



DEVELOPING ^{NEW}
TUBERCULOSIS VACCINES
FOR THE WORLD



Partnering to Support Research Capacity in TB Endemic Countries

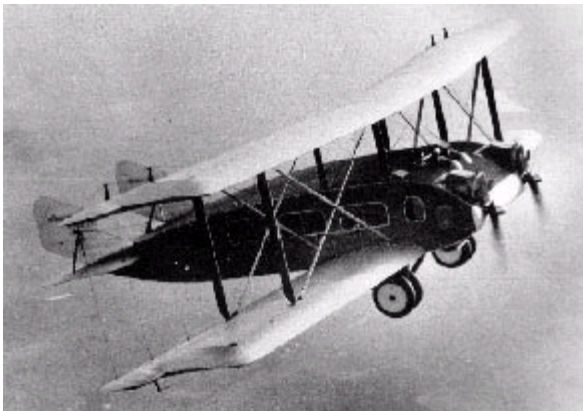
Dr. Tony Hawkrige
Aeras Global TB Vaccine Foundation, Africa Office

Fifth EDCTP Forum
13 October 2009
Arusha, Tanzania

Invention of BCG Vaccine

By Calmette & Guérin
1908-1921

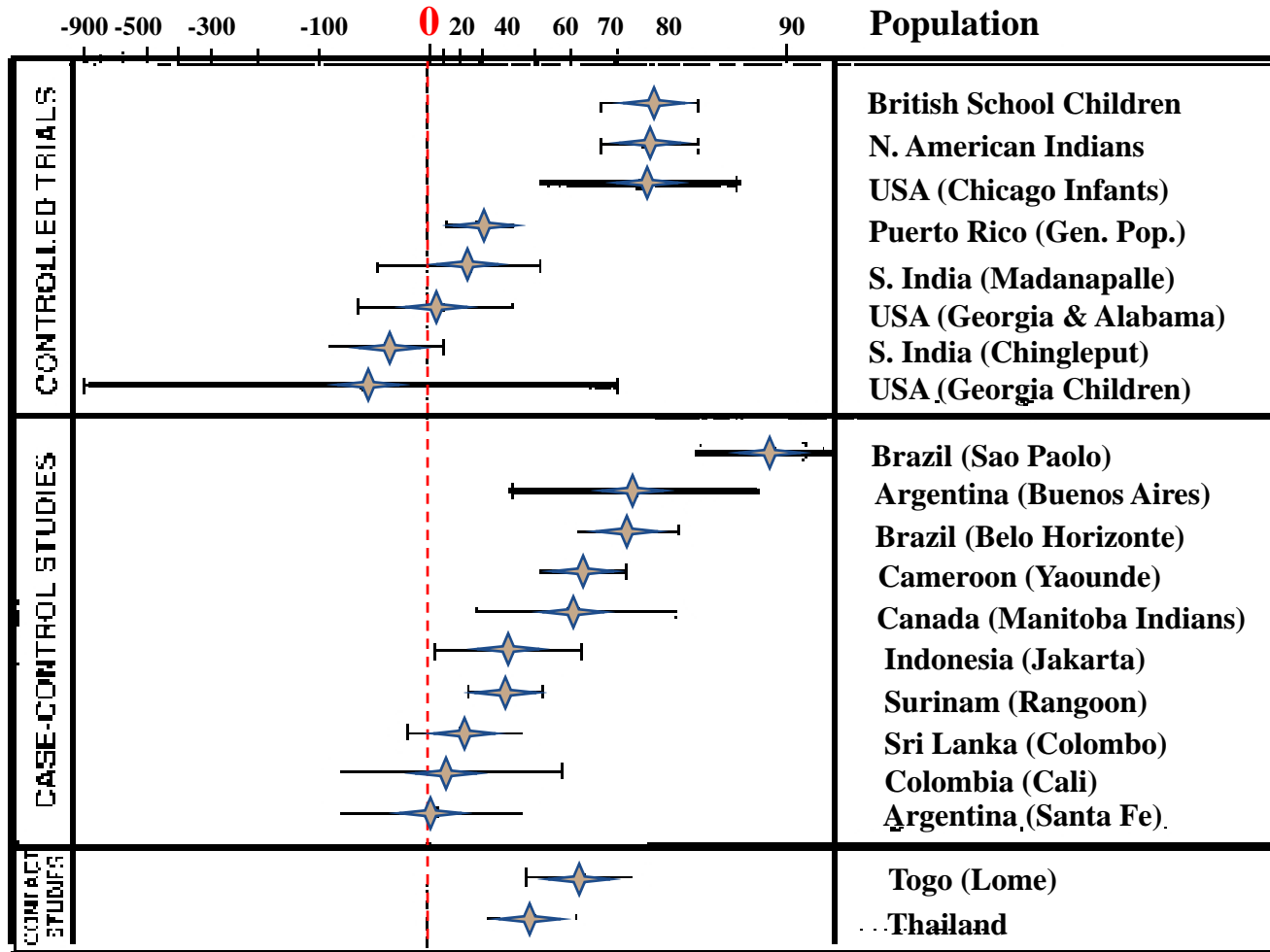
No new TB Vaccine
in almost 90 years





Variable Efficacy of BCG vs. Pulmonary TB

Vaccine Efficacy (%)



We are seeking a vaccine which will ...

- Contribute to eliminating TB as a public health threat, in line with global targets (<1 case /million)
- Be safe and effective in preventing TB in children, adolescents and adults, including persons living with HIV
- Protect against all forms of TB – including MDR and XDR
- Help to reduce the cost and burden of TB on patients, health care systems and national economies



Aeras Global TB Vaccine Foundation

Mission

To develop new, more effective TB vaccines and ensure their availability to all who need them

Goals

- A more effective, safe and affordable TB vaccine by 2016
- Identify correlates and surrogate markers of vaccine induced protection
- Develop second generation TB vaccines with increased potency and broader protection



Aeras Global Vaccine Development Partners

Foundations/ Governments/ NGOs

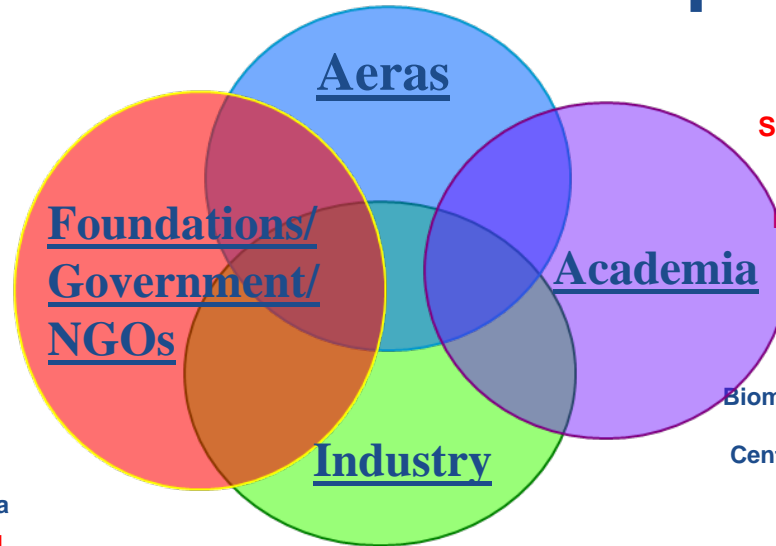
Bill & Melinda Gates Foundation, U.S.
 Ministry of Foreign Affairs of Denmark
 The Netherlands Ministry of Foreign Affairs, the Netherlands
 Fogarty International Center and NIAID, National Institutes of Health, U.S.
 Research Council of Norway, Norway
 Maryland Department of Business and Economic Development, United States
 AIDS Fondet, Denmark
 Cambodian Health Committee, Cambodia

European and Developing Countries Clinical Trials Partnership (EDCTP), European Commission

LHL/ The Norwegian Association of Heart and Lung Patients, Norway
 Planeta Salud, Spain

Manhiça Health Research Centre, Mozambique

Medicine in Need (MEND), U.S.
 Stop TB Partnership, Switzerland
 TB-Alert, United Kingdom
 Wellcome Trust, United Kingdom



Aeras

Foundations/ Government/ NGOs

Academia

Industry

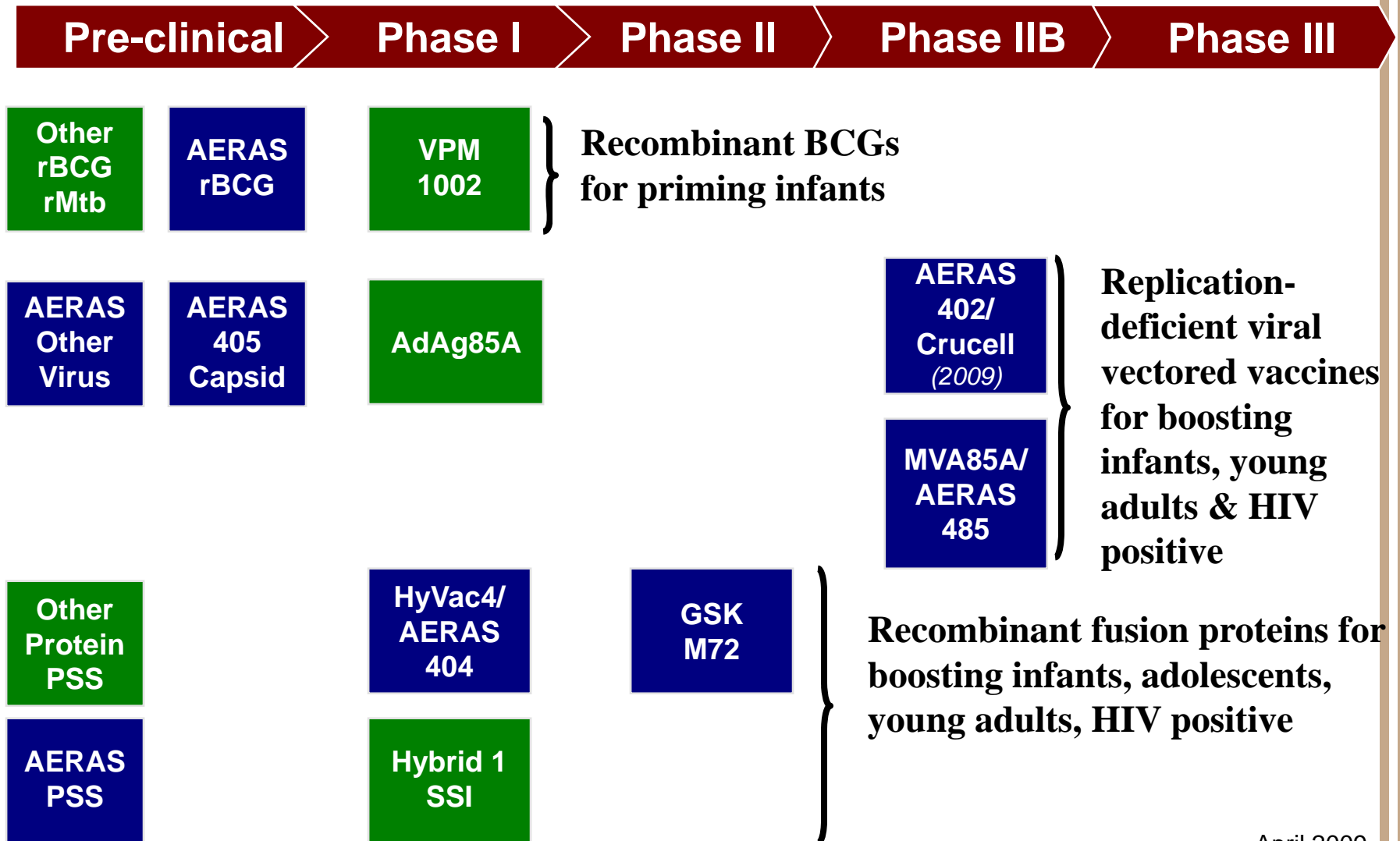
Industry

GlaxoSmithKline Biologicals, Belgium
 Crucell, the Netherlands
 Statens Serum Institute, Denmark
 ImmunoBiology, United Kingdom
 Wuhan Institute of Biological Products, China
 Serum Institute, India
 Thymed, Germany
 Japan BCG Laboratory, Japan
 Korean Institute of TB, Korea
 Cyncron, Denmark
 Immune Solutions, New Zealand
 Sanofi Pasteur, France
 Smittskyddsinstytutet, Sweden
 Emergent BioSolutions, U.S.
 Intercell, Austria
 Bioland, Korea

Academia

Oxford University, United Kingdom
South African TB Vaccine Initiative (SATVI)
 St. Johns Research Institute, India
Makerere University, Uganda
Kenya Medical Research Institute, Kenya
 Karolinska Institute, Sweden
 Wuhan University, China
 Albert Einstein College of Medicine, U.S.
 Arizona State University, U.S.
Aurum Institute, South Africa
 Biomedical Primate Research Center, the Netherlands
 Case Western Reserve University, U.S.
 Centre for International Health, University of Bergen, Norway
 Colorado State University, U.S.
 Emory University, U.S.
 Food and Drug Administration, U.S.
 Foundation for Innovative New Diagnostics (FIND), Switzerland
 Harvard University, U.S.
 International AIDS Vaccine Initiative (IAVI), U.S.
 Johns Hopkins University, U.S.
 KNCV Tuberculosis Foundation, the Netherlands
 Leiden University Medical Center, the Netherlands
 Life Science Research Israel (LSRI), Israel
 Max Planck Institute for Infection Biology, Germany
 National Cancer Institute (NKI), the Netherlands
 Oregon Health Sciences University, U.S.
 Stanford University, U.S.
 Saint Louis University., U.S.
 Tuberculosis Vaccine Initiative (TBVI), Europe
 University of California-San Francisco, U.S.
 University of California-Los Angeles, U.S.
 University of Maryland, College Park, U.S.
 University of Tampere, Finland
 University of Wales, United Kingdom
 Vanderbilt University., U.S.
 Walter Reed Army Institute of Research, U.S.

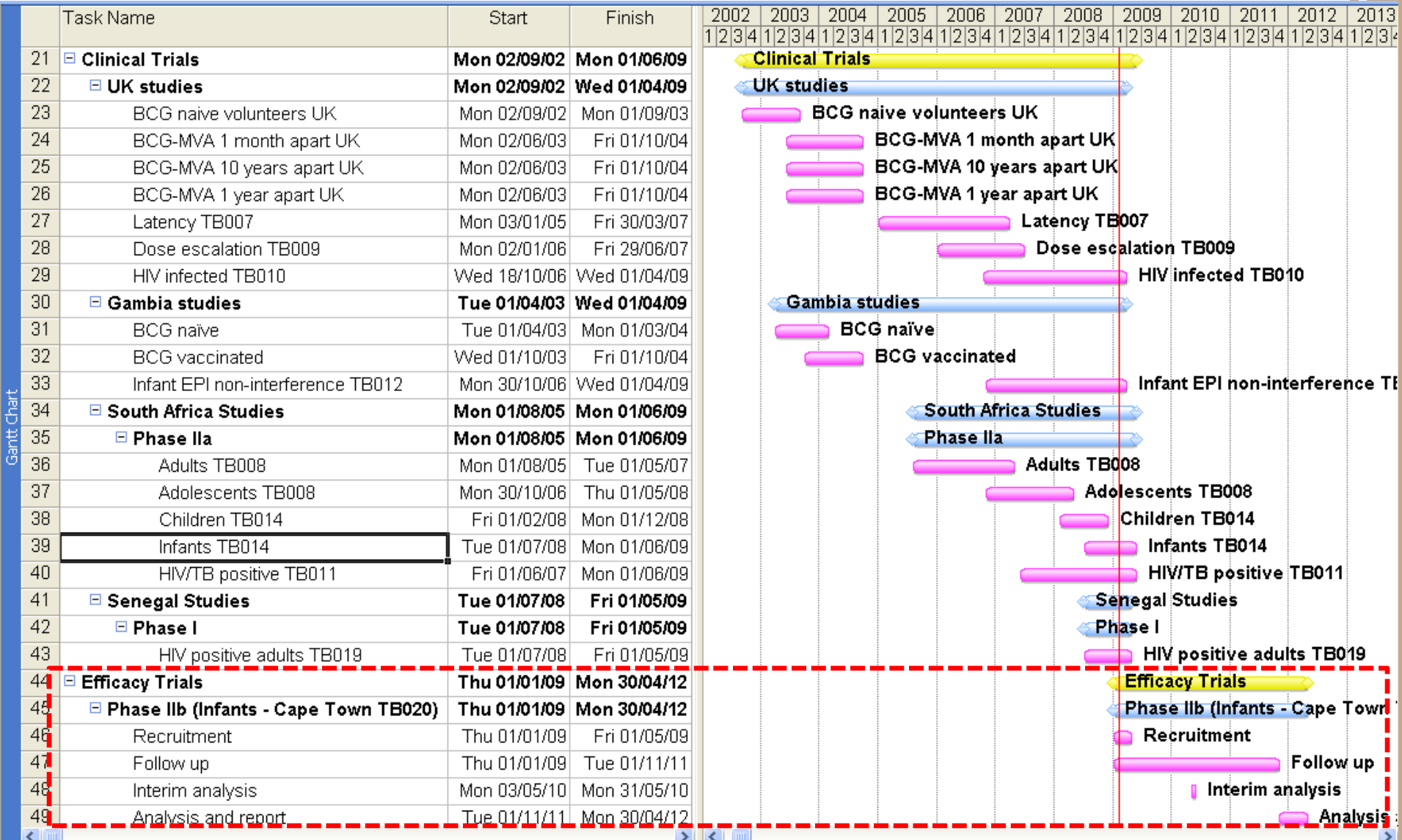
Current TB Vaccine Pipeline





Summary of clinical trials with MVA85A and MVA85A/AERAS485 since 2002

Slide Courtesy of Dr Helen McShane, Oxford University



AERAS-402 / Crucell Ad35 Studies

Trial	Phase	2005	2006	2007	2008	2009	2010	2011	2012	
001	1		Yellow	Yellow	Yellow					AFRICA
003	1		Blue	Blue	Blue	Blue				OTHER
004	1			Yellow	Yellow	Yellow	Yellow			
008	1			Yellow	Yellow	Yellow				
009	1			Yellow	Yellow	Yellow				
010	2			Blue	Blue	Blue	Blue			
012	2				Blue	Blue	Blue			
017	2B					Blue	Blue	Blue		
018	2				Blue	Blue	Blue			
021	1				Yellow	Yellow	Yellow	Yellow		
022	1				Yellow	Yellow				
029	2B					Blue	Blue	Blue	Blue	

Trial	Phase	Populat'n	N	TB	BCG	QFT	HIV	Country	Notes
001	1	Adults	32	Neg	Neg	Neg	Neg	US	Safety in healthy adults
003	1	Adults	40	Neg	Pos	Neg	Neg	SA	Safety in healthy adults
004	1	Adults	12	Neg	Pos	Neg	Neg	India	Safety in healthy adults
008	1	Adults		Neg	Pos	Neg	Neg	US	Prime Boost
009	1	Adults		Neg	Pos	Neg	Neg	US	Prime Boost
010	2	Adults	116	Pos	Pos	Pos	Neg	SA	Safety in TB diseased
012	2	Adults	20	Neg	Pos	Pos/Neg	Neg	Kenya	Safety in TB infected
017	2B	Adults	1000	Neg	Pos	Pos/Neg	Pos	SA	Safety and efficacy in HIV infected
018	2	Infants	54	Neg	Pos	Neg	Neg	SA	Safety in infants
021	1	Adults	13	Neg	Neg	Neg	Neg	US	Apheresis
022	1	Adults	24	Neg	Neg	Neg	Neg	US	High dose
029	2B	Infants	1600	Neg	Pos	Neg	Neg	4 African countries	Safety and efficacy in infants



Mtb72f / M72

Courtesy of Opokua Ofori-Anyinam, GSK, Rixensart

Vaccine	Participants	Safety	Immunogenicity
Mtb72f/ ASO2A	Animals	Demonstrated	Demonstrated
	PPD- adults USA/Belgium; PPD+ adults Switzerland	Acceptable reactogenicity	High; poly functional CD4
M72/ ASO1	PPD- adults Belgium	Comparable to Mtb 72f/ ASO2 and M72/ASO2	High M72-specific polyfunctional response AND persistent (2 years) CD4+ T cell response, statistically higher than either M72/ASO2 or Mtb72F/ASO2
M72/ ASO1 _E	BCG+ Filipino Dose ranging		M72/ASO1 _E (10ug antigen concentration) selected as lead candidate vaccine
	PPD negative and positive South African Adults	Well tolerated	Immunogenic, inducing M72-specific polyfunctional CD4+ and CD8+ T cell responses
	Healthy HIV positive Swiss adults on HAART	Well tolerated	Immunogenic, inducing M72-specific polyfunctional CD4+ T cell responses

HyVac 4 / AERAS-404 Studies

Trial	Phase	2005	2006	2007	2008	2009	2010	2011	2012	
005	1								AFRICA	
006	1								OTHER	
011	1									
025	2									
024	2									

Trial	Phase	Popul'n	N	TB	BCG	QFT	HIV	Country	Notes
005	1	Adults	64	Neg	Neg	Neg	Neg	Sweden	Adjuvant dose escalation
006	1	Adults	60	Neg	Neg	Neg	Neg	Finland	Dose escalation
011	1	Adults	40	Neg	Pos	Neg	Neg	SA	Safety
025	2	Adults	24	Neg	Pos	Pos	Neg	EU	Safety
024	2	Adults	25	Neg	Pos	Pos/Neg	Neg	SA	Safety

Summary so far ...

- Good progress made with several new booster vaccines and promise of new priming vaccines
- One Phase IIB trial already started, 2 more will start within 6 months
- A Phase III trial should start by 2012
- Required numbers will need multiple trial sites across Africa and elsewhere.
- **Do we have enough sites? Are they ready?
What are we doing about it?**

Challenges to Site Development

Sites in areas with very high rates of TB may lack capacity in areas of:

- Execution of protocols according to Good Clinical Practice (GCP)
- Performance of clinical procedures for TB diagnosis
- *M tuberculosis* culture and speciation
- Collection and storage/transport of blood specimens for immunogenicity assays, performance of assays themselves.



Palamaner, India site before development



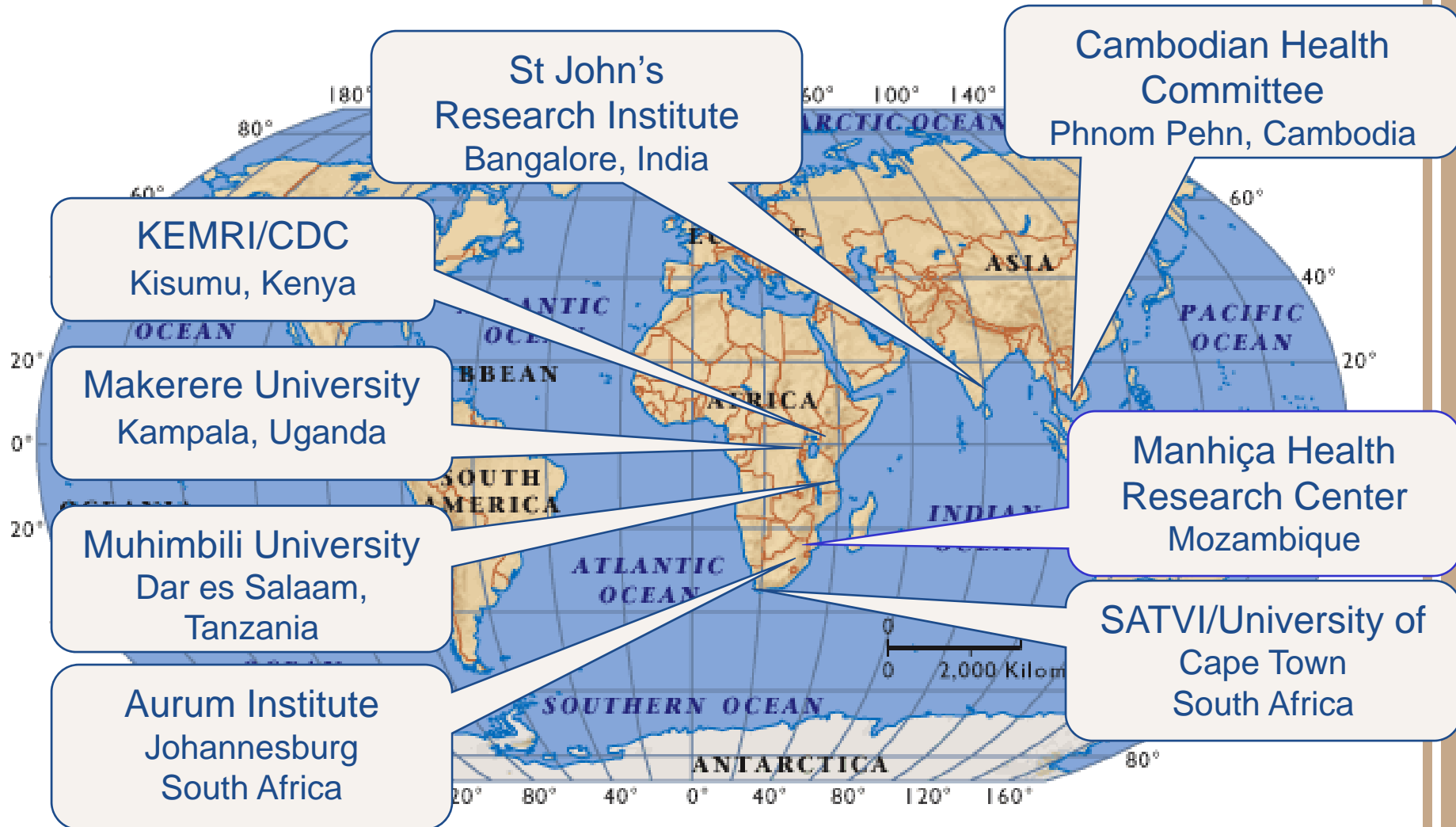
Lab at Palamaner, India site after development

TB Vaccine Site Development Activities

- TB diagnosis laboratory set-up and maintenance
- Epidemiology cohort studies
- Establishment of a Professional Development Program
- Implementation and maintenance of Quality Management Systems
- Data management infrastructure set-up or augmentation
- Clinical trials of vaccine candidates

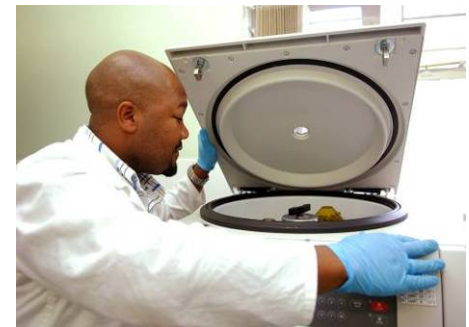


Existing Aeras Partnerships with Clinical Trial Sites



Example of Site Development: South Africa

- Partnership with South African Tuberculosis Vaccine Initiative (SATVI)
- Field site developed in Worcester (~120 km from Cape Town)
- Infrastructure developed:
 - State-of-the-art immunology laboratory
 - Highly skilled staff capable of performing the duties necessary to maintain the infrastructure and execute clinical research
 - Clinical and office facilities
 - Professional Development Program (Siyantinga- “Reach for the Stars”) – program initiated in 2001
 - Resource Center established in 2005



Accomplishments in South Africa

- BCG randomized clinical trial involving 11,680 infants
- Cohort studies involving more than 11,500 infants and adolescents
- Conducting Phase I and Phase II studies of 4 vaccine candidates
- Initiating Phase IIb trial of a new TB vaccine
- 231 staff trained since 2004
- Establishment of a Quality Management System and data capture mechanism
- Most advanced site for large-scale TB vaccine trials in the world



Capacity Building at Other Partner Sites

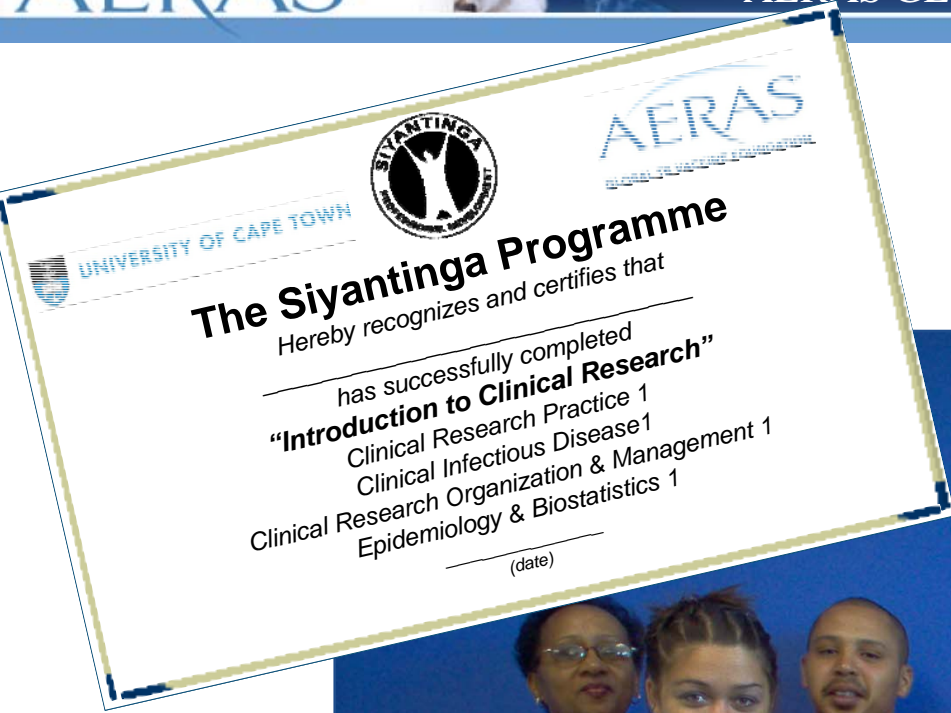
- State-of-the-art immunology and mycobacteriology laboratory established at **India** site, first of the kind in the area for TB diagnosis
- BSL2+ lab commissioned in **Uganda**, lab capacity being developed in **Kenya**
- Professional Development Programs established in **Kenya**, **Uganda** and **India**
- Epidemiological cohort studies initiated in **Kenya** and **Uganda**
- **Kenya**, **Uganda**, **South Africa** and **Mozambique** to participate in planned multicountry Phase II trial



Professional Development Program

A collaborative initiative to develop a model program that builds and sustains capacity of the clinical research staff.





Promoting South-South Collaboration

- **TBVACSIN** (Tuberculosis Vaccine Trial Sites Network) is a network of partners from Africa and Asia currently involved in or intending to be involved in TB vaccine trials.
 - Share experiences between sites related to TB vaccine trial site development
 - Strengthen TB vaccine trial capacity in African and other countries
 - Network includes sites in South Africa, Kenya, Uganda, Mozambique, Tanzania, India, Cambodia and others.
- Coordinated and led by trial sites in Africa. Northern organizations such as Aeras, KNKV Tuberculosis Foundation and KI are members.

Summary: How is Aeras partnering to support research capacity in TB endemic countries?

1. By proposing to sponsor **clinical trials** of TB vaccines there
2. By allocating **resources** to site development in order to assist local investigators to:
 1. **Train** their **teams** in GCP, GLP and other necessary clinical research competencies
 2. **Build or upgrade** TB and immunology laboratories, clinical diagnostic facilities, pharmacies
3. By providing **support** to research units to develop their own teams in areas of e.g. data management, statistical analysis, quality assurance / management, grant writing, publication of results, clinical project management.
4. By supporting research units in TB endemic countries in their efforts to **collaborate** with each other (e.g. TBVACSIN)

*Aeras gratefully acknowledges the support of
the following major donors*

**BILL & MELINDA
GATES foundation**




**Buitenlandse
Zaken**

Netherlands Ministry of Foreign Affairs



Ministry of Foreign Affairs of Denmark





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Back up slides

Current and planned TB Vaccine Efficacy / Proof of concept Trials

- **MVA85A/AERAS-485 – C-020-485**
 - 2,800 **infants** – 90% power for 60% efficacy compared to BCG
 - In collaboration with SATVI, Oxford-Emergent Tuberculosis Consortium (OETC) and Wellcome Trust
 - Started July 2009
- **AERAS-402/Crucell Ad35 – C-017-402**
 - Planned multicenter study in **HIV infected adults** at Aurum (South Africa) and other sites in Africa.
 - In collaboration with Aurum Institute and Crucell
 - Starting Q4 2009
- **MVA85A/AERAS-485 – C-030-485**
 - Planned multicenter study in **HIV infected adults** in Cape Town (South Africa), The Gambia and Senegal.
 - In collaboration with UCT (Wilkinson), The Gambia (Ota), Senegal (Mboup), Oxford-Emergent Tuberculosis Consortium (OETC) and EDCTP
 - Planned to start 2010
- **AERAS-402/Crucell Ad35 – C-029-402**
 - Planned study in **infants** at multiple sites including SATVI (South Africa), Makerere University (Uganda), KEMRI/CDC (Kenya), Manhica Health Research Centre (Mozambique)
 - In collaboration with EDCTP and Crucell

AERAS-402/Crucell Ad35 Studies

Study	Phase/Location, Population	Status	10 ⁸	10 ⁹	10 ¹⁰	10 ¹¹	PL	Tot
C-001	1/US, Adults, (-) BCG, Boost	Completed	8	8	16			32
C-003	1/ZA, Adults, (+) BCG, Boost	Completed	7	7	15		11	40
C-008	1/USA, Adults, Prime/boost	Completed			8		9	17
C-009	1/USA, Adults, Prime/boost	Completed			8		15	23
C-010	2/ZA, Adults, (+) BCG, (+) TB, Boost	Enrolling	10	20	34	40	8	112
C-012	2/KE, Adults, QFN (+/-), (+) BCG, Boost	Completed			16		4	20
C-017	2/ZA Adults, (+) BCG, (+) HIV, Boost	Approved			26	474	500	1000
C-018	1/ZA Infants, (+) BCG, Boost	Enrolling	10	10	10	10	14	54
C-021	1/USA, Adults, Prime/boost Apheresis	Approved			10		3	13
C-022	1/USA, Adults, Boost	Completed			8	12	4	24
C-029	2/ZA, MOZ, KE, UG Infants, (+) BCG, Boost	Submitted				700	700	1400
Total (completed) in Africa			7	7	31	0	15	60
Total (completed)			15	15	71	12	43	156

HyVac 4/AERAS-404 Studies

Study	Phase/Location, Population	Status	AERAS-404	Placebo	Total
C-005	1/S, Adult, (+) BCG, boost antigen/adjuvant combos	Completed	56	8	64
C-006	1/FIN, Adult, (+) BCG, boost antigen/adjuvant combos	Completed	50	10	60
C-011	1/ZA, Adult, (+) BCG, boost antigen/adjuvant combos	Completed	32	8	40
C-025	2/ Adult, Quantiferon (+), boost antigen/adjuvant combos	Planned	20	4	24
Totals			158	30	188

Mtb72 tuberculosis vaccine

- Safety, immunogenicity and efficacy demonstrated in several animal models
 - selection of Mtb72F/AS02A for clinical development
- Phase I/2 studies with Mtb72F/AS02_A in PPD negative healthy adults in USA and Belgium and PPD positive adults in Switzerland
 - Acceptable reactogenicity profile in PPD-negative and BCG-vaccinated adults
 - Highly immunogenic – M72-specific polyfunctional CD4+ T cell responses
 - 2 doses are sufficient to mount a good immune response

Mtb72 tuberculosis vaccine

- M72/AS01 an improved vaccine (Mtb72F/AS02 to M72/AS01)
 - Phase I/2 studies in PPD-negative healthy Belgian adults
 - Well tolerated with comparable reactogenicity to M72/AS02 and Mtb72F/AS02
 - High M72-specific polyfunctional (up to 4 markers) AND persistent (2 years) CD4+ T cell response, statistically higher than either M72/AS02 or Mtb72F/AS02.

M72/AS01_E tuberculosis vaccine

- Antigen and adjuvant dose range study in BCG vaccinated Filipino adults to select a vaccine for further development
 - M72/AS01_E (10ug antigen concentration) selected as lead candidate vaccine
- Well tolerated and immunogenic, inducing M72-specific polyfunctional CD4+ and CD8+ T cell response responses in PPD negative and positive South African adults
- Well tolerated inducing M72-specific polyfunctional CD4+ T cell response responses in healthy HIV positive Swiss adults on HAART comparable to that seen in non-HIV positive populations.

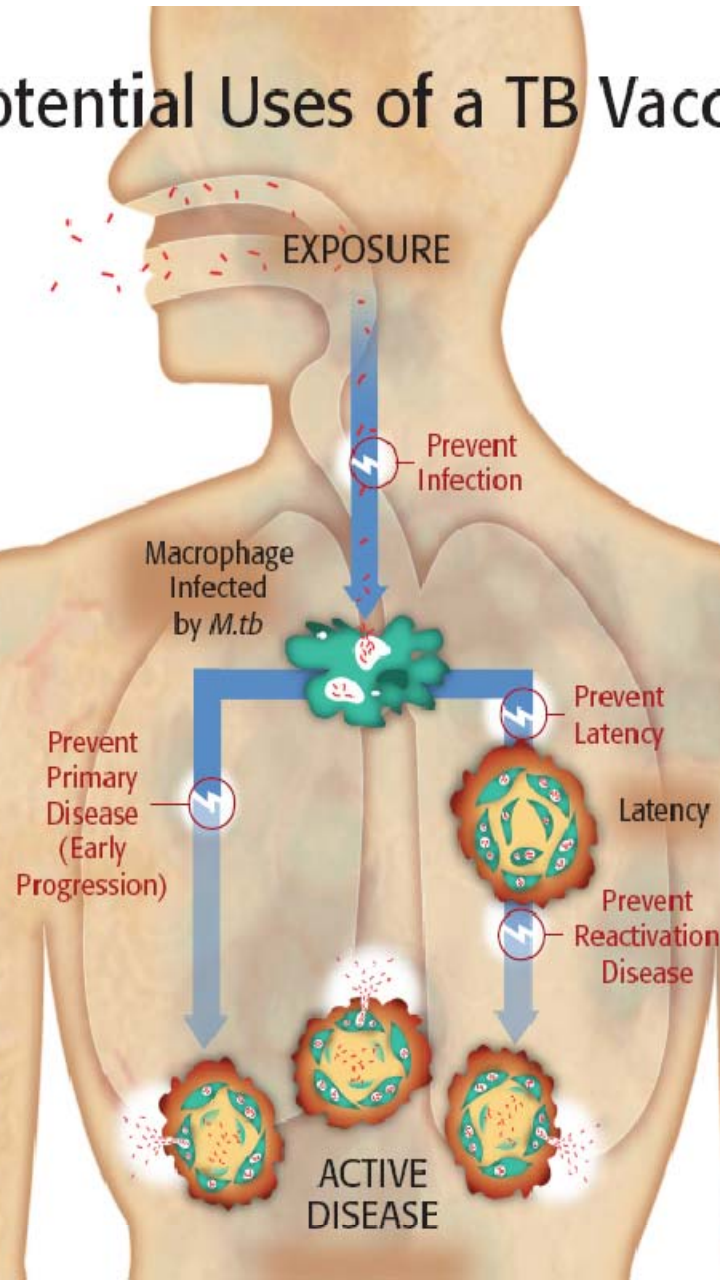
Potential Uses of a TB Vaccine

Block Initial Infection

Prevent Early Disease

Prevent Latent Infection

Prevent Reactivation Disease



Summary

- **A new TB vaccine**
 - will contribute to global health and development
 - is critical for controlling TB pandemic
- **Clinical trial field sites play an essential role in TB vaccine development**
- **Field site development enhances local health infrastructure, research capacity and human capacity**



Safety data – MVA85A

- 7 clinical trials completed; 7 ongoing
- 540 subjects vaccinated, including
 - 24 latently infected
 - 59 HIV infected
 - 306 children and infants
- Well tolerated
- Mild local reactions common (>90%)
- Mild systemic side effects common
- No signs of immunopathology

Vaccine Efficacy Trials

- **MVA85A/AERAS-485**
 - First efficacy trial of a new TB vaccine in infants in more than 80 years (proof of principle)
 - 2,800 infants – 90% power for 60% efficacy compared to BCG
 - In collaboration with SATVI, Oxford-Emergent Tuberculosis Consortium (OETC) and Wellcome Trust
- **AERAS-402/Crucell Ad35**
 - Planned multicenter study including SATVI (South Africa), Makerere University (Uganda), KEMRI/CDC (Kenya), Manhica Health Research Centre (Mozambique)
 - In collaboration with EDCTP and Crucell
- **GSK M72** to be tested late 2010
- **AERAS-rBCG** to be tested in infant Phase III non-inferiority trial vs BCG in 2011

Clinical Trials Field Site Development

- Large-scale community-based clinical trials are conducted in high burden countries
- Aeras partners with local research institutions in order to develop potential Phase III TB vaccine trial sites
- This includes:
 - Building research capacity to perform Good Clinical Practice (GCP) compliant clinical trials
 - Building physical infrastructure
 - Building health care capacity where necessary
- Professional Development Program builds human capacity and contributes to development of local research profession