Commentary: Please sir, I want some more (and something else)

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Stunting has gained unprecedented attention, largely because of the importance of the first 1000 days to lifelong well-being. We know that healthy physical growth is an essential component of normal development and that it does not simply happen. It is the result of awareness, adequate resources and (not or) clean environments, each sustained from conception onwards. Some argue that these conditions are also essential during the development of the progeny’s parents, and possibly even grandparents. Yet it is unlikely that either a lack of knowledge or growth constraints experienced by today’s parents during their own development account substantially for the ongoing persistence of stunting. Rather, it is the enduring discrepancies between what is known about human growth, societies’ aspirations for their children’s well-being and the resources dedicated to child health, that require attention and give heightened significance to the Bangladeshi study by Prof. Christian et al. reported in this issue.

The investigators set out to assess the effects on linear growth of fortified complementary food supplementation in children 6 to 18 months of age, living in rural Bangladesh and at high risk of food insecurity and undernutrition. They assessed the effectiveness of two ‘innovative and well-designed, locally developed and produced products and also an enhanced fortified blended food, in promoting linear growth and reducing stunting and wasting’. They also included a fourth group supplemented with a lipid-based product, Plumpy-doz. Food supplements provided 20–30% of estimated energy needs and met requirements for ‘most’ micronutrients, ‘especially in older children’ who received larger rations. Child feeding, health and hygiene advice was also provided to all caregivers in experimental and control

groups. The study was meticulously designed, executed and analysed. Stunting was significantly reduced: in relative terms, by approximately 10%; in absolute terms, stunting prevalence at 18 months was 44% in the control group and 40% in two of the four experimental groups. These improvements are well within the 3% annual absolute reduction targeted by the World Health Organization (WHO).

Associations between reductions in stunting and positive impacts on child mortality, coupled with the limited nature of the Bangladesh trial intervention and the consistency of its findings with those of past trials, should capture our attention.\textsuperscript{3,4} For example, it is important to reinforce the fact that US dietary reference values (one of various benchmarks used by the investigators) were designed to meet the needs of healthy populations, with healthy histories (for children, this includes healthy gestations) and morbidity levels associated with clean environments. The trial participants were enrolled from communities characterised by excessive levels of low birthweight, high levels of endemic morbidity, inadequate levels of exclusive breastfeeding and poor baseline diets. Yet, despite the participants’ precarious circumstances (fully acknowledged by the investigators), significant improvements in growth were achieved.

The authors describe the results as ‘modest’, even though the significant reduction in stunting was a substantial achievement in the face of the multiple challenges faced daily in the study population. The descriptor also risks inadvertently undermining our conviction in the essentiality of meeting nutritional needs for healthy growth and other developmental processes, not as a magic bullet, but as an essential component of the multiple constituents of awareness, resource adequacy, and clean environments, each indispensable for normal development. Hoping for greater reductions in stunting than were achieved is admirable, but the results of this and past similar trials, evaluations of other strategies for reducing stunting (e.g. prophylactic use of antibiotics) and reflections on what is known about human growth support the conclusion that both ‘more’ and ‘something else’ are required to meet the higher aspirations embedded in the use of the word ‘modest’ to describe the trial results.

Why both ‘more’ and ‘something else?’ The short answer is because of the complex nature of human growth. Growth is influenced heavily by genetics, but it is also responsive to a broad range of environmental influences. For example, a review of human growth concluded that, although hundreds of variants in approximately 180 loci have been associated with adult stature, only about 10% of observed variation in adult height is explained by them: much less than the 80% expected from more traditional heritability studies and the 40% estimated by Sir Francis Galton in his 19th-century studies of mid-parental height.\textsuperscript{5,6} Some have concluded that such gaps reflect inadequate consideration of gene-gene and gene-environment interactions.\textsuperscript{7}

These gaps are often referred to as examples of missing heritability and, along with the trial findings and results of past studies that also focused on reducing stunting by improving nutrient intakes, are collectively instructive. Stature, like many (if not all) other complex, quantitative genetic traits, is influenced by multiple factors, each apparently contributing relatively small effects, with any single factor seldom acting as a bottleneck that when resolved unleashes normalization.\textsuperscript{8,9} In the case of growth, some factors are of classical genetic origin; others likely reflect more expansive structural variants, non-coding RNA, epigenetics, differences in individual microbiomes and a host of environmental factors. Diet, infectious diseases, environmental toxins and childcare practices are among the environmental factors that have historically impacted on growth. Each is important in the sense of being biologically and statistically significant, particularly in settings such as those in which the Bangladesh trial was conducted.

Of these influences, diet is particularly relevant to this discussion. US and all other dietary reference values for children are based on estimates that assume continuous, steady growth. Yet normal growth occurs in a saltatory manner.\textsuperscript{10} Periodic growth spurts have been observed in highly controlled settings to be separated by 2 to 63 growth-free days in infants 3 days to 21 months of age, leaving ‘90 to 95 percent of infancy growth free’. Observed weekly amplitudes were 0.5 to 2.5 centimetres. The mean amplitude was 1 cm, more than twice the longer-term mean velocities reported by Christian et al.\textsuperscript{3}

Longitudinal studies that led to the current international growth standards documented the salutary nature of growth in free-living community settings.\textsuperscript{11} Periods of slow or no growth (observed normally or during illnesses such as infections) are ordinarily followed by periods of accelerated growth. In free-living healthy populations, growth velocities at the 5th and 95th centiles in healthy children 8 to 10 months of age vary by approximately 2-fold, and at 14 to 16 months of age by more than 3-fold. It is likely that greater variability is normal in intervals of less than 2 months and that higher levels of nutrients are needed to support salutary growth than are estimated on the basis of steady, continuous length gains. Furthermore, the salutary dynamic is potentially more intense when conditions of increased morbidity prevail and/or catch-up linear growth with proportional gains in healthy weight is desired to redress past, unresolved shortfalls. This reasoning supports the necessity for sufficient and consistent nutrient intakes in the overall diet to sustain adequate levels of circulating nutrients and nutrient stores necessary to
meet demands of accelerated growth periods and/or catch up in the face of growth-constraining conditions: needs above what are usually estimated. Successfully addressing dietary constraints on growth requires more than meeting recommended nutrient intakes. For example, exposure to foodborne toxins such as aflatoxins must also be minimized. Total diets must be safe and consistently sufficiently nutritious to meet inter- and intra-individual variation in baseline needs, day-to-day variations in food intake, inter-individual variations in the efficiency of nutrient utilization, the added demands of saltatory growth and—in this instance—high endemic morbidity.

With all of these demands, is normal growth or substantial catch-up in the first 2 years possible for children such as those included in the Bangladesh trial? Yes, early studies of undernourished children in metabolic ward settings with follow-up adoptions have demonstrated positive and substantial responsiveness to adequate nutrient intakes, safe baseline diets, clean environments and psychosocial stimulation. Importantly, however, if radical improvements in living conditions are unlikely, raising nutrient intakes to levels enjoyed by healthy children in clean environments makes an important, rather than a modest, difference. The Bangladesh trial documents the importance of improved nutrition, supports the utility and efficacy of locally produced fortified foods and underscores the need for both ‘more’ and ‘something else’.

Conflict of interest: I have no conflicts of interest to disclose.

References