

Environmental enteric dysfunction and child stunting

Sophie Budge, Alison H. Parker, Paul T. Hutchings, and Camila Garbutt

In 2017, an estimated 1 in every 4 (23%) children aged < 5 years were stunted worldwide. With slow progress in stunting reduction in many regions and the realization that a large proportion of stunting is not due to insufficient diet or diarrhea alone, it remains that other factors must explain continued growth faltering. Environmental enteric dysfunction (EED), a subclinical state of intestinal inflammation, can occur in infants across the developing world and is proposed as an immediate causal factor connecting poor sanitation and stunting. A result of chronic pathogen exposure, EED presents multiple causal pathways, and as such the scope and sensitivity of traditional water, sanitation, and hygiene (WASH) interventions have possibly been unsubstantial. Although the definite pathogenesis of EED and the mechanism by which stunting occurs are yet to be defined, this paper reviews the existing literature surrounding the proposed pathology and transmission of EED in infants and considerations for nutrition and WASH interventions to improve linear growth worldwide.

INTRODUCTION

Linear growth failure: a prevalent and complex condition

Linear growth failure, or stunting, is the most prevalent form of undernutrition worldwide. An estimated 155 million, or 23% of children aged < 5 years worldwide are stunted,¹ defined by the World Health Organization (WHO) as a height-for-age (HAZ) score < -2.² Although the global prevalence of stunting has more than halved from 47% in 1985,³ in some of the poorer regions of the world progress has been slow. In East Africa, where there is the second highest regional prevalence, 36.7% of children remain malnourished—representing 1 in every 3 stunted children worldwide.¹

Undernutrition in general is responsible for almost half of all child mortality⁴; stunting in particular bears

other substantial, long-term effects on both individuals and societies. The cumulative effects of the resulting impairments to cognitive and physical development and reduced productive capacity include lower levels of schooling, lower household per-capita expenditure, and decreased national economic output.^{5–7} A review describing the size of developmental loss from stunting estimated that over the course of a year, stunted individuals will earn an average of 22% less than their nonstunted counterparts⁸ (likely conservative), and a World Bank report estimating economic costs of stunting suggests a country's gross domestic product may be reduced as much as 3%.⁷

As such, stunting is both a major cause and effect in the cycle of poverty, particularly given that women who were stunted themselves or of low birth weight are more likely to have stunted children^{9,10}; both genetic and epigenetic research has demonstrated the

Affiliation: S. Budge, A. Parker, and P. Hutchings are with the Cranfield Water Science Institute, Cranfield University, Bedfordshire, United Kingdom. C. Garbutt is with People in Need, Prague, Czech Republic.

Correspondence: A. Parker, Cranfield School of Water, Energy and Environment, Cranfield University, Bedfordshire MK43 0AL, UK. E-mail a.parker@cranfield.ac.uk.

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phenomenon of transgenerational inheritance of environmental insults.¹¹ Child growth does demonstrate an element of plasticity (as seen through catch-up growth); however, it is likely that the adaptive degree of that plasticity in response to environmental cues is also at least partly determined by epigenetic mechanisms.^{11,12} This generational reproduction of stunting is a cycle that is difficult to break; however, key periods of growth from pregnancy through birth and childhood offer windows of opportunity for potential intervention.¹³ To act now is critical to improve outcomes for multiple future generations. This review aims to summarize those factors, in particular those related to water, sanitation, and hygiene (WASH) and gut health. Principally, it explores the role of environmental enteric dysfunction, household sanitation, and differing exposure pathways in infants as critical factors underlying poor growth and the importance of interventions aiming to improve growth in children worldwide.

The pathogenesis of stunting

Throughout development, periods of growth occur in 4 interrelated phases: fetal, infant, childhood, and pubertal. During these periods, actual spurts of growth are short, occurring during only 5% of a healthy infancy¹⁴; however, it is then when nutrient needs are highest, determining growth over the life-course. Maximal growth velocity is normally achieved between birth and 6 months,¹³ a period also critical for long-term cognitive development.¹⁵ From 6 to 24 months, linear growth is determined,¹⁶ so in most developing countries this is when stunting is most prevalent as high nutritional demand from growth meets a nutrient-poor environment.¹⁷ As such, inadequate nutrition from conception onward can cause irreparable damage through impaired physical and cognitive growth; this begins in utero from conception, the effect is sustained throughout pregnancy, and will continue to affect development for at least the first 2 years of life.^{13,18} The first thousand days has therefore been identified as a critical period in which to focus nutrition-specific and -sensitive interventions that aim to address both the immediate and underlying determinants of fetal and child nutrition and growth.^{18,19}

An individual's nutritional status during the first thousand days is dependent on a diverse range of interconnected factors, and, as such, determining the causes of stunting is complex. At the most basic level, stunting from undernutrition is the result of poor dietary intake and repeated infection,²⁰ but multiple underlying proximal and distal determinants mean establishing causality is difficult. Child undernutrition is caused not just by insufficient food quality and quantity but also by poor

care practices and lack of access to healthcare and social services. These determinants were first detailed in the United Nations Children's Fund's (UNICEF's) conceptual framework of child undernutrition > 2 decades ago²¹ and has since evolved to capture new knowledge and evidence.²² Also captured by the WHO Conceptual Framework on Childhood Stunting, other distal, structural socioeconomic and political factors such as political stability and urbanization also play a large role in stunting prevalence, having a long term influence on malnutrition.²⁰ Along with the most proximal causes, including the quality and quantity of food and an individual's digestive capacity and immunity,^{13,20,23} there lies a complicated network in which growth failure can occur. Such a multifaceted condition suggests that an adequate diet is necessary but not sufficient alone to ensure optimal child growth; indeed, the majority of interventions to improve breastfeeding, complementary feeding, or nutritional supplementation have yielded mostly small improvements in HAZ,^{17,24} with an estimated efficacy of +0.79 (z score),²⁵ far from the median deficits seen across sub-Saharan Africa of -2.0.¹⁶ The inability of interventions to combat stunting highlights the complexity of the condition, and it is becoming clearer that other etiological factors must be at play.

Relationship between stunting and water, sanitation, and hygiene

The failure of polarized interventions to reduce stunting may lie in the rationale that the 3 main underlying causes—namely poor quality and quantity of food, poor care practices, and infectious disease—are either directly or indirectly related to inadequate WASH infrastructure and facilities.^{18,19} The following sections aim to describe this relationship between linear growth failure and WASH and the reasons for the limited success of WASH interventions thus far to prevent stunting worldwide.

At the direct, biological level, 3 main pathways between poor WASH and stunting have been proposed: repeated diarrheal episodes, soil-transmitted infections (helminths), and environmental enteropathy.^{19,26}

The secondary, more indirect links between poor WASH conditions and nutritional status relate mainly to the broader socioeconomic environment—for example, access and affordability of WASH services, distance from household to a water point, education, and poverty. These parameters, although highly open to confounding and thus more difficult to ascertain, are no less substantial, affecting the possibility of a safe and clean living environment and reducing the available time an adult has to provide adequate childcare.²⁷ Moreover, poor access to water and sanitation impacts

child educational achievement, resulting in reduced working capital and worsened household food security—further perpetuating undernutrition, stunting, and the cycle of poverty.^{19,28} As such, poor WASH conditions are now more clearly recognized as contributing to child stunting and have increasingly become the focus of targeted interventions aimed at improving both global public health and child growth.

INTERVENING TO IMPROVE LINEAR GROWTH

Water, sanitation, and hygiene interventions

The 2013 Lancet Series identified a set of 10 nutrition-specific interventions that it proposed, if scaled-up from the existing population coverage to 90%, could save an estimated 900 000 deaths in the 34 countries housing 90% of the world's stunted children. Resultantly, stunting prevalence would be reduced by one-fifth worldwide.²⁹ Although this is important, nutrition-sensitive interventions (not analyzed in the report), including WASH, are possibly equally important for the reduction of undernutrition.^{27,29} Water, sanitation, and hygiene interventions include a number of different programs that could be grouped accordingly: water supply (improvements in water quantity and quality), sanitation (particularly safe disposal of feces), and hygiene promotion/education (including hand washing, and food, personal, and environmental hygiene).^{18,19} Of the small but growing evidence base that supports the effect of WASH intervention on stunting reduction, results are mixed: Bhutta et al²⁹ estimated that those at scale with 99% coverage would only reduce stunting prevalence by 2.5%. Some observational studies in different developing contexts have suggested a modest association with linear growth^{30–34}; a study in Peru found a positive association between improved water sources and HAZ, an effect that was greater when the intervention was combined with improved sanitation facilities.³¹ In India, a cross-sectional analysis of health surveys indicated that, with reported optimal handwashing practices, stunting risk decreased.³² Controlled trials had similar findings: a meta-analysis of 5 cluster-randomized controlled trials that assessed interventions in water and hygiene (but not sanitation) found a small but significant impact on HAZ ($P < 0.05$; mean difference, 0.08; 95% confidence interval [CI], 0.00–0.16).²⁷

Water, sanitation, and hygiene interventions to reduce diarrhea

Most commonly, WASH interventions aiming to address malnutrition have focused on reducing incidence of diarrhea because it is frequent in children who live in

conditions of poor sanitation, and incidence during the first thousand days has shown some association with poor linear growth.^{35–37} Indeed, symptomatic infection is common during the first years of life in low-income countries, where within the first thousand days infants suffer on average 6–8 episodes of acute diarrhea.³⁸ Observational studies have suggested that recurring diarrhea or infection are associated with increased risk of stunting.^{35,39,40} In a pooled analysis of 9 studies, the probability of stunting at 2 years increased by 2.5% per episode of diarrhea, and 25% of all stunting in 2-year-olds was attributable to having > 5 episodes of diarrhea in the first thousand days.³⁵ A more recent study found a small difference in height at 2 years in the children who had experienced a “typical” diarrhea burden in the same time period.³⁷ However, other research suggests that the incidence of diarrhea bears little significance on linear growth. This is because between diarrheal episodes, the speed of growth can be higher than the average for that age, meaning ultimately catch-up growth is still achieved.⁴¹ As such the relative contribution of diarrhea to stunting and, resultantly, the potential benefit of related WASH interventions are contentious. The Lancet Maternal and Child Undernutrition Series recently estimated that sanitation and hygiene interventions implemented with 99% coverage would reduce diarrhea incidence by 30%, which would in turn decrease the prevalence of stunting by only 2.4%.²⁵

Handwashing interventions, growing in evidence as a specific component of WASH, have shown similar results. A recent randomized controlled trial of handwashing in Karachi found a significant protective effect from diarrhea,⁴² but not from stunting⁴³; this was also observed in a study in Nepal: although improved handwashing with soap reduced child diarrheal morbidity by 41% ($P = 0.023$), there was no significant change in growth between intervention and control ($P = 0.76$).⁴⁴ This was also demonstrated in results from the recent WASH Benefits trial⁴⁵ (1 of 3^{45–47} trials currently studying the effects of WASH on linear growth), where handwashing showed the largest effect on diarrhea reduction (0.60; 95%CI, 0.45–0.80) but no significant impact on growth versus the control (Bangladesh $P = 0.169$; Kenya $P = 0.478$).^{48,49}

Estimating the overall impact of sanitation on diarrheal disease also shows mixed (and mostly modest) results. A systematic review that pooled estimates for the effect of handwashing on diarrheal diseases gave a risk reduction of 40% (risk ratio, 0.60; 95%CI, 0.53–0.68), reduced to 23% (risk ratio, 0.77; 95%CI, 0.32–1.86) after adjustment for unblinded studies.⁵⁰ A recent meta-analysis estimated that, overall, improved sanitation was associated with only a 12% reduction in diarrhea risk (odds ratio, 0.88; 95%CI, 0.83–0.92).⁵¹ WASH

Benefits Bangladesh indicated that, versus the control, groups receiving a WASH intervention (excluding water) did experience a reduction in reported diarrhea; however, the effect in the combined intervention groups (water, sanitation, handwashing, and nutrition) was no larger.⁴⁸ A recent analysis by the Water, Sanitation, and Hygiene Partnerships and Learning for Sustainability (WASHPaLS) task force concluded that WASH interventions aimed at reducing diarrhea show a mixed effect, with certain intervention categories, such as improved water supply and point-of-use water treatment, seemingly more effective.⁵² The report concluded that the effect of improved overall sanitation on diarrhea is unclear, and although handwashing shows substantial efficacy in some contexts, effects are inconsistent and vary highly across settings.⁵²

Diarrhea and stunting frequently coincide in an individual,^{35,38,40} and this certainly indicates a level of gut disturbance. However, the heterogeneity of results among interventions and the small impact of diarrhea reduction strategies suggest that diarrhea alone is not causing stunting, and there must be other contributory factors that have so far not been addressed.

Limits to the success of water, sanitation and hygiene interventions

Despite reductions in child mortality over the last few decades and some improvements to linear growth, growth faltering and impaired neurodevelopment still persist in low- and middle-income countries,^{1,3} and poor WASH conditions remain connected to a substantial proportion of morbidity and mortality in children aged < 5 worldwide.¹⁸ With such mixed results in a substantial body of research, it has been necessary to isolate other reasons for the continued prevalence of stunting, and, given the complicated nature of the issue, to consider the issue more broadly.

It is becoming clearer that WASH must be viewed more holistically, as “broadly encompassing the hygiene-related aspects of the physical and behavioural environment in which children are being raised.”³³ Thus the partial failure of WASH interventions to reduce stunting may lie in traditional design, which typically aims to reduce diarrhea by standard improvements in sanitation but may not consider other causative factors that sit within the wider etiological framework of stunting. Subsequently, this has meant taking into consideration the need for much more well-rounded intervention design. A recent experimental trial demonstrated that in a food-insecure region in Ethiopia, children gained +0.33 z score in mean HAZ over 5 years if they lived in a WASH intervention area, which allowed for a protected water supply, sanitation

education, soap use, handwashing practices, sanitary facility construction, domestic hygiene, separate housing of animals, and the maintenance of clean water.³⁴ The implication may lie in the completeness of the intervention, which also addressed the potential source of infection from animals. Water, sanitation, and hygiene programs may therefore need to broaden to consider the wider sanitary environment and the implication for child growth: specifically, the risk and significance of pathogen exposure in the domestic environment. The following sections address pathogen exposure as a primary causal factor in the pathway to stunting and implications for future WASH interventions that address sanitation within the home.

ENVIRONMENTAL ENTERIC DYSFUNCTION

The missing piece of the stunting puzzle

The manifestation of stunting is the indication of disturbances to the healthy development of multiple body systems. Of growing interest is the disturbance of the immune system, where it appears certain subclinical alterations mean stunting can occur even in the absence of obvious insults, such as diarrhea.^{53–56} One proposed cause for this is poor sanitary conditions, where chronic pathogen exposure leads to this subclinical shift in gut structure and function.^{23,57,58} The resulting condition has been termed *environmental* or *tropical enteropathy*, or more recently *environmental enteric dysfunction* (EED)⁵⁹—an apparently seasonal,⁶⁰ reversible⁶¹ disorder marked by gut mucosal cell villous atrophy, crypt hyperplasia, increased permeability, and inflammatory cell infiltrate.^{53,58,62} It is not clear that EED is present at birth,⁶³ but by infancy^{64–66} it can affect children across the developing world⁵⁴ and may be crucial to improve linear growth.

By way of process, it is proposed that chronic exposure to enteric pathogens drives T-cell-mediated hyperstimulation of the gut immune system, which remains in an inflammatory, hyperimmune state.⁵³ This, an otherwise appropriate reaction, leads to the aforementioned structural changes in the gut and increased intestinal inflammation and permeability, resulting in disrupted gut immune response; reduced delivery, absorption, and utilization of nutrients; and subsequently, nutritional deficiency.^{53,58,67} Nutritional deficiency in turn impairs the renewal of epithelial tissue and the maturation and proliferation of intestinal cells and pancreatic β cells^{23,67} and results in linear growth faltering.^{55,65,67–69} Concurrently, the low-grade inflammatory state associated with EED appears to inhibit

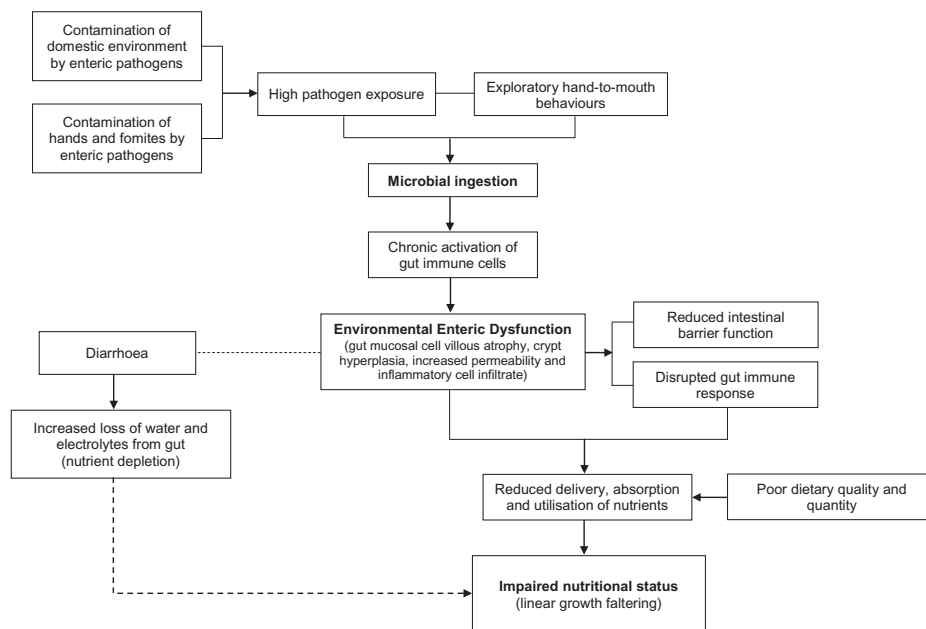


Figure 1 Proposed causal pathway linking environmental enteric dysfunction with linear growth faltering.

endochondral ossification, thereby inhibiting bone growth and directly affecting height.⁷⁰

Epidemiological studies suggest that continuous exposure to bacteria from feces is one principal cause of EED, but it is still unclear how enteric pathogens trigger the development of EED.⁷¹ One proposed mechanism is small intestine bacterial overgrowth; a subclinical disturbance in numbers of bacterial colonization in the upper gastrointestinal tract, small intestine bacterial overgrowth is observed in children in developing countries⁷² and is associated with growth faltering.^{73,74} Alternatively, it is suggested that chronic fecal exposure may cause qualitative changes in gut microbiota⁷¹; studies in Bangladesh and Malawi demonstrated that microbiota immaturity correlated with both malnutrition and stunting.^{75,76} Thus both quantitative and qualitative changes in gut function, which appear to commonly overlap, may contribute to EED.⁷¹

With an etiology in poor sanitation, nonsymptomatic, subclinical effects independent of those of diarrhea, and uncertainty over the causal effect of diarrhea on stunting,^{41–44,77} it is proposed that the primary causal mechanism between poor WASH and stunting is not diarrhea, but EED^{13,33,54} This is illustrated in Figure 1, which describes the proposed pathway linking EED to stunting. If this is the case, stunting prevention will require a multisector approach that not only considers improved WASH, food quality and quantity, and the reduction of acute illness but also addresses disruptions to immune function and gut stasis—that is, prevents the chronic gut inflammation

and malabsorption as seen in EED by improved household sanitation.^{71,78–80}

Enteric infection and linear growth

Stunted infants and young children with EED experience high rates of both symptomatic and asymptomatic enteric infection.^{55,65,67,81} However, although it is not clear how an overstimulated immunity affects pathogen ingestion, in EED, colonization and stunting appear to occur more often without any clinical effects⁸²—even when diarrhoea does not^{53–56}—or only in a small proportion of individuals. In Brazil for example, children with intestinal *E. coli* infection exhibited significant decline in height-for-age ($P < 0.001$), regardless of the presence or absence of diarrhoea.⁸³ Effects of the initial pathogenic infection may explain this. Gut permeability was observed in Bangladeshi children, among whom those from contaminated households had a dramatically higher incidence of stunting and parasitic infection and worsened gut function than those from clean households.⁸⁴ In studies that examined growth in Gambian children, dietary sufficiency and diarrhea were not associated with stunting, but measures of intestinal permeability explained 43% of linear growth.⁶⁶ Specific microbes may also be responsible for the outcome on growth: recent findings from the MAL-ED study⁸⁵ indicated that the sample-based lactulose/mannitol ratio z score tended to be higher (indicating increased permeability of the gut wall) in infants with pathogenic infection, particularly in those who tested for

Cryptosporidium (mean, 0.34) and *Giardia* (mean, 0.20).⁶⁹ As detected in nondiarrheal stool samples, *Giardia* was directly associated with reduced linear growth.⁶⁹ Infection from *Cryptosporidium*, isolated in animal feces, has also been associated with linear growth failure⁵⁶; this was seen in Peru and Brazil, also independent of diarrhea.^{83,86} On the other hand, wide heterogeneity across studies does mean the relationship among microbial infection, EED, and stunting is unclear,⁸⁷ and the exact mechanism by which intestinal permeability and inflammation affect growth is uncertain.⁸⁷ The associations among various aspects of EED and stunted growth appear highly variable, conflicting, and easily confounded⁸⁷ and, as such, far more complicated than much of the literature confidently suggests.

Enteric infection and nutritional status

It is suggested that stunting is a result of the gut disturbances from EED meeting limited dietary quality and quantity within the first thousand days, when nutritional needs are high.⁸⁸ Also, the effect of enteric infection and the associated subclinical disruptions seen in EED may limit responses to any dietary intervention.^{17,23,54} This may explain the partial failure of nutritional supplementation alone to improve linear growth, as described in Figure 1.^{17,54,89}

Improving nutritional intake and breastfeeding practices has understandably been expected to mitigate such associated outcomes, but although such interventions have largely helped to lower child mortality, they have not successfully prevented stunting, and effects seem mostly small.^{17,25,90,91} Even nutritional interventions that have specifically aimed to reduce EED (eg, with probiotics, antibiotics, or dietary supplements) appear to have little improved either EED or growth.⁹²

Certain breast milk constituents, including sialylated oligosaccharides, are shown to enhance gut barrier function and may improve nutrient uptake,⁹³ and it has been demonstrated that early feeding behaviors are associated with biomarkers of EED.⁹⁴ However, although breastfeeding is arguably one of the most effective hygiene interventions,¹⁸ impaired gut health has been observed in stunted infants still breastfeeding at 18 months of age,⁹⁵ and early growth assessments in Gambian infants indicated persistent abnormalities in gut mucosa—and later growth faltering—in infants who were continuously breastfed.⁶⁶ Furthermore, studies have indicated that the average infant harbors 2–4 enteric pathogens at any one time, even during exclusive breastfeeding postpartum.^{96,97} It seems likely that sustained breastfeeding and an improved diet may be able to lessen, but perhaps not overcome, the effects of enteric infection and EED on growth.⁴⁵

A recent retrospective cohort study assessed trends in growth of Gambian infants after 4 decades of intervention.⁸⁰ In a setting where the community has received access to primary and antenatal care, improved WASH facilities, and screening and treatment of undernutrition, stunting halved over the study period from 1976 to 2012, from 57% to 30%.⁸⁰ However, given the unacceptably high prevalence of stunting still remaining in the community,⁷⁹ it is apparent that the level of nutrition could not fully explain the burden. With noteworthy levels of structural gut disruption also noted within the same community,⁹⁸ it is suggested that the chronic inflammation characteristic of EED is likely a major contributory factor to the stall in progress to reduce stunting in this setting, where other potential risk factors were comprehensively addressed.⁷⁹

Increasing evidence of this kind suggests EED is a critical factor underlying poor growth, potentially bearing the greatest effect in the stunting pathway.^{13,65,99} A more focused intervention that specifically aims to reduce pathogen exposure and infection in infants during the first thousand days may more substantially improve linear growth—possibly even independent of dietary intervention.⁴⁵

PATHOGEN EXPOSURE IN INFANTS

In consideration of the broader environment

The fecal-oral route of transmission as described in the F Diagram (fluids, fingers, fields, flies, and food) was proposed some 60 years ago as an important map of causes of enteric infection.¹⁰⁰ An understanding of the principal fecal-oral transmission routes is critical because the rationale for intervening on stunting depends on the potential of each route to cause enteric-related disease and establish EED.^{18,53,57} Importantly, for babies and infants these primary transmission pathways differ, given that their principal food and fluid is breast milk, and exploratory behaviors, including crawling and the sucking and the mouthing of objects, create additional exposures to enteric pathogens.^{101,102} Thus the following sections address pathogen exposure as it pertains to babies, routes of exposure in the domestic environment, and what this might signify for future interventions aimed at reducing linear growth failure.

In developing settings, humans or animals that tread in feces or who openly defecate bring pathogens into the domestic vicinity of infants and babies,¹⁰³ and infants will often come into contact with feces and contaminated objects and soil while crawling and playing.^{33,102,104} The original F Diagram, although fundamental to WASH research and programming, was

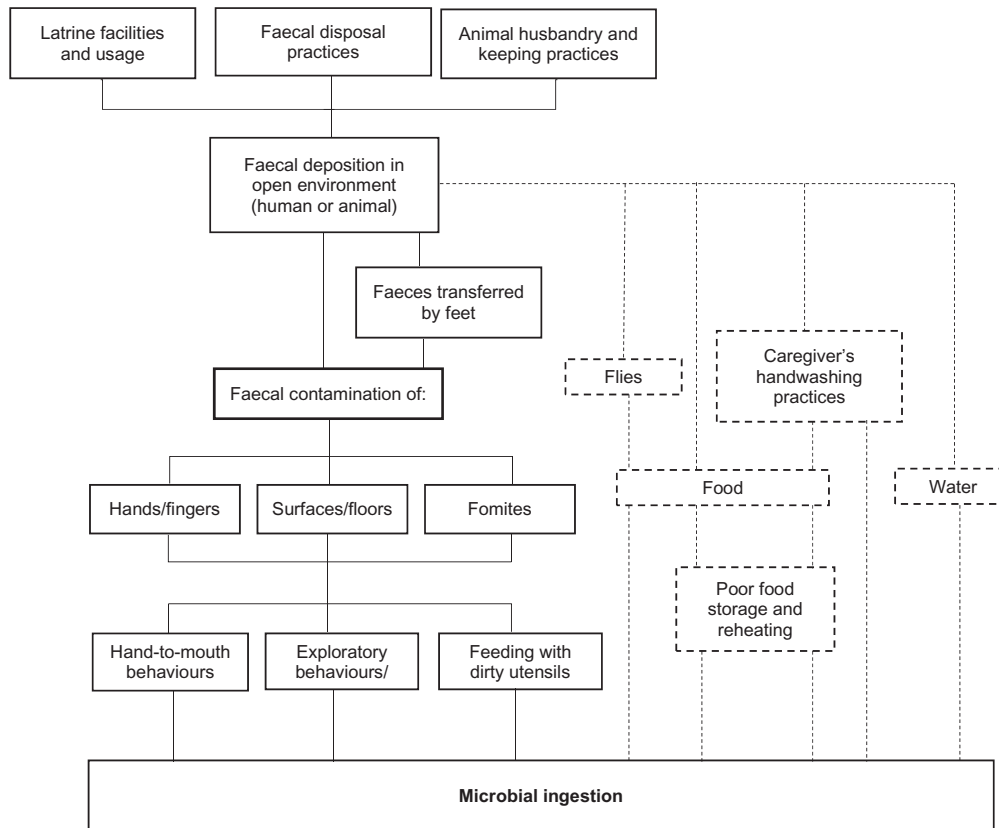


Figure 2 The common pathways by which infants are exposed to, and ingest pathogens in the domestic environment. The dashed lines integrate the traditional 'F diagram' which do not relate specifically to infant behaviours. Adapted alongside the 'F diagram', as published by Wagner, E and Lanoix, J, 1958.¹⁰⁰

developed to illustrate transmission routes from human excreta only and did not consider the contribution to contamination from animals inside and around the home. From both animal and human feces, potential pathways of exposure in infants to pathogens inside the home include unclean (ie, pathogen-contaminated) floors, caregiver and infant hands, food, and fomites. Figure 2¹⁰⁰ incorporates the F Diagram to illustrate the exposure pathways in the domestic environment through which infants are commonly and frequently exposed to and ingest these enteropathogens.

Routes of exposure to infants in the domestic environment

Faecal, and thus pathogenic, contamination of the domestic environment is common in the developing world, and thus infant ingestion of microbes appears widespread. Dirty, contaminated floors, where infants will typically sit to play and crawl, are common. In rural Zimbabwe, all soil samples collected within reach of a crawling infant were highly contaminated with *E. coli*, with counts 3- to 35-fold higher in soil than water.¹⁰² Kitchen floor swabs also tested positive for *E. coli* in

82% of sites tested.¹⁰² In a second study in Zimbabwe, pathogenic *Clostridium difficile* was isolated in 37% of soil and 6% of water samples.¹⁰⁵ A study of 20 peri-urban Tanzanian households detected *E. coli* in samples across the household, with highest concentrations found in soil from the house floor (83%)¹⁰⁶; both general (70%) and human-specific (18%) fecal *Bacteroidales* were detected in samples, as well as pathogenic *E. coli*, enterovirus, and rotavirus genes.¹⁰⁶

Another pathway, the contamination of fomites—items such as toys, bottles, and feeding and cooking utensils—is an important route of exposure in infants and serves as an indicator of faecal contamination at the household level. In Tanzania, Pickering et al¹⁰⁶ found high levels of *E. coli* and *Enterococci* on plastic plates and cups and on children's toys; of all surface samples that harbored an *E. coli* pathotype gene, 62% were cups and plates. In Huascar, a poor semi-urban community near Lima, 35% of sampled household objects, including infant bottle nipples, feeding bottles, spoons, and can openers, tested positive for *E. coli*.¹⁰⁷

A third pathway is contaminated hands, both those of caretaker and infant, which is intrinsically linked to the surrounding level of contamination. In an

forementioned study in Zimbabwe, mothers' and infants' hands were contaminated in 50% and 13% of households, respectively.¹⁰² As an exposure route in itself, hand contamination is difficult to determine in risk and origin because contamination is usually from animals and most studies do not specifically assess human-to-animal contact.¹⁰⁸ However, studies have found associations between increasing levels of direct contact with animals and/or animal fecal contamination and poor health outcomes.¹⁰⁸

Domestic contamination by animals, environmental enteric dysfunction, and linear growth

The issue of contamination from animals is important.¹⁰⁹ In developing countries domestic animals—usually livestock¹¹⁰—are often not contained or separated from the household environment,¹⁰⁸ and the close proximity of animals to infants increases the pathogen load, as well as the likelihood of microbial ingestion.¹¹¹ In rural Zimbabwean infants, ingestion of soil and chicken feces from the floor were identified as a key pathway for fecal-oral transmission of bacteria, and all feces samples tested positive for *E. coli*.¹⁰⁵ In a different setting in rural Zimbabwe, animals, mostly poultry, occupied the kitchens of one-third of households, and one-third had chicken feces on the kitchen floor.¹⁰² It seems inevitable that an unobserved playing infant, who by nature needs to explore the senses of taste and touch to learn, will eventually come into contact with pathogens; in the latter study, 3 infants ingested soil a mean of 11.3 times, and 2 infants ingested chicken feces twice over a 6-hour observational period.¹⁰² An observational study in a poor, peri-urban shanty town in Lima measured the frequency with which infants were exposed to chicken feces and found that feces was ingested on average 4 times during a 12-hour period.¹⁰⁹ Infants rarely had their hands washed after contact and often put their fingers in their mouths; as would be expected, feces-to-hand and feces-to-mouth episodes were highly correlated ($r = 0.94$).¹⁰⁹

Several pathogens isolated from animal feces in particular are related to acute gastrointestinal symptoms in children¹¹² and to which the 2015 Global Burden of Disease report associates approximately one-third of mortality in children aged < 5.¹¹³ With few studies that quantitatively address specific exposure pathways between animal feces and child health and specific health risks, the causal network is not well outlined.¹⁰⁸ However, cohabitation with animals has been associated with negative health outcomes,^{108,114} including stunting.^{114–117} In rural Bangladesh, children in households with animal pens in the sleeping area had significantly higher EED scores (from fecal markers) than those

without (1.0 point difference; 95% CI, 0.13–1.88; $P < 0.05$).¹¹⁶ Households with fewer toys contaminated with *E. coli* were in villages with > 50% toilet coverage, handwashing facilities with soap, no open defecation, safe disposal of child feces, and no animals present in the household.¹¹⁸ Among children in rural Malawi, animals sleeping in the same room was positively associated with EED,⁶⁸ and Ethiopian children in households where poultry were kept indoors overnight experienced reductions in growth.¹¹⁴ In the aforementioned study in Ethiopia that managed to improve growth,³⁴ the broad extensiveness of the WASH infrastructure may have been key to reduced fecal contamination and pathogen exposure, but the lack of animals in the household and safe feces disposal were possibly important. Similarly, in the aforementioned public sanitation program in Mali in which linear child growth increased (but without a reduction in diarrhea), intervention households were half as likely to have visible human feces within the domestic setting, and animal feces were also less likely to be present.¹¹⁹

These figures are not completely indicative of infection risk, and it is not always certain that the pathogen responsible is of animal origin. However, substantial data demonstrate that animal feces is a large contributor to levels of contamination in the home. Considering the common high contamination among the illustrated transmission pathways and the naturally high frequency of hand-to-mouth contact in infants, it is likely that animals are important sources of enteropathogens in the fecal-oral route of disease transmission, in the promotion of EED, and ultimately in linear growth failure.

Reducing pathogen contamination: a focus on animals

What might work best in terms of reducing pathogen exposure is unclear. Penakalapati et al¹⁰⁸ modified the traditional F Diagram to isolate specific primary barriers aimed at reducing exposure to animal feces. Of the 7 interventions they found to purposely address animal control, findings were mostly ineffective.¹⁰⁸ Some studies even suggested that enclosing animals may increase the burden of pathogens by way of increased pathogen concentration; in these studies, infants continued to enter and handle the animals (particularly poultry) and experienced higher rates of *Campylobacter*-related diarrhea than before animal separation.^{114,120,121} Other efforts, including providing metal scoops for feces removal resulted in a minimal difference in fecal contamination from baseline in rural Bangladesh.¹²² This was partly attributed to an inefficiency of the tool but also the observation that domestic animals form such an integral part of rural livelihoods that interventions might

have greater impact by preventing infant exposure through means other than removing feces alone.¹²² Similarly, another study that attempted to confine poultry was also unsuccessful, likely due to household preferences for free-range poultry and eggs and different cultural, structural, and economic barriers.¹²¹

Given the high prevalence of human and animal feces around the home in developing countries,^{102,108,114} the potential for high concentrations of even nonpathogenic bacteria in the gut to cause EED,¹²³ and the clear association among the presence of animal faeces, EED^{68,116} and lower HAZ scores,^{114–117} animal exposure and animal feces must be an important consideration in interventions that aim to reduce pathogen exposure. This is not often a feature of nutrition-sensitive WASH interventions, which have typically overtly focused on improving toilet facilities, water and water sources, and point-of-use water treatment.¹⁰² Furthermore there is little indication that interventions are routinely geared toward reducing exposure to animal feces.^{27,124} This is of particular importance in rural settings, where animals, which are often kept in and around the domestic area, may be overlooked during intervention design—and where, indeed, stunting rates are high, often surpassing those of urban areas.¹²⁵

Implications for future interventions

More evidence is needed on how chronic pathogen exposure over the first thousand days represents an important risk to Early Child Development (ECD), but it is likely that reducing stunting in the most resource-poor areas will require a solution that more substantially blocks exposure to infants. Although it might seem obvious that the risk of pathogen exposure should be a major consideration in intervention design, so far WASH programs and ECD interventions, such as the Essential Package from Save the Children and the Care for Child Development Package from UNICEF, have not specifically tackled the pathogen burden encountered by babies and infants in their home and play environments.

Specifically, possibly due in part to insufficiently comprehensive and collaborative design, existing WASH interventions have not sufficiently addressed the relevant exposure pathways, and thus not protected young infants and children from ingesting fecal pathogens and microorganisms at critical stages of growth.^{33,54,102} Hygienic fecal disposal and handwashing with soap after fecal contact are primary preventions of fecal-oral transmission because they prevent contamination of the domestic environment. However, there are different transmission routes that must be considered in WASH intervention design that

specifically pertain to infants—particularly contamination from animals of the household spaces in which young infants play and sleep, which appears to be more relevant during the first thousand days than contaminated drinking water.^{33,102,104} The evidence exists (and is mounting) for associations among *E. coli* counts in soil from infant play areas, rates of diarrhea, and elevated levels of biomarkers associated with EED.¹⁰¹ Other studies have found substantial levels of diarrheagenic *E. coli* on surfaces and objects that an infant regularly encounters as part of play, including toys and balls.^{101,106,126} These exposure routes represent critical, undisrupted pathways and an important gap for innovative, creative interventions and behavioral change programs.

A “BabyWASH” approach: thinking outside the box

Given that each transmission pathway is closely linked to infant play and exploration, one proposed solution is the creation of an infant and young child play space¹⁰⁴: a clean, safe environment in which babies and infants can freely play that avoids key fecal transmission routes.³³ A specific, designated play area also allows for stricter control of hygiene and sanitation; given that mothers and caregivers in developing settings encounter multiple demands of day-to-day living that limit the time and attention available to their children,^{33,127} they may, for example, miss the necessary instances for handwashing to reduce fecal contact. The provision of a sanitary space in which crawling infants can be left to explore offers the opportunity to interrupt primary transmission routes, while providing an environment that is safe, practical, and conducive to infant growth and development.¹⁰⁴ However, the possible efficacy of such a space is uncertain. WASHPaLS concluded in their report that the potential benefit of a play space depends on a more thorough understanding of the protective biological effect against risk, and that in areas of high contamination risk “extended periods of protection on a mat or within a play yard may not be sufficient to prevent risk posed by even short periods of time.”⁵² It has been argued that the significance of this lies in the importance of household level sanitation in predicting child health. Indeed, a recent study in Bangladesh comparing EED and stunting with household WASH status supports the view that this is more relevant to early growth than improvements in community sanitation.⁸⁴ However, WASHPaLS suggest that unless complete community sanitation coverage is reached (to achieve the desired “herd effect”), improved sanitation at the household level may be insufficient to mitigate pathogen exposure and improve infant health.

Thus a broader challenge here is the promotion of more hygienic living conditions for the entire population: something that may only occur through greater shifts in living arrangements and livelihood systems. This requires bigger, more high-level thinking and more holistic, creative solutions. In light of this, it is proposed that a play space in the form of a community area may be a more effective answer to the issue of microbial exposure and improved growth. As mentioned, in poor, rural environments where women experience substantial time poverty¹²⁸ which may well encroach on their ability to comprehensively care for their child,⁵² a communal space may ease some of this burden. Although it is possible that bacterial contamination would increase in a shared area, a single, common play space may be more easily kept clean. It may also more greatly facilitate, stimulate, and encourage learning, play, and thus cognitive development—a critical aspect of growth.^{33,104} Importantly, a common play space may also increase the potential to leverage community wide participation, thus achieve herd immunity and also community-level behavioral change. Although other trials^{46,48} have piloted a play space on a household level, it is possible that a community approach may show a different result, potentially more effective at preventing the risk (in terms of burden and duration) of exposure, in supporting healthy growth, and in encouraging social behavioural change.

DISCUSSION

Moving forward: clarifying the pathways linking environmental enteric dysfunction to poor growth

In their review, WASHPaLS note a clear finding that “[p]ractitioners and researchers have underestimated potentially key pathways of disease transmission in Wagner & Lanox’s 1958 ‘F-Diagram.’”⁵² It is arguable that the greater oversight is that of the importance of animal fecal contamination, the burden of which may be greater and more important in rural, poor areas where livestock and poultry husbandry are a mainstay. To improve child growth and reduce exposure to enteric pathogens it is thus necessary to focus on “field” transmission routes relevant to infants and young children¹⁸ and a disruption of several key risk pathways, as outlined in Figures 1 and 2. It is apparent from the body of research that the contribution of each exposure pathway to microbial ingestion and enteric infection may be highly context specific, so future studies must seek to further clarify which pathways represent the highest risk in different settings.

Alongside this, studies must try to further quantify the relative magnitude of exposure from each pathway

and, furthermore, how these effects vary by infant age and behavior and growth stages (that is, the change in risk as infant mobility changes). Results from WASH Benefits⁴⁵ indicated that HAZ scores at 2 years were higher in the combined water, sanitation, handwashing, and nutrition intervention versus control (mean difference in score, 0.16; 95%CI, 0.05–0.27).⁴⁹ The effect appeared significant ($P=0.004$) at 2 years after the intervention, when concurrently changing infant behaviors broaden routes of exposure. These findings highlight the importance of WASH components that are specific to the aging of an infant and also consider how exposure pathways and exposure risk change over time. Additional research is needed to understand the efficacy, uptake, constraints, and scale potential of different interventions to reduce pathogen exposure, including but not limited to clean play spaces, improved animal husbandry practices, and domestic sanitation⁵² (and indeed, more nonconventional approaches are certainly required). Research must explore the further benefits of these interventions when coupled with traditional WASH intervention measures, such as improved water supply and quality, improved toilets, and handwashing with soap, as well as the potential difference in effect between household- and community-level interventions.

Moving forward: challenges in the field

To progress this area of research, several key challenges must be addressed. The first is measuring very complex, multicausal change processes and then isolating the factors that are making a difference (if any). Establishing cause and effect appears to be one of the most pertinent issues in clarifying the EED-stunting pathway, particularly because the primary contributory cause of EED is not yet established (and it is unlikely there is just one). Thus there is currently no gold standard or established criteria for defining and measuring EED (although a histological examination via endoscopy and small intestinal biopsy may clarify), with the most widely accepted surrogate marker the lactulose/mannitol test, followed by serum and fecal biomarkers.⁵³ Thus the identification of a biomarker (or surrogate) or a range of biomarkers that are practical and affordable to collect and analyze in the field is necessary, not only to diagnose EED but also to establish prevalence and to quantify the effects of interventions of differing design and across varying settings.

The second challenge is actually delivering a baby-focused WASH intervention—if evidence accumulates that it is effective. The WASH sector in itself faces challenges in delivering interventions that are effective, sustainable, and supported and upheld by the national

political and bureaucratic environment.¹²⁹ Further complicating an already challenging area, the multifaceted nature of a baby-focused WASH intervention requires strong sector integration and holistic programming. The phenomenon of EED spans multiple discipline boundaries, so tackling it will require collaboration and research across diverse specialties, including WASH experts and nutritionists, public health professionals, gastroenterologists, pediatricians, and immunologists. Institutional and bureaucratic barriers may prevent partnerships and cooperation—for example, separate funding regimes, different governmental departments, and different working discourses. The Sustainable Development Goals (SDGs) both encourage and necessitate further cross-sector work and collaboration among different development institutions, and the BabyWASH coalition, a multi-stakeholder platform that was founded to address the issue of sectoral integration, will need to ensure it is practiced and maintained. Indeed, it will be necessary to define exactly what is required by sectoral integration in the field and across institutions and to strengthen and uphold that definition.

Last is the challenge of context. As is described, the relative contribution of risk factors attributed to stunting vary in estimate and prevalence—not only at global and national levels¹³⁰ but potentially down to the individual household level. Although eliminating a few key risk factors may largely reduce the burden of stunting worldwide,¹³⁰ changes in the diet, environment, and health are both quantitative and qualitative, so that, although broad themes appear to be standard, there may be substantial variation worldwide. Recent research into longitudinal determinants of stunting suggested that causative factors vary widely by the child's age and the community's main livelihood practice.¹³¹ Indeed, early commentary on healthcare delivery in developing settings has noted how large variations in landscape, culture, and communities necessitate “a patchwork” of different health facilities.¹³² Further public health research suggests interventions would be more effective if they were decentralized and adapted to specific population groups^{132,133}; as such, at the local level interventions may merit a more focused, tailored design.

Similarly, as with any research question, there exist differences between the clinical and empirical and the contextual and local understanding of both the issue and the solutions. As such, differences in the principal contributing factors to EED, the cultural significance of hygiene, fecal matter, and animal husbandry, and the possible interpretations of messaging will need to be considered at each stage of formation, intervention, and analysis, including at the hypothetical, measurement, and design stages, when building effective behavioral

change campaigns, and later during information dissemination, if interventions are to be both effective and sustainable.

CONCLUSION

Accumulating evidence continues to support the hypothesis that the subclinical changes and inflammation seen in EED may underlie linear growth failure. Although it is important not to ignore the critical role of adequate nutrition in optimal growth, the anabolic contribution of nutrition to linear growth appears severely compromised in the presence of EED-related inflammation,⁷⁰ a common experience in developing settings. Although difficult to explain quantitatively and highly open to issues of confounding, it is likely WASH conditions play an important role in optimal child growth, so WASH interventions that effectively disrupt pathogen exposure, particularly those that address the contribution of animals to domestic contamination, may be necessary for the reduction of stunting in developing countries. Success in some countries supports this,¹³⁴ and several WASH intervention trials currently underway^{45–47} are expected to add to the evidence and further clarify the effects of WASH both independently and together with complementary feeding on linear growth.

Although it seems unlikely that WASH interventions alone will eradicate the current prevalence of stunting, what does seem possible is that a design that is more holistically focused and baby-centric and that aligns WASH, ECD, and improved nutrition into a single intervention may contribute substantially to reducing the burden. Specifically, there is a need for a more considerate, more integrated intervention design that includes not just toilet provision and handwashing promotion but that also focuses on aspects that pertain specifically to infants. Integrating WASH interventions into the nutrition framework is then necessarily a key aspect; SDG 6, although broad in its framework, is not sufficiently comprehensive to consider all of these factors, including the surrounding sanitary and pathogenic environment in which the infant plays and lives (including animal husbandry and animal fecal contamination), caregiver hygiene and feeding practices, improved drinking water, WASH and nutrition education, and behavior change—as well as nutritional factors, such as continued breastfeeding and improved quality and quantity of the diet.^{18,33,54,94} If each of these factors bear equal importance for optimal child growth and development during the first thousand days, a baby-focused, more holistic approach to WASH interventions is certainly needed.^{18,19,104} This, by nature, will require strong coordination, collaboration, and

communication across the WASH and nutrition sectors, a task of some considerable (but not impossible) effort if the SDGs are to be achieved. Given the number, breadth, and ambition of the proposed SDGs to which child growth and development, and thus both nutrition and WASH interventions, relate,¹³⁵ it seems a decisive time for a multisector approach—and indeed a baby-focused approach—for more inspired, creative action to prevent growth failure worldwide.¹³⁶ Critical to this is the willingness and cooperation of policymakers, governments, and stakeholders to ensure interventions are timely, supported, and sustained.

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REFERENCES

- United Nations' Children's Fund, World Health Organization, World Bank. *Joint Child Malnutrition Estimates—Levels and Trends*. Geneva, Switzerland: World Health Organization, 2017. Available at: <http://www.who.int/nutgrowthdb/estimates2016/en/>. Accessed December 15, 2017.
- WHO Multicentre Growth Reference Study Group. *WHO Child Growth Standards: Length/Height-for-Age, Weight-for-Age, Weight-for-Length, Weight-for-Height and Body Mass Index-for-Age: Methods and Development*. Geneva, Switzerland: World Health Organization, 2006.
- Stevens G, Finucane M, Paciorek C, et al. Trends in mild, moderate, and severe stunting and underweight, and progress towards MDG 1 in 141 developing countries: a systematic analysis of population representative data. *Lancet*. 2012;380:824–834.
- United Nations' Children's Fund. *Malnutrition: current status and progress*. 2017. Available at: <https://data.unicef.org/topic/nutrition/malnutrition/#>. Accessed December 15, 2017.
- Black R, Victora C, Walker S, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet*. 2013;382:427–451.
- Martorell R, Horta B, Adair L, et al. Weight gain in the first two years of life is an important predictor of schooling outcomes in pooled analyses from five birth cohorts from low- and middle-income countries. *J Nutr*. 2010;140:348–354.
- World Bank. *Repositioning nutrition as to development: a strategy for large-scale action*. Vol 13. Washington, DC: World Bank, 2006.
- Grantham-McGregor S, Cheung Y, Cueto S, et al. Developmental potential in the first 5 years for children in developing countries. *Lancet*. 2007;369:60–70.
- Martorell R, Zongrone A. Intergenerational influences on child growth and undernutrition. *Paediatr Perinat Epidemiol*. 2012;26:302–314.
- Ramakrishnan U, Martorell R, Schroeder DG, et al. Role of intergenerational effects on linear growth. *J Nutr*. 1999;129:544S–549S.
- Hochberg Z, Feil R, Constancia M, et al. Child health, developmental plasticity, and epigenetic programming. *Endocr Rev*. 2011;32:159–224.
- Burdge GC, Lillycrop KA. Nutrition, epigenetics, and developmental plasticity: implications for understanding human disease. *Annu Rev Nutr*. 2010;30:315–339.
- Prendergast A, Humphrey J. The stunting syndrome in developing countries. *Paediatr Int Child Health*. 2014;34:250–265.
- Lamp I, Veldhuis J, Johnson M. Saltation and stasis: a model of human growth. *Science*. 1992;258:801–803.
- Pongcharoen T, Ramakrishnan U, Digirolamo A, et al. Influence of prenatal and postnatal growth on intellectual functioning in school-aged children. *Arch Pediatr Adolesc Med*. 2012;166:411–416.
- Victora C, de Onis M, Hallal P, et al. Worldwide timing of growth faltering: revisiting implications for interventions. *Pediatrics*. 2010;125:e473–e480.
- Dewey K, Adu-Afarwah S. Systematic review of the efficacy and effectiveness of complementary feeding interventions in developing countries. *Matern Child Nutr*. 2008;4:24–85.
- Action Against Hunger, United Nations' Children's Fund. *WASH/Nutrition: A Practical Guidebook on Increasing Nutritional Impact through Integration of WASH and Nutrition Programs*. Paris: Action Against Hunger, 2017.
- Action Against Hunger. *BabyWASH and the 1,000 Days*. 2017. Available at: <https://www.actionagainsthunger.org/publication/2017/10/babywash-and-1000-days>. Accessed December 12, 2018.
- Blössner M, de Onis M. *Malnutrition: Quantifying the Health Impact at National and Local Levels*. Geneva, Switzerland: World Health Organization; 2005.
- United Nations' Children's Fund. *Strategy for Improved Nutrition of Children and Women in Developing Countries*. Vol 8. New York: UNICEF, 1990.
- United Nations' Children's Fund. *UNICEF's Approach to Scaling up Nutrition for Mothers and Children*. New York: UNICEF, 2015. Available at: https://www.unicef.org/nutrition/files/Unicef_Nutrition_Strategy.pdf. Accessed June 22, 2018.
- Ahmed T, Auble D, Berkley J, et al. An evolving perspective about the origins of childhood undernutrition and nutritional interventions that includes the gut microbiome. *Ann NY Acad Sci*. 2014;1332:22–38.
- Piper J, Chandna J, Allen E, et al. Water, sanitation and hygiene (WASH) interventions: effects on child development in low- and middle-income countries. *Cochrane Database Syst Rev*. 2017;2017:1–40.
- Bhutta Z, Ahmed T, Black R, et al. What works? Interventions for maternal and child undernutrition and survival. *Lancet*. 2008;371:417–440.
- Action Against Hunger. *Water, Sanitation and Hygiene Policy*. 2011. Available at: <https://www.actionagainsthunger.org/publication/2011/06/water-sanitation-and-hygiene-policy>. Accessed December 12, 2018.
- Dangour A, Watson L, Cumming O, et al. Interventions to improve water quality and supply, sanitation and hygiene practices, and their effects on the nutritional status of children. *Cochrane Database Syst Rev*. 2013;8:1–101.
- Matare C, Mbuya M, Pelto G, et al. Assessing maternal capabilities in the SHINE Trial: highlighting a hidden link in the causal pathway to child health. *Clin Infect Dis*. 2015;61:574S–575S.
- Bhutta Z, Das J, Rizvi A, et al. Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? *Lancet*. 2013;382:452–477.
- Merchant A, Jones C, Kiure A, et al. Water and sanitation associated with improved child growth. *Eur J Clin Nutr*. 2003;57:1562–1568.
- Checkley W, Gilman R, Black R, et al. Effect of water and sanitation on childhood health in a poor Peruvian peri-urban community. *Lancet*. 2004;363:112–118.
- Rah J, Cronin A, Badgaiyan B, et al. Household sanitation and personal hygiene practices are associated with child stunting in rural India: a cross-sectional analysis of surveys. *BMJ Open*. 2015;5:e005180–e005180.
- Ngure F, Reid B, Humphrey J, et al. Water, sanitation, and hygiene (WASH), environmental enteropathy, nutrition, and early child development: making the links. *Ann N Y Acad Sci*. 2014;1308:118–128.
- Fenn B, Bulti A, Nduna T, et al. An evaluation of an operations research project to reduce childhood stunting in a food-insecure area in Ethiopia. *Public Health Nutr*. 2012;15:1746–1754.
- Checkley W, Buckley G, Gilman R, et al. Multi-country analysis of the effects of diarrhoea on childhood stunting. *Int J Epidemiol*. 2008;37:816–830.
- Black R, Brown K, Becker S. Effects of diarrhoea associated with specific enteropathogens on the growth of children in rural Bangladesh. *Pediatrics*. 1984;73:799–805.
- Richard S, Black R, Gilman R, et al. Diarrhea in early childhood: short-term association with weight and long-term association with length. *Am J Epidemiol*. 2013;178:1129–1138.
- Fischer Walker C, Perin J, Aryee M, et al. Diarrhea incidence in low- and middle-income countries in 1990 and 2010: a systematic review. *BMC Public Health*. 2012;12:220.
- Black R, Allen L, Bhutta Z, et al. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet*. 2008;371:243–260.
- Guerrant R, Schorling J, McAuliffe J, et al. Diarrhea as a cause and an effect of malnutrition: diarrhea prevents catch-up growth and malnutrition increases diarrhea frequency and duration. *Am J Trop Med Hyg*. 1992;47:28–35.

41. Briend A. Is diarrhoea a major cause of malnutrition among the under-fives in developing countries? A review of available evidence. *Eur J Clin Nutr.* 1990;44: 611–628.
42. Luby S, Agboatwalla M, Painter J, et al. Combining drinking water treatment and hand washing for diarrhoea prevention, a cluster randomised controlled trial. *Trop Med Int Heal.* 2006;11:479–489.
43. Bowen A, Agboatwalla M, Luby S, et al. Association between intensive hand-washing promotion and child development in Karachi, Pakistan: a cluster randomized controlled trial. *Arch Pediatr Adolesc Med.* 2012;166:1037–1044.
44. Langford R, Lunn P, Panter-Brick C. Hand-washing, subclinical infections, and growth: a longitudinal evaluation of an intervention in Nepali slums. *Am J Hum Biol.* 2011;23:621–629.
45. Arnold B, Null C, Luby S, et al. Cluster-randomised controlled trials of individual and combined water, sanitation, hygiene and nutritional interventions in rural Bangladesh and Kenya: the WASH Benefits study design and rationale. *BMJ Open.* 2013;3:1–17.
46. Humphrey J, Jones A, Manges A, et al. The sanitation hygiene infant nutrition efficacy (SHINE) trial: rationale, design, and methods. *Clin Infect Dis.* 2015;61: S685–S702.
47. Brown J, Cumming O, Bartram J, et al. A controlled, before-and-after trial of an urban sanitation intervention to reduce enteric infections in children: research protocol for the Maputo Sanitation (MapSan) study, Mozambique. *BMJ Open.* 2015;5:1–11.
48. Null C, Stewart CP, Pickering AJ, et al. Effects of water quality, sanitation, hand-washing, and nutritional interventions on diarrhoea and child growth in rural Kenya: a cluster-randomised controlled trial. *Lancet Glob Health.* 2018;6: e302–e315.
49. Luby S, Rahman M, Arnold B, et al. Effect of water quality, sanitation, handwashing and nutritional interventions on diarrhoea and child linear growth in rural Bangladesh: a cluster randomized trial. *Lancet Glob Health.* 2018;6:Pe302–e315.
50. Freeman M, Stocks M, Cumming O, et al. Systematic review: hygiene and health: systematic review of handwashing practices worldwide and update of health effects. *Trop Med Int Health.* 2014;19:906–916.
51. Freeman M, Garn J, Sclar G, et al. The impact of sanitation on infectious disease and nutritional status: a systematic review and meta-analysis. *Int J Hyg Environ Health.* 2017;220:928–949.
52. USAID. *Toward a Hygienic Environment for Infants and Young Children: A Review of the Literature.* Washington, DC: USAID Water, Sanitation, and Hygiene Partnerships and Sustainability (WASHPaLS) Project, 2018.
53. Korpe P, Petri W. Environmental enteropathy: critical implications of a poorly understood condition. *Trends Mol Med.* 2012;18:328–336.
54. Humphrey J. Child undernutrition, tropical enteropathy, toilets, and handwashing. *Lancet.* 2009;374:1032–1035.
55. Mondal D, Minak J, Alam M, et al. Contribution of enteric infection, altered intestinal barrier function, and maternal malnutrition to infant malnutrition in Bangladesh. *Clin Infect Dis.* 2012;54:185–192.
56. Kotloff K, Nataro J, Blackwelder W, et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. *Lancet.* 2013;382: 209–222.
57. Schenk E, Samloff I, Klipstein F. Morphology of small bowel biopsies. *Am J Clin Nutr.* 1968;21:944–961.
58. Ramakrishna B, Venkataraman S, Mukhopadhyaya A. Tropical malabsorption. *Postgrad Med J.* 2006;82:779–787.
59. Kusch G, Rosenberg I, Denno D, et al. Implications of acquired environmental enteric dysfunction for growth and stunting in infants and children living in low- and middle-income countries. *Food Nutr Bull.* 2013;34:357–364.
60. Kelly P, Menzies I, Crane R, et al. Responses of small intestinal architecture and function over time to environmental factors in a tropical population. *Am J Trop Med Hyg.* 2004;70:412–419.
61. Lindenbaum J, Harmon J, Gerson C. Subclinical malabsorption in developing countries. *Am J Clin Nutr.* 1972;25:1056–1061.
62. Veitch A, Kelly P, Zulu I, et al. Tropical enteropathy: a T-cell-mediated crypt hyperplastic enteropathy. *Eur J Gastroenterol Hepatol.* 2001;13:1175–1181.
63. Baker S. Subclinical intestinal malabsorption in developing countries. *Bull World Health Organ.* 1976;54:485–494.
64. Campbell D, McPhail G, Lunn P, et al. Intestinal inflammation measured by fecal neopterin in Gambian children with enteropathy: association with growth failure, *Giardia lamblia*, and intestinal permeability. *J Pediatr Gastroenterol Nutr.* 2004;39:153–157.
65. Campbell D, Elia M, Lunn P. Growth faltering in rural Gambian infants is associated with impaired small intestinal barrier function, leading to endotoxemia and systemic inflammation. *J Nutr.* 2003;133:1332–1338.
66. Lunn P, Northrop-Clewes C, Downes R. Intestinal permeability, mucosal injury, and growth faltering in Gambian infants. *Lancet.* 1991;338:907–910.
67. Owino V, Ahmed T, Freeman M, et al. Environmental enteric dysfunction and growth failure/stunting in global child health. *Pediatrics.* 2016;138: e20160641–e20160641.
68. Ordiz M, Shaikh N, Trehan I, et al. Environmental enteric dysfunction is associated with poor linear growth and can be identified by host fecal mRNAs. *J Pediatr Gastroenterol Nutr.* 2016;63:453–459.
69. Kosek M, et al. Causal pathways from enteropathogens to environmental enteropathy: findings from the MAL-ED birth cohort study. *EBio Med.* 2017;18: 109–117.
70. Millward D. Nutrition, infection and stunting: the roles of deficiencies of individual nutrients and foods, and of inflammation, as determinants of reduced linear growth of children. *Nutr Res Rev.* 2017;30:50–72.
71. Watanabe K, Petri W. Environmental enteropathy: elusive but significant subclinical abnormalities in developing countries. *EBio Med.* 2016;10:25–32.
72. Donowitz J, Petri W. Pediatric small intestine bacterial overgrowth in low-income countries. *Trends Molec Med.* 2015;21:6–15.
73. Donowitz J, Haque R, Kirkpatrick B, et al. Small intestine bacterial overgrowth and environmental enteropathy in Bangladeshi children. *MBio.* 2016;7:1–7.
74. Khin-Maung U, Bolin T, Duncombe V, et al. Epidemiology of small bowel bacterial overgrowth and rice carbohydrate malabsorption in Burmese (Myanmar) village children. *Am J Trop Med Hyg.* 1992;47:298–304.
75. Subramanian S, Huq S, Yatsunenko T, et al. Persistent gut microbiota immaturity in malnourished Bangladeshi children. *Nature.* 2014;510:417–421.
76. Blanton L, Charbonneau M, Salih T, et al. Gut bacteria that prevent growth impairments transmitted by microbiota from malnourished children. *Science.* 2016;351:6275.
77. Ejemot-Nwadiaro R, Ehiri J, Meremikwu M, et al. Hand washing for preventing diarrhoea. *Evid-Based Child Health.* 2009;4:893–939.
78. Cumming O, Cairncross S. Can water, sanitation and hygiene help eliminate stunting? Current evidence and policy implications. *Mater Child Nutr.* 2016;12(suppl 1):91–105.
79. Crane R, Berkley J. Progress on growth faltering. *Lancet Glob Health.* 2017;5: e125–e126.
80. Nabwera H, Fulford A, Moore S, et al. Growth faltering in rural Gambian children after four decades of interventions: a retrospective cohort study. *Lancet Glob Heal.* 2017;5:e208–e216.
81. Kosek M, Haque R, Lima A, et al. Fecal markers of intestinal inflammation and permeability associated with the subsequent acquisition of linear growth deficits in infants. *Am J Trop Med Hyg.* 2013;88:390–396.
82. Levine M, Robins-Browne R. Factors that explain excretion of enteric pathogens by persons without diarrhea. *Clin Infect Dis.* 2012;55:S303–S311.
83. Steiner T, Lima A, Nataro J, et al. Enterocoaggregative *Escherichia coli* produce intestinal inflammation and growth impairment and cause interleukin-8 release from intestinal epithelial cells. *J Infect Dis.* 1998;177:88–96.
84. Lin A, Arnold B, Afreen S, et al. Household environmental conditions are associated with enteropathy and impaired growth in rural Bangladesh. *Am J Trop Med Hyg.* 2013;89:130–137.
85. Miller M, Acosta A, Chavez C, et al. The MAL-ED study: a multinational and multidisciplinary approach to understand the relationship between enteric pathogens, malnutrition, gut physiology, physical growth, cognitive development, and immune responses in infants and children up to 2 years of age. *Clin Infect Dis.* 2014;59:S193–S206.
86. Guerrant D, Moore S, Lima A, et al. Association of early childhood diarrhea and cryptosporidiosis with impaired physical fitness and cognitive function four-seven years later in a poor urban community in northeast Brazil. *Am J Trop Med Hyg.* 1999;61:707–713.
87. Harper KM, Mutasa M, Prendergast AJ, et al. Environmental enteric dysfunction pathways and child stunting: a systematic review. *PLoS Neglected Trop Dis.* 2018;12:e0006205.
88. World Health Organization. *Global Nutrition Targets 2025: Stunting Policy Brief: What's at Stake.* Geneva, Switzerland: WHO, 2014.
89. McKay S, Gaudier E, Campbell D, et al. Environmental enteropathy: new targets for nutritional interventions. *Int Health.* 2010;2:172–180.
90. Alemayehu M, Tinsae F, Hailelassie K, et al. Undernutrition status and associated factors in under-5 children, in Tigray, Northern Ethiopia. *Nutrition.* 2015;31: 964–970.
91. Fekadu Y, Mesfin A, Haile D, et al. Factors associated with nutritional status of infants and young children in Somali Region, Ethiopia: a cross-sectional study. *BMC Public Health.* 2015;15:846.
92. Crane RJR, Jones KDJ, Berkley JA. Environmental enteric dysfunction: an overview. *Food Nutr Bull.* 2015;36:S76–S87.
93. Charbonneau M, O'Donnell D, Blanton L, et al. Sialylated milk oligosaccharides promote microbiota-dependent growth in models of infant undernutrition. *Cell.* 2016;164:859–871.
94. Smith E, Manji K, McDonald C, et al. Early breastfeeding initiation, pre-lacteal feeding, and infant feeding are associated with biomarkers of environmental enteric dysfunction. *FASEB J.* 2017;31:959.13
95. Campbell R, Schulze K, Shaikh S, et al. Biomarkers of environmental enteric dysfunction among children in rural Bangladesh. *J Pediatr Gastroenterol Nutr.* 2017;65:40–46.

96. Taniuchi M, Sobuz S, Begum S, et al. Etiology of diarrhea in Bangladeshi infants in the first year of life analyzed using molecular methods. *J Infect Dis*. 2013;208:1794–1802.
97. Gilmartin A, Petri WJ. Exploring the role of environmental enteropathy in malnutrition, infant development and oral vaccine response. *Philos Transac R Soc London Ser B Biol Sci*. 2015;370:pii:20140143.
98. Van Der Merwe L, Moore S, Fulford A, et al. Long-chain PUFA supplementation in rural African infants: a randomized controlled trial of effects on gut integrity, growth, and cognitive development. *Am J Clin Nutr*. 2013;97:45–57.
99. Prendergast A, Kelly P. Review: enteropathies in the developing world: neglected effects on global health. *Am J Trop Med Hyg*. 2012;86:756–763.
100. Wagner E, Lanoix J. *Excreta Disposal for Rural Areas and Small Communities*. Vol 39. Geneva, Switzerland: World Health Organization, 1958.
101. Morita T, Perin J, Oldja L, et al. Mouthing of soil contaminated objects is associated with environmental enteropathy in young children. *Trop Med Int Health*. 2017;22:670–678.
102. Ngure F, Humphrey J, Mbuya M, et al. Formative research on hygiene behaviors and geophagy among infants and young children and implications of exposure to fecal bacteria. *Am J Trop Med Hyg*. 2013;89:709–716.
103. Curtis V, Cairncross S, Yonli R. Review: domestic hygiene and diarrhoea—pinpointing the problem. *Trop Med Int Health*. 2000;5:22–32.
104. Mbuya M, Tavengwa N, Stoltzfus R, et al. Design of an intervention to minimize ingestion of fecal microbes by young children in rural Zimbabwe. *Clin Infect Dis*. 2015;61(suppl. 7):S703–S709.
105. Simango C. Prevalence of *Clostridium difficile* in the environment in a rural community in Zimbabwe. *Trans R Soc Trop Med Hyg*. 2006;100:1146–1150.
106. Pickering A, Julian T, Marks S, et al. Fecal contamination and diarrheal pathogens on surfaces and in soils among Tanzanian households with and without improved sanitation. *Environ Sci Technol*. 2012;46:5736–5743.
107. Black R, Lopez De Roma G, Brown K, et al. Incidence and etiology of infantile diarrhea and major routes of transmission in Huascar, Peru. *Am J Epidemiol*. 1989;129:785–799.
108. Penakalapati G, Swarouth J, Delahoy M, et al. Exposure to animal feces and human health: a systematic review and proposed research priorities. *Environ Sci Technol*. 2017;51:11537–11552.
109. Spears D, Ghosh A, Cumming O. Open defecation and childhood stunting in India: an ecological analysis of new data from 112 districts. *PLoS One*. 2013;8:e73784
110. Dufour A, Bartram J, Gannon V. *Animal Waste, Water Quality and Human Health*. Geneva, Switzerland: WHO, 2012.
111. Berrilli F, D'Alfonso R, Giangaspero A, et al. *Giardia duodenalis* genotypes and *Cryptosporidium* species in humans and domestic animals in Côte d'Ivoire: occurrence and evidence for environmental contamination. *Transac R Soc Trop Med Hyg*. 2012;106:191–195.
112. Zambrano L, Levy K, Menezes N, et al. Human diarrhea infections associated with domestic animal husbandry: a systematic review and meta-analysis. *Trans R Soc Trop Med Hyg*. 2014;108:313–325.
113. Wang H, Naghavi M, Allen C, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388:1459–1544.
114. Headey D, Hirvonen K. Is exposure to poultry harmful to child nutrition? An observational analysis for rural Ethiopia. *PLoS One*. 2016;11:1–16.
115. Bukuya G, Nwoko N. Compound hygiene, presence of standpipe and the risk of childhood diarrhoea in an urban settlement of Papua New Guinea. *Int J Epidemiol*. 1991;20:534–539.
116. George C, Oldja L, Biswas S, et al. Fecal markers of environmental enteropathy are associated with animal exposure and caregiver hygiene in Bangladesh. *Am J Trop Med Hyg*. 2015;93:269–275.
117. George C, Oldja L, Biswas S, et al. Geophagy is associated with environmental enteropathy and stunting in children in rural Bangladesh. *Am J Trop Med Hyg*. 2015;92:1117–1124.
118. Torondel B, Gyekye-Aboagye Y, Routray P, et al. Laboratory development and field testing of sentinel toys to assess environmental faecal exposure of young children in rural India. *Trans R Soc Trop Med Hyg*. 2015;109:386–392.
119. Pickering A, Djebbari H, Lopez C, et al. Effect of a community-led sanitation intervention on child diarrhoea and child growth in rural Mali: a cluster-randomised controlled trial. *Lancet Glob Heal*. 2015;3:e701–e711.
120. Oberhelman R, Gilman R, Sheen P, et al. An intervention-control study of corralling of free-ranging chickens to control *Campylobacter* infections among children in a Peruvian periurban shantytown. *Am J Trop Med Hyg*. 2006;74:1054–1059.
121. Harvey S, Winch P, Leontsini E, et al. Domestic poultry-raising practices in a Peruvian shantytown: implications for control of *Campylobacter jejuni*-associated diarrhea. *Acta Trop*. 2003;86:41–54.
122. Ashraf S, Hussain F, Leontsini E, et al. Continued environmental fecal contamination following implementation of sanitation hardware. *Health Sci Bull*. 2013;11:9–14.
123. Mbuya M, Humphrey J. Preventing environmental enteric dysfunction through improved water, sanitation and hygiene: an opportunity for stunting reduction in developing countries. *Mater Child Nutr*. 2016;12:106–120.
124. USAID. Save the Children. Water, Hygiene and Sanitation (WASH) in Rural Households in Amhara, Oromia, SNNP and Tigray: A Report on the Findings and Recommendations of a Multi-Method Qualitative Research Study for Social and Behavior Change Communication Programming in Ethiopia. Washington, DC: USAID, 2014.
125. Ruel M. *The Natural History of Growth Failure: Importance of Intrauterine and Postnatal Periods*. In R. Martorell and F. Haschke, eds. *Nutrition and Growth*. Nestle Nutrition Workshop Series Pediatric Program. Vol.47. Philadelphia, PA: Lippincott Williams & Wilkins, 2001: 123–158.
126. Vujcic J, Ram P, Hussain F, et al. Toys and toilets: cross-sectional study using children's toys to evaluate environmental faecal contamination in rural Bangladeshi households with different sanitation facilities and practices. *Trop Med Int Health*. 2014;19:528–536.
127. Hampshire K, Casiday R, Kilpatrick K, et al. The social context of childcare practices and child malnutrition in Niger's recent food crisis. *Disasters*. 2009;33:132–151.
128. Kes A, Swaminathan H. *Gender and Time Poverty in Sub-Saharan Africa*. Washington DC: World Bank, 2006.
129. Bartram J, Cairncross S. Hygiene, sanitation, and water: forgotten foundations of health. *PLoS Med*. 2010;7:e1000367.
130. Danaei G, Andrews K, Sudfeld C, et al. Risk factors for childhood stunting in 137 developing countries: a comparative risk assessment analysis at global, regional, and country levels. *PLoS Med*. 2016;13:1–18.
131. Woodruff B, Wirth J, Bailes A, et al. Determinants of stunting reduction in Ethiopia 2000–2011. *Matern Child Nutr*. 2017;13:e12307.
132. Mansfield D, Morris A. "All for health and health for all": a study of basic health care in Peru. *Br Med J (Clin Res Ed)*. 1981;282:1684–1686.
133. Chaparro M, Estrada L. Mapping the nutrition transition in Peru: evidence for decentralized nutrition policies. *Rev Panam Salud Publica*. 2012;32:241–244.
134. De Onis M, Blössner M, Borghi E. Prevalence and trends of stunting among pre-school children, 1990–2020. *Public Health Nutr*. 2012;15:142–148.
135. United Nations. *Open Working Group Proposal for Sustainable Development Goals*. Geneva, Switzerland: United Nations, 2014.
136. World Health Organization, United Nations' Children's Fund, USAID. *Improving Nutrition Outcomes with Better Water, Sanitation and Hygiene: Practical Solutions for Policies and Programmes*. Geneva, Switzerland: WHO, 2015.