TB Vaccines

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satvi SOUTH AFRICAN TUBERCULOSIS VACCINE INITIATIVE

Do we need a new TB vaccine?

Global Toll

9 million people develop TB each year

1.5 million people people die each year

In a single day - equivalent to 15 airliner crashe

New TB drugs are being approved for MDR TB

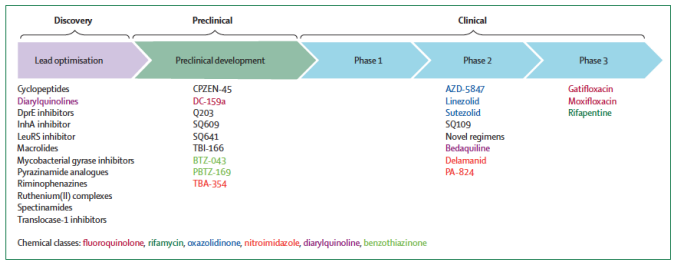
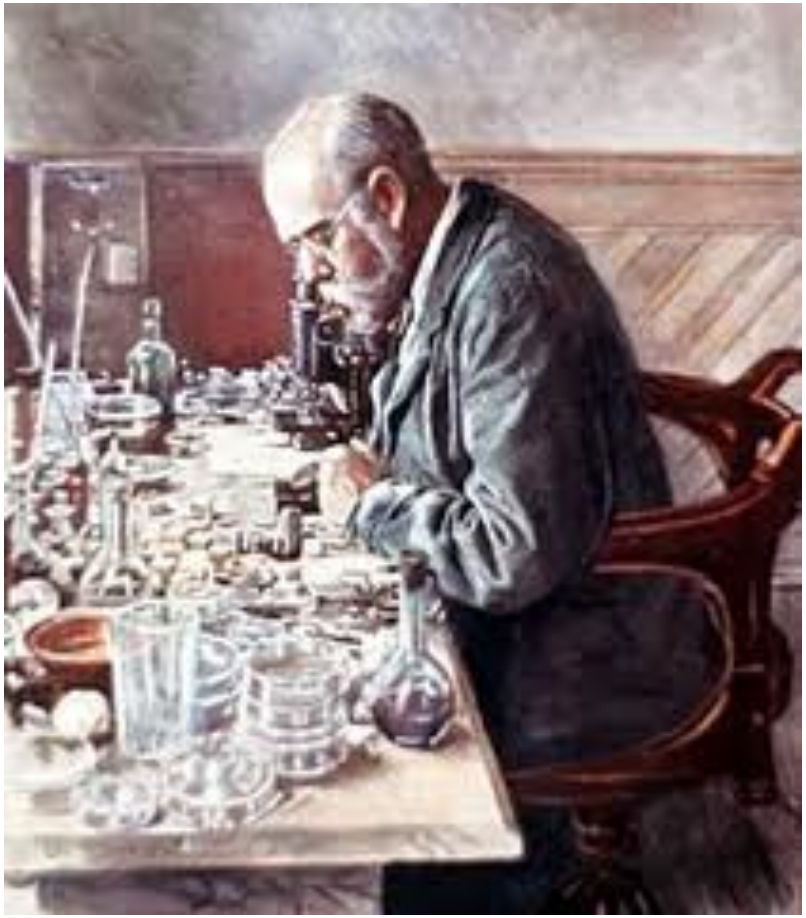


Figure 1: **Global pipeline of new tuberculosis drugs**[123-34,35-48]

Used with permission of the Stop TB Partnership Working Group on New Drugs.

Our only licensed TB vaccine – BCG - was developed in 1921…..

A little history……
1882: Robert Koch discovers the tubercle bacillus



HOW TO PREVENT CONSUMPTION (TUBERCULOSIS) AND OTHER GERM DISEASES

For School Children to Take Home and to Read Every Day.

DON'T FORGET THESE FACTS.

Germs are very small microscopic plants. Germs are found in all *Dust* and *Dirt*. Some germs are harmless, others cause disease. *Germs cause Consumption.* Avoid germs and Prevent Consumption.

TRY TO

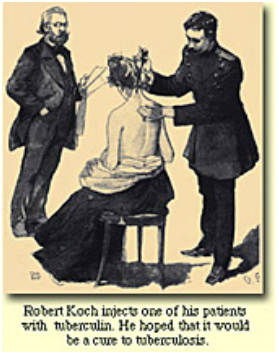
TRY to breathe through the nose rather than through the mouth.
TRY to fill the lungs with pure air, free from dust.
TRY to turn the head away from a person when coughing or sneezing, or hold a handkerchief or your hand over your mouth.
TRY to spit out material coughed up from the lungs.
TRY to spit into a piece of paper or cloth and burn as soon as possible.
TRY to gargle your throat with salt water or some other mild mouth wash after being exposed to any contagious disease.
TRY to clean the nose with a handkerchief.
TRY to keep the hands clean.
TRY to keep your finger nails cut short.
TRY to brush your teeth night and morning.
TRY to eat clean food and drink pure water.
TRY to eat slowly and chew your food well.
TRY to keep moving about when heated from play.
TRY to keep your feet dry.
TRY to sleep in a room with partly-opened windows.
TRY to live in the sunshine.
TRY to be out of doors as much as possible.

TRY NOT TO

Try NOT to take a full breath in a cloud of dust.
Try NOT to cough or sneeze in another's face.
Try NOT to swallow what you raise in coughing.
Try NOT to spit upon the floor or sidewalk.
Try NOT to cough long without seeing a physician.
Try NOT to kiss a sick friend.
Try NOT to pick your nose with your fingers.
Try NOT to eat with dirty hands.
Try NOT to eat things made dirty by the handling of other persons.
Try NOT to eat a piece of candy or apple picked up from the sidewalk or street.
Try NOT to have long and dirty finger nails.
Try NOT to go about with unclean teeth.
Try NOT to drink out of a cup that has been used unless you wash it first.
Try NOT to eat when heated or tired.
Try NOT to eat fast.
Try NOT, when heated, to sit down where it is cold.
Try NOT to play in wet shoes and stockings.
Try NOT to sleep in a warm or hot room.
Try NOT to shut out the sunshine.
Try NOT to form the habit of living around a stove.

Gardner Association for the Prevention and Relief of Tuberculosis.

Robert Koch's "therapeutic vaccine"
Purified Tuberculin Protein (PPD)

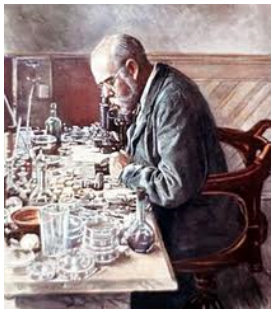

Robert Koch injects one of his patients with tuberculin. He hoped that it would be a cure to tuberculosis.

August 1890

- 10th International Medical Congress in Berlin attended by 8000 participants
- Keynote speech by Koch on opening day
- Urged by Emperor William II to present something spectacular

Guinea pigs, which are known to be highly susceptible to tuberculosis, no longer respond to infection with tubercle bacilli once they had been pretreated with such substances. Moreover, in guinea pigs that suffered from severe tuberculosis, the disease process could be brought to an end without harming the animals. I do not want to draw further conclusions from these experiments, but only to state that the possibility exists to inactivate pathogens in the host without major side effects—a possibility that was thus far considered extremely unlikely.

The substance with which the new treatment against tuberculosis is being performed, is a glycerol extract of pure culture of tubercle bacilli.



- General acclaim. Patients and scientists flocked to Berlin….

The Famous Scientist, His Mistress, and The 1 Million Gold Marks

• Given The Grand Cross of the Red Eagle by the Emperor William II

• The Emperor declared all profits belonged to the discoverer

• Rumoured that the Hoechst Company (later part of Sanofi-Aventis) bought exclusive rights to manufacture tuberculin for 1 million Gold Marks.

One of his contemporaries (Professor of Medicine, Janes Flesch) sa

> The material was sold for 1 million Gold-Marks, without doubt so Koch could get an easy divorce and once again marry a beautiful blonde. Was it his love for this very young lady that urged him to propagate the material prematurely and without the necessary careful evaluation?

Robert Koch's 'cure' for TB: Purified Tuberculin Protein (PPD)

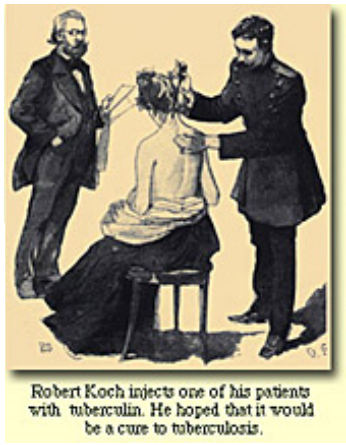

Robert Koch injects one of his patients with tuberculin. He hoped that it would be a cure to tuberculosis.

Table 1 Results of treatment with tuberculin

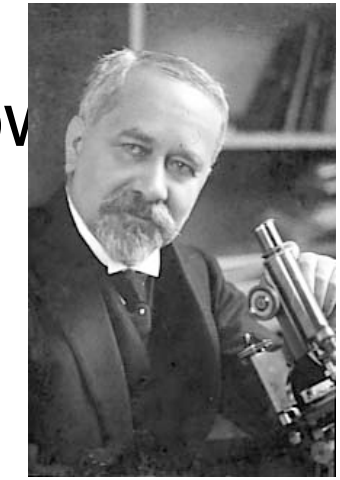
	External tuberculosis	Pulmonary tuberculosis
Cured	15	13
Substantially improved	148	171
Improved	237	194
Unimproved	298	586
Died	9	46

1891: First negative reports of clinical trials

- Total 1769 patients
- More patients died during therapy than were cured
- Most of deaths due to advanced pulmonary TB
- Fewer that 20% of all patients improved substantially
- 50% showed no improvement

Animal models may be misleading….

The Doctor, The Vet, and The Cow



Bacille Calmette-Guerin (BCG) Vaccine

- Albert Calmette (physician) and Camille Guerin (vet)
- Pasteur Institute, Lille, France (1921)
- Attenuated bovine TB strain (*Mycobacterium bovis*)
- Cultured virulent bacilli obtained from a cow with TB mastitis
- Added bile as natural culture detergent → organism unexpectedly lost virulence
- Tested as vaccine in calves, guinea pigs, rabbits, horses, monkeys

BCG vaccine

Natural experiments

Table 1 Tuberculosis Case and Death Rates Among Student Nurses at Ullevål Hospital, Norway, by Tuberculin and BCG Vaccination on Entry, 1927–1946

Tuberculin and Vaccination Status on Entry	No.	Person-years of Observation	Rate/1000 Person-years	
			Cases	Deaths
Tuberculin-positive, not vaccinated	668	1772	12.4	0
Tuberculin-negative, not vaccinated	284	687	141.2	14.6
Tuberculin-negative, vaccinated	501	1450	24.1	2.1

Variation in protection by BCG: implications of and for heterologous immunity

P E M Fine

STUDY	Lat	U/R	Type	VE
NORWAY, gen popn[42]	65	U+R	COH	81%
SWEDEN, gen popn[43]	62	U+R	COH	80%
SWEDEN, military[44]	62	U+R	COH	55%
DENMARK, school[45]	56	U	O/B	94%
IRELAND, school[46]	55	R	O/B	82%
CANADA Indians[47]*	55	R	T	81%
CANADA ALBERTA Indians[48]*	55	R	C.C	57%
CANADA MANITOBA Indians[49]*	55	R	C.C	70%
UK, schoolchildren[50]*	53	U+R	T	77%
UK, gen popn 1973[51]	53	U+R	COH	79%
UK, gen popn 1978[52]	53	U+R	COH	74%
UK, gen popn 1983[7]	53	U+R	COH	75%
UK, Asians[53]*	53	U	C.C	49%
UK, BIRMINGHAM Asians[54]*	52	U	C.C	64%
UK, BIRMINGHAM[55]	52	U	COH	88%
USA, Indians[25]*	52	R	T	79%
USA, CHICAGO infants[56]*	42	U	T	72%
USA, NEW YORK infants[57]	41	U	T	7% →
KOREA, SEOUL[58]	38	U	H/H	74%
ARGENTINA, BUENOS AIRES[59]*	35	U	C.C	73%
USA, GEORGIA school[26]*	33	U+R	T	−56% →
USA, GEORGIA ALABAMA gen popn[60]*	33	U+R	T	16%
ISRAEL, children[61]	31	U+R	COH	38%
SOUTH AFRICA, miners[62]*	27	U+R	T	62%
AUSTRALIA, QUEENSLAND[63]*	20	U+R	C.C	41%
PUERTO RICO[15]*	18	R+U	T	29%
HAITI[64]*	18	R+U	T	80%
BURMA, RANGOON[65]*	17	U	C.C	38%
THAILAND, BANGKOK[66]	14	U	C.C	74%
THAILAND, BANGKOK[67]	14	U	C.C	83%
THAILAND, BANGKOK[68]	14	U	H/H	47%
INDIA, MADANAPALLE[27]*	13	R	T	20%
INDIA, CHINGLEPUT[10]*	13	R	T	−19%
PAPUA NEW GUINEA[69]	10	U+R	C.C	41%
MALAWI, KARONGA[8]	10	R	COH	−11%
INDONESIA, JAKARTA[70]*	6	U	C.C	37%
TOGO LOME[71]	6	U	H/H	66%
COLUMBIA, CALI[72]*	4	U	C.C	16%
CAMEROUN, YAOUNDE[73]	4	U	C.C	66%
KENYA, KISUMU[17]	0	R	C.C	22%

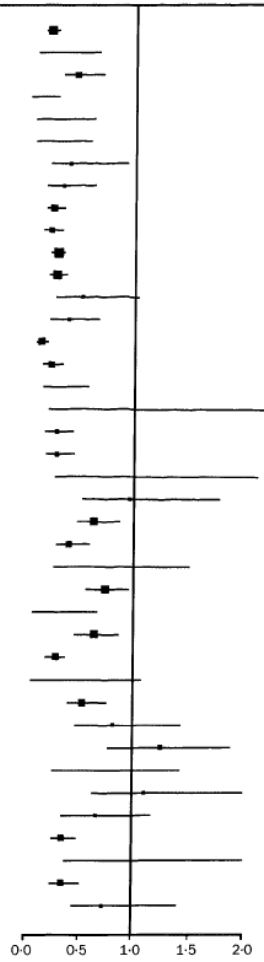


Figure 1: **Summary of published estimates of efficacy of BCG against pulmonary tuberculosis in trials and observational studies, by latitude**

This includes published trials involving random or alternate allocation of vaccine, and both retrospective and prospective observational studies. *Studies included in recent review[11] which concluded that latitude could explain 41% of the between-study variance. Total series of studies shown here also shows strong heterogeneity (χ^2[39df]=394, p<0·00001) and a significant trend with latitude (χ^2[1df]=151, p<0·00001). Lat=latitude in degrees (north or south) from equator; U/R=urban or rural; Type=study type (T=trial, COH=cohort, C·C=case control, O/B=outbreak, H/H=household contact study); OR=odds ratio; VE=vaccine efficacy (1−OR).

Does BCG work?

Trials and observational studies

0 - 81% protection

Vaccine efficacy varies by latitude, age group, type of disease, among other things…..

Young children have been the historical focus of TB vaccine trials

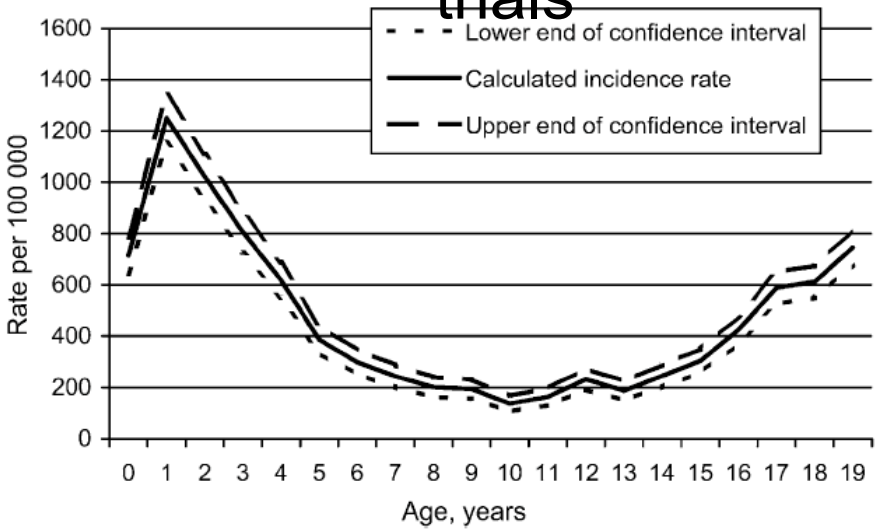


Figure 1 All tuberculosis incidence rate by age (years) in Cape Town, July 2002–June 2003 (n = 5039). Source: City Health Directorate of the City of Cape Town (notified TB cases) and Census 2001 (population estimates).

Young children have higher risk of progression from TB infection to disease

And higher risk of disseminated disease (TB meningitis and miliary TB)

Marais IJTLD 2004

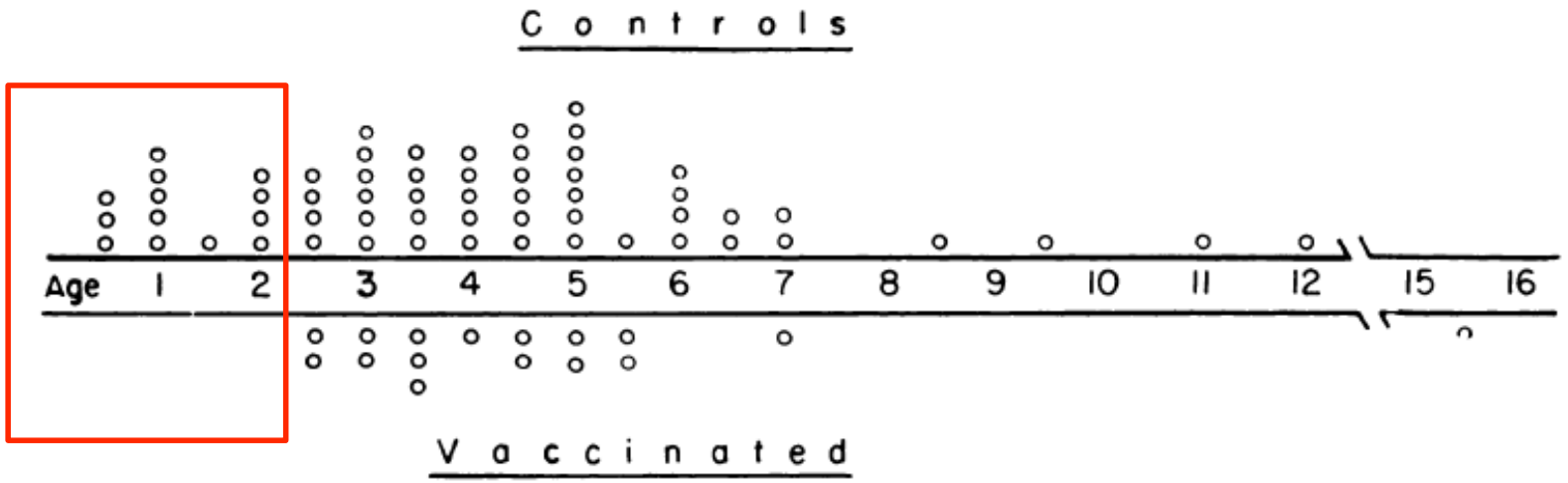


FIG. 1. Comparison of time of development of tuberculosis in the vaccinated and control groups. Each circle represents a case of nonfatal tuberculosis.

BCG VACCINATION AGAINST TUBERCULOSIS IN CHICAGO

A Twenty-year Study Statistically Analyzed

Sol Roy Rosenthal, M.D., Ph.D., Erhard Loewinsohn, M.D., Mary L. Graham, M.D., Dorothy Liveright, Margaret G. Thorne, *and* Violet Johnson, with Statistical Analysis by H. C. Batson, Ph.D.

Institution for Tuberculosis Research of the University of Illinois, the Chicago Municipal Tuberculosis Sanitarium, Research Foundation, and the Cook County Hospital, Chicago

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

The Efficacy of Bacillus Calmette-Guérin Vaccination of Newborns and Infants in the Prevention of Tuberculosis: Meta-Analyses of the Published Literature

Graham A. Colditz, Catherine S. Berkey, Frederick Mosteller, Timothy F. Brewer, Mary E. Wilson, Elisabeth Burdick and Harvey V. Fineberg

Pediatrics 1995;96;29-35

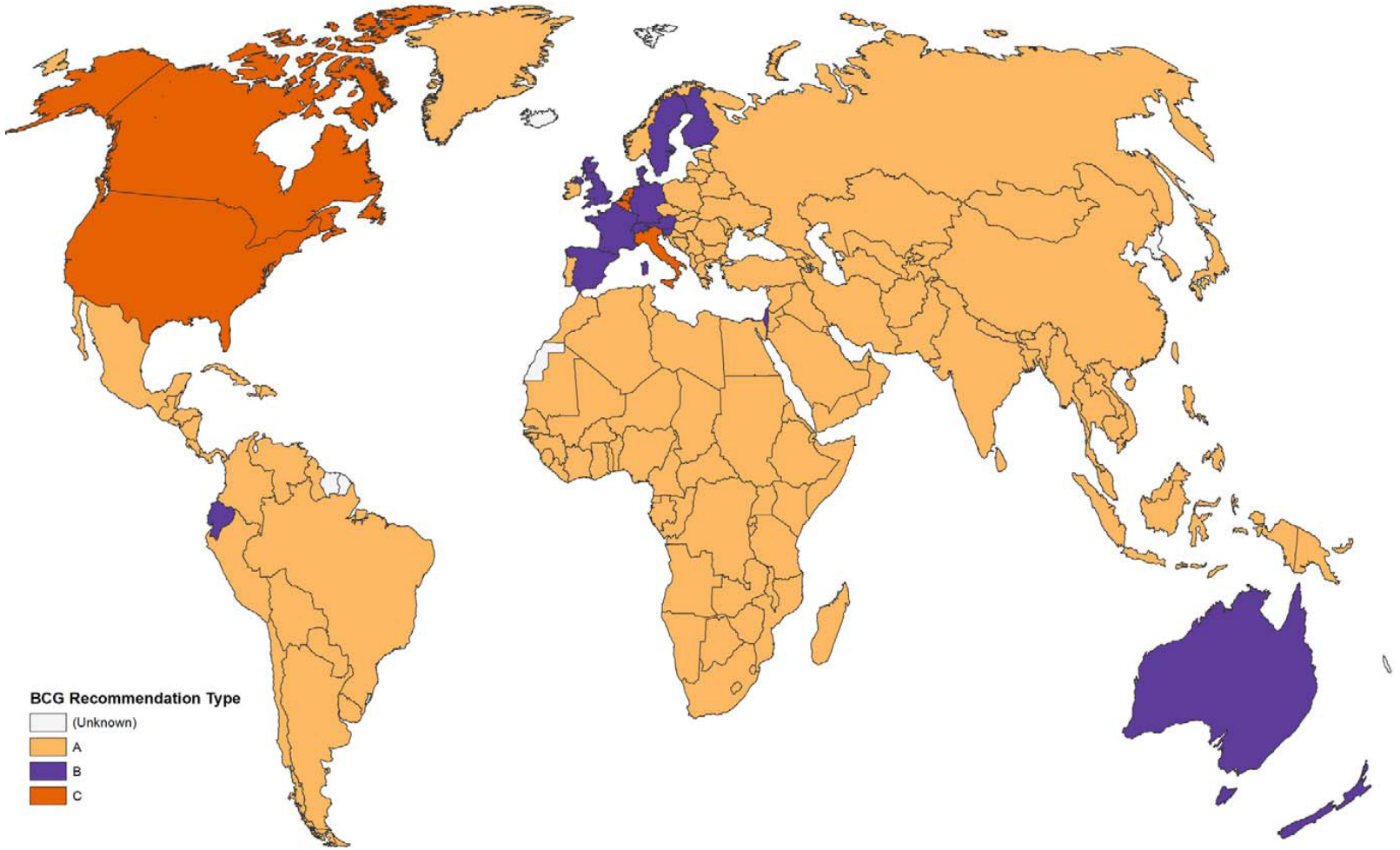
TABLE 6. Estimated Protective Effect (PE) [PE = 1 – RR or PE = 1 – OR] of BCG Vaccination Against Tuberculosis (TB), 95% Confidence Interval (CI) of the Combined Estimate, and Estimate of the Interval Enclosing 95% of the Distribution of the PEs to Be Observed in Future Studies or Trials

Protection Against	Combined PE	95% CI of Combined PE	95% Density of the Trials/ Studies Observed PEs*
TB cases (trials)	.742	(0.616, 0.826)	(0.304, 0.904)
TB cases (case-control studies)	.524	(0.379, 0.635)	(–0.017, 0.777)
TB deaths	.648	(0.118, 0.860)	(–2.698, 0.966)
Lab-confirmed cases	.826	(0.582, 0.928)	(0.114, 0.966)
TB meningitis	.644	(0.300, 0.820)	(–0.560, 0.919)
Disseminated TB	.780	(0.581, 0.883)	(0.285, 0.932)

BCG protects against severe disease in children

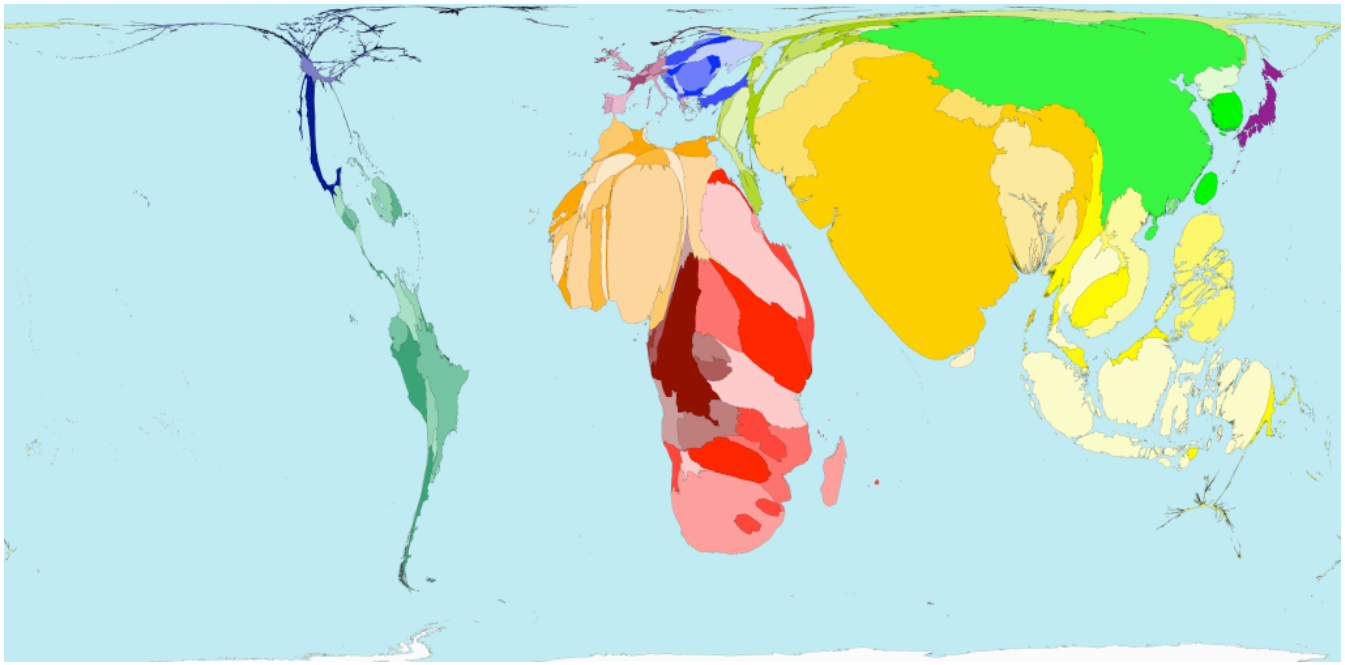
64% efficacy against TBM

78% efficacy against disseminated TB disease



The BCG Atlas

Does BCG work in adults?



Little evidence to suggests that BCG protects against PTB in adults…

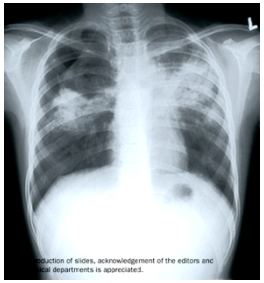
…who are the source of transmission

We need a new TB vaccine strategy

Safe + effective

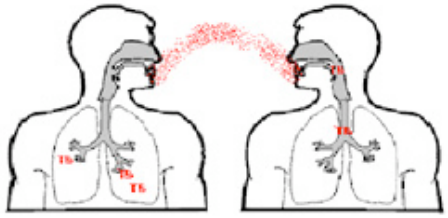
….in infants, children, and adults

….and in HIV infected people



Protection against TB?

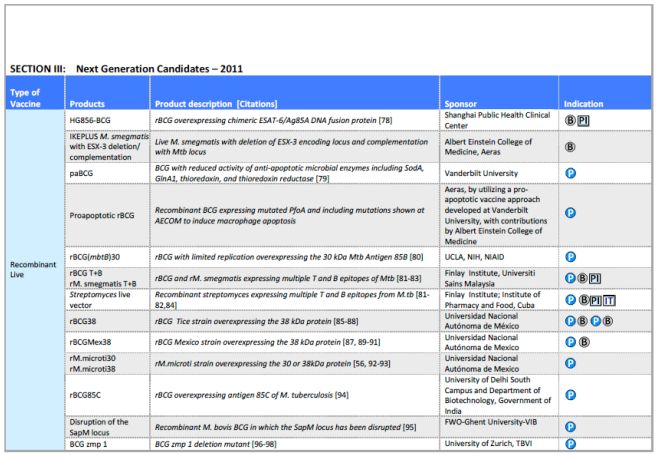
- Primary infection in children?
- Pauci-bacillary childhood disease?
- Disseminated TBM / miliary disease / death?
- Reactivation → adult-type cavitatory PTB?



satvi SOUTH AFRICAN TUBERCULOSIS VACCINE INITIATIVE
http://www.satvi.uct.ac.za
Vaccines to stop TB
IIDMM INSTITUTE OF INFECTIOUS DISEASE AND MOLECULAR MEDICINE

SECTION II: Candidates in Preclinical Studies & GMP – 2011

Type of Vaccine	Products	Product Description [Citations]	Sponsor	Indication
Recombinant Live	BCG Danish ΔpanCD ΔmmaA4	*Non-replicating, Mtb strain auxotrophic for lysine and pantothenate; attenuated for secA2* [58-59]	Albert Einstein College of Medicine	P
	MTBVAC [*ΔphoP, ΔfadD26*]	*Live vaccine based on attenuation of Mtb by stable inactivation by deletion of phoP and fadD26 genes without antibiotic resistance markers in compliance with 2005 and 2010 Geneva consensus safety requirements* [60-64]	University of Zaragoza, Institute Pasteur, BIOFABRI, TBVI	P
Protein	HBHA	*Naturally methylated 21-kDa purified protein from M.bovis BCG* [65-69]	Institute Pasteur of Lille, INSERM, TBVI, Aeras	P B PI IT
DNA	HG85A	*DNA vaccines—Ag85A* [70-74]	Shanghai H&G Biotech	B IT
	Hsp DNA vaccine	*Codon-optimized heat shock protein from M. leprae, a CpG island* [75-77]	Sequella, Shanghai Public Health Clinical Center	B PI IT



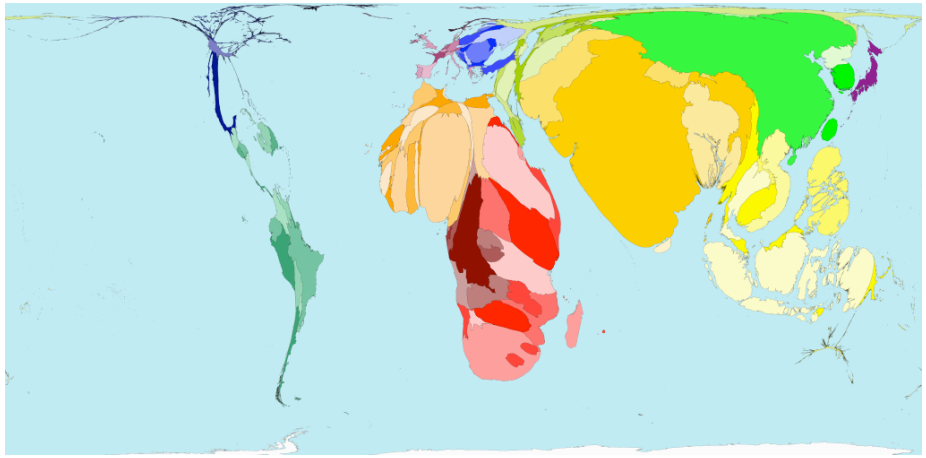
SECTION III: Next Generation Candidates – 2011

Type of Vaccine	Products	Product description [Citations]	Sponsor	Indication
Recombinant Live	HG856-BCG	*rBCG overexpressing chimeric ESAT-6/Ag85A DNA fusion protein* [78]	Shanghai Public Health Clinical Center	B PI
	IKEPLUS *M. smegmatis* with ESX-3 deletion/ complementation	*Live M. smegmatis with deletion of ESX-3 encoding locus and complementation with Mtb locus*	Albert Einstein College of Medicine, Aeras	B
	paBCG	*BCG with reduced activity of anti-apoptotic microbial enzymes including SodA, GlnA1, thioredoxin, and thioredoxin reductase* [79]	Vanderbilt University	P
	Proapoptotic rBCG	*Recombinant BCG expressing mutated PfjoA and including mutations shown at AECOM to induce macrophage apoptosis*	Aeras, by utilizing a pro-apoptotic vaccine approach developed at Vanderbilt University, with contributions by Albert Einstein College of Medicine	P
	rBCG(*mbtB*)30	*rBCG with limited replication overexpressing the 30 kDa Mtb Antigen 85B* [80]	UCLA, NIH, NIAID	P
	rBCG T+B rM. smegmatis T+B	*rBCG and rM. smegmatis expressing multiple T and B epitopes of Mtb* [81-83]	Finlay Institute, Universiti Sains Malaysia	P B PI
	Streptomyces live vector	*Recombinant streptomyces expressing multiple T and B epitopes from M.tb* [81-82,84]	Finlay Institute; Institute of Pharmacy and Food, Cuba	P B PI IT
	rBCG38	*rBCG Tice strain overexpressing the 38 kDa protein* [85-88]	Universidad Nacional Autónoma de México	P B P B
	rBCGMex38	*rBCG Mexico strain overexpressing the 38 kDa protein* [87, 89-91]	Universidad Nacional Autónoma de Mexico	P B
	rM.microti30 rM.microti38	*rM.microti strain overexpressing the 30 or 38kDa protein* [56, 92-93]	Universidad Nacional Autónoma de Mexico	P
	rBCG85C	*rBCG overexpressing antigen 85C of M. tuberculosis* [94]	University of Delhi South Campus and Department of Biotechnology, Government of India	P
	Disruption of the SapM locus	*Recombinant M. bovis BCG in which the SapM locus has been disrupted* [95]	FWO-Ghent University-VIB	P
	BCG zmp 1	*BCG zmp 1 deletion mutant* [96-98]	University of Zurich, TBVI	P

Recombinant Protein	ID93 in GLA-SE adjuvant	*Subunit fusion protein composed of 4 Mtb antigens* [99-100]	Infectious Disease Research Institute	B PI IT
	Latency fusion proteins	*recombinant fusion proteins composed of antigens 85A-85B-Rv3407, Rv3407-Rv1733c-Rv2626c, Rv0867c-Rv-1884-Rv2389c*	Aeras	B
	r30	*30kDa Mtb Ag85B protein purified from rM. Smegmatis* [53-57]	UCLA, NIH, NIAID	B PI
	R32Kda (recombinant 85A)	*Purified recombinant 85A protein from BCG* [101-105]	Bhagawan Mahavir Medical Research Center, LEPRA Society- Blue Peter Research Centre	B PI IT
Viral Vectored	Recombinant LCMV	*Recombinant lymphocytic choriomeningitis virus expressing Ag85A, Ag85B, or Ag85B-ESAT6* [106-107]	University of Geneva, TBVI	P B PI IT
	rhPIV2-Ag85B	*Replication-deficient human parainfluenza type 2 virus expressing Ag85B* [108-110]	National Institute of Biomedical Innovation, Japan; Japan BCG Laboratory	P B
DNA	HVJ-Envelope/HSP65 DNA+IL-12 DNA	*Combination of DNA vaccines expressing mycobacterial heat-shock protein 65 & IL-12* [111-115]	Osaka University	B PI IT
	pUMVC6/7 DNA	*DNA vaccine plasmid vectors pUMVC6 or pUMVC7 expressing Rv3872, Rv3873, Rv3874, Rv3875 or Rv3619c* [116-117]	Kuwait University	P
	DNAacr	*DNA* vaccine expressing α-crystallin, a key latency associated antigen of *M. tuberculosis* [118]	University of Delhi South Campus and Department of Biotechnology, Government of India	B
	rBCGacr/DNAacr	rBCG and DNA vaccines expressing α-crystallin of M. tuberculosis in a heterologous prime boost approach [119]	University of Delhi South Campus and Department of Biotechnology, Government of India	P B
	HG85 A/B	*Chimeric DNA vaccines—Ag85A/B* [70-74]	Shanghai H&G Biotech	B IT
	HG856A	*Chimeric DNA vaccines—ESAT-6/Ag85A; Ag85A/Ag85B* [78]	Shanghai H&G Biotech	B IT
Other	HG856-SeV	*Recombinant Sendai virus overexpressing chimeric Ag85A/B protein*	Shanghai H&G Biotech; Shanghai Public Health Clinical Center; DNAVEC Corporation, Japan	B IT
	LIP1 Ac_2SGL sulfoglycolipid	*Ac_2SGL/PIM2 in DDA/TDB* [120-122]	Centre National de la Recherche Scientifique (CNRS), TBVI	P B PI IT
	LIP2 SL37 (synthetic) sulfoglycolipid	*SL37/PIM2 in DDA/TDB* [123-124]	CNRS, TBVI	P B PI IT

	EspC	*Recombinant protein and/or viral-vectored* [125]	Imperial College London	P B PI IT
	Liporale™ TB	*Live attenuated BCG Danish Strain in a novel stable lipid matrix for oral vaccination* [126-130]	Immune Solutions Ltd.	P B
	Mycobacterial liposomes and proteoliposomes	*Liposomes from M. smegmatis and proteo-liposomes from BCG and M. smegmatis* [131]	Finlay Institute Universiti Sains Malaysia	P B PI IT
	PS- conjugate	*Subunit Mtb polysaccharide protein conjugate*	Albert Einstein College of Medicine	B
	T-BioVax	*Heat shock HspC protein antigen complexes* [132-133]	ImmunoBiology Ltd.	P B IT
	TBVax	*T cell epitope-based DNA-prime/peptide boost vaccine* [134-136]	EpiVax , Inc.	B PI

50 candidate TB vaccines in pre-clinical development….



Sutton's Law Applied to TB Vaccine Trials

South Africa: TB incidence 993 per 100,00

(Global TB Report 2012)

Willie "The Actor" Sutton

Willie "The Actor" Sutton

FBI Ten Most Wanted Fugitives	
Charges	Bank robbery
Description	
Born	June 30, 1901
Died	November 2, 1980 (aged 79) Spring Hill, Florida
Criminal Status	
Added	March 20, 1950
Caught	February 1952
Number	11
Captured	

satvi

Global TB Vaccine Pipeline*

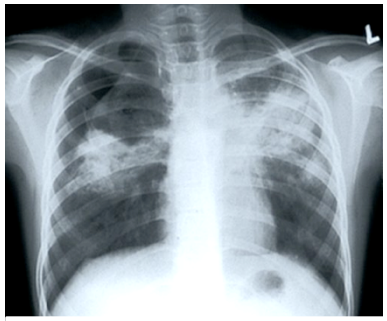
TB Vaccine Types

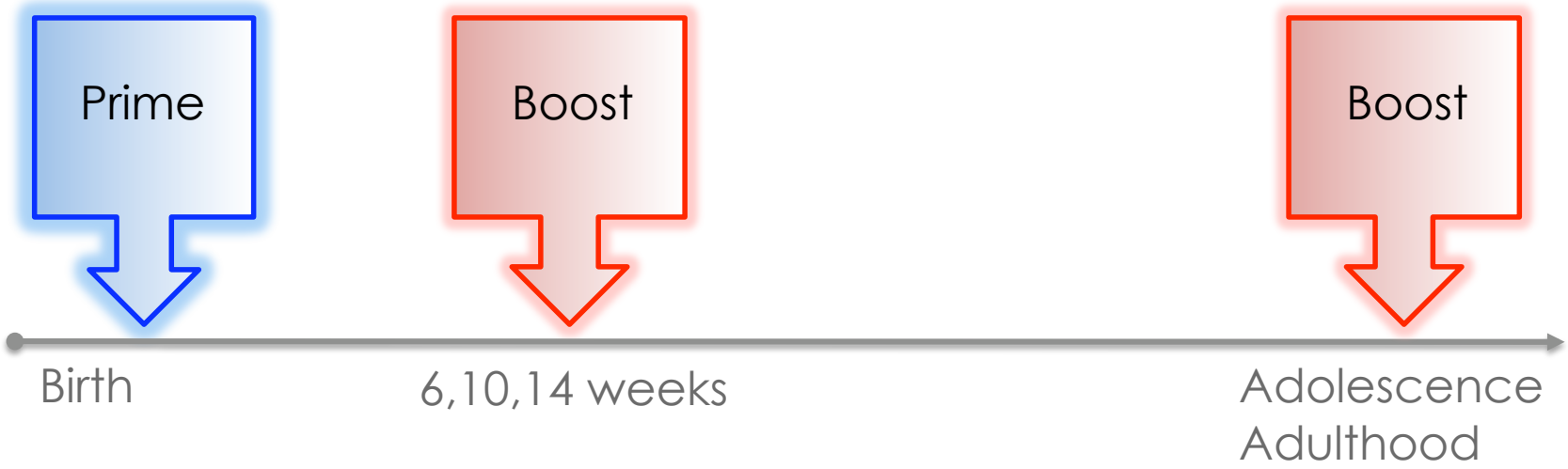
Viral-vectored: MVA85A, AERAS-402, Ad35Ag85A, Ad5Ag85A
Protein/adjuvant: M72, Hybrid-1, Hyvac 4, H56, ID93
rBCG: VPM 1002
Killed WC or Extract: Mw, RUTI

*Adapted to highlight vaccine candidates evaluated at the SATVI site

Stop TB Partnership
Working Group on New TB Vaccines

12 candidate TB vaccines in clinical development





BCG
VPM-1002
MTBVAC

MVA-Ag85A (**MVA85A**)
Mtb32,39 in ASO1E (**M72**)
Ag85B,TB10.4 in IC31 (**H4**)
ESAT-6,Ag85B in IC31 (**H1**)
ESAT-6,Ag85B,Rv2660c in IC31 (**H56**)
Rv2608, Rv3619, Rv3620, Rv1813 in GLE (**ID93**)

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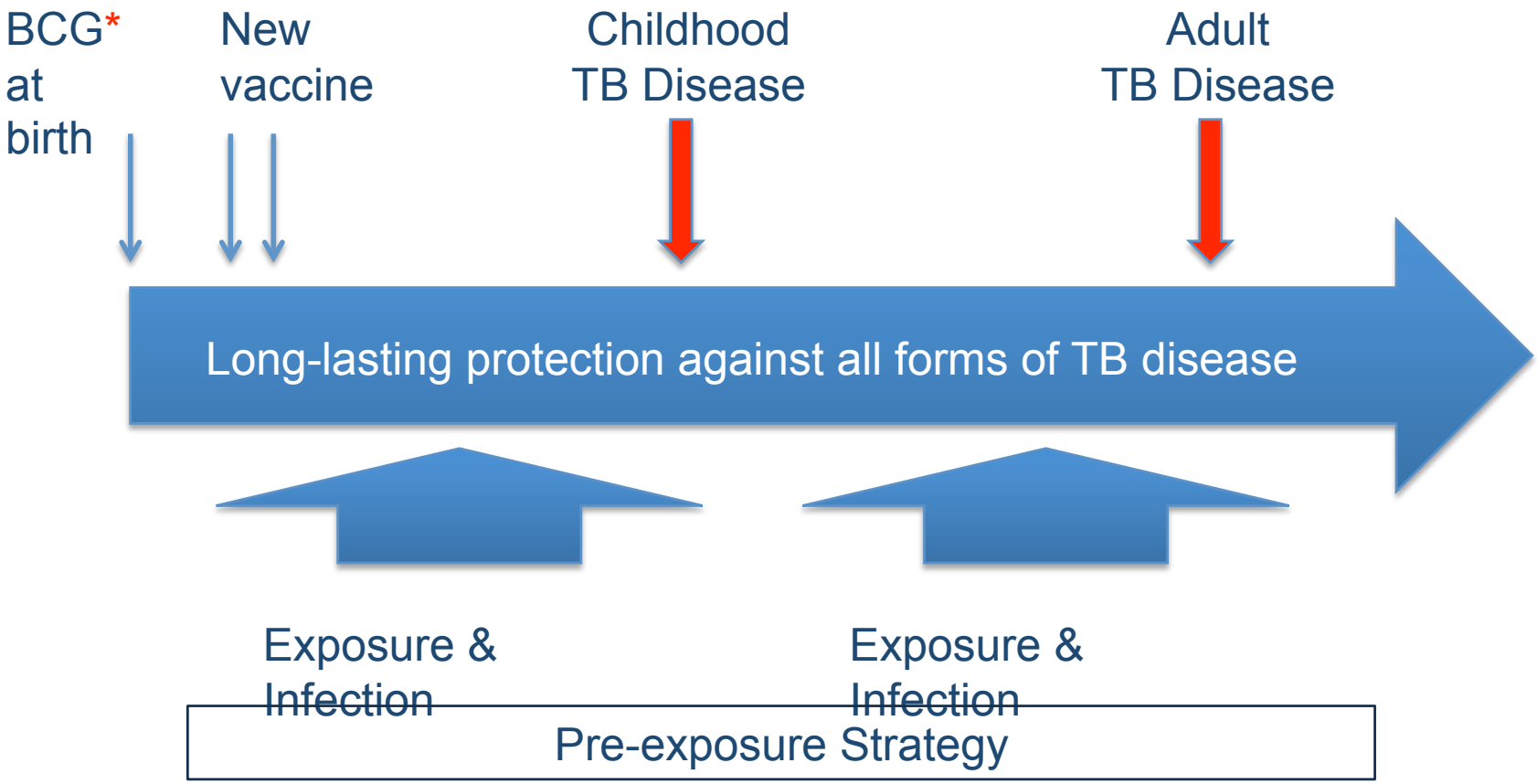
Design: Infant TB vaccination
Prime and boost strategy



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The first infant TB vaccine efficacy trial since BCG….

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

BBC NEWS HEALTH

Tuberculosis vaccine hopes dashed

CBS News: *Tuberculosis vaccine MVA85A fails to protect babies in new study*

SABC News: *Key tuberculosis vaccine fails, more waiting in the wings*

Deutsche Welle: *There is good news. And there is bad news.*

MVA85A did not offer additional protection against TB disease….

	Placebo (n=1395)	MVA85A (n=1399)	Vaccine efficacy
Endpoint 1 (primary efficacy endpoint)	39 (3%)	32 (2%)	17·3% (–31·9 to 48·2)
Endpoint 2 (exploratory efficacy endpoint)	52 (4%)	55 (4%)	–6·9% (–56·1 to 26·9)
Endpoint 3 (exploratory efficacy endpoint)	177 (13%)	196 (14%)	–12·1% (–37·4 to 8·5)

Data are n (%) or % (95% CI). Participants with more than one diagnosis were analysed in each level of diagnosis attained. Vaccine efficacy and corresponding 95% CI was estimated with the Cox regression model (1–estimated hazard ratio).

Table 2: **Primary and secondary efficacy endpoints**

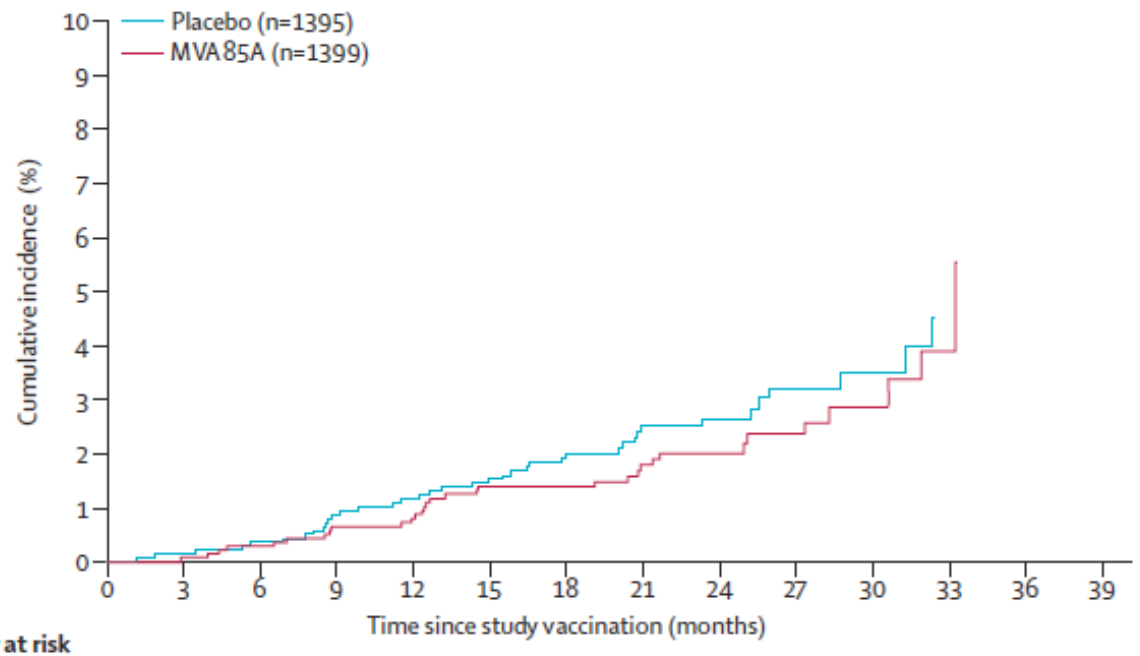

Figure 3: **Cumulative incidence of diagnosis of tuberculosis endpoint 1**

New TB vaccines induce T cells with distinct functional patterns

	MVA85A	A402	M72	H1	HyVac4	H56
Dominant CD4 T cell subset	**IFN-γ +IL-2+TNF+**	No dominance	IFN-γ +IL-2+TNF+; IFN-γ alone	IL-2+TNF+	IL-2+TNF+	IFN-γ +IL-2+TNF+; IL-2+TNF+
Th17	Co-expressed with Th1	None	IL-17 alone	Very few	Very few	Very few
CD8 T cells	None	Potent IFN-γ+TNF+	Some	None	None	None
	Viral vectored		Subunit + Th1 adjuvants			

Whole blood ICS assay
Hawkridge et al., 2008; Scriba et al., JID 2011;
Abel et al., AJRCCM 2010; Day et al., AJRCCM 2013

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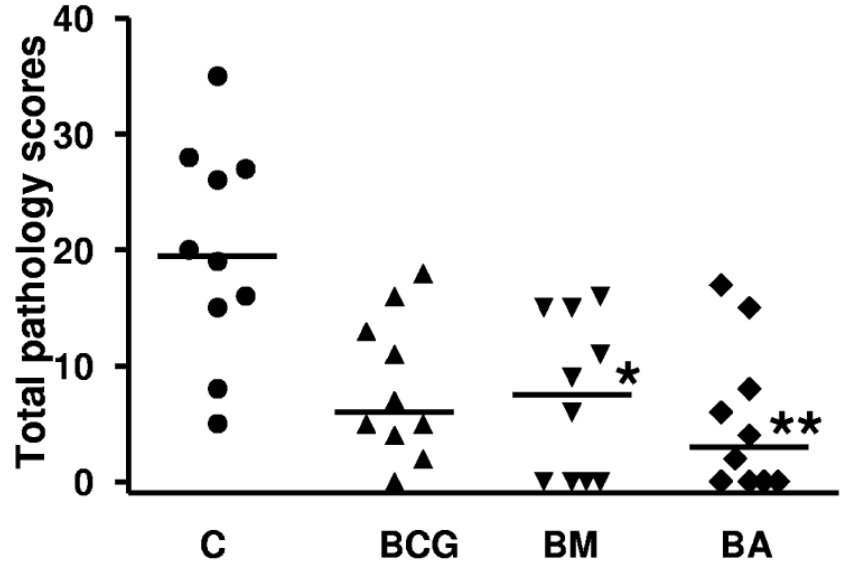
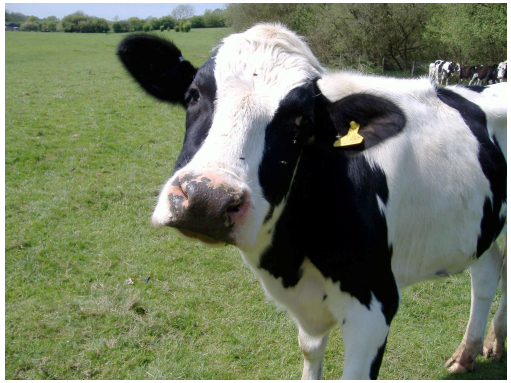
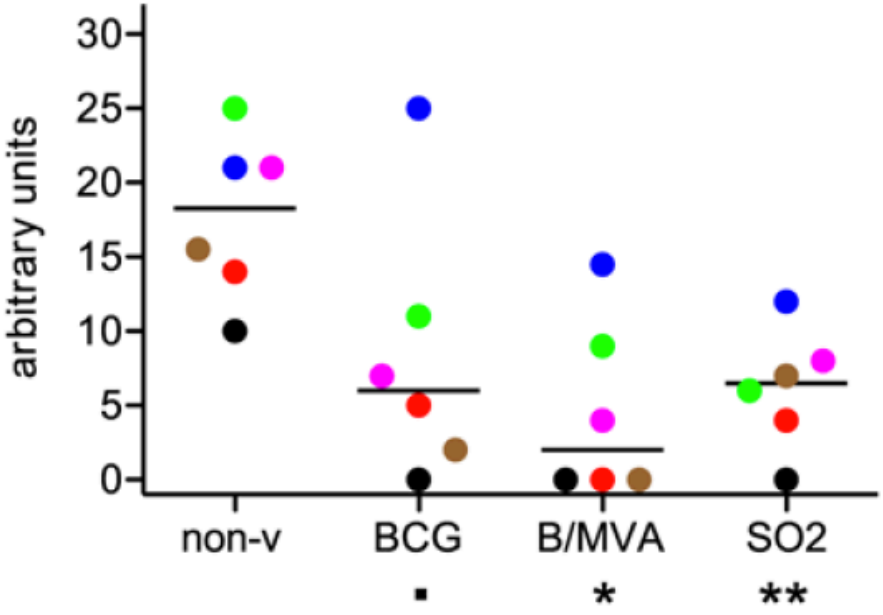
Preclinical development
Animal models of MVA85A



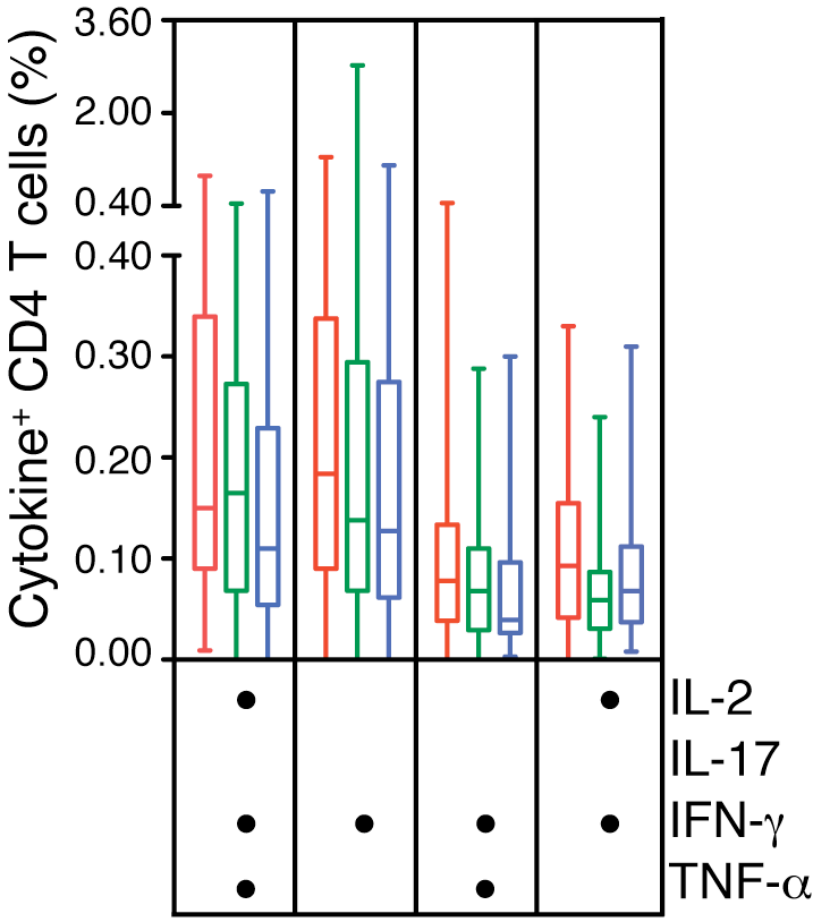


Vordermeier, et al. Infect. Immun. 2009;77:3364.



Verreck, et al. PlosOne 2009;4:e5264.

Classical Th1 cytokine responses after vaccination do not associate with risk of TB disease



From 5,724 enrolled infants:

- TB cases (n=29)
- Community controls (n=55)
- Household controls (n=55)

Many other T cell markers also investigated: none differed between cases and controls

Ben Kagina, many others!

*BCG given at birth. Infants followed for 2 years to assess protection; Whole blood incubation with BCG at 10 weeks of age for 12 hours.

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A major event for new tuberculosis vaccines

www.thelancet.com Published online February 4, 2013 http://dx.doi.org/10.1016/S0140-6736(13)60137-3

*Christopher Dye, Paul E M Fine
HIV/AIDS, Tuberculosis, Malaria and Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland (CD); and Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK (PEMF)
dyec@who.int

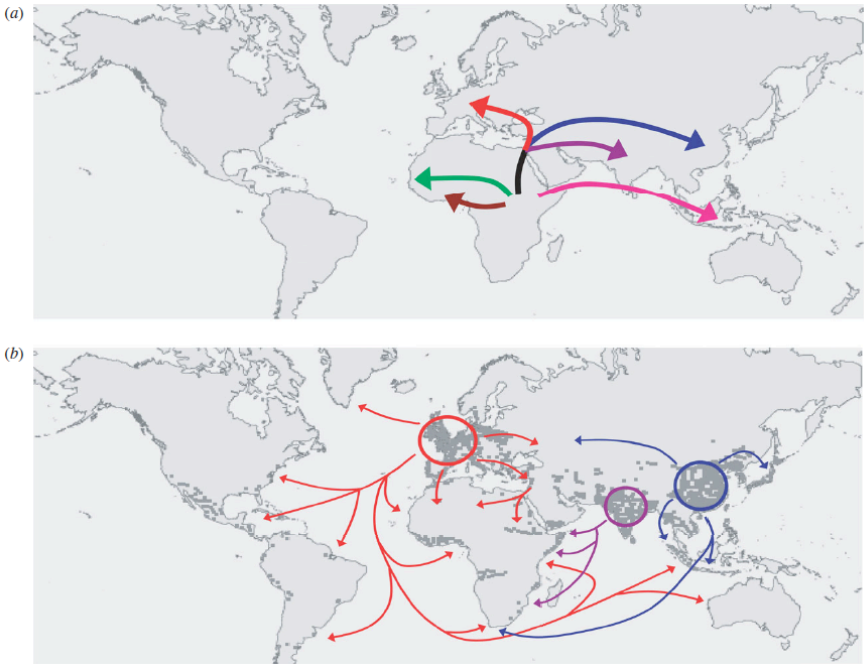
The Good News

Safety of MVA85A viral-vectored vaccine boost. No Koch phenomenon observed.

Questions still to be answered…

Efficacy independent of BCG prime?
Efficacy in different geographical populations?
Efficacy in adolescents/adults?
Efficacy in HIV infected people?
Efficacy against severe/disseminated TB?
Immune mechanism/correlates of risk?
Comparison with other candidate TB vaccines?

"Now is a key moment in tuberculosis vaccine research…..We need to go on playing the high-stakes game."



PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

Phil. Trans. R. Soc. B (2012) **367**, 850–859
doi:10.1098/rstb.2011.0316

Review

Host–pathogen coevolution in human tuberculosis

Sebastien Gagneux*

Department of Medical Parasitology and Infection Biology, Swiss Tropical and Public Health Institute and University of Basel, Socinstrasse 57, 4002 Basel, Switzerland

The spread of MTB lineages
Out-of-and-back-to- Africa

***Homo sapiens* and *Mycobacterium tuberculosis* have co-evolved**

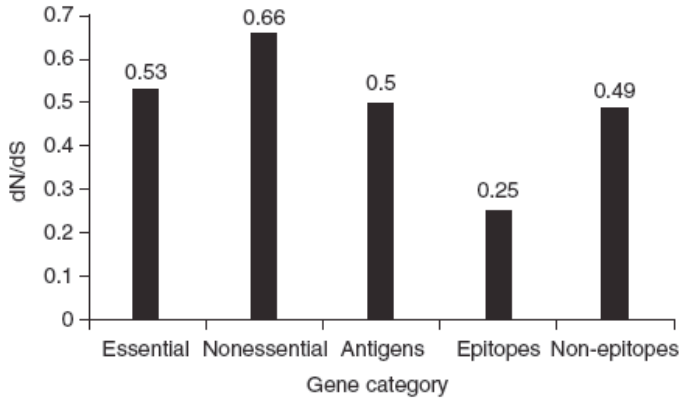
Expect variation in MTB genes encoding antigens – attempt to evade host immune system

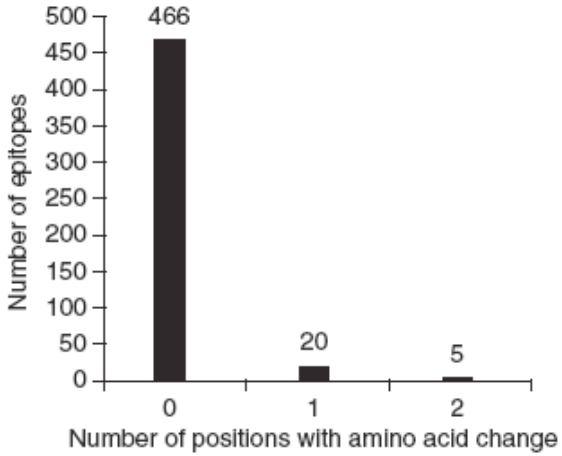
Since MTB interacts with humans through antigen-specific CD4+ or CD8+ T-cells

Expect T cell epitopes to be the most diverse genes in the MTB genome….

Human T cell epitopes of *Mycobacterium tuberculosis* are evolutionarily hyperconserved

Iñaki Comas[1], Jaidip Chakravartti[2], Peter M Small[3], James Galagan[4], Stefan Niemann[5], Kristin Kremer[6], Joel D Ernst[2] & Sebastien Gagneux[1,7,8]





T cell epitopes are highly conserved in the MTB genome

Suggests human T cell recognition offers some evolutionary benefit to the pathogen

Human T cell response

→ Establishment of latency → Subsequent cavitation

→ Transmission to later generations of susceptible hosts

Could vaccine-induced immunity against highly conserved T cell epitopes perversely increase TB transmission long-term?

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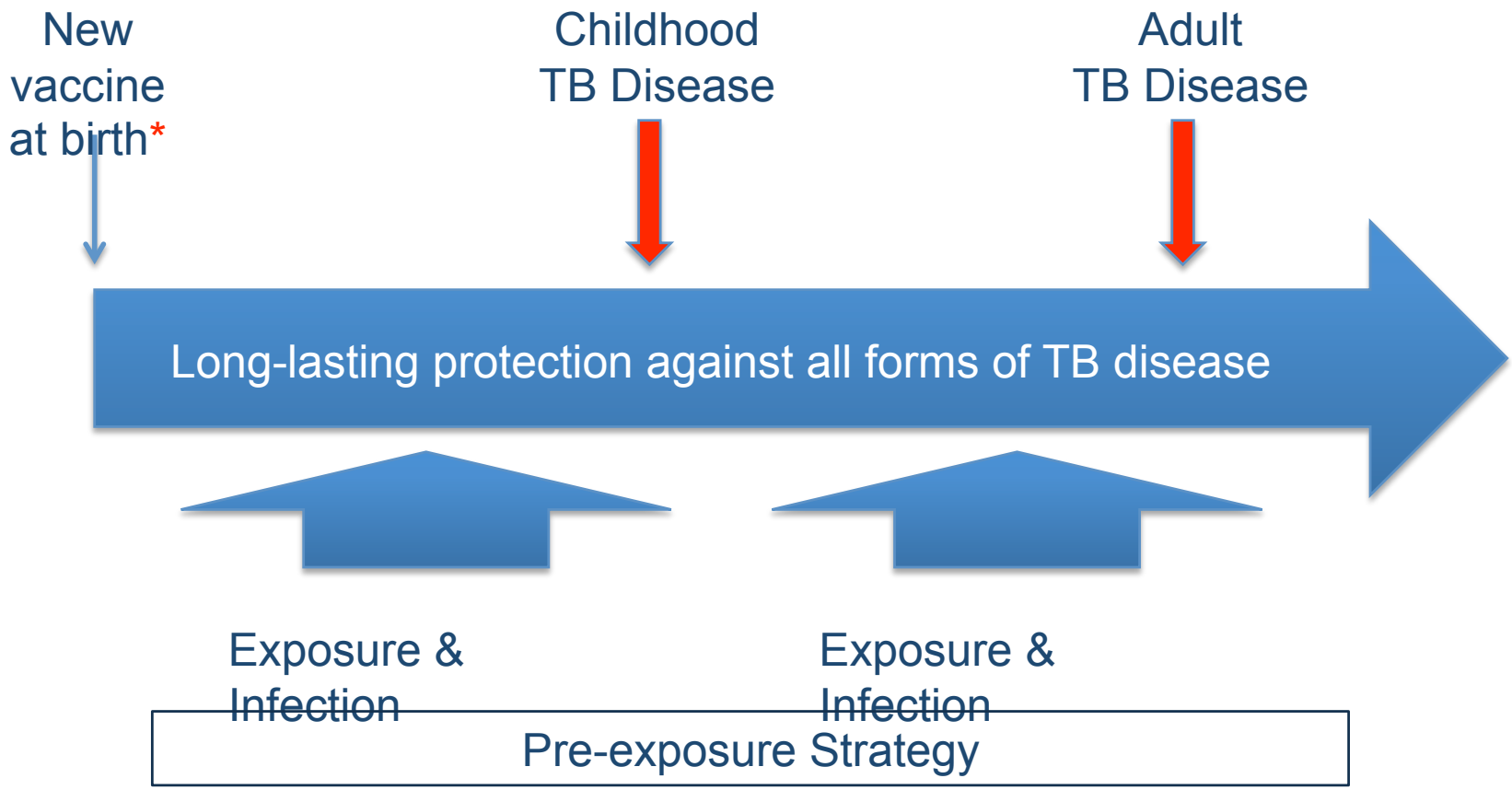
Design: Newborn TB vaccination
BCG replacement strategy “The Holy Grail”



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Contents lists available at SciVerse ScienceDirect

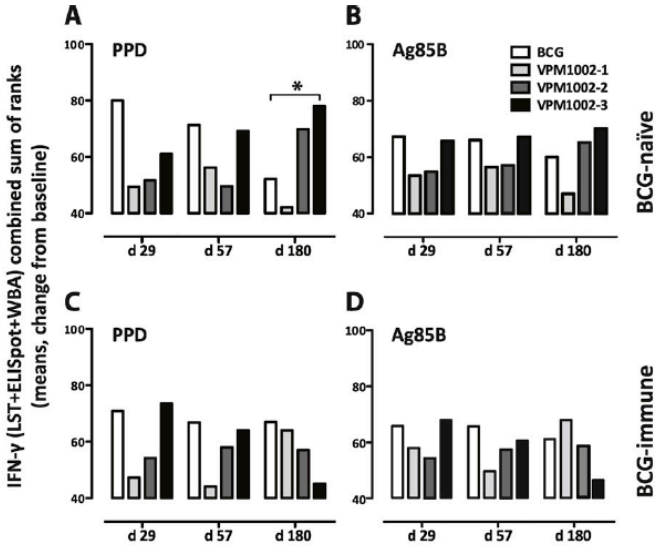
Vaccine

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

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



VPM-1002 = BCG ureC::hly

Recombinant BCG strain expressing listeriolysin, which perforates the phagosomal membrane

To provide optimal pH for biological activity of listeriolysin, the urease C gene was deleted

→ improved release of BCG-derived antigens into the cytosol and increased apoptosis of host cells

Safer than BCG in SCID mice

Safe and well-tolerated in adults

Produces B and T cell responses comparable to BCG

→ Phase II trials in infants

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Contents lists available at ScienceDirect

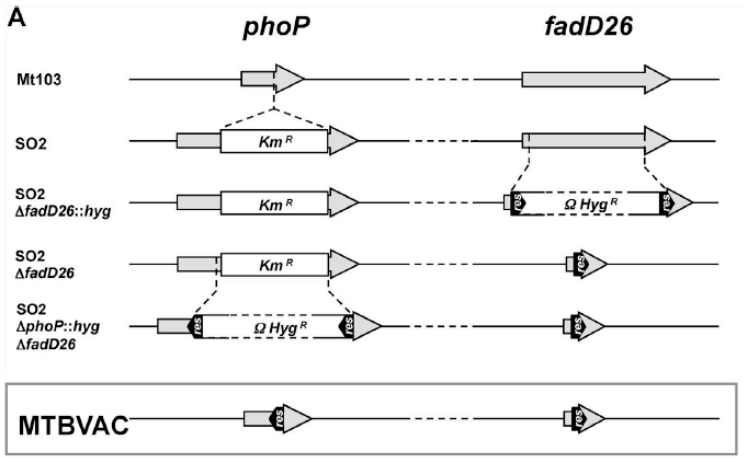
Vaccine

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

Construction, characterization and preclinical evaluation of MTBVAC, the first live-attenuated *M. tuberculosis*-based vaccine to enter clinical trials

Ainhoa Arbues[a,b,1], Juan I. Aguilo[a,b], Jesus Gonzalo-Asensio[a,b,c], Dessislava Marinova[a,b], Santiago Uranga[a,b], Eugenia Puentes[d], Conchita Fernandez[d], Alberto Parra[d], Pere Joan Cardona[b,e], Cristina Vilaplana[b,e], Vicente Ausina[b,f], Ann Williams[g], Simon Clark[g], Wladimir Malaga[h,i], Christophe Guilhot[h,i], Brigitte Gicquel[j], Carlos Martin[a,b,c,*]

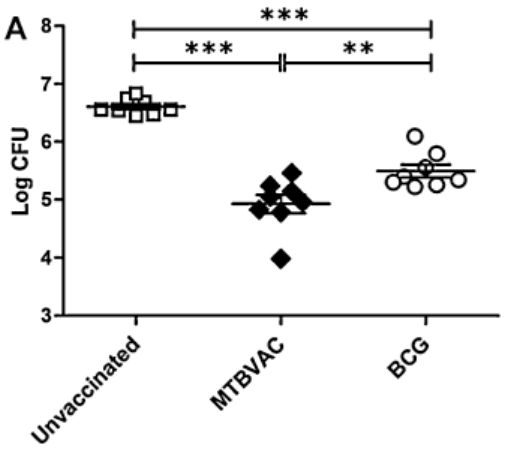
[a] Grupo de Genética de Micobacterias, Dpto. Microbiología, Medicina Preventiva y Salud Pública, Universidad de Zaragoza, C/ Domingo Miral s/n, 50009 Zaragoza, Spain



MTBVAC

M. tuberculosis clinical isolate with 2 independent gene deletions

phoP – transcription factor
fadD26 - essential for the synthesis of a virulence factor



Safety profile similar to BCG and confers superior protection in animals

Currently in first-in-human trial in Switzerland

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Historical infant BCG trials in the pre-chemotherapy era

Clinical course followed the natural history of disease over months or years

→ evaluation of classical features of late-stage TB as trial endpoints

TABLE 14 *B*

CASES OF TUBERCULOSIS IN THE CONTROL GROUP

Primary Disease		Outcome		Source Case and Diagnosis
Age	Diagnosis	Age	Diagnosis	
8 months	Right interlobar thickening	9 months	Postmortem—miliary tuberculosis; tuberculosis RML and hilar lymph node	Father F.A.
1 year	Right hilar infiltration and extension	2 years, 9 months	Postmortem—tuberculous meningitis; miliary tuberculosis; infiltration RLL and hilar lymph node	Mother M.A.
2 years	Right hilar node	2 years, 2 months	Postmortem—tuberculous meningitis; miliary tuberculosis; caseous tuberculosis RML and hilar lymph node	Father F.A.
11 months	Parenchymal infiltration	1 year, 5 months	Postmortem—tuberculous meningitis; caseous tuberculous lung, and hilar lymph node	Mother Min. Father F.A.
1 year, 2 months	Parenchymal infiltration RML, and hilar lymph node	13 years	Infiltration RML and calcification hilar lymph node	Mother M.A.
1 year, 10 months	Hilar node	10 years, 6 months	Calcification LUL and hilar lymph node	Father M.A.
1 year, 7 months	Parenchymal infiltration LUL	4 years, 8 months	Calcification left hilar lymph node	Mother M.A.
5 years, 8 months	Parenchymal infiltration LLL	14 years	Calcification LLL	Mother
1 year, 7 months	Hilar infiltration (right)	17–½ years 9 years, 4 months	Negative Calcification right hilar lymph node	Mother M.A.
2 years, 9 months	Hilar infiltration (right)	5 years	Receding infiltration right hilar lymph node	Father M.A. Mother F.A.
10 years, 10 months	Calcification LLL and hilar node	[illegible], 7 months	Calcification LLL and hilar lymph node	Mother M.A.

LLL—Left lower lobe
LUL—Left upper lobe
RML—Right middle lobe

MV—Many vesicles
FV—Few vesicles
VVes—Vesiculation with blebs

F.A.—Far advanced
M.A.—Moderately advanced
Min.—Minimal

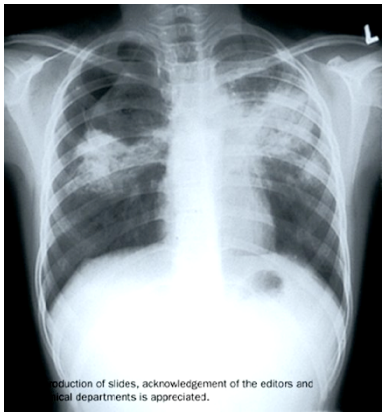
BCG VACCINATION IN TUBERCULOUS HOUSEHOLDS[1]

SOL ROY ROSENTHAL, ERHARD LOEWINSOHN, MARY L. GRAHAM,
DOROTHY LIVERIGHT, MARGARET G. THORNE,
AND VIOLET JOHNSON

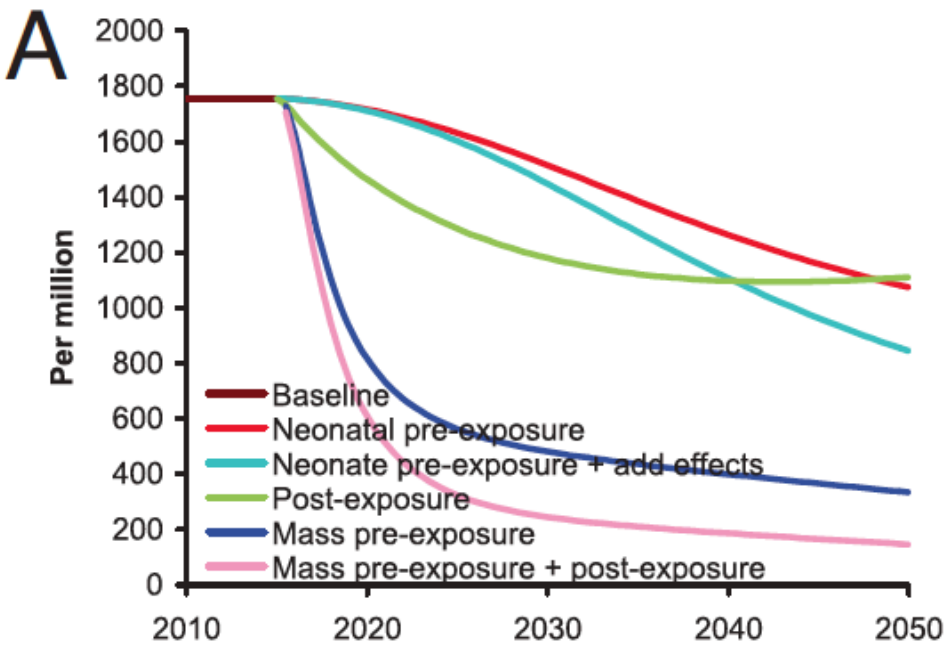
With statistical analysis by H. C. Batson

(Received for publication September 30, 1960)

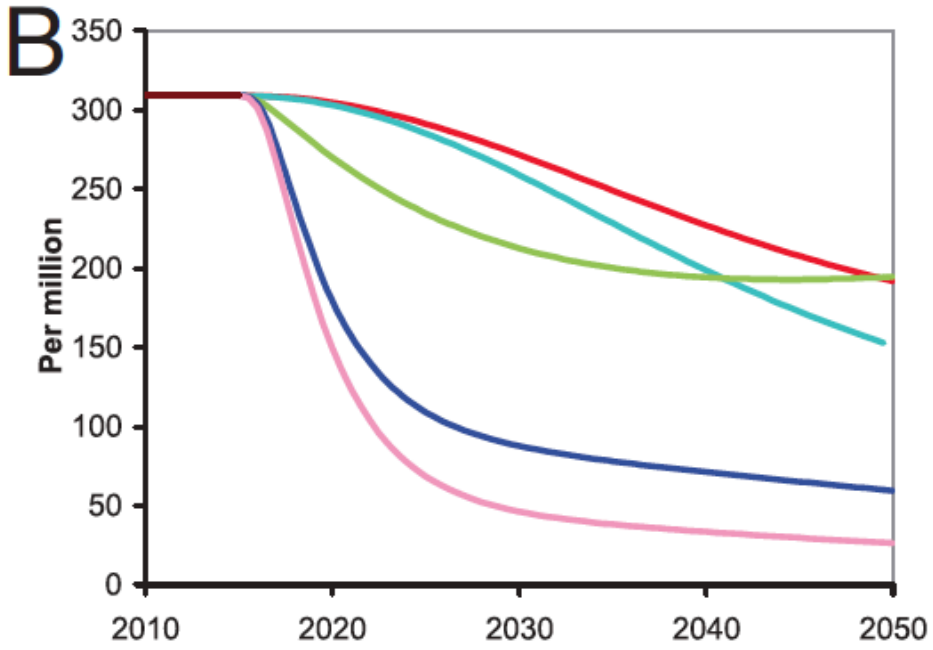
Mass vaccination of adults will be needed to control the epidemic



TB Disease



TB Deaths



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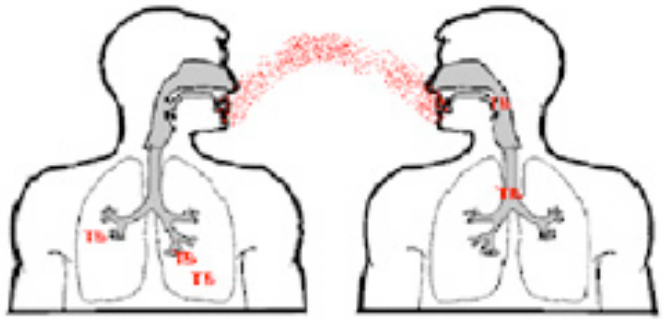
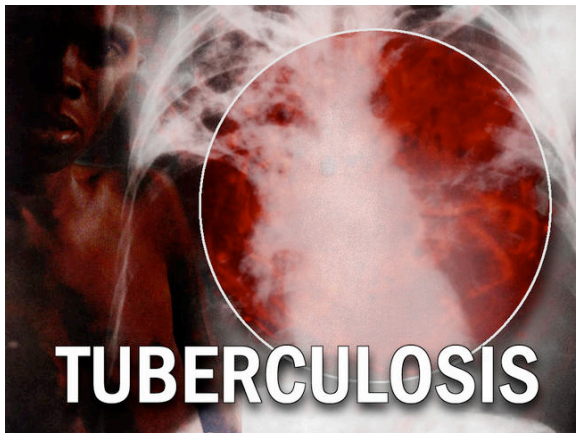
Abu-Haddad, et al. PNAS 2008; 106:13980.

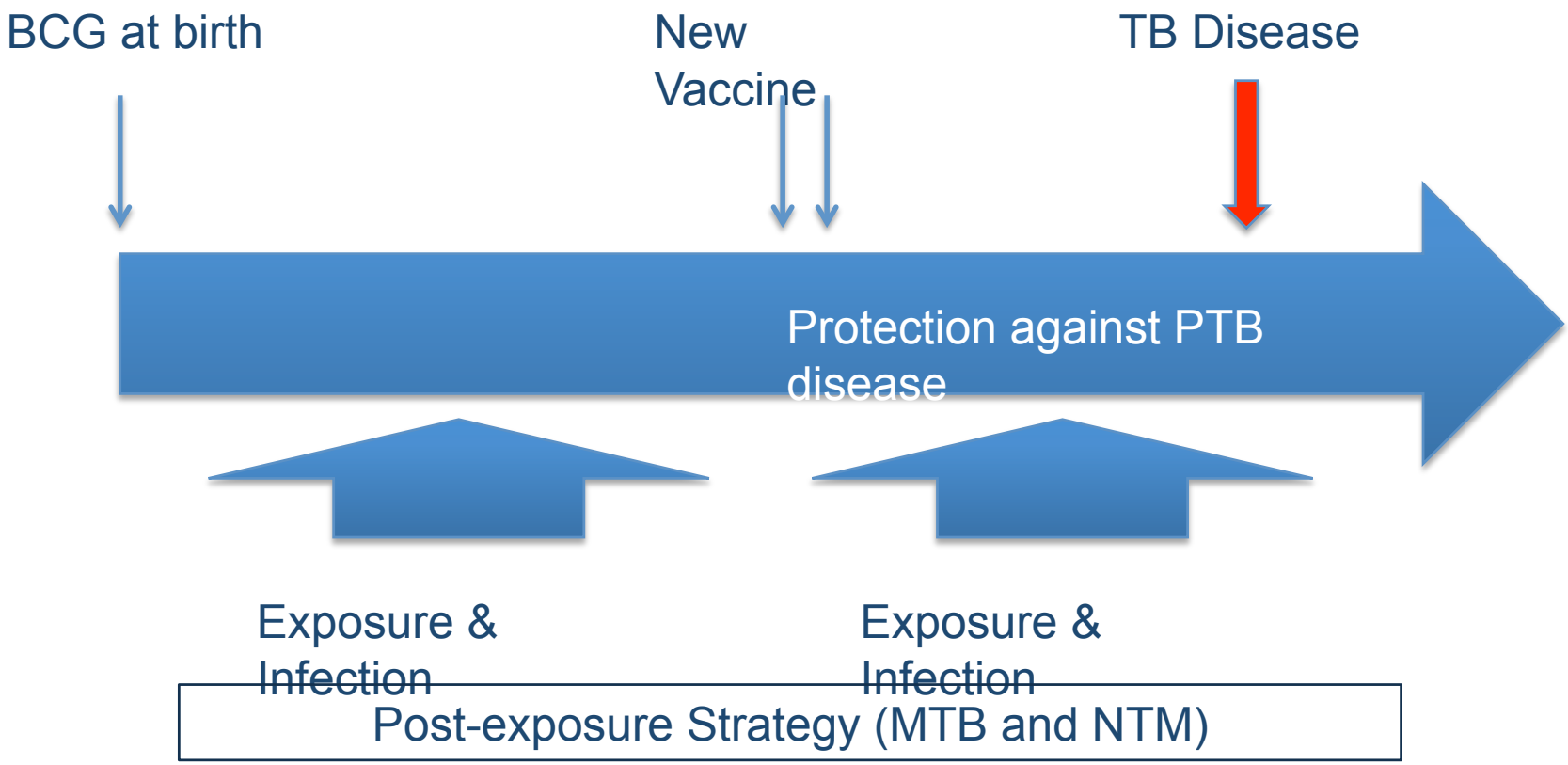
Interrupt of TB transmission

Prevent TB among young adults





Design considerations: Adult TB vaccination
Prime and boost strategy



Defined tuberculosis vaccine, Mtb72F/AS02A, evidence of protection in cynomolgus monkeys

Steven G. Reed[a,b,1], Rhea N. Coler[b], Wilifred Dalemans[c], Esterlina V. Tan[d], Eduardo C. DeLa Cruz[d], Randall J. Basaraba[e], Ian M. Orme[e], Yasir A. W. Skeiky[a,2], Mark R. Alderson[a,3], Karen D. Cowgill[b], Jean-Paul Prieels[c], Rodolfo M. Abalos[d], Marie-Claude Dubois[c], Joe Cohen[c], Pascal Mettens[c], and Yves Lobet[c]

[a]Corixa Corporation, Seattle, WA 98104; [b]The Infectious Disease Research Institute, 1124 Columbia Street, Suite 400, Seattle, WA 98104; [c]GlaxoSmithKline Biologicals, Rue de l'Institut 89, 1330 Rixensart, Belgium; [d]Leonard Wood Memorial Center for Leprosy Research, Cebu City 6000, Philippines; and [e]Mycobacteria Research Laboratories, Department of Microbiology, Immunology and Pathology, Colorado State University, Fort Collins, CO 80523

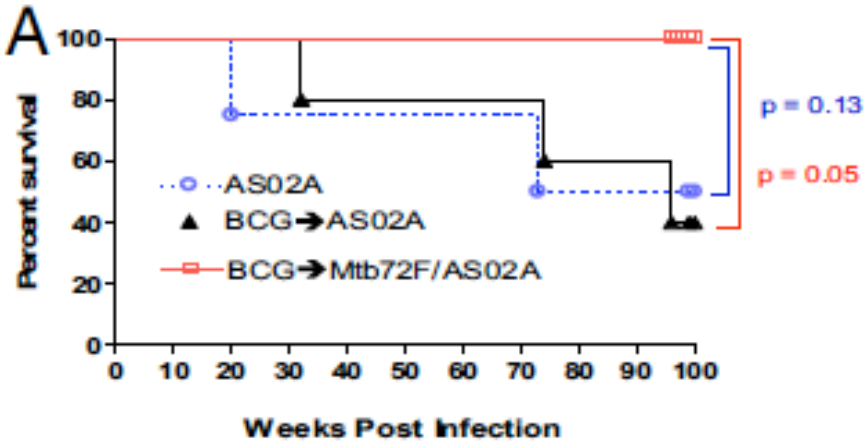
M72

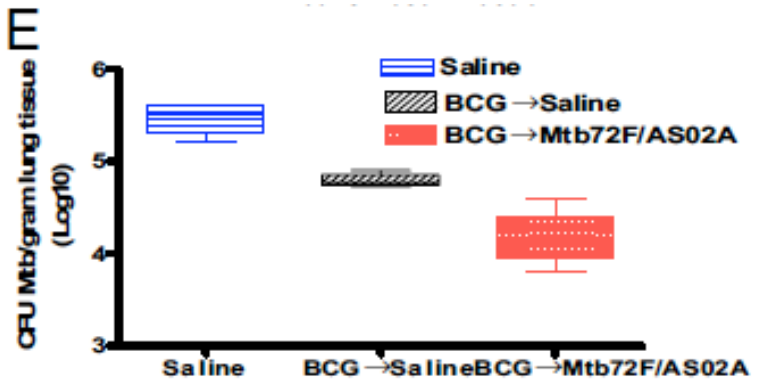
Protein subunit vaccine, derived from the MTB proteins Mtb32 and Mtb39, in GSK proprietary adjuvant AS02A

BCG prime → Mtb72F/AS02A boost: protection superior to BCG alone in non-human primate MTB challenge studies

Safe and immunogenic in humans

Large, multi-centre Phase IIb proof-of-concept efficacy trial…





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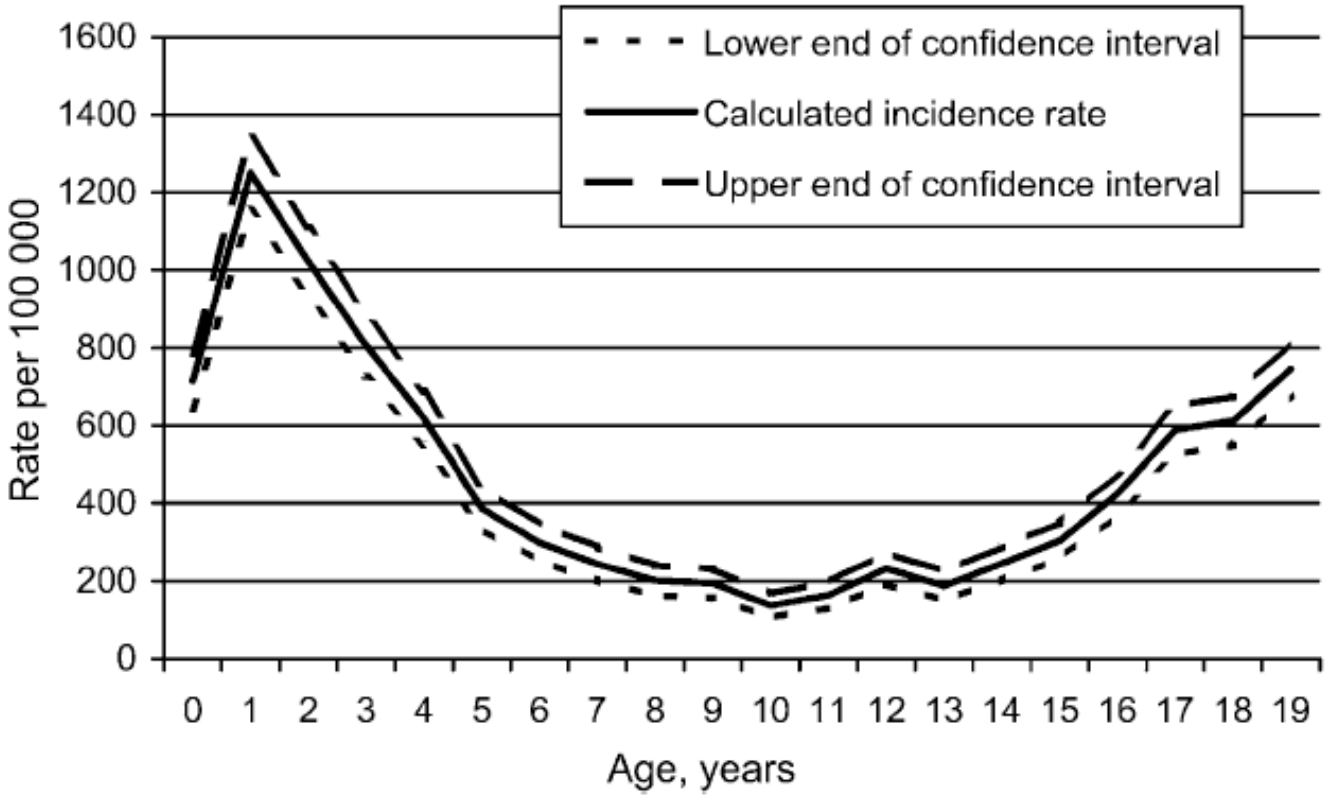
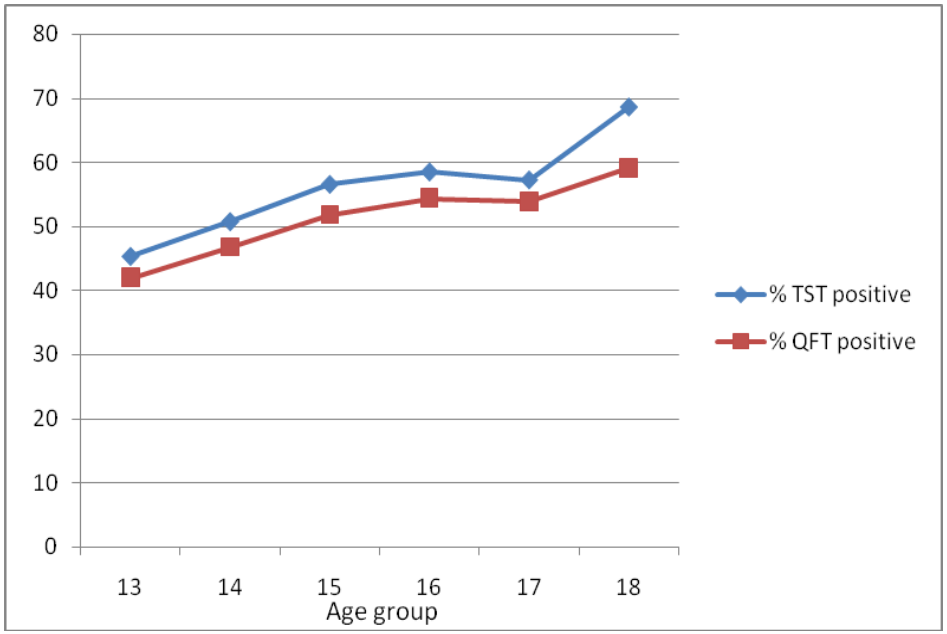


Figure 1 All tuberculosis incidence rate by age (years) in Cape Town, July 2002–June 2003 ($n = 5039$). Source: City Health Directorate of the City of Cape Town (notified TB cases) and Census 2001 (population estimates).

>60% of adolescents are TB infected before they leave High School



Worcester, Western Cape (SATVI)

Hassan Mahomed, many others. TST+ if >5mm.

QFT+ adolescents have 3-fold higher TB disease incidence than QFT-

(640 per 100,000 person years)
Mahomed et al, PLOS ONE 2011

Recent QFT+ converters have 8-fold higher TB disease incidence than persistent QFT- adolescents

(1,460 per 100,000 person years)
Machingaidze et al, AJRCCM 2012

Evaluate new TB vaccines for prevention of infection (and disease) in adolescents

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Identifying Predictors of Interferon-γ Release Assay Results in Pediatric Latent Tuberculosis: A Protective Role of Bacillus Calmette-Guérin?

A pTB-NET Collaborative Study

Robindra Basu Roy[1], Giovanni Sotgiu[2], Neus Altet-Gómez[3], Maria Tsolia[4], Ezia Ruga[5], Svetlana Velizarova[6], and Beate Kampmann[1]

[1]Department of Paediatric Allergy and Infectious Diseases, Imperial College London, London, United Kingdom; [2]Epidemiology and Biostatistics Unit, Department of Biomedical Sciences, University of Sassari, Sassari, Italy; [3]Unitat de Prevenció i Control de la Tuberculosi, Barcelona, Spain; [4]National and Kapodistrian Second Department of Paediatrics, P. and A. Kyriakou Children's Hospital, University of Athens School of Medicine, Athens, Greece; [5]Division of Pediatric Infectious Diseases, Department of Pediatrics, University Hospital, Padua, Italy; and [6]Bulgaria University Pediatric Clinic of Lung Diseases, Hospital St. Sofia, Medical University, Sofia, Bulgaria

What about BCG?

BCG Vaccine may protect against primary MTB infection (QFT conversion) in children

Might novel TB vaccines protect against primary MTB infection?

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PLoS one

The HyVac4 Subunit Vaccine Efficiently Boosts BCG-Primed Anti-Mycobacterial Protective Immunity

Rolf Billeskov*, Tara T. Elvang, Peter L. Andersen, Jes Dietrich*

Department of Infectious Disease Immunology, Statens Serum Institut, Copenhagen, Denmark

H4

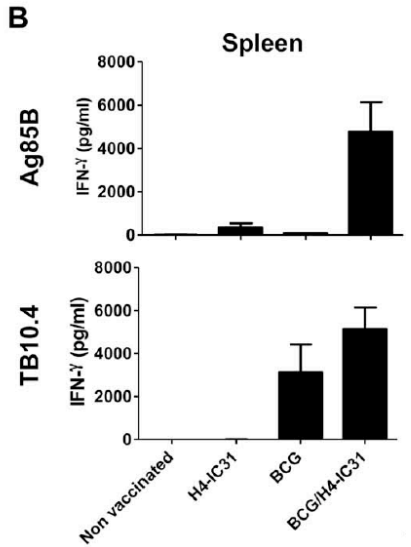
Fusion protein (antigens Ag85B and TB10.4), given in the adjuvant IC31

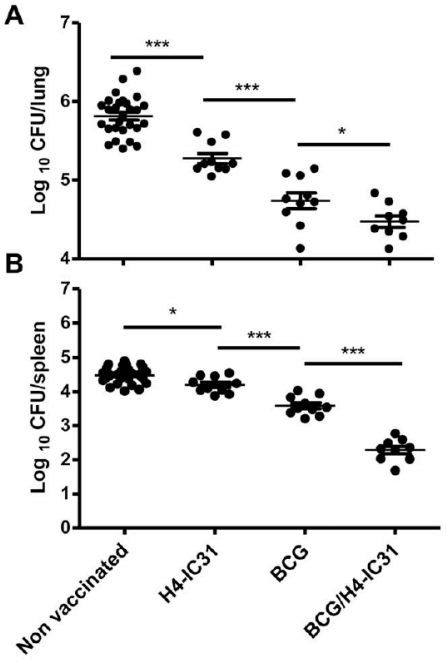
Mouse model

BCG prime with H4 boost → Increased protective anti-MTB immune response dominated by IFN-gamma/TNF-alpha/IL-2 producing CD4 T cells

Safe and immunogenic in QFT- and QFT+ adults

Entering adolescent prevention-of-infection trial…





satvi SOUTH AFRICAN TUBERCULOSIS VACCINE INITIATIVE
http://www.satvi.uct.ac.za

Vaccines to stop TB

IIDMM
INSTITUTE OF INFECTIOUS DISEASE AND MOLECULAR MEDICINE

Global TB Vaccine Pipeline*

TB Vaccine Types

Viral-vectored: MVA85A, AERAS-402, Ad35Ag85A, Ad5Ag85A
Protein/adjuvant: M72, Hybrid-1, Hyvac 4, H56, ID93
rBCG: VPM 1002
Killed WC or Extract: Mw, RUTI

*Adapted to highlight vaccine candidates evaluated at the SATVI site

Stop TB Partnership
Working Group on New TB Vaccines

Take Home Messages

Many new TB vaccine candidates in pre-clinical and clinical development
Animal models problematic in guiding up-selection for clinical development

Children bear the greatest burden of morbidity
Prevention of TB in adults critical to interrupt transmission
Proof-of-concept trials in humans may green light expansion to large Phase III trials

2021 will be the 100th anniversary of BCG vaccine….

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