

BMJ Open Protocol for a case-control study of vitamin D status, adult multidrug-resistant tuberculosis disease and tuberculosis infection in Mumbai, India

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ABSTRACT

Introduction Vitamin D status may be an important determinant of multidrug-resistant tuberculosis (MDR-TB) infection, progression to disease and treatment outcomes. Novel and potentially cost-effective therapies such as vitamin D supplementation are needed to stem the tide of TB and MDR-TB globally, particularly in India, a country that accounts for the largest fraction of the world's TB incidence and MDR-TB incidence, and where vitamin D deficiency is endemic. While vitamin D has shown some promise in the treatment of MDR-TB, its role in the context of MDR-TB infection and progression to disease is largely unknown.

Methods and analysis Through a case-control study in Mumbai, India, we aim to examine associations between vitamin D status and active MDR-TB and to investigate vitamin D status and TB infection among controls. Cases are adult outpatient pulmonary patients with MDR-TB recruited from two public TB clinics. Controls are recruited from the cases' household contacts and from non-respiratory departments of the facilities where cases were recruited. Cases and controls are assessed for serum 25-hydroxyvitamin D concentration, nutrient intake, diet quality, anthropometry and other relevant clinical and sociodemographic parameters. Controls undergo additional clinical assessments to rule out active TB and laboratory assessments to determine presence of TB infection. Statistical analysis investigates associations between vitamin D status and active MDR-TB and between vitamin D status and TB infection among controls, accounting for potential confounding effects of diet, anthropometry and other covariates.

Ethics and dissemination This study has been approved by Harvard T.H. Chan School of Public Health Institutional Review Board; Foundation for Medical Research Institutional Research Ethics Committee and Health Ministry's Screening Committee of the Indian Council for Medical Research. Permission was granted by the Municipal Corporation of Greater Mumbai, India, a collaborating partner on this research. Outcomes will be disseminated through publication and scientific presentation.

Trial registration number NCT04342598.

Strengths and limitations of this study

- This study contributes to filling critical knowledge gaps in our understanding of the relationship between vitamin D status, tuberculosis (TB) infection and active multidrug-resistant TB (MDR-TB) disease to advance efforts to explore vitamin D supplementation as a novel prevention and treatment strategy for TB and MDR-TB.
- The inclusion of two different types of controls provides a scenario for both household contacts of MDR-TB cases (household controls) and the general population in Mumbai (non-household controls); matching non-household controls and cases on age, sex and ward of residence in Mumbai enhances comparability between these groups.
- To address the notable limitation of confounding present in most observational studies, we are conducting a detailed assessment of potential confounders of the association between vitamin D and active MDR-TB disease as well as vitamin D and TB infection, including nutrient intake, overall diet quality, anthropometry and other sociodemographic and clinical variables.
- Previous studies in Mumbai have not reported serum 25-hydroxyvitamin D concentration (25(OH)D) levels of both patients with MDR-TB as well as healthy controls and therefore power calculations had to be completed using serum 25(OH)D levels for MDR-TB cases and controls from a study in Delhi.
- This study is providing critical data to inform future trials to investigate the effect of vitamin D supplementation in the context of MDR-TB exposure and disease.

INTRODUCTION

Worldwide, tuberculosis (TB) is the number one infectious disease killer and one of the top 10 causes of death.¹ At present, 1.7 billion people (22% of the world's population) are infected with latent TB, approximately 5%–10% of whom will develop active TB during their lifetimes. It is estimated that TB

treatment and control efforts cost the world US\$ 21 billion annually, with low-income countries facing a disproportionately high disease burden and limited resources to combat this deadly disease.¹

Drug-resistant TB (DR-TB) is a rapidly growing problem globally and compounds existing infrastructural challenges for eliminating TB.¹ Worldwide, approximately half a million new TB cases in 2018 were resistant to the most effective first-line drug (rifampicin), and of those, 78% were multidrug resistant (resistant to at least two of the first-line drugs).¹ By the end of 2018, an estimated 6.2% of multi DR-TB (MDR-TB) cases were extensively DR-TB (XDR-TB), which includes additional resistance to at least one fluoroquinolone and one second-line injectable drug. MDR-TB is acquired due to inadequate use of first-line therapy for an extended duration (secondary MDR-TB) or from transmission from infected individuals (primary MDR-TB).² In India, it is estimated that 85% of MDR-TB will be primary MDR-TB by 2032, compared with 15% in 2012.² MDR-TB takes longer to treat (18–24 months in the USA, compared with 6 months for drug-susceptible TB (DS-TB)) and is much more expensive to treat than DS-TB. Excluding social costs of lost productivity, in the USA, MDR-TB treatment costs US\$154 000 and XDR-TB treatment costs US\$494 000, compared with US\$18 000 for DS-TB.³ Furthermore, MDR-TB treatment is more physically taxing: while DS-TB treatment is difficult and hepatotoxic on its own, MDR-TB (and particularly XDR-TB) treatment is extremely painful and deleterious to multiple organ systems, with markedly lower treatment success rates.⁴

Epidemiology and management of MDR-TB in India

India currently contributes the largest fraction of global incident TB cases (27%) and global MDR/DR-TB cases (27%); 440 000 HIV-uninfected Indians died of TB in 2018, while 125 000 died in the next country on the list (Nigeria).¹ Worldwide, India also has the highest national fraction of unreported TB cases (contributing an estimated 25% of all unreported cases globally).¹ The first national anti-TB drug resistance survey⁵ conducted in India from 2014 to 2016 revealed MDR/rifampicin-resistant (RR)-TB levels of 2.8% in new cases and 11.6% in previously treated cases. 1.3% of patients with MDR/RR-TB in India have XDR-TB. Notably, in Mumbai, much MDR-TB is in fact pre-XDR: 21.8% of patients with MDR/RR-TB have additional resistance to any fluoroquinolone and 3.6% have resistance to any second-line injection.⁵

According to the 2017 Guidelines on Programmatic Management of Drug-Resistant TB (PMDT) in India,⁶ all presumptive patients with TB, patients with notified TB and non-responders to treatment should undergo drug susceptibility testing. Currently, all patients with TB are routinely offered at least the rifampicin resistance test. Those who are rifampicin resistant undergo additional testing for resistance to isoniazid and are further tested with line probe assay for resistance to second-line injectables and fluoroquinolones. Additionally, they undergo

liquid culture drug susceptibility testing for resistance to five second-line drugs. Patients are diagnosed with MDR-TB if their biological specimen is resistant to both isoniazid and rifampicin with or without resistance to other first-line drugs. Patients with MDR-TB are classified as pre-XDR if they have additional resistance to any/all fluoroquinolones or any/all second-line drugs, but not both. Patients with MDR-TB are classified as XDR if they are additionally resistant to at least one fluoroquinolone and a second-line drug.⁶ Household contacts of active patients with TB are examined to rule out active TB and appropriate preventive therapy is provided to high-risk individuals with TB infection. Currently, there are no guidelines for treatment of TB infection in contacts of active DR-TB cases.⁷

The treatment success rate among patients with MDR-TB in India is consistently about 46% and the death rate is around 20%.⁵ MDR-TB treatment alone is so expensive to treat that an average Mumbai family could spend over half its annual income on a single patient.⁸ The Government of India is committed to combating MDR-TB and DS-TB and has set an ambitious goal of TB elimination by 2025.⁹ However, to reach this goal, novel treatment and prevention strategies are required.⁹

Vitamin D and TB

Vitamin D is a potent modulator of innate and adaptive immunity through its effects on macrophage, dendritic and T-cell function.^{10–11} Observational studies have demonstrated consistent associations between vitamin D status and DS-TB in diverse settings globally.^{12–13} However, multiple syntheses of randomised trials suggest that adjunctive vitamin D treatment has limited effect in improving clinical and immunologic outcomes in active DS-TB^{14–19} despite evidence that specific vitamin D receptor (VDR) polymorphisms are predictive of sputum conversion time in both patients with DS-TB and MDR-TB.^{20–22} A few trials suggest that among subgroups of patients receiving treatment for active MDR-TB, adjunctive vitamin D significantly accelerates sputum conversion^{23–24} (pooled adjusted HR: 13.44, 95% CI 2.96 to 60.90).¹⁹ While intriguing, this pooled result is based on analysis of only 55 patients with MDR-TB, and the effectiveness of this therapy therefore warrants further investigation. As described by Jolliffe and colleagues,¹⁹ the finding is biologically plausible in that in the context of antimicrobial resistance, the effectiveness of host-directed therapies (particularly those that enhance macrophage activity) should be more evident.²⁵ VDR genotypes were associated with rate of sputum conversion in patients with MDR-TB in a population with high HIV prevalence in South Africa.²⁶ Furthermore, given that vitamin D has been found to normalise circulating immunologic signals following their perturbation by DS-TB treatment,²⁷ vitamin D may also provide immunologic support in MDR-TB treatment in addition to its antimycobacterial activity; however, mechanisms have not been studied explicitly.

Several prospective observational studies indicate that vitamin D deficiency is associated with increased risk of contracting any TB infection^{28–32} and of progressing from TB infection^{31,32} to active TB disease, indicating that vitamin D deficiency is more likely a risk factor than a consequence of TB. These findings are supported by *in vitro* evidence of vitamin D's antimycobacterial activity (increased IFN γ production and sensitisation of macrophages in certain populations)^{33,34} and a feasibility randomised trial of 120 Mongolian school children who showed a borderline reduced risk of any TB infection following vitamin D supplementation.³⁵ A subsequent randomised trial of 9810 Mongolian children has recently concluded and will provide the strongest evidence yet of vitamin D's role in preventing TB infection.³⁶ Epidemiologic studies have not yet specifically assessed whether vitamin D supplementation differentially influences DS-TB and DR-TB infectivity or risk of progression. However, some support for this hypothesis is provided by one study in India that noted VDR polymorphisms associated with vitamin D deficiency were correlated positively with MDR-TB, as compared with DS-TB and healthy controls.³⁷

Study objectives/aims

To combat the substantial global burdens of TB and MDR-TB, novel treatment strategies and expanded prevention efforts are critical. Although vitamin D supplementation shows promise in both of these areas, additional observational evidence is needed to support future randomised clinical trials. Therefore, we are undertaking a case–control study in Mumbai, India to clarify associations between vitamin D status, active MDR-TB disease and TB infection to expand the evidence base and inform the design of future trials of vitamin D supplementation for use in MDR-TB infection. This study assesses vitamin D status, diet and anthropometry among adult outpatient MDR-TB cases and controls in Mumbai, India and TB infection among controls. The specific aims are: (1) examine the association between vitamin D status and active MDR-TB infection, (2) investigate the association between vitamin D status and TB infection among controls, (3) collect formative data to inform the design of future randomised clinical trials evaluating vitamin D supplementation and other interventions in MDR-TB treatment and prevention.

METHODS AND ANALYSIS

Study design

To fulfil our first aim, we are conducting a case–control study comparing vitamin D status between pulmonary MDR-TB (including XDR and pre-XDR) cases and controls. Two types of controls are included: (1) household controls (recruited from the cases' household contacts) and (2) non-household controls (recruited from non-respiratory departments in the healthcare facilities where cases are recruited). All controls are screened

to ensure that they do not have active TB disease. For our second aim, we are assessing the association between vitamin D status and TB infection among controls using QuantiFERON-TB (QFT-TB) interferon-gamma release assays.

Study setting and participant population

This study is taking place in Mumbai in Maharashtra state, India, which is an urban area with high incidence of TB and MDR-TB. Cases are recruited from public MDR-TB clinics in the M/E, H/E and M/W wards, working under the PMDT in India.⁶ Our study staff identify and contact cases from a list of new pulmonary patients with MDR-TB (treatment initiated within the past 1 month) with assistance from TB counsellors working at the public health facilities. Drug resistance patterns of cases are abstracted from medical records and are diagnosed by GeneXpert at accredited public health laboratories situated at the facilities where the patients are seeking treatment. **Figure 1** provides an overview of the workflow for participant recruitment and data collection.

Field workers from a local community-based non-governmental organization (NGO) conduct a preliminary household visit to introduce the study to the recruited cases, identify two household contacts per case and schedule interviews with cases and household controls for a future date. Interviews are conducted at the household or at the local health facilities where the cases are recruited. Non-household controls are recruited from medical dermatology departments at the same public hospitals where cases are recruited and are individually matched to the cases by age (± 10 years), sex and ward of residence in Mumbai. Due to the limited pool of eligible household contacts, it is not feasible to individually match household controls to cases, but the relationships of age and sex will be assessed during data analyses.

All participants must be 18–60 years of age and residents of Mumbai for the last 6 months. To be eligible, cases must be (1) receiving outpatient treatment for pulmonary MDR-TB (including XDR and pre-XDR; patients with extrapulmonary TB are included as long as they also have pulmonary TB) according to the national standard of care for no more than 1 month, (2) permanently living with two eligible controls and (3) have no history of MDR-TB episodes in the past 2 years. Both new patients with MDR-TB and patients with prior DS-TB are eligible. The patient must also have disclosed their TB status to their household and consent to their household members being invited to join the study. Within 2–3 days of recruiting each case, two eligible household controls and one non-household control are recruited.

Household controls are eligible if they were a permanent member of the case's household for at least 1 year prior to the case's MDR-TB diagnosis and do not have any signs or symptoms of active TB disease (assessed via questionnaire). Non-household controls are eligible if they have no history of household contact with a patient with TB in the last 2 years and no signs or symptoms of

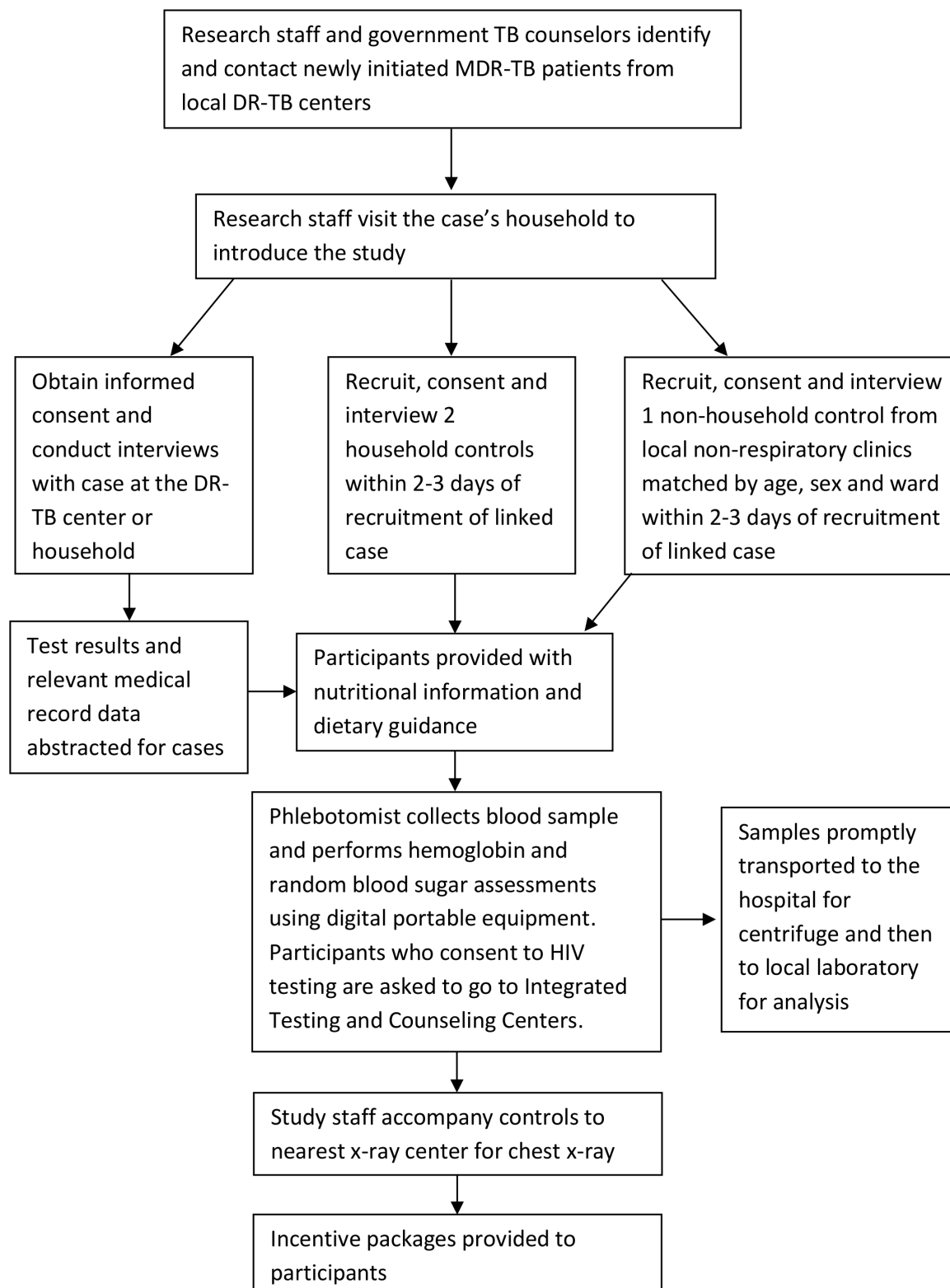


Figure 1 Workflow for recruitment and data collection for MDR-TB cases and controls in Mumbai, India. DR, drug resistant; MDR, multidrug resistant; TB, tuberculosis.

active TB disease. Eligible non-household controls who can be matched to a case (by sex, ward of residence in Mumbai and age) are enrolled directly when they come for consultation to the non-respiratory departments of local hospitals.

Study instruments and assessments

Prior to beginning the interviews, trained interviewers explain the study in detail and obtain written informed consent from each participant. After consent is obtained, study staff administer questionnaires and anthropometric

Table 1 Questionnaires and assessments administered to multidrug resistant tuberculosis cases and controls in Mumbai, India

Assessment	Cases	Household controls	Non-household controls
Serum 25-hydroxyvitamin D (liquid chromatography–mass spectrometry)	✓	✓	✓
QuantIFERON-TB interferon-gamma release assays (QFT-TB IGRA)	NA	✓	✓
Chest X-ray	Data abstraction (hospital records)	✓	✓
Sputum examination	Data abstraction (hospital records)	✓ (only if indicated by symptoms)	✓ (only if indicated by symptoms)
HIV infection	Data abstraction (hospital records)	✓	✓
Haemoglobin	✓	✓	✓
Random blood sugar	✓	✓	✓
Food frequency questionnaire	✓	✓	✓
Clinical questionnaire	✓	✓	✓
Background questionnaire	✓	✓	✓
Anthropometric measurements	✓	✓	✓

assessments in private rooms at the clinic or in a quiet, well-ventilated area of the participant's household. **Table 1** displays the assessments and tests that are administered to cases, household controls and non-household controls. Questionnaires include socioeconomic and demographic variables as well as comorbidities and other clinical information. Existing data for cases and controls are abstracted from hospital records wherever possible. Habitual dietary intake over the past year is assessed using a 195-item general semiquantitative food frequency questionnaire (FFQ), based on an instrument previously developed and validated for use in urban and rural India as part of the Indian Migration Study (IMS),³⁸ which we have modified to more closely reflect foods commonly consumed in Mumbai. After completing the interviews, participants are provided with nutritional information and general dietary guidance to educate them on ways to improve their diet. For all participants, height, weight, waist circumference and mid upper arm circumference are measured and a 5 mL blood specimen is collected by a trained phlebotomist in a vacutainer for laboratory assessments. To measure vitamin D status for all participants, serum 25-hydroxyvitamin D concentration (25(OH)D) is assessed using liquid chromatography–mass spectrometry (LC-MS) at Metropolis Healthcare in Mumbai, which is a local reputable laboratory that maintains a stringent quality assurance programme following the College of American Pathologists and the India National Accreditation Board for Testing and Calibration Laboratories guidelines. The intraassay coefficient of variation (CV) for the LC-MS platform that is used is 7.73%, while the interassay CV is 8.05%. Controls are also assessed for TB infection using QFT-TB tests. Those testing positive for TB infection are referred for further workup at the hospital

to assess comorbidities and to be managed according to the principles laid out at the 2015 Global Consultation on Best Practices in the Delivery of Preventive Therapy for Households Exposed to Drug-Resistant Tuberculosis.³⁹

After completing the interviews, household and non-household controls undergo voluntary HIV testing at nearby government Integrated Counselling and Testing Centres. Study staff accompany controls to nearby digital X-ray centres where they undergo a chest X-ray. If controls are found to have active TB, they are excluded from the study. Controls also undergo sputum examination (if indicated by symptoms). Cases have undergone these tests as part of the standard of care, and data are abstracted. All participants undergo haemoglobin assessments using a Mission ULTRA Digital Hemoglobin Meter and random blood sugar testing using a Contour TS Glucometer. After completing all procedures, modest incentive packages including food and toiletries are provided to the participants.

Ethics and dissemination

This study has been approved by all relevant human research ethics committees in USA and India: Harvard T.H. Chan School of Public Health Institutional Review Board (Ref. No. IRB19-0237); Institutional Research Ethics Committee at the Foundation for Medical Research (Ref. No. FMR/IREC/TB/01/2019) and Health Ministry's Screening Committee of the Indian Council for Medical Research (Ref. No. 2019-7974). Permission was also granted by the Municipal Corporation of Greater Mumbai, India (Ref No. HO/0084/TB). Trained interviewers obtain written informed consent from all participants, ensuring that they understand the purpose of the research, their role in the study and the risks/benefits.

For participants who are illiterate in Hindi, Marathi or English or are not able to sign their name, a thumbprint is used in place of a signature. In the case of illiteracy, study staff explain the study in detail to the participant and informed consent is documented with participation of a witness. The risks of this study are minimal. During the study, participants are provided with information on how to improve their diet as well as vitamin D and general nutritional status. Participants found to be vitamin D deficient, anaemic or with a positive QFT-TB result are referred for the appropriate standard of care. Findings from this study will be presented at national and international research meetings and published in peer-reviewed scientific journals.

Patient and public involvement

Patients and the public are not involved in the design, conduct, reporting or dissemination of this research.

Sample size, power calculations and analysis plan

We used an alpha of 0.05; power of 80%; mean±SD of serum 25 (OH)D in MDR-TB cases of 13.5±10.0 nmol/L³⁷, mean±SD of serum 25(OH)D in healthy controls of 34.9±26.2 nmol/L³⁷ and prevalence of TB infection among Indian adult household contacts of 58.1%⁴⁰ to calculate a sample size of 100 patients with MDR-TB, 200 household contacts (approximately 116 of whom will have TB infection based on the prevalence estimate) and 100 non-household contacts (approximately 58 of whom will have TB infection). This sample size allows detectable differences in 25(OH)D of at least 7.6 nmol/L comparing MDR-TB cases versus all household controls and at least 8.8 nmol/L comparing all TB-infected controls with all TB-negative controls.

To investigate associations between vitamin D status and MDR-TB case status (aim 1), multivariate logistic regression is applied, conditioning on household and controlling for potential confounders. To determine the association between TB infection and vitamin D status (aim 2), unconditional logistic regression is applied among controls, controlling for potential confounders. For both aims, analyses are among all controls combined as well as household controls and non-household controls separately. We are examining vitamin D status continuously and categorically according to cut-offs of 10, 20 and 30 ng/mL.⁴¹ We are exploring a set of covariates to assess potential confounding on the primary exposure and outcome of interest including age, sex, sociodemographic variables, clinical and dietary parameters and anthropometric measurements. FFQ responses are converted to intake per day using empirical portion sizes previously collected during development of the IMS FFQ on which our instrument is based.³⁸ Nutrient intake is calculated using food composition data previously reported for use in analysing the IMS FFQ.⁴² We are estimating intake of macronutrients (energy, protein, total fat and fatty acid fractions, carbohydrate, fibre, alcohol); minerals (Ca, P, Fe, Mg, Na, K, Cu, Mn, Zn, Se, I) and vitamins (A, B1, B2,

B3, B5, B6, B9, B12, C, D and 25-OH-D, E). For foods we added to the IMS FFQ, nutrient values are derived from the 2017 Indian Food Composition Table.⁴³ FFQ data are also being used to tabulate the Global Diet Quality Score,^{44 45} which provides an overall assessment of both nutrient adequacy and diet-related disease risk.

DISCUSSION

MDR-TB is a growing problem and a serious threat to global health security given its airborne transmission, the limited capacity for diagnosis in many settings and the expensive and lengthy treatment that is often associated with challenges in adherence. It has been estimated that by 2050, DR-TB could kill as many as 2.5 million people per year and cost the global economy as much as US\$16.7 trillion.⁴⁶ Although vitamin D shows potential as a strategy for prevention and treatment of MDR-TB,¹⁹ evidence for its efficacy in this regard is limited. Preliminary observational evidence suggests that vitamin D status is associated with duration to sputum conversion and also may be associated with risk of acquiring MDR-TB. Additional detailed observational studies, and potentially randomised controlled trials, are warranted to clarify these associations.

Given the country's high dual burdens of MDR-TB and vitamin D deficiency, India is a priority setting for evaluating these research questions. It is estimated that vitamin D deficiency affects 70%–100% of the Indian population due to a range of environmental, sociological and biological factors.⁴⁷ These include rapid urbanisation and decreasing time spent outdoors; skin pigmentation that is associated with lower vitamin D concentrations; a lack of vitamin D-rich foods and supplements in the diet; cultural practices related to clothing and sun exposure and potentially widespread polymorphisms in the VDR and other aspects of vitamin D metabolism and function.⁴⁷ This case-control study in Mumbai, India aims to clarify the relationship between vitamin D status and active MDR-TB disease as well as vitamin D status and TB infection, which is critical to inform future research, prevention and treatment efforts.

This study has a number of strengths. The inclusion of controls from two distinct source populations allows us to examine associations in household contacts of MDR-TB cases as well as non-household controls, providing a scenario for the general population. Individually matching non-household controls to cases on age, sex and ward of residence enhances comparability between cases and controls. Although we are not able to match household controls to cases due to the limited pool of eligible household contacts, we are taking age and sex into account during data analyses. Additionally, our detailed assessment of intake of macronutrients and micronutrients associated with TB infection and treatment outcomes, overall diet quality, anthropometry and other sociodemographic and clinical variables allows us to explore potential confounders of the associations

between vitamin D and active MDR-TB as well as vitamin D and TB infection.

A limitation of this study is that for our power calculations, we had to use serum 25(OH)D levels for MDR-TB cases and controls from a study in Delhi³⁷ because to our knowledge, no studies in Mumbai have described serum 25(OH)D levels of both patients with MDR-TB and healthy controls. Although vitamin D levels in Delhi may vary from those in Mumbai, this should not significantly affect our power calculation because all we need to parameterise is the detectable difference in expected vitamin D status between study groups, which we were able to do using the data from Delhi. An additional limitation of our study is that given limited resources, we are not measuring serum or plasma parathyroid hormone (PTH). However, our approach is reasonable based on findings from Rathored *et al*³⁷, in which PTH was negatively correlated with 25(OH)D among MDR-TB cases, DS-TB cases and healthy controls as expected (indicating normal calcium homeostasis), and because we are measuring calcium intake (which also influences PTH).

A secondary objective of this study involves collection of key information for the purpose of justifying and informing the design and implementation of future clinical trials evaluating the effectiveness of various interventions, including high-dose vitamin D supplementation as adjunctive therapy to improve MDR-TB treatment outcomes and/or prevent MDR-TB infection in Indian communities. Through implementing the current study, we are documenting local costs and infrastructure necessary for: (1) recruitment of patients with MDR-TB and household contacts, including the burden of disease at various clinics to enable the enrolment of patients in studies of sizeable sample sizes as may be needed in the future (2) laboratory testing of various conditions including vitamin D and other markers of nutritional status, immunologic and inflammatory parameters, active MDR TB of various types and TB infection, (3) intensive-phase and continuation-phase treatment of DS-TB and MDR-TB (including medical and pharmaceutical components of inpatient and outpatient treatment and follow-up) and (4) clinical data management, safety and monitoring and regulatory processes necessary for the conduct of high-quality observational studies and clinical trials. Strong partnerships developed as part of the current study will also be central to the success of future trials and to capacity building at research and government institutions involved.

Early diagnosis and treatment are critical for controlling the rising tide of MDR-TB. Structural macrosocial interventions including those to address poverty and overcrowding are also important. Given the high costs of MDR-TB treatment, which in most cases constitute catastrophic expenses for households, further investment in prevention research is a priority.

This study builds on prior evidence indicating that vitamin D may play an important role in MDR-TB prevention and treatment. Results from this research are critical

to inform the design of future studies and development of novel MDR-TB prevention and treatment strategies, which are urgently needed, especially in India and other low-income and middle-income countries where MDR-TB is a serious threat to public health and national productivity.

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Contributors WF, NM and YD originated the concept for the study and led development of the study design and implementation procedures. AS, ECH, SB, PD and LG were involved in the development of the implementation protocol and data analysis plan. NM, ECH, YD and SB wrote the initial draft of the manuscript. PT and DS provided expert guidance in developing the study design and implementation protocol. SK provided expert guidance in developing the study design and data analysis plan. All authors revised the manuscript for important intellectual content and read and approved the final manuscript.

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REFERENCES

- 1 World Health Organization. *Global tuberculosis report 2019*. Geneva: WHO, 2019.
- 2 Law S, Piatek AS, Vincent C, *et al*. Emergence of drug resistance in patients with tuberculosis cared for by the Indian health-care system: a dynamic modelling study. *Lancet Public Health* 2017;2:e47–55.
- 3 Jackson A. *Protecting the United States from the health security risk of global tuberculosis: CSIS global health policy center*. Washington, DC: Center for Strategic & International Studies, 2017.
- 4 Yang TW, Park HO, Jang HN, *et al*. Side effects associated with the treatment of multidrug-resistant tuberculosis at a tuberculosis

- referral hospital in South Korea: a retrospective study. *Medicine* 2017;96:e7482.
- 5 Ministry of Health & Family Welfare Government of India. Report of the first national anti-tuberculosis drug resistance survey 2014–16; 2018. <https://tbcindia.gov.in/showfile.php?lid=3315>
 - 6 Central TB Division, Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India. Guidelines on programmatic management of drug resistant tuberculosis in India 2017. New Delhi, India; 2017. <https://www.tbfacts.org/wp-content/uploads/2017/12/PMDT.pdf>
 - 7 Central TB Division, Ministry of Health & Family Welfare, Government of India, World Health Organization Country Office for India. Standards of TB care in India; 2014.
 - 8 Udawadia Z, Mullerpattan J, Banka R, et al. The health economics of treating MDR-TB in the Indian private sector. *Eur Respir J* 2016;48:PA1536.
 - 9 Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare India. National strategic plan for tuberculosis elimination 2017–2025. New Delhi, India; 2017. <https://tbcindia.gov.in/WriteReadData/NSP%20Draft%2020.02.2017%201.pdf>
 - 10 Coussens AK, Martineau AR, Wilkinson RJ. Anti-inflammatory and antimicrobial actions of vitamin D in combating TB/HIV. *Scientifica* 2014;2014:1–13.
 - 11 Aranow C. Vitamin D and the immune system. *J Investig Med* 2011;59:881–6.
 - 12 Tessema B, Moges F, Habte D, et al. Vitamin D deficiency among smear positive pulmonary tuberculosis patients and their tuberculosis negative household contacts in Northwest Ethiopia: a case-control study. *Ann Clin Microbiol Antimicrob* 2017;16:36.
 - 13 Maceda EB, Gonçalves CCM, Andrews JR, et al. Serum vitamin D levels and risk of prevalent tuberculosis, incident tuberculosis and tuberculin skin test conversion among prisoners. *Sci Rep* 2018;8:997.
 - 14 Xia J, Shi L, Zhao L, et al. Impact of vitamin D supplementation on the outcome of tuberculosis treatment: a systematic review and meta-analysis of randomized controlled trials. *Chin Med J* 2014;127:3127–34.
 - 15 Grobler L, Nagpal S, Sudarsanam TD, et al. Nutritional supplements for people being treated for active tuberculosis. *Cochrane Database Syst Rev* 2016;6:Cd006086.
 - 16 Zittermann A, Pilz S, Hoffmann H, et al. Vitamin D and airway infections: a European perspective. *Eur J Med Res* 2016;21:14.
 - 17 Wallis RS, Zumla A. Vitamin D as adjunctive Host-Directed therapy in tuberculosis: a systematic review. *Open Forum Infect Dis* 2016;3:ofw151.
 - 18 Wu H-X, Xiong X-F, Zhu M, et al. Effects of vitamin D supplementation on the outcomes of patients with pulmonary tuberculosis: a systematic review and meta-analysis. *BMC Pulm Med* 2018;18:108.
 - 19 Jolliffe DA, Ganmaa D, Wejse C, et al. Adjunctive vitamin D in tuberculosis treatment: meta-analysis of individual participant data. *Eur Respir J* 2019;53. doi:10.1183/13993003.02003-2018. [Epub ahead of print: 07 03 2019].
 - 20 Roth DE, Soto G, Arenas F, et al. Association between vitamin D receptor gene polymorphisms and response to treatment of pulmonary tuberculosis. *J Infect Dis* 2004;190:920–7.
 - 21 Babb C, van der Merwe L, Beyers N, et al. Vitamin D receptor gene polymorphisms and sputum conversion time in pulmonary tuberculosis patients. *Tuberculosis* 2007;87:295–302.
 - 22 Magee MJ, Sun YV, Brust JCM, et al. Polymorphisms in the vitamin D receptor gene are associated with reduced rate of sputum culture conversion in multidrug-resistant tuberculosis patients in South Africa. *PLoS One* 2017;12:e0180916.
 - 23 Tukvadze N, Sanikidze E, Kipiani M, et al. High-Dose vitamin D3 in adults with pulmonary tuberculosis: a double-blind randomized controlled trial. *Am J Clin Nutr* 2015;102:1059–69.
 - 24 Ganmaa D, Munkhzul B, Fawzi W, et al. High-dose vitamin D₃ during tuberculosis treatment in Mongolia. A randomized controlled trial. *Am J Respir Crit Care Med* 2017;196:628–37.
 - 25 Wallis RS, Hafner R. Advancing host-directed therapy for tuberculosis. *Nat Rev Immunol* 2015;15:255–63.
 - 26 Magee MJ, Sun YV, Brust JCM, et al. Polymorphisms in the vitamin D receptor gene are associated with reduced rate of sputum culture conversion in multidrug-resistant tuberculosis patients in South Africa. *PLoS one* 2017;12:e0180916.
 - 27 Coussens AK, Wilkinson RJ, Hanifa Y, et al. Vitamin D accelerates resolution of inflammatory responses during tuberculosis treatment. *Proc Natl Acad Sci U S A* 2012;109:15449–54.
 - 28 Zeng J, Wu G, Yang W, et al. A serum vitamin D level. *PLoS One* 2015;10:e0126014.
 - 29 Keflie TS, Nölle N, Lambert C, et al. Vitamin D deficiencies among tuberculosis patients in Africa: a systematic review. *Nutrition* 2015;31:1204–12.
 - 30 Sarin P, Duffy J, Mughal Z, et al. Vitamin D and tuberculosis: review and association in three rural provinces of Afghanistan. *Int J Tuberc Lung Dis* 2016;20:383–8.
 - 31 Huang S-J, Wang X-H, Liu Z-D, et al. Vitamin D deficiency and the risk of tuberculosis: a meta-analysis. *Drug Des Devel Ther* 2017;11:91–102.
 - 32 Aibana O, Huang C-C, Aboud S, et al. Vitamin D status and risk of incident tuberculosis disease: a nested case-control study, systematic review, and individual-participant data meta-analysis. *PLoS Med* 2019;16:e1002907.
 - 33 Martineau AR, Wilkinson RJ, Wilkinson KA, et al. A single dose of vitamin D enhances immunity to mycobacteria. *Am J Respir Crit Care Med* 2007;176:208–13.
 - 34 Larcombe L, Orr P, Turner-Brannen E, et al. Effect of vitamin D supplementation on Mycobacterium tuberculosis-induced innate immune responses in a Canadian Dené first nations cohort. *PLoS One* 2012;7:e40692.
 - 35 Ganmaa D, Giovannucci E, Bloom BR, et al. Vitamin D, tuberculin skin test conversion, and latent tuberculosis in Mongolian school-age children: a randomized, double-blind, placebo-controlled feasibility trial. *Am J Clin Nutr* 2012;96:391–6.
 - 36 Ganmaa D, Khudyakov P, Buyanjargal U, et al. Prevalence and determinants of Quantiferon-Diagnosed tuberculosis infection in 9810 Mongolian schoolchildren. *Clin Infect Dis* 2019;69:813–9.
 - 37 Rathored J, Sharma SK, Singh B, et al. Risk and outcome of multidrug-resistant tuberculosis: vitamin D receptor polymorphisms and serum 25(OH)D. *Int J Tuberc Lung Dis* 2012;16:1522–8.
 - 38 Bowen L, Bharathi AV, Kinra S, et al. Development and evaluation of a semi-quantitative food frequency questionnaire for use in urban and rural India. *Asia Pac J Clin Nutr* 2012;21:355–60.
 - 39 Harvard Medical School Center for Global Health Delivery Dubai/Vol. 1, No. 1. Global consultation on best practices in the delivery of preventive therapy for household contacts of patients with drug-resistant tuberculosis. Proceedings of the Harvard Medical School Center for Global Health Delivery–Dubai. Dubai, United Arab Emirates Harvard Medical School Center for Global Health Delivery Dubai; 2015. <http://sentinel-project.org/wp-content/uploads/2016/01/Proceedings-on-delivery-of-preventive-therapy-in-DR-TB-contacts.pdf>
 - 40 Chandrasekaran P, Mave V, Thiruvengadam K, et al. Tuberculin skin test and QuantiFERON-Gold in tube assay for diagnosis of latent TB infection among household contacts of pulmonary TB patients in high TB burden setting. *PLoS One* 2018;13:e0199360.
 - 41 Pearce SHS, Cheetham TD. Diagnosis and management of vitamin D deficiency. *BMJ* 2010;340:b5664.
 - 42 Bowen L, Ebrahim S, De Stavola B, et al. Dietary intake and rural-urban migration in India: a cross-sectional study. *PLoS One* 2011;6:e14822.
 - 43 Longvah T, Ananthan R, Bhaskarachary K. *Indian food composition tables*. Hyderabad: National Institute of Nutrition, Indian Council of Medical Research, 2017.
 - 44 Fung TT, Isanaka S, Hu FB, et al. International food group-based diet quality and risk of coronary heart disease in men and women. *Am J Clin Nutr* 2018;107:120–9.
 - 45 Gicevic S, Gaskins AJ, Fung TT, et al. Demographic and socio-economic predictors of diet quality among adults in Bosnia and Herzegovina. *Public Health Nutr* 2019;22:3107–17.
 - 46 All Party Parliamentary Group on Global TB. The price of a pandemic: counting the cost of MDR-TB; 2015. https://51072cd5-c1a2-4ecf-9296-955a4a6c5720.filesusr.com/ugd/309c93_f0731d24f4754cd4a0ac0d6f6e67a526.pdf
 - 47 G R, Gupta A. Vitamin D deficiency in India: prevalence, causalities and interventions. *Nutrients* 2014;6:729–75.