क्षेत्रीय आयुर्विज्ञान संस्थान, इंफाल: मणिपुर
REGIONAL INSTITUTE OF MEDICAL SCIENCES, IMPHAL, MANIPUR
(स्वास्थ्य और परिवार कल्याण मंत्रालय,भारत सरकार के अंतर्गत एक स्वायत्त संस्थान)
(An Autonomous Institute under the Ministry of Health & Family Welfare, Govt. of India

Phone : 0385- 2414720
0385-2414750
e-mail : rims@rims.edu.in
website : www.rims.edu.in

CIRCULAR

Imphal, the 25th June, 2025

No. 121/RIMS-MRU/2025: With reference to the DHR letter no. R.11016/22/2024-HR dated 18.06.2025; it is hereby informed that the **2nd Research Masterclasses 2025**, of the Department of Health Research, Ministry of Health and Family Welfare, Government of India will be conducted virtually, **on 27th June 2025 (Friday).**

2. Being a general holiday, esteemed faculties have the option to attend from their personal online platforms through the link provided. Early login is suggested as the optimum entry at times gets saturated early on.

3. In the larger interest of research endeavor of our fraternity and as a hub center of our institute, the Multi-Disciplinary Research Unit, RIMS, shall remain functional during the transmission period. All the esteemed members of EC, LRAC of MRU, Principal Investigators undertaking MRU funding projects (including under process projects) and interested faculties are invited to take part in the session at MRU itself. (with maintenance of COVID-19 appropriate measures)

Date: 27.06.2025 (Friday);
Time: 3:00 PM onwards
Join Zoom Meeting: (The link for the research masterclass will be shared shortly)
Venue: EC Conference room, MRU, RIMS

4. In compliance with the instruction from DHR, **maximum participation** from the institute is highly encouraged and appreciated. Departments/Colleges/individual faculty participants are requested to share their attendance status with MRU after the session for onward submission to DHR.

5. The research papers to be discussed during the research masterclass are available in the RIMS website: https://www.rims.edu.in/secure/ and also being shared with Departments through their respective e-mail IDs.

25.6.25

Prof. T. Jeetenkumar Singh,
Nodal Officer,
Multi-Disciplinary Research Unit,
RIMS, Imphal

Copy to

1. The P.S. to Director, RIMS for kind information of Director
2. The P.A. to Medical Superintendent, RIMSH for kind information
3. The Dean (Academic), RIMS
4. The Principal, Dental College, RIMS
5. The Principal, College of Nursing, RIMS
6. The HOD, RIMS Imphal.....
7. The Chairman, LRAC, MRU, RIMS
8. The Members, LRAC, MRU, RIMS.....
9. The Members, EC, MRU, RIMS, Imphal.....
10. The Principal Investigator, RIMS .....
11. The IT section, RIMS, Imphal – for uploading the notice in the website and technical support on 27.6.25
12. Guard file.

No. R.11016/22/2024-HR
Government of India
Ministry of Health & Family Welfare
Deptt of Health Research

IRCS Building, 2nd Floor,
Red Cross Road
New Delhi – 110 001
18.06.2025

To
The Dean/ Principal/ Director of Medical Colleges/ Institutes

Subject: Request to attend Research Masterclasses, 2025 for MRU network– reg.

Sir/Madam

DHR-ICMR has initiated a dedicated platform to conduct Research Grand Rounds to strengthen the National research ecosystem through sustained collaboration and knowledge exchange. The objectives of the Research Grand Rounds are as follows:

I. To deliberate on research methodologies, analytical tools, and emerging scientific approaches
II. To strengthen the methodological understanding amongst researchers needed to implement different kinds of research.
III. To foster collaboration and connectivity across research institutions

2. These Research Grand Rounds will be organized as monthly webinars entitled 'Research Masterclass' on last Friday of each month from 3:00-4:30 PM. The speakers for these Research Masterclasses will be eminent research scientists in the country who will be discussing their original research work in details from methodological point of view.

3 The next Research Masterclass is scheduled for 27.06.2025 (Friday) at 3:00 PM. The invited speaker is Prof. Anurag Bhargava, Department of Medicine, Kasturba Medical College Mangalore, Manipal Academy of Higher Education, Manipal, Karnataka. The research paper to be discussed during the research masterclass is enclosed. The link for the research masterclass will be shared shortly.

4. Accordingly, it is requested to kindly disseminate the information in your institution and ensure maximum participation in Research Masterclass. Also, it is requested from your institute to share at least two questions related to research paper attached on the following email: **dhr-mru@gov.in** latest by 24.06.2025. These questions will be discussed with the speaker during masterclass.

Yours faithfully

(Dharkat R. Luikang)
Deputy Secretary

Copy to: The Nodal Officer of Multi-Disciplinary Research Units (MRUs)

Nutritional supplementation to prevent tuberculosis incidence in household contacts of patients with pulmonary tuberculosis in India (RATIONS): a field-based, open-label, cluster-randomised, controlled trial

Anurag Bhargava, Madhavi Bhargava, Ajay Meher, Andrea Benedetti, Banurekha Velayutham, G Sai Teja, Basilea Watson, Ganesh Barik, Rajeev Ranjan Pathak, Ranjit Prasad, Rakesh Dayal, Adarsh Kibballi Madhukeshwar, Vineet Chadha, Madhukar Pai, Rajendra Joshi, Dick Menzies, Soumya Swaminathan

Summary

Background In India, tuberculosis and undernutrition are syndemics with a high burden of tuberculosis coexisting with a high burden of undernutrition in patients and in the population. The aim of this study was to determine the effect of nutritional supplementation on tuberculosis incidence in household contacts of adults with microbiologically confirmed pulmonary tuberculosis.

Methods In this field-based, open-label, cluster-randomised controlled trial, we enrolled household contacts of 2800 patients with microbiologically confirmed pulmonary tuberculosis across 28 tuberculosis units of the National Tuberculosis Elimination Programme in four districts of Jharkhand, India. The tuberculosis units were randomly allocated 1:1 by block randomisation to the control group or the intervention group, by a statistician using computer-generated random numbers. Although microbiologically confirmed pulmonary tuberculosis patients in both groups received food rations (1200 kcal, 52 grams of protein per day with micronutrients) for 6 months, only household contacts in the intervention group received monthly food rations and micronutrients (750 kcal, 23 grams of protein per day with micronutrients). After screening all household contacts for co-prevalent tuberculosis at baseline, all participants were followed up actively until July 31, 2022, for the primary outcome of incident tuberculosis (all forms). The ascertainment of the outcome was by independent medical staff in health services. We used Cox proportional hazards model and Poisson regression via the generalised estimating equation approach to estimate unadjusted hazard ratios, adjusted hazard ratios (aHRs), and incidence rate ratios (IRRs). This study is registered with CTRI-India, CTRI/2019/08/020490.

Findings Between Aug 16, 2019, and Jan 31, 2021, there were 10 345 household contacts, of whom 5328 (94·8%) of 5621 household contacts in the intervention group and 4283 (90·7%) of 4724 household contacts in the control group completed the primary outcome assessment. Almost two-thirds of the population belonged to Indigenous communities (eg, Santhals, Ho, Munda, Oraon, and Bhumij) and 34% (3543 of 10 345) had undernutrition. We detected 31 (0·3%) of 10 345 household contact patients with co-prevalent tuberculosis disease in both groups at baseline and 218 (2·1%) people were diagnosed with incident tuberculosis (all forms) over 21 869 person-years of follow-up, with 122 of 218 incident cases in the control group (2·6% [122 of 4712 contacts at risk], 95% CI 2·2–3·1; incidence rate 1·27 per 100 person-years) and 96 incident cases in the intervention group (1·7% [96 of 5602], 1·4–2·1; 0·78 per 100 person-years), of whom 152 (69·7%) of 218 were patients with microbiologically confirmed pulmonary tuberculosis. Tuberculosis incidence (all forms) in the intervention group had an adjusted IRR of 0·61 (95% CI 0·43–0·85; aHR 0·59 [0·42–0·83]), with an even greater decline in incidence of microbiologically confirmed pulmonary tuberculosis (0·52 [0·35–0·79]; 0·51 [0·34–0·78]). This translates into a relative reduction of tuberculosis incidence of 39% (all forms) to 48% (microbiologically confirmed pulmonary tuberculosis) in the intervention group. An estimated 30 households (111 household contacts) would need to be provided nutritional supplementation to prevent one incident tuberculosis.

Interpretation To our knowledge, this is the first randomised trial looking at the effect of nutritional support on tuberculosis incidence in household contacts, whereby the nutritional intervention was associated with substantial (39–48%) reduction in tuberculosis incidence in the household during 2 years of follow-up. This biosocial intervention can accelerate reduction in tuberculosis incidence in countries or communities with a tuberculosis and undernutrition syndemic.

Funding Indian Council of Medical Research—India TB Research Consortium.

Published Online August 8, 2023 https://doi.org/10.1016/S0140-6736(23)01231-X

See Online/Comment https://doi.org/10.1016/S0140-6736(23)01321-1

Department of Medicine (Prof A Bhargava MD, Prof D Menzies MD), Department of Community Medicine (M Bhargava MD), and Department of Radiology (Adarsh KM MD), Yenepoya Medical College, Mangalore, India; Center for Nutrition Studies, Yenepoya (Deemed to be University), Mangalore, India (Prof A Bhargava, M Bhargava, A Benedetti PhD, G Sai Teja MPhil); Department of Medicine (Prof D Menzies, A Benedetti, Prof A Bhargava), Department of Epidemiology, Biostatistics and Occupational Health (A Benedetti, Prof M Pai MD), McGill International TB Centre (Prof M Pai, Prof D Menzies), McGill University, Montreal, QC, Canada; Indian Council of Medical Research—National Institute for Research in Tuberculosis, Chennai, India (A Meher MPH, B Velayutham MPH, B Watson MSc, G Barik PGDCA); WHO Technical Support Network, Ranchi, India (R R Pathak MPH); State TB Cell, National Tuberculosis Elimination Programme, Ranchi, India (R Prasad MD); National Health Mission, Department of Health, Medical Education and Family Welfare, Ranchi, India (R Dayal MD); National Tuberculosis Institute, Bangalore, India (V Chadha MD); National Tuberculosis Elimination Programme, Ministry of Health and Family Welfare, New Delhi, India (R Joshi DNB);

M S Swaminathan Research Foundation, Chennai, India (S Swaminathan MD)

Correspondence to: Prof Anurag Bhargava, Department of Medicine, Yenepoya Medical College, Center for Nutrition Studies, Yenepoya (Deemed to be University), Mangalore 575018, India
anuragb17@gmail.com

Research in context

Evidence before this study

We searched PubMed and the Cochrane Central Register of Controlled Trials database on Feb 15, 2023, using the terms "undernutrition", "malnutrition", "macronutrient OR micronutrient OR supplementation", and "tuberculosis" and "tuberculosis incidence". We searched for observational studies and clinical trials published between Jan 1, 1950, and Aug 1, 2019, in English only, and identified 14 relevant publications. We also reviewed WHO's global tuberculosis reports since 1997 and used snowballing and hand-searching to retrieve relevant studies. Evidence from a systematic review of six cohort studies suggested undernutrition (as reflected in a BMI) as a consistent risk factor with a strong, inverse, and exponential relationship with tuberculosis incidence and the potential for substantial reduction of tuberculosis incidence per unit change in BMI. Cohort studies from India have shown that food insecurity and undernutrition are prevalent in household contacts and are strong risk factors for progression of latent tuberculosis infection to active tuberculosis disease. Estimation of population-attributable-fractions for risk factors of tuberculosis suggested that globally, undernutrition was the leading risk factor for tuberculosis incidence. We found a negative randomised controlled trial of micronutrients for tuberculosis prevention (vitamin D supplementation in vitamin D deficient children), but no studies on the effect of macronutrients (or combined macronutrient and micronutrient supplementation) on tuberculosis incidence in any population group. The existing evidence supporting efficacy of nutritional interventions for reducing tuberculosis incidence is indirect. At the Papworth village settlement in the UK between 1918 and 1943, among 315 contacts in 135 families with tuberculosis, improved living conditions (eg, adequate nutrition) resulted in a six-fold reduction in tuberculosis incidence. This reduction in tuberculosis incidence occurred in an era without access to tuberculosis drugs or use of the BCG vaccine (ie, pre-chemotherapy and pre-BCG era). Modelling studies based on data from India and other countries with low HIV prevalence suggested that nutritional interventions under different scenarios could reduce tuberculosis incidence by 33–71% over a long-term period.

Added value of this study

This cluster-randomised controlled trial of nutritional supplementation with macronutrients (food rations) and micronutrients is, to our knowledge, the first trial of its kind that was implemented in real-world settings within the National Tuberculosis Elimination Programme. The prevalence of undernutrition was high in the child and adult household contacts of the patients, reaffirming the need for such an intervention. In the setting of high prevalence of undernutrition in the community, this randomised controlled trial shows the efficacy of nutritional supplementation in reducing the incidence rate of tuberculosis by 39% (for all forms of tuberculosis), and a 48% reduction in incidence rate of microbiologically confirmed pulmonary tuberculosis in household contacts in the intervention group compared with the control group.

Implications of all the available evidence

We showed the efficacy of macronutrient and micronutrient supplementation for 6 months in reducing confirmed tuberculosis incidence substantially in a group at high risk for tuberculosis because of close contact with an infectious person and high prevalence of undernutrition. This evidence has implications for policy and practice related to tuberculosis prevention in this current era in which food insecurity is on the increase and the decline of tuberculosis is not in line with WHO's End Tuberculosis targets. Undernutrition is both a biological risk factor and a social determinant and addressing it can be a crucial host-directed tuberculosis-sensitive intervention that can accelerate decline in tuberculosis incidence as well as advance the achievement of Sustainable Development Goals 1 and 2. National programmes should implement a policy of nutritional assessment of household contacts to ascertain the prevalence of undernutrition. Nutritional supplementation in communities with a double burden of tuberculosis and undernutrition should be considered as a mass prophylaxis, and also to increase effectiveness of biomedical interventions to reduce tuberculosis incidence. These results were obtained in a setting of low HIV prevalence, thus they might not be generalisable to a tuberculosis epidemic in a high HIV prevalence region.

Introduction

Tuberculosis is a leading cause of morbidity and mortality, especially in low-income and middle-income countries. The progress achieved in the decline of tuberculosis incidence has faced a setback due to the COVID-19 pandemic. In India, tuberculosis incidence was estimated to be 3 million new cases in 2021 with 494000 deaths, representing 27% of global tuberculosis incidence and 35% of tuberculosis deaths.[1]

The WHO End Tuberculosis strategy[2] recommends combining biomedical interventions with policies on social protection and action on social determinants, such as poverty. Underdnutrition is a biological factor closely associated with poverty and is a risk factor for tuberculosis incidence[3] and tuberculosis mortality.[4] In India, tuberculosis and undernutrition are syndemics[5] with a high burden of tuberculosis coexisting with a high burden of undernutrition in patients[6] and in the population.[7] The National Tuberculosis Elimination Programme has started to address undernutrition in patients via direct benefit transfer since April, 2018.[8]

Undernutrition is the leading risk factor for tuberculosis, with an estimated annual incidence of

www.thelancet.com Published online August 8, 2023 https://doi.org/10.1016/S0140-6736(23)01231-X

19% (2·2 million) globally,[1] and 34% (1·02 million) in India being attributable to undernutrition.[9] A number of cohort studies have consistently shown an inverse exponential relationship between BMI and tuberculosis incidence.[1] Studies have also shown micronutrient deficiencies as risk factors for tuberculosis incidence.[10,11] However, vitamin D supplementation did not reduce tuberculosis incidence in a large randomised controlled trial.[12] To our knowledge, there has been no randomised controlled trial to assess the effect of addressing macronutrient and micronutrient undernutrition on tuberculosis incidence in any population group.[13,14] Reducing Activation of Tuberculosis by Improvement of Nutritional Status (RATIONS) is a cluster-randomised controlled trial and its aim was to assess the effect of nutrition supplementation (macro and micronutrients) on tuberculosis incidence in household contacts of patients with microbiologically confirmed pulmonary tuberculosis in Jharkhand, located in eastern India.[15] We chose cluster randomisation to allow uniform intervention in a cluster as differential nutritional supplementation in households in the same cluster would have been operationally challenging.

Methods

Study design

This is a parallel-arm, field-based, open-label, cluster-randomised, superiority trial of nutritional supplementation in household contacts of patients with microbiologically confirmed pulmonary tuberculosis (the index tuberculosis patient), implemented within the National Tuberculosis Elimination Programme in four districts of the eastern Indian state of Jharkhand. The cluster was a tuberculosis unit, which is a sub-district programme management unit of the National Tuberculosis Elimination Programme that serves a population corresponding largely to an administrative block of the district.

The setting has been described elsewhere[15] and in the appendix (p 2). Jharkhand has a population of 33 million, has low levels of urbanisation (75% of the population live in rural areas), and a high proportion of indigenous communities: 28% compared with 8% national average. Jharkhand has the second highest levels of multidimensional poverty in the country.[16] Jharkhand as a trial site was selected due to a high burden of tuberculosis (52 179 cases notified in 2021, and an annual case notification of 130 of 100 000).[17] In a representative demographic and health survey, Jharkhand had a high population burden of undernutrition with 26·2% in adult women and 39·4% in children as underweight, compared with the national average of 18·7% of adult women and 32·1% of children.[7]

The four districts were chosen based on the annual case finding and logistic feasibility of organising the centralised procurement, and distribution of the intervention. The districts varied in size with West Singhbhum being the largest (7600 sq.km) and Seraikela being the smallest (2600 sq.km). Overall, each block had one tuberculosis unit. The distance of households to the tuberculosis unit could have varied according to the block involved, but as the blocks or tuberculosis unit were randomly assigned to the two groups as described in the methods of this trial, the bias was minimised. The unit of randomisation was the tuberculosis unit. A tuberculosis unit with annual case finding of at least 100 patients with microbiologically confirmed pulmonary tuberculosis was considered eligible (appendix p 4).

Written informed consent was obtained for all index tuberculosis patients and household contacts. Ethics clearance was obtained from the Institutional Ethics Committee of Indian Council of Medical Research—National Institute for Research (ICMR-NIRT number 2018020; grant number 5/8/5/57/TB consortium/Call India Project/2017/ECD-1), with periodic reviews. The ethics committee of Ekjut, a local voluntary organisation involved in community-based research in health,[18] was responsible for the local oversight of serious adverse events, such as deaths in index tuberculosis patients and household contacts that were further communicated to the Institutional Ethics Committee of Indian Council of Medical Research—National Institute for Research. The intervention in this study was food and micronutrients. A data safety and management board was constituted for this trial, and the serious adverse events were not related to the intervention as assessed by the local and NIRT ethics committee. Further, the ethics committee did not advise autopsies.

Participants

Within each cluster, any adult (aged ≥18 years) diagnosed with microbiologically confirmed pulmonary tuberculosis in the National Tuberculosis Elimination Programme, and having at least one eligible household contact, was enrolled in the trial (the index tuberculosis patient; appendix p 8). Their household contacts were assessed for the primary outcome. The eligibility criteria for the household contacts included living in the same house, eating from the same kitchen for one or more nights, or for frequent or extended periods during the day in the preceding 3 months, and not currently on treatment for tuberculosis. Sex data were collected through self-reporting whereby there were three options: male, female, and other.

See Online for appendix

Randomisation and masking

A total of 28 tuberculosis units, each with sizes varying between 80 and 120 households with a patient diagnosed with microbiologically confirmed pulmonary tuberculosis, were randomly allocated (1:1) by block randomisation. Random assignment of the tuberculosis unit or clusters to the intervention or control group was done by a statistician unfamiliar with the trial region based at the National

Institute for Research in Tuberculosis, Chennai, using computer-generated random numbers using Microsoft Excel (version 16.0, 2016). The participants in each tuberculosis unit or cluster were enrolled by the field staff after they were diagnosed with microbiologically confirmed tuberculosis in the unit. The allocation of tuberculosis units to the groups was kept concealed from the principal and co-principal investigators until training of the field staff and their posting was completed.

Procedures

All participants were counselled at enrolment and each follow-up visit regarding a balanced diet using locally available foods, and in the case of the index tuberculosis patients, regarding treatment adherence and cough hygiene in line with national guidelines.[19] Index tuberculosis patients in both groups received a monthly food basket that provided 1200 kcal and 52 grams of protein per day, and pills supplying one recommended dietary allowance of micronutrients daily (appendix p 8). The approximate cost was US$13 per month inclusive of delivery charges (2019 prices; appendix p 7). Index tuberculosis patients in both groups received food baskets for ethical reasons as previous studies in India have shown high prevalence and severity of undernutrition.[6,20]The household contacts in the intervention group received a food basket providing 750 kcal and 23 grams of protein per day per person, and one recommended dietary allowance of micronutrients pills; those younger than 10 years received 50% of this, and a syrup preparation for the micronutrients (appendix p 8). The cost per adult contact was $4·75 per month (2019 prices). The basket was provided to the participants for the duration of treatment—6 months for drug susceptible tuberculosis and 12 months for multidrug-resistant tuberculosis. The intervention was extended if the patient had a BMI of lower than 18·5 kg/m² or any household contact in the intervention group fulfilled the following: an adult household contact with a BMI of lower than 16 kg/m²; children (aged <10 years) with a weight-for-age Z-score of lower than −2SD and adolescents (aged 10–18 years) with BMI-for-age Z-scores of lower than −2SD. This extension was for a period of 12 months or until improvements above these cutoffs, whichever was shorter.

In both groups, public services to which the households were entitled were continued. These services included subsidised food rations (which consisted of only rice in Jharkhand) in the public distribution system, supplementary feeding programmes (mid-day meals in schools and integrated child development services scheme for the pre-schoolers) with no education on nutrition, and the direct benefit transfer under the NIKSHAY Poshan Yojana scheme, in which patients with tuberculosis get ₹500 per month (US$6 per month).[8] Tuberculosis prevention treatment for eligible household contacts was initiated by the staff at the National Tuberculosis Elimination Programme after evaluation as per their existing guidelines, and included mainly children aged 5 years and younger. The National Tuberculosis Elimination Programme guidelines extending eligibility to household contacts after 5 years or more were issued in July, 2021, after enrolment of household contacts was completed.

We selected an International Standardization Organization 22000: 2018 (a food safety management system) certified vendor in Ranchi, Shri Ambaji Food Products Pvt who was a supplier to major retail chains and followed quality norms as per the Food Safety and Standards Authority of India in procurement, storage, packaging, and labelling. We also created sub-depots in all districts where the centrally procured rations were stored for further distribution. Households, especially rural, opted largely for home delivery of the rations, whereas some in urban areas picked them up from the sub-depots at their convenience. We had several processes in place to ensure regular delivery of the rations, such as maintenance of stock registers at the sub-depots, sharing of geolocations with project consultants during the distribution visit, and signing of receipts by the recipient. The ascertainment of delivery of the food rations was further strengthened through random telephone calls and supervisory visits. At each visit, consumption of food was emphasised through counselling, and empty milk powder packets were checked. Weight gain was considered a surrogate indicator of consumption.

The trial overlapped with the COVID-19 pandemic (appendix p 6) and due to the lockdown and related disruptions, enrolment that started on Aug 16, 2019 was extended until Jan 31, 2021, instead of Aug 16, 2020. The protocol was amended from a common follow-up period of 2 years to a common closing period of May 1–July 31, 2022 (appendix p 2); thus, those who had completed 24 months of follow-up continued to be followed quarterly whereas those enrolled in January, 2021, completed at least 18 months of follow-up. This change meant that the planned follow-up of 2 years was possible in only 80% of household contacts recruited until August, 2020. The average cluster size and the intraclass correlation coefficient at the level of cluster and households that we observed in our trial was lower than was assumed, and this resulted in a lower design effect. The study therefore had adequate power despite the truncation of follow-up in a proportion of households (appendix p 10).

Follow-up was defined as time from date of enrolment in the trial until documented tuberculosis disease or censoring (death, loss to follow-up, or end of the study).

Outcomes

The development of incident tuberculosis (all forms, microbiologically confirmed or clinically diagnosed) in the household contacts during the planned follow-up period of 2 years was the primary outcome. We defined a

www.thelancet.com Published online August 8, 2023 https://doi.org/10.1016/S0140-6736(23)01231-X

household contact to have incident tuberculosis if the person was diagnosed with active tuberculosis (microbiologically confirmed or clinically diagnosed) more than 2 months following the initial negative screening and evaluation at enrolment. We defined a household contact to have co-prevalent tuberculosis (all forms) if the person was on tuberculosis treatment, or was symptomatic at baseline or developed symptoms and was diagnosed for tuberculosis on further evaluation within 2 months of enrolment. The ascertainment of the primary outcomes was done by independent medical staff in the government health institutions (primary health centres, community health centres, district hospitals, and medical colleges). The diagnosis of pulmonary or extrapulmonary tuberculosis was made as per National Tuberculosis Elimination Programme guidelines.[19,21] In some cases, especially for smear negative pulmonary tuberculosis, children, and extrapulmonary tuberculosis, facilities with availability of specialists or appropriate diagnostic services such as district hospitals or medical colleges were used.

Undernutrition can increase the frequency and severity of other infections,[22] and these secondary outcomes aimed at examining the effect of nutritional support on non-tuberculosis acute infections during the intervention period. Information on any non-tuberculosis morbidities, such as malaria (based on laboratory diagnosis), diarrhoea, lower respiratory infections (self-reported), and fever related hospitalisations (based on available records), were recorded on follow-up. Death with acute fever (<15 days duration) during the 6-month period of intervention was recorded. In the case of deaths, the field staff recorded the cause of death if medically certified. When it was not medically certified, they recorded the information on the symptoms and circumstances preceding the death and this was reviewed by the project consultant to arrive at a possible cause. The medical certification of cause of death was only available for those who had died in a medical facility, which was the case in a minority of deaths and, in these cases, the field staff had access to the certificate.

Socio-demographic information including ownership of household assets (appendix p 7), tobacco and alcohol use, BCG scar, tuberculosis prevention treatment, and anthropometry were recorded at baseline. At each follow-up visit, monthly for the first year and every 3 months thereafter, the household contacts underwent anthropometry and symptom screening for active tuberculosis. On identifying a household contact with presumptive tuberculosis, the field staff advised household contacts for an evaluation at the nearest government health facility, and reinforced this advice on follow-up in case the contact had not accessed the health facility. This evaluation consisted of a clinical evaluation, a sputum examination by smear microscopy, or a cartridge based nucleic acid amplification test (including GeneXpert [Cepheid, Sunnyvale, CA, USA] and TrueNat [Molbio diagnostics/Bigtec labs, Goa/Bengaluru, India]) depending on the availability. X-rays were done in household contacts, especially in children. Wherever an x-ray was not available or easily accessible, it was done in private centres with costs borne by the trial. In contacts diagnosed with incident tuberculosis, the anti-tuberculosis treatment was initiated in the National Tuberculosis Elimination Programme, while in contacts with persistence or recurrence of symptoms suggesting active tuberculosis despite an initial negative evaluation, a repeat evaluation was advised and facilitated. The contact evaluation was facilitated by covering the transport costs of the participants and ensured by the review processes in the trial.

All attempts, including telephone contact, were made to ensure follow-up, which included asking the other family

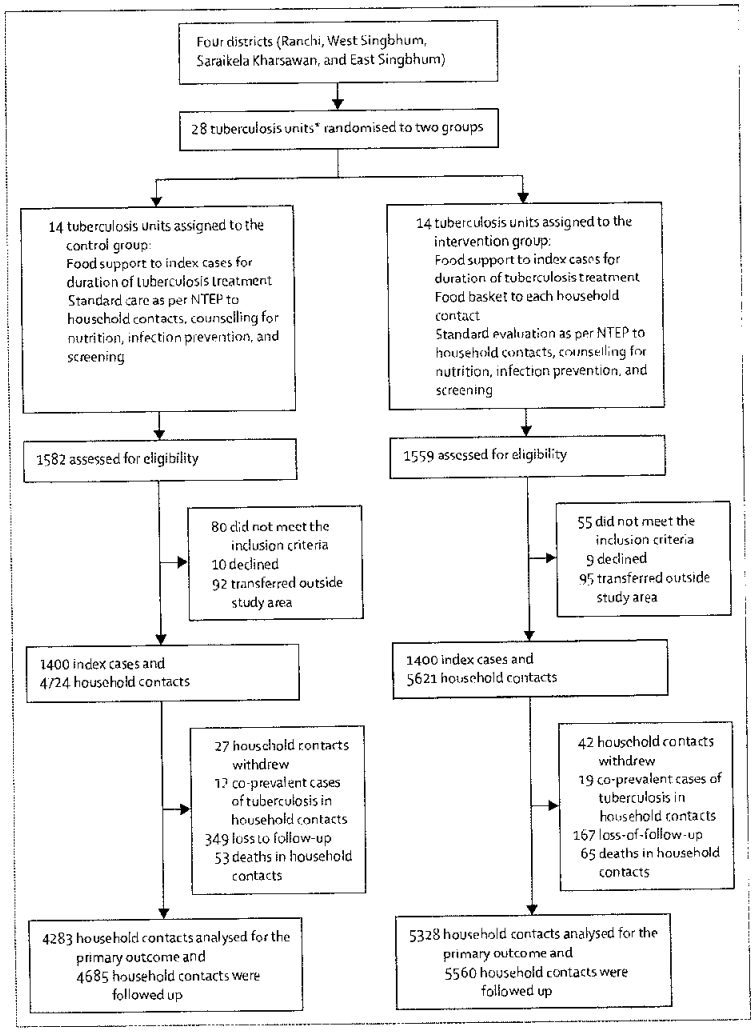

Figure 1: **Trial profile**
NTEP=National Tuberculosis Elimination Programme. *Clusters are the tuberculosis units.

members, neighbours, and the community health worker. If a participant was not available for 2 or more months in the intervention period or for at least 6 consecutive months in the follow-up period, they were considered lost-to-follow-up. Often patients or individual household contacts satisfied this definition of lost-to-follow-up but other family members were available for information on their health status. At the end of the study period, we approached all those who were lost-to-follow-up or who had withdrawn from the study to ascertain any history of diagnosis or treatment for tuberculosis.

The outcomes in the cohort of index patients with tuberculosis who received monthly food baskets during their treatment period with regard to tuberculosis incidence, treatment success, loss to follow-up, treatment failure, and weight gain have been reported separately.[23]

	Control group (n=4724)	Intervention group (n=5621)	Total (N=10345)
Contacts per index case (1400 index patients in each arm)	3·4	4·0	3·7
Age group			
≤5 years (0–60 months)	534 (11·3%)	625 (11·1%)	1159 (11·2%)
6–17 years (61–215 months)	1448 (30·7%)	1665 (29·6%)	3113 (30·1%)
18–59 years (216–719 months)	2513 (53·2%)	3001 (53·4%)	5514 (53·3%)
≥60 years (≥720 months)	229 (4·8%)	330 (5·9%)	559 (5·4%)
Sex			
Male	2121 (44·9%)	2583 (46·0%)	4704 (45·5%)
Female	2603 (55·1%)	3038 (54·0%)	5641 (54·5%)
Marital status			
Single	2628 (55·6%)	3102 (55·2%)	5730 (55·4%)
Married	1845 (39·1%)	2271 (40·4%)	4116 (39·8%)
Separated or widowed	251 (5·3%)	248 (4·4%)	499 (4·8%)
Caste*			
Scheduled tribes	3132 (66·3%)	3989 (71·0%)	7121 (68·8%)
Scheduled castes	354 (7·5%)	451 (8·0%)	805 (7·8%)
Other backward classes	872 (18·5%)	949 (16·9%)	1821 (17·6%)
Other	366 (7·7%)	232 (4·1%)	598 (5·8%)
Occupation†			
Unemployed	237 (5·0%)	188 (3·3%)	425 (4·1%)
MGNREGS, labour, sell forest products, and rickshaw driver	1005 (21·3%)	1307 (23·3%)	2312 (22·3%)
Sell milk, vegetables, livestock, and small-scale trade	48 (1·0%)	75 (1·3%)	123 (1·2%)
Making or selling of baskets, and making or selling alcohol or tobacco	15 (0·3%)	19 (0·3%)	34 (0·3%)
Pensions, employment in mines, or contract jobs	215 (4·6%)	132 (2·3%)	347 (3·4%)
Medium and large-scale trade, and income from land	8 (0·2%)	23 (0·4%)	31 (0·3%)
Student	1627 (34·4%)	2005 (35·7%)	3632 (35·1%)
Home maker	963 (20·4%)	1242 (22·1%)	2205 (21·3%)
Not applicable‡	606 (12·8%)	630 (11·2%)	1236 (11·9%)
Public distribution system§			
Yes	3968 (84·0%)	4825 (85·8%)	8793 (85·0%)
Tobacco			
Yes	347 (7·3%)	552 (9·8%)	899 (8·7%)
Alcohol			
Yes	707 (15·0%)	746 (13·3%)	1453 (14·0%)

(Table 1 continues on next page)

Statistical analysis

When this study was proposed, the estimated incidence rate of pulmonary tuberculosis in the general population in India was 0·22% (217 of 100000 people). The incidence rate ratio (IRR) of tuberculosis in household contacts compared with the general population was reported as 15·9 (IQR 2·6–21·4) in a systematic review, translating to 4% incidence in the household contacts.[24] In view of the higher prevalence of undernutrition in India, and evidence of higher tuberculosis incidence in household contacts,[25] an incidence of 5% during 2 years was assumed. As a historical precedent, improved living conditions with an emphasis on adequate nutrition led to more than 80% decline in tuberculosis incidence in the household contacts at the Papworth village settlement;[26] and an intervention effect of 50% reduction in tuberculosis incidence in the household contacts was assumed for the trial.

Our sample size considered design effect at three levels: the tuberculosis unit level, the families of index cases, and finally their household contacts, and was based on a method suggested for a three-level cluster-randomised trial.[27] We assumed an estimated 100 index patients with microbiologically confirmed pulmonary tuberculosis (80–120 patients) and their families in a cluster, with an intraclass correlation coefficient of 0·01.[28] Family-level clusters were assumed to have an average size of five people based on data on Jharkhand from 2011 census data and an intraclass correlation coefficient of 0·2 for the outcome.[24] Thus, with a design effect of 6·75, a sample size of 28 clusters with 2800 index tuberculosis patients, and 11200 household contacts was estimated to have 80% power to detect 50% reduction of tuberculosis incidence in the intervention group with a type 1 error of 5%.

Field staff collected data on a handheld device using the Research Electronic Data Capture hosted at the ICMR-NIRT. The database underwent periodic quality check to improve accuracy and reduce missing data. A data safety monitoring board conducted periodic review and interim analysis, which was done on May 24, 2022, when we crossed the pre-specified threshold of 50% of expected number of 188 incident tuberculosis cases in household contacts.

The primary comparison of interest was tuberculosis incidence of all forms among the household contacts, and expressed as events per 100 person-years of follow-up in the two groups. The outcomes were assessed at the individual level. Kaplan-Meier survival plots were constructed to display the crude effect of the intervention. The primary analysis used a Cox proportional hazards model to account for varying follow-up times, using robust standard errors to account for clustering under an

intention-to-treat paradigm including those who had been lost to follow-up and had withdrawn from the trial. We reported unadjusted hazard ratios (HRs) and adjusted hazard ratios (aHRs) along with their 95% CIs. To facilitate interpretation, given that HRs are often misinterpreted, we estimated IRR via Poisson regression using a generalised estimating equations approach to account for clustering, with specified independent structure, and used standard errors robust to misspecification of the correlation structure. In the sensitivity analysis we also adjusted for tuberculosis risk factors identified at baseline including age, sex, caste, tobacco and alcohol use, presence of BCG scar, undernutrition status, and asset score. Undernutrition in all household contacts at baseline was operationally defined for the different age groups as follows: for children younger than 5 years (0–60 months), and being underweight was defined as weight-for-age Z-scores less than −2 SD using the WHO child growth standards;[29] for those aged between 6 years and 17 years (61–215 months), underweight was defined as BMI-for-age and sex Z-score less than −2SD using WHO growth reference data,[30] whereas for adults it was defined as BMI of lower than 18·5 kg/m^2.

The assumptions of linearity in the regression models were verified and the proportionality assumption in the Cox proportionality hazards model was checked via Schoenfeld residuals.

In a post-hoc sensitivity analysis, we restricted cases to those with microbiologically confirmed pulmonary tuberculosis and excluded all participants with clinically diagnosed tuberculosis and extrapulmonary tuberculosis.

The secondary outcomes of change in weight in household contacts were compared using a generalised estimating equations approach, accounting for clustering. The secondary outcomes of frequency of non-tuberculosis morbidities and deaths due to infections in the household contacts were compared using the χ^2 test. The analyses were done in Stata (version 17.0) and R (version 4.1.2). This study is registered with CTRI-India, CTRI/2019/08/020490.

Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, and decision to submit for publication.

Results

The trial began on May 14, 2019, after a 3-month preparatory phase. Recruitment began on Aug 16, 2019 and was completed by Jan 31, 2021, and the trial ended on Aug 13, 2022. We had assumed an estimated 11 200 household contacts (5600 in each group), based on 2011 census data, which was the most recent census completed of Jharkhand indicating an average household size of five people (four contacts and one index case). However, the control group had 4724 household contacts

	Control group (n=4724)	Intervention group (n=5621)	Total (N=10 345)
(Continued from previous page)			
Presence of BCG scar			
<18 years	1253/1983 (63·2%)	1731/2291 (75·6%)	2984/4274 (69·8%)
≥18 years	1304/2741 (47·6%)	1695/3330 (50·9%)	2999/6071 (49·4%)
Tuberculosis preventive treatment in children aged <6 years¶			
Initiated or eligible	70/535 (13·1%)	116/626 (18·5%)	186/1161 (16·0%)
Asset cost			
Cost of 23 household assets in Indian Rupees	15 000 (8000–64 750)	16 500 (11 750–73 500)	

Data are n (%) or median (IQR). MGNREGS=Mahatma Gandhi National Rural Employment Guarantee Scheme. *These terms are used by the Indian Constitution and are officially designated groups of people who are the most disadvantaged in that order. †In rural areas, people have multiple occupations, and these are their primary engagements as reported to the field staff. The occupations were grouped based on the income that is usually generated and in consultation with a non-governmental organisation that has worked in the region for a long time. ‡Children aged 5 years and younger and people older than 60 years who declared being unemployed. §Distributes dry food rations at subsidised cost to families living below the poverty line. ¶Tuberculosis preventive treatment eligibility during the trial was in household contacts aged up to 5 years; however, current eligibility has been expanded to household contacts aged older than 5 years.

Table 1: Baseline characteristics of household contacts in the two groups

	Control group (n=4724)	Intervention group (n=5621)	Total (N=10 345)
Incident tuberculosis cases	122 (2·6%)	96 (1·7%)	218 (2·1%)
Sex			
Male	72 (59%)	50 (52·1%)	122 (56·0%)
Female	50 (41%)	46 (47·9%)	96 (44·0%)
Age group			
≤5 years	3 (2·5%)	8 (8·3%)	11 (5·0%)
6–17 years	16 (13·1)	14 (14·6%)	30 (13·8%)
Adults (≥18 years)	103 (84·4)	74 (77·1%)	177 (81·2%)
Types of incident cases			
Microbiologically confirmed*	91 (74·6%)	62 (64·6%)	153 (70·2%)
Clinically diagnosed pulmonary tuberculosis in adults	21 (17·2%)	17 (17·7%)	38 (17·4%)
Clinically diagnosed extrapulmonary tuberculosis (all age groups)	3 (2·5%)	3 (3·1%)	6 (2·8%)
Clinically diagnosed pulmonary tuberculosis in children (0–17 years)	7 (5·7%)	14 (14·6%)	21 (9·6%)
Co-prevalent tuberculosis cases	12 (0·3%)	19 (0·3%)	31 (0·3%)
Deaths†	53 (1·1%)	65 (1·2%)	118 (1·1%)
Lost to follow-up	349 (7·4%)	167 (3·0%)	516 (5·0%)
Withdrawal	27 (0·6%)	42 (0·7%)	69 (0·7%)
Contacts censored at end of study	4161 (88·1%)	5232 (93·1%)	9393 (90·8%)

Data are n (%). *Microbiological confirmation was done with sputum smear microscopy in 56 (61·5%) of 91 patients in the control group and 35 (56·5%) of 62 patients in the intervention group, and this proportion was not statistically significant. Molecular diagnostics were confirmed in 35 patients in the control group (25 patients by GeneXpert and ten patients by TrueNat) and 27 patients in the intervention group (25 positive patients by GeneXpert and two positive patients by TrueNat). †The total number of deaths was 127 inclusive of nine deaths in household contacts with incident tuberculosis that occurred during their follow-up.

Table 2: Outcomes in household contacts

(3·4 per index case), nearly 900 less than the 5621 in the intervention group (4·1 per index patient; figure 1). The number of household contacts per index patient in the intervention group was as predicted from the census data.

Nearly three-fifths (6073 [58·7%] of 10 345) of the patients were adults and there was a higher proportion of women (5641 [54·5%] of 10 345) compared with men. Most individuals were involved in manual work or small trades (table 1); 57·8% (5983 of 10 345) had evidence of BCG vaccination, and 16·0% (186 of 1161) received tuberculosis prevention treatment (table 1). The overall prevalence of low BMI (BMI <18·5 kg/m²) in adults was 36·8% (2232 of 6073) and was higher in the intervention group (38·3% [1275 of 3331] *vs* 34·9% [957 of 2742]; p=0·0070) than the control group, and in women than in men (40·6% [1451 of 3575] *vs* 31·3% [781 of 2498]; p<0·0005). The prevalence of undernutrition in all household contacts (all age groups) measured by the composite indicator of a low BMI in adults, weight-for-age Z-scores of less than −2SD in children younger than 5 years, and BMI-for-age Z-scores of less than −2SD for ages 6–17 years, was 34·2% (3543 of 10 345). The prevalence of people who are overweight or with obesity in adults was 7·7% (465 of 6038). At enrolment, the intervention group had a higher prevalence of undernutrition in adult women and in both sexes in the 6–17 years age group compared with the control group. Weights were available in 4717 (99·9%) of 4724 contacts in the control group, and 5603 (99·7%) 5621 in the intervention group with no missing values in children from 0 months to 60 months. Heights were available in 4256 (90·1%) of 4724 contacts in the control group, and in 5074 (90·3%) of 5621 contacts in the intervention group. 907 (89·4%) of 1015 missing values of heights were in children of 0–60 months of age.

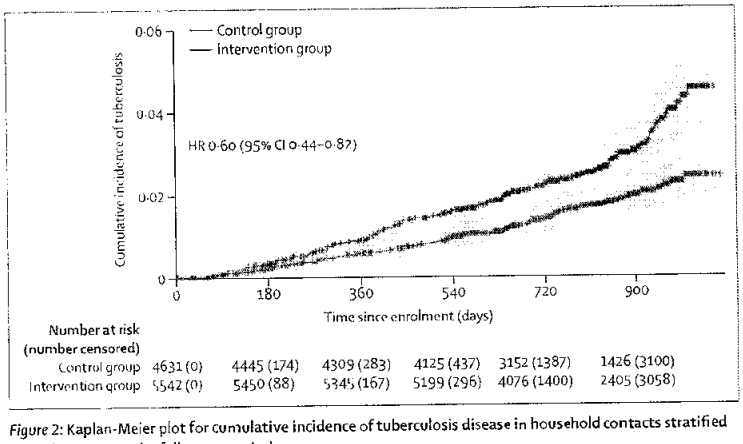

Figure 2: Kaplan-Meier plot for cumulative incidence of tuberculosis disease in household contacts stratified by trial group over the follow-up period
The time shown is the time from the enrolment of contacts in the trial, and shaded lines represent 95% CIs. The planned follow-up of 24 months was extended for some patients due to the COVID-19 pandemic.

Table 2 describes the outcomes in 10 345 household contacts in the trial over a total follow-up period of 21 869 person-years. A total of 249 individuals were diagnosed with active tuberculosis in the household contacts, of whom 31 (12·4%) of 249 individuals had co-prevalent tuberculosis, of whom 19 were in the intervention group and 12 were in the control group (table 2), and 218 (87·6%) individuals had incident tuberculosis. Of the 218 incident cases, 122 of 4712 (2·6%, 95% CI 2·2–3·1) contacts at risk were in the control group and 96 of 5603 (1·7%, 95% CI 1·4–2·1) contacts at risk were in the intervention group. More than 81·2% (177 of 218) of the incidence occurred in adults, and more than two-thirds (70·2% [153 of 218]) were microbiologically confirmed, by sputum smear microscopy (91 [59·5%] of 153 individuals) and cartridge based nucleic acid amplification test (62 [40·5%]; table 2). The median (IQR) time from enrolment to diagnosis of incident tuberculosis disease was 1·4 years (0·8–2·0) and was similar in both groups; 166 (76·1%) of 218 people occurred in the first 2 years after enrolment. 52 people were diagnosed with incident tuberculosis after 2 years (28 in the control group and 24 in the intervention group; figure 2). The overall proportion of loss to follow-up was 5% (516 of 10 345 individuals; higher in the control group: 7·3% [349 of 4724 individuals] *vs* 3·0% [167 of 5621 individuals]; p<0·0001) and withdrawal in household contacts was 0·7% (69 of 10 345 individuals). We could not collect data on participants that were lost to follow-up. The 69 participants who withdrew belonged to 13 families and the withdrawal from the study was due to their migration and relocation in the wake of the COVID-19 pandemic. There were 127 deaths over the entire trial period, of which 34 (26·8%) deaths occurred in the 6-month intervention period, and the number of deaths was equal in both groups. Of these 34 deaths, seven (20·6%) deaths were possibly related to an acute infectious illness (not tuberculosis), based on the symptoms preceding the death reported by the family to the field staff after the death. Nine (26·5%) deaths occurred in those with incident tuberculosis. Most deaths (110 [86·6%] of 127 individuals) occurred at home and were not medically certified. The household contacts who were lost to follow-up or withdrew were largely due to relocation considering the COVID-19 pandemic. 9393 (91%) of 10 345 individuals were censored at the end of the study. 7841 household contacts completed 24 months of follow-up and 2133 completed 33 months until the common closeout period.

The incidence rate in the control group was 1·27 per 100 person-years (95% CI 1·00–1·61) and 0·78 per 100 person-years (0·64–0·96) in the intervention group. The unadjusted IRR was 0·62 (95% CI 0·45–0·84) whereas the unadjusted HR was 0·6 (0·44–0·82). Adjusting this IRR and HR for alcohol and tobacco use, age, sex, caste, underweight status, asset score, BCG status, and family history of tuberculosis in the past did

www.thelancet.com Published online August 8, 2023 https://doi.org/10.1016/S0140-6736(23)01231-X

	Incident tuberculosis per person-years follow-up in the control group (N=4724)	Incidence rate per 100 person-years in the control group (95% CI)	Incident tuberculosis in person-years for follow-up in the intervention group (N=5621)	Incidence rate per 100 person-years in the intervention group (95% CI)	Incidence rate ratio* (95% CI)	Hazard ratio* (95% CI)
Overall	122/9609	1·27 (1·00–1·61)	96/12260	0·78 (0·64–0·96)	0·62 (0·45–0·84)	0·6 (0·44–0·82)
Age group						
0–5 years	3/1120	0·27 (0·09–0·81)	8/1386	0·58 (0·30–1·11)	2·15 (0·60–7·77)	2·02 (0·54–7·61)
6–17 years	16/3008	0·53 (0·30–0·95)	14/3666	0·38 (0·21–0·68)	0·72 (0·32–1·63)	0·70 (0·31–1·61)
≥18 years	103/5481	1·88 (1·49–2·37)	74/7208	1·03 (0·81–1·31)	0·55 (0·39–0·77)	0·53 (0·38–0·74)
Sex						
Male	72/4275	1·68 (1·32–2·15)	50/5630	0·89 (0·66–1·19)	0·53 (0·36–0·77)	0·51 (0·35–0·76)
Female	50/5334	0·94 (0·68–1·29)	46/6629	0·69 (0·51–0·95)	0·74 (0·47–1·16)	0·72 (0·46–1·12)
Types of tuberculosis						
Microbiological confirmation† (n=153)	91/9559	0·95 (0·73–1·24)	62/12208	0·51 (0·38–0·68)	0·53 (0·36–0·79)	0·52 (0·35–0·77)
Clinically diagnosed (n=65)	31/9488	0·33 (0·19–0·56)	34/12176	0·28 (0·18–0·44)	0·86 (0·42–1·74)	0·82 (0·40–1·68)
Nutrition status at baseline						
Underweight*	61/3148	1·94 (1·48–2·54)	64/4468	1·45 (1·09–1·94)	0·75 (0·51–1·12)	0·73 (0·49–1·09)
Normal or above	61/6434	0·93 (0·66–1·31)	32/7769	0·39 (0·27–0·55)	0·33 (0·17–0·65)	0·33 (0·17–0·65)
Caste‡						
Scheduled tribes	85/6415	1·33 (0·99–1·78)	72/8773	0·81 (0·63–1·07)	0·62 (0·42–0·92)	0·60 (0·4–0·91)
Scheduled castes	14/726	1·93 (1·28–2·89)	5/932	0·54 (0·26–1·12)	0·62 (0·42–0·92)	0·28 (9·12–0·65)
Other backward classes	18/1729	1·04 (0·65–1·66)	12/2035	0·59 (0·33–1·06)	0·57 (9·27–1·2)	0·55 (0·26–1·16)
Other	5/738	0·68 (0·45–1·02)	7/520	1·35 (0·68–2·65)	1·99 (0·90–4·39)	2·12 (0·96–4·68)

*Underweight in all ages is a composite category operationally defined as weight-for-age Z-scores less than –2SD for those aged 5 years or younger, BMI-for-age and sex Z-score of lower than –2SD for those aged 6–17 years, and BMI of lower than 18·5 kg/m² for individuals aged at least 18 years. †Microbiologically confirmed tuberculosis included one patient with lymph node tuberculosis who was cartridge based nucleic acid amplification test positive. ‡These terms are used by the Indian Constitution and are officially designated groups of people who are the most disadvantaged in that order.

Table 3: Incidence rate, incidence rate ratios, and hazard ratios among household contacts who developed tuberculosis (all forms)

not change the results and the adjusted IRR (aIRR) was 0·61 (95% CI 0·43–0·85), whereas the aHR was 0·59 (0·42–0·83). These findings translate into a 39% (95% CI 11–54) relative rate reduction for tuberculosis incidence in the intervention group (table 3). Figure 2 shows the Kaplan-Meier curves of cumulative tuberculosis incidence in the two groups plotted against time and shows a significant divergence in the two curves after the first 9 months.

We analysed the overall effect of the intervention on the incidence of 152 cases of microbiologically confirmed pulmonary tuberculosis (table 4) in the two groups and in the subgroups (one of the 153 cases of microbiologically confirmed incident tuberculosis had lymph node tuberculosis). The aIRR of incidence of microbiologically confirmed pulmonary tuberculosis, adjusted for potential confounders described earlier for incident tuberculosis (all forms) was 0·52 (95% CI 0·35–0·79), translating into a 48% reduction in the rate of microbiologically confirmed pulmonary tuberculosis in the intervention group. The corresponding aHR was 0·51 (95% CI 0·34–0·78).

The overall prevalence of low BMI (<18·5 kg/m²) in adults declined to 28·9% (1637 of 5667) after the intervention and was higher in the control group (30·2% [745 of 2463] *vs* 27·8% [892 of 3204]; p=0·047) than the intervention group. This finding represented an absolute (relative) decline in prevalence of underweight adults in nearly 5% (14%) in the control group and nearly 11% (28%) in the intervention group. The household contacts in the intervention group had a higher absolute and relative weight gain across age groups and sex, except the boys aged 5 years and younger. The median percentage weight gain over baseline ranged from 1·6–1·9% in the control group to 2·9–3·5% in the intervention group (p<0·0005) in the adult household contacts (table 5). The difference in the median weight gain at 6 months was 0·7 kg in the adults and 0·4 kg in the 6–17 years age group (p<0·0005; table 5). The weight gains in the trial were affected by weight loss in a significant proportion of contacts (11·7% [1206 of 10 345]) during the intervention period. Although weight loss occurred in both groups and in individuals who were underweight, as well as individuals with normal weight and individuals who were overweight or individuals with obesity, a higher proportion of contacts in the control group and of normal or overweight contacts experienced weight loss (appendix p 10). There was a statistically significant difference between baseline and end of intervention

	Incident tuberculosis per person-years follow-up in the control group (N=4724)	Incidence rate per 100 person-years in the control group (95% CI)	Incident tuberculosis in person-years follow-up in the intervention group (N=5621)	Incidence rate per 100 person-years in the intervention group (95% CI)	Incidence rate ratio* (95% CI)	Hazard ratio* (95% CI)
Overall	90/9557	0·94 (0·72–1·23)	62/12208	0·51 (0·38–0·68)	0·54 (0·37–0·80)	0·53 (0·36–0·78)
Age group						
0–5 years	1/1116	0·09 (0·013–0·63)	0/1374	NA	NA	NA
6–17 years	8/2996	0·27 (0·13–0·55)	8/3656	0·22 (0·12–0·39)	0·82 (0·33–2·06)	0·83 (0·33–2·08)
≥18 years	81/5445	1·49 (1·15–1·93)	54/7178	0·75 (0·55–1·04)	0·51 (0·34–0·76)	0·50 (0·33–0·75)
Sex						
Male	53/4243	1·25 (0·99–1·58)	34/5606	0·61 (0·42–0·88)	0·49 (0·31–0·76)	0·48 (0·31–0·74)
Female	37/5313	0·67 (0·47–1·03)	28/6601	0·42 (0·30–0·61)	0·61 (0·36–1·04)	0·60 (0·35–1·02)
Nutrition status at baseline						
Underweight*	47/3126	1·50 (1·10–2·04)	42/4434	0·99 (0·70–1·40)	0·66 (0·42–1·04)	0·65 (0·41–1·03)
Normal or above	43/6404	0·66 (0·43–1·01)	20/7751	0·22 (0·13–0·37)	0·33 (0·17–0·65)	0·33 (0·17–0·65)
Caste†						
Scheduled tribes	63/6375	0·99 (0·68–1·45)	46/8727	0·53 (0·36–0·77)	0·53 (0·31–0·92)	0·52 (0·30–0·90)
Scheduled castes	11/720	1·53 (0·89–2·61)	3/930	0·32 (0·13–0·83)	0·53 (0·31–0·92)	0·21 (0·07–0·65)
Other backward classes	12/1724	0·70 (0·43–1·12)	10/2033	0·49 (0·24–1·01)	0·71 (0·30–1·70)	0·68 (0·30–1·62)
Other	4/737	0·54 (0·26–1·15)	3/517	0·58 (0·20–1·66)	1·10 (0·30–3·9)	1·14 (0·30–4·37)

Data are number of incidents/number of person-years, unless stated otherwise. NA=not applicable. *Underweight in all ages is a composite category operationally defined as weight-for-age Z-scores less than −2 SD for those aged 5 years or younger, BMI-for-age and sex Z-score of lower than −2SD for those aged 6–17 years, and BMI of lower than 18·5 kg/m² for individuals aged at least 18 years. †These terms are used by the Indian Constitution and are officially designated groups of people who are the most disadvantaged in that order.

Table 4: Incidence rate and incidence rate ratios among household contacts who developed microbiologically confirmed pulmonary tuberculosis

weights in adults in both groups, but this weight gain did not differ across sex (data not shown).

The secondary outcomes related to non-tuberculosis acute infections and their related hospitalisations and mortality in the intervention period are described in the appendix (p 9). The secondary outcomes were similar in the two groups in the frequency of presumed lower respiratory tract infections, diarrhoea, hospitalisations, and deaths related to febrile illness. The food intervention did not lead to any harms reported by the participants.

Discussion

We report the results of, to our knowledge, the first field-based cluster-randomised trial that investigated whether macronutrient supplementation with food rations and micronutrients for 6 months could reduce tuberculosis incidence in household contacts of patients with microbiologically confirmed pulmonary tuberculosis during a follow-up period of 2 years. The trial also investigated the effect of the nutritional intervention on nutritional status, and non-tuberculosis infectious morbidity and mortality in household contacts during the intervention period. The nutritional intervention led to a 39% (aIRR 0·61 [95% CI 0·43–0·85]) relative reduction in the rate of tuberculosis incidence (all forms) and to a 48% (0·52 [0·35–0·79]) relative reduction in the rate of microbiologically confirmed pulmonary tuberculosis in the intervention group. The aHRs obtained on Cox proportional hazards analysis indicate that at any time in the study period, household contacts were significantly less likely to develop tuberculosis incidence (all forms; aHR 0·59 [95% CI 0·42–0·83]) and significantly less likely to develop microbiologically confirmed pulmonary tuberculosis in the intervention group (0·51 [0·34–0·78]). The baseline evaluation revealed prevalence of undernutrition in more than a third of the household contacts, which was higher than the state and national averages, underlining the need for such an intervention. To prevent occurrence of one case of incident tuberculosis during a period of 2 years, an estimated 111 household contacts (30 households) would need to be provided nutritional supplementation. The intervention was also associated with modest gains in weight, which were nearly double in the adults in the intervention group. These modest weight gains translated into a 14–28% reduction in baseline prevalence of individuals who were underweight in adult household contacts. The intervention had no significant effect on the frequency of malaria, diarrhoea, respiratory infections, and hospitalisations and deaths related to febrile illnesses over the intervention period. Nearly 24% of the people with incident tuberculosis were diagnosed after 2 years of follow-up. A systematic review of contact studies has shown that risk of incident tuberculosis is substantial even after 3 years of exposure to the index patient.[24]

www.thelancet.com Published online August 8, 2023 https://doi.org/10.1016/S0140-6736(23)01231-X

The significant reduction of tuberculosis incidence seen in this trial of macronutrient and micronutrient supplementation is in contrast to the trials on micronutrients such as vitamin D in a population with high prevalence of vitamin D deficiency that did not reduce the risk of tuberculosis infection or disease.[12] This reduction is possibly because our intervention addressed the deficiency of calories, proteins, and micronutrient deficiencies. In a cohort study from India, macronutrient undernutrition in household contacts was associated with a six-fold higher rate of tuberculosis incidence.[31] A tuberculosis incidence of 12 per 1000 person-years and incidence proportion of 2% in this cohort was similar to the 12·7 per 1000 person-years and 2·7% in the control group of this study. Modelling studies have shown that modest improvement in nutritional status has a potential of significant reduction in tuberculosis incidence.[32]

Global tuberculosis control faces challenges with tuberculosis incidence increasing for the first time in recent years (3·6% in 2021 compared with an average decline of 2% annually),[1] and a deteriorating situation regarding social determinants such as undernutrition. According to the Food and Agriculture Organization, "the world is moving backwards in its efforts to end hunger, food insecurity and malnutrition in all its forms".[33] This intervention represents a form of mass prophylaxis in a group at high risk of infection and of progression to disease, and could complement biomedical interventions such as tuberculosis prevention treatment and newer tuberculosis vaccines. WHO recommends tuberculosis prevention treatment in people living with HIV, household contacts of people with microbiologically confirmed pulmonary tuberculosis, and clinical risk groups, and had set targets of providing tuberculosis preventive treatment to 30 million individuals by 2022.[34] Of these, only 42% of the tuberculosis prevention treatment target for contacts aged 5 years or younger was achieved, and in the case of contacts older than 5 years, this was only 3% until 2021.[1] Thus, most household contacts are yet to be covered by the tuberculosis prevention treatment, which is operationally challenging in India due to resource-intensive contact evaluations to rule out active tuberculosis, testing to establish tuberculosis infection, and initiation and follow-up of tuberculosis prevention treatment.[35] Tuberculosis preventive treatment coverage in India is 48% and in Jharkhand, it is 29% as per the India tuberculosis report 2022. Jharkhand is the third lowest in the country followed by Arunachal Pradesh and Bihar in the coverage of tuberculosis preventive treatment.[1] Among the tuberculosis prevention treatment regimen, 6 months of isoniazid is efficacious compared with placebo (odds ratio 0·65, 95% credible interval 0·50–0·83) and 3 months of rifapentine-isoniazid is efficacious compared with no treatment (0·36, 0·18–0·73).[36] In a trial of a new vaccine M72/AS01$_E$, the vaccine efficacy was found to be 49·7%.[37] Although our intervention was a host-directed one possibly addressing the immune response to tuberculosis infection, its efficacy in reducing tuberculosis incidence compared favourably with that of conventional tuberculosis prevention treatment involving anti-tuberculosis drugs and approached the Preferred Product Characteristics of at least 50% efficacy in prevention of confirmed pulmonary tuberculosis suggested for newer tuberculosis vaccines.[38]

Strengths include that the trial was conducted in collaboration with and within the National Tuberculosis Elimination Programme, hence the trial population (patients and household contacts) is representative of programmatic cohorts in many Indian states with constitutionally and administratively designated socially and economically disadvantaged groups, such as scheduled castes, scheduled tribes, and other backward classes, and rural communities with a high prevalence of undernutrition and poverty. Another strength was the

	Control group (n=4724)	Intervention group (n=5621)	p value
Adult men			
Weight, kg	52·0 (9·6)	52·4 (9·8)	..
Height, cm	160·2 (7·5)	161·0 (6·9)	..
BMI, kg/m²	20·2 (3·0)	20·2 (3·2)	..
Stunting*	617/1104 (55·9%)	712/1381 (51·6%)	..
Nutrition categories	..	..	..
Severely underweight	59 (5·3%)	80 (5·8%)	..
Mild to moderately underweight	267 (24·2%)	375 (27·2%)	..
Normal BMI	698 (63·2%)	830 (60·1%)	..
People who are overweight or people with obesity	80 (7·3%)	96 (7·0%)	..
Weight gain at 6 months, kg†	0·91 (1·76)	1·70 (1·92)	0·0012
Percent weight gain at 6 months†	1·92% (3·85)	3·45% (3·94)	0·0020
Adult women			
Weight, kg	44·3 (8·7)	43·8 (8·7)	..
Height, kg	149·2 (6·2)	149·1 (6·1)	..
BMI, kg/m²	19·9 (3·6)	19·7 (3·5)	..
Stunting*	854/1623 (52·6%)	1036/1930 (53·7%)	..
Nutritinn categories	..	..	..
Severely underweight	171 (10·5%)	180 (9·3%)	..
Mild to moderately underweight	460 (28·3%)	640 (33·2%)	..
Normal BMI	859 (52·9%)	954 (49·4%)	..
People who are overweight or people with obesity	133 (8·2%)	156 (8·1%)	..
Weight gain at 6 months, kg†	0·83 (1·6)	1·77 (1·92)	<0·0001
Percent weight gain at 6 months†	2·04% (3·86)	4·29% (4·73)	<0·0001
Children aged ≤5 years			
Boys, underweight (weight-for-age lower than −2SD)	120 (44·9%)	168 (49·7%)	..
Boys, weight gain at 6 months, kg†	1·74 (1·25)	1·75 (1·38)	0·85
Boys, percent weight gain at 6 munths†	20·1% (25·1)	18% (18·3)	0·38
Girls, underweight (weight-for-age lower than −2SD)	127 (48·3%)	139 (48·8%)	..

(Table 5 continues on next page)

	Control group (n=4724)	Intervention group (n=5621)	p value
(Continued from previous page)			
Girls, weight gain at 6 months, kg†	1·48 (1·03)	1·75 (1·32)	0·28
Girls, percent weight gain at 6 months†	17·3% (17·5)	18·7% (14·4)	0·49
Children aged 6–17 years			
Boys, thinness (BMI-for-age Z-scores lower than −2SD)	177 (25·3%)	254 (30·1%)	
Boys, weight gain at 6 months, kg†	1·63 (1·41)	2·15 (1·61)	0·0074
Boys, percent weight gain at 6 months†	6·43 (6·08)	8·48 (6·82)	0·0079
Girls, thinness (BMI-for-age Z-scores lower than −2SD)	118 (17·2)	183 (23·2)	
Girls, weight gain at 6 months, kg†	1·67 (1·7)	2·18 (1·59)	0·042
Girls, percent weight gain at 6 months†	6·64% (6·88)	8·98% (8·71)	0·048

Data are n (%) or mean (SD). BMI has been classified as: severely underweight (<16·0 kg/m²), mild to moderately underweight (16–18·49 kg/m²), normal (18·5–24·99 kg/m²), and people who are overweight or people with obesity (≥25·0 kg/m²). *Stunting is defined as sex-specific height-for-age Z-score lower than −2 SD at the age of 18 years as per WHO growth standards. †Estimated using generalised estimating equation. In the control group, weights were missing in seven individuals (0·15%) and heights were missing in 468 individuals (9·9%). In the intervention group, weights were missing in 18 individuals (0·3%) and heights were missing in 547 individuals (9·7%). Of the 1015 missing heights, 907 individuals (89·4%) were in the 0–60 months category. At 6 months, weights of participants were available in 4323 individuals (91·5%) in the control group, and 5430 individuals (96·6%) in the intervention group. Index cases in both groups received a food basket that provided 1200 kcal plus 52 g of protein per day, and household contacts in the intervention group received 750 kcal plus 23 g of protein per day.

Table 5: **Baseline nutritional status and weight gain 6 months after enrolment of household contacts**

food basket that was based on locally available and culturally acceptable food items improved after consultation with local communities, for which future interventions in other communities should be similarly contextualised. The study was adequately powered to detect a difference in the rates of incident tuberculosis. The trial participants and the trial team encountered formidable challenges during the COVID-19 pandemic, but the enrolment, interventions, and follow-up continued uninterrupted. A high proportion of the household contacts with incident tuberculosis were microbiologically confirmed, and the proportion lost to follow-up was also low.

The trial has some limitations. The trial was a pragmatic one implemented in the real-world programmatic conditions and existing health system. Although it was done in a population with high prevalence of food insecurity and undernutrition, we did not individualise the food baskets or ascertain consumption of rations directly. The possibility of food sharing in the control group in which only the index patient with tuberculosis received the food basket cannot be ruled out as evident by the weight gain in household contacts and the reduction in prevalence of undernutrition in the control group. The weight gain in either group did not differ by sex. The nutritional intervention was designed to supplement the usual diet of the families, and the disruption of livelihoods in the COVID-19 pandemic is likely to have affected usual income and diets, and this disruption along with the food sharing might have attenuated its effect in the intervention group. The food intervention reduced undernutrition in the household contacts, but the quantity and duration were not sufficient to eliminate undernutrition in them. In subgroups stratified by baseline nutritional status, the intervention effect in the underweight population overall approached statistical significance, although when the analysis was stratified by age group and nutritional status, the intervention had a significant protective effect in adults who were underweight at baseline. The effect size might not be the same in communities with lower prevalence of undernutrition and deprivation. The COVID-19 pandemic was associated with challenges in diagnosing tuberculosis in household contacts, but these were common to contacts in both groups. The study achieved a smaller sample size and a shorter follow-up period in some households than that targeted; however, this did not result in an underpowered study for the main outcomes because our design effect in the trial proved to be lower than assumed. However, it could have impacted on the analysis of effect in subgroups defined by nutritional status (underweight *vs* normal or individuals who were overweight). Given the nature of the intervention, the investigators, the field staff, and the participants were not masked. The food distribution, anthropometry, and the symptom screening were done by the same field staff. However, the outcome of incident tuberculosis was evaluated by the providers in the government health system who were not associated with the trial team. We did not evaluate the contacts for latent tuberculosis infection except in a small sub-study (unpublished). The trial did not employ cultures for diagnosis of incident tuberculosis as these were not part of the national guidelines,[19] but a significant proportion were diagnosed with the cartridge based nucleic acid amplification test. We had robust data on baseline anthropometric measures, but the follow-up heights in children younger than 18 years were inconsistent due to pandemic-related disruptions. We therefore limited our analysis of changes in nutritional status to weight changes in children, whereas in adults, we could categorise changes in nutritional status based on BMI as well. We did not collect information on the receipt of direct benefit transfers to patients enrolled in this trial, but an imbalance of receipts between the patients in the groups is unlikely. The majority of deaths were not medically certified as they occurred at home. However, the field staff did ascertain the medical condition, symptoms, and circumstances around the death in all cases, although not part of a detailed verbal autopsy protocol.

In communities with a high prevalence of undernutrition, provision of a monthly food basket and micronutrient supplementation to household contacts during the 6-month treatment period of patients with infectious tuberculosis resulted in a 39% reduction in tuberculosis incidence and a 48% reduction in the incidence of microbiologically confirmed tuberculosis (largely pulmonary tuberculosis), with modest improvements in weight and prevalence of undernutrition. This intervention was low cost, operationally feasible, and

should be an essential and integral component of multisectoral strategies that could accelerate reduction in tuberculosis incidence in countries with a syndemic of tuberculosis and undernutrition.

Contributors

AB, MB, and BV were involved in funding acquisition. AB, MB, BV, AnB, SS, MP, and DM were involved in the conceptualisation of the study. AB, MB, AM, GST, GB, and AKM were involved in data curation and AB, MB, and AnB were involved in the formal analysis. Investigations were done by AB, MB, AM, BV, AKM, RRP, RP, and RD. AB, MB, AM, BV, BW, AnB, and VC did the methodology. AB, MB, AM, BV, BW, GB, GST, RP, RD, and RJ were involved in supervision and project administration. The software was the responsibility of AB, MB, AM, GST, BW, and GB. Validation was done by AB, MB, AM, GST, BW, GB, and AnB, and data visualisation was done by AB, MB, and AnB. The original draft was written by AB, MB, AnB, VC, DM, BV, MP, and all authors were involved in reviewing and editing the manuscript. AB, MB, AM, BW, AnB accessed and verified the data.

Declaration of interests

MP serves on the Scientific Advisory Committee of Foundation of Innovative New Diagnostics, which is a non-profit global alliance for diagnostics, and is also an advisor to the Bill & Melinda Gates Foundation. MP has no financial or industry conflicts. All other authors declare no competing interests.

Data sharing

Data will be made available upon reasonable request after planned analyses and reporting have been completed by the investigators.

Acknowledgments

This work was supported by grants from the India Tuberculosis Research Consortium, Indian Council of Medical Research, New Delhi (grant number: 5/8/5/57/TB consortium/Call India Project/2017/ECD-1). We would like to express appreciation of the tremendous efforts of the entire field team who worked in a difficult terrain, and their continued work without any interruption during the COVID-19 pandemic. The cooperation of the district tuberculosis officers of Ranchi, East Singhbhum, West Singhbhum, and Seraikela-Kharsawan and their teams are gratefully acknowledged. We would like to acknowledge the support of Central Coalfields for making available laboratory space and equipment in Ranchi, and to the Letzdream Foundation, New Delhi, for providing support for handheld devices for data entry and two-wheelers for the supervisory team. AB and MB are grateful to the Yenepoya (Deemed to be University) for its wholehearted support, and their colleagues in the Department of Internal Medicine and Community Medicine at the Yenepoya Medical College, who shared their work during their frequent and prolonged visits to Jharkhand for the trial. Last but not least, we wish to thank the participating patients and their families for their cooperation throughout the conduct of this study, and express our admiration for their tremendous resilience in the face of illness and adversity. Our interactions with them have been deeply humbling and enriching.

References

1 WHO. Global tuberculosis report 2022. Geneva: World Health Organization, 2022.
2 WHO. Implementing the end TB strategy: the essentials. Geneva: World Health Organization, 2015.
3 Waitt CJ, Squire SB. A systematic review of risk factors for death in adults during and after tuberculosis treatment. *Int J Tuberc Lung Dis* 2011; 15: 871–85.
4 Lönnroth K, Williams BG, Cegielski P, Dye C. A consistent log-linear relationship between tuberculosis incidence and body mass index. *Int J Epidemiol* 2010; 39: 149–55.
5 Singer M, Bulled N, Ostrach B, Mendenhall E. Syndemics and the biosocial conception of health. *Lancet* 2017; 389: 941–50.
6 Bhargava A, Chatterjee M, Jain Y, et al. Nutritional status of adult patients with pulmonary tuberculosis in rural central India and its association with mortality. *PLoS One* 2013; 8: e77979.
7 International Institute for Population Sciences and ICF. National Family Health Survey (NFHS)-5. Mumbai: India and State Factsheet Compendium, 2020.
8 Ministry of Health and Family Welfare. Government of India Gazette notification for DBT with NIKSHAY. 2017. https://tbcindia.gov.in/show file.php?lid=3304 (accessed Jan 15, 2023).
9 Bhargava A, Bhargava M, Beneditti A, Kurpad A. Attributable is preventable: corrected and revised estimates of population attributable fraction of TB related to undernutrition in 30 high TB burden countries. *J Clin Tuberc Other Mycobact Dis* 2022; 27: 100309.
10 Aibana O, Huang CC, Aboud S, et al. Vitamin D status and risk of incident tuberculosis disease: a nested case-control study, systematic review, and individual-participant data meta-analysis. *PLoS Med* 2019; 16: e1002907.
11 Tenforde MW, Yadav A, Dowdy DW, et al. Vitamin A and D deficiencies associated with incident tuberculosis in HIV-infected patients initiating antiretroviral therapy in multinational case-cohort study. *J Acquir Immune Defic Syndr* 2017; 75: e71–79.
12 Ganmaa D, Uyanga B, Zhou X, et al. Vitamin D supplements for prevention of tuberculosis infection and disease. *N Engl J Med* 2020; 383: 359–68.
13 Sinha P, Lönnroth K, Bhargava A, et al. Food for thought: addressing undernutrition to end tuberculosis. *Lancet Infect Dis* 2021; 21: E318–25.
14 Darnton-Hill I, Mandal PP, de Silva A, Bhatia V, Sharma M. Opportunities to prevent and manage undernutrition to amplify efforts to end TB. *Int J Tuberc Lung Dis* 2022; 26: 6–11.
15 Bhargava A, Bhargava M, Velayutham B, et al. The RATIONS (Reducing Activation of Tuberculosis by Improvement of Nutritional Status) study: a cluster randomised trial of nutritional support (food rations) to reduce TB incidence in household contacts of patients with microbiologically confirmed pulmonary tuberculosis in communities with a high prevalence of undernutrition, Jharkhand, India. *BMJ Open* 2021; 11: e047210.
16 National Multidimensional Poverty Index. Baseline report. New Delhi: Niti Aayog, 2021.
17 India TB. Report 2022. New Delhi: Central TB Division, Ministry of Health and Family Welfare, Government of India, 2022.
18 Tripathy P, Nair N, Barnett S, et al. Effect of a participatory intervention with women's groups on birth outcomes and maternal depression in Jharkhand and Orissa, India: a cluster-randomised controlled trial. *Lancet* 2010; 375: 1182–92.
19 Revised National TB Control Programme. Technical and operational guidelines for tuberculosis control in India. New Delhi: Central TB Division, Ministry of Health and Family Welfare, Government of India, 2016.
20 Padmapriyadarsini C, Shobana M, Lakshmi M, Beena T, Swaminathan S. Undernutrition & tuberculosis in India: situation analysis & the way forward. *Indian J Med Res* 2016; 144: 11–20.
21 INDEX TB guidelines. Guidelines on extrapulmonary tuberculosis for India. New Delhi: Ministry of Health and Family Welfare, Government of India, 2016.
22 Scrimshaw NS, SanGiovanni JP. Synergism of nutrition, infection, and immunity: an overview. *Am J Clin Nutr* 1997; 66: 464S–77S.
23 Bhargava A, Bhargava M, Meher A, et al. Nutritional support for adult patients with microbiologically confirmed pulmonary tuberculosis: outcomes in a programmatic cohort nested within the RATIONS trial in Jharkhand, India. *Lancet Glob Health* 2023. In Press.
24 Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. *Eur Respir J* 2013; 41: 140–56.
25 Trauer JM, Moyo N, Tay EL, et al. Risk of active tuberculosis in the five years following infection . . . 15%? *Chest* 2016; 149: 516–25.
26 Bhargava A, Pai M, Bhargava M, Marais BJ, Menzies D. Can social interventions prevent tuberculosis?: the Papworth experiment (1918–1943) revisited. *Am J Respir Crit Care Med* 2012; 186: 442–49.
27 Teerenstra S, Lu B, Preisser JS, van Achterberg T, Borm GF. Sample size considerations for GEE analyses of three-level cluster randomized trials. *Biometrics* 2010; 66: 1230–37.
28 Fox GJ, Nhung NV, Sy DN, Britton WJ, Marks GB. Household contact investigation for tuberculosis in Vietnam: study protocol for a cluster randomized controlled trial. *Trials* 2013; 14: 342.
29 WHO. WHO child growth standards : growth velocity based on weight, length and head circumference : methods and development. Geneva: World Health Organization, 2009.

30 de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ* 2007; **85**: 660–67.

31 Paradkar M, Padmapriyadarsini C, Jain D, et al. Tuberculosis preventive treatment should be considered for all household contacts of pulmonary tuberculosis patients in India. *PLoS One* 2020; **15**: e0236743.

32 Oxlade O, Huang CC, Murray M. Estimating the impact of reducing under-nutrition on the tuberculosis epidemic in the central eastern states of India: a dynamic modeling study. *PLoS One* 2015; **10**: e0128187.

33 Food and Agriculture Organization of the United Nations. State of food security and nutrition in the world 2022: repurposing food and agricultural policies to make healthy diets more affordable. 2022. https://www.fao.org/documents/card/en/c/cc0639en (accessed April 15, 2023).

34 WHO. WHO operational handbook on tuberculosis: module 1: prevention: tuberculosis preventive treatment. Geneva: World Health Organization, 2020.

35 Fox GJ, Dobler CC, Marais BJ, Denholm JT. Preventive therapy for latent tuberculosis infection-the promise and the challenges. *Int J Infect Dis* 2017; **56**: 68–76.

36 Zenner D, Beer N, Harris RJ, Lipman MC, Stagg HR, van der Werf MJ. Treatment of latent tuberculosis infection: an updated network meta-analysis. *Ann Intern Med* 2017; **167**: 248–55.

37 Tait DR, Hatherill M, Van Der Meeren O, et al. Final analysis of a trial of M72/AS01$_E$ vaccine to prevent tuberculosis. *N Engl J Med* 2019; **381**: 2429–39.

38 WHO. WHO preferred product characteristics for new tuberculosis vaccines. Geneva: World Health Organization, 2018.

Nutritional support for adult patients with microbiologically confirmed pulmonary tuberculosis: outcomes in a programmatic cohort nested within the RATIONS trial in Jharkhand, India

Anurag Bhargava, Madhavi Bhargava, Ajay Meher, G Sai Teja, Banurekha Velayutham, Basilea Watson, Andrea Benedetti, Ganesh Barik, Vivek Pratap Singh, Dhananjay Singh, Adarsh Kibballi Madhukeshwar, Ranjit Prasad, Rajeev Ranjan Pathak, Vineet Chadha, Rajendra Joshi

Summary

Background Undernutrition is a common comorbidity of tuberculosis in countries with a high tuberculosis burden, such as India. RATIONS is a field-based, cluster-randomised controlled trial evaluating the effect of providing nutritional support to household contacts of adult patients with microbiologically confirmed pulmonary tuberculosis in Jharkhand, India, on tuberculosis incidence. The patient cohort in both groups of the trial was provided with nutritional support. In this study, we assessed the effects of nutritional support on tuberculosis mortality, treatment success, and other outcomes in the RATIONS patient cohort.

Methods We enrolled patients (aged 18 years or older) with microbiologically confirmed pulmonary tuberculosis across 28 tuberculosis units. Patients received nutritional support in the form of food rations (1200 kcal and 52 g of protein per day) and micronutrient pills. Nutritional support was for 6 months for drug-susceptible tuberculosis and 12 months for multidrug-resistant tuberculosis; patients with drug-susceptible tuberculosis could receive an extension of up to 6 months if their BMI was less than 18·5 kg/m² at the end of treatment. We recorded BMI, diabetes status, and modified Eastern Cooperative Oncology Group (ECOG) performance status at baseline. Clinical outcomes (treatment success, tuberculosis mortality, loss to follow-up, and change in performance status) and weight gain were recorded at 6 months. We assessed the predictors of tuberculosis mortality with Poisson and Cox regression using adjusted incidence rate ratios (IRRs) and adjusted hazard ratios (HRs). The RATIONS trial is registered with the Clinical Trials Registry of India (CTRI/2019/08/020490).

Findings Between Aug 16, 2019, and Jan 31, 2021, 2800 patients (mean age 41·5 years [SD 14·5]; 1979 [70·7%] men and 821 [29·3%] women) were enrolled. At enrolment, 2291 (82·4%) patients were underweight (BMI <18·5 kg/m²), and 480 (17·3%) had a BMI of less than 14 kg/m². The mean weight and BMI were 42·6 kg (SD 7·8) and 16·4 kg/m² (2·6) in men and 36·1 kg (7·3) and 16·2 kg/m² (2·9) in women. During the 6-month follow-up, treatment was successful in 2623 (93·7%) patients, 108 (3·9%) tuberculosis deaths occurred, 28 (1·0%) patients were lost to follow-up, and treatment failure was experienced by five (0·2%) patients. The median weight gain was 4·6 kg (IQR 2·8–6·8), but 1441 (54·8%) of 2630 patients remained underweight. At 2 months, 1444 (54·0%) of 2676 patients gained at least 5% of baseline weight. Baseline weight (adjusted IRR 0·95, 95% CI 0·90–0·99), BMI (0·88, 0·76–1·01), poor performance status (ECOG categories 3–4; 5·33, 2·90–9·79), diabetes (3·30, 1·65–6·72), and haemoglobin (0·85, 0·71–1·00) were predictors of tuberculosis mortality. A reduced hazard of death (adjusted HR 0·39, 95% CI 0·18–0·86) was associated with a 5% weight gain at 2 months.

Interpretation In this study, nutritional support was provided to a cohort with a high prevalence of severe undernutrition. Weight gain, particularly in the first 2 months, was associated with a substantially decreased hazard of tuberculosis mortality. Nutritional support needs to be an integral component of patient-centred care to improve treatment outcomes in such settings.

Funding India Tuberculosis Research Consortium, Indian Council of Medical Research.

Lancet Glob Health 2023

Published Online August 8, 2023 https://doi.org/10.1016/S2214-109X(23)00324-8

Department of Medicine (Prof A Bhargava MD), Department of Community Medicine (M Bhargava MD), and Department of Radiology (Adarsh KM MD), Yenepoya Medical College, Mangalore, India; Center for Nutrition Studies, Yenepoya (Deemed to be University), Mangalore, India (Prof A Bhargava, M Bhargava, G S Teja MPhil, A Benedetti PhD); Department of Medicine (Prof A Bhargava, A Benedetti) and Department of Epidemiology, Biostatistics and Occupational Health (A Benedetti), McGill University, Montreal, QC, Canada; Indian Council of Medical Research–National Institute for Research in Tuberculosis, Chennai, India (A Meher MPH, B Velayutham MPH, B Watson MSc, G Barik PGDCA, V P Singh MPH, D Singh MPH); State TB Cell, National Tuberculosis Elimination Programme, Ranchi, India (R Prasad MD); WHO Technical Support Network, Ranchi, India (R R Pathak MPH); National Tuberculosis Institute, Bangalore, India (V Chadha MD); National Tuberculosis Elimination Programme, Ministry of Health and Family Welfare, New Delhi, India (R Joshi DNB)

Correspondence to: Prof Anurag Bhargava, Department of Medicine, Yenepoya Medical College, Center for Nutrition Studies, Yenepoya (Deemed to be University), Mangalore 575018, India
anuragb17@gmail.com

Introduction

Tuberculosis is a global public health problem. India had an estimated 3 million cases of tuberculosis and 494 000 tuberculosis deaths among HIV-negative people in 2021.[1] The National Strategic Plan for Tuberculosis Elimination in India has targets of an 80% reduction in

Research in context

Evidence before this study

Undernutrition in patients with active tuberculosis is a risk factor for tuberculosis mortality, drug toxicity, and relapse. We searched for evidence of nutritional support (macronutrients, micronutrients, or both) on treatment outcomes in MEDLINE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews on Nov 15, 2022, using the terms "macronutrients", "micronutrients", "food supplement", "diet supplement", "nutrition support", "nutritional supplementation", and "tuberculosis". Search strings were developed using "OR" and "AND" Boolean operators. We searched for observational studies, clinical trials, and key review articles published between Jan 1, 1950, and Aug 1, 2019, in English. We also retrieved additional studies from the bibliography of articles, and identified 35 relevant publications. A Cochrane review on the effect of macronutrient supplementation on tuberculosis outcomes was inconclusive because randomised controlled trials of macronutrient supplementation were few, small, and unable to achieve an optimal intake of calories and proteins. A relative risk of tuberculosis mortality of 0·34 (95% CI 0·10–1·20) was seen in four randomised controlled trials with 567 participants, indicating a possibly effective intervention. The generation of evidence based on randomised controlled trials is ethically problematic in settings such as India, where severe undernutrition and food insecurity are widely prevalent in patients with tuberculosis.

Added value of this study

To our knowledge, this is the largest single programmatic cohort of predominantly HIV-negative patients with drug-susceptible tuberculosis who underwent comprehensive evaluation of clinical, nutritional, and performance status at enrolment and in whom the effect of a food rations-based nutritional intervention on clinical and nutritional outcomes was documented. The study shows high levels of severe and extremely severe undernutrition in patients at diagnosis, which is a contributor to tuberculosis mortality that is currently unaddressed in most national tuberculosis programmes. Most deaths occurred in the first 2 months, 80% occurred at home, and performance status, nutritional status, haemoglobin, and diabetes were identified to be predictors of death. The effect of nutritional support on tuberculosis mortality in this cohort can be inferred from the survival, with nutritional support, of more than 85% of patients with potentially fatal undernutrition (BMI <13 kg/m^2 in men and <11 kg/m^2 in women), and the 61% reduced hazard of death in those with desirable (5%) weight gain in 2 months. The case fatality ratio was considerably lower than in another National Tuberculosis Elimination Programme cohort with a similar patient population that had no nutritional support. The nutritional intervention was well accepted and was associated with high rates of adherence to treatment and low rates of treatment failure. However, nutritional recovery was incomplete at 6 months in patients with severe undernutrition at enrolment.

Implications of all the available evidence

Nutritional assessment, counselling, and support need to be implemented in settings with a high burden of tuberculosis and undernutrition, such as India, to improve tuberculosis treatment outcomes. Food-based nutritional support during treatment is associated with weight gain, improved performance status, and a decreased hazard of tuberculosis mortality. However, nutritional recovery in patients with severe undernutrition might require graded support for a longer period.

incidence and a 90% reduction in tuberculosis mortality by 2025, compared with the baseline estimates for 2015.[2] The modest progress in reducing tuberculosis mortality since 2015 was reversed during the COVID-19 pandemic.[3]

Preventing tuberculosis mortality requires early diagnosis, provision of high-quality care with comprehensive evaluation, and management of comorbidities.[4] In countries with a high tuberculosis burden such as India, undernutrition is a common comorbidity due to disease-related weight loss acting on a substrate of pre-existing chronic undernutrition. In patients with tuberculosis, undernutrition is often severe, potentially lethal, and, in the absence of nutritional support, persists even after treatment.[5,6] Undernutrition is a consistent risk factor for mortality, drug toxicity, delayed sputum conversion, and recurrence.[5,7,8]

WHO recommends nutritional assessment, counselling, and support as integral components of tuberculosis care.[9,10] These recommendations await adoption in most national programmes.[11] Although modelling studies indicate that addressing undernutrition could reduce tuberculosis mortality,[12] the impact of macronutrient and micronutrient supplementation on treatment outcomes in clinical trials has been inconclusive due to small numbers of participants, heterogeneity, and not reaching optimal intake of calories and proteins.[13] However, a possible reduction in tuberculosis mortality in HIV-negative patients has been noted in small randomised controlled trials of nutritional support.[13]

Reducing Activation of Tuberculosis Through Improvement of Nutritional Status (RATIONS) is an open-label, parallel-arm, cluster-randomised controlled trial involving household contacts of adult patients with microbiologically confirmed pulmonary tuberculosis in Jharkhand state in eastern India.[14] The primary objective of the trial was to estimate the effect of nutritional support in reducing tuberculosis incidence among household contacts of patients in a setting with high prevalence of undernutrition. In this report, we describe

tuberculosis mortality, treatment success, and changes in nutritional and performance status in the patient cohort receiving nutritional support within the RATIONS trial, over the intervention period of 6 months.[14]

Methods

Study design

The RATIONS trial design, detailed methods, recruitment, intervention, follow-up, and outcomes have been described previously.[14] The trial population in this cluster-randomised controlled trial consisted of the household contacts of 2800 patients with microbiologically confirmed pulmonary tuberculosis drawn from 28 tuberculosis units (trial clusters) across four districts of Jharkhand. The 28 clusters were randomly assigned in a 1:1 ratio to receive the intervention of nutritional support (food baskets and micronutrients) for household contacts or no nutritional support for household contacts. The primary outcome in this population was the difference in tuberculosis incidence among household contacts of the two groups over a follow-up period of 2 years from the treatment of the index patient with microbiologically confirmed pulmonary tuberculosis. The trial found a 39% reduction in the incidence of tuberculosis (for all forms of tuberculosis), and a 48% reduction in incidence of microbiologically confirmed pulmonary tuberculosis in household contacts in the intervention group compared with the control group.[14]

All 2800 patients with microbiologically confirmed pulmonary tuberculosis were provided with nutritional support (food baskets and micronutrients) for the treatment period, regardless of their baseline nutritional status or assignment group. They were followed up for the treatment period for the secondary treatment outcomes of tuberculosis mortality (all-cause mortality during the treatment period), treatment success, changes in nutritional and performance status, and occurrence of severe adverse effects (appendix p 2).

The RATIONS trial was embedded within the National Tuberculosis Elimination Programme (NTEP) in four districts of Jharkhand: Saraikela-Kharsawan, West Singhbhum, East Singhbhum, and Ranchi (appendix pp 2–3). Jharkhand (meaning land of trees) has substantial forest cover and a population of 33 million; the population is predominantly rural (75%) and almost a quarter is indigenous, known as scheduled tribes. The state has one of the highest proportions (46%) of population living in multidimensional poverty in India.[15] The prevalence of underweight is 26·2% in women (aged 15–49 years) and 39·4% in children younger than 5 years, compared with the national average of 18·7%.[16] In 2021, the tuberculosis case notification rate was 130 per 100 000 population,[17] and the prevalence of microbiologically confirmed pulmonary tuberculosis was 352 per 100 000 population compared with 316 per 100 000 population for India overall.[18]

Participants

Patients and their household contacts from 28 tuberculosis units of the NTEP were enrolled between Aug 16, 2019, and Jan 31, 2021. The trial ended on Aug 13, 2022. A district is an administrative unit, and a tuberculosis unit is a programme management unit at the subdistrict level that covers 0·15–0·25 million population. All patients aged 18 years or older with microbiologically confirmed pulmonary tuberculosis and initiated on treatment within the previous 2 weeks were considered eligible for inclusion, regardless of their HIV or drug susceptibility status, if they had at least one eligible household contact.[14] An eligible household contact was a person living in the same house as the index patient, and eating from the same kitchen for at least one night or for frequent or extended periods during the day during the 3 months before diagnosis of the index patient; household contacts were ineligible if they were currently on treatment for microbiologically confirmed or clinically diagnosed active tuberculosis (appendix p 4).[14,19]

Ethics approval was obtained from the Institutional Ethics Committee of the Indian Council of Medical Research–National Institute for Research in Tuberculosis (number 2018020). Local oversight was provided by the ethics committee of Ekjut, a non-profit organisation involved in field-based research. Field staff obtained written informed consent from participants.

Procedures

Patients were diagnosed by the NTEP and received antituberculosis treatment and supervision as per the guidelines.[19] Patients in both groups received an identical monthly food basket supplying 1200 kcal and 52 g protein per day, and a micronutrient pill containing the recommended dietary allowance based on national recommendations (appendix pp 4, 6),[20] which cost US$0·49 per day, inclusive of delivery costs. The food rations were delivered at home by the field staff for 6 months for drug-susceptible tuberculosis and 12 months for multidrug-resistant tuberculosis. Delivery was challenging due to the difficult terrain and poor connectivity, and was further complicated by restrictions related to the COVID-19 pandemic. The food rations for an individual patient in the cohort with drug-susceptible tuberculosis were extended by up to 6 months if the BMI was less than 18·5 kg/m² at the end of treatment. All patients received INR 500 per month ($6·1 per month) under the direct benefit transfer scheme of NTEP during treatment.[21]

See Online for appendix

Demographic characteristics, household assets (appendix p 4), and risk factors were assessed at baseline, along with anthropometry, blood pressure, pulse oximetry for oxygen saturation (SpO_2), performance status using a modified Eastern Cooperative Oncology Group (ECOG) scale, and oedema assessed by pressure over shins.[22] The ECOG scale is categorised from 0 to 4, with a score of

0 representing no restriction of physical activity and 4 representing complete confinement to a bed or chair (appendix p 5). Haemoglobin was estimated with use of the Hemocue Hb 201+ system (HemoCue, Ängelholm, Sweden) and severe anaemia was defined as haemoglobin less than 80 g/L. Nutritional status was defined according to BMI as per WHO guidelines, with a BMI of less than 16 kg/m² classified as severe underweight and an additional category of BMI less than 14 kg/m² classified as extremely severe underweight (appendix p 5).[23] HIV status and random blood sugar were retrieved from NTEP data. Participants with random blood sugar greater than 11·1 mmol/L, those with self-reported diabetes, and those on diabetes medication were categorised as having diabetes. Hypoxia was defined as SpO_2 of less than 94% and hypotension was defined as systolic blood pressure of less than 90 mm Hg.

At monthly follow-ups for 6 months, we monitored symptoms, treatment adherence, consumption of food rations, adverse drug reactions, anthropometry, and ECOG performance status. We referred patients with critical values of BMI, blood pressure, oxygen saturation, and ECOG performance status, and those with adverse drug reactions to the nearest public health facility (appendix p 6).[20] Mortality and adverse drug reactions were reported to the field staff during follow-up visits or by telephone. Data collection was done using REDCap (version 12.2.7), hosted by the National Institute of Research in Tuberculosis (Chennai, India).

	Overall (n=2800)	Underweight (BMI <18·5 kg/m²; n=2291)*	Not underweight (BMI ≥18·5 kg/m²; n=489)*
Sex			
Male	1979 (70·7%)	1603 (70·0%)	362 (74·0%)
Female	821 (29·3%)	688 (30·0%)	127 (26·0%)
Age, years, mean (SD)	40·3 (14·5)	40·1 (14·6)	40·4 (13·6)
Men	41·5 (14·3)	41·3 (14·5)	41·7 (13·6)
Women	37·3 (14·5)	37·2 (14·5)	36·5 (13·2)
Caste			
Scheduled tribe	1896 (67·7%)	1613 (70·4%)	270 (55·2%)
Scheduled caste	258 (9·2%)	200 (8·7%)	57 (11·7%)
Other backward classes	551 (19·7%)	424 (18·5%)	121 (24·7%)
Other	95 (3·4%)	54 (2·4%)	41 (8·4%)
Education			
None	1109 (39·6%)	968 (42·3%)	127 (26·0%)
<10 years	1064 (38·0%)	873 (38·1%)	186 (38·0%)
≥10 years	627 (22·4%)	450 (19·6%)	176 (36·0%)
PDS beneficiary†	2356 (84·1%)	1962 (85·6%)	376 (76·9%)
History of alcohol use	1405 (50·2%)	1123 (49·0%)	207 (54·6%)
History of tobacco use	1021 (36·5%)	841 (36·7%)	169 (34·6%)
History of previous tuberculosis	262 (9·4%)	206 (9·0%)	55 (11·3%)
History of previous tuberculosis in family member	395 (14·1%)	312 (13·6%)	83 (17·0%)
Diabetes	139 (5·0%)	80 (3·5%)	57 (11·6%)
HIV infection‡	6/2264 (0·3%)	6/2264 (0·3%)	0/489
Multidrug-resistant tuberculosis at diagnosis§	38/1258 (3·0%)	30/985 (3·0%)	8/264 (3·0%)

Data are n (%) or n/N (%), unless specified otherwise. PDS=public distribution system. *Patient numbers in the columns related to nutritional status might not add up to the overall prevalence of the characteristic because of missing BMI values in 20 patients. †The PDS provides subsidised rations to Indians living below the poverty line. ‡HIV testing was done in 2264 patients. §Multidrug-resistant tuberculosis was diagnosed based on cartridge-based nucleic acid amplification test; 1258 tests were done.

Table 1: Demographic characteristics and comorbidities in patients with microbiologically confirmed pulmonary tuberculosis in the RATIONS trial

Outcomes

The following outcomes of treatment documented by the NTEP were noted: cure or treatment completion (treatment success), deaths during treatment, loss to follow-up, and treatment failure. In addition, minor adverse effects during treatment were noted by field staff. The diagnosis of adverse effects such as drug-induced hepatitis was based on evaluation by physicians in health facilities. We defined treatment outcomes as per NTEP definitions (appendix pp 4–5).[19] Loss to follow-up during the treatment period was defined as patients who interrupted treatment for 1 month or longer. Loss to follow-up for the purpose of trial intervention was considered non-availability for follow-up for 2 months or longer during the treatment period (appendix p 5).[19] Tuberculosis mortality was defined as all-cause mortality in HIV-negative patients during treatment.[3] The case fatality ratio was defined as the number of patients with tuberculosis mortality divided by the number of patients forming the cohort at the beginning of the observed period.[24] The diagnosis of tuberculosis involved smear microscopy (graded as scanty, 1+, 2+, or 3+) and cartridge-based nucleic acid amplification tests (GeneXpert [Cepheid, Sunnyvale, CA, USA] or Truenat [Molbio Diagnostics/Bigtec Labs, Goa/Bengaluru, India]) and the end of treatment evaluation was by smear microscopy as per NTEP guidelines.[19]

Statistical analysis

Continuous variables were summarised as mean (SD) or median (IQR). Differences between groups were assessed using Student's *t* test or Mann-Whitney *U* test, as appropriate. The association between categorical variables was assessed using the χ^2 test or Fisher's exact test. We estimated the 6-month tuberculosis mortality rate and case fatality ratio with 95% CIs and compared these outcomes via adjusted incidence rate ratios (IRRs) among key subgroups (sex, bodyweight, BMI category, and ECOG performance status). Baseline ECOG performance status was dichotomised as poor (score of 3–4) or better (score of 0–2). All of the aforementioned analyses used a marginal Poisson regression model with independence correlation structure, and the results are presented based on the empirical standard errors to account for clustering by tuberculosis unit and using the log of person-time at risk as the offset. The model was adjusted for potential confounders that are known to be associated with the exposure of undernutrition and are independent

predictors of outcomes such as tuberculosis mortality: age, sex, caste, family history of tuberculosis, alcohol use, tobacco use, diabetes, cough duration, sputum smear grade, ECOG category, haemoglobin, and log of value of household assets as a measure of standard of living. We included interactions between baseline bodyweight, and age, sex, and ECOG score in the regression model and used the p value for the regression coefficient to test the interaction. Participants were censored at 180 days. We estimated the change in weight and BMI (absolute and relative), stratified by sex. With use of a Cox proportional hazards model, we compared time to death (via adjusted hazard ratios [HRs]) over 6 months in participants who gained and did not gain weight over the first 2 months. In this analysis, we considered weight gain as a time-dependent covariate, which started at zero for all patients and changed to one if there was desirable (≥5%) weight gain at 2 months.[27] Missing values were imputed via chained equations,[28] using the missingness-at-random assumption. In sensitivity analyses, we also considered a complete case analysis. We assessed the proportional hazards assumption and used a stratified model in the case of violations. Kaplan-Meier survival curves, stratified by ECOG status and bodyweight category at enrolment, were estimated. The analyses were done with STATA (version 17.0) and R (version 4.1.2).

The RATIONS trial is registered with the Clinical Trials Registry of India (CTRI/2019/08/020490).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The patient cohort (n=2800) was recruited between Aug 16, 2019, and Jan 31, 2021 (appendix p 7). At enrolment, the mean age was 41·5 years (SD 14·5) in men and 37·3 years (14·5) in women (table 1). Most individuals belonged to indigenous communities (scheduled tribes), were engaged in manual labour (appendix p 6), and were beneficiaries of subsidised food rations from the public distribution system; almost 40% had no schooling. HIV–tuberculosis co-infection was found in six (0·3%) of 2264 tested participants, and 139 (5·0%) of 2800 participants had diabetes.

The mean bodyweight at enrolment was 42·6 kg (SD 7·8) in men and 36·1 kg (7·3) in women, and mean BMI was 16·4 kg/m² (2·6) and 16·2 kg/m² (2·9), respectively (table 2). More than 80% of participants were underweight, almost half were severely underweight, and 17% had a BMI of less than 14 kg/m². Almost a quarter of participants had a bodyweight of less than 35 kg, and the cohort included 143 men with a BMI of less than 13 kg/m² and ten women with a BMI of less than 11 kg/m². The lowest recorded bodyweight and BMI were 22·0 kg and 8·3 kg/m² in men, and 18·8 kg and 8·6 kg/m² in women.

Only 29 (1·0%) of 2780 patients were overweight or obese

	Patients with available data, n	Characteristic
Bodyweight, kg	2785	..
Men	1968	42·58 (7·76)
Women	817	36·08 (7·25)
Bodyweight category, kg	2785	..
18·0–24·9	..	27 (1·0%)
25·0–29·9	..	172 (6·2%)
30·0–39·9	..	1211 (43·5%)
40·0–54·9	..	1233 (44·3%)
55·0–70·0	..	129 (4·6%)
>70·0	..	13 (0·5%)
Height, cm	2780	..
Men	1965	160·78 (6·38)
Women	815	149·36 (6·00)
Stunting*	2780	..
Men	1965	1067 (54·3%)
Women	815	431 (53·9%)
BMI, kg/m²	2780	..
Men	1965	16·44 (2·59)
Women	815	16·15 (2·90)
BMI category, kg/m²	2780	..
≥25·0 (overweight or obese)	..	29 (1·0%)
18·5–24·9 (normal)	..	460 (16·5%)
<18·5 (underweight)	..	2291 (82·4%)
17·0–18·4 (mild underweight)	..	485 (17·4%)
16·0–16·9 (moderate underweight)	..	455 (16·4%)
14·0–15·9 (severe underweight)	..	871 (31·3%)
<14·0 (extremely severe underweight)	..	480 (17·3%)
Haemoglobin, g/L	2734	104·5 (18·9)
Anaemia†	2734	2411 (88·2%)
Haemoglobin <80 g/L	2734	204 (7·5%)
Sputum smear examination as basis of diagnosis‡	..	2025
Grade scanty to 1+	2025	910 (44·9%)
Grade 2+ to 3+	2025	1115 (55·1%)
CB-NAAT as basis of diagnosis‡	..	775
Modified ECOG performance status	2800	..
0 (able to carry out normal activity)	..	79 (2·8%)
1 (ambulatory but not able to do strenuous activity)	..	1202 (42·9%)
2 (can do self-care, cannot work, up and about <50% of waking hours)	..	1194 (42·6%)
3 (self-care only, confined to bed or chair >50% of waking hours)	..	271 (9·7%)
4 (no ability to carry out self-care, confined to bed or chair)	..	54 (1·9%)
Systolic blood pressure, mm Hg	2753	110·2 (16·7)
Diastolic blood pressure, mm Hg	2753	77·9 (11·9)
Hypotension (systolic blood pressure <90 mm Hg)	2753	286 (10·4%)
Hypoxia (SpO_2 <94%)	2797	249 (8·9%)
Oedema	2800	130 (4·6%)

Data are mean (SD) or n (%). Percentages might not add to 100% due to rounding. Some patients could not be assessed for height or weight due to a disability or an inability to stand. CB-NAAT=cartridge-based nucleic acid amplification test. ECOG=Eastern Cooperative Oncology Group. SpO_2=oxygen saturation. *Stunting in men and women was assumed if the height measured was more than 2 SD below the WHO standards for boys and girls aged 18 years. †Anaemia was defined as haemoglobin <13 g/dL in men and <12 g/dL in women. ‡Some patients underwent both sputum smear examination and CB-NAAT.

Table 2: Anthropometric and clinical characteristics of patients in the RATIONS trial at enrolment

(BMI ≥25 kg/m²). Diagnosis was based on smear microscopy in 2025 patients and on cartridge-based nucleic acid amplification tests in 775 patients. Severe anaemia was noted in 204 (7·5%) of 2734 patients screened, 325 (11·6%) of 2800 had poor performance status, 286 (10·4%) of 2753 had hypotension (systolic blood pressure <90 mm Hg), and 249 (8·9%) of 2797 had hypoxia. Weight data were missing for 15 patients and height data were missing for 20 patients due to difficulty standing or disabilities rendering height measurements inaccurate (appendix p 4); all of these patients had mid-upper arm circumference measurements, with a mean of 16·3 cm (SD 2·2). The total follow-up time was 1337·32 person-years. Treatment was successful (cure or treatment completed) for 2623 (93·7%) of 2800 patients. Of these, 1382 (49·4%) were smear-negative at 6 months (cured) and 1241 (44·3%) completed treatment with clinical improvement without smear examination. At 6 months, 28 (1·0%) patients were lost to follow-up, which was mostly due to relocation during the COVID-19 pandemic; 13 of the 28 patients withdrew from the study, mostly due to migration or personal reasons. Five (0·2%) patients had treatment failure and 36 (1·3%) of 38 patients with multidrug-resistant tuberculosis continued their treatment (two were lost to follow-up).

The most common adverse drug reactions were joint pains in 1259 (45·0%) participants, further loss of appetite in 589 (21·0%), itching in 520 (18·6%), abdominal pain in 485 (17·3%), tingling sensation in limbs in 343 (12·3%), and vomiting and nausea in 311 (11·1%; appendix p 11). Eight (0·3%) patients developed drug-induced hepatitis. None of the adverse drug reactions led to loss to follow-up.

108 deaths occurred during follow-up, including 81 (75%) in men and 27 (25%) in women. No deaths occurred in patients with multidrug-resistant tuberculosis or HIV–tuberculosis co-infection. One death at 187 days in a patient who interrupted and then resumed therapy was omitted in the survival analysis that was censored at 180 days. The overall incidence of tuberculosis mortality was 8·00 per 100 person-years (95% CI 6·41–9·99); the incidence was 8·49 per 100 person-years (6·65–10·83) in men and 6·84 per 100 person-years (4·70–9·95) in women. The overall case fatality ratio was 3·9% (95% CI 3·2–4·6).

The median time to death was 46 days (IQR 18–96) and 58 (54%) deaths occurred in the first 2 months of treatment. Although most patients (83 [77%] of 108) died at home, 54 patients who died had a history of

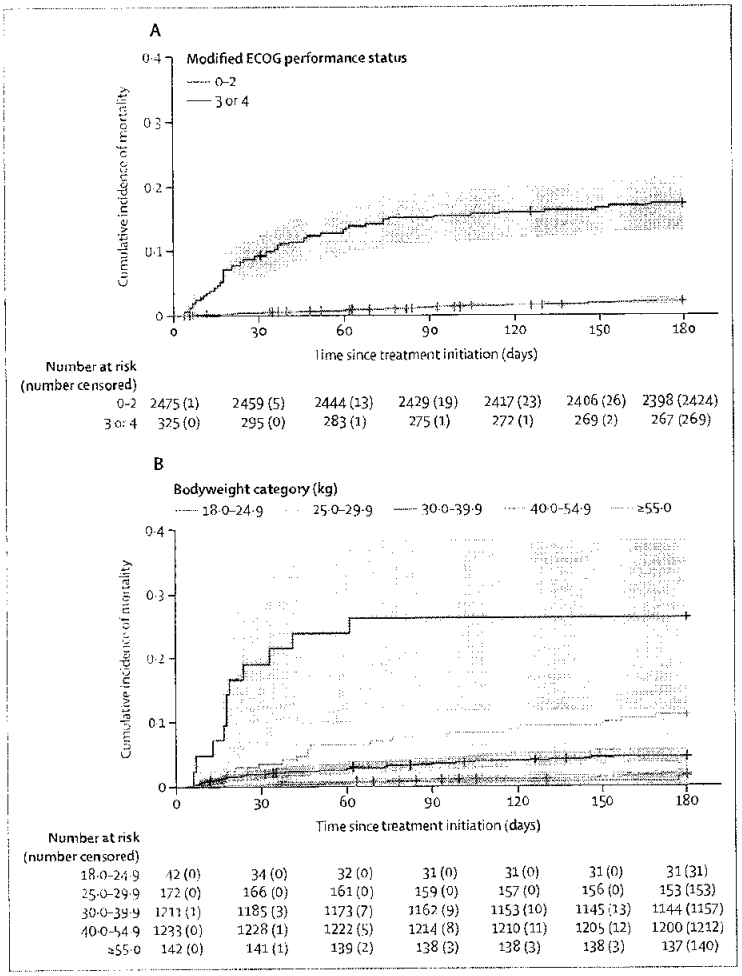

Figure: **Kaplan-Meier plots of cumulative incidence of tuberculosis mortality over 6 months of treatment according to performance status (A) or bodyweight category (B) at enrolment**
ECOG scores were dichotomised into better (score of 0–2) or poor (score of 3 or 4) performance status. The definitions of each ECOG category are described in the appendix (p 5). The number censored is the number of patients who were lost to follow-up or withdrew from the study during the 6-month treatment period. ECOG=Eastern Cooperative Oncology Group.

	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI)
Bodyweight (per kg increase)	0·91 (0·88–0·94)	0·95 (0·90–0·99)
BMI (per kg/m² increase)	0·73 (0·67–0·81)	0·88 (0·76–1·01)
Haemoglobin (per g/dL increase)	0·72 (0·61–0·84)	0·85 (0·71–1·00)
Male sex (vs female sex)	1·24 (0·83–1·86)	1·72 (0·89–3·35)
Age (per year increase)	1·03 (1·02–1·05)	1·01 (1·00–1·03)
Poor performance status (vs better performance status)*	9·50 (5·25–17·19)	5·33 (2·90–9·79)
Diabetes	3·22 (1·76–5·88)	3·30 (1·65–6·72)
Alcohol use	1·70 (1·11–2·61)	1·18 (0·64–2·17)
Tobacco use	0·62 (0·43–0·90)	0·69 (0·43–1·10)

IRRs were estimated using Poisson regression. The model was adjusted for sex, age, caste, bodyweight, log of value of household assets, trial group, ECOG category, diabetes status, cough duration, sputum smear grade, family history of tuberculosis, haemoglobin, alcohol use, and tobacco use. IRR=incidence rate ratio. ECOG=Eastern Cooperative Oncology Group. *Poor performance status was defined as modified ECOG categories 3 and 4, and better performance status was defined as categories 0–2 (appendix p 5).

Table 3: **IRRs of covariates for the event of tuberculosis death in the RATIONS trial**

hospitalisation. No deaths were attributable to COVID-19. In patients with bodyweight of less than 35 kg (n=680), the case fatality ratio was 7·2% (95% CI 5·4–9·4). The lowest weight and BMI at initiation of treatment in survivors were 24·2 kg and 10·7 kg/m² in men and 18·8 kg and 8·6 kg/m² in women, respectively. In men with a BMI of less than 13 kg/m², 123 (86%) of 143 survived, and in women with a BMI of less than 11 kg/m², nine (90%) of ten survived. The case fatality ratios for different categories of ECOG, baseline bodyweight, and BMI are presented in the appendix (p 9).

In univariable analysis, bodyweight, BMI, age, poor performance status, diabetes, alcohol use, haemoglobin, blood pressure, and oxygen saturation were associated with risk of death during treatment (appendix p 10). At enrolment, the bodyweight of patients who died was 5–6 kg lower, their BMI was 2 kg/m² lower, and their performance status was more frequently poor compared with those who survived. The survivors also had higher weight gain at 1 month and 2 months. Kaplan-Meier survival curves (figure) show that the survival in those with lower bodyweight categories or with poor performance status was lower than those in the higher bodyweight categories and with better performance status.

In the adjusted analysis using marginal Poisson regression, nutritional status, diabetes, and ECOG performance status at enrolment were associated with a higher incidence of tuberculosis mortality, when adjusted for important covariates (table 3). The presence of diabetes or a poor performance status was associated with a substantially increased incidence of tuberculosis death (IRR 3·30 [95% CI 1·65–6·72] for diabetes and 5·33 [2·90–9·79] for poor performance status). As a sensitivity analysis, we considered a complete case analysis, which makes a missing-at-random assumption, and the results were similar. The incidence of tuberculosis deaths with 1-kg or 5-kg higher baseline bodyweight was 5% and 23% lower, respectively, independent of other variables. For baseline BMI, the incidence of tuberculosis deaths decreased by 12% with a one-unit increase in BMI, or by 23% for a two-unit increase in BMI (table 3). The interaction of weight with age was statistically significant (p=0·037), suggesting that the protective effect of weight at baseline decreased for older patients. There was no significant interaction with sex or baseline ECOG score.

The overall median weight gain at 6 months was 4·6 kg (IQR 2·8–6·8), and weight gain was higher in men than in women (table 4). A median gain of two units of BMI was recorded in both sexes. At

	All participants	Men	Women	p value
Bodyweight				
Available data, n	2626	1850	776	..
Baseline bodyweight, kg	40·9 (8·1)	42·8 (7·7)	36·2 (7·2)	<0·0001*
Bodyweight at 6 months, kg	45·8 (8·1)	47·9 (7·5)	40·7 (7·0)	<0·0001*
Weight gain in 6 months, kg	4·6 (2·8–6·8)	4·8 (2·9–7·0)	4·2 (2·5–6·2)	<0·0001†
Percentage weight gain over 6 months	11·3% (6·4–17·4)	11·2% (6·4–17·3)	11·6% (6·5–17·6)	0·42†
BMI, kg/m²				
Available data, n	2621	1847	774	..
Baseline BMI	16·4 (2·7)	16·5 (2·6)	16·2 (2·9)	0·0049*
BMI at 6 months	18·4 (2·6)	18·5 (2·5)	18·2 (2·8)	0·0042*
Change in BMI over 6 months	1·9 (1·1–2·7)	1·8 (1·1–2·7)	1·9 (1·1–2·7)	0·72†
Nutritional status at 6 months (BMI category, kg/m²)	..	..	..	0·003‡
Obese or overweight (≥25·0)	45/2630 (1·7%)	28/1853 (1·5%)	17/777 (2·2%)	..
Normal (18·5–24·9)	1144/2630 (43·5%)	845/1853 (45·6%)	299/777 (38·5%)	..
Underweight (<18·5)	1441/2630 (54·8%)	980/1853 (52·9%)	461/777 (59·3%)	..
Mild underweight (17·0–18·4)	670/2630 (25·5%)	473/1853 (25·5%)	197/777 (25·4%)	..
Moderate underweight (16·0–16·9)	361/2630 (13·7%)	247/1853 (13·3%)	114/777 (14·7%)	..
Severe underweight (14·0–15·9)	350/2630 (13·3%)	226/1853 (12·2%)	124/777 (16·0%)	..
Extremely severe underweight (<14·0)	60/2630 (2·3%)	34/1853 (1·8%)	26/777 (3·3%)	..
Modified ECOG performance status at 6 months§	..	..	..	0·17‡
0	2000/2651 (75·4%)	1430/1867 (76·6%)	570/784 (72·7%)	..
1	558/2651 (21·0%)	377/1867 (20·2%)	181/784 (23·1%)	..
2	74/2651 (2·8%)	47/1867 (2·5%)	27/784 (3·4%)	..
3	13/2651 (0·5%)	10/1867 (0·5%)	3/784 (0·4%)	..
4	6/2651 (0·2%)	3/1867 (0·2%)	3/784 (0·4%)	..

Data are mean (SD), median (IQR), or n/N (%), unless specified otherwise. Percentages might not add to 100% due to rounding. ECOG=Eastern Cooperative Oncology Group. *Calculated by Student's *t* test. †Calculated by Mann-Whitney *U* test. ‡Calculated by χ^2 test. §Modified ECOG categories are described in the appendix (p 5).

Table 4: Nutritional status and performance status at enrolment and after 6 months of nutritional support in patients in the RATIONS trial

	Adjusted hazard ratio (95% CI)
Bodyweight at enrolment (per increment of 1 kg)	0·92 (0·87–0·97)
Percentage weight gain at month 2 (per 1% increase from enrolment bodyweight)	0·87 (0·81–0·93)
Weight gain of ≥5% at month 2	0·39 (0·18–0·86)

Models were adjusted for sex, age, and haemoglobin, and were stratified by baseline modified ECOG category and diabetes. Results were similar when adjusting only for sex, age, and haemoglobin. The proportionality hazard assumption was tested; it was often violated by diabetes and modified ECOG category at baseline. In that case, Cox proportionality hazard models were stratified, which was sufficient to ensure that the proportionality hazard assumption held. Missing data were addressed with multiple imputation via chained equations; results of a sensitivity analysis using complete case analysis were similar. ECOG=Eastern Cooperative Oncology Group.

Table 5: **Results of multivariable Cox proportional hazards model examining weight as a time-dependent covariate up to the end of month 2 for the risk of tuberculosis mortality over a treatment period of 6 months**

2 months, the median change in weight was 2·2 kg (1·2–3·6) and in BMI was 0·89 kg/m² (0·49–1·46); 1444 (54·0%) of 2676 patients gained at least 5% of their baseline weight. In 206 (7·7%) of 2674 patients, BMI was unchanged or reduced at 2 months. At 6 months, the proportion of those with normal BMI increased from 16·5% to 43·5%, but 1441 (54·8% remained underweight; this included more than half of men and almost 60% of women. Of the 48·6% of patients who were severely underweight at baseline, 15·6% continued to be so at the end of treatment. In terms of ECOG performance status, the proportion of patients in category 0 (able to carry out normal activity) increased from 2·8% at baseline to 75·4% at the end of treatment (table 3, appendix p 8).

Absolute and relative weight gain in the initial 2 months was associated with a reduced risk of tuberculosis mortality in Cox regression analysis. The adjusted HR of baseline weight was 0·92 (95% CI 0·87–0·97) per 1-kg increment, with adjustment for male sex, age, baseline ECOG category, diabetes, and haemoglobin (table 5). The adjusted HR of bodyweight at 2 months for death during treatment was 0·68 (0·56–0·82) per 1-kg increment. The adjusted HR of percentage weight gain at 2 months for death was 0·87 (0·81–0·93) per 1% increase. We considered a 5% weight gain by 2 months to be desirable;[22] in Cox proportional hazards analysis, a desirable weight gain reduced the hazard (instantaneous risk) of death compared with those who gained less weight (adjusted HR 0·39 [0·18–0·86]; table 5). The results of Cox regression using complete case analysis and multiple imputation using a missing-at-random assumption were almost identical (data not shown).

Discussion

In our cohort of 2800 patients with microbiologically confirmed pulmonary tuberculosis, we observed a high prevalence of undernutrition. Severe undernutrition was seen in almost half of patients, and BMIs that were low enough to pose an immediate threat to life in the absence of nutritional intervention (<13 kg/m² in men and <11 kg/m² in women)[27] were seen in 153 (5·5%) patients at baseline. Most deaths occurred in the intensive phase of treatment, with an overall case fatality ratio of 3·9%. At diagnosis, several indicators that can be easily assessed, such as bodyweight, BMI, haemoglobin, diabetes, and ECOG performance status, were predictors of tuberculosis mortality. Previous cohort studies have reported an association between these predictors and tuberculosis mortality.[5,28–30] Weight gain during treatment, especially at 2 months, was associated with reduced mortality, with the instantaneous risk of death over the treatment period reducing by 13% for a 1% weight gain and by 61% for a 5% weight gain at 2 months.

The nutritional support delivered to patients in the form of food rations and micronutrient pills as an adjunct to antituberculosis treatment was feasible, cost less than $0·5 per day, and was associated with high rates of treatment success, lower loss to follow-up and treatment failure, more than 10% weight gain, and a marked improvement in performance status. These are an improvement over the outcomes reported by the NTEP. In 2022, the NTEP reported the following outcomes for patients notified in the public sector in 2020: treatment success of 83%, tuberculosis mortality of 4·4%, loss to follow-up of 2·5%, treatment failure of 0·6%, regimen changes of 1·8%, and outcomes not evaluated of 1·9%.[17] The national case fatality ratio appears similar to that seen in our study, but states with better health infrastructure, such as Kerala, had higher case fatality ratios (7·9%) than Jharkhand (2·9%).[17] A cohort from NTEP during the COVID-19 pandemic, reported in 2022, had a case fatality ratio of 6·5% in the first 2 months, which was much higher than in our cohorts.[31]

Our study did not randomly assign patients to a control group without nutritional support for ethical reasons. Nevertheless, our results show a predictive effect for undernutrition at enrolment, and a protective effect of weight gain for tuberculosis mortality. Outcomes from two previous large multicentre cohort studies in patients with pulmonary tuberculosis that did not provide nutritional support are relevant because they had similar inclusion criteria, and a low prevalence of HIV and multidrug-resistant tuberculosis. One of these studies was conducted in southern and western India and included private-sector patients,[30] and the other was an NTEP cohort that included participants from states such as Madhya Pradesh with similar socioeconomic indicators to Jharkhand.[32] In the private-sector study, the loss to follow-up was 12%, and 78·5% completed treatment.[30] The NTEP cohort study reported a 6% (93 of 1565) case fatality ratio, 6% loss to follow-up, and 8% treatment failure.[32] However, that study defined treatment failure with documentation of negative cultures at the end of

treatment, unlike in RATIONS.[32] A case fatality ratio of 16 (15%) of 104 in patients with bodyweight of less than 35 kg was reported in another cohort study from the NTEP.[28] Improved treatment success with nutritional support was also seen in a 2021 pilot study in India.[33]

The NTEP reports a high prevalence of undernutrition in people in India with tuberculosis, with median bodyweights of 43 kg in men and 38 kg in women.[34] The weight of men in our cohort was similar, whereas those of women were lower than the NTEP data. A mean weight gain of 3·2 kg was reported in an NTEP cohort,[35] and it was 1·5 times higher in our cohort with nutritional support. An unchanged or decreased BMI at 2 months, associated with a five-fold higher risk of tuberculosis mortality, was observed in 59% of patients in a recent study in which patients did not receive nutritional support.[30] Static or decreasing BMIs at 2 months were observed in only 7% of our cohort, indicating better weight gains. Overall, almost 45% of our patients had a normal BMI (18·5–24·9 kg/m²) at the end of 6 months. The dietary energy surplus over expenditure required to gain 1 kg of weight is approximately 7500 kcal.[36] Not reaching a normal BMI could be due to a high prevalence of severe and extremely severe undernutrition at enrolment, the inability to reach an adequate dietary surplus in view of poverty, COVID-19-induced disruptions, early return to activity, and physiological limits to nutritional recovery over 6 months. In a smaller study of nutritional support from 2021, weight gains were satisfactory but 13% of patients continued to be severely underweight at the end of intervention.[33]

The current study has some limitations. The study design did not include a control patient group without nutritional support because this was deemed unethical in view of the high prevalence of severe undernutrition[5,33] and its association with mortality reported in Indian patients with tuberculosis.[5,27] Our intervention was based on national guidelines and was standardised, rather than being individualised and graded with reference to nutritional status. Our assessment of adherence to food intervention was indirect,[14] and food sharing could have occurred between patients and their contacts without tuberculosis, although nutritional counselling included advice to families that the food basket should be consumed by the patient alone. Tuberculosis cure, which is defined in the national guidelines as a negative smear examination at end of treatment, was not assessed in almost half of patients due to COVID-19-related disruptions.

A strength of this study is that the patient cohort was more than four times larger than has been studied in previous trials, and we evaluated implementation of nutritional support in a real-world, programmatic setting. The intervention was delivered despite a challenging terrain, poor road connectivity, and forest cover, and without interruption during the COVID-19 pandemic. The food basket was developed after discussion with community workers in the preparatory phase and was well accepted. We had low loss to follow-up and few missing values in our anthropometric measurements.

A primarily food-based nutritional support intervention was feasible, low-cost, and was associated with improved clinical outcomes. These findings have implications for the tuberculosis programme in India and other countries with a large burden of tuberculosis and undernutrition. We suggest that national programmes routinely assess nutritional status, haemoglobin, and performance status at diagnosis, in addition to HIV and diabetes screening; implement graded nutritional support as part of patient-centred care; and provide close supervision with the option of referral for inpatient care in the intensive phase, the period with the highest risk of tuberculosis mortality.

Undernutrition is a widely prevalent, serious, and potentially lethal comorbidity in Indian patients with pulmonary tuberculosis. Baseline bodyweight was a risk factor for tuberculosis mortality, and weight gain in the first 2 months, with nutritional support, was associated with a significantly reduced hazard of death during treatment. The provision of nutritional support with food baskets and micronutrients was feasible and was associated with normalisation of performance status in the majority, as well as higher rates of treatment success, lower rates of loss to follow-up, and better weight gain compared with NTEP data.

Contributors

ABh, MB, and BV were involved in funding acquisition. ABh, MB, BV, and ABe were involved in conceptualisation. ABh, MB, AM, GST, BW, GB, and AKM curated the data, and along with them ABe, VPS, DS, and RRP contributed to formal analysis. Investigations were done by ABh, MB, AM, BV, VPS, AKM, and RRP. The methodology was the responsibility of ABh, MB, AM, BV, BW, ABe, and VC. ABh, MB, AM, BV, BW, GB, GST, VPS, DS, RP, and RJ were involved in supervision and project administration. The software was the responsibility of ABh, MB, AM, GST, BW, GB, VPS, and DS. Validation was done by ABh, MB, AM, GST, BW, and ABe, and visualisation was done by ABh, MB, GST, and ABe. ABh, MB, ABe, VC, and RJ were involved in the writing of the original draft and all authors were involved in reviewing and editing the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Data will be made available upon reasonable request (made to the corresponding author) after planned analyses and reporting have been completed.

Acknowledgments

This work was supported by grants from the India Tuberculosis Research Consortium, Indian Council of Medical Research (India vide grant number 5/8/5/57/TB consortium/Call India Project/2017/ECD-1). We appreciate the tremendous efforts of the entire field team who worked in a difficult terrain, and continued work without any interruption during the COVID-19 pandemic. The cooperation of the district tuberculosis officers of Ranchi, East Singhbhum, West Singhbhum, and Seraikela-Kharsawan and their teams is gratefully acknowledged. We acknowledge the support of Central Coalfields for making available laboratory space and equipment in Ranchi, and the Letzdream Foundation for providing support for handheld devices for data entry and two-wheelers for the supervisory team. We acknowledge Anika Juneja (Institute of Public Health, Bengaluru, India) and Carl Britto (Boston Children's Hospital, Boston, MA, USA) for their contributions to the launch of substudies and the trial, and

Kannan Thiruvengadam (National Institute for Research in Tuberculosis, Chennai, India) for maintenance of the RedCap database. We thank Madhukar Pai (McGill University, Montreal, QC, Canada) and Shriprakash Kalantri (Mahatma Gandhi Institute for Medical Sciences, Wardha, India) for their critical input on earlier drafts of this report.

References

1 WHO. Global tuberculosis report 2022. Geneva: World Health Organization, 2022.

2 Ministry of Health with Family Welfare, Government of India. National strategic plan for tuberculosis: 2017–25. March, 2017. https://tbcindia.gov.in/WriteReadData/National%20Strategic%20Plan%202017-25.pdf (accessed Nov 1, 2022).

3 WHO. Global tuberculosis report 2021. Geneva: World Health Organization, 2021.

4 Bhargava A, Bhargava M. Tuberculosis deaths are predictable and preventable: comprehensive assessment and clinical care is the key. *J Clin Tuberc Other Mycobact Dis* 2020; 19: 100155.

5 Bhargava A, Chatterjee M, Jain Y, et al. Nutritional status of adult patients with pulmonary tuberculosis in rural central India and its association with mortality. *PLoS One* 2013; 8: e77979.

6 Zachariah R, Spielmann MP, Harries AD, Salaniponi FML. Moderate to severe malnutrition in patients with tuberculosis is a risk factor associated with early death. *Trans R Soc Trop Med Hyg* 2002; 96: 291–94.

7 Waitt CJ, Squire SB. A systematic review of risk factors for death in adults during and after tuberculosis treatment. *Int J Tuberc Lung Dis* 2011; 15: 871–85.

8 Sinha P, Lönnroth K, Bhargava A, et al. Food for thought: addressing undernutrition to end tuberculosis. *Lancet Infect Dis* 2021; 10: e318–25.

9 WHO. Guideline: nutritional care and support for patients with tuberculosis. Geneva: World Health Organization, 2013.

10 WHO. Management of severe malnutrition: a manual for physicians and other senior health workers. Geneva: World Health Organization, 1999.

11 Darnton-Hill I, Mandal PP, de Silva A, Bhatia V, Sharma M. Opportunities to prevent and manage undernutrition to amplify efforts to end TB. *Int J Tuberc Lung Dis* 2022; 26: 6–11.

12 Oxlade O, Huang CC, Murray M. Estimating the impact of reducing under-nutrition on the tuberculosis epidemic in the central eastern states of India: a dynamic modeling study. *PLoS One* 2015; 10: e0128187.

13 Grobler L, Nagpal S, Sudarsanam TD, Sinclair D. Nutritional supplements for people being treated for active tuberculosis. *Cochrane Database Syst Rev* 2016; 6: CD006086.

14 Bhargava A, Bhargava M, Meher A, et al. Nutritional supplementation to prevent tuberculosis incidence in household contacts of patients with pulmonary tuberculosis in India (RATIONS): a field-based open-label, cluster-randomised, controlled trial. *Lancet* 2023; published online Aug 8. https://doi.org/10.1016/S0140-6736(23)01231-X.

15 NITI Aayog. India national multidimensional poverty index: baseline report. 2021. https://www.niti.gov.in/sites/default/files/2021-11/National_MPI_India-11242021.pdf (accessed Nov 1, 2022).

16 International Institute for Population Sciences. National Family Health Survey (NFHS-5) 2019–21: compendium of fact sheets. 2021. https://main.mohfw.gov.in/sites/default/files/NFHS-5_Phase-II_0.pdf (accessed Nov 1, 2022).

17 Ministry of Health with Family Welfare, Government of India. India TB report 2022. March, 2022. https://tbcindia.gov.in/WriteReadData/IndiaTBReport2022/TBAnnualReport2022.pdf (accessed Nov 1, 2022).

18 Indian Council of Medical Research, National Institute for Research in Tuberculosis, National Health Mission, Ministry of Health and Family Welfare, Government of India, National Tuberculosis Elimination Programme. WHO. National TB prevalence survey in India (2019-2021): summary report. New Delhi: India Office. 2022. https://tbcindia.gov.in/WriteReadData/l892s/2503202216102ONATBPSReport.pdf (accessed Nov 1, 2022).

19 Ministry of Health and Family Welfare, Government of India. Revised national TB control programme: technical and operational guidelines for tuberculosis control in India. 2016. https://tbcindia.gov.in/index1.php?sublinkid=4573&level=2&lid=3177&lang=1 (accessed Nov 1, 2022).

20 Ministry of Health and Family Welfare, Government of India. Guidance document: nutritional care and support for patients with tuberculosis in India. 2017. https://tbcindia.gov.in/WriteReadData/Guidance%20Document%20-%20Nutritional%20Care%20%26%20Support%20for%20TB%20patients%20in%20India.pdf (accessed Nov 1, 2022).

21 Ministry of Health and Family Welfare, Government of India. Government of India gazette notification for DBT with NIKSHAY. https://tbcindia.gov.in/showfile.php?lid=3286 (accessed Nov 1, 2022).

22 de Vallière S, Barker RD. Poor performance status is associated with early death in patients with pulmonary tuberculosis. *Trans R Soc Trop Med Hyg* 2006; 100: 681–86.

23 Alpers DH, Taylor BE, Beir DM, Klein S. Manual of nutritional therapeutics, 6th edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2015.

24 Huddart S, Svadzian A, Nafade V, Satyanarayana S, Pai M. Tuberculosis case fatality in India: a systematic review and meta-analysis. *BMJ Glob Health* 2020; 5: e002080.

25 Khan A, Sterling TR, Reves R, Vernon A, Horsburgh CR. Lack of weight gain and relapse risk in a large tuberculosis treatment trial. *Am J Respir Crit Care Med* 2006; 174: 344–48.

26 Van Buuren S, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R. *J Stat Softw* 2011; 45: 1–67.

27 Henry CJK. The biology of human starvation: some new insights. *Nutr Bull* 2001; 26: 205–11.

28 Santha T, Garg R, Frieden TR, et al. Risk factors associated with default, failure and death among tuberculosis patients treated in a DOTS programme in Tiruvallur district, south India, 2000. *Int J Tuberc Lung Dis* 2002; 6: 780–88.

29 Huangfu P, Ugarte-Gil C, Golub J, Pearson F, Critchley J. The effects of diabetes on tuberculosis treatment outcomes: an updated systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2019; 23: 783–96.

30 Sinha P, Ponnuraja C, Gupte N, et al. Impact of undernutrition on tuberculosis treatment outcomes in India: a multicenter, prospective, cohort analysis. *Clin Infect Dis* 2023; 76: 1483–91.

31 Shewade HD, Nagaraja SB, Vanitha B, et al. Screening for severe illness at diagnosis has the potential to prevent early TB deaths: programmatic experience from Karnataka, India. *Glob Health Sci Pract* 2022; 10: e2100736.

32 Velayutham B, Chadha VK, Singla N, et al. Recurrence of tuberculosis among newly diagnosed sputum positive pulmonary tuberculosis patients treated under the Revised National Tuberculosis Control Programme, India: a multi-centric prospective study. *PLoS One* 2018; 13: e0200150.

33 Singh AK, Siddhanta A, Goswami L. Improving tuberculosis treatment success rate through nutrition supplements and counselling: findings from a pilot intervention in India. *Clin Epidemiol Glob Health* 2021; 11: 11.

34 Padmapriyadarsini C, Shobana M, Lakshmi M, Beena T, Swaminathan S. Undernutrition & tuberculosis in India: situation analysis & the way forward. *Indian J Med Res* 2016; 144: 11–20.

35 Vasantha M, Gopi PG, Subramani R. Weight gain in patients with tuberculosis treated under directly observed treatment short-course (DOTS). *Indian J Tuberc* 2009; 56: 5–9.

36 Wakabayashi H, Yoshimura Y, Maeda K, Fujiwara D, Nishioka S, Nagano A. Goal setting for nutrition and body weight in rehabilitation nutrition: position paper by the Japanese Association of Rehabilitation Nutrition (secondary publication). *J Gen Fam Med* 2021; 23: 77–86.

BMJ Open

The RATIONS (Reducing Activation of Tuberculosis by Improvement of Nutritional Status) study: a cluster randomised trial of nutritional support (food rations) to reduce TB incidence in household contacts of patients with microbiologically confirmed pulmonary tuberculosis in communities with a high prevalence of undernutrition, Jharkhand, India

To cite: Bhargava A, Bhargava M, Velayutham B, *et al*. The RATIONS (Reducing Activation of Tuberculosis by Improvement of Nutritional Status) study: a cluster randomised trial of nutritional support (food rations) to reduce TB incidence in household contacts of patients with microbiologically confirmed pulmonary tuberculosis in communities with a high prevalence of undernutrition, Jharkhand, India. *BMJ Open* 2021;**11**:e047210. doi:10.1136/bmjopen-2020-047210

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-047210).

MB and BV contributed equally.

Received 23 November 2020
Revised 23 April 2021
Accepted 05 May 2021

For numbered affiliations see end of article.

Correspondence to
Dr Anurag Bhargava;
anuragb17@gmail.com

Anurag Bhargava ,[1,2] Madhavi Bhargava ,[2,3] Banurekha Velayutham,[4] Kannan Thiruvengadam,[4] Basilea Watson,[4] Bharati Kulkarni ,[5] Manjula Singh ,[6] Rakesh Dayal,[7] Rajeev Ranjan Pathak,[8] Anindya Mitra,[9] Kiran Rade,[10] KS Sachdeva[11]

ABSTRACT

Introduction India has the largest burden of cases and deaths related to tuberculosis (TB). Undernutrition is the leading risk factor accounting for TB incidence, while severe undernutrition is a common risk factor for mortality in patients with TB in India. The impact of nutritional supplementation on TB incidence is unknown, while few underpowered studies have assessed its impact on TB mortality. We designed an open-label, field-based cluster randomised trial to assess the impact of nutritional supplementation (with food rations) on TB incidence in a group at higher risk of TB infection and disease, viz household contacts (HHC) of patients with microbiologically confirmed pulmonary TB (PTB) in Jharkhand, a state with a high prevalence of undernutrition.

Methods and analysis We shall enrol 2800 adult patients with PTB of the national TB programme, across 28 treatment units in 4 districts, and their approximately 11 200 eligible contacts. The sample size has 80% power to detect the primary outcome of 50% reduction in incidence of active TB in HHC over 2 years of follow-up. Patients and HHC in both the arms will undergo nutritional assessment and counselling. Patients will receive monthly food rations (supplying 1200 kcal and 52 g proteins/day) and multivitamins along with antitubercular treatment. The HHC in the intervention arm will receive food rations (supplying 750 kcal and 23 g proteins/day) and multivitamins while HHC in control arm will be on usual diet. The secondary outcomes in HHC will include effects on nutritional status, non-TB infections. Secondary outcomes in patients are effects on TB mortality, adherence, adverse effects, nutritional and performance status. Substudies will examine micronutrient status and

Strengths and limitations of the study

- ► The Reducing Activation of Tuberculosis by Improvement of Nutritional Status study is the first trial addressing undernutrition to reduce tuberculosis (TB) incidence in communities with high prevalence of poverty, undernutrition and low prevalence of HIV infection.
- ► It is the largest trial to evaluate the impact of nutritional support on TB mortality in a programme-based cohort of patients with pulmonary TB and a high prevalence of undernutrition.
- ► The follow-up period of 2 years will ensure detection of most cases of incident TB in household contacts and recurrence of TB in index cases.
- ► The quantum of food rations per participant is standardised, and in the absence of individual needs assessment, the extent to which the intervention meets individual needs is unknown.
- ► Food sharing in the families in the control arm and extra food consumption from other sources cannot be ruled out.

effects on dietary intake, body composition, muscle strength and immune function.

Ethics and dissemination The institutional ethics committee of ICMR-NIRT, Chennai, approved the study (289/NIRT-IEC/2018). The results will be disseminated in publications and presentations.

Trial registration number Clinical Trial Registry of India: CTRI/2019/08/020490.

INTRODUCTION

Tuberculosis (TB) is a global public health problem leading to significant morbidity and mortality, especially in low and middle income countries. An estimated 10 million people developed TB and 1.2 million (HIV-negative) people succumbed to it in 2019.[1] India was the major contributor to the global TB burden with an estimated 2.6 million new cases (27% of global) and 0.4 million (35% of global) TB deaths in HIV-negative people in 2019.[1]

The United Nations Sustainable Development Goals-3 (SDG-3) has a target for ending the TB epidemic by 2030 and aims to reduce TB incidence and TB deaths by 80% and 90% of the 2015 levels, respectively.[2] As per the National Strategic Plan (2017–2025), the Revised National Tuberculosis Control Programme (renamed as National Tuberculosis Elimination Programme, NTEP) in India has set an ambitious target of achieving the 2030 SDG milestone by 2025, 5 years ahead of the global target.[3]

The end TB strategy will require a mix of biomedical, public health and social interventions to achieve these goals.[2] The strategy requires acceleration of the current decline of 1.5% to 10%–17% per year.[4] The present biomedical approach to TB prevention based on vaccination and TB preventive treatment (TPT) has its limitations. The efficacy of BCG vaccine is limited to prevention of severe forms of childhood TB.[5] The TPT with isoniazid in countries like India currently covers only select groups of contacts like children under 6 years of age and people living with HIV.[6] WHO recently made a conditional recommendation of offering TPT to all household contacts (HHC).[7] However, there are considerable logistical and technical challenges in countries with a high burden of latent TB infection (LTBI).[8]

Rationale for the trial

The end TB strategy recognises the need for new tools, interventions and strategies to address the problem of TB incidence and adverse outcomes.[2] Globally, an estimated 1.7 billion people or 23% of the population have LTBI, which remains latent in 90% in the presence of innate and cell-mediated immunity.[9] Risk factors like HIV, undernutrition, uncontrolled diabetes, smoking and alcohol impair immunity, lead to active TB, and act as drivers of the TB epidemic. Undernutrition results from deficient intake or assimilation of energy and nutrients, often in association with disease-associated inflammation, and is a part of the broader spectrum of malnutrition, which includes both undernutrition, overweight and obesity and deficiencies of micronutrients. Undernutrition in children is commonly defined by the well-accepted WHO indicators of low birth weight in newborns, underweight (low weight for age), stunting (low height for age) and wasting (low weight for height) in preschool children and by age and gender-specific cut-offs for body mass index (BMI) in those aged 6–18 years. In adults, undernutrition is based on a low BMI, which reflects low body energy stores or chronic energy deficiency. The BMI cut-off for underweight proposed by WHO of <18.5 kg/m^2 for populations[10] has also been accepted as a criterion for clinical diagnosis of malnutrition/undernutrition in a recent consensus statement.[11] In addition, there have been proposals for diagnosis of undernutrition based on altered body composition, and for higher BMI cut-offs in patients undergoing significant involuntary weight loss, which require further validation.[11 12]

Undernutrition is the leading cause of impaired immunity globally,[13] with a consistent inverse exponential relationship between nutritional status measured by BMI and TB incidence.[14] According to the global TB report 2020, undernutrition is a leading risk factor accounting for 2.2 million cases (19%), more than HIV and diabetes (accounting for 0.76 and 0.35 million cases, respectively).[1] Undernutrition is also a consistent risk factor for TB mortality, regardless of HIV infection, and drug susceptibility.[15] Its prevalence was as high as 23% in women and 19% in men (BMI: <18.5 kg/m^2) in the most recent National Family Health Survey (NFHS-4) in India.[16] It is higher in the poor, rural residents and those belonging to the scheduled castes and tribes, who also suffer a high burden of TB disease.[16 17] The WHO has estimated that 0.6 million cases of TB in India are attributable to undernutrition,[1] while other studies indicate that this estimate may be higher.[18] A majority of Indian patients with active TB have severe levels of undernutrition (macronutrient and micronutrient), which are associated with twofold–fourfold higher risk of mortality.[19]

A single unit increase in BMI could reduce TB incidence by 14%,[14] and a modelling study has shown that TB incidence and mortality could decline by 40%–71% with nutritional interventions.[20] There is no randomised controlled trial on the effect of nutritional supplementation on TB incidence. The studies on the impact of nutritional supplementation on TB mortality have been limited, small and underpowered.[21]

The Reducing Activation of Tuberculosis by Improvement of Nutritional Status (RATIONS) study is a cluster randomised trial to assess the impact of nutritional supplementation on TB incidence among HHC of patients with microbiologically confirmed pulmonary TB (PTB), living in a community with a high prevalence of undernutrition. They are a group at higher risk of TB infection and disease,[22] with a prevalence of 10-fold–60-fold higher than in the general population.[23] TB incidence was 4.8% in the HHC and 21.4% in child contacts in a previous study from Peru.[24] Food insecurity and undernutrition are strong and modifiable risk factors of TB in

Table 1 Objectives of the RATIONS trial and the outcome variables

Objective	Outcome variables	Index case	HHC
Primary Objective			
Effect of household nutritional supplementation in reducing TB incidence among HHC of patients with microbiologically confirmed PTB	Difference in number of incident cases of active TB (all forms) in the two arms detected by active case finding over a follow-up period of 2 years after diagnosis of index case		✓
Secondary objectives			
Effect of nutritional supplementation on anthropometric indicators over 6 months	Anthropometric indicators such as weight and BMI	✓	✓
Non-TB infectious morbidity and mortality in HHC in both the arms	Malaria, diarrhoea, lower respiratory tract infection, hospitalisation with fever of any cause or death with fever of any cause <15 days in duration		✓
Adherence to anti-TB therapy	Proportion completing the therapy successfully	✓	
Mortality during treatment	Proportion of index cases who died during treatment	✓	
Adverse effects	Severe adverse effects with TB drugs	✓	
Recurrence of TB within 2 years after cure	Relapse rate of microbiologically confirmed TB	✓	
Performance status	Change in ECOG scale at 1 month, 2 months and 6 months compared with baseline	✓	
Dietary substudy			
Evaluate the difference in dietary intake of calories and proteins	Calorie and protein intake at baseline, and end of treatment in intervention and control arms	✓	✓
Micronutrient substudy			
Assess vitamins A and D (25-hydroxyvitamin D) levels	Level of vitamins A and D at baseline	✓	✓
Body composition substudy			
Evaluation of body composition	Estimate fat-free mass, fat mass and other bioimpedance analysis parameters at baseline, and 6 months after treatment	✓	✓
Substudy on grip strength			
Evaluate muscle strength using hand grip dynamometer	Grip strength at baseline and 6 months	✓	
Substudy of immune function			
Evaluate cellular immunity in patients and HHC	Lymphocyte subsets (CD4, CD8, natural killer cells and B lymphocytes), fourth generation IGRA at baseline and end of treatment	✓	✓

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; HHC, household contacts; IGRA, Interferon Gamma Release Assay; PTB, pulmonary tuberculosis; RATIONS, Reducing Activation of Tuberculosis by Improvement of Nutritional Status.

the HHC.[25 26] The trial is being conducted in Jharkhand (meaning 'Land of Forests') a state in eastern India which has a high prevalence of undernutrition in children and adults. According to the National Family Health Survey-4 (2015–6), the state has the highest levels of underweight (47.8%), wasting (29.0%), and the second highest level of stunting(45.3%) in children under 6 years of age in India.[16 27] Similarly, more than two of out of every five (41%) of adult rural women in Jharkhand had a BMI of <18.5 kg/m^2, and had the highest prevalence of anaemia in adult women in India,(65.9%), which is largely related to nutritional deficiencies of iron and folic acid.[16 27]

Objectives

The objectives and the outcome variables have been tabulated in table 1.

Primary objective

The primary objective is to evaluate the effect of household nutritional supplementation in reducing TB incidence among HHC of patients with microbiologically confirmed PTB.

Secondary objectives in HHC

The secondary objective is to evaluate the effect of nutritional supplementation on anthropometric indicators, and non-TB infectious morbidity and mortality.

Secondary outcomes in index cases

To evaluate the effect of nutritional supplementation on adherence to treatment, mortality, frequency of adverse effects due to treatment, performance status of patients as measured by the Eastern Cooperative Oncology Group

(ECOG),[28] and relapse of microbiologically confirmed TB on follow-up.

Substudies: six substudies have been planned in a subset of index cases and HHC

a. Dietary intakes: to evaluate the difference in dietary intake of calories, proteins at baseline, and at the end of treatment in a subsample of the patients in both the arms.
b. Micronutrients: vitamin A (serum retinol) and 25-hydroxyvitamin D levels in a subsample of index patient and HHC at baseline.
c. Body composition: to evaluate the difference in body composition between patients in the two arms at baseline and 6 months by a multifrequency bioelectric impedance analyzer (Bodystat Quadscan 4000).
d. Muscle function (grip strength) in a subsample of index cases at baseline, and end of treatment using a digital handheld dynamometer.
e. Immune function: to evaluate select aspects of immunity in index patient and their HHC before and after treatment using the lymphocyte subsets (CD4, CD8, natural killer cells and B lymphocytes) and kinetics of interferon γ responses (by CD4 and CD8 cells) in a fourth generation Interferon Gamma Release Assay (QuantiFERON-TB Gold Plus: QFT-Plus).
f. Qualitative study in a subset of stakeholders: a qualitative study will also be conducted in a subset of the stakeholders (patients, contacts and field staff) at the end of the intervention period to assess the perceptions and experiences of nutrition intervention.

METHODS AND ANALYSIS

Study design and oversight

This is a cluster randomised open-label parallel-arm, superiority trial of nutritional supplementation in households with microbiologically confirmed patients with PTB in the state of Jharkhand, Eastern India. The study will randomise 28 TB units (TUs) in four districts (Ranchi, East-Singhbhum, West-Singhbhum and Seraikela-Kharsawan) into control and intervention arms, each with 1400 adult PTB patients. It is supported by the India TB Research Consortium of the Indian Council of Medical Research (ICMR) and implemented by the Yenepoya (deemed to be University), in association with the National Institute for Research in Tuberculosis (ICMR-NIRT) and National Institute of Nutrition. The enrolment began on the 16 August 2019.

Study setting: under the NTEP, each district has one district TB centre and there are subdistrict administrative units called TUs. The population is predominantly rural (75%) and indigenous communities classified as 'scheduled tribes' who comprise 28% of the population (national-8%) and are historically disadvantaged groups with regard to social, economic and health indicators. According to NFHS-4, the prevalence of undernutrition in Jharkhand was 23.8% and 31.6% in adult men and women, respectively, significantly higher than the national average.[16] A total of 44 000 TB cases were notified in the year 2017 when this trial was proposed.[29]

Eligibility criteria

The inclusion and exclusion criteria are mentioned in table 2.

Inclusion criteria: adult patients (≥18 years) with microbiologically confirmed PTB (irrespective of drug sensitivity) will constitute the index cases and will be eligible to enrol in the study. The HHC will be persons who have lived in the same house (and eating from the same kitchen), for one or more nights or for frequent or extended periods during the day with the index case during the preceding 3 months.

Exclusion criteria: an index case with no eligible HHC and any HHC currently on treatment for TB will be excluded.

Study interventions

Nature and quantity

The study intervention includes macronutrients and micronutrient supplementation along with nutritional counselling as per national guidelines.[30] The index patients (in both arms) and the HHC (in the intervention arm) will receive a food basket and a recommended daily allowance of vitamins and micronutrients every month, as

Table 2 Eligibility criteria for RATIONS trial participants

Index cases	HHC
Inclusion criteria	
Patients ≥18 years of age with microbiologically confirmed PTB	Persons living in the same house, eating from same kitchen as index case for ≥one night or for frequent or extended periods during the day during the 3 months before diagnosis in index case
Exclusion criteria	
Non eligible HHC	Current smear or GeneXpert or LPA or culture confirmed TB
Time interval between initiation of treatment and enrolment is >14 days	Clinically diagnosed PTB or extra-PTB and currently on treatment

HHC, household contacts; LPA, line probe assay; PTB, pulmonary tuberculosis; RATIONS, Reducing Activation of Tuberculosis by Improvement of Nutritional Status.

Table 3 Nutritional supplementation in the RATIONS trial

	Intervention arm	Control arm
Index case*, quantity per person per month	Nutritional counselling 5 kg of rice 3 kg roasted Bengal gram powder (locally called as sattu) 1.5 kg of milk powder 500 mL vegetable oil One RDA of micronutrient	Nutritional counselling 5 kg of rice 3 kg roasted Bengal gram powder (locally called as sattu) 1.5 kg of milk powder 500 mL vegetable oil One RDA of micronutrient
Household contact†, quantity per person per month	Nutritional counselling 5 kg rice 1.5 kg pulses (split pigeon peas) One RDA of micronutrient per adult/adolescent HHC Half of this amount for children less than 10 years	Nutritional counselling Usual food assistance available to eligible households through public distribution system

*Approximately 1200 kcal of energy and 52 g proteins/day.
†Approximately 750 kcal of energy and 23 g of proteins/day.
HHC, household contacts; RATIONS, Reducing Activation of Tuberculosis by Improvement of Nutritional Status; RDA, recommended dietary allowance.

described in table 3. This will be either delivered by the study staff or may be picked up from a depot as per the participant preference.

Frequency and duration

The food basket will be provided for 6 months for new patients and 12 months for patients with multidrug resistant TB (MDR-TB) (and their HHC in intervention arm). Extension of the intervention period to 12 months, for a patient with non-MDR-TB will be considered if there is evidence of undernutrition (BMI: <18.5 kg/m^2) in the index case even at the end of 6 months. Extension of rations to an HHC will be considered if an adult contact has a BMI of <16 kg/m^2; children (<10 years) have weight-for-age z-score <−2SD and adolescents (10–18 years) have BMI-for-age z-scores <−2SD.

Nutritional counselling and assessing adherence

The patients and the HHC will be counselled about the importance of a balanced diet for the nutritional recovery of the patient and the protection of the health status of the family. The families will be instructed about the optimal utilisation of the food rations in locally acceptable food recipes.The field staff will undertake follow-up visits to monitor weight gain (a proxy indicator for adherence) and check the empty packets of the milk powder as an indicator of consumption by the patient.

Co-interventions permitted during the trial

The patients as well as the HHC will continue to access public distribution system, supplementary feeding programmes (Integrated Child Development Services Scheme, mid-day meals) as usual and additional INR 500/month as direct benefit transfer availed by patients with TB in India. The eligible children under 6 years of age and those with HIV infection who have been advised by the NTEP staff to take chemoprophylaxis with isoniazid after an evaluation will continue to do so.

Risk assessment and referral

The patients will be evaluated for nutritional status, oxygen saturation, blood pressure and presence of complications at baseline and at follow-up. Patients with severe undernutrition with oedema, extremely severe undernutrition (BMI: <14 kg/m^2), breathlessness or low oxygen saturation (SpO_2: <94) will be referred for inpatient care as per national guidelines.[30]

Randomisation and intervention allocation

This is an open label trial; the participants and field staff are not blinded after assignment. All the TUs from the selected districts were line-listed (list of TUs is available in online supplemental file 1) and randomised equally to both the arms by computer-generated random numbers using restricted randomisation by the statistician at ICMR-NIRT, Chennai. The cluster allocation was kept confidential until the end of training of the field staff and the TUs were ready for implementation.

Enrolment of index cases and HHC

Figure 1 describes the study flow. Consecutive patients diagnosed with microbiologically confirmed PTB in selected TUs will be enrolled after due consent process, during a 6–12-month period. Information about the study will be given to the HHC during a home visit by the trial staff and enrolled after elicitation of voluntary written informed consent. The need for adherence to treatment and food rations, cooperation with study procedures, the stability of residence and the willingness to permit home visits will be discussed with the index cases and HHC during enrolment.

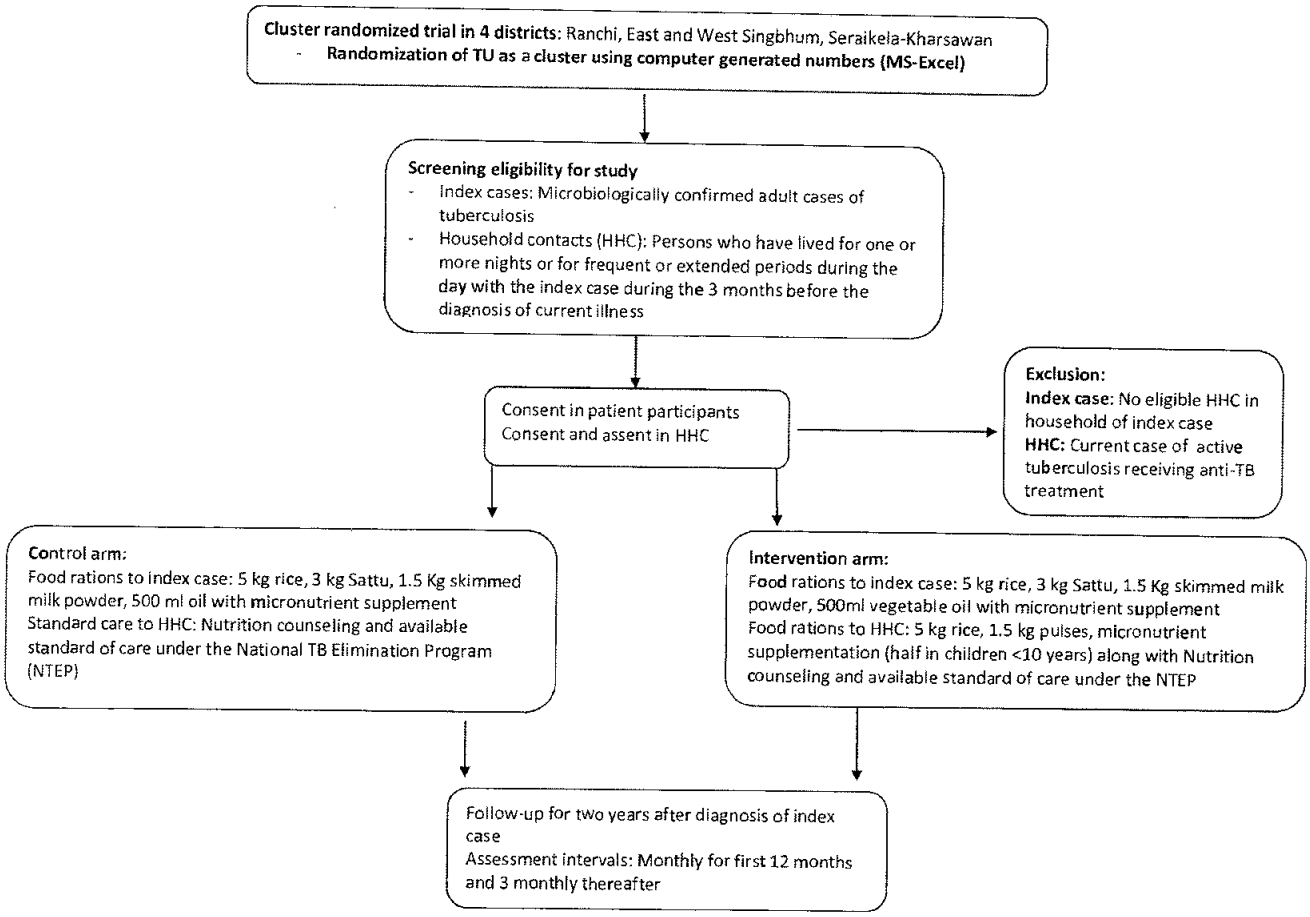

Figure 1 Study flow for the Reducing Activation of Tuberculosis by Improvement of Nutritional Status trial. TU, tuberculosis unit.

Baseline evaluation of index cases and HHC

The study procedures at baseline and follow-up are denoted in table 4. Demographic characteristics, including gender, occupation, caste, marital status, education, socioeconomic assessment with an asset score and education, will be noted. The presence of self-reported risk factors such as diabetes, alcohol consumption and tobacco use, and family/history of TB will also be recorded.

Clinical examination of index cases

Weight will be measured with a digital weighing scale (SECA 803) with accuracy of 100 g, and height using a portable stadiometer (SECA 213) with accuracy of 0.1 cm using standard procedures. Mean of two measurements of weight will be taken for calculation of BMI. Undernutrition is defined as a BMI of <18.5 kg/m^2 according to the underweight definition approved by the WHO.[10] Patients will further be categorised into mild underweight in case the BMI is 17.0–18.49 kg/m^2, moderate underweight if the BMI is 16.0–16.99 kg/m^2 and severely underweight if the BMI is <16 kg/m^2 as suggested by WHO.[31] An additional category of extremely severe underweight is used to classify those with a BMI of ≤14 kg/m^2.[32] Mid-upper arm circumference (MUAC) will be measured to the nearest of 0.1 cm on the non-dominant arm, if the patient is unable to stand. Presence of oedema, blood pressure using a digital instrument (OMRON) and oxygen saturation using pulse oximeter will be noted. Assessment of performance status will be done using ECOG Scale as described in table 5.[28]

Clinical examination in contacts

This will consist of anthropometric measurements like weight, height, MUAC (if unable to stand and in children under 5 years of age), the presence of oedema and BCG scar.

Laboratory evaluation of index cases

The results of the sputum smear microscopy, cartridge-based nucleic acid amplification test (CB-NAAT), Gene Xpert MTB/RIF test, blood glucose and HIV tests (if available) will be retrieved from the NTEP records. Haemoglobin will be measured during the home visit using HemoCue Hb 201$^+$ using standard procedures and precautions. Chest X-ray (CXR) of patients at baseline will be done wherever feasible.

Laboratory evaluation of HHC

Symptom screening for TB will be done in all HHC and CXR will be done wherever feasible as per the NTEP

Table 4 Schedule of enrolment, assessments at baseline and follow-up in the RATIONS trial

	Investigations	Baseline	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M15	M18	M21	M24
	In index cases																	
1	Informed consent	X																
2	Demography, socio-economic status, comorbidities, household characteristics and access to PDS	X																
3	Clinical evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
4	Anthropometry (height, weight and MUAC) and SpO_2, pedal oedema	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
5	*Laboratory evaluation RBS, HIV and Hb	X																
6	Compliance to nutritional supplement in new cases (12 months in MDR-TB)	X	X	X	X	X	X	X	X	X	X	X	X	X				
7	Performance status (modified ECOG Scale)	X	X	X				X	X	X	X	X	X	X				
8	*CB-NAAT	X	(in case of symptoms of recurrent disease)															
9	*CXR	X						X										
	In subsample of index cases																	
1	Dietary recall of calories and protein intake	X						X										
2	Body composition (by BIA)	X						X										

Continued

Table 4 Continued

	Investigations	Baseline	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M15	M18	M21	M24
3	Micronutrient estimation (vitamins A and D)	X																
4	Hand grip strength	X						X										
5	Immunological tests (fourth-generation IGRA, lymphocyte subsets)	X						X										
	In household contacts																	
1	Informed consent	X																
2	Baseline demography, socioeconomic status, comorbid conditions, household characteristics and access to PDS	X																
3	Symptom screen	X	X	X	X	X	X	X			X			X	X	X	X	X
4.	Clinical evaluation if symptomatic	X	In case of symptoms of active TB															
5	Anthropometry (height, weight and MUAC)	X		X	X	X	X	X			X			X	X	X	X	X
6	Compliance to nutritional supplement (intervention arm) (12 months in MDR-TB)	X	X	X	X	X	X	X										
7.	Review of non-TB infectious illnesses†	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
8	Sputum smear, CB-NAAT	In case of symptoms of active TB																

Continued

Table 4 Continued

	Investigations	Baseline	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M15	M18	M21	M24
9	CXR‡	X	In case of symptoms of active TB															
	In subsample of household contacts																	
1.	Dietary recall of calories, protein intake	X						X										
2	Body composition (by BIA)	X						X										
3	Micronutrient estimation (vitamins A and D)	X																
4	Immunological tests (fourth-generation IGRA and lymphocyte subsets)	X						X										

*Through public health system.
†Respiratory infections, diarrhoea, hospitalisation with fever of any cause and death due to fever <15 days duration.
‡For children under 5 years of age, symptomatic contacts.
BIA, Bioimpedance analysis; CB-NAAT, cartridge-based nucleic acid amplification test; CXR, chest X-ray; ECOG, Eastern Cooperative Oncology Group; Hb, haemoglobin; HIV, HIV immunodeficiency virus; IGRA, Interferon Gamma Release Assay; MDR-TB, multidrug resistant tuberculosis; MUAC, mid upper arm circumference; MUAC, mid-upper arm circumference; PDS, public distribution system; RATIONS, Reducing Activation of Tuberculosis by Improvement of Nutritional Status; RBS, random blood sugar; SpO_2, oxygen saturation; TB, tuberculosis.

Table 5 Eastern Cooperative Oncology Group (ECOG) Scale for functional assessment[24]

ECOG categories	Additional description	Score
Able to carry out normal activity without restriction	No physical restriction	0
Unable to do physically strenuous activity, but ambulatory and able to carry out light work	Able to walk around the neighbourhood, but unable to do any income-generating work	1
Ambulatory and capable of all self-care, but unable to carry out any work; up and about <50% of waking hours	Able to walk around the house and backyard	2
Capable of only limited self-care; confined to bed or chair >50% of waking hours	Able to go to the bathroom	3
Completely disabled; cannot carry out any self-care and totally confined to bed or chair	Unable to go to the bathroom	4

guidelines.[6] In case of symptoms of presumptive TB or an abnormal CXR, the HHC will be referred for sputum examination. Children with symptoms/abnormal CXR will be referred for further evaluation by sputum smear and CB-NAAT (if cough is productive) and induced sputum/gastric aspirate, if unable to produce sputum at a referral hospital.

Follow-up of index cases and HHC

The enrolled index cases and their HHC will be followed-up for 2 years after the diagnosis of the index case. Jharkhand is a state with potential seasonal labour migration from rural areas. All attempts (including telephonic contact) will be made to retain follow-up in case of temporary migration with an in-person visit on their return. Participants will be termed as lost to follow-up if in-person or telephonic contact is not made for ≥2 months in the intervention period or for ≥6 months in the follow-up period. All participants lost to follow-up will be approached for an end of study evaluation to ascertain information on the primary and relevant secondary outcomes.

The schedule of follow-up and assessments is described in table 4. Evaluation will be done for current symptoms, any adverse effect related to treatment, adherence to treatment and rations. All HHC will be evaluated for symptoms of active TB on each visit, consumption of rations (in intervention arm) and review of non-TB infectious morbidity and mortality based on symptoms, hospitalisation or death.

Patients will undergo repeat sputum examination on follow-up as per NTEP guidelines. Contacts that develop any symptoms of active TB (pulmonary or extrapulmonary) will undergo appropriate investigations.

The cases of active TB in HHC will be classified as co-prevalent or incident according to the time of diagnosis of the index case. A co-prevalent case is HHC diagnosed with active TB (microbiologically confirmed active TB or as clinically diagnosed TB) at the baseline, or within 2 months of the baseline screening and evaluation of the HHC. An incident case is a new case of TB in an HHC (microbiologically confirmed active TB or as clinically diagnosed) that was diagnosed more than 2 months following the initial negative screening and evaluation. The definition of microbiologically confirmed case and clinically diagnosed cases is as per table 6.

Qualitative study about the nutritional intervention

We will use a phenomenological approach to generate qualitative data through the in-depth interview of TB patients and their HHC. The participants will be purposively selected till conceptual saturation and triangulation is reached, and will be interviewed using topic guides prepared in line with the study objectives. Interviews will be tape-recorded, transcribed verbatim and translated to English. Open Code software will be used to facilitate analysis. This substudy will be conducted at the end of the intervention period.

Discontinuation of study intervention and withdrawal of study participants

Study participants will be asked about consumption of rations and micronutrients at every visit. Rarely, they may choose to discontinue consumption of the study intervention during the intervention period, due to an unrelated illness or perceived adverse effects. The reasons for their discontinuation of study intervention will be recorded, but these participants will remain in the study and undergo protocol-specified follow-up procedures. However, if the participant also explicitly withdraws consent for follow-up and collection of additional information in addition to discontinuation of consumption of study intervention, the withdrawal of consent will be recorded, and only the data collected prior to withdrawal of consent will be used in the study. Study participants will be free to withdraw at any time during the trial. The reasons for the withdrawal will be documented, which may include refusal of follow-up, lost to follow-up, participant request, death or if the study sponsors decide to stop or cancel the study. Unless the participants withdraw consent for further follow-up, attempts will be made to ascertain outcomes as mentioned earlier.

Study outcomes

The primary outcome in HHC is the difference in number of incident cases of active TB (all forms) in the two arms by active case finding over a follow-up period of 2 years. The secondary outcomes are improvement

Table 6 Case definitions for outcomes used in RATIONS trial[6]

Outcome	Case definition
Active TB	Any patient with microbiologically confirmed TB or clinically diagnosed TB
Microbiologically confirmed TB in adults or children	A patient who has a positive sputum smear for *Mycobacterium tuberculosis* and/or ► Sputum/gastric aspirate is positive on CB-NAAT ► And/or positive on culture
Clinically diagnosed PTB	A patient who has symptoms suggestive of TB, is smear negative and/or negative on CB-NAAT, and/or who has CXR is suggestive of TB, and where there is no alternative clinical diagnosis
Clinically diagnosed extra-PTB	A patient who is either negative on microbiological testing and/or CB-NAAT, or where an appropriate specimen is not available, and the findings (clinical/biochemical/cytological/histopathological/radiological or direct visualisation procedures) are suggestive of TB, and where alternative diagnosis has been ruled out
Clinically diagnosed PTB in children	A patient who has symptoms suggestive of active PTB (fever, cough, weight loss or the absence of weight gain), and/or a CXR is suggestive of TB, and there is absence of alternative diagnosis, who is negative on CB-NAAT on gastric aspirate or induced sputum, or when bacteriological confirmation has not been possible

CB-NAAT, Cartridge-based nucleic acid amplification test; CXR, chest X-ray; PTB, pulmonary tuberculosis ; RATIONS, Reducing Activation of Tuberculosis by Improvement of Nutritional Status.

in the nutritional indicators over 6 months, frequency of malaria, diarrhoea, lower respiratory tract infection, hospitalisation with fever of any cause or death with fever of any cause less than 15 days in duration in both the trial arms.

The secondary outcomes in the index cases are successful treatment completion, TB-related deaths, improvement in performance status, adverse effects and recurrence of TB during 2-year follow-up. The ascertainment of primary outcomes of incident TB in contacts is by NTEP staff (not part of the trial team).

Participant timeline

The trial has a preparatory phase of 3 months for site selection, staff recruitment and training, and preparation of manual of procedures. The intervention phase will be 6 months for drug-susceptible cases and 12 months in the MDR-TB. The follow-up phase will continue for 2 years from the initiation of treatment.

Sample size estimation

The estimated incidence rate of PTB in the general population in India is 217/100 000 population (0.208 %).[4] The incidence rate ratio of TB in HHC is 15.9 (IQR: 2.6–21.4) compared with the general population, translating into 4% incidence in the HHC.[22] Assuming a higher burden of TB and undernutrition in India, and recent emerging evidence of significantly higher risk of TB disease following infection in close contacts,[33] we considered TB incidence in HHC to be 5% over the study period. We assume 50% reduction in TB incidence at household level with intervention.[34]

Our sample size considers design effect at three levels; the TU level, the families of index cases and finally their HHC.[35] We assumed approximately 100 index cases (80–120) and their families in a cluster per annum, a correlation coefficient of 0.2 for the outcome in HHC and 0.01 between members of the same cluster,[22] and thus a design effect of 6.75. Thus, a sample size of 28 clusters with 2800 patients and approximately 11 200 contacts equally distributed in both the arms would have 80% power to detect 50% reduction of TB incidence in intervention arm with a type-1 error of 5%.

The substudy sample sizes were estimated based on the assumptions related to the objective of the substudy. The sample size of 250 cases (125/arm) and 250 contacts (125/arm) was based on the prevalence of multiple vitamin deficiencies in patients with PTB,[36] and the prevalence of vitamin D deficiency in apparently healthy individuals in India.[37]

A sample size of 352 contacts (176/arm) was assumed to be needed to detect a 10% difference in mean CD4 counts in the contacts of the two arms after 6 months of intervention, with 90% power. This proportion is about 3% of the HHC and we will enrol a similar 3% of the index cases (50/arm) to assess determine the immune function at baseline and after intervention in them.

The sample size for the dietary intake substudy assumes an SD of 525 kcal, over a wide range of caloric intakes.[38] Assuming a mean difference in caloric intake between both the arms as 400 kcal and 20% loss to follow-up, we will enrol 45 contacts and 45 patients in each arm.

Data collection and management

The data will be collected by field investigators working in close collaboration with the NTEP staff. Study data will be collected and managed using Research Electronic Data Capture, an electronic data capture tools[39] hosted at ICMR-NIRT. The data capture will be done real time using a handheld device, will be subjected to range and logic checks and will be monitored by the project technical

team. A periodic quality check will be performed for accuracy and completeness by the data management team at ICMR-NIRT, which will minimise missing data. Appropriate imputation methods will be used for missing values in the analysis if required. The final dataset will be accessible to the investigators based in Yenepoya (deemed to be University) and ICMR-NIRT and will be deposited in electronic format with the trial sponsor, ICMR, at the end of the study.

All essential trial documents and consent forms will be stored under lock and key at the recruitment site under the supervision of investigators. Electronic data will be password protected and the records will be retained for a period of 5 years after completion of the study.

We will constitute a data safety management board (DSMB) comprising of subject experts in clinical trials, TB and nutrition along with independent biostatistician and ethicist.

Apart from the regular monitoring by the project team, there is periodic reporting to the ICMR, to the institutional ethics committee (IEC) of ICMR-NIRT, the trial advisory committee and the DSMB.

Data analysis

The primary outcome is TB incidence among contacts, expressed as events per 100 000 person-months of follow-up. Follow-up is defined as time from date of randomisation until the earliest endpoint, that is, documented TB disease or censoring (death, loss to follow-up or end of the study).

Cox proportional hazards model, accounting for varying follow-up times and clustering effect, will be used to compare the rate of progression of TB infection to disease among contacts between the arms and to assess its association with risk factors. Unadjusted and adjusted HRs along with their 95% CIs will be reported. The crude effect of the intervention will be calculated using Kaplan-Meier survival plots and compared using the log rank test.

The primary analysis will be intention to treat. Per-protocol analysis will also be done. The models will be adjusted for relevant risk factors (age, smoking, diabetes and duration of exposure) during the sensitivity analysis.

The secondary outcomes of change in weight and z-scores in patients and HHC, and the performance status in patients, will be compared using unpaired and paired t-tests and Bonferroni correction for multiple comparisons. Linear mixed regression models adjusted for age, gender, TU, caste, asset score, family size and baseline weight will be done.

The secondary outcomes of frequency of non-TB morbidities and deaths due to infections in the HHC, and the frequency of deaths, adverse effects, defaults and relapse in the index cases in the two arms, will be compared using the χ^2 test and Cox proportional hazards regression for time to first event.

The patients enrolled in the substudies will be compared in their baseline characteristics as these have been drawn by non-random sampling of patients from the main trial.

The changes in dietary intake of calories and proteins, body composition parameters and lymphocyte will be assessed among index and contacts. Interactions between treatment and change in nutritional and body composition indicators will be tested using likelihood ratio tests.

The effect of subgroups will be analysed based on age, gender, caste, residence, BMI, asset score and possession of below poverty line card, alcohol use and family history of TB. A $p<0.05$ (two-tailed) will be considered statistically significant. All data will be analysed using STATA V.16.1 (StataCorp, Texas, USA).

Interim analysis will be performed on attaining 50% of outcomes in the control arm (approximately 230 cases) with $p<0.0054$ as statistically significant. The final analysis will be done at the end of attainment of planned sample size and completion of follow-up, considering $p<0.0492$ as statistically significant.

Harm

The intervention involves locally consumed food items, which are part of the daily diet and hence no specific adverse events are expected. Patients who have lactose intolerance will be offered alternatives. The possibility of 're-feeding syndrome' in severely undernourished patients will be prevented by training the field staff to offer a graded increase in food intake in such patients.

Ethics, participant information and consent

Ethics clearance has been obtained from IEC of ICMR-NIRT, Chennai (NIRT-IEC number: 2018020), to which all the amendments of the protocol will be communicated. Patients and their HHC who are enrolled in the study will receive a detailed 'Participant Information Sheet' in local language before administering the informed consent. A separate consent form will be used for the adult participants enrolled in the substudy on micronutrient status and immune function. No blood specimen will be stored for any future use. A unique numerical code will be allocated to each participant for purpose of their identification and for maintaining confidentiality. Personal identifiers will be deleted in the final research database for analysis. All forms with personal identifiers will be under lock and key with the trial team.

Responsibility for ancillary care during the trial

Any index case or HHC found to have an acute illness other than TB during the follow-up visits will be facilitated by the field staff to reach the nearest government health set-up.

Patient and public involvement statement

Patients were not directly involved in the development of the research question. The components of food basket were discussed with community health workers during the preparatory phase of the trial. The training of the field staff involved interaction with TB survivors and two of the field staff in the trial are TB survivors.

Dissemination plan

The impact of nutritional support on TB incidence and outcomes in this trial will be of relevance to NTEP, India. The results will be disseminated through publications, conference presentations and briefs for the programme managers, Jharkhand's department of health, policymakers and other stakeholders. We intend to share the published results in simple language with the participants and community leaders.

Trial status

The trial was started on 16 August 2019 after trial registration and an intensive 2 weeks training of 56 field staff, two project consultants and one project director by state NTEP staff, nutritionist and specialists in TB, ethicist, TB champions, communication experts and social scientists. We have enrolled 2488 index cases and 9125 HHC in the trial as of 31 October 2020.

Author affiliations
[1]Department of Medicine, Yenepoya Medical College Hospital, Mangalore, India
[2]Center for Nutrition Studies, Yenepoya University, Mangalore, India
[3]Department of Community Medicine, Yenepoya Medical College Hospital, Mangalore, India
[4]National Institute of Research in Tuberculosis, Chennai, India
[5]National Institute of Nutrition, Hyderabad, India
[6]Division of ECD, Indian Council of Medical Research, New Delhi, Delhi, India
[7]State TB Cell, Ranchi, India
[8]WHO, Technical Support Network, Ranchi, India
[9]State Tuberculosis Demonstration and Training Centre, Ranchi, India
[10]World Health Organisation Country Office for India, New Delhi, India
[11]National Tuberculosis Elimination Programme, India Ministry of Health and Family Welfare, New Delhi, Delhi, India

Acknowledgements We wish to gratefully acknowledge the critical inputs of Professor Dick Menzies, Director McGill International TB Centre and Professor Andrea Benedetti, of McGill University's Departments of Epidemiology, Biostatistics and Occupational Health and Medicine, on early drafts of the protocol. We also wish to thank Dr Soumya Swaminathan, former Director-General, Indian Council of Medical Research, and Chief Scientist (WHO) for her support in exploring nutritional interventions to address the tuberculosis and undernutrition syndemic in India.

Contributors AB conceived the research question. AB, BV, MB, KT and BK designed the study protocol and drafted the manuscript. BW, MS, RD, AM, RRP, KR and KSS reviewed the study protocol and provided critical intellectual content. All authors carefully read and approved the final version of the manuscript.

Funding The Reducing Activation of Tuberculosis by Improvement of Nutritional Status study is supported by the India Tuberculosis Research Consortium, Indian Council of Medical Research, New Delhi, India, vide grant number 5/8/5/57/TB Consortium/Cali India Project/2017/ECD-1. The funder has no role in the study design and writing of the protocol, and will not have any role in collection, management, analysis and interpretation of data; the writing and the decision to submit any future reports for publication.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and **peer review** Not commissioned; externally peer reviewed.

ORCID iDs
Anurag Bhargava http://orcid.org/0000-0001-7187-8759
Madhavi Bhargava http://orcid.org/0000-0001-7480-566X
Bharati Kulkarni http://orcid.org/0000-0003-0636-318X
Manjula Singh http://orcid.org/0000-0001-8656-3768

REFERENCES

1 World Health Organization. *Global tuberculosis report 2020*. Geneva: World Health Organization, 2020.
2 World Health Organization. *Implementing the end TB strategy: the essentials. WHO/HTM/TB/2015.31*. Geneva: WHO, 2015.
3 Central TB Division, Ministry of Health and Family Welfare, Government of India. National strategic plan for TB elimination (2017-2025) 2017 http://tbcindia.gov.in/WriteReadData/NSP%20Draft%2020.02.2017%201.pdf
4 World Health Organization. *Global tuberculosis report 2016*. Geneva: World Health Organization, 2016.
5 Mangtani P, Abubakar I, Ariti C, *et al*. Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials. *Clin Infect Dis* 2014;58:470–80.
6 Revised National TB Control Programme. *Technical and operational guidelines for tuberculosis control in India*. New Delhi: Central TB Division,Ministry of Health and Family Welfare, 2016.
7 WHO consolidated guidelines on tuberculosis. *Module 1: prevention – tuberculosis preventive treatment*. Geneva: World Health Organization, 2020.
8 Paton NI, Borand L, Benedicto J, *et al*. Diagnosis and management of latent tuberculosis infection in Asia: review of current status and challenges. *Int J Infect Dis* 2019;87:21–9.
9 Houben RMGJ, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. *PLoS Med* 2016;13:e1002152.
10 World Health Organization. *Physical status: the use and interpretation of anthropometry: report of a WHO expert Committee*. Geneva: World Health Organization, 1995.
11 Cederholm T, Bosaeus I, Barazzoni R, *et al*. Diagnostic criteria for malnutrition - An ESPEN Consensus Statement. *Clin Nutr* 2015;34:335–40.
12 Cederholm T, Jensen GL, Correia MITD, *et al*. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. *Clin Nutr* 2019;38:1–9.
13 Bhargava A. Undernutrition, nutritionally acquired immunodeficiency, and tuberculosis control. *BMJ* 2016;355:i5407.
14 Lönnroth K, Williams BG, Cegielski P, *et al*. A consistent log-linear relationship between tuberculosis incidence and body mass index. *Int J Epidemiol* 2010;39:149–55.
15 Waitt CJ, Squire SB. A systematic review of risk factors for death in adults during and after tuberculosis treatment. *Int J Tuberc Lung Dis* 2011;15:871–85.
16 International Institute for Population Sciences, ICF. *National family health survey (NFHS-4), 2015–16: India*. Mumbai: IIPS Mumbai, 2017.
17 Mazumdar S, Satyanarayana S, Pai M. Self-Reported tuberculosis in India: evidence from NFHS-4. *BMJ Glob Health* 2019;4:e001371.
18 Bhargava A, Benedetti A, Oxlade O, *et al*. Undernutrition and the incidence of tuberculosis in India: national and subnational estimates of the population-attributable fraction related to undernutrition. *Natl Med J India* 2014;27:128–33.
19 Bhargava A, Chatterjee M, Jain Y, *et al*. Nutritional status of adult patients with pulmonary tuberculosis in rural central India and its association with mortality. *PLoS One* 2013;8:e77979.
20 Oxlade O, Huang C-C, Murray M. Estimating the impact of reducing under-nutrition on the tuberculosis epidemic in the central eastern states of India: a dynamic modeling study. *PLoS One* 2015;10:e0128187.
21 Grobler L, Nagpal S, Sudarsanam TD. Nutritional supplements for people being treated for active tuberculosis. *Cochrane Database Syst Rev* 2016;6:CD006086.
22 Fox GJ, Barry SE, Britton WJ, *et al*. Contact investigation for tuberculosis: a systematic review and meta-analysis. *Eur Respir J* 2013;41:140–56.

23 Enarson DA, Fanning EA, Allen EA. Case-finding in the elimination phase of tuberculosis: high risk groups in epidemiology and clinical practice. *Bull Int Union Tuberc Lung Dis* 1990;65:73–4.
24 Grandjean L, Gilman RH, Martin L, *et al*. Transmission of multidrug-resistant and drug-susceptible tuberculosis within households: a prospective cohort study. *PLoS Med* 2015;12:e1001843.
25 Jubulis J, Kinikar A, Ithape M, *et al*. Modifiable risk factors associated with tuberculosis disease in children in Pune, India. *Int J Tuberc Lung Dis* 2014;18:198–204.
26 Morán-Mendoza O, Marion SA, Elwood K, *et al*. Risk factors for developing tuberculosis: a 12-year follow-up of contacts of tuberculosis cases. *Int J Tuberc Lung Dis* 2010;14:1112–9.
27 Food and Nutrition Security Analysis, India, 2019. Ministry of statistics and programme implementation, the world food programme 2019.
28 de Vallière S, Barker RD. Poor performance status is associated with early death in patients with pulmonary tuberculosis. *Trans R Soc Trop Med Hyg* 2006;100:681–6.
29 Central TB Division, Ministry of Health and Family Welfare, Government of India. *India TB report 2018*. New Delhi: Central TB Division, Ministry of Health and Family Welfare, Government of India, 2018.
30 Central TB Division, Ministry of Health and Family Welfare, Government of India. *Guidance document on nutritional care and support for patients with tuberculosis in India*. New Delhi: Central TB Division, Ministry of Health and Family Welfare, Government of India, 2017.
31 WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004;363:157–63.
32 Alpers DH. *Manual of nutritional therapeutics*. 5th ed. New York: Lippincott Williams & Wilkins, 2008.
33 Trauer JM, Moyo N, Tay E-L, *et al*. Risk of active Tuberculosis in the five years following infection … 15%? *Chest* 2016;149:516–25.
34 Bhargava A, Pai M, Bhargava M, *et al*. Can social interventions prevent tuberculosis?: the Papworth experiment (1918-1943) revisited. *Am J Respir Crit Care Med* 2012;186:442–9.
35 Teerenstra S, Lu B, Preisser JS, *et al*. Sample size considerations for Gee analyses of three-level cluster randomized trials. *Biometrics* 2010;66:1230–7.
36 Oh J, Choi R, Park H-D, *et al*. Evaluation of vitamin status in patients with pulmonary tuberculosis. *J Infect* 2017;74:272–80.
37 Beloyartseva M, Mithal A, Kaur P, *et al*. Widespread vitamin D deficiency among Indian health care professionals. *Arch Osteoporos* 2012;7:187–92.
38 Hall JC. A method for the rapid assessment of sample size in dietary studies. *Am J Clin Nutr* 1983;37:473–7.
39 Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.

PLOS Global Public Health

RESEARCH ARTICLE

Qualitative study of acceptability, benefits, and feasibility of a food-based intervention among participants and stakeholders of the RATIONS trial

Sunita Sheel Bandewar[1‡], Madhavi Bhargava[2,3‡*], Hema Pisal[4], Sharanya Sreekumar[5], Anant Bhan[6], Ajay Meher[7], Anurag Bhargava[3,8,9]

1 Secretary General, Forum for Medical Ethics Society, Mumbai, India, **2** Professor, Department of Community Medicine, Yenepoya Medical College, Mangalore, India, **3** Center for Nutrition Studies, Yenepoya (Deemed to be University), Mangalore, India, **4** Independent Researcher and Anthropologist, Pune, Maharashtra, India, **5** Program Assistant, Forum for Medical Ethics Society, India, **6** Global Health and Ethics Researcher and Consultant, Forum for Medical Ethics Society, Mumbai, India, **7** Senior Programme Manager and Team Lead, Swasthya Swaraj Society, Kalahandi, Odisha, **8** Professor, Department of Internal Medicine, Yenepoya Medical College, Mangalore, India, **9** Department of Medicine, McGill University, Montreal, Canada

‡ These authors are joint senior authors on this work.
* madhavibhargava4@gmail.com

OPEN ACCESS

Citation: Bandewar SS, Bhargava M, Pisal H, Sreekumar S, Bhan A, Meher A, et al. (2025) Qualitative Study of Acceptability, Benefits, and Feasibility of a Food-based Intervention among Participants and Stakeholders of the RATIONS Trial. PLOS Glob Public Health 5(4): e0004219. https://doi.org/10.1371/journal.pgph.0004219

Editor: N. Sarita Shah, Emory University Rollins School of Public Health, UNITED STATES OF AMERICA

Received: January 7, 2025

Accepted: April 4, 2025

Published: April 28, 2025

Data availability statement: All relevant data are within the paper and its Supporting Information files.

Funding: AB and MB secured the grant by the India Tuberculosis Research Consortium,

Abstract

A qualitative study was conducted during the RATIONS trial to explore the perceptions, experiences, and expectations of participants and stakeholders on the acceptability, benefits, and feasibility of the nutritional intervention to complement the trial findings for deeper exploration into why and how of these findings and other allied themes. Using purposive sampling, we recruited 58 individuals for 22 in-depth interviews (IDI) and four focus group discussions (FGDs) between January and June 2022. These included 12 patients with TB, six household contacts, and other stakeholders (18 trial members, 18 government community workers, and four National TB Elimination Program (NTEP) staff). All IDIs and FGDs were audio-recorded, transcribed, and translated. The codes were generated using an inductive process and categorized manually into themes, with direct quotes describing the themes. The intervention was found to be acceptable in terms of cultural compatibility, quality, quantity, and duration; considered beneficial in helping tolerate the adverse effects of medications, weight gain, and resuming work; and was considered life-saving by many during the COVID-19 pandemic. Other observations included food-sharing in the control arm, inability to regain pre-disease functional status despite weight gain, and preference for in-kind support. Community health workers expressed confidence in its feasibility and willingness to take responsibility for its implementation. The NTEP staff considered it feasible if necessary resources were provided. This qualitative inquiry reflected the

Indian Council of Medical Research, New Delhi, India, grant no 5/8/5/57/TB consortium/Call India Project/2017/ECD-1 for the RATIONS trial and the qualitative sub-study. The funders did not have a role in study design, data collection, and analysis, the decision to publish, and in preparing the manuscript.

Competing interests: The authors have declared that no competing interests exist.

perspectives and lived experiences of households experiencing poverty, food insecurity, TB and the stakeholders serving them. Their voices are relevant in framing policy and practice in the NTEP and future research in India and similar low-resource settings. The food-based intervention was perceived as acceptable, feasible, and beneficial for the recipients and the NTEP. Opinion on cash or support in kind was divided; many preferred in-kind support over cash, but others expressed a requirement for both.

Introduction

Tuberculosis (TB) is one of the most widely prevalent infections, affecting 23% of the global population [1]. An estimated 10.8 million people fell ill with TB in 2023, with 1.25 million dying from TB in 2023, the highest with any single pathogen [2]. As a quintessential social disease, poverty is a major factor that affects both the exposure to M. tuberculosis and the outcomes of TB infection [3]. Undernutrition is an important factor associated with poverty that mediates its risk of active TB, leading to immunological dysfunction, referred to as nutritionally acquired immunodeficiency syndrome [4]. It is the leading risk factor for TB incidence worldwide, accounting for as many cases annually as due to HIV and diabetes combined [2]. Also, undernutrition is a widely prevalent comorbidity in persons with TB (PwTB) and is a consistent risk factor for TB mortality [5]. A Cochrane review was inconclusive about the effect of nutritional supplementation on treatment outcomes in PwTB [6]. However, the WHO recommended nutritional assessment and counseling for all PwTB and support to some groups as integral components of TB care [7].

The Reducing Activation of Tuberculosis by Improvement of Nutritional Status (RATIONS) trial, a cluster-randomized trial of nutritional intervention in PwTB and their HHCs, in a setting with a high prevalence of poverty, food insecurity, undernutrition, and a low prevalence of HIV and drug-resistant TB, addressed this evidence gap [8]. This was the first trial globally to estimate the effect of nutritional supplementation on TB incidence in a group at high risk of developing TB [9]. The trial population consisted of 2800 PwTB and 10,345 HHCs [9,10]. For ethical reasons, the documented high prevalence of severe undernutrition in PwTB in India and recommendations for nutritional care in a national policy document [11–13], PwTB in both trial arms received a monthly food basket and micronutrients for the treatment period (Table 1). The HHCs in the control arm (1400 families) received a food basket and micronutrients based on family size for the treatment period of the index PwTB. The primary outcome was the difference in the TB incidence in the HHCs in both arms over a two-year follow-up period [9]. Secondary outcomes included the nutritional and clinical outcomes [10]. This trial was registered with CTRI-India (CTRI/2019/08/020490).

This paper reports the findings from a qualitative sub-study of the RATIONS trial. The sub-study assesses trial participants' and stakeholders' perceptions,

Table 1. RATIONS Study intervention.

	Intervention arm	Control arm
Index case (1200 Kcal of energy and 52 gm proteins)	5 kg of rice 3 kg roasted Bengal gram powder (locally called as *sattu*) 1.5 kg of milk powder 500 ml vegetable oil One RDA of micronutrient	5 kg of rice 3 kg roasted Bengal gram powder (locally called as *sattu*) 1.5 kg of milk powder 500 ml vegetable oil one RDA of micronutrient
Household contact	5 kg rice 1.5 kg pulses (split pigeon peas) One RDA of micronutrient per adult/adolescent HHC Half of this for children less than 10 years.	Nutritional counseling Usual food assistance through the public distribution system

Source: RATIONS Protocol [8]; RDA = Recommended Dietary Allowance.

https://doi.org/10.1371/journal.pgph.0004219.t001

experiences, and expectations on the acceptability and feasibility of this food basket-based intervention. These have relevance to guideline development for programmatic implementation and future research [14].

Methodology

Study design

Study setting and context

The trial was conducted in association with the National Tuberculosis Elimination Program (NTEP) in four districts of Jharkhand in eastern India [8]. Jharkhand ("land of forest") is rich in mineral resources and has a significant forest cover and a hilly terrain. More than three-quarters of its population lives in rural areas, and more than a quarter comprises scheduled tribes (ST), a marginalized set of communities. Two-thirds of the participants in the trial were tribals, reflecting their higher proportion in the selected districts.

Jharkhand has many tribal groups: the Mundas, Gonds, Santhals, Ho, Oraons, and Bhumij [15]. They continue to fare the worst in terms of income, education, health, nutrition, prevalence of TB, access to health services, and nearly half are classified as suffering from Multidimensional poverty [16]. Infant and under-five mortality, nutrition indicators like wasting and stunting in children, and thinness and anemia in adults are higher compared to other social groups [17]. The World Bank reported that 55% of tribal households had some degree of food insecurity throughout the year [18]. The prevalence of TB in tribals is more than double the national average (703/100,000 vs. 316/100,000), and in some communities like the Sahariyas, it is almost 10 times [19–21]. In Jharkhand, agriculture is the backbone of the rural economy, revolving around a single rain-fed rice crop. Food insecurity is worse in the pre-harvest months of September to November due to small land holdings and subsistence farming [18].

Participant types

The participants in the qualitative sub-study (Table 2 and S1 Table) included the PwTB and their HHCs equally represented from the intervention and the control arms, the Sahiyas, the NTEP staff, the trial field staff that anchored the regular follow-up of the families, and the food delivery, two project consultants who supervised the field staff through field visits, checked food stocks, prepared the monthly rations procurement order, and liaised with government program staff. Sahiyas ("female friend" in the local language) is the local name for Accredited Social Health Activists (ASHAs), the community health workers associated with the National Health Mission [22]. Among many preventive and promotive health activities they conduct, the TB component includes case-finding, facilitating diagnosis and treatment, and enrolment in the scheme for direct benefit transfers (DBT), a monthly cash transfer for all PwTB under the Nikshay Poshan Yojana (NPY) to support nutritious food during treatment [23].

Table 2. Participant profile of the qualitative sub-study of the RATIONS trial.

Participant characteristics (N = 58)		N (Percent)
Age group	18-29	13 (22.4)
	30-39	32 (55.2)
	40-49	4 (6.9)
	50-60	9 (15.5)
Sex	Male	34 (58.6)
	Female	24 (41.4)
Education	Not adequately literate	6 (10.4)
	Primary School	5 (8.6)
	High School	21 (36.2)
	Graduate	16 (27.6)
	Post Graduate	8 (13.8)
	Not mentioned	2 (3.4)
Occupational status	Unemployed	8 (13.8)
	Employed	50 (86.2)
Type of participants	Patients with TB	12 (24.1)
	Household contacts*	6 (10.3)
	RATIONS field staff	16# (25.9)
	Sahiyas	18 (31.06)
	RATIONS Project consultants	2 (3.4)
	NTEP Staff	4 (1.8)
Type of data collection (n = 26)	In-depth interview	19 (73.1)
	Focused group discussion@	4 (15.4)
	Group interview	3 (11.5)

* 2 Household Contacts were also Sahiyas; #1 field staff was also a TB survivor; @ 6–10 Sahiyas and 8–10 field staff present in each FGD.

https://doi.org/10.1371/journal.pgph.0004219.t002

Research team attributes

The qualitative sub-study was anchored by social scientists from the Forum for Medical Ethics Society (FMES) with extensive experience in qualitative research and ethics, uniquely providing a third-party independent perspective. The lead trial investigators had experience spread over two decades of working with marginalized tribal communities in central India and researching interactions between TB and nutrition [24]. Their long-term engagement with the NTEP, involvement in the trial conceptualization and its conduct, and experiences with the implementation of the intervention helped the stakeholder mapping, framing the in-depth interview (IDI) and focus group discussion (FGD) guide, and interpreting the data.

Sample size

The eligibility criteria for this study included those above 18 years of age, trial participants (PwTB or their HHC), or stakeholders in the RATIONS/NTEP who agreed to participate in this qualitative study. The sample included an equal number of participants from each arm of the trial, with the representation of households from urban, rural, and remote locations as well as different communities. The trial participants were relatively homogeneous, with more than two-thirds belonging to indigenous communities with similar problems of poverty and food insecurity and challenged by a similar disease and its consequences. We ceased to recruit participants when it was felt that no additional themes or insights were emerging and data saturation was achieved. The qualitative sub-study was located within a large cluster randomized nutritional intervention trial with a substantive quantitative component. The qualitative sub-study was conducted within the context of quantitative information emerging from the trial.

Sampling and recruitment strategy

The study used a purposive sampling framework with participants and stakeholders across urban/rural geography, community groups, and social class. The trial field staff helped recruit PwTB and their HHCs and Sahiyas, while the trial investigators helped recruit the field staff and project consultants. The NTEP program staff were recruited with inputs from the trial team. None of the participants declined participation.

Data collection techniques and tools

The RATIONS trial ended in August 2022, and the data collection for qualitative inquiry was done from January to June 2022. The overall contours of the semi-structured interview guide were adapted suitably for the respective stakeholders. The interview guide was designed in English; however, the interviews were conducted in Hindi. The IDIs of trial participants occurred at their residences, and all FGDs were in community halls (the Panchayat Bhawan) or district headquarters. Participant IDIs began with general questions followed by probes when required (S1 Text). The general questions included, "Can you tell me about your experience as a PwTB/HHC/RATIONS project consultant/NTEP staff? Can you tell me about the food basket? and can you tell me about your main challenges?" The FGDs began with general questions followed by probes when required (S2 Text). These included, "Can you tell me your role in TB care? What do you know about the RATIONS project? How are you engaged in it? and can you tell me about the challenges of RATIONS-like food-based intervention?"

During data collection in the field, all the prevailing infection prevention guidelines of the COVID-19 pandemic were followed. All data collected was face-to-face except online IDIs with the two project consultants and one with senior NTEP staff. All interviews were conducted in Hindi, and in some, the aid of a local interpreter was utilized, and leading questions were avoided as far as possible. The duration was 90 to 120 minutes for IDIs and up to 180 minutes for FGDs.

Data processing and analysis

Interviews were continued till HP and SS identified data saturation. All audio-recorded interviews were transcribed verbatim, translated into English by SS, and cross-checked by SSB. Both repeatedly read these to identify any grammatical errors or consistency of the meaning. Additionally, investigator triangulation was used to understand some of the technical terms related to TB and NTEP and to improve the credibility and validity of the results. This was done by consistently discussing and reconciling the context of keywords, broader concepts, and terminologies among the research team throughout the data collection process. For the analysis, similar responses were coded and grouped. Codes were generated using an inductive process and manually categorized by the social scientists in the team into themes and sub-themes. Direct quotes were employed to describe the themes.

Ethics

Written informed consent was obtained from all participants: the PwTB, HHCs, project staff, the Sahiyas, and the NTEP staff. Appropriate privacy and confidentiality measures were undertaken, and data were anonymized. The RATIONS trial received ethics approval from the Indian Council of Medical Research – National Institute of Research in Tuberculosis ethics committee (ICMR-NIRT: 2018020), Chennai. Only FGD participants were provided refreshments due to its time-intensive nature, and there was no monetary compensation for participation.

Measures and techniques to enhance the quality of data

Any RATIONS trial team member known to the trial participants was not part of the IDI to ensure rigor and credibility. Similarly, during the FGDs with Sahiyas, no government health staff were present. The lead investigators recused themselves during FGDs and IDIs of the field staff and project consultants.

Results

The stakeholders' perspectives that emerged consisted of not only those related to the stated objectives like ascertainment of acceptability, content of food basket, and its benefits in terms of weight gain and ability to work but also the unstated aspects of the intervention. These included positive experiences of being cared for, well-being, personhood, and dignity. The results are organized around the themes that emerged in the content analysis and supported by relevant quotes, also represented in Table 3.

1. Acceptability of the food basket

We explored the participants' views regarding the acceptability of the food basket, palatability, ease of cooking, and quality compared to their usual food, as described below.

1.1 Cultural compatibility. Almost all participants asserted cultural compatibility of the intervention, along with good taste. Some mentioned that 'sattu," although available in the market, is unaffordable and was mainly for special occasions/festivals.

> *"I liked it all. … I used to make sattu balls/laddu and eat. … Milk powder, I mixed water; I made rice and used oil to cook vegetable curry."* (Female PwTB)

The diverse ethnic communities have their own specific food-related cultural practices. They have certain similarities and differences regarding their food preferences. Several meat items were desirable inclusions in the interactions with varied preferences across ethnic communities. This and certain commonalities justified the content of a "desirable" food basket.

> *"Like some (ethnic groups) eat suvar (pork) and some don't. But most eat meat, fish, and eggs … (Therefore,) the food basket could be the same for all. All consume eggs. Santhal, Munda, Mahato, Karmakar, and even Brahmins eat eggs. (And) meat, fish can be there, but not all eat it." (Male PwTB)*

Table 3. Themes of the qualitative inquiry in RATIONS study and representative quotes.

Theme	Representative quote	Participant
Acceptability of the food basket	"We are Munda. We have Munda, Gopa, Kurmi, Lohar (artisans engaged with fabrication and ironwork), and Santhals in this village. Eating habits (of all these ethnic/ artisan groups) are almost the same but (with) some difference."	Male PwTB
Perceived benefits of the food basket	"My mother became better soon with ration. We did not find it difficult to give her the food she needed. She was very weak, but after getting food, her weight increased."	Female HHC
Quantity and content of food basket	"It is good, but some patients say it would have been better if eggs had been given."	Sahiya
Duration of support	"It is given for the patient's welfare, so it can be stopped when the patient becomes healthy. But if the patient is not okay, it should be prolonged."	Female PwTB
Resource constraints in TB-affected households	"…..we would not pay attention to our diet as we go to work and sometimes sleep without food only."	Male PwTB
Food insecurity and the COVID-19 pandemic	"COVID-19-related lockdown worsened the livelihood and food availability. Our patients badly needed the food basket, but the police used to drive the field staff away initially (during lockdown). It was tough."	Male project consultant
Feasibility, mainstreaming, equity, including cash vs. kind	"Send the food ration according to the number of patients in each village and drop it off at the *Panchayat office*. We will collect it and deliver it to the patients. At village level it is easy." "If I were to choose, I would choose food over cash. If you want to give both, that is also fine"	Sahiya
Stigma	"All this (stigma) is present among urban people, not in our villages"	Male Medical Officer, NTEP

https://doi.org/10.1371/journal.pgph.0004219.t003

1.2 Quality of the food basket, its comparison with their regular food. All trial participants unambiguously expressed satisfaction with the quality of the food basket. Many felt it was far better than what they usually eat and mentioned that the public distribution system (PDS) must also provide additional grocery items.

"What they gave was good and tasty. We get sattu in the market, but the sattu they gave we won't get in the nearby shop, not as good." (*Male PwTB*)

We further probed the quality by comparing food baskets with PDS food, one of the largest social welfare schemes of fair-priced government shops on which many poorer families depend across India. These insights are relevant as PDS can be a good strategy for the scale-up of the intervention in the future. Broadly speaking, three distinctive factors emerged in this comparison: the diversity of food items, the quantity, and the quality.

"There is much difference between the rations we receive from the PDS and what they gave. (For example), they (PDS) only give rice, and here (in the trial food basket) we get sattu, milk and better rice." (*Male PwTB*)

2. Perceived benefits of the food basket

2.1 Improvement in weight and strength. The expression of benefits and gratitude varied according to the participant's needs, vulnerabilities, and lived experiences. An important message underscored a positive experience of feeling better, gaining weight, and gaining strength.

"I was a very thin person earlier. This food was good for me as it increased, almost doubled my weight." (*Female PwTB, physical disability, Indigenous community).*

The benefits went beyond 'feeling better' to positively impact other spheres of life, such as schooling, sports, and a sense of well-being.

"I had stopped my studies and playing on the ground when I had the disease. Now, I have started to play volleyball." (*Male PwTB, youth*)

2.2 Better adherence to treatment due to lesser side effects. Participants drew a link between "powerful" TB medicines and the favorable impact of adequate good food from their lived experiences. Many highlighted that TB medicines could have been difficult to consume without the food basket, essential for treatment adherence, vital to achieving a cure, and important programmatic implications.

"If I had not got the ration, it would have been tough for me. The medicines are so powerful that I would have died." (*Male PwTB*)

The complex relationship between undernutrition, TB, side effects of medicines, lack of compliance, and drug resistance was explained by a senior medical officer of tribal origin who has been working in the region for > 25 years:

"Side effects of TB medicines are more in malnourished patients. After some time, he will stop eating food due to vomiting. We will know about it only when we do the follow-up, and then we will restart medicines. This irregularity would ultimately develop drug-resistant TB." (Male Medical Officer)

2.3 Effects on outcomes like death and recurrence of TB. The food basket played a role in patient-centered outcomes. Moreover, these are also important from the NTEP perspective: TB deaths and recurrence. The Sahiyas, who were uniquely placed to compare patients within and outside the trial, shared their observations regarding the benefits of the food basket.

"Those who received food baskets improved completely. They gained weight. Another patient on treatment migrated somewhere, but he died there. … All those who received food baskets are doing well now, but those who did not receive them have got TB again." (FGD Sahiyas)

2.4 Other collateral benefits: the positive community impact. We noted some collateral benefits of the trial team's engagement with the families. For example, a HHC developed TB and was not eligible for a food basket. However, due to the knowledge gained about the type of diet that would be beneficial, the family attempted to maintain a diet like the trial diet. The positive impact on community food practices, thus, goes beyond TB. The home visits by the field staff and periodic checkups were added benefits.

"We would not have come to know about all this, and we would not have this knowledge, such as how TB occurs, how it spreads, what food is needed to prevent it, and which medicine we should take for this disease." (Male HHC)

The lived experiences of individuals brought unique insights into how they perceive the relevance of such an intervention.

"When I had TB, we had to go to STS (Senior Treatment Supervisor), and he would reply to our questions. But no one visited our house to help us understand diet and lifestyle, not when I had TB."(female field staff and TB survivor)

3. Expectations regarding the food basket: quantity and content

During the interaction with patients, their families, and Sahiyas, various expectations regarding the content of the food basket were expressed for a possible roll-out on a large scale. Eggs and non-vegetarian items were often included in this wish list.

"I will take potato, all kinds of vegetables such as tomato, brinjal then dal and rice. If possible, I would like to have meat (once) in a week." (Male PwTB)

Some other Sahiyas mentioned during the same FGD "potatoes, sugar-flavored branded supplements, soyabean." But then immediately, someone in the group quipped that if we demand more, even those getting the food basket will not get it. About the quantity, most felt it was okay, and some wanted more. The trial participants in the control arm appeared to share with others, especially with children.

"The quantity of ration should vary by region. People in the village work hard and need more food. In cities, they sit in the workplace and drink milk and nutritious food, but village people do manual work and eat less nutritious food." (Female HHC)

4. Duration of support, regaining strength, but not enough to resume work

Several study participants expressed that although the food basket was helpful and they had recovered, they have not been able to resume work, often labor-intensive, primarily because they continue to feel weak.

"I was a mason. I felt as if having gained strength but not as much as before disease. The ration provided surely helped improve my health. ... but I feel weak even now and am just staying at home." (Male PwTB)

The food basket was responsive to their nutritional needs, and the benefits transcended TB recovery to improve health, but at times, not sufficient to resume their earlier work. Considering the high prevalence of severe undernutrition in PwTB in the trial, a significant proportion remained underweight at the end of treatment. The food basket was extended for these patients.[10] A patient with TB and diabetes who was underweight and regained normal weight put it across very well,

"if a person becomes healthy, then they can stop giving ration, but if someone is still weak, then they should continue to give them the food for their health."(Male PwTB)

A reflection of the understanding of the complexity of such an intervention by the government, the extent to which it can be done, and the general sense of resource constraints of public spending were evident in the expression that they do not wish to receive the support for a protracted period than the health of the patient warrants.

5. Resource-constrained circumstances of households affected by TB

We encountered trial participants who did not consume milk regularly. Often, participants had limited food items or only one or two meals during the day and nothing else.

"We don't have not much. I ate only one or two meals and used to eat very little then. (Before receiving the food basket) My meal used to be Alu ka sabji (potato side dish), rice (only), and this much (showing with hand)." (Male PwTB)

Several trial participants rarely included sattu and milk in their diet. Some mentioned reasons like limited purchasing capacity, but many did not mention any specific reasons, with an unstated dignified silence that did not escape the interviewers. Limited financial resources, dependence on contractual work, often involving heavy manual labor, and overall subsistence-based livelihoods implied precarious living conditions that can quickly worsen with TB. Loss of livelihood and poor strength to resume work with no reserve to sustain the difficult times worsened the situation for these families. This became especially evident when an incident TB case developed in a household and the intervention could not be provided to them, and the DBT was delayed.

"In my house, there was very little food. Our didi (Sahiya) and everyone else said I must eat good food because medicine is powerful. They said I would get money (not ration). That also I did not get till now." (Male HHC)

6. Food insecurity and the COVID-19 pandemic

With the loss of livelihood and lockdown, the pandemic worsened the already precarious conditions for the community. It shaped the views on the intervention for the trial participants and the field staff who faced many difficulties during the pandemic.

"We had to give food to my father on time, and we had also to feed everyone in the family. So, this food was lifesaving." (Female HHC)

"I like to say that during COVID, people used to say that they survived because of this food; otherwise, we would starve. In the RATIONS trial, we could see sensitive issues such as hunger and poverty very closely."(Male field staff).

7. Feasibility, mainstreaming, and equity

We spoke with the Sahiyas, field staff, and NTEP staff about possible feasibility issues, and many were willing to contribute as they felt it was essential despite the challenges.

7.1 Sahiyas. The Sahiyas were willing to get involved with the logistics if this was rolled out at scale. However, they mentioned that there should be good supportive supervision and monitoring as they do not want to be accused of pilferage.

"As Anganwadi workers (India has an Integrated Child Development Services Scheme where preschool children have informal education and supplementary nutrition, among other things) bring their goods, we will also unite to do the same. We are 4 in a village and will come together and do it in a tempo (small goods carrier vehicle). We will do anything for the patients."(Sahiyas)

7.2 Field staff of the trial. Apart from food delivery, the connection of the field staff with their assigned 80–120 households was an important aspect of care. This takes the issue from beyond feasibility to humane care for patients with problems like TB, where patients often experience stigma and discrimination.

"One patient, when I took his arm to take BP, he started crying. When I asked him about it, he said that the doctor never touched him in the hospital. He made me sit far away and talk and prescribed medicines to me from a distance. You are the first person who has touched and is talking to me face to face."(Male field staff)

The field staff expressed difficulty distributing the food basket on top of the rigorous data collection for a research trial. During the peak of the trial, with enrolment and follow-up of already enrolled patients, the difficult-to-reach areas or the scattered hamlets were especially challenging. But gratification was also expressed by most.

"The geographical situation here is such that the villages are scattered. So how many people can you visit in one day? But it feels good when you do something for someone….. Every job provides you money, but only a few provide ultimate pride and satisfaction." (Female field staff)

For feasibility, it is essential to mention the acceptability of project field staff delivering food baskets at the doorstep. While most participants were happy to have it delivered, there were challenges initially with some families. Villagers would gather and ask many questions due to trust issues. Things improved gradually with the improvement in the health of the trial participants, appropriate explanations by Sahiyas, and other sociocultural methods employed by the field staff.

"We drank their water, ate food that they offered, and they start trusting us once we help them in an illness and facilitate investigations."(Male field staff)

7.3 NTEP staff. The feasibility aspect was also discussed with the NTEP staff, if the intervention was scaled up to include all PwTB at the district level. While most agreed that this is needed, a senior NTEP staff foresaw challenges of procurement, storage, and distribution, which can be overcome by budgeting appropriately for human resources

"Even if done on a big scale, I do not think it should cause many problems because patient numbers will slowly reduce (with this intervention)."(Male STS)

7.4 Who should receive? The equity lens. The equity aspect of who should get it was discussed in various ways: whether food should be given to only microbiologically confirmed PwTB, all PwTB, or their entire households. The responses brought to the fore the challenges that the NTEP staff can face if it is done selectively, especially in food-scarce settings and the foreseeable issue of food-sharing. The Sahiyas expressed that it was uncomfortable for them that some patients who were part of the trial received food and others did not:

"All patients should get food. If food is given to all, the patient will recover quickly, and the disease will not spread. Most of them are poor, so all should get."(Sahiya)

Food sharing was especially common in the control arm, with a female index patient, when there were toddlers or more children in the family. One of the grandmothers, who was also a patient, said,

"I give the milk powder to my grandson when I have it" (Female PwTB)

For extending food to HHCs, the responses were "yes" and "no," each qualified appropriately.

"No, the nutritious food is for the patient's good health; they are taking medicines, and there are side effects. Why give it to the whole family?" (Female HHC).

On further probing these divergent opinions, the choices and preferences were rooted in the understanding of economic constraints. The resource constraints and possible non-feasibility for the government in supporting the food provision for the entire household of all PwTB might explain this divergence in the response. This was despite their own microcosms against the backdrop of difficult personal circumstances and limited financial capabilities.

7.5 Cash and/or kind. Most participants felt that both cash and food in kind are important. But when asked to choose, many felt that food is better than cash, which may get spent on things other than nutrition. The divergent opinion was also based on the presumption that patients will use the money on unnecessary expenses, including the possibility of alcohol. But at the same time, cash could be used for the food of their choice.

"Considering the present situation, Rs 500/- is not much for the patients. Maybe this amount needs to be increased." (Male STS)

"I would choose food and medicine. To get well, we need medicine, and to become healthy, we need food. It will be difficult for TB patients to go outside and buy the food items needed for their health." (Male PwTB)

However, it is important to note that branded and chocolate-flavored powders advertised as energy boosters were commonly mentioned during many interviews.

8. Stigma

Stigma can be reflected in keeping distance from TB patients and their families, and at times, it could even lead to ostracism – subtle or obvious. Stigma was more prominent in urban areas than in rural and tribal communities. Insights from one of the field staff, also a TB survivor, were helpful.

"A girl with TB was of marriageable age, and the family did not disclose this as it would hamper her prospects of marriage. We were told not to visit their house with rations, and they came and collected it." (Female field staff, TB survivor)

However, we also heard voices stating that once TB was cured, there was not much to worry about the marriage prospects of PwTB, especially in the rural and tribal areas. Practices to prevent the spread of infection can also be construed as stigma or can give rise to perceived stigma by the patient.

We probed the possible stigma related to ration being delivered, which has implications for programmatic scale-up.

"Nothing like that. Even when brother (field staff) used to come to give food, neighbors used to ask why they were coming. We just told the reason." (Male PwTB)

Discussion

The qualitative sub-study of the RATIONS trial reaffirmed the felt need for food-based intervention in PwTB and their household contacts. There are valuable additional insights into the possible composition of the food basket, the acceptability, the feasibility, the perceived benefits, and the background conditions like poor nutrition and food insecurity. Many participants alluded to food insecurity, manifesting in the unaffordability of nutrient-dense foods like sattu and milk powder to even cutting back on the number of meals consistent with moderate to severe food insecurity definitions by FAO [25]. Undernutrition is most commonly due to food insecurity, which "is the limited or uncertain availability of nutritionally adequate, safe foods or the inability to acquire foods in socially acceptable ways [26]." The trial had > 80% of the PwTB [10], and > 1/3rd HHCs with undernutrition [9]. The background to this is poverty [16], in which people develop TB, further exacerbated by the inability of the breadwinner to work, which creates a vicious cycle.

Food insecurity is widely prevalent in India [27], including moderate to severe food insecurity in households with PwTB [26,28], which is linked with many adverse outcomes [29]. In the recent comprehensive national nutrition survey, 3 of 5 adolescents did not have access to nutritious foods like fruit or milk even once a week [30]. In the National Family Health Survey-5, more than half of adults did not consume any pulses daily, nearly half did not consume any dairy products or dark green vegetables, more than 80% did not consume any fruits, and more than 90% did not consume any eggs or flesh foods [31]. Household food insecurity was strongly associated with the development of active TB in children (aOR: 11.55) [29]. Food insecurity is also linked to treatment adherence [32], and clinical outcomes in PwTB, with a fivefold higher risk of death [29]. The need for a food basket in such a situation was evident by the term "life-saving" used by some trial participants. Food insecurity is linked to a higher prevalence of mental health issues such as depression and anxiety and impacts treatment success [33].

The acceptability of the food baskets was high and attributed to content and quality. The perceptions about their quantity and duration varied according to individual needs and lived experiences. The composition of the trial food basket was based on the NTEP policy document [13]. Similar food baskets based on dry rations containing cereals and pulses have been well accepted in West Bengal and Madhya Pradesh in India [34–36]. Also, food baskets have been used with good acceptability in Afghanistan [37], Senegal [38], Angola [39], and Brazil [40]. These perspectives and in-depth understanding of "*why things are the way they are rather than how much they are a certain way*" are critical in guiding global recommendations and policymakers [41]. In India, 75% of rural and 50% of rural households have access to cheaper rice and wheat in PDS, which meets the cereal requirements and assumes that the resultant savings will improve their non-cereal intake [42]. Patients appreciated the quality and diversity of the food basket with the versatility of sattu that can be made into a savory or sweet drink, rolled into sweet balls, or stuffed into freshly baked savory Indian bread (Paratha). The food basket breaks the monotony as there is a choice of recipes, which is not the case with ready-to-use therapeutic foods (RUTF), where people may not like the taste or find a preparation too sweet or salty [38]. Locally available and acceptable sources of proteins like sattu need to be identified for scale-up.

The perceived "positive experience" of the food baskets included being able to return to work. Moreover, better adherence, reduced mortality, and reduced side effects are important to patients and NTEP. A very striking feature in Indian PwTB patients is the high prevalence and severity of undernutrition [10–12,43]. Undernutrition and poor weight gain are associated with a higher risk of death, drug toxicity, and recurrence of TB even after a cure [5,44,45]. With severe weight loss and poor weight gain, the ability to return to work is impaired. The persistence of undernutrition (40% continued to remain underweight at 6 months in the trial because of severe undernutrition at baseline) [10], and the presence of post-TB sequelae explains why some patients reported an inability to work as usual at the end of treatment [46]. This observation has an important policy implication regarding extended support for severely underweight patients and the necessary resource planning and program implementation.

Food baskets served as an enabler to better adherence to drugs that were otherwise difficult to tolerate, which has been observed in a systematic review [47]. The role of food insecurity in increasing the frequency and intensity of adverse drug reactions (ADR) has been noted in other countries, including in patients with HIV disease [32,48]. Undernutrition is a risk factor for drug toxicity with anti-TB drugs, but there is a paucity of ADR studies on PwTB with undernutrition as a comorbidity. A cohort of tribal patients in a community with a high burden of TB and undernutrition documented ADR in nearly 90% of PwTB, much more than that in our trial [10,49]. In a recent study in children and adolescents, ADRs were strongly associated with malnutrition, with Grade-3 ADRs exclusively seen in patients with malnutrition [50].

The RATIONS trial used food-based nutritional support and had high levels of acceptability among the beneficiaries. Acceptability in the intended beneficiaries is crucial in an intervention likely to involve investments of manpower, money, and time. There are discussions about introducing peanut-based energy-dense nutrition supplements (EDNS)/RUTF in India for PwTB [51]. A study of the acceptability of peanut-based EDNS in 102 PwTB over a 2-month period reported a 10% refusal and 14% adverse effects, and it provided 60 gm fat and 28 gm protein per day [52]. Unfortunately, this would not address the additional protein requirement in TB and the lost lean body mass. Also, the high-fat content may result in nausea and fat accretion rather than lean mass. In a small study in Africa of RUTF vs. food baskets in PwTB, nearly half reported a preference for food baskets [38]. In studies with peanut-based RUTF in Bangladesh, 40% of caregivers of children and nearly 80% of women found it unacceptable as a food product, citing palatability and smell despite the perception of a therapeutic benefit [53,54]. In Indian children, the acceptability of a 'khichri' (cooked preparation of rice and legumes) was much higher than that of a peanut-based RUTF [55]. RUTFs risk mystifying nutrition and making local communities dependent on higher-priced externally sourced food items. In 2015, a nutritional support program for patients with multi-drug-resistant tuberculosis in Mumbai had a 58% refusal rate as patients were not happy with the ready-to-eat foods offered, and the authorities switched to a food-based intervention [56].

The issue of the duration of food baskets and other alternative contents reflected a nuanced understanding of the feasibility of support. There is a need for an extension of support when the baseline weights are very poor, and there is a physiological limit to necessary weight gain over the treatment period [10].

Regarding the feasibility of implementing nutritional support, there was strong support from the community health workers with the caveat of community involvement and supportive supervision of the process. Additionally, the Sahiyas handed over a written petition at the end of FGD to convey this wish to the NTEP. The trial field staff provided valuable insights into the challenges of making doorstep deliveries of food rations in challenging terrain and hard-to-reach areas. A recent modeling study emphasizes the cost-effectiveness of food-based intervention within a feasible budget with improvement in equity and reducing the TB burden among those who are susceptible [57].

The interviews explored cash transfers, which are an operationally easier alternative to facilitate purchasing nutritious foods and have been operational since 2018 as NPY [23]. Some challenges in cash transfers include patients from the unorganized sector, those depending on daily wages, with no paid sick leave, continued wages, or non-availability of comprehensive health insurance covering outpatient and inpatient care [58]. Earlier studies have shown significant levels of indebtedness, mainly due to indirect costs associated with loss of wages in Indian PwTB [59]. In a recent national cost survey, > 45% of PwTB incurred catastrophic costs (costs >20% of annual household income) [60]. The question of cash transfers vs. food support in kind drew responses that either supported in-kind food support or the provision of both food and cash. The amount of cash in a cash transfer-only model should be adequate for purchasing a nutritious diet with adequate accounting for food inflation. An impact evaluation of the NPY has shown that non-receipt of DBT was associated with more than 4-fold higher odds of unfavorable outcomes [61]. As a positive step, the cash benefit for PwTB is to be doubled [51]. A vital step should be assessing the nutritional impact of these initiatives to shape future policies.

Finally, the qualitative study highlighted some persistent misconceptions that can impact rational and cost-effective nutritional care: the desire to buy branded sugary energy powders with little value for money. This can be attributed to the aggressive marketing of such products in print and audio-visual media, reinforcing the need to add counseling as an important long-term enabler in TB care [7,62].

Strengths and limitations

This qualitative inquiry had numerous strengths. First, it represents voices often under-represented in the literature because they are rural, live in remote areas, and belong to indigenous communities. Second, when qualitative aspects are studied in trials, there is potential bias when studied by the trial investigators. We minimized it by involving social scientists unrelated to the trial. Third, we ensured that the researchers or the field staff who knew the participants were not present during the interviews/discussions. Fourth, in-person interactions at the homes of the trial participants helped shape the understanding of the background conditions, the terrain, and the non-verbal communication that can be affected by online methods. Lastly, interim findings from the quantitative trial component were available to shape the interview guide.

The study had some limitations. The purposive sampling may not have fully represented the spectrum of perceptions, experiences, and opinions. The interviews were conducted primarily in Hindi, and some of the nuances expressed in the local language may have been affected. We did not explore gender issues and the experiences of children and adolescents. Lastly, the sample size of PwTB and HHCs could be considered small compared to the large trial population. However, given the background of poverty and food insecurity exacerbated by TB disease as well as the COVID pandemic in a relatively homogenous population, the interviewers perceived data saturation, a concept studied in the past [63].

Implications for policy, practice, and research

Undernutrition is a recognized and serious comorbidity in Indian PwTB and the most prevalent risk factor for TB incidence in India. India was one of the first countries to adapt the WHO guidelines for nutritional care and support and launched DBT to enable better nutrition for PwTB. The quantitative component of the RATIONS trial, as well as the qualitative inquiry discussed here, are relevant for the NTEP as the program plans to enhance the cash transfer, introduce appropriate nutritional support in kind, as well as expand food baskets to cover TB-affected households. This study has provided insights, perceptions, and experiences of beneficiaries and stakeholders, and evidence of how this food-based intervention can be therapeutic for patients, preventive for contacts, provider of social protection in a setting of food insecurity, and an enabler for adherence to therapy, and return to work.

Conclusions

The qualitative inquiry, the first of its kind, related to food-based intervention in TB-affected households, reflected the voices and lived experiences of poverty, insecurity, and TB, as well as of the stakeholders serving them. These are relevant to framing policy and practice in the NTEP and any future research in this domain. The food-based intervention for the PwTB and their HHCs was perceived as acceptable, feasible, and beneficial for the recipients and the NTEP. The lived experiences expressed as weight gain, recovery of strength to work, and ability to adhere to treatment because of better tolerability of drugs are in line with "patient-centered" outcomes aligning with India's resolve to end TB and the global END TB strategy. Opinion on cash or support in kind was divided; many preferred food support over cash, but others expressed a requirement for both. Beneficiaries had a nuanced understanding of the limitations of the government, but extending coverage to household members and duration of nutrition support when required was suggested.

Supporting information

S1 Table. Demographic characteristics of study participants and participant type in the qualitative sub-study of the RATIONS trial.
(DOCX)

S1 Text. Guidelines and steps followed for the In-depth Interviews.
(DOCX)

S2 Text. Guidelines and steps followed for the Focus Group Discussions.
(DOCX)

S1 Checklist. COREQ Checklist.
(PDF)

Acknowledgments

The authors would like to express appreciation for the tremendous efforts of the entire RATIONS field team, who worked in difficult terrain and continued work without interruption during the COVID-19 pandemic. The cooperation of the district TB officers and their teams is gratefully acknowledged.

Author contributions

Conceptualization: Sunita Sheel Bandewar, Madhavi Bhargava, Anant Bhan, Anurag Bhargava.

Data curation: Sunita Sheel Bandewar, Madhavi Bhargava, Hema Pisal, Sharanya Sreekumar.

Formal analysis: Sunita Sheel Bandewar, Madhavi Bhargava.

Funding acquisition: Madhavi Bhargava, Anurag Bhargava.

Investigation: Madhavi Bhargava, Hema Pisal, Ajay Meher.

Methodology: Sunita Sheel Bandewar, Madhavi Bhargava, Anurag Bhargava.

Project administration: Sunita Sheel Bandewar, Madhavi Bhargava, Sharanya Sreekumar, Ajay Meher, Anurag Bhargava.

Resources: Madhavi Bhargava, Anurag Bhargava.

Supervision: Madhavi Bhargava.

Writing – original draft: Sunita Sheel Bandewar, Madhavi Bhargava, Anurag Bhargava.

Writing – review & editing: Sunita Sheel Bandewar, Madhavi Bhargava, Hema Pisal, Sharanya Sreekumar, Anant Bhan, Ajay Meher, Anurag Bhargava.

References

1. Houben RM, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. PLoS Med. 2016 Oct 25;13(10):e1002152. https://doi.org/10.1371/journal.pmed.1002152
2. Global Tuberculosis Report 2024. Geneva: World Health Organization, 2024. [cited 2024 Dec 14]. (accessed 28th December 2024). Available from: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2024
3. Bhargava A. Bhargava M, Juneja A. Social determinants of tuberculosis: context, framework. and the way forward to ending TB in India. Expert Rev Respir Med. 2021 Jul;15(7):867-883. https://doi.org/10.1080/17476348.2021.1832469 PMID: 33016808
4. Undernutrition Bhargava A., nutritionally acquired immunodeficiency, and tuberculosis control. BMJ. 2016 Oct 12;355:i5407. https://doi.org/10.1136/bmj.i5407 PMID: 27733343
5. Waitt CJ, Squire SB. A systematic review of risk factors for death in adults during and after tuberculosis treatment. Int J Tuberc Lung Dis. 2011;15(7):871–85. https://doi.org/10.5588/ijtld.10.0352 PMID: 21496360
6. Grobler L, Nagpal S, Sudarsanam TD, Sinclair D. Nutritional supplements for people being treated for active tuberculosis. Cochrane Database Syst Rev. 2016 Jun 29;2016(6):CD006086. https://doi.org/10.1002/14651858.CD006086.pub4 PMID: 27355911
7. Guideline: Nutritional care and support for patients with tuberculosis. Geneva: World Health Organisation, 2013. (accessed 28th Dec 2024). Available from: https://www.who.int/publications/i/item/9789241506410
8. Bhargava A, Bhargava M, Velayutham B, Thiruvengadam K, Watson B, Kulkarni B, et al. The RATIONS (Reducing Activation of Tuberculosis by Improvement of Nutritional Status) study: a cluster randomised trial of nutritional support (food rations) to reduce TB incidence in household contacts of patients with microbiologically confirmed pulmonary tuberculosis in communities with a high prevalence of undernutrition, Jharkhand, India. BMJ Open. 2021 May 20;11(5):e047210. https://doi.org/10.1136/bmjopen-2020-047210 PMID: 34016663

9. Bhargava A, Bhargava M, Meher A, Benedetti A, Velayutham B, Sai Teja G, et al. Nutritional supplementation to prevent tuberculosis incidence in household contacts of patients with pulmonary tuberculosis in India (RATIONS): a field-based, open-label, cluster-randomised, controlled trial. Lancet. 2023 Aug 19;402(10402):627-640. https://doi.org/10.1016/S0140-6736(23)01231-X
10. Bhargava A, Bhargava M, Meher A, Teja GS, Velayutham B, Watson B, et al. Nutritional support for adult patients with microbiologically confirmed pulmonary tuberculosis: outcomes in a programmatic cohort nested within the RATIONS trial in Jharkhand, India. Lancet Glob Health. 2023 Sep;11(9):e1402-e1411. https://doi.org/10.1016/S2214-109X(23)00324-8
11. Padmapriyadarsini C, Shobana M, Lakshmi M, Beena T, Swaminathan S. Undernutrition & tuberculosis in India: Situation analysis & the way forward. Indian J Med Res. 2016 Jul;144(1):11-20. https://doi.org/10.4103/0971-5916.193278 PMID: 27834321
12. Bhargava A, Chatterjee M, Jain Y, Chatterjee B, Kataria A, Bhargava M, et al. Nutritional status of adult patients with pulmonary tuberculosis in rural central India and its association with mortality. PLoS One. 2013 Oct 24;8(10):e77979. https://doi.org/10.1371/journal.pone.0077979 PMID: 24205052
13. Guidance document on nutritional care and support for patients with tuberculosis in India. Central TB Division, Ministry of Health and Family Welfare, Government of India; 2017. (accessed 28th December 2024). Available from: https://tbcindia-wp.azurewebsites.net/guidance-document-nutritional-care-support-for-tb-patients-in-india/
14. Using qualitative research to strengthen guideline development [Internet]. (accessed 12th March 2025) Available from: https://www.who.int/news/item/08-08-2019-using-qualitative-research-to-strengthen-guideline-development
15. Tribes of Jharkhand. 2024/12/19/T15:20:15Z. 2024. (accessed 28th December 2024). Available from: https://en.wikipedia.org/w/index.php?title=Tribes_of_Jharkhand&oldid=1263951585%20files/3982/Tribes_of_Jharkhand.html
16. National Multidimensional Poverty Index: Baseline report. New Delhi: Niti Aayog. 2021. (accessed 20 Dec 2024) Available from: https://www.niti.gov.in/sites/default/files/2021-11/National_MPI_India-11242021.pdf
17. Tribal Health Report, India – First Comprehensive Report on Tribal Health in India. (accessed 30 Dec 2024). Available from: https://tribalhealthreport.in/
18. South Asia Food and Nutrition Security Initiative. Food and nutrition security in tribal areas in India. In: World Bank SAg, editor. 2014. (accessed 28 Dec 2024) Available from: https://documents1.worldbank.org/curated/en/620611468173967141/pdf/Food-and-nutrition-security-in-tribal-and-backwards-areas-in-India.pdf
19. Thomas BE, Adinarayanan S, Manogaran C, Swaminathan S. Pulmonary tuberculosis among tribals in India: A systematic review & meta-analysis. Indian J Med Res. 2015 May;141(5):614-23. https://doi.org/10.4103/0971-5916.159545 PMID: 26139779
20. National TB Prevalence Survey in India (2019-2021): Summary Report: Indian Council of Medical Research (ICMR) New Delhi, ICMR-National Institute for Research in Tuberculosis (NIRT) Chennai, Ministry of Health and Family Welfare (MOHFW) Government of India New Delhi, Central TB Division (CTD) and National Tuberculosis Elimination Programme (NTEP), World Health Organisation(WHO) India Office New Delhi. 2022. (accessed 28 Dec 2024). Available from: https://tbcindia.mohfw.gov.in/2023/06/06/national-tb-prevalence-survey-in-india-2019-2021/
21. Rao VG, Bhat J, Yadav R, Muniyandi M, Sharma R, Bhondeley MK. Pulmonary tuberculosis - a health problem amongst Saharia tribe in Madhya Pradesh. Indian J Med Res. 2015;141(5):630–5. https://doi.org/10.4103/0971-5916.159560 PMID: 26139781
22. About Accredited Social Health Activist (ASHA): National Health Mission [Internet]. (accessed 28th December 2024).Available from: https://nhm.gov.in/index1.php?lang=1&level=1&sublinkid=150&lid=226
23. Direct Benefit Transfer Manual for National Tuberculosis Elimination Programme. In: Central TB Division, Ministry of Health and Family Welfare, Government of India, editors. New Delhi, India. July 2020. (accessed on 9th April 2025). Available from: https://tbcindia.mohfw.gov.in/wp-content/uploads/2023/05/23294204DBTManualForNTEP.pdf
24. Samarasekera U. Anurag and Madhavi Bhargava: enhancing TB prevention and care. Lancet. 2023 Nov 11;402(10414):1740. https://doi.org/10.1016/S0140-6736(23)02472-8
25. Hunger and food insecurity | FAO | Food and Agriculture Organization of the United Nations. 2024. (accessed 28th Dec 2024). Available from: https://www.fao.org/hunger/en
26. Ayiraveetil R, Sarkar S, Chinnakali P, Jeyashree K, Vijayageetha M, Thekkur P, et al. Household food insecurity among patients with pulmonary tuberculosis and its associated factors in South India: a cross-sectional analysis. BMJ Open. 2020 Feb 28;10(2):e033798. https://doi.org/10.1136/bmjopen-2019-033798 PMID: 32114470
27. McKay FH, Sims A, van der Pligt P. Measuring Food Insecurity in India: A Systematic Review of the Current Evidence. Curr Nutr Rep. 2023;12(2):358–367. https://doi.org/10.1007/s13668-023-00470-3 PMID: 37022635
28. Jubulis J, Kinikar A, Ithape M, Khandave M, Dixit S, Hotalkar S, et al. Modifiable risk factors associated with tuberculosis disease in children in Pune, India. Int J Tuberc Lung Dis. 2014;18(2):198–204. https://doi.org/10.5588/ijtld.13.0314 PMID: 24429313
29. Richterman A, Saintilien E, St-Cyr M, Claudia Gracia L, Sauer S, Pierre I, et al. Food Insecurity at Tuberculosis Treatment Initiation Is Associated With Clinical Outcomes in Rural Haiti: A Prospective Cohort Study. Clin Infect Dis. 2024 Aug 16;79(2):534-541.
30. Ministry of Health and Family Welfare (MoHFW), Government of India, UNICEF, Population Council. Comprehensive National Nutrition Survey (CNNS) National Report. New Delhi, 2019. (accessed 24 Dec 2024) Available from: https://nhm.gov.in/WriteReadData/l892s/1405796031571201348.pdf

31. Patwardhan SR, Kapoor S, Scott PH, Nguyen S, Chamois SK, Singh S, et al. 2022. Trends and patterns in consumption of foods among Indian adults: Insights from National Family Health Surveys, 2005-06 to 2019-21. POSHAN Data Note 91. New Delhi, India: International Food Policy Research Institute. (accessed 25 Dec 2024) Available from: https://ebrary.ifpri.org/utils/getfile/collection/p15738coll2/id/136530/filename/136743.pdf
32. de Pee S, Grede N, Mehra D, Bloem MW. The enabling effect of food assistance in improving adherence and/or treatment completion for antiretroviral therapy and tuberculosis treatment: a literature review. AIDS Behav. 2014;18(5):S531-41. https://doi.org/10.1007/s10461-014-0730-2 PMID: 24619602
33. Wang Q, Dima M, Ho-Foster A, Molebatsi K, Modongo C, Zetola NM, et al. The association of household food insecurity and HIV infection with common mental disorders among newly diagnosed tuberculosis patients in Botswana. Public Health Nutr. 2022 Apr;25(4):913–21. https://doi.org/10.1017/S1368980020004139
34. Samuel B, Volkmann T, Cornelius S, Mukhopadhay S, MejoJose, Mitra K, et al. Relationship between Nutritional Support and Tuberculosis Treatment Outcomes in West Bengal, India. J Tuberc Res. 2016 Dec;4(4):213–9. https://doi.org/10.4236/jtr.2016.44023
35. Singh AK, Siddhanta A, Goswami L. Improving tuberculosis treatment success rate through nutrition supplements and counselling: Findings from a pilot intervention in India. Clinical Epidemiology and Global Health. 2021;11:100782. https://doi.org/10.1016/j.cegh.2021.100782
36. Howell E, Dammala RR, Pandey P, Strouse D, Sharma A, Rao N, et al. Evaluation of a results-based financing nutrition intervention for tuberculosis patients in Madhya Pradesh, India, implemented during the COVID-19 pandemic. BMC Glob Public Health. 2023 Sep 4;1(1):13. https://doi.org/10.1186/s44263-023-00013-6 PMID: 39681888
37. Pedrazzoli D, Houben RM, Grede N, de Pee S, Boccia D. Food assistance to tuberculosis patients: lessons from Afghanistan. Public Health Action. 2016 Jun 21;6(2):147–53. https://doi.org/10.5588/pha.15.0076
38. Benzekri NA, Sambou JF, Tamba IT, Diatta JP, Sall I, Cisse O, et al. Nutrition support for HIV-TB co-infected adults in Senegal, West Africa: A randomized pilot implementation study. PLoS One. 2019 Jul 18;14(7):e0219118. https://doi.org/10.1371/journal.pone.0219118.eCollection2019
39. Santos E, Felgueiras Ó, Oliveira O, Duarte R. The Effect of a Basic Basket on Tuberculosis Treatment Outcome in the Huambo Province, Angola. Arch Bronconeumol (Engl Ed). 2018 Mar;54(3):167–168. https://doi.org/10.1016/j.arbres.2017.08.013 PMID: 29241985
40. Cantalice Filho JP. Food baskets given to tuberculosis patients at a primary health care clinic in the city of Duque de Caxias, Brazil: effect on treatment outcomes. J Bras Pneumol. 2009 Oct;35(10):992–7. https://doi.org/10.1590/s1806-37132009001000008 PMID: 19918632
41. Lewin S, Glenton C, Munthe-Kaas H, Carlsen B, Colvin CJ, Gülmezoglu M, et al. Using qualitative evidence in decision making for health and social interventions: an approach to assess confidence in findings from qualitative evidence syntheses (GRADE-CERQual). PLoS Med. 2015 Oct 27;12(10):e1001895. https://doi.org/10.1371/journal.pmed.1001895 PMID: 26506244
42. Ghosh SM, Qadeer I. Impact of Public Distribution System on Quality and Diversity of Food Consumption. Economic and Political Weekly. 2021 Jan 30;56(5):52-9.
43. Mahapatra A, Thiruvengadam K, Nair D, Padmapriyadarsini C, Thomas B, Pati S, et al. Effectiveness of food supplement on treatment outcomes and quality of life in pulmonary tuberculosis: Phased implementation approach. PLoS One. 2024 Jul 16;19(7):e0305855. https://doi.org/10.1371/journal.pone.0305855 PMID: 39012889
44. Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. Respirology. 2006 Nov;11(6):699–707. https://doi.org/10.1111/j.1440-1843.2006.00941.x
45. Khan A, Sterling TR, Reves R, Vernon A, Horsburgh CR. Lack of weight gain and relapse risk in a large tuberculosis treatment trial. Am J Respir Crit Care Med. 2006 Aug 1;174(3):344–8. https://doi.org/10.1164/rccm.200511-1834OC
46. Nightingale R, Carlin F, Meghji J, McMullen K, Evans D, van der Zalm MM, et al. Post-TB health and wellbeing. Int J Tuberc Lung Dis. 2023 Apr 1;27(4):248–83. https://doi.org/10.5588/ijtld.22.0514
47. Wagnew F, Gray D, Tsheten T, Kelly M, Clements ACA, Alene KA. Effectiveness of nutritional support to improve treatment adherence in patients with tuberculosis: a systematic review. Nutr Rev. 2024 Sep 1;82(9):1216–1225. https://doi.org/10.1093/nutrit/nuad120 PMID: 37759339
48. Weiser SD, Tuller DM, Frongillo EA, Senkungu J, Mukiibi N, Bangsberg DR. Food insecurity as a barrier to sustained antiretroviral therapy adherence in Uganda. PLoS One. 2010 Apr 28;5(4):e10340. https://doi.org/10.1371/journal.pone.0010340 PMID: 20442769
49. Mishra P, Bhat J, Yadav R, Sharma RK, Rao VG. Adverse Drug Reaction Patterns of First-line Anti-tubercular Drugs among Saharia Tuberculosis Patients: An Observational Study in Particularly Vulnerable Tribal Group of Madhya Pradesh, India. Indian J Public Health. 2023;67(4):542–545. https://doi.org/10.4103/ijph.ijph_865_22 PMID: 38934815
50. Agarwal A, H B S, Mathur SB, Kalra BS, Arora R, Khanna A, et al. Adverse drug reactions in children and adolescents on daily antitubercular regimen: An observational longitudinal study. Indian J Tuberc. 2023;70(Suppl 1):S76–81. https://doi.org/10.1016/j.ijtb.2023.07.004 PMID: 38110265
51. Union Health Minister Unveils Key Initiatives to boost Nutrition Support for TB Patients and their Families. 2024. (accessed 3rd January 2025). Available from: https://mohfw.gov.in/?q=/press-info/7783.
52. Kumar R, Krishnan A, Singh M, Singh UB, Singh A, Guleria R. Acceptability and Adherence to Peanut-Based Energy-Dense Nutritional Supplement Among Adult Malnourished Pulmonary Tuberculosis Patients in Ballabgarh Block of Haryana, India. Food Nutr Bull. 2020 Dec;41(4):438–445. https://doi.org/10.1177/0379572120952306 PMID: 32885665

53. Ali E, Zachariah R, Shams Z, Manzi M, Akter T, Alders P, et al. Peanut-based ready-to-use therapeutic food: how acceptable and tolerated is it among malnourished pregnant and lactating women in Bangladesh? Matern Child Nutr. 2015;11(4):1028–35. https://doi.org/10.1111/mcn.12050 PMID: 23647821

54. Ali E, Zachariah R, Dahmane A, Van den Boogaard W, Shams Z, Akter T, et al. Peanut-based ready-to-use therapeutic food: acceptability among malnourished children and community workers in Bangladesh. Public Health Action. 2013 Jun 21;3(2):128–35. https://doi.org/10.5588/pha.12.0077

55. Dube B, Rongsen T, Mazumder S, Taneja S, Rafiqui F, Bhandari N, et al. Comparison of Ready-to-Use Therapeutic Food with cereal legume-based khichri among malnourished children. Indian Pediatr. 2009 May;46(5):383–8.

56. Mascarenhas A. TB patients not happy with "ready to eat" food packets [Internet]. The Indian Express. 2015 [cited 2025 Mar 19]. Available from: https://indianexpress.com/article/cities/pune/tb-patients-not-happy-with-ready-to-eat-food-packets/

57. McQuaid CF, Clark RA, White RG, Bakker R, Alexander P, Henry R, Velayutham B, et al. Estimating the epidemiological and economic impact of providing nutritional care for tuberculosis-affected households across India: a modelling study. Lancet Glob Health. 2025 Mar;13(3):e488–e496. https://doi.org/10.1016/S2214-109X(24)00505-9 PMID: 39824201

58. Mohan M, Thangaraj JWV, Pandey S, Sri Lakshmi Priya G, Arunachalam S, Sharma R, et al. Need for operational simplicity and timely disbursal of benefits-a qualitative exploration of the implementation of a direct benefit transfer scheme for persons with tuberculosis in India. Infect Dis Poverty. 2024 May 23;13(1):36. https://doi.org/10.1186/s40249-024-01206-3 PMID: 38783334

59. Rajeswari R, Balasubramanian R, Muniyandi M, Geetharamani S, Thresa X, Venkatesan P. Socio-economic impact of tuberculosis on patients and family in India. Int J Tuberc Lung Dis. 1999 Oct;3(10):869–77. PMID: 10524583

60. Jeyashree K, Thangaraj JWV, Shanmugasundaram D, Giridharan SLP, Pandey S, Shanmugasundaram P, et al. Cost of TB care and equity in distribution of catastrophic TB care costs across income quintiles in India. Glob Health Res Policy. 2024 Dec 9;9(1):51. https://doi.org/10.1186/s41256-024-00392-9 PMID: 39648213

61. Jeyashree K, Thangaraj JWV, Shanmugasundaram D, Sri Lakshmi Priya G, Pandey S, Janagaraj V, et al. Ni-kshay Poshan Yojana: receipt and utilization among persons with TB notified under the National TB Elimination Program in India, 2022. Glob Health Action. 2024 Dec 31;17(1):2363300. https://doi.org/10.1080/16549716.2024.2363300 PMID: 39034827

62. Reed G, Hendlin Y, Desikan A, MacKinney T, Berman E, Goldman GT. The disinformation playbook: how industry manipulates the science-policy process-and how to restore scientific integrity. J Public Health Pol. 2021 Dec;42(4):622–34. https://doi.org/10.1057/s41271-021-00318-6 PMID: 34811464

63. Guest G, Bunce A, Johnson L. How Many Interviews Are Enough? An Experiment with Data Saturation and Variability. Field Methods. 2006;18(1):59–82.