The Guidebook
Nutritional Anemia

The Guidebook

Nutritional Anemia

Edited by
Jane Badham
JB Consultancy, Johannesburg, South Africa

Michael B. Zimmermann
Swiss Federal Institute of Technology, Zurich, Switzerland

Klaus Kraemer
SIGHT AND LIFE, Basel, Switzerland

SIGHT AND LIFE
Press

SIGHT AND LIFE Mission Statement
SIGHT AND LIFE is a humanitarian initiative of DSM. It aims to ensure a sustainable and significant improvement in human nutrition and health by encouraging partnerships with universities and intergovernmental and governmental agencies, by generating and exchanging scientific information and by forming lasting networks.

SIGHT AND LIFE Press
c/o SIGHT AND LIFE / DSM Nutritional Products Ltd
PO Box 2116
4002 Basel
Switzerland
Phone: +41 61 68 87494
Fax: +41 61 68 81910
Email: info@sightandlife.org
Internet: www.sightandlife.org

The paper used in this book is acid-free and falls within the guidelines established to ensure permanence and durability.

Cover photo by Ulla Lohmann, Germany
Cover illustration by graphic art studio, Grenzach-Wyhlen, Germany
Typeset and print by Burger Druck, Waldkirch, Germany

ISBN 3-906412-35-0

PREFACE TO THE NUTRITIONAL ANEMIA GUIDEBOOK

Two hundred million children under the age of five, mostly living in sub-Saharan Africa and South Asia, fail to reach their full cognitive, motor and social-emotional potential because of micronutrient deficiencies and inadequate stimulation. These children will probably fail at school, fail to achieve their income potential, and remain trapped in the poverty cycle. A tragic reality.

In May 2002, the General Assembly of the United Nations re-emphasized that control of nutritional anemia should be one of the global development goals to be achieved in the early years of this new millennium. Sadly, there has been little documented progress in the global fight against anemia and WHO data shows that 818 million children under the age of five and women are affected by this public health problem, mainly in developing countries. About one million of them die every year. This shows the magnitude of the problem and highlights the urgent need for action.

SIGHT AND LIFE has always championed interventions to address micronutrient malnutrition, including iron deficiency and nutritional anemias, and, as a result, has published a book, Nutritional Anemia. In a single volume it highlights for the first time all the critical factors in addressing nutritional anemia, with contributions from leading scientists in their respective fields. Each chapter addresses a specific issue in great detail. It has become clear that the effective control of anemia requires integrated solutions that are tailored to the particular needs and opportunities in each country. Components of any such an approach include micronutrient supplementation of the most vulnerable groups (particularly children and women of childbearing age), food fortification, dietary diversification and education, as well as control of diseases such as malaria, worm infections, and other chronic endemic infections. While each of these can help reduce the burden of anemia, none is capable of doing the job on its own.

The purpose of this Guidebook is to give you, the reader, a comprehensive summary of the critical issues from prevalence data and statistics, to economics, through to the diagnosis, functional consequences and background information on each of the micronutrients believed to be directly or indirectly involved in anemia.

This Guidebook does not contain all the information or give all the answers, but its intention is to give an overview of the latest scientific thinking and the challenges facing the world as we go forward in planning, implementing and monitoring interventions to address what is undoubtedly the biggest nutritional problem that the world currently faces.

We trust that the information, knowledge and insights that you will gain from this Guidebook, will enable you to become a part of the solution and actively engage in advocacy, programming or on-going research to make a difference.

Jane Badham
Michael B. Zimmermann
Klaus Kraemer

ABOUT THE EDITORS

Jane Badham

Jane is a dietitian with an MSc in Nutrition from North West University, Potchefstroom Campus, South Africa. She is currently the Managing Director of JB Consultancy, a health communication and strategy company that advises the pharmaceutical industry, food industry, humanitarian organizations, and the media. Jane is also the CEO of the 5-a-Day for Better Health TRUST in South Africa that promotes the increased consumption of vegetables and fruit. She serves on the Board of Directors of the International Fruit and Vegetable Alliance (IFAVA) as well as being part of the organizing team of the African Nutrition Leadership Program (ANLP).

Michael Zimmermann

Michael obtained his MD from Vanderbilt University School of Medicine and his MSc in Nutritional Science at the University of California in Berkeley, both in the USA. He is currently Senior Scientist in the Laboratory for Human Nutrition at the Swiss Federal Institute of Technology in Zurich (ETH), visiting Professor at Wageningen University in the Netherlands, and holds the Unilever Endowed Chair in International Health and Micronutrients. Michael's research focus is nutrition and metabolism, including the effects of micronutrient deficiencies on thyroid function, and he has won many awards for his work.

Klaus Kraemer

Klaus obtained his doctorate in nutritional sciences from the University of Giessen, Germany. He is currently Secretary General of SIGHT AND LIFE, a humanitarian initiative of DSM, involved in a number of activities to ensure a sustainable and significant improvement in human nutrition, health, and wellbeing. Klaus has over 20 years of research experience in the field of health and safety of vitamins, minerals, carotenoids, and nutraceuticals. He serves on several professional societies dedicated to nutrition, vitamins, and antioxidants, has published many scientific articles, and coedited five books.

CONTRIBUTORS TO THE NUTRITIONAL ANEMIA BOOK

Harold Alderman
Africa Region of the World Bank, Washington, DC, USA; halderman@worldbank.org

Jane Badham
JB Consultancy, Health Communication and Strategy Consultants, Johannesburg, South Africa; jbconsultancy@mweb.co.za

Hans-Konrad Biesalski
Institute for Biological Chemistry and Nutrition at the University of Hohenheim, Hohenheim, Germany; biesal@uni-hohenheim.de

Martin Bloem
World Food Programme (WFP), Rome, Italy; martin.bloem@wfp.org

Tommaso Cavalli-Sforza
Nutrition and Food Safety, WHO Regional Office for the Western Pacific, Manila, Philippines; cavalli-sforzat@wpro.who.int

Mary Cogswell
Division of Nutrition and Physical Activity, Centers for Disease Control and Prevention, Atlanta; USA

Ian Darnton-Hill
Nutrition Section, UNICEF, New York, USA; idarntonhill@unicef.org

Omar Dary
A2Z Project, Academy for Educational Development, Washington, DC, USA; odary@aed.org

Bruno de Benoist
World Health Organization (WHO), Geneva, Switzerland; debenoistb@who.int

Saskia de Pee
World Food Programme (WFP), Rome, Italy; sdepee@compuserve.com

Ines Egli
Institute of Food Science and Nutrition, Swiss Federal Institute of Technology (ETH), Zurich, Switzerland; ines.egli@ilw.agrl.ethz.ch

Jürgen Erhardt
University of Indonesia, SEAMEO-TROPMED, Jakarta, Indonesia; erhardtj@gmx.de

Alison D. Gernand
Bloomberg School of Public Health, Johns Hopkins University, Baltimore, USA; agernand@jhsph.edu

Gary R. Gleason
Friedman School of Nutrition Science and Policy, Tufts University, Boston, USA; ggleason@inffoundation.org

Eva Hertrampf Díaz
Institute of Nutrition and Food Technology (INTA), University of Chile, Santiago, Chile; ehertram@inta.cl

Susan Horton
Wilfrid Laurier University, Waterloo, Canada; shorton@wlu.ca

Richard Hurrell
Institute of Food Science and Nutrition, Swiss Federal Institute of Technology (ETH), Zurich, Switzerland; richard.hurrell@ilw.agrl.ethz.ch

Alan Jackson
Institute of Human Nutrition, University of Southampton, Southampton, UK; aaj@soton.ac.uk

Afaf Kamal-Eldin
Department of Food Science, Swedish University of Agricultural Sciences, Uppsala, Sweden; afaf.kamal-eldin@lmv.slu.se

Klaus Kraemer
SIGHT AND LIFE, Basel, Switzerland; klaus.kraemer@sightandlife.org

Sean Lynch
Eastern Virginia Medical School, Norfolk, USA; srlynch@visi.net

M.G. Venkatesh Mannar
The Micronutrient Initiative, Ottawa, Canada; vmannar@micronutrient.org

Erin McLean
World Health Organization (WHO), Geneva, Switzerland; mcleane@who.int

Regina Moench-Pfanner
Global Alliance for Improved Nutrition (GAIN), Geneva, Switzerland; rmoenchpfanner@gaingeneva.org

Christine A. Northrop-Clewes
Northern Ireland Centre for Food and Health, University of Ulster, Coleraine, UK; c.clewes@ulster.ac.uk

Manuel Olivares
Institute of Nutrition and Food Technology (INTA), University of Chile, Santiago, Chile; molivare@inta.cl

Neal Paragas
Institute of Human Nutrition, Columbia University, New York, USA; np2014@columbia.edu

Klaus Schümann
Technical University of Munich, Freising, Germany; kschuemann@schuemann-muc.de

John M. Scott
School of Biochemistry & Immunology, Trinity College Dublin, Dublin, Ireland; jscott@tcd.ie

Nevin Scrimshaw
International Nutrition Foundation, Boston, USA; nevin@cyperportal.net

Richard Semba
School of Medicine, Johns Hopkins University, Baltimore, USA; rdsemba@jhmi.edu

Noel Solomons
Center for Studies of Sensory Impairment, Aging and Metabolism (CeSSIAM), Guatemala City, Guatemala; cessiam@guate.net.gt

Alfred Sommer
Bloomberg School of Public Health, Johns Hopkins University, Baltimore, USA; asommer@jhsph.edu

Elisabeth Stoecklin
R & D Human Nutrition and Health, DSM Nutritional Products Ltd, Kaiseraugst, Switzerland; elisabeth.stoeklin@dsm.com

Brian Thompson
Food and Agriculture Organization (FAO), Rome, Italy; brian.thompson@fao.org

David Thurnham
Northern Ireland Centre for Food and Health, University of Ulster, Coleraine, UK; di.thurnham@ulster.ac.uk

Melody C. Tondeur
Division of Gastroenterology, Hepatology and Nutrition, Hospital for Sick Children, Toronto, Canada, melody.tondeur@sickkids.ca

Maret G. Traber
Linus Pauling Institute & Department of Nutrition and Exercise Sciences, Oregon State University, Corvallis, USA; maret.traber@oregonstate.edu

Ricardo Uauy
Institute of Nutrition and Food Technology (INTA), University of Chile, Santiago, Chile; ricardo.uauy@lshtm.ac.uk

Keith P. West
Bloomberg School of Public Health, Johns Hopkins University, Baltimore, USA; kwest@jhsph.edu

Daniel Wojdyla
Escuela de Estadistica, Universidad Nacional de Rosario, Argentina

Michael Zimmermann
Laboratory for Human Nutrition, Swiss Federal Institute of Technology (ETH), Zurich, Switzerland; michael.zimmermann@ilw.agrl.ethz.ch

Stanley Zlotkin
Departments of Paediatrics and Nutritional Sciences and Public Health Sciences, University of Toronto, Canada; stanley.zlotkin@sickkids.ca

CONTENTS

1

WORLDWIDE PREVALENCE OF ANEMIA IN PRESCHOOL AGED CHILDREN, PREGNANT WOMEN AND NON-PREGNANT WOMEN OF REPRODUCTIVE AGE

Erin McLean, Mary Cogswell, Ines Egli,
Daniel Wojdyla and Bruno de Benoist

What is the problem and what do we know so far?
Anemia is a widespread public health problem associated with an increased risk of morbidity and mortality, especially in pregnant women and young children. It is a disease with multiple causes, both nutritional (vitamin and mineral deficiencies) and non-nutritional (infection) that frequently co-occur. It is assumed that one of the most common contributing factors is iron deficiency, and anemia resulting from iron deficiency is considered to be one of the top ten contributors to the global burden of disease.

The World Health Organization (WHO) has as one of its mandates to inform its Member States about the global health situation. It was decided to update the global estimates of anemia and provide a current picture of the situation, especially in high-risk groups. This was done by generating global and United Nations Regional estimates of anemia prevalence in preschool aged children, pregnant women and non-pregnant women of childbearing age. Data was gathered between 1993 and 2005, using the most recent nationally representative survey for a country or from at least two surveys representative of the countries first administrative boundary. When data was not available for a country, the anemia prevalence was predicted based on regression equations using the country's United Nations Human Development Index and health indicators from the World Health Statistics database. Coverage varied by UN Regions and was highest in northern America, Asia and Africa while it was lower in Europe and Oceania. The estimates are based on the 192 Member States of WHO, so represent 99.8% of the global population.

What do we know about global prevalence of anemia?

- Global prevalence of anemia in preschool aged children is 47.4%.
- Global prevalence of anemia in pregnant women is 41.8%.
- Global prevalence of anemia in non-pregnant women is 30.2%.
- Globally 818 million women (both pregnant and non-pregnant) and young children suffer from anemia and over half of these, approximately 520 million, live in Asia.
- The highest prevalence for all 3 groups is in Africa, but the greatest number of people affected are in Asia.
- In Asia 58% of preschool aged children, 56.1% of pregnant women and 68% of non-pregnant women are anemic.
- More than half of the world's population of preschool aged children and pregnant women reside in countries where anemia is a severe public health problem.
- Countries with a severe public health problem were grouped in Africa, Asia and Latin America and the Caribbean.
- Africa and Asia are the most affected and as these regions are also the poorest, it may reflect the link between anemia and development.
- Compared to North America, anemia is three times more prevalent in Europe and this may be due to the fact that Europe includes countries with a range of social and economic profiles or as a result of low coverage of data in Europe compared to North America or that in north America foods are widely fortified with iron and a high proportion of iron intake comes from fortified foods.

It has to be noted that these estimates are not quantitatively comparable to previous estimates as the methodologies used are different. They do have some limitations but, based on the best available information, they are a good starting point to track progress in the elimination of anemia.

Based on these estimates, the magnitude of nutritional anemia or of iron deficiency anemia is difficult to assess since most of the surveys used do not address the causes of anemia and are solely restricted to the measurement of hemoglobin.

What is the way forward?
Globally, almost half of all preschool aged children and pregnant women and close to one third of non-pregnant women, suffer from anemia. As the estimates represent a large segment of the population, they are likely to reflect the actual global prevalence of anemia within these population groups. However, UN Regional estimates may be more accurate for some populations and some areas since the coverage varies significantly within regions.

Anemia is of greatest concern in children less than 2years of age since their rapid growth requires a high

intake of iron, which frequently is not covered by the diet, especially in low-income countries.

In order to make full use of these prevalence data, information on the cause of anemia should be collected in any survey on anemia so that interventions for anemia control can be better adapted to the local situation and therefore be more effective.

What is the key message?

Anemia remains a significant public health concern. These new estimates are likely to reflect the current situation and are a good starting point for tracking global progress. Future surveys need to include data on the causes of anemia, as lack of this data impairs our ability to correct this significant public health problem.

FACTS:

- Preschool children are aged between 0–4.99 years, non-pregnant women between 15 and 49.99 years and no age defined for pregnant women.
- Hemoglobin concentration cut-offs to define anemia as set by the WHO are 110 g/L for pre-school aged children and pregnant women, and 120 g/L for non-pregnant women.
- The prevalence of anemia as a public health problem is categorized by the WHO as follows:
  - <5% – no problem
  - 5–19% – mild public health problem
  - 20–39% – moderate public health problem
  - >40% – severe public health problem
- Global prevalence of anemia in preschool aged children is 47.4%
- Global prevalence of anemia in pregnant women is 41.8%
- Global prevalence of anemia in non-pregnant women is 30.2%
- Globally 818 million women (both pregnant and non-pregnant) and young children suffer from anemia and over half of these, approximately 520 million, live in Asia.
- The highest prevalence for all 3 groups is in Africa, but the greatest number of people affected are in Asia.
- In Asia 58% of preschool aged children, 56.1% of pregnant women and 68% of non-pregnant women are anemic.
- More than half of the world's population of preschool aged children and pregnant women reside in countries where anemia is a severe public health problem.
- Countries with a severe public health problem were grouped in Africa, Asia and Latin America and the Caribbean.
- Africa and Asia are the most affected and as these regions are also the poorest, it may reflect the link between anemia and development.
- Compared to North America, anemia is three times more prevalent in Europe.

2

THE CASE FOR URGENT ACTION TO ADDRESS NUTRITIONAL ANEMIA

Venkatesh Mannar

What is the problem and what do we know so far?

The United Nations goal of reducing by one third the prevalence of anemia by 2010 is unlikely to be met. Nutritional anemia remains common in many countries of the world and its eradication through effective interventions must be a priority for attention and action. Iron deficiency in early childhood has a significant, negative effect on a child's physical and intellectual development. There has been an intensification of efforts in several countries and this gives encouragement that interventions can be successful and sustainable. It is recognized, however, that there are no easy solutions and effective interventions have their drawbacks, but it would seem that lack of priority of eradicating nutritional anemia by policy makers is the major concern. There is an urgency to act.

What has been achieved?

There are key developments that have occurred in the past 10 years:

- More technical consensus
- Better understanding of conditions needed for effective supplementation
- Sufficient knowledge and experience (especially with pregnant women) to design and implement effective programs
- Programmatic and technical guidelines for effective programming
- Better information on stable and bioavailable iron compounds
- Recognition by the food industry of the need for fortification
- Feasibility of double salt fortification
- Technology to fortify rice with iron and folic acid
- Increased successful work relating to improved varieties of staple crops

- Greater knowledge about the interface between iron status and infection.

What is the way forward?

Concerns are that although iron supplementation has been shown to be effective in controlled experiments, supplementation in field settings does not seem to show a significant improvement in anemia prevalence. In addition, data to support large-scale food fortification is still lacking and has not been systematically documented.

It seems that progress will only be made if:

1. Key issues are addressed and consensus statements developed
2. Bridges are built between science/technology and those who deliver the services
3. The field application of supplementation is strengthened
4. Universal fortification of staple foods with significant levels of nutrients is globally recognized
5. Creative means of increasing the iron content of the diet are explored
6. Enhancing the iron absorption from diets is investigated
7. There is a better understanding of interactions between micronutrients and other dietary components and other causes of anemia
8. Social marketing and supporting behavioral change is encouraged
9. There is a combination of proper regulation and strong and appropriate public education
10. A multi-intervention approach is accepted that includes adequate nutritional intake (supplementation, fortification, dietary modification, biofortification) and reduction of concurrent infection
11. There is more compelling advocacy at all levels, forming of strategic alliances and commitment to action
12. There are global champions to push action forward.

What is the key message?

There is an urgent need for action but that action needs to consider a number of factors if it is to be successful and sustainable.

FACTS:

- Iron deficiency could be preventing 40%-60% of children in developing countries from growing to their full mental potential.
- The WHO identifies iron deficiency as being amongst the ten most serious risks in countries with a high infant mortality coupled with a high adult mortality.
- Interventions to address iron deficiency are one of the most cost effective public health interventions.
- The cost-benefits ratio for iron programs is estimated to be 200:1.
- Amongst a list of 17 possible development investments, the returns of investing in micronutrient programs are second only to those of fighting HIV/AIDS.

3

THE ECONOMICS OF ADDRESSING NUTRITIONAL ANEMIA

Harold Alderman and Susan Horton

Why is economic assessment important?

The economic gains from addressing any micronutrient deficiency come from both cost reductions and from enhanced productivity. They include lower mortality, reduced healthcare costs, reduced morbidity, improved productivity and intergenerational benefits through improved health. In the case of iron deficiency anemia, economic assessment requires determining the costs of iron deficiency in dollar terms in order to determine the consequences in a unit of measurement that is common to other claims on public resources (both health interventions and interventions outside the health arena). This is in partial contrast to the calculation of a program's effectiveness in terms of increases in life expectancy or disability-adjusted life years (DALYs).

It is also important to assess the economic impact of interventions in terms of cost and benefits. In making economic assessments, there are a number of important issues that must be considered:

- There may be more than a single outcome for the intervention (e.g. an intervention in pregnant women may both reduce low birth weights and maternal mortality via changes in maternal hemoglobin);
- Some interventions affect not only anemia but also other health and economic outcomes (e.g. deworming can be effective in both improving hemoglobin levels as well as absorption of vitamin A);
- Measuring cost-effectiveness using the ultimate outcome of interest (e.g. mortality) is usually too costly and time consuming and so often only proximate indicators (e.g. proportion anemic or hemoglobin) are used;

- Cost-effectiveness varies with the scale of the program (e.g. costs may decrease over time if there are fixed costs that can be spread over larger programs);
- There are distinctions between public and private costs (e.g. the cost of a dollar of government revenues is generally more than a dollar to the economy).

How are the economic benefits of addressing anemia assessed?

There are two key approaches that are used:

1. Calculation of the expected gains in economic terms if a case of anemia were prevented. This approach is useful for making comparisons of intervention costs.
2. Estimation of the impact on GNP if anemia rates could be reduced. This approach scales the individual gains and results in a stronger motivation for a change in political will.

Results of economic benefits can either be reported in costs in terms of productivity; give sensitivity estimates; or be reported in terms of DALYs, which are then converted into dollar terms.

Each approach has its advantages and limitations. It is important to recognize that placing precise figures on economic value involves a range of assumptions and requires the adaptation to a country's specific context. These approaches all measure different concepts and so cannot be directly compared.

What are the economic costs of reducing anemia?

In terms of either the cost per DALY saved, or the cost-benefit ratio calculated, iron fortification is one of the most attractive public health interventions available.

- The cost of fortification per person per year is in the range of $0.10 (US) to $1.00.
- Home fortification is relatively new and holds considerable promise for some groups and the costs can be viewed as intermediate between fortification and supplementation.
- Supplementation costs per person are estimated in the range of $2.00–$5.00, noting, however, that often reported costs do not fully cover personnel costs and that results of programs at scale have been disappointing. Operational research is needed to design programs which work cost-effectively in the field.
- Periodic deworming has been estimated in one study to cost US$3.50 to increase school participation by one child year. A combined program of deworming and supplementation, using a number of assumptions, estimated that the intervention could lead to an expected additional income of $29 for a cost of $1.70. Deworming has possibly been overlooked in importance and works synergistically with fortification and supplementation.
- There are few studies that have shown the cost-effectiveness of home gardening and increased production of small animals.
- Biofortification approaches are promising but involve extensive fixed costs for research, but with few, if any, incremental costs of operation over the general costs of producing a crop with increased iron availability. Using a number of assumptions, the strategy could provide global total present value of nutritional benefits of up to $694 million, giving a cost-benefit ratio of 19 or an internal return of 29%.

What are the outcomes of economic assessments that have been undertaken?

It is clear (see FACTS below) that anemia at all stages of the lifecycle is associated with a significant health burden and has a potentially large negative impact on productivity and hence also on income and GDP. The total loss per capita due to physical as well as cognitive losses, amounts to billions annually and is considerable when compared to the modest costs of decreasing nutritional anemia.

What is the key message?

Economic impact studies show that addressing nutritional anemia can have a significant impact on health burden, productivity and income. Determining the overall economic impact (economic gain and cost-effectiveness) of any intervention requires expert knowledge and must be based on the specifics of the program, the country and the desired outcome measurements.

FACTS:

- One study estimates that in developing countries one fifth of perinatal mortality, and one tenth of maternal mortality, is attributable to iron deficiency.
- It is estimated that 1.5% of deaths worldwide are attributable to iron deficiency.
- In terms of DALYs, anemia also accounts for 35 million health life years lost (2.5% of global DALYs lost).
- Iron interventions in adults have shown increased productivity by around 5% in light manual labor and as high as 17% in heavy manual labor.
- An Indonesian study shows effects on income of the self employed of as much as 20% for men and 6% for women.
- A range of studies indicate that a half standard deviation change in IQ impacts on earnings in the region of 5%.

- It can be inferred that due to its effects on cognitive development, anemia potentially reduces adult earnings by 2.5%.
- The cost of fortification per person per year is in the range of $0.10 (US) to $1.00, with a cost-benefit ratio of between 6:1 (physical benefits to adults) and 9:1 (including estimated cognitive benefits to children).
- Supplementation costs per person are estimated in the range of $2.00 to $5.00, noting that often these costs do not fully cover personnel costs.
- Supplementation programs are 5 times more costly than fortification in per DALY terms.
- Deworming has been estimated in one study to cost $3.50 to increase school participation by one child year.
- A combined programs of deworming and supplementation is estimated to impact on earnings, with an additional $29.00 expected for a cost of $1.70.

4

LABORATORY ASSESSMENT OF IRON STATUS

Hans-Konrad Biesalski and Jürgen Erhardt

What is the problem and what do we know so far?

Nutrition has a important role in anemia and of all the nutrients involved, iron is the most crucial. Therefore the assessment of the iron status is very often essential in the diagnosis of anemia. Iron deficiency generally occurs in three sequential stages: depleted iron stores, iron deficient erythropoesis and iron deficiency anemia. All three stages can be analyzed biochemically with the measurement of hemoglobin (Hb), ferritin and soluble transferrin receptor (sTfR). Although there are some clinical indicators and the evaluation of iron intake might be helpful, the diagnosis relies mainly on these biochemical indicators. They are the only ones which give the necessary specificity and sensitivity. Unfortunately the procedures to measure them are costly and mostly not easy to perform.

How accurate and useful are the different biochemical indicators?

To measure the iron status there are three important indicators:

1. Hb: The measurement of Hb is essential for the diagnosis of nutritional anemia and is one of the most common, easiest and least expensive methods. Kits are available from several manufacturers and there are also small portable hemoglobinometers for use in the field. Unfortunately the Hb measurement is not very sensitive and specific for iron deficiency (only the third stage affects Hb synthesis). Thus, to determine if iron deficiency is responsible for anemia, it is usually necessary to include other indicators.
2. Ferritin: It is currently considered the most important indicator of the iron status as even in the first stage of iron deficiency, its concentration decreases. Therefore it is the most sensitive indicator and the cost of ferritin ELISA kits or other methods for the measurement of ferritin are relatively low. It is important to note that ferritin is increased by many factors, including infection and inflammation, thus a high value does not necessarily indicate a good iron status. It is therefore also valuable to measure parameters for acute [c-reactive protein (CRP)] and chronic infection [alpha-1-glycoprotein (AGP)].
3. Soluble Transferrin Receptor (sTfR). The measurement of this indicator is increasingly being used to determine iron deficiency in situations where infection is a factor, as it is much less influenced by this condition. It is not as sensitive as ferritin, but more sensitive than Hb. Until now there is no internationally certified standard available and each method/kit has its own cut off values. sTfR measurements are still much more expensive than ferritin measurements. The ratio of sTfR to ferritin is the most sensitive indicator for the iron status, since it allows the calculation of the iron stores in mg/kg body weight. It is therefore similar to the gold standard of bone marrow staining in defining iron deficiency.

Besides these indicators the following three are sometimes also of interest:

1. Iron saturation of plasma transferrin and mean corpuscular volume (MCV): They are well established indicators and relatively inexpensive to measure but only useful in clinical settings where the equipment to measure them is available.
2. Hematocrit: Is very easy to measure but since it is even less sensitive than Hb for iron deficiency it is not very helpful in diagnosing nutritional anemia.
3. Zinc protoporphyrin (ZnPP): It is a simple and robust measurement and useful in screening for iron deficiency but requires a special machine. It must be noted that lead even at normal environmental exposures can increase ZnPP. In most situations, though, it is not a problem.

What is the way forward?

It is generally agreed that a combination of Hb, ferritin,

sTfR and parameters of infection (CRP, AGP) are the best indicators to measure iron status, but four key elements need to be improved through on-going research: reduction of costs; improvement of throughput; increase of sensitivity/specificity and increase of robustness.

Another key challenge is to make the collection of blood in the field as easy and reliable as possible. The collection of blood samples on filter paper is an alternative to venous blood samples, since it doesn't require centrifugation, freezing or transport of samples in a cold chain. Unfortunately, dried blood spots (DBS) have some limitations and requiring strict procedures to be followed.

What is the key message?
The combination of Hb, ferritin, sTfR and parameters of infection (CRP, AGP) are the best indicators to measure iron status, but to ensure implementation and accuracy of interventions, especially in developing countries, there needs to be more research in reducing the cost, improving the robustness of the measurements and finding easy field methods.

5

AN OVERVIEW OF THE FUNCTIONAL SIGNIFICANCE OF IRON DEFICIENCY ANEMIA

Gary Gleason and Nevin Scrimshaw

What is the problem and what do we know so far?
Iron deficiency anemia is the most widespread micronutrient and overall nutritional deficiency in the world. Iron deficiency occurs in three different stages. The first, depletion of iron stores, has no functional changes. When iron stores are exhausted, however, and tissues begin to have insufficient iron, the resulting condition is iron deficiency. Negative effects amongst those who are iron deficient, but do not have outright anemia, include cognitive impairment, decreased physical capacity, and reduced immunity. Thus there are adverse consequences from iron deficiency even before iron deficiency anemia is present. The final stage is iron deficiency anemia which, when severe, can be fatal.

Iron deficiency anemia during pregnancy is prevalent because additional iron is needed to supply the mother's expanding blood volume (±20% increase) and to support the needs of the growing fetus and placenta. Thus, during the second half of pregnancy, although pregnant women have been shown to absorb more iron from food, even in healthy women the iron requirement cannot be easily met by diet. Anemia in pregnancy is associated with increased maternal and child morbidity and mortality and lower birth weight. Favorable pregnancy outcomes occur 30–45% less often in anemic mothers, and infants of anemic mothers are less likely to have normal iron reserves – so they start life at a disadvantage.

What has been achieved?
Considerable emphasis is placed on reducing iron anemia in infancy and early childhood because of its association with impaired psychomotor performance as well as changes in behavior. Although some of the developmental deficits can be corrected with iron treatment, newer studies suggest that difference in cognitive and social adaptation remain, and are likely to be permanent. The risk of iron deficiency is high during later infancy and young childhood, because the stores received at birth have been used to support normal functions and growth and only about 50% of the iron requirement of a 6 month old can be obtained from breast milk. Thus continued breastfeeding will supply only half the infant's iron needs, and for many children the other half (+4 mg/day) must come from fortified complementary foods or supplementation if anemia is to be avoided. This is further aggravated in infants who were of low birth weight, which is common when the mother is malnourished during pregnancy. Hence the WHO and UNICEF recommendation that low birth-weight infants in populations with high levels of anemia receive supplementary iron beginning at 2 months and continuing up to 24 months. As children grow older and start school, studies have shown that those who are anemic have poorer performance. This has serious implications for the effectiveness of education, especially in developing countries in which anemia is highly prevalent.

Addressing iron deficiency and iron deficiency anemia from pregnancy through to infancy and childhood is critical, and interventions need to start early in the lifecycle.

Research also shows the impact of iron status on:
- Physical capacity – iron deficiency reduces physical performance and has been especially noted in agricultural workers.
- Morbidity from infection due to iron's role in several biological mechanisms involved in the immune response to infections. There remains some debate and unresolved issues, especially the relationship between iron supplementation of young children who are not iron deficient and malaria. More research is

necessary. New recommendations from the WHO are that iron deficiency anemia should be determined in young children in areas where malaria is endemic before they are given iron supplements. There is less controversy with regards to other infections but there are still some cautions. The evidence supports a decreased resistance to infection in iron deficient individuals. However, if they are severely malnourished and anemic, the body mechanisms that withhold iron from pathogens can be overwhelmed by too much iron (particularly administered parenterally). Under these circumstances the pathogen can grow explosively before the immune system can recover from the effects of the iron deficiency with disastrous effects to the individual.

- Temperature regulation – severe iron deficiency lowers the body's ability to maintain body temperature in a cold environment.
- Iron excess and chronic disease - concerns have been raised about the possible relationship between high iron stores and heart disease or cancer. Although the studies that have been undertaken are inconclusive, they indicate the need for more research in this field.

What is the way forward?

In general, the negative effects of iron deficiency on health, physical capacity, work performance, cognitive performance and behavior can be corrected by providing adequate iron. Strategies to assure adequate iron nutrition include a combination of promoting a diverse diet with iron-rich foods, micronutrient fortification of staples and targeted fortification or iron supplementation for groups at high risk or with especially high needs. If moderate to severe iron deficiency anemia occurs in infancy, the effects on cognition may not be reversible. Iron should be viewed as a two edged sword in that either too little or too much can have serious adverse consequence for the individual.

What is the key message?

The functional consequences of iron deficiency, and the longer term economic and social impact, has led to a global target to reduce anemia prevalence by 30% from the year 2000 levels by 2010. As of 2007, there has not been substantial progress in most developing countries and iron deficiency anemia should be addressed as a priority, especially in the highest risk groups; pregnant women, infants, and young children. However, there are some areas where caution is needed to avoid a potentially negative impact of interventions.

FACTS:

- In many developing countries one out of two pregnant women, and more than one out of every three preschool children, are estimated to be anemic.
- In countries where meat consumption is low, up to 90% of women are, or become, anemic during pregnancy.
- It is estimated that 800000 deaths worldwide are attributable to iron deficiency anemia, and it remains amongst the 15 leading contributors to the global burden of disease.
- When measured in DALYs, iron deficiency anemia accounts for 25 million or 2.4% of the total DALYs.
- A normal male body has in total ±4.0 g of iron and a normal woman an average of 2.5 g.
- Approximately 73% of the body's iron is in hemoglobin in circulating red cells and in the muscle protein myoglobin, 12% in iron storage proteins, and another 15% is critically important in dozens of enzymes that are essential for the functioning of all cells and tissues. Below normal hemoglobin levels, physical work capacity is linearly related to hemoglobin levels. This is particularly significant when hemoglobin concentration falls below 100 g/L, which is 20–40 g/L below the lower limit of normal adults.
- Moderate anemia is defined as hemoglobin of 70–90 g/L, and severe anemia as hemoglobin of <70 g/L.
- Favorable pregnancy outcomes occur 30–45% less often in anemic mothers, and infants of anemic mothers are less likely to have normal iron reserves.
- The global target is to reduce anemia prevalence nationally, including iron deficiency, by 30% from the year 2000 levels by 2010. Progress as of 2007 was not on pace in most developing countries to meet this goal.

6

IRON METABOLISM

Sean Lynch

What do we know so far?

Iron plays a vital role in oxygen transport and storage, oxidative metabolism, cellular proliferation and many other physiological processes. It has a key property that allows it to co-ordinate electron donors and to participate in redox processes. This property also accounts for its potential to cause toxic effects through the generation of free radicals. Furthermore, iron is an essential nutrient

for all known pathogens. Freely available, iron may greatly increase their virulence. It is therefore not surprising that the human body has tightly regulated processes for absorbing, transporting and storing iron. They ensure that there is a ready supply for cellular growth and function. At the same time they limit its participation in potentially toxic free radical reactions. They also prevent pathogens from getting ready access to the iron.

Approximately 75% of the iron in the body is present in metabolically active compounds. The remaining 25% constitutes a dynamic store that is turned over constantly. This store ensures an adequate supply for normal organ function despite short-term variations in absorption or loss from the body. It also supplies the immediate needs when requirements are increased. The iron reserves that have then been utilized are then gradually replaced by increased absorption. The circulating transferrin pool supplies almost all functional requirements. It contains only about 3 mg iron in adults, but ten times as much (±35 mg) moves through the pool each day, roughly 80% destined for red blood cell production. Most of the iron that is transferred from the dynamic store to the circulating transferrin pool comes from iron recovered from the processing of hemoglobin in red cells that have reached the end of their approximately four month life spans. Absorbed iron also enters this pool, but it amounts to only about 1–1.5 mg a day. The release of iron into the circulation is tightly regulated in concert with requirements. It can be reduced or accelerated several fold. However the saturation of transferrin with iron (the proportion of the protein that is carrying iron at any one time) is held at approximately 35% in normal individuals with adequate iron reserves.

What recent achievements have improved our understanding of iron metabolism?

The recent discovery of a small cysteine-rich cationic peptide called hepcidin, which is produced in the liver, circulates in the plasma and is excreted in the urine, has revolutionized our understanding of the regulation of iron absorption and storage. Hepcidin appears to have a primary role in ensuring the maintenance of an optimal iron store, in regulating iron delivery to all body cells in concert with their functional requirements and blocking the absorption of unneeded iron through the intestine. It acts as a negative regulator of release from stores and intestinal absorption. High levels reduce the rate of release from stores and absorption from the intestine by binding to the only known cellular iron exporter, ferroportin, causing it to be degraded. The expression of hepcidin is induced independently by the accumulation of storage iron and by inflammation. It is suppressed when iron stores are depleted, and by anemia, hypoxemia and accelerated erythropoiesis. Hepcidin ensures that body tissues receive the right amount of iron to meet their functional needs. However all cells also have the capacity to regulate their own internal iron economy by increasing or decreasing the expression of transferrin receptors which are required for the uptake of iron from the circulating transferrin pool into cells.

It has been known that iron balance is maintained by the control of absorption for a long time. However significant advances in our understanding of the processes regulating absorption have also taken place recently. Absorption occurs primarily in the proximal small intestine through mature enterocytes located at the tips of the duodenal villi. Two transporters, Heme Carrier Protein 1 (HCP1) and Divalent Metal Transporter 1 (DMT1) appear to mediate the entry of most if not all dietary iron into these mucosal cells. Heme iron is always readily absorbed. Intact heme molecules are transported into the enterocytes. However, heme constitutes only a small proportion of dietary iron even for people who eat a lot of meat or fish. Most of the iron is present in other forms referred to collectively as nonheme iron. This iron is transported into the enterocytes by DMT1, but it must first be solubilized and reduced to the ferrous state. Moreover factors in food, particularly phytates and polyphenols, may prevent the binding of nonheme iron to DMT1. As a consequence absorption is inhibited. The possibility that specific receptors for other forms of dietary iron have a significant role in absorption awaits further clarification. As indicated above absorption is regulated by the control of iron export from duodenal enterocytes to the circulating transferrin pool by ferroportin. These enterocytes have a short lifespan and iron that is not transferred to the circulation is lost when the cells exfoliate. Nonheme iron absorption is also regulated at the stage of entry into the enterocytes by modifications in the expression of DMT1.

What are the iron requirements throughout the human lifecycle?

Iron is found in almost all foods. Dietary iron intake is therefore related to energy intake. Iron requirements are highest in the second and third trimesters of pregnancy. This need is met utilizing the maternal stores accumulated prior to conception and during the first trimester owing to the cessation of menstruation as well as markedly increased absorption during the second and third trimesters. Requirements are also high in young children particularly between 6 and 18 months of age. Once birth

iron reserves are exhausted, infants depend on weaning foods for iron because the iron content of human milk is low. Unfortunately, traditional weaning foods in many developing countries are poor sources of bioavailable iron. Children aged 6 to 18 months are therefore frequently iron deficient. Requirements are increased during the adolescent growth spurt and by the onset of menstruation in girls. Finally women of childbearing age are at risk for iron deficiency because of their menstrual iron losses. Iron requirements are least in men and postmenopausal women.

What disorders of iron balance are found?

The three common disorders of iron balance are iron deficiency, iron overload and the anemia of inflammation (also called the anemia of chronic disease).

1. Iron deficiency remains the most common micronutrient deficiency disorder worldwide. It is virtually always an acquired condition resulting from a diet that contains insufficient bioavailable iron. In developing countries traditional foods usually contain large quantities of iron absorption inhibitors, particularly phytates and polyphenols. In addition recent observations suggest that diseases that affect the duodenum especially H. pylori infections and celiac disease may be more prevalent than previously suspected and that they may have an important contributory role. More research is needed to confirm these observations and to establish their possible relevance to the prevention of nutritional iron deficiency. Finally, diseases that cause blood loss, particularly hookworm infections, have an important contributory role leading to the high prevalence of iron deficiency in many developing countries.

2. Iron overload is far less prevalent than iron deficiency. Primary systemic iron overload (hemochromatosis) is almost always the result of an inherited abnormality of the regulation of iron transport that affects hepcidin or ferroportin. The common form of iron overload in Caucasians, HFE hemochromatosis, results from a relative hepcidin deficiency. Secondary iron overload occurs in thalassemia and sideroblastic anemia because the treatment of these conditions requires repeated blood transfusion and accelerated erythropoiesis, which is characteristic of these disorders, reduces hepcidin expression.

3. The anemia of inflammation is characterized by decreased iron release from stores, reduced absorption, low plasma iron and transferrin concentrations, restriction of the available iron supply for red blood cell production and mild or moderate anemia. Increased hepcidin expression accounts for almost all the features of this condition which is generally considered to be a host response that evolved to make iron less available to pathogens.

What is the key message?

Major advances have been made in our understanding of the physiology of human iron metabolism and the pathophysiology of related disorders, although many questions still remain unanswered. Ongoing research in this field is required. The knowledge gained has nevertheless provided a sound scientific foundation for approaches to combating nutritional iron deficiency.

FACTS:

- Humans normally have 40–50 mg iron/kg body weight.
- Approximately 75% of the iron in the body is present in metabolically active compounds; the remaining 25% constitutes a dynamic store that is turned over constantly.
- Iron delivery to the cells of the body is rigorously regulated by the control of absorption and release from stores.
- Hepcidin has a central role in controlling iron balance.
- Iron deficiency, iron overload and the anemia of inflammation are the commonest disorders of iron metabolism. Nutritional iron deficiency results from a diet that contains insufficient bioavailable iron to meet requirements; primary iron overload is caused by inherited genetic mutations that lead to dysregulation of hepcidin or abnormalities in its receptor ferroportin; the anemia of inflammation is the result of increased hepcidin expression induced by inflammatory cytokines.

7

OPTIMIZING THE BIOAVAILABILITY OF IRON COMPOUNDS FOR FOOD FORTIFICATION

Richard Hurrell and Ines Egli

What is the problem and what do we know so far?

In any fortification intervention it is critical to ensure the efficacy of the fortificants used. Bioavailability is of key importance in establishing efficacy. The bioavailability of iron compounds relative to ferrous sulphate (relative bioavailability value, RBV) has been proved useful in

ranking their potential for food fortification. However, the efficacy of iron-fortified foods depends on the absolute absorption of the iron compound which is influenced by its RBV, but is also determined by the amount of fortificant added, the iron status of the consumer and the presence of either inhibitors (e.g. phytic acid) or enhancers (e.g. ascorbic acid) of iron absorption in the meal.

What has been achieved?

The World Health Organization (WHO) has published guidelines on food fortification, which include recommendations for preferred iron compounds and a procedure for defining iron fortification levels.

What iron compounds are recommended?

Although an order of preference for iron compounds is given by the WHO, it must be noted that preference also depends on the vehicle being used, and the guidelines list the most appropriate compounds to add to different vehicles: cereal flours, cereal-based foods, milk products, cocoa products, condiments. Each compound also has specific advantages and disadvantages that must be individually assessed.

Electrolytic iron is the only elemental iron powder recommended. Atomized iron and carbon dioxide reduced iron powders are specifically not recommended due to their low RBV. Hydrogen-reduced iron and carbonyl iron powders may be recommended once there is more information on these compounds. In addition NaFeEDTA is not recommended for complementary food fortification as there are too few studies in young children and the Joint FAO/WHO Expert Committee on Food Additives has set limits in their recommendations.

How important is relative bioavailability (RBV)?

RBV is important for ranking different iron compounds relative to ferrous sulphate whose RBV is set at 100. The ranking is made either on the ability of the iron compound to replete hemoglobin in anemic rats or, more recently, to fractional iron absorption in humans using isotope techniques. As a result, four categories of iron compounds have been developed. Each category and each compound within the category has advantages and disadvantages that must be considered on an individual basis, based specifically on the selected fortification vehicle. Compounds' characteristics can also vary depending on the method of manufacture, and their RBV may also be influenced by the food vehicle and the iron status of the subject, which can sometimes result in unexpectedly low RBV values.

- Category 1: Readily water-soluble and with an RBV of close to 100 in adults. Unfortunately these tend to cause unacceptable color and flavor changes. This category includes ferrous sulphate, ferrous gluconate, ferrous lactate and ferric ammonium citrate.
- Category 2: Poorly water-soluble but dissolve readily in the dilute acid of the gastric juice and so have a RBV of 100. These cause fewer organoleptic changes due to their low water solubility. This category includes ferrous fumarate and ferrous succinate.
- Category 3: Insoluble in water and poorly soluble in dilute acid so cause few if any sensory changes, but have lower and more variable RBV. This category includes ferric pyrophosphate, micronized dispersible ferric pyrophosphate (MDFP), ferric orthophosphate and elemental iron compounds.
- Category 4: The advantage of these compounds is that in the presence of phytic acid, they have an RBV 2–3 fold of that of ferrous sulphate. They are however more susceptible to adverse sensory changes than category 2 or 3 compounds. This category includes amino acid chelates, and NaFeEDTA.

How can one enhance bioavailability of fortification iron?

There are 5 key ways of enhancing the bioavailability of iron added to foods:

1. Ascorbic acid is the most commonly added compound for the enhancement of iron absorption but is sensitive to processing and storage losses. Ascorbic acid acts in a dose dependent way and the general recommendation is a 2:1 molar ratio of ascorbic acid to iron for low phytate products, and 4:1 for high phytate products.
2. Erythorbic acid is a stereoisomer of ascorbic acid and appears to have a better enhancing effect but is more sensitive to oxidation, which may limit its usefulness.
3. Organic acids, although they enhance iron absorption, are not an option (with the possible exception of fruit juices) as the large quantities required for the effect cause unacceptable flavor changes in most vehicles.
4. The EDTA complexes of Na_2EDTA and $CaNa_2EDTA$ are accepted food additives and could be used to enhance iron absorption of water-soluble iron compounds.
5. Degradation of phytic acid (a potent inhibitor of iron absorption) by the addition of exogenous phytases or by the activation of native phytases in cereal grains in an aqueous environment under controlled conditions of pH and temperature, might be appropriate in low cost cereal and legume based complementary foods.

What levels of fortification are recommended?
Key when defining fortification levels is knowledge of the composition of the usual diet in order to estimate dietary iron bioavailability at 5%, 10% and 15%, and to have detailed information on the dietary intake of iron within the target population. The ultimate goal is to calculate the amount of extra daily nutrient required so that only 2.5% of the target population has an intake of below the Estimated Average Requirement (EAR). Care must also be taken when high levels of fortification are required to meet the goal, to ensure that other population groups do not exceed the upper limits.

It is noted that the EAR cut point method should not be used to estimate prevalence of inadequate iron intakes as iron intakes of some population subgroups (e.g. menstruating women and children) are not normally distributed. In these population groups it is recommended to use the full probability approach to define the fortification level. The WHO provides probability tables for this.

What is the key message?
Technically we now know how to design an efficacious iron fortified food. This information is provided in the WHO Guidelines. When designing an iron-fortified food, the food manufacturer must choose the iron compound with the highest RBV which causes no/limited sensory changes in the food and which is cost effective. At the same time, the level of fortification should be based on the needs and eating habits of the consumer. Widespread infections and concurrent deficiencies in other micronutrients may blunt its efficacy. In addition, it must not be forgotten that an efficient manufacturing and distribution system, quality control, monitoring procedures, synergistic health measures and good social marketing must also be in place for any intervention to be successful.

8

COPPER AND ZINC INTERACTIONS IN ANEMIA: A PUBLIC HEALTH PERSPECTIVE

Manuel Olivares, Eva Hertrampf and Ricardo Uauy

What is the problem and what do we know so far?
Both copper and zinc are essential nutrients and deficiencies of both result in anemia. Experimental studies have shown an inhibitory effect of zinc on iron absorption and it has been proposed that they compete for a shared absorptive pathway, but the exact mechanisms involved in the interaction at the absorption level are not fully understood. It has also been demonstrated that large doses of zinc inhibit copper absorption and may produce copper deficit, which indirectly could affect iron status leading to anemia. Zinc and copper have an antagonistic interaction within the erythrocyte. The public health relevance of these interactions has been considered limited in the past, but recent studies show that combined iron and zinc supplementation was less efficacious than single supplementation with iron in reducing the prevalence of anemia and in improving iron status. It should be noted that some studies have not confirmed this potentially detrimental effect but three studies in subjects presumably deficient in iron and zinc, demonstrated a larger increase in hemoglobin after combined iron and zinc supplementation than with iron or zinc supplementation alone.

In the developing world iron deficiency coexists with micronutrient deficiencies and infection, and recent research shows that copper and zinc deficiencies could be a contributing factor in the increased frequency of infections. In addition, acute infections are a well-recognized cause of mild to moderate anemia. Resistance to infections depends on a healthy immune function and copper and zinc are both necessary for the normal function of the immune system. In addition to alterations to the immune system, zinc deficiency may also contribute to an increased susceptibility to pathogens and several studies have shown an increased incidence of diarrhea and acute lower respiratory infection in zinc deficiency. It has also been found that zinc supplementation may reduce the incidence of malaria. However, an immunosuppressive effect has been observed at very high doses of supplemental zinc, but this might be explained in part by secondary copper deficiency induced by excessive zinc. Neutropenia is a frequent clinical manifestation of copper deficiency and this may be the link between an increased frequency of severe lower respiratory infections that have been described in copper deficient infants.

The modification of laboratory indices of iron status are related to the severity of the infectious process. This knowledge has led to the use of serum transferring receptor as an aid in the interpretation of iron status in populations with a high frequency of infections.

What are the basics of copper metabolism?
Copper is an essential nutrient which is absorbed primarily in the duodenum by a mechanism not yet fully understood,

but the chemical form of the copper in the lumen markedly affects its absorption. Apparent absorption varies from 15–80% (usual range 40–60%) and is determined by host and dietary related factors (intake and nutritional status), some of which have yet to be defined. As solubility of the compound increases, copper is absorbed more effectively and it seems that animal protein, human milk and histidine enhance absorption whereas cows milk, zinc, ascorbic acid and phytates diminish absorption.

Copper deficiency is usually the consequence of low copper stores at birth; inadequate dietary copper intake; poor absorption and increased requirements induced by rapid growth or increased copper losses and is often as a result of multiple factors. Acquired copper deficiency is a clinical syndrome occurring mainly in infants, and is more frequent in preterm infants (especially of a very low birth weight) and infants fed exclusively cow's milk based diets and should be suspected in infants with prolonged or recurrent diarrheal episodes. It would seem that the most common cause of overt, clinical copper deficiency is insufficient copper supply during the nutritional recovery of malnourished children. High oral intakes of zinc and iron decrease copper absorption and could predispose to deficiency. Common clinical manifestations are anemia (92%), neutropenia (84%) and bone abnormalities. The hematological changes are attributed to a number of mechanisms and are fully reversed by copper supplementation but are unresponsive to iron therapy alone.

Dietary copper deficit and genetic defects of copper metabolism have significant effects on iron metabolism and red cell resistance to oxidative stress, and thus may contribute to the burden of anemia. In addition, copper is also associated with impaired host defenses and could increase the burden of anemia secondary to infection. Copper deficit should be included in the differential diagnosis of anemia unresponsive to iron supplementation. Copper excess may also contribute to anemia by inducing hemolysis.

What are the basics of zinc metabolism?
Zinc is widely found within cells, which makes the study of zinc dependent mechanisms to determine physiological function difficult, but zinc plays a central role in cellular growth, differentiation and metabolism. Some of the critical functions affected by zinc status include pregnancy outcome, fetal growth and development, linear growth, susceptibility to infection and neurobehavioral development. Zinc is absorbed through the small intestines and is affected by its chemical form and the presence of inhibitors or enhancers and adapts to physiological need. The total body zinc content is 1.5–2.5g and is determined by diet content, zinc nutritional status and zinc bioavailability from food. The main causes of zinc deficiency are low intake, increased requirements, malabsorption, increased losses and impaired utilization. The first descriptions of severely zinc deficient subjects included anemia, but this could possibly be due to combined iron deficiency or the special effect of zinc on red cell maturation. The mechanism of altering erythropoiesis is not fully understood.

Zinc deficit may contribute to the burden of anemia by altering erythropoiesis and decreasing red cell resistance to oxidative stress, impairing host defense. In addition, high doses of zinc supplementation interfere with copper and iron absorption and may also interfere with iron mobilization and impaired immune responses.

What is the key message?
Although the potential public health relevance of zinc and copper interactions with iron remains undefined, they both potentially impact on the burden of anemia, directly and indirectly through infection, and must not be ignored in nutritional anemia interventions.

9

NUTRITIONAL ANEMIA – B VITAMINS

John Scott

What is the problem and what do we know so far?
Although most anemia in developing countries is due to iron deficiency, a proportion may be due to deficiency of vitamins of B complex, principally folate and vitamin B_{12}. This anemia is macrocytic but with the presence of abnormal red cell precursors in the bone marrow called megaloblasts. Concurrent presence of iron deficiency results in an anemia that is often normocytic. This can result in diagnostic difficulties and as a result, what is often attributed to pure iron deficiency may frequently be due in part to folate or vitamin B_{12} deficiency, and the true prevalence of folate of vitamin B_{12} deficiency is difficult to establish.

Some nutrients are not at risk of being deficient because of their adequate level in most diets. Others are of particular risk in certain individuals and under certain conditions. For the B complex vitamins, there is a wide spectrum

of risk with biotin and pantothenic acid seldom being deficient, whereas vitamin B_{12} and folate deficiency is a cause for great concern. Folate and B_{12} have an impact on a number of key health outcomes, both for the mother herself and adverse pregnancy outcomes. The development of the embryo and fetus may be stunted. Impaired cognitive development and increased mortality and morbidity in adult life are a cause for concern, in addition to the well proven case of increased risk for spina bifida, neural tube defects (NTD) and other birth defects.

What has been achieved?

Towards the end of the nineteenth century it was recognized that a macrocytic anemia, with larger than normal circulating red blood cells accompanied by abnormal red cell precursors in the bone marrow, was the result of folate or vitamin B_{12} deficiency and that the two deficiencies are interrelated as a result of their biochemical interdependence. Treatment of folate deficiency, either with food folate or more commonly with the synthetic form folic acid, and treatment of vitamin B_{12} deficiency with vitamin B_{12}, usually produces complete remission of the anemia. However, in the case of vitamin B_{12} deficiency, where advanced neuropathy has already resulted, there may be some residual damage. Generally vitamin B_{12} deficiency is the result of either a direct nutritional deficiency (common in vegans) or malabsorption due to the absence of either gastric acid or intrinsic factor needed for absorption. Nutritional deficiency can be treated either by fortification or supplementation, as can gastric atrophy. Malabsorption due to lack of intrinsic factor requires parenteral treatment.

There is a major concern that vitamin B_{12} deficiency can be incorrectly presumed to be a folate deficiency and thus be treated with folic acid. This will result in normalized DNA biosynthesis giving the impression that the anemia has been successfully treated. However, it does not treat the neuropathy that requires vitamin B_{12}, so the neuropathy will then progress to a more advanced and irreversible stage. Masking of vitamin B_{12} deficiency by folic acid supplementation is dose dependant and is considered not to happen at intakes of <1000 µg (or 1.0 mg) of folic acid per day.

In developing countries, the prevalence of megaloblastic anemia may be significantly under-detected as a result of the very common concomitant prevalence of iron deficiency.

What do we know about folate?

Folate is unstable, not fully bioavailable and is not found in great density in most foods except liver, which is not a large part of most diets. The best source of folate is vegetables, but in developing countries insufficient food intake is common, resulting in a high prevalence of folate deficiency. In addition, there is a large increased requirement for folate during pregnancy and lactation. Compounding the problem even further is the fact that recently a polymorphism, that has a high prevalence in some communities, has been found in one of the folate dependent enzymes that increases folate requirement by as much as 30%. This means that folate deficiency in both developed and developing countries is common and is of particular concern leading up to and during pregnancy. As a result, folic acid supplementation before, during and after pregnancy is now accepted as being critical regardless of the nutritional status of the woman. There is some concern that high levels of folic acid supplementation might accelerate the growth of existing tumors, most commonly cited with respect to colorectal cancer but possibly true of other cancers. The recommendation from the experts is that more research is needed but that there is currently insufficient evidence to halt folic acid fortification. Folic acid fortification is mandatory in over 40 countries and is being considered by many others, mainly driven by public health policies, in order to prevent neural tube defects (NTDs).

What do we know about vitamin B_{12}?

Vitamin B_{12} enters the human food chain exclusively through animal sources either as meat, milk, milk products and eggs. Its synthesis is completely absent in plants of all kinds, only being present in such foods by way of bacterial contamination or fermentation. This is because the enzymes necessary to assemble vitamin B_{12} are only present in bacteria and some algae. For this reason vegetarians and more particularly vegans, are at high risk of insufficient dietary intake. Individuals in many developing countries, who have low intakes of animal based foods due to lack of accessibility and high cost, are also at risk of vitamin B_{12} deficiency.

Most diets, in contrast to folate, have levels of vitamin B_{12} that exceed the recommended daily allowance (RDA) and it is therefore surprising that there is a relatively widespread prevalence of vitamin B_{12} deficiency. This has been ascribed to the presence of hypochlorhydria, due to gastric atrophy and the absence of acid preventing the liberation of vitamin B_{12} from food. Such hypochlorhydria is thought to occur in significant proportions of all populations, being especially common in the elderly, where the prevalence might be as high as 30%. It is also suggested that gastric atrophy might be higher in some ethnic groups. Vitamin B_{12}, as a result of impaired absorption,

can also be the result of true pernicious anemia, which is a specific autoimmune disease that reduces or eventually eliminates the active absorption of vitamin B_{12} from the diet. Its prevalence seems to range from a fraction of a percent to as high as 4.3%, but overall its prevalence is low compared to gastric atrophy. The negative effect of vitamin B_{12} malabsorption is on the absorption of food bound vitamin B_{12} and not on free vitamin B_{12}, contained in supplements or in fortified foods. Those with pernicious anemia must get vitamin B_{12} by injection.

What about the other B vitamins?
Extremes of poor intake of riboflavin (vitamin B_2), pyridoxal (vitamin B_6), niacin (vitamin B_1), thiamine and pantothenic acid can cause deficiencies and are classified as essential nutrients, however, the prevention and the consequence of deficiency or under-provision of folate and vitamin B_{12} are by far the most important public health issues.

What is the key message?
It would appear when addressing anemia that more attention needs to be given to folate status and perhaps even more so to the vitamin B_{12} status of individuals, especially pregnant and lactating women, when addressing anemia.

Results from intervention trials seem to indicate that daily iron together with multiple micronutrients is most effective in improving anemia. By their very nature one cannot unravel which component in a multivitamin preparation may be the one to elicit a response, however fortification with low dose folic acid and vitamin B_{12} offers an attractive, cost-effective way of reducing NTDs and eliminating megablastic anemia in developing countries.

FACTS:
- Folic acid supplementation before, during and after contraception can reduce the prevalence of spina bifida and other neural tube defects by more than half and possibly by as much as three-quarters
- Masking of vitamin B_{12} deficiency by folic acid supplementation is dose-dependant and considered not to happen at intakes of <1000 µg (or 1.0 mg) of folic acid per day.
- The Upper Tolerable Intake Level (UL) for folic acid is set at 1000 µg.
- Research in Canada shows that folate fortification of 100 µg/day has resulted in between 50% and 70% reductions in the prevalence of NTDs.
- Detection of folate deficiency can be undertaken using serum folate or preferably red cell folate but levels need to be very low to be diagnostic.
- Detection of vitamin B_{12} deficiency can be undertaken using serum vitamin B_{12} or more recently recommended holtotranscobalamin, but levels need to be very low to be diagnostic.
- Status biomarkers such as serum homocysteine or methylmalonic acid are helpful but are not capable of a definite conclusion and are usually not available.
- Vitamin B_{12} deficiency is a severe problem on the Indian Subcontinent, in Mexico, Central and South America and certain areas of Africa.
- The prevalence of pernicious anemia is reported as being from a fraction of a percent to as high as 4.3%, but gastric atrophy is far more prevalent and in the elderly is considered common (as high as 30%).

10

VITAMIN A IN NUTRITIONAL ANEMIA

Keith P. West, Jr., Alison D. Gernand
and Alfred Sommer

What is the problem and what do we know so far?
Beyond iron, anemia can be caused or made worse by a number of nutritional deficiencies. In particular, vitamin A deficiency may mediate iron metabolism at several points along the internal iron and reticuloendothelial circuitry to increase the risk of iron deficient-erythropoiesis and anemia. Although controversial, there are four plausible mechanisms by which vitamin A nutriture may affect risk of anemia: influencing tissue storage and release of iron into circulation; having a direct regulatory effect on erythropoiesis; modifying the sequestration and release of tissue iron, associated with responses to infection; and exerting an effect on iron absorption. The greatest body of evidence supports the first two mechanisms. The control of vitamin A deficiency, which often coexists with iron deficiency in undernourished populations, can therefore be important for preventing anemia due to either malnutrition or inflammation associated with infection.

Vitamin A is known to have two basic functions. The first is that of a cofactor which maintains proper function of rod photoreceptor cells in the back of the eye and enables vision under conditions of low light. A deficiency in vitamin A can, thus, lead to night blindness. The second, which is likely to explain the various effects of vitamin A on hematopoiesis, involves regulating nuclear transcription and synthesis of proteins that affect cell growth,

differentiation, metabolism and longevity. Its role is most evident in epithelial linings of the eye that become dry (keratinized) from vitamin A deficiency, which in its most severe form can lead to blinding xerophthalmia. However, vitamin A also helps to regulate functions of many other cell types, including those involved in immunity, bone growth and red blood cell production. These many functions lead to diverse health consequences of vitamin A deficiency (VAD) that have been grouped as a class of disorders (VADD) that include xerophthalmia and its resulting blindness, increased severity of infection, anemia, poorer growth and mortality itself. Because of its extent and severity, vitamin A deficiency remains the leading cause of pediatric blindness and a major nutritional determinant of severe infection and mortality among children in the developing world. In addition, maternal vitamin A deficiency is rising as a major public health concern. Less well appreciated are the degrees and conditions under which vitamin A deficiency may also contribute to anemia, which adds further importance to its prevention.

Vitamin A deficiency results from a diet that is chronically low in foods rich in preformed vitamin A or its precursor carotenoids (especially β-carotene). Food sources of preformed vitamin A include liver, cod liver oil, milk, cheese and fortified foods, while common food sources of provitamin A carotenoids include soft yellow fruits, orange and yellow tubers, and dark green leafy vegetables.

What has been achieved?

On a global scale, enormous strides have been made to reduce the burden of vitamin A deficiency, and resulting risks of blindness and mortality, among children. A concurrent reduction in the risk of anemia has typically been less recognized as a public health benefit of control, despite substantial evidence linking these two conditions. Clinical studies early in the last century, and numerous population surveys in developing countries in the mid-20th century, noted a consistent, positive correlation, ranging from 0.2 to 0.9, between serum retinol and the concentration of blood hemoglobin. During a study in the seventies, eight men deprived of vitamin A over a period of months developed anemia that failed to respond to iron but did so with vitamin A repletion, suggesting that vitamin A is required to mount an adequate hematological response to iron. Subsequent studies in anemic children and women have revealed blunted hemoglobin responses to iron in the presence of marginal or deficient vitamin A status, and markedly improved hemoglobin responses to vitamin A alone or when provided with iron. Vitamin A supplementation appears to stimulate iron metabolism in ways that can improve red cell production or survival. Vitamin A supplementation appears most able to exert its positive effects on hemoglobin level and reduce risk of anemia in vitamin A-deficient populations. Vitamin A may be less effective in controlling anemia in the presence of infections such as hookworm, malaria, tuberculosis or HIV, each of which may affect vitamin A and iron metabolism and, in doing so, obscure hematologic effects of vitamin A. Also, little effect of vitamin A on hematopoiesis may be discernable in nutritionally adequate populations.

What is the way forward?

Vitamin A deficiency continues to be a major nutritional problem in the developing world, affecting vision, resistance to infection, growth and survival. It is increasingly recognized as a contributory cause of anemia. Interventions to reduce nutritional anemia in women and children should consider preventing other nutritional deficiencies that may enhance effects of iron prophylaxis, such as that of vitamin A. Recognizing this linkage may stimulate co-assessment of iron and vitamin A status when investigating anemia in high-risk populations. Researchers should continue to elucidate vitamin A interactions with iron. While vitamin A can be expected to reduce risk of severe infection, its effect on reducing the anemia of infection still requires research since its influence on iron metabolism may be obscured by the types and severity of infections in patients or a population. As research continues, practitioners can expect to achieve, on average, gains in the hematologic status of deficient and anemic populations through vitamin A interventions. While likely to be helpful, it should also be kept in mind that vitamin A can not be expected to have a major effect on anemia due to frank iron deficiency, hookworm and malaria infections, and other causes of chronic, moderate-to-severe inflammation.

What is the key message?

Vitamin A supplementation alone, or in combination with iron, is likely to reduce the burden of anemia in areas where vitamin A deficiency is a public health problem. Supplementation has proven effective as large, infrequent doses, daily or weekly doses, and via diet by consuming vitamin A fortified food. The effects are clearest in the absence of infectious disease and in nutritionally deficient populations.

FACTS:

- Vitamin A deficiency is the leading cause of pediatric blindness and a major nutritional determinant of severe infection and mortality among children in the developing world.

- It is estimated that 125–130 million preschool aged children are vitamin A deficient and 20 million pregnant women have marginal to deficient vitamin A status.
- Vitamin A deficiency disorders include xerophthalmia, increased severity of infection, poor growth, anemia and increased risk of mortality.
- Vitamin A affects hemoglobin levels because it is involved in iron metabolism and red blood cell production.
- Vitamin A deficiency contributes to nutritional anemia, probably by restricting iron use for hemoglobin.
- Supplementation with vitamin A can reduce risk of mild to moderate anemia in vitamin A deficient and anemic populations.
- Hematopoietic benefits of vitamin A are more likely to be seen when anemia is not due to severe infectious diseases such as hookworm, malaria, HIV/AIDS and tuberculosis.

11

OXIDATIVE STRESS AND VITAMIN E IN ANEMIA

Maret Traber and Afaf Kamal-Eldin

What is the problem and what do we know so far?

Anemia can result from a range of nutritional deficiencies, inherited disorders and/or from infections or exposure to certain toxins and medications. Anemia can lead to a variety of health problems since the oxygen required by the body is carried by red blood cells and because oxidative stress, the overproduction of reactive oxygen species and impaired antioxidant potential, can be generated by the iron released from damaged red blood cells. Oxidative stress is associated with anemia. Moreover, a major site of antioxidant defense in blood is the erythrocyte because it contains intracellular enzymatic antioxidants. Low molecular weight antioxidants, especially vitamin E and vitamin C provide additional significant protection.

What is oxidative stress?

Oxidative stress represents an imbalance between the generation of free radicals and reactive oxygen species and protection by antioxidant enzymes and low molecular weight antioxidants. A free radical is any chemical species that contains one or more unpaired electrons capable of independent existence. A species with an unpaired electron has the tendency to react very rapidly with other molecules, and thus cause free radical damage. Free radicals can damage virtually all molecules including protein, DNA, carbohydrates and lipids. Lipid peroxidation is especially dangerous because it is a chain reaction that generates radicals.

What is vitamin E and how does it work?

The term vitamin E refers to the group of eight phytochemicals exhibiting the antioxidant activity of alpha-tocopherol, but only alpha-tocopherol meets human vitamin E requirements. Vitamin E, particularly alpha-tocopherol functions as a lipid soluble, chain-breaking antioxidant and is a potent peroxyl radical scavenger. It halts lipid peroxidantion. In humans, vitamin E deficiency occurs as a result of fat malabsorption because vitamin E absorption is dependent not only on the fat content of the food, but also the mechanisms for fat absorption. Unlike other fat-soluble vitamins, which have specific plasma transport proteins, the various forms of vitamin E are transported non-specifically in lipoproteins in the plasma. There are a number of routes by which tissues can acquire vitamin E; however the mechanisms for the release of alpha-tocopherol from the tissues are unknown. In addition, no organ is known to function as a storage organ for alpha-tocopherol. Unlike other fat-soluble vitamins, vitamin E is not accumulated in the liver to toxic levels, which suggests that excretion and metabolism are important in preventing adverse effects. Vitamin E deficiency does occur as a result of genetic abnormalities in alpha-tocopherol (leading to a syndrome called AVED or Ataxia with isolated vitamin E) and as a result of various fat malabsorption syndromes. The major deficiency symptom is a peripheral neuropathy, but anemia is also a consequence of inadequate vitamin E levels. Both anemia and the peripheral neuropathy appear to occur as a result of free radical damage due to the lack of sufficient alpha-tocopherol.

What is the role of vitamin E in the malnourished?

Vitamin E status can be compromised during anemia as a result of the increased oxidative stress caused by erythrocyte hemolysis. Despite the wide range of types of anemia, oxidative stress is the common denominator.

A hepatic protein is required to maintain normal plasma alpha-tocopherol concentrations and so it is not surprising that vitamin E deficiency symptoms have been reported in children with severely restricted food intake, which not only limits vitamin E intake but also the protein necessary to synthesize the required hepatic protein. The degree to which vitamin E deficiency is associated with kwashiorkor and/or marasmus is not clear because

the evaluation of vitamin E status in malnourished children is difficult and so it is not certain that vitamin E supplementation would be beneficial until the underlying metabolic problem is resolved.

In the case of iron deficiency anemia not only is there decreased production of hemoglobin and other iron-containing proteins but the erythrocyte membranes are also more susceptible to oxidative damage. Research showed that iron supplementation to deficient individuals was found to increase oxidative stress but treatment with a combination of iron and vitamins A, C and E proved effective in normalizing the oxidative stress.

What about vitamin E in thalassemia and sickle cell diseases?

These are both inherited blood hemoglobin disorders that cause anemia. About 90 million people worldwide carry the defective genes leading to thalassemia. The mild to severe anemia associated with thalassemia results from oxidative stress and some recommend supplementation of these individuals with vitamin E and vitamin C. Oxidative stress is also manifested in sickle cell disease, which is a chronic inflammatory disease, thus there may be a benefit for vitamin E supplementation.

What about vitamin E in malaria?

Malaria is endemic in many parts of the world and research shows elevated biomarkers of oxidative stress in malaria infected erythrocytes and that this decreases as the individual recovers. The findings from a number of studies suggest that improved antioxidant defenses will be beneficial in mounting appropriate immune responses. Interestingly however, the research also shows that a level of oxidative stress might be important during the treatment of malaria although it contributes negatively to the general health, possibly inducing anemia as a result of the destruction of the red cells. Thus the individual may benefit from post-treatment vitamin E supplementation.

Does vitamin E have a role to play in HIV and AIDS?

Anemia is common in HIV/AIDS and severe anemia is associated with an increased risk of mortality. A recent review of clinical trials has suggested that currently there are no useful therapeutic strategies to decrease anemia in HIV/AIDS and despite positive reports there are few antioxidant intervention trials, suggesting that there has been limited success since the first trials were reported. Vitamin E has been shown to improve host immune response and so it is reasonable to consider whether vitamin E and vitamin C supplementation would be of benefit to support immune function during various infectious diseases.

What is the key message?

Many anemia types are accompanied by a low vitamin E status. While the deficiency may be caused by inadequate food intakes, they could also be caused by impaired vitamin E transport to tissues or increased oxidative stress. This emphasizes the critical need not only for vitamin E supplementation but also adequate dietary support with respect to all nutrients.

FACTS:

- The term vitamin E refers to the group of eight phytochemicals, exhibiting the antioxidant activity of alpha-tocopherol, which come from the diet, but with only alpha-tocopherol meeting human requirements.
- The United States Food and Nutrition Board have defined the lower limit of plasma alpha-tocopherol at 12 µmol/L for normal, healthy adults.
- Children with plasma alpha-tocopherol at 8 µmol/L resulting from malnutrition have been observed to have vitamin E-responsive neurologic abnormalities.
- About 90 million people worldwide carry the defective genes leading to thalassemia.
- Malaria accounts for about 2.7 million deaths a year and there are about 500 million episodes reported each year.

12

SELENIUM

Richard Semba

What is the problem and what do we know so far?

Anemia is common in older adults and the prevalence of anemia increases with advancing age and is associated with numerous adverse outcomes. About one third of the anemia that occurs in some high-risk populations is unexplained, and selenium deficiency may potentially explain a portion of this unexplained anemia. The relationship between selenium status and anemia has not been well characterized in humans. Selenium deficiency should be considered a possible cause of anemia that requires further investigation and confirmation.

Selenium is an essential trace element and a normal con-

stituent of the diet. Dietary intake varies widely worldwide as the natural selenium levels in foods reflect the concentrations in the soil. The richest dietary sources are organ meat and seafood. Selenium is present mostly in human tissue in the form of two selenium containing amino acids. Its biochemical functions are related to its role in selenoproteins, and several of these are antioxidant enzymes. Selenium absorption is not regulated and only 50–100% of dietary selenium is absorbed. Insufficient intake usually does not have obvious clinical manifestations, although low levels have been linked to increased susceptibility to oxidative stress and increased risk of cancer and even heart disease. The selenium requirement for prevention of chronic disease has not yet been definitively determined.

What has been achieved?

Research has showed that low serum selenium levels appear to be independently associated with anemia among older adults (>65 years). In addition, a strong correlation between low plasma selenium concentrations and low hemoglobin has also been observed in studies in older individuals. However, the direction of the association is not clear but could potentially be through selenium's role in the maintenance of an optimal concentration of glutathione peroxidase, a key antioxidant in erythrocytes, or through increased inflammation and oxidative stress.

What is the way forward?

The observations of an association between low selenium levels and anemia in older men and women raises a potentially important public health question – Has selenium deficiency been overlooked as a cause of anemia? Further research is required in order to gain insight into selenium's potential role in the pathogenesis of anemia.

What is the key message?

Research shows that selenium may be associated with anemia but to gain insight, more focused research is required in this field.

13

INTERACTIONS BETWEEN IRON AND VITAMIN A, RIBOFLAVIN, COPPER AND ZINC IN THE ETIOLOGY OF ANEMIA

Michael Zimmermann

What is the problem and what do we know so far?

It is estimated that about half of all cases of anemia are due to iron deficiency and the remainder is due to other causes such as other nutritional deficiencies, infectious disorders, hemoglobinopathies and ethnic differences in normal Hb. The prevalence of anemia is particularly high in developing countries where micronutrient deficiencies often coexist. A deficiency of one micronutrient may influence the absorption, metabolism and/or excretion of another micronutrient. Of specific interest in anemia are the interactions between iron deficiency and four other micronutrients – vitamin A, riboflavin (vitamin B_2), copper and zinc.

The link between vitamin A deficiency and anemia has been recognized for many years and although improving vitamin A status often increases hemoglobin and reduces anemia, the exact mechanism is unclear. Although data from human studies are equivocal, riboflavin deficiency may also impair erythropoiesis and contribute to anemia. In addition, copper deficiency is also known to impair dietary iron absorption but as copper deficiency is rare in the general population, the interaction may not be of public health importance. Finally, although the data do not suggest zinc deficiency as playing a role in anemia, deficiencies of iron and zinc often coexist and supplements containing both iron and zinc could be of value in vulnerable populations. It is noted however that several studies have suggested that zinc supplementation may reduce iron efficacy.

What is known about the link between iron deficiency and vitamin A?

Vitamin A deficiency affects more than 30% of the global population and the most vulnerable are women of reproductive age, infants and children. This is the same group most vulnerable to anemia. Surveys in developing countries have generally reported positive correlations between serum retinol and hemoglobin concentrations, with stronger associations in populations with poorer vitamin A status. However, data from human studies investigating the influence of vitamin A on absorption is

equivocal and suggest that further research is needed to clarify the actual effect of vitamin A on iron absorption. In addition, the mechanism by which vitamin A exerts its effect on erythropoiesis remains unclear, although several mechanisms have been proposed. Intervention studies suggest that in areas where vitamin A and iron intakes are poor, dual fortification or supplementation is likely to be more effective in controlling anemia than providing vitamin A or iron alone.

What is known about the link between iron deficiency and riboflavin?

Riboflavin is required for many metabolic pathways. Riboflavin deficiency is common in areas where intakes of dairy products and meat are low and school children are a group at high risk for riboflavin deficiency. It appears that riboflavin deficiency, in addition to its other symptoms, may impair erythropoiesis and contribute to anemia as a result of a number of suggested mechanisms. Although these mechanisms have been investigated in animals, there is little human data. The data from the studies that have been undertaken suggest that the effect of riboflavin status on hemoglobin is variable and may be confounded by the multifactorial etiology of anemia. It must be noted that the data from a number of studies, in contrast to earlier studies, do not support a detrimental effect of riboflavin deficiency on anemia.

What is known about the link between iron deficiency and copper?

Copper deficiency is a rare cause of anemia and how the deficiency causes anemia is uncertain. It is, however, known that the resultant anemia is responsive to dietary supplementation with copper but not with iron. It is noted that although copper deficiency impairs dietary iron absorption and results in iron deficiency anemia, copper deficiency is rare in the general population and so is unlikely to be of public health importance.

What is known about the link between iron deficiency and zinc?

Iron deficiency anemia is frequently the result of low dietary iron absorption due to low intakes of meat and high intakes of inhibitors (e.g. phytate, polyphenols). Interestingly, these same dietary factors decrease bioavailability of zinc. Although the data does not suggest zinc deficiency as playing a role in anemia, deficiencies of iron and zinc often coexist and supplements containing both could be of value in vulnerable population groups. It must be noted, however, that several studies have suggested that concurrent zinc supplementation may reduce the efficacy of iron and some studies suggest that when zinc supplements are given with iron supplements, iron status does not improve as much as when iron is given alone. Further research is definitely needed to clarify the effect of joint zinc and iron supplementation.

What is the key message?

The prevalence of anemia is particularly high in developing countries where micronutrient deficiencies often coexist and a deficiency of one micronutrient may influence the status of another. Although more research is needed, vitamin A, riboflavin, copper and zinc may be important in addition to iron in addressing nutritional anemia.

14

ANEMIA IN SEVERE UNDERNUTRITION (MALNUTRITION)

Alan Jackson

What is the problem and what do we know so far?

Anemia is found commonly as an associated feature of many pathological conditions. In most cases, severe malnutrition is also accompanied by anemia, as an integral part of the process of reductive adaptation associated with weight loss, reduced lean body mass and the presence of edema. However, the specific cause of anemia is also complicated by associated deficiencies of specific micronutrients, increased red cell destruction and the ongoing suppression of red cell formation as a result of the inflammatory response to multiple infections. As a result, the anemia associated with established severe undernutrition, or malnutrition with edema during childhood or adulthood is not specific but is usually associated with an inability to effectively utilize iron, leading to an increase in the iron present in the body in both the stored and free form. Therapy with iron at this stage increases mortality. Given the complexity of the possible interactions in the established condition, it can be very difficult to determine the sequence with which one factor might have acted as a primary exposure, subsequently interacting with other factors, which later contribute and play a secondary role.

What has been achieved?

The terms marasmus, kwashiorkor, marasmic-kwashiorkor, protein deficiency, energy deficiency and protein-energy deficiency have all been used at different times to

describe what is now termed severe undernutrition with or without edema. There is emerging consensus that there are two key features that capture the essence of the underlying processes which lead to the state of being malnourished, without necessarily being specific about the detailed aspects of multiple complex underlying causes:

1. An inadequate intake of food, due either to a poor appetite or limited availability of food, leads to a wasting syndrome with a relative loss of weight and associated with a range of complex adaptive changes in all tissues and organs
2. The presence of an underlying specific pathology, such as an infection or a poor quality diet, separately and together might predispose to a reduced food intake and in addition challenge metabolic integrity that predisposes to the formation of edema.

There are four key processes which separately and together contribute to anemia:

1. *Reductive adaptation*
   The anemia is in part an aspect of the body's adaptation to reduced food intake and decreased metabolic activity. It should be differentiated from the anemia associated with chronic disorders. At an early stage erythropoiesis may be normal or increased with a lower hemoglobin resulting from a reduction in the life span of the red cells. In the later, more advanced stage, as tissue metabolism falls, erythropoiesis is no longer stimulated with a decrease in red cell mass.
2. *Specific nutrient deficiencies*
   The multiplication and differentiation of red cell precursors with the formation of mature erythrocytes which eventually appear in the circulation is a complex process which requires the full complement of nutrients and metabolic intermediates. A limitation in any of these nutrients will limit the formation of red cells, their structural integrity and their functional capability. Over and above the needs of other cells, red cells have a special need for those nutrients which are directly involved in the formation of hemoglobin.
3. *Infection*
   There is a complex interaction between infection and poor nutrition with each predisposing to, and making the other worse. In severe malnutrition, the effects of infection on anemia might be directly related to a specific infection or indirectly to a more general inflammatory and immune response. Separately and together, these will limit the availability of nutrients for red cell formation and increase the likelihood of anemia.
4. *Hemolysis, pro-oxidant damage*
   The hostile environment to which the red cell is exposed reflects that experienced by all the other cells in the body. For the red cell, enhanced susceptibility to pro-oxidant damage will predispose to a shortened life span, which increases the extent to which iron has to be held in an innocuous form. An increase in stored and/or free intracellular iron can act as the focus for ongoing pro-oxidant stress and ensuing cellular pathology. An increased loss of red cells in the face of any limitation on red cell production inevitably leads to a reduction in red cell mass, and increased iron in storage.

Anemia, as a reduction is circulating red cell mass, must be the result of a change in the balance between the rates of red cell synthesis and red cell degradation, assuming no external blood loss. The reduction in red cell synthesis may be part of the general adaptive response, or a constraint on the availability of energy or a specific nutrient. Alterations in the rate of degradation would result from the production of cells of poor quality being more vulnerable and thus more likely to have a shortened life span because they exist in the challenging environment produced by infection, nutritional or metabolic derangement.

In the case of red cell synthesis, there may be severe changes in the bone marrow, but potentially these appear to be completely reversible with successful treatment and recovery. However even after recovery of weight, there seems to be a delay in the time needed for complete recovery of the red cell formation, implying an ongoing constraint on erythropoiesis. During acute illness, there appears to be an ongoing drive to red cell formation but with an associated constraint on the effective utilization of the available iron. An important feature of this stage that needs to be emphasized is the notable presence or iron deposits in the reticulo-endothelium, including marrow, liver and spleen. This may be visible as hemosiderin, or using appropriate techniques, identifiable as free iron. This makes the identification and characterization of 'iron deficiency' problematic and has important implications for therapy.

What is the required treatment?

The likelihood of an individual dying from a period of severe undernutrition, or surviving with a reasonable chance of recovery, not only depends on what is done in terms of immediate care, but critically the order in which different interventions are carried out. The identification and classification of severe malnutrition places emphasis on two characteristics, loss of relative weight, and the presence of edema. An inappropriate approach to treatment might focus on correcting the edema through the

use of diuretics, correcting the wasting through the provision of food, or treating abnormal blood biochemistry by direct provision of single nutrients. It is now known that each runs the risk of contributing to increased mortality unless specific attention is given to the correction of the cellular damage associated with complex nutrient deficiencies and imbalances. Although anemia might be a common presenting feature, and have many of the characteristics of an iron-deficient picture, the problem in the short term is one of an inability to effectively utilize the iron that is in the body, rather than an immediate shortage. Therapy with iron at this point increases mortality. With appropriate treatment, as infections are addressed and specific nutrient deficiencies corrected, cellular competence returns. Lean body mass can be progressively restored and the red blood cell mass expanded to draw on the iron held as hemosiderin and ferritin. At some stage during the recovery process the iron in storage is likely to be insufficient to meet the demand and as a more classical picture of iron deficiency emerges, iron supplementation becomes needed and is appropriate.

What is the key message?

Accumulated evidence shows that the anemia of severe malnutrition is the consequence of multiple factors and represents an interaction between adaptation to inadequate food intake and the impact of other stresses associated with infection or dietary imbalance. Constraints on the effective utilization of iron lead to an increase in unutilized iron, despite no increase in the total body burden of iron. Iron supplementation is hazardous in this situation. It is thus essential, in order to avoid causing more harm than good, to understand the broader context of the anemia of severe malnutrition and to ensure the use of appropriate interventions at the appropriate times.

FACTS:

- The terms marasmus, kwashiorkor, marasmic-kwashiorkor, protein deficiency, energy deficiency and protein-energy deficiency have all been used at different times to describe what is now termed severe undernutrition with or without edema.
- Infants and children suffering from severe malnutrition frequently have moderately reduced hemoglobin – 80 to 100 g/L, or reduced hematocrit – 30% to 35%.
- The normal life span of a red blood cell is on average, 120 days but may be shorter in severely malnourished children.
- Despite low hemoglobin there is an increase in both stored and free cellular iron, and supplementation with iron increases mortality.

15

INFECTION AND THE ETIOLOGY OF ANEMIA

David Thurnham and Christine Northrop-Clewes

What is the problem and what do we know so far?

Anemia and disease are both highly prevalent in developing countries. It is known that the inflammatory response to disease stimulates a series of changes in iron metabolism that results in anemia if the inflammation is protracted. It must be noted that the hypoferremia of inflammation does not represent a genuine iron deficiency, but rather a redistribution of iron that can prevail in the face of normal iron stores.

Typically, infants are exposed to infection and inflammation and this is in fact necessary to develop the immune system. However, too frequent exposure will increase the risk of anemia. Parasitic infections also contribute to inflammation and anemia. Thus, in the developing world where there is a high prevalence of diarrhoea, vomiting, fever, malaria, and helminth infections, anemia is common. Attempts to reduce the prevalence of anemia have been ongoing for over two decades, but the condition is still common. One of the reasons for the apparent failure could be that the assumption has been that ‘iron deficiency’ was the only cause. It is now more widely recognized that anemia is a consequence of both inflammation and insufficient bioavailable dietary iron.

What has been achieved?

There is now wider recognition that infection is responsible for a large part of the anemia in developing countries and, as a result, there is an acceptance that infection and the inflammatory response may also play an important role in the initial cause. Frequent exposure to endemic diseases will promote the inflammatory response and hypoferremia and increase the risk of anemia by impairing erythrocyte synthesis and/or a shortening red cell life span. Whether this is accompanied by a metabolic iron deficiency will depend on the ability to maintain iron stores through iron absorption, iron loss and dietary iron bioavailability, in order to maintain normal hemoglobin. It must also be remembered that disease reduces appetite – the more frequently an individual is sick, the more likely they are to be malnourished.

What is the relationship between infection and anemia?

Infants are rarely anemic at birth. The relative hypoxic conditions in utero result in high hemoglobin concentrations at birth but as the oxygenation of infant blood improves, erythropoiesis ceases and hemoglobin concentrations drop over the first two months of life. By the age of 4–6 months, iron stores are marginal or become depleted and the supply and bioavailability of dietary iron becomes critical. Up to 4 months, breast milk is the main source of dietary iron and protective immune factors for growing infants, but as complimentary foods increase, so does exposure to environmental pathogens and the frequency of bouts of illness. Such infants are dependent on good sources of dietary iron to maintain hematological status, since iron absorption will be minimal during periods of anorexia and is blocked by fever and inflammation. Although the frequency of infectious episodes declines as humoral immunity develops and food intake in older children is less influenced by infectious diseases, maintenance of iron stores can be jeopardized by iron losses. Iron in the body is tightly conserved but the risk of schistosomal or hookworm infections increases with age and these parasites can cause chronic bleeding and iron loss. Thus infectious diseases, gut parasites and poor diet combine to deprive children of iron from early infancy. The research shows that even mild anemia impairs cognitive capacity, increases the risk of preterm delivery in pregnancy and reduces work output. It is thus clear that there is the possibility that inflammation may be a key etiological factor responsible for the initiation and for the continuing presence of anemia in developing countries.

Raised acute phase proteins (APP) serve as markers for subclinical inflammation. Three of these proteins are particularly useful. C-reactive protein (CRP) and Alpha1-antichymotrypsin (ACT) are the more acute markers of inflammation; they increase within the first 6 hours of infection, reach their maximum concentrations within 24–48 hours and usually fall as clinical signs start to appear. Alpha1-acidglycoprotein (AGP, also known as orosomucoid) concentrations are much slower to rise and only achieve maximum concentration 2–5 days after infection and thus are more of a chronic marker of inflammation. Where these proteins are increased, they indicate that iron metabolism is disturbed and that the alterations in iron metabolism caused by inflammation may be contributing to the prevalence of anemia in the population. Using these proteins, it is possible to identify persons in an apparently healthy population who may be incubating a disease, have recently recovered from a disease or are in later convalescence.

What is the way forward?

- Infection and inflammation play an important role in the etiology of anemia and it is recommended that the acute phase proteins CRP and AGP should be monitored before and after supplementation and should be measured together with ferritin.
- Research has shown that in many cases, iron supplements give little benefit and might in fact increase the prevalence of infection. This can now be explained by our knowledge of inflammation. If anemia in apparently healthy persons is mainly due to subclinical inflammation, it explains why supplementation with iron is so poorly effective in lowering the prevalence of anemia, as iron does not cure infections. Also, additional dietary iron given to infants exposed to frequent infections may upset the delicate balance of pro- and anti-inflammatory cytokines.
- Research shows that vitamin A supplements reduce some of the inflammation and enable iron mobilization to restore hemopoiesis, and so vitamin A supplementation should precede iron supplementation.
- Research needs to determine whether worms such as Ascaris contribute to anemia through inflammation and it needs to be determined whether the recently discovered hepcidin, which is increased by inflammation and blocks absorption and mobilization of iron, is produced locally in the gut.

What is the key message?

Infection and inflammation play an important role in the etiology of anemia and must not be neglected in any intervention. Iron supplements must be given with caution but the risk of adverse consequences may be modified by vitamin A status. It would, therefore, seem prudent that iron interventions should be preceded by vitamin A supplements with or without anti-helmitic treatment according to local conditions. The area of infection and inflammation is relatively new and its effect on anemia requires more research.

FACTS:

- 2 billion people across the globe are estimated to be anemic.
- 40%–50% of children under 14 years and women of childbearing age in developing countries suffer from anemia.
- Children aged 5–14 and pregnant women are at highest risk of anemia with estimated prevalence of 48% and 52% respectively.
- An estimated 200 million people globally are infected with schistosomiasis and another 600 million live in endemic areas.

- It is estimated that 1.3 billion people globally are affected by hookworm.
- It is estimated that 900 million people in the world are infected with Trichuriasis.
- Approximately 1500 million people globally are infected with Ascaris.

16

MAKING PROGRAMS FOR CONTROLLING ANEMIA MORE SUCCESSFUL

Saskia de Pee, Martin Bloem, Regina Moench-Pfanner and Richard Semba

What is the problem and what do we know so far?

The 1990 World Summit for Children set goals for eliminating micronutrient deficiencies because of their widespread prevalence, and in particular their severe consequences in developing countries, some of which are still emerging. Substantial progress has been made in combating vitamin A deficiency (VADD) and similar or even more progress has been made in combating iodine deficiency disorders (IDD). However, in the case of iron deficiency anemia, the knowledge of the impact on mental development is relatively recent and therefore combating iron deficiency anemia among young children was not a World Summit goal and progress in eradicating iron deficiency anemia has lagged behind.

Why is control of iron deficiency anemia lagging behind?

There have been a number of suggested reasons why iron deficiency and anemia control are not being implemented at a larger scale. These include focusing on what would be needed to implement the preferred approach in a better way so as to increase compliance and coverage; evaluation of alternative supplements and dosing frequencies to improve compliance and hence impact; and assessing what should be communicated to whom in order to gain momentum for control of iron deficiency anemia. It would seem, however, that at the core is the fact that there is a lack of mechanisms at country and global levels to ensure that effective measures are implemented. The situation might, therefore, largely be due to the fact that operational components of controlling iron deficiency anemia are less well developed in comparison to research and development (R&D), and that neither of these are well linked to communication. Communication encompasses generating political support and funding as well as motivating acceptance of better nutrition practices by families and communities through health education and promotion. A balanced program with interconnected components is required to support effective reduction of iron deficiency anemia.

Why is communication regarding controlling iron deficiency anemia difficult?

In the case of the control of VADD and IDD, the approach is 'bullet orientated' in that one simply emphasizes the use of vitamin A capsules and iodized salt respectively. In the case of iron deficiency anemia, the design of the intervention and implementation strategy is not the same for every situation and needs to involve various sectors.

What are the problems addressing nutritional anemia and what are the possible solutions?

Anemia versus iron deficiency

Problem: Anemia is not only due to iron deficiency and iron deficiency does not always lead to anemia.

Background: As a result of this problem, there has been an ongoing debate as to what the intervention goal should be – just reducing iron deficiency and iron deficiency anemia or also reducing anemia due to other causes, such as malaria, helminth infestation, deficiencies of other micronutrients etc. Because an effective approach requires knowledge of the primary causes of anemia, gathering knowledge on this is prioritized and often no action is taken until this is clear.

Solution: Focusing on the following facts should facilitate taking decisions as to which programs to implement:

- Over 2 billion people are anemic and estimates of the number of people affected by iron deficiency are even higher. Therefore, it is unlikely that any population is affected by anemia that is not to some extent due to iron deficiency nor that only iron deficiency underlies the anemia observed.
- The iron needs during infancy and pregnancy are so high that it is virtually impossible to meet these through the diet alone. Only when the diet of infants and pregnant women contains a considerable amount of fortified foods and heme iron, from animal foods, might their needs be met by the diet alone. Thus, iron deficiency in these age groups is almost guaranteed and the question is not whether intervening with iron, multi-micronutrients and/or infection control will have an impact on iron deficiency and anemia, but

rather which strategy is most effective. Instead of determining the precise extent to which each factor plays a role, action should be taken to address the causes that are assumed most important, while concurrently monitoring the impact of these measures on iron deficiency and anemia in the population, in order to adjust and fine tune the program. The rationale for this is that doing nothing does more damage than not treating all cases just because some causes are not yet recognized.

Nutrition, health, development or economic consequences

Problem: For a long time, iron supplementation was promoted as a means to prevent and treat anemia, a largely medical term that did not speak to the minds of policy makers and governments concerned with stimulating economic growth etc.

Background: Anemia was described as a state where not enough oxygen was transported through the body and people suffering from anemia were described to be more easily tired (lethargic), have lower work productivity, lower achievement in school, and severe anemia increased the risk of maternal mortality. This description was mainly tailored to the understanding of nutritionists and medical professionals. However, the consequences on a child's current and future mental capacity, a nation's development, as well as the economic consequences, were not sufficiently advocated among various appropriate sectors such as the economic child welfare, and education sector etc.

Solution: The fact that damage done by iron deficiency to a young child's mental capacity cannot be reversed later in life, and quantifying the loss of GDP when iron deficiency and anemia are left untreated, should be the key messages to mobilize action in combating iron deficiency and anemia across a wide range of sectors.

Medical versus food-based, public-health approach

Problem: When anemia is regarded a medical problem, solutions sought will focus on a medical approach for addressing the problem. This implies identifying the precise cause for each population before taking action, giving a high dosage of nutrients that is sufficient to treat rather than to prevent anemia, and giving messages focused on treating a perceived or assumed problem.

Background: As iron deficiency and anemia are so widespread, existence of the problem can be assumed and action should therefore be taken accordingly. However, at the same time it is difficult to do so at an individual level because most people who suffer from anemia or iron deficiency are not aware of it and they are less likely to take supplements for a long time, as their perception is that these should noticeably improve their condition.

Solution: Because one third of the world population suffers from iron deficiency and anemia, primarily because their diet does not meet their needs, a food-based approach, which aims at increasing the intake of iron and other micronutrients of the whole population and focuses particularly on the most at-risk groups makes the most sense. Such an increased intake should be sustained for a long period of time and should be perceived as a way to promote good health and protect cognitive development. In addition, by increasing everyone's intake of iron, using a food-based approach, women will enter pregnancy with higher stores, which will reduce the gap between needs and intake during pregnancy. The biggest challenge of a food-based approach is to find a way to increase intake sufficiently among the most at-risk groups, young children and pregnant women. The best way to assure consumption of an adequately high amount of micronutrients is by adding fortificants to an individual's bowl of food, a strategy known as home fortification.

Few successful experiences have been described

Problem: The experiences with iron & folic acid supplementation during pregnancy are mixed and decision makers seem to think twice before embarking on further iron deficiency anemia control program for pregnant women and/or young children. Because of this, there are few successful program experiences described, especially for young children.

Background: Most research on iron deficiency and anemia has been conducted by academic institutions and is thus focused on gaining new knowledge on the technical feasibility of interventions, rather than on operational feasibility. The consequence seems to be that program personnel wait for the scientists to conclude what is best, whereas the scientists go on to improve possible interventions and test new preparations, dosing schemes, combinations of micronutrients etc. At the same time, programs that are conducted on a regular basis often do not place enough emphasis on monitoring and evaluation and are hence not doing a good job in communicating successes and lessons learned.

Solution: There should be a greater link between the R&D community and those implementing programs to ensure that greater investment is made in defining the

operational feasibility of promising interventions and to thoroughly monitor and evaluate their implementation. These experiences should be implemented on a sufficiently large scale. Too often relatively small projects are implemented, and conclusions made which are not suitable for scaling up to an entire province or country.

Communicating and interpreting new research findings and exceptions

Problem: New research findings and reports on cases which experienced no benefit or even negative effects of iron or multi-micronutrient supplementation, often lead to conclusions that these supplements should be withheld from everyone because of the possibility that they could also be at risk of these negative consequences.

Background: Scrimshaw has suggested the following misconceptions that could impede implementation of programs:

- The myth that iron deficiency is more difficult to prevent than IDD and VADD. This is largely based on the fact that few successful programs have yet been implemented for iron deficiency control as compared to the control of vitamin A and iodine deficiency.
- The myth that iron supplementation can increase the severity of infections. Three papers have reviewed the evidence in this regard and concluded that only very young children (<2 mo), severely malnourished children with clinical complications, and children in areas where malaria is highly endemic and no good malaria control programs have been implemented should not receive high doses of iron (>10 mg/d) as supplements. Fortified foods can be provided to children in areas with high malaria endemicity. There is not enough evidence at present to know whether home fortificants, most of which provide 10 mg–12.5 mg of iron mixed with one meal, are safe in areas with high malaria endemicity and it has therefore been recommended that these are only provided under carefully controlled circumstances. The increase of diarrhea that was found among children who received iron was too small to be of clinical significance.
- The assumption that thalassemias and other hemoglobinopathies are contra-indications to iron supplementation. In some regions of the world, anemia is complicated by thalassemia and hemoglobinopathies. In severe cases of thalassemia, there may be iron overload. Routine iron supplementation during pregnancy in areas with a high prevalence of thalassemia and hemoglobinopathies results in widely varying hematologic responses. However, there do not seem to be reports on complications arising from routine iron supplementation during pregnancy that are related to thalassemia and hemoglobinopathies in the population.
- The idea that screening is required before supplementation because of the prevalence of hemochromatosis. Homozygotes for hemochromatosis have a very low prevalence (<0.5%) and the gene for the common form of hemochromatosis is only prevalent in populations whose ancestral origins were in Northern Europe. With regard to the risk of iron overload in people suffering from hemochromatosis, the experts do not believe this is a reason to withhold iron from people at risk of iron deficiency living in developing countries.
- The finding that iron fortification and supplementation could increase the risk of heart disease and cancer. A possible relationship between iron status and risk of cardiovascular disease and cancer has been the subject of a number of recent observational studies. As yet, there is no good evidence that such a relationship exists nor that it would be a causal relationship.

Solution: It is most important not to lose sight of the very widespread prevalence of iron deficiency and anemia, or of the severe consequences and the underlying cause of a deficient diet. Whereas research findings should be thoroughly examined and their applicability to the situation among different populations evaluated, they should lead to fine-tuning and better implementation of iron deficiency and anemia control programs rather than to a halt of programs when that means that the majority of the population is left untreated because of a small increased risk among a minority of the population. This situation has recently occurred in response to the finding of a higher mortality among children in a highly malaria endemic area when supplemented with iron in the absence of malaria control measures. That the increased risk was small, that those findings were not observed in a different area where malaria transmission was controlled using treated bed nets and treatment of suspected cases, and that malaria was very highly endemic in the area, did not receive much emphasis in the discussions that followed on the publication of the findings.

What is the way forward?

As the prevalence of iron deficiency and anemia is so widespread and the consequences for individuals and populations so severe, the focus should be on implementing control programs. Advocacy should focus on the benefits for early child development and hence success

later in life and increased productivity which ultimately benefit the economy of the nation.

Programs should promote a food-based approach, including fortification of staple foods and condiments for the general population as well as home fortificants for specific target groups, as these are:

- are more sustainable
- are less perceived as treatment of a condition
- applicable for use in malaria-endemic areas.

When any large-scale program is implemented, it is essential that the coverage, compliance and effectiveness are assessed.

What is the key message?

The control of iron deficiency and anemia is lacking behind that of VADD and IDD. Its control should be accelerated by focusing on the fact that many people lack an adequate amount of iron in their diet, which needs to be addressed through a food-based approach including (home) fortification, and concurrent, with but not dependent on, methods of tackling the other causes of anemia. The consequences of anemia and iron deficiency on cognitive development, productivity and economic development need to be emphasized. And to move forward most effectively, programs and policies should be thoroughly monitored, evaluated and communicated.

17

SUCCESSFUL APPROACHES – SPRINKLES

Stanley Zlotkin and Mélody Tondeur

What is the problem and what do we know so far?

Current INACG/WHO/UNICEF recommendations are to provide daily iron supplementation to all infants of normal birth weight in the first year of life, starting at 6 months, where the prevalence of anemia is below 40%, and to continue supplementation until 24 months where prevalence is 40% or above. The concern is that few options exist for supplementing iron to infants and young children. Syrups (ferrous sulphate) have been the primary strategy, but the unpleasant, metallic after taste, dark staining of teeth and abdominal discomfort, negatively impact on adherence. In addition, technical problems of short shelf life, expensive transportation costs and difficulty in accurately dispensing drops have hampered the success of interventions. The concept of 'home fortification' came about some 10 years ago, when addressing iron deficiency anemia was made a priority, and yet available interventions seemed not to be effective in reaching the most vulnerable populations. This resulted in the development of 'Sprinkles' which are single-dose sachets containing a blend of micronutrient powder, which is mixed directly into food. Studies show Sprinkles to be effective, well tolerated and easy to administer. Currently there are two readily available formulations – 'nutritional anemia formulation' and 'complete micronutrient formulation', but other micronutrients can be added depending on local conditions. Sprinkles use is been investigated to contribute to healthy infant complementary feeding through the concurrent promotion of appropriate weaning practices of pregnant and lactating women and the area of humanitarian aid and emergency settings.

What has been achieved?

The problem of iron deficiency anemia in children largely disappeared in North America following the fortification of commercial foods with iron and other essential micronutrients. Unfortunately, commercially fortified foods have had limited success in developing countries as store-bought foods are not widely available or affordable, especially for young children. Single-dose sachets of micronutrient powder (Sprinkles) were developed to address the problems and limitations of traditional fortification interventions. The iron (ferrous fumarate) is encapsulated within a thin lipid layer that prevents it from interacting with the food, thereby limiting changes to the taste, color and texture of the food. Other micronutrients can be added to the iron, based on local requirements and deficiencies. Caregivers can also be easily instructed in their use and they can be added to any semisolid food, after cooking and before serving. In addition the concept is programmatically feasible and no cultural barriers have been identified.

Staple isotope studies have been carried out to demonstrate the encapsulated iron and zinc's bioavailability. Community based studies in several countries, involving both non-anemic and anemic infants and children, have evaluated the efficacy, bioavailability, dose, acceptability and safety of Sprinkles. Results show:

- Single dose packaging and distribution of a limited supply are deterrents to overdosing and a child would need to consume many sachets (>20/day) before there would be any toxicity concerns. Risk of overdose is lower than with liquid preparations
- Infants with iron deficiency anemia (IDA) absorb iron from Sprinkles about twice as efficiently as iron-

deficient and non-anemic infants
- The 12.5 mg iron dose, as recommended by the WHO, is efficacious and sufficient
- Sprinkles with 12.5 mg of iron given for 2 months is adequate for anemia reduction but should be repeated more than once a year (i.e. 2 months in every 6 month period)
- The only reported side effect is darkening of the stool, which is expected as most of the iron is excreted in the stool
- An average of 70% of required sachets were consumed, indicating a high level of acceptance
- Sprinkles are effective in preventing and treating anemia

What is the way forward?

The impact of iron on enhancing the severity of infections, both parasitic (malaria) and bacterial, remains an important but unresolved issue. It is considered that if rapid absorption of iron exceeds the transferrin binding capacity, there is the possibility of free (non-transferrin bound iron) enhancing pathogen proliferation. The form and dose of iron will impact the rate of absorption. It is postulated that the encapsulated form of iron in Sprinkles, and the fact that they are added to foods will result in a safer alternative to other forms of iron supplementation. However, more research is required.

Research and development of Sprinkles for pregnant and lactating women is underway, as is their use in humanitarian aid and emergency feeding.

Two things are key to the success of Sprinkles, and the scale-up of interventions using them: firstly the securement of sustainable methods of distribution, which reach the most vulnerable populations in underdeveloped countries, and secondly, making sure that the interventions also have a social marketing strategy. Partnering with organizations which specialize in these areas is critical.

The greatest challenge for the future is to advocate for the adoption of Sprinkles in nutrition policies of underdeveloped countries.

What is the key message?

Home fortification using single-dose sachets containing a blend of micronutrient powder, that is mixed directly into food (Sprinkles), is a safe and effective way of reaching vulnerable groups in underdeveloped countries and overcomes many of the limitations of traditional interventions to address nutritional anemia.

FACTS:
- WHO/UNICEF estimates that more than 750 million children around the world have iron deficiency and anemia.
- Symptoms of iron toxicity occur when intake is between 20–60 mg iron per kg of body weight.
- A study has shown Sprinkles to be cost-effective with an estimated DALY saved of $12.20 (US), and cost per death averted $406.
- Cognitive benefits associated with the prevention of iron deficiency anemia which, when translated into academic achievement and ultimate adult employment, are estimated to be $37 gained for each $1 spent.

18

SAFETY OF INTERVENTIONS TO REDUCE NUTRITIONAL ANEMIAS

Klaus Schümann and Noel W. Solomons

What is the problem and what do we know so far?

Anemias are widespread in developing countries and were thought to be primarily of nutrient deficiency origin, although an increasing number of anemias are now recognized as not being of nutritional origin but rather due to chronic disease or hemoglobinopathies. It is important therefore to consider the safety of either therapeutic or prophylactic clinical and public health interventions, as along with the benefits of alleviating deficiencies by providing nutrients, there can also be associated risks in nutrient sufficient or overloaded individuals. The overriding principle of any intervention program is to ensure that it does no harm.

The safety issues and concerns arise because adverse consequences, and even toxic effects, can result either directly of indirectly from excess exposure to the vitamins and minerals involved with nutritional anemia. The greatest concern is that specific individuals or, subgroups within a population, can habitually receive excessive exposure to micronutrients in supplements or fortified foods or have idiosyncratic reactions to other measures involved in the public health control of anemia. It is thus clear that protecting the public's health involves both reducing the risk of nutritional anemia and exempting individuals from possible adverse consequences of the interventions.

It is well recognized that practitioners and public health authorities must ensure certain standards in order to guarantee the safety of any intervention. It is vital to consider the three major intervention strategies:

1. *Supplementation*
   Supplements may contain more than the physiological daily requirements for a nutrient, in particular for iron. In addition issues of quality control in manufacturing, overages and dosing are important. In the case of iron supplementation, it is critical to avoid new imbalances that may arise from iron-induced corrosive effects or oxidative damage as a result of unintended overdosing.
2. *Fortification*
   When exogenous nutrients are placed in food, the variation across a population of the consumption of the fortified foods becomes important. For example in cooking oil or sugar there can be a tenfold variance in the amount of product consumed between the highest and the lowest consumers. It is therefore important that the fortification level should provide safe exposure for the upper distribution of consumers.
3. *Dietary diversification*
   The intervention related to promoting foods as a source of nutrients are not without potential safety issues and might encourage a dietary pattern that is less than healthy, by increasing the intake of foods promoting chronic disease risk. Distorted intakes of red meat as a natural source of bioavailable iron, for example, could increase the risk of colon cancer and many diseases associated with saturated fat exposure.

Any intervention must be targeted. The group with below average intake should be the inherent target of micronutrient intervention programs. It is important to note that if the effort is aimed at raising the mean intake of the population, it may be inefficient (spreading resources where they are not needed), ineffective (not targeting those most in need) and even potentially harmful (pushing some at the upper end of the distribution to an even higher habitual intake). In any intervention program, it is critical that there is a diagnostic assessment and monitoring component.

IRON

What are the safety concerns with iron?

Iron by nature of its physicochemical characteristics and biological interactions, presents a series of challenges for its safe application:

- Gastrointestinal effects: Of importance are the doses of iron to which an individual may be exposed on a daily basis from the combination of foods, fortificants in the diet and supplements. As a result age-related tolerable upper intake levels (UL) have been set in the United States. They are 40 mg/day from infancy to the younger ages and 45 mg/day for adults. The most common side effect of oral iron preparations are gastrointestinal: nausea, vomiting and epigastric discomfort and the lowest observed adverse effect level in a single dose has been set at between 50 mg and 60 mg. Oral iron intake also leads to a harmless black discoloration of the stools and either diarrhea or constipation is also noted in about 6% of individuals.
- Atherogenic effects: There have been some controversial observations correlating dietary iron intake and risk for acute myocardial infarction, but these findings may be confounded by concomitant meal consumption and thus by saturated fat and cholesterol intake.
- Inflammation effects: Iron supplementation increases the indices of oxidative stress.
- Bacterial infections: The problem in this regard is that iron is a nutrient that is required by both the pathogen and the host defense mechanisms. However, it would seem that oral iron supplementation in deficient children is mostly beneficial and reduces infection prevalence.

What should be considered regarding iron supplementation?

- Therapeutic iron supplementation uses oral high doses of between 50 mg and 400 mg iron/day and can be individually monitored and should be continuously geared to a changing demand.
- It is essential that worm infections be treated together with any iron intervention.
- Prophylactic iron supplementation in two population subgroups, pregnant women and infants and toddlers aged 6–24 months, is internationally recommended.
- The prenatal distribution of the combination of iron and folic acid as a combined tablet is valuable.
- Blanket supplementation in young children can be problematic as often dose is not monitored and adapted to changes in demand in deficient children, and in iron-adequate children there is an increased risk of imbalances caused by iron excess. Recent research on iron supplementation in malaria-endemic areas showed disturbing results of an increased incidence of adverse effects and death. Thus iron supplementation of iron deficient children in malaria endemic areas is not recommended.

What about iron fortification?

The fortification of infant formula and complimentary

foods has been common for a long time but the number and array (from traditional staples to beverages and condiments) of other foods with added iron is increasing. Unlike staples, which contribute only a fraction of an individual's daily needs, fortified infant formulas and complimentary foods provide up to 100% of the day's intake and so must be formulated with an appropriate iron density and bioavailability. It is important to note that two different fortification densities are required for children from 6–24 months in order to avoid over exposure in the older age group. Fortification of cereal grains is mandatory in many countries and the levels of addition are around 20 mg to 50 mg/kg, depending on the iron compound used, and generally provide a maximum of 22% of the daily iron needs. It must be noted that the unintended increase in sodium exposure may be a consideration when condiments are fortified. The WHO Guidelines on Food Fortification with Micronutrients are valuable.

What about iron biofortification?

Biofortification refers to the genetic modification of energy-rich food crops such as rice, wheat, maize, potatoes and cassava. This technology uses systematic plant breeding or genetic techniques to develop micronutrient-rich staple foods. In contrast to other methods, the need for centralized processing and complex logistics is avoided. A prerequisite for successful biofortification is that the soil must contain enough trace elements and this might require fertilization to avoid depletion. There are also controversies regarding genetic modification, which might be addressed by conventional plant breeding and selection to optimize micronutrient content and availability.

What about dietary diversification for increased iron intake?

Encouraging populations to diversify their diets to include richer sources of certain widely deficient micronutrients is an important strategy with specific relevance when discussing iron. Encouraging home and school gardening is generally safe from possible excess due to the comparatively low iron content and bioavailability of iron in fruits and vegetables. Other interventions promote greater meat consumption through small ruminant husbandry or subsidizing meat purchase, as well as poultry and fish farming. Excessive consumption is unlikely and the safeness of the intervention relies on sanitary issues and the long-term consequences for chronic diseases associated with high meat intakes.

How does delayed umbilical cord clamping impact on iron status?

Research shows that delaying the clamping of the umbilical cord is an effective prophylactic measure that can increase iron endowment at birth by up to 50% and that offers a benefit of permitting longer periods of breastfeeding. There are some concerns regarding an increased risk for hyperbilirubinanemia but different meta-analyses show conflicting results.

VITAMIN B_{12}

What about the safety of vitamin B_{12}?

Vitamin B_{12} is associated with anemia and its absence results in hypoproliferative anemia with large, immature macrocytic red cells in the circulation. Vitamin B_{12} is remarkable for its high safety margin and no ULs have been set. The traditional treatment for vitamin B_{12} deficiency megaloblastic anemia is a single, intramuscular dose of parenteral cyanocobalamin in the order of 200 µg. The only safety concern surrounds giving injections in the age of blood-borne viral infections and so the use of sterile needles and their safe handling are paramount. Alternatively doses of 1000 µg–2000 µg of oral cyanocobalamin have been found to be as effective.

Prophylactic supplementation of vitamin B_{12} as a policy measure is virtually unknown but vitamin B_{12} fortification is practiced.

FOLIC ACID

What should one consider regarding folate?

Folate has both a primary and secondary relationship with nutritional anemia. It is important to note that the daily recommendations for intake are not based on its hematological function but at a higher level for the prevention of neural tube defects. Excessive folate intake is associated with adverse consequences and the major concern is the potential for masking an underlying vitamin B_{12} deficiency.

For macrocytic anemia due to folate deficiency, a daily supplementation course in doses of 500 µg–5000 µg can be given and it is prudent to concurrently give vitamin B_{12}. When folic acid is given as a prophylactic intervention it is targeted to groups at risk of neural tube defects and the dose is 400 µg either given alone or in combination with iron or iron and other micronutrients. Routine supplementation with iron and folic acid in populations with high rates of malaria is not recommended.

Folic acid fortification is widely practiced and the WHO specifies 1.3 mg/kg of edible foodstuff as the maximal

addition for fortification of staples, and a maximum of 27 µg of folic acid per 40 kcal serving of product for other fortified commercial foods.

VITAMIN A

What are the key safety issues around vitamin A?
Vitamin A deficiency is not a cause per se of nutritional anemia; however, vitamin A adequacy has been shown to act as an adjunct to optimize iron utilization. The UL has been set at 10,000 IU (3,030 µg as retinol) daily. Total vitamin A exposure should be limited to a cumulative dose that maintains a hepatic vitamin A concentration of <300 µg/g, which is considered the threshold of toxicity. Regular daily consumption of 30 mg of vitamin A in the retinoid form is associated with chronic toxicity.

Sustained high intakes of β-carotene (a provitamin A carotenoid) produces a yellow-orange discoloration of the skin but is dermatologically harmless. Some research has shown an increased risk of death when isolated β-carotene was used in supplements in the 30 mg–50 mg daily range in a clinical trials among individuals with a predisposition to lung cancer (smokers, asbestos workers).

What about vitamin A supplementation and fortification?
Vitamin A supplementation is included as part of the regime for the intensive rehabilitation of children with severe protein-energy malnutrition. Strict record keeping is required. It is no longer recommended that high dose supplements of vitamin A be given postpartum to lactating women to support milk vitamin A.

The WHO does not specify a safety limit for fortification of staple foods with vitamin A, although food fortification with vitamin A is common. It is suggested that such fortification should provide at least 15% of the daily vitamin A needs of the target group but should not exceed 30%. For commercial products, the WHO recommends a maximum vitamin A addition of 60 µg per 40 kcal serving.

Is there a role for biofortification of vitamin A?
Biofortification is an emerging area of research in micronutrient interventions and its promotion is coordinated by the Harvest Plus initiative. Provitamin A-rich carrot and sweet potato varieties have been developed and exposure to these forms of β-carotenes should be safe across the population.

RIBOFLAVIN

Are there safety concerns with riboflavin?
Riboflavin deficiency is not a cause of nutritional anemia, however, as with vitamin A, riboflavin is a supportive nutrient to maximize iron-mediated repletion of a full red cell mass. As there are no adverse effects associated with riboflavin, no UL has been assigned.

Oral doses of approximately 2 mg daily are used to treat individuals with hyporiboflavinosis. Generally riboflavin is also added to multinutrient supplements and in fortification of staple cereals where it is typically added at a concentration of up to 200 mg/kg of cereal flours.

COPPER

What are the safety concerns pertaining to copper?
Severe copper deficiency produces a hypochromic, microcytic anemia, but is not a public health problem as primary copper deficiency is rarely seen and occurs almost exclusively in infants and young children subsisting on low copper, milk-based formulas or adults on total enteral or parenteral nutrition. Secondary copper deficiency anemia, however, could be related to interventions with zinc at levels in excess of its tolerable limits.

Copper is a strong emetic, provoking nausea and vomiting when ingested in even low amounts, and chronic excess intake has been associated with abnormal elevation of LDL cholesterol. The UL in the United States is set at 10 mg for adults, compared to 5 mg in the European Union.

Copper deficiency anemia has been successfully treated with daily doses of copper as cupric sulphate of 1 mg–2 mg/day in adults and young children, and doses of up to 9 mg/day in divided doses are safe and tolerable in adults. Where high-dose zinc is given, copper should be included in the formulation to prevent distortion of copper nutriture by the zinc.

MULTIPLE MICRONUTRIENT INTERVENTIONS

What should be considered regarding the safety of multiple micronutrient interventions?
As a result of the fact that nutrient deficiencies often occur in combination, there has been a shift from single nutrient fortification to multiple micronutrient interventions. Research in reproductive settings and in infants, have shown contradictory effects of multinutrient supple-

mentation and it would seem that both biological and nutrient-nutrient interactions may be responsible for this. More research is required as the combination of several nutrients complicates attribution of positive or negative health consequences of specific combinations and in specific settings.

What is the way forward?

The recent studies showing a negative effect of iron supplementation in malaria-endemic areas suggest that research is needed to develop and test adequate end economic procedures for large-scale iron status determination in the field and reminds us that there can be negative consequences of intervention programs. Safety monitoring is critical. In any fortification intervention, the risk profile of the population should be carefully estimated and be repeatedly updated.

What is the key message?

Interventions to address nutritional anemia are designed to have a positive public health outcome. There is, however, the potential to threaten lives and damage the reputation of intervention programs. Ongoing research in all the fields of intervention, (supplementation, fortification and dietary diversification) and with both single and multiple nutrient formulations, must therefore continue. Policy-makers and public health officials must be uncompromising with the principle that any and every intervention program must be safe for all consumers and must result in improved or sustained health for all.

FACTS:

- Iron deficiency accounts for approximately half of the anemias in developing countries, with the other half being proposed as due to a lack of copper, zinc, folate or vitamins A, B_2, B_{12}, or C.
- The overriding principle of any intervention must be 'first do not harm'.
- The usual nutritional supplement doses are:
  - 30–60 mg iron for a 70 kg adult
  - Maximum of 120 mg iron during pregnancy
  - 2 mg iron/kg for children
- Side effects of iron are not usually seen after oral intakes of 30–60 mg.
- An oral dose of 180–300 mg iron/kg body weight can be lethal to humans but oral doses below 10–20 mg iron/kg of body weight represent a no observed adverse-effect-level (NOAEL).
- In the United States, there are age-related ULs (tolerable upper intake levels) for iron. For infants and young child this is set at 40 mg/day and for adults, 45 mg/day.
- The WHO Guidelines on Food Fortification with Micronutrients provides detailed information on fortification levels based on safety, and technological and cost constraints. This can be ordered from the WHO website.
- The WHO Guidelines suggest that no more than 3 mg of fortificant iron be added to a 50 g serving portion of a solid food or 250 ml of beverage – contributing a maximum of 22% of daily iron needs from a diet with high biological availability.
- Iron supplementation in malaria-endemic areas is not recommended due to the results of recent studies that showed an increased incidence of adverse effects and death.
- Traditional treatment for vitamin B_{12} deficiency megaloblastic anemia is a single, intramuscular dose of parenteral cyanocobalamin in the order of 200 µg. Alternately oral doses of 1000 µg–2000 µg of cyanocobalamin have been found to be as effective.
- The UL for folate is set at 1000 µg/day for adults.
- For macrocytic anemia due to folate deficiency, a daily supplementation course in doses of 500 µg to 5000 µg can be given and it is prudent to concurrently give vitamin B_{12}.
- Folic acid as a prophylactic intervention is targeted to groups at risk of neural tube defects and the dose is 400 µg either given alone or in combination with iron or iron and other micronutrients. Note: Routine supplementation with iron and folic acid in populations with high rates of malaria is not recommended.
- The WHO specifies 1.3 mg folic acid/kg of edible foodstuff as the maximal addition for fortification of staples and a maximum of 27 µg of folic acid per 40 kcal serving of product for other fortified commercial foods.
- The WHO specifies 1.3 mg of folic acid/kg of edible foodstuff as the maximal addition for fortification of staples and a maximum of 27 µg of folic acid per 40 kcal serving of product for other fortified commercial foods.
- The UL for vitamin A has been set at 10,000 IU (3,030 µg as retinol) daily.
- Total vitamin A exposure should be limited to a cumulative dose that maintains a hepatic vitamin A concentration of <300 µg/g, which is considered the threshold of toxicity.
- Regular daily consumption of 30 mg of vitamin A in the retinoid form is associated with chronic toxicity.
- The WHO does not specify a safety limit for fortification of staple foods with vitamin A, but it is suggested that such fortification should provide at least 15% of the daily vitamin A needs of the target group but should not exceed 30%.

- For commercial products the WHO recommends a maximum vitamin A addition of 60 µg per 40 kcal serving.
- It is no longer recommended that high dose supplements of vitamin A be given postpartum to lactating women to support vitamin A in milk.
- Oral doses of approximately 2 mg daily are used to treat individuals with hyporiboflavinosis.
- Riboflavin is generally added to multinutrient supplements and in the fortification of staple cereals where it is typically added at a concentration of up to 200 mg/kg of cereal flours.
- The UL for copper in the United States is set at 10 mg for adults compared to 5 mg in the European Union.
- Copper deficiency anemia has been successfully treated with daily doses of copper as cupric sulphate of 1 mg–2 mg per day in adults and young children and doses of up to 9 mg/day in divided doses are safe and tolerable in adults.
- Where high-dose zinc is given, copper should be included in the formulation to prevent distortion of copper nutriture by the zinc.

19

THE IMPORTANCE AND LIMITATIONS OF FOOD FORTIFICATION FOR THE MANAGEMENT OF NUTRITIONAL ANEMIA

Omar Dary

What is the problem and what do we know so far?

Two main approaches are used to address micronutrient deficiencies in populations; supplementation and food fortification. Supplements are highly dense in vitamins and minerals in order to provide large amounts of nutrients in one or few doses. Their formulation can be tailored to the requirements of a specific population group and they are designed to deliver the recommended amount of micronutrients and avoid interactions between micronutrients and absorption inhibitors. They do, however, require a voluntary and educated decision for consumption, and studies show that their population coverage and acceptance is low. A fortified food is an edible product manufactured by the food industry with an enhanced (added vitamins and minerals) nutritional composition. Food fortification could be considered the most favorable and cost-effective approach if it is supported under industrial settings. Nevertheless, even in these cases there are many factors that can limit its potential use and efficacy.

There are WHO Guidelines for Food Fortification, and these identify three approaches:

1. Mass – Addition of micronutrient to foods generally consumed by the general public. Provides greater population coverage but may satisfy only partially the micronutrient needs of the at-risk subgroups.
2. Targeted – Fortification that focuses on coverage of specific, at-risk subgroups. Delivery can be sufficient to satisfy nutritional requirements.
3. Market-driven – Where a food manufacturer takes the initiative to fortify products in order to increase sales and profits. Has a very small coverage in developing countries.

There is, in addition, a relatively new concept, namely household fortification. This is the consumption of dietary supplements (usually in powder forms) mixed with food at meals. In the case of mass fortification, the main advantage over the other interventions is that it uses already existing distribution and trade systems, and therefore the cost is basically restricted to the added vitamins and minerals and the fortification process.

Addressing nutritional anemia in the target group of children younger than 24 months requires special attention and products, such as complementary foods (targeted fortification) and age-specific dietary supplements. There is another important group that requires attention and that is women of reproductive age.

What are the possible limitations of mass fortification?

- Vehicle selection is a critically important factor to be considered. The low cost of using mass fortification only holds true in industrial settings where the product is produced by formal, centralized production centers.
- The dilution factor of the fortificant in the food must be high, i.e. a small amount of fortificant in a large quantity of the food.
- Increase in the price of the product due to fortification should be small, otherwise it will be difficult to get compliance and a level playing field among producers is difficult to establish.
- The content of vitamin and minerals is determined by the individuals who consume the food in large amounts, and hence the additional supply of micronutrient given to the most at-risk individuals, frequently consuming the food in lower amounts, may be insuffi-

cient using only one fortified vehicle. Therefore, complimentary measures might still be required.
- Technological barriers might limit the levels and forms of micronutrients in specific vehicles due primarily to undesirable organoleptic changes. This is the main limitation to supplying sufficient amounts of iron through fortified flours.

How can one assess the potential impact of fortification interventions?

The WHO Guidelines suggest potential benefit estimates using the proportion of the population that moves from below to above the corresponding Estimated Average Requirement (EAR). It is, however, difficult to estimate the distribution profile of EAR in populations and it is therefore suggested that a proxy calculation of the additional EAR obtained from fortified foods is valuable. It is suggested that, as a convention, a food providing at least 20% EAR could be considered a 'good' source and foods providing 40% EAR as an excellent source. The importance of mass fortification could then be estimated by the absolute and relative number of individuals from vulnerable groups that reach those categories of EAR.

What is the role of control and enforcement?

Success of any intervention depends primarily on ensuring that the target population/s receive the micronutrients in the amount and quality required. This makes quality control and assurance actions by producers, and inspection and enforcement by governmental authorities, essential. Values of reference and compliance criteria responding to the reality of the programs have to be set, but unfortunately are frequently neglected in planning programs. Micronutrient and premixes should be certified for both micronutrient amounts and for quality as well as microbiological safety and should be supervised by government authorities.

What is the key message?

Fortified products as well as dietary supplements appear to be a reasonable way to proceed to reduce iron deficiency anemia in developing countries. However, the challenge is to ensure that such strategies are permanent and sustainable. Food fortification has a number of challenges, but these can be addressed and overcome through the setting of standards, quality control, certification and government supervision and enforcement.

FACTS:
- To supply women of reproductive age with the Estimated Average Recommendation (EAR) of most micronutrients (except calcium and vitamin C), the overall cost ranges from $0.25 (US) to $1.00 per year.
- In mass fortification under truly industrial settings, approximately 80–90% of the cost corresponds to the purchase of micronutrients, with the exception of rice where 50–90% of the cost is linked to the production of the fortified kernels.
- In supplementation, the cost of the micronutrients corresponds to only 10–40% of the overall cost. However supplementation requires a distribution system, which is already in place with mass fortification.
- Iron is a difficult nutrient to be provided through mass fortification especially for satisfying the needs of women of reproductive age. Therefore, targeted fortification and preventive supplementation should be kept in mind for the comprehensive management of nutritional anemias.

20

FOOD BASED APPROACHES FOR COMBATING IRON DEFICIENCY

Brian Thompson

What is the problem and what do we know so far?

Iron deficiency is a serious and widespread public health and social problem. Though prevalence rates are often higher amongst women and children, iron deficiency can affect the growth, development and performance of all. The scale and magnitude of the problem, combined with the functional impact such deficiencies have on the quality of life, both physiologically and socioeconomically, require the urgent adoption of known and effective control measures.

We know that in the majority of cases the main cause of micronutrient malnutrition is poor dietary intake, both in terms of the total quantities of food consumed and the contribution made by micronutrient-rich foods to the diet. Consequently the Food and Agriculture Organization of the United Nations (FAO) encourages a range of actions that promote an increase in the supply, access and consumption of an adequate quantity, quality and variety of foods for all populations. In developing countries where micronutrient deficiencies predominantly exist in the context of food insecurity, meeting overall energy needs from a diversified micronutrient-rich diet continues to remain a major challenge. In such cases, where food insecurity is driven by poverty and agricultural underdevelopment, the FAO is focusing support on food-

based strategies, including dietary diversification and food fortification aimed at increasing the availability and consumption of a nutritionally adequate micronutrient-rich diet made up from a variety of available foods to those who are food insecure.

Such broad food-based interventions tend to be neglected in favor of singular fortification and supplementation programs as they are considered attractive for their apparent simplicity and cost-effectiveness. In practice, however, many such programs are proving difficult to manage, more costly than expected to implement, and less effective than promised. Consequently, for combating iron and other micronutrient deficiencies, we need to ensure that a fully comprehensive approach is taken and that dietary diversification is recognized as essential and does not lose out in attracting country and donor interest and support.

What is the way forward?

The promotion of dietary improvement/diversification with a focus on improving the intake of bioavailable iron through greater consumption of animal products, fruit and vegetables, especially vitamin C-rich foods, is the preferred intervention as it can lead to sustainable improvements, not only of iron status but also of intakes of other micronutrients. Neither supplementation nor fortification can be effective on their own. Since food-based approaches have a higher potential for achieving far-reaching and long-lasting benefits for the control of iron and other micronutrient deficiencies, increasing the availability and consumption of a nutritionally adequate diet must be placed high on the development policy agenda.

Micronutrient deficiencies need to be addressed by focusing on a broad set of mutually reinforcing strategies including dietary diversification, fortification, supplementation and public health measures. These together provide maximum coverage and impact and this comprehensive approach needs to be widely implemented if this critical global problem is to be tackled and overcome.

Virtually all traditional dietary patterns can satisfy the nutritional needs of the population. However, one of the main causes of iron deficiency anemia in low-income countries is the low bioavailability of iron in poor cereal and tuber based diets, since these contain high amounts of iron inhibitors. The following are practical actions and interventions that can boost access to and consumption of an adequate and nutritious diet and hence increase the bioavailability of iron, especially to the hungry and those most vulnerable to deficiencies:

- Implement large-scale commercial livestock and vegetable and fruit production to provide accessible micronutrient foods at reasonable prices to all sectors of the population.
- Stimulate the small-scale, community agricultural sector and promote potential dietary sources, including many leafy vegetables and legumes that contain important quantities of iron, with special emphasis on increasing the consumption of animal products with high bioavailable iron and high-in-iron absorption enhancers.
- Improve the micronutrient content of soils and plants to improve the composition of plant foods and improve agricultural practices to enhance yields.
- Develop plant breeding through conventional or with genetic modification (biofortification) to increase the micronutrient content of staple and other crops.
- Introduce crop diversification to promote micronutrient-rich crops.
- Address regulations that prohibit urban gardening or which reduce the availability or sale of fresh foods by street vendors.
- Examine profitability of producing, processing and marketing of micronutrient-rich foods.
- Investigate processing, preservation and preparation practices that reduce losses, increase dietary absorption enhancers and minimize the impact of absorption inhibitors.
- Educational efforts directed at securing appropriate within-family distribution of food, considering the needs of the most vulnerable family members.
- Develop Food Based Dietary Guidelines (FBDGs) and public nutrition education and communication programs to bring about changes in eating practices.
- Improve food quality and food safety and set and enforce regulations for quality control and hygiene.

What is the key message?

Overcoming micronutrient deficiencies can only be achieved if a comprehensive approach is taken which includes ensuring all people have access to and consume adequate quantities of nutritious food. This will not only raise iron status but also the levels of other micronutrients. Dietary diversification and enhancement are an essential part of food-based strategies and key to the long-term success and sustainability of interventions for addressing nutritional anemia. This apporach is in keeping with the right to food, a pledge whose fulfillment means that all people are able to gain access to a varied diet consisting of a variety of foods that provide all the energy and macro- and micronutrients sufficient to achieve a healthy and productive life.

FACTS:

- Food security exists when all people, at all times, have physical, social and economic access to sufficient, safe and nutritious food that meets their dietary needs and food preferences for an active and healthy life.
- An estimated 854 million people are hungry, 20 million children under 5 suffer from severe malnutrition and around 1 million children die due to malnutrition each year. Over two billion people – more than 30% of the world's population – are anemic.
- Asia has the highest number of cases of anemia, while Africa has the highest prevalence rates of anemia in pre-school children.
- Underlying causes of such high levels of malnutrition are poverty and agricultural underdevelopment leading to food insecurity. Meeting overall energy needs and dietary diversity is the major challenge.
- The recommended daily intake (RDI) of iron for men ranges between 9 mg in diets with high bioavailability to 27 mg where bioavailability is only 5%. In premenopausal women (aged 19–50) the RDI for iron is 59 mg.
- Food based strategies, by increasing availability and consumption of a nutritionally adequate micronutrient-rich diet, are the sustainable way to improve nutrition.
- Heme-iron from flesh foods (meats, poultry, fish) is well absorbed with an average absorption of 25%, ranging from 40% during iron deficiency to 10% when iron stores are replete.
- Nonheme-iron, present in plant foods such as cereals, pulses, legumes, grains, nuts and vegetables, has an absorption rate of 2% to 10% depending on the balance of iron absorption inhibitors and enhancers in the meal.
- Addition of vegetables and fruits containing ascorbic acid can double or triple iron absorption. Each meal should preferably contain at least 25mg of ascorbic acid.

21

GLOBAL PERSPECTIVES: ACCELERATING PROGRESS ON PREVENTING AND CONTROLLING NUTRITIONAL ANEMIA

Ian Darnton-Hill, Neal Paragas
and Tommaso Cavalli-Sforza

What is the problem and what do we know so far?

Nutritional anemias, especially iron deficiency anemia, are currently the greatest global nutrition problem. They mainly affect women and children and significantly negatively impact on many nations' chances of improved public health and economic development. Sadly, in the first decade since the UN goal was set to reduce iron deficiency by one third, virtually no progress has been made. Although there is little documented success in addressing the problem at a public health level in less affluent countries, there is many years of programmatic experience and a vast amount of science lie behind the complex picture of iron metabolism. Surprisingly there is still much that is unknown and new areas continue to emerge from the ongoing research.

Poor diets lead to high levels of iron and other micronutrient deficiencies and are aggravated by dietary inhibiting factors such as phytates, high parasite loads and infections such as malaria, sociocultural factors including poverty and gender discrimination, all of which contribute to the high levels of anemia seen in poorer populations.

How is anemia risk affected by age?

Normal hemoglobin distributions vary with genetics, age and gender, at different stages of pregnancy, altitude and smoking. This affects the interpretation of hemoglobin and hematocrit values. In addition, the risk of iron deficiency anemia varies throughout the lifecycle, with several periods of greater vulnerability. This variation is due to changes in iron stores, level of intake, and needs in relation to growth or iron losses. The most vulnerable groups are:

- Children from 6 months to 5 years of age
- Women of childbearing age
- Pregnant women
- The aged.

What is the key reason for the apparent failure in reducing prevalence in many programs?

One of the key reasons is that many programs have been

designed with the assumption that the only cause of anemia is iron deficiency. In fact the main causes of anemia are:

- Dietary iron deficiency;
- Infectious diseases such as malaria, hookworm infections, schistosomiasis, HIV/AIDS, tuberculosis and other chronic diseases including almost any inflammatory illness that lasts several months or longer, and some malignancies;
- Deficiencies of other key micronutrients including folate, vitamin B_{12}, vitamin C, vitamin A, protein, copper and other minerals;
- Inherited conditions that affect red blood cells, such as thalassemia;
- Severe acute hemorrhage (such as occurs in childbirth);
- Chronic blood losses (e.g. in peptic ulcer);
- Trauma.

For effective intervention programs and proper monitoring of their impact, better information is needed, not only of the iron status of populations, but also the other causes of anemia. Even when taking into account all known causes of anemia, a large proportion in many high-risk populations remain unexplained.

Why is there a lack of information?

A reason for the lack of information on the other causes of anemia is that only hemoglobin or hematocrit tests can routinely be performed in field settings, while more precise, multiple biochemical tests are usually only conducted in resource-adequate countries under special research conditions. Advances in laboratory methods to allow for the determination of causes of anemia at low cost, either in the field or later in the laboratory, without refrigeration of samples (dried spots), would greatly contribute to better assess the causes of anemia and allow for more appropriate interventions.

What roles do the private and public sector play in preventing anemia?

One of the main constraints in the fight against anemia and other micronutrient deficiencies, is the limited willingness of governments (and donors) to invest sufficiently to improve diets and reduce social inequalities, as this requires long-term investments to improve the supply, distribution and consumption of animal and vegetable foods, and needs to especially target those who are in greatest need. In addition, health systems in the most affected countries are seriously underresourced. These factors involve not only problems of access and related costs, as the highest undernutrition rates are usually found among those in remote rural areas, but also because these individuals are usually peripheral to the concerns of the urban, political class. It is therefore important to keep undernutrition on the national planning agenda to reinforce the government's responsibility to provide for the good health and nutritional status of all their people. This is a complex task and requires the collaboration of various sectors of society – national government, local government, the private food and health sector, the media, consumers' associations and community organizations.

The role that the food and health industry can play is important for all the key strategies, from efforts to improve the supply, distribution and consumption of animal and vegetable food, to fortification and supplementation. Reduction of anemia is most likely to be achieved through a combination of the three key approaches (supplementation, fortification and dietary diversification), while also aiming to reduce social inequalities – given that anemias are most often the consequence of poverty.

Food fortification: This can offer a partial solution in the medium to long-term and is probably the most cost effective approach, but requires food producers to work with micronutrient premix suppliers and the consumers and public health community to encourage the government to adopt legislation and regulations and to provide effective communication of the importance of this approach through the media so that people to demand it. There have been both success and failures in fortifying foods with iron and commercially fortified foods are not always available or affordable to those most at risk.

Supplementation: These programs should be seen as an opportunity to promote improved diets, as it is a less sustainable means to address deficiencies due to inadequate food intake and/or other factors.

Diet-based interventions: The role of these interventions in addressing nutritional anemia has not been clearly elucidated but there is some interesting work being done in this regard. Limited availability, accessibility and intake of animal source foods at the household level and lack of knowledge about their value in the diet and role in health, contribute to poor diet quality which has a profound impact on the necessary micronutrients that play a role in iron status.

The private and nongovernmental sectors may in many cases have multiple advantages in delivering health care interventions over poorly resourced government serv-

ices. Yet governments must still be held responsible for the wellbeing of the very poorest. In countries where both have worked together with communities, we see the greatest chance of success.

What are the key lessons that have been learnt?

The identified constraints and facilitating factors in addressing nutritional anemia can be broadly grouped as:

- Sociocultural (poverty, gender discrimination);
- Delivery factors (targeting, supplementation, fortification and food-based approaches);
- Systems (health, private sector marketing, logistics);
- End-user (accessibility, compliance).

It would seem that for successful interventions, key factors that are required include improved logistics, better compliance and involvement of multiple stakeholders. In addition any single intervention must be seen as just one part of a comprehensive strategy. Integrated community approaches require combining interventions and need to include mass deworming, health education, improved water and sanitation as well as considering multiple micronutrient supplementation.

There also needs to be a realistic assessment of both accessibility and availability of iron and other relevant micronutrients, whether they are being delivered as supplements, by fortification or by other channels, including poverty reduction programs. This may include assessment of the viability of health systems, feasibility of social marketing and reach of health education.

What is the way forward?

Adequate iron status is necessary for the health of all but especially for infants, young children and pregnant women. The Copenhagen Consensus has attributed high cost-effectiveness to iron and other micronutrient programs. There is now considerable evidence that not addressing iron deficiency and other anemias will cost countries up to 2% of GNP, and impair the intellectual development of their children and future national economic productivity.

International health and national partners need to get firmly behind these statements, so that consistent measures and approaches reinforce one another and so that well planned and monitored interventions become a reality.

What is the key message?

Nutritional anemias are currently the greatest global nutrition problem. A comprehensive, multiple intervention approach is necessary for sustainable success and must include improved social conditions by poverty alleviation measures, as well as the more direct measures of fortification, supplementation and improved health care. Countries, however, must begin interventions themselves and should not wait until all aspects of a comprehensive program are in place, as each individual intervention will have some impact and the need for action is great.

FACTS:

- 200 million under 5 year olds fail to reach their cognitive and socioemotional development, due to undernutrition, including iron deficiency and inadequate stimulation.
- The total attributed global burden of iron deficiency anemia amounts to 841,000 deaths and 35,057,000 DALYs.
- It has been estimated that the median value of productivity losses due to iron deficiency is about $4.00 (US) per capita or 0.9% of GDP.
- It has been calculated that the productivity of adult anemic agricultural workers or other heavy manual laborers is reduced by 1.5% for every 1% decrease in hemoglobin concentrations below established thresholds for safe health.
- Eliminating severe anemia in pregnancy has been estimated to potentially reduce maternal disease burden by 13%.
- 2.5% of any average population is expected to fall below the WHO cut-offs for iron. As a result, iron deficiency anemia is considered a public health problem when the prevalence of low hemoglobin concentrations exceeds 5% of the population.
- Severe anemia in pregnancy is defined as hemoglobin of <70 g/L and requires medical treatment.
- Very severe anemia is defined as hemoglobin of <40 g/L and is a medical emergency.
- Estimates suggest that fortifying flour with iron has the potential to increase national IQ by 5%, increase national GDP by 2% and eliminate 60,000 deaths of pregnant women every year.
- Fortifying with folic acid can significantly reduce the 200,000 cases of neural tube defects every year in newborn babies.

22

CONCLUSION AND RESEARCH AGENDA

Klaus Kraemer, Elisabeth Stoecklin and Jane Badham

Introduction

The United Nations' goal of reducing by one third the prevalence of anemia by 2010 is unlikely to be met. Nutritional anemia remains common in many countries of the world and its eradication through effective interventions must be a priority for attention and action. Anemia impairs individual growth and development, as well as family, community, and national socioeconomic development. There has unfortunately been little documented success in addressing the problem at a public health level over the last decades, although there is now a great deal of programmatic experience and a vast and growing amount of scientific data and new information on iron metabolism and the role of other nutrients in the etiology of nutritional anemia. However, much is still unknown and many new areas requiring attention and research continue to emerge.

This final chapter aims to summarize some of the conclusions drawn from the previous chapters in this volume, draw attention to the unchanged magnitude of the problem and its resulting economic implications, and determine the crucial points for going forward in addressing nutritional anemia by specifying critical factors for future research related to micronutrients and identifying key components that ensure that programs and interventions really work.

Dimension of the problem

Previously, global estimates on the prevalence of anemia did not include nationally representative data from China, which accounts for ~20% of the world's population. In this volume, new global estimates on anemia prevalence for preschool children and nonpregnant and pregnant women have been released, compiled by the World Health Organization (WHO) for its Vitamin and Mineral Nutrition Information System (VMNIS).

Surveys included in the database assessed anemia by measuring hemoglobin using standard methodology and excluded those that used clinical signs to confirm anemia prevalence. Only representative data from countries were included in the analysis and adjusted for WHO cut-offs (Hb <110 g/L for preschool children and pregnant women and Hb <120 g/L for nonpregnant women). For preschool children and women, national surveys cover a large proportion of the population and the data suggest that the global burden of anemia is high, although the proportion of severe anemia still remains unknown. The analysis suggests that almost 50% of preschool children are affected worldwide, with the highest rates in Africa (64.6%) and Asia (47.7%). This number amounts to almost 300 million children under 5 years of age. The anemia prevalence is 41.8% in pregnant women and 30.2% in nonpregnant women. Globally, 818 million women (pregnant and nonpregnant) and children under 5 years of age are affected by anemia. Individual studies from South Asia point to far higher prevalence numbers in pregnant women and adolescent girls.

Four key messages can be concluded from the analysis:

1. More countries should assess anemia prevalence more precisely at the national level and also determine the degree of severity of anemia.
2. Countries should assess iron deficiency in more detail, as it is uncertain how much anemia is due to iron deficiency and how much is due to other causes. It is important to distinguish between anemia due to nutritional causes and anemia as a result of chronic endemic infections, (e.g., malaria, helminth infections, and HIV/AIDS).
3. Subclinical inflammation may be very common in apparently healthy people, and may lead to misclassification of anemia.
4. More comparative evaluation of the advantages and disadvantages of currently available methods for the measurement of iron status (ferritin, sTfR and indicators of infection/inflammation) is required, in addition to reducing the costs of these analyses while maintaining their accuracy.

Weakness and fatigue have long been associated with iron deficiency anemia only. More recent research however points to functional consequences even before the clinical onset of anemia. Longitudinal studies caution that chronic iron deficiency in infancy permanently retards cognitive, motor, and socioemotional development. This is an especially grave concern as more than 200 million children under 5 years of age, mostly living in South Asia and sub-Saharan Africa, fail to reach their cognitive and socioemotional development potential due to malnutrition, including iron and iodine deficiency and inadequate stimulation. These children are likely to fail at school, miss their income potential, and thus remain in the poverty trap. There is consensus among a broad range of scientists from academia and UN agencies that global

and national priority should be given to the prevention of even mild anemia in infants and young children because of the risk of impaired intellectual development. Also of concern is the fact that amongst breastfed infants, only about 50% of their iron requirement during the first 6 months can be obtained from breast milk, indicating a need for early supplementation for all infants.

In the past, the wide-ranging consequences of iron deficiency and anemia have primarily been dealt with as a medical problem, rather than emphasizing the mental and economic consequences. The economic gain from reducing any micronutrient deficiency comes from both cost reduction and from enhanced productivity. This includes reduced mortality, reduced health care costs, reduced morbidity, improved productivity, and intergenerational benefits through improved health. It is clear that anemia at all stages of the life cycle is associated with a significant health burden and has a potentially large negative impact on productivity and hence also income and gross domestic product (GDP) loss; current estimates are as high as $50 billion (US). The total loss per capita due to physical as well as cognitive losses amounts to billions annually and is considerable when compared to the modest costs of decreasing nutritional anemia.

We have derived five key findings from the analysis:

1. Iron interventions in adults have been shown to have productivity impacts of around 5% in light manual labor and as high as 17% in heavy manual labor.
2. It can be inferred that anemia potentially reduces adult earnings (due to its cognitive effects) by 2.5%.
3. Iron fortification is one of the most attractive public health interventions, as seen in the cost per disability adjusted life year (DALY) saved or in the cost-benefit ratio. The cost per person per year for fortification is in the range of $0.10–$1.00 with a cost-benefit ratio of:1:6 (physical benefits to adults) or as high as 1:9 (including estimated cognitive benefits to children).
4. Supplementation costs per person are around $2.00–$5.00 but are five times more costly than fortification in DALY terms and it is noted that the results of large-scale programs have to date been disappointing.
5. More research urgently needs to be done to quantify the economic loss of mental retardation due to iron deficiency anemia.

Critical points in anemia research related to micronutrients

There is no easy solution to overcoming the global scourge of anemia. The etiology of anemia is complex and multifactorial and there appears to be a clear role for multiple micronutrients (vitamins and minerals) in nutritional anemia prevention as well as generally improved nutrition and health. The challenge is to create optimal combinations of micronutrients that will work best together and even synergize each other. No single intervention will revert or prevent anemia in any population. However, there is still limited scientific information about multiple micronutrients in the prevention of nutritional anemia. Moreover, the findings from these clinical studies remain controversial and some need to be interpreted with caution.

Several factors have to be considered when planning future intervention studies with fortified food or supplements in populations with impaired nutritional status and health:

1. *Nutritional factors*

The impact of the composition of the habitual diet including micro- and macronutrients should be evaluated with priority. A poor quality diet, often due to limited intake of animal source food as well as fruits and vegetables, is one of the main causes of multiple micronutrient deficiencies which do not occur in isolation, but rather concurrently. Furthermore, poor bioavailability of nutrients and diets high in plant-based food containing constituents such as phytates and polyphenols limits the absorption of iron and other trace elements.

2. *Health environment and non-nutritional factors*

Infectious diseases such as malaria, tuberculosis, HIV/AIDS, parasitic infections, and certain chronic inflammations are other factors that contribute to anemia and impair nutritional and health status. It is therefore important to take the total health environment into account and to control and/or treat any underlying disease. An integrated intervention approach that considers each population group's epidemiological, socioeconomic, and cultural context is required.

3. *Target population*

The most vulnerable segments of the population are pregnant and lactating women, infants, young children, and adolescent girls. Infancy is the age group in which micronutrient deficiencies start and progress with potentially severe consequences later in life, yet poor nutrition starts in utero. Thus, adequate nutrition and health status should receive high priority during both pregnancy and infancy. The message is clear: a life cycle approach is required, taking the diverse requirements of the different target populations into account.

4. *Recommended intake and composition of micronutrients*
For efficacy of interventions, the optimal dose and composition of micronutrients is still unknown. The potential risks of interactions have to be taken into account when food fortification or supplementation programs are initiated, especially when directed to population groups with a generally poor nutritional status. The interactions between various micronutrients (e.g., iron, zinc, and other minerals, and antinutritional factors inhibiting iron absorption) appear to be especially important. Different combinations and doses as well as new delivery forms of micronutrients still need to be investigated.

5. *Deliveries through the health system*
It is also important to take into account existing prevention programs such as high dose vitamin A, iron/folic acid supplementation, and parasitic disease and malaria control. These programs have to be integrated and monitored carefully in new clinical trials.

6. *Duration*
Long-term outcomes and effectiveness is not yet fully defined with regard to nutrition, health, and general wellbeing and should receive priority. Endpoints of short- and long-term studies vary considerably. Functional outcomes as true indicators of the effects are needed and should be addressed as endpoints in studies.

Making programs and interventions work
Scientific knowledge relating to interventions has expanded beyond iron and now a range of other nutrients (such as vitamin A and multiple micronutrients) as well as infectious disease and parasitic infestation are being considered. In addition, it is now recognized that interventions don't always turn out the way we had hoped; consider the results showing possible negative effects in malaria-endemic areas. So too it has been learned that food-based strategies such as biofortification and dietary diversification are also important. It would seem, that although often a specific angle is emphasized or an approach advocated, the key message should be that all the recognized and documented causes and intervention approaches must work together and that supplementation, fortification (food and home), biofortification, food based approaches, and public health measures have to be viewed and practiced as complementary to one another. For the long-term success and sustainability of nutritional anemia control programs, all the factors and options must be viewed together as a whole and be adjusted to suit the specific local conditions and requirements. Controlling iron deficiency anemia is different from controlling other recognized deficiencies such as VADD and IDD, where 'bullet orientated' approaches of capsules and fortification, respectively, seem to have worked.

It is a sobering statistic that in the year 2000, the number of iron supplements supplied by UNICEF to developing countries was only enough for 3% of all pregnant women in those countries – and that is before one considers compliance. This highlights the view that a key hindrance to achieving the global goals is the fact that operational components of controlling iron deficiency anemia are less well developed in comparison to research and development efforts, and that neither of these are generally linked to communication, which includes political advocacy, funding, motivation for acceptance of better nutrition practices, health education, and promotion. In fact, the greatest challenge probably does not lie in the need for more scientific research, although there are still many unanswered questions and areas for new or renewed focus, but rather in communicating and interpreting the research findings and exceptions so as to fine-tune programs.

Advocacy communication needs to focus on the benefits throughout the life cycle and the associated impact of interventions on improving productivity, which ultimately lead to the economic uplift of both individuals and countries. Emphasizing the fact that the damage to intellectual development caused by iron deficiency in early childhood cannot be reversed later in life and quantifying the loss of GDP when iron deficiency is left untreated should be the key messages to mobilize action across a wide range of sectors for the eradication of iron deficiency and anemia. What we need are effective bridges between science and technology, service providers and political as well as financial decision makers. The problem is not the lack of knowledge about tailored solutions but rather a lack of clear political and financial commitment to undertake interventions to match the magnitude of the problem. The problem is clearly described. What remains is to accept the challenge and accelerate the action.