Child undernutrition, tropical enteropathy, toilets, and handwashing

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Of the 555 million preschool children in developing countries, 32% are stunted and 20% are underweight.[1] Child underweight or stunting causes about 20% of all mortality of children younger than 5 years of age and leads to long-term cognitive deficits, poorer performance in school and fewer years of completed schooling, and lower adult economic productivity.[2] Child underweight state or stunting mainly develops during the first 2 years of life, when mean weight-for-age and length-for-age *Z* scores of children in Africa and Asia drop to about –2·0, with little or no recovery thereafter.[3]

Under the plausible assumption that children grow poorly because they do not eat enough of the right foods, research efforts have focused on identifying dietary solutions. Numerous studies have tested many nutrient-dense foods and supplements, nutrition education interventions, and infant feeding behavioural-change strategies. A recent review[4] of 38 of these studies showed that children receiving one of these dietary interventions gained up to 760 g more weight (0·0–0·76 weight-for-age *Z* score) and grew up to 1·7 cm taller (0·0–0·64 length-for-age *Z* score) than control children by 12 to 24 months. However, none of these interventions achieved normal growth: the growth effect of even the most successful of these studies (~ +0·7 *Z*) is equivalent to about a third of the average deficit of Asian and African children (~ –2·0 *Z*).

Diarrhoea has also been implicated as a cause of poor growth. In a pooled analysis of nine studies with diarrhoea and growth data for 1393 children,[5] the probability of stunting at 24 months of age increased by 2·5% per episode of diarrhoea, and 25% of all stunting in 24-month-old children was attributable to having five or more episodes of diarrhoea in the first 2 years of life. However, other authors have contended that the effect of diarrhoea on permanent stunting is small because growth velocity can be faster than average for age between illness episodes resulting in catch-up growth.[6] Hence, the relative contribution of diarrhoea to undernutrition and, consequently, the potential effect that diarrhoea control programmes (ie, sanitation and hygiene interventions) could have on growth are still unresolved. The *Lancet* Maternal and Child Undernutrition Series estimated that sanitation and hygiene interventions implemented with 99% coverage would reduce diarrhoea incidence by 30%, which would in turn decrease the prevalence of stunting by only 2·4%.[7]

This report suggests: that a key cause of child undernutrition is a subclinical disorder of the small intestine known as tropical enteropathy, which is characterised by villous atrophy, crypt hyperplasia, increased permeability, inflammatory cell infiltrate, and modest malabsorption;[8] that tropical enteropathy is caused by faecal bacteria ingested in large quantities by young children living in conditions of poor sanitation and hygiene; that provision of toilets and promotion of handwashing after faecal contact could reduce or prevent tropical enteropathy and its adverse effects on growth; and that the primary causal pathway from poor sanitation and hygiene to undernutrition is tropical enteropathy and not diarrhoea.

If this is true, the *Lancet* Maternal and Child Undernutrition Series[7] might have substantially underestimated the contribution of sanitation and hygiene to growth because the effect was modelled entirely through diarrhoea. Importantly, because of mortality, and cognitive and economic consequences of child undernutrition, sanitation and hygiene interventions might have been undervalued because they have been mainly appraised for their effect on diarrhoea. Confirmation of these hypotheses might provide evidence to accelerate provision of toilets to the 2·6 billion people (40% of the world's population) who currently lack them, hasten progress towards the Millennium Development Goal to halve this number by 2015, and ultimately yield improvements in child growth, health, and survival.

Several studies done mostly in the 1960s in Asia, Africa, and Central America showed that almost all apparently healthy adults and children in developing countries worldwide had morphological changes or functional signs of tropical enteropathy.[8] Although the cause of tropical enteropathy has not been clearly elucidated, most of these investigators suggested that tropical enteropathy results from exposure to poor environmental sanitation. Further evidence for an environmental cause comes from studies of asymptomatic American soldiers in Vietnam and Peace Corps volunteers in Pakistan who got tropical enteropathy after a few months of residence in these settings and recovered soon after returning to the USA.[8]

Similar to other inflammatory bowel diseases, tropical enteropathy results from unrestrained enteric T-cell activation.[9] However, unlike diseases caused by abnormal hyper-reactivity to a normal exposure (eg, in coeliac disease, enteric T cells are phenotypically hyper-reactive to gluten[10]), tropical enteropathy probably develops when normal T cells are hyperstimulated by abnormally high concentrations of ingested faecal bacteria in the small-intestinal lumen.[11]

Over the past 20 years, investigators at the MRC Dunn Nutritional Laboratory (Cambridge, UK, and Keneba, The Gambia) have studied growth in Gambian children. Dietary inadequacy and diarrhoea were not associated

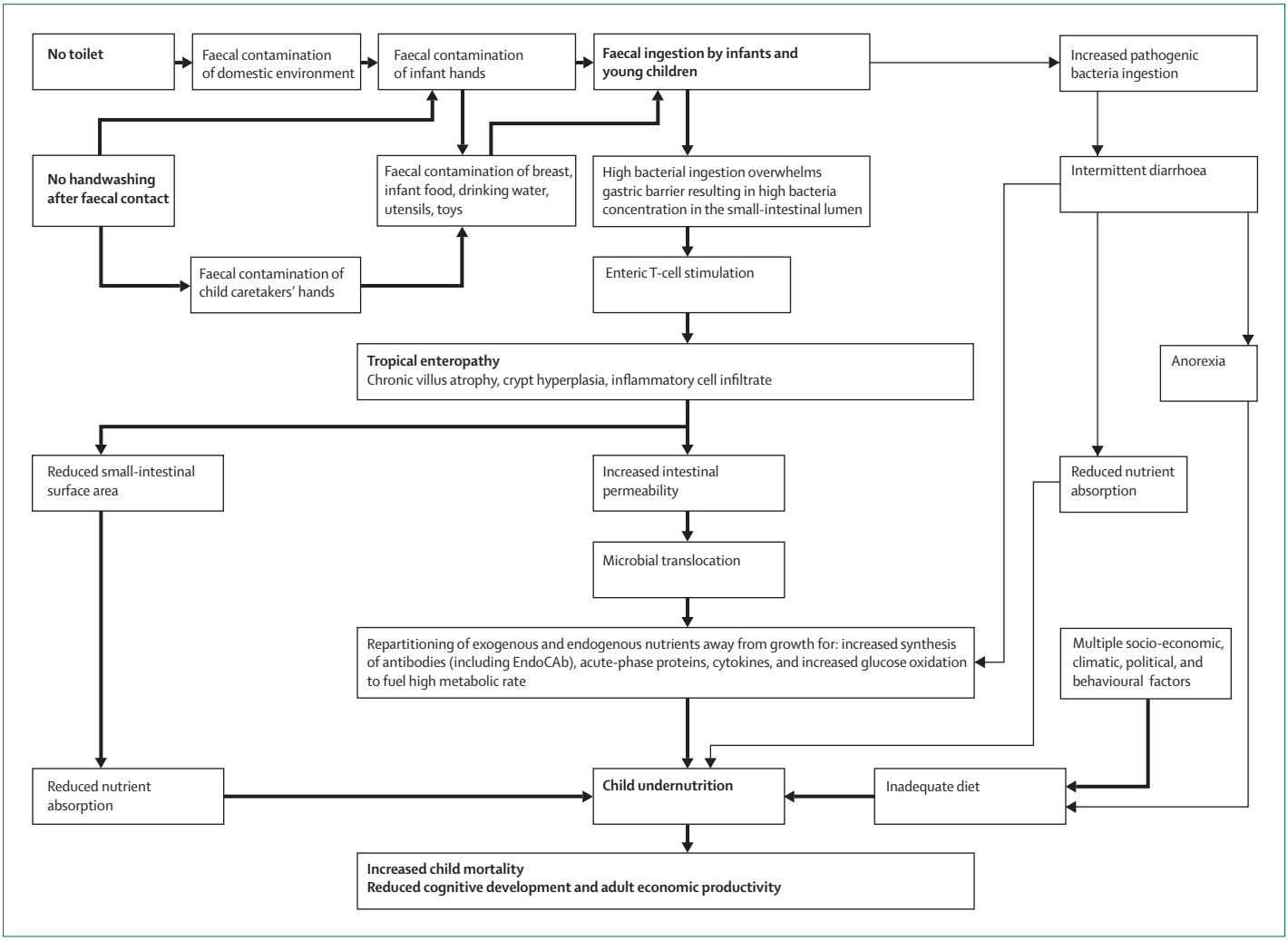

Figure: **Model of the mechanisms from poor sanitation and hygiene to tropical enteropathy, child undernutrition, and child development and survival**
Thick lines indicate primary pathways and thin lines secondary pathways, as hypothesised in this report.

with growth failure, but the lactulose to mannitol urinary excretion ratio—an indicator of intestinal permeability—explained 39% of ponderal and 43% of linear growth.[12] Moreover, gut hyperpermeability was a chronic condition: these children had diarrhoea on 7·3% of days between birth and 2 years of life, but had lactulose to mannitol urinary excretion ratios associated with growth suppression on 76% of days during this period.

In a subsequent study,[13] the same investigators also measured plasma concentrations of total IgG and IgG–endotoxin-core antibody (EndoCAb). Endotoxin is a component of gram-negative bacterial cell walls probably derived from faecal contamination. A permeable gut allows endotoxin translocation into the body, where it stimulates an immune response that stimulates production of EndoCAb. At 2 months of age, the weight-for-age *Z* score, height-for-age *Z* score, lactulose to mannitol ratio, and plasma IgG and EndoCAb concentrations were similar to those in normal infants in the UK. However, by 15 months of age, mean height-for-age *Z* score fell from –0·6 to –1·8, mean weight-for-age *Z* score fell from –0·4 to –2·4, the lactulose to mannitol ratio almost tripled (in normal infants in the UK, this ratio declined during this period), and mean IgG and EndoCAb concentrations were 2-fold and 5-fold higher than normal, respectively. The lactulose to mannitol ratio and IgG and EndoCAb concentrations were correlated with each other and all were negatively correlated with linear and ponderal growth. Using semipartial regression analysis methods, the combined effects of IgG and EndoCAb concentrations explained 51% of linear growth, which increased to 56% when the lactulose to mannitol ratio was also included.

Solomons and colleagues tell a similar story from animal husbandry.[14] In controlled studies, chicks raised amidst faeces, dust, and dander but fed antibiotics grew better than chicks living in similar conditions but not fed antibiotics, and grew as well as chicks raised in

steam-cleaned cages for whom antibiotics had no growth effect.[15] The poor growth of dirty chicks not fed antibiotics was accompanied by high plasma concentrations of interleukin 1, a major mediator of the immune response, which was not observed in dirty chicks fed antibiotics or in clean chicks. On this basis, antibiotics (termed growth permitters in this context) have been used for decades on poultry farms to maximise meat yield. Therefore, when confronted by incessant microbial challenge, both the Gambian infants and chicks studied entered a near-continuous state of growth-suppressing immune response: dietary nutrients were repartitioned away from anabolism in favour of glucose oxidation and synthesis of acute-phase proteins and other immune mediators.[14]

The figure shows a model of these pathways. Children living in poor sanitary conditions ingest high concentrations of faecal bacteria, which colonise the small intestine and induce tropical enteropathy through a T-cell-mediated process. The hyperpermeable gut facilitates translocation of microbes, which trigger the metabolic changes of the immune response. Growth falters when these changes coincide with reduced nutrient absorption by atrophied villi, marginal dietary intake, and the high growth demands of the first 2 years of life.

How can children be protected from faeces? Safe disposal of stools (ie, toilets) and handwashing with soap after faecal contact are the primary barriers to faecal-oral transmission because they prevent faeces from entering the domestic environment. Many randomised trials of handwashing[16] have shown substantial reductions in diarrhoea, although none included the effect of these interventions on tropical enteropathy or child growth. Surprisingly, there are no published randomised trials of toilet provision on child growth or even diarrhoea. Almost all existing evidence that sanitation benefits human health comes from cross-sectional, prospective cohort, case-control, and non-randomised intervention studies. Thus, all have methodological issues, including potential confounding by socioeconomic status, lack of adequate control in before–after programme assessments, and inadequate statistical power when a single control community is compared with a single intervention community.[17] Nonetheless, many of these studies have documented benefits on child growth.[18] Indeed, in an analysis of demographic and health survey data from eight countries, Esrey[19] estimated that improvements in sanitation were associated with length-for-age *Z* score increments of 0·06–0·62 in children living in rural areas and 0·26–0·65 in children living in urban areas, which are similar to the growth effects of dietary interventions reviewed earlier in this report[4] (ie, 0·00–0·64). Moreover, from a mean length-for-age *Z* score (SD) of –1·69 (1·45) in rural children and –1·19 (1·45) in urban children, these increments correspond to 4–37% and 20–46% decreases in stunting prevalence in rural and urban children, respectively, suggesting a considerably greater effect than the 2·4% decrease previously estimated in the *Lancet* Series.[7]

Undoubtedly, the complex problem of child undernutrition will not be solved with toilets and handwashing alone. Interventions focused on gut microbial populations[20] and improved drinking water quality[21] might be important, together with continued efforts to improve infant diets. However, I hypothesise that prevention of tropical enteropathy, which afflicts almost all children in the developing world, will be crucial to normalise child growth, and that this will not be possible without provision of toilets. Randomised controlled trials of toilet provision and handwashing promotion that include tropical enteropathy and child growth as outcomes will give valuable evidence for this premise, and might offer a solution to the intractable problem of child undernutrition.

Conflicts of interest

I declare that I have no conflicts of interest.

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References

1 Black RE, Allen LH, Bhutta ZA, et al. Maternal and undernutrition: global and regional exposures and health consequences. *Lancet* 2008; **371:** 243–60.

2 Victora CG, Adair L, Fall C, et al. Maternal and child undernutrition 2: Maternal and child undernutrition: consequences for adult health and human capital. *Lancet* 2008; **371:** 340–57.

3 Shrimpton R, Victora CG, De Onis M, Lima RC, Blossner M, Clugston G. Worldwide timing of growth faltering: implications for nutritional interventions. *Pediatrics* 2001; **107:** 1–7.

4 Dewey KG, Adu-Afarwuah S. Systematic review of the efficacy and effectiveness of complementary feeding interventions in developing countries. In: Maternal and Child Nutrition. Blackwell Publishing Ltd: Program in International and Community Nutrition, University of California, Davis, CA, USA, 2008; pp 24–85.

5 Checkley W, Buckley G, Gilman RH, et al, The Childhood Malnutrition and Infection Network. Multi-country analysis of the effects of diarrhoea on childhood stunting. *Int J Epidemiol* 2008; **37:** 816–30.

6 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:** 611–28.

7 Bhutta ZA, Ahmed T, Black RE, et al. Maternal and child undernutrition 3: What works? Interventions for maternal and child undernutrition and survival. *Lancet* 2008; **371:** 417–40.

8 Haghighi P, Wolf PL. Tropical sprue and subclinical enteropathy: a vision for the nineties. *Crit Rev Clin Lab Sci* 1997; **34:** 313–41.

9 Veitch AM, Kelly P, Zulu IS, Segal I, Farthing MJG. Tropical enteropathy: a T-cell-mediated crypt hyperplastic enteropathy. *Eur J Gastroenterol Hepatol* 2001; **13:** 1175–81.

10 Halstensen TS, Brandtzaeg P. Activated T lymphcytes in the celiac lesion: non-proliferative activation (CD25) of CD+ a/b cells in the lamina propria but proliferation (Ki-67) of a/b and g_d cells in the epithelium. *Eur J Immunol* 1993; **23:** 505–10.

11 Fagundes Neto U, Martins MC, Lima FL, Patricio FR, Toledo MR. Asymptomatic environmental enteropathy among slum-dwelling infants. *J Am Coll Nutr* 1994; **13:** 51–56.

12 Lunn PG, Northrop-Clewes CA, Downes RM. Intestinal permeability, mucosal injury, and growth faltering in Gambian infants. *Lancet* 1991; **338:** 907–10.

13 Campbell DI, Elia M, Lunn PG. Growth faltering in rural Gambian infants is associated with impaired small intestinal barrier function, leading to endotoxemia and systemic inflammation. *J Nutr* 2003; **133:** 1332–38.

14 Solomons NW, Mazariegos M, Brown KH, Klasing K. The underprivileged, developing country child:environmental contamination and growth failure revisited. *Nutr Rev* 1993; **51:** 327–32.

15 Roura E, Homedes J, Klasing KC. Prevention of immunologic stress contributes to the growth-permitting ability of dietary antibiotics in chicks. *J Nutr* 1992; **122:** 2383–90.

16 Curtis V, Cairncross S. Effect of washing hands with soap on diarrhoea risk in the community: a systematic review. *Lancet Infect Dis* 2003; **3:** 275–81.

17 Blum B, Feachem RG. Measuring the impact of water supply and sanitation investments on diarrhoeal diseases: problems of methodology. *Int J Epidemiol* 1983; **12:** 357–65.

18 Checkley W, Gilman RH, Black RE, et al. Effect of water and sanitation on childhood health in a poor Peruvian peri-urban community. *Lancet* 2004; **363:** 112–18.

19 Esrey SA. Water, waste, and well-being: a multicountry study. *Am J Epidemiol* 1996; **143:** 608–23.

20 Palmer C, Bik EM, DiGiulio DB, Relman DA, Brown PO. Development of the human infant intestinal microbiota. *PLoS Med* 2007; **5:** e177.

21 Clasen T, Schmidt W-P, Rabie T, Roberts I, Cairncross S. Interventions to improve water quality for preventing diarrhoea: systematic review and meta-analysis. *BMJ* 2007; **334:** 782.