Prevention of TB with an inactivated whole cell mycobacterial vaccine

C. Fordham von Reyn MD
Dartmouth Medical School
USA

Prevention of tuberculosis in Bacille Calmette–Guérin-primed, HIV-infected adults boosted with an inactivated whole-cell mycobacterial vaccine

Charles F. von Reyn[a], Lillian Mtei[b], Robert D. Arbeit[c], Richard Waddell[a], Bernard Cole[d], Todd Mackenzie[e], Mecky Matee[b], Muhammad Bakari[b], Susan Tvaroha[a], Lisa V. Adams[a], Charles R. Horsburgh[f], Kisali Pallangyo[b], the DarDar Study Group*

AIDS 2010, 24: 675-685

Immunologic protection against TB in humans

1. Mycobacterial infections (natural)
   - *M. tuberculosis* (Heimbeck, Norway)
   - Non-tuberculous mycobacteria (NTM; Edwards, USA)

2. Mycobacterial vaccines
   - Single dose live *M. bovis* BCG
   - Single dose live *M. microti* (vole bacillus)
   - Multiple dose inactivated whole cell mycobacterial vaccines:
     - MAC/*M. bovis*/MTB combination (VIP, VDS, Italy)
     - *M. bovis* (Jamaica)

Common features: Whole organism, single-dose live or multiple-dose inactivated vaccine, multiple antigens, cross protection within genus

TB vaccine development goal

Goal: Expeditious development of a vaccine to prevent TB in patients with HIV (the major TB risk group in most areas of the world).

Hypothesis: A multiple dose series of an inactivated whole cell NTM vaccine:

- would be safe in HIV

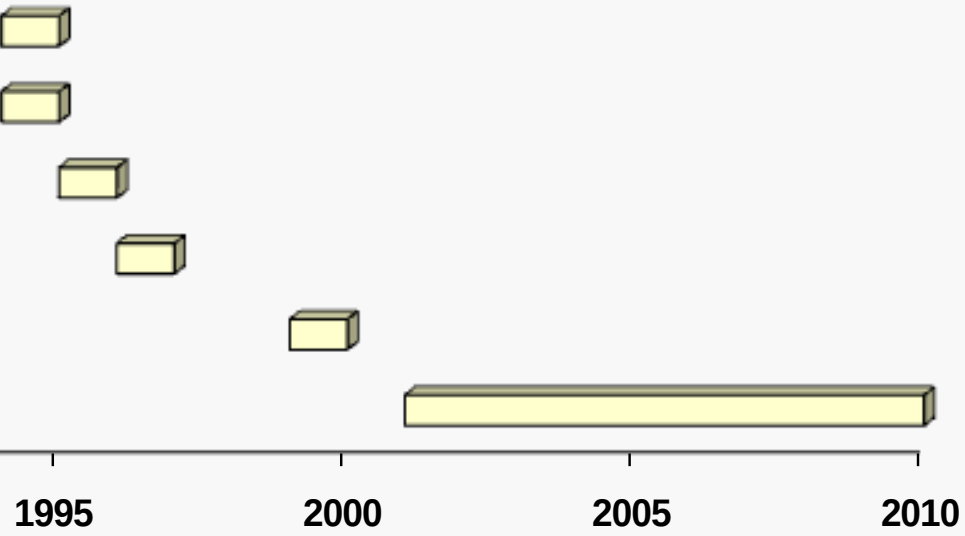
- would be likely to afford protection based on human experience with immunologic protection against TB (multiple Ags, species cross protection)

Inactivated NTM vaccine: SRL 172

- Heat-inactivated whole cell preparation derived from rough variant of an environmental non-tuberculous mycobacterium, *M. vaccae* (MV) isolated by J. Stanford & G. Rook
- Agar-based manufacturing method developed by SR Pharma (now Immodulon, London)
- Animal studies indicated immunogenicity and efficacy in preventing TB (Skinner, Hernandez-Pando, Abou-Zeid)

MV Phase I, II and III Trials

Phase	Site	MV (N)	Control (N)
1	US	9	0
	US	23	12
	US	11	0
2	Zambia	22	22
	Finland	19	20
3	Tanzania	~1000	~1000



Phase II studies in HIV-positives with CD4>200

Study	Design	Assays	Comment
Zambia[1]	5 doses 22 MV, 22 Placebo BCG pos + BCG neg	⇧LPA to MV	Responses greater with prior BCG
Finland[2]	5 doses 19 MV, 20 Placebo BCG pos only	⇧LPA to MV ⇧LPA to MTB ⇧IFNγ to MV	LPA responses greater in 10 HIV negative controls

1. - Waddell et al, Clin Infect Dis 2000
2. - Vuola et al, AIDS 2003

Finland: LPA to *M. vaccae* sonicate

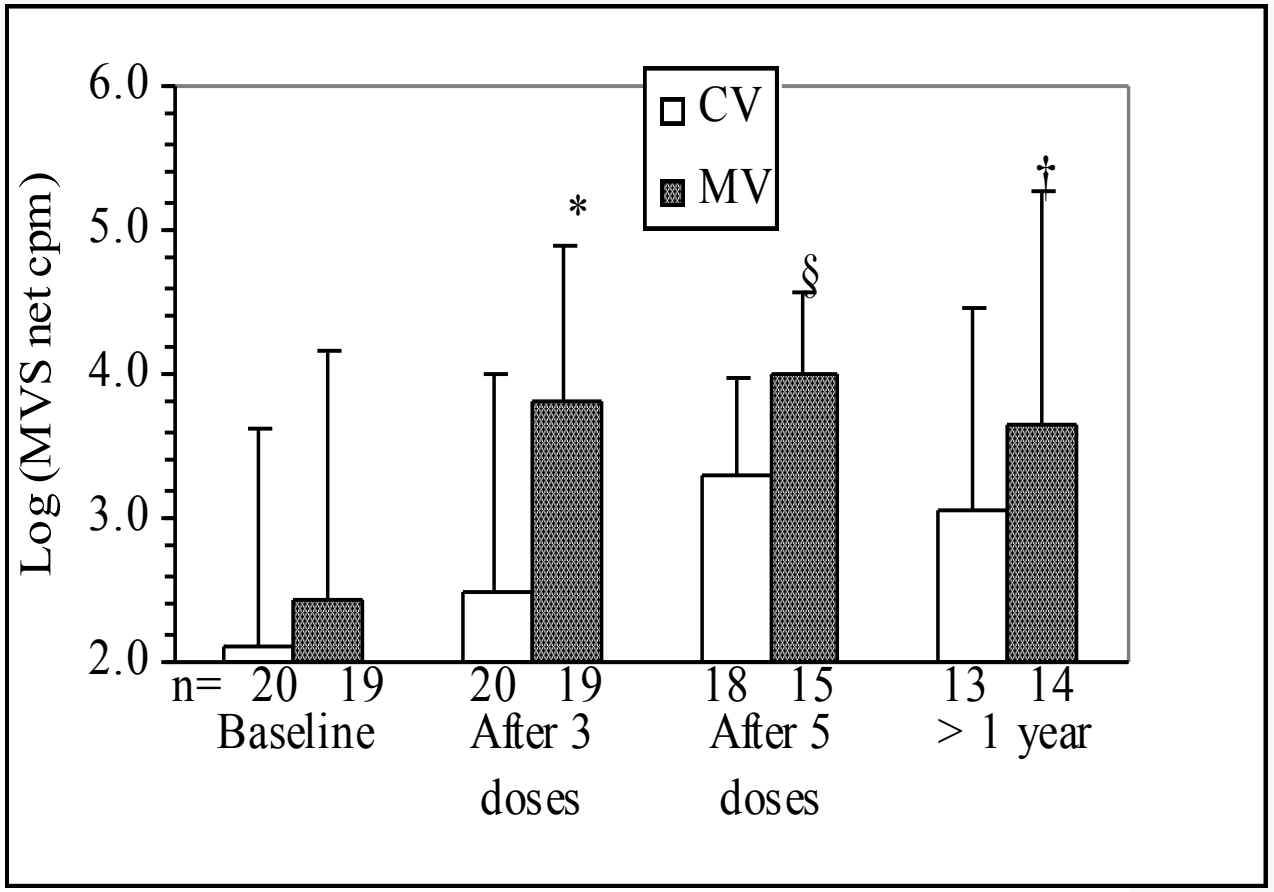
Study population:

HIV pos, BCG pos

CV = control (hep B)

MV = MV SRL 172

LPA = lymphocyte proliferation assay



* P< 0.004, § P = 0.0027, † P = 0.0198

DarDar Study (Dartmouth / Dar es Salaam, Tanzania)

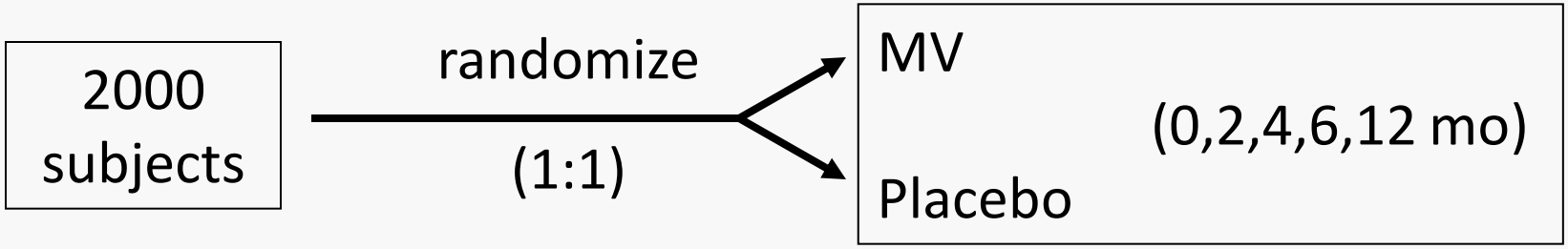
A prime-boost strategy to prevent TB in persons with HIV infection - I

- Hypothesis:
  - MV (boost) of childhood BCG (prime) will reduce disseminated TB by 50% and definite TB by 50%
- Enrollment criteria:
  - HIV-positive
  - CD4 >200
  - BCG scar
  - no active TB (smear, culture, CXR – all negative)
- Sponsor: Division of AIDS (DAIDS), NIH

DarDar Study (Dartmouth/Dar es Salaam, Tanzania)

A prime-boost strategy to prevent TB in persons with HIV infection - II

- Study design:
  - randomized (1:1), double-blind, placebo-controlled
  - regulatory: Tanzania FDA
  - conducted to GCP
- Intervention:
  - 5 intradermal doses of MV SRL 172 (or placebo)



DarDar Study (Dartmouth/Dar es Salaam, Tanzania)

A prime-boost strategy to prevent TB in persons with HIV infection - III

- Immunologic assessments:
  - Tuberculin skin testing
    - INH x 6 mos for subjects with TST >5 mm
  - LPA and IFNγ assays to: MV, ESAT, Ag85, MTB WCL
  - Ab to lipoarabinomannan (LAM)
  - done at baseline and after dose 5 of vaccine
    - 94% of subjects had baseline immune response to mycobacterial antigens (Matee, Lahey et al, J Infect Dis, 2007)
  - annual CD4

DarDar Study (Dartmouth/Dar es Salaam, Tanzania)

A prime-boost strategy to prevent TB in persons with HIV infection - IV

- Clinical follow-up
  - every 3 mo: routine HIV care, active evaluation for new cases of TB (sputum and blood cultures for TB, CXR)
- Endpoints
  - Primary: disseminated TB (blood culture positive)
  - Secondary: definite TB (adjudication board)
    probable TB (adjudication board)

DarDar Study TB Endpoint Definitions

Disseminated

- Positive blood culture

Definite

- pos sterile site culture (other than blood)
- *or* 1 pos sputum culture with >10 cfu
- *or* 2 pos sputum smears or 2 cultures with 1-9 cfu

Probable

- 1 pos sputum smear or culture with 1-9 cfu
  plus either pos CXR or pos Sx
- *or* Sx/signs plus CXR plus response to Rx (“clinical”)


GRIP

Compliance and safety

Loss to F/U: 3% per year

Doses administered:

- MV: 4616 (84% completed 5 doses)
- Placebo: 4603 (83% completed 5 doses)

Koch reactions:

- none, including 312 MV subjects with TST>5 mm

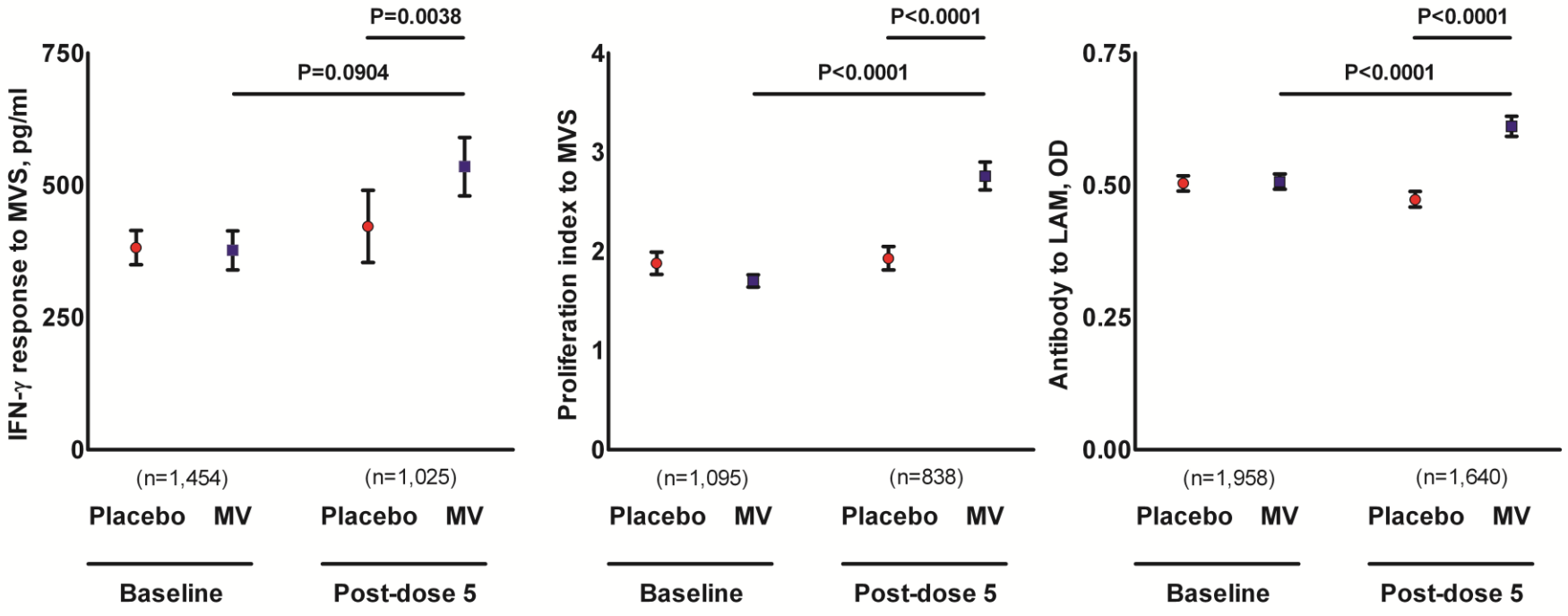
Vaccine site:

- Induration: average 5-6 mm
- Desquamation: 37-58%
- Local drainage: 22-49%
- Sterile abscesses: 3 (0.3% of subjects, 0.06% of doses)

HIV viral load and CD4 after each dose

- No pattern of adverse changes

IFNγ and LPA responses to MV sonicate (vaccine antigen), antibody responses to LAM:



- Lahey, Arbeit, et al Vaccine 2010, in press

Table 3. Study endpoints and protection against tuberculosis.

Endpoint	Intention-to-treat ($n = 2013$)			
	No. of endpoints MV	Placebo	Hazard ratio (95% CI)	*P*
Disseminated tuberculosis	7	13	0.52 (0.21–1.34)	0.16
Definite tuberculosis	33	52	0.61 (0.39–0.96)	0.03
Probable tuberculosis	48	40	1.17 (0.76–1.80)	0.46

CI, confidence interval; MV, *Mycobacterium vaccae*.
[a]Per protocol, at least three doses of MV or placebo.

Median f/u = 3.3 years

- von Reyn et al AIDS 2010

Immunologic predictors of TB risk in placebo recipients

MAJOR ARTICLE

Interferon γ Responses to Mycobacterial Antigens Protect against Subsequent HIV-Associated Tuberculosis

Timothy Lahey,[1] Siddharth Sheth,[1] Mecky Matee,[4] Robert Arbeit,[2] C. Robert Horsburgh,[3] Lillian Mtei,[4] Todd MacKenzie,[1] Muhammad Bakari,[4] Jenni M. Vuola,[5,a] Kisali Pallangyo,[4] and C. Fordham von Reyn[1]

[1]Dartmouth Medical School, Lebanon, New Hampshire; [2]Tufts University School of Medicine and [3]Boston University School of Public Health, Boston, Massachusetts; [4]Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania; [5]National Public Health Institute, Helsinki, Finland

-Lahey et al, J Infect Dis 2010, epub ahead of print

-Lahey et al, poster at this meeting [protection against subsequent TB greatest if baseline IFN-γ response to 3 vs 2 vs 1 vs 0 mycobacterial Ags]

TB vaccine efficacy trials: lessons learned - I

- Vaccine study conduct: Excellent follow-up and adherence to GCP standards possible in low income setting; good compliance with multiple dose vaccine

- Safety in HIV: Multiple Ag inactivated vaccine safe despite prior BCG and high rate of latent TB

- Placebo recipients: opportunity to decipher features of immune protection against TB

TB vaccine efficacy trials: lessons learned - II

- Efficacy in HIV: TB vaccine can be effective in this high risk immunocompromised group

- Endpoints: Definite culture-confirmed TB should be primary endpoint

  - both DarDar Trial and Aronson found no protection against clinical (“probable”) TB

- Surrogate marker: number and diversity of Ags (secreted, cell wall, cytosolic) to which subjects respond may be more important than the specifics of responding cell types to 1 or 2 immunodominant Ags

DarDar Trial - Conclusions

A multiple dose series of heat killed MV (SRL 172) in BCG-immunized subjects with HIV:

- is safe and well tolerated
- prevents definite TB
- generates cellular and antibody responses to mycobacterial antigens

MV- Future directions

- Vaccine immunogenicity and efficacy expected to be greater in healthy subjects

- Large scale broth manufacturing method for scale-up in development with Aeras

Acknowledgement

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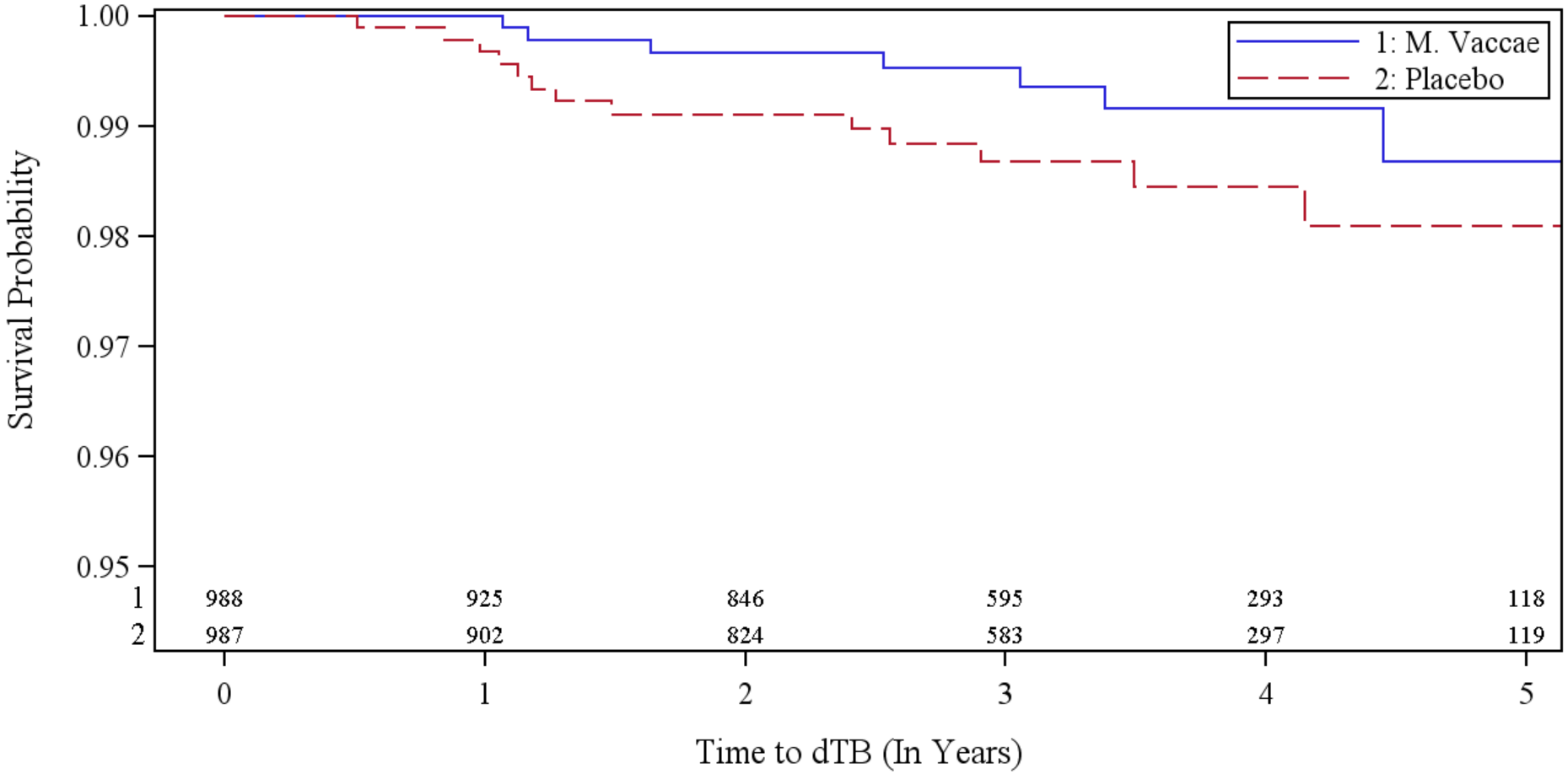
New York	**Barry Kreiswirth**	

Disseminated TB (ITT)

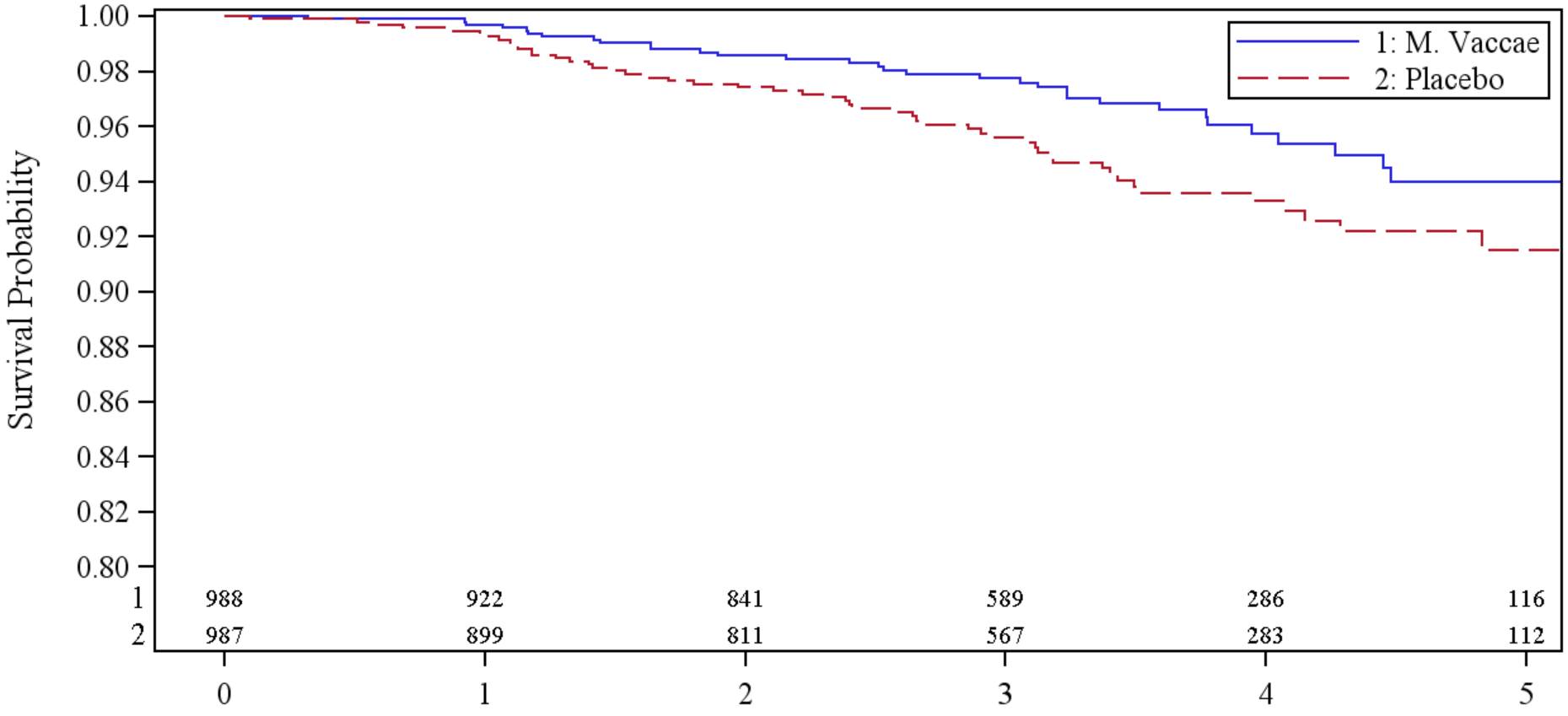
With Number of Subjects at Risk



Group	Num Subjects	Events	Censored	Median	p-value
1: M. Vaccae	988	7	981	.	0.1632
2: Placebo	987	13	974	.	

Definite TB (ITT)

With Number of Subjects at Risk

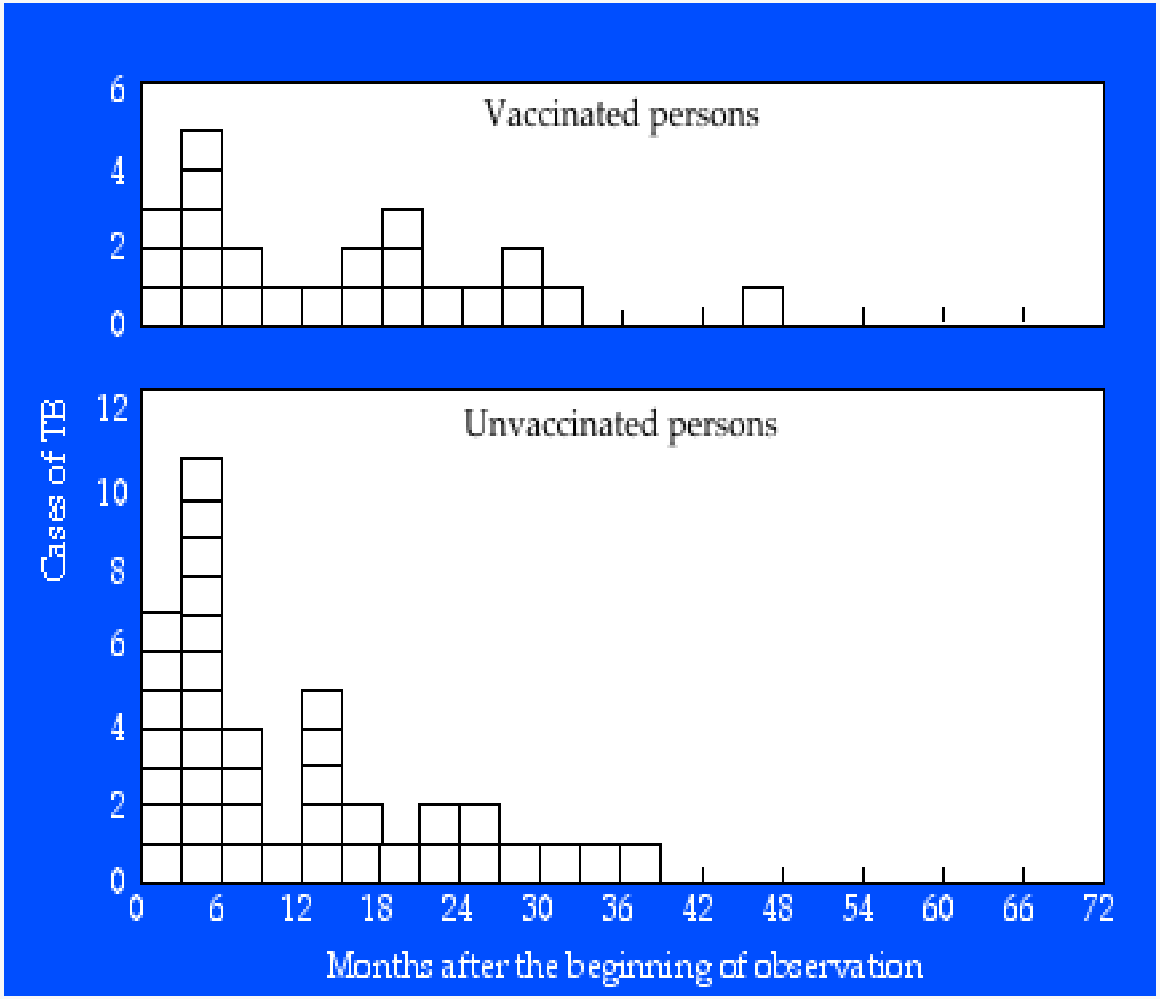


Group	Num Subjects	Events	Censored	Median	p-value
1: M. Vaccae	988	33	955	.	0.0273
2: Placebo	987	52	935	.	

Baseline Subject Characteristics

Characteristic	MV, n=988	Placebo, n=987	p value
Age, mean (sd)	33 .4 (8.0)	33.1 (7.7)	0.48
Female sex	756 (77%)	749 (76%)	0.74
CD4 cells / uL, median (minimum, 25th – 75th percentile, maximum)	425 (200, 316 – 572, 1645)	403 (200, 298 – 578, 2000)	0.30
Log HIV viral load, median (range)	3.96 (1.70 - 5.70)	3.95 (1.70 - 5.70)	0.70
HIV antiviral therapy	25 (2.5%)	33 (3.3%)	0.28
Prior treatment for TB	88 (9%)	81 (8%)	0.58
Tuberculin skin test ≥ 5 mm	312 (32%)	319 (33%)	0.81

Prevention of TB by 5 doses of inactivated *M. bovis*



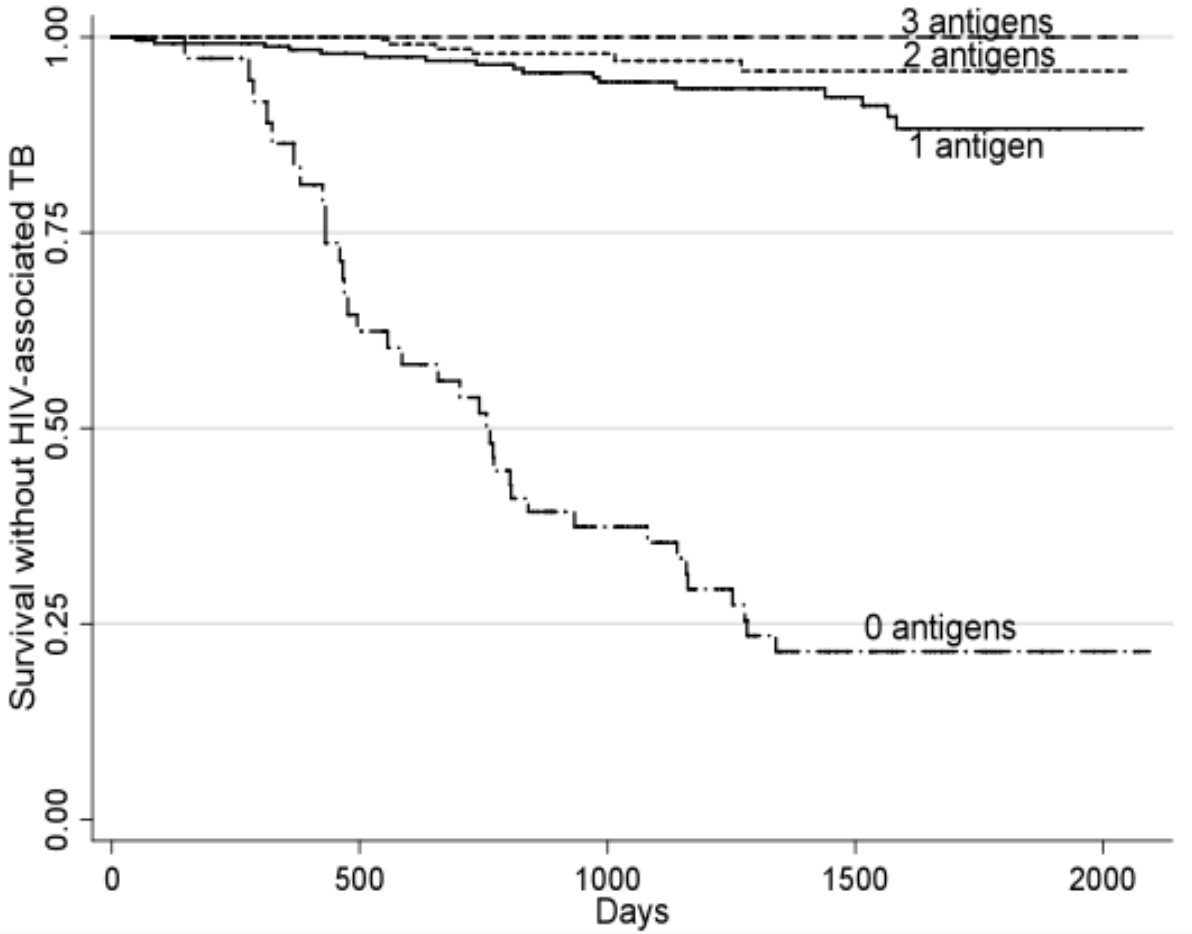
TB disease rates
vaccine: 11% (23/210)
control: 19% (39/206)
efficacy = 42% despite inability to segregate until immunization complete

Opie, Freund et al. 1939, psychiatric hospital in Jamaica

Multiple dose inactive whole cell vaccines effective against other intracellular bacterial pathogens: plague, typhoid

-Opie, 1939

Immunologic predictors of TB risk in placebo recipients



TB risk in placebo recipients reduced in those with IFN-γ response to multiple mycobacterial Ags

- Lahey et al, poster at this meeting