Malnutrition-Infection Syndemics in Pediatric Populations: A Systematic Review

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Abstract

Malnutrition and infectious diseases are in a mutually reinforcing syndemic relationship: in low- and middle-income countries (LMICs), this leads to significant morbidity and mortality among children. The syndemic appears to be different from comorbidity because it acknowledges the biological synergism and common risk factors that exacerbate the negative health outcomes associated with each condition. This systematic review critically and synthetically summarizes epidemiological data, biological mechanisms, clinical outcomes and comprehensive management strategies for malnutrition-infection syndemics in children worldwide. PubMed, Scopus, Web of Science, Science Direct, WHO, UNICEF and FAO were searched systematically with preference to literature published between 2015 and 2024. Studies were chosen for inclusion if they met certain specified criteria and excluded if they did not meet the criteria, all involving children between 0 and 59 months of age. Bidirectional links between malnutrition and infection (including diarrheal disease, pneumonia, malaria and tuberculosis) are consistently supported by the evidence. This relationship is mediated by immunological impairment, disruption of gut microbiota, enteropathy and micronutrient deficiencies. Syndemic interactions are exacerbated due to socioeconomic deprivation, inadequate sanitation, and food insecurity. Whereas uncoordinated or siloed nutrition and infectious disease responses have less impact than integrated nutrition-infection responses. There is a need for multisectoral interventions that will simultaneously address malnutrition rehabilitation, infectious disease prevention and structural determinants of health, to address the malnutrition-infection syndemics. There are still important challenges to address, including long-term developmental outcomes, a mechanistic understanding of the role gut microbiome plays in development and implementation science for integrated interventions.

Keywords: Malnutrition; pediatric infections; syndemic; undernutrition; child mortality; gut microbiota; environmental enteric dysfunction; low- and middle-income countries; integrated management; micronutrient deficiency.

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1. Introduction

Malnutrition and infectious diseases are among the most important challenges to the health of children in the world, but the effects of being malnourished and suffering from infection are more complex than being just cooccurring. They work together in a “synergic” way that interacts with the other dimensions of the conditions, creating biological and social effects in which one condition adds to the other, increasing the physiological and social ill effects beyond the negative effect of either condition alone (Singer, 2009; Tsai et al., 2017). The idea of syndemics, which was developed in the 1990s by Merrill Singer and later described in public health literature, is one that captures this interplay between the clustering of disease and the socioecological environments that promote and incentivize harmful interactions (Mendenhall et al., 2017; Singer & Clair, 2003).

In children under 5 years of age, undernutrition is responsible for about one quarter of all deaths – the vast majority of which is observed in sub-Saharan Africa and South Asia (Black et al., 2013; United Nations Children's Fund et al., 2023). However, infectious diseases such as pneumonia, diarrheal disease, malaria and tuberculosis, continue to be the primary causes of paediatric mortality, affecting the same vulnerable groups that suffer from malnutrition (Liu et al., 2016a; World Health Organization, 2023b). These observations are not random or accidental. Malnourished infants and children are handicapped in their ability to fight infections and recover from them. On the other hand, recurrent infections lower the nutritional reserves, hinder the absorption of nutrients, divert the metabolic resources to immune response and reduce appetite, worsening malnutrition (Rytter et al., 2014; Schaible & Kaufmann, 2007).

However, the link between a child's nutritional status and children's susceptibility to infectious diseases is well recognised, but has been tackled by global health programmes using parallel, vertically driven solutions to the problems of malnutrition and infectious diseases. This silo mentality is also inadequate to end the vicious cycle of malnutrition-infection syndemics (Bhutta et al., 2013a; Ruel et al., 2013), especially in low- and middle-income countries (LMICs) where structural vulnerabilities are sustaining both the malnutrition and the infection. It sees an analytically stronger picture within the 'syndemic' lens for understanding the underlying factors associated with disproportionate burden (social and biological determinants and the role of malnutrition in relation to infection), and a clearer picture about what most likely will generate durable improvements (integrated strategies).

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This systematic review critically synthesises the available evidence on malnutrition-infection syndemics in the paediatric population. It covers epidemiology, biological mechanisms, the importance of certain infections and micronutrient deficiencies, the gut microbiota and environmental enteropathy, socioeconomic factors, clinical consequences, current strategies of prevention and management. Incorporating findings from various sectors, this review will provide input to evidence-based, multi-sectoral public health responses to this key issue.

2. Materials and Methods

2.1 Search Strategy

A systematic literature search was conducted across PubMed, Scopus, Web of Science, ScienceDirect, Springer, Wiley Online Library, BMJ, Elsevier, Nature, Frontiers, MDPI, PLOS, as well as institutional repositories of the World Health Organization (WHO), UNICEF, and the Food and Agriculture Organization (FAO). The search was conducted between January 2015 and December 2024, with inclusion of landmark pre-2015 studies where necessary to establish foundational concepts.

The search strategy employed combinations of the following Medical Subject Headings (MeSH) terms and keywords: "malnutrition AND children," "undernutrition AND infection," "syndemic AND pediatric," "child malnutrition AND infectious disease," "wasting AND diarrhea," "stunting AND immunity," "micronutrient deficiency AND infection," "gut microbiota AND malnutrition," "environmental enteric dysfunction," "severe acute malnutrition AND mortality," "pneumonia AND undernutrition," "malaria AND nutritional status," "tuberculosis AND child malnutrition," and "integrated management AND malnutrition." Boolean operators (AND, OR, NOT) were used to refine searches.

2.2 Inclusion Criteria

Studies were considered if they met the following criteria: i) studies were pediatric studies and included children between 0 and 59 months old; ii) studies focused on the relationship between malnutrition and infectious diseases; iii) published in English in the peer-reviewed journals or reports by the major international health organizations were included; iv) studies included original papers, systematic reviews, meta-analyses, RCTs, cohort studies, case-control studies, and large cross-sectional surveys; and v) studies were published primarily after 2015.

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2.3 Exclusion Criteria

Studies were excluded if they: (1) targeted adults only; (2) provided information specifically on a single nutrient supplement rather than on nutrition and/or infectious diseases; (3) were opinion articles, editorials, commentaries, and lacked supporting empirical research; (4) were not available as full text online; (5) were journal articles in languages other than English and had not been translated.

2.4 Data Synthesis

Instead of summarizing individual studies, the review uses a critical narrative synthesis method, which is characterized by combining and comparing the results of the study thematically in accordance with each study. Inconsistent results from different studies are explained and understood. In the analytic approach of the review, the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) are followed.

3. Understanding the Malnutrition-Infection Syndemic

The syndemic concept extends the understanding of what is meant by "comorbidity," provided that two or more conditions interact and those conditions, in turn, are biologically synergistic and strongly contextually embedded and socially structured (Mendenhall & Singer, 2020; Mendenhall et al., 2017). When applied to children's immunity and malnutrition, this dynamic explains why children with undernutrition are exposed to a wider spectrum of pathogens, more severely ill from infections, and how infections affect children's nutrition through a variety of physiological pathways (Guerrant et al., 2013; Prentice, 2005).

Synergism between malnutrition and infection was recognized by Scrimshaw, Taylor and Gordon in the 1960s, when they showed that it was more lethal than the individual effects of the two factors would be taken together (Scrimshaw et al., 1959). Recent research has greatly extended this understanding. It has now been shown that undernutrition contributes to making infection more severe not only by the effects on immunity, but also by disrupting mucosal barriers, changing the microbiome, affecting the host response to infection, and causing dysregulation of hormones, in a landmark analysis published in The Lancet (Prentice et al., 2013; Tickell & Walson, 2016). These mechanisms do not act separately but rather they act synergistically to exacerbate cascading vulnerabilities that increase in difficulty after being aggravated through each episode of illness.

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It is important to note the social and structural environment that is sustaining this interaction, as outlined by the syndemic framework. Poverty and food insecurity, lack of access to clean water and sanitation, poor healthcare services and social marginalisation are not just background risks; they are organizing risks, bundling malnutrition and infection into specific population groups, and increasing the vulnerability of people across generations (Haddad et al., 2015; Victora et al., 2008). However, syndemic theory also suggests that interventions to prevent and control syndemic effects should recognize both the biological synergy and their social production (Mendenhall & Singer, 2020), which is not well met in global health programming.

4. Global Epidemiology

Malnutrition in children continues to be highly clustered in LMICs, which has important implications for the distribution and scale of syndemic risk. The estimated numbers of stunted, wasted, and overweight children aged under 5 in 2022 were about 148 million, 45 million, and 37 million respectively (UNICEF et al., 2023) based on 2022 joint estimates by the UNICEF, the WHO, and the World Bank. Wasting and stunting often go together, especially a situation of concurrent low income, food insecurity and high prevalence of infectious diseases in sub-Saharan Africa and South Asia (Thurstans et al., 2020; Victora et al., 2021).

The number of severely malnourished children under five (SAM) is estimated at 13.6 million per year with the potential case fatality rate over 30% when treated in a hospital setting without adequate nutritional support because of the profound immunosuppression and susceptibility to infection caused by SAM (Berkley et al., 2016; World Health Organization, 2013b). A systematic review of Lazzerini and Tickell (Lazzerini & Tickell, 2011) demonstrated that most children who die while in the hospital for SAM have infections.

Malnutrition frequently occurs in tandem with infectious diseases and this is not a chance occurrence. Thus, the lowest micronutrient intake observed in sub-Saharan Africa is consistently linked to high-burden of diseases such as malaria, diarrheal disease, and acute respiratory infections (ARI) among populations suffering wasting and stunting (Dewey & Begum, 2011; Müller & Krawinkel, 2005). The Childhood Acute Illness and Nutrition Network (CAN) conducted a large cohort study at multiple locations across the African continent where undernutrition was shown to be independently associated with deaths related to acute illness and

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which increased most when children also wasted and were stunted (Childhood Acute Illness and Nutrition Network (CHAIN), 2020). Likewise, it has been found that children in the poorest quintile (during which they were also at the highest risk of being malnourished) are more likely to suffer from infectious disease morbidity than any other quintile (Joe et al., 2009; Svedberg, 2000). There are also additional complications of overnutrition. The double burden of malnutrition, the coexistence of overweight and undernutrition conditions, and possible compromised immune function and increased vulnerability to specific infections in children with overweight and obesity have been documented in a growing body of research in middle-income settings, and, if present, may occur in children with obesity as well, though the evidence base is not as well developed as for undernutrition (Development Initiatives, 2021; Popkin et al., 2020). Although epidemiological evidence shows that undernutrition has been linked to infectious disease syndemics, this review focuses on undernutrition as this concept is gaining more relevance in the context of double-burden framework.

5. Biological Mechanisms Linking Malnutrition and Infection

Mechanisms linking malnutrition and infection are bidirectional and multiple, interlocking pathways exist and require adequate understanding to design feasible interventions.

Immunological impairment: Undernutrition leads to immunological impairment, which is one of the best studied effects. Protein-energy malnutrition causes atrophy of primary and secondary lymphoid organs such as thymus and spleen, which in turn causes fewer T lymphocytes to be generated and their lessened activity, particularly in CD4+ helper cells (Calder, 2013; Cunningham-Rundles et al., 2005). Concomitantly, defects in cell-mediated immunity are worsened by decreased natural killer cell activity, lowered production of secretory immunoglobulin A at mucosal surfaces and decreased macrophage bactericidal function (Kau et al., 2011). Immunological investigations in malnourished children have been performed, and the results are consistent in showing that not only are immune cells present in low numbers but that those that are present are functionally impaired, on the levels of cytokine signaling, phagocytosis and antigen presentation, for instance (Sanchez-Muñoz et al., 2008).

Mucosal barrier disruption: Disruption of the mucosal barrier is another important pathway. The integrity of the epithelium in the respiratory and gastrointestinal tracts needs sufficient nutrition.

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Undernutrition leads to decreased production of mucous secretions, a decrease in the expression of tight junction proteins, and a decrease in the ability to regenerate epithelial cells which opens up opportunities for pathogens to enter the system (Nanthakumar et al., 2013; Turner, 2009). This is often characterized by leakage of the gut, which allows bacteria to enter the blood in addition to helping to cause chronic systemic inflammation, which also decreases nutritional status through anorexia, elevated basal energy expenditure, and catabolism (Deitch, 1990).

Metabolic responses: Malnourished children also have dysregulated metabolic changes to infection. In mentally healthy people with sufficient nutrition, the immediate reaction to infection prompts shifts in metabolism to allocate energy toward an immune response, a process which includes an initial reduction in appetite, protein breakdown, and reorganization of micronutrient transport. These demands are beyond what is being offered in a child experiencing malnutrition and may cause them to rapidly suffer clinical deterioration (Pappas et al., 2009). This process involves re-distribution of micronutrients (iron and zinc) during infection, which in addition to restricting the growth of the pathogens, also makes immune cells less effective in the condition of deficiencies (Ganz, 2009).

Hormonal dysregulation: Recovery is further complicated by a hormonal imbalance. Growth hormone resistance, hypercortisolism and hypoinsulinemia (which increases insulin-like growth factor-1 [IGF-1] levels) have been reported for malnourished children and influence both linear growth and physiological maturation and regeneration of the immune system (Bhutta et al., 2008). During infection and malnutrition, cortisol excess acts to down-modulate immune function while simultaneously facilitating catabolic processes, thus creating a very negative physiological environment (Thurnham, 1997).

Infections, on the other hand, exacerbate nutritional status, for example through multiple processes. Diarrheal illnesses further promote nutrient loss due to malabsorption and loss through faeces. Each degree Celsius rise in temperature raises BMR by nearly 10% (Powanda & Beisel, 1982). Infection can also directly reduce dietary intake (anorexia) during periods of increased nutritional need. Children who are frequently and chronically ill do not catch up with their growth and development, resulting in an additive effect on stunting. The individual suffering each infection episode thus exacerbates the nutritional drain caused by the preceding infection, and this

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vicious cycle tends to escalate in difficulty to break over time (Prendergast & Humphrey, 2014; Victora et al., 1999).

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6. Common Infectious Diseases Associated with Pediatric Malnutrition

6.1 Diarrheal Diseases

The combination of diarrheal disease with malnutrition is both a cause and a consequence and is best exemplified by this relationship. A total of an estimated 525,000 children under 5 years of age die from diarrhea each year, of which most are in LMICs (World Health Organization, 2023a). Malnourished children have a higher frequency of diarrheas and more severe episodes, are slower to recover from diarrheas and are more likely to develop persistent diarrheas (that last more than 14 days), which in turn can lead to severe nutritional loss (Bhattacharya et al., 2003; Mondal et al., 2012). The findings from several African and Asian sites have shown that wasted children are twice to four times more likely than their adequately nourished counterparts to die from diarrhea (Berkley et al., 2005; Childhood Acute Illness and Nutrition Network (CHAIN), 2020). Mechanistically, malnourished children may be at higher risk of enteric pathogens such as Cryptosporidium, enterotoxigenic Escherichia coli, Shigella, and rotavirus due to an increased vulnerability associated with both impaired barrier function and reduced secretory IgA in the intestine and the altered composition of the microbiome (Liu et al., 2016b; Platts-Mills et al., 2015). Cryptosporidium is of particular interest due to its ability to cause particularly severe and chronic diarrhea in malnourished children and being recognised as a major cause of malnutrition and linear growth faltering in prospective cohort studies (Checkley et al., 2015; Tickell et al., 2017).

6.2 Acute Respiratory Infections

Pneumonia is the largest single cause of death from infectious diseases in young children around the world, contributing to about 14% of all child deaths (McAllister et al., 2019). The good knowledge and understanding of the link between undernutrition and severity of pneumonia.Good knowledge and understanding of relationships between underaquated nutritional status and pointers to the severity of pneumonia Pooled analysis of studies from LMICs showed that stunted and wasted children were at significantly higher risk of being hospitalized with pneumonia and dying relative to non-pregnant children; the risk for wasting was higher than for stunting when adjusted for the effects of other factors (Rice et al., 2000). These biological factors include defects in clearance of mucosa by cilia, decreased pulmonary immune system, and decreased respiratory

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muscle reserve in malnourished children (Bhatt & Mehta, 2016). Vitamin A and zinc deficiencies are of special relevance with regards to respiratory susceptibility; zinc supplementation trials have shown that pneumonia incidence and severity has been reduced in high-risk populations (Brown et al., 2016; Imdad et al., 2011).

6.3 Malaria

The geographic distribution of malaria and malnutrition is similar in most tropical LMICs and their association is complex and little understood. Several cross-sectional and cohort studies have shown increased susceptibility of malnourished children to severe malaria, cerebral malaria, mal-nutrition associated anemia (Ehrhardt et al., 2006; Fillol et al., 2009). But that an allegation on the direction of the relationship is on a discussion. Some reports have shown that malnutrition undermines the development of natural immunity to malaria, making children more susceptible to experience frequent and more severe episodes of the disease that can result in malnutrition (Caulfield et al., 2004; Kabyemela et al., 2008) and other have suggested that the effect of malaria on malnutrition may be due to the hemolysis, suppressed erythropoiesis, and infection-associated anorexia (Nyakeriga et al., 2004; World Health Organization, 2023c). A large prospective cohort study with children was conducted in Kenya and it was concluded that immediate recovery from moderate acute malnutrition placed children at high risk of a delayed acquisition of anti-malarial immunity, thus creating vulnerability for many years after MALN (Nyakeriga et al., 2004). It has implications that are relevant to malaria control programmes among nutritionally vulnerable groups.

6.4 Tuberculosis

Children are especially vulnerable to the influence of tuberculosis and malnutrition. Undernutrition is known to be the greatest risk factors for TB in the world and undernutrition was estimated to contribute a significant burden of TB throughout the world, especially in Asia, Africa, and the Americas (World Health Organization, 2023c). Diseased children are frequently wasted due to the hyper catabolic state, malabsorption or prolonged infection-associated anorexia characteristic of tuberculosis; and mal-nutrition is a significant risk factor for progression from tuberculosis infection to active disease in children (Bhargava et al., 2023; Sabiiti et al., 2022). A systematic review conducted by Bhargava and his co-authors showed that nutritional support during TB treatment was associated with increased weight gain, decreased treatment default, and better

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outcomes and that evidence for the benefits of nutritional support with regards to mortality reduction was limited (Bhargava et al., 2014). The present study highlights the importance of co-management of nutrition and TB, especially among children in high TB burden countries.

7. Types of Malnutrition and Their Relationship with Infection

7.1 Wasting

Wasting (weight-for-height z score below -2) is a marker of acute nutritional deficit, and one of the greatest short-term risk factors for mortality in undernutrition. In wasted children there is deep immunodeficiency, impaired mucosal barrier function and altered metabolism that greatly contribute to their susceptibility and severity to infection (Collins et al., 2000). Severe acute malnutrition is the most severe case of wasting and occurs due to either edematous malnutrition (kwashiorkor) or non-edematous severe wasting (marasmus) and is highly correlated with infections-related mortality (Briend et al., 2012; World Health Organization, 2013b). By reviewing multiple studies, McDonald and colleagues (McDonald et al., 2013) found that SAM was about 9 times more likely to result in all-cause mortality than well-nourished children; the majority of attributable deaths were related to infections. The likely combined effect of wasting and concurrent infection is also very dangerous; studies have consistently found that children wasted due to concurrent infections are synthetically at higher risk of death than those wasted from either cause alone (Childhood Acute Illness and Nutrition Network (CHAIN), 2020; Isanaka et al., 2009).

7.2 Stunting

Although there are some aspects of the relationship between stunting and long-term immune deficiencies and vulnerability to infection that are more complex than those between wasting, stunting is clearly an indicator of chronic nutritional deficit, with an impact on immunity. Stunted children exhibit markers of immune dysregulation such as increased markers of systemic inflammation, which could be an indirect marker of chronic low-grade exposure to infective pathogens, in contrast to just nutritional hemi deficiency (Humphrey, 2009; Mbuya & Humphrey, 2016). A large SHINE trial led in Zimbabwe delivered compelling data that supported the correlation of better WASH, along with child dietary supplementation, and reduced stunting showing that environmental infectious exposures significantly play a role in the etiology of

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stunting (Humphrey et al., 2019). These findings support the evidence base that stunting is a syndrome, addressing it through nutrition interventions alone will not suffice.

7.3 Underweight

Being under weight (WHA: z < -2) is considered a composite indicator in the context of nutrition and is based on both acute and chronic deficiency. The underweight indicator reflects the combination of wasting and stunting, but is not as specific to the process of understanding the mechanisms of interaction between malnutrition and infection as are the more specific indicators of anthropometry (de Onis & Branca, 2016).

8. Role of Micronutrient Deficiencies

Even in children with good macronutrient nutritional levels, micronutrient deficiencies can be considered as critical mediators to the malnutrition-infection syndemics. The role of vitamins A, D, C, B12, zinc, iron and selenium is thought to be strongly immunological, and deficiencies in these micronutrients are known to cause particular immunological vulnerabilities, enhancing the susceptibility to and severity of infections (Gombart et al., 2020; Maggini et al., 2018).

Vitamin A deficiency: It is estimated that some 190 million pre-schoolers worldwide suffer from vitamin A deficiency, which is responsible for markedly higher rates of diarrhea, measles and malaria deaths (World Health Organization, 2009). Vitamin A plays an important role in the differentiation of epithelial cells, mucosal immunity and the activity of innate and adaptive immune cells. A Cochrane systematic review of all Vitamin A supplementation trials found that there was a 24% reduction in all-cause mortality among children 6–59 months of age in populations with Vitamin A Deficiency, plus a marked reduction in diarrhoea and measles, the two most common causes of death, in populations with the highest levels of VAD (Imdad et al., 2017).

Zinc deficiency: It has been estimated that more than one billion people suffer from zinc deficiency worldwide, and this deficiency is especially occurring among children in LMICs (Wessells & Brown, 2012). Neutrophils, natural killer cells and T lymphocytes are important cells that require zinc for their development and function. There has been variability in effects previously reported among randomized controlled trials of zinc supplementation for decreased rates and duration of diarrhea and pneumonia, depending on zinc status and intervention design at baseline (Lassi et al., 2010; Lazzerini & Wanzira, 2016). In the children who were in populations

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with zinc deficiency, a meta-analysis carried out by Haider and Bhutta, reported a 13% reduction in diarrhea incidence and a 19% reduction in pneumonia incidence due to preventive zinc supplementation (Haider & Bhutta, 2009).

Vitamin D deficiency: Vitamin D deficiency has been a rising focus as a regulator of children's susceptibility to infection, property attributed to its effects and action. The effects, and the action, of vitamin D deficiency have led to heightened interest in this condition as a modulator of susceptibility to infection in children. In addition to its classic role in the regulation of calcium metabolism, vitamin D is also an immunomodulator that promotes innate immune response by augmenting antimicrobial peptide synthesis and inhibits adaptive immune response (Aranow, 2011). A systematic review and meta-analysis revealed that vitamin D use during childhood was linked with a statistically significant decrease in the risk for ARI, especially for the children who were deficient at the beginning of the study (Martineau et al., 2017).

Iron deficiency and iron deficiency anemia: It is estimated that 40% of children under five years old worldwide are iron deficient (World Health Organization, 2008) and 35% are iron deficient anemia (Sazawal et al., 2006). The link between iron fortification and infection in LMIC settings is complex with iron being conciously necessary for proper immune cell proliferation and modulation in pregnancy. However, because of concerns for potentially higher risk of malaria during iron supplementation trials in malaria-endemic areas, the role of micronutrient-infection interactions is complex, and context-specific guidance is important (Neuberger et al., 2016; Sazawal et al., 2006). The current WHO guidelines support an iron supplementation programme specifically customised according to the malaria endemicity level and baseline prevalence of anemia in the region (World Health Organization, 2016).

9. Gut Microbiota, Environmental Enteric Dysfunction, and Immunity

One of the greatest steps forward in our understanding on the topic of malnutrition-infection syndemics has been the identification of disruption of gut microbiota and environmental enteric dysfunction (EED) as key intervening pathways.

Gut microbiota: Childhood early life events such as birth type, breastfeeding, infants' feeding habits, antibiotic use, and environmental exposures differentiate the early development of gut microbiota to a predictable pattern (Bäckhed et al., 2015; Dominguez-Bello et al., 2019). The

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microbiome characteristics of malnourished children, such as the decrease in microbial diversity, decrease in abundance of beneficial bacteria including those from the genera Bifidobacterium and Lactobacillus, and relative increase of potentially pathogenic bacteria, are consistently observed (Subramanian et al., 2014; Vonaesch et al., 2018b). Importantly, this microbiome immaturity is not only due to nutritional deficiency, and transfer of microbiota from stunted children has been shown to be sufficient to induce growth faltering in germ-free mice that are otherwise fed nutritionally adequate diets (Smith et al., 2013).

The microbiome-immune interface is two-way. Commensal bacteria play guardians of the barrier, regulators of T cells and maturational influences of mucosal immunity (Thaiss et al., 2016). These functions are disrupted by dysbiosis, which can provide a basis for colonization of enteric pathogens and lead to immune system dysregulation in the whole organism. Bangladesh, Malawi and Zimbabwe studies have all concluded that microbiome immaturity scores are independent risk factors for growth faltering and diarrheal disease, not related to dietary intake (Langdon et al., 2016; Subramanian et al., 2015).

Environmental enteric dysfunction in children who repeatedly have encounters with fecally contaminated environments the small intestine becomes malnourished due to villous blunting, crypt hyperplasia, increased intestinal permeability and chronic mucosal inflammation which give rise to a subclinical entity identified as environmental enteric dysfunction (Keusch et al., 2014; Korpe & Petri WA Jr, 2012). EED decreases the ability of the animal to absorb nutrients, causes systemic inflammation due to bacterial translocation, and redirects metabolic resources to immune activation as opposed to growth. Prendergast and Kelly performed a systematic review that found that EED is most likely a primary factor influencing the occurrence of stunting in high-burden settings and that this influences a significant proportion of the effect of poor sanitation and hygiene on child growth (Prendergast & Kelly, 2012).

Hypothesis testing regarding the relationship between improved WASH conditions and reduced EED and/or the promotion of child growth was carried out in the WASH Benefits trial in Bangladesh and Kenya, and the SHINE trial in Zimbabwe (Luby et al., 2018; Null et al., 2018). These trials demonstrated only modest impacts from WASH alone in reducing stunting, but revealed that the pathogenesis of EED is complex, and multiple synchronous interventions might be necessary (Cumming & Cairncross, 2016). The stoic results from these trials highlight the

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complex influences around EED – and that WASH improvements alone cannot reduce EED – since it depends on much more than just the lack of WASH features in the home.

10. Socioeconomic and Environmental Determinants

The relationship between malnutrition and infections is not exclusively a biological phenomenon, but rather one that is shaped by and dependent on social, economic, and environmental factors that shape exposure to nutrition risk and infectious agents (UNICEF, 2013; Victora & Barros, 2001). Poverty is the primary variable and acts in several mechanisms such as food insecurity, access to health services, shelter, exposure to environmental pollutions, access to education etc.

Food insecurity directly restricts the diets in terms of diversity and adequacy, importantly reducing consumption of animal-source foods, fruits and vegetables which are key to micronutrient sufficiency (Headey & Ecker, 2013). The relation between food insecurity and nutritional outcomes has been consistently linked to stunting and wasting in a variety of contexts, being a dose response relation; a higher food insecurity level is correlated with poorer nutritional outcome (Grebmer et al., 2022; Hackett et al., 2010). But, the stress and the psychosocial challenges arising from food insecurity also affect the caregiver's feeding-responsiveness and infant care practices (Slopen et al., 2010) indirectly.

Low water, sanitation and hygiene facilities allow EED and enteric pathogens to be spread. Globally, there are billions of individuals who continue to be deprived from safely managed drinking water and sanitation services, with children living in households that do not have adequate WASH infrastructure having considerably increased burden of diarrheal disease and growth faltering (Prüss-Ustün et al., 2019; World Health Organization & UNICEF, 2019). Open defecation in comparison (0D) has been linked to high rates of fecal-oral transmission, and infant environmental fecal ingestion via contaminated soil and water sources (Chambers & von Medeazza, 2013).

We have identified household air pollution (caused by cooking with biomass fuels) as an environmental risk factor for susceptibility to respiratory infections that overlaps with malnutrition. Solid fuel household consumption is associated with children being at high risk for pneumonia, and there is evidence that nutritional deficiencies exacerbate the pulmonary inflammatory response to particulates (Dherani et al., 2008; Smith et al., 2014). A systematic

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review revealed that household air pollution was associated with significantly increased pneumonia incidence among children with similar effect estimates as compared with adults exposed to indoor smoking (Burnett et al., 2014).

There are social determinants such as maternal education and empowerment, gender equity, and healthcare access that play a strong moderating role in the risk of syndemic. Maternal education has been strongly linked to child nutrition and helping to prevent child death from infectious diseases, via better nutrition practices, better healthcare use, hygiene behaviors, and increased household income generation (Bain et al., 2013; Semba et al., 2008). Bangladesh, Ethiopia, and India show that every extra year of maternal education has a strong negative correlation with prevalence of undernutrition among children (Abuya et al., 2012).

11. Clinical Outcomes and Long-Term Consequences

Malnutrition–infection syndemics impact a variety of dimensions of functioning across multiple organ systems and developmental domains that can have a long-term impact. The short-term-most important outcome is mortality. SAM combined with SBI carries increased risk of death, compared to either SAM or SBI alone, and the simultaneous presence of concurrent malnutrition and serious bacterial infection (SBI) in the care environment is complex and challenging to manage operating in a resource-limited health environment (Childhood Acute Illness and Nutrition Network (CHAIN), 2020; World Health Organization, 2013b).

Among survivors, there are cascading developmental consequences due to recurring malnutrition-infection cycles. One of the most important long-term complications is **impairment of cognition**. The first 1000 days of life are a particularly critical window for brain development, and subsequent illness exposures during this window have been linked with lower cognitive performance, academic achievement and productivity in adulthood (Grantham-McGregor et al., 2007; Victora et al., 2008). One study in Guatemala showed significant association between early childhood stunting and adult cognitive scores, with part of the effects of stunting being linearized through the history of infections (Hoddinott et al., 2008). Iron deficiency anemia at key periods of brain development is related to deficits in executive function and working memory which remain even after nutritional rehabilitation (Lozoff et al., 2006).

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Linear growth faltering: Once a child starts to exhibit linear growth faltering, it continues to get worse with every infection episode, especially with diarrheal diseases and, like the other indicators, is an effect of a more complex developmental disadvantage relationship than a nutritional indicator (Checkley et al., 2008). The critical period of growth faltering is significant: analysis of data collected in the COHORTS showed that stunting in early childhood (infants and young children aged 2–12 months) was most closely associated with childhood development deficits (Victora et al., 2010).

Immune programming: Early programming by malnutrition may persist through childhood; there is evidence for altered programming of the immune system in malnourished children that may lead to changes in immune system set points, increased vulnerability to infections and non-communicable diseases and decreased immune system function in adulthood (Bourke et al., 2016). The Developmental Origins of Health and Disease (DOHaD) concept offers a conceptual framework on how in early life a nutrition and infection-related insult can program long-term immune and metabolic phenotypes (Barker, 1990).

Impaired vaccine: One of the important clinically critical consequences of the syndemic is impaired vaccine response among malnourished children. Most studies have shown that children with severe malnutrition have poorer acute seroconversion following measles, oral polio (POLIO) vaccine, rotavirus, and cholera vaccines (Oral Cholera) (Huo et al., 2015; Luabeya et al., 2015). This implies significant implications for herd immunity thresholds and the effectiveness of childhood immunisation programmes in high-malnutrition environments where malnourished children are less likely to be adequately immunised after receiving the recommended childhood vaccine course (Benn et al., 2016).

12. Prevention and Integrated Management Strategies

12.1 Nutritional Rehabilitation

Guidelines provided by the WHO have standardised the management of SAM with recommendations to use ready-to-use therapeutic food (RUTF; uncomplicated cases) and F-75 and F-100 therapeutic milk (in-patient) (World Health Organization, 2013a). At scale, community-based management of acute malnutrition (CMAM) has been proven to be effective and more than 75% of children involved in well-implemented programmes recover (Tekeste et al., 2012). Despite

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this, concurrent infections are difficult to manage at SAM and studies indicate that there is a survival benefit in giving antibiotics routinely at the time of SAM diagnosis, a recommendation which is reflected in knowledge of SAM in the WHO treatment guidelines (Irena et al., 2011; Trehan et al., 2013).

12.2 Micronutrient Supplementation

The implementation of programmes of universal vitamin A supplementation in vitamin A non-deficient populations in more than 70 countries has shown reductions in mortality ranging from 12 to 24% in the meta-analyses (Imdad et al., 2017; Mayo-Wilson et al., 2011). Zinc supplementation initiatives have shown to be effective in trials but are constrained to scale up through coverage, compliance and the necessity of situation-specific platforms of delivery (Haider & Bhutta, 2009). Multiple micronutrient powders (MNPs) have been created because of the complexity of concurrent deficiencies and systematic reviews indicate that they can be effective in reducing the prevalence of multiple micronutrient deficiencies, including anemia, with some questions remaining about how useful they are for reducing the prevalence of infection outcomes (Allen & Dror, 2011; De-Regil et al., 2013).

12.3 Breastfeeding and Complementary Feeding

One of the most effective interventions to reduce malnutrition and infection risk in the first six months of life is exclusive breastfeeding. In addition to the macronutrients and micronutrients that are essential for infant nutrition, breast milk contains immunoglobulins, antimicrobial proteins, human milk oligosaccharides (HMO) which help to induce development of a healthy infant microbiome, and bioactive components that regulate infant immune signature development (Ballard & Morrow, 2013; Victora et al., 2016). A systematic review showed that non-breastfed infants faced significantly increased risk of diarrheal and respiratory infections, with the highest risks for the most vulnerable environment (Sankar et al., 2015).

The quality of complementary feeding is as important as when it is offered. Early complementary feeding at 6 months helps to prevent micronutrient deficiencies and growth faltering and should be introduced with foods that are nutritionally adequate, safe, and diversified. Yet in LMICs, complementary foods are often poorly nutritionally balanced, low in micronutrients, and, prepared under hygiene risk conditions, should be addressed concurrently with the food quality and safety, as well as preparation processes (Dewey, 2016; Ruel et al., 2013).

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12.4 Integrated Approaches

Increasing evidence over time demonstrates the greater effectiveness of integrated nutrition and infectious disease interventions over parallel vertical programmes. Lives Saved Tool (LiST) modelling exercises have shown that the package of nutrition-specific interventions (NSIs), which include therapeutic feeding and micronutrient supplementation, and nutrition-sensitive interventions (NSIsw), such as WASH, malaria prevention, immunization, and social protection, can save significantly more children together than either intervention package alone (Bhutta et al., 2013b; Walker et al., 2013).

Large-scale programmes like IMCI approach the intersectionality of malnutrition and infections clearly in clinical management, and in this approach take a single initiative to deal with both concurrently in a single clinical encounter (World Health Organization, 2014). Multiple country evaluations suggest a relationship between better quality of case management and a decrease in mortality when IMCI is implemented, even though fidelity of implementation can be quite variable (Gera et al., 2016). The 2030 Sustainable Development Goals (SDGs) have a policy framework that explicitly connects nutrition, health, water, sanitation, education, and poverty reduction and that is generally consistent with the pattern of the syndemic approach.

Relevant effects of social protection programmes, such as conditional cash transfer (CCT) and unconditional cash transfer (UCT) programmes, have been observed on food security outcomes as well as on access to health services, which is relevant for syndemic prevention. A systematic review identified significant impacts of cash transfer programmes on child stunting and diet diversity in LMICs (Manley et al., 2012). Social protection mitigates the syndemic through raising household food consumption budgets, benefiting caregiver health and well-being and their utilization of health services during illness periods (Leroy et al., 2009).

13. Current Challenges

Despite its increased knowledge and intervention capacity, malnutrition-infection syndemics continue to manifest in considerable scale, with structural issues which cannot be resolved using solely technical solutions. In high-burden areas, there is still a deep and continued lack of capacity in the healthcare systems. The quality of treatment for SAM and associated infections is often suboptimal in pediatric wards of many LMICs, is poorly stocked with medications, and is not

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adequately supported by trained staff; in many community programmes RUTFs are frequently out of stock due to their reliance on a weak supply chain (Action Against Hunger, 2017; Puett et al., 2013).

Strategies for preventing key interventions have not been sufficiently covered. Global progress towards health-related vitamin A coverage improvements has stalled or even regressed in several high-burden countries over recent years, and improvements in WASH coverage have been greater for better-resourced groups than for poorer groups or for those living in rural areas (Prüss-Ustün et al., 2019; UNICEF, 2007). There is a mutual reinforcement between syndemic and vaccination coverage gaps, as vaccines do not provide optimal coverage in high malnutrition environments, and because malnourished children are the least likely to receive vaccines (Luabeya et al., 2015) and have suboptimal vaccine responses.

COVID-19 pandemic added more disruptions to nutrition and IDM programmes. Several sub-Saharan African and South Asian nations have experienced rises in their malnutrition prevalence in 2020 and 2021 due to disruptions of food supply chains, healthcare access and delivery, vaccination programmes and community nutrition programmes (Headey et al., 2020; Roberton et al., 2020). The present crisis has shed light on the weak points of nutrition-health systems integration in LMICs and the need for sustainable and community-based programme delivery.

The threat of climate change is a new threat to progress on malnutrition-infection syndemics. Climatic changes and risks to food security due to altered precipitation, extreme weather events, and rising temperatures may threaten to undermine gains made in nutrition and infectious disease control, especially for malaria and dengue fever outbreaks, in the geographic areas in which these diseases are present (Lloyd et al., 2011; Watts et al., 2018). Children in the highest risk nutritional environments are not only at the greatest risk of experiencing climatic risks but they are also the most vulnerable groups.

14. Research Gaps and Future Directions

Even in the face of the widespread body of evidence reviewed here, there are important gaps that limit the possibilities of designing effective interventions and of developing strategies informed by mechanisms. There is a need for greater investment in some priority areas.

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Mechanistic understanding of gut microbiota-immunity interactions: The mechanistic aspects of the interactions between gut microbiota and immunity in malnourished children need further studies. Even if the association between microbiome immaturity, EED, and growth faltering are known, the causal advances and best targets for therapeutic intervention are not well understood. The potential of prospective cohort studies with integrated metagenomics and metabolomics and immunological profiling has the potential to significantly contribute to the field (Blanton et al., 2017; Vonaesch et al., 2018a).

Long-term developmental consequences: In low-income country settings, little is known about the long-term developmental impact of early malnutrition-infection syndemics. Tracking cognitive, education, economic, and health outcomes into adulthood for high-burden populations through longitudinal studies is desperately needed to estimate the overall developmental burden of the syndemic and to argue for investing in early prevention (Walker et al., 2011).

Implementation science: The need to increase attention to implementation science for integrated, nutrition and infectious disease interventions. Some evidence for efficacy of individual interventions is reasonably robust, but effectiveness of implementing integrated programmes at scale in resource-constrained settings is limited. There is a need for research on the delivery platforms, task shifting, capacity building of community health workers and supply chain management (Dube et al., 2016; Theodoratou et al., 2019).

Overnutrition-infection syndemics: Compared with interactions between undernutrition and infection, the interactions between overnutrition and infection are under-researched in middle-income countries. Understanding how adiposity-associated immune dysfunction interacts with infection risk in these contexts will become ever more relevant in the context in which LMICs are in the midst of a nutritional transition and childhood obesity is increasingly affecting these regions (Development Initiatives, 2021; NCD Risk Factor Collaboration, 2017).

Climate-nutrition-infection interactions: It is necessary to look upstream in climate-nutrition-infection interactions and study them in the future. Future research plans should explicitly account for impacts of climate variability on food security outcomes, vector-borne disease transmission to food security, and impacts of undernutrition on childhood health outcomes to predict and reduce the risk of syndemic impacts from climate change (Lloyd et al., 2011).

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Vaccine efficacy enhancement: Research on vaccine efficacy enhancement strategies for malnourished children will be necessary if this is desired. One of the most important immunological gaps in children is a poor response to vaccines in malnourished children, which could be addressed through co-interventions such as nutritional or immune-modulating agents with public health implications (Benn et al., 2016; Soares-Weiser et al., 2012).

15. Conclusion

The malnutrition and infectious syndemic is one of the most impactful and protracted issues affecting paediatric health around the world. Observational data from epidemiology, immunology, microbiology, and public health show a synergy among these conditions in their effects, synergy in their social and structural conditions of sustainability. How this interaction works, through immunological impairment, disruption of the mucus barrier, dysbiosis of the gut microbiota, EED and micronutrient deficiencies, is now well understood and offers several targets for prevention and treatment.

This mechanistic understanding must be translated into producing relevant public health results by decisively breaking out of the wheel-spinning, programme-by-programme silos and moving towards more comprehensive, multi-sectoral, and synergistic nutrition and health approaches that integrate nutrition rehabilitation, Infectious Disease prevention/treatment, WASH, social protection and the structural determinants of health. The evidence examined in this paper shows that these kinds of integrated approaches are more effective – but seldom implemented worldwide. To realize the promise of integration one has to invest in strengthening health systems, delivering programmes in the community, building infrastructure to support research in high-burden settings, and committing to addressing the structural inequalities that perpetuate the syndemic. Malnutrition-infection syndemics, in the twenty first century, are a failure of science translation and political will and must be eliminated to hit the child health and development targets that are part of the Sustainable Development Agenda (United Nations, 2015).

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All authors (Muhammad Hashir Habib, Muhammad Tahir Habib, Laraib Zahra, and Eisha Nasir) contributed equally to the conception and design of the review, the literature search and screening, data extraction and synthesis, and the drafting and critical revision of the manuscript. All authors read and approved the final manuscript.

Competing Interests

The authors declare that they have no competing interests.

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Not applicable. This is a systematic review of previously published, publicly available literature and did not involve primary data collection from human participants or animals; therefore, ethics approval and consent to participate were not required.

Consent for Publication

Not applicable. This manuscript does not contain any individual person's data in any form (including individual details, images, or videos).

Data Availability Statement

All data generated or analysed during this study are included in this published article and its reference list. No new datasets were generated during the current study.

Abbreviations

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SAM: Severe Acute Malnutrition; MAM: Moderate Acute Malnutrition; LMIC(s): Low- and Middle-Income Country/Countries; WHO: World Health Organization; UNICEF: United Nations Children's Fund; FAO: Food and Agriculture Organization; WASH: Water, Sanitation, and Hygiene; EED: Environmental Enteric Dysfunction; CMAM: Community-based Management of Acute Malnutrition; RUTF: Ready-to-Use Therapeutic Food; IMCI: Integrated Management of Childhood Illness; ARI: Acute Respiratory Infection; SBI: Serious Bacterial Infection; UCT: Unconditional Cash Transfer; CCT: Conditional Cash Transfer; CHAIN: Childhood Acute Illness and Nutrition Network; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; HIV: Human Immunodeficiency Virus; COVID-19: Coronavirus Disease 2019.

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