

UNDERNUTRITION AND TUBERCULOSIS

An updated review of scientific advances through May 2021 for USAID

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Orientation to this Document

- This report is derived largely from searching PubMed to May 2021 with specific MeSH search terms for tuberculosis and for nutrition, including both general terms and separate terms for each micronutrient and as well as each main category of macronutrients but not specific individual foods. The search strategy was intended to be more specific than sensitive, so it was not exhaustive. In addition, relevant references to authoritative sources, such as recent textbooks, monographs, reports, and major public health agencies were searched as well.
- Any language articles were included that had English language abstracts. Articles were restricted to TB in humans with a few exceptions. From these, publications were selected that were unique or, where there were many on the same topic, the best (highest quality evidence, most informative, definitive, credible, impactful, and least redundant) reducing the literature search from thousands of abstracts and hundreds of pages down to about 120 abstracts and 50 pages. From non-periodical literature, paragraphs or passages were quoted that complemented or expanded upon these topics
- The abstracts from primary research literature and passages from authoritative sources were sorted by topic into natural categories from which the structure of this document developed as outlined in the Table of Contents.
- All sources are cited appropriately throughout. Copy/pasted material from non-periodical sources is enclosed in quotes (“ ”) and *attributed to the source document at the end of the passage or paragraph in italics.*
- **Titles are listed in 12 point bold font aligned left** introducing each abstract or paragraph. *Abbreviated author and journal citations follow each abstract.*
- In the interest of brevity, some abstracts were abridged, cutting unnecessary / redundant / boiler plate lines in the introduction and discussion while fully keeping methods and results. [Some passages are highlighted in light blue color type that capture the core info from that reference while reducing reading time by 80%.](#)
- Some paragraphs or sections were spliced together from different parts of a single document, lightly edited for continuity and brevity, and *attributed to its source document at the end of said passage in italics preceded by the words, “Adapted from:”*
- With exceptions, this report focuses on literature after about 2000-2005. The evidence in humans and experimental animals up to 2004 was reviewed in *Cegielski JP, McMurray DN. IJTLID 2004*, and up to 2007 in *McMurray DN, Cegielski JP. Acad. Sci. S. Africa 2007*. The present report extend those earlier reviews to 2021 in an expanded format. Prior to 1968 the scientific literature on nutrition and infection, including tuberculosis, was summarized in *Scrimshaw, Gordon, and Taylor*.
- A small number of older reports are included if they remain the only or one of the only reports on a given topic. Likewise, a small number of animal studies are included for the same reason.
- This report is accompanied by an Executive Summary and Expert Commentary as a separate digital file, condensing the sum total of these abstracts into a 10-page narrative.

I. EFFECT OF UNDERNUTRITION ON TB INCIDENCE RISK

NB: In this section nutritional status is an antecedent risk factor for the development of active TB disease; nutritional status is measured months to years before TB disease develops. Within each section evidence is presented in chronological order.

A. Protein-Energy Malnutrition

Historical declines in tuberculosis in England and Wales: improving social conditions or natural selection? A reinvestigation of the relationship between the decline of tuberculosis and improvement in social conditions in England and Wales during Victorian times.

Design: A retrospective study using data published in the annual reports of the Registrar General from 1853 to 1910. The diseases studied, in addition to tuberculosis were, dysentery and cholera including their total and infant mortality. Social conditions were evaluated from earnings and population density per house. Tuberculosis mortality declined at an annual average rate of 1.71% (95%CI 0.77 to 2.63) whereas total mortality, infant mortality and mortality from cholera and dysentery and house population density showed no statistically significant decline over the same period. Real earnings increased by 1.05% (CI 0.29 to 1.81). Improving social conditions do not provide the total explanation for the decline in tuberculosis during Victorian times. Other factors, principally natural selection, probably played a role. Part of the current increase in tuberculosis may be caused by effective drug therapy eliminating natural selection.

Davies RPO, Tocque K, Bellis MA, Remington T, Davies PDO. Int J Tuberc Lung Dis 1999; 3: 1051–54.

A consistent log-linear relationship between tuberculosis incidence and body mass index

Intro: Low weight for height is an established risk factor for tuberculosis (TB), and recent studies suggest that overweight is a protective factor. No previous systematic review has been done to explore the consistency and establish the gradient of this apparent 'dose–response' relationship.

Methods: A systematic literature review was carried out to identify cohort studies that collected data on weight and height at baseline and that used a diagnosis of active TB as the study outcome. Weight-for-height measures used in the original studies were transformed into body mass index (BMI). Exponential trend lines were fitted to each data set.

Results: Six studies were included. In all of them, there was a log-linear inverse relationship between TB incidence and BMI, within the BMI range 18.5–30 kg/m². The average slope gave a reduction in TB incidence of 13.8% [95% confidence interval 13.414.2] per unit increase in BMI. The dose–response relationship was less certain at BMI <18.5 and >43 kg/m².

Conclusion There is a strong and consistent log-linear relationship between TB incidence and BMI across a variety of settings with different levels of TB burden. More research is required to test the relationship at very low and very high BMI levels, to establish the biological mechanism and to establish the potential impact on the global TB epidemic of changing nutritional status of populations.

Lonnroth K, et al. Int. J. Epidemiol. 2010 Feb;39(1):149-55. doi: 10.1093/ije/dyp308.

Tuberculosis control and elimination 2010-50: cure, care, and social development

Table 3 in this article shows the estimated prevalence and corresponding population attributable fractions (PAF) of selected risk factors for tuberculosis in high-burden countries. An extract is reproduced below. Table 3 includes only factors that are common, can be changed, have strong evidence for a causal relation with tuberculosis, and for which there are quantitative data for the strength of the association. Variation is large across countries in the relative importance of different risk factors. Undernutrition contributes the most to TB incidence. Indoor air pollution has a high PAF, but a causal relation is not yet firmly proven. In most African high-burden countries, HIV is a leading attributable factor. Alcohol misuse and diabetes are increasing in low-income and middle-income countries and might be crucial factors in coming decades. Mathematical modeling studies have shown that a large part of the tuberculosis burden in India, can be attributed to undernutrition (60%), smoking (40%), and diabetes (15%); and that reductions in the prevalence of smoking and indoor air pollution in China could reduce incidence by an additional 14–52% by 2033, in excess of the expected effect of sustained good NTP performance.

Knut Lönroth, et al. Lancet 2010 May 22;375(9728):1814-29. doi: 10.1016/S0140-6736(10)60483-7.

	HIV		Undernutrition		Diabetes mellitus		Alcohol Abuse		Smoking		Indoor air	
	P(>15y)	PAF	P(>15y)	PAF	P(>15y)	PAF	P(>15y)	PAF	P(>15y)	PAF	P(>15y)	PAF
Wtd avg (min-max)	0.8 (0.1-18.1)	11 (1.5-69.7)	16.7 (2.5-78.0)	26.9 (5.2-62.6)	5.4 (1.7-7.7)	7.5 (2.3-13.8)	8.1 (0.1-33.3)	9.8 (0.1-35.0)	26.5 (5.0-49.0)	15.8 (2.7-29.4)	71.2 (7.0-95.0)	22.2 (4.6-27.5)

Adapted from: Lönnerth, et al. Lancet 2010 May 22;375(9728):1814-29.

Nutritional Risk Factors for Tuberculosis Among Adults in the United States, 1971–1992

To determine the impact of nutritional status on TB incidence, the authors analyzed data from the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study (NHEFS). NHANES I collected information on a **probability sample of the US population in 1971–1975. Adults were followed up 1982–1992.** Incident TB cases were ascertained through interviews, medical records, and death certificates. TB incidences were compared across different levels of nutritional status after controlling for potential confounding using proportional hazards regression appropriate to the complex sample design. TB incidence among adults with normal body mass index was 24.7 per 100,000 person-years (95% confidence interval (CI): 13.0, 36.3). In contrast, among persons who were underweight, overweight, and obese, estimated TB incidence rates were 260.2 (95% CI: 98.6, 421.8), 8.9 (95% CI: 2.2, 15.6), and 5.1 (95% CI: 0.0, 10.5) per 100,000 person-years, respectively. **Adjusted hazard ratios were 12.43 (95% CI: 5.75, 26.95), 0.28 (95% CI: 0.13, 0.63), and 0.20 (95% CI: 0.07, 0.62), respectively, after controlling for demographic, socioeconomic, and medical characteristics. A low serum albumin level also increased the risk of TB, but low vitamin A, thiamine, riboflavin, and iron status did not.** A population's nutritional profile is an important determinant of its TB incidence.

Cegielski JP, et al. Am J Epidemiol 2012 July 11; DOI: 10.1093/aje/kws007

Inadequate Diet Is Associated with Acquiring Mycobacterium tuberculosis Infection in an Inuit Community. A Case-Control Study

Background: Tuberculosis predominantly affects socioeconomically disadvantaged communities. The extent to which specific dietary and lifestyle factors contribute to tuberculosis susceptibility has not been established.

Methods: A total of 200 residents of a village in Northern Quebec were investigated during a tuberculosis outbreak and identified to have active tuberculosis, latent tuberculosis infection, or neither. Participants completed questionnaires about their intake of food from traditional and commercial sources, and provided blood samples. Adults were asked about recent smoking and drug and alcohol intake. Nutritional adequacy was evaluated with reference to North American standards. Multiple dietary, lifestyle, and housing factors were combined in a logistic regression model evaluating the contributions of each to disease and infection.

Findings: After adjusting for potential confounding, **new infection was associated with inadequate intake of fruit and vegetables (odds ratio [OR], 2.1; 95% confidence interval [CI], 1.03-4.3), carbohydrates (OR, 4.4; 95% CI, 1.2-16.3), and certain vitamins and minerals. A multivariable model, combining nutrition, housing, and lifestyle factors, found associations between new infection and inadequate fruit and vegetable intake (OR, 2.3; 95% CI, 1.0-5.1), living in the same house as a person with smear-positive tuberculosis (OR, 14.7; 95% CI, 1.6-137.3), and visiting a community gathering house (OR, 3.7; 95% CI, 1.7-8.3). Current smoking was associated with new infection (OR, 9.4; 95% CI, 1.2-72) among adults completing a detailed lifestyle survey.**

Interpretation: Inadequate nutrition was associated with increased susceptibility to infection, but not active tuberculosis. Interventions addressed at improving nutrition may reduce susceptibility to infection in settings where access to healthy foods is limited.

Gregory J Fox, et al. Ann Am Thorac Soc. 2015 Aug;12(8):1153-62. doi: 10.1513/AnnalsATS.201503-156OC. PMID: 26099015

B. Protein

NB: McMurray's work in experimental animals is included here even though it is dated 1980s-90s because it is the only work that examines the effect of **isocaloric** protein deficiency with/without specific micronutrient deficiencies. His low-dose aerosol exposure guinea pig model closely mimics human TB, unlike many other animal models.

Respiratory infection with attenuated *M. tuberculosis* H37Ra in malnourished guinea pigs.

Specific pathogen-free guinea pigs were infected via the respiratory route with viable, attenuated Mycobacterium tuberculosis H37Ra and maintained on purified isocaloric diets: **control, low protein diet, low zinc diet.** Protein-deficient animals exhibited significantly reduced body weight, spleen weight, serum total proteins, and serum albumin. Zinc deficiency was characterized by loss of weight and progressive reductions in plasma zinc concentrations. **The number of viable *M. tuberculosis* H37Ra cells**

was significantly higher in the lungs, spleen, BT lymph nodes of both malnourished groups at 3 weeks, but fell below control viable counts by 5 weeks post-infection. Both the proportion and intensity of delayed hypersensitivity reactions increased steadily between 3 and 5 weeks in control animals, whereas the two malnourished groups were essentially anergic at all intervals, despite systemic infection. The nature of the influence depends upon the interval: In both malnourished groups, the pulmonary infection tended to peak early and decline, whereas the disease developed more slowly in control animals. Apparent control of mycobacterial populations in the tissues was accomplished by malnourished animals in the absence of demonstrable delayed hypersensitivity.

McMurray DN, et al. *Infect Immun.* 1983 Feb;39(2):793-9. doi: 10.1128/LAI.39.2.793-799.1983.

Impact of nutritional deficiencies on resistance to experimental pulmonary tuberculosis. In conclusion, we have presented evidence that reveals multiple abnormalities in the response of chronically protein-deficient guinea pigs to infection with virulent *M. tuberculosis*. The diet-induced defects that we believe are most detrimental in terms of resistance to TB are (1) inability to form mature, well-circumscribed granulomas, perhaps related to a TNF- α defect; (2) decreased clonal expansion of antigen-reactive T cells, perhaps secondary to an IL-2 defect; (3) increased suppression of T lymphocyte activation by alveolar macrophages; and (4) trapping of protective T cells in lymph nodes. Of course, these putative defects are not mutually exclusive, and the existence of one might well influence the appearance of another. Taken together, these data suggest that the protein-deficient guinea pig cannot mobilize antigen-reactive lymphocytes to infectious pulmonary foci, and that those lymphocytes that do accumulate fail to expand clonally, either because of a lack of growth factors (e.g., IL-2) or the presence of suppressive factors (e.g., TGF- β). The precise molecular mediators of these events have yet to be determined.

McMurray DN. *Nutrition Reviews* 1988; 56: S147–S152. Doi: 10.1111/j.1753-4887.1998.tb01633.x

Immunosuppression and alteration of resistance to pulmonary tuberculosis in guinea pigs by protein undernutrition.

The impact of chronic moderate protein deficiency on resistance to pulmonary tuberculosis was studied in a guinea pig model. Inbred and outbred guinea pigs were maintained on isocaloric diets containing 30% or 10% ovalbumin, vaccinated with *Mycobacterium bovis* BCG vaccine and infected by the respiratory route with virulent *Mycobacterium tuberculosis*. Protein deficiency was associated with significant loss of dermal tuberculin hypersensitivity, reduced purified protein derivative (PPD)-driven lymphoproliferation in vitro and diminished interleukin-2 production. The proportion of E rosette receptor (CD2) positive lymphocytes was significantly lower in the blood and thymus of low-protein guinea pigs. Increased levels of circulating anti-PPD antibodies were associated with loss of delayed hypersensitivity in protein-deprived animals. Immune complexes containing these antibodies may act on T cells bearing Fc receptors for immunoglobulin G (γ cells), which appear to exert a suppressive effect on antigen-induced lymphoproliferation of T(non- γ) cells in vitro. These results imply an important immunoregulatory role for γ cells in tuberculosis and suggest one mechanism whereby resistance to tuberculosis is altered in protein malnutrition.

McMurray DN and Bartow RA. *Journal of Nutrition* 1992; 122: 738–743.

C. Lipids

Is adipose tissue a place for *Mycobacterium tuberculosis* persistence?

Background: *Mycobacterium tuberculosis*, the etiological agent of tuberculosis (TB), has the ability to persist in its human host for exceptionally long periods of time. However, little is known about the location of the bacilli in latently infected individuals. Long-term mycobacterial persistence in the lungs has been reported, but this may not sufficiently account for strictly extra-pulmonary TB, which represents 10-15% of the reactivation cases.

Methodology/principal findings: We applied in situ and conventional PCR to sections of adipose tissue samples of various anatomical origins from 19 individuals from Mexico and 20 from France who had died from causes other than TB. *M. tuberculosis* DNA could be detected by either or both techniques in fat tissue surrounding the kidneys, the stomach, the lymph nodes, the heart and the skin in 9/57 Mexican samples (6/19 individuals), and in 8/26 French samples (6/20 individuals). In addition, mycobacteria could be immuno-detected in perinodal adipose tissue of 1 out of 3 biopsy samples from individuals with active TB. In vitro, using a combination of adipose cell models, including the widely used murine adipose cell line 3T3-L1, as well as primary human adipocytes, we show that after binding to scavenger receptors, *M. tuberculosis* can enter within adipocytes, where it accumulates intracytoplasmic lipid inclusions and survives in a non-replicating state that is insensitive to the major anti-mycobacterial drug isoniazid.

Conclusions/significance: Given the abundance and the wide distribution of the adipose tissue throughout the body, our results suggest that this tissue, among others, might constitute a vast reservoir where the tubercle bacillus could persist for long periods of time, and avoid both killing by antimicrobials and recognition by the host immune system. In addition, *M.*

tuberculosis-infected adipocytes might provide a new model to investigate dormancy and to evaluate new drugs for the treatment of persistent infection.

Neyrolles O, Hernandez-Pando R, Pietri-Roussel F, Fornes P, Tailleux L, et al. *PLoS One* 2006; 1: e43.
<https://doi.org/10.1371/journal.pone.0000043>.

Dietary polyunsaturated fatty acids modulate resistance to *Mycobacterium tuberculosis* in guinea pigs.

The purpose of this study was to determine the role of dietary (n-3) and (n-6) fatty acids on immunity and resistance to aerosol infection with virulent *Mycobacterium tuberculosis* in guinea pigs. Weanling guinea pigs were fed purified, isocaloric diets differing only in lipid source, and the effects of diet on specific immune cell functions were evaluated after 3 or 6 wk. Dietary (n-3) fatty acid consumption reduced in vivo skin test and in vitro lympho-proliferative responses ($P < 0.05$) relative to (n-6) fatty acid consumption. The effect of diet on resistance to mycobacterial infection was assessed by enumerating viable mycobacteria in the lungs and spleens of guinea pigs infected with virulent *M. tuberculosis* by the aerosol route. (n-3) Fatty acid-fed guinea pigs had more bacteria in the lungs compared with (n-6) fatty acid-fed guinea pigs at 3 ($P < 0.05$) and 6 wk postinfection ($P < 0.01$). These data document the immunomodulatory effects of (n-3) fatty acid consumption in the context of tuberculosis resistance. The loss of antigen-specific T-cell functions in addition to impaired resistance to mycobacterial disease suggests a susceptible phenotype in (n-3) fatty acid-fed guinea pigs.

McFarland CT, et al. *J Nutrition* 2008; 138: 2123–2128.

Pathogen destruction versus intracellular survival: the role of lipids as phagosomal fate determinants.

“Yet another example of phosphoinositide involvement in the pathogenesis of infectious disease is provided by *Mycobacterium tuberculosis*. *M. tuberculosis* is unable to invade cells actively, but is internalized by macrophages into what is initially a conventional phagosome. Shortly after ingestion, the bacteria deploy a number of weapons that enable them to arrest the maturation process at an early stage, precluding progression to lytic phagolysosomes (99). The bacteria generate a favorable intracellular niche, in part by modulating the acquisition of PI(3)P by the vacuole (95). To limit the production of this inositide, the bacteria secrete the glycosylated PI analog lipoarabinomannan, which inhibits the activation of Vps34 (100). In concert, the bacteria secrete the acid phosphatase SapM, which dephosphorylates PI(3)P. The combined actions of these two effectors lower the vacuolar content of PI(3)P and, in a manner that remains poorly understood, contribute to the arrest of phagosomal maturation at an early stage and favor intracellular survival of *M. tuberculosis*. These are but a few of the strategies used by bacteria to survive intracellularly; additional means of targeting host cell inositides by other pathogens are likely to emerge with future studies.”

Adapted from: Steinberg BE and Grinstein S (2008) *Journal of Clinical Investigation* 118: 2002–2011.

Evolutionary Speculation About Tuberculosis and the Metabolic and Inflammatory Processes of Obesity

This Commentary explores the possibility that the tuberculosis epidemic during previous centuries generated selective pressures that intensified the metabolic syndrome and the inflammatory processes now associated with obesity. These proinflammatory defenses (with immune systems that are especially robust and more easily triggered) in partnership with the metabolic syndrome (insulin resistance, dyslipidemias, and hypertension),¹ may have provided an advantage during the tuberculosis pandemic when food availability was limited and average life span was short. Currently, in developed countries, tuberculosis is relatively uncommon, food is abundant, and life expectancy beyond the reproductive years is substantial; the evolutionarily enhanced immune and metabolic elements now act possibly to intensify the pathological consequences of obesity

Jesse Roth. *JAMA*. 2009;301(24):2586-2588. doi:10.1001/jama.2009.930

Cytological and Transcript Analyses Reveal **Fat and Lazy Persister-Like Bacilli in Tuberculous Sputum**

Tuberculous sputum provides a sample of bacilli that must be eliminated by chemotherapy and that may go on to transmit infection. A preliminary observation that *Mycobacterium tuberculosis* cells contain triacylglycerol lipid bodies in sputum, but not when growing in vitro, led us to investigate the extent of this phenomenon and its physiological basis.

Methods and Findings: Microscopy-positive sputum samples from the UK and The Gambia were investigated for their content of lipid body-positive mycobacteria by combined Nile red and auramine staining. All samples contained a lipid body-positive population varying from 3% to 86% of the acid-fast bacilli present. The recent finding that triacylglycerol synthase is expressed by mycobacteria when they enter in vitro nonreplicating persistence led us to investigate whether this state was also associated with lipid body formation. We found that, when placed in laboratory conditions inducing nonreplicating persistence, two *M. tuberculosis* strains had lipid body levels comparable to those found in sputum. We investigated these physiological findings further by comparing the *M. tuberculosis* transcriptome of growing and nonreplicating persistence cultures with that obtained directly from sputum samples. Although sputum has traditionally been thought to contain actively growing tubercle bacilli, our transcript analyses refute the hypothesis that these cells predominate. Rather, they reinforce the results of the lipid body analyses by revealing transcriptional signatures that can be clearly attributed to slowly replicating or

nonreplicating mycobacteria. Finally, the lipid body count was highly correlated ($R=0.64$, $p=0.03$) with time to positivity in diagnostic liquid cultures, thereby establishing a direct link between this cytological feature and the size of a potential nonreplicating population.

Conclusion As nonreplicating tubercle bacilli are tolerant to the cidal action of antibiotics and resistant to multiple stresses, identification of this persister-like population of tubercle bacilli in sputum presents exciting and tractable new opportunities to investigate both responses to chemotherapy and the transmission of tuberculosis.

Natalie J. Garton¹, *PLoS Medicine* | www.plosmedicine.org 0634-0645 April 2008 | Volume 5 | Issue 4 | e75

Effects of omega-3 and -6 fatty acids on *Mycobacterium tuberculosis* in macrophages and in mice

We recently showed that treatment of macrophages prior to *Mycobacterium tuberculosis* infection with the pro-inflammatory omega-6 lipid, arachidonic acid (AA) enhanced bacterial killing whereas the anti-inflammatory, omega-3 lipid eicosapentaenoic acid (EPA) stimulated bacterial growth. Here we tested if these effects depended on when lipids were added to macrophages: before or during *Mycobacterium* infection. Collectively, our data suggested that a high omega-6 diet might be beneficial against mycobacteriosis, while a high omega-3 diet might be detrimental. AA also stimulated TNF-alpha secretion in *M. tuberculosis*-infected macrophages whereas EPA inhibited this process. AA strongly activated the MAP kinase p38 in uninfected cells but *M. tuberculosis* infected cells blocked the ability of AA to activate p38; AA-dependent killing is therefore independent of p38. We therefore tested diets enriched in omega-3 and omega-6 lipids on a mouse model of tuberculosis. In contrast to the *in vitro* results, the omega-6 tended to increase survival of *M. tuberculosis* in mice, while omega-3- tended to increase pathogen killing. Overall our results together with those previously reported in the literature suggest that it is almost impossible to predict, at the whole organism level, if a diet enriched in omega-3 or -6 will be beneficial or detrimental to intracellular pathogens.

Jordao L, et al. *Microbes Infect.* 2008 Oct;10(12-13):1379-86. doi: 10.1016/j.micinf.2008.08.004. PMID: 18771745

Reversible lipid accumulation and associated division arrest of *Mycobacterium avium* in lipoprotein (VLDL)-induced foamy macrophages may resemble key events during latency and reactivation of tuberculosis.

24 During the dormant phase of tuberculosis, *Mycobacterium tuberculosis* persists in lung 25 granulomas by residing in foamy macrophages (FM) that contain abundant lipid bodies (LB) in 26 their cytoplasm, allowing bacilli to accumulate lipids as intracytoplasmic lipid inclusions (ILI). 27 An experimental model of FM is presented where bone marrow-derived mouse macrophages are 28 infected with *M. avium* and exposed to very low density lipoprotein (VLDL) as a lipid source. 29 Quantitative analysis of detailed electron microscope observations showed the following results: 30 (i) Macrophages became foamy and mycobacteria formed ILI, for which host triacylglycerides, 31 rather than cholesterol, was essential; (ii) Lipid transfer occurred via mycobacteria-induced 32 fusion between LB and phagosomes; (iii) Mycobacteria showed a thinned cell wall and became 33 elongated; (iv) Upon removal of VLDL, LB and ILI declined within hours and simultaneous 34 resumption of mycobacterial division restored the number of mycobacteria to the same level as 35 that found in untreated control macrophages. This showed that the presence of ILI resulted in a 36 reversible block of division without causing a change in mycobacterial replication rate. 37 Fluctuation between ILI either partially or fully extending throughout the mycobacterial 38 cytoplasm was suggestive of bacterial cell-cycle events. We propose that VLDL-driven FM 39 constitute a well-defined cellular system in which to study changed metabolic states of 40 intracellular mycobacteria that may relate to persistence and re-activation of tuberculosis.

Irene Caire-Brandli, et al. *Infect. Immun.* (2013) doi:10.1128/LAI.01196-13

Pharmacodynamic Modeling of Bacillary Elimination Rates and Detection of Bacterial Lipid Bodies in Sputum to Predict and Understand Outcomes in Treatment of Pulmonary Tuberculosis.

Background. Antibiotic-tolerant bacterial persistence prevents treatment shortening in drug-susceptible tuberculosis, and accumulation of intracellular lipid bodies has been proposed to identify a persister phenotype of *Mycobacterium tuberculosis* cells. In Malawi, we modeled bacillary elimination rates (BERs) from sputum cultures and calculated the percentage of lipid body-positive acid-fast bacilli (%LB + AFB) on sputum smears. We assessed whether these putative measurements of persistence predict unfavorable outcomes (treatment failure/relapse).

Methods. Adults with pulmonary tuberculosis received standard 6-month therapy. Sputum samples were collected during the first 8 weeks for serial sputum colony counting (SSCC) on agar and time-to positivity (TTP) measurement in mycobacterial growth indicator tubes. BERs were extracted from nonlinear and linear mixed-effects models, respectively, fitted to these datasets. The %LB + AFB counts were assessed by fluorescence microscopy. Patients were followed until 1 year posttreatment. Individual BERs and %LB + AFB counts were related to final outcomes.

Results. One hundred and thirty-three patients (56% HIV coinfecting) participated, and 15 unfavorable outcomes were reported. These were inversely associated with faster sterilization phase bacillary elimination from the SSCC model (odds ratio [OR], 0.39; 95% confidence interval [CI], .22–.70) and a faster BER from the TTP model (OR, 0.71; 95% CI, .55–.94). Higher

%LB + AFB counts on day 21–28 were recorded in patients who suffered unfavorable final outcomes compared with those who achieved stable cure ($P = .008$).

Conclusions. Modeling BERs predicts final outcome, and high %LB + AFB counts 3–4 weeks into therapy may identify a persister bacterial phenotype. These methods deserve further evaluation as surrogate endpoints for clinical trials.

Sloan DJ, et al. Clin Infect Dis. 2015 Jul 1;61(1):1-8. doi: 10.1093/cid/civ195. Epub 2015 Mar 16. PMID: 25778753

Breaking fat! How mycobacteria and other intracellular pathogens manipulate host lipid droplets

“...dormant bacteria regain growth and virulence when the immune system is weakened, leading to the active form of the disease. [Fatty acids \(FAs\) released from host triacylglycerols \(TAGs\) and sterols are proposed to serve as sole carbon sources during infection.](#) The metabolism of FAs requires beta-oxidation as well as gluconeogenesis and the glyoxylate shunt. Interestingly, the Mtb genome encodes more than hundred proteins involved in the five reactions of beta-oxidation, clearly demonstrating the importance of lipids as energy source. FAs have also been proposed to play a role during resuscitation, the resumption of replicative activities from dormancy. Lipid droplets (LDs) are energy and carbon reservoirs and have been described in all domains. TAGs and sterol esters (SEs) are stored in their hydrophobic core, surrounded by a phospholipid monolayer. Importantly, host LDs have been described as crucial for several intracellular bacterial pathogens and viruses and specifically translocate to the pathogen-containing vacuole (PVC) during mycobacteria infection. FAs released from host LDs are used by the pathogen as energy source and as building blocks for membrane synthesis. Despite their essential role, the mechanisms by which pathogenic mycobacteria induce the cellular redistribution of LDs and gain access to the stored lipids are still poorly understood. This review describes recent evidence about the dual interaction of mycobacteria with host LDs and membrane phospholipids and integrates them in a broader view of the underlying cellular processes manipulated by various intracellular pathogens to gain access to host lipids.”

Caroline Barisch, Thierry Soldati. Biochimie. 2017 Oct;141:54-61. doi: 10.1016/j.biochi.2017.06.001. PMID: 28587792

D. FAT SOLUBLE VITAMINS

1. Vitamin A

Impact of Vitamin A and Carotenoids on the Risk of Tuberculosis Progression.

BACKGROUND: Low and deficient levels of vitamin A are common in low- and middle-income countries where tuberculosis burden is high. We assessed the impact of baseline levels of vitamin A and carotenoids on tuberculosis disease risk.

METHODS: We conducted a case-control study nested within a longitudinal cohort of household contacts (HHCs) of pulmonary tuberculosis case patients in Lima, Peru. We defined case patients as human immunodeficiency virus (HIV)-negative HHCs with blood samples in whom tuberculosis disease developed ≥ 15 days after enrollment of the index patient. For each case patient, we randomly selected 4 controls from among contacts in whom tuberculosis disease did not develop, matching for sex and year of age. We used conditional logistic regression to estimate odds ratios for incident tuberculosis disease by vitamin A and carotenoids levels, controlling for other nutritional and socioeconomic factors.

RESULTS: Among 6751 HIV-negative HHCs with baseline blood samples, 192 had secondary tuberculosis disease during follow-up. We analyzed 180 case patients with viable samples and 709 matched controls. After controlling for possible confounders, we found that baseline vitamin A deficiency was associated with a 10-fold increase in risk of tuberculosis disease among HHCs (adjusted odds ratio, 10.53; 95% confidence interval, 3.73-29.70; $P < .001$). This association was dose dependent, with stepwise increases in tuberculosis disease risk with each decreasing quartile of vitamin A level.

CONCLUSIONS: [Vitamin A deficiency strongly predicted the risk of incident tuberculosis disease among HHCs of patients with tuberculosis. Vitamin A supplementation among individuals at high risk of tuberculosis may provide an effective means of preventing tuberculosis disease.](#)

Aibana O, et al. Clin Infect Dis. 2017 Sep 15;65(6):900-909. doi: 10.1093/cid/cix476. PMID: 28531276

FURTHER READING ON LIPIDS AND LIPID METABOLISM IN M.TUBERCULOSIS
Modulation of the M. tuberculosis cell envelope between replicating and non-replicating persistent bacteria. Stokas H, Rhodes HL, Purdy GE. Tuberculosis (Edinb). 2020 Dec;125:102007. doi: 10.1016/j.tube.2020.102007.
Foam Cells Control Mycobacterium tuberculosis Infection. Agarwal P, Combes TW, Shojaee-Moradie F, et al. Front Microbiol. 2020 Jul 9;11:1394. doi: 10.3389/fmicb.2020.01394.
Triacylglycerols: Fuelling the Hibernating Mycobacterium tuberculosis. Maurya RK, Bharti S, Krishnan MY. Front Cell Infect Microbiol. 2019 Jan 9;8:450. doi: 10.3389/fcimb.2018.00450.
Phospholipid homeostasis, membrane tenacity and survival of Mtb in lipid rich conditions is determined by MmpL11 function. Bothra A, Arumugam P, Panchal V, et al. Sci Rep. 2018 May 29;8(1):8317. doi: 10.1038/s41598-018-26710-z.
Adipocyte Model of M.tb. Infection Reveals Differential Availability of Iron to Bacilli in the Lipid-Rich Caseous Environment. Nandy A, Mondal AK, Pandey R, et al. Infect Immun. 2018 May 22;86(6):e00041-18. doi: 10.1128/IAI.00041-18.
Triacylglycerol: nourishing molecule in endurance of M.tb. Mali PC, Meena LS. J Biosci. 2018 Mar;43(1):149-154.
The transcriptome of Mycobacterium tuberculosis in a lipid-rich dormancy model through RNAseq analysis. Aguilar-Ayala DA, Tilleman L, Van Nieuwerburgh F, et al. Sci Rep. 2017 Dec 15;7(1):17665. doi: 10.1038/s41598-017-17751-x.
Rv2744c Is a PspA Ortholog That Regulates Lipid Droplet Homeostasis and Nonreplicating Persistence in Mycobacterium tuberculosis. Armstrong RM, Adams KL, Zilisch JE, et al. J Bacteriol. 2016 May 13;198(11):1645-1661. doi: 10.1128/JB.01001-15. P
Mycobacterial Metabolic Syndrome: LprG and Rv1410 Regulate Triacylglyceride Levels, Growth Rate and Virulence in M.tb. Martinot AJ, Farrow M, Bai L, et al. PLoS Pathog. 2016 Jan 11;12(1):e1005351. doi: 10.1371/journal.ppat.1005351.
Mycobacteria and the greasy macrophage: getting fat and frustrated. Neyrolles O. Infect Immun. 2014 Feb;82(2):472-5. doi: 10.1128/IAI.01512-13.
Reversible lipid accumulation and associated division arrest of Mycobacterium avium in lipoprotein-induced foamy macrophages may resemble key events during latency and reactivation of tuberculosis. Caire-Brändli I, Papadopoulos A, Malaga W, et al. Infect Immun. 2014 Feb;82(2):476-90. doi: 10.1128/IAI.01196-13.
Mycobacterium tuberculosis uses host triacylglycerol to accumulate lipid droplets and acquires a dormancy-like phenotype in lipid-loaded macrophages. Daniel J, Maamar H, Deb C, et al. PLoS Pathog. 2011 Jun;7(6):e1002093. doi: 10.1371/journal.ppat.1002093.
Carbon flux rerouting during Mycobacterium tuberculosis growth arrest. Shi L, Sohaskey CD, Pheiffer C, et al. Mol Microbiol. 2010 Dec;78(5):1199-215. doi: 10.1111/j.1365-2958.2010.07399.x.
Global adaptation to a lipid environment triggers the dormancy-related phenotype of Mycobacterium tuberculosis. Rodríguez JG, et al. mBio. 2014 May 20;5(3):e01125-14. doi: 10.1128/mBio.01125-14.

2. Vitamin D

Micronutrient status and immune function in tuberculosis. Guinea pigs were fed diets containing varying levels of zinc or vitamin D, and infected 6 weeks later by the respiratory route with virulent Mycobacterium tuberculosis. Zinc-deficient guinea pigs had fewer circulating T cells and reduced tuberculin (PPD) hypersensitivity. The response of peritoneal exudate macrophages to the lymphokine MIF was impaired. Zinc deprivation did not influence disease resistance in BCG-vaccinated or nonvaccinated animals. Vitamin D deficiency adversely affected the tuberculin reaction and ability to control the infection. Lymphocytes from vitamin D-deprived animals did not proliferate normally when cultured with PPD. A diet supplemented with vitamin D enhanced T cell responses to PPD in vivo.

McMurray DN, et al. Ann N Y Acad Sci. 1990;587:59-69. doi: 10.1111/j.1749-6632.1990.tb00134.x.

Vitamin D status and incidence of tuberculosis among contacts of pulmonary tuberculosis patients.

A prospective cohort study was conducted from 2009 to 2012 to assess the relationship between serum baseline 25-hydroxyvitamin D (vitamin D) status and the incidence of tuberculosis (TB) among 572 contacts of 89 pulmonary TB patients in Castellon, Spain. Three new cases of pulmonary TB occurred, with an incidence density of 3.6 per 1000 person-years. Mean vitamin D status was 13.7 ng/ml for cases and 25.7 ng/ml for non-cases. Vitamin D status showed a significant inverse association with TB incidence (adjusted HR 0.88, 95%CI 0.80-0.97). This result is in line with the hypothesis that vitamin D deficiency is associated with TB incidence.

Arnedo-Pena A, et al. Int J Tuberc Lung Dis. 2015 Jan;19(1):65-9. doi: 10.5588/ijtld.14.0348. PMID: 25519792

Vitamin D and tuberculosis: more effective in prevention than treatment?

...individual patient data meta-analysis of the burgeoning number of trials in this field may reveal sub-groups in which adjunctive therapy may confer clinical benefit, such as those with profound vitamin D deficiency, multidrug-resistant disease or particular genotypes of vitamin D receptor. This project is now underway. Whether vitamin D deficiency might predispose to extra-pulmonary dissemination. The original question regarding tuberculosis prevention is currently being addressed in Phase 3 trials – one testing the effectiveness of vitamin D in preventing pulmonary tuberculosis among 4000 HIV- infected adults in Tanzania, and another testing the ability of vitamin D to prevent acquisition of latent M. tuberculosis infection among 8200 schoolchildren in Mongolia. **To our knowledge, trials of vitamin D to prevent active disease in non-HIV-infected adults are currently lacking, and this represents a significant research need.**

Davies PD, Martineau AR. *Int J Tuberc Lung Dis.* 2015 Aug;19(8):876-7. doi: 10.5588/ijtld.15.0506.PMID: 26162349

Vitamin D status and risk of incident tuberculosis disease: A nested case-control study, systematic review, and individual-participant data meta-analysis.

BACKGROUND: Few studies have evaluated the association between preexisting vitamin D deficiency and incident tuberculosis (TB). We assessed the impact of baseline vitamin D levels on TB disease risk.

METHODS AND FINDINGS: We assessed the association between baseline vitamin D and incident TB in a prospective cohort of 6,751 HIV-negative household contacts of TB patients enrolled between September 1, 2009, and August 29, 2012, in Lima, Peru. We screened for TB disease at 2, 6, and 12 months after enrollment. We defined cases as household contacts who developed TB disease at least 15 days after enrollment of the index patient. For each case, we randomly selected four controls from among contacts who did not develop TB disease, matching on gender and year of age. We also conducted a one-stage individual-participant data (IPD) meta-analysis searching PubMed and Embase to identify prospective studies of vitamin D and TB disease until June 8, 2019. We included studies that assessed vitamin D before TB diagnosis. In the primary analysis, we defined vitamin D deficiency as 25-(OH)D < 50 nmol/L, insufficiency as 50-75 nmol/L, and sufficiency as >75nmol/L. We estimated the association between baseline vitamin D status and incident TB using conditional logistic regression in the Lima cohort and generalized linear mixed models in the meta-analysis. We further defined severe vitamin D deficiency as 25-(OH)D < 25 nmol/L and performed stratified analyses by HIV status in the IPD meta-analysis. In the Lima cohort, we analyzed 180 cases and 709 matched controls. **The adjusted odds ratio (aOR) for TB risk among participants with baseline vitamin D deficiency compared to sufficient vitamin D was 1.63 (95% CI 0.75-3.52; p = 0.22).** We included seven published studies in the meta-analysis and analyzed 3,544 participants. **In the pooled analysis, the aOR was 1.48 (95% CI 1.04-2.10; p = 0.03).** **The aOR for severe vitamin D deficiency was 2.05 (95% CI 0.87-4.87; p trend for decreasing 25-(OH)D levels from sufficient vitamin D to severe deficiency = 0.02).** **Among 1,576 HIV-positive patients, vitamin D deficiency conferred a 2-fold (aOR 2.18, 95% CI 1.22-3.90; p = 0.01) increased risk of TB, and the aOR for severe vitamin D deficiency compared to sufficient vitamin D was 4.28 (95% CI 0.85-21.45; p = 0.08).** Our Lima cohort study is limited by the short duration of follow-up, and the IPD meta-analysis is limited by the number of possible confounding covariates available across all studies.

CONCLUSION: Our findings suggest vitamin D predicts TB disease risk in a dose-dependent manner and that the risk of TB disease is highest among HIV-positive individuals with severe vitamin D deficiency. Randomized control trials are needed to evaluate the possible role of vitamin D supplementation on reducing TB disease risk.

Aibana O, et al. *PLoS Med.* 2019 Sep 11;16(9):e1002907. doi: 10.1371/journal.pmed.1002907. PMID: 31509529

3. Vitamin E

Vitamin E Status Is Inversely Associated with Risk of Incident Tuberculosis Disease among Household Contacts.

BACKGROUND: Few studies have previously assessed how pre-existing vitamin E status is associated with risk of tuberculosis (TB) disease progression.

OBJECTIVE: We evaluated the association between baseline plasma concentrations of 3 vitamin E isomers (α -tocopherol, γ -tocopherol, and δ -tocopherol) and TB disease risk.

METHODS: We conducted a case-control study nested within a longitudinal cohort of household contacts (HHCs) of pulmonary TB cases in Lima, Peru. We defined cases as HHCs who developed active TB disease ≥ 15 d after the diagnosis of the index patient, and we matched each case to 4 control cases who did not develop active TB based on age by year and gender. We used univariate and multivariate conditional logistic regression to calculate ORs for incident TB disease by plasma concentrations of α -tocopherol, γ -tocopherol, and δ -tocopherol.

RESULTS: Among 6751 HIV-negative HHCs who provided baseline blood samples, 180 developed secondary TB during follow-up. After controlling for possible confounders, we found that baseline α -tocopherol deficiency conferred increased risk of incident TB disease (adjusted OR: 1.59; 95% CI: 1.02, 2.50; P = 0.04). Household contacts in the lowest tertile of δ -tocopherol were also at increased risk of progression to TB disease compared to those in the highest tertile (tertile 1 compared

with tertile 3, adjusted OR: 2.29; 95% CI: 1.29, 4.09; P-trend = 0.005). We found no association between baseline concentration of γ -tocopherol and incident TB disease.

CONCLUSIONS: Vitamin E deficiency was associated with an increased risk of progression to TB disease among HHCs of index TB cases. Assessment of vitamin E status among individuals at high risk for TB disease may play a role in TB control efforts.

Aibana O, et al. *J Nutr.* 2018 Jan 1;148(1):56-62. doi: 10.1093/jn/nxx006. PMID: 29378042

E. WATER SOLUBLE VITAMINS

4. B Vitamins and Friends

In Cegielski et al. (2012), TB incidence was not associated with urinary thiamine/creatinine or riboflavin/creatinine ratios, considered to be better indicators of insufficiency than simple serum levels. I found no unusual associations between tuberculosis and beriberi (thiamine, B1), ariboflavinosis (B2), pellagra (niacin, B3) or megaloblastic anemia (folate, B12).

5. Vitamin C

Historically, there was no specific association between TB with scurvy. Getz et al (see below) demonstrated that low vitamin C and low vitamin A, but not other micronutrients, predicted a high incidence of TB in a large cohort of mostly Black men in Philadelphia in the 1950s. No other reports focused solely on vitamin C as a risk factor for TB. Vitamin C may potentiate the effect of anti-TB drugs.

F. VITAMINS A & C TOGETHER

A study of the relation of nutrition to the development of tuberculosis; influence of ascorbic acid and vitamin A.

A group of 1,100 men, free from pulmonary tuberculosis at first examination as shown by roentgenographic study, were followed over periods ranging from one month to five years. The average number of years of observation was 1.5 years. Eighty-three per cent of the group were Negroes and 17 per cent were white. All were between 20 and 45 years of age. Periodic roentgenographic examinations and clinical studies and serial nutritional assays were made of the group. The nutritional assay included measurement of the blood once nutrition of hemoglobin, plasma carotene, vitamin A and vitamin C, total serum protein, serum albumin and globulin and serum calcium, phosphorus and phosphatase. The clinical examination, in addition to specific tests for tuberculosis, included calculation of per cent standard weight and, in a large number of instances measurement of bone density.

Twenty-eight persons in the group developed roentgenographic evidence of tuberculosis during the seven years of the investigation. Sixteen of these had active tuberculosis and four of them died during the study. Twelve had lesions which appeared to be inactive when first detected, but in four persons the lesions fluctuated in a visibly favorable way, indicating recent activity.

Nutritional assays of the 28 gave values evenly distributed through the ranges of values for all 1,100 with respect to all; blood elements studied except vitamins A and C. **All cases of clearly active disease occurred in persons with markedly substandard values for vitamins A and C prior to the development of tuberculosis. An inverse relation thus appeared evident in the development of tuberculosis and blood concentration of these vitamins.** The degree of probability that such a relation is significant is indicated by statistical computations in the text. No correlation was evident in the development of tuberculosis and deviation from standard weight or bone density. Appropriate studies indicated a degree of persistence of nutritional pattern ensuring suitability of the population under investigation for this study.

Getz HR, Long ER, Henderson HJ. *Am Rev Tuberc.* 1951 Oct;64(4):381-93. doi: 10.1164/art.1951.64.4.381.

Dietary Intake of Antioxidant Vitamins and Carotenoids and Risk of Developing Active Tuberculosis in a Prospective Population-Based Cohort Study

Antioxidants may protect against oxidative stress, which is associated with tuberculosis (TB) disease. However, direct evidence for a protective association between dietary antioxidants and TB incidence in humans has been lacking. The relationship between intake of antioxidant vitamins (vitamins A, C, D, and E) and individual carotenoids (α -carotene, β -carotene, β -cryptoxanthin, lycopene, and lutein) and TB incidence was examined in the Singapore Chinese Health Study, a prospective cohort study of 63,257 adults aged 45–74 years enrolled during 1993–1998. Baseline intake of these antioxidants was estimated

using a validated semiquantitative food frequency questionnaire including questions on use of dietary supplements. After an average of 16.9 years of follow-up, 1,186 incident active TB cases were identified among cohort participants. Compared with the lowest quartile, reduced risk of active TB was observed for the highest quartile of vitamin A intake (hazard ratio = 0.71, 95% confidence interval: 0.59, 0.85; P-trend < 0.01) and β -carotene intake (hazard ratio = 0.76, 95% confidence interval: 0.63, 0.91; P-trend < 0.01), regardless of smoking status. Lower TB risk was seen for vitamin C intake among current smokers only. Other vitamins and carotenoids were not associated with TB risk. These results suggest that vitamin C may reduce TB risk among current smokers by ameliorating oxidative stress, while vitamin A and β -carotene may have additional antimycobacterial properties.

Sob AZ, et al. AmJ Epidemiol. 2017;186(4):491–500

G. MINERALS

6. Zinc

Zinc: Deficiency Disorders and Prevention Programs

Four main factors are responsible for zinc deficiency in lower income countries: inadequate dietary zinc intake; poor zinc absorption from high-phytate, plant-based diets; disease states that either induce excessive losses or impair utilization of zinc; and increased zinc requirements such as the periods of rapid growth during childhood and pregnancy. In the context of developing countries, the health consequences of zinc deficiency are known based on relatively firm evidence from randomized community-based trials of zinc supplementation among populations at possible risk of zinc deficiency.

1. Impact Of Zinc Deficiency

- a. Child Growth
- b. Child Mortality: 6%-9% reduction, 18% among >12 mos. age
- c. Diarrheal infections - treatment and prevention (20%)
- d. Acute lower respiratory infections - prevention (21%)
- e. Pregnancy

2. Zinc Intervention Strategies

- a. Preventive Zinc Supplementation
- b. Therapeutic Zinc Supplementation in the Treatment of Diarrhea
- c. Food Fortification with Zinc
- d. Mass Fortification of Staple Foods
- e. Targeted Fortification
- f. Dietary Diversification and Modification
- g. Biofortification

Adapted from SY Hess, Encyclopedia of Human Nutrition-3rd ed., London: Elsevier Ltd., 2013, pp. 431-436

Micronutrient status and immune function in tuberculosis.

Guinea pigs were fed diets containing varying levels of zinc or vitamin D, and infected 6 weeks later by the respiratory route with virulent *Mycobacterium tuberculosis*. Zinc-deficient guinea pigs had fewer circulating T cells and reduced tuberculin (PPD) hypersensitivity. The response of peritoneal exudate macrophages to the lymphokine MIF was impaired. Zinc deprivation did not influence disease resistance in BCG-vaccinated or nonvaccinated animals. Vitamin D deficiency adversely affected the tuberculin reaction and ability to control the infection. Lymphocytes from vitamin D-deprived animals did not proliferate normally when cultured with PPD. A diet supplemented with vitamin D enhanced T cell responses to PPD in vivo.

McMurray DN, et al. Ann N Y Acad Sci. 1990;587:59-69. doi: 10.1111/j.1749-6632.1990.tb00134.x.

Respiratory infection with attenuated *Mycobacterium tuberculosis* H37Ra in malnourished guinea pigs.

Specific pathogen-free guinea pigs were infected via the respiratory route with viable, attenuated *Mycobacterium tuberculosis* H37Ra and maintained on purified isocaloric diets: control, low protein diet, low zinc diet. Protein-deficient animals exhibited significantly reduced body weight, spleen weight, serum total proteins, and serum albumin. Zinc deficiency was characterized by loss of weight and progressive reductions in plasma zinc concentrations. The number of viable *M. tuberculosis* H37Ra cells was significantly higher in the lungs, spleen, BT lymphnodes of both malnourished groups at 3 weeks, but fell below control viable counts by 5 weeks postinfection. Both the proportion and intensity of delayed hypersensitivity reactions increased steadily between 3 and 5 weeks in control animals, whereas the two malnourished groups were essentially anergic at all intervals, despite systemic infection. The nature of the influence depends upon the interval: In both malnourished groups, the pulmonary infection tended to peak early and decline, whereas the disease developed more slowly in control animals. Apparent control of mycobacterial populations in the tissues was accomplished by malnourished animals in the absence of demonstrable delayed hypersensitivity.

McMurray DN, et al. Infect Immun. 1983 Feb;39(2):793-9. doi: 10.1128/LAI.39.2.793-799.1983.

7. Selenium

Selenium is important for optimal function of both innate and acquired immune systems, and is involved in defense of animals against bacterial and viral infections. The mechanisms for this role of selenium are likely to be related to its antioxidant function through the selenoproteins GPx, thioredoxin reductases or SEPP. Selenium supplements can improve several indices of immune function, even in individuals whose selenium status is not severely deficient. Studies in mice of strains of Cocksackievirus B3 showed that selenium deficiency and vitamin E deficiency increased the cardiotoxicity of myocarditic strains. In addition nonmyocarditic strains of the virus caused heart lesions as a result of changes in the viral genome in selenium-deficient mice but not in selenium adequate mice. This is relevant to the etiology of Keshan disease, which has been attributed in part to a viral factor. Selenium deficiency also causes mutational changes in another RNA virus, influenza A, and in the protozoan parasite *Trypanosoma cruzi* and *Heligmosomoides polyrus*, enhancing the intensity of infection. In HIV-infected individuals, progression to AIDS and decline in T helper (CD4) cell counts are accompanied by a parallel decrease in blood selenium levels. Selenium deficiency appears to increase the probability of mortality in HIV-infected subjects. Some studies have reported benefits (e.g., anticancer and immunological effects) when supplements are given, even to populations that appear to be generously supplied with the nutrient, whereas others have identified adverse effects. The distinction between nutritional and pharmacological benefits is unclear, and further trials to determine risk–benefit balance at different intake levels are needed in a range of populations and age and gender groups.

Adapted and updated from: Thompson CD. Selenium. Encyclopedia of Human Nutrition, 3rd ed. London: Elsevier. 2013, pp. 186-192.

8. Iron

Associations of iron overload in Africa with hepatocellular carcinoma and tuberculosis: Strachan's 1929 thesis revisited

We analyzed data from the first study of iron overload in Africans, conducted between 1925 and 1928, to determine whether this common condition is associated with death from hepatocellular carcinoma and/or tuberculosis. In the original study, necropsies were performed on 714 adult blacks from southern Africa. Hepatic and splenic iron levels were measured semiquantitatively in 604 subjects and one of five iron grades was assigned. We examined death from hepatocellular carcinoma or from tuberculosis and the variables of age, sex, the presence of cirrhosis or other diagnoses that might be influenced by iron status, and tissue iron grades. **Nineteen percent of men and 16% of women had the highest grade of hepatic iron.** After adjustment for the presence of cirrhosis, hepatic iron grade was the variable most significantly associated with death from hepatocellular carcinoma ($P = .021$). The odds of death from hepatocellular carcinoma in subjects with the highest grade of hepatic iron was 23.5 (95% confidence interval, 2.1 to 225) times the odds in subjects with the three lowest grades. **Splenic iron was the variable most significantly associated with death from tuberculosis ($P < .0001$).** The odds of death from tuberculosis with the highest grade of splenic iron was 16.9 (4.8 to 59.9) times the odds with the two lowest grades. **These findings suggest that iron overload in black Africans may be a risk factor for death from hepatocellular carcinoma and for death from tuberculosis.**

V R Gordeuk, et al. Blood. 1996 Apr 15;87(8):3470-6. PMID: 8605366

Iron homeostasis and progression to pulmonary tuberculosis disease among household contacts.

Early identification of individuals at risk for progressing to active tuberculosis (TB) disease may limit new transmission and improve clinical outcomes. Evidence indicates altered iron homeostasis may identify those at greater risk of disease progression in HIV co-infection. We aimed to investigate iron homeostasis biomarkers as risk factors for progression to TB. Archived plasma samples were analyzed from household contacts of pulmonary TB index cases in The Gambia. Contacts were classified as asymptomatic non-progressors ($n = 17$) or TB-progressors ($n = 10$), which included two HIV-infected participants. Iron homeostasis (hemoglobin, ferritin, hepcidin, soluble transferrin receptor, transferrin) was assessed in all contacts at study recruitment. Plasma was collected a median of 910 days prior to TB diagnosis. Low transferrin around the time of known exposure to infectious TB was a disease progression risk factor among all TB-progressors (Poisson incidence rate ratio: 0.55; 95% CI: 0.35-0.89). Iron homeostasis also differed between early and delayed TB-progressors, with higher ferritin and hepcidin concentrations observed among early TB-progressors (mean ferritin 50.2 vs. 26.2 ng/ml; $P = 0.027$; mean hepcidin 37.7 vs. 5.6 ng/ml; $P = 0.036$). Iron homeostasis is associated with progression to TB among household contacts. Further studies are needed to elucidate mechanisms and determine the clinical utility of monitoring iron homeostasis biomarkers.

Minchella PA, et al. Tuberculosis (Edinb). 2015 May;95(3):288-93. doi: 10.1016/j.tube.2015.02.042. PMID: 25764944

Association of iron deficiency anemia with tuberculosis in Taiwan: A nationwide population-based study

Background: Iron deficiency is associated with decreased cellular immunity, which may predispose patients with iron deficiency anemia (IDA) to increased risk of developing tuberculosis (TB). This study investigated the relationship between newly diagnosed IDA and TB infection in Taiwan.

Methods: The study included data on 21,946 patients with incident IDA and 87,555 non-IDA controls from a national database covering the period 2000-2012. IDA and non-IDA subjects were matched 1:4 on age, gender, and index year. The follow-up period was defined as the time from the initial IDA diagnosis to the date of developing TB or 31 December 2013. Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals, with the control group as the reference.

Results: The adjusted hazard ratio of TB for the IDA group was 1.99 (95% confidence interval, 1.77-2.25) compared with the control group. The subgroup analysis showed that for both genders, all age groups, and patients with diabetes mellitus, hyperlipidemia, hypertension, cancer, chronic obstructive pulmonary disease, and hepatitis B virus infection, the IDA group had significantly higher TB incidence. The association was significantly stronger within the 5 years after new IDA diagnosis for both genders and all age groups.

Conclusions: Higher TB incidence was discovered in the IDA group, especially for patients with comorbidities.

Kuo-An Chu, et al. PLoS One. 2019 Aug 30;14(8):e0221908. doi: 10.1371/journal.pone.0221908.

H. Risk of infection versus risk of progression & nutrition for prevention

Vitamin D and tuberculosis: more effective in prevention than treatment?

“...individual patient data meta-analysis of the burgeoning number of trials in this field may reveal sub-groups in which adjunctive therapy may confer clinical benefit, such as those with profound vitamin D deficiency, multidrug-resistant disease or particular genotypes of vitamin D receptor. This project is now underway. Whether vitamin D deficiency might predispose to extra-pulmonary dissemination. The original question regarding tuberculosis prevention is currently being addressed in Phase 3 trials – one testing the effectiveness of vitamin D in preventing pulmonary tuberculosis among 4000 HIV- infected adults in Tanzania, and another testing the ability of vitamin D to prevent acquisition of latent M. tuberculosis infection among 8200 schoolchildren in Mongolia. To our knowledge, trials of vitamin D to prevent active disease in non-HIV-infected adults are currently lacking, and this represents a significant research need.”

Davies PD, Martineau AR. Int J Tuberc Lung Dis. 2015 Aug;19(8):876-7. doi: 10.5588/ijtld.15.0506.PMID: 26162349

Low body mass index and latent tuberculosis infection: a systematic review and meta-analysis.

Background: The well-documented association between underweight and increased incidence of active tuberculosis (TB) has not been extended to incidence or prevalence of latent tuberculous infection (LTBI).

Design: After identifying studies that reported a categorical measure of body mass index (BMI) and used the tuberculin skin test (TST) or QuantiFERON®-TB Gold In-Tube (QFT) to measure LTBI, a maximum likelihood random-effects model was used to examine the pooled association between LTBI and low BMI (<18.5 kg/m²), compared with 1) normal BMI (18.5-25 kg/m²) and 2) a complementary group of all others, i.e., non-underweight subjects (BMI ≥ 18.5 kg/m²).

Results: Among studies using TST, the odds ratios (ORs) showed a slight, non-statistically significant decrease in the odds of TST positivity in underweight persons compared with both groups (non-underweight, OR 0.88, 95%CI 0.73-1.05; normal weight, OR 0.96, 95%CI 0.77-1.20). Among studies using QFT, the OR suggested slightly decreased, yet non-significant, odds of QFT positivity in underweight compared with non-underweight subjects (OR 0.92, 95%CI 0.68-1.26), and significantly decreased odds of QFT positivity in underweight compared with normal weight subjects (OR 0.84, 95%CI 0.73-0.98).

Conclusion: These results suggest that underweight persons are not at an increased risk of LTBI. Screening this population for LTBI would not increase the yield of identified LTBI.

Saag LA, et al.. Int J Tuberc Lung Dis. 2018 Apr 1;22(4):358-365. doi: 10.5588/ijtld.17.0558. PMID: 29562981.

Prevalence and Determinants of QFT+ Tuberculosis Infection in 9810 Mongolian Schoolchildren.

BACKGROUND: There is controversy regarding the potential influence of vitamin D deficiency, exposure to environmental tobacco smoke, BCG vaccination, season, and body habitus on susceptibility to Mycobacterium tuberculosis (MTB) infection.

METHODS: We conducted a cross-sectional analysis to identify determinants of a positive QuantiFERON-TB Gold (QFT) assay result in children aged 6-13 years attending 18 schools in Ulaanbaatar, Mongolia. Data relating to potential risk factors for MTB infection were collected by questionnaire, physical examination, and determination of serum 25-hydroxyvitamin D (25[OH]D) concentrations. Risk ratios (RRs) were calculated with adjustment for potential confounders, and population attributable fractions (PAFs) were calculated for modifiable risk factors identified.

RESULTS: Nine hundred forty-six of 9810 (9.6%) participants had a positive QFT result. QFT positivity was independently associated with household exposure to pulmonary tuberculosis (adjusted RR [aRR], 4.75 [95% confidence interval {CI}, 4.13-5.46, P < .001]; PAF, 13.1% [95% CI, 11.1%-15.0%]), vitamin D deficiency (aRR, 1.23 [95% CI, 1.08-1.40], P = .002; PAF,

5.7% [95% CI, 1.9%-9.3%]), exposure to environmental tobacco smoke (1 indoor smoker, aRR, 1.19 [95% CI, 1.04-1.35]; ≥ 2 indoor smokers, aRR, 1.30 [95% CI, 1.02-1.64]; P for trend = .006; PAF, 7.2% [95% CI, 2.2%-12.0%]), and increasing age (aRR per additional year, 1.14 [95% CI, 1.10-1.19], P < .001). No statistically significant independent association was seen for presence of a BCG scar, season of sampling, or body mass index.

CONCLUSIONS: Vitamin D deficiency and exposure to environmental tobacco smoke are potentially modifiable risk factors for MTB infection.

Ganmaa D, et al. Clin Infect Dis. 2019 Aug 16;69(5):813-819. doi: 10.1093/cid/ciy975. PMID: 30481273

Vitamin D deficiency is associated with tuberculosis infection among household contacts in Ulaanbaatar, Mongolia.

BACKGROUND: Vitamin D deficiency (VDD) is a known risk factor for tuberculous infection. We investigated if VDD is a risk factor for tuberculous infection among the household contacts (HHCs) of patients with tuberculosis (TB) in Mongolia.

MATERIALS and METHOD: All HHCs of TB patients diagnosed in Khan-Uul District, Mongolia, were enrolled. The serum level of 25-hydroxyvitamin D [25(OH)D] was detected and TB infection determined using QuantiFERON-TB Gold Plus (QFT-Plus). A tuberculin skin test (TST) reading >10 mm was considered to be positive. Epidemiological and bacteriological data were collected from routine surveillance of the National Tuberculosis Programme.

RESULTS: Among study participants, 48.2% (135/285) were QFT-Plus-positive. Of QFT-positive HHCs, 77.0% (104/135) were TST-positive. A low serum level of 25(OH)D was an independent predictor for QFT-Plus positivity (P < 0.001). CD8+ T-cell stimulation measured by QFT-Plus had borderline association with the serum level of 25(OH)D (P = 0.089).

CONCLUSION: We showed a high rate of TB infection among HHCs in Mongolia. QFT-Plus could decrease the number of people requiring TB preventive treatment, in addition to aiding detection of new TB infection. A low serum level of vitamin D was an independent predictor of TB infection, but not a predictor of stimulation of CD8+ T cell s.

Gurjav U, et al. Int J Tuberc Lung Dis. 2019 Aug 1;23(8):919-923. doi: 10.5588/ijtld.19.0047. PMID: 31533882

Effectiveness of a multivitamin supplementation program among HIV-infected adults in Tanzania

Design: We conducted a retrospective cohort study of 67 707 adults enrolled in the Dar es Salaam HIV care and treatment program during 2004-2012 to assess the effectiveness of a routine multivitamin supplementation program.

Methods: The Dar es Salaam HIV care and treatment program intended to provide all adult patients with multivitamin supplements (vitamins B-complex, C, and E) free of charge; however, intermittent stockouts and other implementation issues did not afford universal coverage. We use Cox proportional hazard models to assess the time-varying association of multivitamin supplementation with mortality and clinical outcomes.

Results: The study cohort contributed 41 540 and 129 315 person-years of follow-up time to the antiretroviral therapy (ART)-naive and ART-experienced analyses, respectively. Among 48 207 ART-naive adults, provision of multivitamins reduced the risk of mortality (aHR: 0.69; 95%CI: 0.59-0.81), incident tuberculosis (TB) (aHR: 0.83; 0.76-0.91), and meeting ART eligibility criteria (aHR: 0.78; 0.73-0.83) after adjustment for time-varying confounding. Among 46 977 ART-experienced patients, multivitamins reduced mortality (HR: 0.86; 0.80-0.92), incident TB (aHR: 0.78; 0.73-0.84), and immunologic failure (aHR: 0.70; 0.67-0.73). The survival benefits were greatest during the first year of ART and declined over time (P value <0.001).

Conclusion: Multivitamin supplementation appears to be a simple, effective, safe, and scalable program to improve survival, reduce incidence of TB, and improve treatment outcomes for adult HIV patients in Tanzania.

Sudfeld CR, et al. AIDS. 2019 Jan 27;33(1):93-100. doi: 10.1097/QAD.0000000000002033.

II. EFFECT OF TB ON NUTRITIONAL STATUS

NB: Nutritional status measured at the time of TB diagnosis and during the course of treatment, in other words, development of overt TB is the antecedent resulting in the nutritional status observed at presentation. Includes observational studies of nutritional support during treatment and of treatment outcomes in relation to nutritional status.

>> See Papatheakis P. *Nutrition and Tuberculosis. USAID 2008 for evidence up to 2008* <<

A. MACRONUTRIENTS AND BODY COMPOSITION

Macronutrient intake and body composition changes during anti-tuberculosis therapy in adults.

OBJECTIVE: To evaluate macronutrient intake and body composition in individuals with newly diagnosed TB over time. **DESIGN:** Adults with active pulmonary TB (n = 191; 23 with multidrug-resistant TB (MDR-TB) and 36 culture-negative household contacts (controls) enrolled in a clinical trial of high-dose cholecalciferol (vitamin D3). Macronutrient intake was determined at baseline, 8 and 16 weeks. Serial body composition was assessed by body mass index (BMI; kg/m²) and bioelectrical impedance analysis (BIA) to estimate fat mass and fat-free mass. Descriptive statistics, repeated measures ANOVA for changes over time and linear regression were used.

RESULTS: At baseline, mean daily energy, protein, fat and carbohydrate (CHO) intakes were significantly higher, and body weight, BMI, fat-free mass and fat mass were significantly lower, between TB subjects and controls. These remained significant after adjusting for age, gender, employment status and smoking. In all TB subjects, baseline mean daily intakes of energy, fat and protein were adequate when compared to the US Dietary Reference Intakes and protein significantly increased over time (p < 0.0001). Body weight, BMI, and fat and fat-free mass increased over time. MDR-TB patients exhibited lower body weight and fat-free mass over time, despite similar daily intake of kcal, protein, and fat.

CONCLUSIONS: Macronutrient intake was higher in TB patients than controls, but TB-induced wasting was evident. As macronutrient intake of TB subjects increased over time, there was a parallel increase in BMI, while body composition proportions were maintained. However, individuals with MDR-TB demonstrated concomitantly decreased body weight and fat-free mass over time versus drug-sensitive TB patients, despite increased macronutrient intake. Thus, MDR-TB appears to blunt anabolism to macronutrient intake, likely reflecting the catabolic effects of TB.

Frediani JK, et al. *Clin Nutr.* 2016 Feb;35(1):205-212. doi: 10.1016/j.clnu.2015.02.007. PMID: 25753551

B. MULTIPLE MICRONUTRIENTS CONCURRENTLY

Relationships between serum concentrations of C-reactive protein and micronutrients, in patients with tuberculosis.

Studies on the serum concentrations of micronutrients in tuberculosis (TB), and their relationship to the acute-phase response (APR), are scarce. The serum concentrations of zinc, copper, selenium and vitamins A and E in 46 smear-positive cases of pulmonary TB (PTB) from Ecuador were therefore compared with those in 10 healthy Ecuadorian volunteers, and the correlations between these concentrations and the serum concentration of C-reactive protein (CRP) were evaluated. Compared with the healthy volunteers, the PTB cases had significantly lower serum concentrations of zinc, retinol and selenium, although both groups had moderately high selenium concentrations, and significantly higher serum concentrations of copper. The PTB cases who had >50 mg CRP/l, indicating an acute phase response, had lower serum concentrations of retinol and zinc than the cases with lower CRP concentrations; they were inversely correlated. Thus, in patients with PTB, low levels of zinc and retinol may indicate an ongoing acute phase reaction rather than a deficiency of the micronutrient. It is therefore necessary to consider the extent of activation of the APR when interpreting serum micronutrient concentrations in patients with TB.

Koyanagi A, et al. *Ann Trop Med Parasitol.* 2004 Jun;98(4):391-9. doi: 10.1179/000349804225003424. PMID: 15228720

Evaluation of vitamin status in patients with pulmonary tuberculosis.

In 152 patients with tuberculosis and 137 control subjects, concentrations of vitamin A, vitamin D, vitamin E, homocysteine, and methylmalonic acid were measured using high-performance liquid chromatography (HPLC) or HPLC-tandem mass spectrometry. Patient demographic data and other biochemical parameters were also analyzed.

RESULTS: The serum concentrations of vitamins A, D, and E were significantly lower in patients with tuberculosis than in control subjects (1.4 vs. 2.0 μmol/L, P < 0.001; 10.6 vs. 19.3 ng/mL, P < 0.001; and 22.8 vs. 30.6 μmol/L, P < 0.001,

respectively). In contrast, the methylmalonic acid levels were higher in patients with tuberculosis (134.9 vs. 110.8 nmol/L, $P < 0.001$). The prevalences of vitamin deficiencies were significantly higher in patients with tuberculosis. Moreover, multiple vitamin deficiencies were only observed in patients with tuberculosis (22.4% of all patients with tuberculosis vs. 0% of all control subjects). Positive correlations among vitamin A, D, and E concentrations were observed (vitamins A and D, $r = 0.395$; vitamins D and E, $r = 0.342$; and vitamins A and E, $r = 0.427$, $P < 0.001$). Body mass index, total cholesterol, low-density lipoprotein, iron, and total iron-binding capacity all showed positive correlations with vitamin A, D, and E concentrations.

Ob J, et al. J Infect. 2017 Mar;74(3):272-280. doi: 10.1016/j.jinf.2016.10.009.

Micronutrient levels of tuberculosis patients during the intensive phase, a prospective cohort study.

INTRODUCTION: The objectives of this study were to estimate the micronutrient deficiency levels of tuberculosis patients at the start and end of the intensive phase, and to identify the predictors of micronutrient deficiencies in tuberculosis patients.

METHODS: A prospective cohort study design was implemented. The sample size was calculated using Epi-info software. Systematic sampling technique was used. Descriptive statistics were used to estimate the micronutrient levels. The general linear model was used to predict the determinants of micronutrient level.

RESULTS: At the start of DOTS (directly observed treatment strategy), 64% of tuberculosis patients had a serum iron level less than 60 $\mu\text{g}/\text{dl}$, 41.9% of tuberculosis patients had serum zinc level less than 52 $\mu\text{g}/\text{dl}$, 29.7% of tuberculosis patients had serum selenium level less than 70 ng/dl , 40.5% of tuberculosis patients had serum vitamin d level less than 20 ng/ml , and 60.4% of tuberculosis patients had urine iodine level of less than 60.4 $\mu\text{g}/\text{dl}$. At the end of the intensive phase, 16.7% of tuberculosis patients had a serum iron level less than 60 $\mu\text{g}/\text{dl}$, <1% of tuberculosis patients had serum zinc level less than 52 $\mu\text{g}/\text{dl}$, <1% of tuberculosis patients had serum selenium level less than 70 ng/dl , 20.4% of tuberculosis patients had serum vitamin d level less than 20 ng/ml , and 53% of tuberculosis patients had urine iodine level of less than 60.4 $\mu\text{g}/\text{dl}$. Serum iron level was affected by HIV infection, hookworm infection, and site of tuberculosis infection; serum vitamin d level was affected by HIV infection; and alcohol dependency affected the serum zinc level of tuberculosis patients during the course of tuberculosis treatments.

CONCLUSION: Antituberculosis drugs were effective in normalizing the serum zinc and selenium level, but the serum level of iron, vitamin D and iodine were not normalized by the anti-tuberculosis drugs.

Feleke BE, et al. Clin Nutr ESPEN. 2019 Jun;31:56-60. doi: 10.1016/j.clnesp.2019.03.001. PMID: 31060835

C. VITAMIN A

Vitamin A status and therapy in childhood pulmonary tuberculosis.

Low plasma vitamin A levels (mean, 18.1 +/- 10.3 micrograms/dl, 62% below normal) were demonstrated in South African children with pulmonary tuberculosis. More extensive or severe disease (e.g., additional extrapulmonary tuberculosis) and low levels of retinol binding protein, prealbumin, and albumin were associated with low vitamin A levels. High-dose vitamin A therapy had no effect on disease outcome.

Hanekom WA, et al. J Pediatr. 1997 Dec;131(6):925-7. doi: 10.1016/s0022-3476(97)70046-5. PMID: 9427903

Vitamin A status of patients presenting with pulmonary tuberculosis and asymptomatic HIV-infected individuals, Dar es Salaam, Tanzania.

Serum vitamin A was determined in a cross-sectional study of 100 HIV-positive and -negative tuberculosis patients and 144 blood donors. Tuberculosis patients were seen again after 2 months of treatment. Mean vitamin A was lowest among tuberculosis patients co-infected with HIV, and was lower among HIV-positive than HIV-negative blood donors. Mean vitamin A rose significantly at 2 months in HIV-negative patients, and not in HIV-positive patients. HIV infection was the strongest predictor of low vitamin A. Vitamin A deficiency is common in tuberculosis and HIV infection, particularly in those patients who are dually infected, and nutritional supplementation may be beneficial.

Mugusi FM, et al. Int J Tuberc Lung Dis. 2003 Aug;7(8):804-7. PMID: 12921158

Vitamin A levels in sputum-positive pulmonary tuberculosis patients in comparison with household contacts and healthy 'normals'.

OBJECTIVE: To estimate serum vitamin A in pulmonary tuberculosis (PTB) patients at the start and end of anti-tuberculosis treatment.

DESIGN: Serum vitamin A was estimated in 47 PTB patients (pre and post treatment), 46 healthy household contacts and 30 healthy 'normals'.

RESULTS: Mean serum vitamin A in patients at the start of treatment was 21.2 microg/dl, which was significantly lower than in household contacts (42.2 microg/dl) and healthy 'normals' (48.1 microg/dl). The vitamin A levels in patients increased following treatment.

CONCLUSION: **The low vitamin A levels observed in patients returned to normal at the end of anti-tuberculosis treatment without vitamin A supplementation.**

Rama Chandran G, et al. Int J Tuberc Lung Dis. 2004 Sep;8(9):1130-3. PMID: 15455600

Vitamin A deficiency and other factors associated with severe tuberculosis in Timor and Rote Islands, East Nusa Tenggara Province, Indonesia.

BACKGROUND: Plasma zinc and vitamin A concentrations have been reported to be low in tuberculosis (TB) patients in some studies, although it is not clear whether this constitutes a risk for a more severe clinical presentation among TB patients. The acute phase reaction may also deplete zinc and vitamin A in the plasma. Therefore, we further studied these associations.

METHODS: We carried out a cross-sectional study among newly diagnosed sputum smear-positive TB patients in East Nusa Tenggara. The patients were categorized as either mild TB when Karnofsky Score (KS) > or =80 or severe TB (KS <80).

Body mass index (BMI), mid upper arm circumference (MUAC), chest radiograph, and the results of hemoglobin, erythrocyte sedimentation rate, albumin, C-reactive protein (CRP), zinc and vitamin A in plasma were correlated with TB category.

RESULTS: A total of 300 TB patients participated in the study (63% male and 37% female), and were categorized as mild TB (53%) or severe TB (47%). **Vitamin A, hemoglobin and plasma albumin were significantly lower, and CRP was significantly higher, in severe TB than in mild TB**, and the active lesion area on the chest radiograph was greater among severe TB patients. In a multiple regression analysis, after adjustment for CRP, **low vitamin A (beta=3.2, 95%CI (confidence interval) 1.6-4.9, P=0.000) but not zinc, correlated with the severity of TB. MUAC was better than BMI as a predictor of TB severity (beta=1.3, 95%CI 0.6-6.2, P=0.000).**

CONCLUSIONS: Severe TB was associated with vitamin A deficiency. MUAC can be used as a measure of TB severity.

Pakasi TA, et al. Eur J Clin Nutr 2009 Sep;63(9):1130-5. doi: 10.1038/ejn.2009.25. PMID: 19471295

D. VITAMIN D

Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis

Objective: To explore the association between low serum vitamin D and risk of active tuberculosis in humans.

Systematic review and meta-analysis.

Observational studies published between 1980 and July 2006 (identified through Medline) that examined the association between low serum vitamin D and risk of active tuberculosis.

For the review, seven papers were eligible from 151 identified in the search. The pooled effect size in random effects meta-analysis was 0.68 with 95% CI 0.43–0.93. This 'medium to large' effect represents a probability of 70% that a healthy individual would have higher serum vitamin D level than an individual with tuberculosis if both were chosen at random from a population. There was little heterogeneity between the studies.

Low serum vitamin D levels are associated with higher risk of active tuberculosis. Although more prospectively designed studies are needed to firmly establish the direction of this association, it is more likely that low body vitamin D levels increase the risk of active tuberculosis. In view of this, the potential role of vitamin D supplementation in people with tuberculosis and hypovitaminosis D-associated conditions like chronic kidney disease should be evaluated.

Kelechi E Nnoaham, et al. International Journal of Epidemiology 2008;37:113–119. doi:10.1093/ije/dym247

Vitamin D deficiencies among tuberculosis patients in Africa: A systematic review.

The aim of this study was to explore the existence of vitamin D deficiency (VDD) in tuberculosis (TB) patients living in Africa and to identify its predictor variables. PRISMA guidelines and checklists were used. The sources of the data were Medline/PubMed, Web of Science, Scopus, and Google Scholar databases. We identified 23 articles, of which 15 reported the status of vitamin D in TB with TB. The definition of serum vitamin D status was summarized as severe, deficient, and insufficient when the concentration of 25-hydroxyvitamin (OH)-D ≤ 25 , ≤ 50 , and ≤ 75 nmol/L, respectively. The reports showed that **up to 88.9% and 96.3% of patients with TB tested by radioimmunoassay had VDD and vitamin D insufficiency, respectively.** Statistically significant variables such as lack of sun exposure, inadequate dietary intake, season, clothing, comorbidities, low body mass index, age, skin pigmentation, use of antiretroviral therapy and anti-TB drugs, and socioeconomic status were identified as the main predictor variables of vitamin D status. VDD and vitamin D insufficiency were highly prevalent in TB patients in Africa. Further case-control studies are warranted to clarify the cause-effect relationship between vitamin D and TB and thereby, design valuable strategies to manage VDD among TB patients in Africa.

Keflie TS, et al. Nutrition. 2015 Oct;31(10):1204-12. doi: 10.1016/j.nut.2015.05.003. PMID: 26333888

Vitamin D deficiency in Malawian adults with pulmonary tuberculosis: risk factors and treatment outcomes.

SETTING: Vitamin D deficiency is common in African adults with tuberculosis (TB), and may be exacerbated by the metabolic effects of anti-tuberculosis drugs and antiretroviral therapy (ART). It is unclear whether vitamin D deficiency influences response to anti-tuberculosis treatment.

OBJECTIVES: To describe risk factors for baseline vitamin D deficiency in Malawian adults with pulmonary TB, assess the relationship between serum 25-hydroxy vitamin D (25[OH]D) concentration and treatment response, and evaluate whether the administration of anti-tuberculosis drugs and ART is deleterious to vitamin D status during treatment.

DESIGN: A prospective longitudinal cohort study.

RESULTS: The median baseline 25(OH)D concentration of the 169 patients (58% human immunodeficiency virus [HIV] infected) recruited was 57 nmol/l; 47 (28%) had vitamin D deficiency (<50 nmol/l). Baseline 25(OH)D concentrations were lower during the cold season ($P < 0.001$), with food insecurity ($P = 0.034$) or in patients who consumed alcohol ($P = 0.019$). [No relationship between vitamin D status and anti-tuberculosis treatment response was found. 25\(OH\)D concentrations increased during anti-tuberculosis treatment, irrespective of HIV status or use of ART.](#)

CONCLUSIONS: Vitamin D deficiency is common among TB patients in Malawi, but this does not influence treatment response. Adverse metabolic effects of drug treatment may be compensated by the positive impact of clinical recovery preventing exacerbation of vitamin D deficiency during anti-tuberculosis treatment.

Sloan DJ, et al. Int J Tuberc Lung Dis. 2015 Aug;19(8):904-11. doi: 10.5588/ijtld.15.0071.

Vitamin D and tuberculosis: review and association in three rural provinces of Afghanistan.

OBJECTIVES: 1) To update the 2006 systematic review and meta-analysis by Nnoaham & Clarke exploring the association between serum vitamin D and risk of active tuberculosis (TB) following discrepant evidence; and 2) to identify whether TB and vitamin D are associated in rural Afghanistan.

METHODS: Systematic review and meta-analysis of studies published between January 1980 and June 2014 using Nnoaham & Clarke's methodology. For this case-control study, 90 age- and sex-matched pairs were recruited from rural provinces, and blood 25-hydroxyvitamin D concentrations were measured using enzyme-linked immunosorbent assay.

RESULTS: Sixteen studies were eligible for review. [Eleven showed differences between vitamin D levels in TB patients and controls, two showed partial differences and three showed none. Studies on African and European populations show lower vitamin D levels in TB patients, but results from Asia vary. No significant differences were found in vitamin D levels in our rural Afghan population.](#) Controls had a higher body mass index (BMI) (mean control BMI 21.50 kg/m², mean case BMI 18.86 kg/m², $P < 0.001$), and were more likely to have been employed (40% of controls, 15.6% of cases, $P = 0.002$).

CONCLUSION: Genetic differences may account for the differences among study results in the systematic review. Vitamin D levels are not associated with TB among Afghans living in these rural provinces.

Sarin P, et al. Int J Tuberc Lung Dis. 2016 Mar;20(3):383-8. doi: 10.5588/ijtld.15.0303. PMID: 27046721

Vitamin D Levels in Active TB, Latent TB, Non-TB Pneumonia and Healthy Children: A Prospective Observational Study

BACKGROUND: Growing evidence suggests that vitamin D deficiency might be implicated in the development of active tuberculosis (TB). We evaluated vitamin D levels in children with active TB compared to children with latent TB infection (LTBI), non-TB pneumonia (NTPB) and healthy controls to determine if there was a difference.

METHODS: In this prospective study, vitamin D levels were measured and compared between the four groups and adjusted for age, ethnicity, gender and season of sample collection.

RESULTS: Fifty-seven children were included: 24.6% active TB, 28.1% LTBI, 22.8% NPTB and 24.6% healthy controls. 36.8% of all children tested had an insufficient or deficient vitamin D level. Vitamin D level was significantly lower in active TB compared to other groups ($p = 0.004$).

CONCLUSIONS: Our study showed a correlation between hypovitaminosis D and active pulmonary TB.

Buonsenso D, et al. Fetal Pediatr Pathol. 2018 Oct;37(5):337-347. doi: 10.1080/15513815.2018.1509407. PMID: 30260729

Serum vitamin D levels and risk of prevalent tuberculosis, incident tuberculosis and tuberculin skin test conversion among prisoners.

Poor vitamin D status has been associated with tuberculosis (TB); whether poor status is cause or consequence of disease is uncertain. We conducted a case-control study and two nested case-control studies to determine whether vitamin D levels were associated with active TB, tuberculin skin test (TST) conversion, and risk of progression to the active TB in prisoners in Brazil. In multivariable conditional logistic regression, subnormal vitamin D levels (OR, 3.77; 95% CI, 1.04-13.64) were more likely in prisoners with active TB. In contrast, vitamin D was not found to be a risk factor for either TST conversion (OR, 2.49; 95% CI, 0.64-9.66) or progression to active disease (OR, 0.59; 95% CI, 0.13-2.62). Black race (OR, 11.52; 95% CI, 2.01-63.36), less

than 4 years of schooling (OR, 2.70; 95% CI, 0.90-8.16), cigarette smoking (OR, 0.23; 95% CI, 0.06-0.79) were identified as risk factors for TST conversion. Risk of progression to active TB was found to be associated with cigarette smoking (OR, 7.42; 95% CI, 1.23-44.70). Our findings in the prison population show that poor vitamin D status is more common in individuals with active TB, but is not a risk factor for acquisition of latent TB or progression to active TB.

Maceda EB, et al. Sci Rep. 2018 Jan 17;8(1):997. doi: 10.1038/s41598-018-19589-3. PMID: 29343733

The association between vitamin D status and tuberculosis in children: A meta-analysis.

BACKGROUND: Vitamin D deficiency (VDD) has been implicated in the pathogenesis of tuberculosis (TB), but most studies have not reported a significant association. We conducted a meta-analysis to explore the association between vitamin D status and TB in children.

METHODS: Web of Science, Ovid Medline, and EMBASE were searched for studies in English that discussed vitamin D status and TB in children before January 22, 2018.

RESULTS: From the 585 initially identified studies, we selected those that addressed an association between vitamin D status and TB according to our preselected inclusion criteria. **Our meta-analysis included 10 studies. According to the random effects model, TB was significantly associated with VDD (ORs, 1.70; 95% CI, 1.20-2.42; P<.05) in children. Vitamin D levels were significantly lower in TB patients than in controls, with a mean difference $d = -5.49$ nmol/L (95% CI, -10.42 to -0.55; P<.05), indicating that VDD was significantly associated with TB (OR, 1.78; 95% CI, 1.30-2.44; P<.05) in children.**

CONCLUSION: This study suggests that vitamin D levels are significantly lower in children with TB/latent TB infection than in controls. TB may contribute to VDD in children. Therefore, VDD may be associated with TB in children.

Gou X, et al. Medicine (Baltimore). 2018 Aug;97(35):e12179. doi: 10.1097/MD.00000000000012179. PMID: 30170465

Status of vitamin D and the associated host factors in pulmonary tuberculosis patients and their household contacts: A cross sectional study

Innate immunity plays an important role in pathophysiology of tuberculosis which is influenced by various host factors. One such factor is vitamin D which, along with its associated molecule, can alter the host defense against Mycobacterium Tuberculosis (M.Tb.) via altered production of cathelicidin and nitric oxide, both having bactericidal effect. Therefore, assessment of vitamin D and its associated molecules in tuberculosis patients and household contacts as compared to healthy controls were done and the implication of these findings in susceptibility to tuberculosis (TB) was studied. 80 active TB patients, 75 household contacts and 70 healthy controls were included. Vitamin D receptor (VDR), vitamin D binding protein (VDBP) and inducible nitric oxide synthase (iNOS) mRNA levels were studied using quantitative PCR. Serum VDR, cathelicidin, and iNOS levels were measured using ELISA. Vitamin D and NO levels were measured in serum using chemiluminescence based immunoassay and greiss reaction based colorimetry kit respectively. **Decreased serum levels of vitamin D were observed in active TB patients as compared to healthy controls ($p < 0.001$). VDR and iNOS mRNA levels were found to be significantly lower in active TB patients compared to household contacts and healthy controls ($p < 0.0001$ and 0.005 respectively). VDBP mRNA expression was found to be lower in active TB group as compared to household contacts and healthy controls however the difference was not found to be significant ($p > 0.21$). Although, mRNA expression of VDR, VDR protein and iNOS along with vitamin D levels were significantly ($p < 0.05$) higher in household contacts compared to active TB group. However, levels of iNOS, NO and cathelicidin were found to be higher in TB patients as compared to household contacts and healthy controls ($p < 0.01$, 0.05 and 0.01 respectively). Higher levels of Vitamin D along with VDR and iNOS expression in household contacts as compared to active TB patients suggest vitamin D might have a protective role against TB plausibly decreasing disease susceptibility. Low vitamin D levels in active TB patients warrants further studies to determine the role of vitamin D supplementation in prevention and treatment of TB.**

Panda S, et al. J Steroid Biochem Mol Biol. 2019 Oct;193:105419. doi: 10.1016/j.jsbmb.2019.105419. PMID: 31255688

Risk factors for active tuberculosis in 938 QuantiFERON-positive schoolchildren in Mongolia: a community-based cross-sectional study.

BACKGROUND: There is controversy regarding the relative influence of 'exogenous' versus 'endogenous' factors on the risk of progression from latent tuberculosis infection to active tuberculosis (TB) disease in children.

METHODS: We conducted a **cross-sectional analysis** to identify risk factors for active tuberculosis in QuantiFERON®-TB Gold (QFT-G)-positive children aged 6-13 years attending 18 schools in Ulaanbaatar, Mongolia. Children underwent clinical and radiological screening for active tuberculosis, and data relating to potential risk factors for disease progression were collected by questionnaire and determination of serum 25-hydroxyvitamin D (25[OH]D) concentrations. Risk ratios were calculated using generalized estimating equations with adjustment for potential confounders.

RESULTS: 129/938 (13.8%) QFT-positive children were diagnosed with active tuberculosis. Risk of active tuberculosis was independently associated with household exposure to pulmonary TB (adjusted risk ratio [aRR] 2.40, 95% CI 1.74 to 3.30, $P < 0.001$), month of sampling (adjusted risk ratio [aRR] for March-May vs. June-November 3.31, 95% CI 1.63 to 6.74, $P < 0.001$; aRR for December-February vs. June-November 2.53, 95% CI 1.23 to 5.19, $P = 0.01$) and active smoking by the child (aRR 5.23, 95% CI 2.70 to 10.12, $P < 0.001$). No statistically significant independent association was seen for age, sex, socio-economic factors, presence of a Bacillus Calmette-Guérin (BCG) scar, tobacco exposure or vitamin D status.

CONCLUSIONS: Household exposure to active TB, winter or spring season and active smoking were independently associated with risk of active tuberculosis in QFT-positive children. Our findings highlight the potentially high yield of screening child household contacts of infectious index cases for active tuberculosis in low- and middle-income countries.

Ganmaa D, et al. BMC Infect Dis. 2019 Jun 17;19(1):532. doi: 10.1186/s12879-019-4160-7. PMID: 31208362

E. VITAMINS A+D; A+E

Low plasma levels of cholecalciferol and 13-cis-retinoic acid in tuberculosis: implications in host-based chemotherapy.

OBJECTIVE: The aim of this study was to estimate the concentration of cholecalciferol and 13-cis-retinoic acid (RA) in the plasma and pleural fluid of patients with tuberculosis (TB) against controls.

METHODS: Plasma levels of cholecalciferol and 13-cis-RA were measured in 22 patients with TB and healthy controls and their pleural fluids levels were measured in 6 TB patients and diseased controls by established high-performance liquid chromatography-based procedure.

RESULTS: Cholecalciferol levels in plasma and pleural fluid of patients with TB and healthy controls were 67.45 (10.71) nmol/L and 21.40 (8.58) nmol/L compared with 117.43 (18.40) nmol/L ($P < 0.001$) and 94.73 (33.34) nmol/L ($P = 0.0049$), respectively. 13-cis-RA level in the plasma of patients with TB and healthy controls were 1.51 (0.72) nmol/L and 6.67 (0.81) nmol/L ($P < 0.001$), respectively. 13-cis-RA was not detectable in pleural fluid. The levels of both the agents were lower in patients with TB than in controls.

CONCLUSION: It was observed that in patients with TB there is a combined deficiency of cholecalciferol and 13-cis-RA compared with healthy volunteers. Because cholecalciferol and 13-cis-RA are in equilibrium with active ingredients of vitamins A and D, we feel that there is a combined deficiency of these vitamins in patients with TB. There is an evidence that concomitant vitamin A and D supplementation can kill intracellular Mycobacterium tuberculosis in vitro. Therefore, the observations made in this study can pave the path for a trial of combined supplementation of available formulations of vitamin A and D (cholecalciferol and 13-cis-RA) for novel anti-tubercular drug therapy. Because such an approach is host-based it has potential to treat even multidrug-resistant and extensively drug-resistant forms of TB.

Srinivasan, et al. Nutrition. 2013 Oct;29(10):1245-51. doi: 10.1016/j.nut.2013.03.018. PMID: 23880094

Vitamin A, vitamin E and beta-carotene nutritional status and antioxidase level analysis among tuberculosis patients [Article in Chinese]

OBJECTIVE: To investigate vitamin A (VA), vitamin E (VE) and beta-carotene nutritional status and antioxidase level among tuberculosis patients.

METHODS: Totally 70 tuberculosis patients were randomly selected as the experiment group from Tancheng Tuberculosis Control in 2010. And 70 matched normal persons were selected as the control group. Metrics included body mass index (BMI), hemoglobin (Hb), triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL), superoxide dismutase (SOD), catalase (CAT), VA, VE and beta-carotene.

RESULTS:

- BMI of the experiment group was 19.13, lower than the control group which was 21.95 ($P < 0.05$);
- For blood lipid level, TG, TC, HDL of the experiment group were 1.54, 4.47 and 1.21 mmol/L respectively; significantly lower than the control group which were 1.63, 5.20, 1.30 mmol/L respectively ($P < 0.05$);
- Antioxidase level contrast between two groups showed that SOD and CAT of the experiment group were 78.20 and 5.24 U/ml respectively, significantly lower than the corresponding indexes of the control group were 83.27 and 9.99 U/ml respectively ($P < 0.05$);
- VA, VE of the experiment group were 0.256 and 1.148 microg/ml respectively which were lower than the control group which were 0.385 and 1.182 microg/ml ($P < 0.05$);

CONCLUSION: Nutritional status among the tuberculosis patients is quite poor, especially antioxidase and VA, VE and beta-carotene level are significantly lower than normal people.

Dou Y, et al. Wei Sheng Yan Jiu. 2013 May;42(3):364-8. PMID: 23805508

F. MINERALS

Status of Serum Zinc in Multidrug Resistant Tuberculosis.

Zinc deficiency affects host defense by reducing the number of circulating T cells and phagocytosis activity of other cells which ultimately impair cell mediated immunity. The present study was carried out to estimate serum zinc level in newly detected multidrug resistant tuberculosis (MDR-TB) in adult population. In this study total fifty (50) MDR-TB patients were enrolled conveniently from the in-patients departments of National Institute of Diseases of the Chest Hospital (NIDCH), Bangladesh. Serum zinc was estimated by atomic absorption spectrophotometry method from early morning fasting blood sample. Serum zinc level was assessed according to normal cut-off value 70-120 µgm/dl and 76% studied population were found lower than this value. The mean±SD serum zinc level was observed 60.40±8.91 µgm/dl. No associations were found between serum zinc level with age (p=0.11) and with sex (p=0.085) of the study population respectively. The low level of serum zinc in MDR-TB patients suggested impaired immune status of our study population.

Barman N, et al. Mymensingh Med J. 2016 Jan;25(1):27-30. PMID: 26931245

Assessments of serum copper and zinc concentration, and the Cu/Zn ratio determination in patients with multidrug-resistant pulmonary tuberculosis (MDR-TB) in Côte d'Ivoire.

BACKGROUND: The principal aim of this study was to evaluate the serum concentration of some trace element and determine the Cu / Zn ratio in patients with MDR-TB before and after second line treatment of TB.

METHODS: Blood samples were obtained from 100 MDR-TB patients after confirmation of their diagnosis. The level of zinc and copper were determined using flame air / acetylene atomic absorption spectrometer.

RESULTS: A significant decrease in zinc levels (P <0.05) and an increased Cu / Zn ratio (P <0.05) was observed in MDR-TB patients compared to controls TB free. During treatment a significant reduction in Cu / Zn ratio (P <0.05) was observed compared to the initial result.

CONCLUSIONS: The decrease in serum zinc level and the high Cu / Zn ratio could explain the immune system dysfunction and the high level of oxidative stress in patients with MDR-TB.

Bahi GA, et al. BMC Infect Dis. 2017 Apr 11;17(1):257. doi: 10.1186/s12879-017-2343-7. PMID: 28399817

Changes in serum level of trace elements in pulmonary tuberculosis patients during anti-tuberculosis treatment.

INTRODUCTIONS: In this study, trace elements concentrations and their alterations were determined in TB patients during anti-tuberculosis treatment period.

MATERIALS AND METHODS: We have collected blood samples from a total of 180 TB patients with pulmonary Tuberculosis, and 180 healthy controls in Sistan, Iran. The serum iron, copper, lead, calcium, arsenic and selenium concentrations were detected at the beginning of anti-TB chemotherapy, at the end of 2nd, 4th and 6th month after treatment initiation. Data were then analyzed using SPSS version 20.

RESULTS AND DISCUSSIONS: Although Ca, Pb, and As levels did not change during the treatment period, serum concentrations of Fe, Zn, Cu, and Se were diminished in TB patients significantly during treatment in comparison with controls (P < 0.001). We also found that there was a significant difference in the Cu/Se and Cu/Zn ratios in tuberculosis patients in comparison with healthy individuals (P < 0.001).

CONCLUSIONS: Trace elements serum concentrations are affected by TB infection and anti-TB therapy. Their serum levels were strongly perturbed during infection as well as anti-TB treatment.

Sepehri Z, et al. J Trace Elem Med Biol. 2018 Dec;50:161-166. doi: 10.1016/j.jtemb.2018.06.024. PMID: 30262275

Serum Zinc Concentrations in Patients with Pulmonary Tuberculosis.

This analytical case control study was conducted in the Department of Internal Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh to see the association of serum zinc concentrations with pulmonary tuberculosis (PTB) in adult population (18-60 years) from January 2015 to January 2016. Freshly diagnosed PTB patients before initiating anti-TB chemotherapy as cases (N=43) and TB negative subjects as controls (N=48) were included conveniently in this study with a rigid selection criteria. Serum zinc concentrations were estimated by using atomic absorption spectrophotometer. The mean±SD age and BMI of the case group and control group were 33.30±14.71 and 32.69±11.60 years, 19.88±2.31 and

22.08±2.80 kg/m² respectively. The concentrations of serum zinc were significantly lower (P=0.01) in PTB group (840.9±230.0 µgm/l) compared with the control group (965.6±219.9 µgm/l). There was marked variation of mean±SD serum zinc concentrations between male (1008.95±246.16 µgm/l) and female (937.24±200.35 µgm/l) in control group (P=0.182) though the variation is minimal in PTB group (P=0.724). The serum zinc concentrations showed positive correlation with BMI (P=0.642) but negative correlation with age (P=0.023) in both case and control. The lower serum zinc concentrations (12.06%) in PTB patients indicate relative immune deficiency.

Mazumder MK, et al. Mymensingh Med J. 2018 Jul;27(3):536-543. PMID: 30141443

Serum selenium levels in tuberculosis patients: A systematic review and meta-analysis.

INTRODUCTION: not clear whether selenium supplementation could improve the treatment outcomes in TB patients. We conducted a systematic review and meta-analysis to update existing evidence about selenium levels in TB patients.

METHODS: In this systematic review and meta-analysis, EMBASE, Medline and the International Journal of Tuberculosis and Lung Disease were searched to identify observational studies on selenium and TB published up until April 2018. Studies comparing blood selenium levels in TB patients to controls were included. Data extraction was performed by two investigators. The quality of the studies was assessed using the Newcastle-Ottawa Quality Assessment Scale. Random effects analysis was performed to calculate the pooled effect size and 95% confidence interval (CI).

RESULTS: Of the 605 studies initially identified, only six were eligible. Of them, four were carried out in Asia, and one each in Africa and South America. **The random pooled effect size was 1.6 (CI: 0.9, 2.4) for low levels of selenium among TB patients as compared to individuals without TB. Heterogeneity across the studies was substantial (I²=95.1%).** Potential sources of heterogeneity included study design and selenium measurement methods.

CONCLUSION: Our review provides compelling evidence that serum selenium is lower in TB patients as compared with controls. Therefore, it is advisable to individually assess selenium status in TB patients and decide whether selenium supplement is needed or not.

Muzemba BA, et al. J Trace Elem Med Biol. 2018 Dec;50:257-262. doi: 10.1016/j.jtemb.2018.07.008. PMID: 30262288

G. OXIDATIVE STRESS AND ANTIOXIDANTS

Lipid peroxidation, vitamins C, E and reduced glutathione levels in patients with pulmonary tuberculosis.

The present study examined the relationship between lipid peroxidation and vitamin C, vitamin E and reduced glutathione levels in plasma, erythrocytes and erythrocyte membranes of pulmonary tuberculosis patients and an equal number of age- and sex-matched healthy subjects.

Enhanced plasma, erythrocytes and erythrocyte membrane lipid peroxidation with concomitant decline in vitamin C, vitamin E and reduced glutathione levels were found in pulmonary tuberculosis patients.

The elevated lipid peroxidation and decreased vitamin C, vitamin E and reduced glutathione levels indicate the potential of oxidative damage to erythrocytes and erythrocyte membranes of pulmonary tuberculosis patients.

Vijayamalini M, Manoharan S. Cell Biochem Funct. 2004 Jan-Feb;22(1):19-22. doi: 10.1002/cbf.1039.

Evaluation of lipid peroxidation product, nitrite and antioxidant levels in newly diagnosed and two months follow-up patients with pulmonary tuberculosis

This case-control study followed by a longitudinal cohort study was undertaken to evaluate the level of lipid peroxidation product malondialdehyde (MDA) and nitrite as an indirect measurement of nitric oxide vis-à-vis the levels of antioxidants vitamin C and vitamin E in pulmonary tuberculosis.

Fifty-six sputum smear-positive cases of pulmonary tuberculosis based on Ziehl-Neelsen (ZN) staining and 50 healthy controls without any systemic disease were included in this study. Thirty-five cases were longitudinally followed up with standard antituberculosis chemotherapy (ATT) for two months. Serum levels of malondialdehyde (MDA), nitrite, and plasma levels of vitamins C and E were measured.

The **mean serum MDA level was significantly higher** (8.1 +/- 1.61 nmoles/ml) in PTB patients before commencement of ATT as compared to healthy controls (3.45 +/- 1.7 nmoles/ml) (p=0.0001) and decreased significantly after 2 months of ATT (3.84 +/- 1.28 nmoles/ml) (p=0.0001). The **mean serum nitrite level** (47.19 +/- 18.44 micromol/l) **was significantly elevated** before ATT compared to healthy controls (32.89 +/- 11.94 micromoles/l) and decreased significantly after 2 months of ATT (27.71 +/- 11.97 micromoles/l) (p=0.0001). The **mean plasma levels of vitamins C** (0.88 +/- 0.33 mg/dl) **and E** (0.79 +/- 0.24 mg/dl) in PTB patients before commencement of ATT **were lower than healthy controls** (1.42 +/- 0.38 mg/dl) and (1.35 +/- 0.35 mg/dl), respectively (p=0.001). There was a significant increase in vitamin C levels after 2 months of ATT (1.19 +/-

0.40 mg/dl) compared to before ATT (0.83 +/- 0.31 mg/dl) ($p=0.0001$), but no significant change in mean plasma vitamin E level before and after 2 months on ATT was found.

Elevated malondialdehyde and nitrite levels with concomitant depressed vitamin C and E levels are indicative of lipid peroxidation and oxidative stress. The decrease in levels of malondialdehyde and nitrite with subsequent increase in vitamin C levels after two months of follow-up indicate a good response to treatment with standard ATT.

Lamsal M, et al. *Southeast Asian J Trop Med Public Health*. 2007 Jul;38(4):695-703.

Influence of antimicrobial chemotherapy and smoking status on the plasma concentrations of vitamin C, vitamin E, beta-carotene, acute phase reactants, iron and lipid peroxides in patients with pulmonary tuberculosis

SETTING: Inflammation-related oxidative stress has been implicated in the pathogenesis of lung fibrosis and dysfunction in patients with pulmonary tuberculosis.

OBJECTIVE: To investigate the effects of antimicrobial chemotherapy and smoking status on the plasma concentrations of the anti-oxidative nutrients vitamin C, vitamin E and beta-carotene, as well as those of iron, lipid peroxides and the acute phase reactants C-reactive protein (CRP) and ferritin.

DESIGN: A total of 41 patients with active pulmonary tuberculosis were studied at the outset and after 6 months of antimicrobial chemotherapy.

RESULTS: Initial plasma concentrations of vitamin C and beta-carotene were low, returning to normal after chemotherapy in the non-smokers, but not in the smokers, while those of vitamin E remained low throughout in both groups.

Ferritin and CRP concentrations decreased significantly following chemotherapy, with the former higher in smokers than in non-smokers. Serum lipid peroxides were elevated in patients with pulmonary tuberculosis and were unaffected by chemotherapy or smoking habits, while iron levels were not significantly affected by chemotherapy. Although residual dysfunction and infiltration were evident, pulmonary function (FEV1) and radiographic score improved equally in both smokers and non-smokers following antimicrobial chemotherapy.

CONCLUSIONS: Even after 6 months of apparently successful antimicrobial chemotherapy, pulmonary tuberculosis is associated with increased oxidative stress, which is unrelated to cigarette smoking and characterized by increased levels of circulating lipid peroxides and low concentrations of plasma vitamin E.

Plit ML, et al. *Int J Tuberc Lung Dis*. 1998 Jul;2(7):590-6. PMID: 9661828

Relation of leptin, ghrelin and inflammatory cytokines with body mass index in pulmonary tuberculosis patients with and without type 2 diabetes mellitus

Background: Pulmonary tuberculosis (TB) patients often suffer from anorexia and poor nutrition, causing weight loss. The peptide hormones leptin and its counterpart ghrelin, acting in the regulation of food intake and fat utilization, play an important role in nutritional balance. This study aimed to investigate the association of blood concentrations of leptin, ghrelin and inflammatory cytokines with body mass index (BMI) in TB patients with and without type 2 diabetes mellitus (T2DM). Methods: BMI, biochemical parameters and plasma levels of leptin, ghrelin and inflammatory cytokines were measured before the start of treatment in 27 incident TB patients with T2DM, 21 TB patients and 23 healthy subjects enrolled in this study.

Results: The levels of leptin were significantly higher in TB patients (35.2 ± 19.1 ng/ml) than TB+T2DM (12.6 ± 6.1 ng/ml) and control (16.1 ± 11.1 ng/ml) groups. The level of ghrelin was significantly lower in TB (119.9 ± 46.1 pg/ml) and non-significantly lower in TB+T2DM (127.7 ± 38.6 pg/ml) groups than control (191.6 ± 86.5 pg/ml) group. The levels of TNF- α were higher, while IFN- γ and IL-6 levels were lower in patients than in the control group. Leptin showed a negative correlation with BMI in TB ($r=-0.622$, $p<0.05$) and TB+T2DM ($r=-0.654$, $p<0.05$) groups, but a positive correlation with BMI in the control group ($r=0.521$, $p<0.05$). Contrary ghrelin showed a positive correlation with BMI in TB ($r=0.695$, $p<0.05$) and TB+T2DM ($r=0.199$, $p>0.05$) groups, but negative correlation with BMI in the control ($r=-0.693$, $p<0.05$) group. Inflammatory cytokines were poorly correlated with BMI in this study. Only IFN- γ showed a significant negative correlation with BMI in the control group ($r=-0.545$, $p<0.05$).

Conclusions: This study may suggest that possible abnormalities in ghrelin and leptin regulation (high levels of leptin and low levels of ghrelin) may be associated with low BMI and may account for the poor nutrition associated with TB and TB+T2DM.

Zheng Y, et al. *PLoS One*. 2013 Nov 8;8(11):e80122. doi: 10.1371/journal.pone.0080122. PMID: 24260344

III. EFFECT OF NUTRITIONAL STATUS ON TREATMENT OUTCOMES

NB: Includes observational studies with sputum conversion as the “outcome”

The impact of nutritional state on the duration of sputum positivity of *Mycobacterium tuberculosis*.

Background: The outcome of anti-tuberculosis treatment varies according to patient factors.

Objective: To retrospectively identify risks related to the extension of time to negative sputum culture (Tn) and to determine their clinical significance.

Design: Patients with bacilli susceptible to isoniazid and rifampicin who received initial standard treatment without cessation were recruited into the study. **A total of 630 consecutive in-patients were included in the risk development analysis (development cohort) and another 611 consecutive in-patients in the risk validation analysis (validation cohort).**

Results: Univariate analysis showed that Tn was related to sex, body mass index (BMI), white blood cell count (WBC), serum albumin, fasting blood sugar, haemoglobin A1c, C-reactive protein and total cholesterol levels and sputum smear positivity (SSP). **Multivariate analysis showed that BMI, WBC and SSP were significant risk factors related to extended Tn.** Optimal cut-offs of BMI and WBC for predicting good (Tn < 46 days) and poor responders (Tn ≥ 46 days) according to each risk were determined by receiver operating characteristics analysis. Risks were verified with the validation cohort. Tn increased according to the number of risks; the median Tn for patients with three risks was 21 days longer than that of patients with none.

Conclusion: The nutritional state of a TB patient can be used to predict Tn

Hatsuda K, et al. Int J Tuberc Lung Dis. 2015 Nov;19(11):1369-75. doi: 10.5588/ijtld.14.0963.

Association of Dietary Micronutrient Intake with Pulmonary Tuberculosis Treatment Failure Rate: A Cohort Study

Malnutrition is associated with an increased risk of pulmonary tuberculosis (PTB) treatment failure. Currently, there is no effective adjunctive nutritional therapy. The current objective is to investigate the association of dietary micronutrient intake with PTB treatment outcome. **A cohort study including 1834 PTB patients was conducted in Linyi, China.** The dietary micronutrient intake was assessed through a three-day 24 h dietary recall questionnaire. The treatment outcome was assessed by combinations of sputum smear and computerized tomography results. A multivariate binary regression model was used to assess the associations. The final model was adjusted for potential confounding factors. **A low intake of vitamin C (adjusted OR (95% CI): 1.80 (1.07, 3.04), Ptrend = 0.02) and Zn (adjusted OR (95% CI): 2.52 (1.25, 5.08), Ptrend = 0.02) was associated with a high treatment failure rate. In addition, a low intake of vitamin C and Mn was associated with a severe tuberculosis symptom, as indicated by a high TB score.** Previous meta-analysis of randomized controlled trials (RCTs) reported a null effect of Zn supplementation on PTB treatment. The effect of vitamin C supplementation should be investigated by RCTs.

Ke Xiong, et al. Nutrients. 2020 Aug 19;12(9):2491. doi: 10.3390/nu12092491. PMID: 32824912

Polymorphisms in the vitamin D receptor gene are associated with reduced rate of sputum culture conversion in multidrug-resistant tuberculosis patients in South Africa

BACKGROUND: Vitamin D modulates the inflammatory and immune response to tuberculosis (TB) and also mediates the induction of the antimicrobial peptide cathelicidin. Deficiency of 25-hydroxyvitamin D and single nucleotide polymorphisms (SNPs) in the vitamin D receptor (VDR) gene may increase the risk of TB disease and decrease culture conversion rates in drug susceptible TB. We aimed to determine if SNPs in the VDR gene were associated with sputum culture conversion among a cohort of MDR TB patients in South Africa.

METHODS: We conducted a prospective cohort study of adult MDR TB patients receiving second-line TB treatment in KwaZulu-Natal province. Subjects had monthly sputum cultures performed. In a subset of participants, whole blood samples were obtained for genomic analyses. Genomic DNA was extracted and genotyped with Affymetrix Axiom Pan-African Array. Cox models were used to determine the association between VDR SNPs and rate of culture conversion.

RESULTS: Genomic analyses were performed on 91 MDR TB subjects enrolled in the sub-study; 60% were female and median age was 35 years (interquartile range [IQR] 29-42). Smoking was reported by 21% of subjects and most subjects had HIV (80%), were smear negative (57%), and had cavitory disease (55%). **Overall, 87 (96%) subjects initially converted cultures to negative, with median time to culture conversion of 57 days (IQR 17-114).** Of 121 VDR SNPs examined, 10 were significantly associated ($p < 0.01$) with rate of sputum conversion in multivariable analyses. Each additional risk allele on SNP rs74085240 delayed culture conversion significantly (adjusted hazard ratio 0.30, 95% confidence interval 0.14-0.67).

CONCLUSIONS: Polymorphisms in the VDR gene were associated with rate of sputum culture conversion in MDR TB patients in this high HIV prevalence setting in South Africa.

Association of serum levels of iron, copper, and zinc, and inflammatory markers with bacteriological sputum conversion during tuberculosis treatment.

The present study aimed to evaluate the association between serum levels of iron, copper, and zinc, inflammatory markers, and the smear and culture conversion of *M. tuberculosis* during 60 days of tuberculosis treatment. *Seventy-five male patients with pulmonary tuberculosis* (mean age, 40.0 ± 10.7 years) were evaluated at baseline and again at 30 and 60 days of tuberculosis treatment. Serum levels of iron, copper, zinc, albumin, globulin, C-reactive protein, and hemoglobin, and smear and cultures for *M. tuberculosis* in sputum samples were analyzed. Compared to healthy subjects, at baseline, *patients with PTB had lower serum iron levels, higher copper levels and copper/zinc ratio, and similar zinc levels. During the tuberculosis treatment, no significant changes in the serum levels of iron, zinc, and copper/zinc were observed. Lower serum copper levels were associated with bacteriological conversion in tuberculosis treatment (tuberculosis-negative) at 30 days but not at 60 days (tuberculosis-positive). C-reactive protein levels and the C-reactive protein/albumin ratio were lower in tuberculosis-negative patients than in tuberculosis-positive patients at 30 and 60 days after treatment. Albumin and hemoglobin levels and the albumin/globulin ratio in patients with pulmonary tuberculosis increased during the study period, regardless of the bacteriological results. High serum globulin levels did not change among pulmonary tuberculosis patients during the study. Serum copper levels and the C-reactive protein/albumin ratio may be important parameters to evaluate the persistence of non-conversion after 60 days of tuberculosis treatment, and they may serve as predictors for relapse after successful treatment.* Moraes ML, et al. *Biol Trace Elem Res*. 2014 Aug;160(2):176-84. doi: 10.1007/s12011-014-0046-0. PMID: 24958018

Association between serum selenium level and conversion of bacteriological tests during antituberculosis treatment.

OBJECTIVE: To determine whether serum selenium levels are associated with the conversion of bacteriological tests in patients diagnosed with active pulmonary tuberculosis after eight weeks of standard treatment.

METHODS: We evaluated *35 healthy male controls and 35 male patients with pulmonary tuberculosis*, the latter being evaluated at baseline, as well as at 30 and 60 days of antituberculosis treatment. For all participants, we measured anthropometric indices, as well as determining serum levels of albumin, C-reactive protein (CRP) and selenium. Because there are no reference values for the Brazilian population, we used the median of the serum selenium level of the controls as the cut-off point. At 30 and 60 days of antituberculosis treatment, we repeated the biochemical tests, as well as collecting sputum for smear microscopy and culture from the patients.

RESULTS: The mean age of the patients was 38.4 ± 11.4 years. Of the 35 patients, 25 (71%) described themselves as alcoholic; 20 (57.0%) were smokers; and 21 (60.0%) and 32 (91.4%) presented with muscle mass depletion as determined by measuring the triceps skinfold thickness and arm muscle area, respectively. Of 24 patients, 12 (39.2%) were classified as moderately or severely emaciated, and 15 (62.5%) had lost > 10% of their body weight by six months before diagnosis. At baseline, the tuberculosis group had lower serum selenium levels than did the control group. The conversion of bacteriological tests was associated with the CRP/albumin ratio and serum selenium levels 60 days after treatment initiation.

CONCLUSIONS: Higher serum selenium levels after 60 days of treatment were associated with the conversion of bacteriological tests in pulmonary tuberculosis patients.

Moraes ML, et al. *J Bras Pneumol*. 2014 May-Jun;40(3):269-78. doi: 10.1590/s1806-37132014000300010. PMID: 25029650

Iron status predicts treatment failure and mortality in tuberculosis patients: a prospective cohort study from Dar es Salaam, Tanzania

Background: Experimental data suggest a role for iron in the course of tuberculosis (TB) infection, but there is limited evidence on the potential effects of iron deficiency or iron overload on the progression of TB disease in humans. The aim of the present analysis was to examine the association of iron status with the risk of TB progression and death.

Methodology/principal findings: We analyzed plasma samples and data collected as part a randomized micronutrient supplementation trial (not including iron) among HIV-infected and HIV-uninfected TB patients in Dar es Salaam, Tanzania. We prospectively related baseline plasma ferritin concentrations from 705 subjects (362 HIV-infected and 343 HIV-uninfected) to the risk of treatment failure at one month after initiation, TB recurrence and death using binomial and Cox regression analyses. Overall, low (plasma ferritin < 30 µg/L) and high (plasma ferritin > 150 µg/L for women and > 200 µg/L for men) iron status were seen in 9% and 48% of patients, respectively. *Compared with normal levels, low plasma ferritin predicted an independent increased risk of treatment failure overall (adjusted RR = 1.95, 95% CI: 1.07 to 3.52) and of TB recurrence among HIV-infected patients (adjusted RR = 4.21, 95% CI: 1.22 to 14.55). High plasma ferritin, independent of C-reactive protein concentrations, was associated with an increased risk of overall mortality (adjusted RR = 3.02, 95% CI: 1.95 to 4.67).*

Conclusions/significance: Both iron deficiency and overload exist in TB patients and may contribute to disease progression and poor clinical outcomes. Strategies to maintain normal iron status in TB patients could be helpful to reduce TB morbidity and mortality.

Sheila Isanaka, et al. PLoS One. 2012;7(5):e37350. doi: 10.1371/journal.pone.0037350. PMID: 22606361

The Prevalence of...Iron Deficiency Anemia in New Cases of Smear-positive Pulmonary Tuberculosis and Their Sputum Conversion Rate at the End of Intensive Tuberculosis Treatment Phase

This study aimed to assess the prevalence of iron deficiency anemia (IDA) in patients with acid-fast bacilli (AFB) sputum smear-positive, and sputum conversion in these two groups of patients with absolute and functional IDA at the end of the second month of anti-TB therapy in Zahedan, Iran.

The results of this study revealed that 91 out of 198 (45.9%) sputum positive pulmonary TB patients were anemic, and among those 72 (79.1%) had iron deficiency anemia. The overall prevalence of IDA in this study was 36.3%. In 72 patients with IDA, 54 (75%) had functional while the remainder had absolute IDA 18 (25%). Twenty-one out of 72 (29.2%) of patients with IDA remained sputum positive and among 126 non IDA patients 47 (37.3%) had positive sputum smear at the end of intensive TB treatment phase ($p=0.278$). Approximately, less than half of patients with tuberculosis had anemia among them 79% had iron deficiency anemia. The frequency of functional IDA was three times more than absolute IDA. [There was no statistically significant difference in sputum conversion between two groups of IDA and non-IDA patients after intensive phase of anti-TB therapy.](#)

Malibeh Metanat, et al. Prague Med Rep. 2020;121(1):35-41. doi: 10.14712/23362936.2020.3. PMID: [32191618](#)

III. NUTRITION IN TREATMENT OF ACTIVE TB

A. Protein

Effects of a food supplement rich in arginine in patients with smear positive pulmonary tuberculosis--a randomised trial

In tuberculosis (TB), the production of nitric oxide (NO) is confirmed but its importance in host defense is debated. Our aim was to **investigate whether a food supplement rich in arginine could enhance clinical improvement in TB patients** by increased NO production. Smear positive TB patients from Gondar, Ethiopia (n = 180) were **randomized to a food supplementation rich in arginine (peanuts, equivalent to 1 g of arginine/day) or with a low arginine content** (wheat crackers, locally called daboqolo) during four weeks. The primary outcome was cure rate according to the WHO classification and secondary outcomes were sputum smear conversion, weight gain, sedimentation rate, reduction of cough and chest X-ray improvement as well as levels of NO in urine (uNO) or exhaled air (eNO) at two months. There was **no effect of the intervention on the primary outcome (OR 1.44, 95% CI: 0.69-3.0, p = 0.39) or secondary outcomes. In the subgroup analysis according to HIV status, peanut supplemented HIV+/TB patients showed increased cure rate (83.8% (31/37) vs 53.1% (17/32), p < 0.01). A low baseline eNO (<10 ppb) in HIV+/TB patients was associated with a decreased cure rate. We conclude that nutritional supplementation with a food supplement rich in arginine did not have any overall clinical effect. In the subgroup of HIV positive TB patients, it significantly increased the cure rate and as an additional finding in this subgroup, low initial levels of NO in exhaled air were associated with a poor clinical outcome but this needs to be confirmed in further studies.**

T Schön, et al. Tuberculosis (Edinb). 2011 Sep;91(5):370-7. doi: 10.1016/j.tube.2011.06.002. Epub 2011 Aug 2. PMID: 21813328

B. Lipids

No reports.

C. Randomized controlled trials and systematic reviews/meta-analyses of diet, food and nutritional supplements

The role of diet in the treatment of pulmonary tuberculosis. An evaluation in a controlled chemotherapy study in home and sanatorium patients in South India.

Historically, a diet rich in calories, proteins, fats, minerals and vitamins was generally considered to be an important, if not essential, factor in the treatment of tuberculosis. Safe & effective, specific anti-TB treatment (ATT) so radically altered the management of the disease that the role of diet has to be reconsidered in the light of the recent advances in treatment. An evaluation of the influence of diet in the treatment of pulmonary tuberculosis with isoniazid plus p-aminosalicylic acid undertaken by the Tuberculosis Chemotherapy Centre, Madras, in the course of a controlled comparison of home and sanatorium chemotherapy (patients from poverty-stricken community in Madras). **During the year of treatment the home patients subsisted on a markedly poorer diet, were physically more active and, on the average, gained less weight than the sanatorium patients. Nevertheless, overall response to treatment in the home series closely approached that in the sanatorium series, although there was a tendency for tubercle bacilli to disappear earlier in the latter. None of the dietary factors studied (calories, carbohydrates, total and animal proteins, fats, minerals and vitamins) appears to influence the attainment of quiescent disease among tuberculous patients treated for one year with an effective combination of antimicrobial drugs, and that initial chemotherapy of patients at home can be successful even if the dietary intake is low throughout the period of treatment.**

Ramkrishnan CV, et al. Bull World Health Organ. 1961;25(3):339-59. PMID: 14490066

Randomized controlled trial of nutritional supplementation in patients with newly diagnosed tuberculosis and wasting

Objective: We assessed the effects of early nutritional intervention on lean mass and physical function in patients with tuberculosis and wasting.

Design: Patients who started antituberculous therapy within the previous 2 wk were randomly assigned to receive standard nutritional counseling (control group) or nutritional counseling to increase their intake through diet and high-energy supplements (nutritional supplement group) for 6 wk. Body composition was measured by dual-energy X-ray absorptiometry, and physical function was assessed by maximum grip strength.

Results: Patients in the nutritional supplement group (n = 19) had a significantly greater increase in body weight (2.57 +/- 1.78 compared with 0.84 +/- 0.89 kg, P = 0.001), total lean mass (1.17 +/- 0.93 compared with 0.04 +/- 1.26 kg, P = 0.006), and grip strength (2.79 +/- 3.11 compared with -0.65 +/- 4.48 kg, P = 0.016) than did the control subjects (n = 17) at week 6. During subsequent follow-up, the increase in body weight remained greater in the nutritional supplement group, but this increase was due mainly to a greater gain in fat mass in the nutritional supplement group than in the control group.

Conclusions: Early intervention to increase nutritional intake increases lean mass and physical function. Nutritional intervention after the initial phase of treatment could be less beneficial because it mainly increases fat.

Paton NI, et al. *Am J Clin Nutr.* 2004 Aug;80(2):460-5. doi: 10.1093/ajcn/80.2.460. PMID: 15277171

Nutritional supplements for people being treated for active tuberculosis (Cochrane 2008)

Objectives: To assess the provision of oral nutritional supplements to promote the recovery of people being treated with antituberculous drug therapy for active tuberculosis.

Search strategy: We searched the Cochrane Infectious Disease Group Specialized Register (June 2008), CENTRAL (The Cochrane Library 2008, Issue 2), MEDLINE (June 2008), EMBASE (June 2008), LILACS (June 2008), mRCT (June 2008), the Indian Journal of Tuberculosis (1983 to June 2008), and checked the reference lists of all included studies.

Selection criteria: Randomized controlled trials comparing any oral nutritional supplement given for at least four weeks with no nutritional intervention, placebo, or dietary advice only for people being treated for active tuberculosis.

Data collection and analysis: Two authors independently selected trials, extracted data, and assessed risk of bias. We calculated risk ratios (RR) for dichotomous variables and mean differences (MD) for continuous variables, with 95% confidence intervals (CI). We pooled data from trials with similar interventions and outcomes.

Main results: Twelve trials (3393 participants) were included. Five trials had adequate allocation concealment. Interventions included a high energy supplement, high cholesterol diet, vitamin D, vitamin A, zinc, arginine, multiple micronutrient supplements, combined multiple micronutrient supplements and zinc, combined vitamin A and zinc, and combined vitamin A and selenium. The following supplements were associated with increased body weight at follow up: high energy supplements (MD 1.73 kg, 95% CI 0.81 to 2.65; 34 participants, 1 trial); multiple micronutrients plus additional zinc (MD 2.37 kg, 95% CI 2.21 to 2.53; 192 participants, 1 trial); and vitamin A plus zinc (MD 3.10 kg, 95% CI 0.74 to 5.46; 80 participants, 1 trial). There was no evidence that any supplement affected the number of deaths or number of participants with sputum test positive results at the end of treatment.

Authors' conclusions: There is limited evidence that high energy supplements and some combinations of zinc with other micronutrients may help people with tuberculosis to gain weight. There is not enough evidence to assess the effect of other combinations of nutrients. A number of relevant trials are in progress, and, where appropriate, the results will be incorporated into future updates of this review.

AbbaK, et al. *Cochrane Database Syst Rev.* 2008 Oct 8;(4):CD006086. doi: 10.1002/14651858.CD006086.pub2.

Update in Nutritional supplements for people being treated for active tuberculosis. Sinclair D, et al. *Cochrane Database Syst Rev.* 2011 Nov 9;(11):CD006086. doi: 10.1002/14651858.CD006086.pub3. PMID: 22071828

Nutritional supplements for people being treated for active tuberculosis (Cochrane 2011)

Objectives: To assess the effects of oral nutritional supplements (food, protein/energy supplements or micronutrients) on tuberculosis treatment outcomes and recovery in people on antituberculous drug therapy for active tuberculosis.

Search methods: We searched the Cochrane Infectious Disease Group Specialized Register, CENTRAL (The Cochrane Library), MEDLINE, EMBASE, LILACS, mRCT, and the Indian Journal of Tuberculosis to July 2011, and checked the reference lists of all included studies.

Selection criteria: Randomized controlled trials comparing any oral nutritional supplement given for at least four weeks with no nutritional intervention, placebo, or dietary advice only for people being treated for active tuberculosis.

Data collection and analysis: Two authors independently selected trials, extracted data, and assessed the risk of bias. Results are presented as risk ratios (RR) for dichotomous variables, and mean differences (MD) for continuous variables, with 95% confidence intervals (CI). Where appropriate, data from trials with similar interventions and outcomes have been pooled. The quality of evidence was assessed using the GRADE methods.

Main results: Twenty-three trials, with 6842 participants, were included. **Macronutrient supplementation:** Five trials assessed the provision of free food, or high energy supplements, although none were shown to provide a total daily kilocalorie intake above the current daily recommended intake for the non-infected population. The available trials were too small to reliably prove or exclude clinically important benefits on mortality, cure, or treatment completion. One small trial from India did find a statistically significant benefit on treatment completion, and clearance of the bacteria from the sputum, but these findings have not been confirmed in larger trials elsewhere (VERY LOW quality evidence). The provision of free food or high-energy nutritional products probably does produce a modest increase in weight gain during treatment for active tuberculosis (MODERATE quality evidence). Two small studies provide some evidence that physical function and quality of life may also be improved but the trials were too small to have much confidence in the result (LOW quality evidence). These effects were not seen in the one trial which included only human immunodeficiency virus (HIV)-positive patients. **Micronutrient**

supplementation: Five trials assessed multi-micronutrient supplementation in doses up to ten times the dietary reference intake, and 12 trials assessed single or dual micronutrient supplementation. There is insufficient evidence to judge whether multi-micronutrients have a beneficial effect on mortality in HIV- negative patients with tuberculosis (VERY LOW quality evidence), but the available studies show that multi-micronutrients probably have little or no effect on mortality in HIV- positive patients with tuberculosis (MODERATE quality evidence). No studies have assessed the effects of multi-micronutrients on cure, or treatment completion. Multi-micronutrient supplements may have little or no effect on the proportion of tuberculosis patients remaining sputum positive during the first eight weeks (LOW quality evidence), and probably have no effect on weight gain during treatment (MODERATE quality evidence). No studies have assessed quality of life. Plasma levels of vitamin A appear to increase following initiation of tuberculosis treatment regardless of supplementation. In contrast, plasma levels of zinc, vitamin D and E, and selenium may be improved by supplementation during the early stages of tuberculosis treatment, but a consistent benefit on tuberculosis treatment outcomes or nutritional recovery has not been demonstrated.

Authors' conclusions: There is insufficient research to know whether routinely providing free food or energy supplements results in better tuberculosis treatment outcomes, or improved quality of life. Further trials, particularly from food insecure settings, should have adequate sample sizes to identify, or exclude, clinically important benefits. Although blood levels of some vitamins may be low in patients starting treatment for active tuberculosis, there is currently no reliable evidence that routinely supplementing at or above recommended daily amounts has clinical benefits.

Sinclair D, et al. Cochrane Database Syst Rev. 2011 Nov 9;(11):CD006086. doi: 10.1002/14651858.CD006086.pub3. PMID: 22071828

Update in: Nutritional supplements for people being treated for active tuberculosis. Grobler L, et al. Cochrane Database Syst Rev. 2016 Jun 29;2016(6):CD006086. doi: 10.1002/14651858.CD006086.pub4. PMID: 27355911

Nutritional supplementation increases rifampin exposure among TB patients coinfecting with HIV

Nutritional supplementation effect on the pharmacokinetics of first-line anti-TB drugs is unknown. A cohort of 100 TB patients (58 men; median age, 35 [interquartile range {IQR}, 29 to 40] years, and median body mass index [BMI], 18.8 [17.3 to 19.9] kg/m²) were randomized to receive nutritional supplementation during the intensive phase of TB treatment. Rifampin plasma concentrations were determined after 1 week and 2 months of treatment. The effects of nutritional supplementation, HIV, time on treatment, and body weight were examined using a population pharmacokinetic model. The model adjusted for body size via allometric scaling, accounted for clearance autoinduction, and detected an increase in bioavailability (+14%) for the patients in the continuation phase. HIV coinfection in patients not receiving the supplementation was found to decrease bioavailability by 21.8%, with a median C_{max} and AUC₀₋₂₄ of 5.6 µg/ml and 28.6 µg · h/ml, respectively. HIV-coinfecting patients on nutritional supplementation achieved higher C_{max} and AUC₀₋₂₄ values of 6.4 µg/ml and 31.6 µg · h/ml, respectively, and only 13.3% bioavailability reduction. **In conclusion, nutritional supplementation during the first 2 months of TB treatment reduces the decrease in rifampin exposure observed in HIV-coinfecting patients but does not affect exposure in HIV-uninfected patients.** If confirmed in other studies, the use of defined nutritional supplementation in HIV-coinfecting TB patients should be considered in TB control programs.

Kidola J, et al. Antimicrob Agents Chemother. 2014 Jun;58(6):3468-74. doi: 10.1128/AAC.02307-13.

Adjuvant Efficacy of Nutrition Support During Pulmonary Tuberculosis Treating Course: Systematic Review and Meta-analysis

Methods: English database of the Cochrane Controlled Trials Register, PubMed, EMBASE, and Chinese database of CBM, CNKI, VIP, and WANFANG were searched. Randomized controlled trials comparing nutrition support (given for more than 2 weeks) with no nutrition intervention, nutrition advice only, or placebo-control for TB patients being anti-TB treated were included. Two reviewers conducted data extraction, assessed the quality of the studies independently, and any discrepancies were solved by the third reviewer. Data were entered and analyzed by RevMan 5.2 software, and meta-analysis was done using risk ratios (RR s) for dichotomous variables and mean differences (MDs) for continuous variables with 95% confidence intervals (CI s).

Results: A total of 19 studies (3681 participants) were included. In nutritional support for TB patients, pooled RR and its 95% CI of sputum smears- or culture-negative conversion rate and chest X-ray (CXR) absorption rate were 1.10 (1.04, 1.17) and 1.22 (1.08, 1.39), respectively, the pooled MD and its 95% CI of body mass index (BMI) and time of sputum smears or culture negativity were 0.59 (0.16, 1.2) and - 5.42 (-7.93, -2.92), respectively, compared with the control group. The differences in outcomes of CXR zone affected, TB score, serum albumin, and hemoglobin were not statistically significant (P = 0.76, 0.24, 0.28, and 0.20, respectively) between the intervention group and the control group. No systemic adverse events were recorded.

Conclusions: During anti-TB course, nutrition support may be helpful in treatment of TB patients by improving both sputum smears- or culture-negative conversion rate and BMI, shortening the time of sputum conversion negative. Whether it can improve the final clinical effect, there still needs high-level quality studies to confirm in the future.

Zhuang-Li Si, et al. Chin Med J (Engl). 2015 Dec 5;128(23):3219-30. doi: 10.4103/0366-6999.170255. PMID: 26612299

Nutritional supplements for people being treated for active tuberculosis (Cochrane 2016)

Background: Tuberculosis and malnutrition are linked in a complex relationship. Tuberculosis may cause undernutrition through increased metabolic demands and decreased intake, and nutritional deficiencies may worsen the disease, or delay recovery by depressing important immune functions. At present, there is no evidence-based nutritional guidance for adults and children being treated for tuberculosis.

Objectives: To assess the effects of oral nutritional supplements in people being treated with antituberculous drug therapy for active tuberculosis.

Search methods: We searched the Cochrane Infectious Disease Group Specialized Register, Cochrane Central Register of Controlled Trials (CENTRAL; Issue 1, 2016), MEDLINE (from 1946 to 4 February 2016), EMBASE (from 1980 to 4 February 2016), LILACS (from 1982 to 4 February 2016), the metaRegister of Controlled Trials (mRCT), the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), and the Indian Journal of Tuberculosis up to 4 February 2016, and checked the reference lists of all included studies.

Selection criteria: Randomized controlled trials that compared any oral nutritional supplement given for at least four weeks with no nutritional intervention, placebo, or dietary advice only for people being treated for active tuberculosis. The primary outcomes of interest were all-cause death, and cure at six and 12 months.

Data collection and analysis: Two review authors independently selected trials for inclusion, and extracted data and assessed the risk of bias in the included trials. We presented the results as risk ratios (RR) for dichotomous variables, and mean differences (MD) for continuous variables, with 95% confidence intervals (CIs). Where appropriate, we pooled data from trials with similar interventions and outcomes. We assessed the quality of the evidence using the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach.

Main results: Thirty-five trials, including 8283 participants, met the inclusion criteria of this review. **Macronutrient supplementation:** Six trials assessed the provision of free food, or high-energy supplements. Only two trials measured total dietary intake, and in both trials the intervention increased calorie consumption compared to controls. The available trials were too small to reliably prove or exclude clinically important benefits on mortality (RR 0.34, 95% CI 0.10 to 1.20; four trials, 567 participants, very low quality evidence), cure (RR 0.91, 95% CI 0.59 to 1.41; one trial, 102 participants, very low quality evidence), or treatment completion (data not pooled; two trials, 365 participants, very low quality evidence). Supplementation probably produces a modest increase in weight gain during treatment for active tuberculosis, although this was not seen consistently across all trials (data not pooled; five trials, 883 participants, moderate quality evidence). Two small studies provide some evidence that quality of life may also be improved but the trials were too small to have much confidence in the result (data not pooled; two trials, 134 participants, low quality evidence). **Micronutrient supplementation:** Six trials assessed multi-micronutrient supplementation in doses up to 10 times the dietary reference intake, and 18 trials assessed single or dual micronutrient supplementation. Routine multi-micronutrient supplementation may have little or no effect on mortality in HIV-negative people with tuberculosis (RR 0.86, 95% CI 0.46 to 1.6; four trials, 1219 participants, low quality evidence), or HIV-positive people who are not taking antiretroviral therapy (RR 0.92, 95% CI 0.69 to 1.23; three trials, 1429 participants, moderate quality evidence). There is insufficient evidence to know if supplementation improves cure (no trials), treatment completion (RR 0.99, 95% CI 0.95 to 1.04; one trial, 302 participants, very low quality evidence), or the proportion of people who remain sputum positive during the first eight weeks (RR 0.92, 95% CI 0.63 to 1.35; two trials, 1020 participants, very low quality evidence). However, supplementation may have little or no effect on weight gain during treatment (data not pooled; five trials, 2940 participants, low quality evidence), and no studies have assessed the effect on quality of life. Plasma levels of vitamin A appear to increase following initiation of tuberculosis treatment regardless of supplementation. In contrast, supplementation probably does improve plasma levels of zinc, vitamin D, vitamin E, and selenium, but this has not been shown to have clinically important benefits. Of note, despite multiple studies of vitamin D supplementation in different doses, statistically significant benefits on sputum conversion have not been demonstrated.

Authors' conclusions: There is currently insufficient research to know whether routinely providing free food, or energy supplements improves tuberculosis treatment outcomes, but it probably improves weight gain in some settings. Although blood levels of some vitamins may be low in people starting treatment for active tuberculosis, there is currently no reliable evidence that routinely supplementing above recommended daily amounts has clinical benefits.

Grobler L, et al. *Cochrane Database Syst Rev.* 2016 Jun 29;2016(6):CD006086. doi: 10.1002/14651858.CD006086.pub4. PMID: 27355911

Nutritional supplements for people being treated for active tuberculosis: A technical summary

Tuberculosis and nutrition are intrinsically linked in a complex relationship. Altered metabolism and loss of appetite associated with tuberculosis may result in undernutrition, which in turn may worsen the disease or delay recovery. We highlight an updated Cochrane review assessing the effects of oral nutritional supplements in people with active tuberculosis who are receiving antituberculosis drug therapy. The review authors conducted a comprehensive search (February 2016) for all randomised controlled trials comparing any oral nutritional supplement, given for at least 4 weeks, with no nutritional intervention, placebo or dietary advice only in people receiving antituberculosis treatment. Of the 35 trials (N=8 283 participants) included, seven assessed the provision of free food or high-energy supplements, six assessed multi-micronutrient

supplementation, and 21 assessed single- or dual-micronutrient supplementation. There is currently insufficient evidence to indicate whether routinely providing free food or high-energy supplements improves antituberculosis treatment outcomes (i.e. reduced death and increased cure rates at 6 and 12 months), but it probably improves weight gain in some settings. Plasma levels of zinc, vitamin D, vitamin E and selenium probably improve with supplementation, but currently no reliable evidence demonstrates that routine supplementation with multi-, single or dual micronutrients above the recommended daily intake has clinical benefits (i.e. reduced death, increased cure rate at 6 and 12 months, improved nutritional status) in patients receiving antituberculosis treatment. In South Africa, most provinces implement a supplementation protocol based on nutritional assessment and classification of individuals rather than on disease diagnosis or treatment status.

Grobler L, et al. *S Afr Med J*. 2017 Dec 13;108(1):16-18. doi: 10.7196/SAMJ.2017.v108i1.12839. PMID: 29262971

Increased vegetable and fruit intake is associated with reduced failure rate of tuberculosis treatment: a hospital-based cohort study in China

Increased intake of vegetables and fruits has been associated with reduced risk of tuberculosis infection. Vegetables and fruits exert immunoregulatory effects; however, it is not clear whether vegetables and fruits have an adjuvant treatment effect on tuberculosis. Between 2009 and 2013, a hospital-based cohort study was conducted in Linyi, Shandong Province, China. Treatment outcome was ascertained by sputum smear and chest computerised tomography, and dietary intake was assessed by a semi-quantitative FFQ. The dietary questionnaire was conducted at the end of month 2 of treatment initiation. Participants recalled their dietary intake of the previous 2 months. A total of 2309 patients were enrolled in this study. After 6 months of treatment, 2099 patients were successfully treated and 210 were uncured. In multivariate models, higher intake of total vegetables and fruits (OR 0.70; 95 % CI 0.49, 0.99), total vegetables (OR 0.68; 95 % CI 0.48, 0.97), dark-coloured vegetables (OR 0.61; 95 % CI 0.43, 0.86) and light-coloured vegetables (OR 0.67; 95 % CI 0.48, 0.95) were associated with reduced failure rate of tuberculosis treatment. No association was found between total fruit intake and reduced failure rate of tuberculosis treatment (OR 0.98; 95 % CI 0.70, 1.37). High intake of total vegetables and fruits, especially vegetables, is associated with lower risk of failure of tuberculosis treatment in pulmonary tuberculosis patients. The results provide important information for dietary guidelines during tuberculosis treatment.

Lei Xu, et al. *Br J Nutr*. 2020 Sep 2;1-8. doi: 10.1017/S0007114520003438. PMID: 32873351

D. Fat Soluble Vitamins

Immunotherapy Added to Antibiotic Treatment Reduces Relapse of Disease in a Mouse Model of Tuberculosis.

Immune-modulating drugs that target myeloid-derived suppressor cells or stimulate natural killer T cells have been shown to reduce mycobacterial loads in tuberculosis (TB). We aimed to determine if a combination of these drugs as adjunct immunotherapy to conventional antibiotic treatment could also increase therapeutic efficacy against TB. In our model of pulmonary TB in mice, we applied treatment with isoniazid, rifampicin, and pyrazinamide for 13 weeks alone or combined with immunotherapy consisting of all-trans retinoic acid, 1,25(OH)₂-vitamin D₃, and α -galactosylceramide. Outcome parameters were mycobacterial load during treatment (therapeutic activity) and 13 weeks after termination of treatment (therapeutic efficacy). Moreover, cellular changes were analyzed using flow cytometry and cytokine expression was assessed at the mRNA and protein levels. Addition of immunotherapy was associated with lower mycobacterial loads after 5 weeks of treatment and significantly reduced relapse of disease after a shortened 13-week treatment course compared with antibiotic treatment alone. This was accompanied by reduced accumulation of immature myeloid cells in the lungs at the end of treatment and increased TNF- α protein levels throughout the treatment period. We demonstrate, in a mouse model of pulmonary TB, that immunotherapy consisting of three clinically approved drugs can improve the therapeutic efficacy of standard antibiotic treatment.

Mourik BC, et al. *Am J Respir Cell Mol Biol*. 2017 Feb;56(2):233-241. doi: 10.1165/rmb.2016-0185OC. PMID: 27654457

1. Vitamin A

NB: Numerous reports of vit. A with zinc are included in the zinc section below, starting on p. 59

Vitamin A status and therapy in childhood pulmonary tuberculosis.

Low plasma vitamin A levels (mean, 18.1 +/- 10.3 micrograms/dl, 62% below normal) were demonstrated in South African children with pulmonary tuberculosis. More extensive or severe disease (e.g., additional extrapulmonary tuberculosis) and low levels of retinol binding protein, prealbumin, and albumin were associated with low vitamin A levels. High-dose vitamin A therapy had no effect on disease outcome.

Plasma-soluble CD30 in childhood tuberculosis: effects of disease severity, nutritional status, and vitamin A therapy.

Plasma-soluble CD30 (sCD30) is the result of proteolytic splicing from the membrane-bound form of CD30, a putative marker of type 2 cytokine-producing cells. We measured sCD30 levels in children with tuberculosis, a disease characterized by prominent type 1 lymphocyte cytokine responses. We postulated that disease severity and nutritional status would alter cytokine responses and therefore sCD30 levels. Samples from South African children enrolled prospectively at the time of diagnosis of tuberculosis were analyzed. (Patients were originally enrolled in a randomized, double-blind placebo-controlled study of the effects of oral vitamin A supplementation on prognosis of tuberculosis.) Plasma samples collected at the time of diagnosis and 6 and 12 weeks later (during antituberculosis therapy) were analyzed. sCD30 levels were measured by enzyme immunoassay. The 91 children included in the study demonstrated high levels of sCD30 at diagnosis (median, 98 U/liter; range, 11 to 1,569 U/liter). Although there was a trend toward higher sCD30 levels in more severe disease (e.g., culture-positive disease or miliary disease), this was not statistically significant. Significantly higher sCD30 levels were demonstrated in the presence of nutritional compromise: the sCD30 level was higher in patients with a weight below the third percentile for age, in those with clinical signs of kwashiorkor, and in those with a low hemoglobin content. There was minimal change in the sCD30 level after 12 weeks of therapy, even though patients improved clinically. However, changes in sCD30 after 12 weeks differed significantly when 46 patients (51%) who received vitamin A were compared with those who had received a placebo. Vitamin A-supplemented children demonstrated a mean (+/- standard error of the mean) decrease in sCD30 by a factor of 0.99 +/- 0.02 over 12 weeks, whereas a factor increase of 1.05 +/- 0.02 was demonstrated in the placebo group (P = 0.02). We conclude that children with tuberculosis had high sCD30 levels, which may reflect the presence of a type 2 cytokine response. Nutritional compromise was associated with higher sCD30 levels. Vitamin A therapy resulted in modulation of sCD30 levels over time.

Hanekom WA, et al. *Clin Diagn Lab Immunol.* 1999 Mar;6(2):204-8. PMID: 10066655

All-trans Retinoic Acid Augments Autophagy during Intracellular Bacterial Infection.

Vitamin A deficiency strongly predicts the risk of developing tuberculosis (TB) in individuals exposed to *Mycobacterium tuberculosis* (Mtb). The burden of antibiotic-resistant TB is increasing globally; therefore, there is an urgent need to develop host-directed adjunctive therapies to treat TB. Alveolar macrophages, the niche cell for Mtb, metabolize vitamin A to all-trans retinoic acid (atRA), which influences host immune responses. We sought to determine the mechanistic effects of atRA on the host immune response to intracellular bacterial infection in primary human and murine macrophages. In this study, atRA promoted autophagy resulting in a reduced bacterial burden in human macrophages infected with Mtb and *Bordetella pertussis*, but not bacillus Calmette-Guérin (BCG). Autophagy is induced by cytosolic sensing of double-stranded DNA via the STING/TBK1/IRF3 axis; however, BCG is known to evade cytosolic DNA sensors. atRA enhanced colocalization of Mtb, but not BCG, with autophagic vesicles and acidified lysosomes. This enhancement was inhibited by blocking TBK1. Our data indicate that atRA augments autophagy of intracellular bacteria that trigger cytosolic DNA-sensing pathways but does not affect bacteria that evade these sensors. The finding that BCG evades the beneficial effects of atRA has implications for vaccine design and global health nutritional supplementation strategies. The ability of atRA to promote autophagy and aid bacterial clearance of Mtb and *B. pertussis* highlights a potential role for atRA as a host-directed adjunctive therapy.

Coleman MM, et al. *Am J Respir Cell Mol Biol.* 2018 Nov;59(5):548-556. doi: 10.1165/rmb.2017-0382OC. PMID: 29852080

Zinc and vitamin A supplementation fails to reduce sputum conversion time in severely malnourished pulmonary tuberculosis patients in Indonesia. (See also in Zn and MMN)

BACKGROUND: A previous study showed that combination of zinc and vitamin A reduced sputum conversion time in pulmonary tuberculosis (TB) patients.

OBJECTIVE: We studied the efficacy of which single micronutrient contributed more to the sputum conversion time.

METHODS: In a double-blind randomized community trial, newly sputum smear positive pulmonary TB patients were assigned randomly to receive zinc, vitamin A, zinc + vitamin A or placebo on top of TB treatment.

RESULTS: Initially, 300 patients were enrolled, and 255 finished the treatment. Most patients were severely malnourished (mean BMI 16.5 ±2.2 Kg/m²). Patients in the zinc + vitamin A group showed earlier sputum conversion time (mean 1.9 weeks) compared with that in the other groups; however the difference was not significant. Also, no benefit could be demonstrated of any of the used supplementations on clinical, nutritional, chest x-ray, or laboratory findings.

CONCLUSIONS: This study among severely malnourished TB patients, did not confirm that single or combined supplementation of zinc and vitamin A significantly reduced sputum conversion time or had other significant benefit. Pakasi TA, et al. *Nutr J.* 2010 Sep 28;9:41. doi: 10.1186/1475-2891-9-41. PMID: 20920186

2. VITAMIN D

Experimental animal studies in guinea pigs, 1930-33, showed that vitamin D supplements prevented TB when given at the same time as the animal is inoculated with the infection. This was one of the first indications it may have some effect. For historical interest, see: Meerseman, F. *Rev. Tuberc.*, Paris, 1936, p. 1055 and also Meerseman, F., Thibault, G. "Ibid," 1930, 105, 398, where "Ibid" may refer to: *C.R. Soc. Biol. Paris*, or to *Bull. Soc. med. Hop. Paris*. In the 1940s, many reports were published on the effects of vitamin D for the treatment of cutaneous tuberculosis, a.k.a. lupus vulgaris. The pro-calcifying effect of vitamin D on experimental TB lesions was first noted in 1946. Studies on treatment of pulmonary TB and other extra pulmonary TB and on pulmonary TB started in 1947. [Studies reporting at least some benefit of vit. D \(see below\): Ganmaa AJRCCM 2017, Bekele JIM 2018, Wu BMC Pulm Med 2018, Hasanain IndJTbc 2019, Jolliffe ERJ 2019, Wang Jinyu 2020](#)

Vitamin D, cod liver oil, sunshine, and phototherapy: Safe, effective and forgotten tools for treating and curing tuberculosis infections - A comprehensive review.

Tuberculosis remains an epidemic throughout the world, with over 2 billion people, or more than one third of the world's population, infected with TB. In 2015, there were an estimated 10.4 million new cases of tuberculosis, and 1.8 million deaths, making TB one of the top ten causes of death worldwide. Approximately 95% of new TB cases occur in developing countries, where the costs of treatment force many patients and their families into poverty. The United Nations and the World Health Organization are working to end this global epidemic. [Historically, cod liver oil in the 1840's, phototherapy in the 1890's, sunshine in the 1890's and 1930's, oral vitamin D in doses of 100,000-150,000 international units a day the 1940's, and injectable vitamin D in the 1940's were all shown to be able to safely treat tuberculosis.](#) However, for reasons that are unclear, these treatments are no longer being used to treat tuberculosis. [We will review several reports that documented the clinical efficacy of these seemingly disparate treatments in treating tuberculosis.](#) Taken together, however, these reports show the [consistent efficacy of vitamin D in treating tuberculosis infections](#), regardless of whether the vitamin D was produced in the skin from the effects of phototherapy or sunshine, taken orally as a pill or in cod-liver oil, or put into solution and injected directly into the body. We will discuss how vitamin D, through its action as a steroid hormone that regulates gene transcription in cells and tissues throughout the body, enables the body to eradicate TB by stimulating the formation of a natural antibiotic in white blood cells, the mechanism of which was discovered in 2006. We will speculate as to why vitamin D, cod liver oil, sunshine, and phototherapy are no longer being used to treat tuberculosis, in spite of their proven efficacy in safely treating this disease dating back to the early 1800's. [In fact, in 1903 the Nobel Prize in Medicine or Physiology was awarded to a physician who was able to cure hundreds of cases of long-standing lupus vulgaris \(cutaneous TB\) with refracted light rays from an electric arc lamp.](#) Vitamin D, cod liver oil, sunshine, and phototherapy have never been shown to lose their ability to safely eradicate tuberculosis infections, and deserve consideration to be re-examined as first-line treatments for tuberculosis. These treatments have the potential to help cost-effectively and safely end the global TB epidemic.

McCullough PJ, Lehrer DS. J Steroid Biochem Mol Biol. 2018 Mar;177:21-29. doi: 10.1016/j.jsbmb.2017.07.027. PMID: 28756294

Adjunctive vitamin D for treatment of active tuberculosis in India: a randomised, double-blind, placebo-controlled trial.

BACKGROUND: Vitamin D has immunomodulatory effects that might aid clearance of mycobacterial infection. We aimed to assess whether vitamin D supplementation would reduce time to sputum culture conversion in patients with active tuberculosis.

METHODS: We did this randomised, double-blind, placebo-controlled, superiority trial at 13 sites in India. Treatment-naive patients who were sputum-smear positive, HIV negative, and had pulmonary tuberculosis were randomly assigned (1:1), with centrally labelled, serially numbered bottles, to receive standard active tuberculosis treatment with either supplemental high-dose oral vitamin D3 (four doses of 2.5 mg at weeks 0, 2, 4, and 6) or placebo. Neither the patients nor the clinical and laboratory investigators and personnel were aware of treatment assignment. The primary efficacy outcome was time to sputum culture conversion. Analysis was by modified intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00366470.

FINDINGS: [Between Jan 20, 2010, and Aug 23, 2011, we randomly assigned 247 participants to the vitamin D group \(n=121\) or the placebo group \(n=126\), of whom 211 participants \(n=101 and n=110, respectively\) were included in the primary efficacy analysis. Median time to culture conversion in the vitamin D group was 43.0 days \(95% CI 33.3-52.8\) versus 42.0 days \(33.9-50.1\) in the placebo group \(log-rank p=0.95\). Three \(2%\) patients died in the vitamin D group and one \(1%\) patient died in the placebo group; no death was considered attributable to the study intervention. No patients had hypercalcaemia.](#)

INTERPRETATION: [Our findings show that vitamin D supplementation did not reduce time to sputum culture conversion.](#) Further studies should investigate the role of vitamin D in prevention or reactivation of tuberculosis infection.

Adjunctive vitamin D for treatment of active tuberculosis in India: a randomised, double-blind, placebo-controlled trial.

BACKGROUND: We aimed to assess whether vitamin D supplementation would reduce time to sputum culture conversion in patients with active tuberculosis.

METHODS: We did this [randomised, double-blind, placebo-controlled, superiority trial at 13 sites in India](#). Treatment-naïve patients who were sputum-smear positive, HIV negative, and had pulmonary tuberculosis were randomly assigned (1:1), with centrally labelled, serially numbered bottles, to receive standard active tuberculosis treatment with either supplemental high-dose oral vitamin D3 (four doses of 2.5 mg at weeks 0, 2, 4, and 6) or placebo. Neither the patients nor the clinical and laboratory investigators and personnel were aware of treatment assignment. The primary efficacy outcome was time to sputum culture conversion. Analysis was by modified intention to treat.

FINDINGS: Between Jan 20, 2010, and Aug 23, 2011, we [randomly assigned 247 participants to the vitamin D group \(n=121\) or the placebo group \(n=126\)](#), of whom 211 participants (n=101 and n=110, respectively) were included in the primary efficacy analysis. Median time to culture conversion in the vitamin D group was 43.0 days (95% CI 33.3-52.8) versus 42.0 days (33.9-50.1) in the placebo group (log-rank p=0.95). Three (2%) patients died in the vitamin D group and one (1%) patient died in the placebo group; no death was considered attributable to the study intervention. No patients had hypercalcaemia.

INTERPRETATION: [Our findings show that vitamin D supplementation did not reduce time to sputum culture conversion.](#)

Daley P. *Lancet Infect Dis* 2015 May;15(5):528-34. doi: 10.1016/S1473-3099(15)70053-8. PMID: 25863562

High-dose vitamin D3 in adults with pulmonary tuberculosis: a double-blind randomized controlled trial.

OBJECTIVE: We determined whether adjunctive high-dose vitamin D3 supplementation improves outcomes in individuals with pulmonary tuberculosis disease.

DESIGN: The study was a [double-blind, randomized, placebo-controlled, intent-to-treat trial in 199 individuals with pulmonary tuberculosis disease in Tbilisi, Georgia](#). Subjects were randomly assigned to receive oral vitamin D3 [50,000 IUs (1.25 mg) thrice weekly for 8 wk and 50,000 IU every other week for 8 wk] or a placebo concomitant with standard first-line antituberculosis drugs. The primary outcome was the time for the conversion of a Mtb sputum culture to negative.

RESULTS: Baseline characteristics between groups were similar. Most subjects (74%) were vitamin D deficient (plasma 25-hydroxyvitamin D [25(OH)D] concentration <50 nmol/L). With vitamin D3, plasma 25(OH)D concentrations peaked at ~250 nmol/L by 8 wk and decreased to ~125 nmol/L at week 16. Adverse events and plasma calcium concentrations were similar between groups. [In 192 subjects with culture-confirmed tuberculosis, an adjusted efficacy analysis showed similar median culture-conversion times between vitamin D3 and placebo groups \[29 and 27 d, respectively; HR: 0.86; 95% CI: 0.63, 1.18; P = 0.33\].](#) Eight-week culture-conversion rates were also similar (84.0% and 82.1% for vitamin D3 and placebo, respectively; P = 0.99).

CONCLUSION: [A high-dose vitamin D3 regimen safely corrected vitamin D deficiency but did not improve the rate of sputum Mtb clearance over 16 wk in this pulmonary tuberculosis cohort.](#)

Tukvadze N, et al. *Am J Clin Nutr*. 2015 Nov;102(5):1059-69. doi: 10.3945/ajcn.115.113886. PMID: 26399865

Paradoxical upgrading reaction in extra-pulmonary tuberculosis: association with vitamin D therapy

SETTING: Glasgow, Scotland, UK.

BACKGROUND: Paradoxical reactions in tuberculosis (TB) are a notable example of our incomplete understanding of host-pathogen interactions during anti-tuberculosis treatment.

OBJECTIVES: To determine risk factors for a TB paradoxical reaction, and specifically to assess for an independent association with vitamin D use.

DESIGN: Consecutive human immunodeficiency virus (HIV) negative adult patients treated for extra-pulmonary TB were identified from an Extended Surveillance of Mycobacterial Infections database. In our setting, vitamin D was variably prescribed for newly diagnosed TB patients. A previously published definition of paradoxical TB reaction was retrospectively applied to, and data on all previously described risk factors were extracted from, centralised electronic patient records. The association with vitamin D use was assessed using multivariate logistic regression.

RESULTS: Of the 249 patients included, most had TB adenopathy; 222/249 had microbiologically and/or histologically confirmed TB. [Vitamin D was prescribed for 57/249 \(23%\) patients; 37/249 \(15%\) were classified as having paradoxical reactions.](#) Younger age, acid-fast bacilli-positive invasive samples, multiple disease sites, lower lymphocyte count and vitamin D use were found to be independent risk factors.

CONCLUSION: We speculate that vitamin D-mediated signalling of pro-inflammatory innate immune cells, along with high antigenic load, may mediate paradoxical reactions in anti-tuberculosis treatment.

Barr DA, et al. *Int J Tuberc Lung Dis*. 2017 Jun 1;21(6):677-683. doi: 10.5588/ijtld.16.0927. PMID: 28482963

High-Dose Vitamin D(3) during Tuberculosis Treatment in Mongolia: a RCT.

RATIONALE: Existing trials of adjunctive vitamin D in the treatment of pulmonary tuberculosis (PTB) are variously limited by small sample sizes, inadequate dosing regimens, and high baseline vitamin D status among participants.

OBJECTIVES: To determine the effect of high-dose vitamin D3 on response to antimicrobial therapy for PTB and to evaluate the influence of single-nucleotide polymorphisms (SNPs) in vitamin D pathway genes on response to adjunctive vitamin D3.

METHODS: We conducted a clinical trial in 390 adults with PTB in Ulaanbaatar, Mongolia, who were randomized to receive four biweekly doses of 3.5 mg (140,000 IU) vitamin D3 (n=190) or placebo (n=200) during intensive-phase antituberculosis treatment.

MEASUREMENTS AND MAIN RESULTS: The intervention elevated 8-week serum 25-hydroxyvitamin D concentrations (154.5 nmol/L vs. 15.2 nmol/L in active vs. placebo arms, respectively; 95% CI for difference, 125.9-154.7

nmol/L; $P < 0.001$) but did not influence time to sputum culture conversion overall (aHR 1.09; 95% CI 0.86-1.36; $P = 0.48$).

Adjunctive vitamin D3 accelerated sputum culture conversion in patients with one or more minor alleles for SNPs in genes encoding the vitamin D receptor (rs4334089, rs11568820) and 25-hydroxyvitamin D 1 α -hydroxylase (CYP27B1: rs4646536) (adjusted hazard ratio ≥ 1.47 ; P for interaction ≤ 0.02).

CONCLUSIONS: Vitamin D3 did not influence time to sputum culture conversion in the study population overall. Effects of the intervention were modified by SNPs in VDR and CYP27B1.

Ganmaa D, et al. *Am J Respir Crit Care Med.* 2017 Sep 1;196(5):628-637. doi: 10.1164/rccm.201705-0936OC. PMID: 28692301

Daily adjunctive therapy with vitamin D(3) and phenylbutyrate supports clinical recovery from pulmonary tuberculosis: a randomized controlled trial in Ethiopia.

METHODS: A randomized controlled trial was conducted in Addis Ababa, Ethiopia. Patients with smear-positive or smear-negative TB received daily oral supplementation with 5000 IU vitD3 and 2 \times 500 mg PBA or placebo for 16 weeks, together with 6-month chemotherapy. Primary end-point: reduction of a clinical composite TB score at week 8 compared with baseline using modified intention-to-treat (mITT, n = 348) and per-protocol (n = 296) analyses. Secondary end-points: primary and modified TB scores (week 0, 4, 8, 16, 24), sputum conversion, radiological findings and plasma 25(OH)D3 concentrations.

RESULTS: Most subjects had low baseline plasma 25(OH)D3 levels that increased gradually in the vitD3 + PBA group compared with placebo ($P < 0.0001$) from week 0 to 16 (mean 34.7 vs. 127.4 nmol L⁻¹). In the adjusted mITT analysis, the primary TB score was significantly reduced in the intervention group at week 8 (-0.52, 95% CI -0.93, -0.10; $P = 0.015$) while the modified TB score was reduced at week 8 (-0.58, 95% CI -1.02, -0.14; $P = 0.01$) and 16 (-0.34, 95% CI -0.64, -0.03; $P = 0.03$). VitD3 + PBA had no effect on longitudinal sputum-smear conversion ($P = 0.98$). Clinical adverse events were more common in the placebo group (24.3%) compared with the vitD3 + PBA group (12.6%).

CONCLUSION: Daily supplementation with vitD3 + PBA may ameliorate clinical TB symptoms and disease-specific complications, while the intervention had no effect on bacterial clearance in sputum.

Bekele A, et al. *J Intern Med.* 2018 Sep;284(3):292-306. doi: 10.1111/joim.12767. PMID: 29696707

Effects of vitamin D supplementation on the outcomes of patients with pulmonary tuberculosis: a systematic review and meta-analysis.

We aimed to clarify the efficacy and safety of vitamin D supplementation in PTB treatment.

METHODS: We searched Medline, Embase, Cochrane Central Register of Controlled Trials, Web of Science for double-blind, randomized controlled trials of vitamin D supplementation in patients with PTB that reported sputum conversion, clinical response to treatment, adverse events, or mortality, published from database inception to November 26, 2017.

RESULTS: A total of 1787 patients with active PTB receiving vitamin D supplementation along with standard anti-tuberculosis regimen were included in the eight trials with different doses of vitamin D ranging from 1000 IU/day to 600,000 IU/month at different intervals. Primary analysis revealed that vitamin D supplementation increased the proportion of sputum smear and culture conversions (OR 1.21, 95%CI 1.05~1.39, $z = 2.69$, $P = 0.007$; OR 1.22, 95%CI

1.04~1.43, $z = 2.41$, $P = 0.02$), but did not improve the time to sputum smear and culture conversions (HR 1.07, 95%CI

0.83~1.37, $z = 0.50$, $P = 0.62$; HR 0.97, 95%CI 0.76~1.23, $z = 0.29$, $P = 0.77$). In the secondary analysis, vitamin D improved serum 25(OH)D, plasma calcium concentration, lymphocyte count, and chest radiograph (MD 103.36, 95%CI 84.20~122.53, $z = 10.57$, $P < 0.00001$; SMD 0.26, 95%CI 0.15~0.37, $z = 4.61$, $P < 0.00001$; MD 0.09, 95%CI 0.03~0.14,

$z=2.94$, $P=0.003$); MD -0.33, 95% CI -0.57~-0.08 $z=2.57$, $P=0.01$), but had no impact on adverse events, mortality and other indicators (TB score, BMI, mean mid-upper arm circumference, weight gain, CRP, ESR, and other blood cells) ($P>0.05$).
CONCLUSIONS: Vitamin D supplementation can be considered as a combination therapy in patients with PTB.
Wu HX, et al. BMC Pulm Med. 2018 Jun 28;18(1):108. doi: 10.1186/s12890-018-0677-6. PMID: 29954353

Efficacy and safety of cholecalciferol-augmented anti-tuberculosis therapy for treatment of naïve patients with pulmonary tuberculosis: A randomized, controlled, clinical study.

OBJECTIVE: The aim of this study is to explore the role of adding cholecalciferol to the standard ATT in improving the therapeutic outcome among the naïve patients with pulmonary tuberculosis (TB).

METHODS: A randomized, controlled, clinical study, which included 496 naïve patients with pulmonary TB, was carried out. The patients were randomly allocated to two groups. Group-A included 247 patients who received ATT, while group-B included 249 patients who received ATT with cholecalciferol.

RESULTS: The rate of therapeutic failure among the study population was 29.4%; it was significantly lower among patients of group-B compared to those of group-A (22.1% (95% CI 14.7-26.2) vs 38.1% (95% CI 31.5-46.1), $p=0.036$). In addition, the rate of early therapeutic response was significantly higher among patients of group-B compared to those of group-A (35.3% (95% CI 29.6-42.3) vs 19.4% (95% CI 15.1-24.6), $p=0.041$). Incidence rate of adverse effects was 19.3%; it was higher (although not statistically significant) among patients of group-A compared to those of group-B (21.9% vs 16.9%).

CONCLUSIONS: In conclusion, cholecalciferol-augmented ATT can be more efficacious in treating naïve patients with pulmonary TB compared to the standard ATT.

Hasanain AFA. Indian J Tuberc. 2019 Jan;66(1):111-117. doi: 10.1016/j.ijtb.2018.06.004. PMID: 30797266

Adjunctive vitamin D in tuberculosis treatment: meta-analysis of individual participant data.

METHODS: We meta-analysed individual participant data from randomised controlled trials of vitamin D in patients receiving antimicrobial therapy for pulmonary TB. Primary outcome was time to sputum culture conversion. Secondary outcomes were time to sputum smear conversion, mean 8-week weight and incidence of adverse events. Pre-specified subgroup analyses were done according to baseline vitamin D status, age, sex, drug susceptibility, HIV status, extent of disease and vitamin D receptor genotype.

RESULTS: Individual participant data were obtained for 1850 participants in eight studies. Vitamin D did not influence time to sputum culture conversion overall (adjusted HR 1.06, 95% CI 0.91-1.23), but it did **accelerate sputum culture conversion in participants with multidrug-resistant pulmonary TB (adjusted HR 13.44, 95% CI 2.96-60.90)**; no such effect was seen in those whose isolate was sensitive to rifampicin and/or isoniazid (adjusted HR 1.02, 95% CI 0.88-1.19; p -value for interaction=0.02). Vitamin D accelerated sputum smear conversion overall (adjusted HR 1.15, 95% CI 1.01-1.31), but did not influence other secondary outcomes.

CONCLUSIONS: Vitamin D did not influence time to sputum culture conversion overall, but it accelerated sputum culture conversion in patients with multidrug-resistant pulmonary TB.

Jolliffe DA, et al. Eur Respir J. 2019 Mar 7;53(3):1802003. doi: 10.1183/13993003.02003-2018. PMID: 30728208

Effectiveness of vitamin D supplementation on the outcome of pulmonary tuberculosis treatment in adults: a meta-analysis of randomized controlled trials.

BACKGROUND: we systematically reviewed the literature to investigate whether vitamin D supplementation could improve the effect of anti-TB therapy.

METHODS: We systematically searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials from their inception to February 8th, 2019 for randomized controlled trials on vitamin D supplementation in patients with pulmonary TB receiving anti-TB therapy. The primary outcomes were time to sputum culture and smear conversion and proportion of participants with negative sputum culture. The secondary outcomes were clinical response to treatment and adverse events. A random-effects model was used to pool studies. Data were analyzed using RevMan 5.3 software.

RESULTS: Five studies with a total of 1126 participants were included in our meta-analysis. Vitamin D supplementation did not shorten the time to sputum culture and smear conversion (HR 1.04, 95% CI 0.89-1.23, $P=0.60$; HR 1.15, 95% CI 0.93-1.41, $P=0.20$, respectively) and did not lead to an increase in the proportion of participants with negative sputum culture (relative risk [RR] 1.04, 95% CI 0.97-1.11, $P=0.32$). However, it reduced the time to sputum culture conversion in the subgroup of participants with TaqI tt genotype (HR 8.09, 95% CI 1.39-47.09, $P=0.02$) and **improved the multidrug-resistant**

(MDR) TB sputum culture conversion rate (RR 2.40, 95% CI 1.11-5.18, P=0.03). There was no influence on secondary outcomes.

CONCLUSIONS: Vitamin D supplementation had no beneficial effect on anti-TB treatment, but it reduced the time to sputum culture conversion in participants with tt genotype of the TaqI vitamin D receptor gene polymorphism and improved the MDR TB sputum culture conversion rate.

Zhang J, et al. Chin Med J (Engl). 2019;132(24):2950-2959. doi: 10.1097/CM9.0000000000000554. PMID: 31833904

3. VIT. A and D

Adjunctive vitamin A and D during pulmonary tuberculosis treatment: a randomized controlled trial with a 2 × 2 factorial design

Background and objective: Vitamin A and D have immunoregulatory effects and may improve the response to pulmonary tuberculosis treatment. The interaction of vitamin A and D on pulmonary tuberculosis treatment has not been studied. The objective is to investigate the effects of adjunctive supplementation of vitamin A, D and their interaction on the outcome of pulmonary tuberculosis treatment, primarily time to sputum smear conversion.

Methods: We conducted a randomized controlled trial with a 2 × 2 factorial design in Qingdao, China. Eight hundred patients were enrolled to receive standard pulmonary tuberculosis therapy alone (control), or together with vitamin A (2000 IU d-1), or vitamin D (400 IU d-1) or a combination of vitamin A (2000 IU d-1) and D (400 IU d-1) during the intensive-phase of pulmonary tuberculosis treatment.

Results: 761 patients were included in the tuberculosis symptom analysis; 521 patients with positive baseline sputum smear results were included in the sputum smear analysis. The allocation to vitamin A or D did not significantly influence the time to sputum smear conversion [vitamin A: adjusted hazard ratio: 1.021, 95% CI: (0.821, 1.271); vitamin D: adjusted hazard ratio: 0.949, 95% CI: (0.760, 1.185)]. No significant interaction was observed between vitamin A and D supplementation (p = 0.660). Vitamin D supplementation significantly relieved the tuberculosis symptoms as indicated by decreased TBscore [mean difference: -0.2, 95% CI: (-0.4, 0)] in week 2 to 4.

Conclusions: Adjunctive supplementation of vitamin A and/or D did not improve the time to smear conversion in pulmonary tuberculosis patients. However vitamin D supplementation significantly improved tuberculosis symptoms during the first month of pulmonary tuberculosis treatment.

Wang Jinyu, et al. Food Funct. 2020 May 1;11(5):4672-4681. doi: 10.1039/c9fo02751c. PMID: 32406431

4. VITAMIN E

Effect of vitamin E and selenium supplementation on oxidative stress status in pulmonary tuberculosis patients.

BACKGROUND AND OBJECTIVE: Increased production of reactive oxygen species secondary to phagocyte respiratory burst occurs in pulmonary tuberculosis (TB). The present study evaluated the efficacy of vitamin E-selenium supplementation on oxidative stress in newly diagnosed patients treated for pulmonary TB.

METHODS: A double-blind, placebo-controlled trial including patients with newly diagnosed TB was conducted. The intervention group (n = 17) received vitamin E and selenium (vitamin E: 140 mg alpha-tocopherol and selenium: 200 microg) and the control group (n = 18) received placebo. Both groups received standard anti-TB treatment. Assessment of micronutrient levels, oxidative markers and total antioxidant capacity were carried out at baseline and 2 months after the intervention.

RESULTS: Malondialdehyde levels were significantly reduced in the intervention group (P = 0.01), while there was minimal reduction in the control group. The mean plasma level of total antioxidants was increased significantly (P = 0.001) in both the intervention and the control groups.

CONCLUSION: A 2-month intervention with vitamin E and selenium supplementation reduces oxidative stress and enhances total antioxidant status in patients with pulmonary TB treated with standard chemotherapy.

Seyedrezaqadeh E, et al. Respirology. 2008 Mar;13(2):294-8. doi: 10.1111/j.1440-1843.2007.01200.x. PMID: 18339032

Immune boosting role of vitamin E against pulmonary tuberculosis.

The current study aimed to assess the effect of supplementation of Vitamin E on the immune status of human subjects against pulmonary tuberculosis. A total of 80 patients with pulmonary TB were divided into treatment group (vitamin E) and control group (Anti-tuberculosis regime). Presence of acid fast bacilli in sputum sample, Erythrocyte sedimentation rate, total leucocytes counts, body mass index and mid arm muscle circumference (MAMC) were recorded as per standard protocol.

Levels of vitamin E, IgG, IgM and T-Cell count were determined before and after treatment. The results showed that 16% males and 33% females were underweight who consumed 1145 kcal energy instead of 2270 kcal per day and 19.5 gram protein instead of 78.6 grams. A non significant effect of vitamin E on ESR and TLC values was observed but **significant increase in level of immunoglobulins (IgG, IgM) and T-cell types (CD4+ and CD8+)** was observed in patients as compared to control group. Results indicate that vitamin E plays important role in enhancing immunity of patients against TB.

Hussain MI, et al. *Pak J Pharm Sci.* 2019 Jan;32(1(Supplementary)):269-276. PMID: 30829203

E. Water Soluble Vitamins

1. Thiamine, vitamin B1

Vitamin B1 Helps to Limit *Mycobacterium tuberculosis* Growth via Regulating Innate Immunity in a Peroxisome Proliferator-Activated Receptor- γ -Dependent Manner.

Vitamin B1 (VB1) has a protective effect against oxidative retinal damage induced by anti-tuberculosis drugs. However, it remains unclear whether VB1 regulates immune responses during *Mycobacterium tuberculosis* (MTB) infection. We report here that VB1 promotes the protective immune response to limit the survival of MTB within macrophages and in vivo through regulation of peroxisome proliferator-activated receptor γ (PPAR- γ). VB1 promotes macrophage polarization into classically activated phenotypes with strong microbicidal activity and enhanced tumor necrosis factor- α and interleukin-6 expression at least in part by promoting nuclear factor- κ B signaling. In addition, VB1 increases mitochondrial respiration and lipid metabolism and PPAR- γ integrates the metabolic and inflammatory signals regulated by VB1. Using both PPAR- γ agonists and deficient mice, we demonstrate that VB1 enhances anti-MTB activities in macrophages and in vivo by down-regulating PPAR- γ activity. Our data demonstrate important functions of VB1 in regulating innate immune responses against MTB and reveal novel mechanisms by which VB1 exerts its function in macrophages.

Hu S, et al. *Front Immunol.* 2018 Aug 16;9:1778. doi: 10.3389/fimmu.2018.01778.

2. Riboflavin, vitamin B2

Functional Heterogeneity and Antimycobacterial Effects of Mouse Mucosal-Associated Invariant T Cells Specific for Riboflavin Metabolites. (vit. B2)

Mucosal-associated invariant T (MAIT) cells have a semi-invariant TCR V α -chain, and their optimal development is dependent upon commensal flora and expression of the nonpolymorphic MHC class I-like molecule MR1. MAIT cells are activated in an MR1-restricted manner by diverse strains of bacteria and yeast, suggesting a widely shared Ag. Recently, human and mouse MR1 were found to bind bacterial riboflavin metabolites (ribityllumazine [RL] Ags) capable of activating MAIT cells. In this study, we used MR1/RL tetramers to study MR1 dependency, subset heterogeneity, and protective effector functions important for tuberculosis immunity. Although tetramer(+) cells were detected in both MR1(+/+) and MR1(-/-) TCR V α 19i-transgenic (Tg) mice, MR1 expression resulted in significantly increased tetramer(+) cells coexpressing TCR V β 6/8, NK1.1, CD44, and CD69 that displayed more robust in vitro responses to IL-12 plus IL-18 and RL Ag, indicating that MR1 is necessary for the optimal development of the classic murine MAIT cell memory/effector subset. In addition, tetramer(+) MAIT cells expressing CD4, CD8, or neither developing in MR1(+/+) V α 19i-Tg mice had disparate cytokine profiles in response to RL Ag. Therefore, murine MAIT cells are considerably more heterogeneous than previously thought. Most notably, after mycobacterial pulmonary infection, heterogeneous subsets of tetramer(+) V α 19i-Tg MAIT cells expressing CXCR3 and α 4 β 1 were recruited into the lungs and afforded early protection. In addition, V α 19iC α (-/-)MR1(+/+) mice were significantly better protected than were V α 19iC α (-/-)MR1(-/-), wild-type, and MR1(-/-) non-Tg mice. Overall, we demonstrate considerable functional diversity of MAIT cell responses, as well as that MR1-restricted MAIT cells are important for tuberculosis protective immunity.

Sakala IG, et al. *J Immunol.* 2015 Jul 15;195(2):587-601. doi: 10.4049/jimmunol.1402545.

3. Niacin, nicotinic acid, vitamin B3

Like riboflavin, niacin and nicotinic acid are central to metabolism and biochemistry. *M. Tuberculosis* constitutively produces niacin, unlike other mycobacteria, which is the basis of the biochemical niacin test to speciate mycobacteria. *M.tb.* is niacin-positive. Nicotinic acid is a precursor of several anti-TB drugs: INH is isonicotinic acid hydrazone, ethio/prothionamide and pyrazinamide also derive from nicotinic acid. Niacin has anti-TB activity itself but at doses that elicit unpleasant side effects. In rare instances, pellagra (niacin deficiency) has been associated with isoniazid treatment in communities with marginal niacin status, especially those with corn-based staples.

Big brains, meat, tuberculosis and the nicotinamide switches: co-evolutionary relationships with modern repercussions on longevity and disease?

Meat eating has been an important trigger for human evolution however the responsible component in meat has not been clearly identified. Here we propose that the limiting factors for expanding brains and increasing longevity were the micronutrient nicotinamide (vitamin B3) and the metabolically related essential amino-acid, tryptophan. Meat offers significant sourcing challenges and lack causes a deficiency of nicotinamide and tryptophan and consequently the energy carrier nicotinamide adenine dinucleotide (NAD) that gets consumed in regulatory circuits important for survival, resulting in premature ageing, poor cognition and brain atrophy. If a trophic supply of dietary nicotinamide/tryptophan is so essential for building brains, constraining their size and connectivity, we hypothesise that back-up mechanisms to ensure the supply evolved. One strategy may be increasing the reliance on gut symbionts to break down celluloses that produces NADH and only nicotinamide indirectly, and may cause diarrhoea. We suggest that a direct supplier was the chronic mycobacterial infection tuberculosis (TB) that is a surprise candidate but it co-evolved early, does not inevitably cause disease (90-95% of those infected are healthy), and secretes (and is inhibited by) nicotinamide. We hypothesise that TB evolved first as a symbiont that enabled humans to cope with short-lived shortages of meat and only later behaved as a pathogen when the supply deteriorated chronically, for those in poverty. (TB immunology and epidemiology is riddled with paradoxes for a conventional pathogen). We test this in pilot data showing that sharp declines in TB (and diarrhoea) - 'environmental enteropathy' strongly correlate with increasing meat consumption and therefore nicotinamide exposure, unlike later onset cancers and Parkinson's disease that increased in incidence, perhaps - as we propose a hypothetical hypervitaminosis B3 (to include obesity and the metabolic syndrome) - as the trade-off for increased brain power and longevity, a recently evolved human characteristic. *Williams AC, Dunbar RI. Med Hypotheses. 2014 Jul;83(1):79-87. doi: 10.1016/j.mehy.2014.04.003.*

4. Pantothenic acid, vitamin B5

Pantothenic acid is effective in a mouse model of TB and in vitro. Its anti-tb activity was investigated in the early years of TB drug discovery along with streptomycin and viomycin. Also, extensive publications in Russian language literature.

Vitamin B5 Reduces Bacterial Growth via Regulating Innate Immunity and Adaptive Immunity in Mice Infected with Mycobacterium tuberculosis.

Studies have found that vitamin B5 (VB5) can promote epithelial cells to express inflammatory cytokines. We aimed to examine the proinflammatory and antibacterial effect of VB5 in macrophages infected with *Mycobacterium tuberculosis* (MTB) strain H37Rv and the therapeutic potential of VB5 *in vivo* with tuberculosis. We investigated the activation of inflammatory signal molecules (NF- κ B, AKT, JNK, ERK, and p38), the expression of two primary inflammatory cytokines (tumor necrosis factor and interleukin-6) and the bacterial burdens in H37Rv-infected macrophages stimulated with VB5 to explore the effect of VB5 on the inflammatory and antibacterial responses of macrophages. We further treated the H37Rv-infected mice with VB5 to explore VB5's promotion of the clearance of H37Rv in the lungs and the effect of VB5 on regulating the percentage of inflammatory cells. **Our data showed that VB5 enhanced the phagocytosis and inflammatory response in macrophages infected with H37Rv. Oral administration of VB5 decreased the number of colony-forming units of H37Rv in lungs of mice at 1, 2, and 4 weeks after infection. In addition, VB5 regulated the percentage of macrophages and promoted CD4+ T cells to express interferon- γ and interleukin-17; however, it had no effect on the percentage of polymorphonuclear neutrophils, CD4+ and CD8+ T cells.** In conclusion, VB5 significantly inhibits the growth of MTB by regulating innate immunity and adaptive immunity.

He W, et al. Front Immunol. 2018 Feb 26;9:365. doi: 10.3389/fimmu.2018.00365. PMID: 29535733

5. Pyridoxine, vitamin B6

Vit. B6 is routinely used in TB treatment together with INH to prevent neuropathy, with CYS to prevent CNS toxicity, and with linezolid to prevent neuropathy. There were no updates here.

6. Biotin, vitamin B7

Biotin is essential to M.tb. metabolism. M.tb. synthesizes its own biotin, does not scavenge from host. In fact, the biotin biosynthesis pathway is a target for anti-TB drug development.

The Role of Biotin in Bacterial Physiology and Virulence: a Novel Antibiotic Target for Mycobacterium tuberculosis.

Biotin is an essential cofactor for enzymes present in key metabolic pathways such as fatty acid biosynthesis, replenishment of the tricarboxylic acid cycle, and amino acid metabolism. Biotin is synthesized de novo in microorganisms, plants, and fungi, but this metabolic activity is absent in mammals, making biotin biosynthesis an attractive target for antibiotic discovery. In particular, biotin biosynthesis plays important metabolic roles as the sole source of biotin in all stages of the Mycobacterium tuberculosis life cycle due to the lack of a transporter for scavenging exogenous biotin. Biotin is intimately associated with lipid synthesis where the products form key components of the mycobacterial cell membrane that are critical for bacterial survival and pathogenesis. In this review we discuss the central role of biotin in bacterial physiology and highlight studies that demonstrate the importance of its biosynthesis for virulence. The structural biology of the known biotin synthetic enzymes is described alongside studies using structure-guided design, phenotypic screening, and fragment-based approaches to drug discovery as routes to new antituberculosis agents.

Salaemae W, et al. Microbiol Spectr. 2016 Apr;4(2). doi: 10.1128/microbiolspec.VMBF-0008-2015.

Investigation of (S)-(-)-Acidomycin: A Selective Antimycobacterial Natural Product That Inhibits Biotin Synthase.

The synthesis, absolute stereochemical configuration, complete biological characterization, mechanism of action and resistance, and pharmacokinetic properties of (S)-(-)-acidomycin are described. Acidomycin possesses promising antitubercular activity against a series of contemporary drug susceptible and drug-resistant M. tuberculosis strains (minimum inhibitory concentrations (MICs) = 0.096-6.2 μ M) but is inactive against nontuberculosis mycobacteria and Gram-positive and Gram-negative pathogens (MICs > 1000 μ M). Complementation studies with biotin biosynthetic pathway intermediates and subsequent biochemical studies confirmed acidomycin inhibits biotin synthesis with a K_i of approximately 1 μ M through the competitive inhibition of biotin synthase (BioB) and also stimulates unproductive cleavage of S-adenosyl-L-methionine (SAM) to generate the toxic metabolite 5'-deoxyadenosine. Cell studies demonstrate acidomycin selectively accumulates in M. tuberculosis providing a mechanistic basis for the observed antibacterial activity. The development of spontaneous resistance by M. tuberculosis to acidomycin was difficult, and only low-level resistance to acidomycin was observed by overexpression of BioB. Collectively, the results provide a foundation to advance acidomycin and highlight BioB as a promising target.

Bockman MR, et al. ACS Infect Dis. 2019 Apr 12;5(4):598-617. doi: 10.1021/acinfed.8b00345.

The Biotin Biosynthetic Pathway in Mycobacterium tuberculosis is a Validated Target for the Development of Antibacterial Agents.

Mycobacterium tuberculosis, responsible for Tuberculosis (TB), remains the leading cause of mortality among infectious diseases worldwide from a single infectious agent, with an estimated 1.7 million deaths in 2016. Biotin is an essential cofactor in M. tuberculosis that is required for lipid biosynthesis and gluconeogenesis. [M. tuberculosis relies on de novo biotin biosynthesis](#) to obtain this vital cofactor since it cannot scavenge sufficient biotin from a mammalian host. The biotin biosynthetic pathway in M. tuberculosis has been well studied and rigorously genetically validated providing a solid foundation for medicinal chemistry efforts. This review examines the mechanism and structure of the enzymes involved in biotin biosynthesis and ligation, summarizes the reported genetic validation studies of the pathway, and then analyzes the most promising inhibitors and natural products obtained from structure-based drug [design and phenotypic screening](#).

Bockman MR, et al. Curr Med Chem. 2020;27(25):4194-4232. doi: 10.2174/0929867326666190119161551. PMID: 30663561

7. Folic acid (folate), vitamin B9

Folate status in tuberculosis: a study in the Guinea Savanna of Nigeria.

Serum folate (SF) and red cell folate (RCF) measurements were carried out by a microbiological (L. casei) method on 152 patients before treatment and on 94 patients (58 defaulted) at varying intervals during treatment. Mean SF (3.9 micrograms/l) of tuberculous subjects was significantly lower than that of the normal mean (6.8 micrograms/l; P less than 0.001) but their mean RCF (212.9 micrograms/l) was not significantly different from the normal mean RCF (220 micrograms/l). These findings indicate at least a state of incipient folate depletion. Though the mean RCF was normal, 32 patients had low RCF values of less than 120 micrograms/l while in 16 patients RCF levels were less than 100 micrograms/l. Only 10 ill subjects--all with disseminated disease--showed both very low SF (less than 2.0 micrograms/l) and low RCF (less than 120 micrograms/l). Thus, established folate deficiency was also clearly demonstrated in a proportion of the affected individuals. In the patient population as a whole, however, no relationship was detected between folate levels (SF, RCF) and (a) extent of disease (b) haemoglobin or haematocrit. Antituberculous treatment was accompanied by a rise in mean SF and RCF which, however, were still less than the normal mean values.

Mycobacterium tuberculosis folate metabolism and the mechanistic basis for para-aminosalicylic acid susceptibility and resistance.

Herein, we discuss previous studies that demonstrate PAS-mediated disruption of iron acquisition, as well as recent genetic, biochemical, and metabolomic studies that have revealed that PAS is a prodrug that ultimately corrupts one-carbon metabolism through inhibition of the formation of reduced folate species. We also discuss findings from laboratory and clinical isolates that link alterations in folate metabolism to PAS resistance.

Minato Y, et al. *Antimicrob Agents Chemother.* 2015 Sep;59(9):5097-106. doi: 10.1128/AAC.00647-15

8. Cobalamin, vitamin B12

M. Tb uses vitamin B12 like we do. It both scavenges and synthesizes vitamin B12.

Vitamin B(12) metabolism in Mycobacterium tuberculosis.

Mycobacterium tuberculosis is included among a select group of bacteria possessing the capacity for de novo biosynthesis of vitamin B12, the largest and most complex natural organometallic cofactor. The bacillus is also able to scavenge B12 and related corrinoids utilizing an ATP-binding cassette-type protein that is distinct from the only known bacterial B12-specific transporter, BtuFCD. Consistent with the inferred requirement for vitamin B12 for metabolic function, the M. tuberculosis genome encodes two B12 riboswitches and three B12-dependent enzymes. Two of these enzymes have been shown to operate in methionine biosynthesis (MetH) and propionate utilization (MutAB), while the function of the putative nrdZ-encoded ribonucleotide reductase remains unknown. Taken together, these observations suggest that M. tuberculosis has the capacity to regulate core metabolic functions according to B12 availability - whether acquired via endogenous synthesis or through uptake from the host environment - and, therefore, imply that there is a role for vitamin B12 in pathogenesis, which remains poorly understood.

Gopinath K, et al. *Future Microbiol.* 2013 Nov;8(11):1405-18. doi: 10.2217/fmb.13.113.

Ileocaecal tuberculosis: an under-recognised cause of vitamin B(12) deficiency.

A combination of anaemia and knuckle pigmentation should always raise concern for megaloblastic anaemia. As the terminal ileum is the site of vitamin B12 absorption and also the commonest site of abdominal tuberculosis, a clinical triad of prolonged fever, knuckle pigmentation and right lower quadrant abdominal tenderness should suggest ileocaecal tuberculosis in endemic areas.

Pannu AK, Palanisamy DR. *Trop Doct.* 2019 Apr;49(2):143-144. doi: 10.1177/0049475518816590.

Serum cobalamin concentration in tuberculosis. A study in the Guinea savanna of Nigeria.

The concentration of serum cobalamin (SB12) was estimated in tuberculous Nigerian patients so as to define the role of this vitamin in the pathogenesis of the anaemia of tuberculosis. Complete data in 147 infected subjects before and during treatment and in 50 asymptomatic blood donors revealed no significant difference between mean serum cobalamin (mean SB12) concentrations of patients of both sexes and the asymptomatic controls. No differences were demonstrated between mean SB12 of groups of patients subdivided on the basis of degree of anaemia. Moreover, there was no significant correlation between Hb and SB12. Mean SB12 was essentially similar in patients with localised (300.7 pmol/l) and disseminated (311.1 pmol/l) disease. In the 121 patients with pulmonary tuberculosis, mean SB12 of those with one affected lung (291.9 pmol/l) was not significantly different from those with infection of both lungs (303.5 pmol/l). Antituberculosis therapy did not cause a fall in mean SB12. This study does not provide evidence of any significant abnormality in serum cobalamin concentration in Nigerians suffering from localised or disseminated tuberculosis.

Knox-Macaulay HH. *Trop Geogr Med.* 1990 Apr;42(2):146-50.

2. Vitamin C

***Mycobacterium tuberculosis* is extraordinarily sensitive to killing by a vitamin C-induced Fenton reaction**

Drugs that kill tuberculosis more quickly could shorten chemotherapy significantly. In *Escherichia coli*, a common mechanism of cell death by bactericidal antibiotics involves the generation of highly reactive hydroxyl radicals via the Fenton reaction. [Here we show that vitamin C, a compound known to drive the Fenton reaction, sterilizes cultures of drug-susceptible and drug-resistant *Mycobacterium tuberculosis*, the causative agent of tuberculosis. While *M. tuberculosis* is highly susceptible to killing by vitamin C, other Gram-positive and Gram-negative pathogens are not.](#) The bactericidal activity of vitamin C against *M.*

tuberculosis is dependent on high concentrations, high ferrous ion levels and reactive oxygen species production and causes a pleiotropic effect affecting several biological processes. This study enlightens the possible benefits of adding vitamin C to an anti-tuberculosis regimen and suggests that the development of drugs that generate high oxidative burst could be of great use in tuberculosis treatment.

Catherine Vilchèze, et al. *Nat Commun.* 2013; 4: 1881. doi: 10.1038/ncomms2898

Combination of anti-tuberculosis drugs with vitamin C or NAC against different *Staphylococcus aureus* and *Mycobacterium tuberculosis* strains.

BACKGROUND: Hepatotoxicity due to anti tuberculosis drugs, rifampin and isoniazid, is a major problem in tuberculosis patients. Vitamin C, an antioxidant, and N-acetyl cysteine (NAC), a scavenger of active metabolites, reduce the hepatotoxicity. The aim of present study was to investigate the effect of vitamin C and NAC individually on the antibacterial activity of anti tuberculosis drugs against *Mycobacterium tuberculosis* and *Staphylococcus aureus* strains.

METHODS: The MICs of each compound against all strains were determined in 96 wells plate. Rifampin was tested at serial two fold concentrations alone or in combination with NAC or vitamin C.

RESULTS: The MIC of rifampin against different strains of *S. aureus* was 0.008-0.032 µg/ml. The MIC of rifampin and isoniazid against *M. tuberculosis* strains were 40 and 0.2 µg/ml, respectively. Vitamin C and NAC had no antibacterial activity against all strains. MIC of rifampin was reduced two fold by combination with vitamin C for all *S. aureus* strains, while NAC did not affect the antibacterial activity of rifampin. [Vitamin C and NAC had remarkable effects on the antibacterial activity of anti-tuberculosis drugs against *M. tuberculosis*.](#)

CONCLUSIONS: Synergistic effects were observed between rifampin or isoniazid and vitamin C against all tested strains. However, combination therapy of rifampin and isoniazid with NAC was not being effective. This study highlighted the advantages of combination of anti-tuberculosis drugs and vitamin C to eradicate the microbial infections.

Khameneh B, et al. *Microb Pathog.* 2016 Apr;93:83-7. doi: 10.1016/j.micpath.2015.11.006.

Vitamin C Potentiates the Killing of *Mycobacterium tuberculosis* by the First-Line Tuberculosis Drugs Isoniazid and Rifampin in Mice.

We previously discovered that high concentrations of vitamin C sterilize cultures of drug-susceptible and drug-resistant *Mycobacterium tuberculosis*. Here, we tested subinhibitory concentration of vitamin C in combination with TB drugs against *M. tuberculosis* in vitro and in a mouse model of *M. tuberculosis* infection. In vivo, we showed that the vitamin C level in mouse serum can be increased by intraperitoneal injection of vitamin C to reach vitamin C levels close to the concentrations required for activity in vitro. [Although vitamin C had no activity by itself in *M. tuberculosis*-infected mice, the combination of vitamin C with the first-line TB drugs isoniazid and rifampin reduced the bacterial burden in the lungs of *M. tuberculosis*-infected mice faster than isoniazid and rifampin combined in two independent experiments. These experiments suggest that the addition of vitamin C to first-line TB drugs could shorten TB treatment.](#) Vitamin

C, an inexpensive and nontoxic compound, could easily be added to the TB pharmacopeia to substantially improve chemotherapy outcome, which would have a significant impact on the worldwide TB community.

Vilchèze C, et al. *Antimicrob Agents Chemother.* 2018 Feb 23;62(3):e02165-17. doi: 10.1128/AAC.02165-17.

Multifaceted remodeling by vitamin C boosts sensitivity of *Mycobacterium tuberculosis* subpopulations to combination treatment by anti-tubercular drugs.

Bacterial dormancy is a major impediment to the eradication of tuberculosis (TB), because currently used drugs primarily target actively replicating bacteria. Therefore, decoding of the critical survival pathways in dormant tubercle bacilli is a research priority to formulate new approaches for killing these bacteria. Employing a network-based gene expression analysis approach, we demonstrate that [redox active vitamin C \(vit C\) triggers a multifaceted and robust adaptation response in *Mycobacterium tuberculosis* \(Mtb\) involving ~ 67% of the genome. Vit C-adapted bacteria display well-described features of dormancy, including growth stasis and progression to a viable but non-culturable \(VBNC\) state, loss of acid-fastness and reduction in length, dissipation of reductive stress through triglyceride \(TAG\) accumulation, protective response to oxidative stress, and tolerance to first line TB drugs. VBNC bacteria are reactivatable upon removal of vit C and they recover drug susceptibility properties. Vit C synergizes with pyrazinamide, a unique TB drug with sterilizing activity, to kill dormant and replicating bacteria, negating any tolerance to rifampicin and isoniazid in combination treatment in both in-vitro and intracellular infection models. Finally, the vit C multi-stress redox models described here also offer a unique opportunity for concurrent screening of compounds/combinations active against heterogeneous subpopulations of Mtb. \[These findings suggest a novel strategy of vit C adjunctive therapy by modulating bacterial physiology for enhanced efficacy of combination chemotherapy with existing drugs, and also possible synergies to guide new therapeutic combinations towards accelerating TB treatment.\]\(#\)](#)

Sikeri K, et al. *Redox Biol.* 2018 May;15:452-466. doi: 10.1016/j.redox.2017.12.020

F. Minerals

Minerals differ fundamentally from vitamins because they are inorganic elements, mostly metals, not complex biological molecules. They cannot be synthesized by biological systems. They must be acquired from the environment. We stand upright thanks to calcium and phosphorous. Apart from structural roles, minerals play central roles in hundreds or thousands of biochemical reactions and metabolic processes many of which are the same or similar between pathogenic prokaryotes and their eukaryotic hosts. Pathogenic microbes require these same metals for many of the same biochemical pathways as host, but each also has distinct requirements, pathways, and biologically active forms for the metal ion. Host and pathogen compete for the same minerals that are ingested and absorbed and stored by the host. For example, human cells, organelles and proteins sequester iron away from the bacillus as part of their defense against the pathogen; while *M.tb.* secretes highly avid iron scavenging proteins to secure its iron requirements. Thus, deficiency in the host may be worse for the microbe than for the person, having a net clinical benefit. A person's iron deficiency can be treated after their TB is cured. Conversely, a surplus in the host can promote the pathogen's growth and replication, as in TB in people with iron overload. Thus, treating iron deficiency with supplemental iron can exacerbate TB, malaria, certain fungi and other I.D. caused by pathogens with specific iron requirements. Underscores the need for controlled trials because in vivo situation may be counterintuitive.

1. Iron

Historical review:

Iron, mycobacteria and tuberculosis

Ratledge C. Tuberculosis (2004) 84: 110-130.

Targeting iron acquisition by *Mycobacterium tuberculosis*

In *M.tb.*, siderophore molecules used for iron acquisition are good targets because pathogen survival and virulence is directly related to iron availability. Indeed, a key host defense mechanism is the production of siderocalins that sequester iron-laden siderophores, and *M. tuberculosis* replicates poorly in the absence of these siderophores. A number of investigators have recently targeted siderophores or their synthesis for the development of novel anti-tubercular therapeutics. One group has synthesized 'dominant negative' mycobactin siderophore analogues that significantly inhibit bacterial growth. Several other groups have developed agents that directly inhibit enzymes involved in siderophore synthesis. A different approach is to target the iron dependent regulator protein (IdeR) that represses siderophore synthesis genes and virulence factors when sustainable iron levels have been achieved. Loss of the repression leads to iron overload and oxidative damage. In contrast, enhanced IdeR repression at low iron levels attenuates *M. tuberculosis* virulence in mice. The structural basis for iron activation and IdeR binding to DNA has been recently reported and these insights have enabled the structure-based design of agents that target IdeR function. Small peptides that either enhance IdeR repression or inhibit IdeR dimerization demonstrate that IdeR activity can be rationally modulated.

Ryan R Monfeli, Craig Beeson. Infect Disord Drug Targets. 2007 Sep;7(3):213-20. doi: 10.2174/187152607782110031. PMID: 17897057

Iron overload and tuberculosis: a case for iron chelation therapy

Elevated levels of iron impair immune defense mechanisms, and specifically the macrophage function of innate immunity. Iron enhances *Mycobacterium tuberculosis* infection, *M. tuberculosis* replication, progression to clinical disease and death from tuberculosis (TB). Chelation of iron in individuals with an excessive iron burden may reduce *M. tuberculosis* viability and replication, restore host defense mechanisms and could find application in the prevention and treatment strategies in settings where both iron overload and TB are prevalent. The objective of this paper was to summarize recent literature on the role of iron in TB pathogenesis and to examine the potential of iron chelation therapy. [The literature confirms a key role for iron in mycobacterial virulence. The ability of chelation to enhance host effector mechanisms and to inhibit replication of various pathogens justifies further studies into iron chelation as a potential additive therapy for TB.](#)

L. Cronje, L. Bornman. Int J Tuberc Lung Dis. 2005 Jan;9(1):2-9. PMID: 15675543

Further reading about iron homeostasis and acquisition in *M.tb.*, iron sequestration as a host defense, iron targeting strategies for host-directed therapy, iron overload and chelation, and diagnostic tests based on iron to distinguish active from quiescent TB. These reports are at the in vitro level and have not (yet) made the transition to human experimental, therapeutic, or programmatic implementation.

1. Iron Homeostasis in Mycobacterium tuberculosis: Mechanistic Insights into Siderophore-Mediated Iron Uptake. *Sritharan M. J Bacteriol.* 2016 Aug 25;198(18):2399-409. doi: 10.1128/JB.00359-16. PMID: 27402628
2. Iron homeostasis in Mycobacterium tuberculosis is essential for persistence. *Pandey M, et al. Sci Rep.* 2018 Nov 26;8(1):17359. doi: 10.1038/s41598-018-35012-3. PMID: 30478257
3. Heparin inhibits intracellular Mycobacterium tuberculosis bacterial replication by reducing iron levels in human macrophages. *Abreu R, et al. Sci Rep.* 2018 May 8;8(1):7296. doi: 10.1038/s41598-018-25480-y.
4. Iron Acquisition in Mycobacterium tuberculosis. *Chao A, et al. Chem Rev.* 2019 Jan 23;119(2):1193-1220. doi: 10.1021/acs.chemrev.8b00285. (Discusses potential for novel therapeutics).
5. Genome-wide Phenotypic Profiling Identifies and Categorizes Genes Required for Mycobacterial Low Iron Fitness. *Dragset MS, et al. Sci Rep.* 2019 Aug 6;9(1):11394. doi: 10.1038/s41598-019-47905-y. PMID: 31388080
6. The Capacity of Mycobacterium tuberculosis To Survive Iron Starvation Might Enable It To Persist in Iron-Deprived Microenvironments of Human Granulomas. *Kurthkoti K, et al. mBio.* 2017 Aug 15;8(4):e01092-17. doi: 10.1128/mBio.01092-17.
7. A major role for ferroptosis in Mycobacterium tuberculosis-induced cell death and tissue necrosis. *Amaral EP, et al. J Exp Med.* 2019 Mar 4;216(3):556-570. doi: 10.1084/jem.20181776. PMID: 30787033
8. Altered drug efflux under iron deprivation unveils abrogated MmpL3 driven mycolic acid transport and fluidity in mycobacteria. *Pal R, et al. Biometals.* 2019 Feb;32(1):49-63. doi: 10.1007/s10534-018-0157-8. (Discusses potential for synergism with anti-TB drugs)
9. Modulating Iron for Metabolic Support of TB Host Defense. *Phelan JJ, et al. Front Immunol.* 2018 Oct 15;9:2296. doi: 10.3389/fimmu.2018.02296. PMID: 30374347
10. A combination of iron metabolism indexes and tuberculosis-specific antigen/phytohemagglutinin ratio for distinguishing active tuberculosis from latent tuberculosis infection. *Luo Y, et al. Int J Infect Dis.* 2020 Aug;97:190-196. doi: 10.1016/j.ijid.2020.05.109. PMID: 32497795
11. Biomarkers of iron metabolism facilitate clinical diagnosis in Mycobacterium tuberculosis infection. *Dai Y, et al. Thorax.* 2019 Dec;74(12):1161-1167. doi: 10.1136/thoraxjnl-2018-212557. PMID: 31611342

2. Zinc, often with other micronutrients

Mycobacteria, metals, and the macrophage.

Mycobacterium tuberculosis is a facultative intracellular pathogen that thrives inside host macrophages. A key trait of M. tuberculosis is to exploit and manipulate metal cation trafficking inside infected macrophages to ensure survival and replication inside the phagosome. Here, we describe the recent fascinating discoveries that the mammalian immune system responds to infections with M. tuberculosis by overloading the phagosome with copper and zinc, two metals which are essential nutrients in small quantities but are toxic in excess. M. tuberculosis has developed multi-faceted resistance mechanisms to protect itself from metal toxicity including control of uptake, sequestration inside the cell, oxidation, and efflux. The host response to infections combines this metal poisoning strategy with nutritional immunity mechanisms that deprive M. tuberculosis from metals such as iron and manganese to prevent bacterial replication. Both immune mechanisms rely on the translocation of metal transporter proteins to the phagosomal membrane during the maturation process of the phagosome. This review summarizes these recent findings and discusses how metal-targeted approaches might complement existing TB chemotherapeutic regimens with novel anti-infective therapies.

Neyrolles O, et al. Immunol Rev. 2015 Mar;264(1):249-63. doi: 10.1111/immr.12265. PMID: 25703564

A double-blind, placebo-controlled study of vitamin A and zinc supplementation in persons with tuberculosis in Indonesia: effects on clinical response and nutritional status.

To investigate whether vitamin A and zinc supplementation increases the efficacy of antituberculosis treatment with

respect to clinical response and nutritional status.

DESIGN: In this double-blind, placebo-controlled trial, patients with newly diagnosed tuberculosis were divided into 2 groups. One group (n = 40) received 1500 retinol equivalents (5000 IU) vitamin A (as retinyl acetate) and 15 mg Zn (as zinc sulfate) daily for 6 mo (micronutrient group). The second group (n = 40) received a placebo. Both groups received the same (WHO) antituberculosis treatment. Clinical examinations, assessments of micronutrient status, and anthropometric measurements were carried out before and after 2 and 6 mo of antituberculosis treatment.

RESULTS: At baseline, 64% of patients had a body mass index (in kg/m²) < 18.5, 32% had plasma retinol concentrations < 0.70 micromol/L, and 30% had plasma zinc concentrations < 10.7 micromol/L. After antituberculosis treatment, plasma zinc concentrations were not significantly different between groups. Plasma retinol concentrations were significantly higher in the micronutrient group than in the placebo group after 6 mo (P < 0.05). [Sputum conversion \(P < 0.05\) and resolution of X-ray lesion area \(P < 0.01\) occurred earlier in the micronutrient group.](#)

CONCLUSION: [Vitamin A and zinc supplementation improves the effect of tuberculosis medication after 2 mo of antituberculosis treatment and results in earlier sputum smear conversion.](#)

Karyadi E, et al. Am J Clin Nutr. 2002 Apr;75(4):720-7. doi: 10.1093/ajcn/75.4.720. PMID: 11916759.

The effect of therapeutic zinc supplementation among young children with selected infections: a review of the evidence

OBJECTIVE: To evaluate the impact of zinc supplementation as an adjunct in the treatment of diarrhea, pneumonia, malaria, and tuberculosis in children under 5 years of age.

METHODS: A comprehensive literature search of electronic databases to identify randomized, controlled trials on the topic was undertaken in January 2008. Eligible studies identified on search were reviewed by the authors and data extraction was done. Statistical analyses were performed with the use of Review Manager software.

RESULTS: Current analysis of the adjunctive therapeutic benefit of zinc in acute diarrhea corroborates existing reviews and provides evidence of reduction in the duration of acute diarrhea by 0.5 day (p = .002) in children under 5 years of age. However, zinc supplementation is found to have no beneficial impact in infants under 6 months of age. A beneficial effect of zinc as an adjunctive treatment is also found in persistent diarrhea, the duration of which is reduced by 0.68 day (p < .0001). [Evidence of the benefit of zinc supplementation in pneumonia and malaria is insufficient, whereas no studies are available in children with tuberculosis.](#)

CONCLUSIONS: [The existing literature provides evidence of a beneficial effect of therapeutic zinc supplementation in the reduction of the duration of acute and persistent diarrhea. However, evidence for its impact on pneumonia, malaria, and tuberculosis in children under 5 years of age is insufficient and needs further evaluation.](#)

Haider BA, et al. Food Nutr Bull. 2009 Mar;30(1 Suppl):S41-59. doi: 10.1177/15648265090301S104. PMID: 19472601

Zinc and vitamin A supplementation fails to reduce sputum conversion time in severely malnourished pulmonary tuberculosis patients in Indonesia. (Same abstract in vit. A and multiple micronutrients)

BACKGROUND: A previous study showed that combination of zinc and vitamin A reduced sputum conversion time in pulmonary tuberculosis (TB) patients.

OBJECTIVE: We studied the efficacy of which single micronutrient contributed more to the sputum conversion time.

METHODS: In a double-blind randomized community trial, newly sputum smear positive pulmonary TB patients were assigned randomly to receive zinc, vitamin A, zinc + vitamin A or placebo on top of TB treatment.

RESULTS: Initially, 300 patients were enrolled, and 255 finished the treatment. Most patients were severely malnourished (mean BMI 16.5 ±2.2 Kg/m²). Patients in the zinc + vitamin A group showed earlier sputum conversion time (mean 1.9 weeks) compared with that in the other groups; however the difference was not significant. Also, no benefit could be demonstrated of any of the used supplementations on clinical, nutritional, chest x-ray, or laboratory findings.

CONCLUSIONS: [This study among severely malnourished TB patients, did not confirm that single or combined supplementation of zinc and vitamin A significantly reduced sputum conversion time or had other significant benefit.](#) *Pakasi TA, et al. Nutr J. 2010 Sep 28;9:41. doi: 10.1186/1475-2891-9-41. PMID: 20920186*

Randomized controlled trial of zinc and vitamin A as co-adjuncts for the treatment of pulmonary tuberculosis. (See also under multiple micronutrients)

OBJECTIVE: To assess the efficacy of weekly zinc or zinc plus retinol as adjuncts for the treatment of pulmonary tuberculosis.

METHODS: Double-blind, randomized, placebo-controlled trial in 350 patients >15 years old with smear-positive tuberculosis in Nigeria. In addition to antituberculous treatment, patients were randomly allocated to weekly supplements of zinc (90 mg), zinc plus retinol (5000 IU) or placebos for 6 months. Primary outcomes were time to sputum smear conversion and resolution of radiographic abnormalities.

RESULTS: After 8 weeks of treatment, 68% had achieved sputum smear conversion, and the median conversion time was 6.5 weeks. Hazard ratios (HR, 95%CI) for sputum conversion relative to the placebo group were not significant for zinc (1.07, 0.92-1.29) or zinc plus retinol (0.89, 0.76-1.07). Significant predictors of time to sputum conversion were lung abnormality score, sputum smear grade, age and serum C-reactive protein. There were no significant differences between supplement groups in clinical, radiological or laboratory outcomes at 2 months or 6 months. There were 9, 9 and 2 deaths in patients receiving zinc, zinc plus retinol or placebos, respectively. Mortality in those who received zinc (HR 1.71, 0.88-3.58) or zinc plus retinol (HR 1.54, 0.78-3.26) did not differ significantly from those who received placebos. Most deaths occurred in patients co-infected with HIV.

CONCLUSIONS: [Supplementation with zinc or zinc plus retinol did not lead to better outcomes than placebos.](#)

Lawson L, et al. Trop Med Int Health. 2010 Dec;15(12):1481-90. doi: 10.1111/j.1365-3156.2010.02638.x. PMID: 20958890

Randomized controlled trial of zinc and vitamin A as co-adjuvants for the treatment of pulmonary tuberculosis.

OBJECTIVE: To assess the efficacy of weekly zinc or zinc plus retinol as adjuncts for the treatment of pulmonary tuberculosis.

METHODS: Double-blind, randomized, placebo-controlled trial in 350 patients >15 years old with smear-positive tuberculosis in Nigeria. In addition to antituberculous treatment, patients were randomly allocated to weekly supplements of zinc (90 mg), zinc plus retinol (5000 IU) or placebos for 6 months. Primary outcomes were time to sputum smear conversion and resolution of radiographic abnormalities.

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CONCLUSIONS: Supplementation with zinc or zinc plus retinol did not lead to better outcomes than placebos.

Lawson L, et al. Trop Med Int Health. 2010 Dec;15(12):1481-90. doi: 10.1111/j.1365-3156.2010.02638.x. PMID: 20958890

Adjunctive micronutrient supplementation for pulmonary tuberculosis.

OBJECTIVE: To assess the effect of micronutrient supplementation on tuberculosis (TB) patient outcomes.

MATERIAL AND METHODS: The randomized, double-blinded, placebo-controlled study was conducted in pulmonary TB patients undergoing directly observed treatment short course/ tratamiento acortado estrictamente supervisado (TAES/ DOTS) at IMSS in Ciudad Juarez, Chihuahua, Mexico, who were recruited during August 2005-July 2006. Consecutive patients received zinc and vitamin A supplements or matched placebo for four months. Dietary intake, blood zinc and vitamin A,

immune response (IFN-gamma, TNF-alpha, and IL-10 mRNA), and sputum smear conversion were measured.

RESULTS: [The proportion of micronutrient compared to placebo group subjects with a negative sputum smear by month 3 was significantly increased \(p= 0.03\).](#) This occurred subsequent to increased TNF-alpha and IFN-gamma and decreased IL-10 observed at month 2. Micronutrient supplementation appeared to accelerate the beneficial therapeutic effect of chemotherapy.

CONCLUSIONS: [The earlier elimination of bacilli from sputum was associated with improved zinc status and Th1 immune response. The therapeutic effect of vitamin A was less evident.](#)

Armijos RX, et al. Salud Publica Mex. 2010 May-Jun;52(3):185-9. doi: 10.1590/s0036-36342010000300001. PMID: 20485880

The effect of vitamin A and zinc supplementation on treatment outcomes in pulmonary tuberculosis: a randomized controlled trial.

OBJECTIVE: To assess the efficacy of vitamin A and zinc supplementation on sputum smear and culture conversion and time to culture detection in adults with sputum smear-positive pulmonary tuberculosis.

DESIGN: Participants attending a primary care tuberculosis clinic in Cape Town, South Africa, were randomly assigned to receive micronutrients (single dose of 200,000 IU retinyl palmitate plus 15 mg Zn/d for 8 wk) or matching placebo.

RESULTS: The participants (n = 154) were randomly assigned to the micronutrient (n = 77) or placebo (n = 77) group. Twenty participants were HIV infected (13%), and 12 participants had an unknown HIV status (8%). No differences in time to smear or culture conversion were observed between the treatment groups by Kaplan-Meier analysis (P = 0.15 and P = 0.38, respectively; log-rank test). Log-logistic regression analysis found no significant group interaction effect in time to culture detection over the 8-wk period (P = 0.32). No significant differences in weight gain (2.3 ±3.5 compared with 2.2 ±2.4 kg, P = 0.68) or radiologic resolution were observed between the treatment groups.

CONCLUSION: Supplementation with vitamin A and zinc did not affect treatment outcomes in participants with pulmonary tuberculosis at 8 wk.

Visser ME, et al. *Am J Clin Nutr.* 2011 Jan;93(1):93-100. doi: 10.3945/ajcn.110.001784.PMID: 21068353

Effect of micronutrient supplementation on treatment outcomes in children with intrathoracic tuberculosis: a randomized controlled trial. (Zn v. MVI v. Zn+MVI v. placebo)

OBJECTIVE: To assess effect of micronutrient supplementation in children treated with antituberculosis therapy (ATT).

DESIGN: A randomized, double-blind, placebo-controlled trial that used a 2 × 2 factorial design was undertaken at 2 teaching hospitals in Delhi. Children with newly diagnosed intrathoracic tuberculosis were enrolled, and they received ATT together with daily supplementation for 6 mo with either zinc alone, micronutrients without zinc, micronutrients in combination with zinc, or a placebo. Main outcomes were weight gain and an improvement in a chest X-ray (CXR) lesion assessed at 6 mo of treatment.

RESULTS: A total of 403 children were enrolled and randomly assigned. A microbiological diagnosis of tuberculosis was confirmed in 179 children (44.4%). The median (95% CI) increase in weight-for-age z score at 6 mo was not significantly different between subjects who received micronutrients [0.75 (0.66, 0.84)] and those who did not receive micronutrients [0.76 (0.67, 0.85)] and between subjects who received zinc [0.76 (0.68, 0.85)] and those who did not receive zinc [0.75 (0.66, 0.83)]. An improvement in CXR was observed in 285 children, but there was no difference between those receiving zinc and no zinc or between those receiving micronutrients and no micronutrients after 6 mo of ATT. However, children who received micronutrients had a faster gain in height over 6 mo than did those who did not receive micronutrients (height-for-age z score $\Delta = 0.08$; $P = 0.014$).

CONCLUSIONS: Micronutrient supplementation did not modify the weight gain or clearance of lesions on CXR in children with intrathoracic tuberculosis. Micronutrient supplementation during treatment may improve height gain in children with intrathoracic tuberculosis.

Lodha R, et al. *Am J Clin Nutr.* 2014 Nov;100(5):1287-97. doi: 10.3945/ajcn.113.082255. PMID: 25332327

Elemental Ingredients in the Macrophage Cocktail: Role of ZIP8 in Host Response to Mycobacterium tuberculosis.

M.tb resides in a phagosomal niche within macrophages, where trace element concentrations impact the immune response, bacterial metal metabolism, and bacterial survival. The manipulation of micronutrients is a critical mechanism of host defense against infection. In particular, the human zinc transporter Zrt-/Irt-like protein 8 (ZIP8), one of 14 ZIP family members, is important in the flux of divalent cations, including zinc, into the cytoplasm of macrophages. It also has been observed to exist on the membrane of cellular organelles, where it can serve as an efflux pump that transports zinc into the cytosol. ZIP8 is highly inducible in response to *M.tb* infection of macrophages, and we have observed its localization to the *M.tb* phagosome. The expression, localization, and function of ZIP8 and other divalent cation transporters within macrophages have important implications for TB prevention and dissemination and warrant further study. In particular, given the importance of zinc as an essential nutrient required for humans and *M.tb*, it is not yet clear whether ZIP-guided zinc transport serves as a host protective factor or, rather, is targeted by *M.tb* to enable its phagosomal survival.

Pyle CJ, et al. *Int J Mol Sci.* 2017 Nov 9;18(11):2375. doi: 10.3390/ijms18112375. PMID: 29120360

Zinc depletion induces ribosome hibernation in mycobacteria.

Bacteria respond to zinc starvation by replacing ribosomal proteins that have the zinc-binding CXXC motif (C+) with their zinc-free (C-) paralogues. Consequences of this process beyond zinc homeostasis are unknown. Here, we show that the C-ribosome in *Mycobacterium smegmatis* is the exclusive target of a bacterial protein Y homolog, referred to as mycobacterial-specific protein Y (MPY), which binds to the decoding region of the 30S subunit, thereby inactivating the ribosome. MPY binding is dependent on another mycobacterial protein, MPY recruitment factor (MRF), which is induced on zinc depletion, and interacts with C- ribosomes. MPY binding confers structural stability to C- ribosomes, promoting survival of growth-arrested cells under zinc-limiting conditions. Binding of MPY also has direct influence on the dynamics of aminoglycoside-binding pockets of the C- ribosome to inhibit binding of these antibiotics. Together, our data suggest that zinc limitation leads to ribosome hibernation and aminoglycoside resistance in mycobacteria. Furthermore, our observation of the expression of the proteins of C- ribosomes in *Mycobacterium tuberculosis* in a mouse model of infection suggests that ribosome hibernation could be relevant in our understanding of persistence and drug tolerance of the pathogen encountered during chemotherapy of TB.

Li Y, et al. *Proc Natl Acad Sci U S A.* 2018 Aug 7;115(32):8191-8196. doi: 10.1073/pnas.1804555115. PMID: 30038002

Role of combined zinc, vitamin A, and fish oil supplementation in childhood tuberculosis.

This objective of this study was to determine benefit of one month combined supplementation (zinc, vitamin A, fish oil) along with anti-tuberculosis drugs (ATD) on increasing serum leptin levels and decreasing tumor necrosis factor-alpha (TNF-alpha) in children with tuberculosis (TB). A quasi experimental study was conducted on 22 children (aged 5-14 years) with a positive acid-fast bacilli (AFB) smear. The children were divided into 2 groups. Nutritional supplementation and ATD were given to group I while ATD only were given to group II.

Group I had a higher significant increase in serum leptin levels than group II ($p=0.034$). Group I had a significantly greater decrease in TNF-a levels than group II ($p=0.032$). No significant differences in retinol or zinc levels were seen between the two, but both groups had an increase after treatment. Both groups had a significant increase in BMI ($p<0.001$) post-treatment compared to pre-treatment.

Supplementation with zinc, vitamin A and fish oil is associated with a significant increase in leptin levels and a significant decrease in TNF-alpha levels among children treated for TB. No significant benefit was seen in BMI among children receiving supplementation compared to those without it, although ATD resulted in a significant increase in BMI in both groups.

Nenni V, et al. Southeast Asian J Trop Med Public Health. 2013 Sep;44(5):854-61. PMID: 24437320

3. Selenium

Effect of vitamin E and selenium supplementation on oxidative stress status in pulmonary tuberculosis patients.

BACKGROUND AND OBJECTIVE: Increased production of reactive oxygen species secondary to phagocyte respiratory burst occurs in pulmonary tuberculosis (TB). The present study evaluated the efficacy of vitamin E-selenium supplementation on oxidative stress in newly diagnosed patients treated for pulmonary TB.

METHODS: A double-blind, placebo-controlled trial including patients with newly diagnosed TB was conducted. The intervention group ($n = 17$) received vitamin E and selenium (vitamin E: 140 mg alpha-tocopherol and selenium: 200 microg) and the control group ($n = 18$) received placebo. Both groups received standard anti-TB treatment. Assessment of micronutrient levels, oxidative markers and total antioxidant capacity were carried out at baseline and 2 months after the intervention.

RESULTS: Malondialdehyde levels were significantly reduced in the intervention group ($P = 0.01$), while there was minimal reduction in the control group. The mean plasma level of total antioxidants was increased significantly ($P = 0.001$) in both the intervention and the control groups.

CONCLUSION: A 2-month intervention with vitamin E and selenium supplementation reduces oxidative stress and enhances total antioxidant status in patients with pulmonary TB treated with standard chemotherapy.

Syedrezazadeh E, et al. Respirology. 2008 Mar;13(2):294-8. doi: 10.1111/j.1440-1843.2007.01200.x. PMID: 18339032

G. Multiple Micronutrients

Effect of micronutrient supplementation on treatment outcomes in children with intrathoracic tuberculosis: a randomized controlled trial. (Zn/MVI/Zn+MVI/placebo)

OBJECTIVE: To assess effect of micronutrient supplementation in children treated with antituberculosis therapy (ATT).

DESIGN: A randomized, double-blind, placebo-controlled trial that used a 2×2 factorial design was undertaken at 2 teaching hospitals in Delhi. Children with newly diagnosed intrathoracic tuberculosis were enrolled, and they received ATT together with daily supplementation for 6 mo with either zinc alone, micronutrients without zinc, micronutrients in combination with zinc, or a placebo. Main outcomes were weight gain and an improvement in a chest X-ray (CXR) lesion assessed at 6 mo of treatment.

RESULTS: A total of 403 children were enrolled and randomly assigned. A microbiological diagnosis of tuberculosis was confirmed in 179 children (44.4%). The median (95% CI) increase in weight-for-age z score at 6 mo was not significantly different between subjects who received micronutrients [0.75 (0.66, 0.84)] and those who did not receive micronutrients [0.76 (0.67, 0.85)] and between subjects who received zinc [0.76 (0.68, 0.85)] and those who did not receive zinc [0.75 (0.66, 0.83)]. An improvement in CXR was observed in 285 children, but there was no difference between those receiving zinc and no zinc or between those receiving micronutrients and no micronutrients after 6 mo of ATT. However, children who received micronutrients had a faster gain in height over 6 mo than did those who did not receive micronutrients (height-for-age z score $\Delta = 0.08$; $P = 0.014$).

CONCLUSIONS: Micronutrient supplementation did not modify the weight gain or clearance of lesions on CXR in children with intrathoracic tuberculosis. Micronutrient supplementation during treatment may improve height gain in children with intrathoracic tuberculosis.

Lodha R, et al. Am J Clin Nutr. 2014 Nov;100(5):1287-97. doi: 10.3945/ajcn.113.082255. PMID: 25332327

The effect of micronutrient supplementation on treatment outcome in patients with pulmonary tuberculosis: a randomized controlled trial in Mwanza, Tanzania.

OBJECTIVE: The aim of the study was to assess the effects of micronutrient supplementation on culture conversion in tuberculosis (TB) patients.

DESIGN: The study was a randomized, double-blind placebo-controlled 2 x 2 trial of zinc and multi-micronutrient (MMN) supplementation in pulmonary TB patients in Tanzania.

RESULTS: A total of 499 pulmonary TB patients were included in the trial after being confirmed sputum-positive by microscopy or culture. At 8 weeks, 25% were sputum-smear positive but only 11% were culture-positive ($P < 0.0001$). No significant differences were observed in culture conversion rate among those allocated to MMN or placebo (89.5 vs. 86.2%, $P = 0.29$) at 8 weeks, although at week 4 those allocated to MMN had a slightly reduced culture conversion rate (42.8 vs. 52.8%, $P = 0.058$). Zinc had no effects on culture conversion. MMN increased weight gain by 0.78 kg [95%CI: 0.12--1.43] at week 8, while zinc supplementation had no effect. The effects of MMN and zinc did not interact and neither MMN nor zinc interacted with human immunodeficiency virus status, sex and culture-intensity at baseline.

CONCLUSION: Neither zinc nor MMN supplementation had significant effects on culture conversion, but MMN supplementation increased weight gain in TB patients.

Range N, et al. *Trop Med Int Health*. 2005 Sep;10(9):826-32. doi: 10.1111/j.1365-3156.2005.01463.x. PMID: 16135188

The effect of multi-vitamin/mineral supplementation on mortality during treatment of pulmonary tuberculosis: a randomised two-by-two factorial trial in Mwanza, Tanzania.

The objective of this study was to assess effects of multi-vitamin/mineral (MVM) and zinc (Zn) supplementation during TB treatment on mortality. Patients diagnosed with sputum-positive pulmonary TB in Mwanza, Tanzania, were randomised, using a two-by-two factorial design, to Zn (45 mg) or placebo, and MVM (vitamins A, B, C, D, E, and selenium and copper) or placebo. Survival status was ascertained at the end of the 8-month TB treatment and supplementation period.

Of 499 TB patients, 213 (43 %) had HIV. The mean weight gain at 7 months was 6.88 kg (95 % CI 6.36, 7.41). Zn and MVM combined, but neither alone (interaction, $P = 0.03$), increased weight gain by 2.37 kg (95 % CI 0.91, 3.83), irrespective of HIV status. Survival status at 8 months was determined for 422 patients (84.6 %), of which fifty-two (12.3 %) had died. Among fifty-two deaths, there were no effects of MVM (relative risk (RR) 0.73; 0.43-1.23) and Zn (RR 0.76; 0.46-1.28). However, among HIV co-infected patients, marginally significant effects of both MVM (RR 0.60; 0.34-1.05) and Zn (RR 0.63, 0.37-1.08) were seen, and MVM and Zn combined reduced mortality (RR 0.29; 0.10-0.80; interaction ratio 0.52).

In conclusion, supplementation with MVM, including Zn, during treatment of pulmonary TB may reduce mortality in those co-infected with HIV. A randomised trial of the effect of the combined intervention used in this study should be conducted in a different setting to confirm the finding.

Range N, et al. *Br J Nutr*. 2006 Apr;95(4):762-70. doi: 10.1079/bjn20051684. PMID: 16571156

A randomized trial of multivitamin supplementation in children with tuberculosis in Tanzania

Background: Children with tuberculosis often have underlying nutritional deficiencies. Multivitamin supplementation has been proposed as a means to enhance the health of these children; however, the efficacy of such an intervention has not been examined adequately.

Methods: 255 children, aged six weeks to five years, with tuberculosis were randomized to receive either a daily multivitamin supplement or a placebo in the first eight weeks of anti-tuberculous therapy in Tanzania. This was only 64% of the proposed sample size as the trial had to be terminated prematurely due to funding constraints. They were followed up for the duration of supplementation through clinic and home visits to assess anthropometric indices and laboratory parameters, including hemoglobin and albumin.

Results: There was no significant effect of multivitamin supplementation on the primary endpoint of the trial: weight gain after eight weeks. However, significant differences in weight gain were observed among children aged six weeks to six months in subgroup analyses ($n = 22$; 1.08 kg, compared to 0.46 kg in the placebo group; 95% CI=0.12, 1.10; $p = 0.01$). Supplementation resulted in significant improvement in hemoglobin levels at the end of follow-up in children of all age groups; the median increase in children receiving multivitamins was 1.0 g/dL, compared to 0.4 g/dL in children receiving placebo ($p < 0.01$). HIV-infected children between six months and three years of age had a significantly higher gain in height if they received multivitamins ($n = 48$; 2 cm, compared to 1 cm in the placebo group; 95% CI=0.20, 1.70; $p = 0.01$; p for interaction by age group=0.01).

Conclusions: Multivitamin supplementation for a short duration of eight weeks improved the hematological profile of children with tuberculosis, though it didn't have any effect on weight gain, the primary outcome of the trial. Larger studies with a longer period of supplementation are needed to confirm these findings and assess the effect of multivitamins on clinical outcomes including treatment success and growth failure.

Mehta S, et al. *Nutr J*. 2011 Oct 31;10:120. doi: 10.1186/1475-2891-10-120.

H. Program considerations and examples, including adherence studies and modeling studies

Adherence to HIV and TB care and treatment, the role of food security and nutrition

Food security and nutrition play an important role in HIV and TB care and treatment, including for improving treatment outcomes, adherence and uptake of HIV and TB care. This [AIDS and behavior supplement on "Adherence to HIV and TB care and treatment, the role of food security and nutrition"](#) provides an overview of the current evidence and knowledge about the barriers to uptake and retention in HIV and TB treatment and care and on whether and how food and nutrition assistance can help overcome these barriers. It contains nine papers on three topic areas discussing: (a) adherence and food and nutrition security in context of HIV and TB, their definitions, measurement tools and the current situation; (b) food and nutrition insecurity as barriers to uptake and retention; and (c) food and nutrition assistance to increase uptake and retention in care and treatment. Future interventions in the areas of food security, nutrition and social protection for increasing access and adherence should be from an HIV sensitive lens, linking the continuum of care with health systems, food systems and the community, complementing existing platforms through partnerships and integrated services.

Joan M Claros. AIDS Behav. 2014 Oct;18 Suppl 5:S459-64. doi: 10.1007/s10461-014-0870-4.

The Enabling Effect of Food Assistance in Improving Adherence and/or Treatment Completion for Antiretroviral Therapy and Tuberculosis Treatment: A Literature Review

Socioeconomic costs of HIV and TB and difficulty maintaining optimal treatment are well documented. Social protection measures such as food assistance may be required to offset some of the treatment related costs as well as to ensure food security and maintain good health of the affected individual and household. Programmes have started placing greater emphasis on treatment adherence and are looking for proven interventions that can optimize it. [This paper looks at the effect of food assistance for enabling treatment adherence and reviews studies that used food assistance to promote adherence. Eight of ten studies found that provision of food can improve adherence and/or treatment completion for HIV care and treatment, ART and TB-DOTS. This indicates that food provision is not only a biological, but also a behavioral intervention, and underscores that unresolved food insecurity can be an impediment to treatment adherence and consequently to good treatment outcomes.](#)

Saskia de Pee, et al. AIDS and Behavior 2014; volume 18, pages 531–541

Estimating the Impact of Reducing Under-Nutrition on the Tuberculosis Epidemic in the Central Eastern States of India: A Dynamic Modeling Study.

BACKGROUND: Tuberculosis (TB) and under-nutrition are widespread in many low and middle-income countries. Momentum to prioritize under-nutrition has been growing at an international level, as demonstrated by the "Scaling Up Nutrition" movement. Low body mass index is an important risk factor for developing TB disease. The objective of this study was to project future trends in TB related outcomes under different scenarios for reducing under-nutrition in the adult population in the Central Eastern states of India.

METHODS: A compartmental TB transmission model stratified by body mass index was parameterized using national and regional data from India. We compared TB related mortality and incidence under several scenarios that represented a range of policies and programs designed to reduce the prevalence of under-nutrition, based on the experience and observed trends in similar countries.

RESULTS: The modeled nutrition intervention scenarios brought about [reductions in TB incidence and TB related mortality in the Central Eastern Indian states ranging from 43% to 71% and 40% to 68% respectively, relative to the scenario of no nutritional intervention. Modest reductions in under-nutrition averted 4.8 \(95% UR 0.5, 17.1\) million TB cases and 1.6 \(95% UR 0.5, 5.2\) million TB related deaths over a period of 20 years of intervention, relative to the scenario of no nutritional intervention. Complete elimination of under-nutrition in the Central Eastern states averted 9.4 \(95% UR 1.5, 30.6\) million TB cases and 3.2 \(95% UR 0.7-, 10.1\) million TB related deaths, relative to the scenario of no nutritional intervention.](#)

CONCLUSION: [Intervening on under-nutrition could have a substantial impact on TB incidence and mortality in areas with high prevalence of under-nutrition, even if only small gains in under-nutrition can be achieved. Focusing on under-nutrition may be an effective way to reduce both rates of TB and other diseases associated with under-nutrition.](#)

Oxlade O, et al. PLoS One. 2015 Jun 5;10(6):e0128187. doi: 10.1371/journal.pone.0128187. PMID: 26046649

Protein-calorie malnutrition, macronutrient supplements, and tuberculosis

Background: Protein-calorie malnutrition (PCM) is a risk factor for tuberculosis (TB) disease and may affect treatment outcomes. There is currently no recommended macronutrient intervention for improving the outcome of anti-tuberculosis treatment.

Methods: We reviewed current literature on PCM and low body mass index (BMI) as risk factors for tuberculous infection and TB disease, and their effects on anti-tuberculosis treatment. We summarize clinical trials of macronutrient supplementation in the treatment of TB.

Results: PCM is a well-established risk factor for TB disease; however, data on malnutrition and the risk of tuberculous infection are limited. Malnutrition is associated with an increased risk of mortality and relapse of active TB. Clinical trials of macronutrient supplementation during treatment confirm a 2-3 kg improvement in weight gain at 2 months, and may result in improvement in physical function, sputum conversion and treatment completion, but they have not been powered to assess effects on mortality or relapse.

Conclusion: Assessment of dietary intake, food security, and baseline BMI should be standard practice in anti-tuberculosis treatment, along with dietary counselling. As macronutrient supplementation may have modest benefits and is not associated with adverse events, patients with BMI values <18.5 kg/m² should be provided with balanced macronutrient supplementation whenever possible.

J R Koethe, C F von Reyn. Int J Tuberc Lung Dis. 2016 Jul;20(7):857-63. doi: 10.5588/ijtld.15.0936. PMID: 27287634

Nutrition support for HIV-TB co-infected adults in Senegal, West Africa: A randomized pilot implementation study

Background: Food insecurity can contribute to poor adherence to both tuberculosis treatment and HIV antiretroviral therapy (ART). Interventions that target food insecurity have the potential to increase treatment adherence, improve clinical outcomes, and decrease mortality. The goals of this study were to compare the feasibility, acceptability, and potential impact of implementing two different forms of nutrition support for HIV-TB co-infected adults in the Casamance region of Senegal.

Methods: We conducted a randomized pilot implementation study among HIV-TB co-infected adults initiating treatment for TB (ClinicalTrials.gov Identifier: NCT03711721). Subjects received nutrition support in the form of a local food basket or Ready-to-Use Therapeutic Food (RUTF), distributed on a monthly basis for six months.

Results: A total of 178 monthly study encounters were completed by 26 HIV-TB co-infected adults; 14 received food baskets and 12 received RUTF. For both the food basket and RUTF, 100% of subjects obtained the supplement at every study encounter, transferred the supplement from the clinic to their household, and consumed the supplement. The food basket had greater acceptability and was more likely to be shared with members of the household. Adherence to TB treatment and ART exceeded 95%, and all outcomes, including CD4 cell count, hemoglobin, nutritional status, and food security, improved over the study period. All subjects completed TB treatment and were smear negative at treatment completion. The total cost of the local food basket was approximately \$0.68 per day versus \$0.99 for the RUTF.

Conclusion: The implementation of nutrition support for HIV-TB co-infected adults in Senegal is feasible and may provide an effective strategy to improve adherence, treatment completion, and clinical outcomes for less than 1 USD per day. Further studies to determine the impact of nutrition support among a larger population of HIV-TB co-infected individuals are indicated.

Noelle A Benzekri, et al. PLoS One. 2019 Jul 18;14(7):e0219118. doi: 10.1371/journal.pone.0219118. PMID: 31318879

Community directed interventions for malaria, tuberculosis and vitamin A in onchocerciasis endemic districts of Tanzania.

In recognising the success attained through community-directed treatment with Ivermectin, there has been a growing interest to use a similar approach for delivery of interventions against other communicable diseases. This study was conducted in 2007 to evaluate the impact of community directed intervention (CDI) on delivering five health interventions namely Vitamin A supplementation (VAS), community-directed treatment with Ivermectin (CDTi), distribution of insecticide-treated nets (ITN), directly observed treatment of tuberculosis (DOTS), and home-based management of malaria (HMM). The study was carried out in onchocerciasis endemic districts of Kilosa, Muheza, Lushoto, Korogwe and Ulanga districts in Tanzania. A total of 250 households were involved in the study for the period of two years. During the first year, one new intervention was added in each study district. A second new intervention was then added in the same manner during the second study year. In the control district all interventions, with the exception of Ivermectin distribution, continued to be delivered in the traditional manner throughout the study period. Results showed that Ivermectin treatment coverage in the CDI districts (88%) was significantly ($P < 0.005$) higher than in the control district (77%). The coverage of VAS was 84 +/- 7%, showing very little difference between control and intervention districts ($P > 0.05$). The DOTS treatment completion rate was observed only in Korogwe where 4 out of 7 patients had completed their treatment. The proportions of pregnant women and <5 years children sleeping under ITN in the CDI districts (range: 83-100%) were significantly higher ($P < 0.05$) than those in the control district (40-43%). There was also a higher proportion of malaria cases referred in the intervention districts (42%) than in the control district (21%) ($P < 0.005$). Likewise, the proportion of <5 years children who were presumptively diagnosed with malaria and received appropriated treatment within 24 hours in the intervention districts (17-29%) was higher than those in the control district (4%) ($P < 0.005$). The costs incurred per integrated programme in the intervention districts were much lower than those

in the control district. In conclusion, our results showed higher coverage of interventions in the CDI districts without necessarily increasing the cost.

Kisinzua WN, et al. Tanzan J Health Res. 2008 Oct;10(4):232-9. doi: 10.4314/thrb.v10i4.45079. PMID: 19402585

Community directed approach beyond ivermectin in Tanzania: a promising mechanism for the delivery of complex health interventions.

The Community Directed Intervention (CDI) is currently used for Ivermectin distribution for the treatment of onchocerciasis in Africa. This study was carried out to [determine the extent to which the CDI process can be used for the delivery of other health interventions with different degrees of complexity](#). The study was conducted in five districts of Kilosa, Muheza, Lushoto, Korogwe and Ulanga in Tanzania and involved communities, health facility and district healthcare providers. Implementation of CDI across these health interventions involved addressing six major processes, namely, stakeholder processes, health system dynamics, engaging communities, empowering communities, engaging CDI implementers and broader system effects. Community and health systems changes were triggered, such that the inherent value of community involvement and empowerment could be internalized by communities and health workers, leading to a more receptive health system. The CDI process was accepted at the community levels as many were willing and ready to adopt the approach. Health workers at community levels were readily available and supportive of the process. Additionally, noted were the verified willingness and ability of community implementers to deliver multiple interventions; confirmed efficiency of CDI leading to cost savings at health systems level; increasing interest of the health system in CDI; interest of health workers in the process of integrated planning. However, there were factors that may have a negative influence on the CDI process. Drug and supply policy for CDI process was lacking at the national and district levels. The presence of parallel community-based programs that provide financial incentives for community members to run them discouraged Community-directed distributors who in most cases are volunteers. In conclusion, the results have clearly and evidently demonstrated the potential of CDI approach for [effectively and efficiently control of other diseases such as malaria, tuberculosis and childhood illnesses](#). The study has provided unique information on the feasibility and effectiveness of integrated delivery of interventions at the community level.

Mutalemwa P, et al. Tanzan J Health Res. 2009 Jul;11(3):116-25. doi: 10.4314/thrb.v11i3.47697.

IV. NUTRITION IN THE PREVENTION OF TB

Effectiveness of a multivitamin supplementation program among HIV-infected adults in Tanzania

Design: We conducted a retrospective cohort study of 67 707 adults enrolled in the Dar es Salaam HIV care and treatment program during 2004–2012 to assess the effectiveness of a routine multivitamin supplementation program.

Methods: The Dar es Salaam HIV care and treatment program intended to provide all adult patients with multivitamin supplements (vitamins B-complex, C, and E) free of charge; however, intermittent stockouts and other implementation issues did not afford universal coverage. We use Cox proportional hazard models to assess the time-varying association of multivitamin supplementation with mortality and clinical outcomes.

Results: The study cohort contributed 41 540 and 129 315 person-years of follow-up time to the antiretroviral therapy (ART)-naive and ART-experienced analyses, respectively. Among 48 207 ART-naive adults, provision of multivitamins reduced the risk of mortality (aHR: 0.69; 95%CI: 0.59-0.81), incident tuberculosis (TB) (aHR: 0.83; 0.76-0.91), and meeting ART eligibility criteria (aHR: 0.78; 0.73-0.83) after adjustment for time-varying confounding. Among 46 977 ART-experienced patients, multivitamins reduced mortality (HR: 0.86; 0.80-0.92), incident TB (aHR: 0.78; 0.73-0.84), and immunologic failure (aHR: 0.70; 0.67-0.73). The survival benefits were greatest during the first year of ART and declined over time (P value <0.001).

Conclusion: Multivitamin supplementation appears to be a simple, effective, safe, and scalable program to improve survival, reduce incidence of TB, and improve treatment outcomes for adult HIV patients in Tanzania.

Sudfeld CR, et al. AIDS. 2019 Jan 27;33(1):93-100. doi: 10.1097/QAD.0000000000002033.

Active Tuberculosis in HIV-Exposed Tanzanian Children up to 2 years of Age: Early-Life Nutrition, Multivitamin Supplementation and Other Potential Risk Factors

Background: Early-life nutritional exposures have rarely been examined in relation to pediatric TB among HIV-exposed children. We investigated independent associations of early-life nutritional exposures with active TB among HIV-exposed children up to 2 years of age.

Methods: Participants were children from a randomized controlled multivitamin supplementation trial conducted in Dar es Salaam, Tanzania, from August 2004 to May 2008, who received daily multivitamin supplements or placebo for 24 months.

Results: Lower mean corpuscular volumes [relative risks (RR): 0.48, 95% confidence interval (CI): 0.27, 0.87] and higher birth weights (RR: 0.61, 95% CI: 0.37, 0.99) were protective against active TB, whereas multivitamin supplementation was not associated with TB risk (RR: 0.87, 95% CI: 0.65, 1.16).

Conclusions: Knowledge of nutrition-related risk and protective factors for TB in HIV-exposed children could enhance preventive and case-finding activities in this population, contributing to efforts to reduce the global TB burden.

Olofin IO, et al. J Trop Pediatr. 2016 Feb;62(1):29-37. doi: 10.1093/tropej/jmv073. Epub 2015 Oct 22.

Correlates of isoniazid preventive therapy failure in child household contacts with infectious tuberculosis in high burden settings in Nairobi, Kenya - a cohort study

Study to elucidate correlates to IPT strategy failure in children below 5 years in Nairobi. A prospective longitudinal cohort study in informal settlements in Nairobi, where children under 5 years in household contact with recently diagnosed smear positive TB adults were enrolled. Contacts underwent baseline clinical screening exclude TB and/or pre-existing chronic conditions. Contacts were then put on daily isoniazid for 6 months and monitored for new TB disease, compliance and side effects. At baseline, 428 contacts were screened, and 14(3.2%) had evidence of TB disease, hence excluded. Of 414 contacts put on IPT, 368 (88.8%) completed the 1 year follow-up. Operational challenges were reported by 258(70%) households, while 82(22%) reported side effects. Good compliance was documented in 89% (CI:80.2-96.2). By endpoint, 6 (1.6%) contacts developed evidence of new TB disease and required definitive anti-tuberculosis therapy. The main factor associated with IPT failure was under-nutrition of contacts (p = 0.023). IPT effectiveness could be optimized through nutrition support of contacts.

Okwara FN, et al. BMC Infect Dis. 2017 Sep 16;17(1):623. doi: 10.1186/s12879-017-2719-8. PMID: 28915796

Efficacy of vitamin D(3) supplementation for the prevention of pulmonary tuberculosis and mortality in HIV: a randomised, double-blind, placebo-controlled trial.

BACKGROUND: The primary aims of this study were to assess the effect of vitamin D3 supplementation on the risk of mortality and incidence of pulmonary tuberculosis among adults initiating antiretroviral therapy (ART).

METHODS: This was a randomised, double-blind, placebo-controlled trial of vitamin D3 supplementation among adults living with HIV who initiated ART and had serum 25-hydroxyvitamin D concentrations of less than 30 ng/mL at four large HIV care and treatment centres in Dar es Salaam, Tanzania. Patients were excluded if they were younger than 18 years, pregnant at the time of randomisation, or were enrolled in any other clinical trial. Patients were randomly assigned 1:1 to

receive either weekly oral 50 000 IU vitamin D3 supplements (cholecalciferol) for the first month of ART followed by daily 2000 IU vitamin D3 supplements or a matching weekly and daily placebo regimen. The randomisation list was computer-generated by a non-study statistician with sequence blocks of ten that were stratified by study clinic. Complete allocation concealment was ensured and patients, field team, and investigators were masked to group assignment. The trial follow-up duration was 1 year and the primary efficacy outcomes were death and incident pulmonary tuberculosis. An intention-to-treat analysis was followed for all-cause mortality; participants diagnosed with or receiving treatment for pulmonary tuberculosis at randomisation, or suspected to have tuberculosis at randomisation and who later had that diagnosis confirmed, were excluded from analyses of pulmonary tuberculosis incidence. Safety was assessed in the intention-to-treat population.

FINDINGS: Between Feb 24, 2014, and Feb 24, 2017, 6250 adults initiating ART had serum 25-hydroxyvitamin D screening, 4000 of whom were enrolled in the trial and followed up for 1 year (follow-up of all participants was completed on March 7, 2018). 2001 patients were randomly assigned to the vitamin D3 supplementation group, and 1999 to the placebo group. 415 deaths were recorded: 211 in the vitamin D3 group and 204 in the placebo group. Among all randomly assigned participants, there was no overall effect of vitamin D3 supplementation on the risk of mortality (hazard ratio [HR] 1.04, 95% CI 0.85-1.25; $p=0.73$). There was also no difference in the overall incidence of pulmonary tuberculosis between the vitamin D3 (50 events in 1812 patients analysed) and placebo groups (64 events in 1827 patients; HR 0.78, 0.54-1.13; $p=0.19$). The vitamin D3 regimen did not increase the risk of hypercalcaemia (three events in the vitamin D3 group and two events in the placebo group; relative risk 1.25, 95% CI 0.43-3.66; Fisher's exact $p=1.00$). 101 hospital admissions were reported in the vitamin D3 group and 94 in the placebo group (incidence rate ratio 1.06, 95% CI 0.80-1.41; $p=0.66$).

Sudfeld CR, et al. Lancet HIV. 2020 Jul;7(7):e463-e471. doi: 10.1016/S2352-3018(20)30108-9. PMID: 32621874

Vitamin D Supplements for Prevention of Tuberculosis Infection and Disease.

METHODS: We randomly assigned children who had negative results for *M. tuberculosis* infection according to the QuantiFERON-TB Gold In-Tube assay (QFT) to receive a weekly oral dose of either 14,000 IU of vitamin D3 or placebo for 3 years. The primary outcome was a positive QFT result at the 3-year follow-up, expressed as a proportion of children. Secondary outcomes included the serum 25-hydroxyvitamin D (25[OH]D) level at the end of the trial and the incidence of tuberculosis disease, acute respiratory infection, and adverse events.

RESULTS: A total of 8851 children underwent randomization: 4418 were assigned to the vitamin D group, and 4433 to the placebo group; 95.6% of children had a baseline serum 25(OH)D level of less than 20 ng per milliliter. Among children with a valid QFT result at the end of the trial, the percentage with a positive result was 3.6% (147 of 4074 children) in the vitamin D group and 3.3% (134 of 4043) in the placebo group (aRR 1.10; 95%CI 0.87-1.38; $P=0.42$). The mean 25(OH)D level at the end of the trial was 31.0 ng per milliliter in the vitamin D group and 10.7 ng per milliliter in the placebo group (mean between-group difference, 20.3 ng per milliliter; 95% CI, 19.9-20.6). Tuberculosis disease was diagnosed in 21 children in the vitamin D group and in 25 children in the placebo group (aRR 0.87; 95% CI, 0.49-1.55). A total of 29 children in the vitamin D group and 34 in the placebo group were hospitalized for treatment of acute respiratory infection (aRR 0.86; 95% CI 0.52-1.40). The incidence of adverse events did not differ significantly between the two groups.

CONCLUSIONS: Vitamin D supplementation did not result in a lower risk of tuberculosis infection, tuberculosis disease, or acute respiratory infection than placebo among vitamin D-deficient schoolchildren in Mongolia.

Ganmaa D, et al. N Engl J Med. 2020 Jul 23;383(4):359-368. doi: 10.1056/NEJMoa1915176. PMID: 32706534

VITAMIN D AND OTHER INFECTIONS

Vitamin D supplementation for preventing infections in children under five years of age.

OBJECTIVES: To evaluate the role of vitamin D supplementation in preventing pneumonia, tuberculosis (TB), diarrhoea, and malaria in children under five years of age. This includes high-, middle-, and low-income countries.

SEARCH METHODS: We searched the Cochrane Infectious Diseases Group Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Library, MEDLINE, EMBASE, LILACS, the WHO International Clinical Trials Registry Platform (ICTRP; <http://www.who.int/ictrp/en/>), ClinicalTrials.gov and the ISRCTN registry (<http://www.isrctn.com/>) up to 16 June 2016.

SELECTION CRITERIA: We included randomized controlled trials (RCTs) that evaluated preventive supplementation of vitamin D (versus placebo or no intervention) in children under five years of age.

DATA COLLECTION AND ANALYSIS: Two review authors independently screened the titles and abstracts, extracted the data, and assessed the risk of bias of included trials.

MAIN RESULTS: Four trials met the inclusion criteria, with a total of 3198 children under five years of age, and were conducted in Afghanistan, Spain, and the USA. Prevalence of vitamin D deficiency varied widely in these populations

(range: 73.1% in Afghanistan, 10 to 12% in USA, and 6.2% in Spain). The included trials evaluated mortality (two trials), pneumonia incidence (two trials), diarrhoea incidence (two trials), hospitalization (two trials), and mean serum vitamin D concentrations (four trials). We do not know whether vitamin D supplementation impacts on all-cause mortality because this outcome was underpowered due to few events (risk ratio (RR) 1.43, 95% confidence interval (CI) 0.54 to 3.74; one trial, 3046 participants, low quality evidence). For pneumonia, episodes of 'radiologically confirmed' first or only episode of pneumonia were little different in the supplemented and unsupplemented group (Rate Ratio: 1.06, 95% confidence interval (CI) 0.89 to 1.26; two trials, 3134 participants, moderate quality evidence), and similarly for children with confirmed or unconfirmed pneumonia (RR 0.95, 95% CI 0.87 to 1.04; one trial, 3046 participants). In these two trials there were no obvious differences between supplemented and unsupplemented children regarding episodes of diarrhoea. In the single large trial from Afghanistan, the trial authors reported that vitamin D supplementation was associated with an increase in repeat episodes of pneumonia confirmed by chest radiograph (RR 1.69, 95% CI 1.28 to 2.21; one trial, 3046 participants), but not reflected in the outcome of confirmed or unconfirmed pneumonia (RR 1.06, 95% CI 1.00 to 1.13; one trial, 3046 participants). For hospital admission measured in one small trial, there was no difference detected (RR 0.86, 95% CI 0.20 to 3.62; one trial, 88 participants; very low quality evidence). The mean serum vitamin D concentrations were higher in supplemented compared to unsupplemented children at the end of supplementation (MD 7.72 ng/mL, 95% CI 0.50 to 14.93; four trials, 266 participants, low quality evidence). These results were driven primarily by two smaller trials with large magnitudes of effect. In the other two bigger trials, serum vitamin D concentrations were elevated in the intervention group for most of the trial duration but not at the end of supplementation. This may be due to time elapsed at measurement from the last dose, incomplete compliance, or increased need of vitamin D with infant age. We did not find any trial that reported on the incidence of TB, malaria or febrile illness, duration of pneumonia, duration of diarrhoea, severity of infection, and cause-specific mortality (due to TB, diarrhoea, or malaria).

AUTHORS' CONCLUSIONS: Evidence from one large trial did not demonstrate benefit of vitamin D supplementation on the incidence of pneumonia or diarrhoea in children under five years. To our knowledge, trials that evaluated supplementation for preventing other infections, including TB and malaria, have not been performed.

Yakoob MY, et al. Cochrane Database Syst Rev. 2016 Nov 9;11(11):CD008824. doi: 10.1002/14651858.CD008824.pub2. Update of doi: 10.1002/14651858.CD008824. PMID: 27826955