BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE

BCG Re-vaccination

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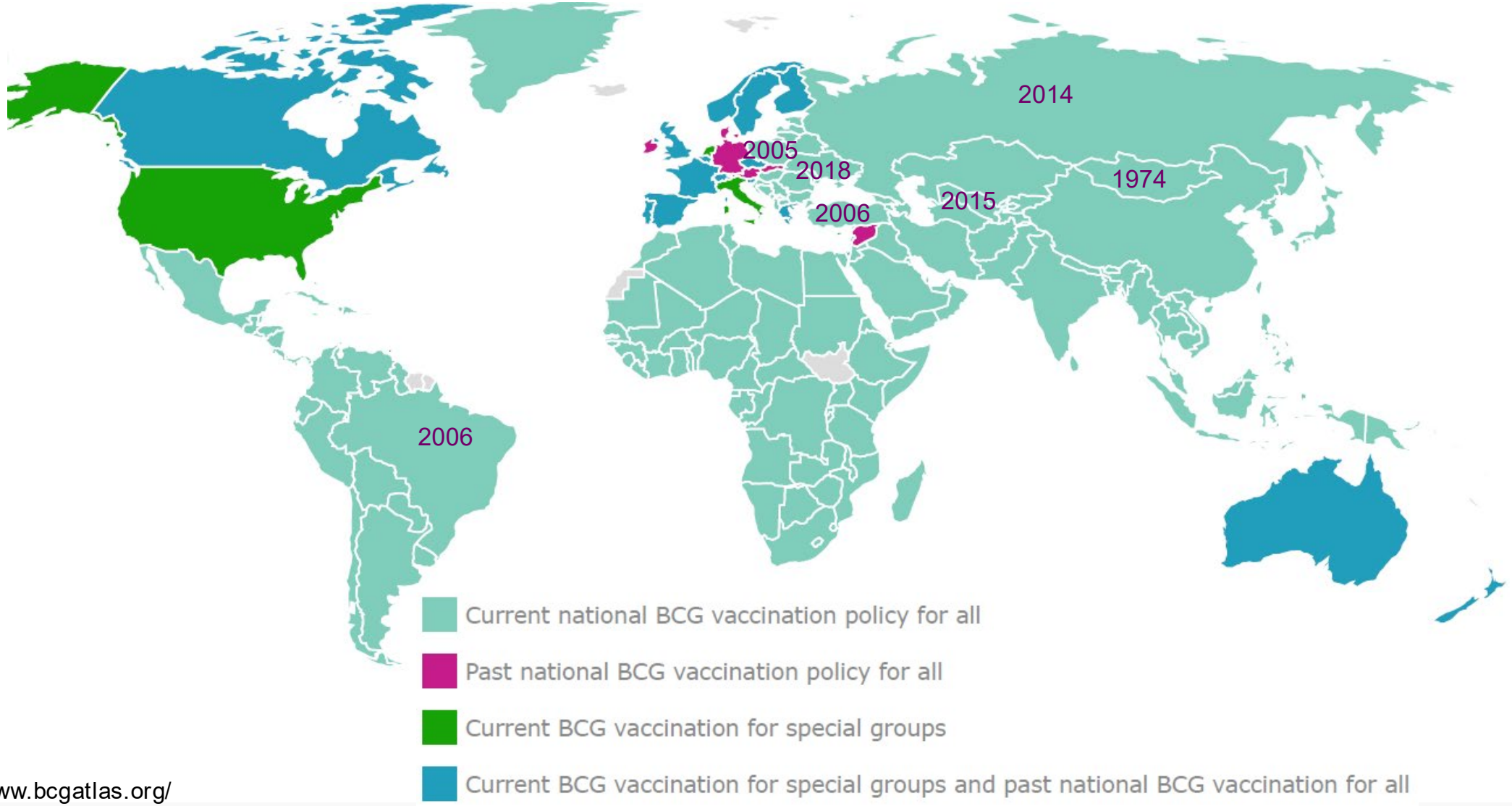
Innovations for Tackling Tuberculosis in the Time of COVID-19

The National Academies of Sciences, Engineering, and Medicine

100 Years of BCG: Vaccination Policies Around the Globe



http://www.bcgatlas.org/

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

Primary BCG Vaccination Protects Skin Test Negative Young Adults from TB

Ulleval Nurses Study, Oslo

TABLE IV.—RATES OF TUBERCULOUS DISEASE AMONG ULLEVÅL NURSES, 1924-1946

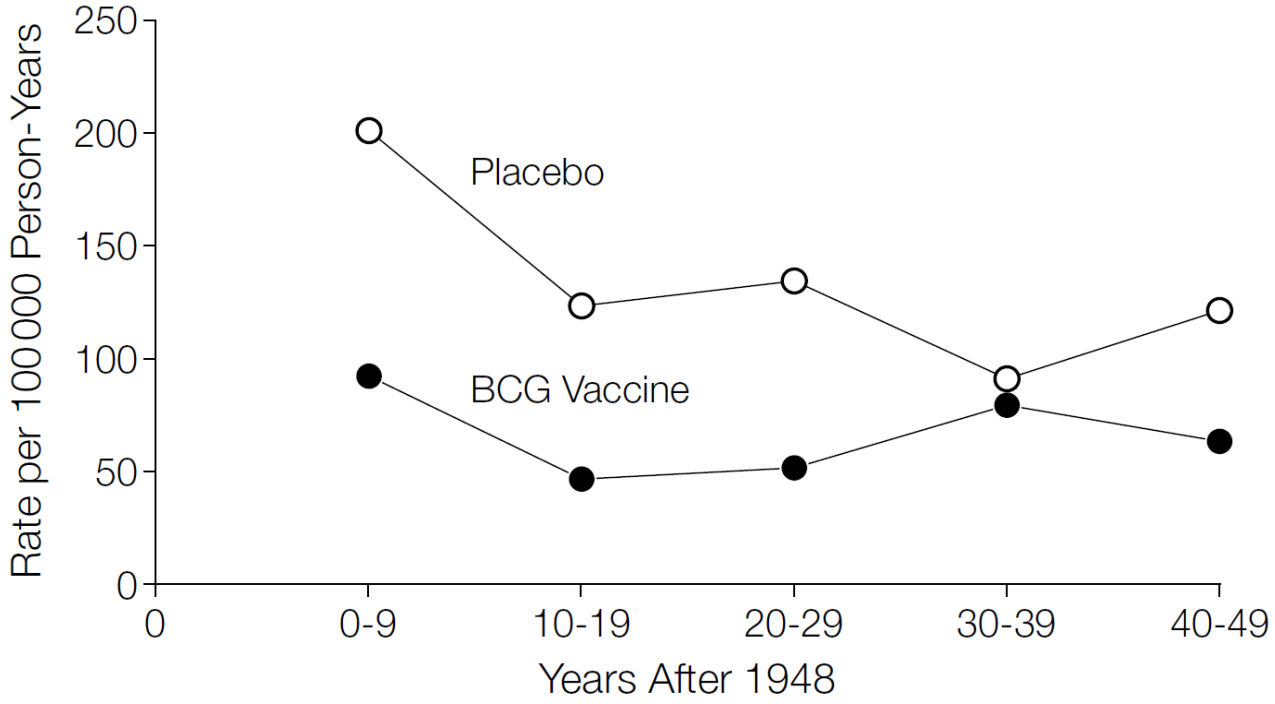
	Nos.	Observation years	Tuberculosis Disease	Deaths	Rate per 1,000 observation years Morbidity	Mortality
Pupil nurses in training						
P+ ..	668	1,772	22	0	12·4	0
BCG ..	501	1,450	35	3	24·1	2·1
P— ..	284	687	97	10	141·2	14·6

VE=83%

Heimbeck, 1948, DOI: 10.1016/s0041-3879(48)80096-6

Primary BCG Vaccination Protects Skin-test Negative Children & Adolescents From TB

American Indian & Alaska Native Study



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

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

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

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

Differences In BCG Strains, Geography, Incidence & Observed Vaccine Efficacy

LONG-TERM RESULTS OF BCG VACCINATION IN THE SOUTHERN UNITED STATES[1]

G. W. COMSTOCK[2] AND C. E. PALMER

(Received for publication September 20, 1965)

INCIDENCE OF TUBERCULOSIS AMONG CONTROLS AND VACCINEES

Study Category	Study Population	Number of Cases	Average Annual Incidence per 100,000
Total			
Controls	17,854	32	12.8
Vaccinees	16,913	26	11.0

Percentage reduction in tuberculosis among vaccinees: 14.2

Comstock & Palmer, 1966, DOI: 10.1164/arrd.1966.93.2.171

BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early adult life

FOURTH REPORT TO THE MEDICAL RESEARCH COUNCIL BY ITS TUBERCULOSIS VACCINES CLINICAL TRIALS COMMITTEE *

Trial group	Number of participants	Cases of tuberculosis		Protective efficacy (%)
		Number starting within 15 years	Annual incidence per 1 000 participants [b]	
Negative, unvaccinated	12 699	240	1.28	
Negative, BCG-vaccinated	13 598	56	0.28	78.4
Positive to 3 TU	15 514	204	0.89	
Positive only to 100 TU	6 153	52	0.57	

MRC UK, 1972, PMID: 4537855

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 protection observed

BCG-REVAC Trial, Brazil

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

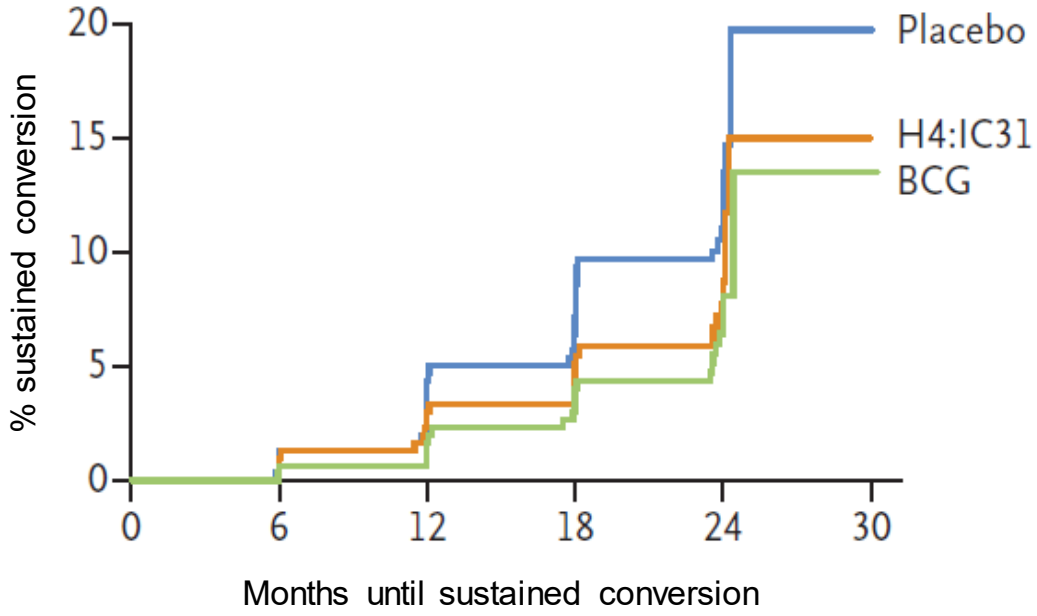
Evidence of an effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: Second report of the BCG-REVAC cluster-randomised trial

	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%

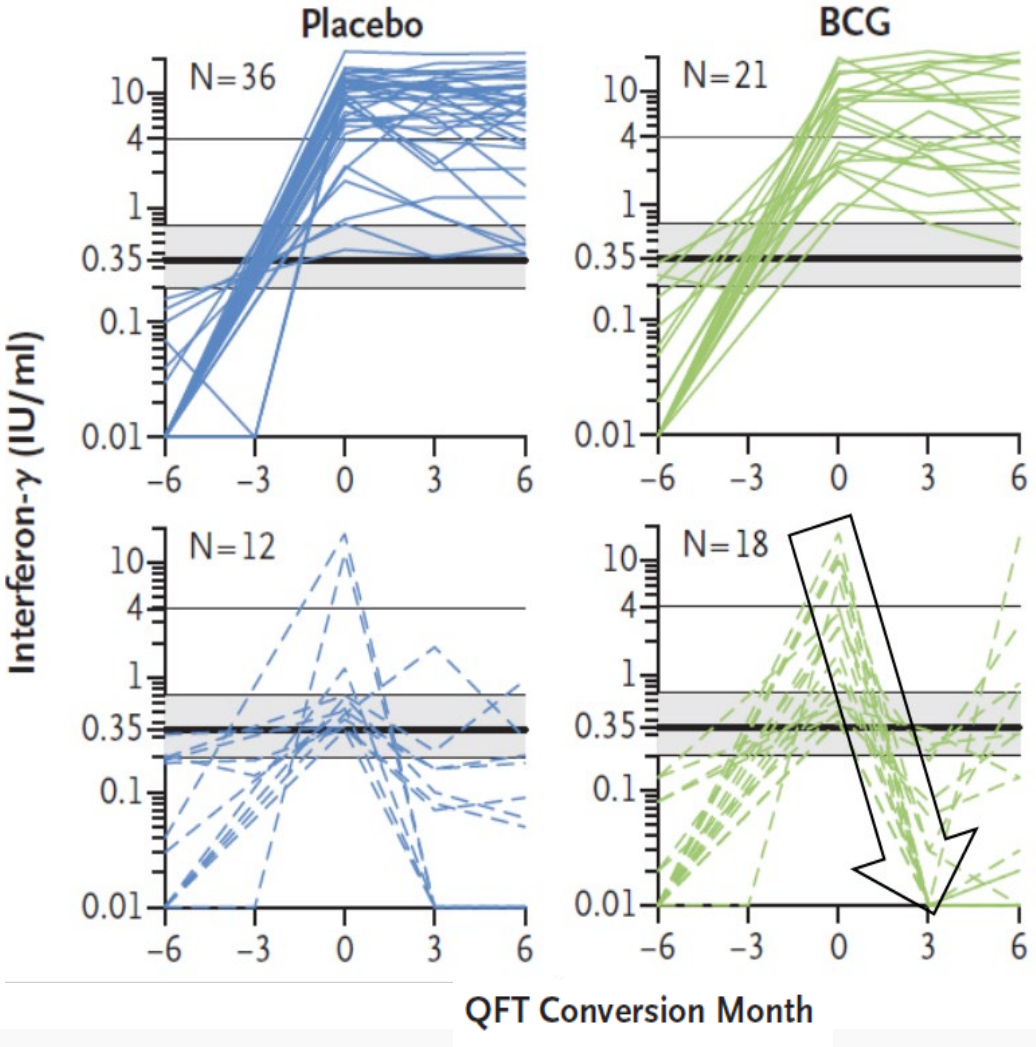
- Cluster-randomized trial, BCG vs no intervention
- No TST prior to BCG re-vaccination
- One or no BCG scar for inclusion
- Passive follow-up
- No protection observed in the overall population
- Modest effect in younger children & further from equator
- Effect of environmental mycobacteria?

Prevention of (sustained) *Mtb* infection with H4:IC31 or BCG Revaccination (Aeras C-040-404)

- N=990, IGRA-negative at enrollment, 1:1:1
- Primary endpoint: initial IGRA-conversion
  - BCG: Vaccine efficacy (VE) not statistically significant
- Secondary endpoint: sustained IGRA-conversion
  - initial conversion and IGRA+ 3 and 6 months post initial conversion
  - **BCG VE was 45% (95% CI 6.4-68%, p=0.03)**

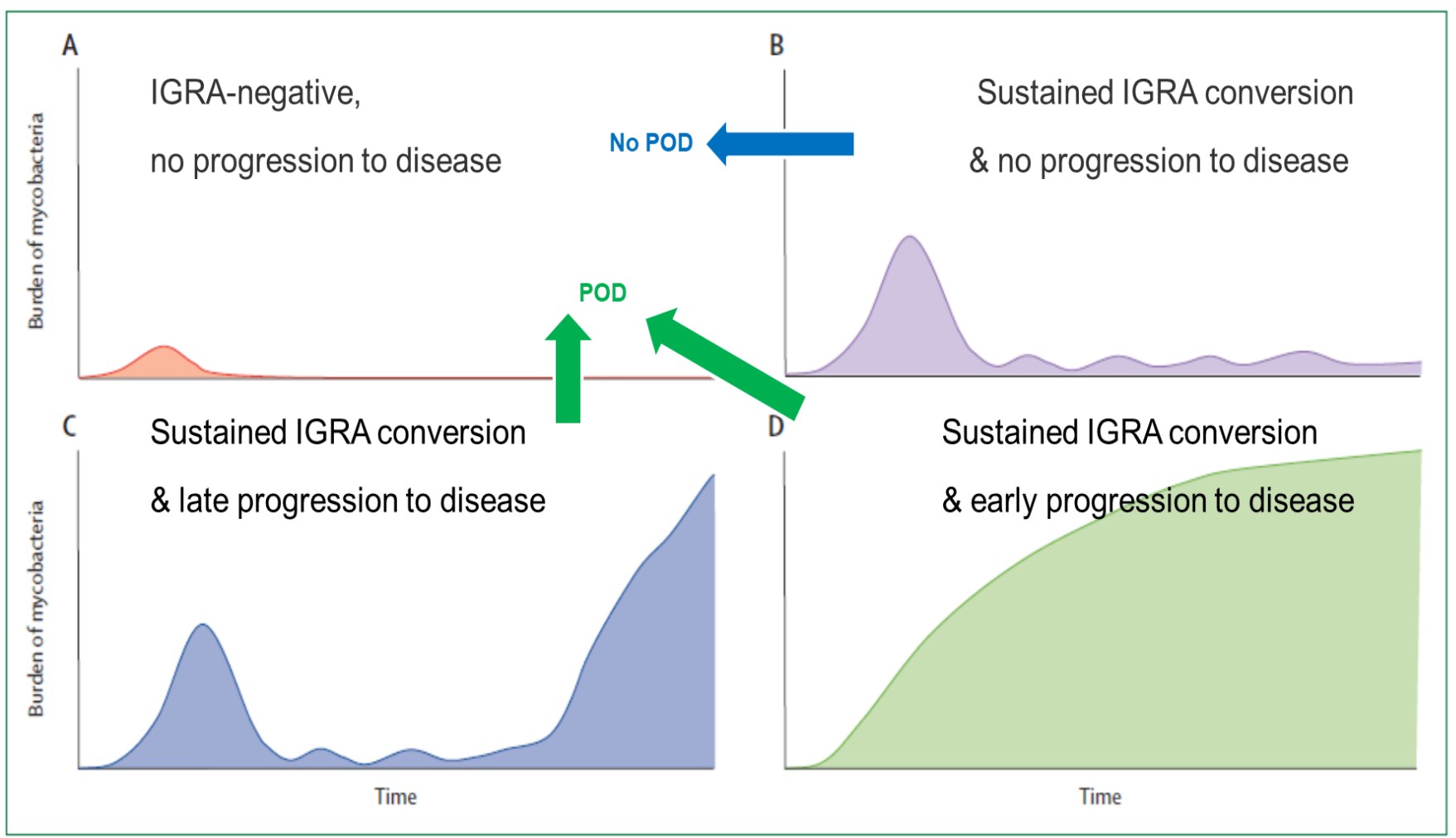


- IGRA conversion rate: 10% per 100 person years



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

Is IGRA reversion indicative of *Mtb* clearance & does it lead to prevention of disease (POD)?



>90% of *Mtb* infections

<10% of *Mtb* infections

Seddon et al, 2019, DOI: 10.1016/S1473-3099(18)30787-4

GATES MRI BCG ReVax Trial

Goal: generate data that can potentially support policy change for BCG revaccination

Randomized (1:1), placebo controlled, Phase 2b trial in South Africa, using BCG vaccine from AJ Vaccines / Biovac Institute (Danish 1331)

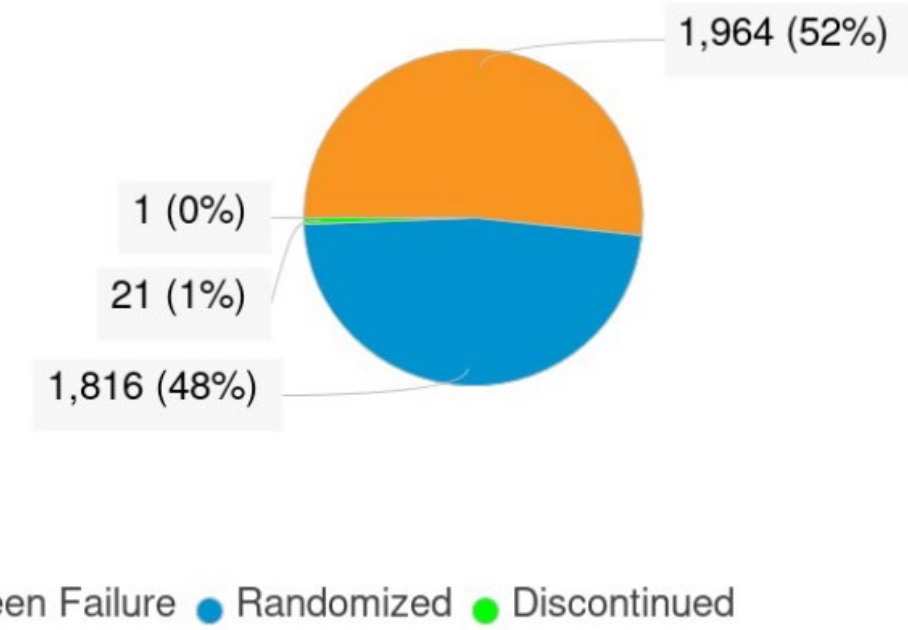
- Approx.1,800 IGRA-negative participants 10-18 years of age
- IGRA every 6 months for 48 months, plus 2 post-conversion visits

Primary objective:

- Demonstrate the efficacy of BCG revaccination for the prevention of sustained *Mtb* infection (POSI)
  - Event-triggered analysis once 118 cases are observed, time-to-event, p<0.025

Other objectives (selected):

- Evaluate safety & reactogenicity
- Evaluate durability of efficacy
- Explore and/or develop candidate correlates of risk (CoRs) and correlates of protection (CoPs)



Clinicaltrials.gov NCT 04152161

BCG Immune Correlates for POSI (based on Aeras C-040-404 trial)

CELLULAR IMMUNITY

- Antigen-specific T cells and NK cells (McElrath)
  - Intracellular cytokine staining
- Donor-unrestricted T cells (DURTs, MAITs) (McElrath)
  - Tetramer staining
- scRNAseq (Shalek)

INNATE / TRAINED IMMUNITY

- Whole blood composition (Nemes)
  - DLC-ICE
- scATACseq (Barreiro)
- EpiToF (Utz/Khatri)

HUMORAL IMMUNITY

- Antibody titer, subclass and avidity (Tomaras)
  - Binding antibody multiplex assay
- Antibody function (Alter)
  - Systems serology
- Antibody-mediated *Mtb* growth inhibition (Alter)

OMICS ANALYSES

- Bulk RNAseq (Scriba)

CoP effort led by Nicole Frahm, Gates MRI

Correlates of Risk & Correlates of Protection

1. Describe CoRs & CoPs for sustained infection, based on Aeras/IAVI BCG Revax samples
    1. Then test candidate CoRs & CoPs using samples from MRI BCG ReVax
2. Describe CoRs & CoPs for TB, based on M72 Phase 2b samples
    1. Then test identified CoRs & CoPs for TB using M72 Phase 3 samples
3. Identify CoRs & CoPs that are shared between POSI and POD data sets

Will this be sufficient to convince policy makers?

Other potential data sources:

- Ongoing and planned Phase 3 programs, e.g., SII Phase 3 program for VPM1002 (rBCG)
- Real world evidence from (discontinuation of) BCG revaccination programs

Summary

- BCG revaccination is associated with a higher rate of IGRA reversion, possibly indicative of a protective immune response, and potentially leading to *Mtb* clearance
- It is unknown what percentage of BCG re-vaccinated individuals who reverted to IGRA-negative would have been at risk of progression to TB disease had they not reverted, i.e., a link between POSI and POD has not yet been established
- BCG revaccination could potentially contribute to accelerating the end of the epidemic (available & affordable) but a potential policy change will likely depend on linking POSI to POD
- The evidence generated from the BCG ReVax study has the potential to provide useful data for vaccine policy makers. The potential impact of geography, environmental mycobacteria, and differences in commercially-available vaccines will play a role in policy deliberations.
- Additional evidence may come from additional RCTs (e.g., rBCG Phase 3) or from real world data
- If robust CoRs & CoPs can be established for TB vaccines, the impact on vaccine development could be transformational (faster, less expensive, easier to iterate)

THANK YOU