Epalinges, SOHF, Lausanne, 02-09-2014

Tuberculosis vaccine trials in 2014: current strategies and challenges

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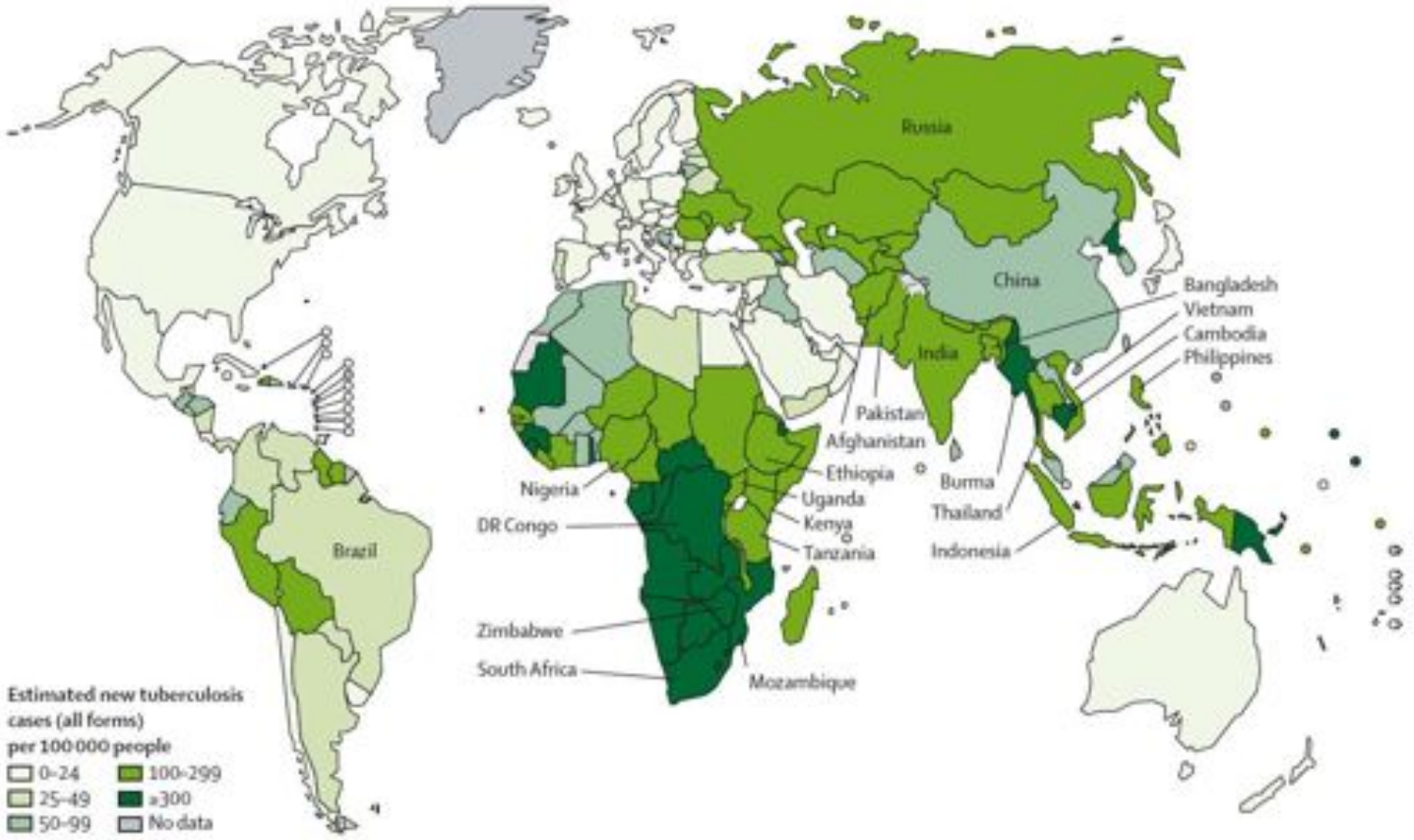
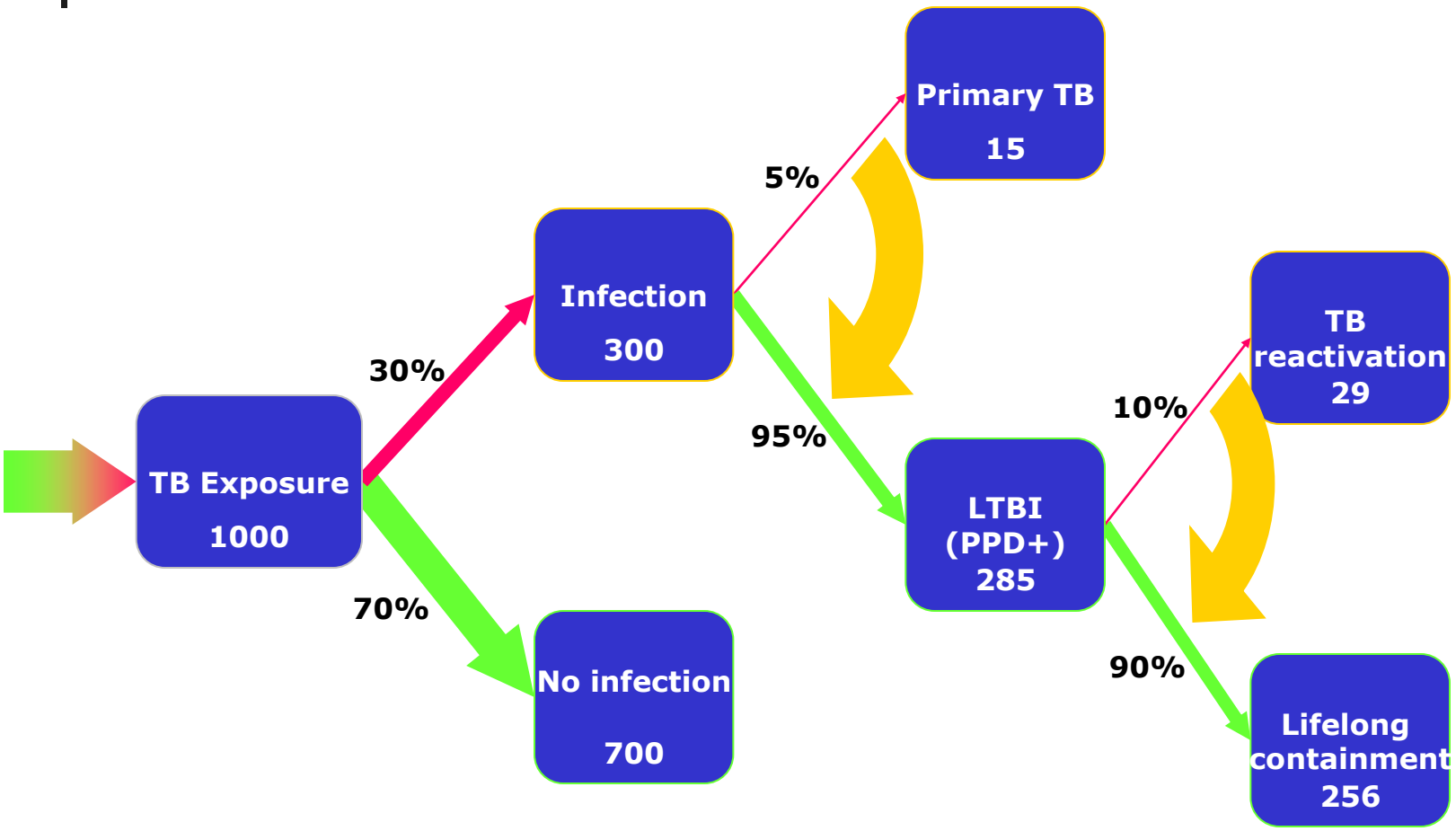
Epidemiology



WHO, 2013

Natural history of TB infection



Therapeutic consequences

- Increasing number
  - Of coinfections with HIV
  - Of resistance to conventional anti-TB drugs
- Need for new drugs
- Need for efficient and safe vaccines (potentially HIV infected, immunocompromized recipients!)

BCG

- Today only commercialized vaccine
- Attenuated strain from *Mycobacterium bovis*
  - Calmette and Guérin 1921
    - Good protection in children
  - Mass vaccination during the 50ies (WHO)
    - Single ID injection in PPD- et PPD+ children immediately after birth
    - >3 x10^9 subjects currently vaccinated
    - 76% of all children
- Efficacy of BCG controversial, in particular in developing countries

BCG efficacy

- Recent meta-analysis
  - 73% et 76% efficacy against TB meningitis and miliary TB in **children** during the first 5 years of life
  - Cost-effective
  - Some parallel protection against leprosy
- BUT!
- In adults
  - Highly controversial efficacy
  - Efficacy from 0% to 80%
    - Pulmonary TB is associated with the highest costs for control
- Studies from India (Chingleput) and from Malawi
  - Efficacy 0% !!

Trunz, Lancet 06; Ponnighaus, Lancet 92; Colditz, JAMA, 94

Global strategy of vaccine development

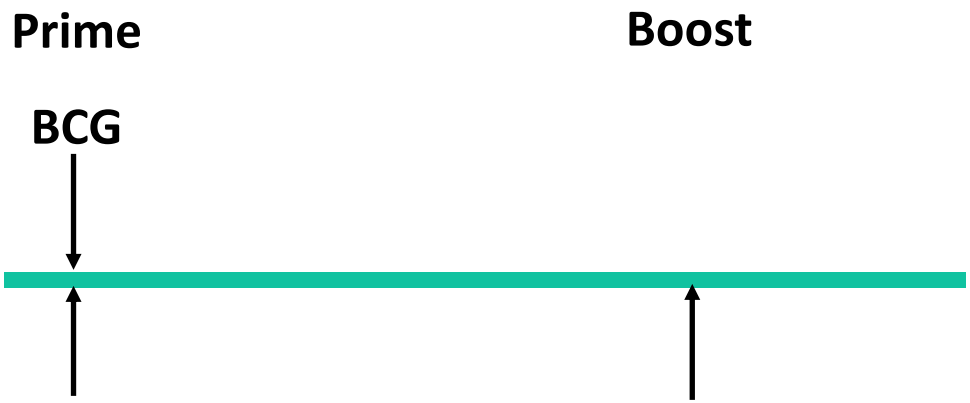
- It would be unethical to interrupt BCG vaccination in developing countries considering the benefits in children
  - Use BCG
    - Prime/boost approaches
    - Prolong the duration of protection
  - Improve BCG
    - Genetic approaches on BCG (Ag complementation) or MTB (attenuation)
- Prevention of primary TB in children, adolescents and adults
- Prevention of reactivation of latent cases

TBVAC.ORG

TBVI
TuBerculosis Vaccine Initiative

Development of an effective vaccine

Prime-boost strategy



AERAS
Global TB Vaccine Foundation

BILL & MELINDA GATES foundation

''super'' BCG (MTB attenuated)

safer, more immunogenic, long lasting protection, protection against highly virulent *Mtb*

Subunit vaccine

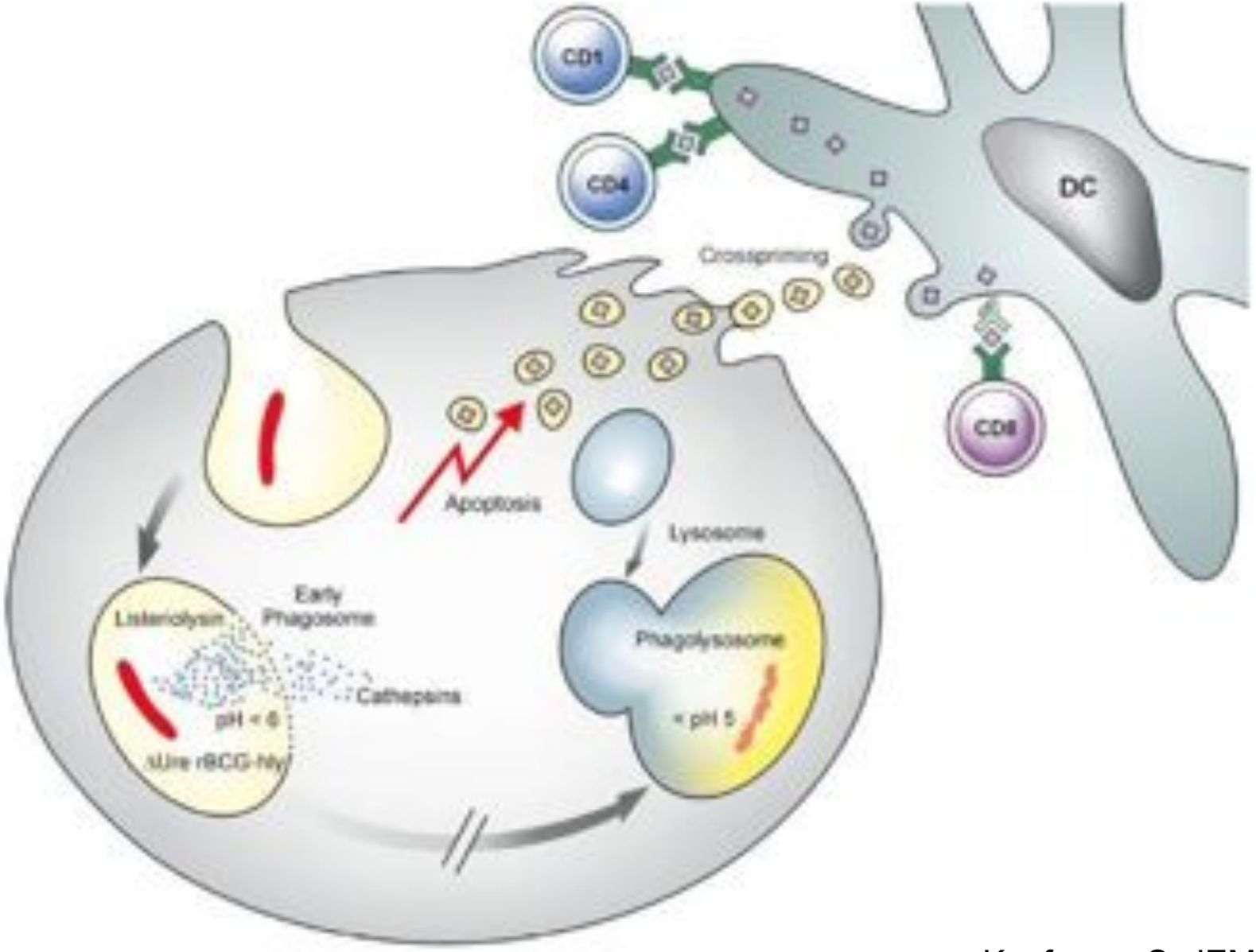
non-live candidate Ag, recombinant protein plus adjuvant or viral vector

The development of new TB vaccines

Attenuated live vaccines

- Recombinant BCG VPM1002 (SH Kaufmann et al.)
  - rBCGΔUreC:Hly+
    - Deletion of the urease gene and insertion of listeriolysine from *Listeria monocytogenes*
  - Improved cross-presentation
  - Potential induction of specific CD8 T cells

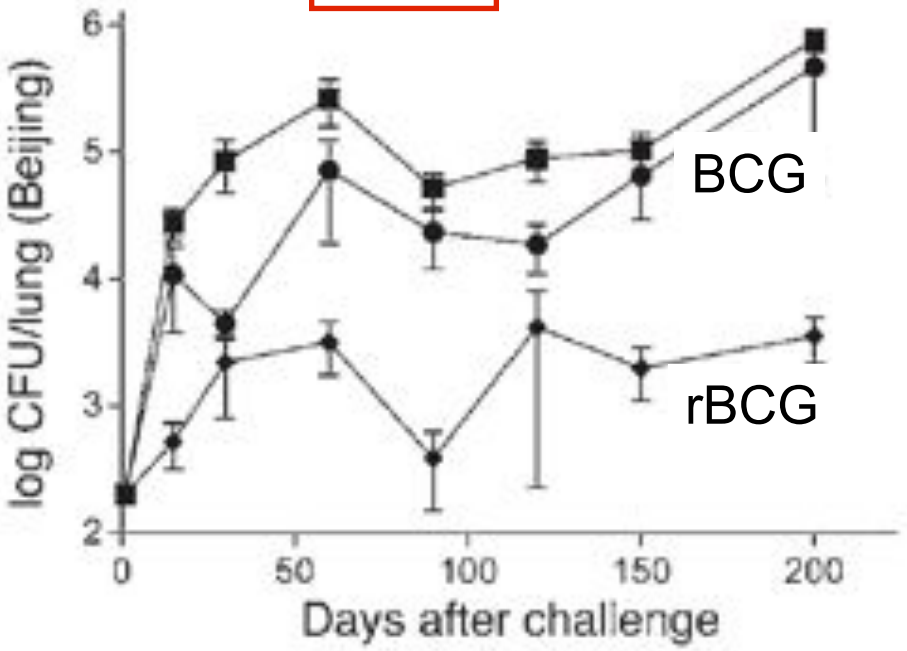
Crosspriming of DC by rBCG



Kaufmann S, JEM 05

rBCG is more efficient and safer than BCG Beijing

Balb/c



SCID

BCG

rBCG

Grode et al., JCI, 05

rBCGΔUreC:Hly+

- Phase I completed (Berlin) in healthy PPD negative and positive healthy subjects
  - Good clinical tolerance
  - Good imunogenicity including CD8 and Th17 cell generation
- Currently in Phase IIb in newborn

Desel et al., J Inf Dis, 11; Grode, Vaccine, 2013

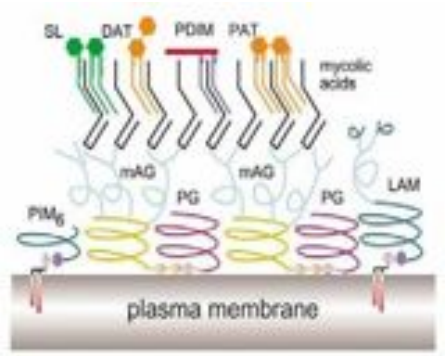
Other approaches with attenuated recombinant mycobacteria

- rBCG30 (Horwitz et al.,05)
  - Overexpression of Ag85B (mycolyltransferase)
    - Disappointing immunogenicity in Phase I although protection in the guinea pig
- Attenuated rMTB (C. Martin et al., Saragozza)
  - Deletion of virulence gene *Phop et fadD26*
    - Attenuated replication in SCID
    - Promising protective effect in mouse and guinea pig
    - Phase I in Lausanne, 2013

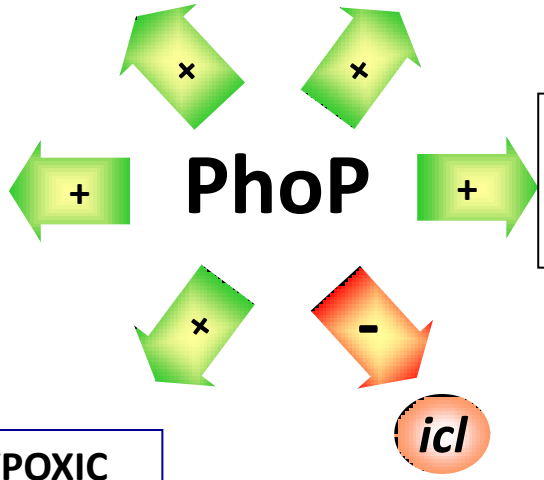
Double mutated phoP-/fadD26 -BASED VACCINE

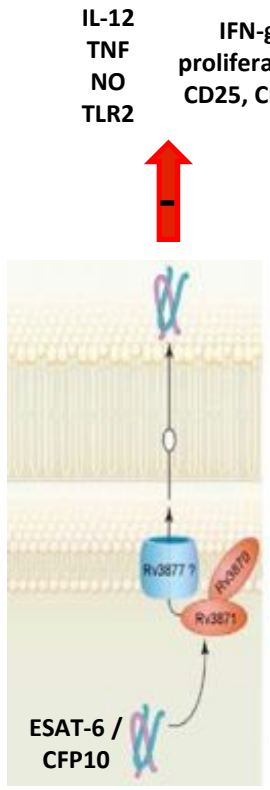
RESEARCH & DISCOVERY

PhoP control the replication of Mtb inside MΦ



Gonzalo Asensio *et al.* JBC 2006





Frigui *et al.* PLoS Path 2008

+

fadD26 (cell envelope fatty acid biosynthesis)

Gonzalo-Asensio *et al.*
PLoS ONE 2008

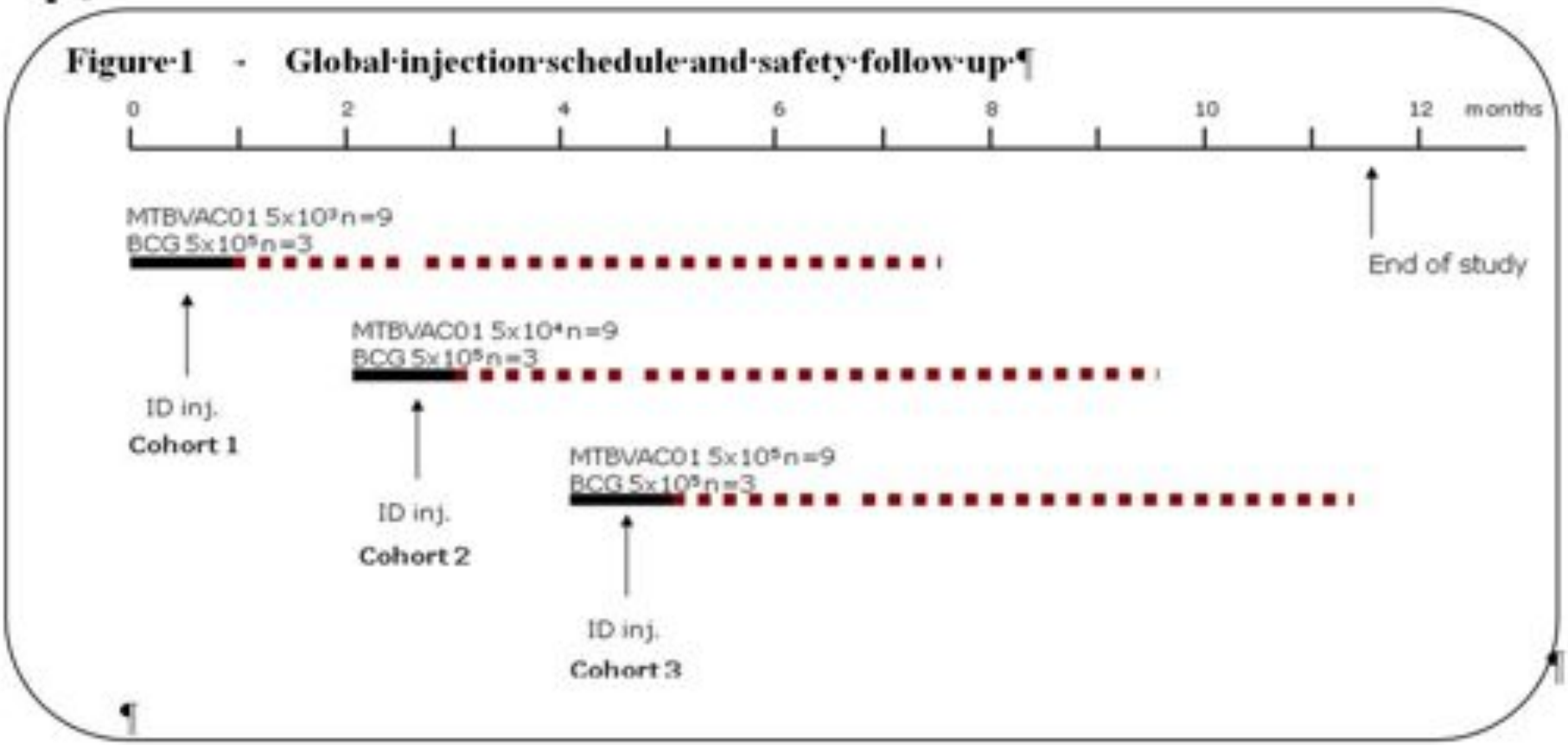
MTBVAC01 PHASE 1

- Double blind, controlled, randomized, dose-escalation study
- Study population:
  - Adult males/ females, aged 18-45 years
  - BCG naive, PPD-negative, HIV-negative volunteers,
  - No evidence of active TB
- Primary objective: Safety and reactogenicity
- Secondary objective: Immunogenicity
  - To evaluate the cell-mediated immune (CMI) response
  - To evaluate the humoral response (Ag85B, ESAT-6)
- Phase I started in Q1 2013

MTBVAC PHASE 1

DOUBLE BLIND, CONTROLLED, RANDOMIZED, DOSE-ESCALATION STUDY

- **3 cohorts of 12 subjects randomised to receive either the study vaccine MTBVAC (n=9) or BCG as control (n=3).**



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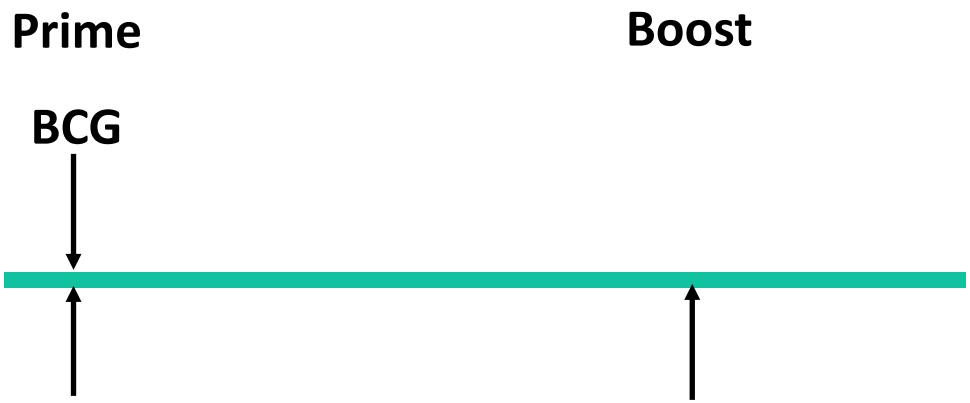

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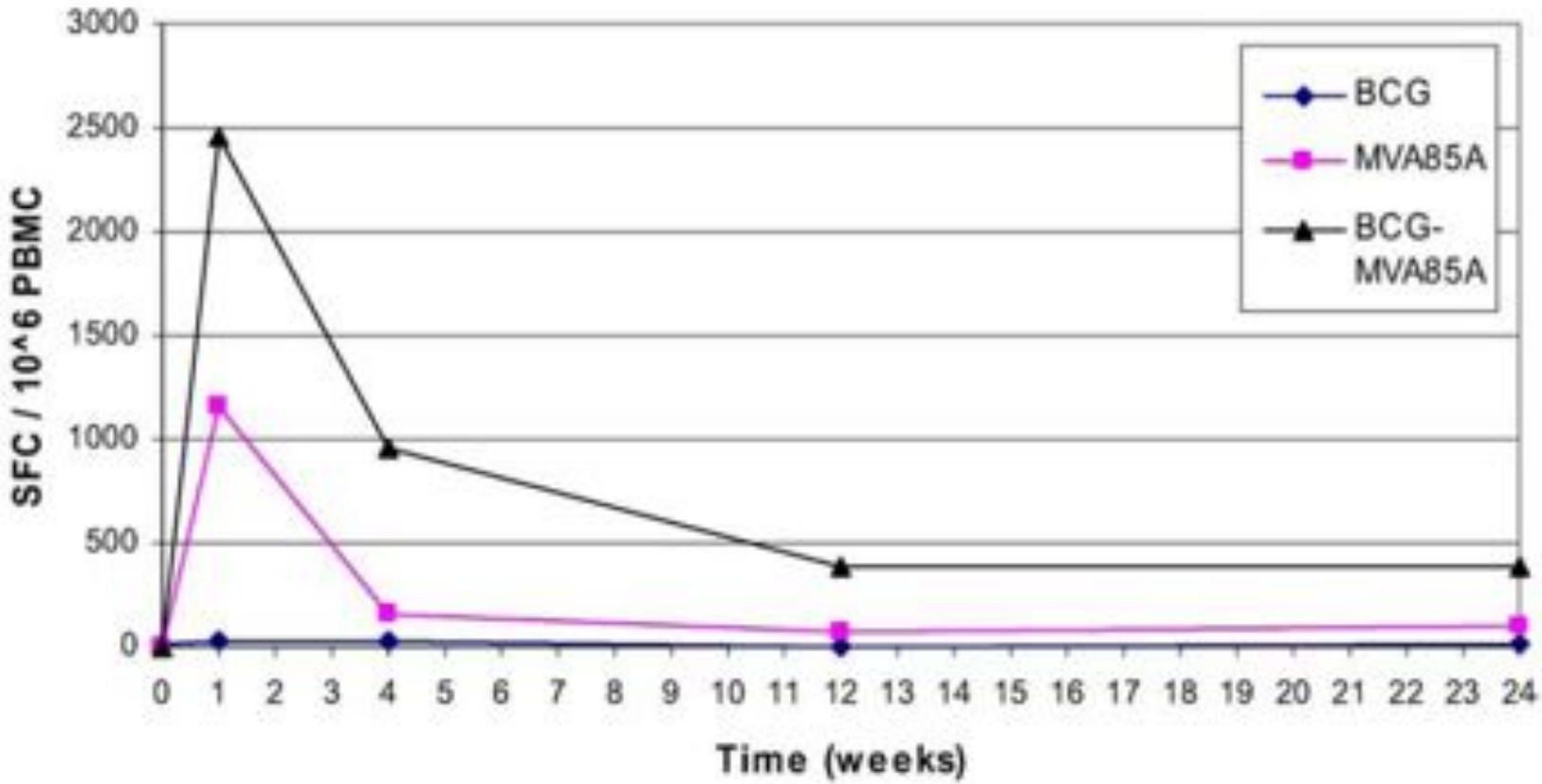
DNA vaccine MVA85A

- Modified Vaccinia Ankara (MVA)
  - Helen McShane, A. Hill et coll., Oxford U
- Express MTB Ag85A (MVA85A)
  - Reinforce protective effect of BCG in mice and macaques (F. Verrreck et coll.)
  - CD4 and CD8 responses in the mouse (JI 03)
- Phase I
  - PPD- et PPD+ volunteers, safe and immunogenic
- Phase II in endemic area in children, adolescent and adults, in HIV+ (McShane Nat Med 04)

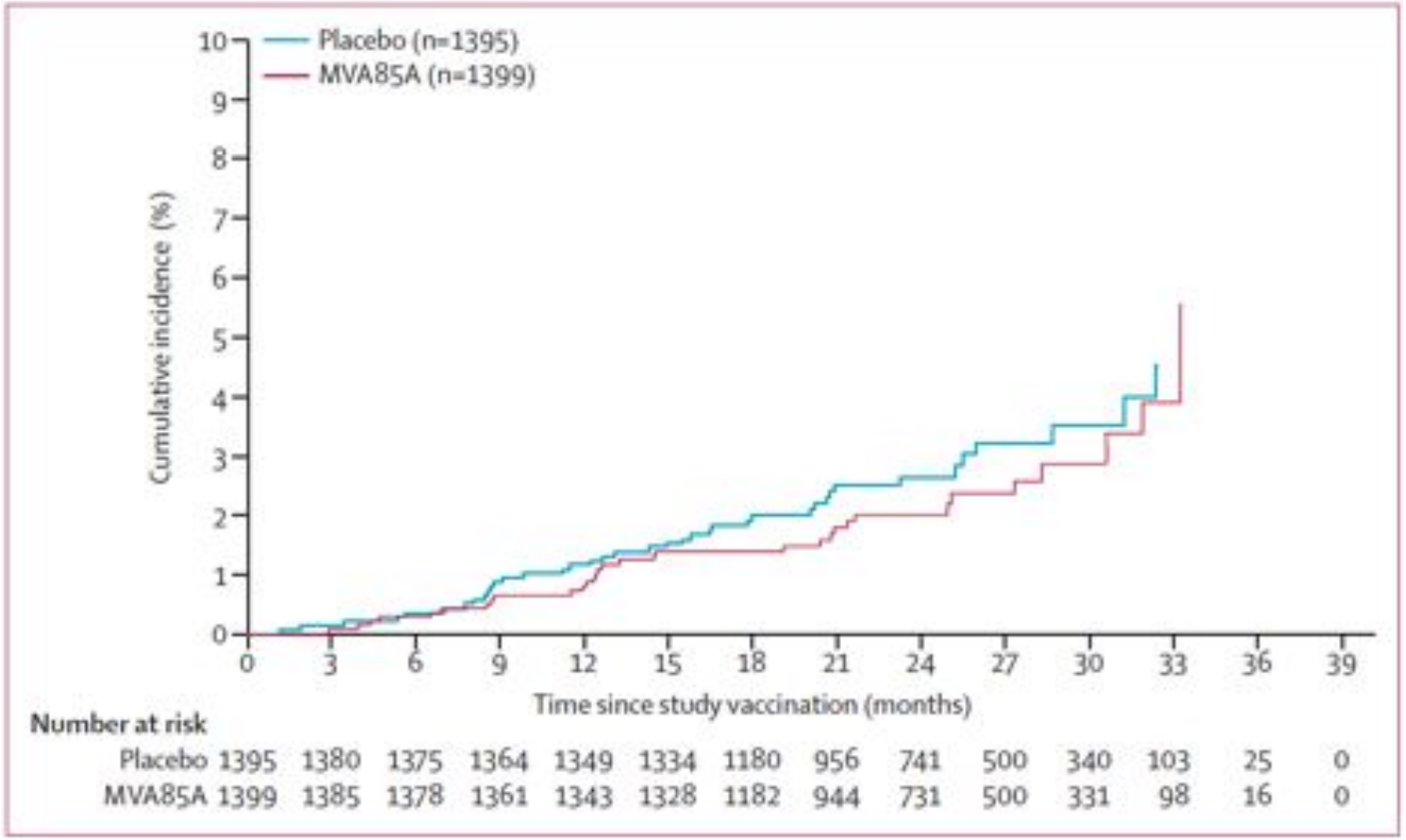
Induction of IFNγ post heterologous prime/boost strategy BCG/ MVA85A (Phase I, UK)



McShane, Microbes Infect 2005

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

M Tameris et al., Lancet 2013



Subunit vaccines

- Hybrid-1 (ESAT6/Ag85B) (Ottenhof et al., LUMC/SSI)
  - Phase I PPD-, adjuvant IC31 (TLR9 ligand)
  - Strong, long lasting Th1 IFNγ response , van Dissel Vaccine 2010
- Mtb72 (GSK) (see below)
- Strategy
  - To reinforce and prolong immune responses to BCG with recombinant subunit vaccines and appropriate adjuvant

Candidate TB vaccine M72/AS01$_E$

- **M72/AS01$_E$**
  - is composed of an improved recombinant fusion protein Mtb72 with GSK's proprietary Adjuvant System AS01$_E$
    - AS01$_E$ is a Th1-inducing adjuvant system containing MPL and QS21 in a proprietary liposome solution

  - has been evaluated in PPD-negative and PPD-positive adults
    - Shown to be well tolerated and highly immunogenic

Spertini et al., Tuberculosis 2013; Thacher Gambillara et al., AIDS, 2014

The safety and immunogenicity of the candidate M72/AS01$_E$ tuberculosis vaccine in HIV-positive adults

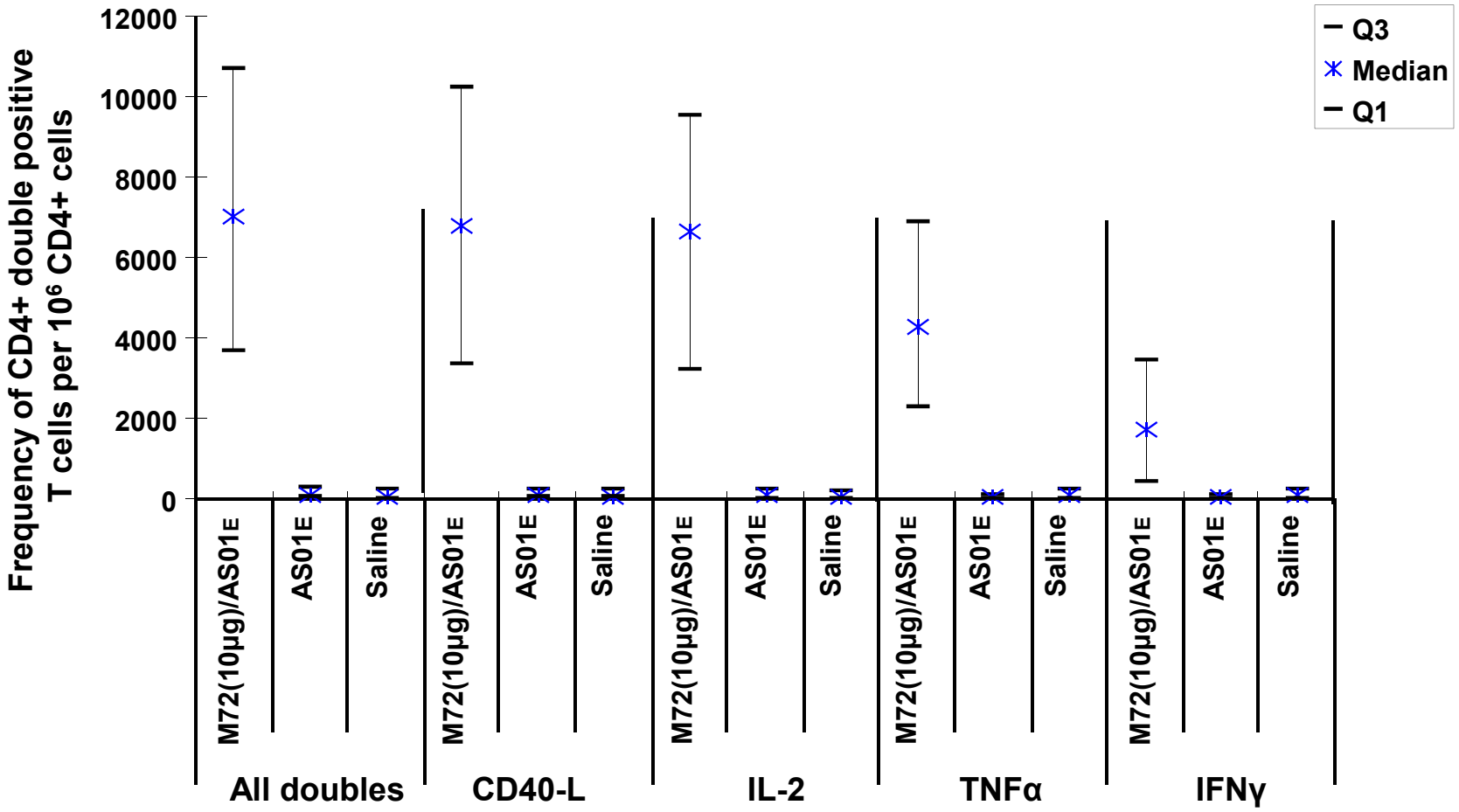
AIM

- To assess safety, reactogenicity and immunogenicity of M72/AS01$_E$
  - in adults aged 18 to 50 years, with well-controlled chronic HIV infection on Highly Active Antiretroviral Therapy (HAART).

RESULTS – Safety and reactogenicity

- No vaccine related Serious AE
  - 2 SAEs reported: appendicitis and cellulitis of leg
- No clinically significant changes in biochemical and hematologic parameters
- There was no effect of vaccination on individual HAART regimens.
- No clinically relevant vaccine-related variation in CD4+ T cell count and viremia

Functional characterisation of M72-specific CD4+ T cells expressing at least two cytokines on Day 60



Conclusions

- This study indicates that the M72/AS01$_E$ candidate TB vaccine is highly immunogenic and well tolerated in this population of HIV-positive adults.

- This promising vaccine profile justifies further evaluation in HIV disease endemic settings.

- Move to Phase IIb (adolescents)

Conclusions

- BCG is only efficient in children in prophylaxis and at short term
- Recent vaccine developments tend
  - To replace BCG with genetically modified mycobacteria (prime)
  - to consolidate immune responses to BCG following a prime/boost approach (subunit vaccines)
- Perspectives
  - New generations of vaccines (post-exposure, therapeutic in part) may also target latency/starvation antigens

Thanks for your attention