7TH GLOBAL FORUM ON TB VACCINES | 8-10 October 2024 Rio de Janeiro, Brazil

Driving innovation from discovery to access

BCG revaccination: Lessons learned and implications for the field

BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE

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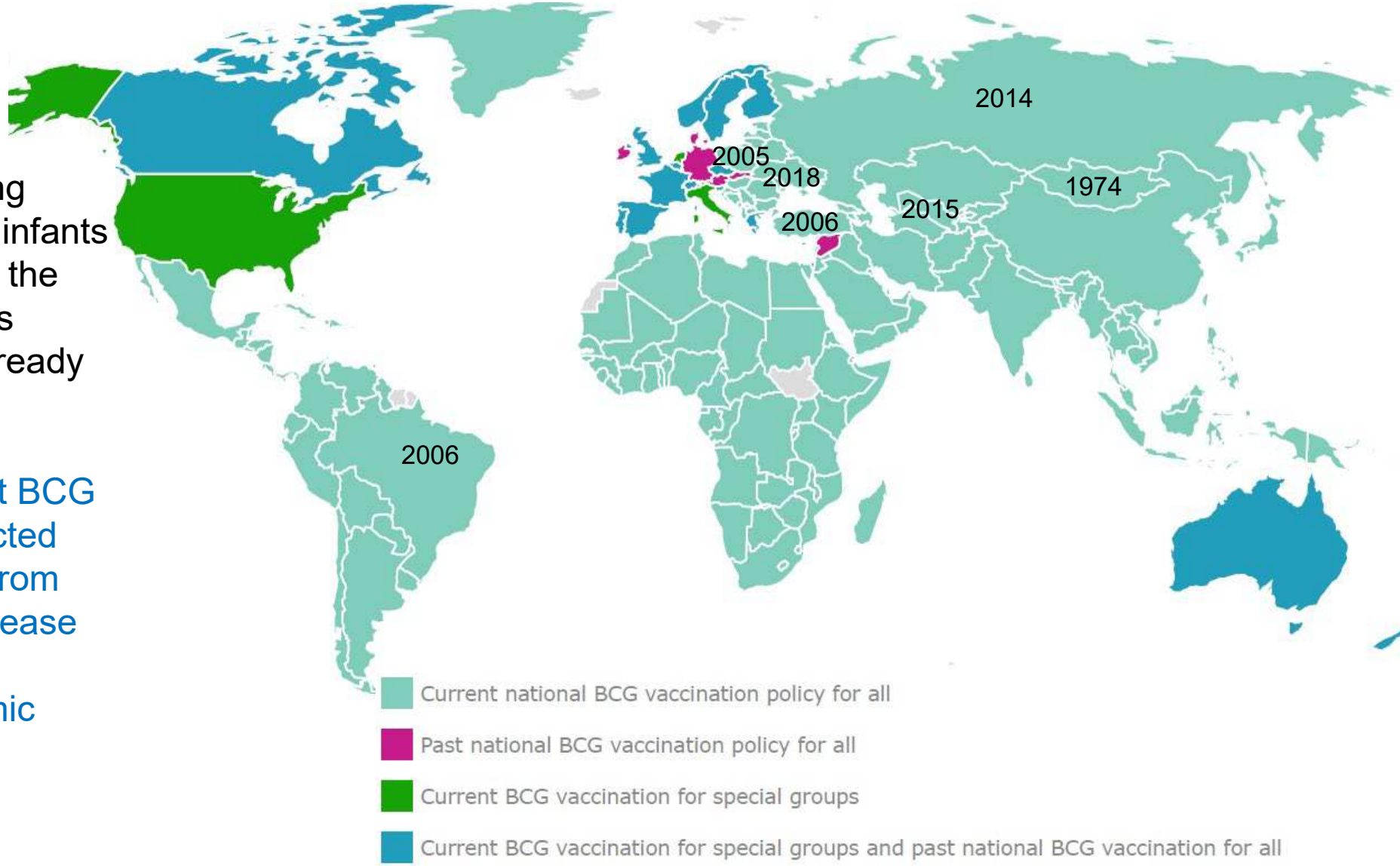
BCG – the only licensed TB vaccine; in use since 1921

Prevents severe TB in young children and is delivered to infants in most countries, including the highest TB burden countries
Variable to no efficacy in already Mtb-infected individuals

- Widespread use of infant BCG has not effectively protected adolescents and adults from developing active TB disease and has not adequately controlled the TB epidemic

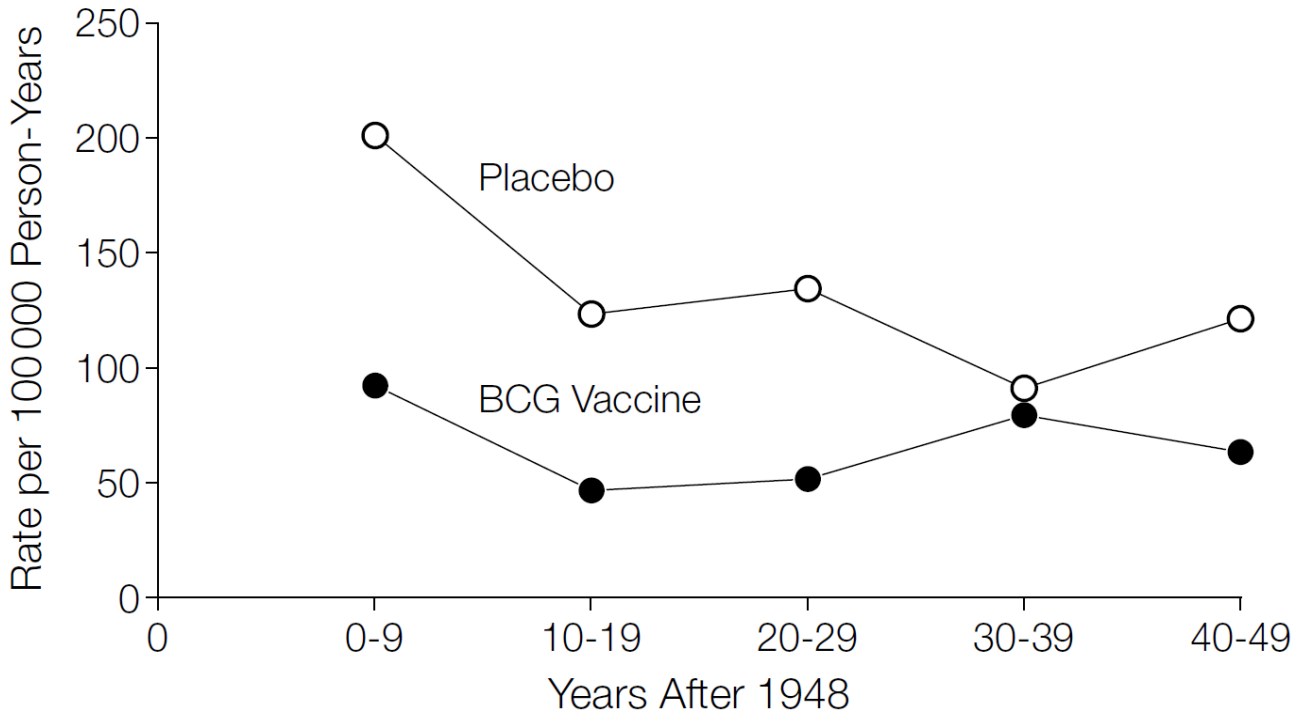


http://www.bcgatlas.org/

Year (selected countries) = year the country stopped recommending revaccination

Primary BCG Vaccination Protects Skin-Test Negative Children From TB

American Indian & Alaska Native Study, trial intervention 1935 - 1938



No. of Tuberculosis Cases					
Placebo	25	14	14	8	5
BCG Vaccine	13	6	6	8	3
Vaccine Efficacy, %	54	62	62	12	48

Age @ Vx	N
<5	846
5-9	1283
10-14	738
15-19	141

Overall incidence of TB:
1.38/1,000 person years (placebo)
0.66/1,000 person years (BCG)

Aronson & Aronson, 1952, DOI: 10.1001/jama.1952.02930210018006 ; Aronson et al, 2004, DOI: 10.1001/jama.291.17.2086.

The observed efficacy of BCG for Prevention of Disease (POD) in children and adults varies greatly between studies & geographies

Trial and subjects	Duration of observation (years)	Percentage protection	Reference
North American Indians	9—11	80	25
Chicago : infants	12—23	75	11
Georgia : school children	20	None	8
Puerto Rico : population below 20 years	5½—7½	31	26
Georgia and Alabama : general population	14	14	10
Great Britain : school children	15	78	12
Madanapalle, South India: general population	9—14	31	27
Chingleput, South India : general population	7½	None	Present trial

ICMR, 1979, PMID: 535944

Karonga Prevention Trial, Malawi

Started 1986, >23,000 subjects in BCG revax group

Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed *Mycobacterium leprae* vaccine for prevention of leprosy and tuberculosis in Malawi

Case criteria	n	Scar-positive participants: BCG (23 456) *vs* placebo (23 307)		
		Incidence rate ratio (95% CI)	Number of cases	
			BCG	Placebo
Certain and probable tuberculosis	407	1·04 (0·73–1·48)	65	62
Pulmonary tuberculosis	376	1·13 (0·78–1·63)	60	53
Glandular tuberculosis	31	0·56 (0·19–1·66)	5	9
Total certain tuberculosis*	225	1·43 (0·88–2·35)	39	27
Total certain pulmonary tuberculosis*	201	1·74 (1·00–3·03)	35	20

- No TST prior to BCG re-vaccination
- Enhanced passive follow-up
- No prevention of disease (POD) observed

BCG-REVAC Trial, Brazil

Started 1996, >115,000 children in BCG revax group

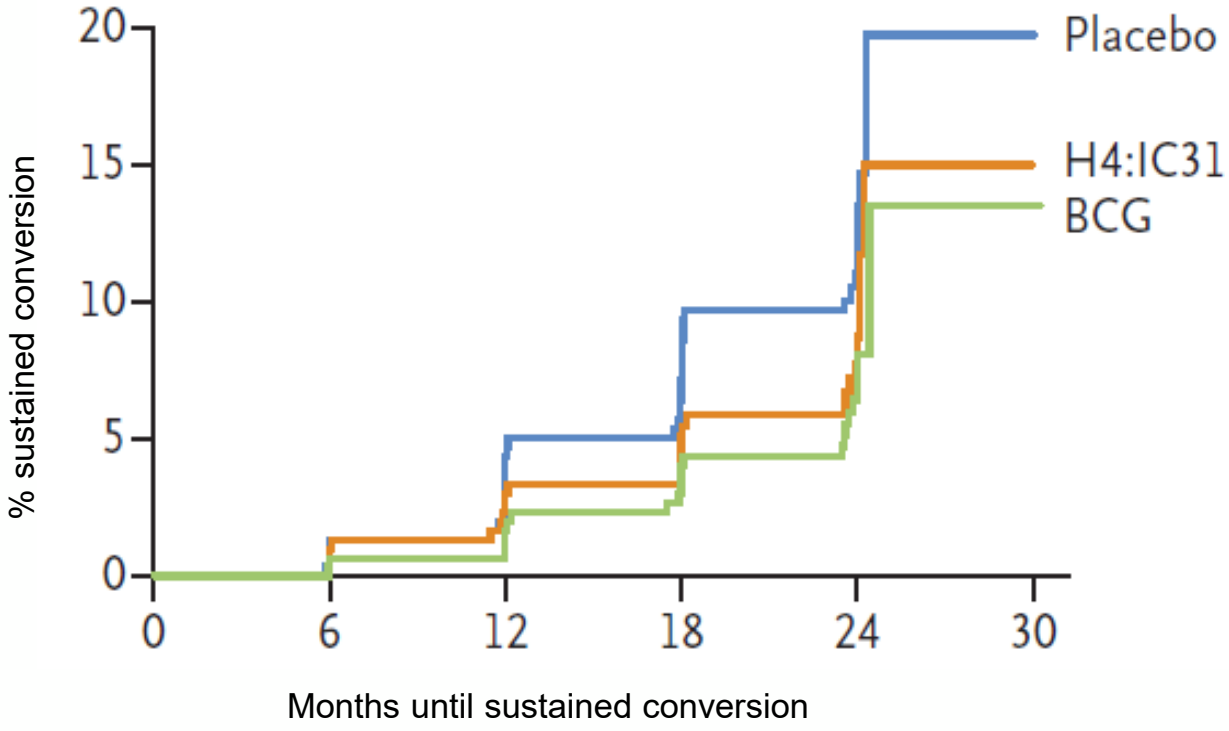
Evidence of an effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: Second report of the BCG-REVAC cluster-randomised trial

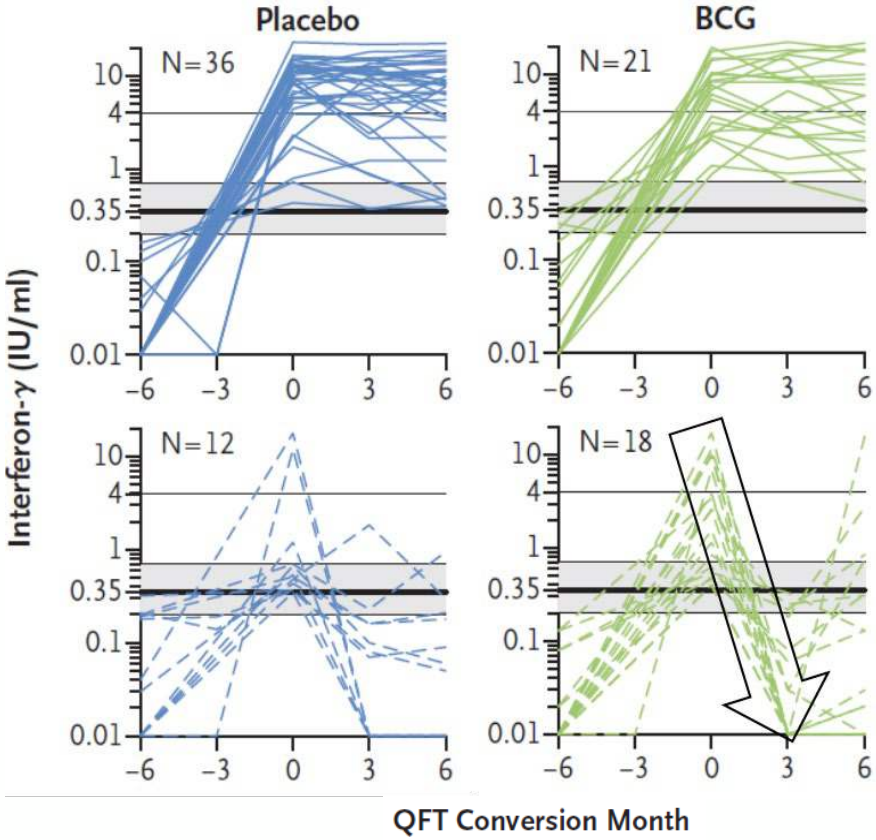
	VE	95% CI
Salvador 7-14 yoa	19%	3 to 33%
Salvador <11 yoa	33%	3 to 54%
Manaus 7-14 yoa	1%	-27 to 23%
Total	12%	-2 to 12%

- Cluster-randomized trial, BCG vs no intervention
- No TST prior to BCG re-vaccination
- One or no BCG scar for inclusion
- Passive follow-up
- No efficacy for POD observed in the overall population
- Modest effect in younger children & further from equator
- Effect of environmental mycobacteria?

Aeras BCG Revaccination Trial (Aeras C-040-404)

- N=990, QuantiFERON-TB Gold (QFT)-negative participants 12-17 years of age, 1:1:1
- Primary endpoint: initial QFT conversion: Vaccine efficacy (VE) = 20% (95% CI -21-47%, p=0.29)
- Secondary endpoint: sustained IGRA conversion: VE=45% (95%CI 6.4-68%, p=0.03)

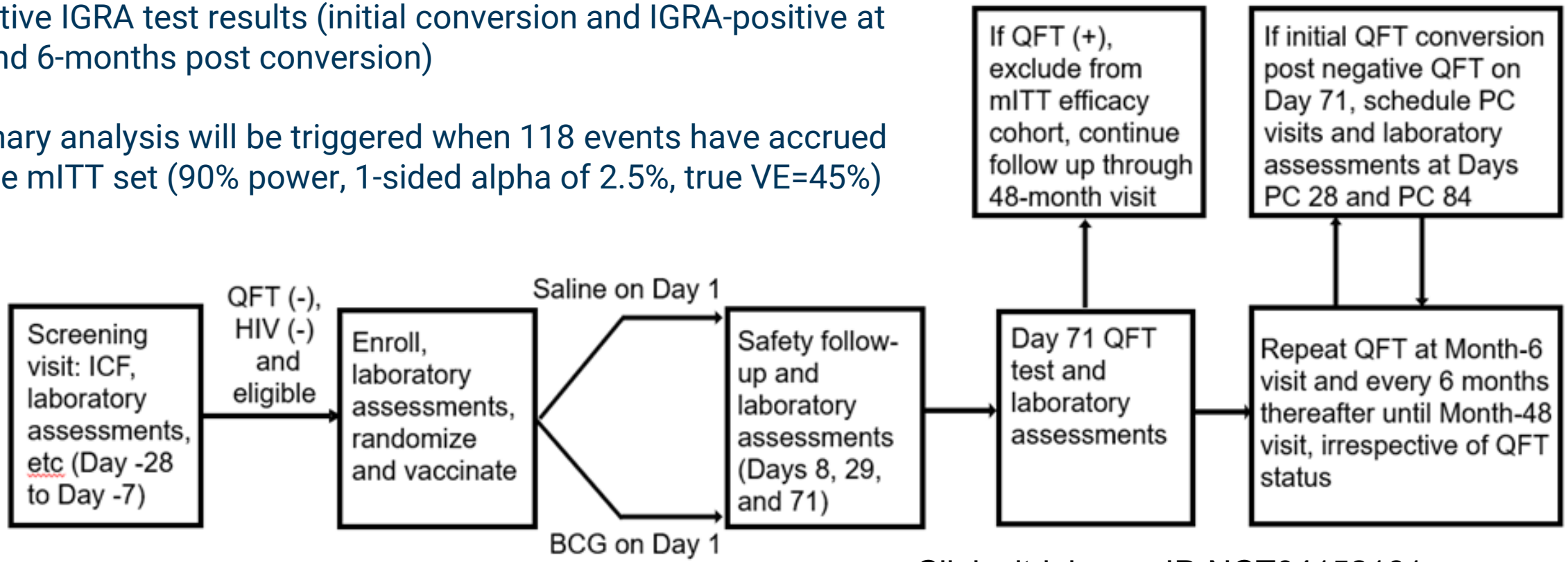




Nemes et al, NEJM 2018, DOI: 10.1056/NEJMoa1714021

Gates MRI BCG ReVax Trial

- **Trial population:** Approx. 1,800 adolescents 10 through 18 years of age, IGRA-negative & HIV-negative at enrollment, randomized 1:1 to BCG or placebo
- **Primary Endpoint:** Sustained IGRA conversion, based on 3 positive IGRA test results (initial conversion and IGRA-positive at 3- and 6-months post conversion)
- Primary analysis will be triggered when 118 events have accrued in the mITT set (90% power, 1-sided alpha of 2.5%, true VE=45%)



Clinicaltrials.gov ID NCT04152161

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Safety and Efficacy of BCG Revaccination for the Prevention of Sustained *Mycobacterium tuberculosis* Infection

Alexander C Schmidt[1], Lee Fairlie[2], Elisabeth Hellström[3], Angelique Kany Kany Luabeya[4], Keren Middelkoop[5], Kogieleum Naidoo[6], Gonasagrie Nair[5], Anele Gela[4], Elisa Nemes[4], Thomas J Scriba[4], Amy Cinar[1], Nicole Frahm[1], Robin Mogg[1], David Kaufman[1], Michael W Dunne[1], and Mark Hatherill[4]

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[6] CAPRISA MRC-HIV-TB Pathogenesis and Treatment Research Unit, Centre for the AIDS Programme of Research in South Africa, Durban, South Africa

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Summary

- Treatment groups were well balanced with respect to demographics and baseline characteristics
- The trial was well executed, with good community engagement and community support.
- BCG Revaccination was well tolerated; no safety concerns.
- Revaccination with BCG was not efficacious for the prevention of initial QFT conversion or sustained QFT conversion, i.e., BCG revaccination did not prevent *Mtb* infection

Effect of BCG vaccination against *Mycobacterium tuberculosis* infection in adult Brazilian health-care workers: a nested clinical trial

Paulo Cesar Pereira dos Santos, Nicole Louise Messina, Roberto Dias de Oliveira, Patricia Vieira da Silva, Marco Antonio Moreira Puga, Margareth Dalcolmo, Glauce dos Santos, Marcus Vinícius Guimarães de Lacerda, Bruno Araújo Jardim, Fernando Fonseca de Almeida e Val, Nigel Curtis, Jason R Andrews, Julio Croda**

- Health care workers, median age 39 years, 74% female, QFT prevalence at baseline approx. 10%

	BCG group	Placebo group	Risk ratio (95% CI)	p value
Primary outcome				
QFT conversion (positivity threshold ≥0·35 IU/mL)	34/996 (3·4%)	32/989 (3·2%)	1·09 (0·67–1·77)	0·791
Secondary outcome				
Sustained conversion (positivity threshold ≥0·35 IU/mL)	15/996 (1·5%)	19/989 (1·9%)	0·80 (0·41–1·57)	0·510

Lancet ID, 2024, doi: 10.1016/S1473-3099(23)00818-6

BCG revaccination: Lessons learned and implications for the field

- BCG revaccination did not provide significant protection from TB in the overall trial population in large trials conducted in Brazil, India, and Malawi. Analyses of subsets of trial participants (e.g., *Mtb*-infected vs not infected) is complex, in part because of missing data on *Mtb* infection status at enrollment

- BCG revaccination of QFT-negative adolescents and adults does not prevent *Mtb* infection, as assessed by QFT conversion

- Currently, there is no compelling evidence to support BCG revaccination as a public health intervention for the prevention of TB

- BCG vaccination of infants does prevent TB and should continue

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M72/AS01$_{E-4}$ Product Overview

- Recombinant fusion protein plus GSK proprietary adjuvant system
- 2-vial presentation (reconstitution of antigen + adjuvant) x 2 doses (1 mo. apart)

M72 is a 72kDa recombinant fusion protein derived from the two *M. tuberculosis* antigens

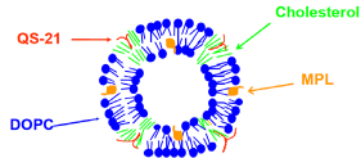
- Mtb39a : membrane-associated protein, putative evasion factor
- Mtb32a : secreted protein, putative serine protease

Composition of M72 lyophilized formulation per dose

Ingredient	Quantity per dose*	Function	Reference
M72	10 µg	Active ingredient	GSK Bio 300723
Sucrose	25 mg	Cake stability	Ph. Eur. 0204
Polysorbate 80	0.1 mg	Protein recovery	Ph. Eur. 0428
Tris	0.97 mg	Buffering agent	Ph. Eur. 1053

* Does not include overage
Ph. Eur.: European Pharmacopoeia
Pharmaceutical form: freeze-dried, white pellet

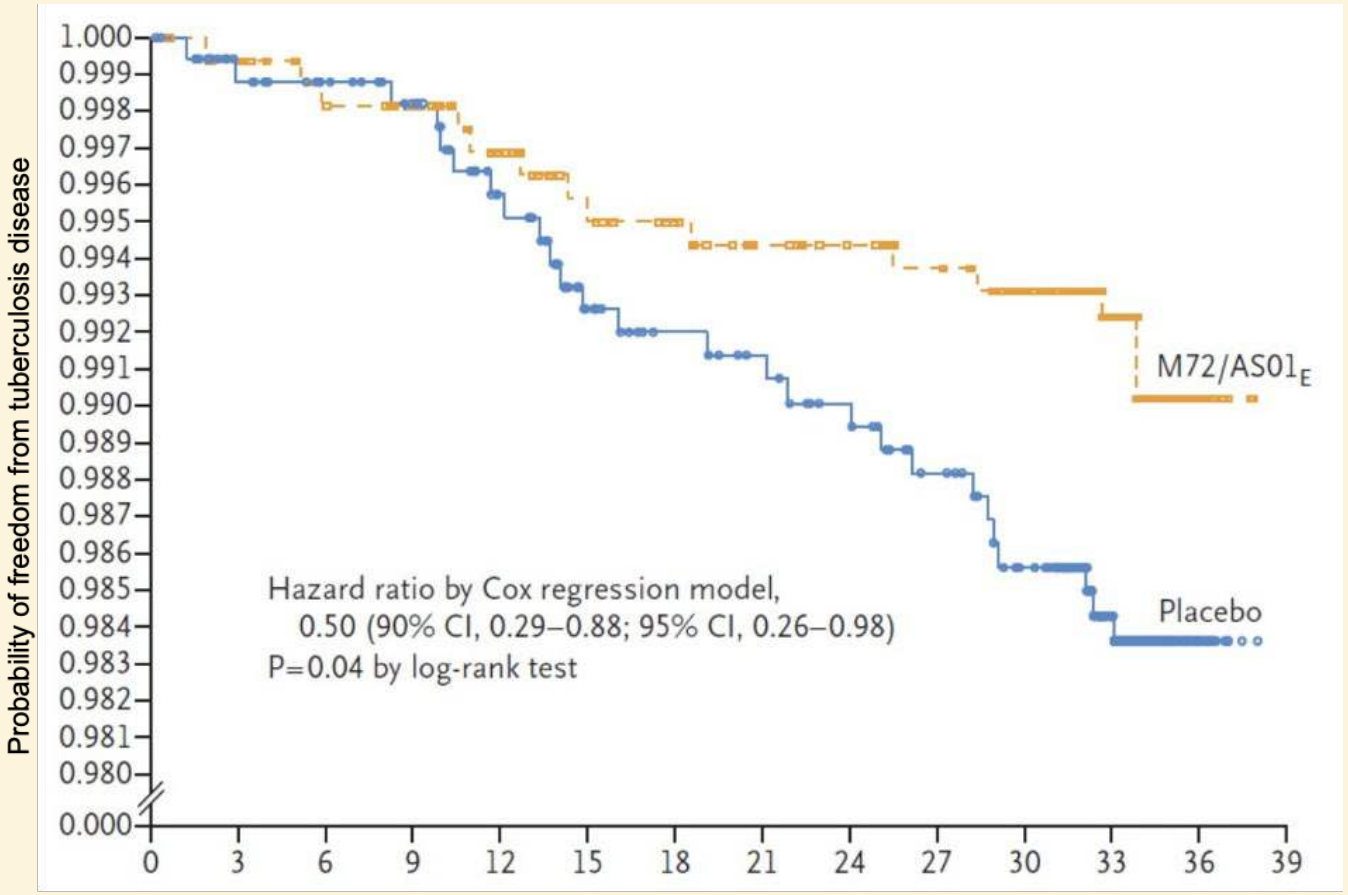
AS01$_{E-4}$ adjuvant system (GSK proprietary) is composed of immunoenhancers, liposome and other excipients

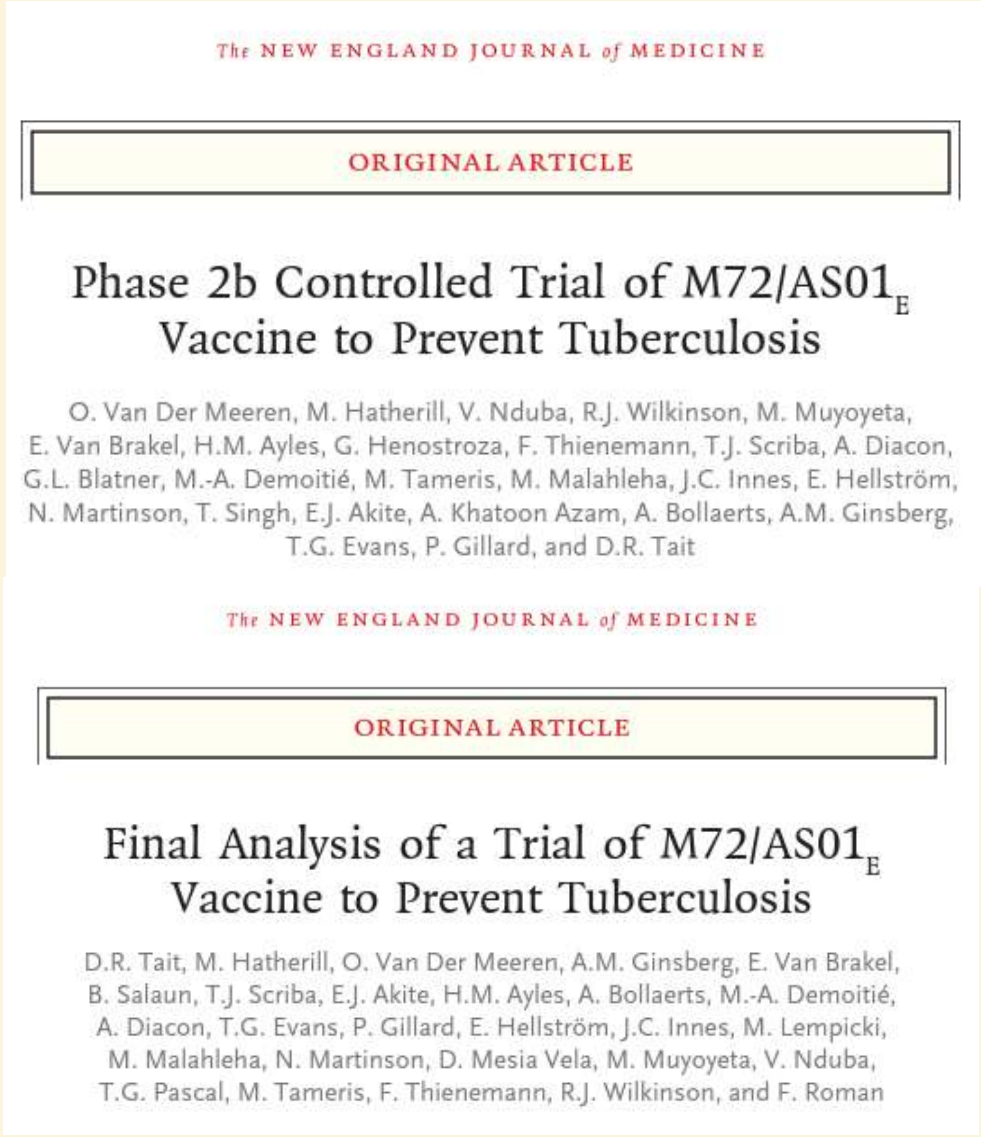


- QS-21 (a triterpene glycoside purified from the bark of Quillaja Saponaria Molina)
- MPL (3-D Monophosphoryl lipid A)
- DOPC
- Cholesterol
- Buffer

M72/AS01$_E$ Phase 2b trial

- VE: reduced active pulmonary TB by 50%
- Acceptable safety profile





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 2b Controlled Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

O. Van Der Meeren, M. Hatherill, V. Nduba, R.J. Wilkinson, M. Muyoyeta, E. Van Brakel, H.M. Ayles, G. Henostroza, F. Thienemann, T.J. Scriba, A. Diacon, G.L. Blatner, M.-A. Demoitié, M. Tameris, M. Malahleha, J.C. Innes, E. Hellström, N. Martinson, T. Singh, E.J. Akite, A. Khatoon Azam, A. Bollaerts, A.M. Ginsberg, T.G. Evans, P. Gillard, and D.R. Tait

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Final Analysis of a Trial of M72/AS01$_E$ Vaccine to Prevent Tuberculosis

D.R. Tait, M. Hatherill, O. Van Der Meeren, A.M. Ginsberg, E. Van Brakel, B. Salaun, T.J. Scriba, E.J. Akite, H.M. Ayles, A. Bollaerts, M.-A. Demoitié, A. Diacon, T.G. Evans, P. Gillard, E. Hellström, J.C. Innes, M. Lempicki, M. Malahleha, N. Martinson, D. Mesia Vela, M. Muyoyeta, V. Nduba, T.G. Pascal, M. Tameris, F. Thienemann, R.J. Wilkinson, and F. Roman

M72/AS01$_{E-4}$ Phase 2b Results

Table 1. Vaccine Efficacy of M72/AS01$_E$ as Compared with Placebo against Pulmonary Tuberculosis in Adults with Evidence of Tuberculosis Infection.*

Cohort and Case Definition	M72/AS01$_E$			Placebo			Vaccine Efficacy	
	No. of Participants†	Person-yr of Follow-up	Rate per 100 Person-yr (90% CI)	No. of Participants†	Person-yr of Follow-up	Rate per 100 Person-yr (90% CI)	% (90% CI)	% (95% CI)
According-to-protocol efficacy cohort								
First definition	13	4427.62	0.3 (0.2 to 0.5)	26	4463.06	0.6 (0.4 to 0.8)	49.7 (12.1 to 71.2)	49.7 (2.1 to 74.2)
First definition: sensitivity analysis‡	7	4429.29	0.2 (0.1 to 0.3)	22	4467.51	0.5 (0.3 to 0.7)	68.0 (34.7 to 84.3)	68.0 (25.1 to 86.3)
Second definition	8	4429.69	0.2 (0.1 to 0.3)	21	4467.51	0.5 (0.3 to 0.7)	61.7 (24.1 to 80.6)	61.7 (13.5 to 83.0)
Third definition	19	4427.62	0.4 (0.3 to 0.6)	30	4463.06	0.7 (0.5 to 1.0)	36.3 (–3.2 to 60.7)	36.3 (–13.2 to 64.1)
Fourth definition§	19	4427.62	0.4 (0.3 to 0.6)	32	44			
Fifth definition§	26	4434.21	0.6 (0.4 to 0.8)	38				
Modified fifth definition	25	4434.21	0.6 (0.4 to 0.8)	36				
Total efficacy cohort								
First definition	13	5055.30	0.3 (0.2 to 0.4)	28				
Second definition	8	5057.38	0.2 (0.1 to 0.3)	22				
Third definition	20	5055.30	0.4 (0.3 to 0.6)	32				
Fourth definition	20	5055.30	0.4 (0.3 to 0.6)	34				
Fifth definition	28	5061.90	0.6 (0.4 to 0.8)	38				
Modified fifth definition	27	5061.90	0.5 (0.4 to 0.7)	36	5			

The first case definition (blue box) for the primary endpoint (definite pulmonary TB) required **≥ 1** positive sputum test. The sensitivity analysis of the primary endpoint (red box) required **≥ 2** positive sputum tests.

The more stringent case definition (≥ 2 positive sputum tests) will be used as primary case definition for the Phase 3 VE trial.

M72/AS01$_E$ Phase 3 Efficacy Trial

Design

- Placebo-controlled, double-blind, 1:1 randomized trial
- N = 20,000, 15 to 44 years of age

Assumptions

- Vaccine Efficacy (VE) against Disease (D) in IGRA+ cohort is ≥ 55%
- Null hypothesis: H0: VE(D) ≤ 10% (α < 2.5%, lower bound of 95% CI > 10%)
- TB incidence: 0.4% per year in IGRA+
- *Mtb* infection rate: 3% per year

Cohort	N
HIV-, IGRA+ Cohort	18,000
HIV-, IGRA- Cohort	1000
HIV+ Cohort	1000
Total	20,000

End of Trial

- Primary endpoint analysis once 110 cases of lab-confirmed TB are observed
- > 90% power to demonstrate VE of 55% with LB > 10%

Thank you