TB vaccine progress

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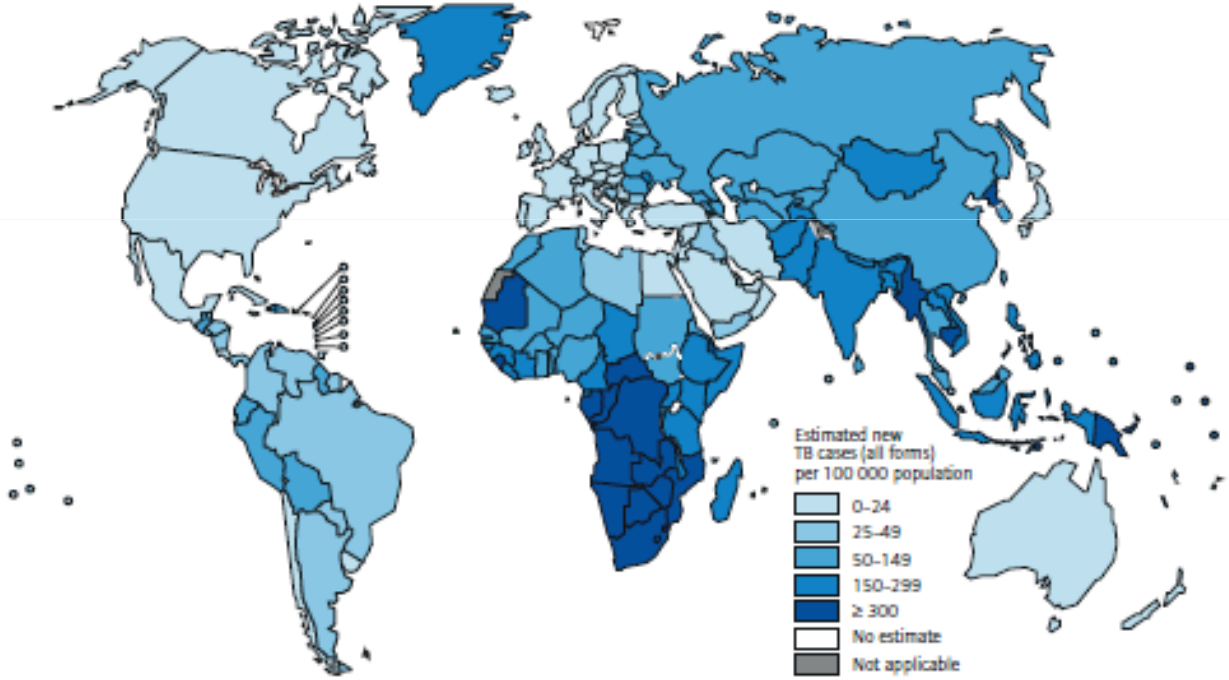
Background

- 8.7 million people were diagnosed with TB in 2011 of whom 1.4 million died (WHO Global Tuberculosis Control, 2012).

FIGURE 2.5 **Estimated TB incidence rates, 2011**



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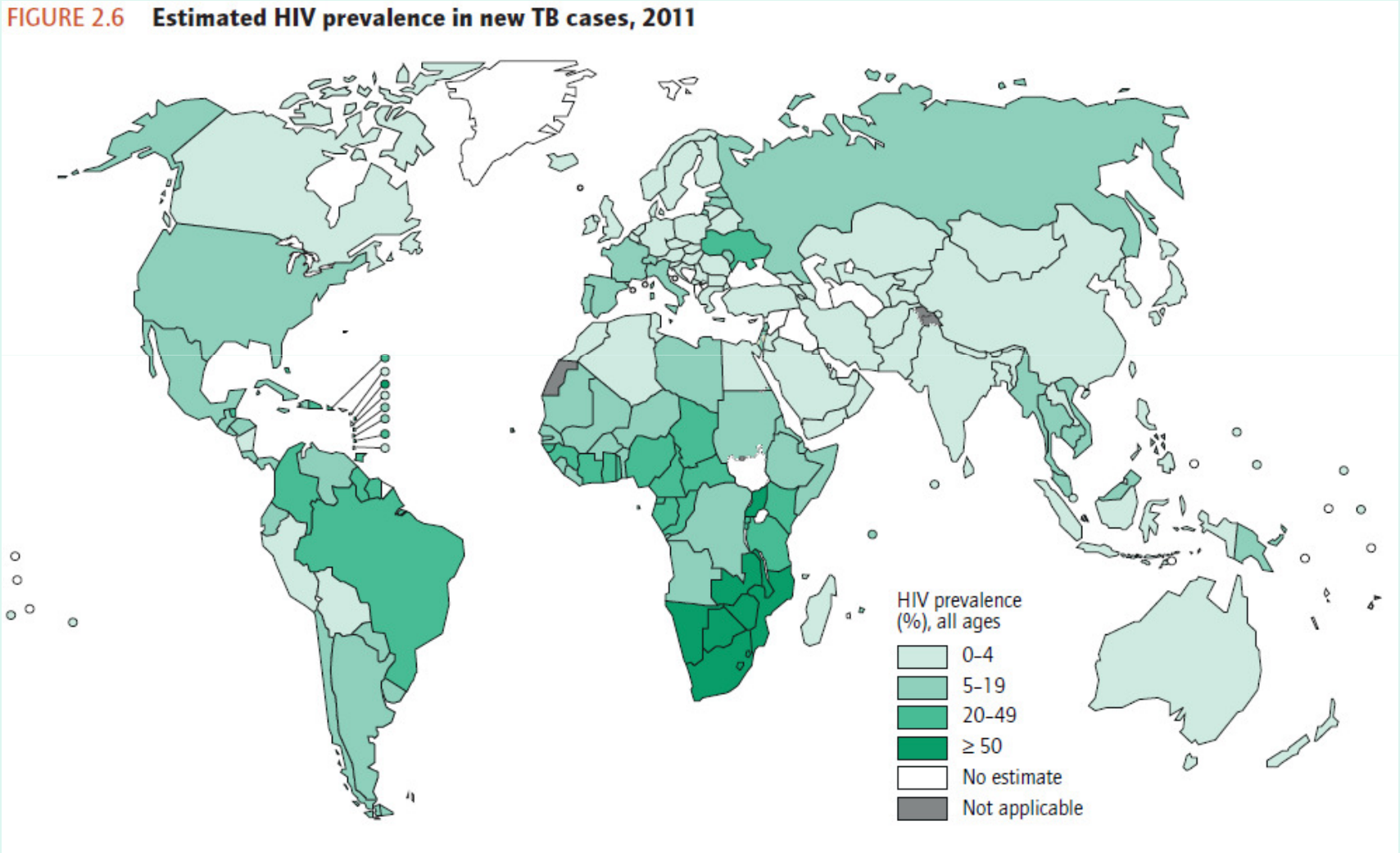
The role of HIV in TB



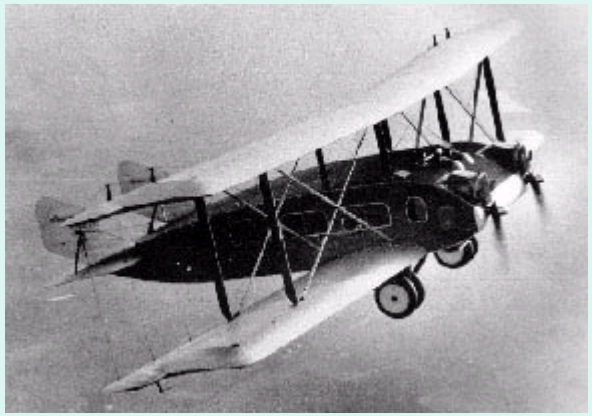
Invention of BCG Vaccine

By Calmette & Guérin

1908-1921

No new TB Vaccine

in almost 90 years



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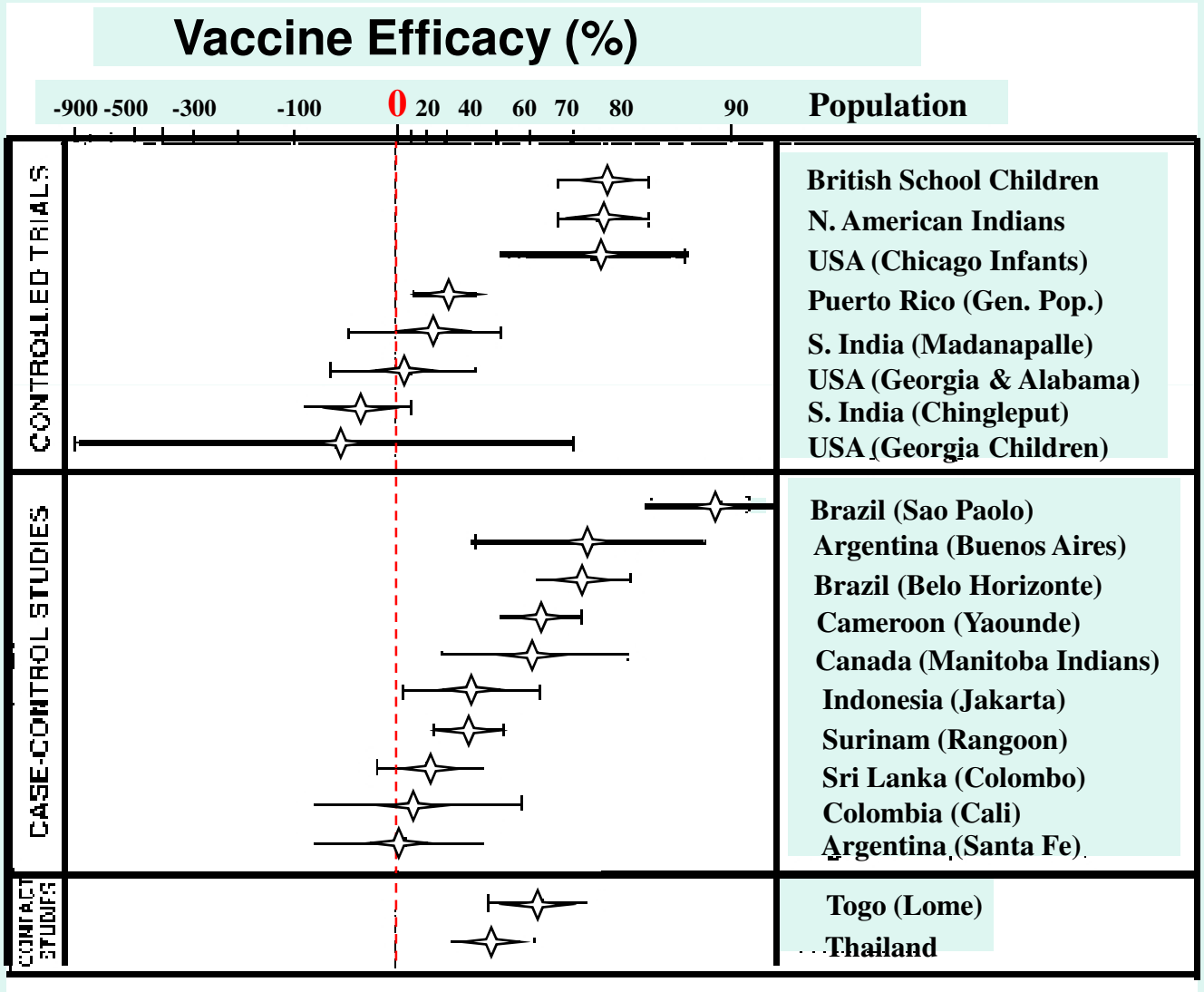
Variable Efficacy of BCG vs. Pulmonary TB



Global Plan to Stop TB, 2006-2015

- "Encouraging and consistent scientific results from the laboratory and from early field trials indicate that **the introduction of new, effective TB vaccines will be an essential component of any strategy to eliminate tuberculosis (TB) by 2050**. New TB vaccines to prevent childhood and adult forms of tuberculosis, to reduce tuberculosis in persons co-infected with HIV, and to shorten drug treatment regimens will fundamentally alter our approach to TB control."

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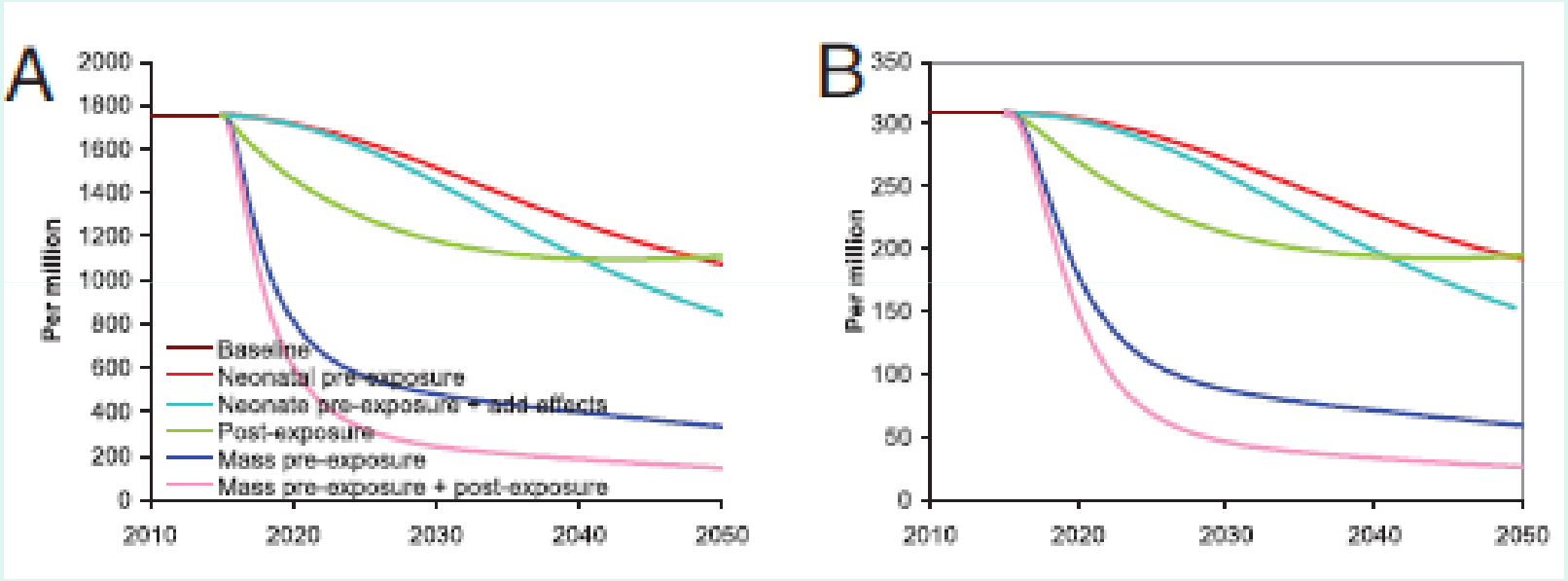
Potential benefit of new TB vaccines (Abu-Raddad et al PNAS 2009)



New TB vaccine development

- There are a number of potential TB vaccine candidates that have been identified at a basic science level.
- Of these, **12 have entered clinical trials**, 2 in Phase IIB (MVA85A and Aeras 402), one is in Phase III (Mw) and one has completed a phase III (M Vaccae).

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The TB vaccine pipeline (end 2011)

SECTION I: Candidates Tested in Clinical Trials

Status	Products	Product Description [Citations]	Sponsors	Indication	Type of Vaccine	Target Populations
Phase III	*Mw* [*M. indicus pranii* (MIP)]	*Whole cell saprophytic non-TB mycobacterium* [1-3]	Department of Biotechonology (Ministry of Science & Technology, Government of India), M/s. Cadila Pharmaceuticals Ltd.	IT	Whole cell, Inactivated or Disrupted	–
Phase IIb	MVA85A/AERAS-485	*Modified vaccinia Ankara vector expressing Mtb antigen 85A* [4-8]	Oxford-Emergent Tuberculosis Consortium (OETC), Aeras, EDCTP, Wellcome Trust	B PI IT	Viral Vectored	BCG-vaccinated infants and adolescents; HIV-infected adults
	AERAS-402/Crucell Ad35	*Replication-deficient adenovirus 35 vector expressing Mtb antigens 85A, 85B, TB10.4* [9-13]	Crucell, Aeras, EDCTP, NIH	B	Viral Vectored	BCG-vaccinated infants, children and adults
Phase II	M72 + AS01	*Recombinant protein composed of a fusion of Mtb antigens Rv1196 and Rv0125 & adjuvant AS01* [14-17]	GSK, Aeras	B PI	Recombinant Protein	Adolescents/adults, infants
	Hybrid-I+IC31	*Adjuvanted recombinant protein composed of Mtb antigens 85B and ESAT-6* [18-22]	Statens Serum Institute (SSI), TBVI, EDCTP, Intercell	P B PI	Recombinant Protein	Adolescents; adults
	VPM 1002	*rBCG Prague strain expressing listeriolysin and carries a urease deletion mutation* [23-27]	Max Planck, Vakzine Projekt Management GmbH, TBVI	P B	Recombinant Live	–
	RUTI	*Fragmented Mtb cells* [28-32]	Archivel Farma, S.L..	B PI IT	Whole cell, Inactivated or Disrupted	HIV+ adults, LTBI diagnosed
Phase I	AdAg85A	*Replication-deficient adenovirus 5 vector expressing Mtb antigen 85A* [33-37]	McMaster University	P B PI	Viral Vectored	Infants; adolescents; HIV+
	Hybrid-I+CAF01	*Adjuvanted recombinant protein composed of Mtb antigens 85B and ESAT-6* [19-20, 38-40]	SSI, TBVI	P B IT	Recombinant Protein	Adolescents, adults
	Hybrid 56 + IC31	*Adjuvanted recombinant protein composed of Mtb antigens 85B, ESAT-6 and Rv2660* [41-42]	SSI, Aeras, Intercell	P B PI	Recombinant Protein	Adolescents, adults
	HyVac 4/AERAS-404, + IC31	*Adjuvanted recombinant protein composed of a fusion of Mtb antigens 85B and TB10.4* [43-46]	SSI, sanofi-pasteur, Aeras, Intercell	B	Recombinant Protein	Infants
	ID93/GLA-SE	*Subunit fusion protein composed of 4 Mtb antigens* [99-100]	Infectious Disease Research Institute (IDRI), Aeras	B PI IT	Recombinant Protein	Adolescents, adults

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(www.stoptb.org)

Understanding the candidates

- Timing of administration
- Prime vs boost
- Live or inactive

Timing of vaccine administration

- Pre infection (MVA85A, Aeras 402. Aeras 404/ Hyvac 4, M72, rBCG30, VPM1002, Aeras rBCG)
- Post infection (H56, ID93)
- Therapeutic (RUTI, Mw).

Prime vs boost

- Prime vaccines to replace BCG – rBCG30, VPM1002, Aeras rBCG, MTBVAC.
- Boost vaccines to augment the benefit of BCG MVA85A, Aeras 402, Hyvac 4, M72.
- Heterologous – prime and boost are different.
- Ultimately, one or the other or a combination may be the solution.
- ?boost vaccine on its own in HIV infected persons.

Live versus inactive

- Live recombinant BCGs (rBCG30, VPM1002, Aeras rBCG) – need to be more effective but safer.
- Live vectored (MVA85A [modified vaccinia ankara] and Aeras 402 [ad 35]) – replication deficient.
- Antigen protein based – M72, Aeras 404/ Hyvac 4
- Killed vaccines – M Vaccae, RUTI

TB vaccine trial designs

- Phase 1 numbers have varied from 36-54
- Some have used placebo or control vaccines and others not (no control).
- Infants – best to have a control because of common adverse events and SAEs.
- Target groups – starting with healthy adults, then adolescents to children and infants. HIV positive and TB infected/ TB treated persons have also been included in safety trials.

Trial designs continued

- Age de-escalation from adults straight to infants now accepted.
- Dose finding studies a common element in phase 1 and 2a studies.
- Non-interference studies with respect to other vaccines also part of the clinical development of certain vaccines.

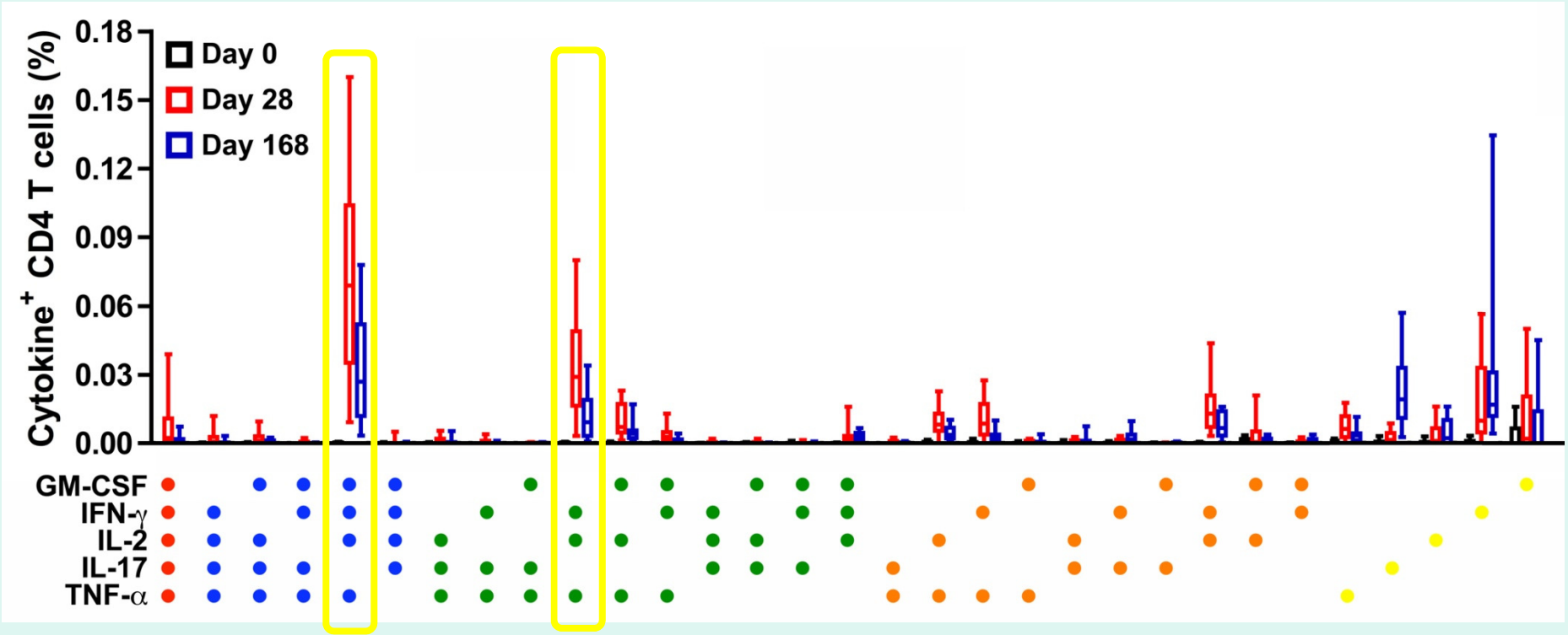
Safety Results

- Local reactions – injection site swelling, redness, pain, scaling
- Systemic effects – fever, malaise, liver function test and full blood count abnormalities – generally resolving within a short period.
- Few related serious adverse events (SAEs) to date.
- No “Koch phenomenon” incidents identified so far.

Immunology

- CD4 and CD8 responses
- Polyfunctional cells.
- Correlates of protection?

CD4 T cell cytokine patterns induced by a boost vaccine, MVA85A



Polyfunctional T cells

Willem Hanekom, Tom Scriba, Nazma Mansoor, others at SATVI

*Infant vaccine recipients, previously BCG-vaccinated, not Mtb-infected.
12 hours incubation of whole blood with vaccine antigen peptides.

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In trials of new TB vaccines, we see distinct patterns of T cell activation

	MVA85A	A402	M72	H1
Dominant CD4 T cells	IFN-γ+IL-2+TNF	No dominance	IFN-γ+IL-2+TNF; IFN-γ alone	IL-2+TNF
CD4 IL-17 induction?	IL-17+IFN-γ+IL-2+TNF	None	IL-17 alone	Very few
CD8 T cell induction?	None	Potent	Some	None

Viral vectored

Subunit + Th1 adjuvants

Willem Hanekom, many others

Whole blood ICS assay

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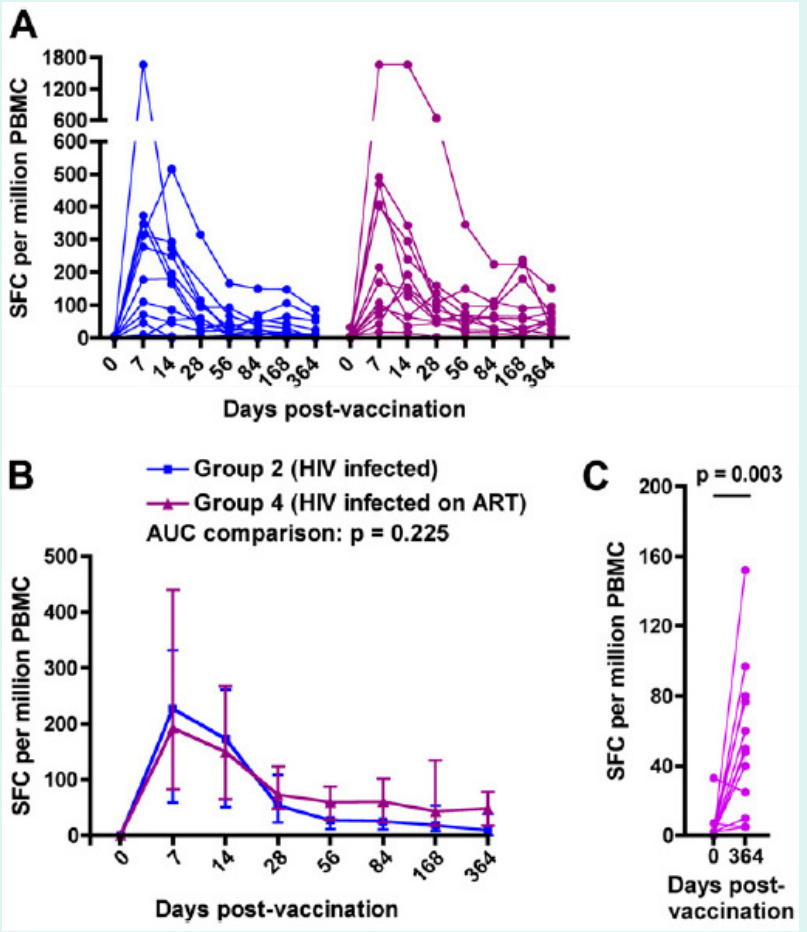
Immune responses to MVA85A in HIV infected

Measurements and Main Results: MVA85A was well tolerated and no vaccine-related serious adverse events were recorded. MVA85A induced robust and durable response of mostly polyfunctional $CD4^+$ T cells, coexpressing IFN-γ, tumor necrosis factor-α, and IL-2. Magnitudes of pre- and postvaccination T-cell responses were lower in HIV-infected, compared with HIV-uninfected, vaccinees. No significant effect of antiretroviral therapy on immunogenicity of MVA85A was observed.

Scriba et al, AJCCRM 2012



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Trial site development

- First phase 1's done in developed countries.
- Next phases in developing countries with a view to phase III trials.
- High TB rates needed for reasonable sample size estimations.
- But more than this is needed……

Trial site development (contd)

- Good infra-structure – roads, water, electricity.
- Good public care services (for TB and HIV).
- Well trained staff – GCP, GLP trained.
- Accredited laboratories.
- Ethics and regulatory structures.
- Medical/ paediatric expertise.
- Internal QAC/QC – external monitoring is standard.
- Stakeholder support – communities, Dept of Health

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Today vs yesterday

- The regulatory environment make trials today very different from what they were when the first BCG trials were done – more costly but with better designs and better protection for participants

Challenges

- Cost of trials
- Ongoing site development
- Lack of a immunological correlate of protection. Need for clinical endpoints for efficacy determination
- TB diagnosis in children – need better diagnostics
- Regulatory environment – approval processes/ accreditation of labs/ monitoring/ audits.

Conclusion

- There are a variety of candidates in trials (12) or in pre-clinical development (32) – a good position to be in.
- Results are promising thus far and we have reason to be optimistic. First infant efficacy data will be available in February 2013.
- Estimates of when a new vaccine would be available is by 2020.

Acknowledgements

- WHO STOP TB working group on TB vaccines (www.stoptb.org)
- Tony Hawkridge – use of slides.
- SATVI team

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