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Integration of childhood TB into guidelines for the management of acute malnutrition in high burden countries

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Introduction: Childhood tuberculosis (TB) and undernutrition are major global public health challenges. In 2015, although an estimated 1 million children aged <15 years developed TB, the majority of the cases remain undiagnosed, partly due to a lack of awareness and capacity by providers who serve as the first point of care for sick children. This calls for better integration of TB with child health and nutrition services. TB can cause or worsen undernutrition, and undernutrition increases the risk of TB.

Methods: Guidelines for the management of acute malnutrition from 17 high TB burden countries were reviewed to gather information on TB symptom screening, exposure history, and treatment.

Results: Seven (41%) countries recommend routine TB screening among children with acute malnutrition, and six (35%) recommend obtaining a TB exposure history.

Conclusion: TB screening is not consistently included in guidelines for acute malnutrition in high TB burden countries. Routine TB risk assessment, especially history of TB exposure, among acutely malnourished children, combined with improved linkages with TB services, would help increase TB case finding and could impact outcomes. Operational research on how best to integrate services at different levels of the health care system is needed.

Tuberculosis (TB) is a major public health challenge, now surpassing human immunodeficiency virus (HIV) infection as a leading cause of death from infectious disease globally. With one million estimated cases, children aged <15 years accounted for approximately 10% of the 10.4 million incident TB cases in 2015, and 210 000 children died.[1] However, only 39% of child TB cases were reported, highlighting significant underdiagnosis and under-reporting of childhood TB.[1]

Despite increased awareness within the TB community and the launch of a Roadmap for Childhood Tuberculosis in 2013,[2] there is a significant policy–practice gap in implementing guidelines, capacity building at the country level, and decentralization and integration of TB services into broader child health programs to better reach children where they access the health care system.[3] This means targeting programs and services at the community and primary health care level, and health care providers caring for those at high risk for TB. It also means actively engaging key stakeholders in child health and survival, including the nutrition sector.[4,5]

TUBERCULOSIS AND MALNUTRITION

Approximately 45% of deaths in children aged <5 years are attributable to undernutrition,[6] which may be acute or chronic, and categorized as moderate or severe. Children with undernutrition are at increased risk of death from infectious diseases and, conversely, severe infectious diseases in early childhood can affect nutritional status.[6] Undernutrition increases the risk of TB and TB can cause or worsen undernutrition.[7] One study estimated that 26% of overall TB cases in 22 high-burden countries are attributable to undernutrition.[8]

Data on TB prevalence among acutely malnourished children vary widely: 2–24% of acutely malnourished children in high TB burden settings have been diagnosed with TB.[9–13] The wide range observed between studies can be partly attributed to the use of varying screening strategies and access to TB diagnostics, as well as varying clinical capacity for childhood TB diagnosis and treatment among hospitalized children. Even at referral hospitals, access to diagnostic tests may be limited,[14] highlighting the need for improved access to services across all levels of the health care system, including appropriate referral pathways. These data also highlight the role of TB as a comorbidity among children with acute malnutrition, emphasizing the need to routinely screen for TB and manage those at risk of TB appropriately. Asking about contacts with persons with TB is included as part of the initial history for children with severe malnutrition, as outlined in the 1999 World Health Organization (WHO) manual on the management of severe malnutrition.[15] In the WHO 2013 update on the management of severe acute malnutrition (SAM), TB screening is mentioned in the context of HIV infection.[16] We performed a review of the guidelines on acute malnutrition from high TB burden countries to identify whether and how TB is integrated within nutrition guidelines.

METHODS

We searched country-level guidelines from high TB burden or high TB incidence countries for the management of acute and severe acute malnutrition. Guidelines were obtained from the Community-based Management of Acute Malnutrition (CMAM) Forum website,[17] as well as country contacts. The CMAM Forum supports the scale-up of services for acute malnutrition through the collation of existing technical guidance, creation of technical briefs, and highlighting ongoing research and research gaps.[17]

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KEY WORDS
pediatrics; tuberculosis; malnutrition; infection; integration

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TABLE 1 Summary of country-level guidelines

Country, year	Type of guideline		Level of care		
	Acute malnutrition (SAM and MAM)	SAM	In-patient	Out-patient	Community
Afghanistan, 2014	X		X	X	X
Bangladesh, 2008		X	X		
Bangladesh, 2011	X			X	X
Brazil, 2005		X	X		
Cambodia, 2011	X		X	X	X
Democratic Republic of Congo, 2012	X		X	X	X
Ethiopia, 2007		X	X	X	X
India, 2011		X	X		
Kenya, 2009	X		X	X	X
Mozambique, 2011	X		X	X	X
Myanmar, 2008	X		X	X	X
Nigeria, 2011	X		X	X	X
Pakistan, 2010	X		X	X	X
The Philippines, 2015		X	X	X	X
South Africa, 2015	X		X	X	X
United Republic of Tanzania, 2013	X		X	X	X
Uganda, 2010	X		X	X	X
Viet Nam, 2013	X		X	X	X

SAM = severe acute malnutrition; MAM = moderate acute malnutrition.

All guidelines for the management of acute malnutrition were reviewed using the key words TB, tuberculosis, HIV, screening, Mantoux, tuberculin, tuberculin skin test (TST), and chest radiograph (CXR), to obtain information on 1) TB screening and diagnosis, 2) assessment of TB exposure, and 3) anti-tuberculosis treatment.

Data were entered using MS Excel (Microsoft, Redmond, WA, USA). Among acutely malnourished children, if guidelines included obtaining a symptom history and testing for TB using the TST and/or CXR as a part of the initial assessment, this was counted as a recommendation for TB screening. If guidelines did not specifically mention TB, but the initial assessment of acutely malnourished children included TST and/or CXR, these countries were also counted as recommending TB screening. If the initial assessment consisted of only obtaining a symptom history, including cough or fever, without specifically recommending any tests for TB, these countries were not counted as recommending TB screening. Guidelines that recommended asking care givers of an acutely malnourished child whether the child had had any household or other contacts with TB were considered as recommending screening for TB exposure. Guidelines were also reviewed to determine whether and how anti-tuberculosis treatment was addressed in the context of acute malnutrition.

RESULTS

Guidelines on the management of acute malnutrition for 19 countries were obtained, and a total of 18 guidelines from 17 different countries were reviewed (Table 1). Guidelines from Indonesia are a translation of the WHO guidelines; the WHO guidelines are also used in Zambia (personal communication with country-level contacts), and were therefore not included.

Screening for tuberculosis and tuberculosis contacts

Guidelines from all 17 countries mentioned TB as a comorbidity in the context of acute malnutrition; however, only seven (41%) countries recommended routine screening for TB in acutely malnourished children (Table 2). Recommendations for TB screening varied, ranging from a general recommendation to screening for TB according to specific recommendations, including an evaluation with TST and CXR for all children with SAM. Guidelines from South Africa also recommended considering TB among children with moderate acute malnutrition (MAM) and SAM, whereas Bangladesh recommended TB screening in the context of specific signs or symptoms such as cough for >2 weeks, chest infection that fails to respond to antibiotics, or history of contact with a TB case, which could already count as TB risk assessment. Furthermore, several countries recommended asking about non-specific signs and symptoms such as cough or fever when evaluating children with acute malnutrition, but these were not counted as a specific recommendation for TB screening. Six (35%) countries recommended assessing TB exposure by asking about contacts with TB when evaluating children with acute malnutrition.

Anti-tuberculosis treatment

Information on anti-tuberculosis treatment differed between the sets of guidelines, with no clear recommendations on where and when TB treatment should be initiated and managed. Guidelines from Ethiopia recommended that children with SAM and TB receive anti-tuberculosis treatment at a nutrition center rather than having their malnutrition treated at a TB center. Guidelines from Cambodia recommended that children admitted with SAM and TB be treated in a TB room, but receive their feeds from the malnutrition unit. No guidelines provided specific information on medication regimens, dosages, or duration of anti-tuberculosis treatment in their malnutrition guidelines, except for the Brazilian guidelines, which included a regimen for the treatment of TB meningitis. Two (12%) countries recommended referring children to TB services if indicated, and two (12%) countries recommended that children already on anti-tuberculosis treatment be counseled to continue treatment and that adherence be monitored when children were seen for nutrition services.

TABLE 2 Country-specific TB information

Country, year	Screen/evaluate for TB	Exposure history: TB contact	TB treatment
Afghanistan, 2014	No	No	No
Bangladesh, 2008	Yes	No	Per NTP
Bangladesh, 2011	No	No	No
Brazil, 2005	No	Yes	No
Cambodia, 2011	Yes	No	No
Democratic Republic of Congo, 2012	Yes	No	No
Ethiopia, 2007	No	No	Per NTP
India, 2011	Yes	Yes	Per NTP
Kenya, 2009	No	No	No
Mozambique, 2011	No	Yes	No
Myanmar, 2008	No	No	No
Nigeria, 2011	No	No	No
Pakistan, 2010	No	No	No
The Philippines, 2015	No	Yes	Per NTP
South Africa, 2015	Yes	No	No
United Republic of Tanzania, 2013	Yes	Yes	No
Uganda, 2010	Yes	No	No
Viet Nam	No	Yes	No
Total number of countries (n = 17, 100%)	7 (41%)	6 (35%)	4 (24%)

TB = tuberculosis; NTP = national TB program.

Guidelines from six countries mentioned that TB medications could be toxic in patients with acute malnutrition; guidelines from five of these countries further specified that TB medications could damage the liver and pancreas. Guidelines from the Democratic Republic of Congo, Ethiopia, Kenya, and Mozambique specified that acute malnutrition should be treated before initiating anti-tuberculosis treatment, except in cases of miliary TB or TB meningitis, due to abnormal liver and kidney function and altered drug metabolism in patients with acute malnutrition.

DISCUSSION

TB and undernutrition contribute to significant morbidity and mortality in children, particularly in low- and middle-income countries.[1,6] Although the exact mechanism underlying the association between malnutrition and TB is unknown,[18] undernutrition is a risk factor for TB,[7] and routine TB risk assessment among acutely malnourished children, combined with improved linkages with TB services, would help increase TB case finding and improve outcomes for children with TB and undernutrition. To address the burden of TB and undernutrition, there has been increasing focus by advocates of both conditions on decentralizing care to the community and primary health care levels, and integration with services where children with these conditions often present for care.[5] Community-based detection and treatment of uncomplicated SAM in combination with facility-based treatment can have a major impact on mortality,[19] and TB can be integrated into existing community-based programs.[20,21] Risk assessment for TB has recently been added to community health worker manuals by the WHO and the United Nations Children's Fund, including those for integrated community case management, and is recommended for roll-out in high TB and HIV burden settings.[22]

Global-level recommendations exist; for example, guidelines recently published by Action Against Hunger recommending the integration of TB and undernutrition services, the screening of children with severe malnutrition for underlying causes of acute malnutrition and referrals for further evaluation if TB and/or HIV are suspected.[23] The assessment of a child with SAM should at least include asking about TB exposure (contact history), as already outlined in the 1999 WHO Manual for Severe Malnutrition.[15] A positive contact history should, depending on the setting, level of care, and capacity of health care workers, lead to referral and/or further investigation for TB. All children hospitalized for SAM should be further evaluated for TB, especially if there is history of contact with an adult case, poor growth despite good food intake, chronic cough, or respiratory infection that fails to respond to antibiotics.[24]

Based on our review of guidelines from 17 high TB burden countries, the majority of the countries do not recommend routine initial screening for TB among acutely malnourished children; even among the seven (41%) countries that recommend screening for TB, recommendations vary from a general recommendation to screen for TB to detailed guidance on diagnostic tests. Children who fail to respond to treatment for acute malnutrition should always be evaluated for TB, and 13 (76%) countries recommend an evaluation in this context.

Evidence and data needs

Integration of services is an important strategy for addressing childhood TB and SAM, and a crucial step towards more comprehensive, child-centered care. Active surveillance and case finding of children with SAM can lead to earlier identification of SAM and community-based treatment for the majority of children,[19,25] highlighting the need for TB guidelines to also include screening for acute malnutrition and defining referral pathways. Recent guidance on community-based management of acute malnutrition has led to the scale-up of interventions to diagnose and treat acute malnutrition, from screening in the community to hospitalization for SAM with complications,[19,26] providing opportunities at multiple levels of the health care system to evaluate for comorbidities, including TB (Table 3).

Careful consideration needs to be given to the specific interventions that should be recommended at different levels of care,

TABLE 3 Key interventions for TB as part of services for acute malnutrition

Level of health care system*	TB assessment
Community, primary, secondary, tertiary	For each child at diagnosis of acute malnutrition: • Ask about exposure to TB: has the child been in contact with a person with TB/on anti-tuberculosis treatment? • Perform TB symptom screen: cough >2 weeks, reduced playfulness, etc. • Assess HIV status • If TB is suspected, perform diagnostic work-up for TB (e.g., clinical, CXR, bacteriologic testing). Refer to higher level of care if cannot perform diagnostic work-up • Repeat TB assessment in children who do not respond to nutritional rehabilitation

*Each country should delineate the specific pathway to TB diagnosis at all levels of the health care system.
TB = tuberculosis; HIV = human immunodeficiency virus; CXR = chest X-ray.

and to defining target groups of children to be screened. Children with signs or symptoms of TB or positive exposure history might have to be referred to a higher level of care if further clinical evaluation or diagnostic testing cannot be completed. Evaluating for TB at various levels of nutrition services would also require thorough and systematic adherence to guidelines and protocols, simple management tools, as well as mentoring and supervision. This can be challenging, particularly in resource-limited settings.[12,13] In India, evaluating for TB among children treated for SAM at nutrition rehabilitation centers resulted in a TB diagnosis for 2–9% of children, and highlighted several challenges, such as lack of qualified health care providers, limited availability of CXR and TST, and difficulties with sputum collection.[12,13] These hurdles could be overcome by increasing the capacity of health care workers to diagnose TB clinically in the absence of diagnostic tests and/or the improvement of referral systems. In Malawi, among 300 children hospitalized for SAM and thoroughly investigated for TB using standard research case definitions,[27] over 25% had signs of TB exposure, <1% were microbiologically confirmed, and 7% had a probable and 66% a possible diagnosis of TB.[9] While a probable diagnosis should result in treatment, children with less clear criteria might benefit from observation and further assessment as they continue their nutritional rehabilitation, but additional data are needed. The significant variability in country-level guidelines regarding TB screening among acutely malnourished children also highlights the need for further clarity, standardized approaches, and best practices on how to best integrate TB and nutrition services at different levels of the health care system (Table 4).

Children with TB often present with signs or symptoms consistent with other conditions, including respiratory infections; TB-endemic countries also have a high burden of pneumonia.[28,29] Data on the epidemiology of childhood TB with acute pneumonia are limited, irrespective of nutritional status; nevertheless, a systematic review found that 7.5% of children with pneumonia had culture-confirmed TB in high-burden settings.[28] Individual studies showed that up to 20% of children hospitalized for severe pneumonia might have TB.[29] Among children with severe malnutrition, respiratory symptoms, and CXR findings consistent with pneumonia, TB was diagnosed microbiologically in 7%, and clinically in an additional 16% of children;[30] one review reported TB in 21% of children with SAM and pneumonia.[31] This highlights the need to evaluate specifically for TB among children with malnutrition and respiratory symptoms.[28,31]

Over one third of guidelines reviewed specify that TB medications can have toxic effects in children with acute malnutrition. Children with malnutrition have altered drug metabolism;[32] however, based on a systematic review of the efficacy, safety, and pharmacokinetics of antibiotics in children with SAM, further research is needed to guide optimal antibiotic treatment for these children.[33] Data on the pharmacokinetics of TB medicines among malnourished children are also needed, as differences have been reported.[34–37] Further research into anti-tuberculosis treatment in the setting of malnutrition can guide the development of recommendations for the optimal timing for the initiation of treatment, dosing, and follow-up of children with malnutrition and TB.

Further research on factors associated with TB among children with malnutrition can help guide targeted screening for TB and improve diagnosis, particularly in high-burden and low-resource settings. Although extensive screening for TB may not be available at every point of contact within a nutrition program, asking about contacts with TB is important and is recommended as part of the evaluation for a child with severe malnutrition.[15] A more comprehensive symptom-based screening approach may also be feasible to integrate within nutrition services at the peripheral health care level, with referral to higher levels of care for symptomatic children for diagnosis.[38] Children aged <5 years who are TB contacts should be started on preventive therapy once TB disease has been ruled out, as the risk of disease progression remains high, especially among malnourished children.[38]

We were not able to review guidelines from all high TB burden countries, but we did review guidelines from the majority of these countries. It is important to note that guidelines may not reflect what actually occurs in practice at the country level, and there

TABLE 4 Research needs

Understand the TB burden among children with acute malnutrition seen/managed at different levels of care
Improved TB diagnostics, particularly in children with acute malnutrition
Risk factors for TB specific to children with acute malnutrition
Pharmacokinetics, safety, and efficacy of TB medications in children with acute malnutrition
Optimal timing of initiation of TB medications in children with acute malnutrition and monitoring for side effects
Best practices for better integrating TB in the management of malnutrition, including referral systems
Initiation and follow-up of anti-tuberculosis treatment in TB services or nutrition services
Impact of early assessment for and appropriate management of TB on malnutrition outcomes

TB = tuberculosis.

may also be in-country variations in implementing guidelines. Information from the field would provide further information on the actual implementation of guidelines, including TB assessment, prevalence, and outcomes among acutely malnourished children.

CONCLUSION

Undernutrition and TB are closely linked, highlighting the need for improved integration of services. However, integration of TB into nutrition services, including TB exposure history and a symptom-based screening approach, can help identify children at greatest risk for TB disease for further evaluation, and help reduce mortality among children with TB and acute malnutrition.

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Cadre : La tuberculose (TB) de l'enfance et la malnutrition sont des défis majeurs de santé publique dans le monde. On estime qu'un million d'enfants âgés de <15 ans ont eu une TB en 2015, mais la majorité des cas sont restés non diagnostiqués, en partie à cause du manque de connaissance et de capacité des prestataires de soins qui sont le premier point de contact pour les enfants malades ; ceci demande une meilleure intégration de la TB avec les services de santé de l'enfant et de nutrition. La TB peut causer ou aggraver la malnutrition et la malnutrition augmente le risque de TB.
Methodes : Les directives pour la prise en charge de la malnutrition aiguë de 17 pays durement frappés par la TB ont été revues afin de rassembler des informations relatives au dépistage des symptômes de TB, des antécédents d'exposition et de traitement.
Résultats : Sept (41%) pays recommandent un dépistage de routine de la TB parmi les enfants ayant une malnutrition aiguë et six (35%) recommandent de rechercher des antécédents d'exposition à la TB.
Conclusion : Le dépistage de la TB n'est pas systématiquement inclus dans les directives relatives à la malnutrition aiguë dans les pays durement frappés par la TB. Une évaluation de routine du risque de TB, particulièrement des antécédents d'exposition à la TB, parmi les enfants atteints de malnutrition aiguë, combinée à de meilleurs liens avec les services de TB contribuerait à augmenter la découverte des cas de TB et améliorer leur évolution. Une recherche opérationnelle sur la meilleure façon d'intégrer les services à différents niveaux du système de santé est nécessaire.

Marco de referencia: La tuberculosis (TB) durante la infancia y la desnutrición representan graves problemas de salud pública en el mundo. Se estima que un millón de niños de edad de <15 años contrajeron la TB en el 2015, pero la mayoría de los casos permaneció sin diagnóstico, debido en parte a la falta de sensibilización y a la escasa capacidad de los profesionales de salud que atienden en primera línea a los niños enfermos; esta situación exige una mejor integración de los servicios de atención de la TB y los servicios que se ocupan de la salud y la nutrición de los niños. La TB puede causar o agravar la desnutrición y esta a su vez aumenta el riesgo de contraer la TB.
Métodos: Se analizaron las directrices de manejo de la desnutrición aguda de 17 países con alta carga de morbilidad por TB, con el objeto de reunir información sobre la detección sistemática de los síntomas, los antecedentes de exposición y el tratamiento de la TB.
Resultados: Siete países recomendaban la detección sistemática de la TB en la práctica corriente en los niños con desnutrición aguda (41%) y seis países recomendaban obtener los antecedentes de exposición a la enfermedad (35%).
Conclusión: La recomendación de la detección sistemática de la TB no es constante en las directrices de manejo de la desnutrición en los países con alta carga de morbilidad por esta enfermedad. La práctica corriente de una evaluación del riesgo de TB, sobre todo de los antecedentes de exposición en los niños aquejados de desnutrición aguda, aunada a mejores vínculos con los servicios de atención de la TB contribuiría a aumentar el rendimiento de la búsqueda de casos y mejorar los desenlaces. Sería muy útil realizar investigaciones operativas sobre la mejor manera de integrar los servicios en los diferentes niveles del sistema de atención de salud.

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