Nutritional Supplementation to Prevent Infection in Household Contacts of Tuberculosis Patients

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SUMMARY

This was a field-based, open-label, cluster-randomized controlled trial, in which household contacts of 2800 patients with microbiologically confirmed pulmonary tuberculosis across 28 tuberculosis units of the National Tuberculosis Elimination Programme across four districts of Jharkhand, India, were enrolled. The tuberculosis units were randomly allocated 1:1 by block randomization to the control group or the intervention group. 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, for the primary outcome of incident tuberculosis (all forms). 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. The authors 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. The authors conclude that nutritional intervention was associated with substantial (39-48%) reduction in tuberculosis incidence in the household during the two years of follow-up.

CRITICAL APPRAISAL

Evidence-Based Medicine Viewpoint

This cluster-randomized controlled trial (RCT) [1] examined the impact of nutritional supplementation provided to household contacts of adults with pulmonary tuberculosis, on the incidence of tuberculosis disease in them. The elements of the research question can be broken down to: Population/Problem (P): Household contacts of adults with microbiologically confirmed pulmonary tuberculosis; Intervention (I): Nutritional supplementation for 6 months; Comparison (C): No nutritional supplementation; Outcomes (O): Incidence of all types of tuberculosis; Timeframe of outcome measurement (T): Two years; and Setting (S): Community setting among people living in 'tuberculosis units.' The unit of randomization was the tuberculosis unit (and not individual participants) in four districts of Jharkhand.

The participants eligible for inclusion were household contacts of any adult with microbiologically confirmed pulmonary tuberculosis (index case) as per the criteria in the National Tuberculosis Elimination Programme (NTEP). A 'household contact' was defined as those living in the same house, consuming food from the same kitchen for any length of time, and not already receiving tuberculosis therapy. There were no other exclusion criteria specified by the authors.

The sample size was meticulously calculated, taking into consideration the population incidence of pulmonary TB, number of index cases within a tuberculosis unit, incidence of TB among household contacts, estimated decline in TB with the intervention, design effect, average family size in the

target population, and the usual alpha error. The calculation suggested that a sample size of 11200 household contacts randomized into two arms would have at least 80% power to detect a 50% decline in the incidence of TB with the intervention.

The intervention was daily 'nutritional supplementation' amounting to 750 kcal, 23 g protein, & one recommended dietary allowance (RDA) of micronutrients, per household contact. Those <10y old received half of this. It was administered as a monthly ration that could be either home-delivered, or collected from specific locations. The comparison group of participants did not receive these rations. However, the index case in both groups received daily nutritional supplements amounting to 1200 kcal, 52g protein, and one RDA of micronutrients. Household contacts received supplementation throughout the duration of treatment of the index case (viz 6 months for drug sensitive TB, and 12 months for drug resistant TB). However, supplementation could be extended for up to 12 additional months in adult contacts with BMI <16 kg/m^2, adolescents with BMI Z score <2, and younger children with weight-for-age Z score <2. Apart from the intervention, both groups were treated similarly.

The primary outcome was development of TB (any type) among the household contacts. Other outcomes were pulmonary TB, other TB, other acute infections (notably malaria, diarrhea, lower respiratory tract infection, hospitalization for fever), change in weight among contacts, and mortality with acute fever during the intervention period. Cost of the intervention (including delivery and implementation) was calculated.

The intended follow-up period was 2 years, with monthly visits during the first year, and 3-monthly thereafter (i.e., total 16 follow-up time points). However, due to COVID exigencies, the protocol was modified, extending the follow-up period to a common closing period. Therefore, some participants could be followed-up for longer than 2 years; whereas almost one-fifth could be followed up for only 18 months. Each contact was followed-up until they developed TB, or their data were censored.

The main results among household contacts are summarized in **Box I**.

Critical appraisal of the RCT

Critical appraisal using the current Cochrane Risk of Bias (RoB) II tool for cluster RCTs [2] is summarized in **Table I**. There was low RoB in three domains, and some concerns in two domains. Considering the criteria in the GRADE-ing of evidence [3], this trial would qualify for downgrading by at the most one point for the issues highlight in the RoB assessment. There is no significant imprecision, or indirectness noted. Thus the trial can be considered to contribute moderate to high quality evidence.

The trial had numerous methodological refinements raising confidence in the reported findings. The state of Jharkhand was chosen for specific reasons that are described well. The selected districts were not chosen randomly, but were apparently based on the case load and logistic feasibility of implementing the intervention. The trial was aligned with the prevalent NTEP system and procedures, facilitating applicability of the findings. A local non-Governmental organization was involved in data collection of serious adverse events and deaths. A Data Safety and Management Board was established for the trial, although there was no interim analysis. The trial investigators incorporated multiple logistic refinements to ensure appropriate delivery of nutritional supplementation, and also attempted to ensure appropriate consumption. There are no grave ethical concerns in the trial design or implementation.

Additional refinements included the use of clear definitions for terms such as index case, household contact, tuberculosis unit, duration of intervention, incident TB, co-prevalent TB, lost to follow-up, etc. At enrolment and during the trial, the index cases were counselled regarding consuming a balanced diet, adhering to therapy, and cough hygiene. Meticulous attempts were made to ensure appropriate follow-up and track those who were unavailable.

Despite these refinements, some aspects are unclear. For example, the basis for choosing to supplement diet with specifically 750 kcal and 23g protein is unclear. Similarly, the rationale for providing exactly half of this to all children <10 y old (irrespective of age) is also unclear.

The age-wise analysis of incident TB among contacts confirms that the beneficial effect of nutritional supplementation was driven by reduction in TB only in adults. There was no such benefit among young children <5y or

Box I Main Results Among Household Contacts in the Study

TB (any type)

96/5602 vs 122/4712 equivalent to 1.7% (CI 1.4, 2.1) vs 2.6% (CI 2.2, 3.1)[a]

Incidence rate of TB (per 100 person-years)

0.78 (CI 0.64, 0.96) vs 1.27 (CI 1.00, 1.61)[a]

Incidence rate of microbiologically confirmed TB (per 100 person-years):

0.51 (CI 0.38, 0.68) vs 0.95 (CI 0.73, 1.24)[a]

Incidence rate of clinically diagnosed TB (per 100 person-years):

0.28 (CI 0.18, 0.44) vs 0.30 (0.19, 0.56)

Incidence of other acute infections, and deaths due to febrile illness, was apparently similar in the two groups.

[a]$P<0.05$

Table I Critical Appraisal of the Trial Using the Current Cochrane Risk of Bias (RoB) II Tool for Cluster Randomized Controlled Trials

Domain and Comments	*Assessment*
RoB arising from the randomization process	
• The allocation sequence (for tuberculosis units) was generated by a remotely located statistician using computer generated random numbers.	*Low RoB*
• Block randomization was used, however block size(s) is/was not specified.	
• The allocation ratio was 1:1. Although tuberculosis units (and not individuals) were randomized, the data of individuals were reported.	
• Allocation was concealed from the investigators, although it is unclear how this was done, and also whether it remained concealed until the clusters were assigned to the intervention. However, it is unlikely that participants could have self-selected themselves to either trial arm.	
• Baseline characteristics viz. age distribution, gender distribution, caste status, occupational background, access to the pubic distribution system, personal habits (tobacco use, alcohol consumption), economic status, and proportion of children receiving prophylaxis; were comparable suggesting adequacy of the randomization process.	
• However, there a statistically significant difference in the baseline prevalence of undernutrition among adults (38.3% vs 34.9%) and children, although this was not shown in the Table of baseline characteristics.	
• Although trial participants were neither identified not recruited before the clusters were randomized, it may not create bias in this study. It is also unlikely that participant selection was affected by knowledge of the intervention assigned to the cluster.	
RoB due to deviations from the intended interventions	*Low RoB*
• Participants were aware that they were in a trial; however the nature of the intervention was such that participants could not be blinded to their allocation.	
• Similarly, the trial personnel also were aware of the allocation of individual clusters (and thereby households). These personnel were responsible for periodic symptom screening of contacts (to direct them towards diagnostic tests).	
• There were no apparent deviations from the assigned intervention.	
• It is unclear whether knowledge of the assigned interventions could have altered the behavior of participants (as no calculations of their caloric or protein intake during the intervention period, and thereafter, were made). Adults in both trial arms gained weight during the intervention period (suggesting a potential for behavioral alteration), although the intervention group showed a statistically significant greater weight gain. Further, the limited number of children in both groups had comparable weight gain, reiterating the same concept.	
• If there were deviations from the intended allocation (i.e. participants in the comparison group consumed additional nutrition on their own), it would have resulted in a narrower (if not nil) difference between the trial arms. Since there was still a statistically significant difference, it suggests a robust result.	
RoB due to missing outcome data	*Some concerns*
• It is unclear whether data from all the clusters randomized were available for analysis, as the authors reported data by participants rather than clusters.	
• After randomization, there were 5621 participants in the intervention group, and 4724 in the comparison group. Data for the primary outcome were available in 5328 (94.8%) and 4283 (90.7% respectively).	
• Data were missing in the remainder due to withdrawal, co-prevalent TB, deaths during the intervention period (all three were comparable between groups) and loss to follow-up. However, there was almost 2.5 times greater loss to follow-up in the comparison group (3.0% vs 7.4%). The reasons and impact of this are unclear. It is reasonable to wonder whether the missing data could have altered the estimate of benefit of the intervention (if they had unfavorable outcome). Although the authors stated that an intention-to-treat (ITT) analysis was performed considering those with missing data, it is unclear how this was done.	
• When the study was terminated, there were 167 (3.0%) and 349 (7.4%) participants respectively, whose follow-up data were unavailable.	
RoB in measurement of the outcome	*Some concerns*
• The method of measuring the outcome was appropriate, and there does not appear to be any inter-group difference in the method of ascertaining the outcome.	
• Those recording the primary outcome were independent of the trial personnel, however it is unclear if they were blinded to the intervention. It is also unclear whether they were aware that a trial was in progress.	

- As TB was diagnosed clinically in over 25% household contacts, knowledge of the allocation could have influenced the outcome.

RoB in in selection of the reported result *Low RoB*

- The outcomes reported were decided a priori.
- Additional post hoc analyses included splitting TB cases as 'microbiologically confirmed' and clinically diagnosed. However, given that this is permissible under the NTEP, it is acceptable.
- None of the other outcomes appear to have been selected for reporting, based on the result.

older children 6-17y. This is disappointing from the perspective of pediatricians. Further, even among adults, the benefit was observed only among males, and especially those who were not undernourished at baseline.

One of the major challenges in this study is the possibility of food sharing within a household. Given that only index cases in the comparison group received supplementation, it is possible (even probable) that some of it may have been shared with family members. This is indicated by the nearly 2% weight gain over 6 months amongst adult household members, irrespective of gender. This gain which was about half of that recorded amongst adults in the intervention group, needs explanation. Further, the overall prevalence of poor nutrition (defined by low BMI) declined more in the comparison than the intervention group.

Similarly, children between 6 to 17y (male and female) in the comparison group gained about 6.5% weight over 6 months. Although this could be simply due to natural growth among children, the possibility of food sharing cannot be ruled out, especially as the gain was only 2% lower than in those receiving the intervention. Given these concerns, it would have been logical for the authors to report the weight gain in the index cases. If there was no food sharing, the gains would have been similar in both groups. Of course, additional analysis of inter-group weight gain patterns by the number of household contacts would have thrown further light on this issue. Unfortunately, these data were not reported.

Children <5y (both boys and girls) showed almost 20% weight gain over 6 months, and surprisingly the gain was similar amongst those in the intervention as well as comparison groups. The comparable weight gain in both groups raises several questions viz., *i*) Could it be because young children in the comparison group also received some supplementation, either through food sharing or behavior change within families? *ii*) Could it be because young children in the intervention group were deprived of the nutritional supplementation allocated to them, because of diversion to others in the household? *iii*) Had increase in weight *z* scores been reported instead of absolute weight gain, it would have been feasible to interpret whether the gain was due to natural growth (in which case *z* scores would remain unchanged) or nutritional supplementation (*z* scores would increase). Unfortunately this was not reported.

In this trial, incident TB among household contacts was determined by screening for symptoms to make a presumptive diagnosis of TB, followed by referral to a health facility for clinical examination and sputum evaluation. Sputum was examined by microscopy or nucleic acid amplification. Thus it is unclear how symptomatic contacts who did not produce sputum were evaluated. Although the NTEP may not have a provision for such situations, this would be expected in a well-designed and conducted trial. The issue is particularly relevant to young children, wherein sputum is not usually available, and multiple gastric aspirate/lavage specimens are required for diagnosis.

There are several interesting findings reported in the publication [1] but not sufficiently highlighted or explored. For example, among children younger than 5 years, incident TB was over three times more frequent amongst those who received nutritional supplementation (8.3% vs 2.5%) despite them being 1.5 times more likely to have received INH prophylaxis. This unusual situation is of great interest to pediatricians and public health specialists, and warrants further exploration.

Despite the well-established National guideline [4] recommending INH prophylaxis for children <6y in contact with adult pulmonary TB (prevalent during the trial period), it appears that only 1 in 6 such children actually received it. This indicates a gap between programmatic policy vs practice. The broader implication is that if nutritional supplementation were to be initiated at the programmatic level, there is risk of similar gaps in practice once the stringent project related oversight is replaced by routine implementation.

It is important to note that current guidelines recommend INH preventive therapy to contacts across all age groups [5]. This raises two subsidiary questions: *i*) If the programmatic implementation of this remains similar to that among children, little may be achieved by it; and *ii*) On the other hand, if it is implemented in a robust manner, would there be need of nutritional supplementation to prevent the development of TB?

Although the trial overall showed lower incidence of TB among contacts receiving nutritional supplementation, this appears to be restricted to those with microbiologically confirmed TB. Among those with clinically diagnosed TB, there was no inter-group difference among adults, whereas it was actually almost three times higher among children (<18y). This unusual observation has not been explored.

It is interesting that although females outnumbered males amongst household contacts (11:9 ratio), the reverse was true for those who developed incident TB, with approximately 55% cases being male. The median time for the development of TB among contacts was almost 17 months. In fact, almost a fourth of the cases among contacts were diagnosed beyond 2 years of follow-up. This suggests a few interesting possibilities. If the contacts were being infected by the index case, it should have occurred during the peak of infectivity viz., within the first few weeks after starting treatment of the index case. Therefore confirmatory diagnosis after several months, and that too almost a year after the index case stopped therapy, suggests slow progression from infection to disease. The alternate explanation that contacts were getting infected from some other source is even less plausible. This also raises the question of how long the contacts of successfully treated cases should be followed up, to be confident that they do not develop TB.

There were 31 contacts who had co-prevalent TB (i.e., TB was detected even before the intervention was implemented). This means that their family members were exposed to two index cases. It would have been interesting (and relevant) to record the incidence of TB in such families.

What could be the mechanism whereby nutritional supplementation for 6 months, prevented the development of TB for over 2 years? Could it be that short-term enhanced nutrition somehow altered the immune status, resulting in long-term protection? As there was no reduction in the incidence of other infections, if 'immunity' were responsible, could it be restricted to cell-mediated immunity? Would the 'immunity' wane over time? Although nutritional supplementation of contacts was done for six months (in the majority), the benefit of reduction in TB became apparent only after 9 months, i.e. well after cessation of the intervention. If nutrition-facilitated, enhanced cell-mediated immune function, is it acquired slowly? Pathophysiologic studies may be required to address these questions.

It is encouraging that there did not appear to be any drug resistant TB among 2800 adults. This is useful information from the public health perspective.

It appears that the monthly cost of nutritional supplementation per adult contact was about Rs 338/- (1USD = 71.17 INR on the project start date) [6] or approximately Rs 11/- per day. This remarkably low cost included delivery costs as well. However, the monthly cost of providing less than double the supplementation, to index cases was almost thrice the cost i.e.. Rs 925/-, or Rs 30/- per day.

Conclusion: This methodologically robust, low risk-of-bias randomized trial suggests that nutritional supplementation offered to household contacts of adult TB cases, could reduce the incidence of TB among adult family members, although there may not be any impact on children. The issues highlighted above suggest although the intervention appears promising, there are several challenges to be overcome for successful implementation a s a public health strategy.

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REFERENCES

1. 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;402:627-40.
2. Revised Cochrane risk-of-bias tool for cluster-randomized trials (RoB 2 CRT); Version 18 March, 2021. Accessed Oct 21, 2023. Available from: *https://drive.google.com/file/d/1leTmLEEg1SgmO9NrxMj2J34AEwZL-Kyl/view*
3. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. What is "quality of evidence" and why is it important to clinicians? BMJ. 2008;336:995-8.
4. Revised National Tuberculosis Control Programme. National Strategic Plan for Tuberculosis Elimination 2017–2025. Accessed Oct 21, 2023. Available from: *https://tbcindia.gov.in/WriteReadData/NSP%20Draft%2020.02.2017%201.pdf*
5. Ministry of Health and Family Welfare. Guidelines for Programmatic Management of Tuberculosis Preventive Treatment in India 2021. Accessed Oct 21, 2023. Available from: *https://tbcindia.gov.in/ showfile.php?lid=3625*
6. Currency conversion: US Dollar. Accessed Oct 21, 2023. Available from:*https://www.xe.com/currencytables/? from=USD&date=2019-08-16#table-section*

Pediatric Tuberculosis Specialist's Viewpoint

Among all the risk factors that accelerate tuberculosis infection, undernutrition tops the list, especially in childhood tuberculosis. The World Health Organization (WHO) recommends integration of childhood tuberculosis preventive and diagnostic services with community nutritional services to address tuberculosis and undernutrition syndemic [1]. In the study under discussion [2], children aged below 17 years constituted 40% of cohort in this controlled study of nutritional supplementation of household contacts (HHCs)

of microbiologically confirmed pulmonary tuberculosis. Children younger than five years, who are known to have the highest risk of tuberculosis infection and disease progression, formed 11% of the study population.

The authors have shown an overall reduction of incidence of tuberculosis by 39% in the nutritional supplementation group compared to the control group (0.78 vs 1.27) [2]. However, paradoxically, incident tuberculosis cases were higher in intervention group compared to control group in children < 5 years, who are the most vulnerable HHCs (0.58 vs 0.27). There was no disparity either in nutritional status or tuberculosis preventive therapy (TPT) between the groups. What can explain this?

Surprisingly, authors have not discussed this paradoxical finding. There was only a modest reduction of incident rate in children of ages 6-17 years (0.38 vs 0.53). This calls for deeper look into the strategy to find out the factors responsible for the same. What is worrisome for pediatricians is, only 16% of children younger than five years exposed to confirmed pulmonary tuberculosis were initiated on TPT, which is an essential strategy to prevent pediatric tuberculosis. This could have confounded the results in them. Hence, along with nutritional intervention, other strategies like TPT, and early detection and treatment of adult tuberculosis, have to be strengthened to achieve the goal.

Despite these limitations in children, overall reduction in incident tuberculosis and further reduction in microbiologically, confirmed pulmonary TB in adults by nutritional supple-mentation will have indirect impact on control of pediatric tuberculosis.

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REFERENCES

1. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 5: management of tuberculosis in children and adolescents. World Health Organization; 2022. Accessed Sep 30, 2023. Available from: *https://www.who.int/publications/i/ item/9789240046764*
2. 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;402:627-40.

Public Health Specialist's Viewpoint

Tuberculosis remains one of the most significant public health problems in India, with more than 3 million people affected annually, about 1.3 million out of them estimated to be children [1]. Despite it being such a significant problem in India and in other low- and middle-income countries (LMICs), there have been limited advances in its prevention, diagnosis or treatment.

Most high-income countries controlled tuberculosis without a vaccine or treatment, primarily by equitable improvements in nutrition, living and working conditions of its citizens. National Tuberculosis Elimination Program (NTEP) commits to eliminate tuberculosis by the year 2025, relying predominantly on a treatment-based approach to control and eliminate the disease.

This rigorously conducted study [2] provides evidence of effectiveness of nutrition supplementation of household contacts. At 39% reduction of all forms of tuberculosis incidence among households, it promises to be one of the most effective public health interventions to control the disease. In the absence of an effective vaccine, strong evidence of its effectiveness, and low costs in administering (<5 USD per household contact), there is a compelling reason to integrate this strategy within NTEP. Given the syndemic of tuberculosis and malnutrition, there is also a critical need for focused multi-sectoral efforts to enhance availability of nutritious food in food scarce regions of India, such as where this study was conducted.

Since the diagnosis of tuberculosis in NTEP relies heavily on sputum examination, there is an inadequate identification of tuberculosis among children, who often swallow their sputum. It is estimated that there are closer to 1.5 lakh cases of childhood tuberculosis annually, that are not reported within NTEP. In this study, which relied on the existing program mechanisms of detecting tuberculosis, very few children younger than five years (n=11) were found to have tuberculosis during a 2-year follow-up. This underscores the urgent need for diagnostic tools, simplified algorithms, and training of program staff for detection of childhood tuberculosis.

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REFERENCE

1. Ministry of Health and Family Welfare, Government of India. Collaborative Framework to address the burden of tuberculosis among children and adolescents. Government of India, 2021. Accessed Sep 30, 2023. Available from: *https://tbcindia. gov.in/showfile.php?lid=3632*
2. 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;402:627-40.