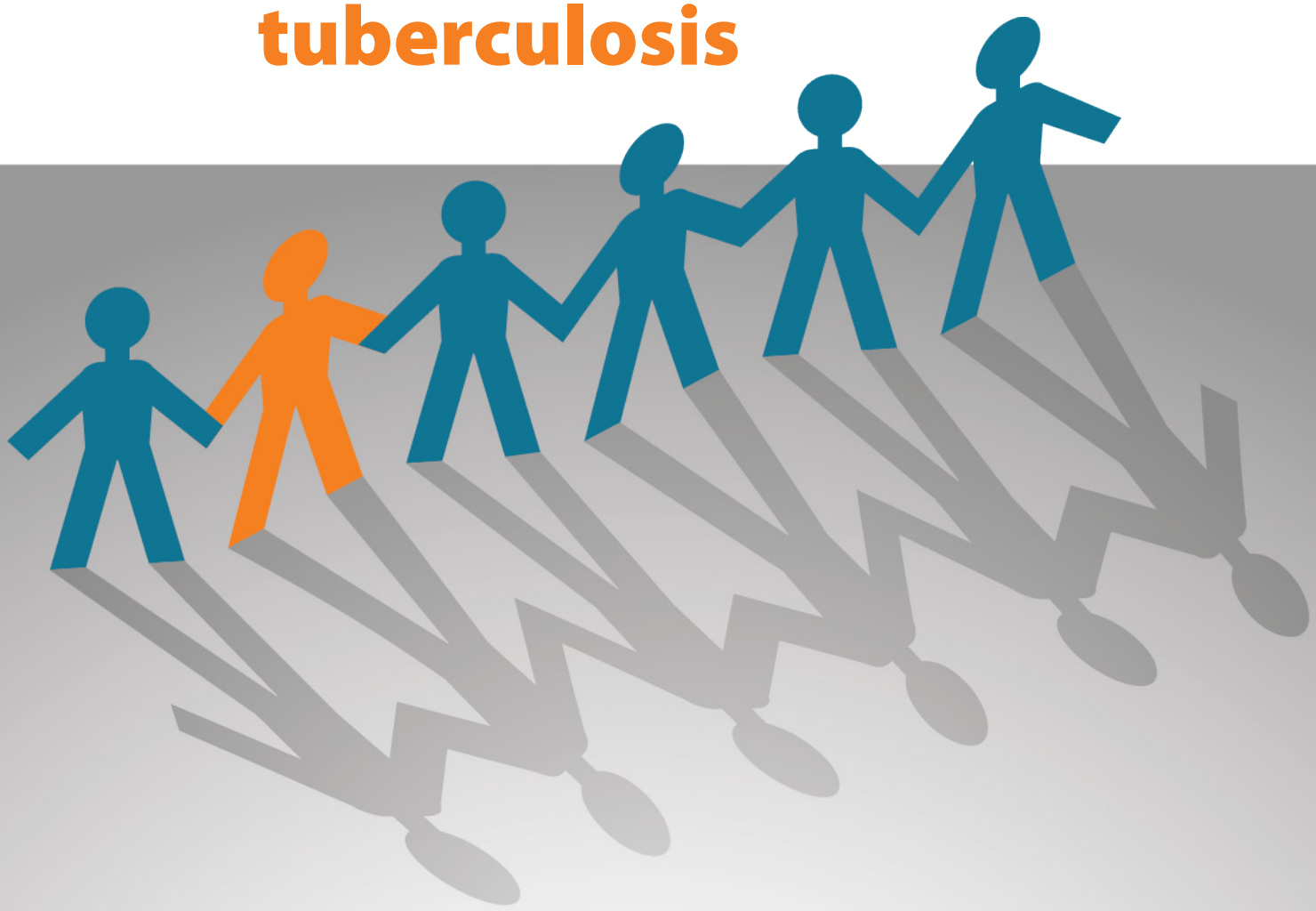
Guideline:

Nutritional care and support for patients with tuberculosis



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Abbreviations

ART	antiretroviral therapy
BMI	body mass index
DOTS	Directly Observed Treatment – Short course
eLENA	WHO e-Library of Evidence for Nutrition Actions
EVIPNet	WHO Evidence-Informed Policy Network
GRADE	Grading of Recommendations Assessment, Development and Evaluation
MDR-TB	multidrug-resistant tuberculosis
PICO	population, intervention, control, outcomes
TB	tuberculosis
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

Executive summary

Purpose of the guideline[1]

Undernutrition increases the risk of tuberculosis (TB) and in turn TB can lead to malnutrition. Undernutrition is therefore highly prevalent among people with TB. It has been demonstrated that undernutrition is a risk factor for progression from TB infection to active TB disease and that undernutrition at the time of diagnosis of active TB is a predictor of increased risk of death and TB relapse. However, the evidence concerning the effect of nutritional supplementation on TB prevention and health outcomes among people with TB had not previously been systematically reviewed. This guideline provides guidance on the principles and recommendations for nutritional care and support of patients with TB as part of their regular TB care. However, it does not consider the provision of food as part of a package of enablers to improve TB treatment adherence or as means to mitigate the negative financial consequences of TB. Member States have requested guidance from the World Health Organization (WHO) on nutritional care and support for patients with TB, in support of their efforts to achieve the Millennium Development Goals. The primary audience for the guideline is health workers providing care to people with TB. However, the guideline is also intended for a wider audience, including policy-makers, their expert advisers, and technical and programme staff at organizations involved in the design, implementation and scaling-up of nutrition actions for public health.

Guideline development methodology

WHO developed the present evidence-informed recommendations using the procedures outlined in the *WHO handbook for guideline development (1)*. The steps in this process included: (i) identification of priority questions and outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of recommendations, including research priorities; and (v) planning for dissemination, implementation, impact evaluation and updating of the guideline. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was followed, to prepare evidence profiles related to preselected topics, based on up-to-date systematic reviews.

The guideline development group for nutrition interventions, the Nutrition Guidance Advisory Group, comprised content experts, methodologists, representatives of potential stakeholders and consumers. These experts participated in three WHO technical consultations concerning this guideline, held in 2009–2011, two in Geneva, Switzerland, and one in Amman, Jordan. Members of the external experts' and stakeholders' panel were identified through a public call for comments, and this panel was involved throughout the guideline development process.

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[1] A WHO guideline is any document, whatever its title, containing WHO recommendations about health interventions, whether they be clinical, public health or policy interventions. A recommendation provides information about what policy-makers, health-care providers or patients should do. It implies a choice between different interventions that have an impact on health and that have ramifications for the use of resources. A full guideline is one that provides complete coverage of a health topic or disease. It is expected to include recommendations in relation to all aspects of the topic (e.g. surveillance, diagnosis, public health and clinical interventions) and to be fully based on systematic reviews of the evidence for each aspect. All publications containing WHO recommendations are approved by the WHO Guidelines Review Committee.

Available evidence

Three systematic reviews were updated to inform this process. One Cochrane systematic review assessed the effects of oral nutritional supplements (food, protein/energy supplements or micronutrients) on TB treatment outcomes and nutritional recovery in people on anti-tuberculous drug therapy for active TB. The review included 23 trials and concluded that there is insufficient research to determine whether the routine provision of food or energy supplements results in better TB treatment outcomes, or improved quality of life. Although blood levels of some vitamins may be low in patients starting treatment for active TB, there is currently no reliable evidence that routine micronutrient supplementation at or above recommended daily amounts has clinical benefits. Another systematic review investigated the optimal composition of diet for patients receiving treatment for active TB. This review included only two studies, both on energy requirements in people on TB treatment. The review concluded that the evidence is too weak to judge whether, or by how much, the daily energy intake needs are increased in people with active TB. A third review assessed the effects of nutritional interventions on the progression from TB infection to active TB. No trial was included in the review. There is no evidence on reduced risk of progression because of nutrient supplementation.

The overall evidence base on effects of nutritional supplements for TB prevention and care is limited and the overall quality is low or very low for most outcomes. There is no evidence on improvement of TB treatment outcomes, or prevention of progression from TB infection to active disease, when using nutritional supplementation as an addition to standard care.

Principles

Five guiding principles[1] are key for providing nutritional care and support as an integral part of TB care and prevention.

1. All people with active TB should receive TB diagnosis, treatment and care according to WHO guidelines and international standards of care. When malnutrition is identified at the time of TB diagnosis, TB is considered a key causal factor that needs to be addressed. It is essential that nutrition assessment and assistance do not divert resources from optimal TB diagnosis and care. Concerns about weight loss or failure to gain weight during TB treatment should trigger further clinical assessment (e.g. resistance to TB drugs, poor adherence, comorbid conditions) and nutrition assessment of the causes of undernutrition, in order to determine the most appropriate interventions.

[1] A guiding principle in health is a rule that has to be followed, or that may be desirable to follow, and cannot be proved or contradicted, unless propositions are made that are even clearer. It is a comprehensive and fundamental law, doctrine or assumption guiding health care and is understood by its users as the essential characteristics of health care and its designed purpose. A respect of the principles is needed in order for the health care to be used effectively. A guiding principle reflects a set of values that contextualize the provision of care in programmatic settings. Such values cannot be subjected to formal research but reflect preferences regarding public health approaches and goals. The principles are intended to inform and assist national technical groups and international and regional partners providing health care.

2. An adequate diet, containing all essential macro- and micronutrients, is necessary for the well-being and health of all people, including those with TB infection or TB disease.
3. Because of the clear bidirectional causal link between undernutrition and active TB, nutrition screening, assessment and management are integral components of TB treatment and care.
4. Poverty and food insecurity are both causes and consequences of TB, and those involved in TB care therefore play an important role in recognizing and addressing these wider socioeconomic issues.
5. TB is commonly accompanied by comorbidities such as HIV, diabetes mellitus, smoking and alcohol or substance abuse, which have their own nutritional implications, and these should be fully considered during nutrition screening, assessment and counselling.

Recommendations

Patients with TB should be nutritionally assessed and receive the same nutritional care and support as other individuals or populations of similar nutritional status, in agreement with all relevant WHO recommendations.

The recommendations are grouped on four areas related to nutritional care and support, to cover especially vulnerable populations, with an additional area for contact investigation.

Recommendation	Quality of evidence	Strength of recommendation
Nutrition assessment and counselling All individuals with active TB should receive (i) an assessment of their nutritional status and (ii) appropriate counselling based on their nutritional status at diagnosis and throughout treatment.	not available	strong[1]
Management of severe acute malnutrition School-age children and adolescents (5 to 19 years), and adults, including pregnant and lactating women, with active TB and severe acute malnutrition should be treated in accordance with the WHO recommendations for management of severe acute malnutrition *(2)*.	very low	strong

[1] A *strong* recommendation is one for which the guideline development group is confident that the desirable effects of adherence outweigh the undesirable effects. Implications of a strong recommendation for patients are that most people in their situation would desire the recommended course of action and only a small proportion would not. Implications for clinicians are that most patients should receive the recommended course of action, and adherence to this recommendation is a reasonable measure of good-quality care. With regard to policy-makers, a strong recommendation means that it can be adapted as a policy in most situations, and for funding agencies it means the intervention represents an appropriate allocation of resources (i.e. large net benefits relative to alternative allocation of resources).

Recommendation	Quality of evidence	Strength of recommendation
Children who are less than 5 years of age with active TB and severe acute malnutrition should be treated in accordance with the WHO recommendations for the management of severe acute malnutrition in children who are less than 5 years of age *(3)*.	very low	strong
Management of moderate undernutrition School-age children and adolescents (5 to 19 years), and adults, including lactating women, with active TB and moderate undernutrition, who fail to regain normal body mass index after 2 months' TB treatment, as well as those who are losing weight during TB treatment, should be evaluated for adherence and comorbid conditions. They should also receive nutrition assessment and counselling and, if indicated, be provided with locally available nutrient-rich or fortified supplementary foods, as necessary to restore normal nutritional status *(2)*.	low	conditional[1]
Children who are less than 5 years of age with active TB and moderate undernutrition should be managed as any other children with moderate undernutrition. This includes provision of locally available nutrient-rich or fortified supplementary foods, in order to restore appropriate weight-for-height *(4)*.	very low	strong
Pregnant women with active TB and moderate undernutrition, or with inadequate weight gain, should be provided with locally available nutrient-rich or fortified supplementary foods, as necessary to achieve an average weekly minimum weight gain of approximately 300 g in the second and third trimesters.	very low	strong
Patients with active multidrug-resistant TB and moderate undernutrition should be provided with locally available nutrient-rich or fortified supplementary foods, as necessary to restore normal nutritional status.	very low	strong

[1] A *conditional* recommendation is one for which the guideline development group concludes that the desirable effects of adherence probably outweigh the undesirable effects, although the trade-offs are uncertain. Implications of a conditional recommendation for patients are that, while many people in their situation would desire the recommended course of action, a considerable proportion would not. Implications for clinicians are that they should help patients make a decision that is consistent with their values. With regard to policy-makers, a conditional recommendation means that there is a need for substantial debate and involvement from stakeholders before considering the adoption of the recommendation, and for funding agencies it means that the intervention may not represent an appropriate allocation of resources (i.e. alternative uses of resources may produce greater benefits).

Recommendation	Quality of evidence	Strength of recommendation
Micronutrient supplementation		
A daily multiple micronutrient supplement at 1× recommended nutrient intake should be provided in situations where fortified or supplementary foods should have been provided in accordance with standard management of moderate undernutrition *(2, 4)*,[1] but are unavailable.	very low	conditional
All pregnant women with active TB should receive multiple micronutrient supplements that contain iron and folic acid and other vitamins and minerals, according to the United Nations Multiple Micronutrient Preparation *(5)*, to complement their maternal micronutrient needs.	very low	conditional
For pregnant women with active TB in settings where calcium intake is low, calcium supplementation as part of antenatal care is recommended for the prevention of pre-eclampsia, particularly among those pregnant women at higher risk of developing hypertension, in accordance with WHO recommendations *(6)*.	very low	strong
All lactating women with active TB should be provided with iron and folic acid and other vitamins and minerals, according to the United Nations Multiple Micronutrient Preparation (*5*), to complement their maternal micronutrient needs.	very low	conditional
Contact investigation		
In settings where contact tracing is implemented, household contacts of people with active TB should have a nutrition screening and assessment as part of contact investigation. If malnutrition is identified, it should be managed according to WHO recommendations *(2–4)*.	very low	conditional

[1] Pyridoxine supplementation is recommended along with isoniazid treatment for all pregnant (or breastfeeding) women, as well as for people with conditions such as HIV infection, alcohol dependency, malnutrition, diabetes, chronic liver disease or renal failure. Pyridoxine provision together with isoniazid treatment was not analysed for this guideline.

Key remarks

- There is no evidence that nutritional management of acute malnutrition of patients with active TB should be different than for those without active TB.
- Concerns about weight loss or failure to gain weight should trigger further clinical assessment (e.g. resistance to TB drugs, poor adherence, comorbid conditions) and nutrition assessment, in order to determine the most appropriate interventions.
- Closer nutritional monitoring and earlier initiation of nutrition support (before the first 2 months of TB treatment are completed) should be considered if the nutritional indicator is approaching the cut-off value for a diagnosis of severe undernutrition.

Research priorities

Guideline group members and stakeholders identified several research priorities to improve the body of evidence at the basic, clinical, epidemiological and operational levels, on the nutritional care and support for patients with TB.

1. Scope and purpose

The aim of this guideline is to help improve health outcomes for people with tuberculosis (TB), through improved nutritional care and support. The objectives of the guideline are to provide guidance on nutritional assessment, advice and treatment, for integration into clinical care for people with TB. Five guiding principles for nutritional care and support for people with TB are presented. The focus is on nutrition assessment, counselling and management to improve the clinical care of people with TB. These should be considered an essential part of services for people with TB and can be adapted according to countries' burden of disease and health-care infrastructure, including human resources capacity.

It is recognized that food assistance[1] is sometimes used in TB programmes for purposes other than nutritional care, especially in food-insecure settings. Specific guidance regarding the role of food assistance as part of a larger package of services intended to improve access and adherence to treatment and to mitigate the financial and social consequences of TB will be addressed elsewhere.

The primary audience for the guideline is health workers providing care to people with TB. However, the guideline is also intended for a wide audience, including policy-makers, their expert advisers, and technical and programme staff managing national and subnational TB programmes and nongovernmental agencies that deliver TB services, and for policy-makers involved with scaling up TB prevention, diagnosis and treatment, including adherence to and completion of therapy. This document presents the guiding

[1] The definition of food assistance includes, in some cases, all interventions that address food insecurity and nutrition (including in-kind food aid, cash transfers and some forms of production and market support), while in other it is limited to direct food- and cash-based transfers.

principles, key recommendations and a summary of the supporting evidence. Further details of the evidence base are provided in Annexes 1 and 2 and other documents listed in the references.

2. Background

TB is a contagious disease related to poverty, undernutrition and poor immune function. TB morbidity and mortality are highest in developing countries. In 2012, there were an estimated 8.6 million new cases of TB (13% coinfected with HIV). There were 950 000 deaths due to TB among people who were HIV negative and another 320 000 among people who were HIV positive *(7)*. While TB is more common among men than women, it is one of the top killers of women worldwide; including HIV-positive women, half a million women died from TB in 2012. There were an estimated 0.5 million TB cases and 74 000 TB deaths among children less than 15 years of age in 2012 *(7)*.

More than 15 years of intensive effort to improve TB diagnosis, treatment and control have been successful in reducing TB prevalence and death rates. Between 1995 and 2012, 56 million TB patients were successfully treated in quality-assured national TB programmes, and over 20 million lives were saved through DOTS (Directly Observed Treatment – Short course) and the Stop TB Strategy *(7)*. Still, the incidence of TB globally is declining only slowly and TB remains a major public health threat in most parts of the world *(8)*.

Addressing comorbid conditions has value for improving access and response to TB treatment and it should be considered as part of the standard of care for people with TB. The aim of comprehensive care should be to improve general health and quality of life. The role of food and nutritional care is integral to successful health promotion and disease prevention. Undernutrition is both an important risk factor for, and a common consequence of, TB. It is therefore a common comorbid condition for people with active TB and is associated with increased risk of mortality and poor treatment outcomes *(8–12)*. There is very limited evidence available to suggest that nutrition support, such as provision of supplemental or fortified food or specific nutrients, in addition to standard TB treatment, improves TB-specific treatment outcomes. However, nutrition assessment and care are critical components of improving rehabilitation and quality of life.

The integration of recommendations regarding nutrition care and support may include scaling up and strengthening nutrition care infrastructure, coordinating public health services and investing in capacity-building and training of health-care workers in the use of evidence-informed approaches to nutrition assessment and counselling. Opportunities exist to coordinate with other health programmes, such as HIV, childhood immunization and reproductive services.

Nutrition and tuberculosis

An essential dietary nutrient is a substance that a person needs to consume in order to live, grow and be healthy. Nutrients are required to regulate body processes and build and repair tissues and thereby promote health and prevent disease. Macronutrients (protein, carbohydrate and fat) are generally consumed in large amounts. Carbohydrate

and some fat are converted to energy, while protein and some fat are used to make structural and functional components of human tissue. Micronutrients (vitamins and minerals) are consumed in small amounts and are essential for metabolic processes. Macronutrients and micronutrients work together to contribute to tissue regeneration and cellular integrity.

Malnutrition is a general term that refers to either overnutrition or undernutrition or both. Undernutrition refers to a state when the nutritional status of the person is suboptimal and thereby health and growth may be limited. Undernutrition may be due to illness that impairs nutrient intake and metabolism, or result from inadequate intake of macronutrients, micronutrients or both *(10, 11, 13, 14)*.

Undernutrition is commonly associated with illness and infections such as gastrointestinal disorders and malabsorption, pneumonia, TB and HIV *(15)*. Food insecurity can be a cause of malnutrition, as can alcohol misuse and illicit drug use *(15)*, and a number of other conditions. In any case, both the underlying condition associated with undernutrition and the malnutrition itself warrant evaluation and treatment *(15)*.

The association between TB and undernutrition has long been known. TB makes undernutrition worse and undernutrition weakens immunity, thereby increasing the likelihood that latent TB will develop into active disease *(10)*. Most individuals with active TB are in a catabolic state and experience weight loss *(9, 16, 17)* and some show signs of vitamin and mineral deficiencies at diagnosis *(18–21)*. Weight loss among those with TB can be caused by several factors, including reduced food intake due to loss of appetite, nausea and abdominal pain; nutrient losses from vomiting and diarrhoea *(22, 23)* and metabolic alterations caused by the disease. Low body mass index (BMI) (lower than 18.5 kg/m^2) and lack of adequate weight gain with TB treatment are associated with an increased risk of death *(9, 24)* and TB relapse *(25, 26)* and can be an indication of severity of TB, poor treatment response and/or the presence of other comorbid conditions.

Macronutrient requirements in active TB

Active TB, like other infectious diseases, is likely to increase energy requirement, and data on the actual level of increase in energy requirements caused by HIV infection may be used as a guide. Studies show that subjects who receive food supplements during TB treatment tend to gain more weight compared with those not receiving food supplements, but the increase in weight gain has not been associated with improvement of TB treatment outcomes *(17, 27)*.

There is currently no evidence to suggest that the proportion of dietary energy from macronutrients (e.g. protein, carbohydrate and fat), otherwise known as macronutrient distribution, is different for people with active TB than for those without TB. It is generally recommended that all people consume approximately 15–30% of energy as protein, 25–35% as fat and 45–65% as carbohydrate *(28)*.

Micronutrient requirements in active TB

Low circulating concentrations of micronutrients, such as vitamins A, E and D, and the minerals iron, zinc and selenium have been reported from cohorts of patients

beginning treatment for active TB *(29–32)*. These usually return to normal after 2 months of appropriate TB treatment. Since studies have not been done on dietary intake near the time of diagnosis, it is unclear whether the low concentrations are related to low dietary intake, to metabolic processes or to the disease itself. It is unknown whether the observed return to normal concentrations is dependent on the quality of dietary intake.

Available guidance for treatment of malnutrition/undernutrition

BMI is the most commonly used indicator to measure the degree of thinness and fatness in adults over 18 years of age, while BMI-for-age-and-sex Z-score is used in children and adolescents aged 5–19 years *(15)*. Weight-for-length or weight-for-height Z-score is the recommended indicator for children who are less than 5 years of age, with mid-upper arm circumference being used to identify cases in need of life-saving nutrition management.

Severe acute malnutrition

Severe acute malnutrition is a common cause of morbidity and mortality in many settings. Nutritional therapy aims to reduce the risk of death, shorten hospitalization and facilitate rehabilitation and a full recovery. Please see the World Health Organization (WHO) recommendations for definition and treatment of severe acute malnutrition in children, adolescents and adults *(2–4)*.

Moderate undernutrition

In 2012, WHO published a technical note on *Supplementary foods for the management of moderate acute malnutrition in infants and children 6–59 months of age (4)*. Currently WHO recognizes that the dietary management of moderate acute malnutrition in children should normally be based on the optimal use of locally available nutrient-dense foods. In situations of food shortage, or where some nutrients are not sufficiently available through local foods, specially formulated supplementary foods are usually required to supplement the regular diet; for those cases, the technical note provides orientation on the composition of supplementary foods.

The current recommendation for moderate undernutrition in adolescents and adults is to provide supplemental foods in the outpatient setting until BMI is normalized. The approach is that individuals with moderate undernutrition have different nutritional needs than either people without undernutrition or those with severe acute malnutrition. An individualized approach that addresses the various causes of moderate undernutrition is needed, since the appropriate therapy depends on the cause of undernutrition. For most people with active TB, assuming sufficient food is available, effective TB therapy will improve nutritional status by improving appetite and food intake, reducing energy/nutrient demands, and improving metabolic efficiency.

Nutrition care or management of persons with active TB with moderate undernutrition, similarly to other persons with moderate malnutrition, includes assessing their nutritional status, identifying and treating the underlying causes of malnutrition and improving the nutrient intake through education, counselling, food assistance and other activities *(2)*.

Social determinants of malnutrition and TB

Because undernutrition increases the risk of progression from TB infection to active TB disease, food insecurity and poor general nutritional status in the population are important contributors to the global burden of TB disease *(8, 10, 11)*. Catastrophic health expenditure is a common consequence of TB diagnosis, treatment and care, which can lead to a worsening of food insecurity for TB patients and their families during the course of the disease. At least 75% of all TB cases are among people who are 15–54 years of age and in their prime working years *(7)*. TB is a major cause of poverty aggravation because people with TB often face the double burden of reduced income and increased expenses: they are often too sick to work and their families have to pay expenses associated with treatment *(33)*.

TB and pregnancy

Low birth weight, a predictor of infant morbidity and mortality, is more common in infants borne by women with TB *(34–38)*. Infants of mothers with TB have increased risks of premature birth and perinatal death, while the mothers are more likely to have complications during pregnancy, with disorders of hypertension during pregnancy being the more common *(35–37, 39, 40)*. Initiation of TB treatment earlier in the pregnancy is generally related to better maternal and infant outcomes *(37, 39)*.

Adequate weight gain during pregnancy, which is associated with improved birth weight, is a concern in women with TB. In a study in Papua New Guinea, more than 80% of pregnant women with TB who did not receive TB treatment during pregnancy, or were treated for less than 4 weeks, lost weight or did not gain adequate weight during pregnancy. The majority of women receiving treatment for more than 4 weeks gained weight adequately; however, 38% did not gain adequate weight or lost weight in spite of longer TB treatment *(39)*.

Pregnant women with TB have been noted to be at increased risk of developing pre-eclampsia *(35, 40, 41)*. Health-care providers should be made aware of this risk and follow the WHO nutrition recommendations for women at risk of developing pre-eclampsia and eclampsia *(6, 42)*. In populations where calcium intake is low, calcium supplementation as part of antenatal care is recommended for the prevention of pre-eclampsia among pregnant women, particularly among those at higher risk of hypertension.

Regardless of the presence of TB, the maternal requirement for micronutrients during pregnancy tends to be 25–50% higher, depending on the nutrient, than the pre-pregnancy requirements *(43, 44)*. While there have not been any randomized controlled trials of micronutrient supplements in pregnant women with TB, multiple micronutrient supplements given during pregnancy in non-HIV infected populations have been effective in reducing rates of low birth weight, small-for-gestational-age infants, and anaemia *(45–47)*. A Cochrane review of multiple micronutrient supplementation in HIV-infected women during pregnancy found that women who received the multiple micronutrient supplement including iron and folic acid had significantly better birth outcomes compared with those who received only iron and folic acid or no supplementation *(48, 49)*. Infants of HIV-infected mothers given multiple micronutrient supplements had higher birth weights, and were less likely to have low birth weight, or to have been born severely pre-term or small-for-gestational-age *(48, 49)*.

A healthy well-nourished woman should gain between 10 kg and 14 kg during pregnancy, to increase the likelihood of delivering a full-term infant weighing at least 3.3 kg *(50)*. To support an average weekly weight gain of approximately 420 g and an average monthly gain of 1.7 kg in the second and third trimesters, a woman usually consumes 360 kcal/day (1.5 MJ/day) in the second trimester and 475 kcal/day (2.0 MJ/day) in the third trimester, in addition to usual food *(50)*. To support the additional protein requirements during pregnancy, women are advised to consume an additional 9 g/day of protein during the second trimester and 31 g/day in the third trimester. A pregnant adolescent needs 1.5 g protein/kg pregnant body weight to support her own needs as well as those of the fetus *(51)*. Underweight pregnant women (BMI less than 19 kg/m^2) can eat additional food, in order to achieve a total weight gain between 12.5 kg and 18 kg, with an average weekly weight gain of 510 g and an average monthly gain of 2 kg in the second and third trimesters *(52)*.

TB and child household contacts

Owing to their proximity and frequency of contact, children with TB are usually infected by someone in their immediate household *(53)*. When the positive case in the household is detected, screening for TB amongst household members is a means to detect TB early in children and other close contacts. Young children are particularly vulnerable, owing to their relatively immature immune systems *(53)*. Undernourished children are at particular risk. Undernutrition and younger age individually increase the risk of household contacts of TB patients developing active TB disease *(53, 54)*.

Child contact screening in many low- to middle-income countries may not be a priority, so children who are infected may be missed. An additional complication for screening household contacts for TB infection is the fact that children with mild to moderate malnutrition become anergic, meaning that they cannot mount an immunologic response to the TB skin test *(14)*. This increases the likelihood of missing the TB diagnosis where skin testing is used. These children represent a potentially significant number of future TB cases *(53, 55)*.

In the only nutrition intervention study identified in household contacts, family members of TB patients who received nutrition advice alone had almost six times the risk of developing active disease, compared with those who received a vitamin and mineral supplement with dietary advice *(56)*. This study was conducted in New York City between 1941 and 1946, before the advent of TB chemotherapy. While intervention studies in child household contacts have not been conducted after the introduction of chemotherapy, improved nutrition among household contacts of TB patients, especially in children who are less than 10 years of age, might reduce the risk of contacts developing active disease.

3. Guideline development process

This guideline was developed in accordance with the WHO evidence-informed guideline development procedures, as outlined in the *WHO handbook for guideline development (1)*.

Advisory groups

A WHO Steering Committee for Nutrition Guidelines Development, led by the Department of Nutrition for Health and Development was established in 2009, with representatives from all WHO departments with an interest in the provision of scientific nutrition advice, including the Global TB Programme (GTB) and the Departments of Maternal, Newborn, Child and Adolescent Health, and Reproductive Health and Research. The steering committee guided the development of this guideline and provided overall supervision of the guideline development process (Annex 4). Two additional groups were formed: an advisory guideline group and an external experts' and stakeholders' panel.

The Nutrition Guidance Advisory Group was established in 2009 (Annex 5). A subgroup on nutrition in the life-course was established for the biennium 2010–2011. Its role was to advise WHO on the choice of important outcomes for decision-making and in the interpretation of the evidence. The Nutrition Guidance Advisory Group includes experts from various WHO expert advisory panels *(57)* and those identified through open calls for specialists. Efforts were made to include content experts, methodologists, representatives of potential stakeholders (such as managers and other health professionals involved in the health-care process) and consumers. Representatives of commercial organizations may not be members of a WHO guideline group.

The external experts' and stakeholders' panel was consulted on the scope of the guideline, the questions addressed, and the choice of important outcomes for decision-making, as well as with regard to review of the completed draft guideline (Annex 6). This was done through the WHO Nutrition and United Nations System Standing Committee on Nutrition (SCN) *(58)* mailing lists that together include over 5500 subscribers, through the WHO nutrition web site *(59)*, and through contacting technical agencies involved in national and international TB control.

Scope of the guideline, evidence appraisal and decision-making

Since there were no internationally agreed recommendations on what nutrition care or food assistance TB patients should receive, or on how national TB programmes can contribute to improving a population's nutritional status, the Department of Nutrition for Health and Development and the Global TB Programme (GTB) planned to develop such recommendations and guidelines jointly. A scoping meeting for the development of recommendations on nutritional support/food assistance to prevent TB and improve health status among TB patients was held in Geneva, 2–4 November 2009 *(60)*. An initial set of questions (and the components of the questions) to be addressed in the guideline was the critical starting point for formulating the recommendation. The questions were drafted by technical staff at the Evidence and Programme Guidance Unit, Department of Nutrition for Health and Development, and the Policy, Strategy and Innovations unit, Global TB Programme, based on policy and programme guidance needs of Member

States and their partners. The population, intervention, control, outcomes (PICO) format was used (Annex 3). The questions were discussed and reviewed by the WHO Steering Committee for Nutrition Guidelines Development, and feedback was received from five stakeholders.

A Nutrition Guidance Advisory Group meeting was held on 16–18 November 2010 in Amman, Jordan, to finalize the scope of the questions and rank the critical outcomes and populations of interest. The guideline development group discussed the relevance of the questions and modified them as needed. The guideline group scored the relative importance of each outcome. The final key questions on this intervention, along with the outcomes that were identified as critical and important for decision-making are listed in PICO format in Annex 3.

One Cochrane[1] review *(27)*, and two supplementary reviews were used to summarize and appraise the evidence *(62, 63)*. WHO technical staff, together with methods experts of the guideline group, prepared evidence summaries according to the Grading of Recommendations Assessment, Development and Evaluation *(64)* (GRADE) approach to assess the overall quality of the evidence *(65)*.

Both the systematic reviews and the GRADE evidence profiles for each of the critical outcomes were used for drafting this guideline. However, GRADE tables were only developed for those questions for which there were published studies included in the reviews. Some recommendations were developed based on recommendations previously made by WHO on nutritional care and support. The draft recommendation was discussed by the WHO Steering Committee for Nutrition Guidelines Development and the guideline development group, at a second guideline development consultation, held in Geneva between 28 November and 1 December 2011. The procedures for decision-making were established at the beginning of the meetings, including a minimal set of rules for agreement and voting. At least two thirds of the guideline development group had to be present for an initial discussion of the evidence and proposed recommendation and remarks. The guideline development group secretly voted on the direction and strength of the recommendation, using a form designed for this purpose, which also included a section for documenting their views on (i) the desirable and undesirable effects of the intervention; (ii) the quality of the available evidence; (iii) values and preferences related to the intervention in different settings; and (iv) the cost of options available to health-care workers in different settings. Each member had one vote if not advised otherwise, after managing any potential conflict of interests. Abstentions were not allowed.

The WHO Secretariat collected the forms and disclosed the summary of the results to the guideline development group. If there was no unanimous consensus, more time was given for deliberations and a second round of voting was possible. If there was no full agreement, a two thirds vote of the guideline development group would have been

[1] The detailed methods used in each Cochrane systematic review, as well as their search date, are published and available through the Cochrane Library. As part of the Cochrane pre-publication editorial process, this review was commented on by external peers (an editor, and two referees external to the editorial team) and the group's statistical adviser. The *Cochrane handbook for systematic reviews of interventions (61)* describes in detail the process of preparing and maintaining Cochrane systematic reviews on the effects of health-care interventions.

required for the approval of the proposed recommendation. Divergent opinions, if any, were recorded in the guideline. Voting forms will be kept on file by WHO for 10 years. Consensus was reached for all recommendations. WHO staff present at the meeting, as well as other external technical experts involved in the collection and grading of the evidence, were not allowed to vote. There were no strong disagreements among the guideline group members.

A draft of the revised principles and recommendations was disseminated for external peer review in February 2012. Reviewers were asked to examine the principles and recommendations, to ensure that there were no important omissions, contradictions or inconsistencies with scientific evidence or programmatic feasibility; and to assist with clarifying the language, especially in relation to implementation and how policy-makers and programme staff might read them. Reviewers were advised that no additional recommendations could be considered and that they were being asked to undertake this exercise in their personal capacity and not as representatives of any agency or institution. External reviewers proposed several comments to make the recommendations clearer. There was no major disagreement. The draft principles and recommendations were circulated to all involved WHO technical staff; all TB regional advisers in all WHO regional offices; selected national TB programmes; several technical agencies working on TB control, including KNCV Tuberculosis Foundation, the Centers for Disease Control and Prevention and the International Union Against TB and Lung Disease; and a network of external experts for TB and nutrition, respectively. All interested stakeholders became members of the external experts' and stakeholders' panel but were only allowed to comment on the draft guideline after submitting a signed declaration of interests form. Feedback was received from these stakeholders. WHO staff addressed each comment and then finalized the guideline and submitted it for clearance by WHO before publication.

Management of conflicts of interest

According to the rules in the WHO *Basic documents (66),* all experts participating in WHO meetings must declare any interest relevant to the meeting, prior to their participation. The conflicts of interest statements for all guideline group members were reviewed by the responsible technical officer and the relevant departments before finalization of the group composition and invitation to attend a guideline group meeting. All guideline group members and participants of the guideline development meetings submitted a declaration of interests form along with their curriculum vitae, before each meeting. In addition, they verbally declared any interest at the beginning of each meeting and they agreed to the publication of their declaration, if relevant, in the guideline prior to their involvement. The procedures for management of conflicts of interests strictly followed WHO *Guidelines for declaration of interests* (*WHO experts*) *(67)*. On reviewing the responses, none of the declared interests were likely to influence the discussions of the meeting. Therefore, no special provisions or mechanisms to deal with these interests were considered necessary. External experts representing partner organizations, representatives from the Department of Nutrition for Health and Development and Global TB Programme, and from selected national TB programmes, participated in the meeting and review processes. All external experts were also required to submit a curriculum vitae and complete a declaration of interest.

4. Summary of the evidence

Systematic reviews were conducted to address the following questions (see Annex 3 for questions in PICO format)

1. What is the optimal composition of the diet for patients receiving treatment for active TB?
2. Should macronutrient supplements be recommended to improve TB treatment and health outcomes for well-nourished or undernourished patients (children, adolescents, adults and pregnant and lactating women) being treated for active TB?
3. Should micronutrient (alone, combined or as a multiple micronutrient) supplements be recommended as a component of normal care in well-nourished or undernourished patients (children, adolescents, adults and pregnant and lactating women) being treated for active TB for improving TB treatment and nutrition outcomes?
4. Are there population-level nutritional interventions that could reduce the progression from latent to active TB in household contacts of patients with active TB?

Optimal composition of the diet for patients receiving treatment for active TB

This question was considered a background question and the findings from the review of the literature on the subject were integrated in the background section of this guideline. The only aspect of the diet composition considered for inclusion in the questions in a PICO format and systematic review of the literature was that of energy requirements.

When assessing energy requirements in patients with TB and other pulmonary diseases *(63),* only two observational studies were included in the review on energy requirements in people on TB treatment, with a total of 40 persons with TB. The studies found that basal metabolic rate was 14% higher in the patients compared with the controls (see GRADE Table 1, Annex 1). One study measured energy expenditure in six TB subjects with 10% weight loss at diagnosis, compared with six healthy controls; the second study's objective was to investigate whether the leptin concentration in 32 TB patients is higher during active TB disease versus recovery and how it related to energy metabolism. In this study, there was no comparison group. Both studies were of very low quality. The evidence is limited to judge whether, or by how much, the daily energy requirements are increased in people with active TB.

Macronutrient and micronutrient supplementation for patients with active TB

One Cochrane systematic review assessed the effects of oral nutritional supplements (food, protein/energy supplements or micronutrients) on TB treatment outcomes and recovery in people on antituberculous drug therapy for active TB *(27)*. Twenty-three trials, with a total of 6842 participants, were included in the review on these two subjects (see GRADE Tables 2 and 3, Annex 1).

In relation to macronutrient supplementation, five trials assessed the provision of free food, or high-energy supplements, although none were shown to result in a total daily kilocalorie intake above the current daily recommended intake for the non-infected

population. The available trials were too small to reliably prove or exclude clinically important benefits on mortality, TB cure or completion of TB treatment. One small trial from India did find a statistically significant benefit on completion of TB treatment, and clearance of the bacteria from the sputum, but these findings have not been confirmed in larger trials elsewhere (very low quality evidence).

The provision of free food or high-energy nutritional products may produce a modest increase in weight gain during treatment for active TB (moderate quality evidence). Two small studies on people coinfected with TB and HIV provide some evidence that physical function and quality of life may also be improved but the trials were too small to have much confidence in the result (low quality evidence). These effects were not seen in the one trial that included only HIV-positive patients.

In relation to micronutrient supplementation, five trials assessed multi-micronutrient supplementation in doses up to 10 times the dietary reference intake, and 12 trials assessed single or dual micronutrient supplementation.

There is insufficient evidence to judge whether multi-micronutrients have a beneficial effect on mortality in HIV-negative patients with TB (very low quality evidence), but the available studies show that multi-micronutrients probably have little or no effect on mortality in HIV-positive patients with TB (moderate quality evidence).

No studies have assessed the effects of multi-micronutrients on TB cure, or completion of TB treatment. Multiple micronutrient supplements may have little or no effect on the proportion of TB patients remaining sputum positive during the first 8 weeks (low quality evidence), and probably have no effect on weight gain during treatment (moderate quality evidence). No studies have assessed quality of life. Plasma levels of vitamin A appear to increase following initiation of TB treatment, regardless of supplementation. In contrast, plasma levels of zinc, vitamin D and E, and selenium may be improved by supplementation during the early stages of TB treatment, but a consistent beneficial effect on outcomes of TB treatment or nutritional recovery has not been demonstrated. There is insufficient evidence to know whether routinely providing free food or energy supplements results in better TB treatment outcomes or improved quality of life. Although blood levels of some vitamins may be low in patients starting treatment for active TB, there is currently no reliable evidence that routinely supplementing at or above recommended daily amounts has clinical benefits.

Population-level nutritional interventions to reduce the progression from latent to active TB

A literature review was conducted to investigate whether household contacts with poor nutritional status were at higher risk of contracting or developing active TB disease. No intervention study was included. Six studies on the risk for children in contact with people with active TB were identified. Two of the studies found that malnutrition and younger age individually increased the risk of household contacts developing active TB. One study was cross-sectional and it was difficult to determine the direction of influence between active TB and failure to thrive. Two studies were not designed to measure differences in variables by household contact and the last study found that vitamin D deficiency was associated with increased risk of development of active disease in close contacts *(62)*.

Although undernutrition is a risk factor for progression from TB infection to active TB disease, it is not known whether or with how much macro- or micronutrient supplementation reduces the risk of progression. Among young children who have had recent contact with a case of active TB, it is not known whether nutritional supplementation in combination with treatment of latent TB infection reduces the risk of progression to active TB more than treatment for latent TB infection alone.

The overall evidence base on effects of nutritional supplements for TB prevention and care remains very weak. It is not known whether nutritional supplementation, as an addition to standard care, improves health outcomes among people with TB, or prevents progression from TB infection to active disease. Owing to a lack of evidence that people with TB should receive nutritional care and support that is different from that which should be provided to others, the recommendations in this guideline are fully consistent with WHO's general recommendations on nutritional care and support *(2–4)*.

Implications for future research

Discussion with Nutrition Guidance Advisory Group members and stakeholders highlighted the limited evidence available in themes related to the areas listed next.

1. ***Nutrient requirements***

    a. Energy requirements in TB patients compared with persons without TB, considering TB treatment, coexistent HIV, phase of treatment and multidrug-resistant tuberculosis (MDR-TB)

    b. Requirements/utilization of proteins, as well as fat requirements

    c. Risk of micronutrient deficiencies in people with active TB in relation to people without TB

    d. Proportional causes of malnutrition in people with TB

    e. The natural course of weight change during the intensive phase of TB treatment in drug-sensitive TB and MDR-TB, in people with different levels of malnutrition, and in settings with varying levels of food security

2. ***Supplementation***

    a. The effect of macronutrient intake/food supplementation in addition to treatment alone, on TB treatment outcomes

    b. The effect of macronutrient supplementation or routine supplementation with micronutrients at 1× recommended nutrient intake in pregnant women with active TB, on neonatal complications

    c. Benefits of macro- or micronutrient supplementation on growth and development in the 5–19-year age groups with active TB, compared to those without TB

    d. Definition of nutritional parameters/TB-specific outcomes to be measured in nutritional supplementation trials

3. ***Programmes***

   a. The effect of implementation of the new WHO nutrition and TB recommendations on nutritional recovery/TB treatment outcomes in TB patients

   b. The relative importance of food assistance (compared with other enablers) as an enabler to adherence

4. ***Assessment and counselling***

   a. Aspects of nutritional counselling that enhance the effectiveness and uptake of advice on nutritional outcomes

   b. The best measure of nutritional status in pregnant women, with and without TB, considering both maternal and infant outcomes

   c. The optimal BMI for healthy maternal and infant outcomes in pregnant women with TB

5. Key principles

The Nutrition Guidance Advisory Group agreed on five key guiding principles[1] that should be considered together with the evidence-informed recommendations. The principles are intended to inform and assist national technical groups, international and regional partners providing TB care, TB treatment services, and/or maternal and child health services in countries affected by TB, in formulating national or subnational nutritional recommendations.

Key principle 1. All people with active TB should receive TB diagnosis, treatment and care according to WHO guidelines and international standards of care

Appropriate diagnostic procedures, support for TB patients to complete treatment, and an appropriate combination of TB medications is crucial for curing the disease. The Stop TB Strategy provides the goals, objectives and indicators for TB care and control *(68)*. The *International Standards for Tuberculosis Care* is a widely accepted level of care that all practitioners should achieve in managing patients who have TB *(69)*. All essential elements of TB diagnosis and treatment should be provided free of charge to patients, in order to improve access to treatment and minimize the financial burden of the TB treatment on patients and households.

[1] A guiding principle in health is a rule that has to be followed, or that may be desirable to follow, and cannot be proved or contradicted, unless propositions are made that are even clearer. It is a comprehensive and fundamental law, doctrine, or assumption guiding health care and is understood by its users as the essential characteristic of health care and its designed purpose. A respect of the principles is needed in order for the health care to be used effectively. A guiding principle reflects a set of values that contextualize the provision of care in programmatic settings. Such values cannot be subjected to formal research but reflect preferences regarding public health approaches and goals. The principles are intended to inform and assist national technical groups and international and regional partners providing health care.

When undernutrition is identified at the time of TB diagnosis, TB should be considered a key causal factor that needs to be addressed. It is essential that nutrition assessment and assistance do not divert resources from optimal TB diagnosis and care.

***Key principle 2.* An adequate diet, containing all essential macro- and micronutrients, is necessary for the well-being and health of all people, including those with TB infection or TB disease**

Consuming a well-balanced and adequate diet is key to maintaining optimal health and physical function at all ages. Nutritional status is an important determinant of resistance to infection and of general well-being. It is well established that nutritional deficiency is associated with impaired immunity. While malnutrition increases susceptibility to infection, infection can lead to metabolic stress and weight loss, further weakening immune function and nutritional status *(13)*. Vitamins A, C, D, E, B_6 and folic acid and the minerals zinc, copper, selenium and iron all play key roles in metabolic pathways, cellular function and immune function. The concentration of these nutrients may have a role in an individual's defence against TB *(13, 70)*. Undernutrition is a strong contributor for active TB worldwide, and reduction in undernutrition in the general population could dramatically reduce the incidence of TB *(11)*.

***Key principle 3.* Because of the clear bidirectional causal link between undernutrition and active TB, nutrition screening, assessment and management are integral components of TB treatment and care**

Many people diagnosed with TB are undernourished at the time of diagnosis and nutrition intervention and care begin with a nutrition assessment.

Nutrition assessment (anthropometric,[1] biochemical,[2] clinical and dietary) is a prerequisite for the provision of good nutritional care. The results from screening and assessment inform counselling, which is usually done at the time of diagnosis and throughout treatment. Trained primary and lay health-care workers in primary and community health care can play an effective and integral role in nutrition screening and can identify patients affected by undernutrition and in need of further assessment.

At diagnosis, nutrition screening and assessment should include anthropometric and clinical measurements. If undernutrition is diagnosed, dietary assessment is also indicated. The following are required:

- age-appropriate anthropometric measurements and classification of nutrition status *(71–75)*:
  - height and weight:
    - in children who are less than 5 years of age, determination of weight-for-length or weight-for-height Z-score, using the WHO child growth standards *(74)*

[1] Anthropometric measurements use measurements of the body to assess nutritional status.

[2] The most common nutritional biochemical assessments are for anaemia and serum albumin.

- in children and adolescents aged 5–19 years, determination of BMI-for-age-and-sex Z-score, using the WHO growth reference data for 5–19 years *(15, 74)*
- in adults over 18 years of age, determination of BMI

- mid-upper arm circumference:
  - in children who are less than 5 years of age and pregnant women

- history of weight loss and signs of undernutrition, such as visible wasting or oedema
- clinical assessment for comorbid conditions and concurrent treatments
- diet assessment if nutritional status indicates malnutrition.

At TB follow-up, assessment should include, at a minimum:

- anthropometric measures of weight, calculation of BMI and determination of weight and BMI change since diagnosis or last visit
- classification of nutrition status *(71–75)*.

In patients classified as having moderate undernutrition, or severe acute malnutrition, further risk factor and dietary assessment will be necessary, such as:

- poor TB treatment adherence and/or response, resistance to TB drugs
- clinical assessment for other non-dietary causes of malnutrition, including identification of important comorbidities like HIV, diabetes mellitus or alcohol or drug abuse
- biochemical assessment where possible
- dietary assessment, including assessment of food security.

Weight loss or failure to regain or maintain a healthy weight, at any stage of disease should trigger further assessment and appropriate interventions. Weight status is particularly important for people with MDR-TB, who require a very long duration of treatment and are more likely to require chronic care and palliative care.

The goal of nutrition counselling is to improve the dietary intake during recovery, to compensate for the increase in energy expenditure associated with recovery and weight regain; support the increase in cellular production and immune responses; support repair of damaged and diseased tissues *(76)*; and manage the symptoms and side-effects of TB drugs, such as nausea and vomiting, anorexia, diarrhoea and altered taste.

Practical ways to meet macro- and micronutrient requirements through locally available and culturally appropriate foods should be provided.

Key principle 4. ***Poverty and food insecurity are both causes and consequences of TB, and those involved in TB care therefore play an important role in recognizing and addressing these wider socioeconomic issues***

Food insecurity, which is common in TB patients, and concomitant poor nutritional status, contribute to the global burden of active TB. As an integral part of TB care and control, the health sector should recognize and help address generalized malnutrition, food insecurity and other socioeconomic determinants and consequences of TB.

Food insecurity can contribute to poor access and adherence to TB treatment. Although evidence for the positive impact of food intervention on access and adherence to TB treatment is currently limited, interventions that address food security have the potential to improve access and adherence to TB treatment, as well as to support nutritional recovery through provision of nutritious foods. Such interventions can also help mitigate some of the financial and social consequences of TB. While food and nutrition are essential to the health and well-being of all individuals, food assistance may be neither the best or most appropriate enabler for access and adherence to TB treatment, nor the best way to alleviate the catastrophic economic and social costs of TB. It is important to consider the context. Where access and adherence are suboptimal, the causes, including food insecurity, can be assessed and addressed with a suitable package of enablers, which may include food assistance. The health sector and TB programmes can link with food security programmes and the social protection services to ensure that those with active TB, and their families, have access to existing systems for adequate food assistance and social benefits. TB programmes can assess and minimize unnecessary costs to the patient, in order to minimize the economic and social consequences for those affected.

Key principle 5. ***TB is commonly accompanied by comorbidities such as HIV, diabetes mellitus, smoking and alcohol or substance misuse, which have their own nutritional implications, and these should be fully considered during nutrition screening, assessment and counselling***

Addressing comorbid conditions is of value not only for their potential contribution to nutritional status but also for improving access and response to TB treatment. Comorbid conditions should be considered as a part of a comprehensive clinical package for people with TB and/or undernutrition, the aim of which should be to improve general health and quality of life. Nutritional counselling, advice and support may have to be adjusted to the specific nutritional requirements of other comorbid conditions.

The immunosuppression associated with HIV has increased the incidence of active TB, especially in Africa where latent TB is common and HIV prevalence is high *(19)*. HIV also increases the risk of reactivation of TB and the risk of undernutrition *(19)*. Guidance is available for nutritional care and support for people living with HIV/AIDS *(77)*. The increasing prevalence of diabetes mellitus in low- and middle-income countries is contributing to the sustained high incidence of TB disease. Diabetes mellitus triples the risk of developing TB and can worsen the clinical course of TB. TB can make management of blood glucose more difficult. Therefore, individuals with both TB and diabetes mellitus require careful clinical care. To optimize management of both diseases, TB must

be diagnosed early in people with diabetes, and diabetes must be diagnosed early in people with TB (*78*). Diet is an important component of the management of diabetes mellitus and should be part of nutrition counselling of TB patients.

6. Recommendations

Nutrition assessment and counselling

- All individuals with active TB should receive (i) an assessment of their nutritional status and (ii) appropriate counselling based on their nutritional status at diagnosis and throughout treatment (strong recommendation, no evidence).

Management of severe acute malnutrition

- School-age children and adolescents (5 to 19 years), and adults, including pregnant and lactating women, with active TB and severe acute malnutrition should be treated in accordance with the WHO recommendations for management of severe acute malnutrition *(2)* (strong recommendation, very low quality evidence).
- Children who are less than 5 years of age with active TB and severe acute malnutrition should be treated in accordance with the WHO recommendations for the management of severe acute malnutrition in children who are less than 5 years of age *(3)* (strong recommendation, very low quality evidence).

Management of moderate undernutrition

- School-age children and adolescents, and adults, including lactating women, with active TB and moderate undernutrition, who fail to regain normal BMI after two months' TB treatment, as well as those who are losing weight during TB treatment, should be evaluated for adherence and comorbid conditions. They should also receive nutrition assessment and counselling, and, if indicated, be provided with locally available nutrient-rich or fortified supplementary foods, as necessary to restore normal nutritional status *(2)* (conditional recommendation, low quality evidence).
- Children who are less than 5 years of age with active TB and moderate undernutrition should be managed as any other children with moderate undernutrition. This includes provision of locally available nutrient-rich or fortified supplementary foods, in order to restore appropriate weight-for-height *(4)* (strong recommendation, very low quality evidence).
- Pregnant women with active TB and moderate undernutrition, or with inadequate weight gain, should be provided with locally available nutrient-rich or fortified supplementary foods, as necessary to achieve an average weekly minimum weight gain of approximately 300 g in the second and third trimesters (strong recommendation, very low quality evidence).
- Patients with active MDR-TB and moderate undernutrition should be provided with locally available nutrient-rich or fortified supplementary foods, as necessary to restore normal nutritional status (strong recommendation, very low quality evidence).

Micronutrient supplementation

- A daily multiple micronutrient supplement at 1× recommended nutrient intake should be provided in situations where fortified or supplementary foods should have been provided in accordance with standard management of moderate undernutrition *(2, 4)*, but are unavailable (conditional recommendation, very low quality evidence).
- All pregnant women with active TB should receive multiple micronutrient supplements that contain iron and folic acid and other vitamins and minerals, according to the United Nations Multiple Micronutrient Preparation *(5)*, to complement their maternal micronutrient needs (conditional recommendation, very low quality evidence).
- For pregnant women with active TB in settings where calcium intake is low, calcium supplementation as part of antenatal care is recommended for the prevention of pre-eclampsia, particularly among those pregnant women at higher risk of developing hypertension, in accordance with WHO recommendations *(6, 42)* (strong recommendation, moderate quality evidence).
- All lactating women with active TB should be provided with iron and folic acid and other vitamin and minerals, according to the United Nations Multiple Micronutrient Preparation *(5)*, to complement their maternal micronutrient needs (conditional recommendation, very low quality evidence).

Contact investigation

- In settings where contact tracing is implemented, household contacts of people with active TB should have a nutrition screening and assessment as part of contact investigation. If malnutrition is identified, it should be managed according to WHO recommendations (*2–4*) (conditional recommendation, very low quality evidence).

Remarks

- Nutritional assessment is an essential prerequisite to the provision of nutritional care.
- There is no evidence to recommend that nutritional management of severe acute malnutrition should be different for those with active TB than for those without active TB.
- There is no evidence to recommend that nutritional management of severe acute malnutrition should be different in children with active TB than for those without active TB.
- Concerns about weight loss or failure to gain weight should trigger further clinical assessment (e.g. resistance to TB drugs, poor adherence, comorbid conditions) and nutrition assessment of the causes of undernutrition, in order to determine the most appropriate interventions.

- Closer nutritional monitoring and earlier initiation of nutrition support (before the first 2 months of TB treatment are completed) should be considered if the nutritional indicator is approaching the cut-off value for a diagnosis of severe acute malnutrition.
- There is no evidence to recommend that nutritional management of moderate undernutrition should be different for children (less than 5 years of age) with active TB than for those without.
- Efforts should be made, within the sound principles of nutrition assessment, counselling and support, to ensure that TB patients are receiving the recommended intake of micronutrients, preferably through food or fortified foods. If that is not possible, micronutrient supplementation at 1× the recommended nutrient intake is warranted.
- There is insufficient evidence to recommend that antenatal supplementation of calcium, iron and folic acid should be any different for pregnant women with active TB than for those without TB. However, since pregnant and lactating women with HIV have improved maternal and birth outcomes when taking a multiple micronutrient supplement, pregnant women with TB were considered comparable to those with HIV in their potential benefit from having a multiple micronutrient supplement.
- If pregnant or lactating women with moderate undernutrition are receiving a fortified supplementary food product, then the micronutrient content of this product will have to be taken into account when considering a multiple micronutrient supplement, in order to avoid over-supplementation of micronutrients.
- Screening for malnutrition, especially in children who are less than 5 years of age, is recommended at all health-care encounters and this should include contact investigation of TB.

7. Dissemination, adaptation and implementation

Dissemination

The current guideline will be disseminated through electronic media such as slide presentations, CD-ROMs and the World Wide Web, either through the WHO nutrition and SCN mailing lists or the WHO nutrition web site *(59)*, WHO Global TB Programme web site *(79)* and the WHO e-Library of Evidence for Nutrition Actions (eLENA) *(80)*. eLENA compiles and displays WHO guidelines related to nutrition, along with complementary documents such as systematic reviews and other evidence that informed the guidelines, biological and behavioural rationales, and additional resources produced by Member States and global partners. In addition, the guideline will be disseminated through a broad network of international partners, including WHO country and regional offices, ministries of health, WHO collaborating centres, universities, other United Nations agencies and nongovernmental organizations involved in TB care and control, and nutritional care and support, respectively. WHO will convene regional and subregional

workshops to introduce the final recommendations and to assist national authorities to adopt them. The evidence base in support of the revised principles and recommendations will be published and made available on CD-ROM. Feedback on the principles and recommendations will be documented on these occasions.

Adaptation and implementation

As this is a global guideline, it should be adapted to the context of the Member States. Prior to implementation of these principles and recommendations, a public health programme should have well-defined objectives that take into account available resources, existing policies, suitable delivery platforms and suppliers, communication channels and potential stakeholders. Ideally, these recommendations should be implemented as part of an integrated programme for TB care and support. To ensure that WHO global guidelines and other evidence-informed recommendations for nutrition interventions are better implemented in low- and middle-income countries, the Department of Nutrition for Health and Development works with the WHO Evidence-Informed Policy Network (EVIPNet) programme *(81)*. EVIPNet promotes partnerships at country level between policy-makers, researchers and civil society, to facilitate policy development and implementation through use of the best available evidence.

Monitoring and evaluation of guideline implementation

A plan for monitoring and evaluation, with appropriate indicators, is encouraged at all stages. The impact of this guideline can be evaluated within countries (i.e. monitoring and evaluation of the programmes implemented at national or regional scale) and across countries (i.e. adoption and adaptation of the guideline globally).

For evaluation at the global level, the WHO Department of Nutrition for Health and Development has developed a centralized platform for sharing information on nutrition actions in public health practice implemented around the world. By sharing programmatic details, specific country adaptations and lessons learnt, this platform provides examples of how guidelines are being translated into nutrition actions.

8. Plans for updating the guideline

This guideline will be reviewed in 2020. If new information is available at that time, a guideline review group will be convened to evaluate the new evidence and revise the recommendation if needed. The Department of Nutrition for Health and Development and the Global TB Programme at the WHO headquarters in Geneva, Switzerland, along with their internal partners, will be responsible for coordinating the guideline update, following formal *WHO handbook for guideline development (1)* procedures. WHO welcomes suggestions regarding additional questions for evaluation in the guideline when it is due for review.

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Annex 1 GRADE summary of findings tables

Energy requirements in patients newly diagnosed with TB

Patient or population: male and female adults
Settings: all settings, including emergencies
Intervention or exposure: patients with tuberculosis

Outcomes	Relative effect or mean difference (95 % CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
Resting energy expenditure (Kcal/kg)	**MD 7 Kcal/kg higher** (27% higher)	12 (1 trial)	⨁⊖⊖⊖ **very low**[1-4]	
Total energy expenditure (kcal/kg)	**MD 12.7 Kcal/kg higher** (7% higher)	12 (1 trial)	⨁⊖⊖⊖ **very low**[1-5]	

*GRADE Working Group grades of evidence**:**
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we have moderate confidence in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

[1] Raj 2006 (India) compared six healthy volunteers with six newly diagnosed afebrile patients with pulmonary TB. The ^{13}C-labelled bicarbonate method was used.

[2] Although the control group had significantly higher BMI at baseline than the patients with TB (21.1 vs 16.5, $P<0.01$), this is not a risk of bias but a necessary element of a study of this nature: comparing undernourished TB patients with normal weight healthy individuals.

[3] It is difficult to generalize to the whole TB population from a sample of six.

[4] This study is seriously underpowered to confidently detect differences in energy expenditure. This result represents a 27% increase in resting energy expenditure per kg body weight. The statistical significance is not given.

[5] This study is seriously underpowered to confidently detect differences in energy expenditure. This difference (a 7% increase in total energy expenditure per kg body weight) was described as 'not significant' by the authors. The *P* value was not given.

*For details of these studies see supplementary information *(63)*.

Table 2

Macronutrient supplements for improving TB treatment and nutrition outcomes

Patient or population: patients with improving TB treatment and nutrition outcomes
Settings: all settings, including emergencies
Intervention: macronutrient supplements

Outcomes	Relative effect (95 % CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
All-cause death (follow-up: 6 months)	**RR 0.4** (0.07 to 2.25)	202 (2 studies)	⨁⊖⊖⊖ **very low**[1-5]	
Cured (follow-up: 6 months)	**RR 0.91** (0.59 to 1.41)	102 (1 study)	⨁⊖⊖⊖ **very low**[1,4,6]	
Treatment completion (follow-up: 6 months)	**RR 1.08** (0.88 to 1.33)	365 (2 studies)	⨁⊖⊖⊖ **very low**[2,3,7-10]	
Change in quality of life score (at 8 weeks)	Not estimable	34 (2 studies)	⨁⨁⊖⊖ **low**[2,11-13]	
Mean weight gain	Not estimable	597 (5 studies)	⨁⊖⊖⊖ **moderate**[1,2,7,11,14-16]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval**; RR:** risk ratio**;**

*GRADE Working Group grades of evidence**:**
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we have moderate confidence in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

[1] One study in India randomized 103 patients aged >12 years with TB to receive monthly ration packs or nutritional advice alone. The macronutrient supplement was a cereal and lentil mixture calculated to provide 930 kcal and 31.5 g protein per day. The mean BMI at baseline was 17.2 in the supplement group and 18.2 in the controls.
[2] One study in India randomized 100 adults with TB to receive a daily locally appropriate food supplement or nutritional advice alone. The supplement consisted of 'sweet balls' providing 6 g protein and 600 kcal per day. The mean BMI at baseline was 17.1 in the supplement group and 17.9 in the controls.
[3] One study adequately concealed allocation and one did not. The studies were open.
[4] Studies are only available from India. As nutritional status and food availability are likely to differ widely between settings, this result is not easily generalized to other settings.
[5] These trials are severely underpowered to detect a clinically important effect if there is one. The optimal sample size is about 2000 participants. Martins 2009 did not report any deaths occurring after randomization.
[6] This trial is severely underpowered to detect a clinically important effect if there is one. The optimal information size to detect an effect is over 700 participants.
[7] One study in Timor-Leste randomized 270 adults with TB to receive a daily hot meal or nutritional advice alone. The daily meal during the intensive phase consisted of: a bowl of meat, kidney beans and vegetable stew with rice; and during the consolidation phase: a food parcel of unprepared red kidney beans, rice, and oil adequate for one meal, The population was significantly undernourished at baseline with 80% having a BM1 <18.5, and 30% <16.
[8] One study found a statistically significant benefit in favour of supplementation while the other did not.
[9] These two studies are from Timor-Leste, and India. As nutritional status is likely to differ between settings these results are not easily generalised to other settings or subpopulations.
[10] The point estimate (1.08) indicates a small benefit with supplementation, however the 95% CI of the absolute effect includes the possibility of no effect with the intervention.
[11] One study compared high-energy nutritional supplements (≈ 900 kcal) plus nutritional advice versus nutritional advice alone in 36 adults in Singapore. The mean BMI at baseline was 16.7 in the supplement group and 17.9 in the control group.
[12] Only two very small trials, one from Singapore and one from India measured quality of life scores. The results cannot be generalized with any certainty.
[13] The presented data appear highly skewed and could not be pooled.
[14] One study in the United Republic of Tanzania randomized 865 adults with TB plus HIV coinfection to receive six high-energy protein biscuits or one. The mean BMI at baseline was 18.7 in the supplement group versus 18.5 in controls. The result, of a small benefit, is not statistically significant.
[15] One study included only HIV-positive patients and although the trend was towards a benefit this did not reach statistical significance.
[16] At 6 weeks the Singapore study found the mean weight to be 1.78 kg higher with supplements. At 8 weeks the study in Timor-Leste found the mean weight to be 1.7 kg higher with supplements, and at 12 weeks one of the studies in India found the mean weight to be 2.6 kg higher with supplements. All three results are statistically significant.

* For details of studies included in the review, see *(27)*.

Table 3

Multiple micronutrient supplements for improving TB treatment and nutrition outcomes

Patient or population: patients with improving TB treatment and nutrition outcomes
Settings: all settings, including emergencies
Intervention: multiple micronutrient supplements

Outcomes	Relative effect (95 % CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
Mean change in handgrip strength (at 2 months)		771 (1 study)	⨁⨁⊖⊖ **low**[1,2]	
Quality of life	Not estimable		See comment	not reported

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval**; RR:** risk ratio**;**

*GRADE Working Group grades of evidence**:**
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we have moderate confidence in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

[1] One study in the United Republic of Tanzania enrolled 865 adults with TB. Researchers gave all participants a daily high-energy biscuit containing: 4.5 g protein, 615 kJ, 120 mg phosphorous, 120 mg calcium, 36 mg magnesium, 70 mg sodium, 150 mg potassium, and traces <1 mg of iron and zinc. The intervention group then received an additional: 1.5 mg vitamin A, 20 mg thiamine, 20 mg riboflavin, 25 mg vitamin B_6, 50 µg vitamin B_{12}, 800 µg (0.8 mg) folic acid, 40 mg niacin, 200 mg vitamin C, 60 mg vitamin E, 5 µg vitamin D, 0.2 mg selenium, 5 mg copper, 30 mg zinc.

[2] This was a single study from the United Republic of Tanzania. The findings are not easily generalized to other settings.

*For details of studies included in the review, see *(27)*.

[1] One study in India randomized 103 patients aged >12 years with tuberculosis to receive

Annex 2 Summary of the Nutrition Guidance Advisory Group's considerations for determining the strength of the recommendation

Nutrition assessment and counselling

Quality of the evidence:	Not available
Values and preferences:	The panel determined that since people with active TB are often underweight and have experienced weight loss by the time of diagnosis, and that low BMI is associated with increased mortality, nutrition screening and assessment is required to determine appropriate nutrition intervention and care.
Benefits:	Are likely
Harms:	Are unlikely
Acceptability and feasibility:	Health-care workers will need training on targeted nutrition screening and assessment, classification of nutritional status and nutrition counselling. Appropriate devices to measure height/length, weight and mid-upper arm circumference, and charts to determine weight-for-height and BMI are required. Acceptability of nutrition assessment may be a challenge in areas where health-care workers do not have access to food supplements to give if an individual is found to be undernourished. Sparse human and equipment resources may decrease the feasibility of this recommendation in some settings.
Resource implications:	The resource implications for TB programmes for assessment and counselling are considered low to moderate, and in some settings this recommendation may not be achievable.

Management of severe acute malnutrition

Management of adults with active TB and severe acute malnutrition

Quality of the evidence:	Very low
Values and preferences:	In the absence of direct evidence that treatment of severe acute malnutrition in people with TB improves TB outcomes, the panel determined that people with active TB and severe acute malnutrition should be treated in the same manner as severely malnourished people without TB, and that the established standards of care should be applied.

Benefits:	Are likely, especially because severe acute malnutrition in people with TB increases mortality risk. Although there is no direct evidence of the benefits of management of severe acute malnutrition in TB patients, there is evidence of benefit in those without TB.
Harms:	Are unlikely
Acceptability and feasibility:	In hospital and non-hospital settings where appropriate therapeutic food products for adults may be unavailable, available products used for children, such as F-100 or ready-to-use therapeutic foods, could be used.
Resource implications:	The resource implications of this recommendation for TB programmes are considered moderate to high and in some settings may not be achievable. Severe acute malnutrition is frequently managed by nutrition programmes, so linking TB services with referral and treatment to appropriate health services responsible for treating severe acute malnutrition may be recommended.

Management of children with severe acute malnutrition and active TB

Quality of the evidence:	Very low
Values and preferences:	While there is substantial evidence of effective nutritional management in children with severe acute malnutrition without TB, there is no direct evidence that treatment of severe acute malnutrition in children who are less than 5 years of age with TB improves TB outcomes. The panel determined that in the absence of direct TB-related evidence, children who are less than 5 years of age with active TB and severe acute malnutrition should be treated the same as severely undernourished children without TB, and the established standards of care should be applied.
Benefits:	Are likely, especially considering that mortality is high in children with severe acute malnutrition
Harms:	Are unlikely
Acceptability and feasibility:	The effectiveness of therapeutic foods for treating severely undernourished children is well established, and such products are generally widely available, though not in all regions.
Resource implications:	The resource implications of this recommendation for TB programmes are considered moderate to high and

in some settings may not be achievable. Management of severe acute malnutrition in children should be managed by nutrition programmes in health centres or in community-based programmes. TB programme officers should ensure nutrition referral and treatment by appropriate health-care providers.

Management of moderate undernutrition

Management of adults with moderate undernutrition and active TB

Quality of the evidence: Low

Values and preferences: The panel highly valued the need to restore weight and physical functioning and prevent progression to severe acute malnutrition.

The panel valued highly the risks to future growth and development in children and adolescents with moderate undernutrition and TB. The panel also valued highly the potential maternal health risks and infant risks of altered growth and development as a consequence for lactating women with moderate undernutrition and TB.

To allow time for anti-tuberculosis therapy to promote weight gain through a reduction in the energy demands of untreated disease and restoration of appetite, the delay in provision of fortified supplementary food is a compromise between what might be considered optimal care in some settings and the high resource costs of universal provision of supplementary food.

Benefits: Five randomized controlled trials compared the effect of macronutrient supplements with nutritional advice alone on weight gain in people with TB *(82–86)*. Macronutrient supplementation probably does improve weight gain during the intensive phase of treatment (moderate quality evidence), although one trial exclusively in HIV–TB coinfected patients found no difference at any time point.

Two studies also report that supplements may improve some measures of quality of life but the studies are too small to give much confidence in this result (low quality evidence).

The available evidence has not yet demonstrated any clear benefits of macronutrient supplementation on TB treatment outcomes.

Harms:	Are unlikely
Acceptability and feasibility:	In many settings, appropriate locally available nutrient-rich or fortified foods may not be available, and there are no established recommendations for the general management of moderate undernutrition in many age and life-stage groups. Fortified food products for treatment of malnutrition in children who are less than 5 years of age are generally available in most settings and may be available for use in adults. The 2-month delay in provision of supplementary food is different from recommendations for children who are under 5 years of age, pregnant women, people with HIV coinfection, and people with MDR-TB. Some programmes may opt to simplify their protocols by providing supplementary food or therapeutic food for all groups with moderate undernutrition at the initiation of treatment. This may be particularly relevant where food assistance is a part of an enabler package to improve access and adherence to TB diagnosis and treatment. As well as limited financial resources, sparse human resources may decrease the feasibility of this recommendation in some settings.
Resource implications:	The resource implications of this provision for TB programmes are considered high and in some settings may not be achievable. Management of moderate undernutrition can be integrated with other health services or nutrition programmes.

Management of children with moderate undernutrition and active TB

Quality of the evidence:	Very low
Values and preferences:	The panel highly valued the risks to current and future growth and development in infants and children with moderate undernutrition and TB. While there is no direct evidence that treatment of moderate undernutrition in children with TB who are less than 5 years of age improves TB outcomes, the panel considered that, in the absence of direct evidence, children who are less than 5 years of age with active TB and moderate undernutrition should be treated the same as children with moderate undernutrition without TB, and the established standards of care should be applied.

Benefits:	Likely, as for undernourished children without TB
Harms:	Are unlikely
Acceptability and feasibility:	The effectiveness of therapeutic foods for treating children with undernutrition is well established. The products are generally available but may not be available in some settings.
Resource implications:	The resource implications of this recommendation for TB programmes are considered moderate to high and in some settings may not be achievable. Management of moderate undernutrition can be integrated with other health services or nutrition programmes.

Management of pregnant women with moderate undernutrition and active TB

Quality of the evidence:	Very low
Values and preferences:	The panel highly valued the observational association between maternal undernutrition in women with TB and increased maternal and neonatal complications. The panel also recognized the difficulty of detecting moderate undernutrition in pregnant women, in whom BMI and mid-upper arm circumference can be difficult to interpret.
Benefits:	The trials of nutritional supplementation for TB patients did not include pregnant women. However, from observational evidence, weight loss during pregnancy is common *(36, 38, 87)* and even with treatment many fail to gain the optimal weight necessary to reduce the risks of low-birth-weight infants, premature birth or intrauterine growth restriction.
Harms:	Are unlikely
Acceptability and feasibility:	Nutrition support, outside of folic acid and iron supplementation, is not a routine part of antenatal care and may place additional burdens on antenatal care and TB programmes. It may be difficult to clinically track weekly or monthly weight gain during pregnancy in many settings. Effective implementation will require effective coordination between these antenatal and TB services. As well as financial resources, sparse human resources may decrease the feasibility of this recommendation in some settings.
Resource implications:	The resource implications are likely to be moderate.

Management of moderate undernutrition among patients with active multidrug-resistant tuberculosis

Quality of the evidence:	Very low
Values and preferences:	The panel highly valued the need to restore weight and physical functioning and to prevent the progression to severe acute malnutrition. The panel also recognized that people with MDR-TB are an especially vulnerable group.
Benefits:	The supplementation trials that have been conducted are not known to have included people with MDR-TB. However, five randomized controlled trials compared the effectiveness of macronutrient supplements against nutritional advice alone on weight gain in people with TB. Macronutrient supplementation probably does improve weight gain during the intensive phase of treatment (moderate quality of evidence). Two studies also report that supplements may improve some measures of quality of life but the studies were too small to have much confidence in this result (low quality of evidence). The available evidence has not yet demonstrated any clear benefits of macronutrient supplementation on TB treatment outcomes or effects in people with MDR-TB.
Harms:	Are unlikely
Acceptability and feasibility:	In many settings, locally available nutrient-rich or fortified food products for adults may be unavailable, and there are no established recommendations for the general management of moderate undernutrition in various age and life-stage groups. Specialized food products used for children may be considered for use in adults. The human resources necessary to administer this recommendation may draw valuable resources from other areas.
Resource implications:	The resource implications of this provision for TB programmes are considered moderate because the number of cases with MDR-TB is usually lower than the number of drug-susceptible cases.

Micronutrient supplementation

Micronutrient supplementation in patients with active TB and moderate undernutrition

Quality of the evidence:	Very low
Values and preferences:	The panel highly valued meeting and maintaining established standards of the daily micronutrient intake necessary to maintain good health and the known harms associated with deficiencies. The panel also highly valued that many people in low-resource and food-insecure settings have a high likelihood of inadequate micronutrient intake, particularly considering their normal plant-based diet.
Benefits:	Low serum levels of essential micronutrients have been commonly reported from cohorts of patients beginning treatment for active TB. However, randomized micronutrient supplementation trials have, as yet, failed to show any significant or consistent clinically important benefit for TB treatment outcomes with doses at or above 1× recommended nutrient intake *(88–92)*. In the early stages of treatment, micronutrient supplementation may improve plasma levels of zinc, selenium and vitamins D and E, but this has not been shown to have any clinically significant benefit on TB treatment. Plasma levels of vitamins A and D and zinc appear to normalize by the end of treatment, regardless of supplementation. A multiple micronutrient supplement includes vitamin B_6, which protects against isoniazid-induced peripheral neuropathy, and has the added benefit of provision of other micronutrients in addition to vitamin B_6.
Harms:	Supplementation is very unlikely to be harmful but micronutrient supplements could increase the financial burden on TB patients unless they are provided free of charge.
Acceptability and feasibility:	Given the already high pill burden experienced by people undergoing treatment of TB, and the lack of convincing evidence for benefit on TB treatment outcome from micronutrient supplementation, patients may choose not to purchase or consume micronutrient supplements.
Resource implications:	The resource implications for programmes to provide this supplementation are considered low.

Micronutrient supplementation in pregnant and lactating women with active TB

Quality of the evidence:	Very low
Values and preferences:	The panel determined that the increased physiological requirements during pregnancy and lactation, and the likelihood of undernutrition and inadequate dietary intake, make it extremely unlikely that TB patients would require fewer micronutrients than the HIV-positive population. Since there is no evidence of micronutrient supplementation in pregnant and lactating women with TB, the evidence of benefits with multiple micronutrient supplementation in pregnant women with HIV was considered adequate to justify supplementation during TB treatment. The panel also considered that, in the absence of direct evidence that pregnant women with either active TB or signs of undernutrition should receive more or less calcium, folic acid or iron, the established standards of care should be applied.
Benefits:	Trials assessing supplementation in pregnant women with TB have not been conducted. However, trials in pregnant women with HIV infection have shown that multiple micronutrient supplementation at ≥1× the recommended nutrient intake improves both infant and maternal outcomes. There is some evidence that pregnant women with TB are at increased risk of pre-eclampsia and should receive a calcium supplement in accordance with the WHO recommendation for pregnancy *(6, 42)*. For the prevention of pre-eclampsia, the current WHO recommendation is to provide calcium supplementation during pregnancy in areas where dietary calcium intake is low, and for pregnant women at higher risk of developing pre-eclampsia *(42)*.
Harms:	Harms to the mother or child are unlikely.
Acceptability and feasibility:	Given the already high pill burden experienced by people undergoing treatment of TB, combined with the additional calcium and United Nations Multiple Micronutrient Preparation supplementation *(5)*, women may choose not to purchase or consume micronutrient supplements. WHO recommends that all pregnant women living in areas with high rates of anaemia be provided with iron

and folic acid supplements during pregnancy, regardless of maternal iron status. These are routinely given to pregnant women through antenatal programmes. Because the United Nations Multiple Micronutrient Preparation is a prenatal supplement that includes iron and folic acid, additional supplementation of these two nutrients is not needed for women with TB receiving the United Nations Multiple Micronutrient Preparation supplement. In areas of high TB and/or HIV prevalence, programmes may elect to give all pregnant women the United Nations Multiple Micronutrient Preparation supplement rather than the iron and folic acid singly, in order to simplify administration and to not make a special case for women with TB or HIV. Calcium supplementation during pregnancy is recommended to reduce the risk of pre-eclampsia, and continued supplementation after delivery is not needed.

Folic acid and iron are already provided in most settings as a routine part of antenatal care; calcium supplementation is a new WHO recommendation and most likely will be in various stages of implementation in different countries. Regardless, acceptability and feasibility are moderate to high for additional multiple micronutrient supplements, especially if women are educated as to their benefits on both maternal and infant outcomes.

Resource implications: The resource implications of this recommendation for TB programmes are considered low, and this would ideally be implemented through antenatal care. Coordination with antenatal services is required.

Contact investigation

Nutrition assessment, care and support for household contacts of people with active TB

Quality of the evidence: Very low

Values and preferences: The panel highly values the observational evidence that young children and people who are undernourished are at the highest risk of progression to active TB disease. This is particularly important for young children who are less than 5 years of age, who have a higher risk of disease progression, independent of malnutrition. Nutrition screening and assessment can identify high-risk contacts who require rigorous evaluation for active and latent TB.

Benefits:	There is evidence that people who are malnourished are at higher risk of progression from latent to active TB, compared with those who are not malnourished *(49, 53–55)*. No trials in the area of effective chemotherapy have assessed the impact of nutrition support for TB contacts and the subsequent risk of active disease.
Harms:	Are unlikely
Acceptability and feasibility:	In many settings, contact tracing is not implemented; however, in settings where contact investigation is already conducted, screening for undernutrition using simple methods (height, weight, BMI, mid-upper arm circumference) in this high-risk group is likely to have high acceptability and feasibility.
Resource implications:	The resource implications of this provision for TB screening programmes are considered low.

Annex 3 Questions in population, intervention, control, outcomes (PICO) format

1. What is the optimal composition of the diet for patients receiving treatment for active TB?

a. Do patients who are newly diagnosed with TB have increased energy requirements?

Population	• Infants • Children • Adolescents • Adults • Pregnant or lactating women
Intervention	Individuals with TB
Control	Healthy individuals
Outcomes	*Critical* • Resting energy expenditure • Total energy expenditure
Settings	All settings, including emergencies

2. Should macronutrient supplements be recommended to improve TB treatment and health outcomes for well-nourished or undernourished patients being treated for active TB?

a. Does macronutrient supplementation, as food or high-energy supplements, improve TB treatment outcomes?

b. Does macronutrient supplementation, as food or high-energy supplements, improve nutritional recovery and quality of life?

Population	• Infants • Children • Adolescents • Adults • Pregnant or lactating women

	Subpopulations • By nutritional status: underweight/not underweight • By HIV infection: HIV negative/HIV positive • By receiving antiretroviral therapy (ART) (if HIV): on ART/no ART • By resistance: MDR-TB/XDR-TB (extensively drug-resistant TB) • By vulnerability: homeless/alcoholic/ intravenous drug use • By income classification: low-, middle- or high-income country • By food security: food secure or food insecure • By internationally displaced persons/ refugee status
Intervention	• On-site daily rations • Off-site daily rations • Weekly ration • Monthly ration • Nutrient-dense supplements
Control	• Standard care • With/without dietary advice • Head-to-head trials
Outcomes	*Critical* *TB outcomes* • All-cause death (end of treatment) • Treatment success (end of treatment) • Cure (6–8 months) (18–24 months for MDR-TB) • Completed treatment *Nutritional recovery* • Weight gain (absolute/%), age-specific measurement *Quality of life* • Many available measures/scales
Settings	All settings, including emergencies

3. Should micronutrient supplements be recommended as a component of normal care in well-nourished or undernourished patients being treated for active TB for improving TB treatment and nutrition outcomes?

a. Does routine daily multi-micronutrient supplementation improve TB treatment outcomes?

b. Does routine daily multi-micronutrient supplementation improve nutritional recovery and quality of life?

Population	• Infants • Children • Adolescents • Adults • Pregnant or lactating women *Subpopulations* • By nutritional status: underweight/not underweight • By HIV infection: HIV negative/HIV positive • By receiving ART (if HIV): on ART/no ART • By resistance: MDR-TB/XDR-TB • By vulnerability: homeless/alcoholic/ intravenous drug use • By income classification: low-, middle- or high-income country • By food security: food secure or food insecure • By internationally displaced persons/ refugee status
Intervention	• Single micronutrient supplement: o Vitamin A o Vitamin C o Vitamin D o Vitamin E o Zinc o Iron o Selenium • Multi-micronutrient supplements
Control	• Standard care • With/without dietary advice • With/without placebo

Outcomes	*Critical* *Nutritional recovery* • Mean change in handgrip strength *Quality of life* • Many available measures/scales
Settings	All settings, including emergencies

4. Are there population-level nutritional interventions that could reduce the progression from latent to active TB in household contacts of patients with active TB?

Population	• Household contacts of patients with active TB o Infants o Children o Adolescents o Adults o Pregnant or lactating women *Subpopulations* • By nutritional status: undernourished/not undernourished
Intervention	• Single micronutrient supplement: o Vitamin A o Vitamin C o Vitamin D o Vitamin E o Zinc o Iron o Selenium • Multi-micronutrient supplements • Food fortification • Food distribution
Control	• Standard care • With/without dietary advice • With/without placebo
Outcomes	*Critical* *Reduced incidence of active TB*
Settings	All settings, including emergencies

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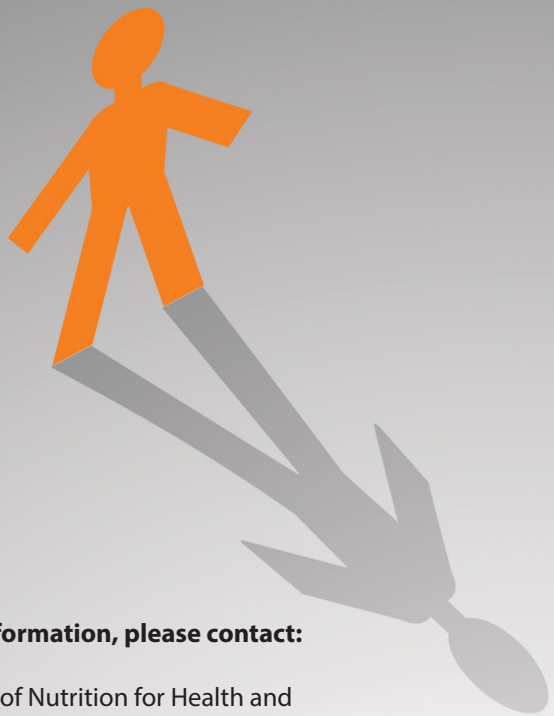

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