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
Drug-resistant TB (DR-TB) is a rapidly growing problem globally and compounds existing infrastructural challenges for eliminating TB. 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). 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). In India, it is estimated that 85% of MDR-TB will be primary MDR-TB by 2022, compared with 15% in 2012. 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. Furthermore, MDR-TB treatment is more physically taxing; while DS-TB treatment is difficult and hepatico 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.

**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). Worldwide, India also has the highest national fraction of unreported TB cases (contributing an estimated 25% of all unreported cases globally). The first national anti-TB drug resistance survey 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.

According to the 2017 Guidelines on Programmatic Management of Drug-Resistant TB (PMDT) in India, 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 injectable 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. 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.

The treatment success rate among patients with MDR-TB in India is consistently about 46% and the death rate is around 20%. 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. The Government of India is committed to combating MDR-TB and DS-TB and has set an ambitious goal of TB elimination by 2025. However, to reach this goal, novel treatment and prevention strategies are required.

**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. Observational studies have demonstrated consistent associations between vitamin D status and DS-TB in diverse settings globally. However, multiple synthesis of randomised trials suggest that adjunctive vitamin D treatment has limited effect in improving clinical and immunologic outcomes in active TB despite evidence that specific vitamin D receptor (VDR) polymorphisms are predictive of sputum conversion time in both patients with DS-TB and MDR-TB. A few trials suggest that among subgroups of patients receiving treatment for active MDR-TB, adjunctive vitamin D significantly accelerates sputum conversion. Observational studies have also shown that vitamin D may provide immunologic support in MDR-TB treatment in addition to its antimycobacterial activity; however, mechanisms have not been studied explicitly.

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Several prospective observational studies indicate that vitamin D deficiency is associated with increased risk of contracting any TB infection and of progressing from TB infection 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) and a feasibility study comparing vitamin D status between pulmonary TB cases and controls, recruited from the cases’ household for at least 1 year without prior history of MDR-TB and MDR-TB patients with prior DS-TB are included as long as they also have pulmonary TB) according to the national standard of care for no more than 1 month, permanently living with two eligible controls and 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.

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 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) and a feasibility study comparing vitamin D status between pulmonary TB cases and controls, recruited from the cases’ household for at least 1 year without prior history of MDR-TB and MDR-TB patients with prior DS-TB are included as long as they also have pulmonary TB) according to the national standard of care for no more than 1 month, permanently living with two eligible controls and 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.

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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...
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. Assessments 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), 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 QuantiFERON-TB interferon-gamma release assays (QFT-TB IGRA) and 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.

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                      | ✓     | ✓                  | ✓                      |
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/L;37 mean±SD of serum 25(OH)D in healthy controls of 34.9±26.2 nmol/L;37 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.31 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,47 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.48 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.49 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 Delhi 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., 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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