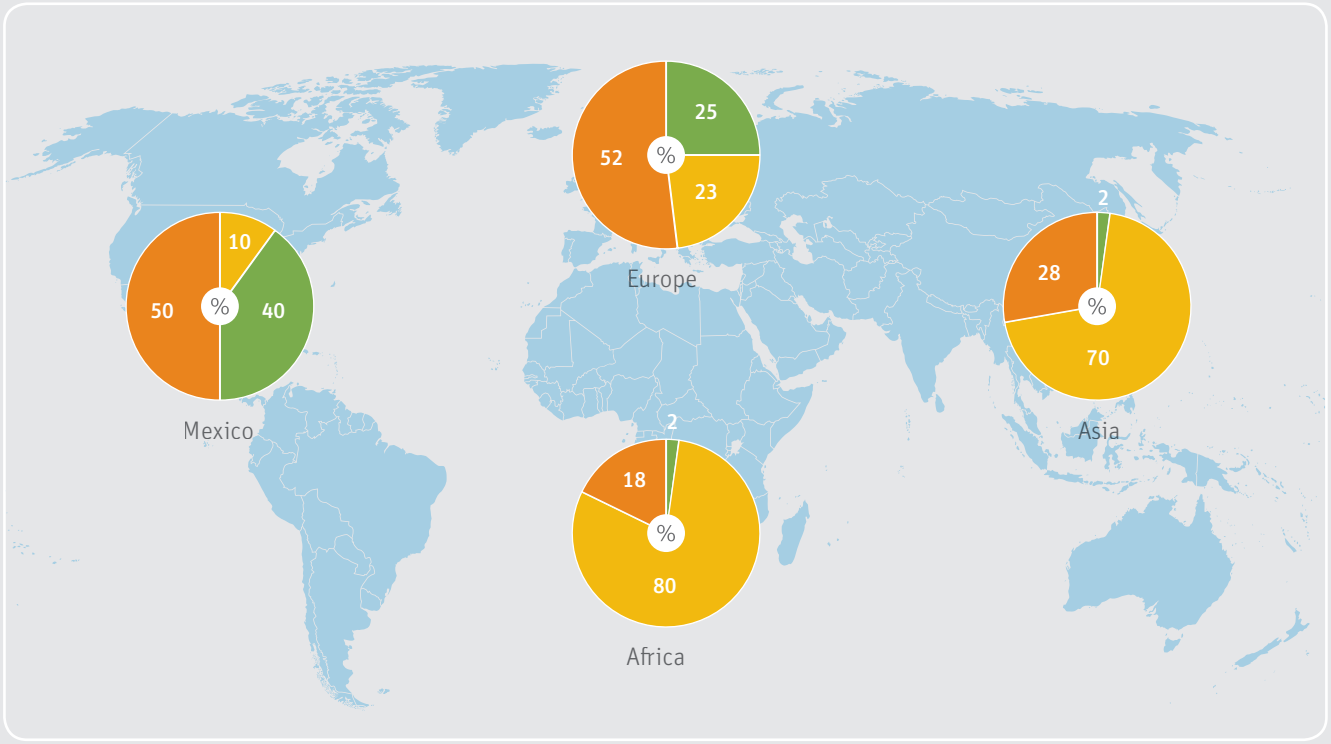
Each person has approximately 50,000 common genetic single nucleotide polymorphisms (SNPs; differences in the

"spelling" of the genetic code of a gene), and some of these SNPs occur in genes that control metabolism and result in metabolic inefficiencies that alter nutritional requirements or responses.

The nutritional requirements for choline

To illustrate this concept, it is useful to examine the nutritional requirements for choline, which was designated as an essential nutrient for humans in 1998.[8] In carefully controlled clinical studies testing the importance of dietary choline, most (~80%) of men and postmenopausal women developed organ dysfunction (fatty liver, liver damage, or muscle damage) when deprived of choline. In contrast, fewer than half of the premenopausal women in the study became sick.[9,10] Depending on the composition of the population studied, investigators could have concluded that choline was, or was not, an essential nutrient. Multiple factors contributed to the differences in the symptomology of dietary choline deficiency. For example, people have the ability to biosynthesize choline (as phosphatidylcholine) through a series of reactions that involve an enzyme coded for by the *PEMT* gene. Expression of *PEMT* is regulated by estrogen, and this explains why young women (with higher concentrations of estrogen) have a reduced dietary requirement for choline compared to men and postmenopausal women.[10,11] Why, then, did almost half of young women still need to eat choline?[10] These women had SNPs that interfered with the estrogen response element in *PEMT*, making the gene unresponsive to estrogen[11–14] and making the young women with this genetic variant reliant on diet for their choline needs. More than 70% of US women from North Carolina have 1 variant allele, and > 20% have two variant alleles for this *PEMT* SNP.[12] It is important to realize that people inherit SNPs from their ancient ancestors; therefore, prevalence of SNPs can vary greatly between populations. **Figure 1** illustrates how one of the functional SNPs in *PEMT* is distributed around the world. Thus, it is easy to understand why nutrition studies could yield different results depending on which populations are studied. Nutrigenetic analyses are needed to enable the identification of choline-sensitive (responders) and choline-insensitive (non-responders) subgroups of people.

FIGURE 1: The prevalence of a functional single nucleotide polymorphism in the gene PEMT (rs12325817) varies in different populations.



The PEMT (rs12325817) polymorphism involves a substitution of a C for a G in the genetic code. Having a C substituted in this gene results in diminished induction of gene expression by estrogen, and having both copies of the gene substituted with a C abrogates the response to estrogen almost completely.

Using data from the 1000 Genomes database (www.1000genomes.org), it is clear that the proportion of people with CC alleles (green), GC alleles (orange), and GG alleles (yellow) is very different in people of different genetic heritage.

Nutritionally relevant single nucleotide polymorphisms (SNPs)

Many other pathways of nutrient metabolism are affected by genetic variation, and these nutritionally relevant SNPs are present in many people. Homozygosity for the variant *C677T* allele in the methylenetetrahydrofolate reductase gene *(MTHFR)* creates a metabolic inefficiency that increases the dietary requirement for folate.[15] Twenty percent of Mexican Americans[16] and 14% of Caucasian Americans[17] have two variant alleles for this SNP. Thus, genotyping can be used to identify likely responders and non-responders to folic acid treatment. Similarly, the metabolic consequences of common SNPs may well have contributed to the different interpretations of vitamin D_3 clinical trials discussed earlier: vitamin D is activated by hydroxylation reactions catalyzed by the products of the *CYP2R1* and *CYP27B1* genes. Common SNPs in either of these genes reduce enzyme throughput and hence the availability of activated vitamin D.[18,19] Activated 1,25-$(OH)_2$-vitamin D_3 must bind to the vitamin D receptor (VDR), and common SNPs in the VDR gene that codes for this receptor further diminish the response to vitamin D.[18,20] People with these SNPs are 2.5 times more likely to be vitamin D insufficient.[18] Knowledge of individuals' genetic variations and associated metabolic inefficiencies could help identify responders and non-responders to vitamin D interventions. These are just a small selection of the many common nutritionally relevant SNPs that result in metabolic variation between individuals. There is a great deal more research that needs to be done before we have identified all of these SNPs, and the expansion of the catalog of nutritionally relevant SNPs is the goal of the research center that I direct.

Nutritionally relevant SNPs probably only result in a phenotype in people who are nutritionally challenged. If people can eat enough of the relevant nutrient, a metabolic inefficiency may not cause a problem. However, metabolic inefficiencies become very important when the availability of the nutrient is marginal (and sometimes they can become important when the diet intake of a nutrient is excessive if the metabolic inefficiency alters removal of the nutrient or its metabolites). This highlights an important concept: investigators need to assess dietary intake as well as genotype when they try to identify nutritionally relevant SNPs. Two conditions may be necessary before an abnormal phenotype exists: presence of an SNP that causes a metabolic inefficiency, and low (or high) dietary intake of the relevant nutrient. Analyses using genetic data alone can miss nutritionally relevant SNPs because when people with high and low dietary intake of the nutrient are lumped together, the effect of the SNP is obscured. Genome-wide association studies (GWAS) miss important nutritionally relevant SNPs because these studies usually do not also consider the SNPs' interactions with dietary intake.

The role of the gut microbiome

Genetic variations are not the only reason that people differ metabolically; they are just the easiest to measure. Differences in the gut microbiome also change how people process nutrients and metabolize them. For example, when fecal microbiota from obese or lean twins were transplanted into mice, the mice that received the obese person's microbiota developed an obesity-associated metabolic phenotype while the lean twin's microbiota transmitted a lean metabolic phenotype.[21] Recently, an interesting study demonstrated that eating artificial sweeteners induced changes in the gut's microbial populations, and this altered microbiome resulted in perturbed glucose metabolism in the host.[22]

Reducing the "noise" in nutrition research

In summary, there is a fundamental problem with the idea that humans are metabolically the same, and with the resulting assumption that responses to nutrients should be distributed along a normal bell-shaped curve. Rather, there is biologically determined metabolic variation that results in discrete subpopulations that are nutrient-sensitive (responders) and nutrient-insensitive (non-responders) to nutrient interventions. Current experimental designs for nutrition intervention studies often yield inconsistent results because they lump together these responders and non-responders, creating "noise" that obscures the effects of the intervention. Identification and recruitment of high-risk vs. low-risk subjects is standard practice for clinical trials of pharmaceuticals, where risk factors (obesity, *BRCA1* mutations) for particular diseases (diabetes, breast cancer) are well known. The challenge for nutrition researchers is to build the catalog of mechanisms whereby metabolic variation can be predicted in people. The next generation of nutrition intervention studies should use this information to identify and recruit nutrient-sensitive subjects, and thereby avoid obscuring therapeutic effects by combining data from this subgroup with data from non-responders. When lacking this knowledge, designs for nutrition trials need to include genetic, microbiome and other measures that allow for *post-hoc* identification of responders, and use this information to build the metabolic-variation knowledge base needed so that investigators can reduce the "noise" in their nutrition research.

> "There is a fundamental problem with the idea that humans are metabolically the same"

Conflict of Interest Disclosures

The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Zeisel reports hono-

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Perspectives in Nutrigenomics and Nutrigenetics

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Introduction

The efficacy and safety of nutritional intervention is dependent on a thorough understanding of **(1)** which nutrients may be deficient or in excess in a population, **(2)** the pathologies induced by specific nutritional imbalances at the genomic, transcriptomic, proteomic and metabolic levels, and **(3)** appropriate diagnostic tools to monitor outcomes at the population and genetic subgroup level. The emerging sciences of nutrigenomics and nutrigenetics which address these issues are expected to contribute substantially to the elimination of malnutrition and to the optimizing of health outcomes to a greater extent than would otherwise be possible by using conventional approaches alone.

Definitions of nutrigenetics and nutrigenomics

Nutrigenetics is the science of the effect of genetic variation on cellular and organism response to dietary intervention. In contrast, the aim of **nutrigenomics** science is to understand how nutrients and bioactive food compounds affect gene expression and maintenance of genome integrity. Exploitation of this genomic information, along with high-throughput "omic" technologies, allows the acquisition of new knowledge aimed at obtaining a better understanding of nutrient-gene interactions depending on genotype, with the ultimate goal of developing nutrition strategies for optimal health and disease prevention at the individual, genetic subgroup and population level.

Therefore, the fundamental hypotheses underpinning the science of nutrigenetics and nutrigenomics are the following:

- Nutrition may exert its impact on health outcomes by directly affecting expression of genes in critical metabolic pathways and/or indirectly by affecting the incidence of genetic mutation at the base sequence or chromosomal level, which in turn causes alterations in gene dosage and gene expression.
- The health effects of nutrients and nutriomes (nutrient combinations) depend on inherited genetic variants that alter the uptake and metabolism of nutrients and/or the molecular interaction of enzymes with their nutrient cofactor or metabolites and hence the activity of biochemical reactions.
- Better health outcomes can be achieved if nutritional requirements are customized for each individual or genetic subgroup, taking into consideration both inherited and acquired genetic characteristics depending on life stage, dietary preferences and health status.

Perspective on potential implications for nutrition

A nutrigenetic and nutrigenomic approach has important consequences to the way public health strategies aimed at nutrition are designed and implemented. For example, dietary reference values (e.g., recommended dietary allowance or safe upper limits) are designed for the general population and not optimized for genetic subgroups which may differ critically in the activity of transport proteins for a micronutrient and/or enzymes that require that micronutrient as a cofactor. The ultimate goal is to **(1)** match the nutriome (i.e., nutrient intake combination) with the genome profile so that DNA integrity, gene expression, metabolism and cell function can occur normally and in a homeostatically sustainable manner, and **(2)** provide better mechanistic interpretation of data from epidemiological and clinical intervention studies regarding health impacts of dietary factors that may help to refine recommendations so that they can also be specifically targeted to individuals and genetic subgroups.

"A nutrigenetic and nutrigenomic approach has important consequences to the way public health strategies aimed at nutrition are designed and implemented"

TABLE 1: Examples of common polymorphisms in genes that affect vitamin transport / metabolism and / or function of an enzyme for which the micronutrient is a cofactor

Micronutrient	Gene	Function of protein or enzyme	Polymorphism	Molecular or health effect of polymorphism
Vitamin A	BCMO1	Cleaves β-carotene into two molecules of all-*trans*-retinal	R267S: rs12934922; A379V: rs7501331	A β-carotene supplementation study with healthy female volunteers indicated that carriers of the 379V and 267S/379V variant alleles had 160% and 240% higher fasting β-carotene concentrations compared to wild-type carriers. More importantly, the conversion efficiency of BCMO1 for β-carotene was 32% reduced in carriers of the 379V variant allele and 69% reduced in carriers of the 267S/379V variant allele compared to the wildtype.[12,13]
Folate	MTHFR	Converts 5,10-methylene-tetrahydrofolate to 5-methyl-tetrahydrofolate (5-MTHF)	C677T: rs1801133	The C677T polymorphism of MTHFR reduces the activity of the enzyme by 50% in TT homozygotes and increases the risk of hyperhomocysteinemia, a risk factor for pregnancy complications, cardiovascular disease and dementia.[9–11]
Vitamin B_{12}	MTR	Converts 5-MTHF and homocysteine to methionine and tetrahydrofolate. B_{12} is the cofactor for MTR	A2756G: rs1805087	Although the functional effect of this polymorphism methionine synthase has not been established, some studies have shown a relatively higher concentration of plasma homocysteine among individuals with the AA genotype. The AA genotype is also associated with more chromosomal DNA damage and reduced disease-free longevity.[14–15]
Vitamin C	SLC23A1	SVCT1, encoded by the gene *SLC23A1*, is predominantly responsible for high capacity vitamin C transport across membranes	rs6596473 rs11950646	Skibola et al observed an increased risk of follicular lymphoma associated with two SNPs (rs6596473 and rs11950646), one of which (rs6596473) is associated with decreased plasma ascorbate levels.[16,17]
Vitamin D	GC	GC codes for the vitamin D binding protein which transports vitamin D throughout the body	rs2282679	rs2282679 within the GC gene is significantly associated with concentrations of GC protein with the minor allele associated with lower levels of vitamin D in plasma.[18]
Vitamin E	ABCA1	The *ABCA1* gene belongs to a group of genes called the ATP-binding cassette family, which provides instructions for making proteins that transport molecules across cell membranes	rs11789603 rs2274873	rs11789603 and rs2274873 polymorphisms predict the plasma chylomicron α-tocopherol level of a subject in response to an α-tocopherol-rich meal.[19,20]

We now live in an era when it is becoming increasingly affordable to have one's genome determined, providing information on a wide spectrum of critical mutations (e.g., single-nucleotide mutation, insertions-deletions, block substitutions, inversions or copy number variants) in critical genes involved in nutrient metabolism and /or pathways requiring micronutrients as cofactors.[1] Gender itself is a critical genetic variation that affects micronutrient requirements for health maintenance.[2] The key challenge is to determine whether it is possible to utilize this information meaningfully to provide reliable and predictable personalized dietary recommendations for specific health outcomes.

An important emerging aspect of nutrient-gene interaction studies with the potential for both intra- and trans-generational effects is epigenetics.[3] Epigenetics refers to the processes that regulate how and when certain genes are turned on and off, while epigenomics pertains to analysis of epigenetic changes in

a cell or entire organism. Epigenetic processes have a strong influence on normal growth and development, and this process is deregulated in diseases such as cancer. Diet on its own, or by interaction with other environmental factors, can cause epigenetic changes that may turn certain genes on or off. As a result, epigenetic silencing of genes that would normally protect against a disease could make people more susceptible to developing that disease later in life. The epigenome which may be to a limited extent heritable and modifiable by diet is the pattern of global and gene-specific DNA methylation, histone modifications and chromatin-associated proteins which control expression of housekeeping genes and suppress the expression of parasitic DNA such as transposons (jumping genes).[4]

Nutrient-gene interactions

About 70% of enzymes require minerals or vitamins as cofactors for their function or, for example in the case of zinc finger proteins, the mineral forms an integral part of its structure.[5] Therefore, even in the absence of loss of function gene mutations, deficiency in the cofactor will cause a transport protein or enzyme to malfunction. The knock-on effects of such deficiency may spread to affect other genes. For example, zinc is required for the function of the DNA repair protein OGG1 which repairs oxidized guanine in DNA, but its malfunction will result in accumulation of 8-oxoguanine, which leads to point mutations or down-regulation of gene expression if CpG islands are affected.[6,7] The latter was shown to be an important cause of changes in gene

FIGURE 1: DNA damage biomarkers that have been successfully used to investigate the effect of nutritional deficiency or excess on genome integrity [22]

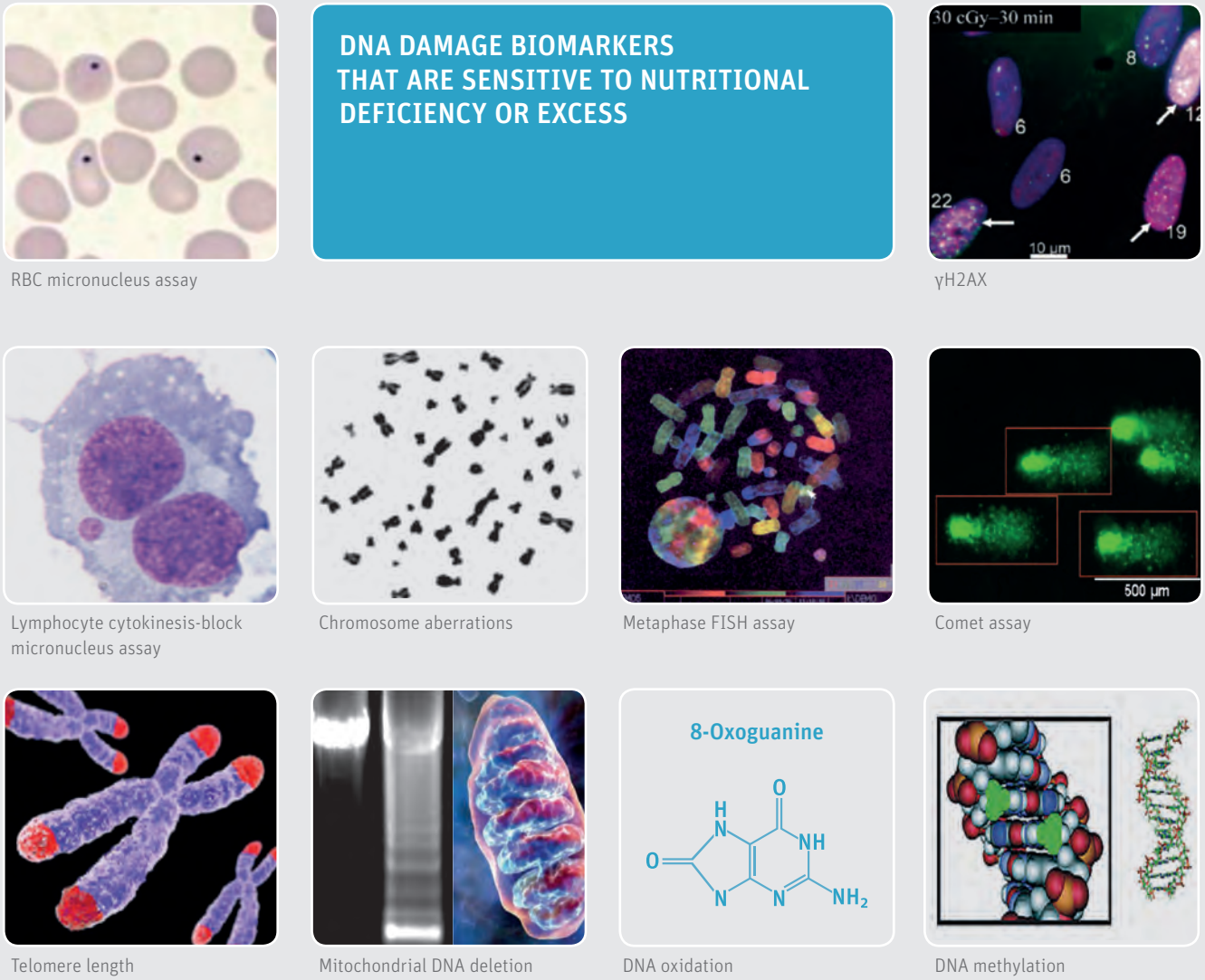
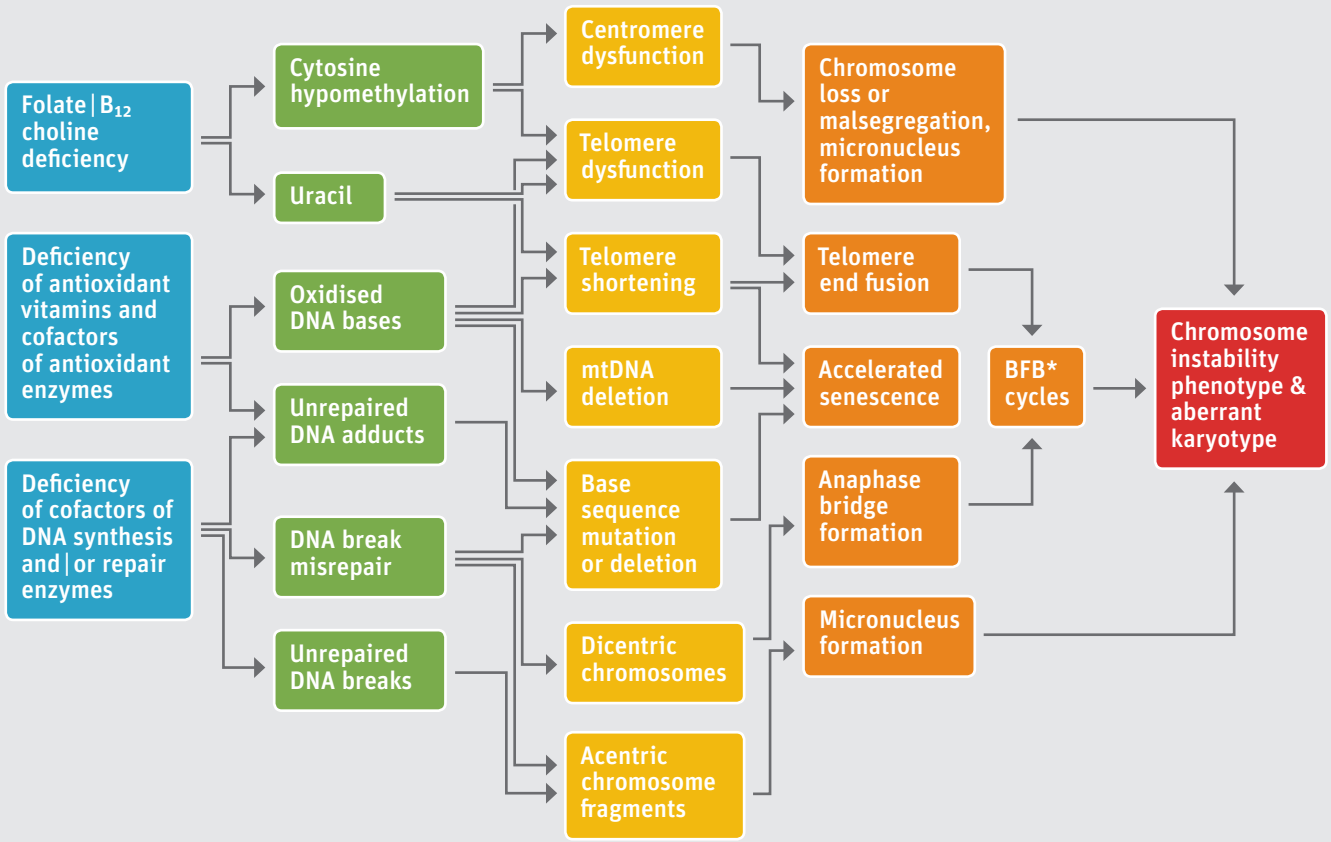


FIGURE 2: Possible mechanisms by which micronutrient deficiencies could cause damage to the genome [22]



***BFB** = breakage-fusion-bridge cycles.

expression with age in the human brain.[8] Another complex case is that of one-carbon metabolism in which folate is converted to various forms to play its role as a methyl donor in pivotal reactions such as the synthesis of thymidine from uridine required for DNA synthesis or repair and the conversion of homocysteine to methionine, which ultimately drives cell proliferation and maintenance of DNA methylation and gene regulation after its conversion to the methyl donor S-adenosylmethionine.[9]

Common polymorphisms affect nutritional requirements

For each micronutrient, there exist common polymorphisms in key genes that limit its transport, its metabolism to an active form, and the ability of tissues to store and/or mobilize it when needed. Some of these common polymorphisms and their effects are listed in **Table 1**. One that has been most investigated in thousands of epidemiological and intervention studies is the C677T polymorphism in the methylene-tetrahydrofolate reductase (MTHFR) gene, which requires riboflavin (vitamin B_2) as cofactor and is essential to convert 5,10-methylene-tetrahydrofolate (5,10-MTHF) to 5-methyl-tetrahydrofolate (5-MTHF), the form of folate that is transported in the blood and is required to convert homocysteine to methionine.[10] Interactive effects between the C677T polymorphism, 5,10-MTHF and vitamin B_2 ultimately determine the bioavailability of folate for DNA or methionine synthesis, affecting chromosomal stability, reproductive outcomes and risk for degenerative diseases of old age.[9–11] Other examples of common polymorphisms in genes that affect bioavailablity and bioefficacy of vitamin A, folate, vitamins B_{12}, C, D and E are given in **Table 1**.

DNA damage prevention and dietary reference values

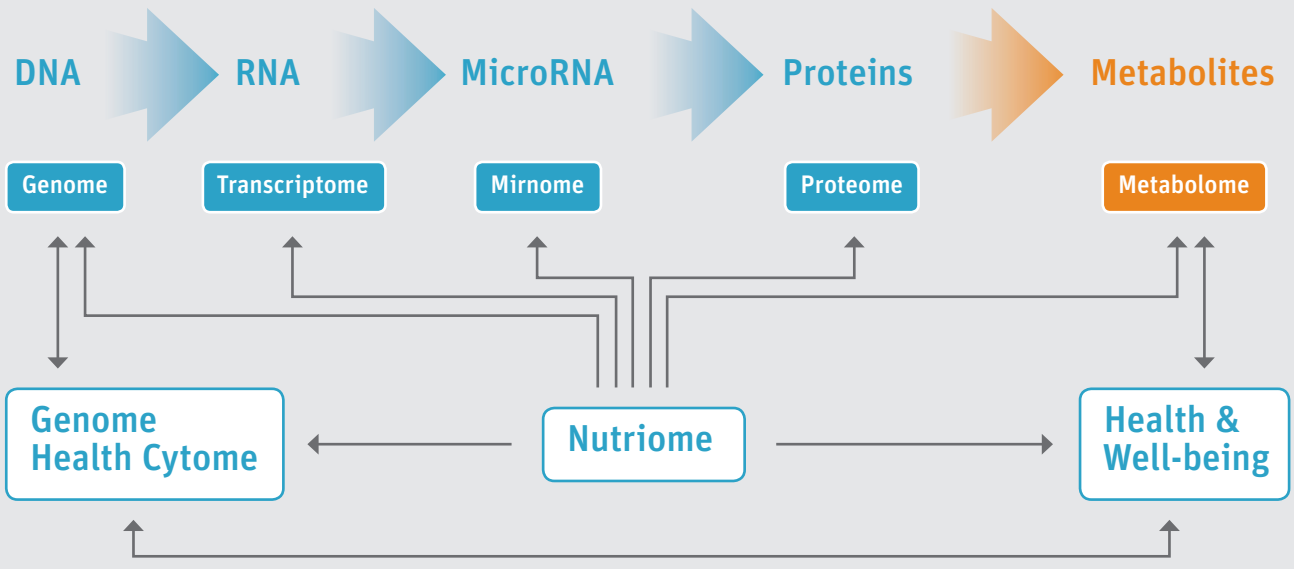
Damage to the genome is the most fundamental pathology which can be measured at the molecular, chromosomal or cytological level (**Figure 1**).[21] The capacity of cells to replicate their genetic material accurately is critical for all stages of life, including fertility, conception, development during the first 1000 days of life, growth during childhood, intellectual development, immune function and tissue regeneration during adulthood, and

prevention of cancer and accelerated ageing. Several micronutrients play an important role in protecting against DNA damage events, induced by endogenous and exogenous factors, by acting as cofactors or substrates for enzymes that detoxify genotoxins as well as enzymes involved in DNA repair, methylation, and synthesis (**Figure 2**).[22] In addition, it is evident that either micronutrient deficiency or micronutrient excess can modify genome stability and that these effects may also depend on nutrient-nutrient and nutrient-gene interaction, which is affected by genotype. For example, excess riboflavin aggravates the level of DNA damage when folate is deficient and such effects are modulated by the common C677T polymorphism in the MTHFR gene.[23,24] These observations have led to the emerging science of genome health nutrigenomics, which is based on the principle that DNA damage is a fundamental cause of disease that can be diagnosed and nutritionally prevented on an individual, genetic subgroup, or population basis. Given the fundamental importance of genome integrity maintenance, it was proposed that dietary reference values should also be defined by the impact of nutritional deficiency or excess on genome integrity at the chromosomal, telomere, mitochondrial and DNA base sequence level.[21,22] Chromosomal aberrations can be measured in lymphocytes, and in fact this was the method used to show for the first time that protein calorie malnutrition increases chromosomal damage 5.5-fold in children.[25] Another method that is commonly used is measurement of micronuclei which arise from chromosome fragmentation or chromosome malsegregation during mitosis, and this method was shown to be sensitive to a wide range of deficiencies (e.g., folate, vitamin B_{12}, zinc deficiency) and also increased in obesity.[26,27,28] DNA strand breaks measured by comet or γH2AX assays and oxidation of guanine are also sensitive tools to assess genome damage effects of malnutrition.[29,30,31] More and more studies are also measuring effects on telomere length showing associations with nutritional deficiencies such as those of zinc, folate, vitamin D and omega-3 fatty acids.[32–35] Of these biomarkers, only telomere and micronucleus assays have been adequately validated, at this point in time, with respect to associations with nutritional status (both cross-sectionally and by controlled intervention) and with developmental and degenerative diseases (both via case-control and prospective cohort studies).[22]

Other "omic" biomarkers of nutritional status

Apart from DNA damage biomarkers, it is possible to utilize transcriptomic, proteomic and metabolic biomarkers to assess the impact of nutritional deficiency, excess or intervention. For example, a network of expressed genes associated with environmental exposures, nutritional intake and ageing can be successfully used to identify biomarkers that relate to the interactive effects of nutrition with life-stage and other environmental factors and to test the plausibility of a connection between nutritional factors and observed genomic changes.[36,37,38] For instance, nutritional deficiencies that increase oxidative stress might be linked with changes in expression of genes susceptible to guanine oxi-

FIGURE 3: The various "omic" biomarkers that are currently used to investigate the impact of nutrients and diets on human health at the cellular and organism level. This figure is an adaptation of that reported by DeFlora and Izzotti.[44,45]



dation in their promoter sequences.[7,8] Furthermore, it is becoming increasingly evident that cellular and metabolic responses to environmental changes including nutritional deficiency or excess are also mediated by micro RNA (miRNA) and that the miRNA "ome" may provide specific fingerprints of nutrient exposure. For example, it has been shown that the miRNAs miR-222, miR-10a and miR-let7b are up-regulated when folate, retinoic acid and vitamin D are deficient, respectively.[39] In a similar vein, plasma proteome analysis is yielding protein markers which are associated with specific deficiencies. For instance, the plasma proteins, RBP4, VDBP, RGS8, Cp and SEPP1 are associated with deficiencies in retinol, vitamin D, α-tocopherol, copper and selenium respectively.[40,41] Together with established metabolic biomarkers of nutritional deficiencies, it has now become possible to identify a network of biomarkers across all of the "omes" that can better diagnose the specific deficiencies, their interactions and likely pathologies at the genome level.[42,43]

Conclusions

The science of nutrigenomics and nutrigenetics is still in its infancy but its potential to improve our understanding of how to diagnose and treat nutritional deficiency or imbalance is already evident. More effort is required to utilize this rich knowledge appropriately to **(1)** better inform, validate and test the design of dietary pattern and fortification recommendations and **(2)** properly measure and rectify poor nutrition in both developing and developed countries, taking into consideration the genetic background of communities and the food supplies that are available to them. The various "omic" biomarkers that are now available need to become more accessible for epidemiological/intervention studies and, furthermore, they should be standardized and validated to improve their translation into public health practice.

> "The science of nutrigenomics and nutrigenetics is still in its infancy but its potential is already evident"

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Proteomics and Metabolomics: The Final Frontier of Nutrition Research

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Introduction

Revolutionary new technologies allow us to penetrate scientific frontiers and open vast new territories for discovery. In astronomy, the Hubble Space Telescope has facilitated an unprecedented view outwards, beyond our galaxy. Wherever the telescope is directed, scientists are making exciting new observations of the deep universe. Another revolution is taking place in two fields of "omics" research: proteomics and metabolomics. In contrast, this view is directed inwards, towards the complexity of biological processes in living organisms. Proteomics is the study of the structure and function of proteins expressed by an organism. Metabolomics is the study of small, low molecular weight metabolites and their cellular processes. The study of individual proteins and metabolites has a long tradition, but a collective approach to their study developed only recently. The terms "proteome" and "metabolome" were first mentioned in the published scientific literature in 1996[1] and 1998,[2] respectively. The German botanist Hans Winkler (1877–1945) coined the related term "genome" more than seven decades earlier.[3]

Proteomics and metabolomics in the post-genomic era

In 2003, the Human Genome Project – which had the goal of mapping all the genes of the human genome – was declared complete.[4] In the post-genomic era, two major challenges in the life sciences include the elucidation of all the proteins and metabolites in the human body. The proteome and metabolome have a level of complexity that far exceeds the genome. In humans, ~20,000 protein-coding genes give rise to ~100,000 proteins and an estimated one million different protein modified forms.[5,6] The many forms of proteins arise from mutations, RNA editing, RNA splicing, post-translational modifications, and protein degradation; the proteome does not strictly reflect the genome. Proteins function as enzymes, hormones, receptors, immune mediators, structure, transporters, and modulators of cell communication and signaling. The metabolome consists of amino acids, amines, peptides, sugars, oligonucleotides, ketones, aldehydes, lipids, steroids, vitamins, and other molecules. These metabolites reflect intrinsic chemical processes in cells as well as environmental exposures such as diet and gut microbial flora. The current Human Metabolome Database contains more than 40,000 entries[7] – a number that is expected to grow quickly in the future.

The goals of proteomics include the detection of the diversity of proteins, their quantity, their isoforms, and the localization and interactions of proteins. The goals of metabolomics include mapping the function of metabolic pathways, many of which remain partially or completely uncharacterized,[8] as well as detecting and measuring the diversity and dynamic changes of metabolites. This fundamental work should help lead to the discovery of new biological mechanisms, biomarkers, drug targets, and pathways of disease. Proteomics and metabolomics are vital steps in the progress of science towards translational research, clinical trials, and personalized medicine. The research fields of cancer, neurology, endocrinology, and cardiovascular disease have been in the vanguard in using proteomic and metabolomic approaches in scientific investigation. In contrast, the field of nutrition has been slow in applying these powerful techniques.

> "Proteomics and metabolomics are vital steps in the progress of science"

The technology to investigate the immense complexity of the proteome and metabolome has advanced rapidly within the last several years. Newer mass spectrometers have greater sensitivity, higher reproducibility, better comprehensiveness, and more rapid throughput, allowing the identification and quantification of thousands of proteins and metabolites in tissues and samples. Mass spectrometers are at the heart of the laboratory (**Textbox 1**). The Orbitrap mass analyzer was commercially available in 2005[9] and gave rise to subsequent generations of Orbitrap mass spectrometers.[10–12] The comprehensive analysis of proteins and lipids has been increased dramatically by sequential windowed data-independent acquisition of the total high resolution mass spectra (SWATH-MS) on triple time-of-flight mass spectrometers.[13,14] Multiple reaction monitoring (MRM; also known as selected reaction monitoring), a targeted mass spectrometry technique, can use triple quadrupole, or QTRAP™, mass spectrometers to measure sets of proteins.[15] MRM allows precise, antibody-free quantitation of proteins in a multiplexed fashion. Targeted metabolomic approaches can be conducted using QTRAP™.[16,17] Nuclear magnetic resonance spectroscopy can also be used to measure metabolites, with the advantage of minimal sample preparation but the major disadvantage of low sensitivity.[18]

Technological breakthroughs are accelerating the research

Currently it is possible to measure thousands of proteins in biological samples – something that was not feasible several years ago.[19] These advances are due not only to the new innovations in mass spectrometry, but also to improvements in sample preparation such as depletion of highly abundant proteins, thus allowing detection of low abundance proteins (the "deep proteome"),[20] more effective electrophoresis and chromatography protocols, and better tools for quantification (**Textbox 2**).[21–23] Protocols are also improving for detection of post-translation modifications (PTMs), such as phosphorylation, glycosylation, acetylation, ubiquitination and sumoylation. PTMs are important to study since they reflect the diversity of protein function. Many of the PTMs are difficult to study because they are labile to sample processing and mass spectrometry. For example, O-GlcNAcylation, an important PTM that rivals phosphorylation in abundance and distribution, has been especially challenging to detect and measure.[24] Many proteins have functions that are unknown or not well understood. By studying the proteins with which a particular protein interacts, it is possible to deduce biological functions and pathways.[25] Protocols have recently been developed for proteomic analysis of dried blood spots[26] and formalin-fixed, paraffin-embedded tissues.[27]

Textbox 1

What is a mass spectrometer?

A mass spectrometer is simply an instrument that weighs molecules. Mass spectrometry is a technique that separates charged molecular species based upon their mass-to-charge ratio (m/z). The instrument provides a mass spectrum, which gives:

(1) The number of components;
(2) m/z for each component;
(3) sequence information (tandem mass spectrometry); and
(4) abundance information.

Spectra are used to identify specific molecules and their relative amounts. There are many different kinds of mass spectrometers. Most laboratories involved in protein biomarker discovery studies or investigations of protein interactions have at least two mass spectrometers for liquid chromatography-tandem mass spectrometry (LC-MS/MS), an Orbitrap or TripleTOF for discovery work and a QTRAP™ for targeted quantitation of proteins.

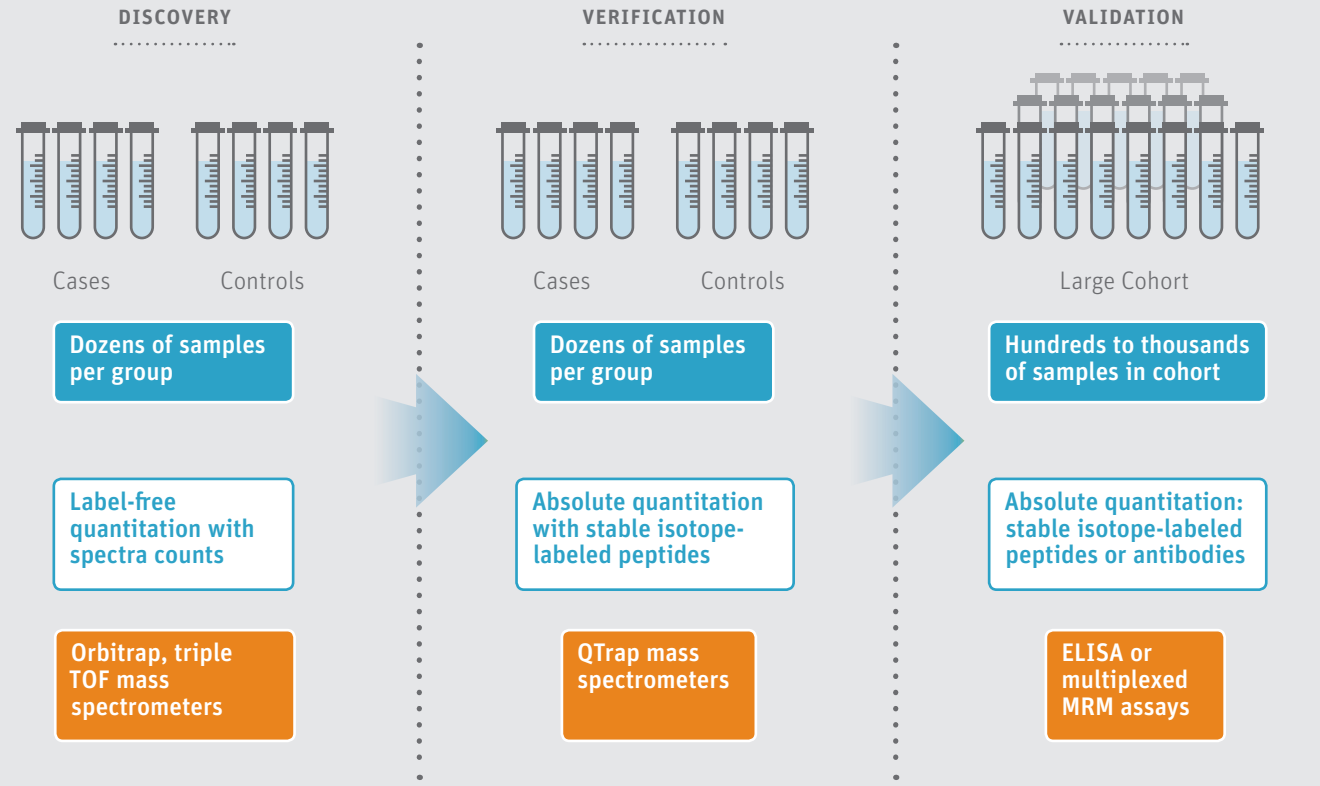
Textbox 2

Key messages

- The diversity of the proteome and metabolome are far greater than the genome, and probably hold the keys to understanding the biology of health and disease.
- Recent advances in sample preparation, instrumentation, and bioinformatics have revolutionized proteomics and metabolomics.
- It is now possible to measure thousands of proteins and hundreds of metabolites in biological samples – something that was not possible even several years ago.
- Proteomics and metabolomics are entering a large growth phase and offer great opportunities for young investigators.

Many recent metabolomic studies have used so-called "targeted" approaches in which a panel of well-characterized and validated metabolites is measured using liquid chromatography-mass spectrometry (LC-MS).[28–30] Given the complexity of various metabolites, there is no single analytical platform to

FIGURE 1: An example of a workflow using a proteomic approach to identify specific biomarkers and pathways in plasma samples



In the hypothesis-free discovery phase, a case-control design is used to identify dozens to hundreds of proteins that are higher or lower in concentrations between the two groups. The verification phase involves absolute quantitation of the candidate proteins between the two groups using stable isotope labeled standard peptides. The proteins that are verified require further validation in large cohort studies. ELISAs or multiple reaction monitoring assays (MRM) can be devised for measuring these specific proteins. Workflows may vary depending upon the clinical phenotype under investigation.

measure the complete metabolome. At present, about 200–1,000 metabolites can be measured using LC-MS in commercial labs or some academic labs, depending upon the type of sample.

Bioinformatics has played a vital role in the acceleration of proteomics and metabolomics. Raw MS data from proteomic analyses can be analyzed using open source search engines such as X!Tandem, OMSSA, or proprietary databases such as Mascot and Sequest. The software assigns sequence information for peptides based upon the spectra, and then protein identifications based upon the specific peptides. Authoritative and comprehensive protein databases include neXtProt[5] for human proteins and UniProt.[31] Annotated databases such as Gene Ontology (GO)[32] and pathway databases such as Kyoto Encyclopedia of Genes and Genomes (KEGG)[33] and Database for Annotation, Visualization and Integrated Discovery (DAVID)[34] are particularly useful. Online resources and databases of metabolites include Metabolomics Workbench, METLIN, and BiGG.[35]

> "Bioinformatics has played a vital role in the acceleration of proteomics and metabolomics"

Phases of investigation in biomarker discovery

Proteomics and metabolomics are used to discover new biological pathways and biomarkers that are associated with specific diseases or conditions. A typical workflow for the identification of novel protein biomarkers proceeds in two phases of investigation: a hypothesis-free discovery phase followed by verification and validation phases (**Figure 1**). The discovery phase may typically utilize a case-control study design with at least thirty subjects per group. The two groups are compared in order to determine which proteins or metabolites are differentially expressed between the two groups so as to identify potential candidate biomarkers. In the case of proteomics, the comparison of

FIGURE 2: Examples of mass spectrometers and instrumentation for proteomic and metabolomic studies, author's laboratory team

a. We use a 5600+ TripleTOF (AB Sciex) mass spectrometer for discovery phase proteomic and lipidomic studies. Dr Alexey Lyashkov operating the instrument.

b. For targeted proteomic and metabolic studies, we use a 5500 QTrap (AB Sciex) mass spectrometer. Dr Pingbo Zhang checking the instrument.

c. A laboratory automated robotic workstation allows efficient, accurate, and high throughput sample handling. Beckman Coulter Biomek NX^{P} robot.

protein concentrations is usually based upon label-free methods, such as spectral counts. Further verification is needed using precise gold standard quantitation measurements such as MRM using stable isotope-labeled peptide standards and LC-MS/MS on a QTRAP™. It is possible to measure several dozen different plasma proteins in a single multiplexed assay using MRM.[36,37]

For proteins, the validation phase involves applying MRM or devising more conventional assays, such as enzyme-linked immunosorbent assays (ELISA) for measurement of specific proteins, and then measuring the biomarkers across one or two large cohort studies. The case-control study design, with careful attention to selection of cases and controls[35,38] and sample size and power,[39] provides a rigorous strategy for discovering new biological pathways, biomarkers, and therapeutic targets. The choice of a well-defined clinical phenotype is critical in the study design of proteomic or metabolomic biomarker studies. For example, bone density assessed by dual-energy X-ray absorptiometry would be preferable to plasma 25-hydroxyvitamin D concentrations as a clinical outcome measure in older adults. Quality standards have been developed for reporting information from proteomic studies.[40,41] Since LC-MS assays for metabolites provide absolute quantitation, discovery/verification can be followed by validation in large cohort studies.

There was great enthusiasm and expectations a decade ago about the potential of proteomics and metabolomics to lead to the discovery of new circulating biomarkers. However, these fields did not deliver immediate returns in this earlier period because of existing limitations in study design, sample preparation, mass spectrometry instrumentation, and bioinformatics. Even the term "biomarker" became viewed in a slightly jaded light. Some notable successes are beginning to emerge, such as validated plasma protein biomarkers for hematopoietic stem cell transplantation,[42] and 2-aminoadipic acid as a predictor of type 2 diabetes.[43] It should be emphasized that proteomics and metabolomics are not just about biomarkers. These fields are providing fundamental knowledge of cellular processes, molecular interactions, and localization of biological pathways.

> "Proteomics and metabolomics are providing fundamental knowledge of cellular processes, molecular interactions, and localization of biological pathways"

Current challenges in proteomics and metabolomics

There are three practical challenges to using proteomic and metabolomic approaches in research.

First, there are a limited number of laboratories with the scientific expertise and instrumentation to conduct these studies. Mass spectrometry core facilities in some universities may be able to meet the needs of nutrition investigators. Some investi-

gators have built up their own labs for proteomic and metabolomic investigations (**Figure 2**).

Second, it is very expensive and time-consuming to prepare samples and conduct sample analyses using LC-MS/MS on mass spectrometers. In most laboratories, mass spectrometers are running 24 hours a day, operated by highly specialized experts who have many years of experience in dealing with these complicated instruments. Core labs generally charge high rates for instrument time, given the great cost for the acquisition and maintenance of mass spectrometers.

Third, proteomic and metabolomic investigations often yield a bewildering wealth of data that require expertise in bioinformatics and biostatistics. The immense complexity of data is often perceived as a "bottleneck" in proteomics and metabolomics research. There are a growing number of specialists with training in bioinformatics. Bioinformatic software, search engines, and methodologies are evolving rapidly. When the final results are placed in the hands of the investigator, the ultimate and most important challenge is in the interpretation of the proteins and metabolites that have been identified in the study. The investigator should learn to "expect the unexpected." The application of such powerful tools may uncover novel biological pathways and relationships – exciting discoveries that can move the field forward.

How does one get started in proteomics or metabolomics? Institutions such as the Cold Spring Harbor Laboratories, the Wellcome Trust, and the Seattle Proteome Center offer specialized courses in proteomics. The European Bioinformatics Institute and West Coast Metabolomics Center give courses in metabolomics. Many universities now have regular courses in proteomics and metabolomics. The main international forum for proteomics research is the Human Proteome Organization (HUPO), which was founded in 2001. The main goal of HUPO is to identify and characterize the diversity of human proteins.[44] HUPO has specific disease and organ-specific proteomic initiatives, such as brain,[45] liver,[46] and eye.[47] The Metabolomics Society, incorporated in 2004, promotes the application of metabolomics in the life sciences. Although proteomics and metabolomics are at currently at the frontier of nutrition research, the fields are on the ascendancy and should provide unprecedented opportunities for young investigators. Some nutrition research groups have already taken up the challenge.[48-50] As noted by the German scientist Georg Christoph Lichtenberg (1742–1799): "Where the frontier of science once was is now the center."

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The Promise of Mobile Health

Connecting people, compressing time and creating opportunities

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Key messages

- Over the past decade, a mobile phone "revolution" has occurred, connecting populations across the most remote and rural parts of the globe.
- The reality of ubiquitous connectivity, at relatively low cost, has spurred an associated explosion of innovations in public services optimization, from health care and nutrition to agriculture extension support.
- mHealth solutions, for example, target health system gaps to deliver incremental gains or, in some instances, completely overcome barriers hindering widespread population coverage of interventions of known efficacy.

The mobile revolution

In these final months leading to the 2015 Millennium Development Goal deadline, we find ourselves redoubling efforts to reach the UN targets set in September 2000. Over the past decade, these shared goals have galvanized the global community, across national boundaries and political agendas, to strive for certain universal targets – from dramatically reducing global poverty and improving equitable access to education to achieving substantial reductions in infant, child and maternal mortality.

As of March 2015, these ambitions are further challenged by a global population that exceeds 7.2 billion, putting further pressure on efforts to reduce inequities. These challenges start at the very beginning of life (providing a clean and safe birth, attended by competent care-providers) through childhood (ensuring timely vaccination against major causes of death) into adolescence (providing education and access to adequate nutrition that prepares young men and women for a productive future). Into adulthood, these encompass access to employment, appropriate financial remuneration, competent and affordable healthcare, access to quality nutrition, and protection from disease.

The "bottom billion"

With a denominator of over 7 billion, it is not difficult to rationalize why inequities in health, education or nutritional equity persist and why national or global institutions struggle to deliver on their promises. Populations, rural and urban, socially or economically disenfranchised, where incomes continue to stagnate at less than US$1.25 per day have been characterized as the "bottom billion" or the "ultra poor".

One basic component linking these challenges is that of measurement – making every life count, irrespective of where a child is born or a pregnant woman dies. If these overt events remain difficult to enumerate, then one can only imagine the hurdles in quantifying the global burden of hidden hunger, a term used to describe invisible micronutrient deficiencies which contribute, in large part, to the morbidity, mortality and loss of productivity in billions of human beings around the world.

Measurement and equitable enumeration has remained a lofty, unattainable goal, largely blamed on a lack of reliable data systems and expensive research methodologies – until now. By the end of 2010, the International Telecommunication Union (ITU) estimated that over 90% of the world's population lived within reach of a mobile phone network, with over 143 countries having access to high-speed Internet services. In 2013, this UN agency estimated that 6.8 billion mobile phone subscriptions reflected an 89% penetration in the developing world alone. By the end of 2014, this number has been revised to 95.5%, a 6% expansion in one year alone (see **Figure 1**).

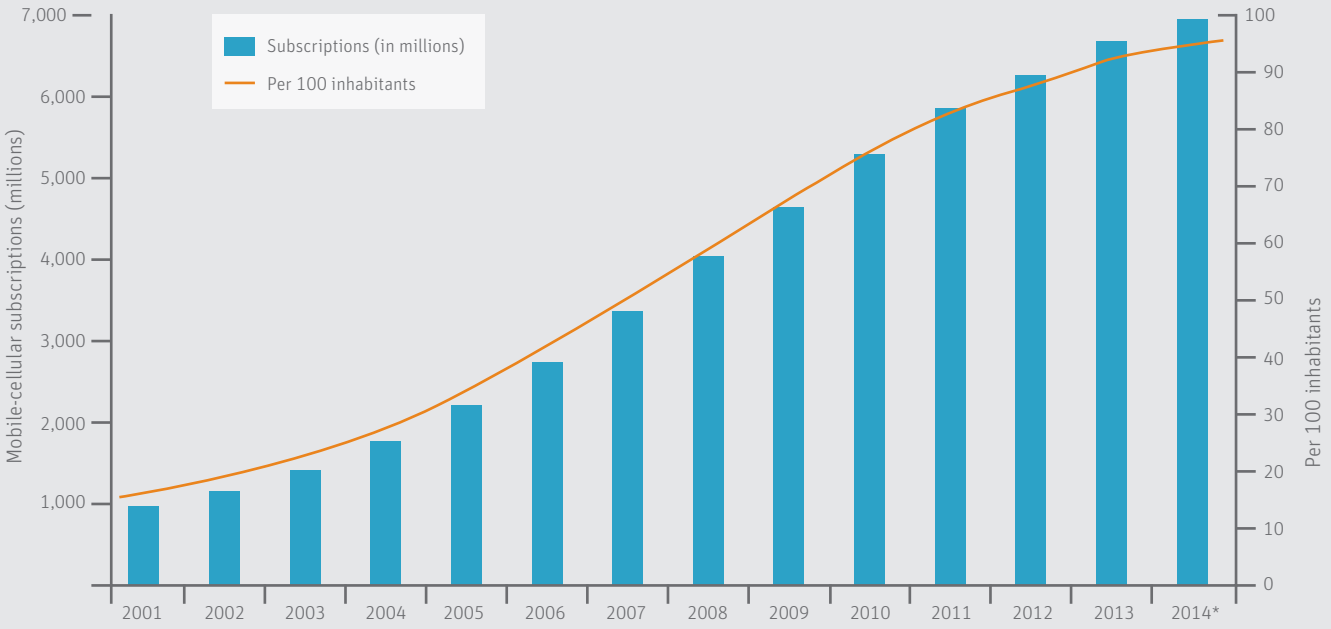
Husband and wife in rural Gaibandha, Bangladesh, hold up their own mobile phones, in a population which has reached over 100% national mobile connectivity coverage

"Measurement has remained a lofty, unattainable goal – until now"

A sea change in global development

This rapid, market-driven technological revolution has spawned a sea change in global development. Initially, organizations like the Grameen Bank in Bangladesh capitalized on mobile technology as an innovative small-enterprise solution for landless women to provide connectivity to their villages. These business models are rapidly becoming obsolete as mobile penetration increases and access to phones becomes ubiquitous. In the past decade, entirely new fields of research and implementation science have emerged, prefaced by an 'm', representing the novel 'mobile' facet of their approach: mHealth, mBanking, mAgriculture, mLearning, mNutrition, and so on.

FIGURE 1: Global mobile-cellular subscriptions total and per 100 inhabitants, 2001–2014



Note: *Estimate
Source: ITU World Telecommunication/ICT Indicators database, 2015, (www.itu.int/en/ITU-D/Statistics/Documents/facts/ICTFactsFigures2014-e.pdf, accessed April 2015).

Connecting people to information systems

Mobile technologies are also rejuvenating the domain of telemedicine and electronic health (eHealth), which were previously largely "tethered" systems, focused on facility-based record-keeping, supply chain monitoring and, sometimes, decision-support. Mobile technologies serve to untether these systems from their facilities. They widen the reach and versatility of the eHealth infrastructure to support frontline health workers, where and when they need access to patient information, while also allowing them to contribute to the clinical record from the field.

Access to information has, for many years, also been reserved to the upper echelons of society – the privilege of the wealthy and educated. As the cost of connectivity continues to plummet, we are witnessing in many of our research sites in low-income settings a transformation in the ease with which families can connect to necessary information, sometimes simply by a phone call, when they need it most. Farmers call neighboring markets to identify the best price before selling their crops, whereas parents may call a clinical provider to ask about whether they should seek care at a facility for a child's illness. In many countries, health and nutrition information services have been launched by governments and NGOs to provide periodic reminders by text message or recorded audio, especially during pregnancy and the postpartum period. The Mobile Alliance for Maternal Action, or MAMA, is one such global initiative that has reached over a million subscribers in Bangladesh, and has transitioned to being a government-led national system in South Africa.

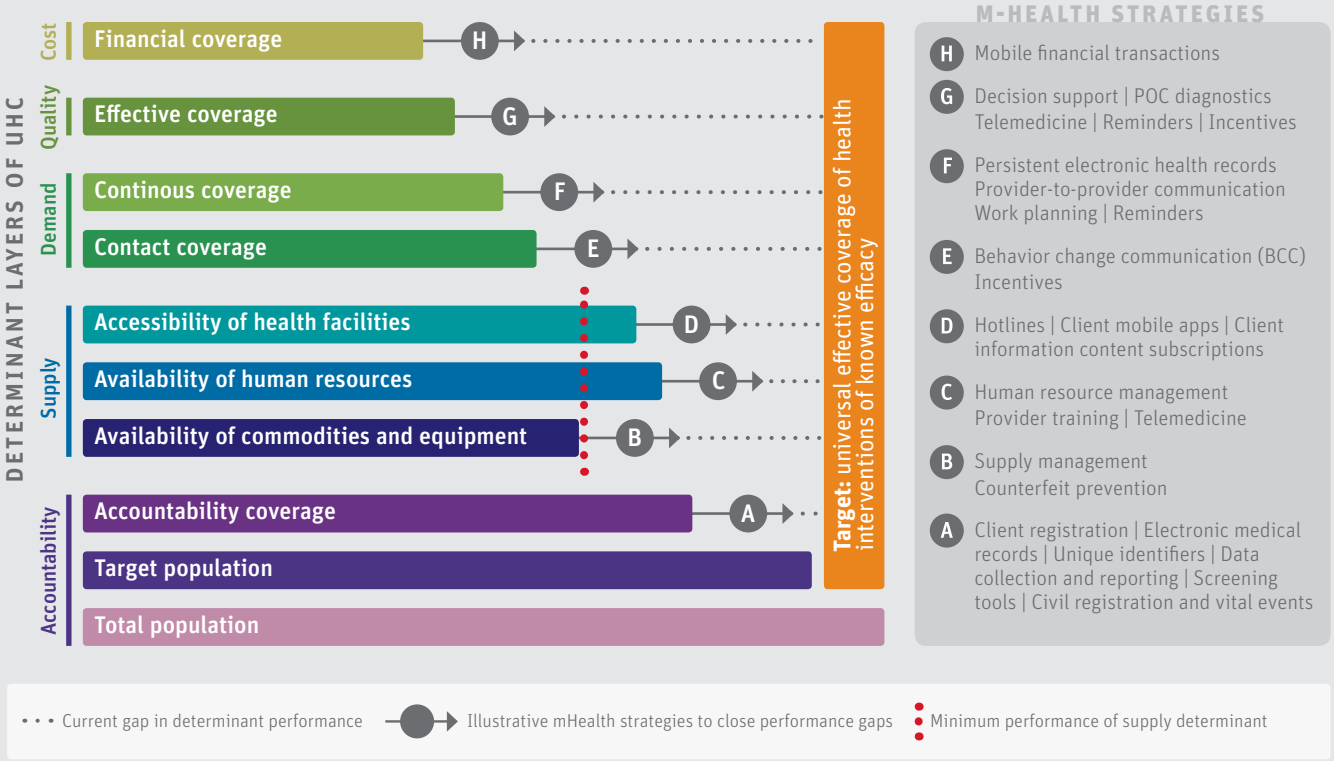
> "We are witnessing a transformation in the ease with which families can connect to necessary information when they need it most"

The endgame: Absorption of mHealth into mainstream systems

This is, to many of us, the most exciting endgame for mobile health, or mHealth – a pragmatic and, increasingly, tested series of solutions to help us bridge the Last Mile, to accelerate progress towards the Millennium Development Goals (MDGs) by 2015 and the post-MDG agenda of universal health coverage (UHC).

Over the past five years, hundreds of pilot projects across the globe have tested mHealth strategies to increase the capacity of community health workers and improve the quality of

FIGURE 2: Cascading model to prioritize and select integrated mHealth strategies for achieving UHC



This framework shows how eight key ingredients are required before a target population (a subset of the total population at the bottom of the cascade) can all receive the quality, timely and adequate care they need. These components of health sytem performance are grouped into categories of accountability, supply, demand, quality and cost. As illustrated, each layer not only builds on the performance of the layer below it but also falls short (dotted lines) of the optimal, desired level. A suite of mHealth strategies (labeled A through H) exists that could contribute to efforts in strengthening any given category. This framework helps facilitate dialogue between mHealth innovators and health system policy-makers to strategically plan how independently developed solutions can work an integrated approach to addressing health system challenges across numerous layers.

Credit: From Mehl G, Labrique A. Prioritizing integrated mHealth strategies for universal health coverage. Science 12 September 2014: 1284–1287 [DOI:10.1126/science.1258926]. Reprinted with permission from AAAS.

care received by the populations they serve. From this field of a "thousand flowers" of innovation, a healthy bouquet of solid enterprise solutions have emerged and are being used in countries at regional and national levels.

These systems enable tasks that were previously thought to be logistically impossible – enumeration of populations; registration of pregnancies, births and deaths; scheduling of antenatal, postpartum, and immunization visits with accountability for missed or delayed contacts; and providing at least a rudimentary health record. Importantly, these systems also provide a means to improve system efficiencies, from worker management to monitoring supply chains (including identifying counterfeit medications), as well as real-time monitoring and reporting of vital events and system performance. Most importantly, the most vital function of mobile phones, often lost in the whirlwind of innovation – voice communication – is a central, yet underrecognized, facet of the mHealth revolution, allowing workers to access peer and supervisor guidance when and where they need it. We have argued, in a recent Science article, that mobile strategies may serve as important incremental contributors towards strengthening health systems' post-MDG targets of achieving universal health coverage (Figure 2).[1]

> "The most vital function of mobile phones – voice communication – is a central facet of the mHealth revolution"

Connecting frontline workers to the systems they support

Frontline health workers who are often the first and only point of care for most of the "bottom billion" and for the world's rural

poor have been disconnected from the parent health systems they serve. Their isolation and often rudimentary training limited the capacity of this cadre to provide more than basic care, often disjointed from the broader health system within which they function. Mobile systems now exist to address gaps which, until recently, seemed intractable. Strategies such as BBC Media Action's "Mobile Academy" have provided continued skills development and training to frontline health workers, which integrate them as fully fledged members of their health systems. mHealth systems have empowered families with the information they need to maintain their health, and knowledge about the services they should expect from the government or health providers. Exciting strategies that bridge the worlds of mHealth and mFinance offer novel approaches to demand-side financing and performance-based incentive schemes.

In the footsteps of giants

In 2015, we find ourselves armed with a growing number of "enterprise grade" mHealth systems, with a rapidly expanding evidence-base for what mHealth works under various conditions. Mobile technologies continue to grow in sophistication and shrink in cost, providing fuel to several visions. We can imagine, in the not-too-distant future, a mobile phone being part of the core set of tools provided to every new community health worker, or a temporary phone, connected to essential downstream services and health information, being given to pregnant women as part of their antenatal services, just as a multivitamin supplement is made available. Through these visions, we build on the legacies established by public health giants John B Grant, whose work established the models for training China's "barefoot doctors" in the 1960s and 1970s, and Carl Taylor, founder of the academic discipline of International Health and proponent of the vision that empowered communities and frontline health workers can shape their own futures. Without mHealth, these leaders changed the delivery of care to disconnected populations across the globe. Imagine what can be accomplished under a new paradigm of universal connectedness.

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Getting a Grip on Complexity: Systems Nutrition

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The need to characterize the complexity of nutritional interactions

Malnutrition, either by lack or excess of nutritional components, poses challenges to global health. To improve nutrition-related health, there is a clear need to characterize the complexity of interactions between nutrients and the network of pathways, mechanisms, processes and organs that drive human health. Furthermore, it is evident that physical health is not a stand-alone aspect of nutrition-related health, but that mental and social health intimately interact with physical health. To move the global nutrition agenda forward, we advocate Systems Nutrition research using composite biomarkers of health and system intervention models covering the relevant physiological, mental and social domains.

Introduction

Over the past century, our understanding of the role of nutrition, including that of micronutrients, in relation to health has made tremendous progress. This was primarily achieved by a combination of epidemiological studies assessing micronutrient intakes and experiments *in vitro* and *in vivo* focusing on single targets or pathways affected by single micronutrients. As a result, significant progress has been made in meeting the need of numerous populations for vitamin A, zinc, iodine, and omega-3 fatty acids,[1] resulting in sufficiency in intake and status for these micronutrients and associated improvements in health status in large parts of the world.

Despite this progress, however, there is still a great need for further improvements in global health. More adequate nutrition could be a major contributor here. In order to achieve this, we must gain insights into the functional relationships between micronutrients and the complexity of biological processes that need to function optimally and in coherence so as to support the maintenance of health in the context of a specific environment (**Figure 1**). In the first instance, this needs to be done for physiological processes, but it also touches upon mental and socioeconomic aspects. Nutrition research should thus evolve into a systems view towards measurements of the micronutrient status and health of people, as well as a systems modeling approach to interventions, taking the cultural and social context into consideration.

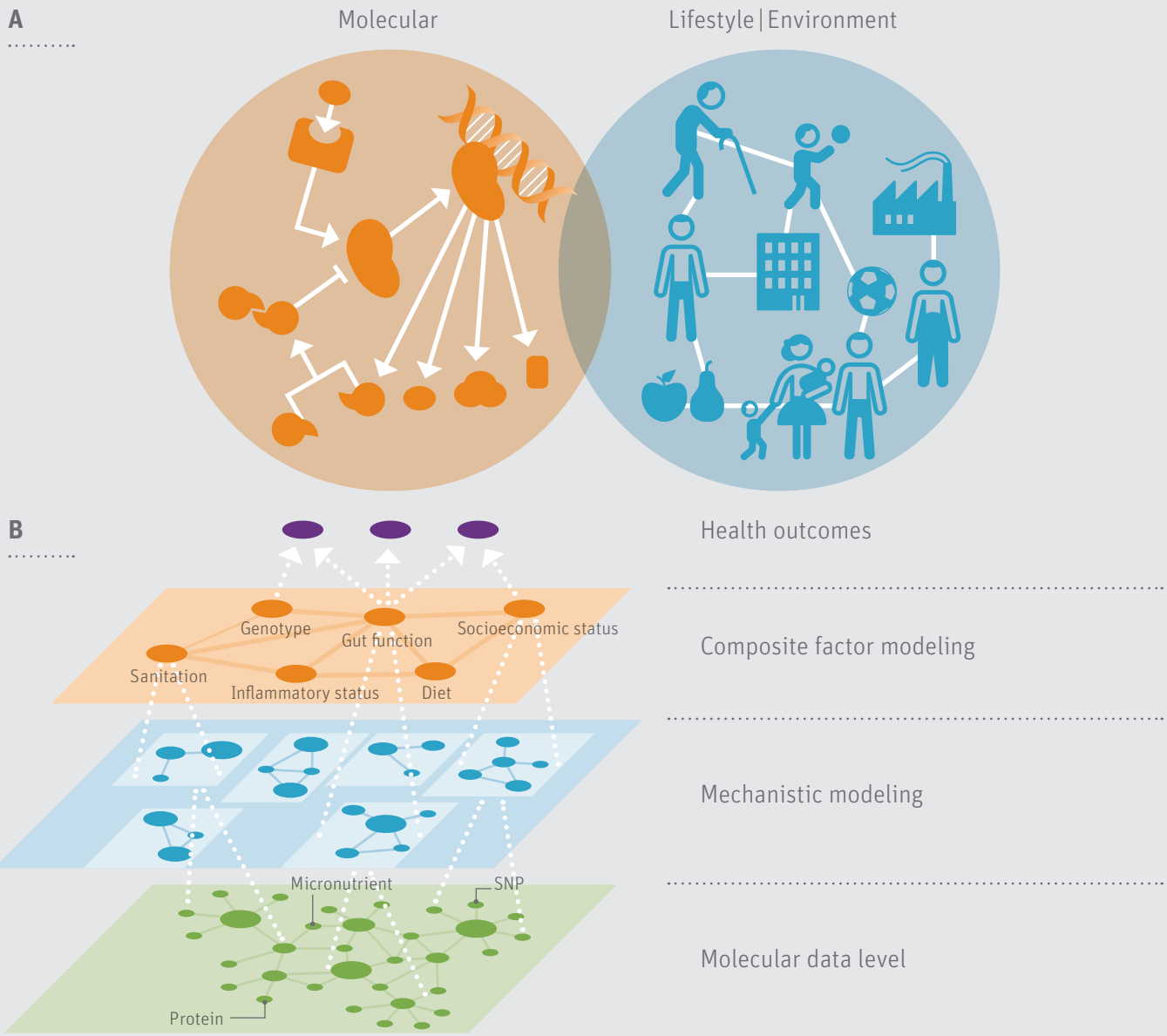
> "We need to gain insights into the functional relationships between micronutrients and the complexity of biological processes"

Micronutrient-supported metabolic health

Providing scientific evidence of the beneficial or detrimental relationships between dietary components and health has proven difficult. This is partly due to the subtleties of the effects of diet on health, but a more fundamental cause lies in the design of studies and the biomarkers used to determine health effects. Currently, substantiation is based on demonstrating that diet, or dietary ingredients, prevent(s) specific diseases by reducing disease risk biomarkers or surrogate endpoints derived from dietary intervention studies and epidemiological studies – in other words, it is based on the link of dietary components to the absence of disease.

There is a growing awareness that health is not merely the absence of disease but also involves adaptation to continuously changing environmental conditions. New definitions of health

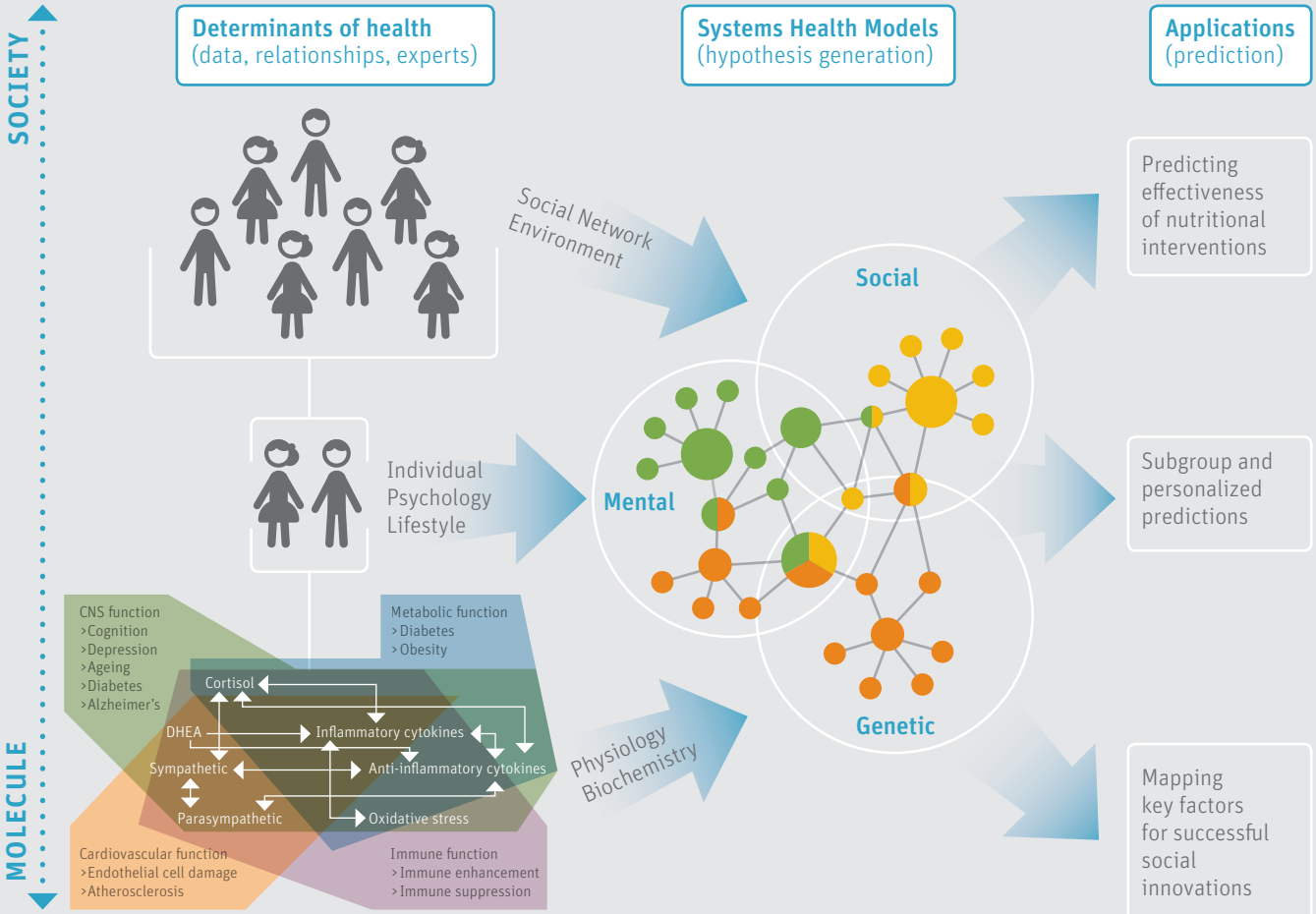
FIGURE 1: Health defined by gene-environment interaction. As the impact of nutrition on health and disease is defined by genetics and molecular pathways in close interaction with environmental factors, in-depth understanding and subsequent intervention developments necessitate an integrated view of both domains (**A**). This integrated view can subsequently be captured in multi-level models driving the identification of biomarkers (**B**).



emphasize the ability to adapt and self-manage in the face of physical, social and emotional challenges.[2] In the physiological domain, a healthy organism is capable of maintaining physiological homeostasis through changing circumstances, which is termed "allostasis".[3] In the context of metabolic health, we term this ability to adapt "phenotypic flexibility".[4]

Chronic stress may induce adaptation processes that go beyond the limits of normal phenotypic flexibility, leading to progressive inflexibility, which in turn contributes to the onset of disease. An excess or lack of food components in the diet introduces challenges to phenotypic flexibility. Micronutrients and bioactives play key roles in mechanisms underlying phenotypic flexibility, while excess of energy, high glucose and fructose intakes or certain trans-fatty acids cause a decline in phenotypic flexibility. Micronutrients are involved in many specific biochemical pathways with dedicated functions in the organism, which have mostly been studied in isolation. They act as co-factors in metabolic homeostasis (e.g., B vitamins) and in enzymes of importance for defense mechanisms (e.g., Se, Zn, Cu, Fe). Furthermore, they have antioxidant function (vitamins C and E), exert

FIGURE 2: Systems health models to get a grip on the complexity of nutrition. Comprehensive diagnoses of the problem at multiple levels of organization are integrated into systems health models. The models allow the simulation and optimization of systems nutrition intervention strategies.



an anti-inflammatory action (essential polyunsaturated fatty acids EPA, DHA), or are involved in hormonal regulation (iodine). These pathways and functions are interconnected in complex metabolic networks, driving overarching processes of metabolism, oxidation and inflammation that need to function optimally for maintaining optimal health. Together, this well-orchestrated machinery allows the organism to adapt to the continuously changing environment, of which food itself takes a major share, or to maintain phenotypic flexibility.

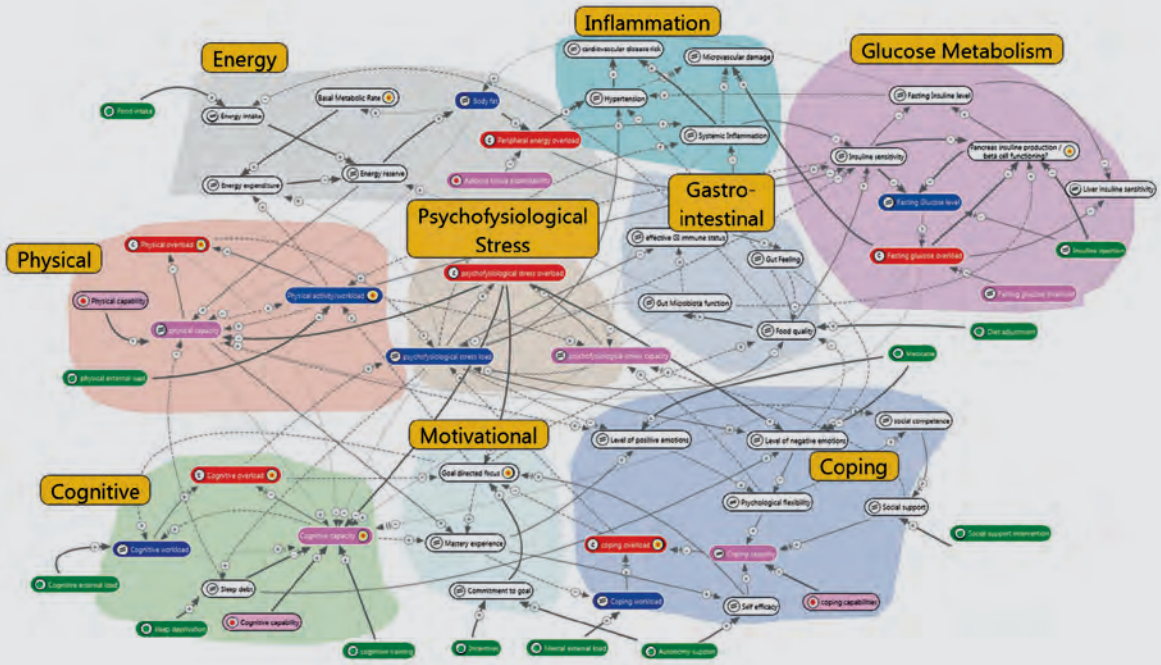
Biomarkers of health

As indicated above, many of the current insights into micronutrient-related health are based on epidemiological studies reporting a combination of estimated micronutrient intake, biomarkers of micronutrient status – which often do not reflect actual body pools of micronutrients – and biomarkers associated with disease or disease risk. The literature reviewed typically reports on group averages, often not taking into consideration aspects such as genetic background, gender, age, nutritional status including micronutrient status, food intake, physiological status, psychological stress and physical activity.

Human health is based on a complex network of interactions between pathways, mechanisms, processes and organs. Many of these processes have to function in a continuously changing environment (diet, infections, stress, temperature, exercise etc.), and thus strive to maintain internal homeostasis by adapting to these changes.[4] Due to a wide variety of reasons (genetic, epigenetic, exposure, diet, stress, exercise etc.) individuals differ in their "wiring" of phenotypic flexibility and therefore will react differently to acute and chronic stressors and develop a personal trajectory of metabolic-inflammatory health and disease.[4]

Acknowledging the importance of maintaining phenotypic flexibility as a key feature to optimal health calls for new research on the relationship between nutrition and health, in par-

FIGURE 3: Example of a systems model for intervention simulation. The model depicted, based on the MARVEL methodology,[8] describes key variables and their qualitative and semi-quantitative interactions in multiple domains relevant to metabolic health. This example was built based on actual data as well as expert knowledge input.



ticular using "biomarkers of health", related to the dynamics of the regulatory processes concerning the processes described above. These "biomarkers of health" would ideally comprise key molecules in all pathways, making up the overarching processes of relevance to phenotypic flexibility. As such, multi-biomarker panels will emerge that act as composite descriptors of physiological processes.

> "Acknowledging the importance of maintaining phenotypic flexibility calls for new research on the relationship between nutrition and health"

For example, in the case of vascular health, such a composite marker could be composed of flow-mediated dilation, a functional marker of endothelial function and blood pressure, resilience markers for endothelial damage after a metabolic challenge test such as sVCAM, sICAM, and E-selectin response, and total cholesterol.[5] Furthermore, these markers can be complemented with specific single nucleotide polymorphisms (SNPs) related to increased risk of cardio-metabolic disease development. By combining this into an integrated readout, a flexibility marker for vascular health can be obtained that has a broader value, both for substantiating the effects of food and nutrition on health and for healthcare.

Systems intervention models

In addition to improving the understanding of interactions of micronutrients with molecular pathways, the investigation of the interaction of environmental factors affecting phenotypic flexibility processes is a key step envisioned in bringing the understanding of global nutritional health to the next level. Environmental factors such as excess calories, poor sanitation, and mental stress have been known to affect physiological processes important for maintenance of phenotypic flexibility and, as such, health. This can be achieved by in-depth assessment of metadata for each nutritional study and the subsequent use of these data in combination with all available molecular and clinical data in complex data analysis approaches using state-of-the-art bioinformatics and multi-level modeling.[6]

The insights derived from these approaches will not only help to bring about scientific understanding of micronutrient-health relationships, but should also lead to better interventions aimed at improving global health. We have recently proposed

a program called Essential Nutrients for Optimal Underpinning of Growth and Health (ENOUGH) for the application of systems nutrition in global nutrition.[7]

In this respect, the key to moving the global nutrition agenda forward is to adopt the paradigm that physical health is not a stand-alone aspect of nutrition-related health, but that mental and social health intimately interact with physical health (**Figure 2**). Malnutrition is a complex issue, arising from the interplay between many individual, social, and political factors. This intrinsically implies that deriving effective intervention programs not only requires biological knowledge of the interaction of nutrients with pathways underlying health and disease, but also needs a sound understanding of the nutrition-health relationship in the context of the environmental drivers of the other aspects of health.

In addition to many non-linear interactions, there are multiple feedback loops between, and different time scales for, each of these drivers. This makes it hard to derive optimal interventions by simply looking at the data-driven models. Recent developments in qualitative/semi-quantitative modeling may open ways to generate intervention simulation models describing the nutrition-health interactions, including all relevant drivers and potential success determinants. Building such a model starts with the mapping of all relevant relationships, including strengths and speeds.

This mapping is based on the exploration of perspectives of all relevant stakeholders to identify all important factors. As stakeholders are building towards a shared understanding, this process, called group model building, will facilitate future discussions on implementation of interventions. Subsequently, this map is turned into a model with the presence of reinforcing loops and balancing loops. Reinforcing loops indicate processes that can get out of control quickly, while balancing loops indicate processes which are stable under certain conditions (**Figure 3**). This reveals which factors cause large changes and might be important to measure, control and possibly intervene in.

> "Recent developments in qualitative | semi-quantitative modeling may open ways to generating nutrition-health interaction models that allow simulation of intervention effects"

This model will allow the stakeholders to simulate the effect of multiple combinations of interventions on a set of defined goals. The simulated intervention effects depend on all the relationships, with their specific strengths and speeds, which are present in the model. Although the output of these simulations is understandably hypothetical, it may be a starting-point for selecting the high-potential interventions in a given setting, as well as identification of key aspects to address so as to allow for an optimal and sustainable intervention result.[8]

Concluding remarks

Without doubt, the reductionist approach towards understanding the mechanisms and health effects of individual micronutrients has greatly impacted global nutrition-related health. The current state of data generation and data analytical technologies enables the generation of insights into the complexity of interactions between nutrients and physiology. This will lead to identification of biomarkers of health that will allow harmonization of Systems Nutrition studies that will feed into generically applicable systems interventions models. We strongly believe that getting a grip on complexity is the next essential step towards a healthier world.

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A Food Systems Approach for Food and Nutrition Security

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Too often, the global discourse on food security focuses on how we will grow enough food to feed a population of 9 billion people by 2050. This neglects to acknowledge that broader food and nutrition security requires more than just producing enough calories. It concerns how we can ensure access for each individual to a quality and safe diet with adequate macro- and micronutrients. It also neglects the fact that we already face a major problem today, with billions of people suffering from malnutrition in various forms.

At the World Food System Center at ETH Zurich, we believe that this discourse, and the design of appropriate solutions to ensure food and nutrition security both now and in the future, could benefit from a broader adoption of a food systems approach.

How do we understand a food system?

We conceptualize a food system as comprising the various activities and actors in food value chains involved in transforming inputs into outcomes, which for a sustainable food system should include food and nutrition security, environmental quality, and human well-being.[1,2,3] A food system includes, is shaped by, and interacts with, a variety of boundary conditions, namely the environmental, social, political and economic conditions and realities which determine how it can function at a particular place of interest (see **Figure 1**). These boundary conditions are not static; rather they interact with trends and change drivers across national and geographic borders. For example, what types of crops can be grown in a particular area and their nutritional quality is determined by the climatic conditions, atmospheric composition, soil quality and resource availability, which can all be potentially impacted over time by climate change.[4]

What does this mean for decision making?

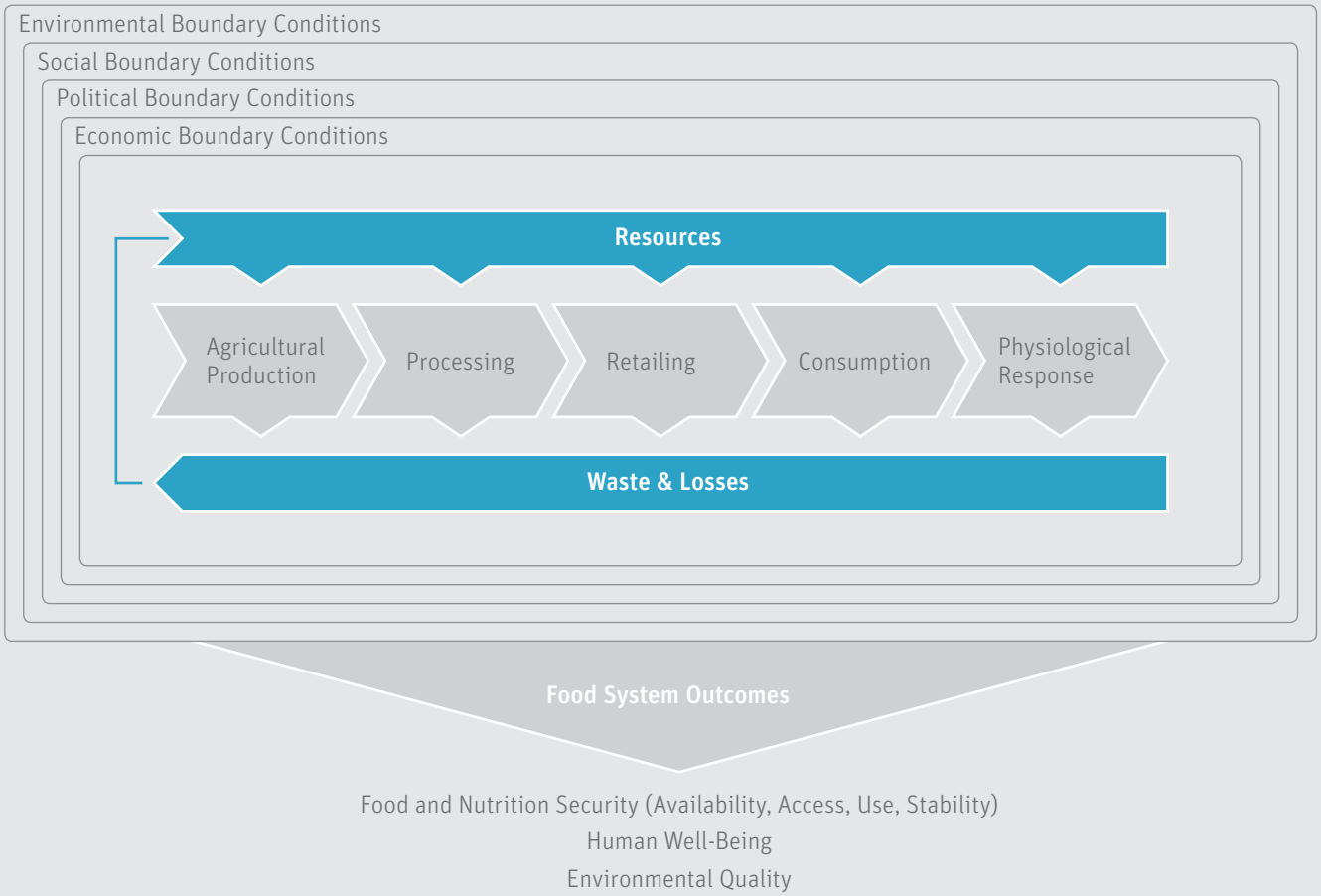
The food systems concept helps to highlight the relationships, interactions and dependencies that come into play whenever we try to address food and nutrition security.[3] It allows us to appreciate that food systems are complex adaptive systems, meaning that the whole system has properties greater than the sum of its parts, that there are high levels of connectedness and interaction across scales and levels and with diverse agents, and that outcomes may be reached by many possible pathways which are influenced by many factors.[3,5] This complexity makes policy and intervention design highly challenging, as the interconnectedness and dynamics can easily lead to unanticipated outcomes and unintended consequences.

All too often, we see examples of unintended consequences that result from interventions that have been designed without taking the broader system into account. This can also happen due to interactions between different systems – for example, energy and food systems. A case in point is the United States ethanol policy, which resulted in an increased demand for corn as a feedstock for biofuel production. This contributed to increased prices for corn for human food and livestock feed, which, combined with other factors, impacted food security in other countries.[6]

> "All too often, we see examples of unintended consequences that result from interventions designed without taking the broader system into account"

Aside from unintended consequences, complex system interactions may also result in interventions not fully achieving the intended outcome. For example, modeling the scale-up of a package of ten nutrition-specific interventions to 90 percent coverage in high-burden countries revealed that, collectively, these interventions could reduce the burden of stunting by only 20 percent.[7] Although significant, this also highlights the fact that for broader impact there is a need for combined nutrition-

FIGURE 1: Key Elements of a Food Systems Concept[1]



specific and nutrition-sensitive interventions that are designed from a systems perspective to holistically address food and nutrition security and to build long-term health and resilience.[8] Systems approaches can help us identify critical leverage points and design interventions across sectors in a way that identifies underlying causes and builds on synergies. This can mean that small interventions can build on tipping points to have bigger contributions to overall food system outcomes.[5]

How do we understand a food systems approach?

A food systems approach relates to a more holistic way of thinking and of working. Often it begins with taking a step back to look beyond a specific focus area so as to understand the broader system and goals. An example of this can be found in initiatives that support actors from the agriculture, health, nutrition and development sectors to come together and explore the role of biodiversity in food systems to support resilient production systems, livelihoods, dietary diversity and nutritional outcomes.[9]

Such approaches require working in inter- and trans-disciplinary ways, which calls for individuals and institutions to build new networks of partners and to design new ways of working together and communicating with one another. This often demands additional management and coordination activities, which should be factored into funding programs from donor and government agencies. All of this necessitates the streamlining of terminology and the building of a shared understanding of the benefits and limitations of different methodological approaches.

A systems approach often begins with multi-stakeholder problem-framing and problem-mapping exercises which aim to use collective knowledge to identify system elements, interactions and leverage points, and to start to analyze trade-offs. New quantitative and qualitative tools that build on these conceptual models are needed for further analysis. A number of systems modeling techniques that have traditionally been applied in other fields are now contributing to food systems analysis, such as agent-based modeling, system dynamics modeling, and companion modeling (ComMod) approaches.[10] Further work is needed to identify and develop new tools and adapt those already available to food systems contexts.

In order for the above to be successful, there is a need for new sets of co-located data that allow cross-sectoral design and analysis of interventions.[9] This means that further efforts are needed to ensure that measurements of human health and well-being are gathered in the same locations and at the same scales as other data related to agriculture, environment and markets.

How do we try to implement this in our work at the World Food System Center?

The Swiss Federal Institute of Technology in Zurich (ETH Zurich) recently made a strategic decision to support such approaches at an institutional level through the establishment of the World Food System Center (WFSC). As a research university, the core contribution of ETH Zurich to addressing food and nutrition security is through the generation of new knowledge and the training of the next generation of leaders and decision-makers. At the WFSC, we focus on trying to leverage this through supporting systems approaches that bring together researchers and external partners to work together in inter- and trans-disciplinary settings. Internally, the Center coordinates a network of 37 research chairs from seven different departments of the university and provides management support, funding and platforms for these network members to engage in research, education and outreach activities that address food system challenges. Aside from connecting these members internally, we link individuals, groups and projects with external partners from a variety of sectors to engage in the research process.

To support the integration of systems approaches into research for food and nutrition security, the Center is now establishing flagship research projects. These aim to be larger scale collaborations that bring together experts from multiple disciplines and sectors and take a systems approach. The Center works with the researchers to coordinate the process, help build up new networks, connect and involve stakeholders from different sectors, and integrate relevant methods and tools from both the social and the natural sciences. The first project being established focuses on assessing and designing resilience for food systems. The ultimate aim of this project is to provide a practical framework, guideline and toolkit that can be used by a variety of food system stakeholders to identify leverage points and design interventions that can improve system resilience in order to *"provide sufficient, appropriate and accessible food to all in the face of various and unforeseen disturbances."*[11]

Systems approaches require working across disciplines, sectors and scales, which demands new networks of collaborators, methods and tools. This year, the WFSC will host a conference that will bring together a group of thought leaders from academia, industry, international organizations, government agencies and the not-for-profit sector to share lessons learnt in addressing food and nutrition security. The conference will include a focus on resilience and a workshop that harnesses the collective expertise of the diverse group to develop indicators for the operationalization of a resilience framework for food systems. The intention is to build this event into a regular series that creates a global forum to support systems approaches for food and nutrition security through a network of collaborators who can share methods, tools, experiences and lessons learnt.

"Systems approaches require working across disciplines, sectors and scales, which demands new networks of collaborators, methods and tools"

Looking to the future, it is critical that the next generation of leaders and decision-makers are equipped with the knowledge, tools, skills and networks to understand and manage complexity to improve food system outcomes. At the WFSC we support this through an annual training program open to students, junior researchers and young professionals from all disciplines, cultures and countries. The two-week program, last year hosted in India and Switzerland, follows the structure of the food system and includes lectures, workshops, group work, field trips, role plays, design approaches and hands-on field work. Through exchange with experts and peer-to-peer learning, the participants gain new knowledge and skills and explore their role in working with and influencing complex food systems. This experience helps prepare them to connect their work to bigger issues and influencing factors, and builds their competence to collaborate across disciplines, sectors and scales.

Delivering food and nutrition security over the long term

Building resilient food systems that deliver food and nutrition security over the long term is one of the defining challenges of our time. Only through systems approaches, building new partnerships and collaborating across boundaries will we be able handle multifactorial problems and design interventions that ensure positive long-term impacts. We hope that our work here at ETH Zurich, together with our partners, can play a role in contributing to these integrated approaches.

"Building resilient food systems is one of the defining challenges of our time"

Food systems require a multisectoral approach

A food system comprises the various activities and actors in food value chains involved in transforming inputs into outcomes, which for a sustainable food system should include food and nutrition security, environmental quality, and human well-being.[1,2,3]

There is typically no single solution or disciplinary approach that is appropriate for all levels and contexts. For this reason, a systems approach that brings together experts from different academic fields and representatives from different sectors to work together collaboratively is critical for designing appropriate interventions that positively support food system outcomes. This means moving beyond a focus on one sector – for instance, only agriculture or only nutrition – to consider together the interactions with other sectors such as health, food, environment, energy, and development. A food systems approach uses inter- and trans-disciplinary methods that consider activities, outcomes, interactions, and feedbacks and attempt to engage all relevant stakeholders. This requires new tools, new ways of thinking and new ways of working together.

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Pune Experience

Influence of early life environment on risk of non-nommunicable diseases (NCDs) in Indians

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Background

India is one of the capitals of the world for diabetes and coronary artery disease.[1] At the KEM Hospital Diabetes Unit in Pune, India, we have been actively involved in studying the susceptibility of Indians to these disorders. Our early research described the characteristics of Indian type 2 diabetic patients: younger age and lower BMI but higher waist-hip ratio and higher insulin resistance compared with European patients.[2,3,4] This was the beginning of the 'thin-fat' Indian concept which provided an explanation for higher susceptibility of Indians to diabetes compared to Europeans despite a lower BMI.[5]

Over the past 25 years, we have progressed to define life-course evolution of the Indian phenotype through a number of prospective studies and tested the contribution of genetics, epigenetics, nutrition and other environmental factors to this phenotype (**Figure 1**).

Birth weight and rise of non-communicable diseases (NCDs)

In our earlier studies, we studied characteristics of malnutrition-related diabetes mellitus (MRDM) in Indians. David Barker in 1991 persuaded us to test his low birth weight hypothesis in India. After all, India is the world's capital of low birth weight (LBW), contributing 30% to the world's LBW babies every year. Studies in the UK showed an inverse association between birth weight and later risk of NCDs, notably diabetes and cardiovascular disease.[6]

Our first "developmental origin of health and disease (DOHaD)" study (Pune Children's Study) confirmed that low birth weight children were more insulin-resistant at four years of age.[7] At eight years, we found that children born with low birth weight who had become heavier during childhood had the highest level of cardiovascular disease (CVD) risk factors[8] (**Figures 2 and 3**). These findings highlighted that an imbalance between intrauterine and childhood nutrition could be an important contributor to the risk of NCDs.

Maternal nutrition and fetal growth

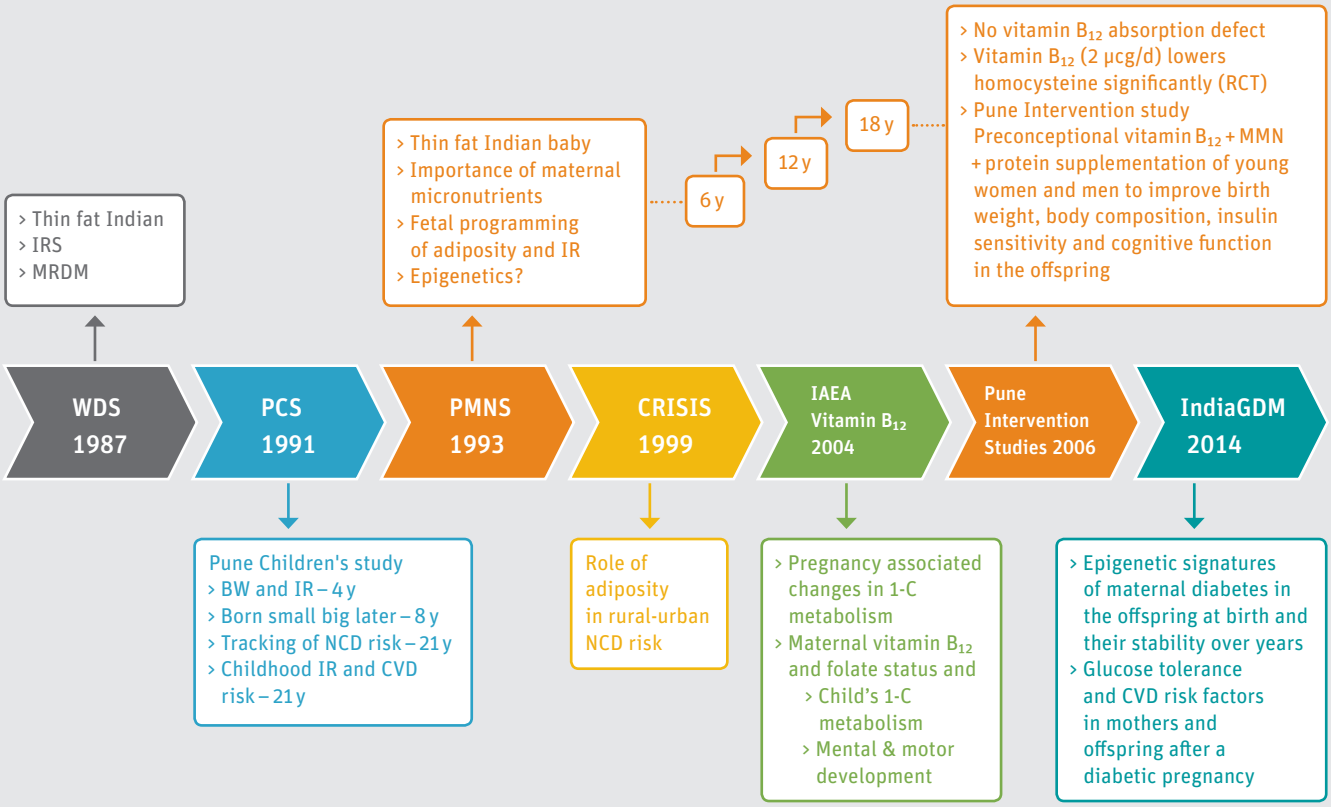
Having established a role for poor fetal growth in diabetes and CVD susceptibility, we investigated the factors contributing to poor intrauterine growth of Indian babies (PMNS, 1993).[9] In more than 800 pregnancies in 6 villages near Pune, we studied mother's nutrition, physical activity, metabolism and fetal growth by ultra-sonography. Babies were measured in detail at birth and were followed up every 6 months for anthropometry and at 6, 12 and 18 years for diabetes, cardiovascular and neurocognitive risk measurements (**Figure 4**).

The mothers were on average 42 kg (BMI 18.1 kg/m^2) at the start of the pregnancy and belonged to a farming community. Babies weighed on average 2.7 kg and were 'thin' by ponderal index (24.1 kg/cm^3) compared to European babies (weight 3.5 kg, ponderal index 28.2 kg/cm^3). Subscapular skin fold thickness of Indian babies was similar and the MRI of abdominal fat (subcutaneous and visceral) higher in Indian babies. Rather than the macronutrients, micronutrients in mother's diet influenced baby's size.[9] Higher frequency of intake of green leafy vegetables, fruit and milk, and higher red cell folate levels were associated with larger birth size. This made us focus on maternal micronutrient status as a determinant of offspring growth and development.

> "Rather than the macronutrients, micronutrients in mother's diet influenced baby's size"

Pregnant PMNS mothers had high prevalence (30%) of hyperhomocysteinemia (> 10 µmol/L), due to vitamin B_{12} rather than folate deficiency. Seventy percent of mothers had vitamin B_{12} insufficiency (< 150 pmol/L) and 31% were severely deficient (< 100 pmol/L). In contrast, fewer than 1% had low erythrocyte folate status (< 283 nmol/L). Ninety percent of these women had high methyl malonic acid (MMA) (> 0.26 µmol/L), which is a specific indicator of vitamin B_{12} deficiency. Higher maternal total homocysteine (tHcy) predicted lower birth weight for gestational age.[10] These findings suggested a role for one-carbon metabolism in fetal growth.

FIGURE 1 | OVERVIEW OF PUNE STUDIES: The figure summarizes studies in the Diabetes Unit, KEM Hospital, Pune over the last 25 years which generated the concept of the 'thin-fat Indian' and intergenerational transmission of the risk of non-communicable diseases by maternal micronutrient nutrition disturbances.



WDS: Wellcome Diabetes Study
PCS: Pune Children's Study
PMNS: Pune Maternal Children Study
CRISIS: Coronary Risk of Insulin Sensitivity in Indian Subjects
IAEA: International Atomic Energy Agency; Observational study for Vitamin B_{12} deficiency in pregnant women
IndiaGDM: Gestational Diabetes Study in Indians under Indo Danish-collaboration
IRS: Insulin Resistance Syndrome
MRDM: Malnutrition Related Diabetes Mellitus
IR: Insulin Resistance

FIGURE 2: Relationship between birth weight and glucose and insulin in 4-year-old children in Pune Children's Study[7]

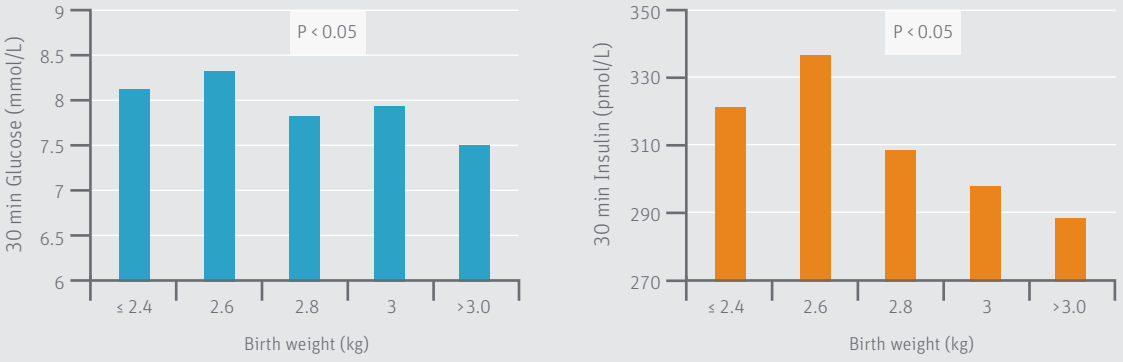
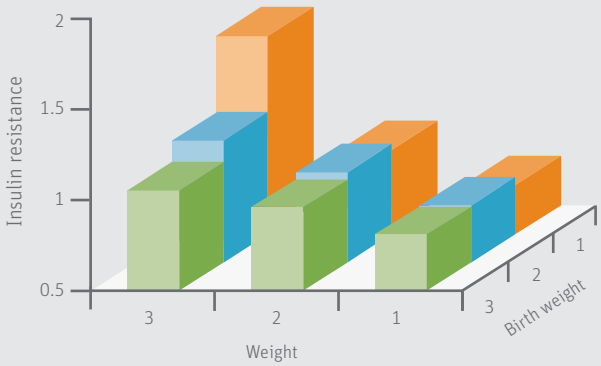


FIGURE 3: Relationship between birth weight (terciles), weight (at 8 years) and insulin resistance in 8-year-old children in Pune Children's Study.[8] Adiposity, glucose, blood pressure and lipids showed a similar association (not shown)



Maternal one-carbon metabolism and offspring health

One-carbon (1-C) metabolism refers to a network of interrelated biochemical pathways that donate and regenerate 1-C units, including the methyl group (**Figure 5**).[11,12,13] Across the life course, the dietary supply of the methyl donors folate, vitamin B_{12}, betaine, methionine and choline is essential for normal growth, development and physiological functions. Maternal diet is the primary source of nutrient availability to the conceptus.[14] Optimal organogenesis, growth and development of the fetus is dependent on the maternal diet and supply of nutrients. **Figure 5** shows possible molecular mechanisms contributing these effects.

Data from the Pune Maternal Nutrition Study highlighted that a relationship exists between maternal methyl donor vitamin nutrition and these also predict neurocognitive function, body composition and insulin resistance during childhood,[15,16] suggesting a critical role of 1-C metabolism in long-term health of the offspring.

> "Data from the Pune Maternal Nutrition Study suggest a critical role of 1-C metabolism in long-term health of the offspring"

Use of genetic markers to establish causality (Mendelian Randomization)

Proving causality from observational research is not easy. Conventionally this is done by interventional research, which is difficult to execute, takes a long time, and is expensive. A recently proposed alternative method is the use of relevant genetic markers which are reliably related to the nutritional exposure of interest. Because the genetic polymorphisms are randomly distributed at conception, they are not confounded by subsequent exposures or lifestyle. Demonstrating a significant association between a genetic marker and the outcome of interest therefore suggests causality.[17] Maternal 5,10-methylene-tetrahydrofolate reductase (MTHFR) genotype (C677T, A1298C) was tested in two Indian birth cohorts (PMNS, n=702 and Mysore Parthenon Study, n=526). Maternal MTHFR T677T predicted high plasma tHcy concentrations in the mother and lower birth weight of the offspring, independent of maternal BMI, socioeconomic status, gestational age and offspring MTHFR genotype. Higher maternal folate concentrations overcame the effect of maternal MTHFR 677TT genotype on birth weight. This suggests that maternal homocysteine status influences birth weight, and that improving maternal vitamin B_{12} and folate status may reduce intrauterine growth retardation (IUGR) and its long-term consequences.[18]

Intervention studies

Micronutrients and growth

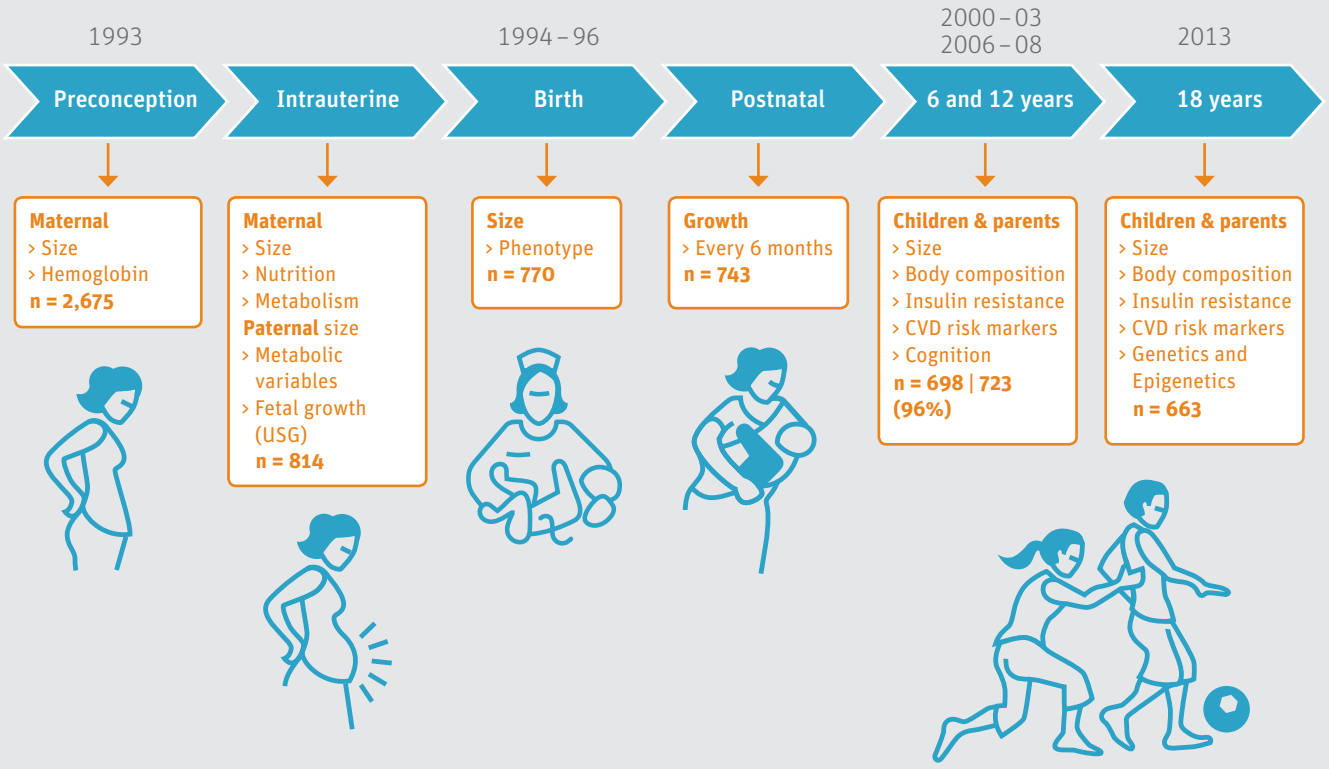
In observational studies and randomized control trials, micronutrients generated inconsistent results. The majority of the trials were in developed countries. A Cochrane review[19] concluded that despite a significant reduction in maternal anemia with micronutrient supplementation, there was only a small and non-significant effect on the incidence of LBW (relative risk [RR] 0.73; 95% CI: 0.47–1.13). However, these trials have to be interpreted in light of the nutritional status of the population: in undernourished populations (India and South Africa), there was a substantial increase in birth weight.[20,21]

Multiple micronutrients in fetal growth and pregnancy complications

Meta-analyses of the effects of antenatal multiple micronutrient supplements (MMS) in 12 randomized controlled trials (RCTs)[22,23] revealed a small but significant increase in birth weight (22.4 g, 95% CI 8.3, 36.4) and an 11% reduction in LBW (CI 3, 19). There were no significant effects on preterm births or prenatal mortality.

A recent Cochrane review[24] shows that MMS during pregnancy significantly decreased the number of LBW infants by 14% and small-for-gestational-age (SGA) by 13%. This review also further indicated that MMS compared with iron and folate supplementation resulted in a significant 11% decrease in the number of LBW and 13% decrease in SGA babies. The impact on pre-term birth, miscarriage, pre-eclampsia, maternal mortality and perinatal mortality were statistically non-significant.

FIGURE 4: Pune Maternal Nutrition Study



Recently married women were enrolled in study before conception. Both parents were characterized during the index pregnancy. Children born to these women are serially followed for growth every 6 months and for body composition, glucose tolerance and CVD risk factors every 6 years

Folic acid and neural tube defects

Prevention of neural tube defects (NTD) by periconceptional folic acid supplementation is considered a major achievement in public health nutrition. This was based on the landmark trials in the UK and Hungary and was supported by Chinese trials. This led to mandatory folic acid fortification of flour in many countries. It is of note that the trials were predominantly in non-vegetarian populations.

We investigated the role of maternal nutritional and genetic markers related to 1-C metabolism in the etiology of NTD in India. Mothers of NTD fetuses had higher plasma tHcy and lower holo-transcobalamin (TC) concentrations but similar folate and vitamin B_{12} concentrations to those in the mothers who delivered normal babies. The commonly associated maternal polymorphism C677T in the MTHFR gene did not predict risk of NTD in the offspring, but C776G polymorphism in transcobalamin II gene (TCN2) was strongly predictive of NTD in the offspring. This study has for the first time demonstrated a possible role for maternal vitamin B_{12} deficiency in the etiology of NTD in India over and above the well-established role of folate deficiency.[25] Policy-makers need to take these facts into account.

Evidences from animal models

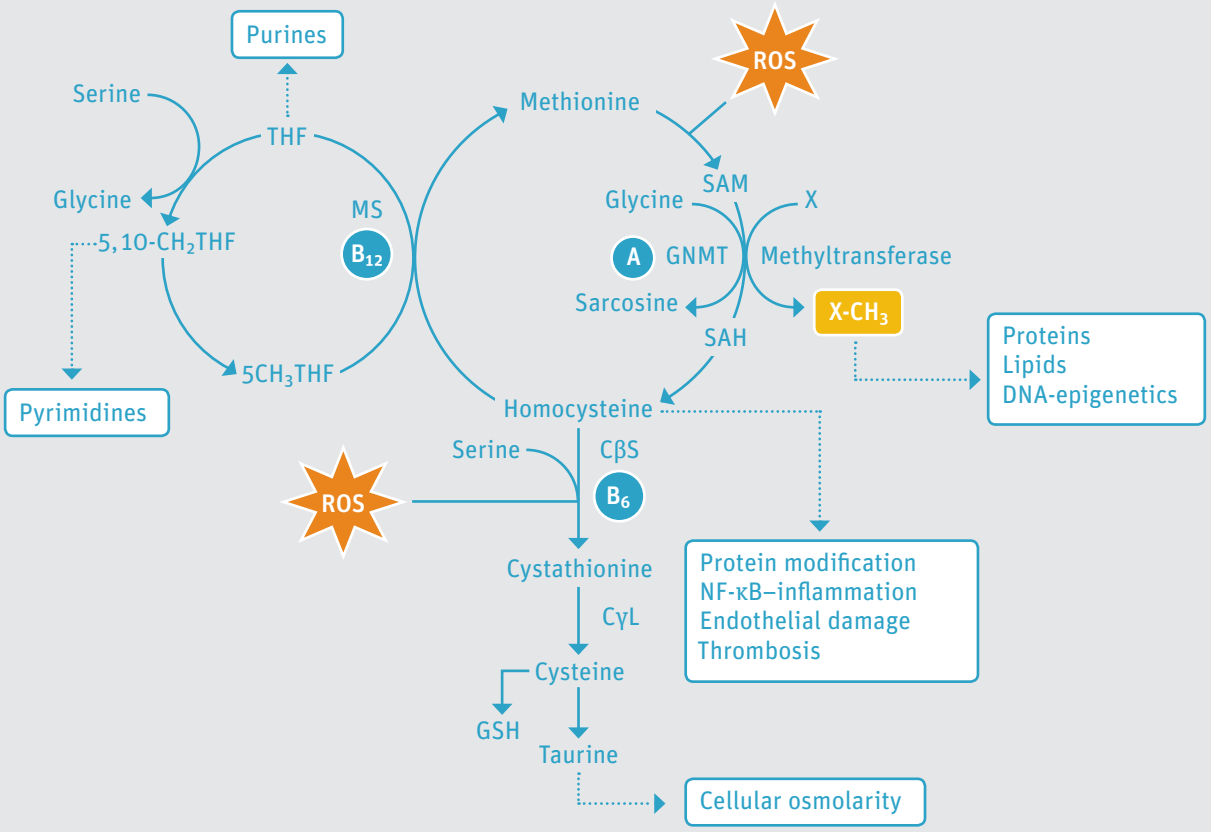
Animal studies have highlighted the role for maternal methyl donor intake and her 1-C metabolism in influencing fetal growth, body composition and programming of risk of blood pressure and diabetes. This has been done in Agouti mice,[26] sheep[27] and Wistar rats.[28] Molecular studies have demonstrated a possible role of DNA methylation in influencing fetal phenotypes.

Intervention studies in India

Pune Intervention Study

We found that vitamin B_{12} deficiency in our population is mainly caused by low dietary intakes, not malabsorption, and can be treated with physiological oral doses (2 µg daily) over 6–12 months.[29,30] We therefore commenced an intervention study as the next logical step to investigate whether improving maternal vitamin B_{12} status improves fetal growth and potentially interrupts the intergenerational transmission of diabetes risk. Previous intervention studies of maternal supplementation started in mid-pregnancy and would have missed the processes that occur around conception and early gestation such as epigenetic programming, placentation, and fetal organogenesis. We decided to start the intervention pre-conceptionally to influence these pro-

FIGURE 5: Vitamin B_{12}, folate and one-carbon metabolism



1-C metabolism is important in many processes involved in fetal growth and development. These include nucleic acid synthesis, DNA methylation and epigenetic regulation, generation of ROS, methylation of proteins and lipids which effect various cellular processes and functions. 1-C metabolism is governed by a number of dietary nutrients including vitamins B_{12}, B_6, B_2, folate.

cesses. Recent evidence suggests that the nutritional status of fathers influences the epigenetic processes in their offspring,[31] and we therefore included boys as well as girls in the trial.

The adolescents are individually randomized to receive a daily supplement for at least 3 years or until their first delivery (whichever is earlier) containing: **1)** vitamin B_{12}, 2 µg; or **2)** vitamin B_{12}, 2 µg + multiple micronutrients (MMN) + 5 g milk protein; or **3)** a placebo. The MMN composition is guided by the UNIMAPP formulation,[32] providing approximately 1 RDA of 15 vitamins and minerals, but with 2 µg vitamin B_{12} instead of 1 µg. Iron and folic acid is prescribed separately for all participants according to Indian guidelines.[33]

The results of this trial will have significant public health implications in a setting with widespread vitamin B_{12} deficiency but relative folate sufficiency. Moreover such "primordial" prevention offers a hope of curtailing the escalating diabetes epidemic in future generations in contrast to current prevention strategies. This trial will test the basic tenet of the DOHaD hypothesis. The RCT design allows us confidence that our findings will be causally relevant. The extended program will create an unparalleled repository of precious biological samples for future "omics" studies.

Mumbai Maternal Nutrition Project

The Mumbai Maternal Nutrition Project[34] was a randomized controlled trial of micronutrient-rich foods before and throughout pregnancy among women living in urban slums based on the studies in Pune. A snack made from green leafy vegetables, fruit and milk was provided each day as an addition to the normal diet. Women in the control group received similar snacks made from vegetables of low micronutrient content.

Six thousand five hundred and thirteen pre-pregnant women were recruited, and 2,067 babies were born. Overall, the intervention increased birth weight by 26 g (not statistically significant, p=0.20) but with a slightly larger effect (48 g, p=0.05) if women started the supplement >3 months before conception. There was a striking interaction with maternal BMI; the supplement had no effect on newborn weight among mothers in the

lowest BMI group (< 18.6 kg/m2, 7 g, p=0.84), but had an effect among women in the middle (18.6–21.8 kg/m2, 79 g, p=0.07) and highest BMI groups (> 21.8 kg/m2, 113 g, p=0.008). The intervention also reduced the prevalence of gestational diabetes (~7% vs 13%, p=0.01). The babies are being followed up for growth and cardiovascular risk factors.

Role of genetics and epigenetics

Fetal growth and development are influenced by an interaction between genetic factors and the intrauterine environment. The size of the newborn is influenced not only by inheritance of genes but also by maternal size, nutrition and metabolism. Hattersley et al[35] showed this through the interaction between the glucokinase gene and maternal hyperglycemia. It is increasingly appreciated that epigenetic changes, which refer to heritable modifications in the genome not associated with a change in the base sequence,[36] are at the center of programming. These changes may be mediated by methylation of DNA, acetylation of histones, and through the role of micro RNAs, all of which modify gene expression. These could potentially result in the production of different phenotypes from the same genotype by altering gene expression and increasing or decreasing the amount of encoded protein.

Our studies will provide relevant information in the near future.

> "The size of the newborn is influenced not only by inheritance of genes but also by maternal size, nutrition and metabolism"

Conclusion

In the past thirty years, we have defined the characteristic phenotype of Indians which explains their high susceptibility to diabetes and related disorders. In addition to genetic factors, we have additionally described a role for intergenerational fetal programming. This is influenced by modifiable environmental factors such as maternal nutrition, which influences the epigenome of the developing fetus. Our finding of the importance of maternal methyl donor nutrition and 1-C metabolism in fetal growth is exciting because of the potential influence it may have on DNA methylation. We are in the process of gathering this data. Our research has highlighted a role for improving the nutrition of young girls so as to curtail the epidemic of NCDs. Early-life interventions may be more cost-effective in preventing the NCD epidemic than controlling the lifestyle factors in later life.

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profile

The Bigger Picture

A Day in the Life of Andrew Prentice and Fatou Sosseh

Prof. Andrew Prentice is Head of MRC Keneba, a rural field station situated in the Kiang West region of The Gambia. He and Chief Midwife Fatou Sosseh discuss their work at the center and its relevance to the nutritional welfare of mothers and babies worldwide.

Sight and Life (S&L): *Andrew, you are Head of MRC International Nutrition Group. Could you tell us a little about the history of the MRC and its current activities?*

Andrew Prentice (AP): The UK Medical Research Council (MRC), for which I work, has been investing in research in Africa for many decades. Its involvement here in The Gambia goes back to 1948, and research in the Keneba Center was started by Professor Sir Ian McGregor in 1950. Its initial focus was malaria. In 1974, my predecessor here, Roger Whitehead, joined. Roger greatly expanded the center. I started living in Keneba in 1978 and took charge of the center in 1999, and it's been full steam ahead ever since. We run a very broad research portfolio centered on maternal and child health. Our main focus is The Gambia and Sub-Saharan Africa, but we also do a lot of discovery science which we hope will be important world-wide, to high-income as well as low-income countries. We're highly unusual in that we have a state-of-the-art clinic and laboratory situated in the heart of The Gambian bush, which allows us to do some extremely specialized research.

S&L: *You were born in Uganda. In what ways does this influence your thinking and work?*

AP: I adore Africa. I was born in Uganda, schooled in Kenya, attended university in the UK, and then returned to Africa. I therefore feel an African in everything except the color of my skin. My first exposure to nutrition was in Uganda, working for Roger Whitehead, who was based there at the time. My job was as a baboon trapper for a research colony – quite a risky occupation, but extremely interesting! The role of the baboons was as an animal model to help us explore the nature of extreme protein energy malnutrition.

> "Improving the human capital of Sub-Saharan Africa requires us to pay attention to nutrition throughout the life-cycle"

S&L: *How has the problem of nutritional deficiencies in Sub-Saharan Africa evolved during the time you have been involved with MRC?*

AP: Understanding the etiology, and treatment, of protein energy malnutrition was the main focus of the center's activities thirty or forty years ago. We still do work in this area, but there have thankfully been few famines in the region in recent decades and health situations are generally improving, and our focus is now on hidden hunger, which generally relates to micronutrient deficiencies. Nutritional deficiencies underlie – whether directly or indirectly – approximately a third of all child deaths in this region. The best metric for infant nutritional well-being is stunting, and so we track this closely so as to be able to understand the nutritional supply here. We also understand today that the nutritional status of the child in the womb has a profound effect on its lifelong health. Improving the human capital of Sub-

① Fatou Sossej, Chief Midwife at the Keneba Center, cradles a newborn baby born at home.

② A mother holds her prematurely born baby in the Edward Francis Small (EFSTH) Teaching Hospital, The Gambia. EFSTH is located in Banjul, the capital of The Gambia and it is the main referral hospital for the country.

③ Three generations side by side: A grandmother, mother and baby in The Gambia.

④ Young girls born in The Gambia. The Keneba Center has done much to improve survival rates for both mothers and newborns.

⑤ Andrew Prentice with a young baby.
"I feel an African in everything except the color of my skin."

⑥ A newborn in Kanong Kunda, The Gambia.

Saharan Africa therefore requires us to pay attention to nutrition throughout the life-cycle, and particularly before a woman conceives. This has a huge influence on our work.

S&L: *In what ways, Andrew?*

AP: Thankfully we are seeing a huge reduction in infant and child mortality. Infant and child mortality in our region has dropped tenfold in the past forty years due to a range of measures, including vaccination. However, the proportion of stillbirths and neonatal deaths, as well as of disabilities, is growing. We therefore have a major focus now on pregnancy and the newborn. Stillbirths and early neonatal deaths are complex and have multifactorial causes, and we are making a major investment in trying to understand them. There are some simple things that can be done to avoid these early deaths in a rural setting such as this, and these are in place. Traditional birth assistants spend a week with birthing mothers, and give them help with breastfeeding and baby care. But there is much more that we need to understand.

S&L: *Fatou, you are Chief Midwife at the Keneba Center. Can you tell us something about the day-to-day life of the center?*

Fatou Sosseh (FS): We conduct research here, so activities such as anthropometry and conducting fetal ultrasounds are very important. We also teach study participants the importance of nutrition and of personal and environmental hygiene. We work in 36 villages in the area around the center. Here we provide a free health check service for pregnant women. The local women are often reluctant to disclose that they are pregnant on account of superstitious fears that they may lose their child. We're doing our best to educate women out of this superstition. We also always have a number of research studies running in the center at any one time, and we recruit women from the local villages into these studies. These are some of the best-studied babies in the world, in fact!

S&L: *What is the relationship between the Keneba Center and the Gambian government?*

FS: We are funded by the UK Medical Research Council, the Bill & Melinda Gates Foundation, and other sources, but we work very closely with the Gambian government. There is a government health center some 23 kilometers from Keneba, and we operate in close liaison with the team there. It's a very fertile relationship that has been sustained over 67 years now.

S&L: *What prompted you to become a nurse?*

FS: Ever since my girlhood, I have always had a passion for caring for people, especially those who are sick. I was born in the city, but I've been working in this rural area for 21 years now, primarily as a midwife.

S&L: *What are the qualities required of a midwife?*

FS: It's a very diverse role. You need to care for people. You must listen to their needs, understand their problems, and try to help them. It can be difficult to gain women's confidence in this remote rural area, but it's essential in order to do the job. It's really important to see women as early in the pregnancy as possible, and I'm now seeing them as early as eight weeks. The local tendency is to assume that one or two antenatal visits are sufficient, which is of course not the case. The more antenatal care women receive, the better.

> "To be a midwife, you need to care for people. You must listen to their needs, understand their problems, and try to help them"

S&L: *Where do the mothers actually give birth?*

FS: We have a delivery room in the Keneba Center for the more complicated births, but our core service is antenatal care rather than actual delivery. Most women therefore give birth at home, assisted by a traditional birth assistant, or TBA. The advantage of running antenatal clinics is that we can predict which births might be difficult and can put appropriate measures in place to mitigate the risks for mother and baby.

S&L: *Could you tell us more about the TBAs?*

FS: The TBAs receive refresher training from MRC Keneba every six months and assist with deliveries in the local community, as well as offering advice on breastfeeding. We oversee them, but they are not part of our team. The vast majority are illiterate, so their training is very basic. They are mostly elderly, and they have a great deal of experience with childbirth.

S&L: *What are the major risks to which women giving birth at home are exposed?*

FS: One of the major risks is bleeding, which is very common. Another is asphyxiation of the baby. Potential breach births and cases of eclampsia are identified during antenatal screening,

and the women in question do not give birth at home. If a home delivery does become especially difficult, we can be contacted, and we will arrange transfer of the mother to an appropriate health facility. Mobile phones have had a huge impact here. The Gambia is a flat country and mobile reception is very good here, so communications have improved vastly in recent times.

S&L: *Do locals generally favor a home birth, or is this the sole option for most women?*

FS: Some women might actively prefer a hospital birth, but there are many practical obstacles to this. To give birth in a hospital, they would have to travel to the coast, not knowing the exact day of delivery and not having their family and friends with them. They would also have to incur the expense of living in the city prior to going into labor. And who would look after the other children and the farm while the mother is away? So the case for home birth almost makes itself in many instances. Poverty is a key factor in most decisions.

S&L: *What are the key things that mothers preparing to give birth at home need to know about good ante- and postnatal care?*

FS: One of the most important things is having antenatal reviews early. If they book in for these in good time, they can be seen at the health clinic four times before giving birth. This allows us to identify any potential problems and give them the information they need to deal with the situation. It's also very important to give the baby the colostrum and not discard it, as used to be the practice. So we encourage new mothers to give the baby the breast as quickly as possible. In the past, a verse from the Koran would be written on wood using charcoal and ink, the verse would be washed off with water and mixed with honey, and the solution was given to the baby as its first nourishment. It was of course full of germs and extremely detrimental to the baby's health. What we now know is that the establishment of the microbiome in the gut after birth – a "signature" mixture of bacterial organisms essential for health – should be based on the bacteria present in the mother's body, and not on the hands of the man who wrote the Koranic verse. This is significant, because the vast majority of the population in The Gambia, and almost 100 per cent here in the countryside, is Muslim.

S&L: *Do you run awareness-raising and educational campaigns to support the dissemination of best practice in antenatal and postnatal care? How are these received?*

FS: There are health programs on the radio, but we always talk to mothers when we visit them, or when they come into the clinics. We cover subjects such as the importance of hand-washing, how to breastfeed, what types of food to give the infant, the prevention of diarrhea, and generally how to look after the baby at home.

S&L: *What can be done to improve the already high standards you uphold here at the Keneba Center, Fatou?*

FS: I've always been passionate about midwifery myself, and despite my age, I'm very interested in reading and taking courses to further develop my knowledge and skills. The urban areas of The Gambia exert a considerable gravitational pull of the populations of rural areas, so it's very hard to keep good people here. That's a perennial challenge for us. We are a research center first and foremost, and our motto is "No survey without service". We're not a hospital, however, and are not funded as such, and so we have to strike the best balance we can between serving people's critical health needs here and conducting research that will benefit mothers and babies all around the world, and not just in The Gambia.

> "We have to strike the best balance we can between serving people's critical health needs here and conducting research that will benefit mothers and babies all around the world"

S&L: *Is there anything else you'd like our readers to know?*

FS: Simply that Andrew has done a terrific job and made enormous improvements to the center since he's been here. I'd like to thank him for his outstanding work.

AP: Let me reciprocate and say how greatly Fatou's involvement in the medical aspect of our work has increased during the time she's been here and what a tremendous job she's done. She has, among other things, helped deliver over 10,000 babies! I dread to think how many wouldn't have survived without her assistance.

S&L: *Back to you, Andrew. Speaking as someone who knows Africa extremely well, what would you like the rest of the world to understand about the continent and the challenges it faces?*

FS: If we turn our attention to South America for a moment, we can see that that continent is going through the so-called economic and nutritional transition. When this happens, a lot of nutrition-related diseases disappear – anemia, stunting and

underweight, for instance, which have gone down very rapidly in the past 20–30 years. Here in Africa, we have what is termed the "remittance economy". Most families have a member living and working abroad and sending money home. Whether their work is legal or illegal, the money they are making available to their families is transforming the nutrition landscape here. The little shops here in Keneba are much better stocked than they were 30 years ago. But we still don't understand the fundamental relationships between cause and effect in nutrition. For instance, we're still struggling with the problem of how to give iron supplementation safely. There's also a vigorous debate among nutritionists at present as to whether the huge efforts that governments and agencies have been putting into vitamin A supplementation should be scaled down. At the same time, we've done a lot of very exciting research – here, in the Gambian bush – into the nutritional status of the baby *in utero*, and especially in the first hours and days of life. The nutrition a mother receives just before and after she conceives can have a very profound effect on the baby in her womb, and on the health of that individual for the rest of his or her life. So if we can engineer an optimal diet for pregnant women, we'll make massive gains in the reduction of pregnancy-related defects. So we are living in very exciting times, able to apply the big science of Europe and America to the issues of the developing world so as to create solutions that will benefit the developed and the developing world alike. That's what really excites me about the work we're doing here in Keneba.

> "We are living in very exciting times, creating solutions that will benefit the developed and the developing world alike"

S&L: *Andrew, Fatou: Many thanks for your time, and the best of luck with your endeavors!*

AP: Thank you.
FS: Thank you.

Andrew Prentice and Fatou Sosseh *were interviewed by Jonathan Steffen*

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The MRC International Nutrition Group

Nutritional deficiencies in low-income countries impair the growth and development of children, reduce their resistance to infections, and contribute to almost half of all child deaths worldwide.

Maternal malnutrition during pregnancy and lactation harms the fetus and infant with both short- and long-term consequences for their health. Future generations are also affected. The MRC International Nutrition Group (ING) works to reduce this burden with a focus on the world's poorest populations, especially in Sub-Saharan Africa.

Our mission

Our mission is to gain novel insights into the basic mechanisms linking diet and disease in order to develop more effective community and clinical interventions.

The MRC International Nutrition Group is based at the London School of Hygiene & Tropical Medicine and has a major research center at MRC Keneba in The Gambia, West Africa.

We also work in Kenya and Tanzania, with additional collaborative studies in other low-income countries, especially Bangladesh. Our primary collaborative center in the UK is MRC Human Nutrition Research in Cambridge, through which we also run comparative studies in China.

MRC Keneba is embedded within the MRC Unit, The Gambia, and works with its other themes on Vaccines & Immunity and Disease Control & Elimination. We work with the Ministry of Health and Social Welfare through close collaborations with The Gambian National Nutrition Agency (NaNA).

Source: www.ing.mrc.ac.uk/, accessed March 2015.

"The *Sight and Life* magazine is a valued resource and it keeps me and my colleagues updated on both developments and news that ensures we remain in touch even though we live and work in Africa."
Susan Tswane, South Africa

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Thanks for this magazine.
Mr Dominic M Mogere,
CEO | CHRCC | Kericho, Kenya

Professor Darwin Karyadi (1933–2014)

Remembering a National Hero of Nutrition in Indonesia

Soekirman
Bogor Agricultural University, Indonesia;
Indonesian Nutrition Foundation for Food Fortification (KFI); and Indonesian Nutrition Institute (IGI)

It was with shock and great sadness that I and many of my colleagues in Indonesia learned that Professor Darwin Karyadi had passed away in Jakarta on October 6, 2014. Prof. Karyadi had formerly been Director of the Center for Research and Development of Nutrition (CRDN) at the Ministry of Health in Bogor, Indonesia, a position he had held for more than 25 years.

A passion for creating collaborations

As Director of CRDN, Darwin Karyadi was the first person to establish collaborations with international research institutions. In the 1970s, he collaborated with Prof. Nevin Scrimshaw from MIT and the World Bank to conduct research on iron deficiency anemia and productivity among rubber plantation workers in West Java (Am J Clin Nutr 1979;32:916–25). He also initiated a WHO-SEARO (World Health Organization, South East Asia Regional Office) nutrition research collaboration in the 1980s known as the WHO Collaborating Centre for the Identification, Development and Propagation of Methods for the Control of Nutritional Blindness and Anemia. This aimed to establish a research network among the WHO-SEARO, especially on vitamin A and anemia studies. Various laboratory trainings on vitamin A were conducted in CRDN Bogor involving numerous participants from Bangladesh, Vietnam, Nepal, Myanmar and other Asian countries.

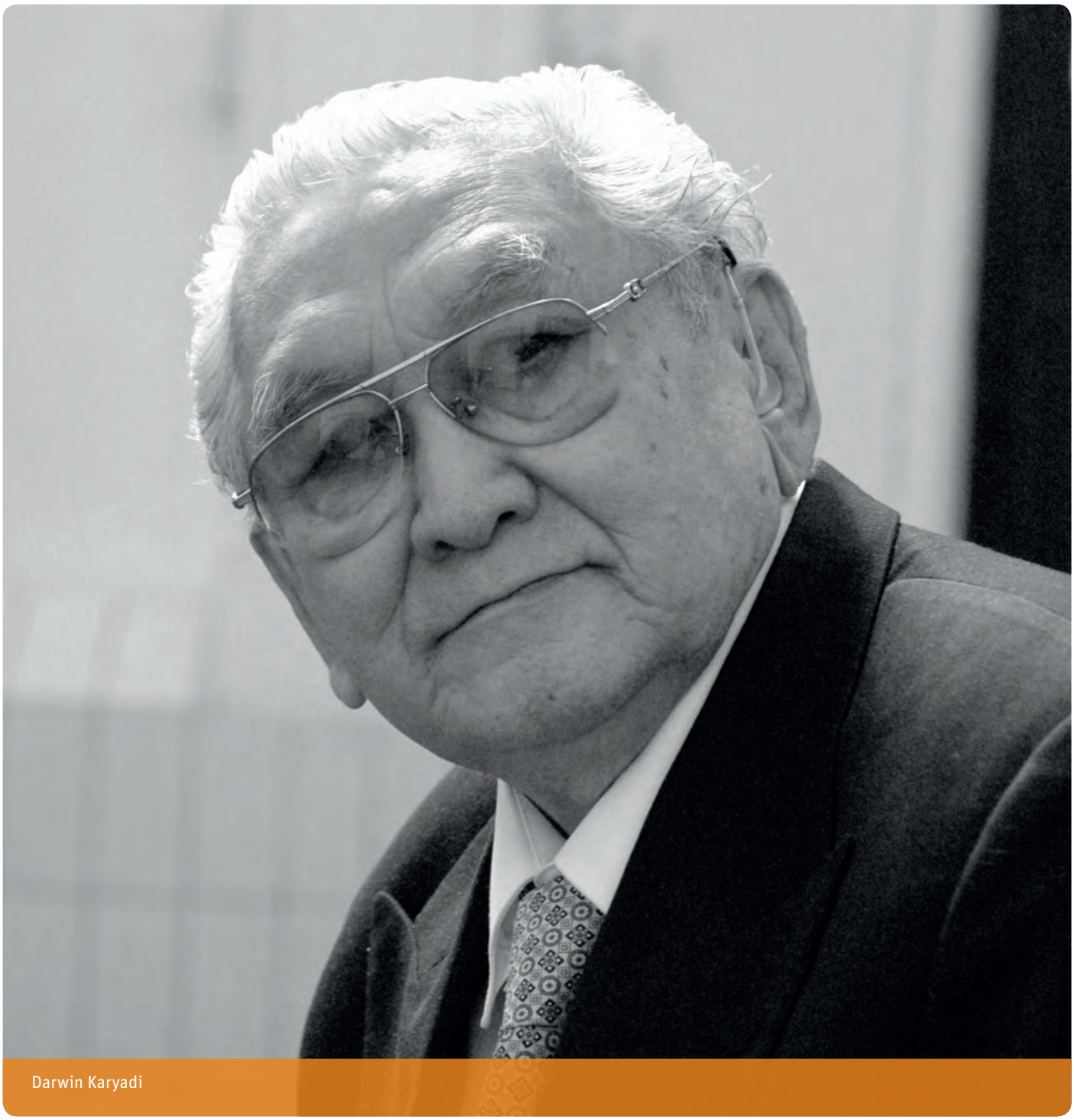
Darwin Karyadi was also the first CRDN director to collaborate with Helen Keller International (HKI) Indonesia. This was on MSG fortification with vitamin A. It occurred in the 1980s and was the first effort to reduce the xerophthalmia rampant in Indonesia at the time. The vitamin A studies were expanded with vitamin A supplementation in West Java and Aceh in collaboration with HKI and Johns Hopkins University. The latter were published in the Lancet 1986:1;1169–73 and the ACC-SCN Nutrition Policy Discussion Paper 1992, No 13.

Fostering new innovations as a nutrition scientist

As Vice Director of a Nutrition College (*Akademi Gizi*) at the Ministry of Health in Bogor, Darwin Karyadi also helped train nutrition professionals from Indonesia and elsewhere in South East Asia. He introduced the traditional food *tempeh* to the world at many international conferences; *tempeh* is the most popular vegetable protein source for most Indonesians (Nutr Rev 1996;54(11):S94–S98). As a member of the National Research Council, Prof. Karyadi contributed to the recognition of nutrition not only among academics but also among politicians in Indonesia. The Country Medal of Honor, presented by President Susilo Bambang Yudhoyono in 2005, recognized him as a Nutrition Hero of Indonesia.

> "Darwin was laid to rest at the Kalibata National Heroes Cemetery"

Darwin Karyadi graduated as medical doctor from the University of Indonesia Faculty of Medicine, receiving a Fellowship in Nutrition in 1963. He was awarded his doctorate in medicine by the University of Indonesia in 1974. He was Vice Director of Bogor Nutrition College from 1960 to 1965, and became Director of Central Research and Development of Nutrition, Bogor, at the Ministry of Health from 1965 to 1993. On retiring, he was ap-



Darwin Karyadi

pointed Director of the SEAMEO-TROPMED network, University of Indonesia, Jakarta (1994–2000).

Darwin was laid to rest at the Kalibata National Heroes Cemetery in Jakarta at the age of 80. He is survived by his beloved wife, Lies, to whom he was married for 52 years; two sons (Elwin and Erwan); a daughter (Elvina), who follows his path in medicine and nutrition; two daughters-in-law (Lily and Lelan); a son-in-law (Isaac); and five lovely grandchildren (Tania, Dio, Tasya, Delvin and Verina). His family keenly feel their loss, but he is very much alive in all their hearts.

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Voyaging On in Search of Evidence to Benefit the Nutrition Community

III World Congress on Public Health Nutrition

Noel W Solomons
CESSIAM, Guatemala City, Guatemala

With the central theme of "Public Health Nutrition: The Core of International Development for Cooperation," the III World Congress on Public Health Nutrition (III WCPHN) was held November 9–12, 2014, in Las Palmas, Gran Canaria, Spain. The previous WCPHNs had been held in Barcelona in 2006 and Oporto in 2010. The President of the Congress and Chair of the International Scientific Committee was Prof. Lluis Serra-Majem. Eight hundred and forty-eight participants from 62 countries attended the meeting. The program comprised a total of 180 hours of activities, including plenary lectures, symposia, workshops, debates, and oral and poster presentations, along with a social program featuring the culinary and performing-arts culture of the Canary Islands. Tributes were offered to the memories of the late Nevin S Scrimshaw, José María Bengoa and Rainer Gross. A focus on the younger generation of the nutrition community was reflected in a satellite reunion assembly of professionals who had been part of the Nutritional Leadership Programs in Europe, Africa, South Asia and Latin America.

Hidden hunger in the "First World"

For the readership of *Sight and Life*, micronutrients would probably be of leading interest; the Program offered seven sessions focused in this arena. This began with the Inaugural Lecture, presented by Prof. Hans Konrad Biesalski of Hohenheim University in Stuttgart, with the provocative title of "Hidden Hunger in the 'First World' – how is economic crisis affecting undernutrition?" The speaker provided examples from iron, folate and vitamin A as problem nutrients in affluent populations, linking these to the recent economic crisis. It underscored the lessons that higher-income nations can learn from their less economically developed counterparts.

Three Plenary Symposia continued the micronutrient theme. "Cost-effectiveness of market-driven fortification to address Hidden Hunger" presented the economic modeling of the benefits of investing adequate vitamin A and iron nutrition in health and productivity. "How can phytase improve public health nutrition?" focused on experimental animal and human data on how enzymes that degrade dietary phytate can improve the bioavailability of iron and zinc and improve growth. Third in the series was "Folate-preventable congenital anomalies: using the WHO research strategy to guide effective actions in public health."

III Rainer Gross Prize awarded to Prof. David Thurnham

Satellite symposia were directly sponsored. DSM Nutritional Products presented "Vitamin E: New emerging data – the way forward," which highlighted new evidence making this vitamin relevant to global public health. The Global Alliance for Improved Nutrition (GAIN) sponsored "The challenges of interventions against micronutrient deficiency" featuring the efforts and obstacles in rolling out an effective fortification agenda. The Puleva Nutrition Institute sponsored a Spanish-language symposium, "Vitamins, bone and public health," which went beyond vitamin D to other fat-soluble vitamins of relevance to skeletal health. Finally, the III Rainer Gross Prize was awarded to Prof. David Thurnham for his work on the awareness of how inflammation distorts the assessment of micronutrient status.

The Program endeavored to examine evidence surrounding contemporary and unresolved issues of health relevance, such

Panel discussion at the III World Congress on Public Health Nutrition. From left to right: Rosario Garcia (on podium), Klaus Schuemann, Noel Solomons, David Thurnham and Ursula Gross.

as childhood obesity, artificial sweeteners, sugar consumption, physical activity, the Mediterranean diet and human hydration. Other sessions addressed research financing, research quality, leadership and opportunities for public-private initiatives. The debate program highlighted controversies in both an entertaining and informative manner; the themes were: **1)** "Taxing foods as public health measure"; **2)** "Experiments or observations"; and **3)** "Wine versus beer".

> "The Program endeavored to examine evidence surrounding contemporary and unresolved issues of health relevance"

On a historical note, the expeditions of Christopher Columbus would break their journey in the Canary Islands as the last supply stopover prior to continuing their voyage westwards in discovery of the unknown. In this context, an announcement from the Congress President is worthy of attention. Prof. Serra-Majem commented: "I am also proud to announce this new integrative and rigorous organization: The International Association of Community Nutrition (IACON), which will be constructing an international and interdisciplinary framework to help coordinate evidence-based, sustainable solutions for the most important nutritional-related diseases and conditions worldwide." IACON and its Congresses are dedicated to the premise that nutritional science is the centerpiece for the necessary new discoveries that will improve public health nutrition policy and programs. We departed the Canary Islands, therefore, to continue our respective journeys toward obtaining the relevant evidence to benefit the nutrition of communities and nations around the globe.

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How can Phytase Improve Public Health Nutrition?

III World Congress on Public Health Nutrition

Barbara Troesch
DSM Nutritional Products, Kaiseraugst, Switzerland

At a symposium on November 11, 2014, held during the III World Congress of Public Health Nutrition in Las Palmas de Gran Canaria, Spain, experts discussed the role phytase could potentially play in public health nutrition. Richard Hurrell from ETH Zurich, who chaired the meeting with the author of this contribution, opened the session by explaining that the speakers would address how this enzyme could help improve mineral status of infants and children, thereby potentially improving growth.

What is the potential role of phytase?

Saskia de Pee of the UN World Food Programme (WFP) emphasized the significance of iron and zinc deficiency for the burden of disease, particularly in developing countries, where diets contain few or no animal-source products. In those regions, staple foods as well as complementary foods are typically plant-based and contain high levels of absorption inhibitors such as phytate. She referred to a review of the topic by Gibson et al,[1] concluding that dephytinization of plant-based foods combined with animal-source foods and/or fortification was necessary to ensure sufficient supply of iron, zinc and calcium for infants. For the WFP, ensuring adequate amounts of bioavailable iron from such diets while at the same time limiting the amount of added iron is a clear priority – given the supposed negative effects on child morbidity of unabsorbed iron in particular. The addition of phytase could be one potential solution to this problem, but according to Saskia de Pee, further studies should address the feasibility and cost of phytase in food processing as well as in foods ready for consumption. Moreover, additional information about the potential role of phytase with regard to linear growth in younger children is needed.

From left to right: Olayiwola Adeola, Parul Christian, Barbara Troesch, Damiet Koenders, Saskia dePee and Richard Hurrell.

> "Ensuring adequate bioavailable iron while limiting the amount of added iron is a clear priority for the World Food Programme"

Consuming active phytase: what evidence is there?

This question was addressed by Richard Hurrell, who explained that the inhibitory effect of phytate on mineral absorption could be countered by the removal of the phytate, by its enzymatic degradation, or by adding compounds such as EDTA that prevent phytate-mineral binding. Traditionally, enzymatic phytate degradation was ensured by activation of endogenous enzymes through soaking, germination and fermentation or else by adding an exogenous phytase during food processing. However, with a phytase from *Aspergillus niger* (Tolerase™ G) that remains active at the low pH in the stomach, phytate can also be degraded during stomach transit time. It has been shown that iron absorption from a high-phytate maize porridge can be significantly increased when the enzyme is added just before consumption.[2] Similarly, Tolerase™ G can also enhance zinc absorption from a millet-based porridge, making the addition of phytase to complementary foods a simple but potentially efficient strategy to enhance mineral bioavailability.[3]

Plaza Las Canteras, Gran Canaria, with the Alfredo Kraus Auditorium – the venue for the III World Congress on Public Health Nutrition.

What are the potential applications for phytase?

Damiet Koenders from the DSM Biotechnology Center presented various applications that hold promise for the use of phytase either during processing or just before consumption. Based on the available evidence, she concluded that the use of phytase as a food ingredient in products such as micronutrient powders, lipid-based nutrient supplements and condiments such as fish or soy sauce can be recommended. Phytase can also be used for flour fortification – in which case the degradation could take place during the processes of bread-making. She also explained that the Joint FAO/WHO Expert Committee on Food Additives assigned an "Acceptable Daily Intake – not specified" to phytase (Tolerase™), which indicates its safety for use. Moreover, phytase was listed in the Codex Alimentarius Guidelines on Formulated Complementary Foods for Older Infants and Young Children as a recommended strategy to reduce phytate content and thereby increase mineral bioavailability. Damiet Koenders concluded that the endorsement of these two bodies enabled intergovernmental organizations to use phytase in high-phytate foods, even for infants. For its use in specific countries the national situation needs to be assessed, but according to her, in many countries the use of phytase is already approved or no legal barriers exist.

> "In many countries, the use of phytase is already approved"

What can we learn from animals?

Exogenous phytase has been used to improve physical performance in non-ruminant animals by releasing otherwise unavailable phosphorus as well as various minerals. Consequently, a vast range of evidence on its effect on growth is available, particularly from pigs and poultry. Olayiwola Adeola from Purdue University reviewed this evidence to draw conclusions about the role phytase could play in reducing stunting in infants. In his opinion, the degradation of phytate can be expected to improve phosphorus retention, protein solubility and consequently retention, and also mineral bioavailability. Moreover, the generation of inositol, thought to mimic insulin in the body, could potentially have a beneficial effect on cellular glucose uptake, protein deposition efficacy and therefore overall growth. However, extrapolation from studies in animals to humans has its limitations, and the role of phytase on growth in infants and

young children can only be resolved with evidence from this target population. Still, given the importance of zinc, calcium, phosphorus and possibly iron on growth; the role phytase plays in their bioavailability from plant-based foods; and the high prevalence of stunting in many regions of the world, it would be a missed opportunity not to pursue this further.

What is known in humans?

Last but not least, Parul Christian from the Johns Hopkins Bloomberg School of Public Health reviewed the limited evidence available on the effect of phytase on linear growth in humans. Even though it has been postulated that zinc deficiency plays an important role in the development of stunting early in life, the effect of interventions with zinc supplements has so far been ambiguous. This might be partly due to the poor absorption of zinc, but also due in part to the multifactorial causes of stunting. Therefore fortification with multiple nutrients, such as micronutrient powders or other ready-to-use fortified foods, might be more promising. However, this will only be the case if the bioavailability of the added micronutrients can be optimized using enhancers such as ascorbic acid for iron or phytase for iron, zinc and other minerals. Parul Christian concluded that further research is required to show the impact of adding phytase to lipid-based fortified foods, as well as other ready-to-use or fortified blended foods, on linear growth and the prevention of stunting.

> "Further research is required to show the impact of adding phytase to fortified foods on linear growth"

Conclusion

Even though more studies could always shed further light on any research topic, the data available from animals and humans already gives an indication of the important role phytase could play in growth in areas where plant-based foods predominate in the diets of infants and young children. Moreover, the role of phosphorus has so far not been studied, as it is abundantly present in Western-type diets. However, in the plant-based foods consumed by infants and young children in low- and middle-income countries, a large part of phosphorous is phytate-bound and therefore poorly available. Given the importance of phosphorus in bone formation and consequently growth, the addition of phytase can be expected to provide an additional benefit.

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Targeting Microbiota 2014: Friend or Foe?

Barbara Troesch
DSM Nutritional Products, Kaiseraugst, Switzerland

Pierre-Henri Gouyon (left) believes that "Nothing in biology makes sense except in the light of evolution"

At the 2nd World Congress on Targeting Microbiota at the Institut Pasteur in Paris, on October 16–17, 2014, experts discussed recent progress and current issues related to the diverse microorganisms that live on or in our bodies or that could be used to produce substances providing a benefit for our health. Given the scope of this article, I will take the liberty of reporting only on selected issues addressed during the conference that coincide with my personal and professional interests.

Not to be underestimated

The conference was opened by Marvin Edea, Chairman of the Scientific Committee and member of the Task Force Targeting Microbiota at the Institut Pasteur. He drew parallels with the expectations triggered by studies assessing the health benefits of antioxidants and the hopes raised by the findings on the role of microbiota in human health. He advised against expecting a simple solution for all, given the complexity of the ecosystem and the extent of individual diversity. This complexity was reflected in a wide range of topics covered by specialists from fields such as microbiology, immunology, evolutionary biology, and medicine.

The driving force

The scene was set by Pierre-Henri Gouyon of the National Museum of Natural History in Paris, with the quote "Nothing in biology makes sense except in the light of evolution" from the evolutionist Dobzhansky. He explained that while the ultimate goal of transferring one's genes to the next generation often leads to competition, it could (as seen in the case of the human gut microbiota) also encourage cooperation within or between species. More than once during these two days, the example of the mitochondria, which is thought to be the result of ever closer symbiosis between an arcane microbe and a more advanced cell, was mentioned as a success story illustrative of the benefits of cooperation.

> "While transferring one's genes to the next generation often leads to competition, it could also encourage cooperation"

The intriguing relationship between mitochondria and microbiota

It is thought that our mitochondria derive from an arcane microorganism that was incorporated into the eukaryotic host. Consequently, it shares many features with modern single-cell organisms, such as the double membrane, the circular genome and the protein expression machinery. Moreover, mitochondrial DNA is transferred from the mother to the child, while the colonization of the newborn's gut also originates from the maternal microbiota. As part of the host defense, intracellular microorganisms are eliminated via autophagy, which is also an important process to eradicate defective mitochondria.

Microbiota in the light of public health

Industrialized countries have witnessed a steady decline in bacterial infections, with a parallel increase in the incidence of non-

Findings on the role of microbiota in human health have raised the hopes of scientists

communicable diseases (NCD). At the same time, it has been shown that obese people tend to manifest a loss of microbial richness in the gut, a condition which is thought to increase the risk of various NCDs. When addressing the impact of the microbiome research on public health, S Dusko Ehrlich (INRA, Metagenopolis) explained that consequently the microbiome could on one hand be used as a marker for various pathologies and on the other be a target for, among other things, nutritional interventions to correct this atrophy. However, he also highlighted that the complexity and the variability of the microbes found in our bodies meant that there would hardly be one standard preventive solution that benefitted everyone.

> "The microbiome could be used as a marker for various pathologies and simultaneously be a target for nutritional interventions to correct this atrophy"

Of mice and men

Nadine Cerf-Benoussan of the Institut Imagine in France explained that while the super-organism composed of human and microbe brought many advantages in evolutionary terms, the large number and the diversity of microorganisms also posed a risk and had to be held in check. Her work in germ-free mice showed that re-colonization led to a wide spectrum of immune responses, which seem to balance each other, thereby maintaining the intestine in some sort of equilibrium. They showed that a small number of bacteria species were responsible for triggering mechanisms that led to the complete maturation of the gut immune barrier after birth. In their mice, they identified one in particular, the segmented filamentous bacterium (SFB), which seems to send signals to the host, thereby probably optimizing the immune response towards other microorganisms.

Keeping the balance

The delicate balance between the microorganisms and their host was also the predominant topic of the presentation by Gerard Eberl from the Institut Pasteur, who spoke of the host's "choice between tolerance and inflammation in the face of mutualists and pathogens." The host has four major adaptive immune responses at its disposal, which could broadly be characterized as directed at **1)** intracellular organisms, **2)** parasites, allergens and wound healing, and **3)** extracellular bacteria, or else **4)** be (anti-) inflammatory. The balance between these is established early in life, and it has been suggested that a lack of exposure to infections in infancy and childhood leads to epigenetic changes that result in increased sensitivity to allergies. However, the decision between "tolerance" and "inflammation" was also influenced by other external factors such as diet; adequate levels of retinoic acid could shift the response from pro- to anti-inflammatory.

Discussion and conclusions

Research in recent years has greatly improved our understanding of the microbiota and their role in human health and disease. However, the complexity and the multifactorial nature of the system pose a major obstacle to putting this new-found knowledge to practical use. Still, the opportunities that lie within this accumulation of bacteria are too great to be neglected and will likely keep scores of scientists busy for the foreseeable future.

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Special Feature

"We Must Not Be the Generation that Breaks the Promise Entrusted to Us"

Shawn K Baker, Director of Nutrition, Bill and Melinda Gates Foundation, with a baby

Issue 1/2014 of *Sight and Life* featured "A Day in the Life of Shawn Baker," Director of Nutrition at the Bill & Melinda Gates Foundation. In November 2014, Shawn spoke at a roundtable meeting held within the framework of the Second International Conference on Nutrition (ICN2) in Rome, Italy. Shawn's observations are so pertinent for the global nutrition community that we reprint them here with our sincere thanks to him.

Thank you Madam Ambassador, Honorable Co-Chair Persons.

When Anna [Lartey] and Francesco [Branca] asked that I speak at this roundtable, I felt very honored. But I also felt quite a bit of trepidation. As I will develop a bit further in my remarks, I think that many of us who work in nutrition move out of our comfort zone when we speak about "governance". It is comfortable to debate requirements for different vitamins and minerals, or the merits of one set of interventions versus the other, or the results of the latest efficacy trial. However, when we speak of governance, we move from our comfort zone of being good technocrats into the realm of politics. This is painful, but necessary – since, at the end of the day, the challenges of nutrition are now far less about the science, and much more about the politics of making it happen.

So I started preparing for this roundtable by asking myself a series of questions. The first question I had is very basic: "Why do we need governance for nutrition?"

"Governance" is a very serious word, and I wanted to question if we needed something so serious.

I will go back to a presentation that Francesco made in Delhi last week. From the WHO multicenter growth reference standards research, and the follow-up InterGrowth study, we have the conclusive evidence base that children from all regions in the world have the same potential for physical growth and cognitive development in utero and early childhood.

To me, this is fundamental evidence of our common humanity, and that the nutrition necessary to realize this potential is the birthright of every child.

> "The nutrition necessary to realize our common human potential is the birthright of every child"

Unfortunately, we have seen ample evidence in the last few days that we are denying hundreds of millions of children this fundamental birthright. We are therefore undermining their

chances to survive, and to thrive. We are undermining the futures of their families, their communities, their nations, and even the whole world.

So I think that we have passed the first hurdle. I convinced myself that a problem so fundamental needs governance that is commensurate with the gravity of the problem.

The second question I posed myself is: "What are the particular challenges of nutrition governance?" Other sectors seem to have done pretty well – when I think about HIV, or malaria, for example. Are there things about nutrition that make it complicated?

When we look at examples where effective governance, resulting in robust action, has emerged, it is where there has been recognition of a "clear and present danger." For HIV, the entire world felt at risk. Political leaders had family members affected, and in the US and Europe activists were scaling the walls of parliaments. For SARS in the recent past, or in the tragic headlines of today in the case of Ebola, again, the entire world feels at risk. During the 2008 food price crisis, politicians feared food riots and political upheaval.

Unfortunately, despite the immense damage it causes, malnutrition is largely a "hidden" problem. It is hidden because nutritional deficits are usually not visible. It is hidden by its ubiquitous nature, which makes it "the norm" in many countries. And it is hidden because the people most affected by undernutrition are those who have the least voice. It is even further hidden because, as we have seen in the Global Nutrition Report, it is so poorly measured.

> "Despite the immense damage it causes, malnutrition is largely a 'hidden' problem"

It is further complicated because it is hard to figure out who is in charge. If I am a head of state and there is a disease outbreak in my country, I call my Minister of Health. If there is an invasion, I call my Minister of Defense. If my country falls to the bottom of rankings of school performance, I call my Minister of Education. Again, as we have seen in the Global Nutrition Report, many, if not most, countries are facing a nutrition crisis. But who is in charge? Who is accountable?

In that sense, I think that nutrition has more parallels with climate change than many other issues where governance has driven action. Similar to climate change, it requires action and accountability that is orchestrated across many sectors. Nutrition also requires long-term commitment – and to be long-term, that commitment has to be political, but not partisan, so that it withstands any change in government and is embraced as a non-negotiable by all parties.

So I convinced myself that nutrition does indeed warrant governance, and that nutrition has governance needs that are quite special. I then asked myself: "What is governance?" It is one of those words we throw around a lot, but we all probably have a different interpretation of what it means. I looked up a number of definitions, some quite short and sweet, like Merriam-Webster's: "The way that a city, company, etc., is controlled by the people who run it." Some definitions were much more complicated. The one I found most useful actually was on Wikipedia: "All processes of governing, whether undertaken by a government, market or network, whether over a family, tribe, formal or informal organization or territory and whether through laws, norms, power or language." It relates to "the processes of interaction and decision-making among the actors involved in a collective problem that lead to the creation, reinforcement, or reproduction of social norms and institutions." That reminded me of one of the announcements earlier in the week at the Global Gathering of the Scaling Up Nutrition Movement, from our colleagues from Francophone Africa, that a new United Republic for Nutrition had been founded – with the social norms that malnutrition would not be permitted.

And so now you start to see why Anna and Francesco's request made me quite fearful. I suspect that many of us in the room today were trained as nutritionists, or public health specialists, or agronomists. We revel in the relative comfort of our world of science. We might stray from time to time into the murkier world of policy. But we really do not feel at ease in the really messy world of politics. But, to truly make a change, we need to embrace the fact that nutrition needs to be addressed, not just at the technical and policy level, but also, and perhaps especially, at the political level.

> "To truly make a change, nutrition needs to be addressed at the political level"

Then my last question, and this is the one that Anna and Francesco probably wanted me to opine on – sorry, I am a bit slow at times – is: "What are the characteristics we should aspire to in nutrition governance?"

I see five essential characteristics:

1. It needs to make the problem visible. Visible and urgent. It needs to change the narrative, and recast norms so that malnutrition is no longer acceptable. This will include better measurement, so that we can no longer hide behind the excuse of poor data. We can no longer hide behind the term "chronic" to ignore the urgent need to take action – because malnutrition's damage to children is irreversible.

2. It has to be inclusive and empower the diverse sectors and stakeholders to act. It must provide concrete, actionable guidelines, so that each actor knows what to contribute. And it must generate resources and capacity so that each actor can contribute. It must drive increased investments from domestic and development assistance sources to get behind evidence-based interventions.
3. On the flip side, it has to hold these diverse sectors and stakeholders accountable. It must set a common definition of success, agree on contributions of each actor, and measure their follow-through. We have a good starting-point, with the World Health Assembly targets for 2025, which the world has already committed to. Our governance needs to focus on delivering on these targets and hold us accountable.
4. It needs to be political, but not partisan. It needs to bridge partisan interests, so that momentum for nutrition is maintained for the long term, regardless of the transitions in governments or the changes in leadership in organizations.
5. It needs to be focused on results for the people the governance is serving. It must be a means to an end, the end of malnutrition, not an end in itself. It should not seek to create new bureaucracy, but rather to make all of us work better, so as to meet the needs of the people we serve.

I wanted to close my comments today with one of my favorite quotes from Nelson Mandela. Referring to the Millennium Development Goals, President Mandela queried: "Will our generation's legacy be more than a series of broken promises?"

> "Will our generation's legacy be more than a series of broken promises?"
>
> *Nelson Mandela*

We stand at the cusp of the world defining the successors to the Millennium Development Goals. I think for many of us who have participated in the two and a half days of the Global Gathering of the Scaling Up Nutrition Movement, and the first two days of the Second International Conference on Nutrition, we feel that there has never been a greater promise to deliver on nutrition. Clearly, anchoring nutrition within the upcoming Sustainable Development Goals is one more step in building on that promise. To do so, we need to ensure the goals are aligned to the World Health Assembly targets, that key issues such as breastfeeding are included, and that our governance ensures the follow-up and accountability to ensure they are achieved.

Whatever the nature of any nutrition governance, we must be clear that its purpose is to make sure that we are not the generation that breaks the promise that has been entrusted to us: the promise that all children, everywhere, realize their potential for physical growth and cognitive development.

Thank you.

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About ICN2

The Second International Conference on Nutrition (ICN2) was a high-level intergovernmental meeting that focused global attention on addressing malnutrition in all its forms. Over 2,200 participants attended the meeting, including representatives from more than 170 governments, 150 representatives from civil society and nearly 100 from the business community. In addition to plenary sessions held on November 19, 20 and 21, several pre-conference events for parliamentarians, civil society and the private sector, as well as round tables and side events, provided a forum for participants to delve deeper into specific nutrition issues. The two main outcome documents – the Rome Declaration on Nutrition and the Framework for Action – were endorsed by participating governments at the conference, committing world leaders to establishing national policies aimed at eradicating malnutrition and transforming food systems to make nutritious diets available to all.

Source: www.fao.org/about/meetings/icn2/en/, accessed March 2015.

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Affordable Nutritious Foods for Women (ANF4W): Overview

Innovative approaches for alleviating micronutrient deficiencies in women of childbearing age

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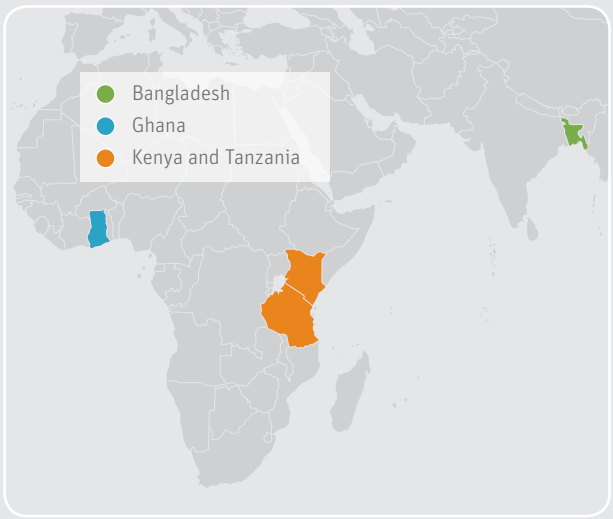
ANF4W project description

The Affordable Nutritious Foods for Women (ANF4W) project is an incubator for testing innovative market-based approaches that can create and promote a sustainable supply of, and demand for, affordable micronutrient-rich foods aimed at reducing micronutrient deficiencies in women of childbearing age (15–49 years). The project is currently being implemented in four countries, and its approaches include fortification of supplementary food, agronomic biofortification, and staple food fortification. In Ghana, ANF4W currently supports local food processors in the development of micronutrient fortified food prototypes targeted at women of childbearing age.

ANF4W is co-funded by the German Federal Ministry for Economic Cooperation and Development (BMZ) and the Bill & Melinda Gates Foundation. It is implemented by the Deutsche Gesellschaft für Internationale Zusammenarbeit (GIZ) GmbH, within the framework of development partnerships with the private sector (develoPPP.de).[1] The current project phase runs from February 2013 to May 2017.

FIGURE 1: ANF4W partner countries



"The Affordable Nutritious Foods for Women (ANF4W) project is an incubator for testing innovative market-based approaches"

The project encompasses three intervention areas:

a) Increasing **availability** of micronutrient-rich foods.
This intervention area seeks to secure availability of micronutrient-rich food in the partner countries by increasing their local production.

b) Improving **access** to micronutrient-rich foods.
This intervention area aims at providing better access to micronutrient-rich foods for women of childbearing age by enhancing distribution channels to the local level and ensuring the affordability of the food products, especially in rural areas.

c) Promoting **utilization** of micronutrient-rich foods.
The first two areas would not be successful if the micronutrient-rich foods provided were not consumed, for whatever reasons. This intervention area therefore promotes appropriate consumption of micronutrients by women of childbearing age through nutrition awareness communication and marketing. It also encourages health behaviors which prevent micronutrient deficiencies or otherwise reduce the burden of deficiencies in the population.

The following section will showcase ANF4W activities in Ghana, describing how availability, access and utilization of micronutrient rich foods are attained.

ANF4W in Ghana: developing new targeted fortified supplementary foods

In Ghana, ANF4W is being implemented in cooperation with *Sight and Life*, Ajinomoto Co. Inc. (headquartered in Japan), McCann Health, and the Global Alliance for Improved Nutrition (GAIN). ANF4W's strategy in Ghana is to develop affordable fortified supplementary food products together with Ghanaian food processors, which will be targeted specifically at women of childbearing age. The project has conducted studies on a range of local conditions or factors that play a role in a local stakeholder's ability to create and supply an affordable nutritious product. These are as follows.

A **focused ethnographic study** assessed women's eating habits and beliefs around food. The study identified feeding and purchasing patterns, as well as beliefs and knowledge about nutrition that inform the potential food concepts that could be further developed into targeted food products. For example, the study found that pregnant and lactating women spend on average US$ 3 per week on ready-to-eat foods, and that these foods are likely not to be shared with others.

An **agricultural value-chain analysis** identified affordable and locally available agricultural commodities in Ghana that could be used as ingredients for the supplementary food prototypes. Criteria used for selection included nutritional quality (nutrient content, anti-nutritional factors and contaminants), affordability, availability, accessibility, and value-chain dynamics. Fifteen agricultural commodities were shortlisted, including millet, cowpeas, yam, fruits, plantain, tomatoes and garden eggs.

A **distribution channel analysis** reviewed possible delivery channels that could facilitate market penetration and uptake of the food product by the target consumer. The analysis considered factors that drive distribution costs, and ultimately retail and institutional purchase prices were considered. Three main distribution models for ANF4W were identified:

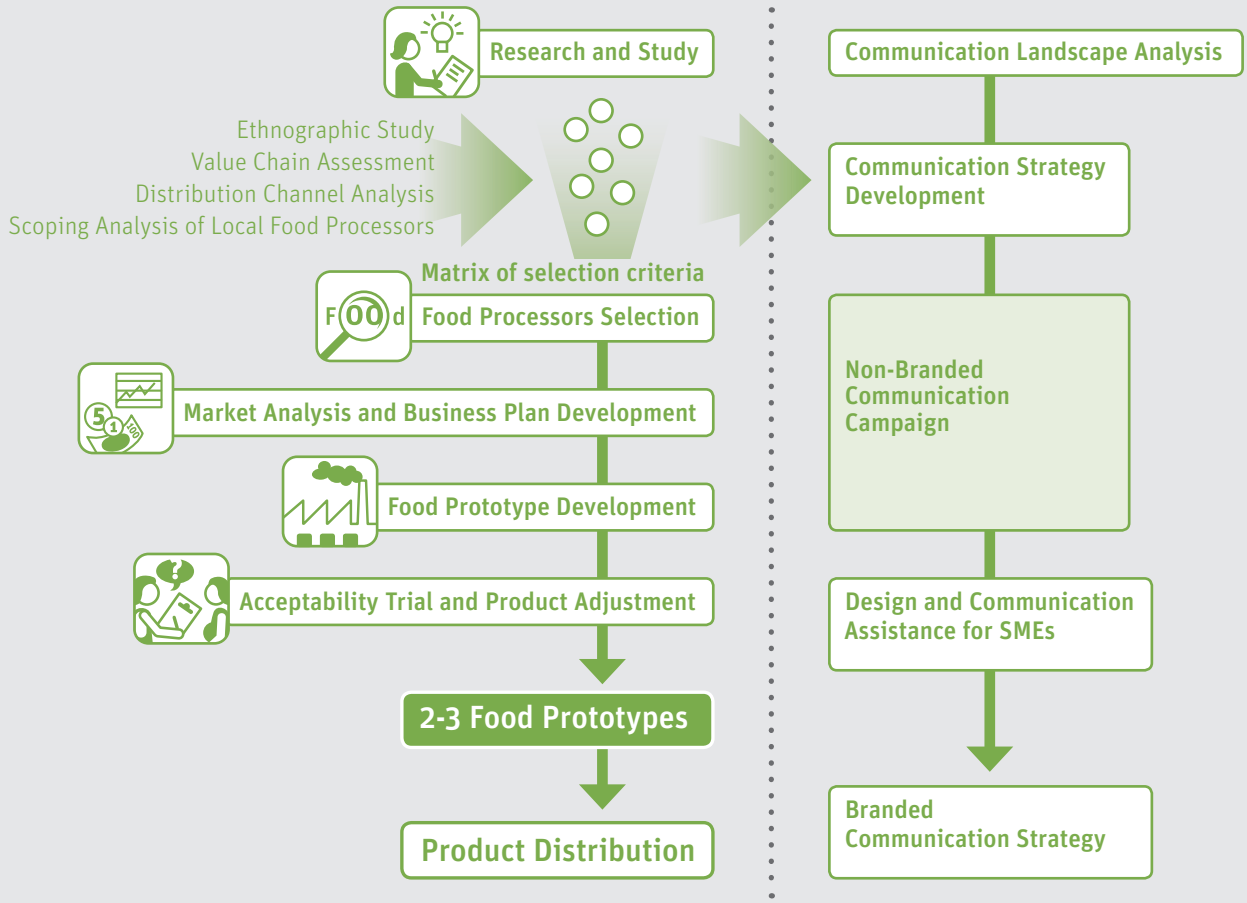
- **Fast-moving consumer goods distribution models (FMCG).** These rely on extensive marketing and strong brand building.
- **Direct sales models.** These use direct and personal interaction with the consumer. They provide an opportunity to educate the consumer about product benefits.
- **The FMCG-pharmaceutical hybrid model.** This uses both product marketing and direct consumer interaction.

The project will also explore beauty salons, where women spend a lot of time, as a potential point of distribution. The fortified food products would be placed in the beauty salons, where ideally the beautician could be an advocate or ambassador for these products.

A scoping analysis of local food processors distinguished suitable Ghanaian food processors that ANF4W could collaborate with to develop targeted fortified supplementary foods. The analysis focused on assessing local food processors' capacities, requirements and expectations regarding targeted fortified food product development, and local food processors' technical and financial capacities. Eight firms were shortlisted, based on their willingness to collaborate with ANF4W, and their readiness (in terms of technical knowledge, available infrastructure, and access to finance) to develop targeted fortified supplementary food products. Engagement with local small and medium-sized enterprises (SMEs) is pivotal in ensuring transfer of knowledge and know-how from the international private-sector firms, thus promoting sustainability of local markets.

Additionally, a communication landscape analysis explored critically important concepts of individual and societal norms

FIGURE 2: ANF4W Ghana Conceptual Framework



around nutrition, which could be used to develop creative and meaningful communication strategies that can fundamentally change behaviors and social norms. The non-product-specific nutrition awareness communication strategy will therefore not only raise awareness of the importance of micronutrients for women of childbearing age, but will also address barriers to successful uptake of future food products by women. Figure 2 conceptualizes the ANF4W approach in Ghana.

Based on the results from the various studies conducted, a matrix of criteria selection was developed, and potential nutritious and affordable food concepts were ranked accordingly. Criteria included nutrient value, cultural acceptability, local availability of ingredients, required infrastructure (equipment, storage, etc.), costs of production and distribution etc. Food concepts that were identified include a beverage, snack bar and sauce.

Next steps

Before the end of the current project phase, ANF4W will engage with local food processors in developing food prototypes from the viable food concepts identified. The expected results of this approach include:

- **Increasing availability of micronutrient-enriched foods.**
  Private sector partner companies have provided technical expertise (including quality assurance and quality control measures) to selected local food companies enabling them to produce micronutrient-rich foods.
- **Improving access to micronutrient-enriched foods.**
  Local food processors deliver food products to local vendors via existing distribution channels; local vendors sell new fortified food products; health authorities explore ways of subsidizing food products for women of childbearing age.
- **Promoting utilization of micronutrient-rich foods.**
  Private partners support local food processors in marketing targeted fortified food products; women of childbearing age make informed dietary purchasing decisions.

"ANF4W will engage with local food processors in developing food prototypes from the viable food concepts identified"

The project is currently seeking additional funding to increase its impact. This involves improving evidence of its effect on the nutritional status of women and thereby learning lessons for the potential transfer of the approach to other countries.

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Federal Ministry for Economic Cooperation and Development

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(Figures as at December 31, 2013)

Affordable Nutritious Foods for Women (ANF4W): Value Chain

Agricultural Value Chain Analysis for Developing Affordable Nutritious Foods for Women in Ghana

Kalpana Beesabathuni
Sight and Life, Delhi, India

Key messages

- Affordable, nutritious foods are currently lacking in Ghana.
- An agricultural value chain analysis (AVC) was conducted as one of various studies to identify elements that influence the ability of local food processors to create such products.
- Affordable commodities were identified, and agricultural practices that affect the quantity and quality of food supply were explored.
- The agricultural value chains traditionally developed to improve farmer incomes and food security are now assessed with human nutrition as a key criterion.
- More than 31 commodities were evaluated.
- A relative ranking of commodities was provided for a porridge or snack bar food concept.

The author would like to thank the following for their invaluable contribution and support: Jedidah Tetteh (independent researcher), Till Ludwig (GIZ), Leonie Vierck (formerly GIZ) and Eva Monterrosa (*Sight and Life*).
This study was funded by the Deutsche Gesellschaft für Internationale Zusammenarbeit (GIZ) GmbH Sector Project on Agricultural Policy and Food Security.

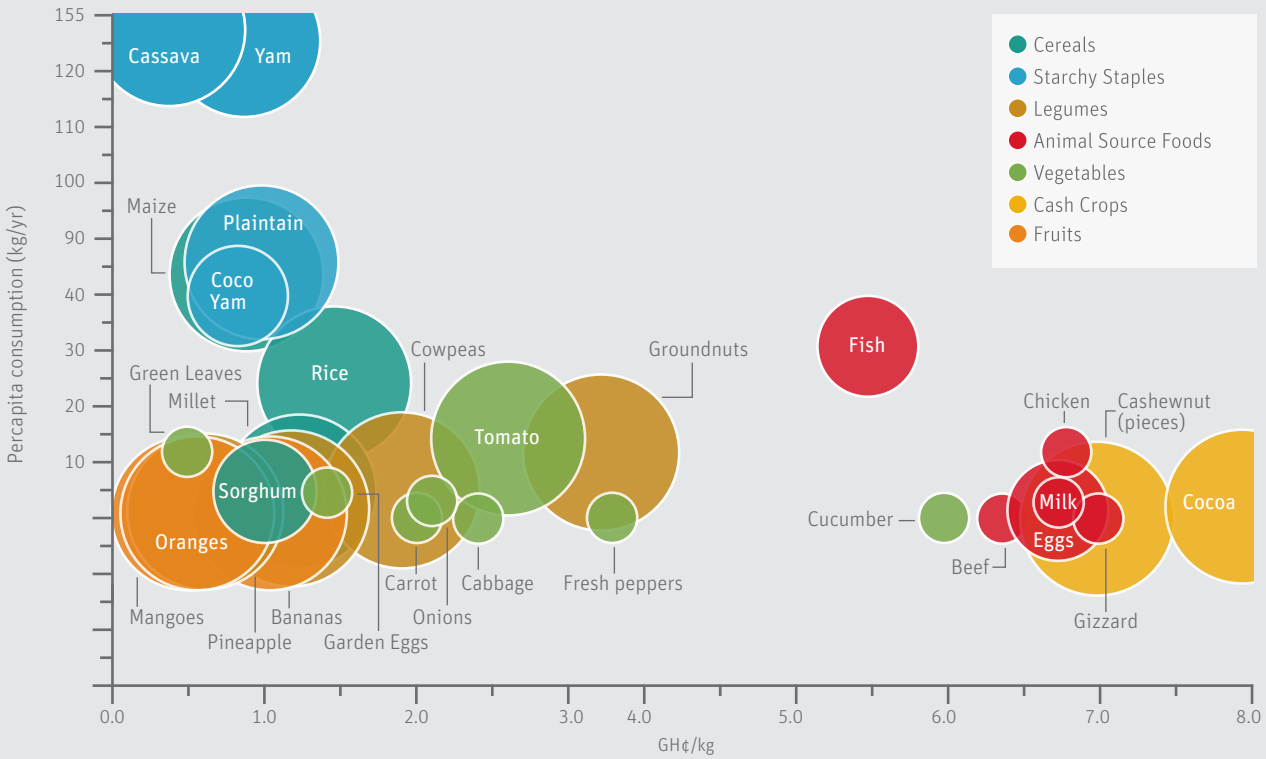
Introduction

The Affordable Nutritious Foods for Women (ANF4W) project aims to improve the intake of micronutrients by women of reproductive age (WRA, 15–49 years of age), with a view to the critical window of opportunity represented by the first 1,000 days of a child's life. It uses market-based approaches, complemented by nutrition awareness activities, to create and promote a sustainable supply of nutritious foods and food products. The project is currently being implemented in four countries – Bangladesh, Ghana, Kenya and Tanzania – and its approaches include agronomic biofortification and staple and supplementary food fortification.

ANF4W is co-funded by the German Federal Ministry for Economic Cooperation and Development (BMZ) and the Bill & Melinda Gates Foundation. It is implemented by the Deutsche Gesellschaft für Internationale Zusammenarbeit (GIZ), within the framework of development partnerships with the private sector (develoPPP.de). The current project phase runs from July 2013 to May 2017.

> "The agricultural value chains are now assessed with human nutrition as a key criterion"

FIGURE 1: Map of agricultural commodities assessed in Ghana during phase 1



Note: Compiled by author based on expert interviews and statistics from MoFA, FAOSTAT (2011–2012). Size of the bubble depicts ease of procurement or availability for food processing. Affordability is measured in wholesale prices (Ghana cedi/kg) and per capita consumption in kg per annum. Size of bubble denotes availability of the commodity or ease of procurement for food processing.

In Ghana, ANF4W supports local food processors in the development of supplementary fortified food products. In identifying different elements that play a role in the ability of local food processors to create an affordable nutritious product, an agricultural value chain analysis (AVC) was conducted. The AVC's goal is to identify affordable agricultural commodities in Ghana, and to understand how agricultural practices affect the quantity and quality of food supply available to local food processors. This evaluation also adds understanding of value chain constraints, and of opportunities to encourage local production of commodities which improve the nutrition of vulnerable groups. In so doing, the agricultural value chains traditionally developed to improve farmer incomes and food security are now assessed with human nutrition as a key criterion.

The study blends secondary and primary research. The desk study utilized more than 100 sources followed by 51 stakeholder and expert interviews in the Brong-Ahafo, Greater Accra, Volta, Eastern, and Northern regions. Stakeholders included donor agencies, non-governmental organizations, entrepreneurs, food processors, farmers, market women, aggregators, traders, wholesalers and retailers.

Selection of commodities

Commodities were selected and screened in two phases. Criteria used for selection included nutritional quality (content of nutrients, anti-nutritional factors and contaminants), affordability, availability, accessibility and value chain dynamics. Out of 31 commodities selected in the first phase across 7 categories – cereals, legumes, tubers, cash crops, animal-source foods, fruits and vegetables (see Figure 1) – 15 commodities were evaluated in depth in the second phase. These are millets, rice, cowpeas, soybeans, yam, cassava, plantains, anchovies, mangoes, pineapples, oranges, cassava leaves, moringa leaves, tomatoes and garden eggs. Spices available in the open market were also assessed for their nutritional quality and affordability.

Findings

All plant-based commodities have a high level and a wide range of anti-nutritional factors. Anti-nutritional factors are food constituents that have a negative impact on the solubility or digestibility of required nutrients and thereby reduce the amounts of bioavailable nutrients and available energy in the foods. Climatic and edaphic factors such as temperature, moisture content, soil

TABLE 1: Definition of qualitative and quantitative indicators and variables

Indicator | Variable	Description
Affordable nutrition (GHC/mg)	Affordability measured by wholesale price and nutrient density measured by amount of bioavailable protein, minerals and vitamins are combined into the criteria affordable nutrition. Its unit of measurement is bioavailable nutrients (mg) per unit wholesale price (Ghana Cedi or GHC). These criteria would be useful to assess amount of investment required to improve nutrition. Minerals include Ca, Fe, Zn, Cu, Se, P, Mg. Water-soluble vitamins include B_1, B_2, B_3, B_6, B_9, B_{12}, C. Fat-soluble vitamins include A, D and E. The higher the score, the more favorable is the outcome.
Commodity quality	This is measured by content of anti-nutritional factors and contaminants. Both these sub-criteria have equal weights. The lower the content, the better the quality of the commodity.
Accessibility	Accessibility is heavily drawn from information about value chain dynamics. Trends in production, consumption, import, export, cost of production, distribution and marketing influence access to commodities. This criterion is a composite score of availability, level of aggregation, wholesale price growth rates, and wholesale price volatility.
Availability	Availability accounts for trends in production, consumption and trade, whether production areas are widespread, and the seasonal nature of the crop.
Aggregation	Aggregation describes the level of aggregation of a commodity and whether market hubs are present where aggregators sell the produce to food processors. High availability and high level of aggregation are preferred, as they facilitate the easy procurement of raw materials.
Wholesale price CAGR	Growth rate and volatility of wholesale price have an effect on availability and access to commodities for low-income groups. Low wholesale price cumulative growth rate (CAGR) and volatility are preferred, as they stabilize the cost of raw materials and hence the final price of ANF4W.
Wholesale price volatility	Wholesale price volatility was calculated for four years, from 2009 to 2012. Here volatility is the standard deviation of returns, where the return is defined as the proportional change in price from one period to the next. The return is measured as the difference in the logarithm of prices from one period to the next.
Value chain dynamics	Favorable value chain dynamics are important to obtain a sustainable supply of raw materials for ANF4W as well as an opportunity to make the value chains gender-sensitive, to integrate smallholder women farmers and to be socially inclusive.
Poverty sensitivity	Poverty sensitivity is measured by the number of smallholder farmers. The number of smallholder farmers is a product of population, the percentage of the labor force involved in agriculture, the proportion of smallholder farmers, and the proportion of arable land allotted to selected commodities. Commodity value chains that have a high number of smallholder farmers are preferred.
Gender sensitivity	Gender sensitivity is measured by the level of participation of women in farming and small-scale processing. Field interviews indicated a high level of participation by women in small-scale processing of certain commodities such as plantains. These women can potentially be both producers and/or consumers of ANF4W.
Level of investment	The level of investment is determined by the number of public and private players investing in activities along the value chain.
Enabling environment	The enabling environment is a measure of infrastructure, industry bodies and policies that boost efficiencies along the value chain.

pH, mineral constituents and other factors can affect the levels of anti-nutrients. There is very limited information on precise levels of anti-nutrients in commodities produced in Ghana. Cereals are rich in the amino acid methionine but low in lysine, while pulses and legumes are rich in lysine and low in methionine. A blend of both flours is likely to have a higher Digestible Indispensable Amino Acid Score (DIAAS, a measure of protein quality) value than pure cereal or pure legume flours.

There is a loss in nutrients as the commodity moves through the value chain. Vitamin C loss is the most documented, ranging from 20% to 100% depending upon the type of commodity, storage time and exposure to heat, light and oxygen. Controlling growth and spread of mycotoxins continues to be a challenge in Ghana. Though aflatoxin is most prevalent in maize and groundnuts, aflatoxins were also detected in sorghum, soybean meal and cassava flour. Several studies indicated the presence of pesticide residues in vegetables and fruits.

Most of the commodities chosen, except for rice and pineapples, are thinly traded (imported and exported) between Ghana and other countries. There is a high demand for imported rice in urban areas and fresh pineapples for exports. However, imported rice has little relevance for ANF4W, as local rice can be used to make processed foods. Cassava and soybeans are being considered as important for food security, and as tradable crops they receive a high level of investment due to the increasing demand for them, both for human consumption and for industrial purpos-

A market woman selling legumes and cereals

es. The rising cost of energy, and hence of transportation, was cited as the key driver affecting the wholesale prices for most of the selected commodities. Storage, post-harvest losses exist for all the commodities. Poor infrastructure, extension services and agricultural practices affect the yields for most of the crops.

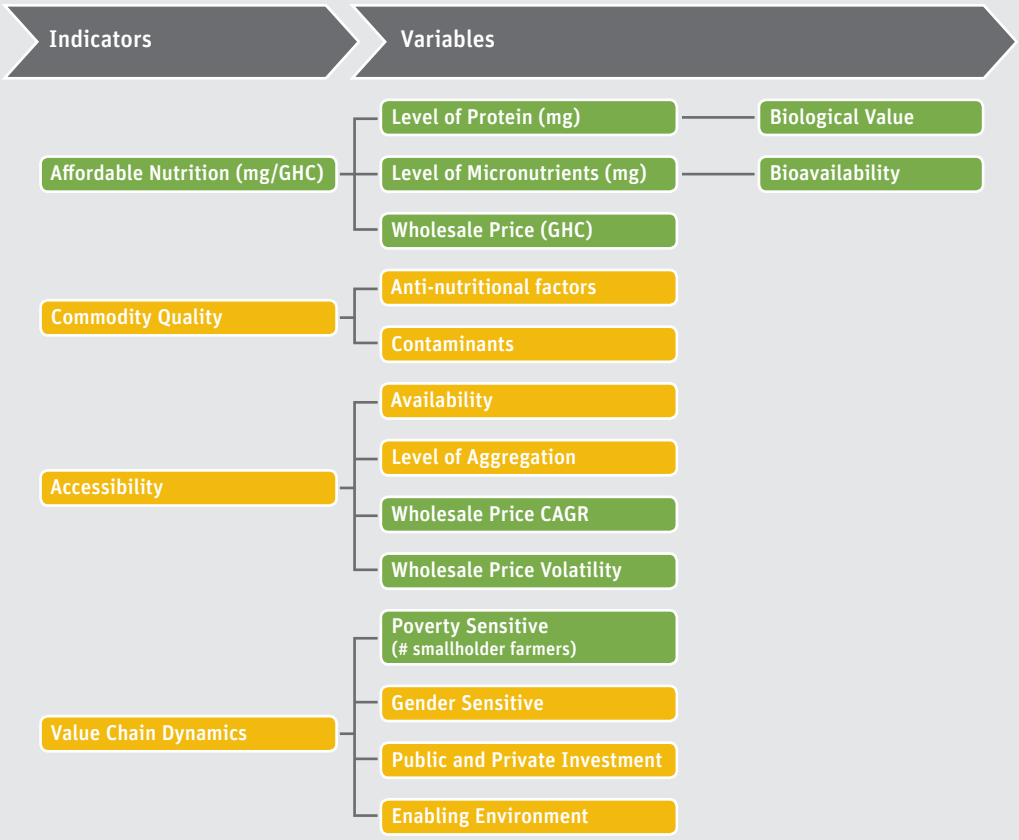
Open market retailers of the selected commodities are mostly women. Market power is chiefly concentrated at the wholesale levels for all the commodities except for anchovies. For this commodity, traders at landing sites, called "queen mothers", have the most influence.

Recommendations

Commodities were ranked using a mix of qualitative and quantitative criteria – affordable nutrition, commodity quality, accessibility and value chain dynamics (see **Figure 2, Table 1**). The overall relative ranking of commodities that are recommended for making porridge or a snack bar are rice > soybean > cowpeas = anchovies > millets > yam > cassava > plantains.

The negative impact of anti-nutrients can be best minimized by various food processing techniques or through the addition of

FIGURE 2: Indicators and variables included in ranking commodities



Note: Equal weights were given to all indicators and variables so as to arrive at a composite score for ranking the commodities. **GHC** = Ghana Cedi

Plantains on sale at Techiman Central Market

additives such as phytase and vitamin C. Training and increasing awareness of the risk of contamination among actors along the value chain is required in respect of all of these commodities. Social marketing and the creation of a certification scheme with a logo on food products guaranteeing nutritional quality (density of macro- and micronutrients, low content of anti-nutritional factors and toxins or contaminants) could act as an incentive for processors to invest in traceable value chains and catalyze demand from consumers.

Legumes, soybean and cowpeas were recommended by several stakeholders, not only for their nutritional value and other uses but also for their attribute of nitrogen fixation, which can improve soil fertility and yield, and can reduce inputs.

> "Creating a certification scheme with a logo guaranteeing nutrition quality could act as an incentive for processors to invest in traceable value chains"

It is recommended to partner with actors such as the Bill & Melinda Gates Foundation and USAID, who are actively developing rice value chains in Ghana to offer a "double dividend" investment. The majority of the rice production (> 90% by volume) comes from smallholders. Women who are dominant in the rice value chain are both income generators and consumers of nutritious food products. This concept of "double dividend" investment could also be applicable to women farmers, "market queens" and "market women" who control wholesale and retail in open markets for most of the commodities. They could be suppliers of raw materials, processors, advocates and consumers of ANF4W.

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Pilot Microfranchise Program in South Africa

Empowering women while facilitating the distribution of innovative fortified products

Sarah Dickerson
Sight and Life intern, South Africa

Sight and Life intern Sarah Dickerson (left) together with microfranchisee Angelina Betha (center) and Thabiso Phoku from DSM South Africa at the certificate presentation following successful completion of the micronutrient fortification training

What is microfranchising, and why is it important to a humanitarian nutritional think tank that seeks to improve the nutritional well-being of some of the world's most vulnerable populations?

The answer is simple: A microfranchise is a scaled-down franchise that sells products inexpensive enough to be purchased by low-income customers in developing countries.

Sometimes these products are nonessential, such as make-up, perfume, or toiletries, but they can also be health products, such as medicine, mosquito nets, or nutritious foods. For many years, *Sight and Life* has given humanitarian support in the form of multiple micronutrients (i.e., fortified biscuits or micronutrient powder added to school feeding schemes) to a number of early learning centers and primary schools. In order to make these humanitarian support initiatives more sustainable, a pilot microfranchise program was recently created, whereby women could sell innovative nutrition products developed by DSM South Africa. The program was elaborated and tested in a disadvantaged community where *Sight and Life* enjoyed previously established relationships.

The importance of good nutrition in childhood

The model for the program was designed to teach franchisees about the importance of good nutrition in childhood and the value of the fortified products. It aimed to equip them with the skills needed to sell, serve customers and manage product stock (these essential skills would be useful beyond the duration of the program). As designated in the model, participants would be given ongoing support and guidance once they began selling the products. The first phase of the pilot would last for six months. The second phase would involve selling for a further four months, after which the program would be evaluated.

To ensure the success of this pilot program, special emphasis was placed on both the preparation and the implementation stages. Ivory Park was selected as the program location due to the fact that it was an economically disadvantaged township within driving distance of Johannesburg and because *Sight and Life* already had connections with some of the community leaders (namely the Dutch-based Tshwaranang Foundation [www.tshwaranang.nl]). Women in the community were invited to attend an information session, the goal of which was to outline the requirements of participating in the program and to gauge their interest. Some 45 women were then invited to pay US$ 5 to participate in the training course, as a demonstration of commitment to becoming a microfranchisee. Of the 25 women who agreed to pay, 16 completed the weeklong training course.

Training topics

The topics covered in the training were broad so as to equip the participants with the basic skills required to start the journey

Microfanchisees receive training from Taurai Nyakunu (extreme right), who ran the project from August to December 2014

toward becoming successful entrepreneurs. The first lesson provided nutritional information on both healthy eating and the products to be sold. This was followed by modules that addressed basic math, how to keep a stock inventory and a sales spreadsheet, the steps involved in the sales process, and the locations within Ivory Park that participants could target to maximize product sales. The final module addressed goal-setting, the importance of saving, and how participants could stay motivated. Participants who attended at least four out of five classes became the first microfranchisees, and received certificates of participation and product samples. These product samples were distributed to the community to generate interest in the products and to further assess acceptability.

> "Participants who attended at least four out of five classes became the first microfranchisees"

Two fortified products – a beverage powder and an instant maize porridge developed by DSM South Africa under the MixMe™ trademark – were the start-up products. The microfranchisees would buy the products at a specified price and sell them at an agreed price that allowed them to make a small profit. All microfranchisees who filled out feedback forms expressed satisfaction with their sales training, and 100% of the customers surveyed (who numbered more than 50) enjoyed the taste of both products.

The first supply of products

Each microfranchisee then received their first supply of products – 15 sachets of porridge (five sachets of each flavor – banana, strawberry and vanilla) and 10 sachets of the orange-flavored beverage power. After the microfranchisees were given their supply of products, they expressed great excitement, which continued – and in many cases grew – once they began selling. Microfranchisees now meet with a project coordinator on a weekly basis. This allows them to place orders, receive new supplies, fill in sales and profit sheets, receive further mentoring and share opportunities and challenges with each other. Initial feedback forms completed by both customers and microfranchisees look promising, and an evaluation of the pilot program's effectiveness is currently under way.

> "Initial feedback forms completed by both customers and microfranchisees look promising"

Potential for scale-up

There is cautious optimism that this program could be scaled up both in Ivory Park and other areas, which supports the theory that microfranchise is a potentially sustainable solution to poverty and unemployment. If the project can continue to accomplish this while also facilitating the distribution of innovative micronutrient products to the most vulnerable, then *Sight and Life* may have incubated a two-pronged approach to tackling poverty-related problems. Ultimately, the program could even serve as a global case study.

Editor's note:

At the end of 2014, Sight and Life and DSM South Africa founded a social business, Sizanani Mzanzi (Zulu for "Help each other South Africa"). Since the pilot was concluded successfully in December 2014, branding of the new company has taken place. Currently, the acceptability of the new logo and packaging designs for three products (pregnancy supplement, porridge, beverage) is being assessed in focus groups.

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Report from Kenya

Fortification with Micronutrient Powder to Address Malnutrition in Rural Kenya

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Malnutrition is a serious public health problem in most rural communities of Sub-Saharan Africa, contributing significantly to the morbidity and mortality of children under five years of age. This burden of malnutrition is reflected in all of the Millennium Villages Project (MVP) sites, including Sauri Millennium Village (MV) and Dertu MV in Kenya. Sauri is a rural community of about 70,000 people in Siaya County, Nyanza province in western Kenya, while Dertu is a mostly pastoral community in Garissa Country, northeastern Kenya. The MVP is an integrated rural development project jointly implemented by the Earth Institute at Columbia University and the Millennium Promise Alliance in ten countries in Sub-Saharan Africa. The MVP aims to demonstrate if and how poor remote communities can achieve the Millennium Development Goals with an estimated investment of US$60 per capita per year (16 cents per day) for five to ten years. The MVP's integrated model employs a multi-sectoral development strategy to simultaneously address the many underlying causes of extreme poverty, including food production, access to health care, education, infrastructure and business development.

A baseline survey conducted in Sauri in 2005 revealed that, among the 300 households interviewed, roughly 60.2%* of children under five were stunted (i.e., low height-for-age, an indicator of chronic malnutrition) and roughly 7.5%* of children under five were wasted (i.e., low weight-for-height, a sign of acute malnutrition). The prevalence of underweight – a composite indicator of chronic and acute malnutrition defined as low weight-for-age – among children under five in these households was 25.3%.* In Dertu MV, the prevalence of stunting, wasting and underweight among children under five surveyed was 38.7%,* 20.0%,* and 38.6%* respectively at baseline (2006). Additionally, the rates of anemia were an astonishing 100% in Dertu and 77% in Sauri among the children under five surveyed. The high prevalence of malnutrition in Sauri and Dertu MVs at baseline suggested that local diets were not sufficient for meeting the micronutrient needs of young children, who, along with pregnant and lactating women, are the most vulnerable to macro- and micronutrient deficiencies.

Bolstering each pillar of food security

The Millennium Villages Project works in conjunction with communities and governments to bolster each pillar of food security – availability, access, and utilization of nutrient-rich foods – by engaging different sectors. Improved seeds, agricultural extension programs, and investments in irrigation have led to higher crop yields and agricultural biodiversity to ensure availability of nutritious foods. The MVP's infrastructure and business development initiatives promote income-generating activities that enable greater access to diverse foods. In addition, community members are counseled on better utilization of nutrient-dense foods through cooking demonstrations, school-based nutrition campaigns, and a robust Community Health Worker program. However, food security alone is insufficient to prevent child malnutrition. Inadequate care and poor water, sanitation and hygiene (WASH) conditions cause morbidities that lead to malnutrition, which in turn undermines the immune system, leaving children more vulnerable to infections and disease. While the MVP aims to address most or all of the factors in the nutrition impact pathway, including strengthening the primary health care system and increasing access to safe water and improved sanitation facilities, malnutrition remains a persistent and complex challenge that affects all but two countries globally.[1]

*Preliminary, unpublished data. The MVP nutrition data from baseline to the present, including new 2015 data, will be analyzed in greater detail as part of the final evaluation of the new project which is now under way and will be published in 2016.

A mother in Sauri Millennium Village, Kenya, feeds her child porridge fortified with MNP

"Malnutrition remains a persistent and complex challenge"

Over the first three years of the project, the MVP, which aims to address all aspects of the nutrition impact pathway, observed substantial reductions in stunting prevalence. Across nine of the MV sites, stunting prevalence among children under two was, on average, 43% lower in 2008–9 than at baseline.[2] However, the early gains in nutritional outcomes were difficult to replicate in subsequent years, and progress began to stagnate.

In August 2012, the MVP partnered with *Sight and Life* to find ways to continue improving the nutritional status of children in Sauri and Dertu. The 1,000 days between conception and a child's second birthday is widely recognized as a critical window of opportunity to positively impact a child's cognitive development, physical growth, and long-term health. Accordingly, *Sight and Life* and the MVP chose to focus on point-of-use fortification with micronutrient powders (MNP) for children six to 23 months of age, which was later declared by the World Health Organization (WHO) as one of the Essential Nutrition Actions for improving maternal, newborn, infant, and young child health in 2013.

MixMe™ micronutrient powder

DSM's MixMe™ micronutrient powder contains 15 vitamins and minerals considered essential for healthy development and growth, including vitamin D for bone development and iron for cognitive development, and zinc for overall growth.[3] It is packaged in single serving, one-gram sachets for daily use and can be easily mixed into a small amount of soft or semi-solid complimentary food for the child to consume. Noted by the WHO for their long shelf-life and limited transport and storage concerns, MNPs have been found to reduce iron deficiency and anemia in infants and young children.[4]

"MNPs have been found to reduce iron deficiency and anemia in infants and young children"

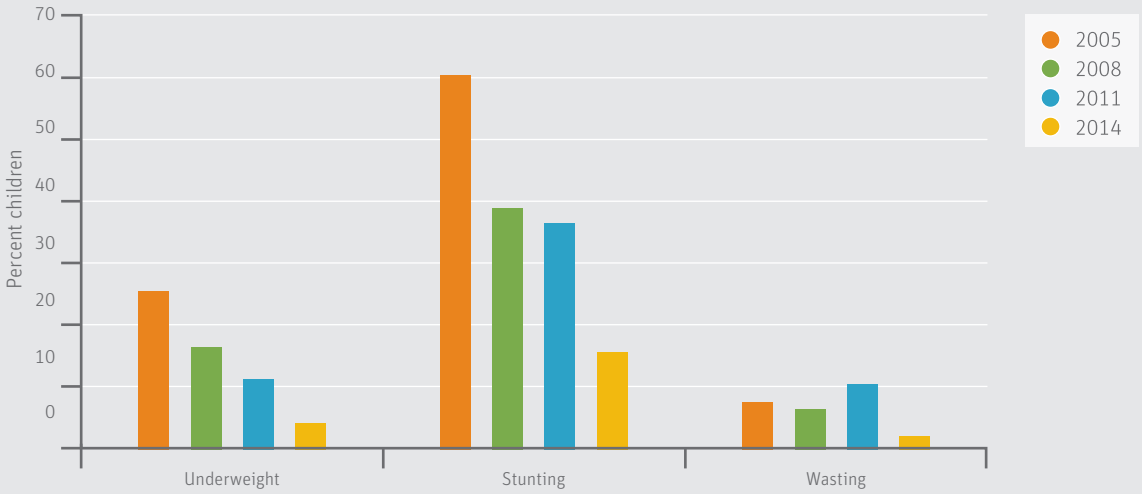
To initiate the new project, the Sauri and Dertu MVP teams first met with community members and government officials to present the initiative and collectively design a plan for implementation. Information, education, and communication (IEC) materials on infant and young child feeding (IYCF) and point-of-use fortification with MixMe™ were developed, translated into the local languages, tested with community health workers and community members, revised, and finalized. Additionally, the project team developed monitoring and evaluation tools including registers, ration cards, monitoring logs, and monthly report forms for understanding compliance. Next, community health workers and their supervisors were trained on distributing MNP, IYCF counseling, and demonstrating proper use.

In Sauri, the MVP team and District Health Management team took advantage of a door-to-door polio campaign to sensitize mothers and caregivers of young children about the upcoming MNP initiative. In Dertu, where communities are predominantly pastoralist and nomadic, community-based health care workers conducted the sensitizations during routine household visits. In total, over 3,500 children aged six to 23 months were enrolled in and around Sauri and Dertu Millennium Villages and received MixMe™ sachets to improve their micronutrient intake.

Acceptance by the community

MixMe™ was generally well-accepted by community members, most of whom noted that it is easy to use, convenient, lightweight, and simple to transport and store. Most mothers were also pleased that the MNP did not alter the taste or texture of foods. However, four mothers stated that their children did not like the taste of the MNP and that one child experienced diarrhea after consuming the powder. Other negative feedback included the absence of instructions in the local language on the packaging, the fact that the sachets may resemble condom packaging, and difficulty understanding the nutrition content as conveyed on the box. Overall, the intervention was well received by com-

FIGURE 1: Sauri Millenium Village



munity members and there was high demand for MixMe™ to be provided to all children under five, not just those from six to 23 months of age.

A nutrition survey conducted in Sauri in 2014 showed remarkable reductions in stunting, wasting and underweight prevalence among children under five in the research area. Unfortunately, due to insecurity in northern Kenya, the survey was not administered in Dertu, and so a similar comparison cannot be drawn.

A note of caution

Since home fortification with MixMe™ was only one of many nutrition-specific and nutrition-sensitive interventions implemented by the MVP, it is important to interpret the data with caution and not attribute these results directly to the MNP intervention or any other specific intervention. However, the significant reduction in all indicators of chronic and acute malnutrition between 2011 and 2014 may suggest that an integrated, multisectoral approach could contribute to improved nutritional outcomes among children under five years of age. The Millennium Villages Project is grateful to *Sight and Life* for its generosity and support.

> "An integrated, multisectoral approach could contribute to improved nutritional outcomes"

Lessons learned from the planning, implementation and monitoring of this project were discussed with key nutrition partners at the Kenyan Ministry of Health in Nairobi. These discussions contributed to the country's National Nutrition Action Plan, launched in 2012, which includes home fortification with MNP as a strategy to achieve its third objective, to reduce the prevalence of micronutrient deficiencies.

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What's New?

Did you know? You can now visit the recently updated *Sight and Life* website **www.sightandlife.org** on a regular basis to get the latest news about what is happening in the field of nutrition. Check out our new blog at **www.sightandlife.org/blog.html!** You can also follow us on **Facebook** and **Twitter @sightandlife.**

01

#EVERYChild 2015

We must end the neglect and abuse of children

As the deadline date for the Millennium Development Goals (MDGs) fast approaches, the discussion around the Sustainable Development Goals (SDGs) that will replace them is well underway. There is much jostling for what will be included, and for those of us dedicated to the field of nutrition, how this vital component will be incorporated and recognized as central is the question on all our lips.

UNICEF has launched a manifesto that lays out actions necessary to ensure that the significant gains made for many children under the MDGs are not lost but built upon and extended to all children in the SDGs. The manifesto rightly states that "it is vital that every child is included – and that children everywhere are at the heart of the new global agenda." While championing for nutrition to be more deeply embedded in the SDGs, we also need to carry the flame for the broader issues that affect children, continually pointing out how nutrition impacts each one of them.

Here are the seven themes that UNICEF puts forward in its #EVERYChild 2015 manifesto to demand and drive change:

1. End violence, neglect, exploitation and abuse of children.
2. Put ending child poverty in all its dimensions at the heart of poverty eradication efforts.
3. Renew the global effort to end preventable child and maternal deaths.
4. Pay more attention to the "second decade of life"– adolescence.
5. Leverage the growing "Data Revolution" to support the rights of every child.
6. Improve investments in all children, especially the most vulnerable and marginalized.
7. Break the cycle of chronic crises affecting children.

To read more, please visit *http://uni.cf/1El21K7.*
You can also look forward to the second 2015 edition of Sight and Life magazine to find out more about the SDGs.

02 The Difference Between a Child Surviving and a Child Thriving

The dictionary defines "survive" as "to continue to live or exist, especially in spite of danger or hardship", and so – although the image this conjures is of some sort of success – it leaves one feeling somewhat unfulfilled. "Thrive" is, however, defined as "to grow or develop well or vigorously," and there are numerous vivid synonyms including *flourish, prosper, blossom, advance* and *make strides*. These make one smile and evoke a sense of real achievement.

We doubt, then, that anyone would want anything less for the world's children than for them to thrive and have a future that gives them the opportunity to live life to the full. Nelson Mandela once wrote: "There can be no keener revelation of a society's soul than the way in which it treats its children." A symposium on nutrition in the first 1,000 days of a child's life hosted by GAIN brought together a number of stakeholders that included WHO, the Bill & Melinda Gates Foundation and DFID to explore the challenges of scaling up infant and young child nutrition programs through innovation and new delivery models. Three key needs were highlighted:

1. The need for more evidence and data pertaining to infant and young child nutrition
2. The need for ensuring that, when developing solutions, we also focus on sustainability
3. The need for behavior change components to interventions and tracking behaviors to create change

There is no doubt that as we move forward from the MDGs to the SDGs we have to do more to ensure that children not only survive but that they also thrive.

To read more about the symposium go to
www.gainhealth.org/knowledge-centre/good-nutrition-difference-child-surviving-thriving/

03 Global Food Policy Report – Where We Are and Where We Are Headed

IFPRI is known for its excellent publications, and the fourth Global Food Policy Report (2014–2015) is no exception, making fascinating reading on major food policy developments and events. It is available in many novel and interactive formats, and the map and data widget allows the reader to instantly visualize the state of the world from the perspective of a range of indicators, such as global hunger or land productivity. Drawing on rigorous research, IFPRI researchers and other distinguished food policy experts consider a wide range of crucial questions. As well as looking back over 2014, they also look forward and offer analysis of the potential opportunities and challenges associated with achieving food and nutrition security in 2015.

The good news during 2014 included: reaching the MDG of halving poverty; world food prices falling to their lowest level since 2010; ICN2; continued increased membership of the SUN Movement; significant commitments to combating climate change; continued efforts towards improving nutrition and food security; and the start of debate on the draft post-2015 SDGs. That said, there were also a number of setbacks, including: the Ebola outbreak; continued conflicts and civil war; and the stark reality that hundreds of thousands continue to suffer from hunger and malnutrition due to disruptions in food production, marketing, and trade.

Read more and be inspired to do more by going to
http://bit.ly/1Dl9f4c

04 Worth Reading ... Worth Receiving ...

15 years on – Bill & Melinda Gates Annual Letter

In 2000, Bill and Melinda Gates started their foundation with the idea that by backing innovative work in health and education, they could help dramatically reduce inequity. Read (and listen to) how they believe they have succeeded, and their ambitious goals for what they believe is possible 15 years from now **at** *http://bit.ly/1y7W44k*. **Follow** *@billgates* and *@melindagates* on Twitter or like them on Facebook for more inspiration.

Keep updated on the Global Nutrition Report

To keep informed of the on-going developments following the launch of The Global Nutrition Report, sign up to their newsletter **by going to** *http://global-nutritionreport.org/*. Also, **like** 'Global Nutrition Report Roundtable Events' on Facebook or **follow them via** *@ifpri* on Twitter.

Alive &Thrive

The Alive & Thrive initiative has released endline survey results showing significant improvements in infant and young child feeding practices in Bangladesh and Viet Nam as a result of its comprehensive behavior change programs. In Bangladesh, from 2010 to 2014, the percentage of infants under six months who were exclusively breastfed increased from 49 to 86 percent in areas that received the comprehensive intervention package, and the proportion of children who consumed a diverse diet increased by 30 percentage points. In Viet Nam, the prevalence of ex-clusive breastfeeding (initially lower than 20 percent) nearly tripled. To keep updated on the initiative's results, and to access their excellent resources, sign on to receive their newsletter and **visit their website** *http://aliveandthrive.org/*. **Follow them** on Facebook or *@aliveandthrive* on Twitter.

Gearing Up for Nutrition Targets and Indicators for the Post-2015 Sustainable Development Goals (SDGs)

As we head towards the new SDGs, The United Nations Standing Committee on Nutrition (UNSCN) has released both a policy brief and a full technical report outlining recommended nutrition indicators and mapping them to proposed SDG goals and targets. At a minimum, the brief urges that the SDG framework needs to include the indicators that measure all six global nutrition targets. These are based on evidence as to what is needed to comprehensively address malnutrition and were endorsed by the World Health Assembly in 2012. The document highlights the centrality of nutrition in development and the need for it to be given a prominent role in the Sustainable Development Framework Explicit.
To download the brief and technical report, please go to *http://bit.ly/1Q1374E*.

05 The Nutrition and Agriculture Link

A rice farmer in India

Getting Nutritious Foods to People through Biofortification

Seven different biofortified crops have been released in 27 countries, where they are being cultivated and consumed by over 1.3 million farm families, and a number of countries at the ICN2 highlighted biofortification amongst their strategies towards ending global hunger and malnutrition by 2025. Now available is the report of the 2nd Conference on Biofortification held last year in Kigali, Rwanda, which includes an excellent infographic, which can be downloaded at *www.harvestplus.org/content/nutritious-staple-food-crops-who-growing-what*, showing what crops have been released where, and where testing and evaluation is currently under way. The "Kigali Declaration on Biofortified Nutritious Foods" was also signed at the end of the conference. It states that *"now is the time to scale up these crops and ensure that those who suffer most from micronutrient deficiencies have consistent access to them,"* and it outlines a call to action to achieve this goal. The full declaration can be found at *http://bit.ly/1GCR754*.

Cultivating Nutritious Food Systems

GAIN has released a publication that follows nutrition along the agricultural value chain – from seed to harvest and on to storage, transport, wholesale, retail and, ultimately, the plate – highlighting the successes and challenges where agriculture and nutrition are working together. In the introduction, the author, Bonnie McClafferty, writes that *"Despite the sensibility that the agriculture and nutrition sectors must work together, the practitioners of those two camps scarcely wave at one another as they pass on opposite sides of the street."* This snapshot report, as it is referred to, is a thought-provoking read that everyone working in nutrition should look at. Why? Because, as the report rightly says, *"few of us have any idea about what it takes to grow a successful crop, much less how agriculture affects the nutritional quality of foods."* If we are to address our nutrition challenges in a world increasingly affected by climate change and ensure sustainable interventions, we need to know about these things!

To start your journey, please go to *http://bit.ly/1aBju81*.

06 The Ever Expanding Rays of the SUN

The third in the series of Scaling Up Nutrition in Practice briefings has been published. It deals with the all-important topic of social mobilization, advocacy and communication.

It is amazing to read how 33 countries have established SUN civil society alliances; 28 have organized nutrition events involving high-level government officials; 16 have engaged parliamentarians in actively advocating for nutrition; 15 have developed country-specific advocacy tools to raise awareness about nutrition at a high level; and 11 have comprehensive government or joint social mobilization, advocacy and communication strategies in place.

> "Looking back on the battle against malnutrition, it has become clear what a key role advocacy has played. When backed by a solid evidence base, and presented in a clear and powerful way, advocacy can bring about tangible and lasting change."
>
> *Tom Arnold, SUN Movement Coordinator ad interim*

This is the start of what success looks like. But bringing people together around a common agenda, putting the necessary policies and laws in place, implementing and aligning programs, and mobilizing resources takes a great deal of concentrated effort and commitment. So learning from other countries, which are all at different stages, helps generate ideas and potentially prevents repetition of the same mistakes.

In the words of Roxana Quader, SUN Focal Point for Bangladesh: *"Raising a common voice for nutrition, in partnership with Bangladesh's many stakeholders, is essential for effective mobilization of leaders from all walks of life. With a shared vision, we can make nutrition everyone's business and strive for a healthy, progressive, sustainable Bangladesh."*

To download the briefing and read more news from SUN, please go to *http://scalingupnutrition.org/*

07

UN Special Rapporteur on Right to Food: Looking Back and Looking Forward

Olivier De Schutter's term of office as the UN Special Rapporteur on the Right to food has ended, and in his parting remarks he noted that a number of significant changes regarding the understanding of hunger and malnutrition and the interventions required to address them have taken place. "*We now recognize that poor, food-deficit countries should be supported not by trade and aid alone, but first and foremost by supporting them in their ability to feed themselves,*" said De Schutter. He went on to emphasize the recognized need to shift to more sustainable modes of production and consumption and the broadening of the discussion to include topics such as agroecology and how to reduce waste.

De Schutter will now be involved with establishing the International Panel of Experts on Sustainable Food Systems (IPES-Food), which works to build bridges between the scientific community and public and private decision-makers and also ensures a permanent dialogue with civil society. He is succeeded by Hilal Elver, Research Professor and Co-Director of the Project of Global Climate Change, Human Security and Democracy based at the University of California at Santa Barbara. Hilal Elver is a specialist on environmental issues.

For more on the Special Rapporteur and her first official visit to the Philippines, please go to *http://bit.ly/1FEI42d.*

Did You Know?

The Special Rapporteur on the Right to food is an independent expert appointed by the UN Human Rights Council, and presents an annual report to the UN Human Rights Council. For the Special Rapporteur, the right to food is the right to have regular, permanent and unrestricted access, either directly or by means of financial purchases, to quantitatively and qualitatively adequate and sufficient food corresponding to the cultural traditions of the people to which the consumer belongs, and which ensure a physical and mental, individual and collective, fulfilling and dignified life free of fear.

Specific functions include:

- Monitoring the situation of the right to food throughout the world
- Identifying general trends related to the right to food and undertaking country visits
- Communicating with states and other concerned parties with regard to alleged cases of violations of the right to food
- Promoting the full realization of the right to food through dialogue with relevant actors

08 What the World Eats, Where our Food comes from and the Cost of Living

What the world eats

We have discovered three wonderful interactive websites that will get you thinking ...

National Geographic has a fascinating interactive website that shows how diets around the world vary and the changes in dietary intake over the last 50 years. Did you know that in the United States the average individual daily food consumption amounts to 3,641 calories, with 37% coming from sugar and fat, while in Sudan it is almost half of that of the USA, at 1,695 calories, with 35% coming from grains rather than sugar and fat? Makes one think!

www.nationalgeographic.com/what-the-world-eats/

The Guardian developed a great knowledge test for World Food Day last year to see if you know where different foods come from, can rank countries by rates of undernutrition, and negotiate a tricky picture round. It's really interesting and tricky as well, so give it a go and see how well you do!

http://bit.ly/1gxGEg9

Business Insider has an excellent infographic depicting the cost of living in every part of the world. The top three countries for the cost of living are Switzerland, Norway and Venezuela, and the bottom three are India, Nepal and Pakistan. See where your country ranks ...

http://read.bi/1xd65Y4

09

Sight and Life Project Partner Receives Honor

Henny Stege with his wife Trees, proudly wearing the Order of Orange-Nassau

Every year, the head of the Dutch royal family – currently King Willem-Alexander – bestows the Order of Orange-Nassau on Dutch citizens who deserve recognition from society for the special way in which they have carried out their activities. We at *Sight and Life* are delighted to report that Henny Stege, one of the founders of the NGO Tshwaranang, with which we have worked closely for a number of years in South Africa, was awarded this honor at an event at the Dutch Embassy in Pretoria, South Africa, at the end of April.

When Henny and his wife Trees (who has received the same honor) first visited South Africa, the plight of many of its people pulled at their hearts – so much so that they left the comfort of their home country and moved to South Africa, embracing an uncertain future there. Since then, Henny has become much loved and greatly respected, and together with Trees has expanded their outreach from one humble project to an organization known as "Tshwaranang" that is responsible for advancing the quality of life of thousands of South Africans.

Joining hands

The very name Tshwaranang – joining hands – aptly describes Henny. He not only offers his own hands (Henny will take on any task required to get a job done). He also has an amazing ability to join hands with others across races, cultures and divides to reach out above all to the marginalized, orphaned, children and the elderly, and to get others involved, committed and passionate about the work of the foundation. Henny has an energy that many people half his age can only dream of: his smile comes from deep in his heart, and his dedication to helping the most vulnerable is unwavering, even in the face of exceptional odds.

Sight and Life's support for the work of Tshwaranang has grown over the years. Initially it supported the eye clinic Ke A Bona and supplied fortified biscuits for grandmothers at the community center in Ivory Park. (At a time when they themselves start to need care, grannies are often left to care for children who have lost one or both parents to AIDS). Later, *Sight and Life* supplied MixMe™ micronutrient powder for some 150 children at Sedimosang crèche. *Sight and Life's* help expanded again to assist with building an equipped kitchen and supplying MixMe™ for 2500 pre-school children at Ebomeni School. Then came feeding 1200 children at the Drake Koka School. Now *Sight and Life* is working with other projects in a more remote area of the country. Often the meals these children are fed at their crèche or school are the only ones they receive in a day other than, perhaps, a slice of bread and a cup of tea.

We love our visits to these projects, not only to see how our support creates brighter futures for the children but also because the *Sight and Life* team always departs with the feeling that we have received more than we have given! We salute both Henny and Trees and the amazing work that they do.

Books
Reviews & Notices

Editor's note: This section contains reviews of books, publications, and websites that, whether brand new or classic, we hope will be of interest to our readers. Notices of relevant new publications that do not actually constitute reviews will from henceforth be published on **www.sightandlife.org.**

Publication Notice

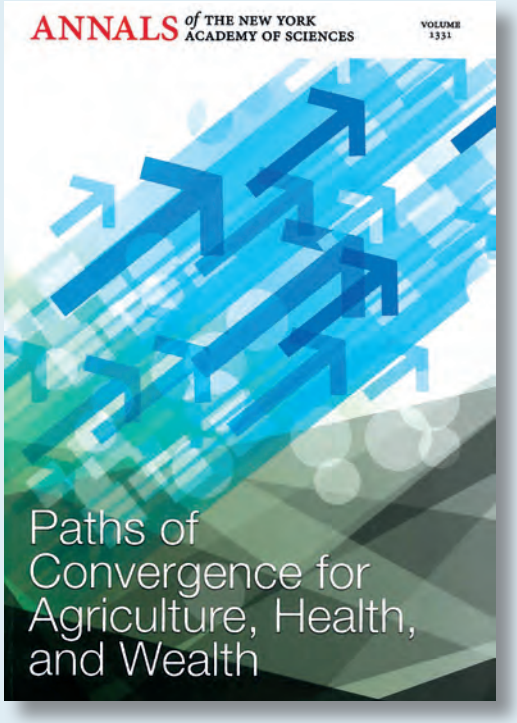
Paths of Convergence for Agriculture, Health, and Wealth: Solutions at Scale to the Triple Burden of Malnutrition

Annals of New York Academy of Sciences, Volume 1331. Pages 1–295 (onlinelibrary.wiley.com/doi/10.1111/nyas.2014.1331.issue-1/issuetoc)
Special issue edited by Laurette Dubé, Patrick Webb, Narendra K Arora and Prabhu Pingali

Bringing solutions at scale to the complex challenges of malnutrition requires both behavioral change and ecosystem transformation at the nexus of farm, food and health systems. Food choices lie at the core of well-entrenched benefits and problems associated with Western lifestyles, income uses and chronic diseases. Focusing on enhancing dietary quality across traditional, as well as modern, food systems may support a convergence towards more sustainable and healthy food production and consumption environments. This special feature of the *Annals of the New York Academy of Sciences* focuses on this potential for convergence thinking and practice. Articles are structured around four themes, with academic papers having a "roadmap" companion paper reporting on the current status of associated convergence-building projects.

Articles in Theme 1 bring evidence **on the need for convergence and on underlying mechanisms at the individual and societal levels.** The multiplicity of mechanisms underscores a major challenge in articulating paths of convergence at scale that go beyond what has been possible so far. Of particular relevance is the article by Portella and Silveira that examines the determinants of food choice and eating behavior in the especially vulnerable population of children born with fetal growth restrictions, these being highly vulnerable to all three facets of malnutrition over the life-course.

Theme 2 addresses strategy for **mainstreaming convergence as a driver of business engagement and innovation.** Reaching solutions to malnutrition at scale calls not only for scaling up, but also for extending private-sector engagement. Business engagement can be, for example, at the level of nutrition-sensitive product formulation and marketing, in inclusive organization and value-chain design and practice, through commercial and social entrepreneurship engaging with communities, or again via financial investments at scale. Of particular relevance is the academic paper and roadmap companion paper by Dubé and her collaborators that intro-



duces food-convergent innovation, implying the joint optimization of economic growth and human development in both their core profit-making and corporate social responsibility activities, making business a catalyst for change throughout society.

Articles presented in Theme 3 address **convergence in policy and governance** and tackle the present disconnect between policy-making in economic sectors, on the one hand, and human development sectors, on the other. Of particular relevance is the paper by Kirton et al that analyzes the political process for the global initiative for addressing mother and child health.

The final set of articles lays the foundations for better **convergence in metrics and methods.** The articles under this theme start to build bridges between knowledge systems and models in health, and those used in policy-making by agricultural, social, and economic actors at local, national, and global levels. Of particular interest is a paper by Pingali and Ricketts that proposes a minimum set of nutrition indicators to be included in nationally representative agricultural (and multi-topic) household surveys.

"The insights provided by the papers have the potential to encourage actors throughout society to enhance the supply of, and demand for, nutritious foods."

The insights provided by the papers assembled in the Annals special issue *Paths of Convergence for Agriculture, Health and Wealth* have the potential to enable all actors throughout society to enhance the supply of nutritious foods and demand for healthier diets in both traditional and modern food systems. The focus is placed on identifying economically viable solutions to the triple burden of malnutrition and associated ill health. Its production and open access, as well as the associated science, policy and innovation agenda, have been financially supported by the Bill & Melinda Gates Foundation (Agriculture Division) and the Rockefeller Foundation (Bellagio programs for writing residency and workshop).

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A world free from malnutrition.

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Sight and Life is a humanitarian think tank. Inspired by a vision of a world that is free from malnutrition, it helps to improve the lives of some of the world's most vulnerable populations. It does this by supporting innovation that aims to eradicate malnutrition.

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