



Efficacy, effectiveness and duration of protection of BCG vaccination

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**World Health
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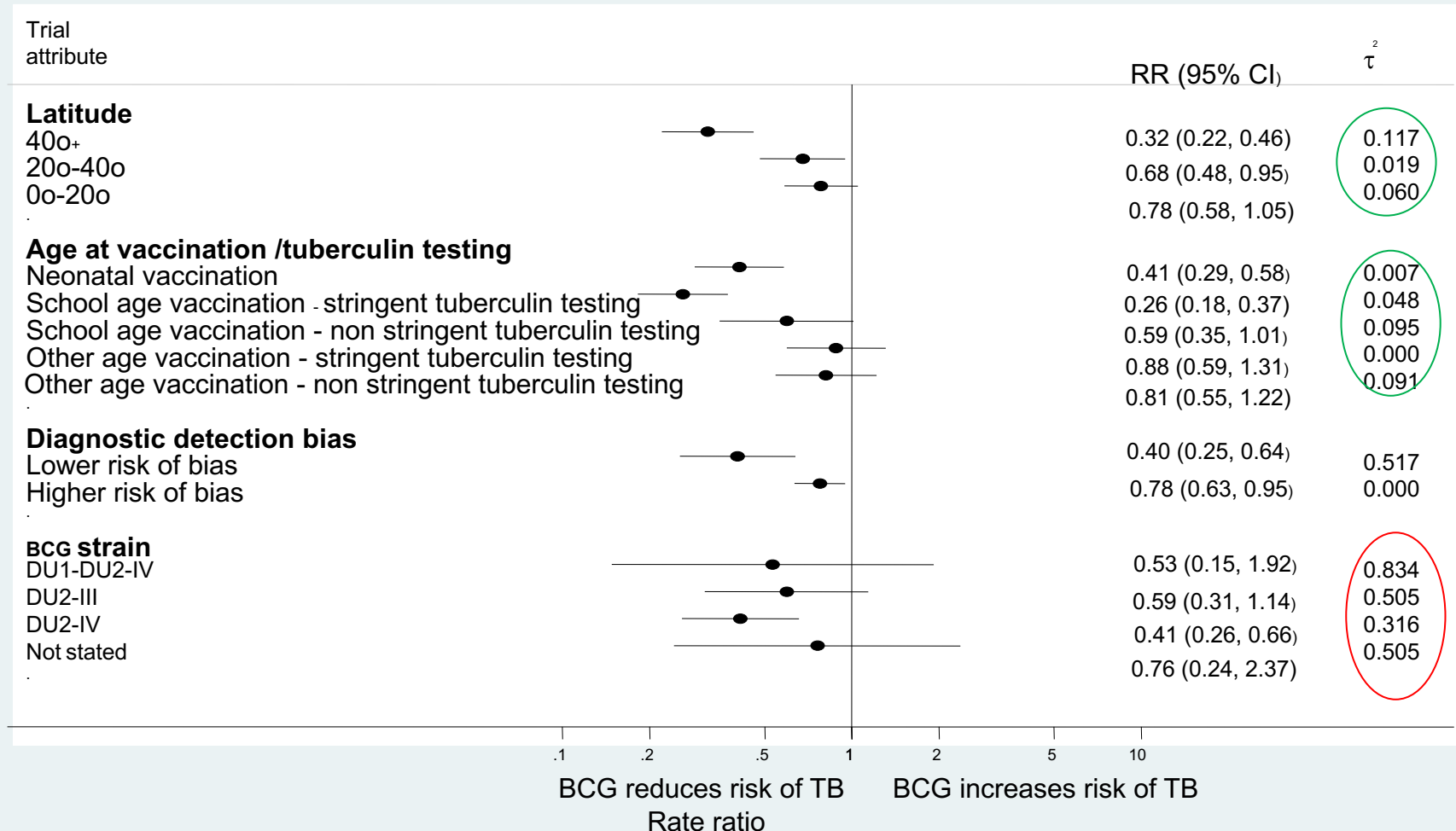
Background

- BCG is one of the most widely used vaccines. There is evidence that it provides consistent protection against severe childhood forms of tuberculosis (TB). Protection against pulmonary TB appears to be stronger at higher latitudes.
- Recent research has evaluated the efficacy, effectiveness and duration of protection of BCG against various forms of TB (pulmonary [PTB], miliary and meningitis) and *M tb* infection
- This evidence is important to guide current policy and practice regarding use of BCG for the mitigation of various forms of TB.

Overview of existing systematic reviews

Author and year	No of studies/RCTs	TB Outcomes
Rodrigues <i>et al</i> (1993)	8 obs studies/10 RCTs	PTB, meningeal, miliary TB
Colditz <i>et al</i> (1994)	12 obs studies/14 RCTs	PTB, TB mortality
Colditz <i>et al</i> (1995)	11 obs studies/5 RCTs(infant)	PTB, meningeal, mortality
Sterne <i>et al</i> (1998)	10 RCTs	Duration protection TB
Trunz <i>et al</i> (2006)	18 obs studies	Meningeal, miliary
Abubakar <i>et al</i> (2013)	76 obs studies/18 RCTs	PTB, meningeal, miliary
Mangtani <i>et al</i> (2014)	Further analyses of 18 RCTs	PTB, meningeal, miliary

Meta-analysis BCG protection (RR) against PTB: RCTs



(Abubakar et al. 2013; Mangtani et al. 2014) No stratification $\tau^2 = 0.38$ ie heterogenous

BCG protection against PTB, results of meta-regression of RCTs

	No. trials	Rate ratio (95% CI)	Ratio of rate ratios Univariable model	p-value	τ^2	Ratio of rate ratios Multivariable model	p-value ($\tau^2=0$)
Latitude							
40°+	8	0.31 (0.21- 0.46)	1.00 (ref)			1.00 (ref)	
20°-40°	5	0.68 (0.41- 1.13)	2.17			1.17	
0°-20°	5	0.77 (0.52- 1.13)	2.45	0.008	0.086	1.73	0.054
Age at Vaccination / Tuberculin Testing Stringency							
Neonatal	5	0.39 (0.24- 0.64)	1.00 (ref)			1.00 (ref)	
School age / stringent	4	0.26 (0.17- 0.40)	0.66			0.76	
School age / non stringent	2	0.62 (0.38- 1.01)	1.58			0.80	
Other age / stringent	3	0.94 (0.51- 1.73)	2.38			1.60	
Other age / non stringent	4	0.85 (0.58- 1.24)	2.16	0.003	0.044	1.75	0.013
Diagnostic Detection Bias							
Lower risk of bias	13	0.43 (0.30- 0.62)	1.00 (ref)			1.00 (ref)	
Higher risk of bias	5	0.95 (0.50- 1.81)	2.22	0.036	0.232	1.60	0.045

Meta-analysis BCG protection against PTB, Observational studies

Similar latitude trends to RCTs

7/8 case control studies neonatal BCG VE= 0.50 (0.33 to 0.76)

1/8 studies other age BCG VE = 0.84 (0.23 to 3.07)

12 Cohort studies

Subgroup	Number of Studies	RR (95% CI)
<u>Latitude</u>		
>40°	7	0.12 (0.06 to 0.25)
20-40°	3	0.31 (0.11 to 0.87)
0-20°	2	0.75 (0.19 to 2.94)
<u>Age at vaccination</u>		
Neonatal	3	0.20 (0.07 to 0.56)
School age	6	0.36 (0.17 to 0.76)
Other	3	0.05 (0.01 to 0.22)

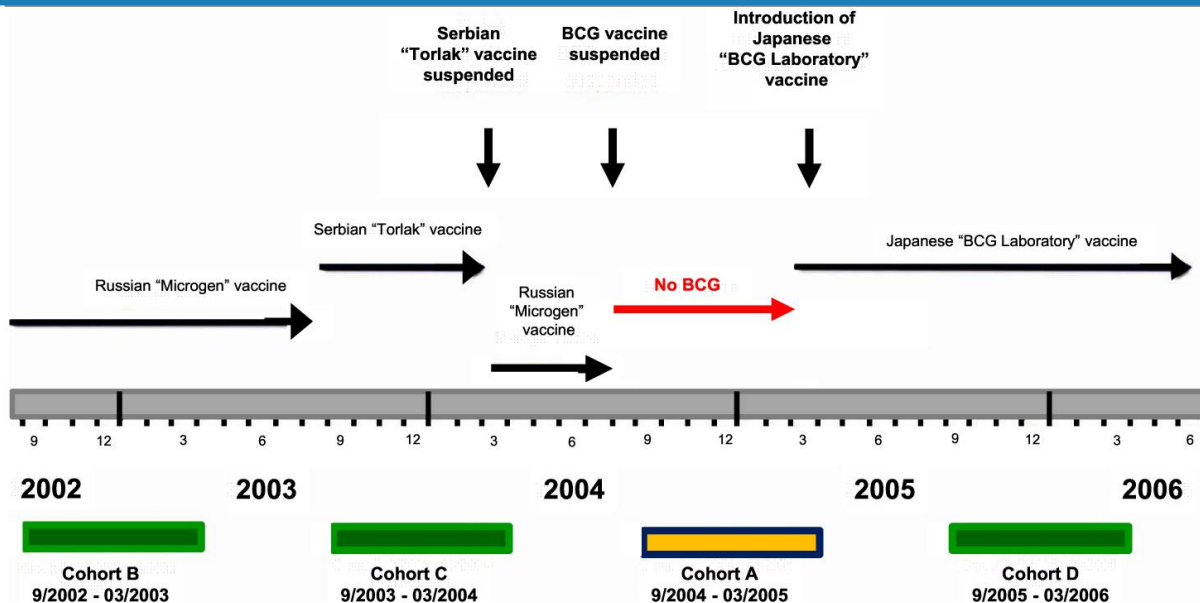
BCG vaccine efficacy against meningeal or miliary TB (all studies)

<u>Variable</u>	<u>N Trials</u>	<u>Univariable Rate Ratios (95% CI)</u>	
<u>Latitude</u>			Meta-analysis of RCTS Similar patterns by latitude and risk of diagnostic detection bias seen
40°+	4	0.09 (0.01; 0.73)	
20°-40°	1	5.28 (0.01; 4143)	
0°-20°	1	0.54 (0.01; 39.97)	
<u>Age at Vaccination / Tuberculin Testing Combined</u>			Observational studies: variance between studies reduced when stratifying by latitude, age at vaccination, and risk of diagnostic detection bias
Neonatal	2	0.10 (0.00; 60173)	
School age / stringent	2	0.08 (0.00; 104.89)	
School age / non stringent	1	0.54 (0.00; 178373)	
Other age / non stringent	1	5.28 (0.00; 1.87x10 ⁹)	
<u>Diagnostic Quality</u>			
Lower risk of bias	4	0.09 (0.02; 0.42)	
Higher risk of bias	2	1.06 (0.07; 15.32)	

Overview of studies since May 2009

Author and year	Participants	Outcome	Design	VE (95% CI)
Favorov et al., 2012	Children (Kazakhstan)	TB (all) (culture+ve)	Ecological	Varies by yr different strain used 51-92%
Michelsen et al 2014	Children (Greenland)	TB (all) IGRA+ve	Cohort Xsectional	50% (15,68) 20% (no summary)
Roy et al., 2014	Children (several)	IGRA+ve	Sys review Outbreaks	19% (8,29)
Van-Dunem et al., 2015	HIV-infected children (Angola)	TB (all)	Case-control	30% (-75,72)
Nguidop-Djomo et al., 2016	Teens/young adults (Norway)	TB (all), PTB Duration	Cohort	2-20 yrs after BCG TB all ~60% PTB ~65%
Mangtani et al., 2017	School-age children (UK)	TB (all) Duration	Case-control	10-20 yrs after BCG ~50%

Comparison of TB rates (RRs) by year with different BCG strains compared to a year no BCG (Favorov et al., 2012)



Confidence intervals overlap culture-confirmed cases

All >70% effective against TB meningitis

Limitations:

- Variations in tuberculosis incidence over time
- Possible changes in diagnostic and notification practices
- Extent of catch-up vaccination in those unvaccinated not known

Effectiveness against

Clinical TB notifications

Culture confirmed TB

BCG-Japan	69% (61-75)	92% (39-99)
BCG-Serbia	43% (31-53)	82% (21-96)
BCG-Russia	22% (7-35)	51% (neg-83)

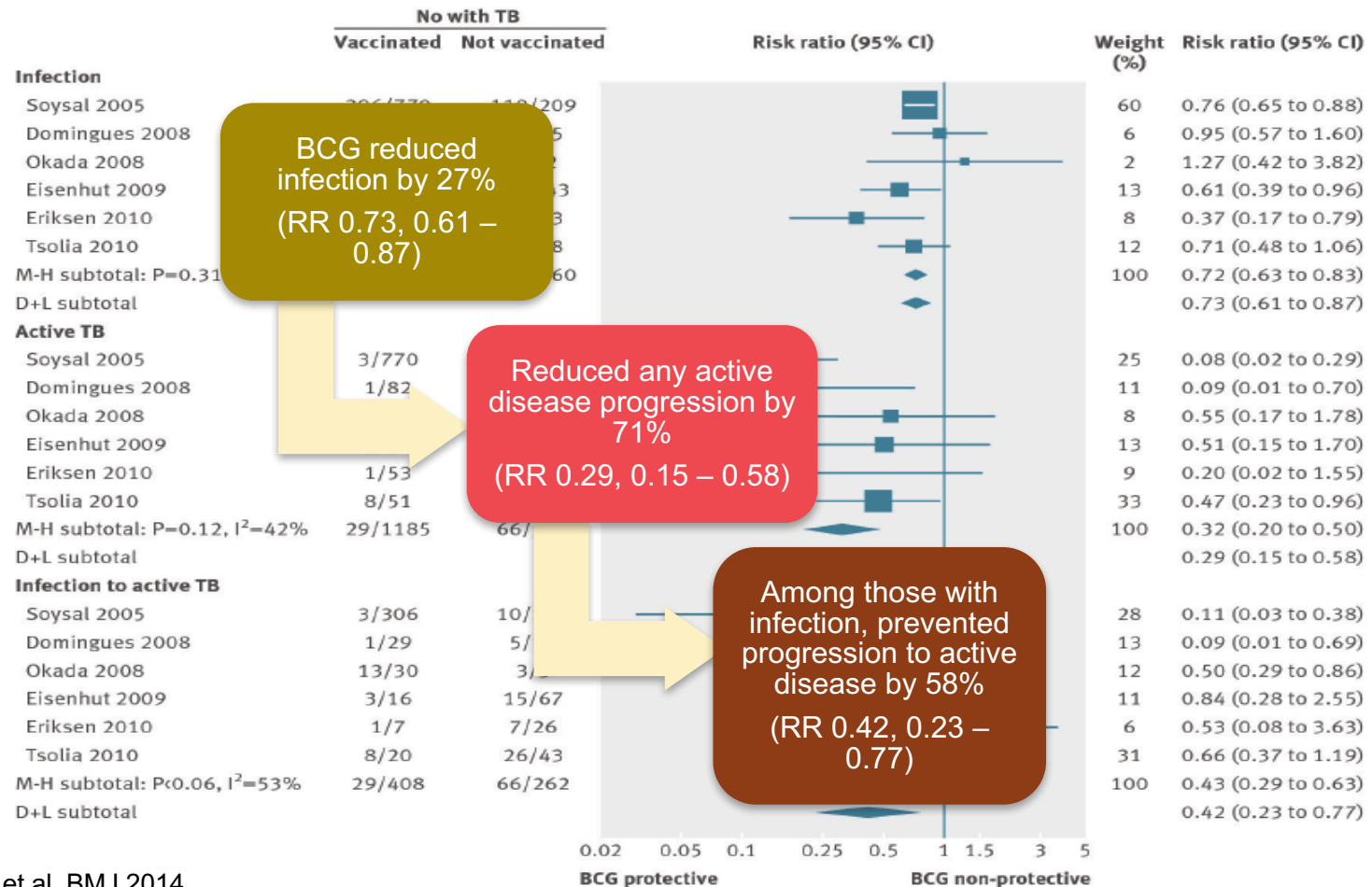
Meta-analysis protection against primary *M tb* infection with BCG (Roy et al 2014)

- 14 studies, BCG vaccinated children exposed to persons with open pulmonary TB had **19% less *Mtb* infection** than unvaccinated children (95% CI 8 – 29%)
- Also found:
 - Greater protection in higher quality studies of low Newcastle-Ottawa score VE 32%
 - Possible greater protection in higher latitudes?
 - latitude 0° - <20°, VE 13%,
 - latitude 20° - < 40°, VE 12%
 - latitude 40°+, VE 26%

Roy et al., 2014 BMJ 2014; doi: <https://doi.org/10.1136/bmj.g4643>

Meta-analysis protection against primary *M tb* infection with BCG (Roy et al 2014)

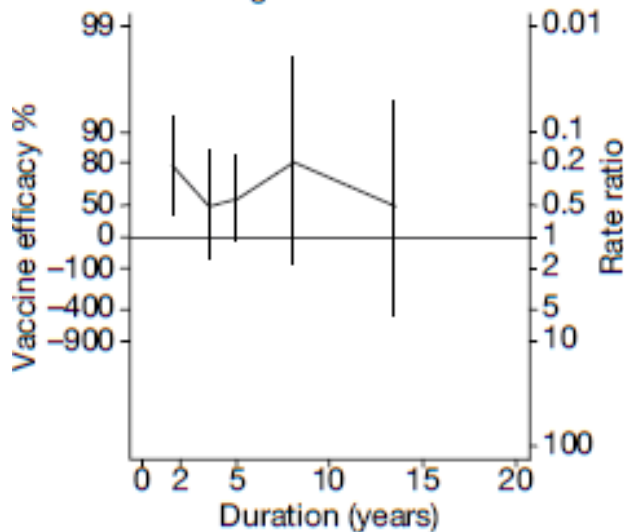
In a subset of 6 studies



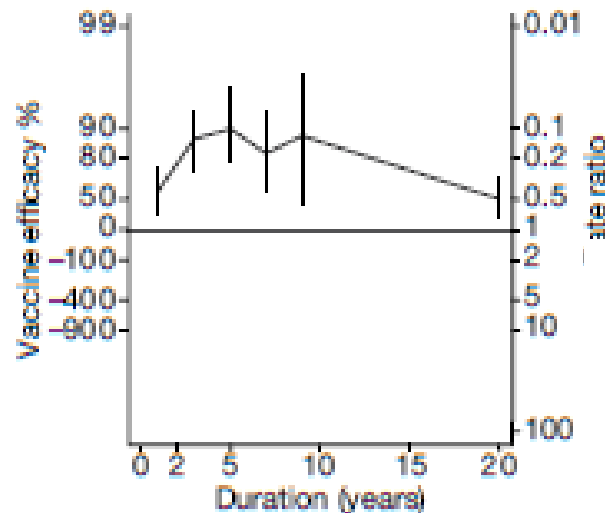
Roy A et al. BMJ 2014

Duration of protection (PTB) RCTs and an observational study

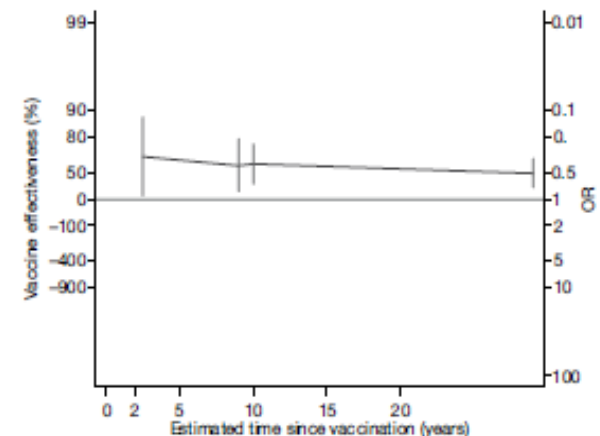
Chicago infants (Hospital)
Infant BCG RCT*



Native American and Alaskan Natives
Stringent testing school-age RCT



Nagpur Hospital
infant BCG CC study

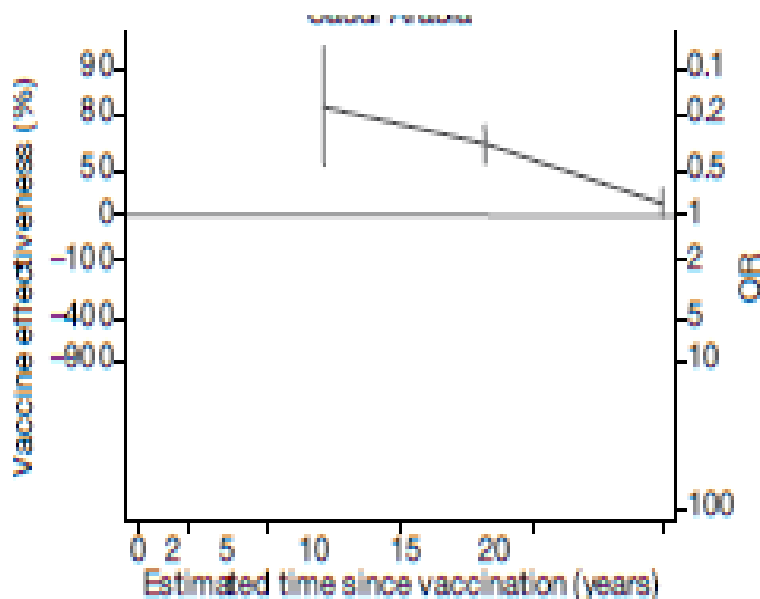


*Similar pattern TB (all)

Abubakar et al. 2013 HTA

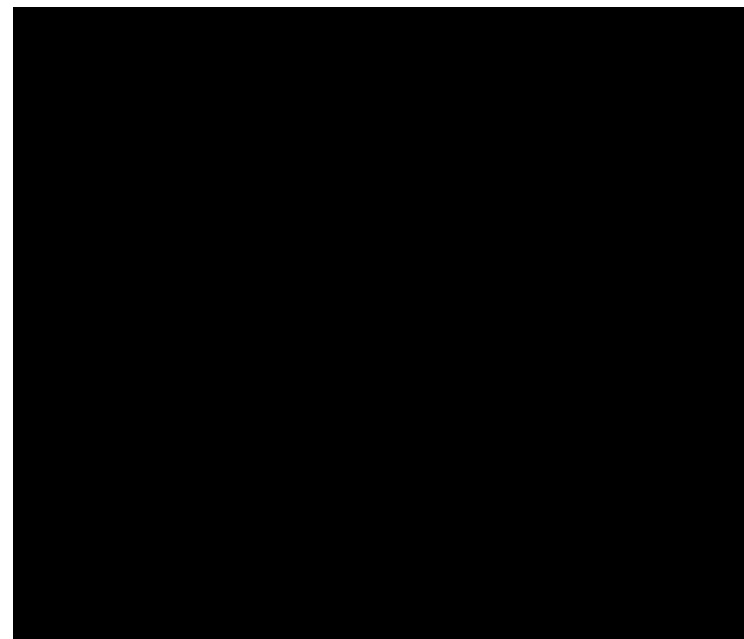
Duration protection TB (all) *infant BCG* observational studies

Saudi Arabia cc study

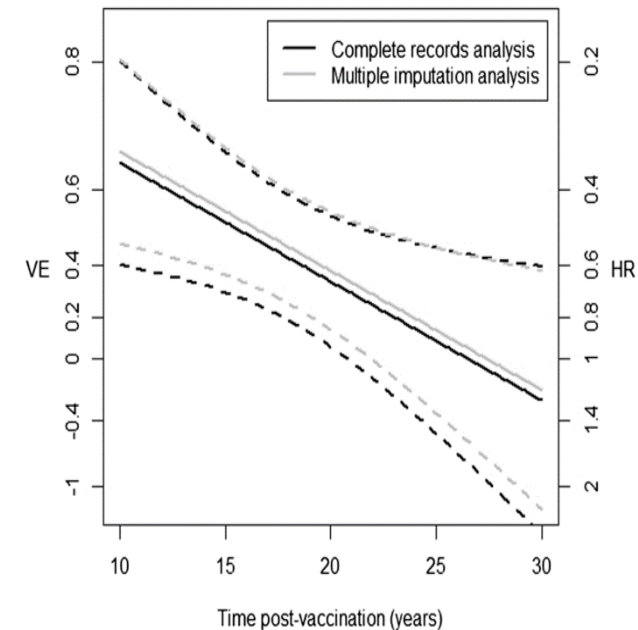
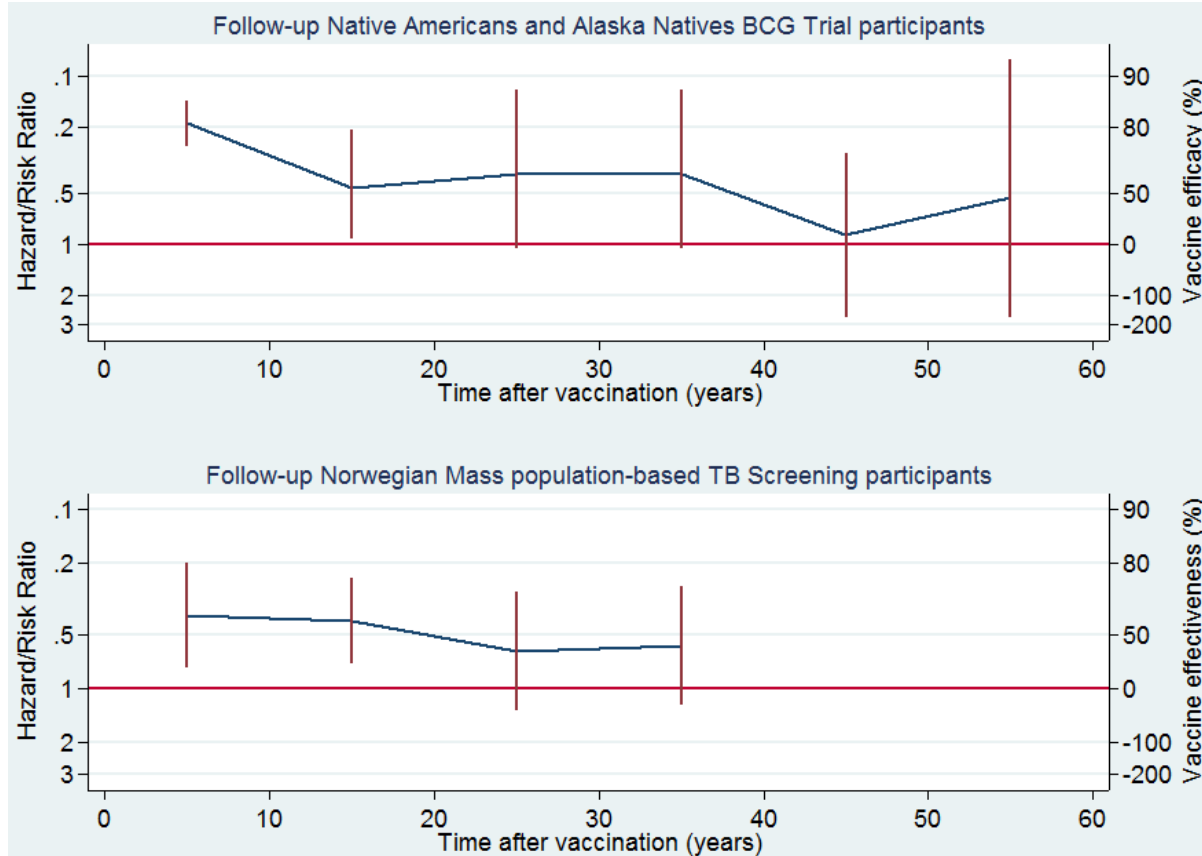


Abubakar *et al.* 2013 HTA

Brazil revac cohort study



Duration protection against TB (all) *school-age/young adult BCG*



Top panel RCT **after stringent testing** Aronson NE et al 2004 JAMA;
Bottom panel cohort **not after stringent testing** Nguipdop-djomo P et al 2015 LID

Case-control study **not after stringent testing** Mangtani et al., 2017 Int J Epidemiol.
doi:10.1093/ije/dyx141

Conclusions

- This new evidence of additional protective effects of BCG vaccination to prevent TB infection and progression to active TB disease, has implications for its overall effect on the control of TB.
- Evidence from RCTs shows that BCG is protective against PTB, especially when given in the neonatal period, or in school age children who are TST negative on stringent testing. More evidence in low latitude settings would be useful.
- Duration of protection up to 20 years in some populations. More evidence required in high TB burden settings.

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