Nestlé Nutrition Institute Workshop, March 29 – 31, 2019

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Global Landscape of Nutrition Challenges in Children

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Foreword

Malnutrition among children remains a persistent problem around the world. The latest UNICEF data reports that nearly half of all deaths in children under 5 years of age can be attributed to undernutrition. Poor linear growth, or stunting, affects over 150 million children around the world, one-third of whom live in India. Among the 50 million children who are wasted, half are in South Asia, yet this region is also home to a large proportion of the 40 million children who are overweight.

These disquieting results raise several questions. Despite international guidelines on early childhood feeding, why does this problem persist? Are novel interventions needed? There is already an extensive body of literature from studies that have tested different combinations of interventions, including dietary, behavioral, educational, and political. Although the results from these trials can be confusing, one thing is clear: addressing any factor (or a limited number of factors) in isolation is not enough. In attempting to tackle the problem of childhood malnutrition, we are merely scratching the surface of the greater problem of poverty.

Malnourished children are the end result of a chain of events that began generations earlier, including malnourished parents, lack of education, unsanitary living conditions, unhealthy behaviors, and ineffective policies. The contrast between the guidelines versus local feeding practices, in order to identify suitable interventions that can strike a balance between effectiveness and safety. The second session focused on the role of milk in early childhood. Despite of undisputable critical importance of breastfeeding, we still need to learn more of its composition and biological function. The biggest challenges comes after the exclusive breastfeeding period when nutrition choice depends not only on the level of caregivers knowledge on appropriate for child age nutrition but also on the socio-economic, cultural and environmental factors. The final session took a step broader in order to identify the environmental influences of nutrition. Infection from unhygienic surroundings combined with inter-generational nutritional deficits are major forces that can shape the epigenome and the infant gut microbiome. Together, these aspects of the global landscape of nutrition provide a roadmap towards combating nutritional deficiencies in vulnerable children around the world.

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Pediatric Nutrition: Challenges and Approaches to Address Them

Chairperson: Lynnette Neufeld (Global Alliance for Improved Nutrition)

Spanning global trends and homing in on specific population data, the first session opened with Lynnette Neufeld’s review on the importance of understanding the local challenges faced by the target population in order to design appropriate intervention strategies. Although international guidelines on early childhood feeding exist, there remains a disparity between recommendations and reality. Margaret Bentley examined the role played by feeding practices, particularly during the complementary feeding period. Although behavior is a key driver of feeding practices and dietary habits in young children, it remains one of the most difficult targets to modify. Usha Ramakrishna reviewed the key learnings from studies that used behavioral interventions. Food composition tables are important tools that can help to pinpoint nutritional deficiencies in a population, as discussed by Fernanda Grande. Finally, all nutritional interventions should strike a balance between effectiveness and safety. Sant-Rayn Pasricha ended the session with an updated overview of universal iron intervention programs from a safety perspective.

Global Landscape of Malnutrition in Infants and Young Children

Lynnette Neufeld (Global Alliance for Improved Nutrition) examined local trends in stunting and overweight as a means to address these challenges in specific populations. How can knowledge of these global trends be applied towards specific action plans to combat stunting or overweight? Although global and regional data are valuable for tracking our progress and for informing policy-makers, these general trends cannot be used to address nutrition challenges in specific populations. In order to make a difference at the local level, we must uncover the specific nutrition deficiencies faced by each population. In India, for example, the prevalence of stunting varies greatly according to district (from 12.4% to 65.1%). Similar disparities are present in other countries including Indonesia and Vietnam.

There is an urgent need for rigorous data collection that is nationally and subnationally representative, regularly collected and standardized across countries.

Why are some populations affected by stunting while others nearby suffer from overweight? The reason is because nutrition is strongly influenced by individual, household, and societal factors. The divergence in stunting across the Indian districts is affected by geography, household size and assets, maternal factors (age at marriage, education, body mass index) and adequacy of the individual diet. Other factors that should be explored include poor sanitation, lack of healthcare and inadequate breastfeeding. Therefore, global trends must be reinforced by knowledge at the local level: only by understanding the specific challenges faced by the local population can we successfully implement action plans to combat both stunting and overweight in children.
**When Does It All Begin?**

**What, When and How Young Children are Fed**

Although the types of foods and beverages young children consume are important, how they are fed influences future dietary preferences and eating behavior. Margaret Bentley (University of North Carolina Chapel Hill) examined the importance of early childhood feeding practices.

The first two years of life are a critical period for developing proper nutrition and shaping future eating behaviors. International guidelines recommend exclusive breastfeeding until six months of age, followed by the introduction of nutritionally adequate complementary foods. Yet there is a wide discrepancy in caregiver adherence to these guidelines. The feeding of infants and toddlers greatly varies depending on the social environment, access to information and quality foods, and cultural beliefs.

**Future research should aim to track both global food and beverage consumption among children under two years old and its impact on growth and development.**

India has seen major changes in the patterns of breastfeeding and complementary feeding over the past decade. The initiation and duration of breastfeeding has improved, thereby decreasing the odds of infant mortality. But child feeding data have identified a deficiency in complementary feeding. There was a 10% decrease in children aged 6-23 months who received solid or semi-solid food and breast milk. A key influencer during complementary feeding is caregiver feeding style, which determines not only what foods and drinks are offered, but whether young children accept these foods. Lack of responsive feeding has been shown to be associated with overweight, reduced breast-feeding, and a higher risk of inappropriate feeding. Another important gap exists with respect to beverage consumption in early childhood. With the rise in consumption of sugar-sweetened beverages, it will be important to track global beverage consumption alongside food consumption and dietary diversity. These findings underscore the importance of the complementary feeding period as an opportunity for intervention. More effective complementary feeding programs need to be applied in order to achieve similar improvements in complementary feeding practices as those attained for breastfeeding.

**Improving Children’s Diet: Approach and Progress**

A wide variety of interventions have been tested with the goal of improving the diet of young children. Usha Ramakrishna (Emory University) highlighted the successes and challenges learned from key intervention trials that focused on behavioral interventions.

Although access to quality foods remains a problem in resource-poor settings, behavioral change has been identified as a cornerstone for improving child feeding practices during the first two years of life. This presentation reviewed the key findings from trials conducted in Sub-Saharan Africa, South and South-East Asia, focusing on interventions that used behavioral change techniques (BTCs).

In reviewing the results across the different trials, several key findings emerged. First, many trials suffered reporting deficiencies, such as lack of detail given on design of the study interventions. Other gaps included information on cost and feasibility, all of which have important implications for the adoption, replication and scale-up of effective strategies. Another concern was the limited data on strategies that targeted preschool-aged children (5-5 years).

Among five large multi-country studies, the Alive & Thrive study in Bangladesh successfully delivered behavioral interventions across multiple platforms to enhance dietary quality in children. This study combined intensive interpersonal communication with the mobilization of mass media and the community. Results from the study reported significant improvements in a variety of child diet indicators including the proportion of young children aged 6-24 months who consumed a minimally adequate diet and attained a minimum dietary diversity. Through the mobilization of a strong community-based, non-governmental organization, this study reached over 8 million mothers. Key factors that contributed to the success of the program were the inclusion of various stakeholders, availability of funds and technical support from multiple donors, use of well-defined interventions and indicators, and streamlined tools to help in implementation. The lessons learned from the Alive & Thrive study provide guidance for future trials that target dietary behavior as a means for improving childhood nutrition.

**The Importance of Food Composition Data for Estimating Micronutrient Intake: What Do We Know Now and Into the Future?**

Fernanda Grande (Food and Agriculture Organization of the United Nations) reviewed the role of food composition tables in identifying population intake deficiencies.

Food composition tables (FCT) provide essential information needed to convert food consumption data into energy and nutrient intakes. Not only do these tables assemble data on the nutrient content of the foods of a particular country or region, they also form the basis for many activities involving health and nutrition, food security, and agriculture. The main factors that affect the quality of FCT are coverage of foods and their components, details included in the food description, and how well the foods analyzed represent the actual food supply. At the minimum, FCT should be provided at the country level since the composition of foods differs according to geographical location.

There are a number of challenges related to the use of FCT. First, although most countries have published at least one FCT, the majority of these tables are outdated. In addition, these tables vary greatly in terms of data quality, food and nutrient coverage, analytical methods used, and accessibility. The use of low-quality FCT may introduce errors in food intake assessments, resulting in under- or over-estimation of the intake of a particular micronutrient. It is important to understand that many natural factors can affect the composition of a specific food. For example, the level of maturation, soil quality and harvest season can influence the vitamin A content of sweet potato. Therefore, these foods should be reported with their specific nutrient profile instead of as a general entry in the tables.

What can be done to improve the quality of FCT worldwide? The FAO International Network of Food Data Systems (INFOODS) coordinates food composition activities with the goal of improving FCT data quality and availability around the world. Some of the actions of INFOODS include capacity development and publication of guidelines and regional and international FCT. The improvement of FCT is a first step towards developing policy and nutrition programs designed to address nutrition deficiencies.

**Balancing Safety and Potential for Impact in Micronutrient Interventions**

Sant-Rayn Pasricha (Walter and Eliza Hall Institute of Medical Research) discussed the use of universal iron interventions from a safety perspective. Worldwide, almost 300 million children under 5 years are anemic. Iron deficiency was originally thought to account for half of these cases, leading international policy-makers to recommend the universal distribution of iron-based interventions for young children (either iron supplements or iron-containing multiple micronutrient powders).

However, more recent data suggests that iron deficiency anemia is less prevalent than was originally anticipated. Furthermore, the results from recent effectiveness studies indicate that the impact of these interventions is low; there is inadequate evidence to support the hypothesis that universal iron interventions provide benefits on functional health outcomes in children. Conversely, several randomized controlled trials have identified an increased risk of infection associated with the use of iron interventions, particularly malaria and diarrhea. Interestingly, the populations with the highest burden of anemia are also those with the highest rates of these infections. Other potential risks of iron intervention are well known but not well described in the target populations. For example, universal iron distribution programs are largely unmonitored and the incidence of iron toxicity is undocumented. In some populations, long-term provision of iron supplements may increase the risk of iron overload.

Currently, two large placebo-controlled trials are ongoing in Bangladesh and Malawi. The outcomes of these trials will clarify the functional benefits of universal iron interventions in terms of key measures such as child development, well-being, growth and hemoglobin and iron status. Until then, the implementation of universal iron intervention programs should be undertaken with caution.

Identifying whether universal iron interventions provide a net benefit or harm to populations is challenging.
Role of Milk in Early Life

Chairperson: Kim Michaelsen (University of Copenhagen)

Milk is a key source of nutrients during infancy and early childhood. Due to ethical and technical challenges, our knowledge of the nutritional composition of breastmilk is limited. Lindsay Allen reviewed the advances made in our understanding of the composition of human milk from healthy mothers. Cow’s milk also plays an important role in healthy growth and development during the first years of life. In addition, it has a role to play in the prevention and treatment of protein-energy malnutrition. Kim Michaelsen discussed the benefits and challenges of using cow’s milk in the nutrition of older infants and young children. In addition, Michaelsen explored the role of milk-derived proteins to support growth in malnourished children. However, addressing malnutrition in children with food-based interventions is not enough to interrupt the vicious cycle. Malnutrition is perpetuated across the generations, requiring multi-factorial interventions. Chittaranjan Yajnik focused on the evolution of vitamin B12 deficiency throughout the life cycle, highlighting the key findings from the Indian population (from the Pune Study) that could be applied to other at-risk populations. A growing number of people are turning towards vegetarian or vegan diets for themselves and their children. Research is ongoing to identify the optimal balance of plant proteins in products designed to support catch-up growth and dairy proteins in products designed to support catch-up growth. Nevertheless, dairy protein plays an important role in products for the treatment and prevention of malnutrition. In comparison to products derived from plant proteins, dairy protein-derived products contain fewer anti-nutrients. The disadvantage is that dairy protein products are expensive. Research is ongoing to identify the optimal balance of plant and dairy proteins in products designed to support catch-up growth.

Breastmilk as the First Source of Micronutrients

Despite the importance of breastmilk as the main source of nutrients during infancy, there are significant gaps in our knowledge of its composition and evolution during lactation. Lindsay Allen (University of California Davis) reviewed cutting-edge research on the nutritional composition of breastmilk. In general, the nutrient content of the breastmilk of a well-nourished woman is sufficient to support optimal growth and development of the infant. But towards the end of the first 6 months, it is thought that some nutrients may not be adequately supplied by breastmilk. These include iron, zinc, vitamin B12, and vitamin D.

What evidence is available to support this assumption? It is difficult to make conclusions about the nutritional adequacy of human milk, because there is little normative data on the nutritional status of infants during the first years of life. The nutrition status of infants is not usually studied until after 6 months of age. To confound the problem, adult cut-off points for defining adequacy versus deficiency are often used, simply because none exist for infants. In poorer populations, however, the data suggests the presence of deficiencies already by age 6 months. These deficiencies are usually ascribed to lack of exclusive breastfeeding, or illness and infections. Recent technological advances have made it possible to measure multiple micronutrients in human milk. These indicate large differences in milk micronutrient concentrations across populations and enable us to study the effects of maternal supplementation on milk composition and infant health status. However, there are several hurdles to overcome. The effects of maternal supplementation vary depending on the nutrient, and the timing of milk sampling can affect the concentrations of the nutrients measured. Results from the ongoing Mothers, Infants and Lactation Quality (MILQ) study will hopefully answer some of these questions. In addition, the study will gather data on the values for milk concentrations of nutrients, which will ultimately aid in improving nutrient intake recommendations for infants, young children and lactating women.
Use of Plant Proteins to Treat and Prevent Acute Malnutrition

Combinations of plant proteins can be used as a cost-effective alternative to dairy ingredients for the prevention and treatment of moderate and severe acute malnutrition. Mark Maraner (Washington University School of Medicine) explained how:

Wasting is the physiological process that leads to acute malnutrition. A key characteristic of this process is reduction of the body’s lean and functional tissues. Particularly in children, generalized wasting of the muscle and organs affects stamina and mobility, and renders the child more vulnerable to infections.

Protein is an important component of specialized foods designed to treat moderate acute malnutrition (MAM) and severe acute malnutrition (SAM). For this target population, a key consideration is the presence of the 11 essential amino acids which cannot be synthesized endogenously by humans, but which must be absorbed by the gut. Therefore, protein quality refers to the essential amino acid content of a particular food or food product. For these reasons, animal source proteins, in particular milk protein, are frequently prescribed as ingredients in foods to treat MAM and SAM. In clinical trials that have used different foods of varying protein quality to treat MAM and SAM, there are correlations between protein quality and the rates of weight gain and recovery. In SAM patients, use of milk protein results in greater weight gain and recovery.

What are the alternatives to using proteins derived from milk? Among the plants, cowpea, common bean and soybean have the highest amount and quality of protein and thus are candidates for foods for the treatment of acute malnutrition. Current research is focusing on promising new options, such as crystallized amino acids, to expand the range of home-based therapy for young children with moderate or severe acute malnutrition.

In young children and adolescents, not only their weight and growth but also their psychomotor development is strongly influenced by the form and quality of their nutrition.
Gut Microbiota and Malnutrition

The intestine is one of the key organ systems to be affected by malnutrition. Ruari C. Robertson (Queen Mary University of London) explored the effects of child malnutrition on the gut microbiome.

In early life, the gut microbiome plays an important role in regulating the structure of the intestinal barrier, nutrient absorption, cell signaling, infection resistance and immune tolerance, among other key functions related to growth. The microbiome-for-age Z-score (MAZ) is a strong predictor of healthy child growth. Stunting is associated with a dysregulation of the gut microbiome, which is reflected as a decompartmentalization of the intestinal tract. Commensal microbial taxa of oropharyngeal origin are found lower in the gastrointestinal tract than normal. It is thought that the presence of these microbes outside of their ecological niche may stimulate a chronic inflammatory cascade leading to environmental enteropathic dysfunction (EED) and growth faltering.

The programmed maturation of the gut microbiome in the first 2 years of life, as measured by the microbiome-for-age Z-score, is highly predictive of healthy child growth.

Does the gut microbiome present a feasible target for alleviating the burden of child undernutrition? Thus far, interventions targeting the gut microbiome in undernourished children have yielded inconclusive results. Antibiotics have shown beneficial effects on linear growth but antimicrobial resistance limits their widespread use. Probiotics have also shown promising results in reducing diarrhea and increasing weight, but more work is needed to identify the optimal timing and strains to use. In severely wasted children, standard therapeutic feeding fails to improve the MAZ score, suggesting that current feeding protocols are not enough to restore the gut microbiome. Future work should apply the key learnings that have already led to novel therapies for patients with chronic intestinal and metabolic disorders towards alleviating the clinical burden of child undernutrition.

Intergenerational Influences on Child Development: An Epigenetic Perspective

The effects of poor maternal nutrition are inevitably transferred from mother to child. Matt Silver (London School of Hygiene and Tropical Medicine) reviewed the epigenetic mechanisms involved.

Modifications to the epigenome of the developing fetus is a known mechanism through which inter-generational nutritional signals can be transmitted. A well-studied event is the addition of methyl groups to DNA. These are faithfully copied during cell division and can influence gene expression without altering the underlying DNA sequence. Indeed, the human genome contains areas called metastable epialleles (MEs): methylation of these regions occurs in early embryogenesis and is particularly sensitive to environmental influences. An example of a ME is the POMC gene which is involved in appetite regulation.

The periconceptional period is a critical window of time when the establishment of epigenetic marks in the offspring is particularly sensitive to differences in maternal and possibly paternal nutrition. Data from a rural population in The Gambia represented that of a natural experiment similar to the Dutch Hunger Winter. In this case, fluctuations in energy balance and maternal nutrition showed a distinct bimodal pattern that corresponded to the dry and rainy seasons. The work of Silver’s group showed that the season of conception and maternal blood levels of certain nutritional biomarkers can predict DNA methylation in infants at a number of MEs. These findings provide further insight into how nutritional signals in the environment may be transferred from mother to child.

The WASH Benefits Bangladesh, WASH Benefits Kenya and SHINE Trials

Jean Humphrey (Johns Hopkins Bloomberg School of Public Health) summarized the findings from three key proof-of-concept WASH trials.

The WASH Benefits Bangladesh, WASH Benefits Kenya and Sanitation, Hygiene, Infant Nutrition Efficacy (SHINE) Zimbabwe trials were cluster-randomized trials to test the independent and combined effects of improved water and sanitation/hygiene (WASH) and improved infant and young child feeding (IYCF) on child linear growth and hemoglobin concentration. The goals of the trials were two-fold: first, to minimize fecal ingestion, and second, to optimize infant diet. Altogether the trials enrolled over 19,000 pregnant women and followed up their 15,500 infants for up to 18 or 24 months.

Several key findings emerged. In all the trials, the IYCF intervention improved infant linear growth scores. This result supports the existing literature on the beneficial effects of complementary feeding interventions on linear growth. The WASH interventions, however, failed to improve linear growth. One possible reason is that the interventions used were not enough to reduce exposure to environmental pathogens sufficiently to improve growth. An interesting finding was that WASH interventions reduced diarrhea in Bangladesh but not in Kenya or Zimbabwe. This could be due to differences in the frequency of the study visits to participants (6 times per month in Bangladesh versus monthly in the African sites). These findings suggest that in order to achieve a high adherence to WASH behaviors to reduce diarrhea, very frequent behavior change promotion is needed.

The results from these studies remind us of how little we know about preventing the transmission of environmental pathogens in early childhood and the significance to childhood linear growth. Achieving WHO growth standards in the world’s poorest children will require multiple efforts at the level of water, sanitation, and feeding.

Innovative WASH interventions that are less reliant on behavior change and much more effective in reducing fecal exposure may be required to optimize child health and growth.
It is non-negotiable that nutrition is playing a crucial role in health and disease especially in population at risk. Thanks to new technologies and progress in other areas of biomedical research, we are beginning to gain a more complete picture of normal human growth and development during the early childhood. We begin to know more on the role played by breast milk and later on other milk and milk based products in supporting healthy child growth and development. Further information from long-term population studies, such as those for vitamin B12, are shedding light the evolution of specific nutritional deficiencies across the human life cycle. Advances in genomic research are helping to clarify the areas of the human genome that are most susceptible to nutritional signals. This could pave the way for developing biomarkers that can be used to track growth outcomes across the generations. A deeper understanding of the gut microbiome may open up new areas for intervention.

The double burden of malnutrition including stunting and overweight/obesity affects many countries around the world. Malnourished children are the product of an environment shaped by forces beyond the control of their parents or families. These include lack of clean water, poor sanitation and health facilities, lack of knowledge, and inadequate policies. Via the mechanisms of epigenetics, these forces combine to transfer the signals from the environment across the generations, thereby perpetuating the vicious circle. Instead of trying to pinpoint one or even several key targets, we must focus on reducing the overall burden of malnutrition by addressing key aspects of the problem in a logical and comprehensive manner.

Integrated nutrition interventions that target specific deficiencies are needed, such as micronutrient fortification/supplementation, as well as products based on animal- or plant-derived proteins. Such interventions should be carefully tailored to meet the nutritional requirements of the children involved. But in order to achieve sustained improvements, such interventions should be combined with other strategies that address the broader risk factors in the child’s physical and social environment. As the malnutrition includes not just wasting and stunting, but also overweight and obesity, we need to focus not only on ensuring an adequate nutrient supply, but also on improving the quality of diets. Indeed, childhood malnutrition is a red flag signifying a knowledge gap within the child’s family and sociocultural sphere. Education programs that target mothers and caregivers should therefore be provided along with any nutrient-based intervention, to emphasize the importance of dietary quality, health and hygiene. The establishment of infrastructures such as a clean water supply, sanitation, and healthcare services are needed to sustain any achievements over the long term.

Thus, the solutions to all forms of malnutrition need to treat nutrition as a multi-sectorial challenge. The dialogue must extend across different stakeholders, including the community, non-governmental agencies, the private sector, as well as local and national governments. Investing in actions that will make a difference to the early years of a child’s life will have far-reaching benefits in terms of reduction of public health costs and the enhancement of human capital, ultimately strengthening the development of a nation.