Inactivated *Mycobacterium obuense*

A whole cell non-tuberculous mycobacterial vaccine booster

SRL172 (agar)

DAR-901 (broth)

C. Fordham von Reyn, MD – Geisel School of Medicine at Dartmouth

Keiko Nakamura, MD, PhD – Tokyo Medical and Dental University

Robert D. Arbeit, MD – Tufts University School of Medicine

GHIT Fund

Global Health Innovative Technology Fund

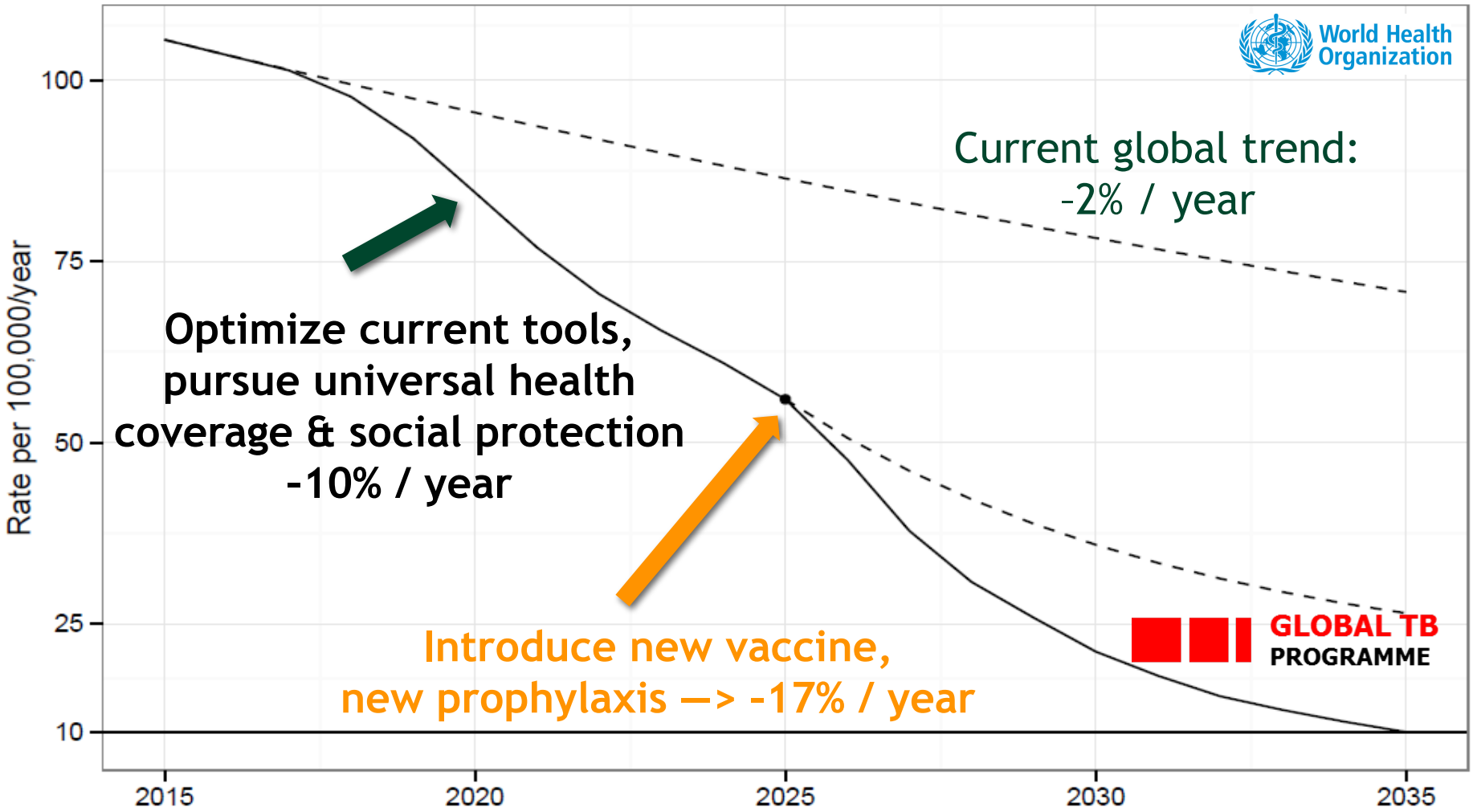
Greetings from Dartmouth, New Hampshire, USA

DARTMOUTH COLLEGE

Vox Clamantis in Deserto

- Dartmouth College, founded 1769, 9th oldest in the US
- Dartmouth Medical School, founded 1784, 4th oldest in the US

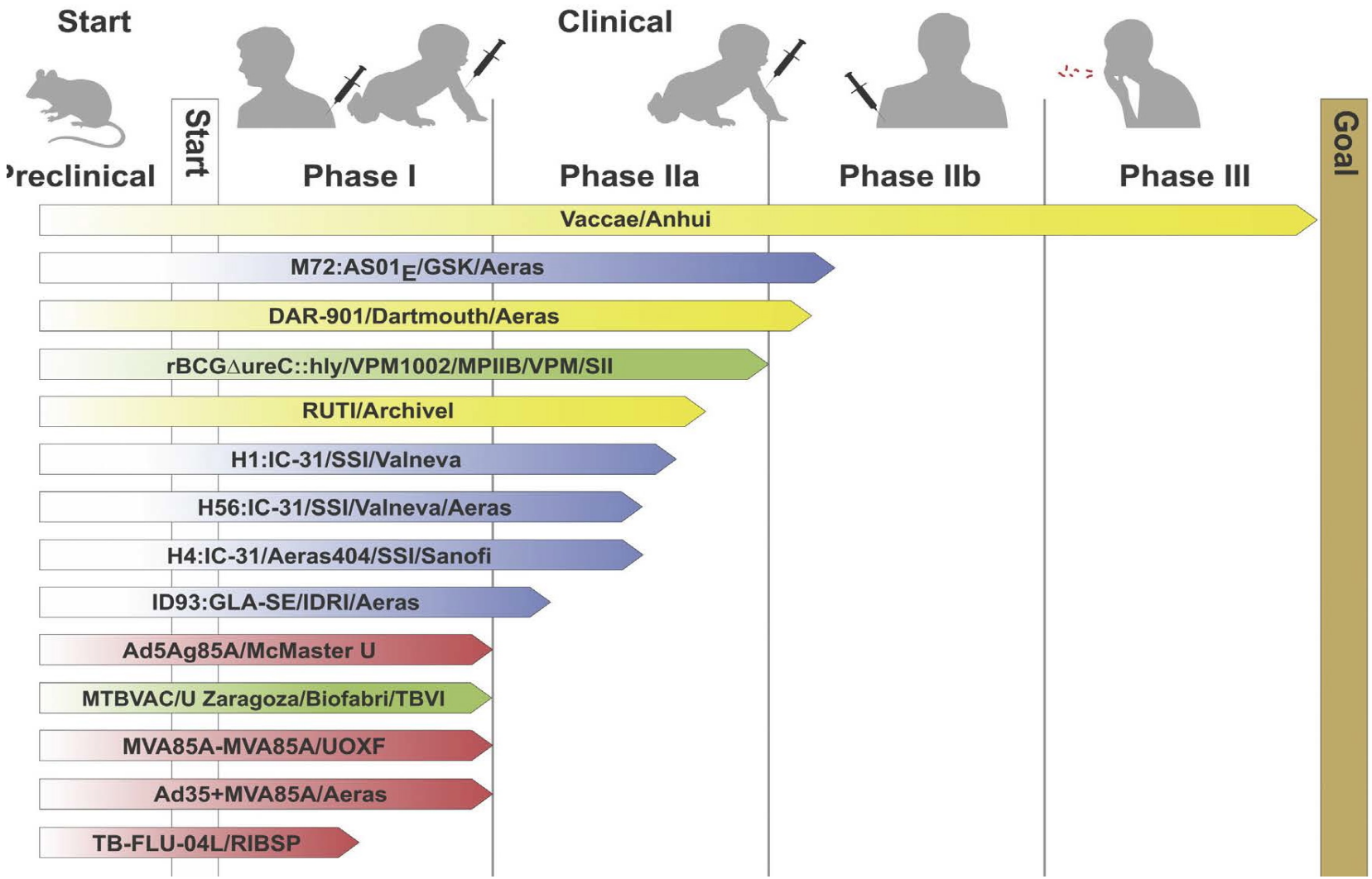
Global TB elimination by 2035
(World Health Organization)



Objective and Goals

1. To develop DAR-901 as the first new TB vaccine to meet Preferred Product Characteristics (PPCs) developed by the World Health Organization (WHO) in October 2017:
    - Booster for BCG in adolescents/adults
    - Efficacy ≥50% against TB disease
    - Safe, including in HIV
2. To establish a pharmaceutical partnership to complete the final stages of development
3. To license DAR-901 by 2025, the WHO target date for introduction of a new TB vaccine.

New TB vaccines in clinical trials



Kaufman, von Reyn. 2016

SRL 172 – A multiple dose boosting vaccine

Heat-inactivated, whole-cell preparation derived from rough variant of an environmental non-tuberculous mycobacterium (NTM)

The organism

- *Mycobacterium obuense* (first described from Obu, Japan)
- Vaccine strain was isolated from soil in Uganda by Stanford and Rook (UK)

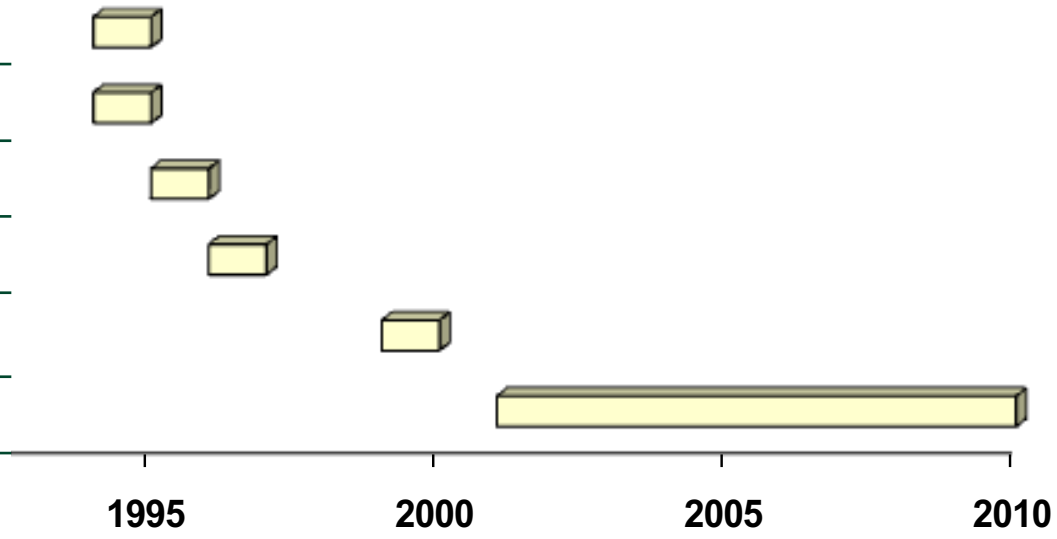
GMP vaccine manufactured by SR Pharma *(agar-based method)*

- 0.1 mL intradermal dose administered in multiple dose series
- Demonstrated safe and well-tolerated in humans

SRL 172 – Dartmouth Phase 1, 2 and 3 Trials

(multiple dose)

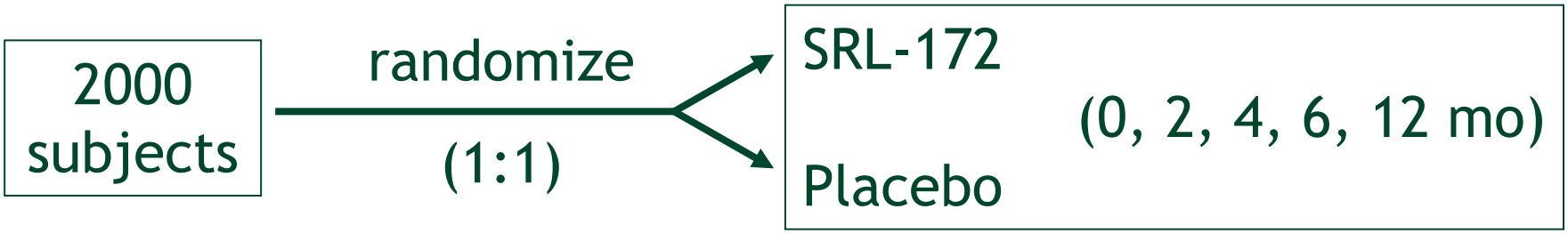
Phase	Site	SRL172 (N)	Control (N)
1	US HIV -	9	0
	US HIV+	23	12
	US HIV+	11	0
2	Zambia	22	22
	Finland	19	20
3	Tanzania	~1000	~1000



- Dartmouth group conducted an entirely independent SRL-172 development program, including safety, immunogenicity, and efficacy studies.
- All studies investigator-initiated (funding: NIH, EGPAF, Sigrid Juselius Foundation)
- All results presented in peer-reviewed publications

SRL172 Phase 3 booster vaccine study
2001-2008 (DarDar trial)

- **Placebo-controlled, randomized (1:1), double-blind, GCP**
- **Eligibility**: BCG scar, HIV positive, CD4≥200
- **Location**: Dar es Salaam, Tanzania
- **Intervention**: 5 intradermal doses of SRL 172 (or placebo)
- **Endpoints**
  - Primary: TB bacteremia (disseminated)
  - Secondary: All culture positive TB




GRIP

SRL-172 Phase 3 Results

At year 7, DSMB recommended the trial be stopped based on efficacy in preventing definite TB.

DAR-901 is the only new TB vaccine in development to have shown efficacy in humans.

Table 3. Study endpoints and protection against tuberculosis.

	Intention-to-treat ($n=2013$)			
Endpoint	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

Median follow-up = 3.3 years

von Reyn et al. AIDS 2010; 24:675-85

DAR-901

Target product profile

- BCG booster for adolescents and adults

Broth-grown manufacturing process developed

- Robust, scalable, high yield fermentation process
- Cost $1.5-2 per dose

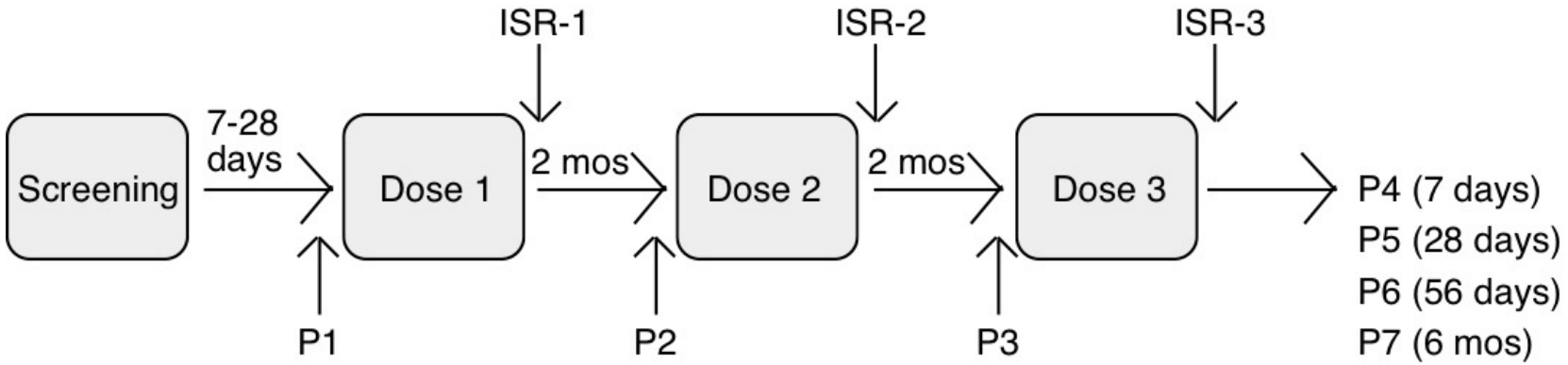
Pre-clinical studies completed

- Animal toxicology studies
- IFNγ and antibody dose response in 2 murine species
- TB challenge study in BCG-primed mice
  - Boost with 1 mg DAR-901 x3 confers greater protection against TB challenge than boost with BCG *

IND filed with US FDA

* Lahey et al. PLoS One, 2016

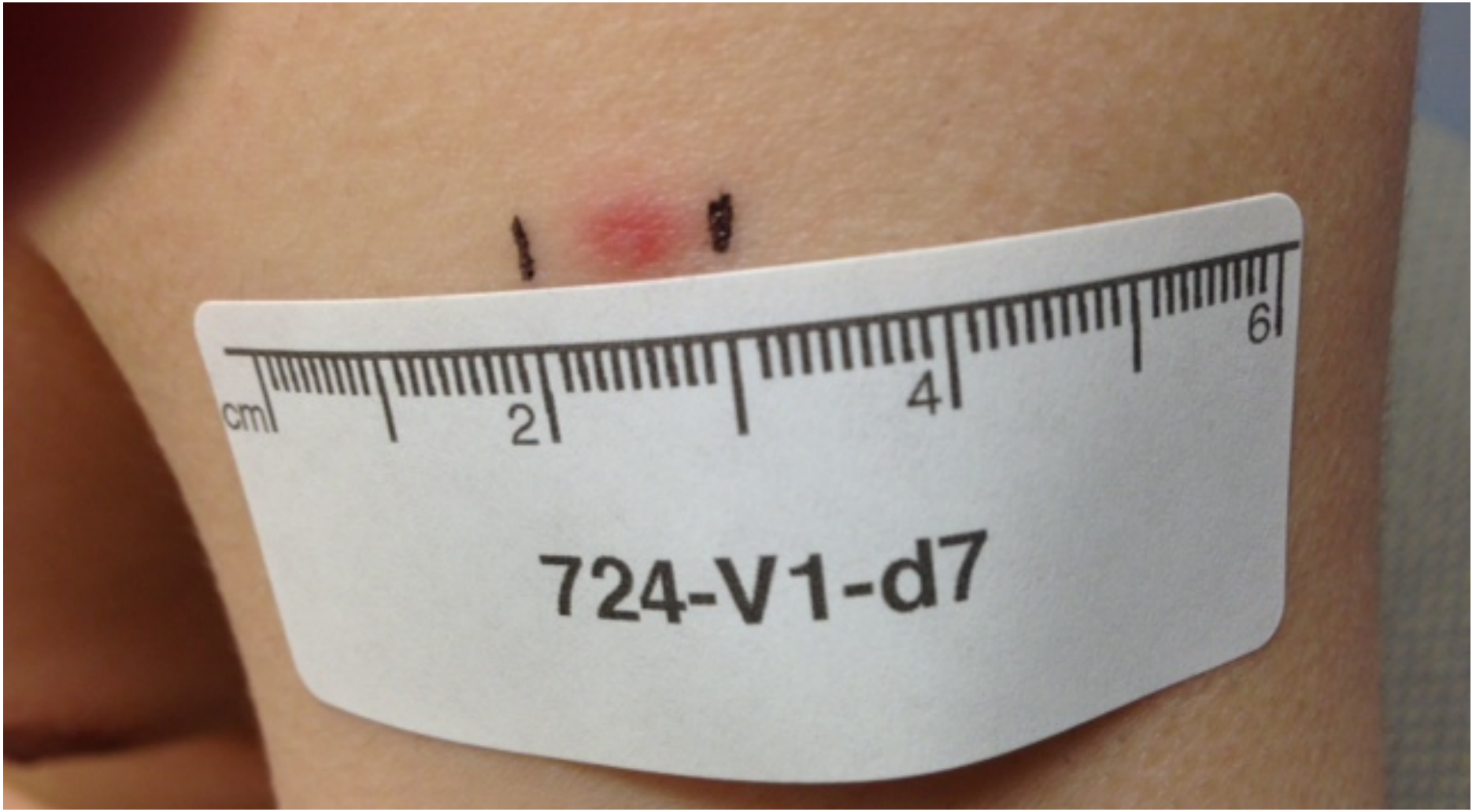
DAR-901 Phase 1 dose escalation



P = phlebotomy: P1, P2, P3 obtained prior to respective doses
ISR = injection site reaction examination 7 days after each dose

- 59 adult subjects in US with prior BCG: IGRA neg, IGRA pos, HIV neg, HIV pos
- Dose escalation cohorts 0.1, 0.3, 1 mg → 1 mg best response
- Three-injection series 1 mg DAR-901 was safe, well tolerated, and immunogenic
  - Injection site reaction (ISR) at 7 days, median 6-10 mm erythema
  - Cellular and humoral immune responses comparable to 5 doses of SRL-172
- Partnership support: Dartmouth, Aeras, Byrne Foundation

von Reyn et al. PLoS One 2017

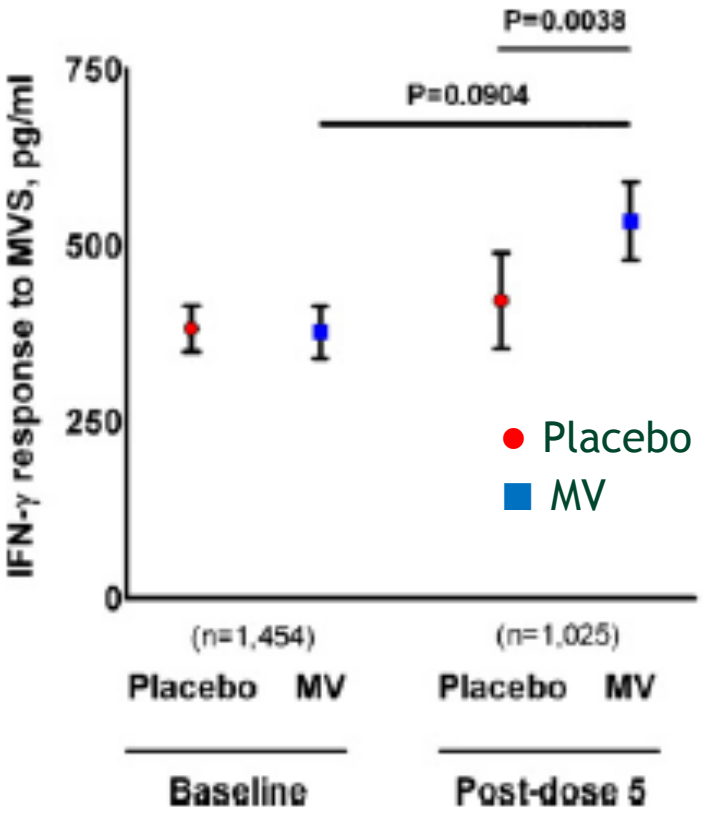


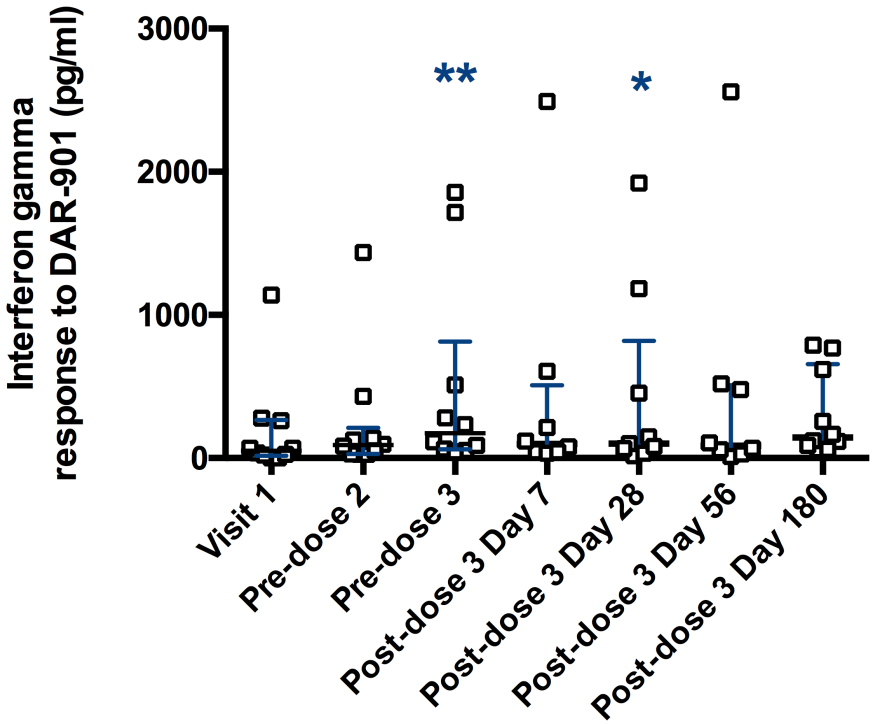
DAR-901: Injection site 7 days after intradermal injection

IFN-γ Responses to Vaccine Sonicate

SRL172 x 5 (agar)
Phase 3, N = >400

DAR-901 x 3 (broth)
Phase 1, N = 10





DAR-901 Phase 2b prevention of infection trial in adolescents in Tanzania (DAR-PIAT)

Goal: Prevent new TB infection (defined by neg IGRA → pos IGRA)

Sample size: 650 adolescents age 13-15

Eligibility: BCG scar, negative IGRA at baseline and 2 months

Design: Randomized (1:1) to DAR-901 or placeboat 0,2,4 mos

Follow-up: repeat IGRA at 2, 12, and 24 months

Status: Apr 2016 – Start
Feb 2017 – 632 complete 3 doses; safe, well-tolerated
Dec 2018 – Last subject, last visit (scheduled)

GHIT Fund

Global Health Innovative Technology Fund

DAR-PIAT: Baseline IGRA results

Baseline IGRA	n (%) (N=931)	Baseline TB Status*	Trial Eligibility
Positive	152 (16%)	Infected	Ineligible
Negative	757 (81%)	Uninfected	Eligible

Risk factors for IGRA positive vs IGRA negative
(multivariable analysis)

- Encounters with traditional alcohol beverage drinkers.
- House with one living room
- Limited sunlight in living room or bedroom
- Residing close to health facility
- Contact with TB patient at school

(Maro, Nakamura, et al, submitted 2017)

* Based on interpretation of IGRA result

DAR-901 Development Plan

Q4 2018	Complete Phase 2b Prevention of Infection (POI) trial in Tanzania [GHIT partnership]
Q1 2020	Establish design & venue for Phase 3 Prevention of Disease (POD) trial [GHIT partnership]
Q1 2025	Complete Phase 3 POD trial [pharmaceutical partner & GHIT]

DAR-901 Summary

Advantages for a pharmaceutical partner

- De-risked product in advanced stage of development
- Extensive safety data, including in HIV
- Efficacy demonstrated in fully powered Ph3 RCT
- Robust, economical manufacturing method
- License available from (non-profit) Dartmouth College, USA
- Development support from GHIT
- Meets WHO PPC and is on target for 2025 registration
- US FDA registration would provide Priority Review Voucher
- Global market: Billions of adolescents and adults
- Unique opportunity to make a high-profile contribution to global health
- Market entry for non-communicable diseases in low income countries
- Potential for vaccine-based prevention of pNTM in developed countries

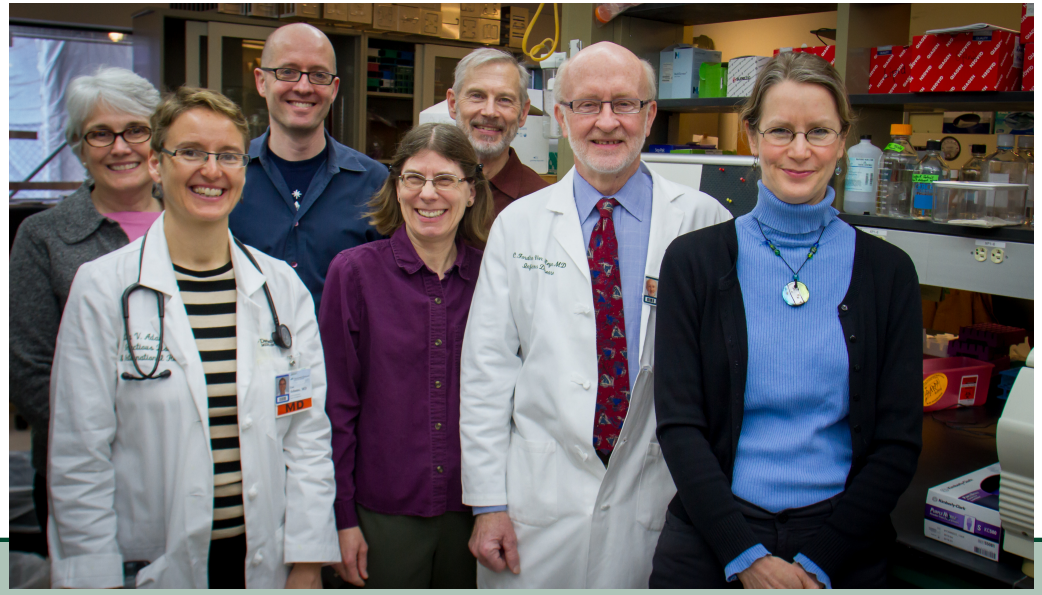
ありがとうございました

Thank you for your attention

And our thanks to GHIT
for critical support in the development of DAR-901

GHIT Fund

Global Health Innovative Technology Fund



End here

Options for Phase 3 POD Trial Design*

Characteristic	Trial A	Trial B
Population	Healthy household contacts	HIV patients
No. per arm	8000	2000
Duration – enroll	1 yr	2 yr
Duration – follow-up	3 yr	3 yr
Location	India	Tanzania
No. of sites	10	2

*Both options assume the following:

- Randomized (1:1) Vaccine : Placebo
- Endpoint: Xpert, culture, or smear positive TB
- Vaccine efficacy 50%, power = 0.8

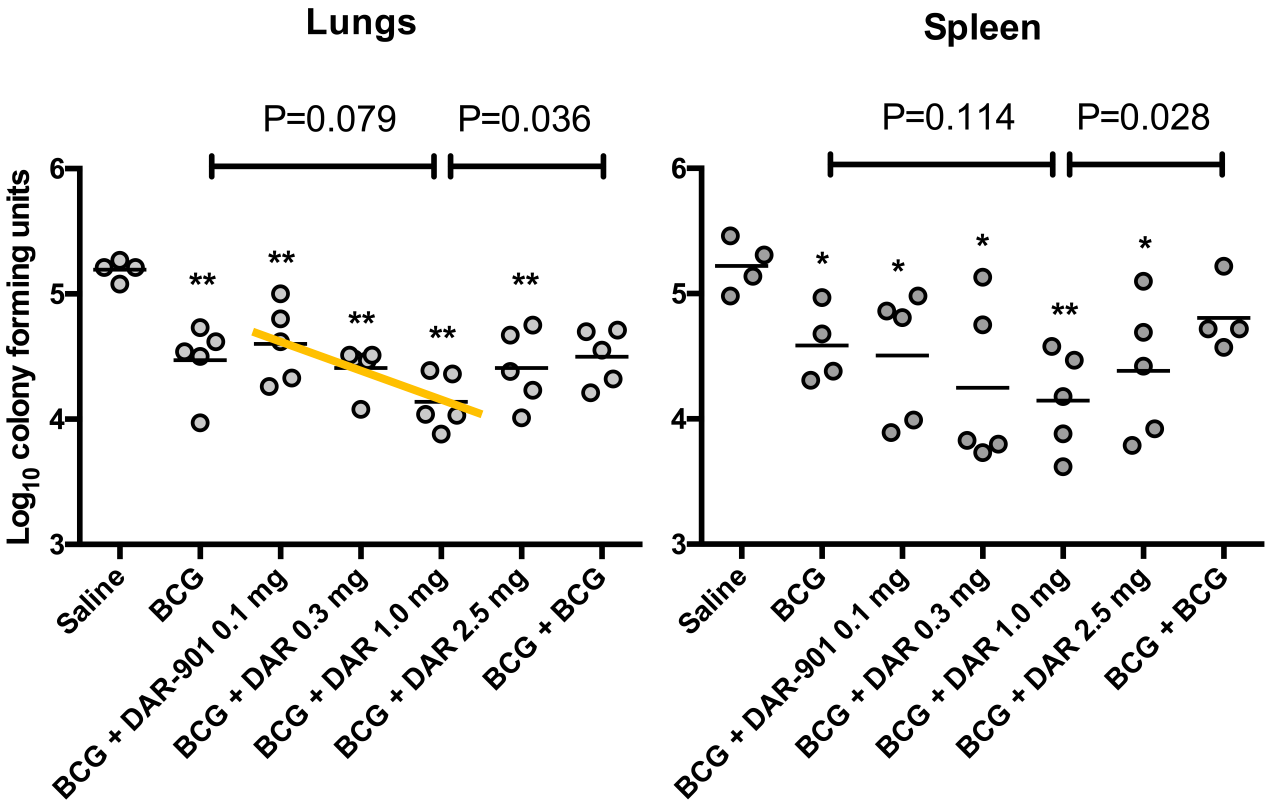
DAR-901 boost superior to BCG boost

Mice primed with BCG, boosted with BCG *or* DAR-901, then challenged with live MTB

Key Findings

Dose response with increasing DAR-901 dose

1 mg DAR-901 boost superior to BCG boost (P = 0.036 lungs P = 0.028 spleen)



Lahey et al; Plos One, 2016

BCG booster will have a greater effect on TB rates than new BCG prime

- Study using low income countries with endemic Tb and modeling reduction in TB cases with a new vaccine at different levels and durations of efficacy.
- A new effective booster vaccine gives greater reduction in TB cases in first 10 years.

Strategy	Efficacy over 10 yrs	Reduction in TB cases	Cost effective vaccine price
New BCG prime (infant)	80%	2%	≤$1.36
Booster for BCG (adult)	40%	40%	≤$6.44

Booster vaccine efficacy of 20% would be cost-effective at $1.19

Knight, PNAS, 2014

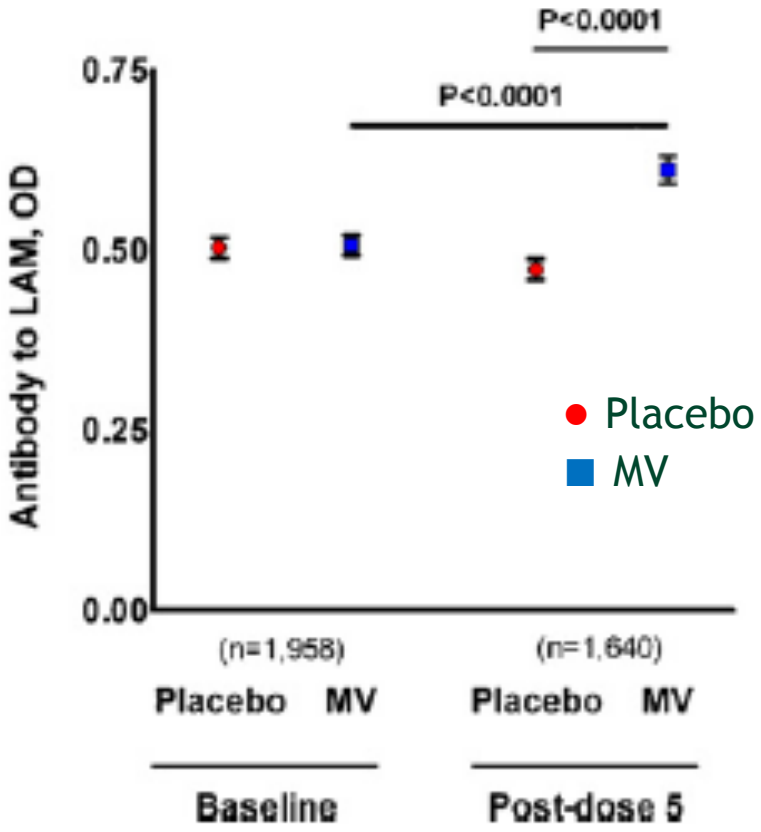
Acknowledgements

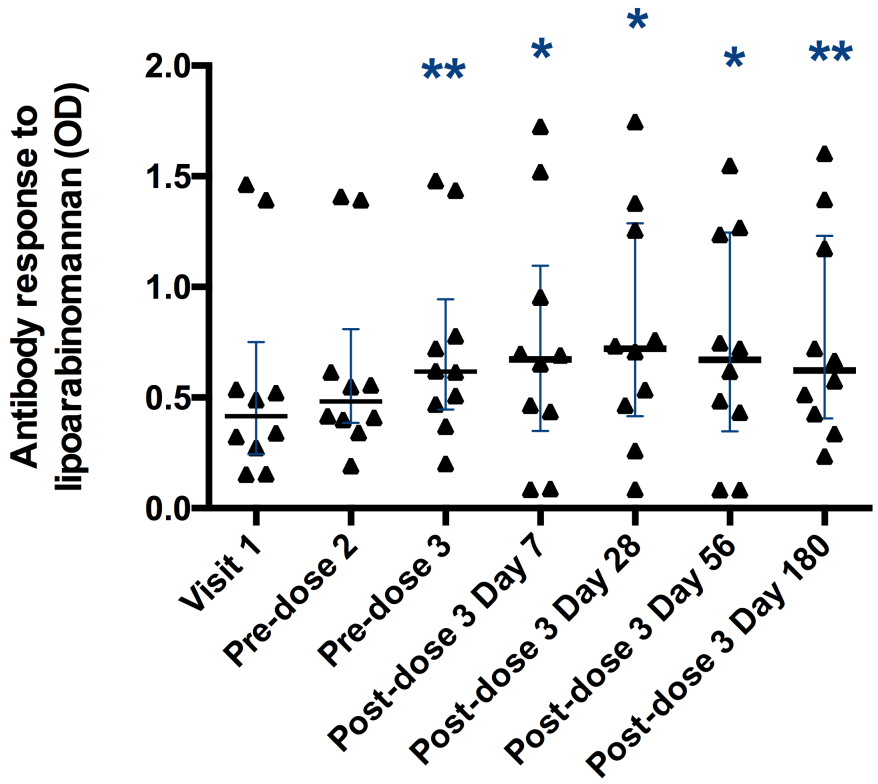
Dartmouth	Richard Waddell **Timothy Lahey*** Sue Tvaroha Wendy Wieland-Alter Ruth Connor Leway Kailani Lori Sostowski	Lisa Adams Todd Mackenzie Mark Carey Peter Wright Brenda Haynes Jill Mortali Karen Prive
Tanzania	Patricia Munseri Lillian Mtei Kisali Pallangyo Muhammad Bakari	Maryam Amour Isaac Maro Albert Magohe Mecky Matee
Boston	**Robert D. Arbeit***	C. Robert Horsburgh
Aeras	Tom Evans, Ann Ginsberg Dave Hokey, Dominick Laddy	Veerabadran Dheenadhayalan Bernard Landry
Finland	Juhani Eskola, Matti Ristola	Jenni Vuola
London	**Ajit Lalvani***	
Other	John Modlin (Seattle) Karim Manji (Dar)	Dan Hoft (St. Louis)

Antibody to LAM

SRL172 x 5 (agar)
Phase 3, N = >400

DAR-901 x 3 (broth)
Phase 1, N = 10





The current vaccine: BCG

Live, attenuated *Mycobacterium bovis* bacille Calmette Guerin (BCG) — is the **most widely used vaccine** in the world.

In endemic countries, immunization at birth is routine

Efficacy of BCG in infancy ("prime")

- 50-80% protection through childhood
- After age 15-20, protection wanes

Efficacy of second BCG ("boost")

- 0%

New TB vaccines in development

- **BCG prime for infants**
- **BCG booster for adolescents/adults**