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.

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See **Comment** page 588

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 494 000 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

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.[4] 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 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 members, neighbours, and the community health worker.

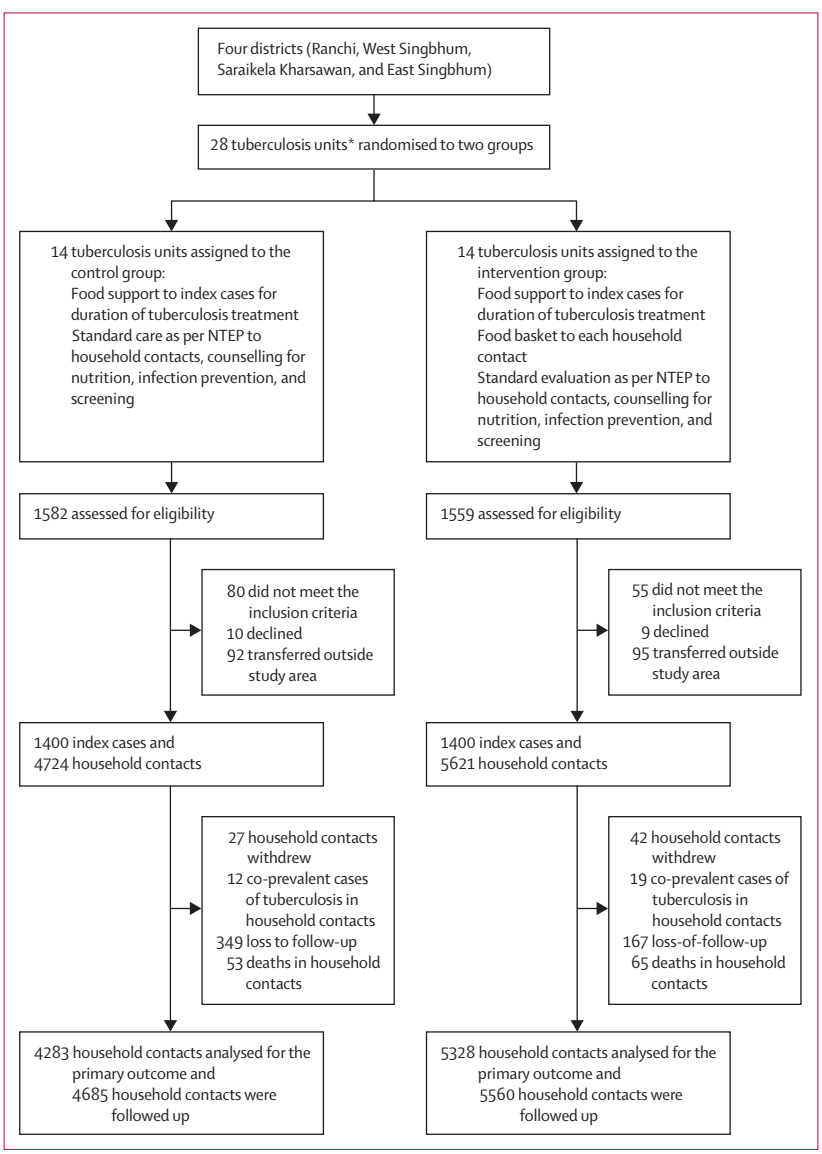

Figure 1: **Trial profile**
NTEP=National Tuberculosis Elimination Programme. *Clusters are the tuberculosis units.

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=10 345)
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 100 000 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 11 200 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 188 incident tuberculosis cases, constituting 50% of the expected number of 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/m².

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.

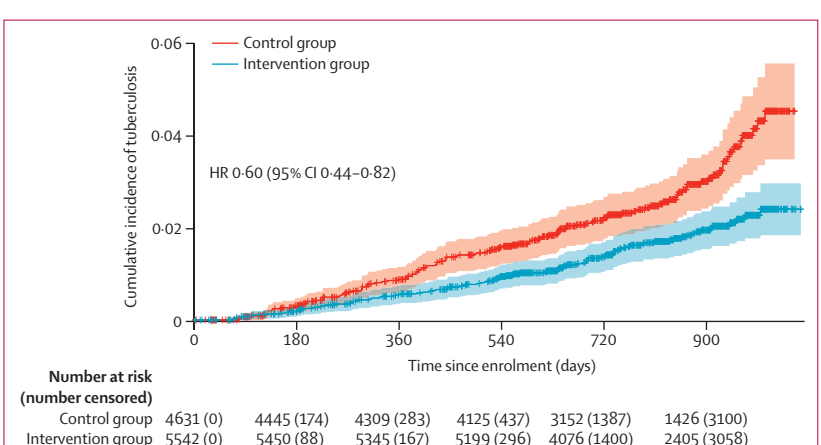

Figure 2: **Kaplan-Meier plot for cumulative incidence of tuberculosis disease in household contacts stratified by trial group over the follow-up period**
The time shown is the time from the enrolment of contacts in the trial, and shaded lines represent 95% CIs. The planned follow-up of 24 months was 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 not change the results and the adjusted IRR (aIRR) was 0·61 (95% CI

	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)**

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

	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/m^2 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**

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]

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.[17] 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/$ASO1_E$, 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

	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%)	..
Nutrition 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 months†	20·1% (25·1)	18% (18·3)	0·38
Girls, underweight (weight-for-age lower than −2SD)	127 (48·3%)	139 (48·8%)	..
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

(Table 5 continues on next page)

	Control group (n=4724)	Intervention group (n=5621)	p value
(Continued from previous page)			
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/m^2), mild to moderately underweight (16–18·49 kg/m^2), normal (18·5–24·99 kg/m^2), and people who are overweight or people with obesity (≥25·0 kg/m^2). *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**

undernutrition and poverty. Another strength was the 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.

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