Promoting Healthy Growth: What Are the Priorities for Research and Action?[1,2]

Ellen Piwoz,* Shelly Sundberg, and Jenny Rooke
Global Health Program, Bill and Melinda Gates Foundation, Seattle, WA

ABSTRACT

Healthy growth from conception through the first 2 y of life is the foundation for adequate organ formation and function, a strong immune system, physical health, and neurological and cognitive development. Recent studies identified several low-cost interventions to address undernutrition during this age period and noted the lower returns on investment of intervening after this critical period. Although these interventions should be implemented widely, it is recognized that existing nutrition solutions, even if universally applied, would only avert a minority fraction of the estimated death and disability due to undernutrition. This paper reviews some of the knowledge and learning needed to close this "impact gap." Five areas are prioritized for future research: *1*) study healthy growth from a lifecycle perspective, because maternal, fetal, and newborn outcomes are connected; *2*) understand why growth faltering begins so early in breast-fed infants in the developing world; *3*) apply new tools and technologies to study long-recognized problems such as the interaction between nutrition and infection; *4*) explore new hypotheses for understanding nutrient assimilation and use to discover and develop intervention leads; and *5*) understand the role of the environment in healthy growth and the potential synergistic benefits of multi-sectoral interventions. Policymakers are urged to invest in nutrition-specific and -sensitive interventions to promote healthy growth from conception through the first 2 y of life because of their immediate and long-term health and development benefits. *Adv. Nutr. 3: 234–241, 2012.*

Introduction

Healthy growth from conception through the first 2 y of life is the foundation for adequate organ formation and function, a strong immune system, physical health, and neurological and cognitive development. In short, much of what we hope to achieve through global health and development efforts requires well-nourished populations who can learn, earn, and innovate. For many years, the global nutrition community has been focused on the problem of underweight, via growth monitoring and promotion programs and advocacy around the Millennium Development Goal 1, which has a target of reducing global underweight by one-half from 1990 to 2015 (1,2).

As a result of these efforts, we know a great deal about how to achieve weight gain and indeed quite a few countries are on track to achieve their Millennium Development Goal 1 targets (2), which is a positive accomplishment. But weight gain for its own sake is not necessarily healthy for all and it is especially unhealthy when it is not accompanied by adequate linear growth, which is something we know far less about than we should, particularly for newborns, infants, and young children who live in environments with high pathogen and infectious disease burdens.

In 2008, the Lancet medical journal published a series of papers on Maternal and Child Undernutrition, including a comprehensive review of the evidence of impact from existing nutritional interventions (3). In these analyses, the burden of disease due to stunting, severe wasting, intrauterine growth restriction, suboptimal breastfeeding, and micronutrient deficiencies was also estimated (4). These papers identified a number of low-cost interventions to address undernutrition from the fetal period through the first 2 y of life (also referred to as the −9 to 24-mo period). However, it was also reported that existing nutrition solutions, even if universally applied, would only avert a minority fraction (25–36%) of the estimated death and disability due to these forms of undernutrition (3). We refer to this as the impact gap.

This paper examines the knowledge, learning, and new or additional interventions needed to close the impact gap

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* To whom correspondence should be addressed. E-mail: ellen.piwoz@gatesfoundation.org.

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described above. We review the literature on the processes that lead to healthy human growth and potential implications of shifting policy and program attention from reducing underweight to reducing stunting. This shift is warranted in light of new data on the global burden, timing, and long-term health and development benefits of healthy linear growth accompanied by adequate weight gain. The paper does not address the important challenge of preventing and treating moderate and severe wasting, for which effective intervention protocols exist.

What is healthy growth and why focus on it?

It is first useful to note that the concept of healthy growth reflects a shift away from the term "optimal growth," due largely to an inability to define any absolute targets for "optimal" growth or an optimal size, rendering those terms not particularly useful. Instead, in this review, we adopt a working definition of healthy growth as normal linear growth relative to the WHO Child Growth Standards. Other growth parameters such as lean body mass and weight relative to height were acknowledged as extremely important aspects of healthy growth but more complicated to measure at a population level. Patterns of growth that favor length over weight have benefits for survival; further, healthy linear growth correlates with positive future health and functional outcomes (5).

Individuals who fall 2 SD below median height-for-age of the WHO reference standard are defined as stunted. Stunting is more common than underweight or wasting (low weight-for-height); it currently affects ~171 million or 27% of children < 5 y of age globally (6). South Asia represents 58% of the global stunting burden. About 35% of the stunting burden is in Africa, where the condition is increasing in absolute numbers against a background of gradually decreasing stunting prevalence globally (**Fig. 1**). Poor linear growth in early life is associated with poor cognition and educational performance, low adult wages, lost productivity, and increased risk of nutrition-related chronic diseases when accompanied by excessive weight gain later in childhood (5,7,8). Stunting is also a risk factor for increased morbidity and mortality from infectious diseases, though other anthropometric indicators such as underweight and wasting more strongly predict immediate health risks (4).

The extent to which failure to grow is an adverse outcome in and of itself or an indicator of other processes that contribute to poor health and development is not well understood. What is known is that the onset of linear growth faltering is much earlier than previously recognized, most likely beginning in the fetal period and continuing until about 24 mo of age (9). Thus, there is a need to intervene early in order to have immediate as well as long-term impacts.

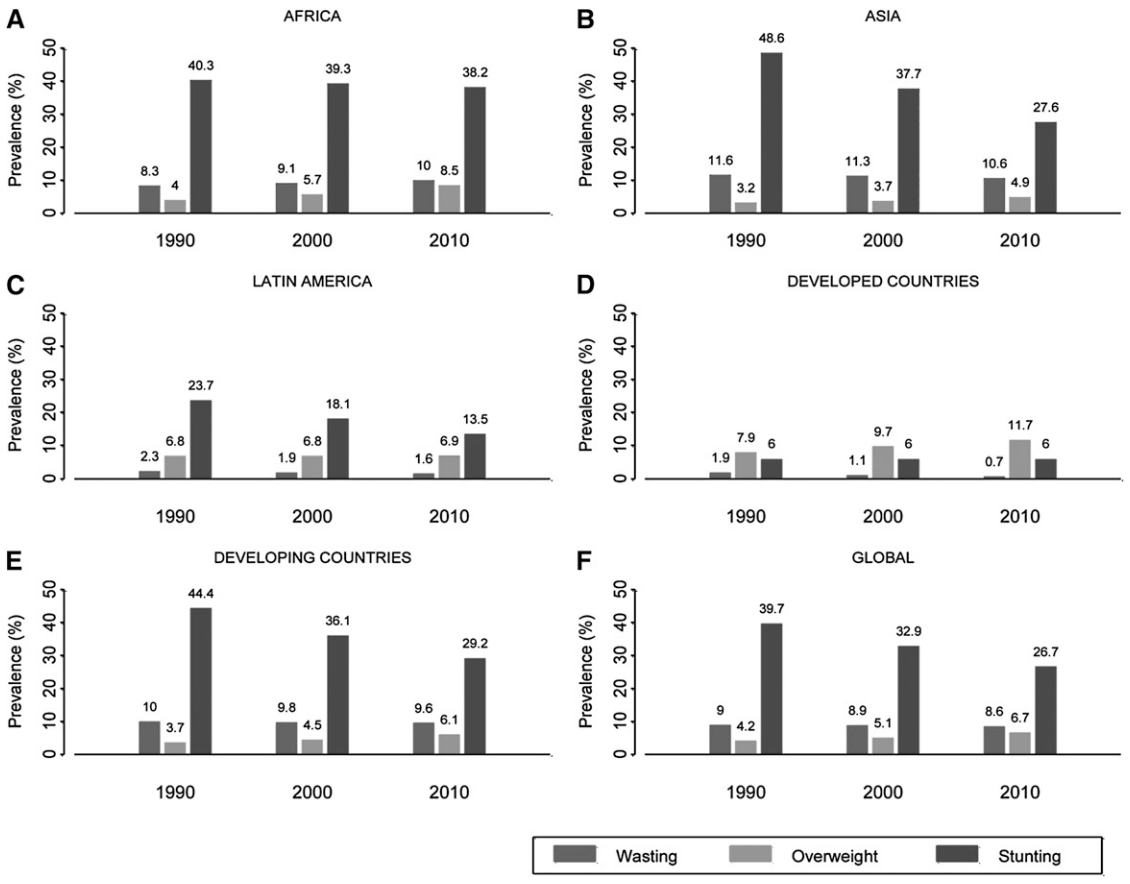

Figure 1 Global and regional prevalences of stunting, wasting, and overweight. Adapted with permission from (6, 44).

Requirements for achieving healthy linear growth

The primary drivers of linear growth differ throughout childhood. In early childhood, nutrition stores, diet, and overall health (e.g., infection status, immune health) are the key influences. In later childhood, by contrast, growth hormones take on a prominent role, whereas during puberty, sex hormones are the main driver (10). Given the importance of early growth for future outcomes, this review focuses on available data on requirements for achieving healthy growth in this period.

Adequate nutrition, including micronutrients

Avoiding undernutrition by ensuring an adequate intake of nutrients, including micronutrients essential for bone, cartilage, and connective tissue formation, is essential for healthy growth. However, defining adequate nutrition, especially for at-risk populations in the developing world, is not at all straightforward. Methods for estimating nutrient requirements for healthy growth have evolved over the past several decades. Although we know a great deal about requirements for certain Type I nutrients (i.e., those nutrients whose tissue concentrations decline during deficiency), it is the relatively difficult to measure those Type II nutrients (i.e., those nutrients that are preserved in tissues when deficient) that appear to be most critical for linear growth (**Table 1**) (11). Furthermore, we have limited information on intakes and adequacy of these nutrients and thus the extent to which they contribute to growth faltering is unknown. Other knowledge gaps include micronutrient requirements during infancy and the impact of maternal prepregnancy nutritional status on birth and other postnatal outcomes.

Available requirements are typically defined for healthy children; the resulting recommendations reflect what is necessary "for the healthy to stay healthy." Such recommendations may overestimate what is needed in some cases (i.e., they do not define a minimum requirement) and in others may grossly underestimate the additional intakes necessary to compensate for chronic stressors affecting nutrient assimilation and use. Some estimates suggest that children in developing countries may have nutritional requirements that are 60–100% higher than those for children in the developed world due to infection, lower bioavailability and absorption of nutrients, and other stressors (12). Data further suggest that these stressors may cause children to stop growing entirely, independent of food intake, though the causal pathways for this growth inhibition are poorly understood; conversely, studies have shown that psychosocial stimulation can have an independent effect on growth in the first 3 y of life (13). As an added complexity, nutrients can have both positive and negative effects on immune function and little is known about diet and immune system interactions (14).

Table 1 Type I and II nutrients

Type I nutrients	Type II nutrients
Selenium	Nitrogen
Iron	Sulfur
Calcium	Essential amino acids
Thiamine	Potassium
Vitamin A	Sodium
Vitamin C	Magnesium
Vitamin D	Zinc
Vitamin E	Phosphorus
Nicontinic acid	
Cobalamin	
Pyridoxine	
Iodine	
Copper	
Manganese	
Riboflavin	
Vitamin K	
Folate	

Immune health/infection status

Reasonable freedom from acute and chronic infection during early childhood is important for achieving healthy growth. Important factors in this dependency include the metabolic demands of infection detracting from resources spent on healthy growth and the timing of insults. Achieving healthy growth depends on both the absence of negative factors (e.g., immunotoxins) and the presence of necessary components (e.g., healthy immune organs, reliant on key nutrients). Immunity is an evolutionarily well-protected function; growth faltering in the context of repeat infection may be in part the result of an adaptive mechanism for protecting immune function (15).

Healthy gut

The role of a healthy gut in achieving healthy growth is sometimes underappreciated. The gut is both a major component of the body's absorption of nutrients, acting as the interface between nutrient intake and growth, and a critical element of a well-functioning immune system. A gut that is free from persistent inflammation is likely to be an essential element for achieving healthy growth. So too is a healthy gut microbial population, important for both keeping pathogens in check and optimizing absorption and utilization of nutrients (16). There is increasing evidence to support the hypothesis that environmental enteropathy and its attendant increased permeability and reduced surface area may be a causal factor in impaired growth in developing world settings, highlighting the complex interactions between nutrition, infection, immune health, and the gut (17).

Timing

Timing is also critical but frequently overlooked. As noted above, factors that influence linear growth processes begin in fetal life and continue to play a crucial role, especially in the first 24 mo after birth; thus, the essential conditions for healthy growth would ideally be present from conception (or before). Conversely, interventions initiated after this critical time period may be delivered too late to achieve maximum benefit and in some instances could be detrimental, leading to accelerated maturation and closing of the growth plates, halting linear growth, and consequently increasing the risk of overweight and obesity (18). Importantly,

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linear growth occurs in spurts; often, weight gain is consolidated first, followed by increase in length (19). Thus, linear growth appears to be a function of "readiness to grow" windows crossed with nutrition and environmental insults. If diet is inadequate or poor health or stress is a factor at key growth windows, linear growth may be affected.

The issue of growth timing can also be considered in a larger sense, i.e., the consequences of unhealthy growth across generations. Short adult women are more likely to have obstructed labor, more likely to give birth to low-birth weight infants, and are at higher risk for maternal death (20). However, although birth weight is correlated across generations, it is also known that health and nutritional interventions can break this intergenerational cycle (21,22), calling out the immediate and longer term benefits of addressing this issue.

Interventions to prevent stunting

As described above, stunting represents the outcome of a complex interaction between undernutrition, poor gut health, infectious disease, and compromised immune function and, as a result, intervening to prevent stunting is particularly tricky. It is difficult to attribute improvements in linear growth to a single intervention, given the complexity of factors that contribute to it. In considering available interventions and their potential impact on stunting, one may find it useful to frame these in terms of either nutrition-specific or nutrition-sensitive interventions (23).

Nutrition-specific interventions

In this review, nutrition-specific interventions are those that directly affect nutrient intake. Analyses by Bhutta et al. (3) suggest strong evidence of impact for these interventions: promotion and support for optimal breastfeeding and appropriate complementary feeding practices (quality, frequency, quantity) and provision of complementary foods, micronutrient supplements, fortification, or combinations thereof. The role of preconception and antenatal interventions on postnatal growth may be significant, but evidence of the magnitude of this benefit is limited. Simple provision of food, irrespective of quality, has had mixed results on linear growth in early childhood. Among complementary feeding intervention studies, those that have had the largest impact on linear growth have included milk powder (24); together with observations from many developed and developing countries that milk intake is an independent predictor of height, this suggests that milk may contain unique factors that stimulate linear growth (25). The impact of complementary feeding educational interventions has similarly varied by context; such approaches have had the most impact on linear growth when conducted in populations with sufficient resources to respond to the messages and when messages promote regular consumption of animal source foods (24). Programs that target food as a preventive intervention are more effective at improving linear growth than programs providing food as treatment (26), again highlighting the importance of timing.

Interventions that provide only micronutrients, e.g. in powders for home fortification, have shown little or no effect on linear growth, suggesting that micronutrients alone may not be sufficient to stimulate linear growth, or that these supplements did not contain the right mix of growth-limiting nutrients (27). Exceptions have been observed, however, particularly in the case of zinc. A recent meta-analysis estimated that zinc supplements (10 mg/d for 24 wk) increase linear growth in children < 5 y by 0.37 cm (0.25 SD), which is a smaller effect size compared to other complementary feeding interventions (0.49–0.54 cm) (28,29).

The most successful complementary feeding interventions report an increase in height-for-age of ~0.7 Z-score, or roughly one-third to one-half of the growth deficit in a stunted child (24). Although this does not account for the additional potential positive impact of prenatal nutritional interventions, it is clear that nutrition-specific interventions alone are insufficient to promote healthy linear growth, given the complex nature of the problem.

Nutrition-sensitive interventions

Nutrition-sensitive interventions are those aimed at improving nutritional status through other (nondietary) means, including improvements in health, environment, or social and economic conditions. These interventions may improve nutrition through reduced disease exposure, better healthcare, or greater purchasing power. Nutrition-sensitive interventions span multiple sectors and may include economic, agricultural, social protection, and water, sanitation and hygiene (WSH) programs. Although nutrition-sensitive interventions can have a measureable impact on linear growth, the effects are less readily observable. The fraction of the stunting burden that can be averted via nutrition-sensitive actions alone is unknown; also uncertain is the additive compared to synergistic impact of combining nutrition-specific and nutrition-sensitive intervention approaches.

The central role of nutrition-sensitive interventions for promoting healthy growth was highlighted in a case study of Brazil (30). The prevalence of stunting in Brazil decreased from 37 to 7% over 33 y, 1974–2007; inequities in stunting between the richest and poorest were also reduced. Brazil's success in reducing stunting was attributed to 4 key factors (in order of relative importance in statistical analyses): increased household income through targeted conditional cash transfers (CCT) programs, increased maternal schooling, increased use of health care, and improved water and sanitation services. These 4 factors accounted for two-thirds of the observed decline in the prevalence of stunting.

Development programs such as CCT have the potential to promote healthy linear growth through both nutrition-specific and nutrition-sensitive pathways but in general have had only a modest impact on linear growth. In Mexico, stunting decreased from 27 to 16% over the period 1988–2006, largely due to targeting and coverage of a CCT program and increased use of healthcare (31). Conversely, a review of 5 Latin American CCT programs showed only modest effects;

at issue may be the lack of clear nutrition objectives and targeted interventions in such programs in general (32).

Healthcare-focused interventions can have a positive effect on linear growth by reducing some of the stressors that impeded it. In particular, in light of the crucial role of the gut mucosa in both nutrient absorption and immune health, healthcare interventions that manage infection and its sequelae could have a major impact on promoting healthy growth in developing world settings. Such interventions, to be maximally effective, will need to manage sick children so as to achieve optimal repair of the gut epithelium, not necessarily targeted or achieved by current disease management practices. For example, in children with severe diarrhea, repeat biopsies demonstrate that intestinal inflammation and damage persists well after cessation of the diarrheal episode (33). Longer duration of treatments aimed at achieving downregulation of the inflammatory response may be called for.

WSH interventions may have a far greater potential to improve linear growth than previously understood. Bhutta et al. (3) estimated that 2.4% of stunting is due to unsafe water and poor sanitation, but the analysis focused only on the impact of diarrheal disease (caused by unsafe water/poor sanitation) on linear growth and did not consider the growth-limiting effects of subclinical inflammation due to persistent exposure to fecal pathogens. Increased immune stress and impaired nutrient absorption, as noted previously, are likely to take an additional toll, suggesting that improved WSH could have more significant impact on linear growth than is currently appreciated. As an example, recent data indicate that children presenting with diarrhea spend roughly 10 times more days with subclinical gut inflammation than with diarrhea itself (34).

Agriculture programs have tended to show limited nutritional impact when nutritional outcomes are measured, which is rarely. Agriculture's impact on nutrition flows through several different pathways, including via income, women's time allocation, and consumption of household food production. Agricultural-led income growth has been an important driver of nutritional improvement in many countries over the past several decades, but economic growth alone is not sufficient to fully address the undernutrition problem. There are many underlying determinants of undernutrition that mediate the relationship between income growth and nutrition. These factors include child feeding practices, women's control of economic resources, and health status. Although increasing agricultural productivity gives rural households the income and increased food availability to enable improvements in their families' food consumption, nutrition interventions are necessary to ensure that increased income and food availability at the farm level are translated into better nutrition. Reviews of past projects conclude that agricultural interventions that work directly with women farmers and include a nutrition education component are more likely to have positive impact on nutritional outcomes (35).

Timing of interventions

Not unexpectedly, linear growth is most affected by interventions (nutrition-specific and -sensitive) delivered during the −9 to 24-mo period. To date, only nutrition interventions up to 3 y have been shown to deliver long-term economic productivity effects (36). Once faltering in linear growth has occurred, catch-up growth may be possible, depending on the number and nature of reasons for failure, but the composition and quality of this growth is most likely not as good as preventing stunting to begin with (37). Evidence suggests that it is difficult to achieve catch-up growth; only modest improvements in Z-scores were observed after 24 mo in several long-term cohort studies (38).

In summary, current data suggest that both nutrition-specific and nutrition-sensitive interventions may be required to promote healthy growth in the developing world. However, many unknowns persist, including the range of growth-limiting nutrients throughout the world, the potential impact of improved antenatal nutrition, and the impact of combined nutrition-sensitive and -specific interventions (and whether they provide synergistic benefits).

Implications for policy and program action

Policy

Countries and programs are in very different places regarding awareness of the importance of healthy growth and assessment of stunting as an indicator of health and nutrition. Legacy programs may not reflect the latest knowledge on the importance of linear growth and its determinants; as a result, programs may divert scarce resources to suboptimal interventions and/or neglect to evaluate linear growth altogether. Bringing the concept of healthy growth more to the forefront in the global conversation enables the discourse to focus on key issues such as timing (early intervention), diet quality, multi-sectoral linkages, and immediate as well as long-term benefits. In the future, there needs to be a greater appreciation that undernutrition is not solely a consequence of poverty but rather is an important component of (and a critical barrier to) societal and economic development. The most effective strategies for conveying these concepts to key decision makers, leading to greater investments in nutrition-specific and nutrition-sensitive interventions, require future documentation.

Programs

The full range of interventions should be considered when designing programs to promote healthy growth. The most significant causal factors and thus the most leveraged potential interventions are likely to vary in different contexts. Effective programs will need to reach across disciplinary boundaries to draw on diverse expertise and promote collaborative problem-solving approaches. To date, agricultural and WSH programs have not typically sought to assess health, nutrition, or biological outcomes. This is understandable, given that most of these programs do not have explicit nutrition objectives; indeed, at present there are weak incentives in most cases for such programs to focus on nutrition and a weak evidence base for how to effectively do so. Further, the institutional structures of governments, nongovernmental organizations, and donors are rarely conducive to designing and executing

thoughtful, efficient, multi-sectoral programs. It will be important to include key nutrition indicators, such as linear growth, in these programs; the resulting data will shed light on the relative importance of these interventions for healthy growth. Ideally, nutrition-sensitive programs can be explicitly designed to measure nutrition outcomes and in some cases to maximize those nutrition outcomes alongside other program objectives.

Research priorities for healthy growth

Focusing attention on healthy growth has helped us to prioritize new areas of inquiry and in some cases has brought us back to issues that were once in vogue but for various reasons were abandoned by the research community. Many of the research priorities are "buckets" of issues rather than answerable questions, as discussed below.

Return to studying healthy growth from a lifecycle perspective, because maternal, fetal, and newborn outcomes are connected

To better understand the processes underlying early wasting and stunting, we need to return to studying growth from a lifecycle perspective, placing far greater emphasis on understanding how antenatal exposures affect fetal nutrient transfers and development, and the subsequent impact this has, particularly on linear growth and growth of associated tissues, muscle mass, and organs. Data suggest that stunting is apparent at birth (9). We need to know far more about why this occurs and how it can be effectively prevented. Of particular interest are a better understanding of maternal conditions that impair adequate placental formation, nutrient transfer, as well as the partitioning and utilization on nutrients between mother and infant. Research to develop multi-country fetal growth standards will help us define a healthy fetal growth phenotype and relate unhealthy fetal growth and development as well as environmental exposures to outcomes at birth and later in life (39). Understanding the interplay between maternal nutritional status, other disease exposures, and placental and fetal development may help us develop more effective antenatal and possible preconception interventions, for healthy growth as well as other conditions of pregnancy.

Understand why growth faltering begins so early in breast-fed infants living in the developing world

Other symposia papers highlight that wasting occurs very early in some populations (40,41). We need to better understand why this occurs. Is it due to suboptimal breastfeeding practices alone, or could it be that other exposures are influencing this, and what can we do about it? Analyses done for the Lancet Series (3) suggest that whereas exclusive breastfeeding saves many lives from infectious diseases, it paradoxically was not associated with improved linear growth. This is surprising, because breast milk is rich in many growth-promoting nutrients. Is the reason because the measures of breastfeeding practices are crude, relying on recall methods that do not capture true practices, or is it due to other conditions, such as an inherited infant gut environment, that are not optimal for producing and promoting healthy growth?

Apply new tools and technologies to the study of long-recognized problems

There are many investigative tools and technologies available today that would enable us to better understand the interplay between nutrition and infection and how these affect growth. These include, e.g., methods for measuring how the immune system works, performing cell analysis, and sequencing DNA. Researchers should be incentivized through competitive calls, such as the Gates Foundation's recent Grand Challenges Exploration call for proposals to Explore Nutrition for Healthy Growth of Infants and Children, to use these tools to explore new hypotheses and gain a better understanding of long-recognized yet understudied nutrition-infection interactions.

Explore new hypotheses and avenues for understanding how nutrients are assimilated and used

One example that has recently garnered considerable attention is the role of the gut microbiome in health and nutrition. There are trillions of microbes inhabiting our gut. Some provide for de novo vitamin biosynthesis and others permit energy harvest from otherwise indigestible foods. They also interact with and entrain our immune system, and their transplantation can actually confer metabolic changes in the new host, as recently demonstrated (16). Understanding how the gut microbiome interacts with and is influenced by early diet could lead to new interventions to promote healthy growth (42).

Understand the role of the environment in influencing healthy growth and the potential synergies from multi-sectoral interventions

The environment influences many aspects of human growth and development. The preceding example suggested that the gut microbial community may play a critical role in healthy growth. Gut health is also environmentally influenced and means for measuring and promoting gut health require further research. Growth faltering coincides with increasing indicators of gut permeability, presumably due to increasing levels of inflammation resulting from environmental exposures (17). The exposures may not be sufficient to produce observable diarrhea, yet they may be sufficient to divert nutrients away from growth processes to fighting inflammation, thus stopping growth while other business critical to survival was being tended to. Jean Humphrey (34) recently speculated that environmental enteropathy is perhaps a more important cause of stunting than inadequate diets. Her paper reminded us that observations on the role of inflammation go back many decades, yet our programmatic strategies and interventions have largely ignored these plausible pathways. It was surprising to learn from this paper that there have never been any definitive studies looking at the independent and combined effects of WSH

interventions with direct nutritional ones to assess and demonstrate possible synergies, and studies looking at the individual and combined effects of multi-sectoral interventions have been surprisingly absent from the literature over the last 20 y. These kinds of data are necessary to close the impact gap for nutrition.

Conclusion

The World Bank estimated in 2009 that it would require $12 billion/y to scale up the proven nutritional interventions in the 36 highest burden countries (43). One-half of this sum, or $6 billion, was for food to prevent and treat moderate and severe wasting and stunting. The Scaling Up Nutrition movement launched in September 2010 to generate country-level commitment to implement proven interventions is gaining traction, but we are still in economically hard times and the cost of food is creeping upwards daily. Given this situation, it is imperative that while we encourage support for Scaling Up Nutrition, we also rigorously engage in research to discover lower cost, more effective, and scalable solutions promote healthy growth.

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