Vitamin D supplementation versus placebo for treatment of pulmonary tuberculosis: a meta-analysis

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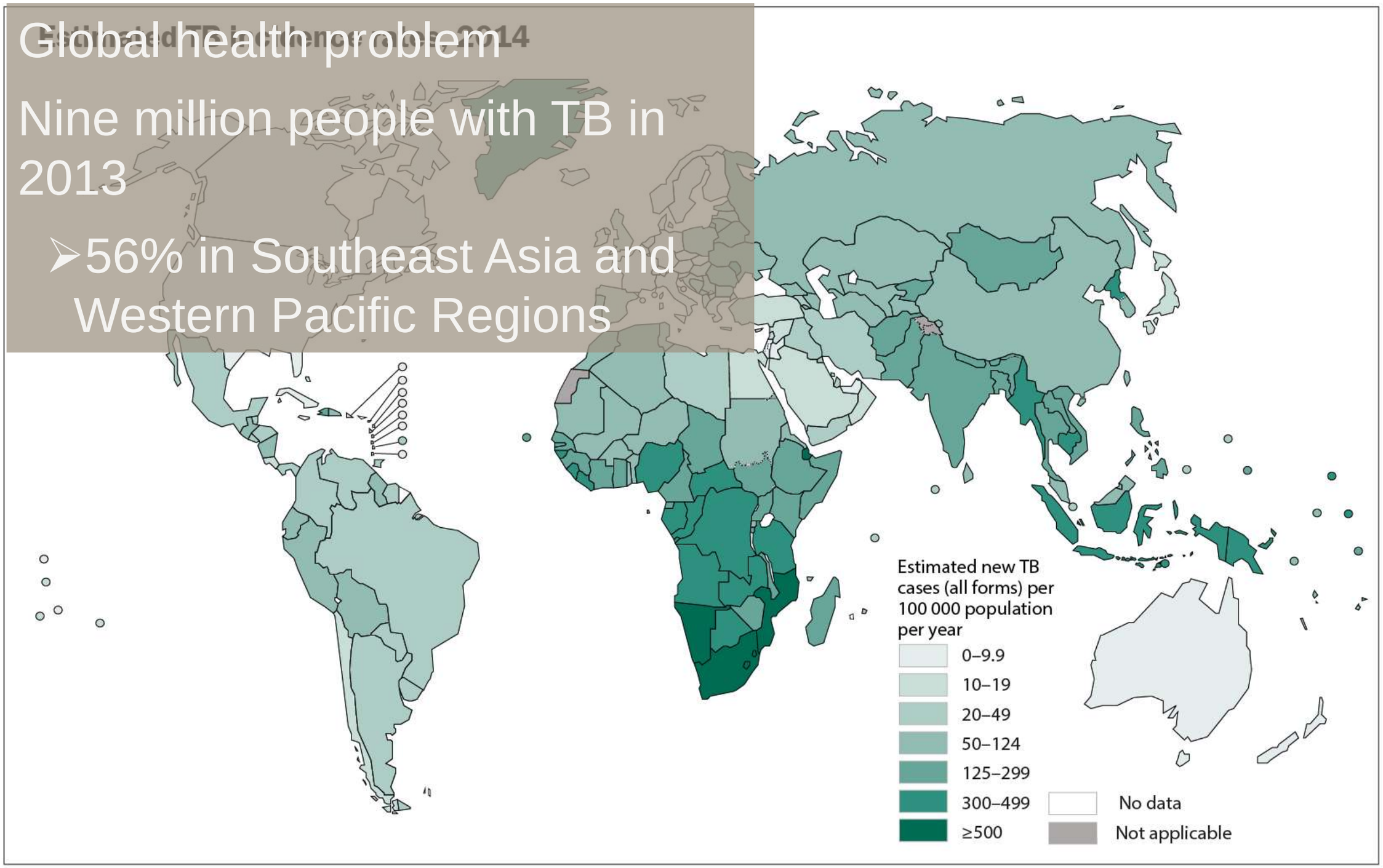
Global health problem

Nine million people with TB in 2013

- 56% in Southeast Asia and Western Pacific Regions



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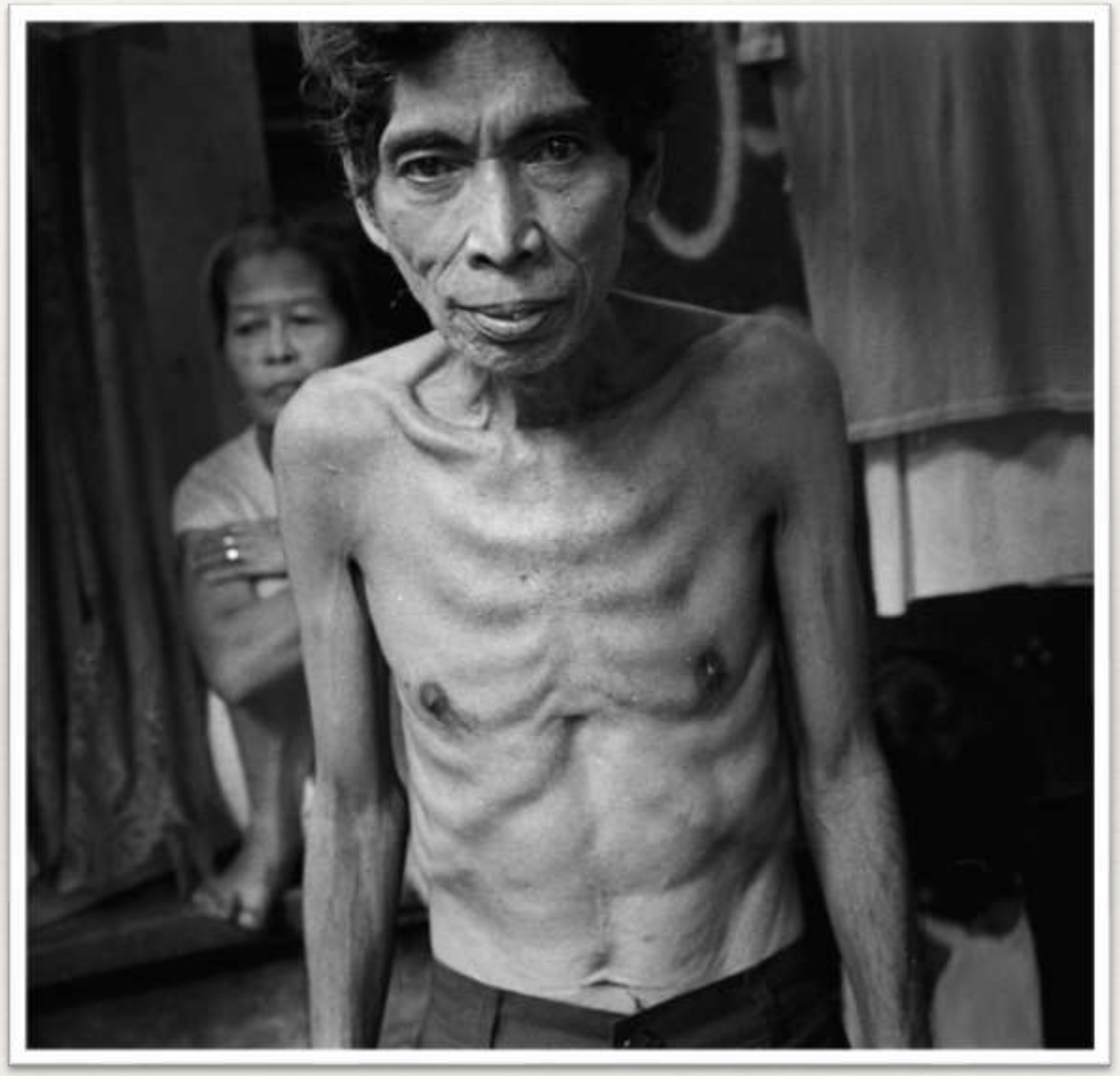
Data Source: *Global Tuberculosis Report 2015*. WHO, 2015.

World Health Organization

Image: WHO 2014. http://gamapserver.who.int/mapLibrary/Files/Maps/Global_TBincidence_2014.png

Pulmonary tuberculosis

- Leading cause of mortality and morbidity



WHO. Global tuberculosis report 2014 (WHO/HTM/TB/2014.08). 2014.
Vianzon et al. Western Pacific Surveillance and Response Journal 2013: 4(2)
Image Source: Sabado, G. http://multivu.prnewswire.com/mnr/bd/50624/

Vitamin D and Tuberculosis

- Augments immune response to M. tuberculosis[1]
  - Induces nitric oxide, NADPH-dependent oxidases, and phagolysosome fusion[2]
  - Suppresses matrix metalloproteinases[3]

[1] Maartens G, Wilkinson RJ. Lancet 2007; 370: 2030-2043
[2] Sly LM et al. J Biol Chem 2001; 276: 354826: 3. Hmama Z et al. Journal of Cell Science. Rockett KA, Infection and Immunity.
[3] Coussens A et al. Immunology 2009; 127: 539

Objectives

- To investigate the effect of vitamin D supplementation on treatment outcomes of adult patients with active pulmonary tuberculosis.
- Specifically:
  - rate of **sputum smear conversion** at weeks 4 and 8
  - median time to **culture conversion**
  - development of severe **adverse events**
  - development of **hypercalcemia**

Systematic Literature Search

"Randomized Controlled Trial"[Publication Type] AND (("Tuberculosis, Pulmonary"[Mesh] OR ("tuberculosis"[MeSH Terms] OR "tuberculosis"[All Fields])) AND ("Vitamin D"[Mesh] OR ("vitamin d"[MeSH Terms] OR "vitamin d"[All Fields] OR "ergocalciferols"[MeSH Terms] OR "ergocalciferols"[All Fields])))

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Study Selection

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Data Extraction

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Assessment of Study Quality

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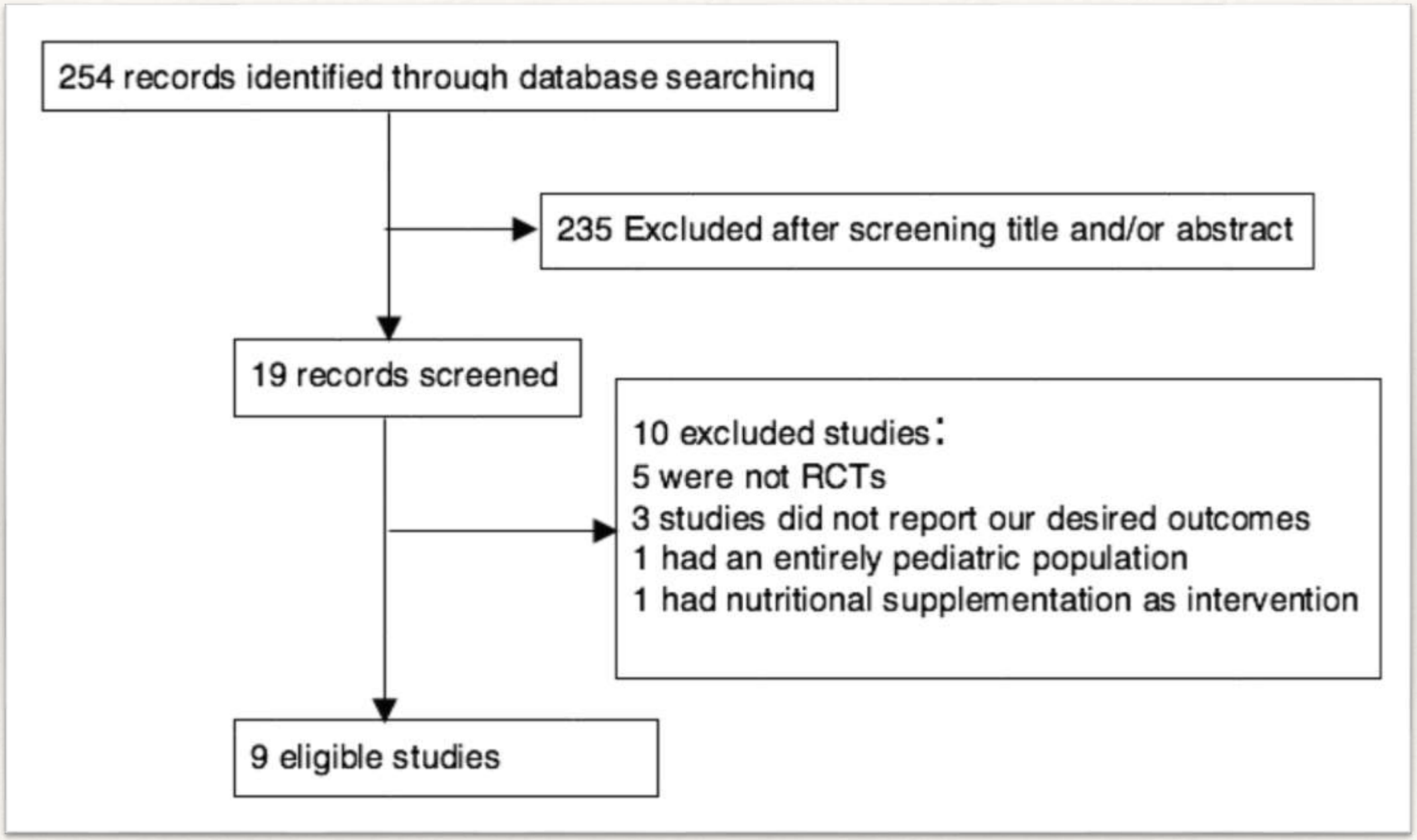
Statistical Analysis

- **Inclusion criteria**
  - All randomized controlled trials, both published and unpublished, using vitamin D supplementation for PTB treatment
  - should have reported at least one of these outcomes: rate of sputum smear conversion, time to culture conversion, and adverse events
  - adult patients (≥15 years old)

- **Exclusion criteria**
  - Not RCTs
  - No reports of the abovementioned outcomes.

Results

Search Strategy



Studies included

- **9 studies** (published 2009 to 2015)
- **1,601 participants** with pulmonary tuberculosis
  - standard anti-TB treatment with vitamin D supplementation (treatment arm); and standard anti-TB treatment with or without placebo
  - Vitamin D doses varied across various studies
  - Follow up period: 8 to 32 weeks

Study (publication year), study design, country	Age (years, mean)	Participants in intervention arm (vitamin D supplementation), n	Participants in the control arm (placebo), n	Duration of follow up (weeks)	Dose or concentration of Vitamin D supplement given
Kota et al (2011), RCT, India	Treatment: 38.4 SD 19.6 Control: 40.2 SD 17.7	15	15	12	60000 U weekly
Daley et al (2015), RCT, India	Treatment: 41.6 SD 15.1 Control: 43.7 SD 15.3	101	110	8	Vitamin D1 oil 100000 IU once every 2 weeks
Wejse et al (2009), Guinea-Bissau	Treatment: 37 SD 13 Control: 38 SD 14	187	178	32	Vitamin D (cholecalciferol) at months 0, 5, 8
Nursyam et al (2001), Indonesia	Treatment: 29.85 SD 11.08 Control: 32.55 SD 11.6	34	33	12	Vitamin D 0.25mg daily
Martineau et al (2011), London, UK	Treatment: 30.7 Control: 30.5	62	64	8	Vitamin D3 2.5 mg at 14, 28 and 42 days

Study (publication year), study design, country	Age (years, mean)	Participants in intervention arm (vitamin D supplementation), n	Participants in the control arm (placebo), n	Duration of follow up (weeks)	Dose or concentration of Vitamin D supplement given
Ralph et al (2013), Indonesia	Treatment: 29 Control: 99	101	99	8	Vitamin D 50000 IU + placebo L-arginine (as one of the four arms in the study)
Salahuddin et al (2013), Pakistan	Treatment: 27.8 SD 13.2 Control: 28.3 SD 14.1	132	127	12	Vitamin D 3 600,000 IU IM for 2 doses
Tukvadze et al (2015), Georgia	Treatment: 34.1 SD 12.4 Control: 32.4 SD 10.6	100	99	16	oral vitaminD3 [50,000 IUs (1.25mg) thrice weekly for 8 weeks and 50,000 IU every other week for 8 weeks
Mily et. Al. (2015), Bangladesh	Treatment 26.7 SD 8.1 Control: 28.1±9.9	72	72	24	5000 IU of vitD3 (Cholecalciferol) once daily

Quality of included studies

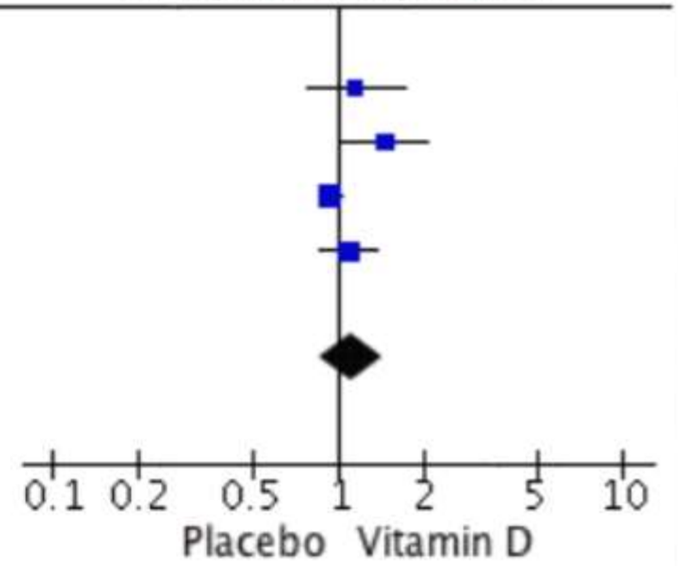
Study	Randomization (2)	Blinding (2)	An account of all patients (1)	Total Jadad score
Kota et al (2011), RCT, India	1	0	1	2
Daley et al (2015), RCT, India	2	2	1	5
Wejse et al (2009),	2	2	1	5
Nursyam et al (2001), Indonesia	1	1	1	3
Martineau et al (2011), London, UK	2	1	1	5
Ralph et al (2013), Indonesia	2	2	1	5
Salahuddin et al (2013), Pakistan	2	2	1	5
Tukvadze et al (2015), Georgia	2	2	1	5
Mily et al (2015). Bangladesh	2	2	1	5

Rate of sputum smear conversion at 4 weeks

Study or Subgroup	Vitamin D Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Kota et al 2011	0	15	0	15		Not estimable
Martineau et al	29	62	26	64	18.8%	1.15 [0.77, 1.71]
Mily et al 2015	38	62	27	64	21.0%	1.45 [1.03, 2.06]
Ralph et al 2013	72	81	81	85	33.4%	0.93 [0.85, 1.02]
Salahuddin et al 2013	71	132	63	127	26.8%	1.08 [0.86, 1.37]
Total (95% CI)		**352**		**355**	**100.0%**	**1.11 [0.86, 1.43]**
Total events	210		197			

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 13.20$, df = 3 (P = 0.004); $I^2 = 77\%$

Test for overall effect: Z = 0.80 (P = 0.42)

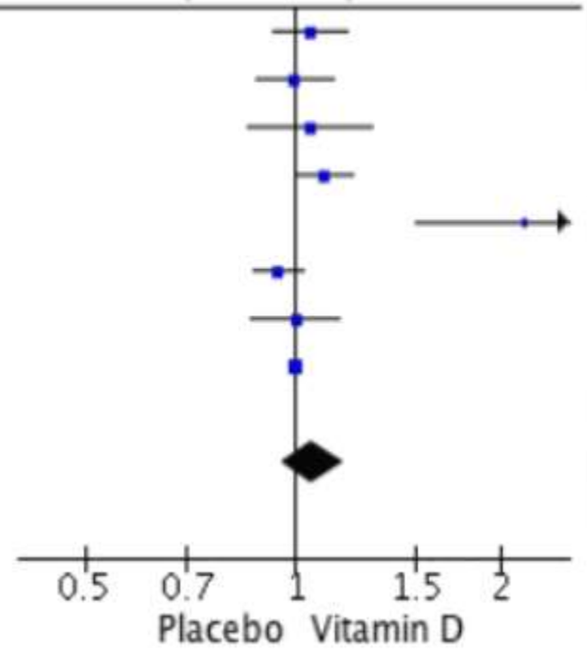


Rate of sputum smear conversion at 8 weeks

Study or Subgroup	Vitamin D supplementation Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Daley et al 2015	85	101	88	110	13.3%	1.05 [0.93, 1.19]
Kota et al 2011	15	15	15	15	13.3%	1.00 [0.88, 1.13]
Martineau et al	47	62	46	64	9.9%	1.05 [0.86, 1.30]
Mily et al 2015	61	62	57	64	14.6%	1.10 [1.01, 1.21]
Nursyam et al 2001	34	34	15	33	5.3%	2.16 [1.49, 3.13]
Ralph et al 2013	73	81	81	85	14.8%	0.95 [0.87, 1.03]
Salahuddin et al 2013	97	132	93	127	12.4%	1.00 [0.87, 1.16]
Wejse et al 2009	123	123	124	124	16.4%	1.00 [0.98, 1.02]
Total (95% CI)		**610**		**622**	**100.0%**	**1.06 [0.96, 1.18]**
Total events	535		519			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 63.13$, df = 7 ($P < 0.00001$); $I^2 = 89\%$

Test for overall effect: Z = 1.13 (P = 0.26)

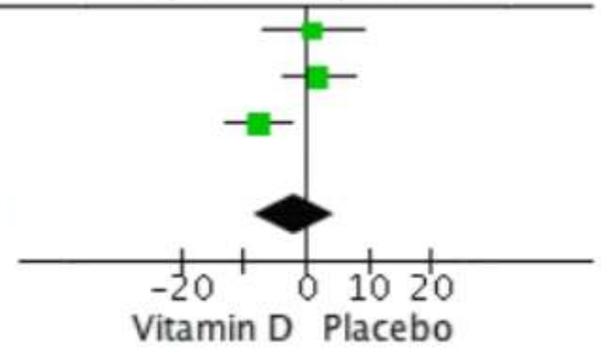


Median time to culture conversion

Study or Subgroup	Vitamin D Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Daley et al 2015	43	32.63	101	42	26.78	110	28.0%	1.00 [-7.10, 9.10]
Martineau et al	29	16.49	62	27	17.23	64	35.1%	2.00 [-3.89, 7.89]
Tukvadze et al 2015	36	12.86	97	43.5	23.56	95	36.9%	-7.50 [-12.88, -2.12]
Total (95% CI)			**260**			**269**	**100.0%**	**-1.78 [-8.28, 4.72]**

Heterogeneity: $Tau^2 = 22.26$; $Chi^2 = 6.27$, df = 2 (P = 0.04); $I^2 = 68\%$

Test for overall effect: Z = 0.54 (P = 0.59)



Severe adverse events

Author	Events in treatment	n in treatment	Events in control	n in control
Daley et al.	0	101	2	108
Wejse et al.	10	90	14	86
Martineau et al.	7	60	2	57
Ralph et al.	4	75	3	61
Tukvadze et al.	0	97	1	94

Adverse events: anorexia, vomiting

Hypercalcemia

Author	Events in treatment	n in treatment	Events in control	n in control
Martineau et al.	2	62	0	62
Ralph et al.	15	64	14	50
Tukvadze et al.	3	94	7	88

Summary

- No benefit in vitamin D supplementation in increasing sputum smear conversion rates at weeks 4 and 8 (not statistically significant)
- Vitamin D may shorten median time to sputum culture conversion by as much as 8.28 weeks (not statistically significant)
- Vitamin D was not associated with severe adverse events nor development of hypercalcemia

Limitations

- Significant heterogeneity among studies
- No universal definition of adverse events
- No standardized definition of clinical improvement available to this day

Recommendations

- Further studies are needed to explore whether vitamin D supplementation at varying doses could shorten treatment and if baseline vitamin D levels have any effect of time of treatment.
- A standardized TB scoring system in place will standardize evaluation of clinical improvement.