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Childhood malnutrition: Toward an understanding of infections, inflammation, and antimicrobials

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Abstract

Background—Undernutrition in childhood is estimated to cause 3.1 million child deaths annually through a potentiating effect on common infectious diseases, such as pneumonia and diarrhea. In turn, overt and subclinical infections, and inflammation, especially in the gut, alter nutrient intake, absorption, secretion, diversion, catabolism, and expenditure.

Objective—A narrative overview of the current understanding of infections, inflammation, and antimicrobials in relation to childhood malnutrition.

Methods—Searches for pivotal papers were conducted using PUBMED 1966–January 2013; hand searches of the references of retrieved literature; discussions with experts; and personal experience from the field.

Results—Although the epidemiological evidence for increased susceptibility to life-threatening infections associated with malnutrition is strong, we are only just beginning to understand some of the mechanisms involved. Nutritional status and growth are strongly influenced by environmental enteric dysfunction (EED), which is common among children in developing countries, and by alterations in the gut microbiome. As yet, there are no proven interventions against EED. Antibiotics have long been used as growth promoters in animals. Trials of antibiotics have shown striking efficacy on mortality and on growth in children with uncomplicated severe acute malnutrition (SAM) or HIV infection. Antibiotics act directly by preventing infections and may act indirectly by reducing subclinical infections and inflammation. We describe an ongoing

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Authors' contributions

All authors contributed to discussion and development of the ideas contained in this manuscript. James A. Berkley wrote the first draft, which was reviewed and edited by all of the other authors.

Conflicts of interest

The authors declare no conflicts of interest.

multicenter, randomized, placebo-controlled trial of daily cotrimoxazole prophylaxis to prevent death in children recovering from complicated SAM. Secondary outcomes include growth, frequency and etiology of infections, immune activation and function, the gut microbiome, and antimicrobial resistance. The trial is expected to be reported in mid-2014.

Conclusions—As well as improving nutritional intake, new case management strategies need to address infection, inflammation, and microbiota and assess health outcomes rather than only anthropometry.

Keywords

Antibiotics; infection; immunity; microbiome; nutrition

Introduction

Undernutrition in childhood, including fetal growth restriction, stunting, wasting, deficiencies of vitamin A and zinc, and suboptimal breastfeeding, has recently been estimated to cause 3.1 million child deaths annually, representing 45% of all childhood mortality [1]. Most of these deaths are from infections, such as pneumonia and diarrhea. Overt infections that are not fatal and subclinical infections alter nutrient intake, absorption, secretion, diversion, catabolism, and expenditure and thereby affect growth. Environmental enteric dysfunction (EED) is also emerging as a widespread and important cause of chronic inflammation in the developing world that contributes to this cycle. We aimed to give an overview of the current understanding of infections, inflammation, and antimicrobials in relation to childhood malnutrition.

Methods

Searches for pivotal papers were conducted using PUBMED 1966–January 2013; hand searches of the references of retrieved literature; discussions with experts; and personal experience from the field.

Results

Epidemiology of infection in relation to malnutrition

The increased childhood mortality associated with undernutrition is almost entirely due to the elevated risk of death from common infectious diseases such as pneumonia, diarrhea, and bacterial sepsis. Pooled global data show that the increased susceptibility occurs across the nutritional status spectrum. Among young children in community settings, a mild degree of acute malnutrition is associated with slightly increased risks, while moderate acute malnutrition (MAM) and severe acute malnutrition (SAM) are associated with correspondingly greater risks [2, 3]. Although SAM is associated with the greatest risk of death, worldwide it is relatively uncommon. Moderate wasting and stunting are far more common and are responsible for the greatest proportion of childhood mortality attributable to undernutrition. This was elegantly shown in an analysis of data from Senegal by Garenne and colleagues in 2006 [4].

A vicious cycle between malnutrition and infection has been long recognized (fig. 1A). Episodes of infection potentiate undernutrition via anorexia, reduced nutrient absorption, nutrient losses (such as vitamin A and proteins in diarrhea), diversion of nutrients to inflammatory responses, and tissue repair. Diarrhea is associated with malabsorption and marked losses of protein, vitamin A, zinc, and other micronutrients. All infections are associated with net protein loss with diversion of amino acids to acute phase and immune response proteins. Activation of inflammatory cascades also causes reduced appetite and loss of lean tissue and fat. Thus, episodes of infection, especially diarrhea, result in both linear and ponderal growth-faltering.

Catch-up growth may be seen between infectious episodes, provided adequate nutritional intake is maintained and the interval between infections is long enough [5, 6]. Specific pathogens may cause more persistent growth-faltering because they result in chronic infections, chronic inflammation, or gut mucosal damage; these include HIV, tuberculosis, cryptosporidiosis, and giardiasis.

Mechanisms of susceptibility to infection

Although the epidemiological evidence for increased susceptibility to infection associated with malnutrition and for growth-faltering during and following infections is strong, our understanding of the cellular and molecular immunologic mechanisms, and of potentially differential impacts of acute versus chronic undernutrition, is limited at present. For example, one of the most frequently described immunologic abnormalities in acute malnutrition is impaired cell-mediated immunity, as evidenced by reduced response to skin test with tuberculin or candida antigens. Although this has conventionally been ascribed to “T-cell anergy” (partly because of limited *in vitro* evidence of impaired T-cell mitogen response), an important recent study showed that such defects may result from reduction in the provision of appropriate help by cells of the innate immune system rather than by a T-cell-integral deficit [7]. Although numerous small and highly heterogeneous studies have demonstrated various (and variable) abnormalities in innate immune function associated with acute malnutrition, the overall picture of innate responsiveness *in vivo* remains unclear. The developing understanding of the critical role of innate players in integrating divergent environmental stimuli in the initiation and modulation of immune responses suggests that this may be an important area for future work.

On the other hand, it is important to recognize that the presence of multifarious acute and chronic infections in the context of reduced skin and mucosal integrity in children living in deprived conditions will likely result in measurable immune abnormalities, regardless of the presence of malnutrition. These factors, and their presence at varying levels in both cases and properly selected controls, represent extremely important potential confounders in all human studies of immune responses to malnutrition. It is noteworthy that antibody responses to routine childhood vaccinations, the generation of which is considered a proxy for a whole pathway of immune activation, appear to be preserved in malnourished children [8]. Longitudinal studies during nutritional rehabilitation of cohorts of malnourished children who are carefully characterized clinically, immunologically, and in terms of diarrhea infection, could help to resolve this issue.

There have been a number of important recent immunologic breakthroughs that have direct relevance for understanding the relationship between infection and nutrition. These include the recognition that retinoic acid (a vitamin A metabolite) signaling pathways are functionally essential to the generation of Th1 and Th17 responses in a murine model [9], the emergence of the critical dynamic role of hepcidin in regulating iron trafficking during infection and its interaction with innate effector mechanisms [10], and the discovery of the Th22 T-cell subclass, which appears to be important in the regulation of intestinal inflammation and is potentially subject to regulation by some dietary factors [11].

Other factors influencing nutrition and infection

The interaction between undernutrition and infection is influenced by a syndrome of chronic enteropathy with reduced mucosal barrier function, called environmental enteric dysfunction (EED), which may affect the majority of children living in developing countries [12]. Importantly, markers of enteropathy have been associated with stunting in studies in Gambia and Malawi [13, 14], and stunting itself is associated with mortality and impaired development. The etiology and epidemiology of EED have not yet been fully described, and although household living conditions appear important [15], any relationships between EED and infections with specific enteric pathogens, weaning practices, or specific nutritional factors have not been established. Clinical trials of a gut-specific antimicrobial, rifamixin, and of a probiotic organism, *Lactobacillus* GG, in Malawi had no effect on enteropathy [16]. Interactions between inflammation and growth may not be entirely gut-specific, since other chronic inflammatory conditions in childhood, such as juvenile arthritis, are also associated with growth impairment.

It is becoming clear that the gut microbiome plays an important role in growth and nutritional status through processing nutrients and immunological and metabolic signaling. The composition of gut microbiota varies with age, and between developed and developing country settings [17]. In a landmark study, Smith and colleagues have recently shown that germ-free mice colonized by gut microbiota from Malawian children with kwashiorkor exhibited an immature gut metabolic profile and became wasted when fed a typical Malawian diet (unlike mice colonized with the microbiome of a non-malnourished co-twin, which did not lose weight). Nutritional rehabilitation resulted in a temporary restoration of metabolic maturity [18].

Intergenerational, preconceptional, and antenatal factors and the development of the infant immune system are also likely to be important and have recently been reviewed by Prentice and colleagues [19].

Antimicrobials in SAM

Since 1999, the World Health Organization (WHO) has recommended that all severely malnourished children receive a broad-spectrum antibiotic, regardless of whether or not clinical features of infection are present. The rationale behind this is that acute infections can be difficult to diagnose accurately, since malnourished children may not show the usual clinical signs of infection [20]. In fact, the use of antimicrobials in malnourished children without overt signs of infection was published as early as 1957. In Nairobi, Dr. Lorna

MacDougall conducted a trial of aureomycin versus placebo among 72 severely malnourished children without signs of infection and demonstrated a threefold increase in daily weight gain [21].

Antibiotics have long been used as animal growth promoters in the agricultural sector. In early experimental work with chicks, it was observed that addition of procaine penicillin to the diet improved growth when chicks were kept in “dirty” conditions, but not if they were housed in clean conditions, and a “transmissible infectious agent” was suspected to be affecting growth [22]. In a subsequent trial published in 1963 by Eyssen and de Somer, chicks temporarily lost weight when fecal contamination was introduced into their quarters, but this effect was eliminated by administration of virginiamycin (fig. 2) [23]. This suggests a direct effect of antibiotics on nutritional status in response to insults from an unhealthy environment.

The need for a routine course of oral antibiotics in children with uncomplicated SAM with good appetite and no signs of infection has been questioned, and some therapeutic programs and clinics have not prioritized oral antibiotics. In Malawi, Manary and colleagues initiated a formal, double-blinded, randomized, controlled trial in three arms: placebo, amoxicillin (recommended by WHO), or an oral third-generation cephalosporin, cefnidir [24]. The decision to include a cephalosporin was informed by the antimicrobial sensitivity patterns observed in bacteria isolated from children admitted to a nearby hospital, where resistance to amoxicillin was common. The results showed a highly statistically significant reduction in mortality during 12 weeks of follow-up from 7.4% in the placebo arm to 4.8% in the amoxicillin arm and 4.1% in the cefnidir arm. There were no statistically significant differences in outcome between the two antibiotic arms. Growth was improved with antibiotics, leading to greater gain in mid-upper-arm circumference (MUAC) in children receiving antibiotics than in those receiving placebo and a non-statistically significant increase in height gain. In an effort to replicate the conditions of normal practice at the study sites, HIV testing of participants was not routinely conducted, despite a relatively high prevalence of HIV infection compared to many other areas in sub-Saharan Africa. This has led to discussion about the generalizability of the results to settings with lower HIV prevalence and/or assured HIV testing programs. Furthermore, there are concerns over the widespread use of a cephalosporin as first-line therapy in the community because of its ability to induce resistance. At a therapeutic program in Niger where ceftriaxone was used for complicated SAM in place of the recommended penicillin and gentamicin combination, there was a huge rise in the prevalence of carriage of gram-negative bacteria carrying genes for extended-spectrum beta-lactamase production giving resistance to multiple antibiotic classes [25].

In the groundbreaking CHAP trial in Zambia of cotrimoxazole prophylaxis among HIV-infected children, not only did cotrimoxazole almost halve mortality [26], but it was also associated with improved growth [27]. The protective efficacy of cotrimoxazole against death in HIV-infected children is striking, given that it does not target the underlying immunodeficiency of HIV infection. Other immunomodulatory effects are likely, especially in view of the fact that cotrimoxazole has been shown to retain activity against pathogens

(both bacterial and malaria) that demonstrate resistance to its direct antimicrobial effect *in vitro*.

The mechanisms by which these trials not only reduced mortality, but improved growth, are not clear. They may include treatment of active (but covert) infection; prevention of colonizing microorganisms causing disease; reduction of inflammatory responses, resulting in less nutrient diversion and less cytokine-mediated impairment of growth through hormonal control; nonantibiotic effects, including direct anti-inflammatory effects; reduction in enteropathy; and alterations in gut microbiome.

With these mechanisms in mind, and drawing on the wealth of experience in management of pediatric HIV, we hypothesized that long-term antimicrobial prophylaxis might improve both survival and growth in children admitted to hospital with complicated SAM (fig. 3). A study evaluating long-term outcomes in Kilifi, Kenya, among children discharged from hospital had identified underweight children as having very high mortality in the year after discharge [28], similar to that found in Malawi during long-term follow-up of HIV-uninfected children who were enrolled in the PRONUT trial of pre-/probiotic-enhanced, ready-to-use therapeutic food (RUTF) (approximately 18% mortality within 1 year of “stabilization”) [29]. The factors associated with postdischarge mortality are likely to include incomplete correction of nutritional deficiencies; delayed immune reconstitution; chronic immune stimulation and gut inflammation; a diet inadequate for immunologic recovery; inadequately treated infections, including tuberculosis, viral infections, and occult bacterial infections; a high burden of exposure to pathogens; and ongoing poverty and food insecurity. Because of its diverse mechanisms of action, it is possible that cotrimoxazole chemoprophylaxis could impact many of these potential problems. It has the added benefits of proven prophylactic efficacy in the Zambian HIV trial; known efficacy in prophylaxis in immunodeficiency conditions, including dysfunctional neutrophil function; an established side effect profile in African populations; low cost; and widespread availability because of its use in HIV programs.

We are currently conducting a double-blind, randomized, placebo-controlled trial of daily cotrimoxazole prophylaxis among HIV-uninfected children who are admitted to two rural and two urban hospitals in Kenya with complicated SAM (NCT00934492). The trial includes children from 2 months to 5 years of age who are admitted to hospital usually because of severe pneumonia or severe diarrhea and severe malnutrition, identified by MUAC or the presence of edema. Infants as young as 2 months are included, because it is increasingly recognized that infants under 6 months of age represent a significant proportion of the case load of severe malnutrition [30]. In Kenya, as in many other developing countries, complementary foods are commonly introduced as early as 2 months of age, often with low nutritional value and the inherent risks of microbial contamination. In our trial, children are randomly allocated to daily cotrimoxazole or placebo for 6 months and followed up for 12 months. They are given standard medical and nutritional care following WHO and national guidelines. The trial has greater than 90% power to detect a 33% reduction in mortality during 12 months of follow-up. Secondary endpoints include toxicity, growth, frequency and microbial causes of readmission to hospital, markers of inflammatory response and growth regulators, phagocyte function, changes in gut microbiota, and nasal

and rectal carriage of resistant bacteria. Recruitment was completed in March 2013, and the last participant will be followed up to March 2014.

Conclusions

It is clear that an enormous burden of child mortality results from malnutrition, as a consequence of its potentiating effect on common infectious diseases. Most deaths, on a population basis, are related to mild or moderate malnutrition. Despite improvements in nutritional status in many countries in recent years, many populations include a large proportion of young children whose nutritional status places them at elevated risk. We do not yet have a full understanding of the mechanisms that cause increased susceptibility to infection and how to tackle them. However, a combination of inadequate nutritional intake, exposure to infections, and the home environment results in a complex interplay involving chronic gut inflammation and alterations in the gut microbiota and its associated metabolic functions.

Our current understanding of the relationships between undernutrition and infection is summarized in fig. 1B. Traditional intervention strategies are largely focused on increasing nutritional intake. The current view, however, is that in addition to nutritional interventions, new approaches are needed that will also address infection, inflammation, and a disturbed intestinal microbiome. Finally, when assessing interventions, clinical outcomes such as episodes of infection should be measured, rather than anthropometric features alone.

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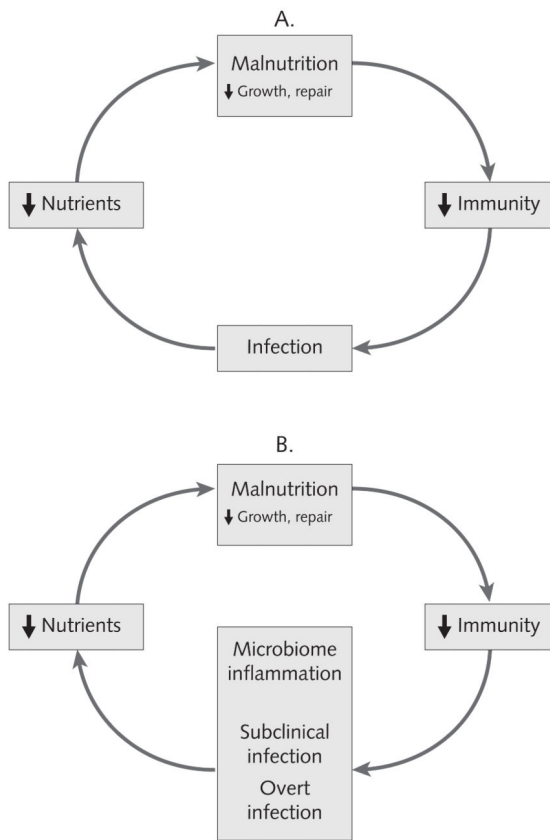
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References

1. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, Ezzati M, Grantham-McGregor S, Katz J, Martorell R, Uauy R, Maternal Child Nutrition Study Group. Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet*. 2013; 382:427–51. [PubMed: 23746772]
2. Black RE, Allen LH, Bhutta ZA, Caulfield LE, de Onis M, Ezzati M, Mathers C, Rivera J, Maternal Child Undernutrition Study Group. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet*. 2008; 371:243–60. [PubMed: 18207566]
3. Bejon P, Mohammed S, Mwangi I, Atkinson SH, Osier F, Peshu N, Newton CR, Maitland K, Berkley JA. Fraction of all hospital admissions and deaths attributable to malnutrition among children in rural Kenya. *Am J Clin Nutr*. 2008; 88:1626–31. [PubMed: 19064524]
4. Garenne M, Maire B, Fontaine O, Briand A. Distributions of mortality risk attributable to low nutritional status in Niakhar, Senegal. *J Nutr*. 2006; 136:2893–900. [PubMed: 17056819]
5. Guerrant RL, Schorling JB, McAuliffe JF, de Souza MA. 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. [PubMed: 1632474]
6. Hoare S, Poppitt SD, Prentice AM, Weaver LT. Dietary supplementation and rapid catch-up growth after acute diarrhoea in childhood. *Br J Nutr*. 1996; 76:479–90. [PubMed: 8942357]

7. Hughes SM, Amadi B, Mwiya M, Nkamba H, Tomkins A, Goldblatt D. Dendritic cell anergy results from endotoxemia in severe malnutrition. *J Immunol.* 2009; 183:2818–26. [PubMed: 19625645]
8. Savy M, Edmond K, Fine PE, Hall A, Hennig BJ, Moore SE, Mulholland K, Schaible U, Prentice AM. Landscape analysis of interactions between nutrition and vaccine responses in children. *J Nutr.* 2009; 139:2154S–218S. [PubMed: 19793845]
9. Pino-Lagos K, Guo Y, Brown C, Alexander MP, Elgueta R, Bennett KA, De Vries V, Nowak E, Blomhoff R, Sockanathan S, Chandraratna RA, Dmitrovsky E, Noelle RJ. A retinoic acid-dependent checkpoint in the development of CD4+ T cell-mediated immunity. *J Exp Med.* 2011; 208:1767–75. [PubMed: 21859847]
10. Drakesmith H, Prentice AM. Hepcidin and the iron-infection axis. *Science.* 2012; 338:768–72. [PubMed: 23139325]
11. Leung JM, Davenport M, Wolff MJ, Wiens KE, Abidi WM, Poles MA, Cho I, Ullman T, Mayer L, Loke P. IL-22-producing CD4+ cells are depleted in actively inflamed colitis tissue. *Mucosal Immunol.* 2014; 7:124–33. [PubMed: 23695510]
12. Korpe PS, Petri WA Jr. Environmental enteropathy: critical implications of a poorly understood condition. *Trends Mol Med.* 2012; 18:328–36. [PubMed: 22633998]
13. Campbell DI, Lunn PG, Elia M. Age-related association of small intestinal mucosal enteropathy with nutritional status in rural Gambian children. *Br J Nutr.* 2002; 88:499–505. [PubMed: 12425730]
14. Weisz AJ, Manary MJ, Stephenson K, Agapova S, Manary FG, Thakwalakwa C, Shulman RJ, Manary MJ. Abnormal gut integrity is associated with reduced linear growth in rural Malawian children. *J Pediatr Gastroenterol Nutr.* 2012; 55:747–50. [PubMed: 22732897]
15. Lin A, Arnold BF, Afreen S, Goto R, Huda TM, Haque R, Raqib R, Unicomb L, Ahmed T, Colford JM Jr, Luby SP. Household environmental conditions are associated with enteropathy and impaired growth in rural Bangladesh. *Am J Trop Med Hyg.* 2013; 89:130–7. [PubMed: 23629931]
16. Galpin L, Manary MJ, Fleming K, Ou CN, Ashorn P, Shulman RJ. Effect of *Lactobacillus GG* on intestinal integrity in Malawian children at risk of tropical enteropathy. *Am J Clin Nutr.* 2005; 82:1040–5. [PubMed: 16280436]
17. Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, Magris M, Hidalgo G, Baldassano RN, Anokhin AP, Heath AC, Warner B, Reeder J, Kuczynski J, Caporaso JG, Lozupone CA, Lauber C, Clemente JC, Knights D, Knight R, Gordon JI. Human gut microbiome viewed across age and geography. *Nature.* 2012; 486:222–7. [PubMed: 22699611]
18. Smith MI, Yatsunenko T, Manary MJ, Trehan I, Mkakosya R, Cheng J, Kau AL, Rich SS, Concannon P, Mychaleckyj JC, Liu J, Hout E, Li JV, Holmes E, Nicholson J, Knights D, Ursell LK, Knight R, Gordon JI. Gut microbiomes of Malawian twin pairs discordant for kwashiorkor. *Science.* 2013; 339:548–54. [PubMed: 23363771]
19. Prentice AM, Moore SE, Fulford AJ. Growth faltering in low-income countries. *World Rev Nutr Diet.* 2013; 106:90–9. [PubMed: 23428686]
20. Christie CD, Heikens GT, McFarlane DE. Nosocomial and community-acquired infections in malnourished children. *J Trop Med Hyg.* 1988; 91:173–80. [PubMed: 3404564]
21. Macdougall LG. The effect of aureomycin in undernourished African children. *J Trop Pediatr.* 1957; 3:74–81. [PubMed: 13463966]
22. Coates ME, Dickinson CD, Harrison GF, Kon SK, Cummins SH, Cuthbertson WF. Mode of action of antibiotics in stimulating growth of chicks. *Nature.* 1951; 168:332. [PubMed: 14875083]
23. Eyssen H, de Somer P. The mode of action of antibiotics in stimulating growth of chicks. *J Exp Med.* 1963; 117:127–38. [PubMed: 19867220]
24. Trehan I, Goldbach HS, LaGrone LN, Meuli GJ, Wang RJ, Maleta KM, Manary MJ. Antibiotics as part of the management of severe acute malnutrition. *N Engl J Med.* 2013; 368:425–35. [PubMed: 23363496]
25. Woerther PL, Angebault C, Jacquier H, Hugede HC, Janssens AC, Sayadi S, El Mniai A, Armand-Lefevre L, Ruppe E, Barbier F, Raskine L, Page AL, de Rekeneire N, Andremont A. Massive increase, spread, and exchange of extended spectrum beta-lactamase-encoding genes among intestinal Enterobacteriaceae in hospitalized children with severe acute malnutrition in Niger. *Clin Infect Dis.* 2011; 53:677–85. [PubMed: 21890771]

26. Chintu C, Bhat GJ, Walker AS, Mulenga V, Sinyinza F, Lishimpi K, Farrelly L, Kaganson N, Zumla A, Gillespie SH, Nunn AJ, Gibb DM, CHAP trial team. Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): A double-blind randomised placebo-controlled trial. *Lancet*. 2004; 364:1865–71. [PubMed: 15555666]
27. Prendergast A, Walker AS, Mulenga V, Chintu C, Gibb DM. Improved growth and anemia in HIV-infected African children taking cotrimoxazole prophylaxis. *Clin Infect Dis*. 2011; 52:953–6. [PubMed: 21427404]
28. Moïsi JC, Gatakaa H, Berkley JA, Maitland K, Mturi N, Newton CR, Njuguna P, Nokes J, Ojal J, Bauni E. Excess child mortality after discharge from hospital in Kilifi, Kenya: A retrospective cohort analysis. *Bull World Health Organ*. 2011; 89:725–32. [PubMed: 22084510]
29. Kerac M, Bunn J, Seal A, Thindwa M, Tomkins A, Sadler K, Bahwere P, Collins S. Probiotics and prebiotics for severe acute malnutrition (PRONUT study): A double-blind efficacy randomised controlled trial in Malawi. *Lancet*. 2009; 374:136–44. [PubMed: 19595348]
30. Kerac M, Blencowe H, Grijalva-Eternod C, McGrath M, Shoham J, Cole TJ, Seal A. Prevalence of wasting among under 6-month-old infants in developing countries and implications of new case definitions using WHO growth standards: A secondary data analysis. *Arch Dis Child*. 2011; 96:1008–13. [PubMed: 21288999]

**FIG. 1.**

A. Historical view of the vicious cycle of malnutrition and infection. B. Our current understanding also involves subclinical infection, intestinal inflammation, and altered gut microbiota

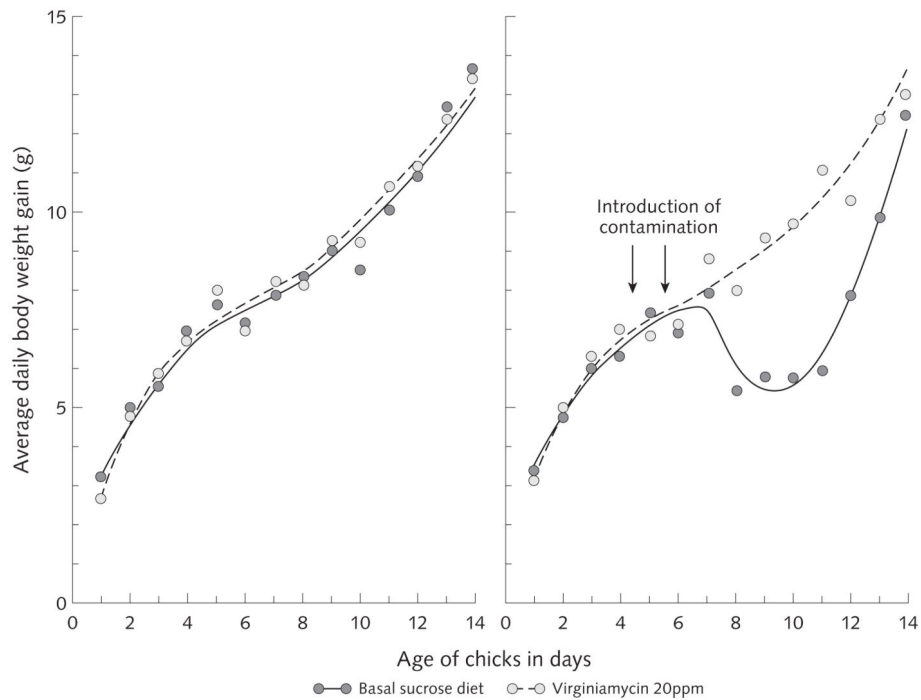


FIG. 2.

Effect of an antibiotic on the weight of chicks housed in a clean environment (new quarters) before and during introduction of contamination from chicks housed in a dirty environment (old quarters) © H. Eyssen and P. de Somer, 1963. Originally published in *The Journal of Experimental Medicine* 117:127-38

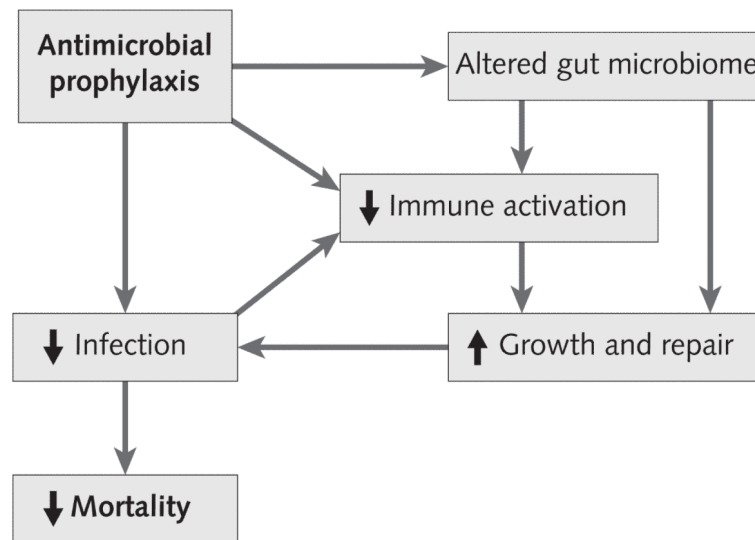


FIG. 3. Hypothesis underlying a randomized, double-blind, controlled trial of daily cotrimoxazole prophylaxis following stabilization in HIV-uninfected children with complicated severe acute malnutrition (SAM)