จุฬาลงกรณ์มหาวิทยาลัย
Chulalongkorn University
Pillar of the Kingdom

TB Vaccine Development
~In Anticipation of AEC~

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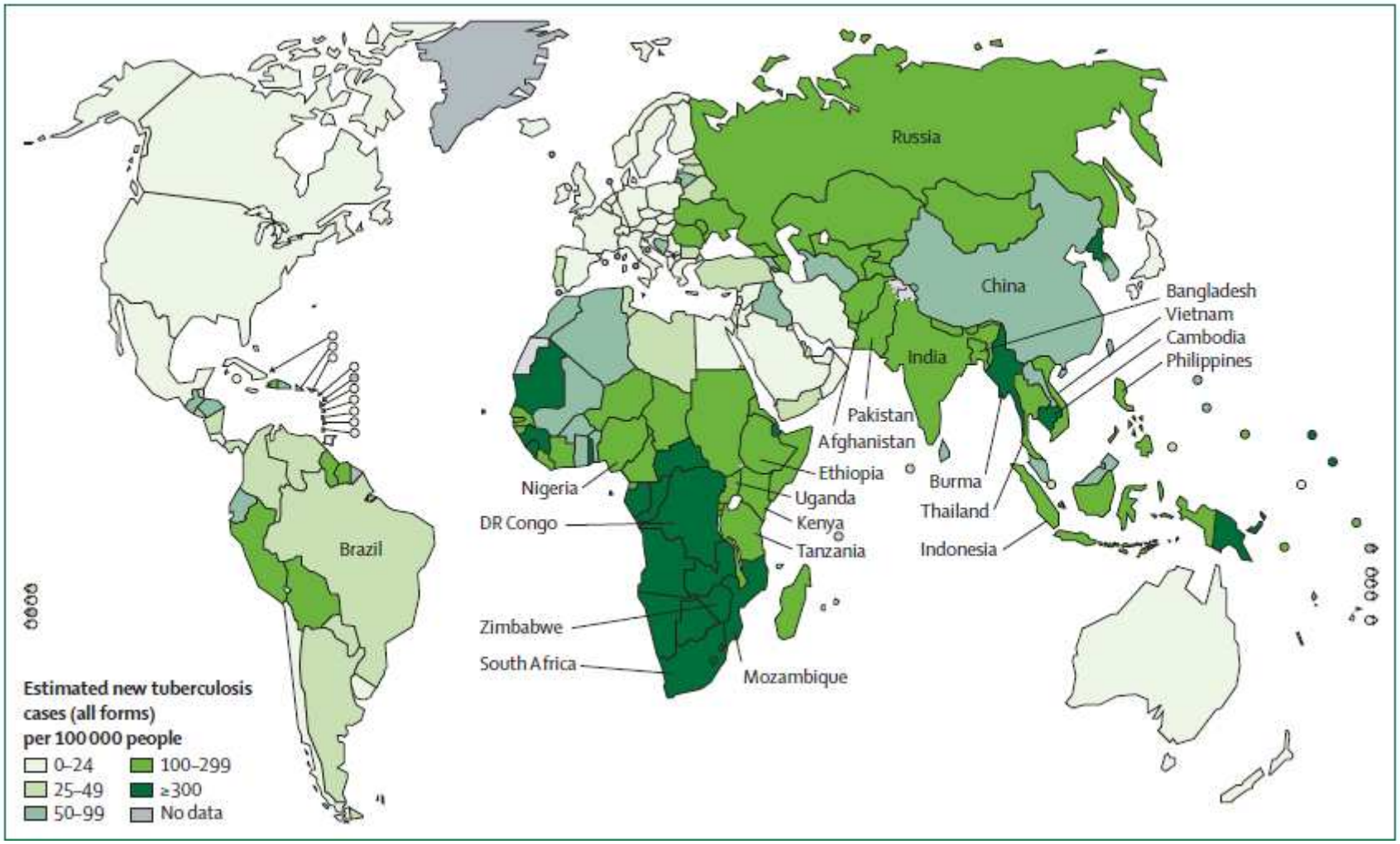
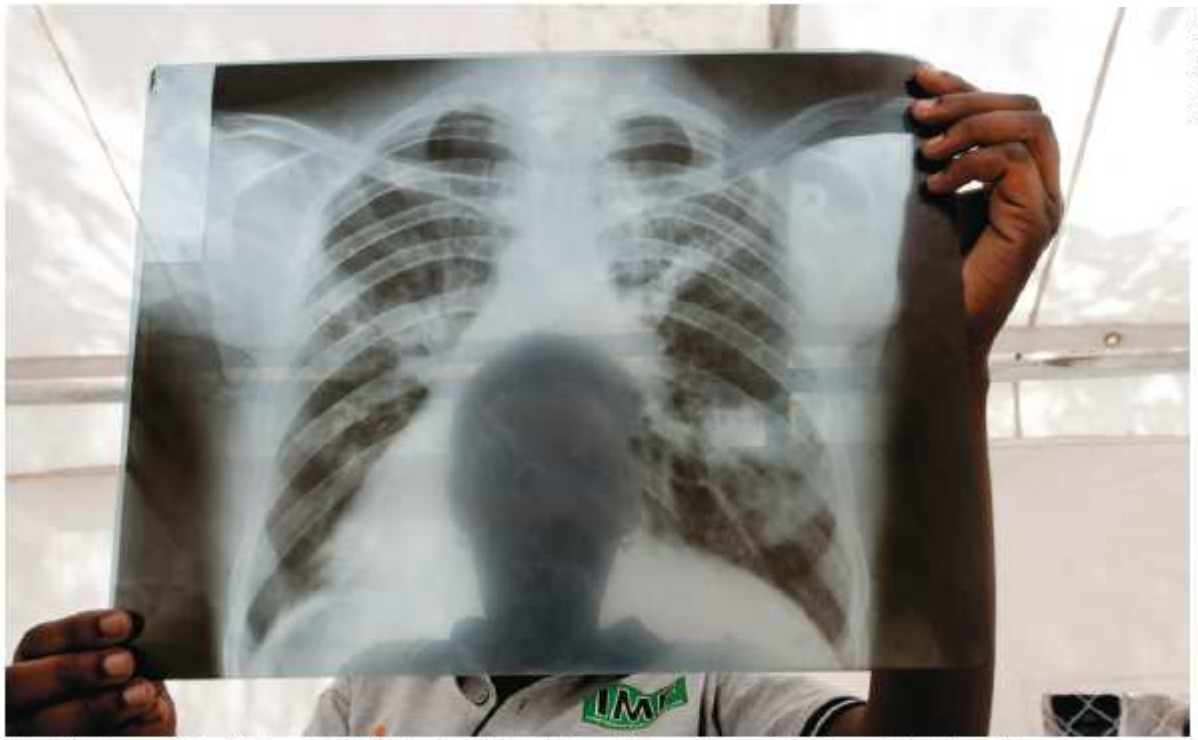
BIOTEC: 02/04/13

Estimated TB Incidence in 2010



WHO Report 2010

| NATURE | VOL 493 | 3 JANUARY 2013



J. MATTHEWS/SCIENCE

A chest X-ray from a patient with tuberculosis (TB) in Lira, Uganda. Uganda is one of 22 countries accounting for roughly 80% of new TB cases each year.

TB'S REVENGE

BY LEIGH PHILLIPS

The world is starting to win the war against tuberculosis, but drug-resistant forms pose a new threat.

"WE MUST INVEST IN VACCINE RESEARCH IF OUR ULTIMATE GOAL IS TO BE ABLE TO PREVENT THE DISEASE."

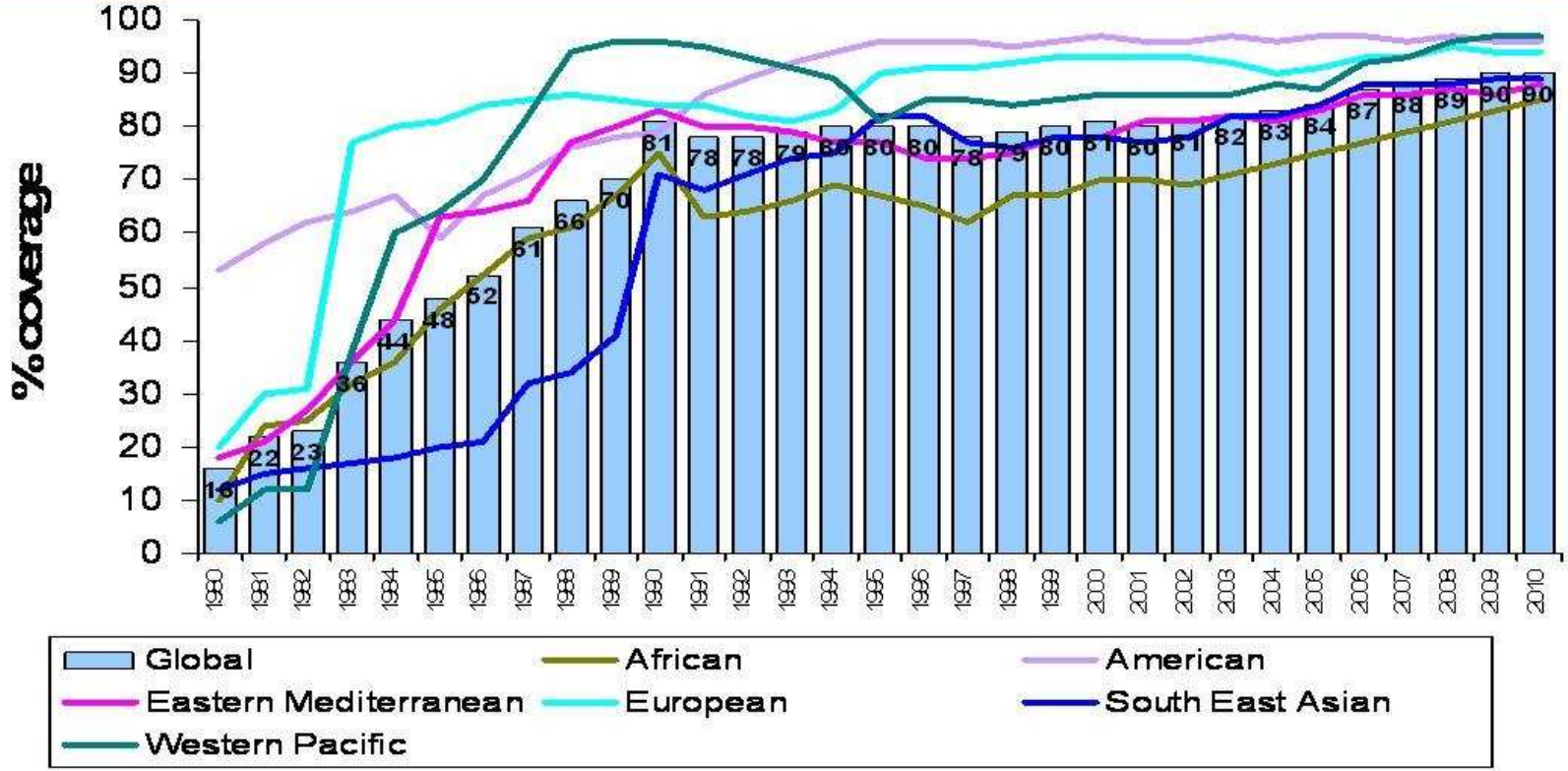
TB Vaccines

- The Stop TB Partnership (WHO) announced the goal of eliminating tuberculosis by the year 2050 (one new TB case per million) (Geneva, WHO Press, 2006)
- Tuberculosis research makes remarkable progress in past 10-15 years
- Lacks of understanding of what constitutes a protective immunity in TB are major obstacles

Current Vaccine: BCG

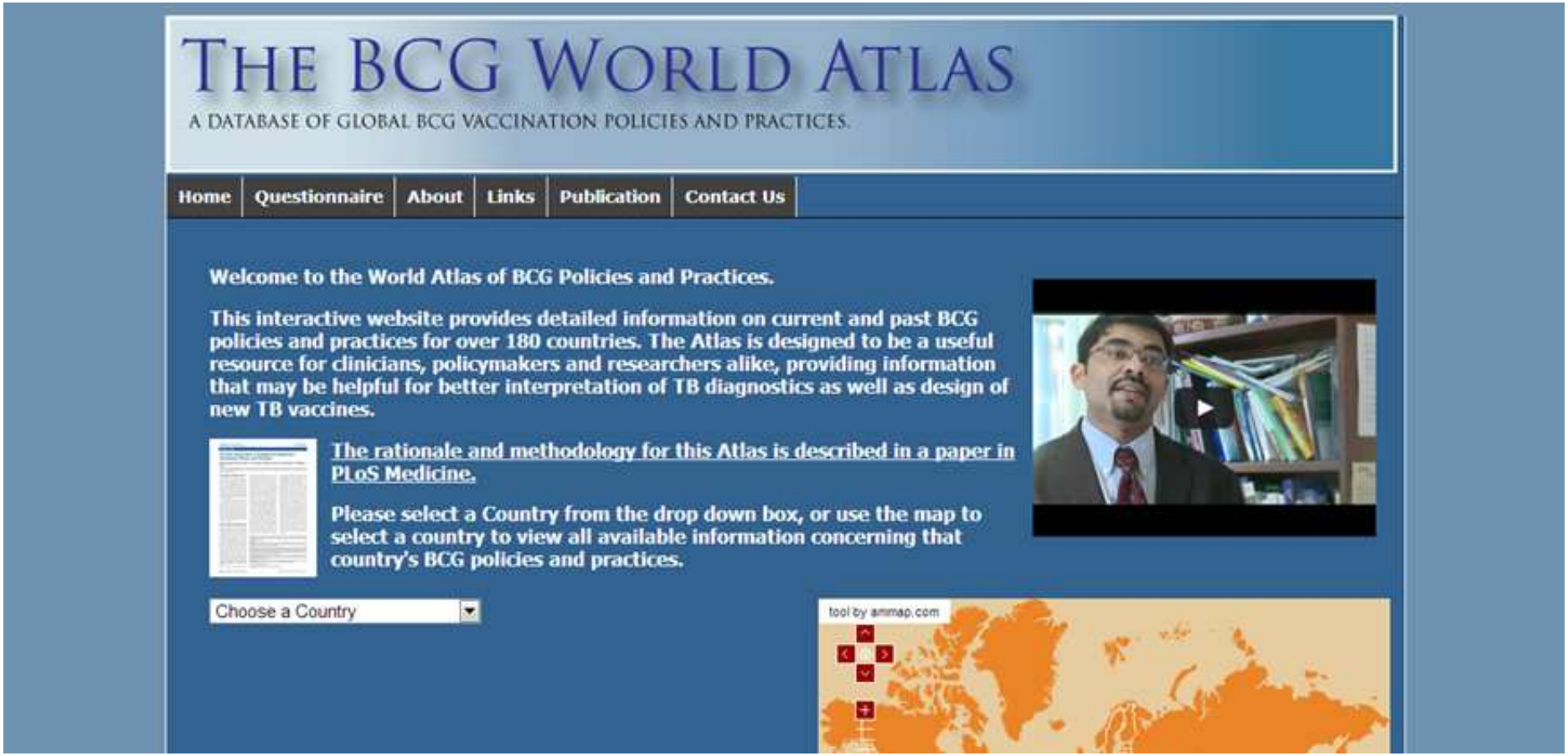
- The one and only available TB vaccine since 1921
- Most widely administered vaccines worldwide
- Effective in protection against severe forms of childhood TB
- Fails to protect against adult pulmonary TB
- Has not reduced global burden of TB
- Can cause BCG-related disease in HIV^+ newborns

Global Immunization 1980-2010, BCG coverage at birth
global coverage at 90% in 2010



Source: WHO/UNICEF coverage estimates 2010 revision. July 2011; 193 WHO Member States. Date of slide: 2 August 2011

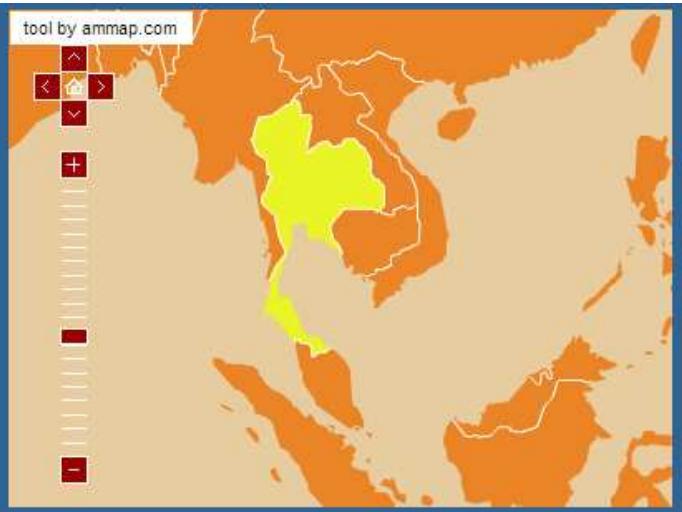
BCG World Atlas: A Database of Global BCG Vaccination Policies and Practices



Zwerling et al., PLoS Med (2010)

Thailand

Country	Thailand
Region	East Asia & Pacific
TB Incidence (per 100 000 per year) * †	137
TB Incidence (Count) * †	93000
TB Prevalence (per 100 000 per year) * ‡	189
TB Prevalence (Count) * ‡	130000
Income group (World Bank)	Lower middle income
Current BCG vaccination?	Yes
BCG Recommendation Type	A
Which year was vaccination introduced?	1977
Year BCG stopped?	N/A
Timing of 1st BCG?	At birth
Multiple BCG?	No
Timing of BCG #2	N/A
Timing of BCG #3	N/A
Multiple BCG in the past?	Yes
Timing of old BCG #2	
Timing of old BCG #3	
Year booster BCG stopped	
BCG Strain	Tokyo, Thai Red Cross
Is TST done post BCG?	No
Year of BCG cooverage estimate	2003
BCG coverage (%)	99%
Year of changes to BCG schedule	1987 & 1991
	1987: changed strain from Danish to Tokyo (same manufacturer)



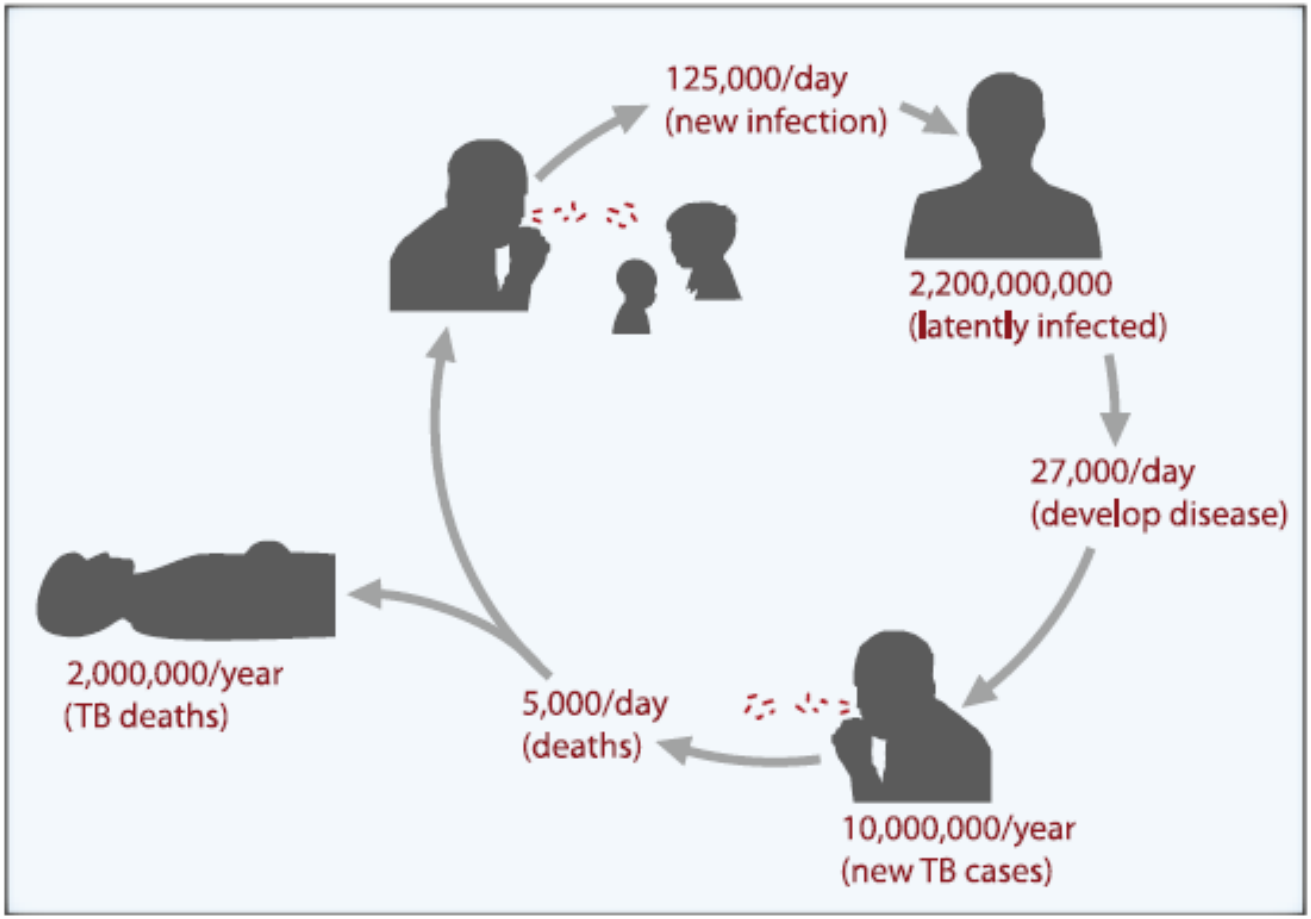
BCG Recommendation Types

Type	Description
A	This country currently recommends BCG vaccination for everyone at a certain age. (Example: BCG at birth or for school-age children, etc.)
B	This country used to recommend BCG vaccination for everyone, but currently does not.
C	BCG vaccination was never recommended for everyone in this country. (i.e.: never gave BCG or given only to high risk groups such as health care workers.)

Data Availability

Entry	Description
NA	This entry is not applicable to this country.
(Blank)	This data was not available

Vicious Cycle of TB

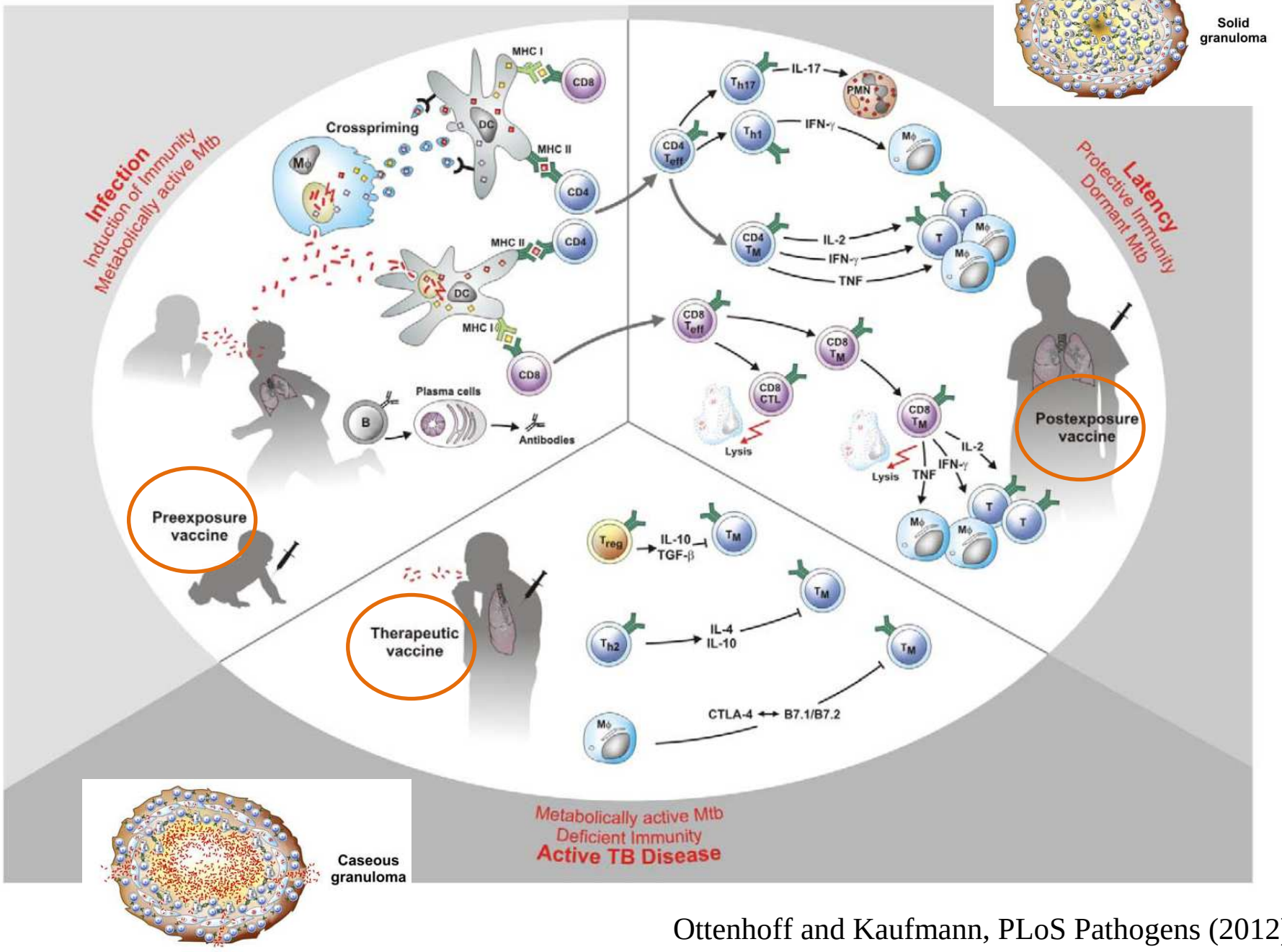


Kaufmann, Immunity (2010)

Necessity of New TB Vaccines

- Nearly 9 million new cases and 1.7 million deaths per year
- Vaccine that prevent pulmonary TB in all age groups is in need to significantly reduce disease incidence
- TB vaccine pipeline was empty in 1990s but now we have more than 12 novel vaccine candidates in human clinical trials

Immunology of TB and Vaccines



Ottenhoff and Kaufmann, PLoS Pathogens (2012)

Designing New TB Vaccines

- Lacks of reliable correlates of protection (biomarkers) and human challenge model → empirical testing of vaccine candidates
- Two basic types:

  (1) Live vaccine to replace BCG: rBCG or attenuated *M. tuberculosis*

  (2) Booster vaccine for BCG: subunit vaccines

Live Vaccine

- Replacement of the conventional BCG vaccine

  (1) live recombinant BCG (rBCG)

  (2) live attenuated *M. tuberculosis* (ΔPhoPΔfad strain)

  Should be:

-safer or equivalent to BCG

-more immunogenic

-inducing long lasting protection and inducing protection against highly virulent strains (MDR/XDR TB or *Beijing* strains)

Subunit Vaccines

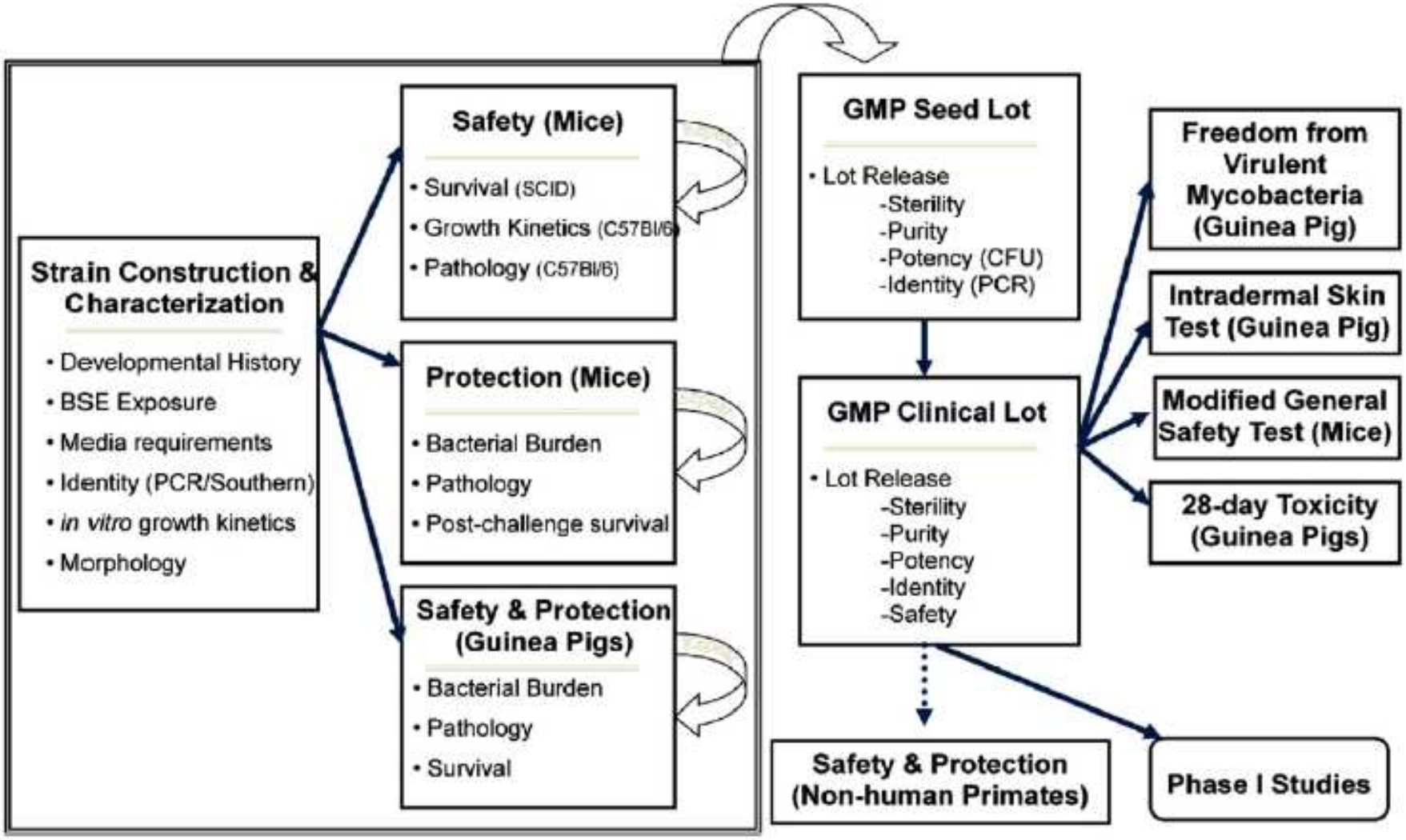
- Priming vaccines or booster vaccines in combination with BCG vaccine

  (1) recombinant proteins with adjuvants

  (2) non-replicating viral vectors

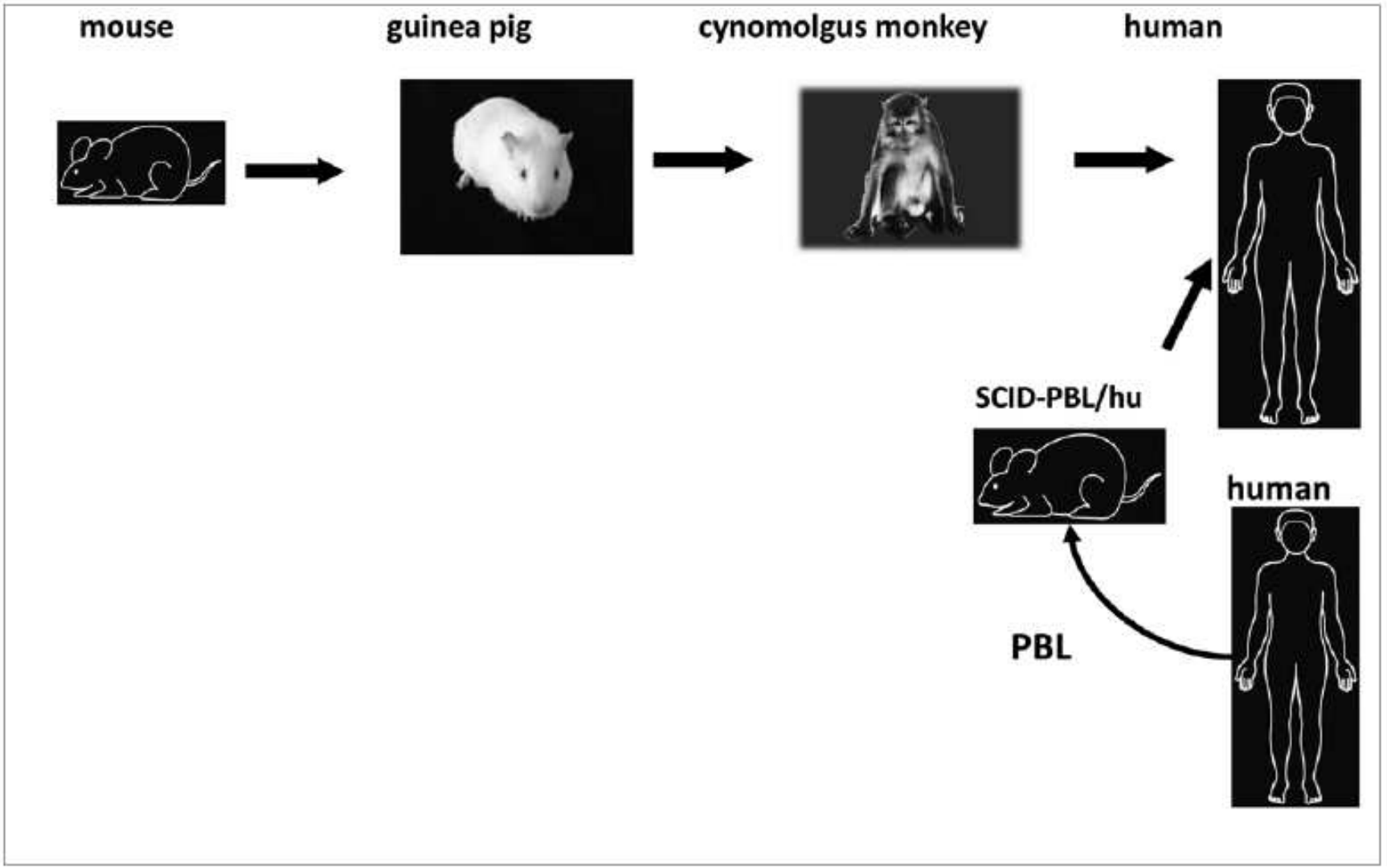
  (3) DNA vaccines

Preclinical TB Vaccine Development



Walker et al., 2010 (Vaccine)

TB Vaccine Trials in Animal Models



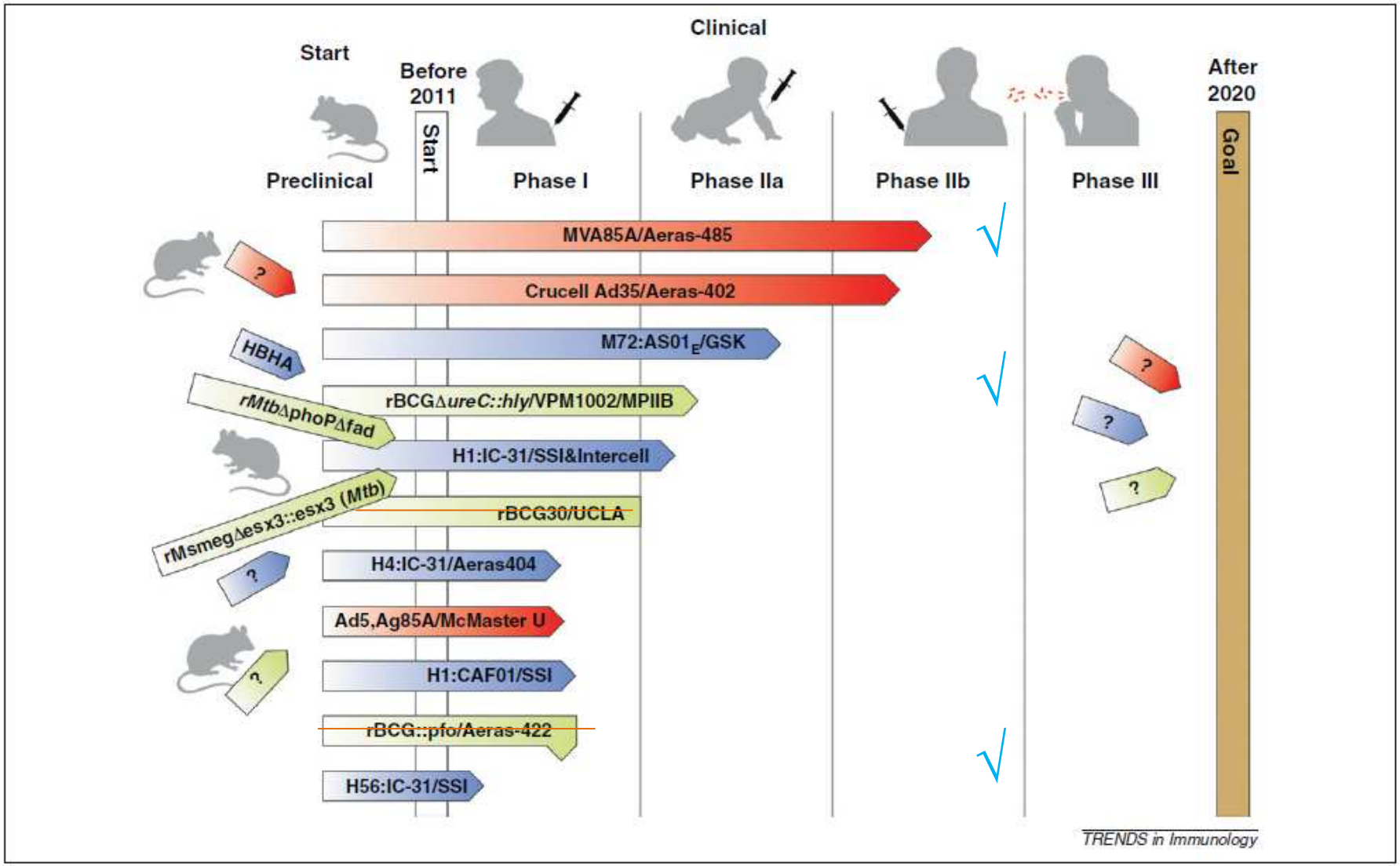
Okada and Kita, 2010 (Human Vaccines)

Table 1. Most advanced TB vaccine candidates in clinical trials.

Type	Candidate	Description	Clinical Trial Status
Recombinant BCG for pre-exposure prime vaccination	VPM 1002	rBCG-expressing listeriolysin and urease deletion	Phase IIa ongoing
	~~rBCG30~~	~~rBCG-expressing Ag85B~~	~~Phase I completed/on hold~~
	~~Aeras-422~~	~~rBCG-expressing perfringolysin and Ag85A, 85B, Rv3407~~	~~Phase I terminated due to~~ side effects
Viral-vector for pre-exposure booster vaccination	Oxford MVA85A/Aeras-485	Modified vaccinia Ankara-expressing Ag85A	Phase IIb ongoing
	Crucell Ad35/Aeras-402	Replication-deficient adenovirus 35-expressing Ag85A, Ag85B, TB10.4	Phase IIb ongoing
	AdAg85A	Replication-deficient adenovirus 5-expressing Ag85A	Phase I
Fusion protein in adjuvant for pre-exposure booster vaccination	Hybrid 1+IC31	Fusion of Ag85B and ESAT-6 in adjuvant IC31	Phase I, soon entering IIa
	Hybrid 56+IC31	Fusion of Ag85B, ESAT-6 and Rv2660c in adjuvant IC31	Phase I ongoing
	Hybrid 1+CAF01	Fusion of Ag85B and ESAT-6 in adjuvant CAF01	Phase I ongoing
	M72+AS01 or AS02	Fusion of Rv1196 and Rv0125 in adjuvant AS01 or ASO2	Phase IIa ongoing
	Aeras-404: HyVac4+IC31	Fusion of Ag85B and TB10.4 in adjuvant IC31	Phase I
Whole bacterial vaccine for therapeutic vaccination	RUTI	Detoxified *M. tuberculosis* in liposomes	Phase IIa ongoing
	M. vaccae	Inactivated *M. vaccae*	Phase III completed

Ottenhoff and Kaufmann, PLos Patho (2012)

Development Pipeline for New TB Vaccines (as of 2012)



Kaufmann, Trends Immunol (2012)

www.thelancet.com Published online February 4, 2013 http://dx.doi.org/10.1016/S0140-6736(13)60177-4

Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial

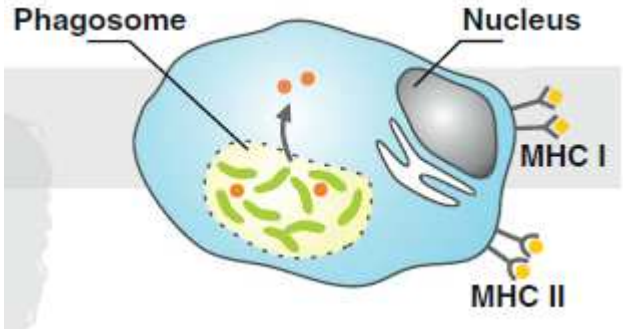
Michele D Tameris*, Mark Hatherill*, Bernard S Landry, Thomas J Scriba, Margaret Ann Snowden, Stephen Lockhart, Jacqueline E Shea, J Bruce McClain, Gregory D Hussey, Willem A Hanekom, Hassan Mahomed†, Helen McShane†, and the MVA85A 020 Trial Study Team

-Modified vaccinia Ankara virus-expressing Ag85A
-the first new tuberculosis vaccine in 90 years
-Developed as a heterologous prime boost for BCG
-Improved BCG-induced protection in animals
-Induced antigen-specific Th1 and Th17 in infants
-Phase IIb: infants (4-6 m/o HIV- with BCG vaccination)
Enrolled 2797 infants
-Well tolerated and induced modest CMIR
-Endpoints: incident of TB/Quantiferon TB Gold Conversion

NO PROTECTIVE EFFICACY (up to 37 months)

VPM1002: (BCG *ΔureC::hly*)

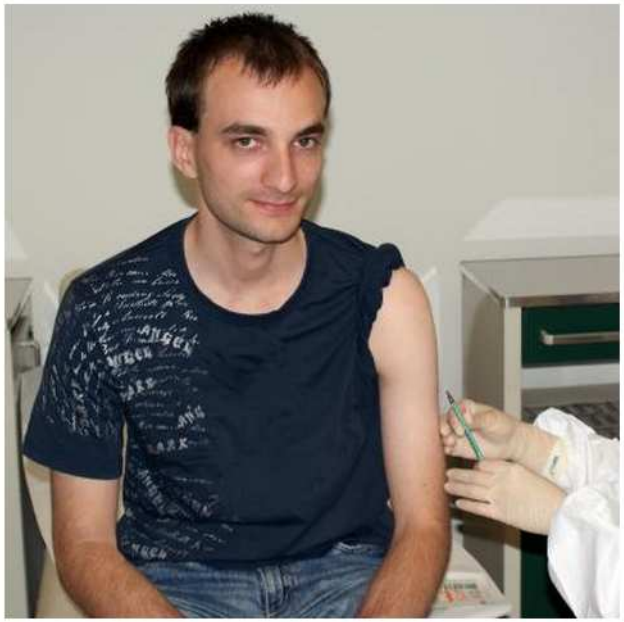
- MPIIB/Vakzine Projekt Management GmbH/TBVI
- Genetically engineered to express listeriolysin from *L. monocytegenes* as a fusion protein with Ag85B under *hsp60* promoter
- Deletion of urease C to keep pH in phagosome to 5.5
- Better protection against *Beijing* strains



Safety and immunogenicity of the recombinant BCG vaccine VPM1002 in a phase 1 open-label randomized clinical trial

Leander Grode[a,1], Christian A. Ganoza[b,1], Christiane Brohm[a,1], January Weiner 3rd[b], Bernd Eisele[a], Stefan H.E. Kaufmann[b,*]

[a] *Vakzine Projekt Management GmbH, Hannover, Germany*
[b] *Department of Immunology, Max Planck Institute for Infection Biology, Berlin, Germany*



First patient for the clinical trial of "VPM1002."

-Total of 80 healthy male volunteers
-Varying doses: $5x10^3$-$5x10^5$CFUs ID
-No AEs and well tolerated
-Induced IFNγ producing and multifunctional T cells and antibody in BCG-naïve and BCG-immune settings

Currently in Clinical Phase 2a

Multi-state Subunit Vaccine for Post-exposure Vaccine

nature medicine

Received 12 October 2010; accepted 7 December 2010; published online 23 January 2011; doi:10.1038/nm.2285

A multistage tuberculosis vaccine that confers efficient protection before and after exposure

Claus Aagaard[1,6], Truc Hoang[1,6], Jes Dietrich[1], Pere-Joan Cardona[2], Angelo Izzo[3], Gregory Dolganov[4], Gary K Schoolnik[4], Joseph P Cassidy[5], Rolf Billeskov[1] & Peter Andersen[1]

Early antigens (Ag85B and ESAT-6)
Latency-associated protein (Rv2660c)

} CAF01 Adjuvant

synthetic two-component liposomic adjuvant comprising the quaternary ammonium dimethyl-dioctadecyl-ammonium (DDA) and the immune modulator trehalose 6,6'-dibehenate (TDB)

-Better containment of late-stage infection
-Control reactivation and lower bacterial load

A recombinant *Mycobacterium smegmatis* induces potent bactericidal immunity against *Mycobacterium tuberculosis*

Kari A Sweeney[1,2], Dee N Dao[1,2,6], Michael F Goldberg[2,6], Tsungda Hsu[1,2], Manjunatha M Venkataswamy[2], Marcela Henao-Tamayo[3], Diane Ordway[3], Rani S Sellers[4], Paras Jain[1,2], Bing Chen[1,2], Mei Chen[1,2], John Kim[1,2], Regy Lukose[1,2], John Chan[2,5], Ian M Orme[3], Steven A Porcelli[2,5] & William R Jacobs Jr[1,2,5]

NATURE MEDICINE VOLUME 17 | NUMBER 10 | OCTOBER 2011

- Deletion of Esx-3 from *M. smegmatis*
- Introducing *M. tuberculosis* Esx-3 into this mutant
- Strong bactericidal immunity
- Sterile eradication

Obstacles in Developing New TB Vaccines

- Lack of knowledge on what constitutes a protective host immune response
- Lack of good animal models
- Lack of surrogate endpoint markers (correlates of protection)
- Lack of funding (everywhere and especially in Thailand)

Research in New TB Vaccines in Thailand

- Almost none exists
- Some grant application attempt was made to government funding agency but ended unsuccessfully
- Recombinant BCG vaccine/DNA vaccine/Subunit vaccine
- Discovery step (pre-clinical vaccine development)

Vaccine 31 (2013) 784–790

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Enhancement of immune response to a DNA vaccine against *Mycobacterium tuberculosis* Ag85B by incorporation of an autophagy inducing system

Jomkhwan Meerak[a,b], Supason P. Wanichwecharungruang[c], Tanapat Palaga[a,*]

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[b] Division of Microbiology, Department of Biology, Faculty of Science, Chiang Mai University, Huaykaew Road, Chiangmai 50200, Thailand
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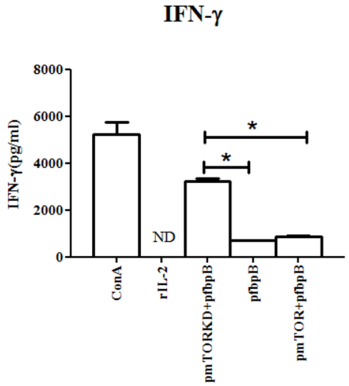
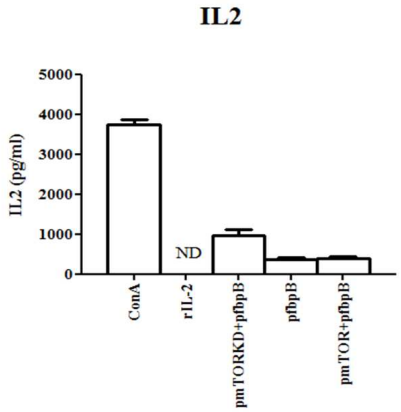
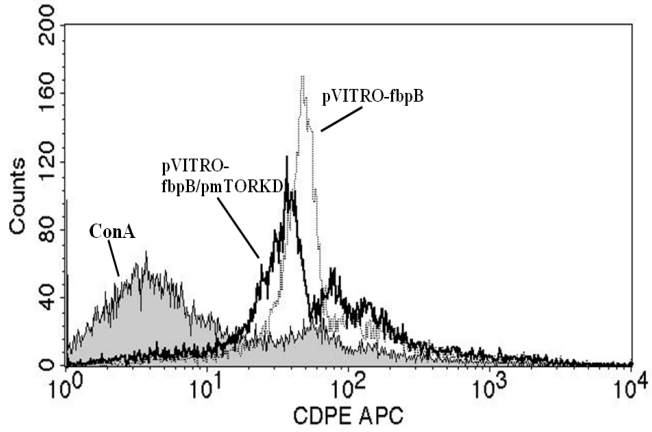






Do We Need to Invest in New TB Vaccines?

- There is no guarantee that the current vaccine candidates will go all the way
- Need to keep the pipeline full of new candidates
- Different geographic and ethnic settings
- Different *M. tuberculosis* lineages
- No active TB vaccine research in ASEAN

DNA Vaccine

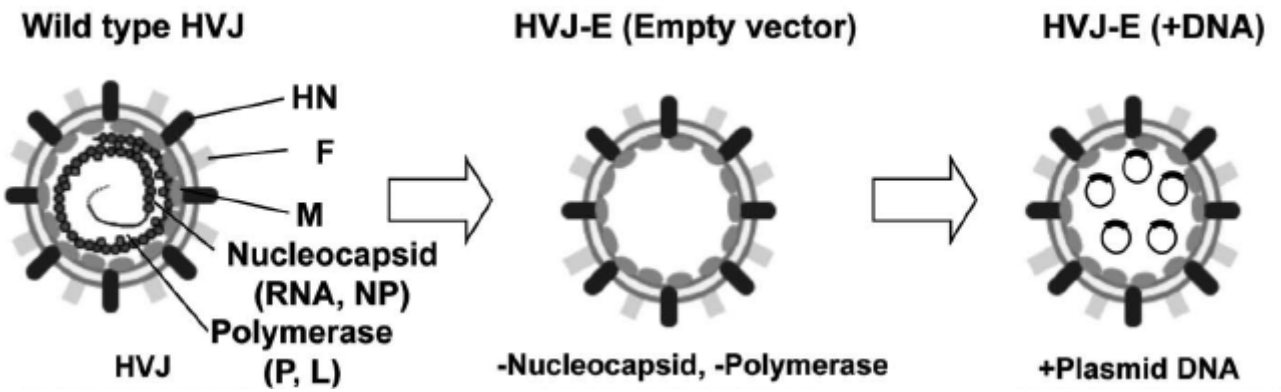


Table 1. The development of Novel vaccines for *M. tuberculosis* using animal model

Vaccine	Mouse	Guinea pig	Monkey	SCID-PBL/hu	Human
HVJ-Envelope/HSP65 DNA+IL-12 DNA	Prophylactic Effect 10,000-fold than BCG	effective	effective		plan (phase I, II)
	Therapeutic Effect	plan	effective	effective	
	Therapeutic Effect against MDR-TB XDR-TB	plan	plan		
HVJ-liposome/HSP65 DNA+IL-12 DNA	prophylactic Effect 100-fold effective than BCG	effective	effective (100% survival)		
recombinant 15 K granulysin	Therapeutic Effect		plan		
15 K granulysin DNA	Therapeutic Effect		plan		

HVJ-Envelope/HSP65 DNA+IL-12 DNA vaccine was evaluated by using mouse, guinea pig, monkey and SCID-PBL/hu model. Therapeutic efficacy as well as prophylactic efficacy was shown in this vaccine. HVJ-liposome/HSP65 DNA+IL-12 DNA vaccine and granulysin vaccine were also evaluated by using these models.

Okada et al., Human Vaccine (2011)

Group	Priming Vaccine (single)	Booster Vaccine (twice)
Group 1.	BCG Tokyo	HSP65+ IL-12 / HVJ-E
Group 2.	BCG Tokyo	(-)
Group 3.	Saline	(-)

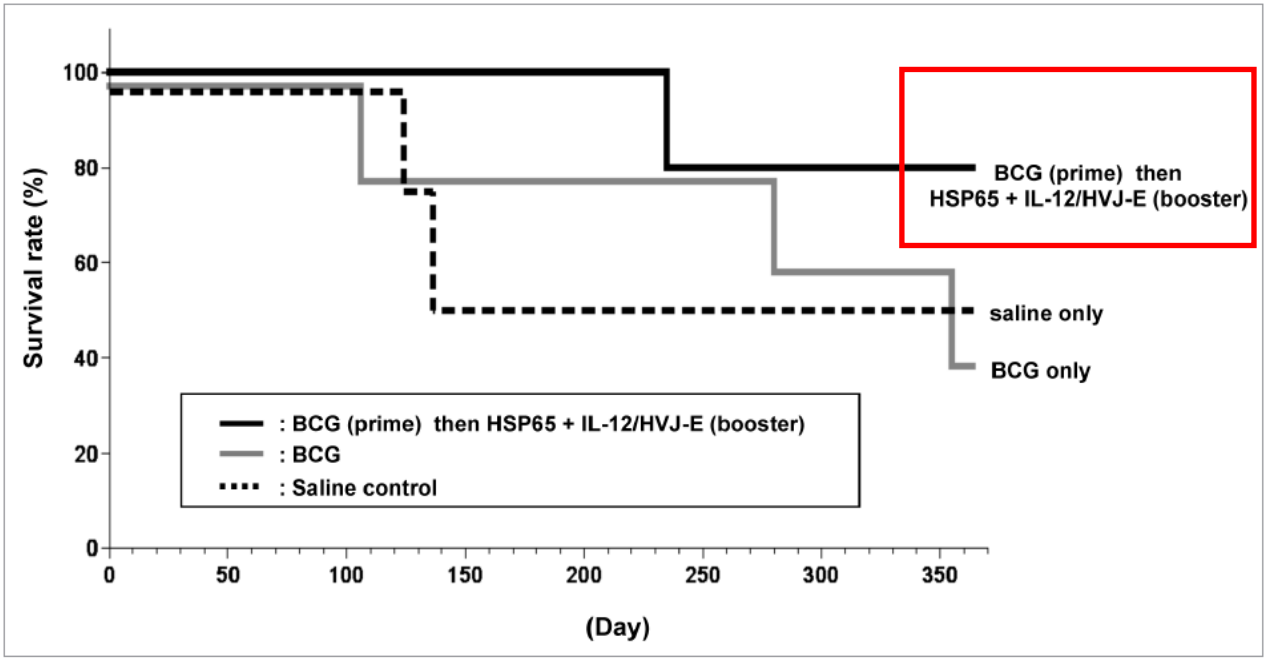
priming → (4 months) → booster → booster → (1 month) → TB challenge

Monkey
5 animals/group

4 months | 3 w | 1 month | 1 year

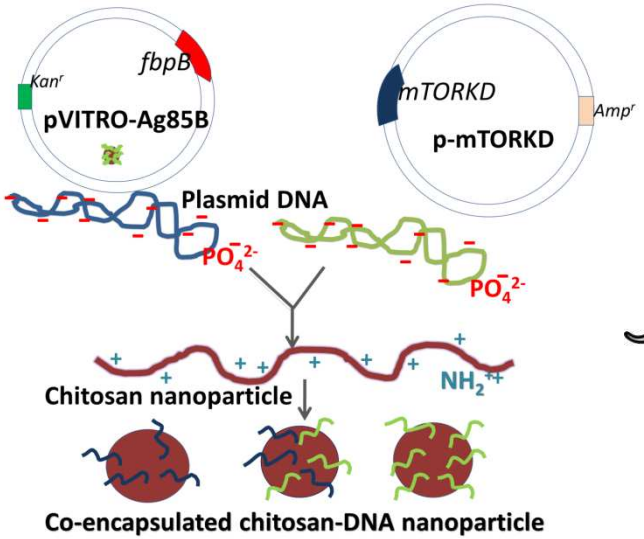
Priming | Booster | TB Erdman 5X10^2 Intratracheal instillation

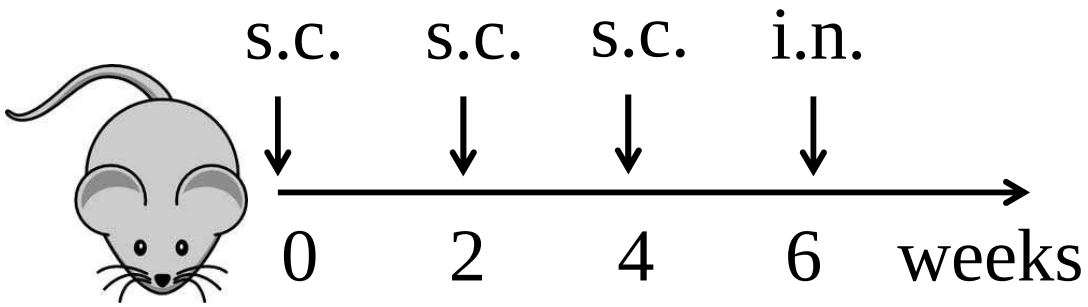
Survival
Immune response

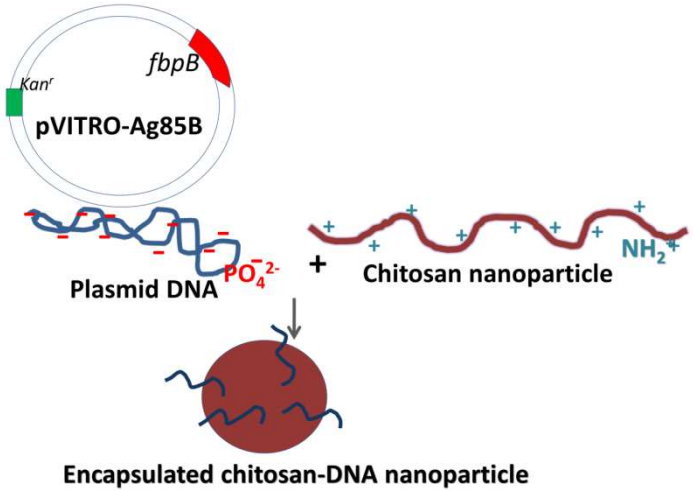


Kita et al., Human Vaccines (2011)

DNA Vaccine to Enhance Immunogenicity against Ag85B







Priming via subcutaneous and boost with nasal route

Meerak and Palaga, 2012

Challenges for Initiating New TB Vaccine (Globally and Locally)

- Preclinical evaluation of vaccine candidates (mice, guinea pigs, NHP): Facility for animal studies
- Predictive parameters (biomarkers) for vaccine efficacy
- Financing of preclinical and clinical development
- (Re)awakening of TB vaccine research
- Human resources: training and incentives (local)

Funding, political and multinational support with increase public awareness of the needs for new TB vaccine

Tuberculosis Vaccine Initiative

Next Generation of Vaccine Candidates

- Most current vaccine candidates are administered pre-exposed to prevent active TB
- The goal is not to achieve sterile clearance
- Vaccines that can result in sterile eradication and therapeutic vaccines (post exposure) are the next generation candidates (with the rise in TB/HIV co-infection)

New Antigens; Therapeutic Vaccines; Environment of Host

Table 2. Total R&D Funding by Disease

Disease	Amount (US$)	% of Total Funding
HIV/AIDS	1,083,018,193	42.30
Malaria	468,449,438	18.30
Tuberculosis	410,428,697	16.03
Kinetoplastids	125,122,839	4.89
Diarrhoeal diseases	113,889,118	4.45
Dengue	82,013,895	3.20

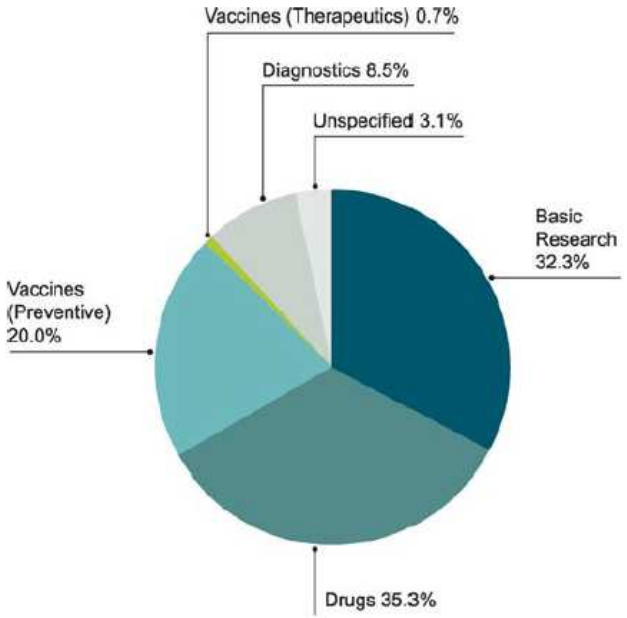


Figure 4. TB R&D Funding in 2007
doi:10.1371/journal.pmed.1000030.g004

Moran et al., PLoS Medicine (2009)