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Tuberculosis in children with severe acute malnutrition

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Abstract

Introduction: With growing attention globally to the childhood tuberculosis epidemic after decades of neglect, and with the burden of severe acute malnutrition (SAM) remaining unacceptably high worldwide, the collision of these two diseases is an important focus for improving child health.

Areas covered: This review describes the clinical and public health implications of the interplay between tuberculosis and SAM, particularly for children under the age of five, and identifies priority areas for improved programmatic implementation and future research. We reviewed the

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literature on PubMed and other evidence known to the authors published until August 2021 relevant to this topic.

Expert opinion: To achieve the World Health Organization's goal of eliminating deaths from childhood tuberculosis and to improve the abysmal outcomes for children with SAM, further research is needed to 1) better understand the epidemiologic connections between child tuberculosis and SAM, 2) improve case finding of tuberculosis in children with SAM, 3) assess unique treatment considerations for tuberculosis when children also have SAM, and 4) ensure tuberculosis and SAM are strongly addressed in decentralized, integrated models of providing primary healthcare to children.

Keywords

Childhood tuberculosis; tuberculosis; severe acute malnutrition

1. Introduction

Especially in resource-limited settings and for children under the age of five years, both tuberculosis (TB) and severe acute malnutrition (SAM) are major causes of mortality. Children under five years are the age group with highest risk to progress from TB infection to disease, to have disseminated forms of TB such as miliary TB and meningitis, and to die from untreated disease [1]. There is growing recognition of malnourished children as a key high-risk group for TB, with recent calls to focus on malnourished children for targeted TB case finding efforts [2]. The World Health Organization (WHO) emphasized the association between malnutrition and child TB in its 2018 *Roadmap towards ending TB in children and adolescents* [3].

For children aged 6–59 months, SAM includes marasmus, kwashiorkor, and marasmic kwashiorkor and is defined by the WHO as a mid-upper arm circumference (MUAC) of less than 11·5 cm, a weight-for-length or -height z-score (WLHZ) less than −3 (table 1), or the presence of any bilateral pitting oedema [4]. SAM is classified as uncomplicated or complicated, with uncomplicated cases managed without hospitalization in a community-based setting and complicated cases requiring stabilization as inpatients [4]. Other types or severities of malnutrition (see Table 1) including moderate acute malnutrition (MAM), chronic malnutrition, various micronutrient deficiencies, and even obesity, are also clinically important. This review, however, primarily focuses on SAM given that of the various types of malnutrition, SAM has the highest short-term mortality and is thought to be most strongly associated with infections such as TB [5].

Analogous to the emphasis and special considerations for co-infection of HIV and TB, co-prevalent child TB and malnutrition also have unique epidemiological, programmatic, and clinical considerations [6]. There is substantial epidemiologic overlap between TB and SAM and bidirectional impact on the prevalence and mortality. Increased awareness of the association between childhood TB and SAM and improved management of co-occurring disease are important for improving child health globally. This review describes the clinical and public health implications of the interplay between TB and SAM, particularly for

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children under the age of five years, and identifies priority areas for improved programmatic implementation and future research.

2. Methods

We based this review on international reports, international guidelines, and published work. We identified published work for this review through searches of PubMed with the search terms “tuberculosis”, “TB”, “wasting”, “severe acute malnutrition”, and “children” published from the database inception to August 2021. We reviewed the reference lists of selected articles to identify additional manuscripts. Relevant evidence known to the authors was also included. The final reference list was generated on the basis of originality and relevance overall to this review subject matter. Preference was given to publications from the past 20 years, as more widespread global use of standard definitions of SAM and child TB has been promoted by the WHO during this time [7,8]. Only publications in English with full texts available were included. We did not conduct a formal assessment of risk of bias for the studies reported on in this review.

3. Epidemiology

3.1 Burden of TB and SAM on Children

According to the WHO, there were an estimated 10 million incident TB cases worldwide in 2019. Children <15 years of age represented 12% of incident cases but 16% of the estimated 1·4 million deaths from TB [9]. Mathematical modelling suggests that of the children <15 years of age that die from TB, 80% are <5 years of age [10]. Global and regional estimates of the burden of SAM are limited by inconsistent definitions and underreporting, with the epidemiology of edematous SAM, or kwashiorkor, particularly poorly defined [11]. Severe wasting (WLHZ less than −3) affects an estimated 16·6 million children under the age of five years worldwide [12]. Severe wasting has a hazard ratio of 11·6 (95% confidence interval, CI: 9·8 to 13·8) for mortality compared to a reference category of WHLZ -1 or greater [13]. Global deaths attributable to severe wasting for children under the age of five in 2011 were estimated at 516,000 [14].

Both geographically and across the lifespan, the parallels between overall mortality, TB disease, and SAM are not coincidental. Although there is much variability within and between countries, the burden of SAM and TB in children are greatest across Africa and Asia [10,14]. The HIV epidemic remains a major driver of child mortality in sub-Saharan Africa, and in this region, the co-prevalence of HIV with TB and SAM is particularly important [15]. Overall, the risk of mortality in children is highest in the first few years of life; this is also true for both TB and SAM [1,10,16,17].

3.2 Prevalence of TB in Children with SAM

Data from cross sectional studies of children with SAM report wide ranging prevalence of TB disease, from 0·4% with microbiologic diagnosis at a tertiary hospital in Zambia up to 44% initiated on TB treatment at a tertiary hospital in neighboring Malawi (Table 2) [18,19]. Three studies in Table 2 only reported the more restrictive diagnosis of microbiologically confirmed TB [20–22]. Two of the studies did not report how TB cases were defined

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[17,23]. Of the remining six studies, five of the studies defining TB cases clinically or as decision to start therapy reported >20% TB prevalence, [18,24–27]. The other study using a clinical case definition reported a TB prevalence of 1·6% [19]. As described below, child TB is a challenging diagnosis, particularly in children with SAM; therefore, TB prevalence is highly dependent upon the case definition used. A post-mortem autopsy study of children <15 years of age with in-hospital mortality at Zambia's national referral center reported that less than half of the TB cases identified on autopsy were diagnosed prior to death and 80% of autopsy-confirmed TB cases had SAM [20]. This suggests that TB is particularly underdiagnosed in children with SAM. Of the five studies in Table 2 assessing associations with mortality, three reported significant associations between diagnosis of TB and increased mortality in children with SAM, including the two largest studies with 9540 and 2008 total children included [19,22]. Two reported crude hazard ratios of 2·98 (95% CI: 1·55–5·70) and 2·1 (95% CI: 1·2–3·6) for morality in those with tuberculosis compared to those without [17,22]. The other study reported an adjusted odds ratios of 1.4 (95% CI: 1·0–2·1) for diagnosis of TB in those that died during the study period compared to those that remained alive [19]. Two smaller studies (405 and 113 total children) reported no difference in mortality between those with SAM diagnosed with TB or not, though overall mortality was high in these studies at 17% and 12% [24,25]. These findings highlight that children with SAM should be a high-priority target population for active case finding of TB.

3.3 Prevalence of SAM in Children with TB

As shown in Table 3, although definitions for malnutrition vary across various studies reporting the prevalence of malnutrition in children diagnosed with TB in various studies, malnutrition is common in children with TB disease [28–39]. Prevalence of malnutrition in these studies ranged from 7·1% in a study of children in South Africa that used a strict definition of SAM to 75·2% in a study of children in Pakistan that utilized a broader definition of malnutrition based on underweight (weight-for-age less than 5th percentile) [34,38]. Three studies including children co-infected with TB and HIV reported SAM prevalence of 22·4%, 24·7%, and 25·4% [32,35,36]. Six studies assessed associations between malnutrition and mortality among children diagnosed with TB. All studies reported significantly increased mortality in the malnourished children with unadjusted odds ratios of 2·9 (95% CI: 2·1–4·1), 2·1 (95% CI: 1·5–2·9), 3·0 (95% CI: 1·1–8·3), and 9·6 (95% CI: 1·8–51) for studies specifically assessing mortality [30–33]. The two studies assessing a composite outcome of treatment failure, default from treatment, or mortality reported malnutrition to have unadjusted odds ratios of 25 (95% CI: 3·1–197) and 8·0 (95% CI: 2·3–28) [37,39]. For three of these studies these associations were lost in adjusted analyses [32,33,39]. For two of these studies malnutrition remained independently associated with poor outcome [30,37]. One of these studies did not report adjusted odds ratios [31].

There is a notable lack of data on associations between type of SAM and TB. One study described that the most common type of SAM in those with TB was kwashiorkor at 47%, though no data showing type of SAM in those without TB was reported for comparison [19]. A second study reported highest odds of TB diagnosis in children with marasmic SAM (OR 3·5, 95% CI: 1·3 to 9·7) [25].

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Existing data clearly demonstrates that TB is common in children with SAM, and vice-versa. Evidence also suggests that mortality increases when these conditions co-exist in a child. However, we note that detailed comparisons between studies of TB and SAM prevalence and their associations may be limited by inconsistent definitions or methods of diagnosis of TB or SAM. Important areas for future epidemiologic research on the relationship between TB and SAM include 1) a more detailed understanding of the risk of developing and dying from these two diseases when one disease or the other or both are present and 2) assessments of how type of SAM (and other types of malnutrition such as MAM) associates with risk of TB disease and mortality from TB.

4. Screening and Diagnosis of TB in Children with SAM

Case finding is a crucial step in the cascade of care for patients with TB; however, TB in children remains largely underdiagnosed. Only 31% of the estimated incident cases of TB in children under the age of five are diagnosed and reported each year, with 96% of TB deaths in children occurring in those never accessing treatment, i.e. most likely never diagnosed [3,10]. TB case finding strategies traditionally focus on two high risk groups: people living with HIV and people in close contact to individuals with TB [40,41]. In settings where there is high prevalence of TB and SAM in children, greater emphasis on TB case finding for children with SAM is likely to be high-yield, if strategies for identifying TB cases are available.

WHO guidelines for the management of SAM reinforce the importance of the four symptom screen (any cough, fever, poor weight gain, or contact history with a TB case) for identifying HIV-infected children requiring investigation for TB [4]. However, these guidelines do not recommend a strategy for TB screening in HIV-uninfected children with SAM. A recent review of national guidelines for management of acute malnutrition from 17 high TB burden countries found that the majority did not specifically recommend either routine screening for TB (10 of 17) or obtaining a TB exposure history (11 of 17) [42]. Ultimately, the lack of guidelines and recommendations for screening for TB in this high-risk population may be due to a current lack of evidence for best practices.

Major factors that complicate TB diagnosis in children include: 1) symptoms tend to be less specific in children and overlap with those of other common childhood diseases; 2) specimen sampling collection methods, such as sputum induction or gastric aspiration, are often invasive and resource intensive; 3) microbiological tests for children often have sub-optimal sensitivity due to the paucibacillary nature of childhood TB (ideally tests need to be inexpensive, accessible, and usable at the point of care, allowing for actionable information for patient care); and 4) reliance on a clinical diagnosis of tuberculosis, without microbiological evidence of disease, can be challenging in areas where the burden of disease is greatest, with healthcare workers at the primary care level typically having minimal training and support for diagnosing and managing childhood TB [3]. In children with SAM, with lethargy so common and blunting of symptoms such as fever and cough also common, the issue of symptom overlap is further magnified.

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Strategies for diagnosing childhood TB have been reviewed extensively [6,43,44]. There are many promising new microbiological assays (most notably nucleic acid amplification tests), specimen sampling techniques, and imaging strategies in development [2,45]. Accessibility of various strategies for diagnosing child TB varies widely by settings, and some strategies may be particularly useful in children with SAM (table 4).

4.1. Clinical Diagnosis Considerations

HIV infection or history of close TB contact should lead to high suspicion for TB in children with SAM. Initial evaluation of a child with SAM should assess the recent nutritional intake of the child and food insecurity in the household. SAM is typically a consequence of deficient caloric intake, sanitation, and hygiene in the face of extreme poverty and social upheaval [46]. The absence of this history should increase suspicion for TB, other occult infections such as HIV, and non-infectious illnesses such as malignancy and metabolic disorders. There is often adequate programmatic support and established practice to screen for HIV in children with SAM in many settings, but the diagnosis of TB is often missed. WHO recommends that the lack of an expected improvement in weight or oedema during SAM nutritional rehabilitation, which includes not only therapeutic feeds but also empiric antibiotics, should prompt clinicians to consider diagnoses such as TB and HIV [4,42,47]. There is no clear evidence that poor response (weight gain) to adequate nutrition (either over longer time or over days during SAM nutrition rehabilitation) is indicative of TB, but given that this is considered by clinicians in high-burden settings and noted in international guidelines, further investigation to better define this relationship would be useful. Poor response to early nutritional rehabilitation for SAM is not uncommon, nor is mortality within the first week of nutritional rehabilitation. Therefore, the impact of empiric TB therapy either in the context of failed response to nutritional rehabilitation, or even at the time of presentation with SAM for certain patients, is an important and practical area for future research. Given the high mortality seen in children with both TB and SAM, the benefits of empiric TB therapy in children with SAM may outweigh the risks, particularly in certain contexts such high TB-burden settings, settings with limited TB diagnostics, and in the presence of risk factors that can be easily screened for (e.g. poor response to therapeutic feeds and close TB contact). However, risks of empiric TB therapy in this population with complex physiology would need to be carefully considered.

4.2 Urine Lipoarabinomannan Assays

The urine lipoarabinomannan assay Alere Determine TB-LAM (LF-LAM; Abbott, Lake Forest, IL, USA) is a commercially-available, relatively inexpensive, point-of-care test that has been recommended by the WHO since 2015 for the diagnosis of TB in people with advanced HIV [48]. LF-LAM has been shown to predict mortality in a cohort of hospitalized HIV-infected, antiretroviral-naïve children less than 13 years of age in Kenya [49]. However, with low sensitivity, LF-LAM has limited utility for use in broader populations [50]. The Fujifilm SILVLAMP TB LAM (FujiLAM; Fujifilm, Tokyo, Japan) is a novel LAM point-of-care test. A recent study of children hospitalized with suspected TB in Cape Town suggested the accuracy of both these assays may be higher in children with malnutrition (defined in this study as weight-for-age z-score, WAZ < -2) [51]. A recent larger study conducted in four African countries reported accuracy of FujiLAM and LF-LAM for 181 malnourished

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children (WAZ or body mass index, BMI, for age z-score < −2) being evaluated for TB in outpatient clinics. Sensitivity and specificity were estimated at 41·4% (13·1–75·9%) and 85·1% (76·6–91·2%), respectively, for LF-LAM and 83·0% (57·8–100%) and 80·0% (71·6–86·8%), respectively, for FujiLAM [52]. In another small, retrospective study of 45 children with SAM at a rural hospital in Mozambique, all 17 of those with clinical diagnosis of TB were LF-LAM positive and of those determined not to have TB, LF-LAM was not done in 5, negative in 23, and not positive in any patients [27]. These findings demonstrate the promise of these assays that utilize non-invasively collected samples for TB case finding in settings were TB and malnutrition commonly co-occur in children.

4.3 Ultrasound

Chest radiography has traditionally been, and remains as, a key investigation for the diagnosis of TB in children; however, it is often unavailable in low-resource settings where TB and SAM tend to be more prevalent. There is growing interest in the use of ultrasound imaging to improve TB diagnosis. Point-of-care ultrasonography (POCUS), performed at bedside by non-radiologist clinicians, may be particularly useful in resource-limited settings where there is limited access to chest radiography and interpretation of imaging by radiologists. A recent study comparing ultrasonography of the chest and chest radiography demonstrated increased detection of pleural effusions and enlarged mediastinal lymph nodes in children diagnosed with TB and higher inter-reader agreement with POCUS compared to chest radiography [53]. Other studies have shown ultrasonography is particularly useful for identifying evidence of abdominal TB in children living with HIV [54–56]. As malnourished children are also immunodeficient, and may be more susceptible to extrapulmonary TB, both urine LAM assays and POCUS could be especially valuable for rapid case detection in low resource inpatient and outpatient units caring for malnourished children.

4.4 Tests of Infection

Immunological tests of TB infection, such as tuberculin skin test (TST) and interferon gamma release assays (IGRAs), can help support the diagnosis of TB disease in certain scenarios. Multiple human and animal studies have demonstrated that malnutrition is associated with reduced TST positivity [5,57]. A study of Bangladeshi children demonstrated an association between BMI-for-age z-score and both decreased responses (31·2% for malnourished versus 20·1% for non-malnourished, p=0·036) and increased indeterminate results for IGRA compared to both positive (p=0·0006) and negative (p=0·0003) IGRAs [58]. Other studies have reported more complex results suggesting differences in accuracy of different types of IGRA tests with varying nutritional status of children [59]. Performance of available tests of infection in malnourished children would be better delineated in larger studies. TST and IGRA negative results cannot rule out TB disease, and this is especially true in malnourished children.

Improved evidenced-based strategies to evaluate for TB in children with SAM could lead to improved outcomes for this high-mortality population. Similarly, given the high incidence of SAM in children with TB, early and ongoing assessment of nutritional status as a standard component of TB management would likely benefit outcomes. New strategies that maximize accuracy, but can also feasibly be implemented in resource-limited settings, are

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urgently needed to 1) screen for TB, 2) improve clinical, microbiologic and radiographic diagnosis of TB, and 3) detect TB infection, among children with SAM. A large diagnostic cohort study in children hospitalized with SAM in Zambia and Uganda aiming to develop a two-step screening and diagnostic algorithm for TB in children with SAM is currently being implemented (NCT04240990). As a unique high-risk group for TB, specialized guidelines for TB case finding in children with SAM need to be developed as has been done for children living with HIV and children in close contact with a case of infectious TB. Until there is sufficient evidence for the development of these guidelines, it is appropriate for public health officials and clinicians to apply general guidance from the WHO on screening and diagnosis of TB in children to those with SAM. The WHO will release new guidelines for the management of TB in children in early 2022.

5. Pharmacology of Antituberculosis Drugs in Children with SAM

5.1 Pharmacokinetics

Children undergo dynamic changes during growth and development that influence their ability to absorb, distribute, metabolize, and eliminate drugs [60]. Malnutrition may lead to pathophysiological changes that can alter typical drug pharmacokinetics [61]. Diarrhea and vomiting, which are common in children with SAM, may result in unretained drug or variable absorption and transit time through the gut. Hypoproteinemia and oedema may alter the volume of distribution of drugs and the unbound (free) fraction [61]. It is largely unknown if malnutrition alters liver or kidney function, the key organs responsible for metabolism and elimination of xenobiotics [61]. There is no evidence to suggest that children with SAM have reduced capacity to metabolize antituberculosis drugs.

Body mass is often the most influential source of variability in drug clearance in children [62]. This is supported by biological principles of basal metabolic rate, which correlate allometrically with body mass, assuming drug metabolism and metabolic rate are driven by the same size factors [62]. While this may hold for children of full maturity and normal nutritional status, the relationship between body size and drug clearance in a child with SAM is unknown [62]. Relating drug clearance to total body weight assumes slower drug clearance in a child with SAM compared to a normal weight child and may underestimate a child with SAM's capacity to eliminate a drug, resulting in subtherapeutic drug exposure.

Supplemental Table 1 summarizes six population and 22 clinical studies of first-line antituberculosis drug pharmacokinetics in malnourished children published since 2006, when the WHO's initial guidance on management of TB in children was published [8]. No study reported antituberculosis drug pharmacokinetics in children with WHO-defined SAM. One study defining 'severe malnutrition' as weight-for-height/length <70% of expected or BMI-for-age <5th percentile found no difference in area under the curve (AUC) from 0 to 4 hours or highest drug concentration (C_{max}) did not differ for any drug by nutritional status [63]. The median WHLZ in children with 'severe malnutrition' was −1·9, which does not meet the WHO definition of SAM [63]. Of the remaining studies, five found significant associations with other metrics of malnutrition: BMI-for-age z-score < −2 predicted low rifampin and isoniazid concentrations [64]. Low weight-for-age was associated with lower rifampin AUC [65]. Pyrazinamide AUC was lower in children 1 to 12 years of age

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with MAM but higher in infants <12 months of age with WAZ <−2 [66,67]. MAM was associated with lower ethambutol AUC and C_{max} [68]. One population pharmacokinetics study identified increased bioavailability with increased body weight but no effect of nutritional status in a mostly malnourished population (median WAZ −2·2) [69].

While some studies have identified a significant association between a child's nutritional status and antituberculosis pharmacokinetics, generally with poor nutritional status associated with lower drug exposure, many studies have reported no statistically significant associations. Inconsistent findings could be due to several factors including (1) insufficient power due to small sample sizes, (2) inherently high pharmacokinetic variability due to the wide range of ages and weights, (3) study design (e.g. truncated sampling times), (4) the definition and distribution of malnutrition in the study, and (5) the prevalence of HIV coinfection, given the triple link between HIV-TB-SAM [69].

5.2 Pharmacodynamics

Understanding the relationship between drug exposure (i.e., pharmacokinetics) and response (i.e., pharmacodynamics) is important to guide optimal drug dosing in children with SAM. SAM may impact the exposure-response relationship of anti-tuberculosis drugs; for example, higher drug exposures may be needed to achieve the same outcome (e.g., to overcome a weakened immune response) or the therapeutic range may be narrower due to a lower threshold for toxicity. No studies have reported on the optimal target drug exposure for efficacy or safety in children with SAM.

Only five of the 22 clinical pharmacokinetics studies reported TB outcomes (Supplemental Table 1). Lower weight-for-age predicted poor TB outcomes in one study at currently recommended doses [63]. Two articles of the same Ghanaian cohort reported two child deaths; both children were HIV-positive with SAM [70,71]. Combined with evidence from studies showing that poor nutrition status increases risk of mortality in children treated for TB, it is possible that antituberculosis drug pharmacodynamics are impacted in SAM [31,32,34,35,39].

Rifampicin AUC is the strongest predictor of TB outcomes in children with pulmonary TB, where an AUC over one week of 185 mg*h/L had a 5% probability of unfavorable outcome. The authors concluded that higher rifampicin doses were necessary, especially for the lightest children (e.g., 20 mg/kg for 4–7 kg compared to 15 mg/kg), but no specific recommendations were provided by nutritional status [69]. A modelling and simulation study utilized this rifampicin AUC target to evaluate a nutritional status-based algorithm in a real-world global population of children under 5 years of age. They predicted that more than 40% of children with SAM would fall below the target, indicating >5% probability of unfavorable outcome, which improved to 75% target attainment and ~1% probability of unfavorable outcome when dosing was stratified by nutritional status [72]. This study assumed no effect of malnutrition on pharmacokinetics apart from body weight and no difference in pharmacodynamics by nutritional status; therefore, the impact of a stratified dosing approach could be far greater if SAM influences either.

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First-line antituberculosis drug safety has been previously reviewed, indicating generally better safety in children than adults [73,74]. Age and pyrazinamide use, but not nutritional status, were risk factors for drug-induced hepatotoxicity in 117 children with TB [75]. In another pediatric study (n=41), age, sex, HIV status, nor nutritional status were associated with drug-induced liver injury [76]. The safety of higher rifampicin doses (>20 mg/kg) has recently been studied; no grade 3 or higher adverse events attributed to rifampicin were reported in 40 children [77]. The safety of higher antituberculosis drug doses in children with SAM remains unknown.

5.3 Future considerations

There are significant gaps in the literature regarding the impact of SAM on antituberculosis drug pharmacology in children. An improved understanding is unlikely with the typical pediatric study designs in TB, which are usually observational with small sample sizes (n<100, but often <50) assessing one dosing schema across a wide range of ages (0–18 years) and body weights (4–50 kg). With this design, even if 50% of enrolled children have SAM, there will be insufficient power to reliably capture the influence of SAM due to the complex and dynamic factors driving pharmacokinetics and pharmacodynamics in children. One approach to overcome these challenges is to pool data from several clinical trials or observational studies and perform individual participant data meta-analysis with powerful quantitative analytical tools (e.g., nonlinear mixed effects modelling). A large database of pharmacokinetics and treatment outcomes that includes diverse populations with substantial SAM prevalence and children living with HIV would be needed and is possible with currently published studies. Well-designed clinical trials including children with SAM and controls without SAM that evaluate pharmacokinetics and post-treatment outcomes are also necessary. Clearly, malnourished children have poorer TB outcomes, but the driving mechanism(s) and solutions remain unclear. With high-quality models incorporating pharmacokinetics and outcomes data, we can describe these mechanisms and inform dosing approaches that may improve outcomes for children with SAM.

6. Other Treatment considerations

Beyond administration of anti-tuberculosis drugs, other adjunctive therapies may be considered to optimize TB treatment in children with SAM. As isoniazid can cause pyridoxine deficiency, with the most common manifestation being neuropathy, pyridoxine supplementation is recommended for malnourished children being treated for TB [78]. Therapeutic feeds that provide specialized macro- and micronutrient supplementation are the backbone of the management for SAM. The WHO guidelines for management of TB in children emphasize the importance of additional energy intake during the intensive phase (first two months) of TB treatment [78]. Overall, there is very little evidence describing the impact of nutrient supplementation on TB outcomes in children.

A recent systematic review assessed the impact of nutritional supplementation for people being treated for TB but focused mostly on adult studies. The evidence suggested moderately improved weight gain during treatment for active TB in those provided macro-nutrient supplementation compared to controls, although this finding was somewhat

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inconsistent across reviewed studies. There was insufficient data to draw conclusions about the impact of macronutrient supplementation on mortality or TB cure. In reviewing the impact of micro-nutrient supplementation, the results were heterogenous with no clear impact on clinical outcomes (i.e. cure, mortality, sputum conversion) but probable improvement in serum levels of particular supplemented micronutrients [79]. A randomized, placebo-controlled study of Tanzanian children <5 years of age with TB reported that multivitamin supplementation during the first eight weeks of anti-tuberculosis therapy led to no significant effect on weight gain, but there was a greater increase in hemoglobin levels and, for those living with HIV, a greater increase in height [80]. We are unaware of any studies assessing the impact of nutritional supplementation on TB treatment outcomes in children with SAM. This is an important area for future research.

In many settings, HIV infection is common in children with SAM or TB. Management of HIV-TB coinfection in children has recently been reviewed, as have particular challenges for malnourished children [6,15]. Some major considerations for the management of HIV-TB coinfection include the risk of immune reconstitution inflammatory syndrome and drug interactions [6].

7. Integrated Child Health Incorporating TB & SAM

National programs for diseases like HIV, TB, and SAM are typically separate entities with varying levels of collaboration. Lack of collaboration leads to inefficiencies and frustration for both patients and healthcare providers and worse outcomes for children. A recent review details the importance of child TB case finding and management as part of integrated service delivery models and primary care for child health [81]. This idea is a key action in the WHO's *Roadmap towards ending TB in children and adolescents* [3]. The community-based and inpatient management of SAM is based upon well-defined guidelines from the WHO [4,47]. These are widely adopted nationally by most countries with a high burden of SAM, with specialized programs within hospital and community settings to identify and care for children with SAM. Therefore, children with SAM are in many ways a distinct clinical cohort, and there is opportunity to improve care of those with co-prevalent TB by leveraging programmatic resources for TB case finding and TB management. Similarly, TB programs must provide care that is integrated with local nutritional rehabilitation programs. An important first step in the management of co-prevalent SAM and TB is case finding. Children diagnosed with SAM must be carefully assessed for TB. Those diagnosed with TB must have their nutritional status assessed so they can be linked to nutrition services when appropriate.

Existing vertical approaches to the management of TB and SAM must be coordinated to optimize outcomes of these important co-prevalent conditions, ideally with a primary healthcare model that comprehensively addresses the needs of children. The Integrated Management of Childhood Illness (IMCI), promoted by the WHO, provides an excellent framework for decentralized, primary healthcare for children under the age of five years. IMCI has a strong focus on nutrition, but some have argued that IMCI does not have enough emphasis on TB [81]. Particularly in resource-limited settings where the burden of SAM and

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TB are greatest, policy-level and implementation research is needed to shift paradigms and optimize integrated models of healthcare that address SAM and TB in children.

8. Conclusion

This review brings to light the important relationship between TB and SAM in children. With growing attention globally to the childhood TB epidemic after decades of neglect, and with the burden of SAM remaining unacceptably high worldwide, the collision of these two diseases is an important focus for improving child health. Public health officials and clinicians much understand the unique considerations for co-prevalent TB and SAM, and much research is needed throughout the domains described above to mitigate the vast suffering of young children from these diseases.

9. Expert opinion

Given the detrimental impact both TB and SAM have on the wellbeing of children globally and the tendency of these two conditions to co-occur, the intersection of TB and SAM has important public health and clinical implications, many of which are unrealized and holding back progress in global child health. The COVID-19 pandemic is expected to continue to disrupt economies and health systems for the foreseeable future, and this will greatly challenge efforts to control TB and malnutrition in children [82,83]. These new challenges occur against a background where TB in children has long been neglected as a priority and severe malnutrition has remained unacceptably common in low- (and even middle- and high-) income countries. However, optimism comes from new emphasis by international leaders on tackling these two major drivers of morbidity and mortality in children, demonstrated by the United Nations Sustainable Development Goals 2 and 3 focusing on ending hunger and the epidemic of TB, respectively [84]. During these particularly challenging times, global progress in protecting children from TB and SAM over the next decade and beyond will be dictated be strong leadership that prioritizes the health of all children, including the most disadvantaged.

As diagnosis of HIV immediately prompts consideration of TB, and vice-versa, the same mindset is needed for TB and SAM in children, particularly where these two conditions tend to be more prevalent. Although countries typically have separate programs for TB and HIV services, in recent years, albeit to varying degrees of success, increased emphasis has been placed on collaboration between TB and HIV service programs and integrated TB-HIV service delivery [85]. This serves as a model for integration of TB services with malnutrition programs. When implemented properly, integration of TB and SAM services has the potential to more efficiently utilize healthcare resources, decrease barriers in access to care, and improve outcomes of children managed for TB and SAM.

Additional research and interventions that target children with TB and SAM are long overdue but urgently needed to improve outcomes among this underserved high-risk population of children (Table 5). Child TB case finding is a major challenge, including for those with SAM, but various factors suggest dramatic improvements in this area are likely to occur over the upcoming years. First, the WHO now emphasizes malnourished children

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as a high-risk group for TB, and this is expected to increase awareness of the importance of case finding in this population [3]. Second, greater roll-out of child-friendly strategies for diagnosing TB in children, including urine LAM and point of care ultrasound, which may be particularly useful in children with SAM, will improve clinicians' confidence diagnosing child TB. Of course, finding children with TB is only half the battle and has little meaning if these children aren't effectively treated. Optimizing the treatment of drug-susceptible and drug-resistant TB in children is an active area of research [86,87]. The advances in treatment close on the horizon will benefit children with TB and SAM as well, though as we emphasize in this review, careful considerations should be made for the proper dosing of antituberculosis medications in children with SAM to maximize treatment response and minimize side effects in these children suffering from two life-threatening conditions. This means we must emphasize the inclusion of children with SAM in studies of antituberculosis drug pharmacokinetics, efficacy, and safety.

Indeed, the magnitude of either of these two problems alone is enormous, and the challenges multiply when TB and SAM co-occur and reinforce each other. TB and SAM tend to occur most frequently in marginalized populations of children living in poverty with poor access to healthcare. Massive numbers of children globally suffer from these two preventable and treatable conditions. An improved understanding of the public health and clinical implications of co-occurring TB and SAM in children, as described in this review, will galvanize efforts to implement well-researched case finding and management strategies and promotes essential research in the key areas described.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Article highlights:

- Understanding the association between childhood tuberculosis (TB) and severe acute malnutrition (SAM), and improved management of co-occurring disease, is important for improving child health globally.
- TB is common in children with SAM, and vice-versa, with mortality tending to increase when these two diseases co-occur.
- Diagnosis of TB in young children is a major challenge globally, and TB case-finding strategies targeted at children with SAM may be high-yield, though diagnosis of TB in children with SAM has unique considerations that are described.
- The pharmacokinetics and pharmacodynamics of antituberculosis drugs in children with SAM may be significantly different compared to nourished children, and understanding these differences is essential for optimizing treatment of TB in children with SAM.
- Policy-level and implementation research is needed to shift paradigms and optimize integrated models of healthcare that address TB and SAM in children.

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Table 1.

Malnutrition terms used as defined by the WHO [4].

Severe acute malnutrition (SAM)	Oedema of both feet and/or severe wasting * (see age-specific definitions below)
Complicated SAM	SAM with any poor appetite, severe oedema (bilateral feet, hands, and periorbital oedema), medical complications or danger signs (e.g. hypothermia, infections, severe dermatosis, diarrhea with dehydration, intractable vomiting, convulsions, lethargy, high fever). Recommended to be stabilized initially as inpatients.
Uncomplicated SAM	Case of SAM without complicating features listed above. Recommended to be managed in community-based settings.
Moderate acute malnutrition (MAM)	WLHZ −2 to −3 OR MUAC 11·5 to 12·4 cm for those age 6 to 59 months (13 to 14·5 cm for those 5 to 9 years)
Kwashiorkor	Any symmetric pitting oedema not explained by other medical condition
Severe wasting *	WLHZ < −3 or MUAC <11·5 cm for those age 6 to 59 months (<13 cm for those 5 to 9 years)
Underweight	WAZ < −2
Stunting	Height for age z-score < −2

* The term ‘wasting’ is generally synonymous with ‘marasmus’.

Z-scores are relative to the WHO Child Growth Standards medians. MUAC: mid-upper arm circumference; WAZ: weight for age z-score; WHLZ: weight for length or height z-score

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Table 2.

Summary of studies describing TB disease in children with severe acute malnutrition.

Author (Year)	Country	Specific SAM Population	Age of Children with SAM (months)	Number with SAM	Number (%) with TB	Source of microbiologic diagnosis
Bates (2016) [20]	Zambia	Inpatients <15 with in-hospital mortality	Median 19 IQR 12 – 45	60	8 (13·3)	Histopathology
Bhat (2013) [21]	India	Inpatients <5	49% between 12 – 35 months	1173	19 (1·6)	34 had AFB smear done on sputa (all negative)
Chisti (2014) [24]	Bangladesh	Inpatients <5 with radiological pneumonia	Median 10 IQR 5 – 18	405	Confirmed: 27 (6·7) Total: 87 (21·5)	Xpert MTB/RIF & MGIT culture on induced sputum & gastric aspirates
De Maayer (2011)[25]	South Africa	Inpatients	Median 10 Range 1 – 34	113	Confirmed: 5 (4) Suspected & started on ATT: 27 (24)	AFB smear & culture on induced sputum & gastric aspirates on all with suspected TB
Girum (2017) [17]	Ethiopia	Inpatients <5	Median 24 IQR 12 – 36	545	41 (7·5)	NR
Ide (2019)[26]	Sierra Leone	Inpatients <5	Median 11 SD 9·9	74	15 (20)	Intermittent use of Xpert MTB/RIF
Kumar (2014) [23]	India	Inpatients <5	Mean 14	104	23 (22·1)	NR
LaCourse (2015) [19]	Malawi	Inpatients <5	Median 18·5 IQR 12·1 – 25·6	300	Confirmed: 2 (0·7) Probable: 20 (6·7%) Started on ATT: 132 (44)	Xpert MTB/RIF and MGIT culture on induced sputum
Munthali (2017) [18]	Zambia	Inpatients <5	Median 17 IQR 22 to 55	9540	Confirmed: 37 (0·4) Total: 151 (1·6)	ZN smear on gastric aspirates
Osório (2020) [27]	Mozambique	Inpatients <5	Mean 17 SD 5·0	45	Confirmed: 2 (4·4) Total: 17 (37·8)	Culture on nasopharyngeal aspirates
Wagnew (2018)[22]	Ethiopia	Meta-analysis of four studies of inpatients <5	NR	2008	126 (6·3)	NR

AFB: acid-fast bacilli; ATT: anti-tuberculosis therapy; IQR: interquartile range; NR: not reported; SD: standard deviation; ZN: Zeihl Neelsen

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Table 3.

Summary of studies describing malnutrition in children with TB disease.

Author (Year)	Country	Specific TB Population	Age (years)	Number of patients	Number (%) malnourished*	Measurement of malnutrition
Aygun (2019) [28]	Turkey	Patients <18 at TB clinic	Mean 9·9 SD 5	163	80 (49·1)	Weight for age <3rd percentile
Blount (2014) [29]	Vietnam	Patients <16 at national referral hospital	Median 5 IQR 2 – 10	103	16 (15·5)	WAZ < −3
Buck (2013) [30]	Malawi	HIV-infected patients <18 at HIV clinic	Median 3·8 IQR 1·5 – 7·4	1561	350 (22·4)	SAM (WLHZ, MUAC, & oedema)
Drobac (2012) [31]	Peru	Patients <15 at referral hospital	Median 9 IQR 5 – 12	2392	890 (37·2)	Weight for age <3rd percentile
du Preez (2018) [32]	South Africa	Patients <13 at district hospital	74% <3	113	8 (7·1)	SAM
Ebonyi (2016) [33]	Nigeria	HIV-infected patients <14 at HIV clinic	Median 3·6 IQR 1·8 – 6·0	260	66 (25·4)	WAZ < −3
Hesseling (2005) [34]	South Africa	HIV-infected patients <14 with culture-confirmed TB at referral hospital	Median 2·0	93	23 (24·7)	<80% IBW in presence of oedema or <60% IBW in absence of oedema
Hicks (2014) [35]	South Africa	Patients <15 at referral hospital with drug resistant TB, 77% HIV infected	Median 8 IQR 4 to 12	84	42 (50·0)	Weight for age <3rd percentile
Laghari (2018) [36]	Pakistan	Patients <15 in DOTS registry	Mean 7·4 SD 4·4	2167	1629 (75·2)	Weight for age <5th percentile
Nansumba (2017) [37]	Uganda	Patients <15 at referral hospital	44% <2, 29% 2–4, 26% >4	144	30 (20·8%)	WHZ < −3
Seddon 2012 [38]	South Africa	Patients <15 at referral hospital with drug resistant TB	Median 4·2 IQR 1·6 to 9	111	41 (36·9%)	Weight for age <3rd percentile
Wobudeya (2019) [39]	Uganda	Patients <15 at TB clinic	Median 3·0 IQR 1·3 to 6·1	713	76 (10·7)	WAZ < −3

ATT: anti-tuberculosis therapy; DOTS: directly observed treatment, short-course; IBW: ideal body weight or weight for age 50th percentile; IQR: interquartile range; MUAC: mid-upper arm circumference; SD: standard deviation; WAZ: weight for age z-score; WLHZ: weight for height z-score; WHZ: weight for height z-score

*Calculated percentage includes enumeration of patients with missing data in denominator

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Table 4.

Strategies for diagnosis of TB disease in children arranged by resource intensity, divided by those possibly unique for children with SAM and those that apply to all children undergoing workup for TB.

	Especially Important with SAM	All Children
Less Resource Intensive  **More Resource Intensive**	• Response to empiric treatment and weight gain on therapeutic feeds • Urine LAM • POCUS	• Clinical history including history of TB contact • Assess symptom resolution/progression with follow-up visits, +/- empiric treatment for alternative diagnoses (eg. antibiotics for bacterial pneumonia) • Tuberculin skin test • Chest radiography • Smear microscopy • Nucleic acid amplification tests (eg. Xpert MTB/Rif Ultra) • Interferon gamma release assays • Mycobacterial cultures (eg. MGIT)

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Table 5:

Proposed research priorities for co-prevalent SAM and TB in children.

- Prospective cohort studies of children with SAM, especially at different levels of care, to further detail:
  - prevalence of TB in this population
  - relative risk of incident TB
  - association between response to therapeutic feeds (ie. weight gain) and TB diagnosis or response to anti-tuberculosis therapy for diagnosed TB
  - differences in TB risk and mortality with different types of SAM and MAM
- Develop practical, evidence-based systematic screening strategies for TB in children with SAM
- Improve implementation of nutritional status screening and linkage to nutritional services for children diagnosed with TB
- Develop accurate, low-cost, non-invasive strategies for diagnosis of TB in children with SAM
- Assess utility of empiric ATT in children with SAM with key risk factors for TB (HIV, TB contact, lack of food insecurity or other clear aetiology of malnutrition)
- Determine optimal dosing of ATT for children with SAM by inclusion of, or focus on, malnourished children in pharmacokinetic and pharmacodynamic studies and meta-analysis of existing data
- Improve strategies for early confirmation of TB treatment response
- Develop decentralized approaches, supported by translational and implementation research, integrated into existing local child health programs (eg. IMCI) for case finding and case management