SEVERE CHILDHOOD MALNUTRITION

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ABSTRACT

Severe childhood malnutrition predominantly occurs among children under 5 years of age living in impoverished conditions and among at-risk populations in low- and middle-income countries. Risk factors include poverty, poor living conditions with pervasive deficits in sanitation and hygiene, frequent infectious and environmental insults, food insecurity with poor prenatal maternal and foetal nutritional status, and suboptimal nutritional intake in infancy and early childhood. Major forms of malnutrition include stunting, wasting, and kwashiorkor; this review focuses on severe wasting and kwashiorkor, sometimes referred to as severe acute malnutrition. Children with any form of severe malnutrition, and especially those with multiple forms, are at markedly elevated risk of serious illness and death, primarily from acute infectious diseases. International growth standards form the basis of diagnosis and provide therapeutic endpoints based on anthropometry. Early detection and outpatient therapy of wasting and kwashiorkor with ready-to-use therapeutic food forms the cornerstone of modern therapy; only the small percentage of children with *complicated* severe malnutrition require inpatient care to address life-threatening infections and metabolic abnormalities, and for re-feeding with milk-based formulas. However, normalization of all physiological and metabolic functions is challenging, and children remain at high risk for relapse and mortality after discharge. Further research to better understand the pathophysiology of severe malnutrition, especially the mechanisms causing kwashiorkor, and to develop new interventions for prevention and treatment are urgently needed to reduce global child mortality associated with severe malnutrition.

[H1] INTRODUCTION

Tackling malnutrition is a major global health priority relevant to numerous Sustainable Development Goals (SDGs) and is highlighted directly in SDG Goal 2 to 'End Hunger, achieve food security and improved nutrition and promote sustainable agriculture'[1]. Several forms of malnutrition are recognised, including stunting, characterized by reduced linear growth; wasting (including moderate wasting and severe wasting, or marasmus), characterized by relatively low body tissue mass, but also marked by a host of other physiological abnormalities; and kwashiorkor, characterized by diffuse peripheral oedema. Table 1 summarizes some of the current anthropometric criteria for classifying overt malnutrition in children 6-59 months of age. This review focuses on severe malnutrition, which is common in resource-poor, fragile, and conflict-affected states and important given its association with child mortality globally[2].

It is important to note that the current classification is based on body size or the presence of oedema, which does not indicate aetiology or the precise nutritional deficits. This classification scheme serves the practical purpose of effectively screening and identifying malnutrition in public health settings, but inevitably does not address each and every specific nutrient deficiency a child may have, or indeed the biological variability between children. Such differences, while real, have no impact on current empiric management strategies that aim to address the predominant macronutrient and micronutrient deficiencies and possible infections that may affect such children.

'Severe acute malnutrition' is a popular term which has replaced an earlier term 'protein energy malnutrition', used to describe children with severe wasting (or marasmus) and kwashiorkor (or nutritional oedema). In this review, we use the composite term 'severe malnutrition' to emphasise its multifactorial aetiology, strong association with mortality[2], the fact that different types of malnutrition shown in Table 1 often co-exist in the same child over time[3], and that such concurrence further exacerbates mortality risk[4]. It is notable that recent clinical trials systematically enrolling children with severe 'acute' malnutrition by current criteria consistently show they are also severely stunted[5-9].

We concentrate on the largest and most vulnerable group – children under 5 years of age – reflecting SDG 2.2 target that the global community will "…by 2030 end all forms of malnutrition, including achieving by 2025 the internationally agreed targets on stunting and wasting in children under five years of age…"[1]. Other important populations are also affected but are beyond the scope of this review, such as malnourished pregnant women (with implications for intrauterine growth)[10] and malnutrition among older persons[11,12] and in those with disabilities[13,14].

[H1] EPIDEMIOLOGY

The key epidemiological aspect of severe malnutrition is its distribution across high child mortality countries, and major contribution to that mortality. Global estimates of prevalence vary between agencies and by methodology (Box 1).

The most commonly used figures are from the WHO, UNICEF, and World Bank inter-agency estimates which provide both levels and trends for child growth and malnutrition[15]. These joint monitoring program estimates are based on standard anthropometric indices. The Lancet Nutrition series[2] estimated that 165 million children under 5 were stunted in 2011, 101 million were underweight, and 52 million were wasted, of whom 19 million were severely wasted. These data have since been updated. Table 2 summarizes the current regional and global distribution of various forms of malnutrition among children under 5 based on 2015 estimates[15]. In contrast, the global burden of kwashiorkor remains uncertain, due to its wide geographic variability and the failure to include oedema assessment in most large nutritional surveys[16]; some estimates from regions of southern and eastern Africa suggest that kwashiorkor may account for 50-70% of cases of severe malnutrition[5].

The other major global metrics initiative, the Global Burden of Disease (GBD) estimates the number of deaths and disabilities directly related to malnutrition and treats stunting and wasting as risk factors. The 2015 GBD estimates suggested that 174,000 deaths among children under 5 were due to `protein energy malnutrition', with a global decline in the prevalence of severe malnutrition from a high of 25.5 million in 1990 to 22.5 million in 2015[15]. However, it is possible that 1990 represented a peak compared to prior years where figures were uncertain and HIV less prevalent. This influence is especially relevant for Sub-Saharan Africa, where HIV and severe malnutrition are strongly linked[17].

Malnutrition, especially severe malnutrition, is associated with high risk of mortality. The Lancet Nutrition Series[2] estimated that in the year 2011 some 875,000 deaths were attributable to wasting (12.6% of all under-5 child deaths) with 516,000 (7.4%) related to severe wasting (marasmus). In ten longitudinal studies involving more than 55,000 child-years of follow-up and 1,315 deaths in children under 5 years of age, all degrees of stunting, wasting, and underweight were associated with increased risk[4]. Children who are both

wasted and stunted have a substantially higher mortality risk – by several orders of magnitude – compared with those who have either wasting or stunting only[4]. Direct causes of malnutrition-associated deaths include infectious diseases such as diarrheal diseases, pneumonia, measles, and malaria, as well as metabolic disturbances such as hypoglycaemia and refeeding syndrome (see Management)[18,19]. Table 3 summarizes the known hazard ratios of deaths due to major childhood infectious diseases associated with various types of malnutrition[2].

As indicated in **Figure 1,** there are important geographical variations in severe malnutrition. This probably reflects variations in the distribution and effects of multiple risk factors including social and environmental factors (such as poverty, poor education, limited healthcare access, and a contaminated environment[20-23]), dietary factors (such as food insecurity[24], both chronic or acute, such as during famines; suboptimal breastfeeding; and complementary feeding practices[25]); high burden of infections (acute infections such as in the respiratory tract and diarrhoea[26]; as well as chronic infections such as HIV and TB[17,22]).

[H1] MECHANISMS/PATHOPHYSIOLOGY

[H2] Determinants of severe malnutrition

The loss of muscle and fat tissue that clinically characterizes wasting can be caused by inadequate protein and energy intake in the context food of insecurity, poor diets and disease. However, as has been well emphasized in the long-standing UNICEF conceptual framework, severe malnutrition is rarely related to single causal factors and arises from an interplay between social, political, and economic factors, chronic infections, and inflammation (both in the gut and systemically); loss of nutrients, such as through the intestinal tract; as well as increased energy expenditure, such as during infection or inflammation. In some circumstances gender issues and lack of female empowerment are important drivers of malnutrition. Additionally, severely malnourished children are also commonly seen in settings of population displacement and conflict[27] which worsen the impact of many of the aforementioned underlying and immediate factors and are associated with poor remedial strategies.

[H2] Mechanisms

[H3] Wasting and kwashiorkor

Ever since the initial descriptions of severe malnutrition, studies have aimed to understand the mechanisms underlying severe weight deficits, oedema, and their associated organ-specific and metabolic pathophysiology. Historical comparisons are difficult given changing case definitions over time[28] and the wide range of clinical manifestations reflecting differing pathologies. An overview of the diverse organ systems affected by severe malnutrition is shown in **Figure 2**.

Our knowledge on the mechanisms and metabolic changes associated with wasting comes mainly from literature on prolonged starvation and cachexia, i.e. wasting induced by a chronic illness[29]. During short-term starvation, free fatty acids and ketone bodies are primarily oxidized using available fat stores, together with some muscle protein oxidation to provide glucose for the brain and other important synthetic functions. After prolonged periods of starvation when body fat has been depleted, muscle protein is more extensively oxidized to maintain essential metabolic processes. Short-term regulation of muscle and fat tissue break down and synthesis also depends on insulin and glucagon, whereas longer-term regulation is mediated by other hormones such as growth hormone and thyroid hormone, catecholamines and corticosteroids.

Cytokine release as part of an inflammatory response in cachexia, especially TNF-α, interleukin-1 and interleukin-6, can negatively influence body composition through downregulation of appetite and food intake and direct catabolic effects on skeletal muscle and adipose tissue. Increased activation of the ubiquitin–proteasome-dependent pathway is the major proteolytic process that degrades myofibrillar proteins in cachectic conditions[29,30]. The function of the proteasome is to degrade damaged or unneeded proteins through proteolysis after being tagged by ubiquitin. More recently, autophagy which plays an essential role in degradation of damaged proteins, has also been implicated[31]. Ongoing activation of autophagy can be detrimental for muscle cells by removing important cellular components for muscle metabolism and contraction. However, the specific role of these pathways in severe wasting in children in low and middle-income countries (LMICs) have not been studied in detail.

Despite longstanding knowledge of the disorder, the underlying mechanisms behind the pathogenesis of kwashiorkor are still poorly understood. In the earliest report by Cecily Williams, she documented that children in Ghana with kwashiorkor were fed mostly a monotonous corn diet, deficient in essential amino acids such as lysine and tryptophan[32]. However, few studies have identified any specific nutritional deficiencies associated with the development of kwashiorkor, with usually no major differences in food group intake between children who developed kwashiorkor compared to those that did not, or those who developed wasting[33-35]. Despite numerous hypotheses, the aetiology of the development of oedema – the hallmark of kwashiorkor – remains undefined. The degree of hypoalbuminemia and recovery upon nutritional management in kwashiorkor correlates poorly with the degree of oedema or speed of its resolution[36]. Dietary intervention studies using animal models have demonstrated that features of kwashiorkor such as hypoalbuminemia, can be induced by a diet very low in protein and high in mono- and disaccharides[37-39]. Oedema, however, is rarely seen in animal models. Therefore, controversy remains as to the contribution of factors other than hypoalbuminemia to oedema in kwashiorkor[39,40]. The different mechanisms involved in the pathophysiology of kwashiorkor and functional changes related to severe wasting and kwashiorkor are described in more detail below[41].

[H3] Immunology/infections.

Children with severe malnutrition are highly susceptible to a variety of life-threatening infections[2,42], a consequence of what is effectively a functional secondary immunodeficiency. The clinical presentation of children with severe malnutrition to medical services may be due to serious infection, rather than malnutrition alone. Unlike typically recognised primary or secondary immunodeficiency conditions, there are multiple potential mechanisms of immune dysfunction in individuals with malnutrition[43,44].

Skin, respiratory, and gastrointestinal mucosal barrier integrity and function are often impaired, and in addition to excess risk of diarrhoea are often compounded by a chronic subclinical enteric dysfunction in close association with altered gut microbiota[45-47]. Severely malnourished children exhibit raised markers of systemic immune activation and intestinal inflammation with elevated levels of pro-inflammatory cytokines, such as TNF-α, IL1, IL6,

and IL12[48-50], which may also contribute to wasting and linear growth failure through the NFkB/IGF-1 axis, also seen in other childhood inflammatory conditions such as arthritis and inflammatory bowel disease. Systemic immune activation or immunostimulation in severe malnutrition may be caused by a range of conditions such as acute or chronic infection, an inflammatory enteropathy, translocation of microbial components[51,52], or dysregulated immune responses[53].

There is also evidence of T-cell dysfunction in severe malnutrition. Reduced neutrophil microbicidal activity[54], dendritic cell numbers, antigen priming and presentation[55], and reduced levels of proteins in the complement cascade are also observed[44]. Thymic atrophy, T-cell hyporesponsiveness, and impaired proliferation result from one or more of: chronic immune activation, the interplay between glucose and amino acid, and regulatory hormones, such as leptin for T-cell metabolism[53,56,57]. Although some changes may be reversible with nutritional rehabilitation[58], the dynamics of improved susceptibility to infection and reduction in immune activation have not been well characterised.

[H3] Endocrinology and metabolism.

Severe malnutrition affects many aspects of macro-nutrient metabolism and endocrine function[59,60]. Studies using stable isotope techniques in Jamaica and Malawi have attempted to characterize dynamic metabolic changes. A concept postulated by Whitehead and Alleyne in 1972 was that, in contrast to marasmus where the starvation-induced response of subcutaneous fat loss and muscle wasting was preserved, kwashiorkor was associated with a dysadaptive metabolic response. It was thought that a high carbohydrate, low protein diet led to a continuous glycolytic response and that a protein catabolic response was inadequate to meet the amino acid requirements necessary to maintain essential protein synthetic pathways[61]. Manary[62] and Jahoor[63,64] demonstrated that protein breakdown was indeed lower in children with kwashiorkor compared to marasmus and children in a recovered state. They also documented reduced essential and some non-essential amino acid concentrations, a deficit even more pronounced in kwashiorkor[65,66].

Apart from amino acid metabolism, lipid metabolism is also differentially affected in kwashiorkor and marasmus. Adipocyte lipolysis is tightly regulated with a central role for

insulin which inhibits hormone-sensitive lipase. Inflammation has been demonstrated to lead to enhanced adipose tissue lipolysis, which is related to release of cytokines such as TNF-α[67]. During starvation, when insulin levels are low, lipolysis is also stimulated and a number of studies have analysed the effect of severe wasting and oedematous malnutrition on lipolysis[68,69]. In a small cohort, free fatty acid flux as a measure of lipolysis was found to be elevated in children with severe malnutrition compared to controls[68]. However, a more recent elegant study by Badaloo et al., found no indication of elevated lipolysis in children with severe malnutrition at admission compared to nutritional recovery[69]. They did document a reduced free fatty acid (palmitate) flux and oxidation in children with kwashiorkor compared to marasmus. A caveat of the study is that children were studied in the semi-fasted state when insulin levels were likely low and lipolysis was stimulated and it is unknown how lipolysis was affected in the post-prandial state.

Glucose homeostasis is also disturbed in children with severe malnutrition, with hypoglycaemia being common, although frequent or continuous glucose measurement studies have not yet been performed to characterise this fully[59,70]. Kwashiorkor is associated with reduced endogenous glucose production compared to marasmus or healthy children, likely contributing to the development of hypoglycaemia[71]. This finding is consistent with the hypothesis of Whitehead and Alleyne[61]. Glucose utilization by muscle and other tissues is also affected. Utilization is mainly regulated by insulin; a number of studies have documented hypoinsulinaemia-related impaired glucose clearance in both kwashiorkor and marasmus[72-74]. This does not appear to be mediated by insulin resistance, as seen in type II diabetes mellitus, as insulin sensitivity seems to be preserved in children with severe malnutrition**.**

The observed effects of severe malnutrition on nutrient metabolism have influenced the development of dietary formulations to help metabolically stabilize affected children and subsequently support optimal growth. Specific nutrition-related recommendations such as frequent feeding to avoid hypoglycaemia and limiting protein and energy intake initially until metabolic homeostasis is restored have become important elements of existing management guidelines.

Many of the changes in nutrient metabolism have been linked to specific alterations in endocrine function. A striking feature is the blunted endocrine pancreatic response, although the endocrine pancreatic functional changes might be to some degree physiological as insulin sensitivity appears to be enhanced and therefore the need for insulin reduced. However, glucose intolerance found in these children suggests the insulin response is, to some degree, inappropriate. The mechanisms of impaired endocrine pancreatic function are poorly understood and pre-clinical models have implicated a more polarized membrane potential, changes in cAMP/protein kinase A, and in activity of the insulin receptor and its substrate[75-77]. No clear data exists on pancreatic glucagon responses, which is responsible for stimulating glucose production. Glucagon concentrations (semi-fasted) have been reported to be either mildly reduced during the acute phase of malnutrition compared to recovery or elevated in marasmus compared to controls[71,78], but stimulation tests or systematic glucagon responses during hypoglycaemia have not been performed.

Cortisol levels have generally found to be elevated or similar to non-malnourished children, likely related to stress, indicating that this axis is preserved in severe malnutrition and likely not responsible for the development of hypoglycemic episodes[49,79,80]. Most studies have documented a reduction in thyroid function in children with severe malnutrition[81,82]. Leptin concentrations are low in children with severe malnutrition reflecting the degree of adipose tissue loss. Leptin plays a direct role in immune function, metabolism and appetite regulation, and was shown recently to be inversely associated with mortality[49].

[H3] Oxidative Stress.

Oxidative stress, defined by an imbalance in the production of reactive oxygen species and anti-oxidant defences, has also been associated with severe malnutrition, in particular kwashiorkor. Studies since the 1980's indicated that children with severe malnutrition have reduced concentrations of anti-oxidants, including vitamin E and glutathione, again more pronounced in children with kwashiorkor[83-87]. While reduced intake of anti-oxidants likely contributes to lower anti-oxidant concentrations, they are are likely in part also related to reduced synthesis rates such as for glutathione [63]. Excessive oxidative stress can impair cellular function and lead to cell death and organ dysfunction. Golden et al., postulated that an imbalance between produced reactive oxygen species and antioxidant defences could

play a role in the pathophysiology of kwashiorkor[84]. While a pilot study suggested potential beneficial effects of treating severely malnourished children with anti-oxidants[85], a large randomized trial of an antioxidant mixture of riboflavin, vitamin E, selenium, and N-acetylcysteine in Malawi failed to decrease rates of kwashiorkor[88].

Clinical and animal model data suggest that peroxisomes and mitochondria, especially those in the liver, may also play a role in oxidative stress[37,89]. Reactive oxygen species such as hydrogen peroxide and superoxides are the main inducers of oxidative stress. Mitochondria are the main producers of reactive oxygen species (0.2-0.5% of oxygen is converted into reactive oxygen species)[90]. An imbalance between reactive oxygen species production and detoxification by peroxisomes damages mitochondria and overall cellular function, ultimately reducing the ATP production in the liver. Mitochondrial dysfunction and energy supply depletion, together with specific nutrient deficiencies, may influence the response to an intercurrent infection and contribute to the development of multi-organ failure[37,91-93], which needs further characterisation.

A model of the various metabolic changes observed in severe malnutrition is depicted in **Figure 3**.

[H3] Other pathophysiological alterations.

Cellular Na^+/K^+ ATPase pumps to maintain physiological fluid, electrolyte, and substrate differentials across cell membranes may be impaired resulting in increased membrane permeability (e.g., in kwashiorkor) or reduced energy availability (e.g. in severe wasting). The Na^+/K^+ ATPase pump activity may be consequently elevated in kwashiorkor and reduced in severe wasting as part of an adaptation to reduce energy expenditure[94,95].

[H2] Specific organ manifestations

[H3] Cardiac function and haemodynamics.

Historic data and clinical experience suggested that cardiac output and blood pressure could be reduced in starvation[96]. Cohort studies in small numbers of children in the 1960's and 1970's reported cardiac muscular atrophy and decreased cardiac output[97], especially in kwashiorkor[98]. The mechanisms behind the cardiac atrophy in malnutrition have not been

well studied. Work in a calorie restriction animal model demonstrated that the cardiac atrophic response was related to a proportional decrease of different subcellular components of cardiomyocytes. More recent studies using echocardiography have reported normal cardiac output when corrected for body surface area[99,100], with only impairments in the most severely ill children, likely related to sepsis. The largest study to date excluded severely ill children, examined them on average 4 days after admission and found no major differences in cardiac function between hospitalized severely malnourished and non-malnourished children[100,101].

[H3] Hepatic function.

Severe malnutrition, in particular kwashiorkor, is associated with changes in hepatic metabolic function. A striking feature of kwashiorkor is the presence of hepatic steatosis (fatty liver)[32]. Limited studies suggest that it is likely not related to impaired secretion of lipids by the liver in the form of very low-density lipoproteins[102]. Increased fatty acid release from adipose tissue that can be taken up by the liver in kwashiorkor has been reported in some[68,103], but not all[69] studies, perhaps related to whether analyses were done in the fasted state. Another hypothesis to explain the hepatic steatosis is impairment of hepatic lipid oxidation[69]. This is difficult to assess *in vivo* in children, but some data including reports using post-mortem samples and animal models provide evidence that mitochondrial function, mainly responsible for hepatic lipid oxidation, may be impaired[71,102,104,105]. Most recently, metabolomic approaches have supported these observations with elevated levels of acylcarnitines, which can be consistent with a lipid oxidation defect[49,106]. As discussed above, strong links exist between oxidative stress and mitochondrial function and could be related to impaired hepatic metabolic function[37]. Impairment in mitochondrial function would be expected to impact hepatic synthetic pathways, and reduced glucose synthesis in kwashiorkor was also found to be correlated with mitochondrial activity[71]. Finally, synthesis of the hepatically produced albumin was reduced in children with kwashiorkor[107]; whether other hepatic synthetic processes such as the production of coagulation factors are affected has not been studied.

[H3] Enteropathy.

Although there is much interest in the potential association of stunting with enteropathy[108], intestinal dysfunction also accompanies severe malnutrition. In recent years, increased attention has been given to intestinal function and disturbances in the commensal enteric microbiome in children with severe malnutrition. Diarrhoea is also common in malnourished children and associated with poor clinical outcomes[109-111]. Several factors might contribute to diarrhoea in individuals with malnutrition including intestinal infections and inflammation contribute to overt secretory and osmotic diarrhoea[50]. In addition, poor nutrient digestion due to impaired hepatobiliary and exocrine pancreatic function could also contribute to nutrient malabsorption and diarrhoea[112-115]. Finally, malnutrition leads to small intestinal villous blunting, thereby reducing intestinal absorptive capacity, including impaired mono- and disaccharide absorption[116].

Recent work has clearly demonstrated that children with severe malnutrition have distinct alterations in their intestinal microbiome which can impact intestinal inflammation and function and growth [117]. It has been shown that the faecal microbiome from children with kwashiorkor in Malawi was developmentally immature and less diverse when compared to their non-malnourished twins[118]. In this seminal and elegant study, investigators transplanted the faecal microbiota into the intestinal lumen of mice and found that they developed more profound weight loss than mice transplanted with microbiota from non-malnourished children which was associated with signs of disturbed metabolic pathways. In a separate birth cohort in Bangladesh such immature microbiota was also linked with wasting[119]. Other work comparing the microbiome between oedematous and wasted children reported a more limited separation in microbiome composition[120]. A potential limitation is antibiotic treatment prior to stool collection, which profoundly affects the microbiome composition. There is growing interest in the interaction between the bacterial microbiome, the virome[121], and eukaryotic organisms. However, the functional consequences of microbiome alterations in children with severe malnutrition have yet to be well characterized.

[H3] Renal function.

Studies examining renal function in severely malnourished children have been limited. Given frequent diarrhoea and dehydration, the pre-renal contribution to reduced glomerular

filtration may play a significant role. Early studies reported especially low glomerular filtration rates in dehydrated children with malnutrition[81] and subsequent studies have shown impaired glomerular filtration rates as well as signs of tubular dysfunction with reduced urine osmolality[122].

[H3] Brain function.

Severe malnutrition is associated with acutely altered cerebral function and behavioural changes. Children with marasmus are often apathetic with slowed movements and reduced speech. Kwashiorkor may also present with irritability apart from lethargy. Underlying mechanisms are uncertain. Cerebral atrophy has been documented in children with kwashiorkor[123,124]. Although the association between growth in early life and development has been well documented, relatively few studies have focused on the long term developmental impacts of severe malnutrition. Poor levels of development in children after an episode of severe malnutrition have been reported[125], as have the benefits of psychosocial interventions to improve development[126]. However, differing case definitions and treatment strategies makes it challenging to disentangle the direct impact of severe malnutrition from the many other risk factors and adversities that affect children also experience. Further studies are needed on this topic, in particular to understand the long-term effects of severe malnutrition on the different domains of development. In contrast, cognitive deficits associated with stunting are well described: one estimate is that for every 10% increase in stunting, the proportion of children reaching the end of primary school drops by 7.9%[127,128].

[H1] DIAGNOSIS, SCREENING AND PREVENTION

Although case definitions (**Table 1**) for epidemiological, biological and clinical purposes focus on anthropometry[129], it is vital to appreciate that malnutrition is actually a functional problem, and has been defined as *'*a state resulting from lack of uptake or intake of nutrition leading to altered body composition, decreased body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease'[130]. Anthropometry is used because such deficits are challenging to directly measure and is thus a proxy, rather than a direct measurement of malnutrition. Importantly, there is no 'gold standard'; different anthropometric measures capture different aspects and durations of

458 the underlying functional deficit. Some relate more closely to body composition and clinical
459 outcomes than others.
460
461 Accepted diagnostic criteria for severe acute malnutrition have changed over time. Initially,
462 measurement of weight-for-age (WFA), comparing the weight of the child to the weight of
463 children of the same age in a reference population, was used. Severe malnutrition was then
464 defined by a weight below 60% of the reference weight[131]. This definition was later refined
465 with the addition of oedema as an additional criterion[28]. In an attempt to focus on the
466 highest risk group of the most acutely malnourished children rather than those with low
467 WFA who were mainly stunted, it was then proposed to use weight-for-height, which
468 compares the weight of the child to the weight of well-nourished children of the same
469 length or height. The WHO recommended expressing weight-for-height in terms of Z-scores
470 (WHZ), thus measuring the difference with the median in standard deviations[132]. US
471 National Center for Health Statistics growth references were dominant until the 2006 WHO
472 Multi-Country Growth Reference study replaced it and other growth standards describing
473 how various populations *do* grow, with a 'gold standard' of how children *should* grow under
474 optimal health, environmental, and nutritional conditions[133]. Severe acute malnutrition was
475 then defined as a WHZ more than 3 standard deviations below the reference for median
476 length or height or bilateral pitting oedema[134].
477
478 The prognostic value of these WHZ recommendations were not confirmed by community
479 studies of untreated children conducted after this index was introduced. Previously, a
480 review of all studies on the relationship between anthropometric indices and mortality in
481 1994 concluded that '*in comparing across studies and across the various comparative*
482 *criteria, the most consistent observation is that weight for height is the least effective*
483 *predictor of mortality'*[135]. These studies showed that unadjusted mid-upper arm
484 circumference (MUAC) was more discriminatory for subsequent mortality than other
485 indices. This was shown in Bangladesh[136,137], Senegal[138], Democratic Republic of Congo[138],
486 Uganda[139], and the Gambia[140]. This association between MUAC and the risk of death may be
487 due to the preferential selection of children who are younger and who are *both* stunted and
488 wasted, and thus are particularly at risk[141]. This association of MUAC with mortality led

WHO to introduce a MUAC less than 115 mm as independent diagnostic criterion for severe acute malnutrition in children aged 6-59 months in 2013[142] (**Table 1**).

In practice, given the challenges of measuring WHZ frequently or at large scale in the community, programmes tend to use a MUAC less than 115 mm for screening severe wasting among children aged 6 months to 5 years, along with the assessment of oedema to diagnose kwashiorkor. Oedema is assessed by depressing firmly down to the 3rd to 4th tarsal bones with the pad of the examiner's thumb on the dorsal aspect of the child's foot for 3-5 seconds and then observing for pitting oedema for 2-3 seconds. The presence of symmetric bilateral pedal pitting oedema in a vulnerable child in a high-risk population, regardless of other anthropometric values, generally is sufficient to constitute the diagnosis of kwashiorkor. More severe or longstanding oedema is more likely to be observed more proximally on the child's body. Oedema is graded by WHO as 1+ if limited to the feet and lower legs, 2+ if present in the arms, or 3+ if found on the face, although this classification scheme is of relatively limited direct clinical utility. An alternative option to identifying children with either MUAC or WHZ is to increase slightly the MUAC cut-off to pragmatically define severe malnutrition. Although additional children identified by increasing MUAC are not the same as those identified by WHZ, this approach has the important advantage of better identifying children with a higher mortality risk than using both MUAC and WHZ[143].

MUAC had been proposed since the 1960's as a simple approach to diagnose malnutrition[144]. For decades its use was limited as it did not identify the same malnourished children as WFH[129]. However, following the development of community based management of severe malnutrition as an effective intervention to prevent these deaths, MUAC has become more frequently used programmatically.

The diagnosis of severe malnutrition among infants under 6 months old presents special challenges. It has only recently become apparent that there is a much larger burden of malnutrition in this age group than previously assumed[145]. The WHO currently recommends using weight-for-length Z scores (WLZ) to identify at-risk infants, but only because there is paucity of evidence on other criteria. Few prospective studies to date have examined the discriminatory performance of anthropometric measures against risk of subsequent death.

As in older children, MUAC identifies a slightly different group of infants, but has superior performance for mortality prediction than WLZ in the Gambia[140]. A MUAC threshold of less than 110 mm has been proposed based on a clinical trial in Kenya that confirms that this identifies a group of infants with very high mortality risk[6,146].

[H2] Screening

Using MUAC or the presence of oedema to diagnose severe malnutrition (**Figure 4**) makes its detection relatively straightforward. The best approach is to measure MUAC frequently, ideally every month or every time a child is unwell. The prognostic value of all anthropometric indices improves for short term follow-up[135] and in particular for MUAC[147]. A promising approach is to give MUAC tapes with a cut-off at 115 mm to mothers and to show them how to detect malnutrition by measuring MUAC[148,149]. The technique is simple enough to be taught rapidly[149] and involving mothers at this stage allows malnutrition to be detected early, before the onset of complications and reduces the need for initial inpatient treatment[148]. However, the use of MUAC for screening and managing severe malnutrition still has significant room for global expansion, delayed due to only relatively recent guideline development by normative bodies such as WHO and UNICEF, contributing to poor uptake by local practitioners and professional bodies.

[H2] Prevention

Given its high morbidity and mortality, preventing severe malnutrition is clearly one of the most important goals in global health. Nevertheless, this remains rather elusive in most impoverished and humanitarian settings and requires programs to address maternal and child malnutrition holistically. Many countries have been able to reduce severe malnutrition and stunting dramatically over the years in aggregate terms and also through the reduction of inequities[150-152]. In most instances, this has required a combination of economic growth, public sector programs focused on reducing inequities, and investments in nutrition-sensitive and -specific interventions.

No single intervention (neither nutrition-sensitive or -specific) has been shown to effectively reduce the rates of severe malnutrition or stunting for individual children[153,154]. Rather, packages of public health approaches are needed, including: improved consistent access to

clean water, sanitation, and hygiene; improved agricultural productivity to minimize food insecurity for children and their families (including especially pregnant and lactating women); timely universal vaccination; early and efficient access to primary health facilities and care for acute illnesses such as pneumonia, diarrhoea, measles, and malaria; an emphasis on exclusive and continued breastfeeding; and attention to effective complementary feeding. Each is likely to impact malnutrition generally, and in turn rates of severe malnutrition, even as these benefits are extremely hard to quantify[155].

A comprehensive prevention package at the individual level should ideally begin with teenage girls and young women prior to childbearing, with comprehensive health education and nutritional interventions aimed at optimizing their overall physical health, nutritional status, and psychosocial readiness for pregnancy and childbirth[156]. During pregnancy, providing the full complement of evidence-based prenatal and perinatal support, including micro- and macronutrient supplementation, anti-infective therapy (for both prophylaxis and acute infections), early and frequent counselling and education about neonatal nutrition and care, among other measures[157] is believed to lead to a generally improved health status for both mother and infant.

Optimizing macronutrient intake during infancy begins with the prompt initiation of breastfeeding in the neonate, followed by exclusive breastfeeding for the first six months of life, the progressive introduction of nutritious and diverse complementary foods after six months, and continued breastfeeding for at least two years[158]. Context-specific micronutrient programs may include vitamin A, iron, and multiple micronutrient powder or small quantity lipid-containing nutrient supplements (LNS), and zinc for cases of acute diarrhoea. The primary health system should ensure that all children living in at-risk communities undergo frequent growth monitoring with intervention for acute malnutrition, receive all recommended immunizations, and have ready access to essential interventions such as oral rehydration salts for diarrhoea, antibiotics for pneumonia, antimalarials, and appropriate antiretroviral therapy and opportunistic infection prophylaxis for HIV-infected and -exposed children[159]. Early and comprehensive intervention for children with moderate malnutrition is important for limiting the incidence of severe malnutrition, as it is assumed they are at increased risk for further progression to severe malnutrition[160].

As an example of the inability for limited vertical programs to make consistent impacts on childhood malnutrition, the largest and most comprehensive multicentre trial of small quantities of LNS failed to demonstrate significant benefits with regards to stunting or wasting when provided in Malawi[161,162] and showed only modest benefits in Ghana[163,164]. The same intervention did have better impact on stunting and wasting in Burkina Faso[165]; however this trial also included treatment for diarrhoea and malaria, emphasizing the importance of interventions that extend beyond nutritional therapy alone.

[H1] MANAGEMENT

[H2] Overview

The goals of management are to prevent short-term mortality, achieve sustained nutritional recovery in order to reduce susceptibility to life-threatening infections and to support neurocognitive development. Despite their striking clinical differences, treatment recommendations for kwashiorkor and wasting have several elements in common (Box 2). Much of the current management of severe malnutrition is based on expert opinion and relatively small observational studies developed over many iterations in the 1970s and 1980s, without necessarily being based on modern randomised clinical trials[166-168]. However, their promulgation in a series of WHO guidelines and training programs has made them practical and adopted widely. Indeed, they have become so engrained in practice that it may be considered unethical to conduct randomised controlled trials without documenting equivalence or superiority to this agreed standard of care. This systematic approach over the last few decades made it possible for the development of RUTF and its widespread use, making care for severe malnutrition even more able to be implemented widely. Many of these principles of management have also emerged from the emergency context; translating these to the relatively stable LMICs where severe malnutrition is a daily burden on health systems, remains a challenge requiring integration into all levels of the health system[169].

The effectiveness of RUTF in decreasing mortality cannot be overstated. The early RUTF trials comparing children treated in the community with RUTF with those treated in hospitals initially aimed only to ensure that mortality in the community was not higher than

in the hospital. As those early studies showed not just similar, but actually even *lower*, mortality among those treated in the community, these community treatment programmes rapidly expanded, as this approach dramatically increased treatment coverage and proved to be a remarkably powerful way to reach previously untreated children. Many community programmes subsequently were able to confirm lower mortality rates when compared to historical data from the hospital-based approach. For these reasons, this massive development of community-based programmes largely took place in the absence of formal randomized controlled trials comparing children treated with RUTF with untreated children, as of course this would be unethical. Of note, for the same reasons, the efficacy of hospital-based treatment of mortality has never been formally established. RUTF provides nutrients at levels which are nearly impossible to reach without the use of supplements[170]. For this reason, no attempt was made either to assess directly the effect of RUTF on weight gain compared to a diet based on local foods. Comparison to local diets supplemented with additional vitamins and minerals have shown a higher proportion of recovery and weight gain in children treated with RUTF[7,171].

[H2] Nutritional management in the community

Until the 2000's, all children with severe malnutrition were usually managed as inpatients with milk-based feeds and empiric broad-spectrum parenteral antibiotics, assuming that nutritional metabolic complications and serious, sub-patent infection were always present[134]. Management has been revolutionised by the recognition that if identified early enough, children may be clinically stable even if anthropometrically malnourished *('uncomplicated malnutrition'*). This contrasts those with more severe disease who are sick as well as malnourished *('complicated malnutrition'*). Uncomplicated malnutrition can be safely treated in the community via a proactive, public health-based approach to care. This is made possible by community screening using mid-upper arm circumference and by feeding with lipid-based ready-to-use therapeutic foods (RUTF) at a dose of 175 kcal/kg/day whose low water content means they can be safely stored for long periods[172,173]. RUTF was developed to provide essentially the same nutritional content as the F-100 therapeutic milk formula used in hospital settings but in a dehydrated form that can be administered at home with no preparation or cooking and minimal risk of contamination[174]. The underlying formulation of F-100 was derived and optimized from metabolic studies of hospitalized

severely malnourished children. Essential to its efficacy is that its high levels of micronutrients and macronutrients likely to be deficient in a severely malnourished child. These also include potassium and other electrolytes, often lacking in traditional diets and whose deficiencies are exacerbated by intercurrent infections and diarrhoea. This formulation is effective in facilitating rapid catch-up weight gain but may not correct all metabolic disturbances a child is suffering from.

Decentralized services closer to patients' homes help avoid the costs and risks of nosocomial infection of inpatient care[175,176]. This strategy has enabled severely malnourished children without overt signs of infection or other complications (generally more than 90% of all severely malnourished children) to be treated in the community (**Figure 5**)[173]. Outcomes among children with uncomplicated severe malnutrition treated in the community are markedly better than among children of similar anthropometric status who are sick and require hospitalisation[7,134,177-179]. Improving coverage, earlier case detection, and addressing costs are key targets for health-systems research.

[H2] Management of complicated severe malnutrition

Children with complicated severe malnutrition are managed as inpatients to address life-threatening complications. Under current recommendations, children are discharged from inpatient care when serious complications have resolved (rather than after achieving specific anthropometric targets), to continue therapeutic feeding as an outpatient, and then supplementary feeding for moderate malnutrition (**Figure 6**)[156]. Transition from hospital to home requires ensuring the parent/caregiver understands the treatment phases, what is expected from them, as well as linkage to available nutritional, medical, and social services.

Children with complicated severe malnutrition, usually admitted to hospital because of severe infection, typically have a case fatality of 12% to >20%[111,168,180-182]. HIV infection, present in 15-29% of children admitted with severe malnutrition in sub-Saharan Africa, is associated with an approximately 3-fold increased risk of inpatient mortality[180,182,183]. Attempts at reducing mortality in complicated severe malnutrition have met with limited success[180-182,184-186], presenting a clear need for research to improve care[17,166].

Children with severe malnutrition are physiologically 'brittle'. Management must address life-threatening medical conditions such as infections as well as nutritional and metabolic demands. Nutritional management aims to address disturbed carbohydrate and energy metabolism affecting blood glucose, ATP, and body temperature[37,72,187-189], as well as both the distribution of fluid and electrolytes between intra/extracellular and intra/extravascular compartments. Regular, and initially relatively low energy dense, feeding aims to prevent and treat hypoglycaemia, reduce sodium, and increase potassium and phosphate levels. Hyperosmolar feeds and intravenous fluids are avoided whenever possible[190].

[H2] Therapeutic feeds

Therapeutic feeds have been designed for nutritional and metabolic stabilisation and rehabilitation aim to address anticipated caloric needs, stage-appropriate protein requirements, electrolyte and micronutrient deficiencies, while initially limiting exposure to nutrients such as iron that may be harmful to infected or metabolically unstable children. The composition of feeds for complicated severe malnutrition is based on a large body of observational work[191]. However, precise nutrient requirements and bioavailability are not well established, and may vary by setting and co-morbidities. Trials of revised formulations of milk-based therapeutic feeds are awaited.

Feeding for children with complicated severe malnutrition is begun cautiously with milk feeds containing relatively low levels of protein, low levels of sodium, and high levels of potassium provided initially, all designed to match the child's lowered metabolic capacity (F-75 milk: 130 mL/kg/day providing 97.5 kcal/kg/day and 1.2 g protein/kg/day and micronutrients). This is aimed at improving metabolism, gut motility and nutrient absorption; clinical improvement during this stabilisation phase will be manifested by improved appetite and reduced oedema (if present). Once there is restoration of appetite and improvement in signs of infectious complications, children transition to ready-to-use therapeutic foods or higher energy/protein milk feeds (F-100 milk: 150-220 mL/kg/day providing 150-220 kcal/kg/day and 4.4-6.4 g protein/kg/day and micronutrients) in order to gain weight during the rehabilitation phase. No other food should be given – except breastmilk (which should be given before therapeutic feeds to keep stimulating the maternal milk supply). Additional micronutrients (including zinc for diarrhoea) beyond what

713 is included in F-75/F-100/RUTF are generally unnecessary without specific signs of
714 deficiency[190].
715
716 Diarrhoea due to carbohydrate malabsorption may occur with therapeutic feeding[116,192,193].
717 Severe refeeding syndrome (Box 3) is a potential concern, although this risk may be
718 lessened when children are allowed to demand-feed on F-75, F-100, or RUTF, governed by
719 appetite, rather than being aggressive fed by nasogastric tube beyond their hunger or
720 thirst[182,194,195]. However, no randomised trials of formulation, amount, or duration of F-75
721 and F-100 have been published, before or since its introduction.
722
723 Severely malnourished infants under 6 months old are currently fed with breast milk, infant
724 formula, or diluted F-100 milk, often using a technique called 'supplementary suckling'
725 whereby a key aim of treatment is also to (re)establish effective exclusive breastfeeding
726 wherever possible[196]. Further research is needed to provide a stronger evidence base for
727 the effectiveness of this strategy and other components of their management[197].
728
729 RUTF has no mandatory recipe or formulation, but minimum micro- and macronutrient
730 concentrations, quality control, and microbiological safety standards are outlined by WHO
731 and UNICEF[177]. The predominant formulation of RUTF consists of peanut paste, milk
732 powder, sugar, oil, and micronutrients, with similar overall nutritional content to F-100 milk.
733 The high relative cost of RUTF is largely due to its milk powder content; this may be only
734 partially overcome by local production, which has its own barriers including the high costs of
735 constructing and maintaining appropriate production facilities, the importation of expensive
736 ingredients, and high local taxes[198-201]. Trials of RUTF without milk powder suggest inferior
737 efficacy on growth[202,203]. Recent trials also suggest that the essential polyunsaturated fatty
738 acid (PUFA) composition of RUTF is not optimal[8,204], but a more favourable, reduced n-6
739 PUFA or enhanced long-chain n-3 PUFA RUTF product presents challenges for shelf-life, and
740 their effects on growth and neurodevelopment is uncertain.
741
742 RUTF is not intended to replace F-100 milk, but rather to enable much earlier treatment of
743 uncomplicated cases in the community with greatly expanded coverage at lower cost than
744 inpatient admission, thereby reducing overall mortality from malnutrition. After completion

of treatment, transition from RUTF to the home diet and environment is a potential point of faltering, but, aside from standardised supplementary feeding, strategies to decrease this risk have not been assessed in trials.

[H2] Antibiotics

Current guidelines recommend empiric antibiotics for all severely malnourished children because of concern that they may not initially present with obvious signs of infection, and may deteriorate suddenly without prior fever or warning signs[205,206]. No prospective clinical trials demonstrating the need for antibiotics among children with complicated severe malnutrition have been published. However, there are reports of *in vitro* non-susceptibility to beta-lactam antibiotics and gentamicin, the recommended first line agents. Interpretation of these studies is challenging because of bias from usually being from tertiary centres and/or not distinguishing community from hospital-acquired infections[207].

For outpatient management, routine antibiotics have been questioned on the basis of cost and risks of enhancing antimicrobial resistance. In Malawi, 2,767 children in a community health centre-based therapeutic feeding program were randomised to amoxicillin or a third-generation oral cephalosporin, cefdinir, or placebo; these antibiotics were associated with a 36% and 44% reduction in mortality compared to placebo respectively, and more rapid recovery[5]. Compared to other centres, there was a relatively high prevalence of kwashiorkor. In Niger, 2,414 children with uncomplicated marasmus, excluding children previously treated for malnutrition, were randomised to oral amoxicillin or placebo in an outpatient feeding program attached to a referral hospital[208]. Mortality was very low (0.5%), without difference between randomised groups. Amoxicillin was associated with faster recovery and a 14% reduction in the relatively high proportion of children referred to hospital. The evidence from these trials supports continuing the use of empiric antibiotics in this context[207,209]. However, further research addressing the full spectrum of severely malnourished children, in other settings, on the effects of treatment on antimicrobial resistance, on the potential for more targeted prescribing with point-of-care biomarkers, and on costs to the health system and families is needed.

[H2] Other interventions

Profuse watery diarrhoea, hypovolaemia, and shock are common and associated with high mortality in severely malnourished children, despite current management guidelines[109,167,210]. The optimal composition and rate of intravenous or oral fluid therapy, or other supportive therapies in settings without access to advanced paediatric intensive care is unclear and controversial[166], as only two small trials have been undertaken in this population[211,212]. A large clinical trial in Africa has indicated that aggressive fluid management of children without diarrhoea but with some signs of shock is harmful in non-severely malnourished children[213], and therefore this is almost certainly the case in malnourished children. Studies are yet to be done that distinguish shock arising from sepsis from hypovolaemia due to diarrhoea in the context of the disturbed physiology of severe malnutrition. These studies, followed by trials are needed to inform management strategies that could be implemented in the hospital settings where children with complicated severe malnutrition are treated.

Chronic systemic and intestinal inflammation is a feature of severe malnutrition, infection, and environmental enteric dysfunction[50]. Mortality risk appears to be more closely related to markers of systemic rather than intestinal inflammation; however bacterial intestinal translocation and aberrant immune function may contribute to both. Gut-protective therapies targeting inflammation, microbial translocation, malabsorption, intraluminal nutrient processing and normalising the intestinal microbiome may yield novel and effective interventions. Trials to date of oral pre- or probiotics have not altered inpatient outcomes, but suggest there could be later benefits[9,214], and in the future, are likely to be better directed by improved knowledge of microbiome ontogeny and functions[121,215,216]. Other potential strategies under research include anti-inflammatory agents[217] and gut-trophic nutrients, including alanyl-glutamine[166,218] and other dipeptides.

[H1] QUALITY OF LIFE

Severely malnourished children typically live in settings of pervasive poverty, low female literacy, food insecurity, inadequate water and sanitation, overstretched health systems and often have dismal futures[2,219,220]. The acute management interventions described here and practiced in the field do not fundamentally alter these risks. That many acutely malnourished children are also severely stunted at presentation[5,7,208,221], indicates chronic

809 ill-health and malnutrition. Studies in Malawi, Kenya, the Gambia, and Bangladesh have all
810 revealed that anthropometric recovery alone is not enough: following discharge from
811 inpatient care for severe malnutrition, there is a high rate of mortality, predominantly from
812 pneumonia and diarrhoea[221-224]. Elevated mortality risk is also evident following treatment
813 in community-based nutrition programmes[173,225]. Reasons are likely to include: a home
814 environment that includes the exposures mentioned above; undiagnosed chronic illness;
815 and the fact that attending healthcare for illness episodes or ongoing therapeutic feeding
816 may be critically limited in disadvantaged populations by access, stigma, and high
817 opportunity costs[225-229]. They may also have some pre-existing vulnerability that results in a
818 vicious cycle of illness, malnutrition and hence even greater vulnerability to infection (e.g. a
819 mild immune deficit that would cause little problem in a resource-rich, low infectious
820 disease setting)[230]. Certainly, not all siblings growing up in the same family seem to be
821 equally affected by the same home environment[224].
822
823 During treatment and recovery from severe malnutrition, weight and MUAC usually increase
824 rapidly; however, height does not – it is typically only sufficient to maintain the baseline
825 height-for-age Z score[5,9,208,221,224]. Body composition during recovery from severe
826 malnutrition has been assessed using bio-impedance and double-labelled water studies.
827 Children treated for severe malnutrition typically have less lean mass (fat-free mass) than
828 non-malnourished children in the community[203,231,232]. Children in Malawi followed up an
829 average of 7 years after hospitalisation for severe malnutrition had reduced lean tissue
830 rather than excess fat and were more stunted, but had similar head circumference as well
831 as respiratory and cardio-metabolic function compared to controls[231]. In these Malawian
832 children, and similar children in Senegal, those with prior severe malnutrition also had
833 weaker hand grip and lower exercise tolerance than controls[231,233]. This 'thrifty' growth
834 pattern raises concerns that early childhood severe malnutrition may predispose to non-
835 communicable diseases (NCDs) later in life. However, in these studies, stunting and other
836 insults may have been present prior to the known episode of severe malnutrition. While the
837 effect of in-utero exposure to a wide range of later life NCDs is by now well
838 established[234,235], the duration of that window of plasticity and the consequent impact of
839 infant and child malnutrition on later life NCDs is still unclear[236].
840

Severe malnutrition and stunting are known to be associated with delayed child neurodevelopment, behavioural problems, lower school achievement, and reduced adult capital[2,237-239]. Clinical trials in Jamaica and Bangladesh have reported that psychosocial stimulation or prolonged home visiting programmes after hospital discharge among infants and young children with severe wasting or kwashiorkor significantly improved infant development scores in the short-term, as well as achievement and IQ into adolescence[125,240-243]. Several micronutrients are potentially vital for cognitive development, including polyunsaturated fatty acids, thiamine, choline, vitamin D, folate, iron, copper, selenium and iodine[237,239,244,245]. Micronutrient deficiencies may vary among severely malnourished children by age, location, and underlying causes of malnutrition. However, none of these micronutrients have yet undergone clinical trials with neurodevelopmental endpoints in the context of severe malnutrition.

Further studies are needed on the optimal duration of treatment, factors limiting lean tissue synthesis (including the role of high-quality dietary protein), how zinc and other micronutrients may modulate tissue deposition, psychosocial stimulation, physical activity, and later effects on health risks in adolescence and adulthood[125,126,232,246-248].

[H1] OUTLOOK

While this paper has highlighted many of the negative consequences and costs of malnutrition, it is important to underscore the huge gains in understanding its epidemiology and management at scale. In recent years, community-based management of acute malnutrition has revolutionised treatment programmes and has made it a realistic goal to reach large numbers of children with effective nutritional and clinical care in various settings. Children with severe malnutrition with a high risk of death can be easily identified, and most of them can be successfully treated at the community level by parents with assistance from community health workers and outreach services. In terms of what appropriate prevention and management of severe malnutrition could achieve, modelling 90% scale up of evidence based interventions suggested that 61% of wasting could be prevented and almost 350,000 child deaths averted annually[249]. Major international initiatives like No Wasted Lives[250] are working towards ambitious targets for this. There is much still to do, but progress towards lowering child mortality is being made. As more

children survive, and as poverty (a major driver of malnutrition) decreases in many countries, new challenges will emerge. It is now no longer enough to just help children *survive* an episode of severe malnutrition. We must also, following the Global Strategy for Women's, Children's and Adolescent's Health (2016-2030), help them *thrive*[249]. For this, we must continue to transform both curative and preventative services. More efforts are needed on previously neglected populations such as infants aged <6 months [251] and children with underlying disability[252] and other identified vulnerabilities. More focus is needed on preventing relapse and readmission - though how to achieve this remains an all too open question. A large recent trial in Kenya exploring prophylactic co-trimoxazole for high risk children discharged from hospital was unfortunately negative[6]. Perhaps other broad-spectrum antibiotics or other strategies given with the same rationale of supporting a long period of immune system recovery might have helped. Improved post-discharge social support and social safety nets to address food security are additional future areas to explore. Box 4 summarizes some of the key research gaps in relation to severe malnutrition which builds on some recent relevant exercises [262, 263.]

While much of the knowledge and many of the tools already exist to make huge inroads into the problem of severe malnutrition, this review highlights several key aspects of complicated severe malnutrition that need a better understanding of pathophysiology and the efficacy of potential interventions to save lives in these very high-risk children. Gaining an understanding of the pathophysiology of kwashiorkor may also lead to phenotype-specific therapeutic interventions to improve outcomes. This requires research using some of the high quality modern tools for assessing metabolism and function that are available. Additionally, while much of the older research on the pathophysiology malnutrition has been informative and hypothesis-generating, it commonly does not meet today's standards for evidence quality in terms of participant selection, avoidance of bias, and sample size. Going forward, there is a need to continue to test well-founded hypotheses in appropriately designed randomised trials with appropriate biomarkers, information on mechanisms, and sound clinical measures.

The overarching priority is to make severe malnutrition just as much a thing of the past in African and Asian countries as it is in Europe and North America today. Achieving the SDGs

for health and nutrition will only be possible through addressing severe malnutrition. However, to do this we must recognize that the current status of severe childhood malnutrition is wholly unacceptable and reducing the burden of morbidity and mortality associated with it is a global moral imperative. As we pen these words the world is once again witnessing a human disaster of famine and severe malnutrition in major parts of Africa. We have the evidence that can make severe malnutrition history across the world with the knowledge that we have. To do this will require political will, investment in peace building and reducing man-made and natural disasters, issues that should unite the world.

Box 1. Factors that can affect estimates of the epidemiology of malnutrition.

Global data and epidemiology of malnutrition must be understood in the light of methodological challenges and contextual factors.

Firstly, acute malnutrition is often highly seasonal, peaking around the pre-harvest rains, when food is scarce and burden of infectious diseases higher (*e.g.*, more malaria and diarrhoea due to rain). In many instances, the interface of food insecurity, population displacement, and drought produce the conditions leading to famine. Hence, cross-sectional prevalence surveys for malnutrition must always be interpreted in the light of the time of year when conducted and concomitant events.

Secondly, while prevalence estimates from cross-sectional surveys are suitable for slow-changing conditions like stunting, they are poor at capturing the rapidly changing nature of severe and moderate malnutrition, which have a relatively acute onset and rapid resolution. Malnutrition can also recur, without record or health services contact at each episode. Incidence is therefore the most informative measure of acute malnutrition[253], but is rarely well documented due to ascertainment difficulties[254]. Addressing this limitation, prevalence-to-incidence 'conversion factors' are sometimes used – especially to estimate caseloads for planning treatment services[255]. There are efforts underway to improve surveillance systems for severe malnutrition[256-258].

Thirdly, there are measurement issues in surveys that can affect estimates. Mid-upper arm circumference and oedema, both case-defining criteria, are not measured in many field surveys, resulting in prevalence underestimates since they do not necessarily overlap with wasting as defined by low weight-for-length[16,228,259]. Additionally, even when included, oedema may be missed in rapid surveys with poorly trained surveyors[16].

Finally, infants under 6 months old may also be missed from surveys, either by design, or because mid-upper arm circumference standards for this age group have not been established. It is not always clear if surveys of 'child under 5 year malnutrition' do or don't include infants <6months.

Box 2. Management of severe acute malnutrition

The management of children with severe malnutrition encompasses several components:

- Identifying and managing immediately life-threatening infections and complications
- Therapeutic feeding with macro- and micronutrients to achieve homeostasis and overcome nutrient deficits
- Treatment of sub-clinical infections and underlying conditions, such as HIV or TB
- Emotional stimulation of the child and psycho-social support for parents or carers
- Linkage to medical, nutritional and social services during therapy and convalescence

Box 3. Refeeding syndrome

Refeeding syndrome has been long recognized to potentially contribute to poor clinical outcomes. A switch from a catabolic to an anabolic state induced by rapidly increased nutrient intake leads to a surge in insulin secretion, which can acutely cause hypoglycaemia, and extra-cellular electrolytes to be driven into the intracellular compartment. This can lead to dangerously low blood concentrations of potassium, magnesium, and phosphate, resulting in lethargy, seizures, muscle weakness, impaired cardiac function, and respiratory failure[260]. The precise incidence of refeeding syndrome is unknown, related to the lack of a precise definition as well as an inability in most settings to accurately measure electrolytes and other biomarkers. Insufficient electrolyte intake and gastrointestinal and renal losses can affect electrolyte concentrations, making it challenging to relate abnormal plasma levels directly to refeeding syndrome. A recent Ugandan study found hypophosphatemia in 76% of severely malnourished children 2 days after admission, and it was associated with mortality[182].

The concept of refeeding syndrome influenced the development of the main milk-based formulation used for stabilization: F-75, which is characterized by low protein content and reduced energy, mostly from carbohydrates, as well as added phosphate potassium, magnesium, and other micronutrients including vitamin A and zinc in particular. However, with energy mostly from carbohydrates, glucose becomes the predominant fuel source. This potentially leads to a surge in insulin secretion and high demand of phosphorylated intermediates of glycolysis and could precipitate severe hypophosphatemia. It is unknown whether further reducing the caloric intake or energy from carbohydrates during the initial hospitalization would reduce refeeding syndrome.

Box 4

Selected research priorities in severe malnutrition.

1. Epidemiology: Burden assessment based on incidence, not prevalence
2. Causes of death in malnutrition, including infection and failure of energy metabolism
3. Pathophysiology of kwashiorkor and implications for management of kwashiorkor versus severe wasting
4. Mechanisms of functional immune impairment in severe malnutrition and their dynamics with nutritional rehabilitation
5. Long term impact on body composition, metabolism and neurodevelopment of severe malnutrition and its treatment, with and without Preterm/LBW
6. Preventive strategies that work at scale and at low cost. Research priorities to improve the management of acute malnutrition in infants aged less than six months (MAMI) https://www.ncbi.nlm.nih.gov/pubmed/25898252
7. Improved risk stratification to help identify which patients need inpatient care, which need empiric antimicrobials, and which antimicrobials should be selected
8. Treatment: Simplification of treatment protocols. Development of treatment protocols which can be carried out at the community level with minimal supervision
9. New formulations of RUTF that optimize fatty acid content and other nutritional parameters to maximize survival, weight gain, correction of metabolic perturbations, and long-term cognitive, physical, and immunological development
10. Research on strategies for integration of severe malnutrition preventive protocols in fragile and humanitarian settings.

Figure 1: Global maps of (A) wasting prevalence and (B) population, by country.
Based on Source: Global Targets Tracking tool, version 3.0 (May 2017)
http://www.who.int/nutrition/trackingtool/en/

Figure 2: Numerous organ systems are affected in severe malnutrition. A large body of work spanning many decades have characterized functional impairments in most organ systems in marasmus and kwashiorkor. However, the mechanisms behind many of the phenotypic signs and symptoms of severe malnutrition have not been fully elucidated.

Figure 3: Schematic diagram of metabolic changes that occur in children with (A) Kwashiorkor and (B) Marasmus. Reduced pancreatic insulin secretion contributes to a catabolic state in both kwashiorkor and marasmus. In marasmus, this leads to a lipolytic and proteolytic response and release of free fatty acids (FFA) and amino acids (AA) into the bloodstream. FFA are taken up by muscle tissue and used for oxidation and ATP production. These nutrients are also in part taken up by the liver and used for ATP production and synthesis of essential proteins and glucose. In kwashiorkor, this adaptive response is disturbed cause a reduced release of FFA and AA from adipose and muscle tissue, respectively. Mitochondrial damage in the liver impairs nutrient oxidation and thereby ATP production affecting normal synthesis processes such as production of albumin, glucose or glutathione.

Figure 4: (A) Child with severe wasting. Visible wasting and redundant skin due to significant loss of lean body mass is visible in a child **(B) Child with kwashiorkor.** Obvious oedematous swelling of the lower extremities with flaky paint dermatitis.

Figure 5: Overview of management of severe and moderate malnutrition.
Children should be screened for moderate or severe malnutrition at all health service contacts, and community screening may also be done, especially in humanitarian crises. Moderate malnutrition is typically treated with supplemental foods, in addition to their normal diet. Children with severe malnutrition are classified as complicated or uncomplicated based on either signs of infection that warrant hospital admission, or failure of appetite which indicates metabolic disturbance and that outpatient treatment is unlikely

to be successful. Children with uncomplicated severe malnutrition are usually treated with ready-to-use therapeutic foods (RUTF) which are given instead of the normal diet. A course of oral antibiotics is given, along with other treatments such as deworming and treatment for other non-life threatening infections. Children with complicated severe malnutrition require admission to an inpatient facility with adequate paediatric emergency care as well as an inpatient nutritional rehabilitation care program.

Figure 6: Approach to integrating medical and nutritional management of complicated severe malnutrition. The challenges of management of seriously ill children with severe malnutrition require integration of structured, high-quality paediatric care, focusing on identifying and treating the most immediately life-threatening problems, as laid out in the WHO Emergency Triage and Treatment (ETAT) guidelines, together with providing nutritional support to first help restore abnormal physiology then achieve rehabilitation. These must happen in parallel and are multidisciplinary. Rapid screening for severe malnutrition among seriously ill children can be done using MUAC and checking for edema. This influences key early aspects of care including fluid management and prevention of hypoglycemia and hypothermia. Severely malnourished children remain exceptionally vulnerable during treatment and may deteriorate rapidly without clear prior warning signs. Monitoring and frequent re-evaluation is essential. Where prevalent, co-morbidities such as TB and HIV should be actively sought. Where community-based management of uncomplicated severe malnutrition is available, the decision to discharge form hospital is based on appetite and resolution of complications, rather than anthropometric parameters, and should be jointly by nutrition and clinical staff. Parents and carers should be helped to understand the treatment process in hospital and after discharge and know what is available to them and what is expected of them.

Table 1: Anthropometric criteria for various subtypes of non-micronutrient malnutrition in children aged 6 to 59 months[142].

	Weight-for-length or weight-for-height† Z-score*	Mid-Upper Arm Circumference (MUAC)	Nutritional oedema	Weight-for-Age Z-score (WAZ)	Length for-Age† Z-score (LAZ)
Global Acute Malnutrition (GAM)	<-2	<125mm	Yes		
Moderate Malnutrition*	<-2 to ≥-3	≥115mm to <125mm	No		
Severe Malnutrition					
- *Severe Wasting***	<-3	<115 mm	No		
- *Kwashiorkor*	any	any	Yes		
Chronic Malnutrition					
Underweight					
Moderate Underweight				<-2 to ≥-3	
Severe Underweight				<-3	
Stunting					
Moderate Stunting					<-2 to ≥-3
Severe Stunting					<-3

‡ Z-scores refer to standard deviations from a reference population median. E.g -1 z-score = 1 standard deviation below reference median

† For older children, typically those >2years age, height is commonly measured instead of length, giving weight-for-height or height-for-age.

*Diagnosed by weight for length/height and/or MUAC criteria; also called “moderate wasting”.

**Diagnosed by weight for length/height and/or MUAC criteria; also called “marasmus”.

Table 2: Stunting, wasting, severe wasting, underweight and overweight in estimates in children under 5 years of age from the UN by UN sub-regions in 2015[261] .

UN regions and sub-regions	Stunting (<-2 SD height-for-age)		Wasting (<-2 SD weight-for-height)		Severe wasting (<-3 SD weight-for-height)	
	%	Millions	%	Millions	%	Millions
Africa	31.6 24.1-39.4	58.5 53.7-63.2	7.6 6.5-8.8	14.1 12.0-16.2	2.3 1.9-2.8	4.3 3.4-5.1
Eastern	37.5 33.8-41.3	24.1 21.7-26.5	6.6 4.8-9.1	4.2 3.1-5.8	1.7 1.2-2.4	1.1 0.8-1.6
Middle	31.2 24.1-39.4	8.4 6.5-10.6	7.8 6.0-10.1	2.1 1.6-2.7	2.5 1.5-4.1	0.7 0.4-1.1
Northern	18.0 11.8-26.3	5.0 3.3-7.3	7.7 4.3-13.2	2.1 1.2-3.7	3.3 1.9-5.6	0.9 0.5-1.6
Southern	28.4 24.2-33.1	1.8 1.6-2.1	5.4 2.7-10.4	0.3 0.2-0.7	1.1 0.4-3.2	0.1 0.0-0.2
Western	32.1 27.4-37.1	19.2 16.4-22.2	8.9 7.5-10.5	5.3 4.5-6.3	2.5 1.8-3.5	1.5 1.1-2.1
Asia	24.3 21.1-27.5	88.0 76.5-99.5	9.4 7.9-10.8	33.9 28.6-39.2	3.3 2.4-4.1	11.9 8.8-14.9
Central	13.8 10.5-18.1	1.1 0.8-1.4	3.8 3.1-4.6	0.3 0.2-0.4	1.5 0.9-2.6	0.1 0.1-0.2
Eastern	6.0 5.5-6.5	5.3 4.9-5.8	2.0 1.9-2.1	1.8 1.7-1.9	0.5 0.4-0.5	0.4 0.4-0.5
South-central	33.6 28.1-39.1	63.0 52.7-73.3	13.7 11.1-16.3	25.7 20.8-30.5	4.3 3.5-5.1	8.1 6.6-9.6
South-eastern	26.3 19.6-34.4	15.2 11.3-19.9	9.2 6.7-12.7	5.3 3.9-7.3	5.2 2.2-12.1	3.0 1.3-7.0
Southern	34.4 28.9-40.4	61.9 52.0-72.7	14.1 11.6-17.0	25.4 20.9-30.7	4.4 3.7-5.4	8.0 6.6-9.7
Western	16.2 8.6-28.3	4.5 2.4-7.9	3.9 1.3-11.3	1.1 0.4-3.1	1.2 0.3-4.0	0.3 0.1-1.1
Latin America & Caribbean	11.3 7.7-15.0	6.1 4.1-8.0	1.3 0.9-1.8	0.7 0.5-1.0	0.3 0.2-0.4	0.2 0.1-0.2
Caribbean	5.5 2.7-10.9	0.2 0.1-0.4	3.1 1.8-5.0	0.1 0.1-0.2	1.1 0.7-1.8	0 0.0-0.1
Central America	15.6 9.7-24.2	2.6 1.6-4.0	1.0 0.8-1.4	0.2 0.1-0.2	0.2 0.2-0.4	0 0.0-0.1
South America	9.9 6.1-15.6	3.3 2.0-5.2	1.3 0.8-2.3	0.4 0.3-0.8	0.2 0.1-0.4	0.1 0.0-0.1
Oceania	38.2 20.8-59.2	0.5 0.3-0.8	9.2 5.7-14.4	0.1 0.1-0.2	3.2 1.2-8.0	0 0.0-0.1
High Income	2.6 1.8-3.7	1.7 1.2-2.4	0.7 0.4-1.5	0.5 0.2-1.0	0 0.0-0.1	0 0.0-0.1
Upper Middle Income	7.1 5.3-9.5	13.3 9.9-17.8	2.1 1.7-2.5	3.9 3.3-4.7	0.5 0.4-0.6	0.9 0.8-1.2
Lower Middle Income	32.6 28.1-37.5	102.8 88.5-118.1	11.5 8.6-15.3	36.4 27.1-48.3	4.0 3.1-5.1	12.6 9.9-16.0
Low Income	37.3 35.1-39.6	37.9 35.6-40.2	7.8 6.2-9.8	7.9 6.3-9.9	2.2 1.6-2.9	2.2 1.7-2.9

Global	23.2 21.3-25.1	156.0 143.2-168.7	7.4 6.6-8.3	49.8 44.0-55.6	2.5 2.0-2.9	16.5 13.3-19.6

Table 3: Hazard Ratios (HR) and 95% Confidence Intervals (CI) for all cause and cause-specific deaths associated with anthropometric measures in children under 5 years old.

	All Deaths HR (95% CI)	Pneumonia Deaths HR (95% CI)	Diarrhoea Deaths HR (95% CI)	Measles Deaths HR (95% CI)	Other Infectious Deaths HR (95% CI)
Height / Length-for-Age Z-Score					
< -3	5·5 (4·6, 6·5)	6·4 (4·2, 9·8)	6·3 (4·6, 8·7)	6·0 (3·0, 12·0)	3·0 (1·6, 5·8)
-3 to < -2	2·3 (1·9, 2·7)	2·2 (1·4, 3·4)	2·4 (1·7, 3·3)	2·8 (1·4, 5·6)	1·9 (1·0, 3·6)
-2 to < -1	1·5 (1·2, 1·7)	1·6 (1·0, 2·4)	1·7 (1·2, 2·3)	1·3 (0·6, 2·6)	0·9 (0·5, 1·9)
≥ -1 (control)	1·0	1·0	1·0	1·0	1·0
Weight-for-Length Z-Score					
< -3	11·6 (9·8, 13·8)	9·7 (6·1, 15·4)	12·3 (9·2, 16·6)	9·6 (5·1, 18·0)	11·2 (5·9, 21·3)
-3 to < -2	3·4 (2·9, 4·0)	4·7 (3·1, 7·1)	3·4 (2·5, 4·6)	2·6 (1·3, 5·1)	2·7 (1·4, 5·5)
-2 to < -1	1·6 (1·4, 1·9)	1·9 (1·3, 2·8)	1·6 (1·2, 2·1)	1·0 (0·6, 1·9)	1·7 (1·0, 2·8)
≥ -1 (control)	1·0	1·0	1·0	1·0	1·0

Adapted from Black, et al[2]

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