Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Ganmaa D, Uyanga B, Zhou X, et al. Vitamin D supplements for prevention of tuberculosis infection and disease. N Engl J Med 2020;383:359-68. DOI: 10.1056/NEJMoa1915176

SUPPLEMENTARY APPENDIX

Contents

Study Personnel

Principal Investigator: Dr Davaasambuu Ganmaa (Harvard T.H. Chan School of Public Health)

Co-Principal Investigator: Prof Adrian R. Martineau (Queen Mary University of London)

Trial Steering Committee: Prof Walter C. Willett (Harvard T.H. Chan School of Public Health), Prof Edward L. Giovannucci (Harvard T.H. Chan School of Public Health), Prof Donna Spiegelman (Yale School of Public Health), Dr Nymdawa Naranbat (Gyals Medical Laboratory, Ulaanbaatar), Dr Danzan Malchinkhuu (National Center for Maternal and Child Health of Mongolia) and Prof. Barry Bloom (Harvard T.H. Chan School of Public Health).

Data and Safety Monitoring Board: Prof Michael F. Holick (Boston University), Prof C. Robert Horsburgh (Boston University), Prof Sarah M. Fortune (Harvard T.H. Chan School of Public Health), Prof Perenlei Enkhbaatar (University of Texas), Dr Erdenebaatar Chadraa (Minnesota State University) and Dr Paige L. Williams (Harvard T.H. Chan School of Public Health).

End-point Committee: Dr James A. Seddon (Imperial College London) and Prof Ben J. Marais (University of Sydney)

Statisticians: Dr Xin Zhou (Yale School of Public Health), Prof Donna Spiegelman (Yale School of Public Health) and Dr Polyna Khudyakov (Harvard T.H. Chan School of Public Health).

Management team: Uyanga Buyanjargal, Enkhjargal Tsendjav,
Enkhjargal Tsendjav, Batbayar Ochirbat, Narangerel Dashdondog, Enkhsaikhan Lkhagvasuren, Tserenbat Minjuur, Altai Sainbuyan, Munkh-Erdene Surenjav, Gantsetseg Garmaa, Enkhmaa Davaasambuu, Boldbaatar Sonom, Ganbat Ganbaa and Gantungalag Ganbaatar.

Laboratory team: Badamtsetseg Jargalsaikhan, Delgerekh Baigali, Oyunsuren Munkhjargal, Sunjidmaa Bolormaa, Suren Nemuuzaya, Munkhzaya Ankhbat, Dolgion Ganbaatar, Nyam-Erdene Narmandakh, Enkhtuvshin Khorolgarav and Tserendolgor Tsendsuren.

Data management team: Narankhuu Yansanjav, Yanjmaa Jutmaan, Sumiya Erdenebaatar, Oyunbaatar Khatanbaatar, Ariunzaya Batnasan, Tsolmon Mendsaikhan and Munguntsetseg Batkhuu.

Study doctors: Erdenetuya Ganbaatar, Munkhzul Baatar, Nyamkhishig Pagma, Khurelbaatar Chuluundorj, Baysgalan Purev, Buyankhishig Burneebaatar, Oyun-Erdene Sereeter, Buyankhishig Khukhbandi, Odgerel Namsraijav, Narantuya Khandsuren, Oyungerel Tsog, Gunjidmaa Ochirchultem, Battogtokh Sambuu, Bayarbold Boldbaatar, Altansuvd Lkhamjav, Bujinlkham Semjeeperenlei, Munkhtumur Dashnyam, Munkhtsetseg Choijav, Buyandalai Khukhbandi, Undarmaa Lkhaachin, Uranchimeg Batsuuri, Zul-Ochir Buyantogtokh, Lkhagvasuren Sandagdoj, Bolor-Erdene Jamsranjav, Lkhagvadulam Peljee, Chuluunbaatar Gendenpil and Byambasuren Sharav.

Logistics team: Dul Bayarjargal, Munkhbayar Luvsannyam, Tumurbaatar Danzan, Baldantseren Tseel, Battsengel Dorjbal, Amarjil Ragchaa and Ganbayar Zagdbazar.

Field team: Unaganshagai Adiya, Oyunbileg Otgonchuluun, Maral Oyunsuren, Ariunzaya Saranjav, Saruul Serdamba, Mungunchimeg Dorjsuren, Tumen-Ulzii Tumurbaatar, Enkhtsetseg Tserenkhuu, Badamkhand Lkhagvadorj, Oyundari Amarbat, Oyunbileg Gankhuyag, Khaliun Ganzorig, Chuluun-Erdene Achtai, Barkhas Batkhuu, Davaatseren Baatar, Bumaa Ariunsanaa, Bolortuya Batbileg, Bilguun Gandold, Demchigmaa Namsraijav, Enkhsuvd Gandold, Zulgerel

Enkhbat, Nomin Enkh-Amgalan, Munkhbadrakh Jamsranjav, Tumurkhuyag Samdan, Dandar Sergelen, Tsolmon Mendsaikhan, Sanjaadorj Tsogtsaikhan, Oyunbold Batjargal, Tsolmon Erdenebileg, Khulan Ganbat, Altangerel Davaajargal, Amarzaya Bold, Bayraa Oidov, Byambasuren Sharav, Bolortuya Narankhuu, Bukhdelger Damdinbazar, Ganchimeg Ganaasuren, Ganchuluun Chantsaldulam, Otgonlkhagva Dondov, Oyunzorigt Ichinkhorloo, Unurbayar Batsuuri, Munkhbayar Buyanjargal, Tamir Davaa, YumjirmaaSodnomdarjaa, Adiyasuren Badarch, Khaliun Ganzorig, Khandmaa Gantulga, Khishigdelger Erdenechuluun, Khishignemekh Munkhbat, Tsakhim-Erdene Tsendjav, Tsend-Ayush Avirmed, Tserenkhand Dagvadorj, Chintungalag Erdenebaatar, Enkhzaya Erdenetuya, Enkhmaa Bold, Erdenelochin Nordov, Uyanga Battsooj, Uranchimeg Naymsuren, YanjmaaSodnomdorj, Yanjinlkham Gonchigsuren, Ulziibadrakh Purvee, Munkhtuya Chuluun, Idermunkh Baasansambuu, Nomundari Lkhagvasuren, Sukhbaatar Serjkhand, Tumenjargal Enkhzaya, Odontsetseg Sosorburam, Ochirmaa Bulgan, Oyundelger Tsevegmid, Khanddari Batsukh, Tamir Batsaikhan, Janchivrentsen Batsaikhan, Baigalituul Ganabazar, Uulensor Bat-Amgalan, Munkhzaya Dashnyam, Tserenchunt Batchuluun, Delgeremurun Batkhurel, Buyanaa Dashnajid, Shinetsetseg Batbayar, Enkhjin Adiyasuren, Tserenlkham Bayanbat, Javzanpagma Tserensodnom, Oyuntsetseg Baldandorj, Myagmarsuren Tseren-Ochir, Altantuul Dashsambuu, Bolormaa Amgalan, Oldokh Bayasgalan, Bileg-Erdene Ankhzul, Sukhbaatar Serjmyadag, Otgontsetseg Ganbaatar, Daariimaa Ganbat, Munkhaya Chuluun, Munkhdolgion Narmandakh, Idermunkh Baasansambuu, Makhpal Adilbek, Uyanga Ganbat, Munkh-Orgil Bold, Tsatsral Munkhbaatar, Davaajav Baasanjav, Amgalankhuu Orkhontuul, Anu-Ujin Byambaa, Ariundalai Tsogbadrakh, Amgalanzaya Erdenebaatar, Altansuvd Dondog, Ankhchimeg Purevdorj, Ariunsaikhan Batsaikhan, Batzaya Batchuluun, Battsesteg Bazarsad, Bolor Batbayar, Bolormaa Duurenjargal, Bolortuul Ganbaatar, Bulgan Munkhbat, Bulgan Khishigdavaa, Buyunmandakh Munkh-Undram, Gantuul Narmandakh, Gantsetseg Choinyambuu, Daniela Hamack, Idersaikhan Shinebayar, Lundiamaa Enkhbat, Lkham-Erdene Byambadoo, Munkhtsetseg Gankhuyag, Nandin-Erdene Erdenebaatar, Nomin Ganbaatar, Nyamsuren Togtokh, Nyamtsend Otgonbaatar, Nyamdorj Norovsambuu, Lkhamnorjin Rentsenjugder, Odgerel Tsogbadrakh, Oyunpurev Erdenechimeg, Oyun-Undram Enkhbaatar, Ulziikhishig Davaasuren, Puevdulam Darkhanbaatar, Suvd-Erdene Tsetseg-Ulzii, Surenkhor Dash, Tovuusuren Baasankhuu, Tungalag Altan, Tumenjargal Turmunkh, Uugangerel Chuluunsukh and Uugantsetseg Enkhbadarakh.

Supplementary Methods

TRIAL SETTING

The study was conducted in eighteen public schools located within a 12 km radius in six districts of Ulaanbaatar, Mongolia (Bayanzurkh, Songino-Kharkhan, Bayangol, Khan-Uul, Chingeltei and Sukhbaatar). Mongolia is an East Asian country situated between China and Russia with a population of approximately 3.1 million people, of whom 1.2 million (39%) reside in the capital city, Ulaanbaatar. School attendance is mandatory for children aged 6-16 years. Incidence of TB disease in Mongolia is estimated at 428 cases per 100,000 population per annum[1] and prevalence of HIV infection is very low at 0.02%.[2]

ETHICAL APPROVAL AND TRIAL REGISTRATION

The study was approved by Institutional Review Boards at the Mongolian Ministry of Health, the Mongolian National University and the Harvard T. H. Chan School of Public Health, USA (IRB reference number 14-0513), and registered with ClinicalTrials.gov (NCT02276755).

STUDY DESIGN AND AUTHOR CONTRIBUTIONS

DG and ARM designed the study. Data were gathered by DG, BU, GG, BD, DE, DK, SA, ES, BB, JY, TE, AM, MT, OB, GE, BA and JT. Data were analyzed by XZ, DS and ARM. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. DG and ARM wrote the first draft of the paper. All authors contributed to the interpretation of the results, review and approval of the manuscript, and the decision to submit it for publication. *T*here were no agreements concerning confidentiality of the data between the sponsor and the authors or the institutions named in the credit lines.

ELIGIBILITY CRITERIA AND BASELINE ASSESSMENT

Inclusion criteria were age 6-13 years at screening, attendance at a participating school, provision of written informed consent for the child to participate from his/her parent/guardian and provision of written informed assent to participate by the child. Exclusion criteria were the presence of LTBI, as evidenced by a positive QFT test result at screening; known HIV sero-positivity, primary hyperparathyroidism, sarcoidosis or previous TB infection or disease; taking cytotoxic therapy or other immunosuppressant medication, enzyme-inducing anticonvulsant therapy, cardiac glycoside, any preparation containing 1-alpha-hydroxylated vitamin D at any dose or vitamin D at a dose of more than 10 micrograms/day; planning to move away from Ulaanbaatar within 3 years of enrolment;

and presence of clinical signs of rickets, assessed by school doctors who checked for leg bowing, knock knees, pectus carinatum and thickened wrists and ankles.

Fieldworkers enrolled participants and collected information from each child's parent or guardian for the following variables using an electronic questionnaire on the RedCAP database: age, sex, ethnic origin, highest education level attained by either parent, type of residence, home ownership, monthly household income, indoor tobacco smoking in the household, active smoking by the child themselves, and presence of an index case of pulmonary TB living in the household during the child's lifetime. School doctors ascertained the BCG status of participating children by clinical examination for a vaccination scar. Height was measured to the nearest 0.1 cm using a portable stadiometer (SECA, Hamburg, Germany). Weight was measured to the nearest 0.1 kg using a Digital Floor Scale (SECA). Body mass index (BMI) was calculated using the formula BMI = weight (kg) / (height $[m]^2$). A 5 ml venous blood sample was drawn: 3 ml were collected into nil, TB antigen and mitogen QuantiFERON-TB Gold High Altitude tubes (1 ml per tube; Qiagen, Hilden, Germany), and 2 ml were collected into a tube containing clot activator for separation and storage of serum for subsequent determination of baseline 25-hydroxyvitamin D concentration. Children found to have positive QuantiFERON-TB Gold results at screening were excluded from the trial and referred to the Mongolia National Centre for Communicable Disease for clinical and radiographic screening for TB disease. QuantiFERON-positive children in whom TB disease was excluded were not preventively treated for latent tuberculosis infection, in line with WHO recommendations.[3] QuantiFERON-negative children proceeded to randomization.

RANDOMIZATION AND MASKING

Eligible participants were individually randomized to receive a weekly capsule containing vitamin D_3 or placebo for three years, with a one-to-one allocation ratio; full details of the randomization process are provided in the Supplementary Appendix. Randomization was stratified by school of attendance (a potential predictor of risk of QFT conversion) as follows. Prior to the start of recruitment, Dr Polyna Khudyakov (Harvard School of Public Health) prepared a single school randomization list comprising 18 pairs of 2-letter randomization codes, with each pair allocated to a single school identifier (e.g. School 1 was allocated codes 'AA' and AB', School 2 was allocated codes 'AC' and AD'). One 2-letter randomization code within each pair was then randomly assigned to the vitamin D arm of the trial, and the other was assigned to the placebo arm, using a computer-generated random sequence (e.g. 'AA' was assigned to 'vitamin D', 'AB' was assigned to placebo, 'AC' was assigned to placebo, 'AD' was assigned to 'vitamin D'). Dr Khudyakov also prepared eighteen separate participant

randomization lists (one for each participating school). Each of these participant randomization comprised 999 5-digit numbers, each consisting of a 2-digit school identifier from 01 to 18 that was constant for, and unique to, each list, followed by a 3-digit participant identifier from 001 to 999 (e.g. 01-001, 01-002, 02-001, 02-002). These 5-digit numbers were then randomly assigned to one or other of the 2-letter randomization codes allocated to that school in blocks of ten, using a computer-generated random sequence (e.g. for School 1, sequence was 01-001-AA, 01-002-AB, etc.; for School 2, sequence was 02-001-AC, 02-002-AD, etc.).

Active and placebo capsules were shipped to Mongolia in boxes that were labelled 'vitamin D' or 'placebo' according to their contents. On arrival, these capsules were packed into bottles, each containing either 1,000 vitamin D capsules or 1,000 placebo capsules. The school randomization list was then used to label these bottles with 2-letter randomization codes according to their contents (i.e. bottles containing vitamin D capsules were labelled with 'AA', 'AD' or another 2-letter code assigned to the vitamin D arm of the trial, while bottles containing placebo capsules were labelled 'AB', 'AC' or another 2-letter code assigned to the placebo arm of the trial). Bottling and labelling was performed by Mr Kevin Zinchuk (Brigham and Women's Hospital, Boston MA), Dr Sabri Bromage (Harvard TH Chan School of Public Health, Boston MA), and Dr Davaasambuu Enkhmaa (National Center for Maternal and Child Health, Ulaanbaatar, Mongolia); none of these individuals was involved with data collection. Children screened at each school were assigned consecutive 5-digit numbers at enrolment by study field workers, and if they were subsequently found to be eligible for randomization (i.e. if their baseline QFT result was negative) then the participant randomization list for their school of attendance was used to determine their allocation, i.e. they received study medication from bottles labelled with the 2-letter code linked to their 5-digit ID in the participant randomization list for the duration of the trial. For example, participant 01-001 would receive study medication labelled 'AA' (i.e. vitamin D), 01-002 would receive medication labelled 'AB' (i.e. placebo), 02-001 would receive medication labelled 'AC' (placebo), and 02-002 would receive medication labelled 'AD' (vitamin D) throughout the trial. Copies of the school randomization list were held by members of the DSMB, Dr Khudyakov and Mr Zinchuk. Neither participants nor trial staff had access to it, and treatment allocation was concealed from participants, care providers and all trial staff (including senior investigators and those assessing outcomes) so that the double-blind was maintained. The school randomization list was emailed to ARM and XZ following completion of the trial, who used it to un-blind allocation and to analyze the trial: they were not therefore masked to group assignment during statistical analysis.

INTERVENTION

Participants received a single, once-weekly soft-gel capsule manufactured by Tishcon Corp (Westbury, NY) containing either 14,000 IU (0.35 mg) of vitamin D_3 in olive oil or matching placebo containing olive oil only, over three years. Active and placebo capsules had identical appearance and taste.

ADMINISTRATION OF STUDY MEDICATION

During term-time, study capsules were administered at schools under the direct observation of field workers. Immediately prior to the start of school holidays, children's parents or guardians were provided with a supply of their child's study medication, and asked to supervise weekly administration until the child returned to school. The study team contacted parents every two weeks by telephone or text message over school holidays to remind them to administer study medication.

FOLLOW-UP ASSESSMENTS

At each weekly visit, participants were asked if they had experienced symptoms of upper respiratory infection (cold symptoms, 'flu symptoms, sore throat, earache) and/or lower respiratory infection (bronchitis, pneumonia or cough) lasting for at least 24 hours since the previous study visit. They were also asked whether they had taken any antibiotic for respiratory infection in the previous week; brand names of antibiotics in common use locally were specified as prompts. During school holidays, details of adverse events were captured every two weeks via telephone. Weight was measured at quarterly intervals. Any child reporting symptoms suggestive of TB disease (fever or cough lasting more than 2 weeks) or losing more than 5% body weight was assessed by a study doctor; where TB disease was suspected, the child was referred to the Mongolian National Center for Communicable Diseases for clinical and radiographic screening for TB disease.

LABORATORY TESTING

QuantiFERON-TB Gold assays were performed according to manufacturer's instructions at the Global Laboratory, Ulaanbaatar, Mongolia, which participates in the QuantiFERON Quality Assurance Program of the Royal College of Pathologists of Australasia. Serum 25(OH)D concentrations were determined using an enzyme linked fluorescent assay (VIDAS 25OH Vitamin D total, Biomerieux, Marcy-l'Étoile, France). The coefficient of variation was 7.9%, mean bias was 7.7% and the limit of quantitation (LOQ) was 8.1 ng/ml. Non-zero 25(OH)D values were standardized using a set of 40 DEQAS serum samples as previously described by the Vitamin D Standardization Program (VDSP).[4] Values below the LOQ were assigned a value equal to the LOQ divided by the

square root of 2 (5.7 ng/mL).[5] Season-adjusted (deseasonalized) values were then calculated for each participant from their individual standardized 25(OH)D concentration and date of blood sample collection, using a sinusoidal model with values derived from standardized values for all participants.[6]

STATISTICAL METHODS

Statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC). All analyses were performed according to intention to treat, and significance was tested at the 5% level. Treatment effects for dichotomous outcomes were estimated using the Mantel-Haenszel risk ratio, stratified by school, and presented as school-adjusted risk ratios with 95% confidence intervals (CI). The effect of allocation on mean end-study IFN-γ concentration in supernatants of antigen-stimulated whole blood was evaluated using analysis of covariance, with adjustment for baseline value and indicators for school of attendance, and presented as baseline-adjusted mean difference with 95% CI. The effect of allocation on incidence of adverse events was presented as incidence rate ratios with 95% CI. Because we did not include a provision for correcting for multiplicity when conducting tests for secondary outcomes, their results are reported as point estimates and 95% confidence intervals. The widths of these confidence intervals have not been adjusted for multiplicity, so they should not be used to infer definitive treatment effects for secondary outcomes. Interim safety analyses, where Data and Safety Monitoring Board (DSMB) members reviewed accumulating serious adverse event data by study arm, were performed at 6-monthly intervals. At each review the DSMB recommended continuation of the trial. No interim efficacy analysis was performed. To explore the impact of missingness of a small number of participants lost to follow-up, inverse probability weighted Mantel-Haenszel risk ratios were estimated for respiratory infection outcomes.[7] The probability of being retained to end of follow-up was estimated using stepwise logistic regression. For QFT outcomes, the candidate covariates used in the logistic model to estimate the probability of not being lost to follow-up included school, age, gender, ethnic origin, parental education, type of residence, home ownership, monthly household income, household environmental tobacco smoke, previous household PTB contact, BCG scar, body mass index (BMI)-for-age z-score, height-for-age z-score, baseline serum 25(OH)D concentration, treatment allocation and the interaction between treatment allocation and baseline characteristics. School, age, gender, and allocation were forced into the final model; other characteristics and interaction terms for inclusion in the final model were chosen by stepwise regression at significance level 0.05, and included type of residence, home ownership and BMI-for-age z-score. For outcomes relating to incidence of tuberculosis disease and ARI, 32 participants had less than one day of follow-up and

were excluded from the primary intention-to-treat analysis. The same set of covariates as in the analysis of QFT outcomes was used in the logistic model to estimate the probability of being followed for at least one day. Covariates for inclusion in the final logistic model were chosen by stepwise regression at significance level 0.05, and included monthly household income as well as school, age, gender and treatment allocation.

Table S1: Mean IFN-γ concentration in end-study QFT supernatants by allocation: antigen tube minus nil tube

		Placebo	Vitamin D	Adjusted mean difference (95% CI)[(1)]
Mean IFN-γ concentration, antigen-minus-nil, IU/ml (s.d.) [n]	Overall	0.08 (0.67) [4,043]	0.07 (0.59) [4,074]	-0.01 (-0.04 to 0.02)
	Baseline 25(OH)D <10 ng/ml	0.13 (0.82) [1,304]	0.09 (0.59) [1,288]	-0.04 (-0.09 to 0.02)
	Baseline 25(OH)D ≥10 ng/ml	0.06 (0.59) [2,736]	0.06 (0.59) [2,785]	0.00 (-0.03 to 0.03)

1, adjusted for school of attendance and baseline value

Table S2. Incidence of Upper and Lower Acute Respiratory Infections, by Allocation

		Vitamin D	Placebo	Adjusted RR (95% CI)[1]
Proportion reporting symptoms of upper respiratory infection on at least one occasion (%)	Overall	3623/4401 (82.3)	3633/4418 (82.2)	1.00 (0.98 to 1.02)
	Baseline 25(OH)D <10 ng/ml	1133/1387 (81.7)	1157/1414 (81.8)	1.00 (0.96 to 1.03)
	Baseline 25(OH)D ≥10 ng/ml	2489/3013 (82.6)	2473/3000 (82.4)	1.00 (0.98 to 1.03)
Proportion reporting symptoms of lower respiratory infection on at least one occasion (%)	Overall	2183/4401 (49.6)	2228/4418 (50.4)	0.99 (0.95 to 1.03)
	Baseline 25(OH)D <10 ng/ml	725/1387 (52.3)	775/1414 (54.8)	0.95 (0.88 to 1.01)
	Baseline 25(OH)D ≥10 ng/ml	1458/3013 (48.4)	1452/3000 (48.4)	1.00 (0.95 to 1.06)

1, adjusted for school of attendance

Table S3. Incidence of Respiratory Infections, by Allocation: Sensitivity Analysis Exploring Impact of Missingness of Participants Lost to Follow-Up

				Primary analysis	Sensitivity analysis
		Vitamin D	Placebo	Adjusted RR (95% CI)[1]	Adjusted RR (95% CI)[2]
Tuberculosis infection					
Proportion QFT-positive at the 0.35 IU/ml IFN-γ threshold (%)	Overall	147/4074 (3.6)	134/4043 (3.3)	1.10 (0.87 to 1.38)	1.10 (0.88 to 1.36)
	Baseline 25(OH)D <10 ng/ml	64/1288 (5.0)	64/1304 (4.9)	1.01 (0.72 to 1.42)	1.00 (0.73 to 1.39)
	Baseline 25(OH)D ≥10 ng/ml	83/2785 (3.0)	70/2736 (2.6)	1.17 (0.86 to 1.61)	1.18 (0.87 to 1.59)
Proportion QFT-positive at the 4.0 IU/ml IFN-γ threshold (%)	Overall	23/4074 (0.6)	35/4043 (0.9)	0.67 (0.39 to 1.12)	0.65 (0.39 to 1.07)
	Baseline 25(OH)D <10 ng/ml	7/1288 (0.5)	17/1304 (1.3)	0.41 (0.17 to 0.99)	0.41 (0.18 to 0.93)
	Baseline 25(OH)D ≥10 ng/ml	16/2785 (0.6)	18/2736 (0.7)	0.90 (0.46 to 1.77)	0.88 (0.46 to 1.68)
Tuberculosis disease					
Proportion starting treatment for TB disease (%)	Overall	21/4401 (0.5)	25/4418 (0.6)	0.87 (0.49 to 1.55)	0.87 (0.49 to 1.55)
	Baseline 25(OH)D <10 ng/ml	10/1387 (0.7)	15/1414 (1.1)	0.67 (0.30 to 1.47)	0.67 (0.30 to 1.47)
	Baseline 25(OH)D ≥10 ng/ml	11/3013 (0.4)	10/3000 (0.3)	1.17 (0.50 to 2.75)	1.17 (0.50 to 2.75)
Proportion with confirmed or probable TB disease, as adjudicated by endpoint committee (%)	Overall	13/4401 (0.3)	13/4418 (0.3)	1.05 (0.49 to 2.27)	1.05 (0.49 to 2.26)
	Baseline 25(OH)D <10 ng/ml	6/1387 (0.4)	8/1414 (0.6)	0.75 (0.26 to 2.14)	0.75 (0.26 to 2.13)
	Baseline 25(OH)D ≥10 ng/ml	7/3013 (0.2)	5/3000 (0.2)	1.47 (0.47 to 4.61)	1.46 (0.47 to 4.61)
Acute respiratory infections					
Proportion with at least one hospitalization for treatment of acute respiratory infection (%)	Overall	29/4401 (0.7)[3]	34/4418 (0.8)[4]	0.86 (0.52 to 1.40)	0.86 (0.52 to 1.40)
	Baseline 25(OH)D <10 ng/ml	8/1387 (0.6)	10/1414 (0.7)	0.81 (0.32 to 2.09)	0.81 (0.32 to 2.08)
	Baseline 25(OH)D ≥10 ng/ml	21/3013 (0.7)	24/3000 (0.8)	0.86 (0.48 to 1.55)	0.86 (0.48 to 1.55)
Proportion with at least one self-reported acute respiratory infection (%)	Overall	3783/4401 (86.0)	3793/4418 (85.9)	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.02)
	Baseline 25(OH)D <10 ng/ml	1195/1387 (86.2)	1205/1414 (85.2)	1.01 (0.98 to 1.04)	1.01 (0.98 to 1.04)
	Baseline 25(OH)D ≥10 ng/ml	2587/3013 (85.9)	2585/3000 (86.2)	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.02)

Proportion taking at least one course of antibiotics to treat acute respiratory infection (%)	Overall	1272/4401 (28.9)	1292/4418 (29.2)	0.99 (0.93 to 1.05)	0.99 (0.93 to 1.05)
	Baseline 25(OH)D <10 ng/ml	392/1387 (28.3)	399/1414 (28.2)	0.99 (0.88 to 1.12)	1.00 (0.88 to 1.12)
	Baseline 25(OH)D ≥10 ng/ml	880/3013 (29.2)	892/ 3000 (29.7)	0.98 (0.91 to 1.06)	0.98 (0.91 to 1.06)

1, adjusted for school of attendance.

2, for QFT outcomes, the candidate covariates used in the logistic model to estimate the probability of not being lost to follow-up included school, age, gender, ethnic origin, parental education, type of residence, home ownership, monthly household income, household environmental tobacco smoke, previous household PTB contact, BCG scar, body mass index (BMI)-for-age z-score, height-for-age z-score, baseline serum 25(OH)D concentration, treatment allocation and the interaction between treatment allocation and baseline characteristics. School, age, gender, and allocation were forced into the final model; other characteristics and interaction terms for inclusion in the final model were chosen by stepwise regression at significance level 0.05, and included type of residence, home ownership and BMI-for-age z-score. For outcomes relating to incidence of tuberculosis disease and acute respiratory infections, 32 participants had less than one day of follow-up and were excluded from the primary intention-to-treat analysis. The same set of covariates as in the analysis of QFT outcomes was used in the logistic model to estimate the probability of being followed for at least one day. Covariates for inclusion in the final logistic model were chosen by stepwise regression at significance level 0.05, and included monthly household income as well as school, age, gender and treatment allocation.

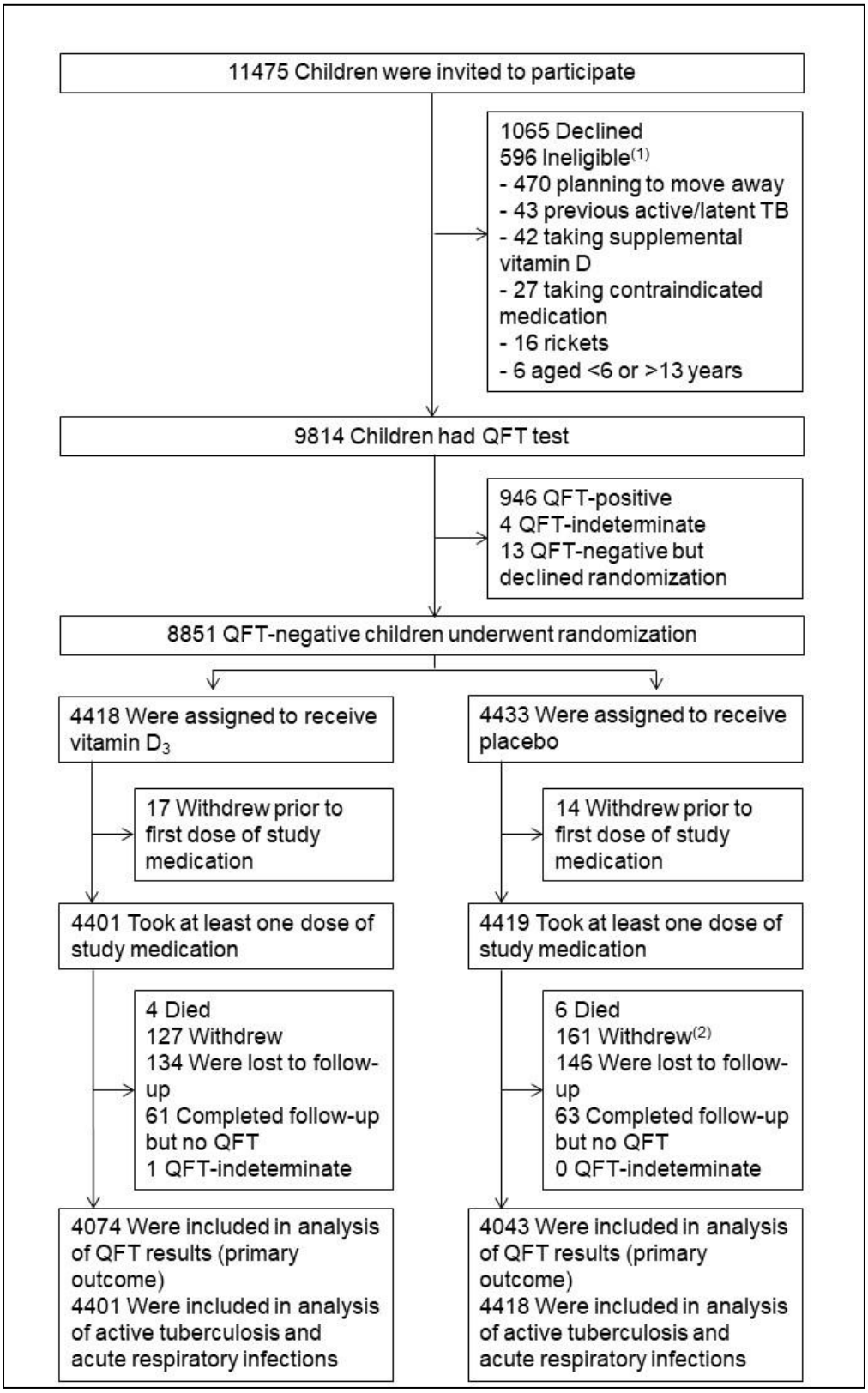
Table S4: Serious adverse events by allocation

Nature of serious adverse event	No. events, placebo arm[1]	No. events, vitamin D arm[2]
Death, acute leukemia	1	1
Death, drowning	1	1
Death, rupture of pulmonary artery aneurysm	1	0
Death, traumatic injury	1	2
Death, unknown cause	2	0
Hospitalization, acute appendicitis	7	8
Hospitalization, acute epididymitis	1	1
Hospitalization, acute respiratory infection	34	30
Hospitalization, allergic reaction	2	0
Hospitalization, allergic rhinitis	1	1
Hospitalization, alopecia areata	0	1
Hospitalization, anemia	1	0
Hospitalization, arthritis	1	0
Hospitalization, asthma exacerbation	1	1
Hospitalization, atopic dermatitis	2	0
Hospitalization, cardiac failure due to congenital heart disease	0	1
Hospitalization, chickenpox	20	17
Hospitalization, chronic constipation	1	0
Hospitalization, chronic fatigue syndrome	3	3
Hospitalization, chronic gastritis	0	2
Hospitalization, chronic pancreatitis	0	1
Hospitalization, elective surgery	21	14
Hospitalization, epistaxis	1	0
Hospitalization, furunculosis	0	1
Hospitalization, gastric perforation	0	1
Hospitalization, gastroenteritis	4	0
Hospitalization, glomerulonephritis	1	1
Hospitalization, hemorrhagic vasculitis	3	0
Hospitalization, hepatic cirrhosis	0	1
Hospitalization, hydronephrosis	1	0
Hospitalization, idiopathic abdominal pain	3	0
Hospitalization, idiopathic headache	1	0
Hospitalization, idiopathic rash	1	0
Hospitalization, intra-cranial hypertension	1	0
Hospitalization, meningitis	0	1
Hospitalization, neuritis	3	3
Hospitalization, osteomyelitis	0	1
Hospitalization, psoriasis	4	1
Hospitalization, pyelonephritis	1	3
Hospitalization, pyrexia of unknown origin	1	1
Hospitalization, renal failure	1	0
Hospitalization, shigellosis	5	0
Hospitalization, shingles	1	1
Hospitalization, thrombocytopenia	1	0
Hospitalization, traumatic injury	56	56
Hospitalization, vasculitis	0	1
Hospitalization, viral hepatitis	2	1
Hospitalization, vitiligo	0	1
Total number of serious adverse events	**192**	**158**

1, these events arose in 188 participants randomized to placebo.

2, these events arouse in 146 participants randomized to vitamin D

Figure S1: Screening, Randomization, and Follow-up of the Participants



1, the total number of reasons for ineligibility is 604 because 8 children fulfilled two ineligibility criteria simultaneously. 2, one participant withdrew within 24 hours of taking the first dose of study medication, and did not contribute follow-up data to analyses of active tuberculosis and acute respiratory infections.

References

1. Tuberculosis country profile: Mongolia. 2018. (Accessed 10/16/2018, at https://extranet.who.int/sree/Reports?op=Replet&name=%2FWHO_HQ_Reports%2FG2%2FPROD%2FEXT%2FTBCountryProfile&ISO2=MN&LAN=EN&outtype=html.)
2. Jagdagsuren D, Hayashida T, Takano M, et al. The second molecular epidemiological study of HIV infection in Mongolia between 2010 and 2016. PLoS One 2017;12:e0189605.
3. World Health Organisation. Guidance for national tuberculosis programmes on the management of tuberculosis in children: second edition. Geneva: World Health Organisation; 2014.
4. Sempos CT, Betz JM, Camara JE, et al. General Steps to Standardize the Laboratory Measurement of Serum Total 25-Hydroxyvitamin D. J AOAC Int 2017;100:1230-3.
5. Schleicher RL, Sternberg MR, Looker AC, et al. National Estimates of Serum Total 25-Hydroxyvitamin D and Metabolite Concentrations Measured by Liquid Chromatography-Tandem Mass Spectrometry in the US Population during 2007-2010. J Nutr 2016;146:1051-61.
6. Sachs MC, Shoben A, Levin GP, et al. Estimating mean annual 25-hydroxyvitamin D concentrations from single measurements: the Multi-Ethnic Study of Atherosclerosis. Am J Clin Nutr 2013;97:1243-51.
7. Little RJ, D'Agostino R, Cohen ML, et al. The prevention and treatment of missing data in clinical trials. N Engl J Med 2012;367:1355-60.