

# **(Reducing Activation of Tuberculosis by Improvement Of Nutritional Status)**

## **RATIONS**

Supported by the India TB Research Consortium ICMR

Presentation for Liverpool School of Tropical Medicine,  
February 15, 2024

Impact of nutritional supplementation in reducing TB incidence in household contacts of PTB patients in communities with high level of undernutrition

Impact of nutritional support in improving TB treatment and other outcomes in patients with active pulmonary TB

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**Co-Principal Investigators: Dr. Madhavi Bhargava, YMC; Dr. Banurekha Velayutham, NIRT**

# Work on TB and nutrition before RATIONS: a 20 year journey

OPEN ACCESS Freely available online



## Nutritional Status of Adult Patients with Pulmonary Tuberculosis in Rural Central India and Its Association with Mortality

Anurag Bhargava<sup>1\*</sup>, Madhuri Chatterjee<sup>2</sup>, Yogesh Jain<sup>3</sup>, Biswaroop Chatterjee<sup>4</sup>, Anju Kataria<sup>3</sup>, Madhavi Bhargava<sup>5</sup>, Raman Kataria<sup>3</sup>, Ravi D'Souza<sup>6</sup>, Rachna Jain<sup>3</sup>, Andrea Benedetti<sup>7</sup>, Madhukar Pai<sup>8</sup>, Dick Menzies<sup>7</sup>

Undernutrition and the incidence of tuberculosis in India: National and subnational estimates of the population-attributable fraction related to undernutrition

ANURAG BHARGAVA, ANDREA BENEDETTI, OLIVIA OXLADE, MADHUKAR PAI, DICK MENZIES

## Can Social Interventions Prevent Tuberculosis? The Papworth Experiment (1918–1943) Revisited

Anurag Bhargava<sup>1</sup>, Madhukar Pai<sup>1</sup>, Madhavi Bhargava<sup>2</sup>, Ben J. Marais<sup>3</sup>, and Dick Menzies<sup>4</sup>

Tuberculosis deaths are predictable and preventable: Comprehensive assessment and clinical care is the key

Anurag Bhargava<sup>a,b,d,\*</sup>, Madhavi Bhargava<sup>c,d</sup>



Ministry of Health & Family Welfare Government of India  
DOYS  
GOI  
YENEPYLA UNIVERSITY  
World Health Organization India

Guidance Document:  
**Nutritional**  
care and support  
for patients with  
**Tuberculosis in India**

**N-TB Calculator**  
Nutritional assessment and counseling tool for adult patients with tuberculosis

HEIGHT Input height (cm)  
160

WEIGHT Input weight (kg)  
30

ENTER

**N-TB: Results**

- Extreme underweight
- Severe underweight
- Moderate underweight
- Mild underweight
- Normal
- Overweight
- Obese

BMI VALUE **11.7 kg/m<sup>2</sup>**

GET STARTED

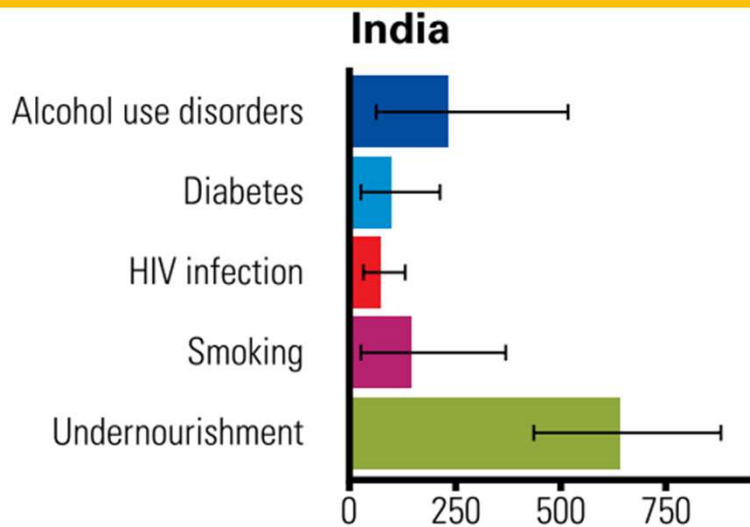
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YENEPYLA UNIVERSITY  
Madill International TB Centre

World Health Organization India

Next >

# What are the major risk factors for TB disease ? Globally and in India?

## Undernutrition : A socially determined biologic risk factor



Globally:  
19% TB cases attributable to undernutrition

India:  
34%-45% of TB cases attributable to undernutrition

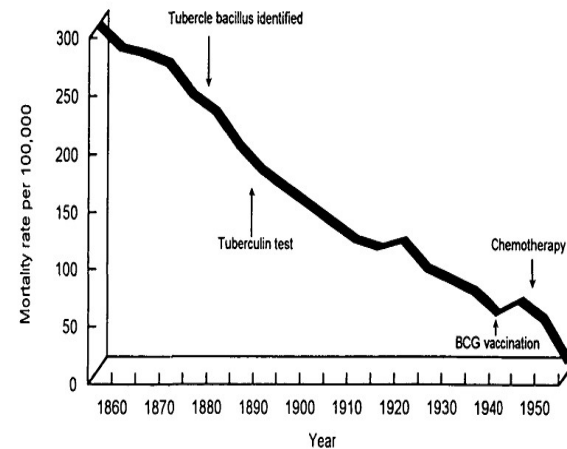
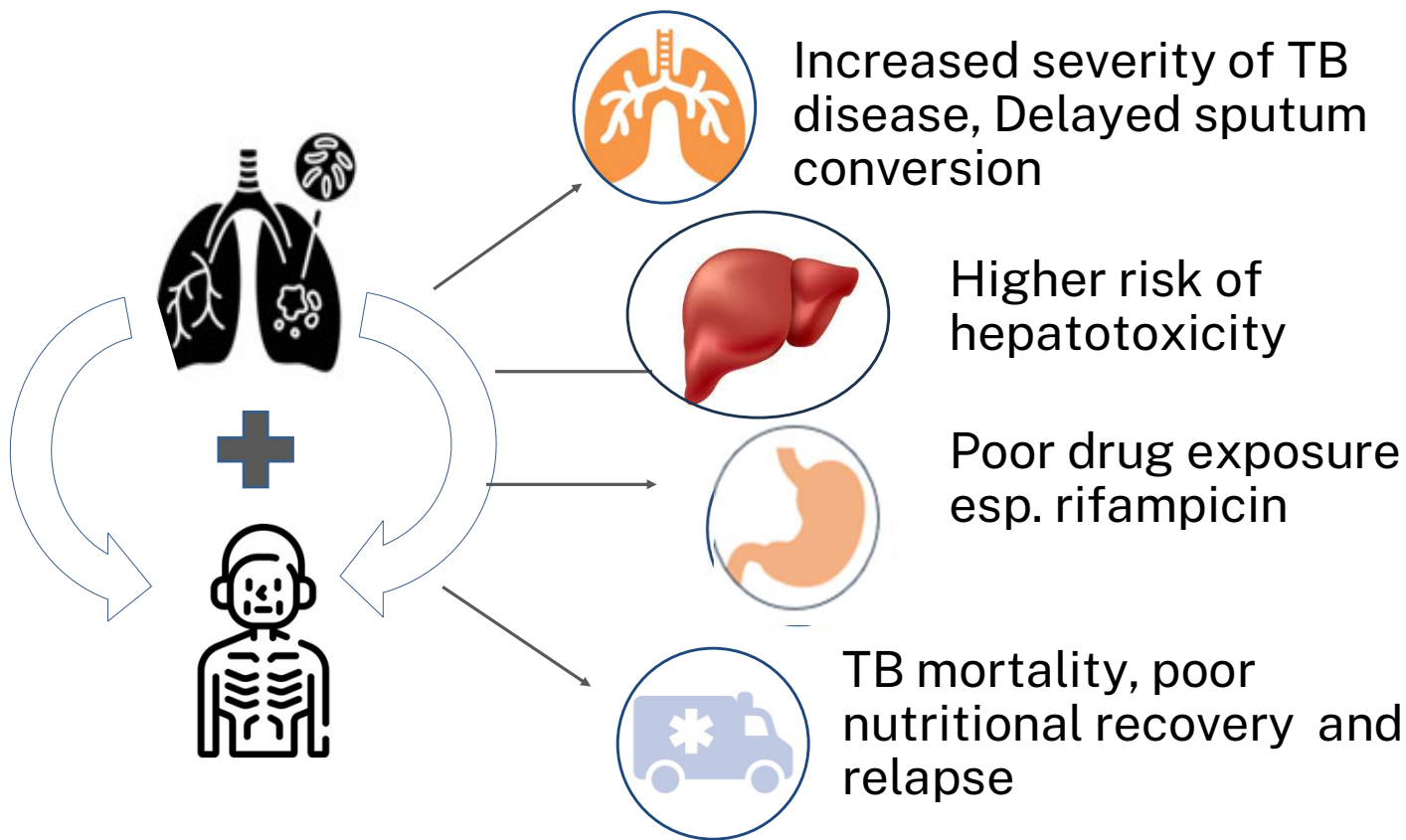


FIGURE 1. Annual tuberculosis mortality rates in England and Wales, 1850–1960. BCG, Bacillus Calmette-Guérin. (Adapted from the following source: Kass EH. Infectious diseases and social change. *J Infect Dis* 1971;123:110–14).

UK decline in TB mortality between 1850-1950)  
Historical decline in TB mortality and TB incidence with improved living conditions

*Global TB report WHO 2020. Bhargava A, Bhargava M, Beneditti A, Kurpad A. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases. 2022;27:100309.*

# Undernutrition impact on TB disease & its treatment outcomes: A socially determined severe co-morbidity



According to NTEP (India) data for adult TB

50 % of Indian adult men weigh < 43 kg

50% of Indian adult women weight < 38 kg

Weight gain poor in absence of nutritional support

# Prevalence of Undernutrition

## Significance of prevalence of BMI < 18.5 kg/m<sup>2</sup> – WHO

India has a twin burden of people at risk of TB:

- A large reservoir of persons with TB infection (300 million)
- Large pool of persons with undernutrition, an important risk factor for TB

NFHS -5 : LOW BMI

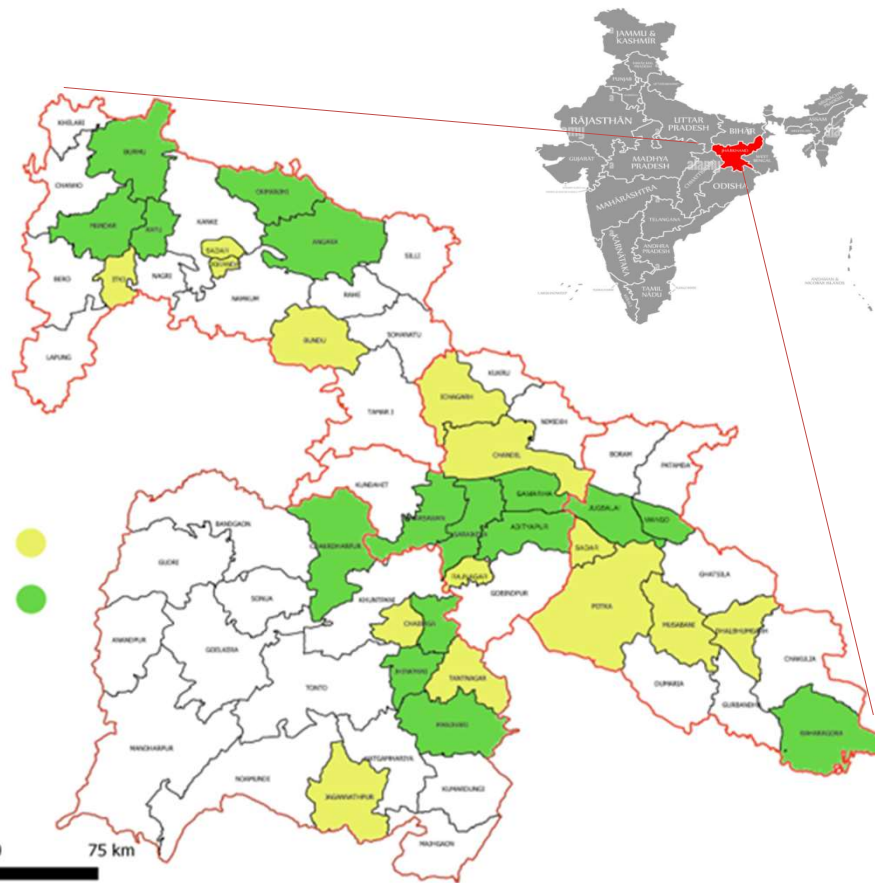
- Adult women: 19 %
- Adult men : 16.2 %
- Higher in lower wealth index
- Higher in vulnerable sub groups
- National TB Prevalence: 316/100,000
- **In some tribal communities: 3294/100,000**
- National TB incidence: 217/100,000
- **In some tribal communities Tribals: 1504/100,000**

% adults with BMI <18.5
5-9%: Low prevalence (warning sign, monitoring required)
10 – 19%: Medium prevalence (poor situation)
20 – 39%: High prevalence (serious situation)
≥40%: Very high prevalence (critical situation)

*Physical status: the use and interpretation of anthropometry. WHO Technical Report Series 854. 1995. p 361-362. International Institute for Population Sciences (IIPS) and ICF. National Family Health Survey (NFHS)-5, Mumbai; 2020 National TB Prevalence Survey in India(2019-2021): Indian Council of Medical Research (ICMR), New Delhi. Rao VG et al. Indian J Med Res 2015. Thomas BE, et al. Indian J Med Res. 2015;141(5):614-23.*



# Trial setting: Jharkhand (The land of trees)



## Trial Area

- 4 districts: Ranchi, Seraikela Kharsawan, East Singhbhum, West Singhbhum
- 28 TB units; 2100 sq km

## Trial Timeline

- Start date of trial: 14<sup>th</sup> May 2019
- Start of Enrolment : 16<sup>th</sup> Aug 2019
- Trial duration: 3 years
- End date: 13<sup>th</sup> August 2022 (3 months no-cost extension)

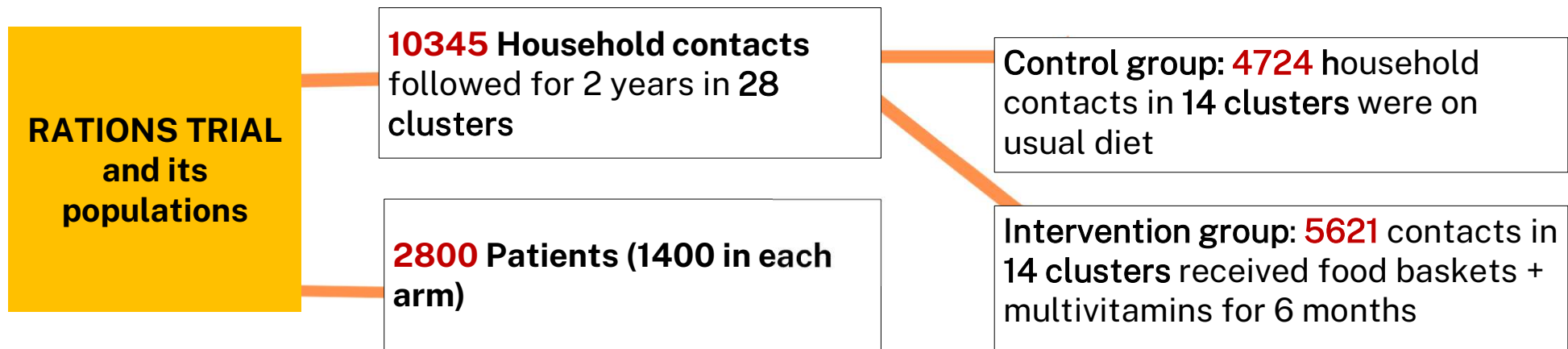




## Trial setting: Jharkhand (The land of trees)



# Study population



## Objectives

### Primary Objective

Difference in incident cases in Household Contacts in both arms in 24 month of follow-up

### Secondary Objectives

- TB mortality
- Changes in weight, BMI, functional status
- Loss to follow-up
- Severe adverse effects to TB drugs

## Study Intervention

Study arms	Intervention
Intervention arm	<p>Patient: 5 Kg Rice + 3 Kg <i>Sattu</i> + 1.5 Kg milk powder + 500 ml Oil + multivitamins per capita per month (1200 Kcal + 52 gm protein per day)</p> <p>Family: 5 Kg Rice +1.5 Kg pulses+ Multivitamins per capita per month (750 Kcal + 23 g proteins per day)</p> <p><i>Sattu: Powdered roasted split chickpeas common in local cuisine</i></p>
Control arm	<p>Patient: 5 Kg Rice + 3 Kg Sattu + 1.5 Kg milk powder+ 500 ml Oil + multivitamins</p> <p>Family: Nutritional assessment + dietary advice</p>

For ethical reasons, no control arm as far as patients are concerned

## Distribution: > 1100 tons/>1 million Kg of food material

- Rice: 646 tons
- Yellow split pigeon peas: 421 tons
- Roasted Bengal gram flour: 50 tons
- Milk powder: 25 tons
- Oil: 8.4 tons
- Micronutrient pill

Cost (basket + MN + delivery charges, prices correspond to 2019 costs):

- Patient basket : INR 1100/month
- Adult contact: INR 325/month



# Food delivery and supportive supervision



## Ensuring intervention delivery and consumption

Weight gain was our surrogate marker for consumption in a food-insecure community

We anticipated variable degree of food sharing

*We did not “directly observe the consumption of intervention”*

### Processes for regular delivery

- Network of sub-depots
- Stock registers
- Sharing of geolocations
- Counter-signing by recipients

### Checks at household level:

- Reinforcement by counselling at each visit
- Checking empty milk powder packets at each visit
- Availability of investigator phone number in PIS

### Triangulation: regular meetings & feedback

- Random supervisory visits
- Phone calls intermittently to household members
- Feedback from Sahiyas and village leaders
- Feedback from Program Staff

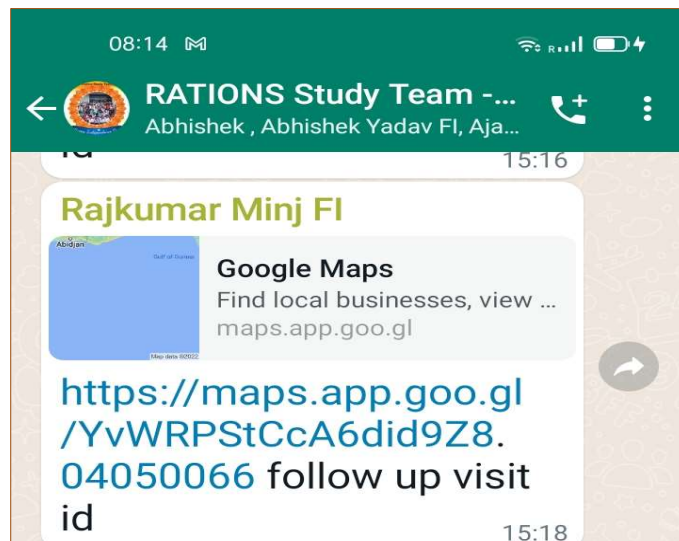
## Enrolment, baseline evaluation, follow-up

- **Enrolment** : start:16.08.2019, end: 31.01.2021
- **Baseline evaluation**:
  - Demography, Anthropometry
  - Symptom screening in all household contacts
  - Clinical: Pedal edema, BP, SpO<sub>2</sub>, ECOG score in patients
- **Triage and referral Criteria**: BMI (<14/<sup>15</sup><16 with edema), hypotension, low SpO<sub>2</sub>, poor mobility, severe anemia
- **Follow-up** of the household: Monthly for first year, quarterly thereafter

### ECOG categories:

- 0**: Working with normal mobility
- 1**: Mobile but not working
- 2**: Self-care, up <50% of the day (able to walk around house)
- 3**: Self-care only, bed/chair bound >50% of the day (able to go to the bathroom)
- 4**: No ability to carry out self-care, confined to bed/chair

# Comprehensive evaluation and triage: Requirement of care in any life-threatening disease



Patient's Id. : 01020080  
Patient's Name : [REDACTED]  
Gender : Male  
Age : 52 years  
D.O.B. : 01/01/1968  
Anthropometry :  
Weight : 31.10 kg  
Height : 154.5 cm  
BMI : 13 kg/m<sup>2</sup>  
Heart Rate : 126  
BP : 82/52  
Spo2 : 94  
Hb : 4.2 g/dl  
Hb Test Date : 19/01/2020  
ECOG Score : 3  
Tb. Diagnosis Date : 14/01/2020 (CBNAAT Positive)  
Treatment Start Date : 18/01/2020  
Enrollment Date : 19/01/2020  
Ration Delivery Date : 19/01/2020

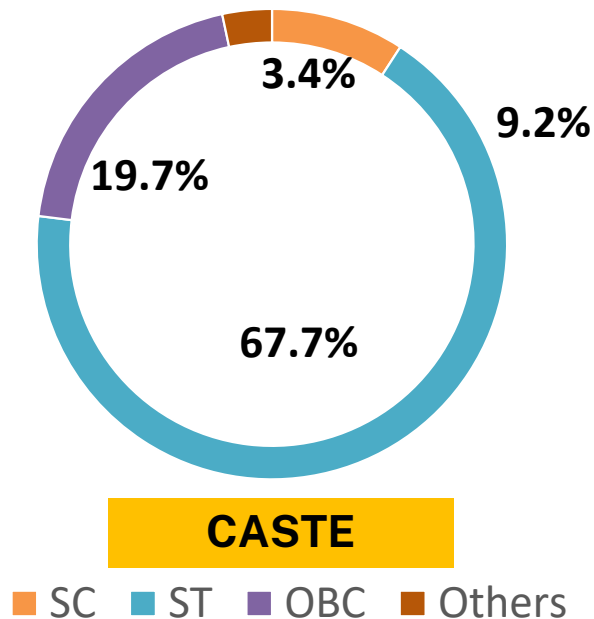
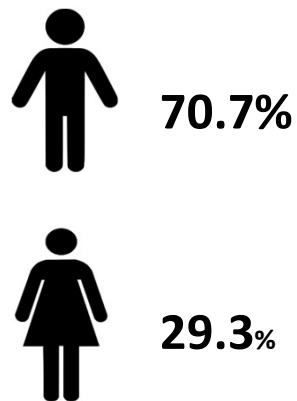




**RESULTS**

## Baseline characteristics of patients with TB

- Underweight (BMI<18.5 kg/m<sup>2</sup>): **82%**
- History of TB in family members – **14%**
- History of Tobacco use – **36.5%**
- History of alcohol : -**50.2%**
- MDR: **3%**
- HIV: **0.3%**
- Diabetes – **5%**



### The severely ill patients with TB:

- Severely underweight (BMI<16 kg/m<sup>2</sup>): **48.6%**
- Extremely severely underweight (BMI<14 kg/m<sup>2</sup>): **17%**
- Hypotension – **10.4%**
- Hypoxia: **9%**
- Anemia : **88%**
- Severe anemia: **7.5%**

Activity levels by ECOG at **baseline**

Able to do normal work: **3%**

Limited activity or bed bound: **12 %**

## Baseline characteristics of contacts

- People who had access to PDS: **85%**
- Tobacco consumption: **9%**
- Alcohol consumption: **14%**
- Presence of BCG Scar: **70%**
- Tuberculosis preventive treatment\*: **16%**



Children <5 years: 11%  
Children 6-17 years: 30%



Adults: 59%

## Prevalence of Underweight in contacts at enrolment: overall 34%

	Control	Intervention
Adults	<b>35%</b>	<b>39%</b>
Children	<b>47%</b>	<b>49%</b>
Adolescents	<b>21%</b>	<b>27%</b>

# Outcomes in contacts of the RATIONS trial

## PRIMARY OUTCOME

Overall TB Incidence:

- **218/10,314 at risk**  
(2.1%) contacts over 21,869 person years of follow up

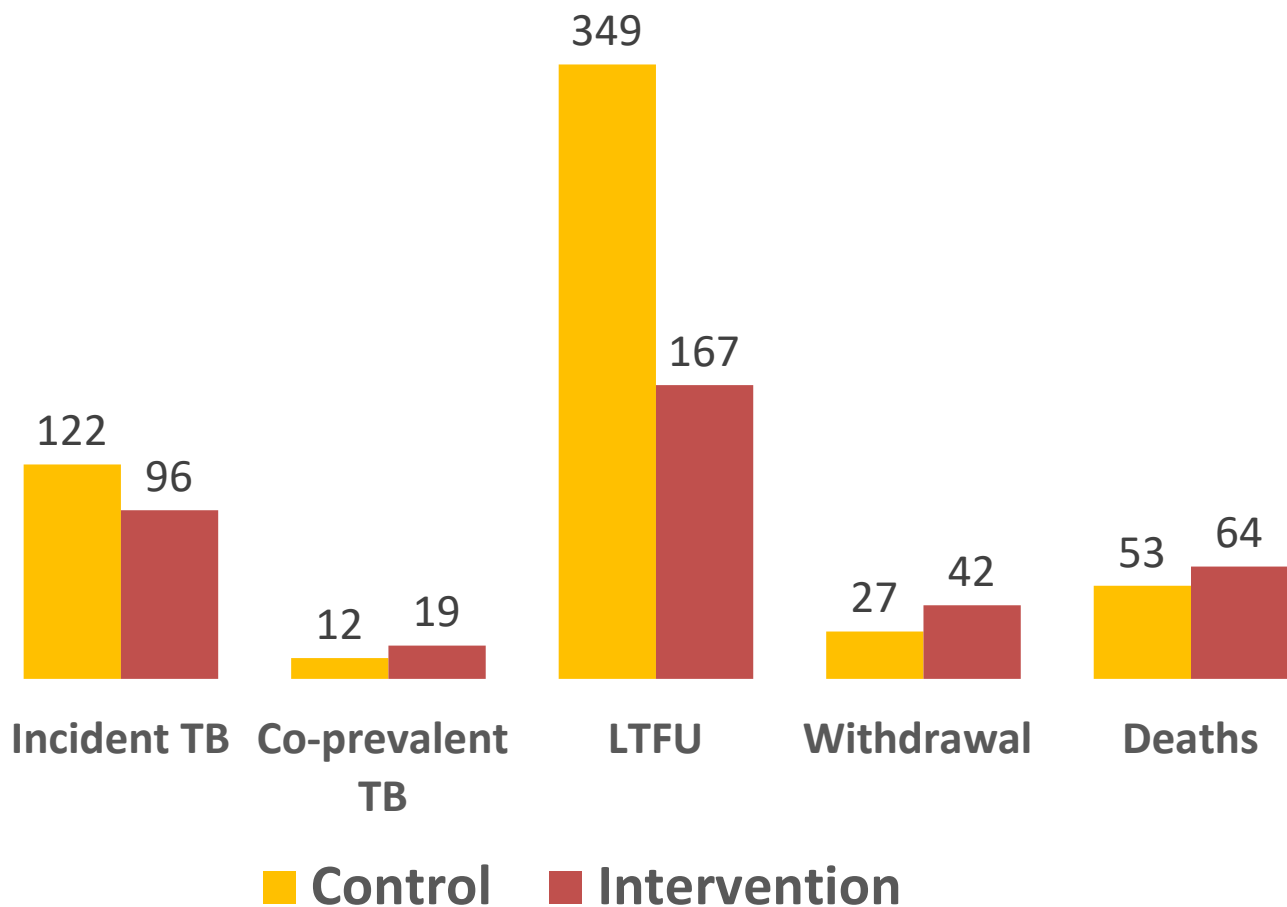
By Arms:

- **96/5602 (1.7%):** Intervention arm
- **122/4 (2.6%):** Control arm

TB incidence rate:

Incident TB (All forms): **1.27** /100 p-years (C) vs. **0.78**/100 p-years (I)

Incident TB (Microbiologically confirmed PTB): **0.95**/100 p-years (C) vs. **0.51**/100 p-years (I)



**Primary outcome: All forms of TB : 39% reduction in Incidence rate**  
**Microbiologically confirmed PTB: 48% reduction in Incidence rate**

	Adjusted Incidence rate ratio (95% Cis)	Adjusted Hazard ratio (95% Cis)
TB incidence (All forms) (N=218)	<u><b>0.61</b></u> (0.46,0.89)	<u><b>0.59</b></u> (0.49,0.83)
TB incidence microbiologically confirmed PTB (N=152)	<u><b>0.52</b></u> (0.35,0.79) <small>21</small>	<u><b>0.51</b></u> (0.34,0.78)

IRR estimated by GEE and Poisson regression and accounted for clustering.

**Model adjusted for age, gender, caste, tobacco , alcohol, BCG status, family history, TPT**

# PRIMARY OUTCOME: TB incidence in household contacts

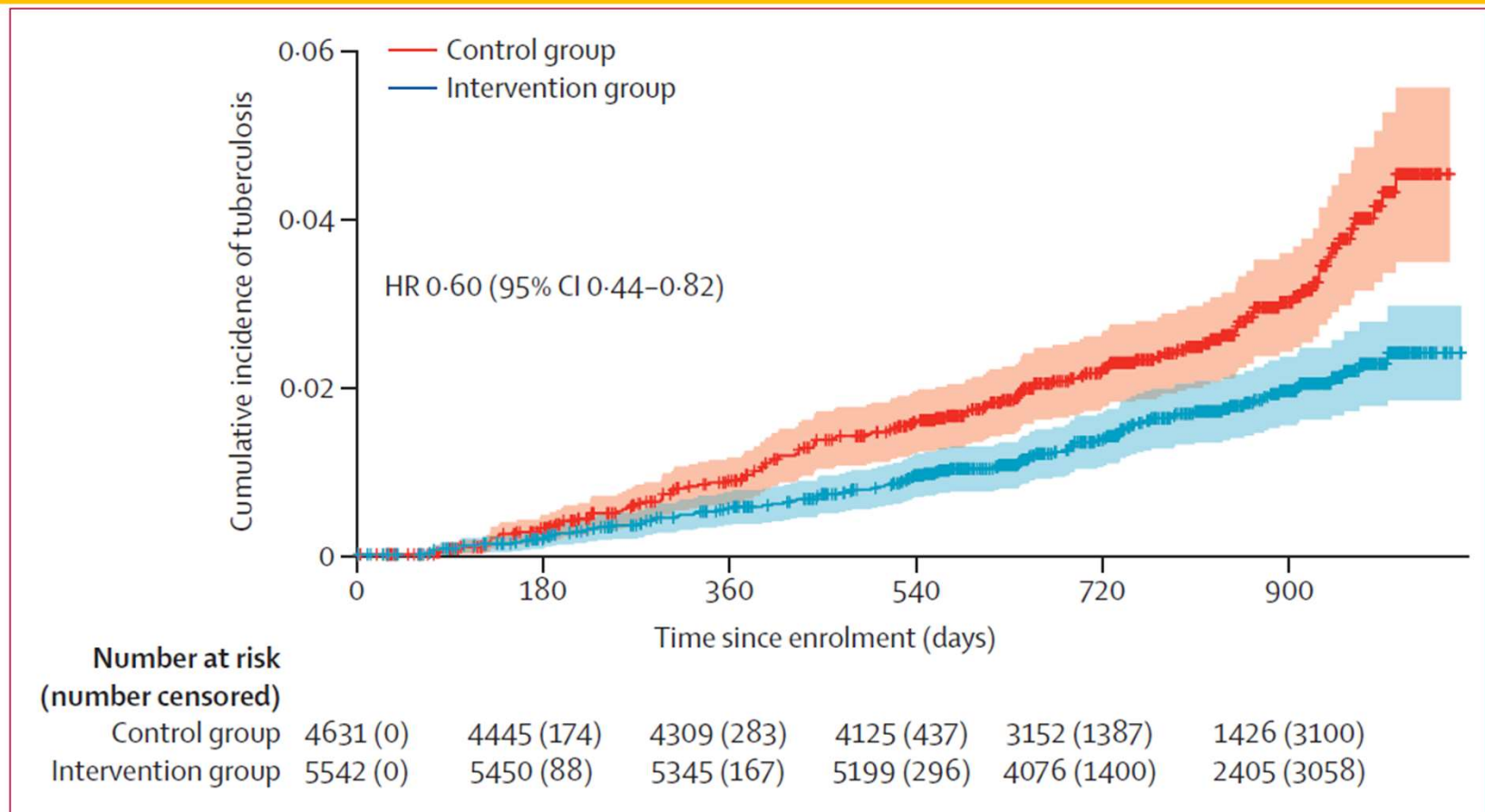
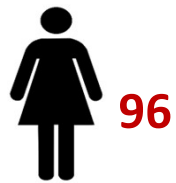


Figure 2: Kaplan-Meier plot for cumulative incidence of tuberculosis disease in household contacts stratified by trial group over the follow-up period

## Characteristics of incident TB in household contacts



<5 years): **11**  
6-17 years: **30**



Adults: **177**

## TYPES OF INCIDENT TB IN CONTACTS

- Microbiologically confirmed: **153**  
Control: **91**; Intervention: **62**
- Clinically diagnosed PTB (adults): **38**
- Extrapulmonary: **6**
- Clinically diagnosed (children): **21**

## Median weight gain in household contacts (kilograms)

### INTERVENTION ARM

- Adults (18-59): **1.5 kg (0.5, 2.9)**
- Adults (>60): 1.1 kg (men) & 1.3 kg (women)
- Children (<5) 1.4 kg (boys), 1.5 kg (girls)
- Children (>5) 1.9 kg (boys); 2 kg (girls)

### CONTROL ARM

- Adults (18-59): **0.8kg (0, 1.7)**
- Adults (>60): 0.6 kg
- Children (<5): 1.4 kg (boys), 1.3kg (girls)
- Children (>5) 1.5 kg (boys); 1.6 kg (girls)

## Treatment outcomes in 2800 patients at 6 months

Treatment success: **94%**

- Cure: **49%**
- Treatment completed: **45%**
- Median weight gain: **4.6 kg (2.6, 6.8)**

Unfavorable outcomes: **5%**

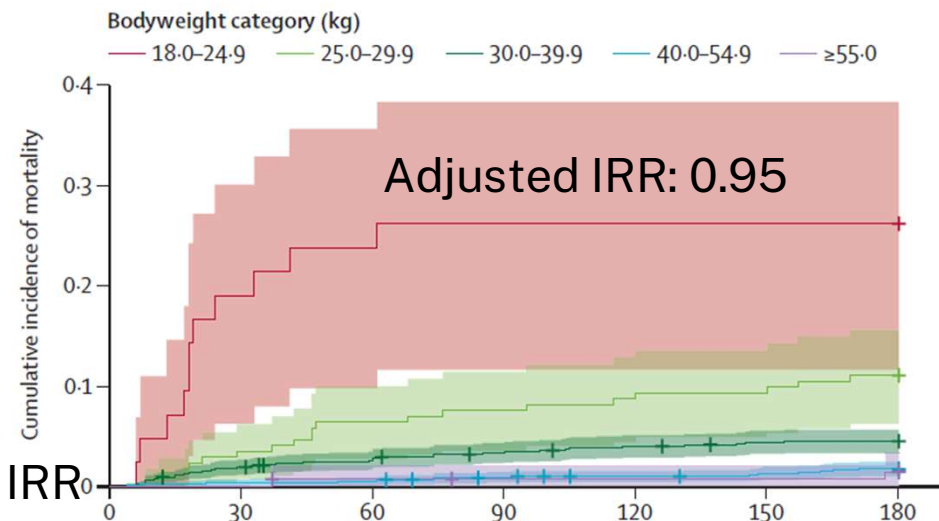
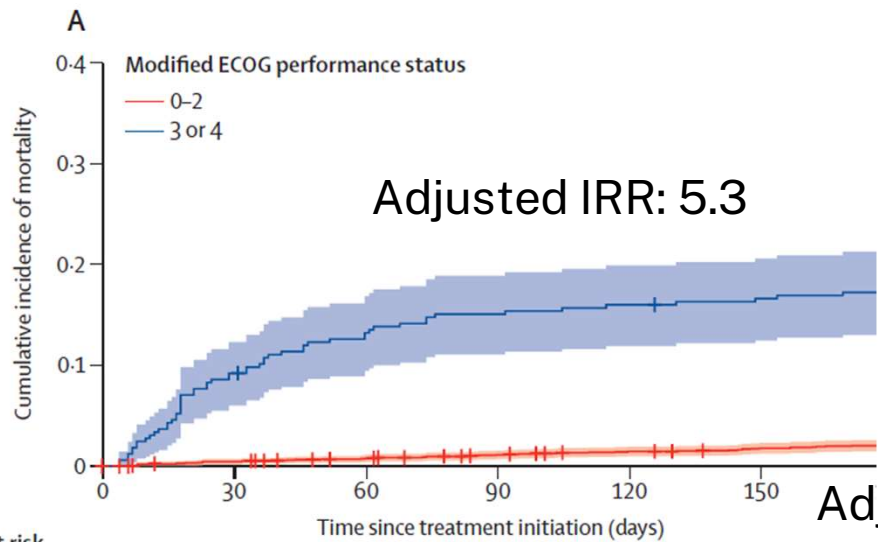
- Death during treatment: **3.9 %**
- Treatment failure: **0.2 %**
- Loss to follow-up: **1 %**

## Predicting and preventing TB deaths: Baseline weight, functional status, diabetes and weight gain in first 2 months are crucial

- Predictors of deaths: Low body weight, poor performance status and diabetes
- Most deaths occurred at home (**77%**)
- **Most deaths in first 2 mos. Median Time to death was 46 (18,96)**
- Preventing TB deaths:
- **5%** weight gain in first 2 months reduced the hazard of death by **60%**.
- **In cohorts without nutritional support, 60% had static or decreasing BMIs in 2 months (Sinha P et al. CID. 2022) and this was associated with 5 fold risk of death**



# Predictors of TB Deaths: Weight, Performance status, Diabetes



Adjusted IRR  
for diabetes:  
3.3

- Performance status is easy to assess in field settings by trained health workers
- 23% reduction in mortality for 5 kg difference in baseline body weight or 2 unit difference in baseline BMI
- Lowest weights & BMIs in survivors: 18.8 kg and 8.6 kg/m<sup>2</sup> (♀), 24.2 kg and 10.7 kg/m<sup>2</sup> (♂)

## Case fatality ratio according to weight, ECOG status

Weight <30 kg: 12 %

Weight 30-39 kg: 4.5 %

Weight 40-54 kg: 1.8 %

Weight 55-69kg: 1.6 %

Weight >70 kg: 0%

Category 0: 0%

Category 1: 1.6%

Category 2: 2.8%

Category 3: 12.6%

Category 4: 40.7%

## Weight gain according to baseline BMI

BMI < 14 kg/m<sup>2</sup> : 6.7 (3.7) kg

BMI 14 -15.9 kg/m<sup>2</sup> : 5.4 (3.1)

BMI 16 -16.9 kg/m<sup>2</sup> : 4.5 (2.8)

BMI 17 -18.4 kg/m<sup>2</sup> : 4.2 (2.9)

BMI 18.5 -24.9 kg/m<sup>2</sup> : 3.7 (2.9)

BMI >25 kg/m<sup>2</sup> : 2.4(3.5)

# Impact of nutrition in TB-deaths & comparison with other cohorts

- The overall mortality of the RATIONS trial was **3.9%**
- Significantly lower than the mortality rate of **5.9%** in the comparison cohorts (Banu et al)
- In those <35 kg: it was **half** that of comparison cohort (7.2% vs. 14%)

## Impact of nutritional support on functional status

Activity levels by ECOG at **baseline**

Able to do normal work: **3%**

Limited activity or bed bound: **12 %**



Activity levels by ECOG at **6 months**

Able to do normal work: **75 %**

Limited activity or bed bound: **0.7 %**

## Key learning from RATIONS trial for TB Prevention

Nutritional supplementation valuable tool in TB prevention in countries with TB-Undernutrition syndemics

- 1 in every 3 contacts was underweight and at higher risk of developing TB
- Nutritional supplementation to family in communities with serious levels of undernutrition reduced the incidence of TB by nearly 40-50%.
- The efficacy of protection (48%) from lung TB approached that of the recently developed vaccine, 49.7% (M72/AS01<sub>E</sub>)
- It can complement other strategies for TB prevention (TPT) and vaccination
- When given for 6 months, it reduced prevalence of undernutrition by 28%
- 30 households (111 household contacts) would need to be provided supplementation to prevent 1 case of TB **(NNS)**

• Tait DR, Hatherill M, Van Der Meeren O., et al. Final Analysis of a Trial of M72/AS01E Vaccine to Prevent Tuberculosis. *N Engl J Med.* 2019;381(25):2429-39.

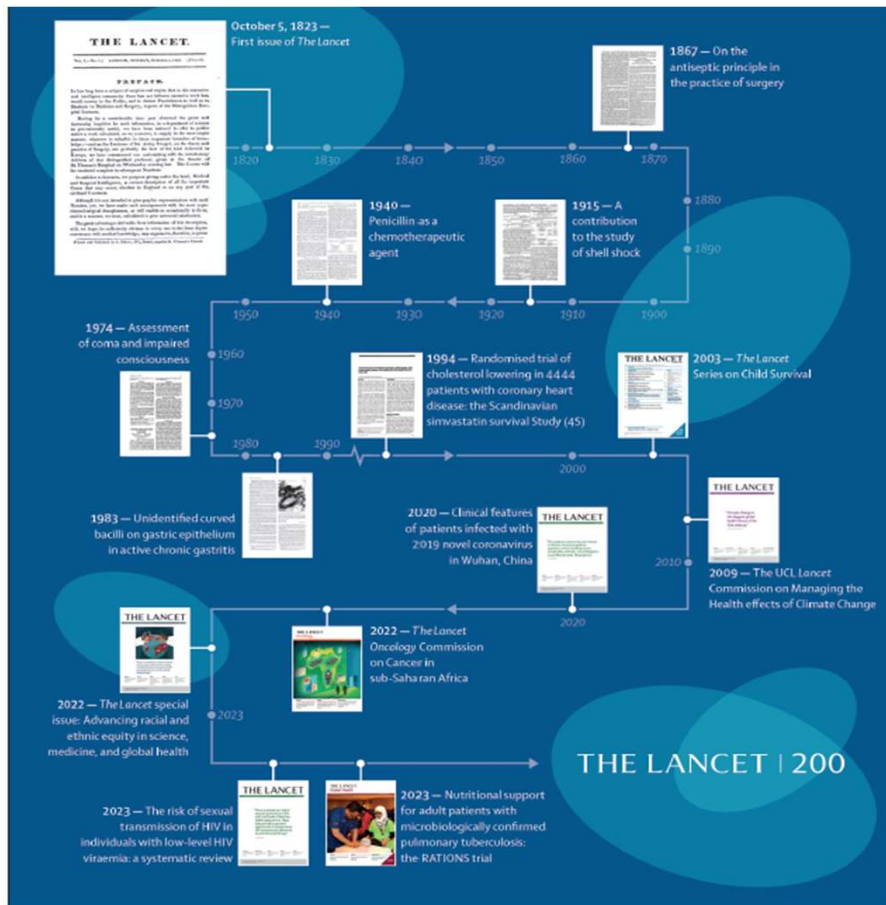
## Key learning from RATIONS trial for TB Care

TB care: Effective TB treatment + Nutritional support= Better outcomes

Nutritional support is an essential *not* component of comprehensive patient centred care

- Patients need comprehensive evaluation-anthropometric, hemoglobin, clinical, performance status at baseline and close supervision for those at high risk
- Comorbidities like diabetes should be better managed with integrated care.
- A simple triage tool based on vital signs, anthropometry, clinical signs and performance status can aid identification of patients with severe disease.
- Nutritional support with food rations was feasible & acceptable
- Better treatment completion, weight gain and return to work
- Reduced deaths by 35% compared to recent cohorts.
- 5% weight gain in the first 2 months protected against TB deaths
- To prevent 1 TB death, 48 patients need to be supplemented **(NNS)**
- To prevent 1 TB death in patients <35 kg, 14 need to be supplemented **(NNS)**

# Some recent developments



Title of UpToDate Section on TB Prevention:

- BCG vaccination
- Nutrition Supplementation

UpToDate Search UpToDate McGill University Menu

Prevention of tuberculosis: BCG immunization and nutritional supplementation

Topic Graphics (2)

**NUTRITIONAL SUPPLEMENTATION**

Mainnutrition is an important risk factor for TB; numerous natural history studies suggest that nutritional supplementation reduces this risk [156-158]. (See "Epidemiology of tuberculosis", section on 'Nutritional status'.)

- **Macronutrient supplementation**
  - **Household contacts** - Nutritional supplementation may be an important intervention to reduce the risk of TB among household contacts of patients with TB disease.
 

In a cluster-randomized trial in Jharkhand, India (a region with annual TB rate of 130 per 100,000, high burden of undernutrition, and low HIV prevalence), 10,345 household contacts of patients with pulmonary TB disease were randomly assigned to a nutritional intervention group or a control group [159]. The intervention included a food basket comprising 750 kcal per day (including 23 g of protein) plus micronutrients per adult, and half that amount for children <10 years of age. During two years of follow-up, fewer cases of microbiologically diagnosed TB (the majority based on a positive sputum smear) were observed among the intervention group (96 versus 122 incident cases, or 1.7 versus 2.1 percent); this represented a protective efficacy of 39 percent (adjusted incidence rate ratio 0.61, 95% CI 0.43-0.85); there were no adverse effects. The individuals who referred participants for TB evaluation were not blinded to randomization assignment.
  - **General population** - Experience from natural history studies support general use of macronutrient supplementation to reduce the risk of TB in malnourished populations.



# Acknowledgements

- ITRC-Indian Council of Medical Research, New Delhi
- Central TB Division, New Delhi
- State TB Cell & District TB Officers of the 4 districts
- Entire RATIONS team
- Sahiya (women field workers of government) network
  
- Our respective dept of Medicine & Community Medicine, Yenepoya Medical College
- Yenepoya (Deemed to be University) Administration
- Central Coal Fields Limited, Jharkhand for Lab space
- Ekjut, Jharkhand (local ethics committee oversight)

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**Patients and communities  
who teach us everyday  
with their resilience and  
humanity in the face of  
sickness and precarity**