



Global progress in vaccine development

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Vaccination

- The most cost-effective health intervention
 - Smallpox
 - Poliomyelitis
- WHO's Expanded Programme on Immunisation
 - up to 95% of children vaccinated
 - BCG, DTP, polio, measles \pm hepatitis B
 - HPV
 - Vaccines for cancer, Alzheimer's, addiction.



Basic Types of Vaccine

Live → Attenuated → Inactivated → Subunit

Decreasing Pathogenicity

Decreasing Immunogenicity/Efficacy



Missing Vaccines: The Big Three

- **HIV / AIDS**
- **TB**
- **Malaria**



Why so difficult?

- Pathogen diversity
- Infection is not protective
- Cellular immunity
- Immunological correlates
- Animal models
- Commercial market
- Cost



Progress is being made...



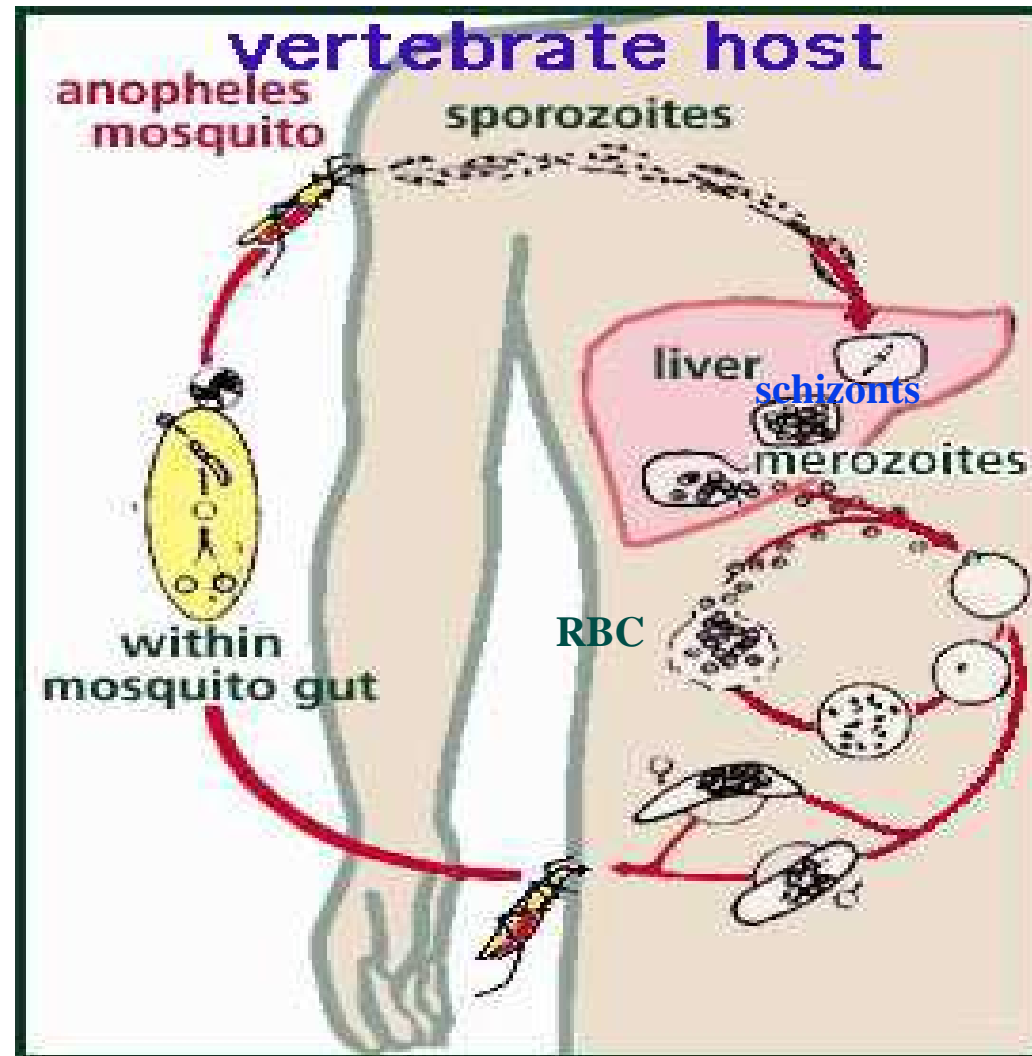
Malaria





Malaria

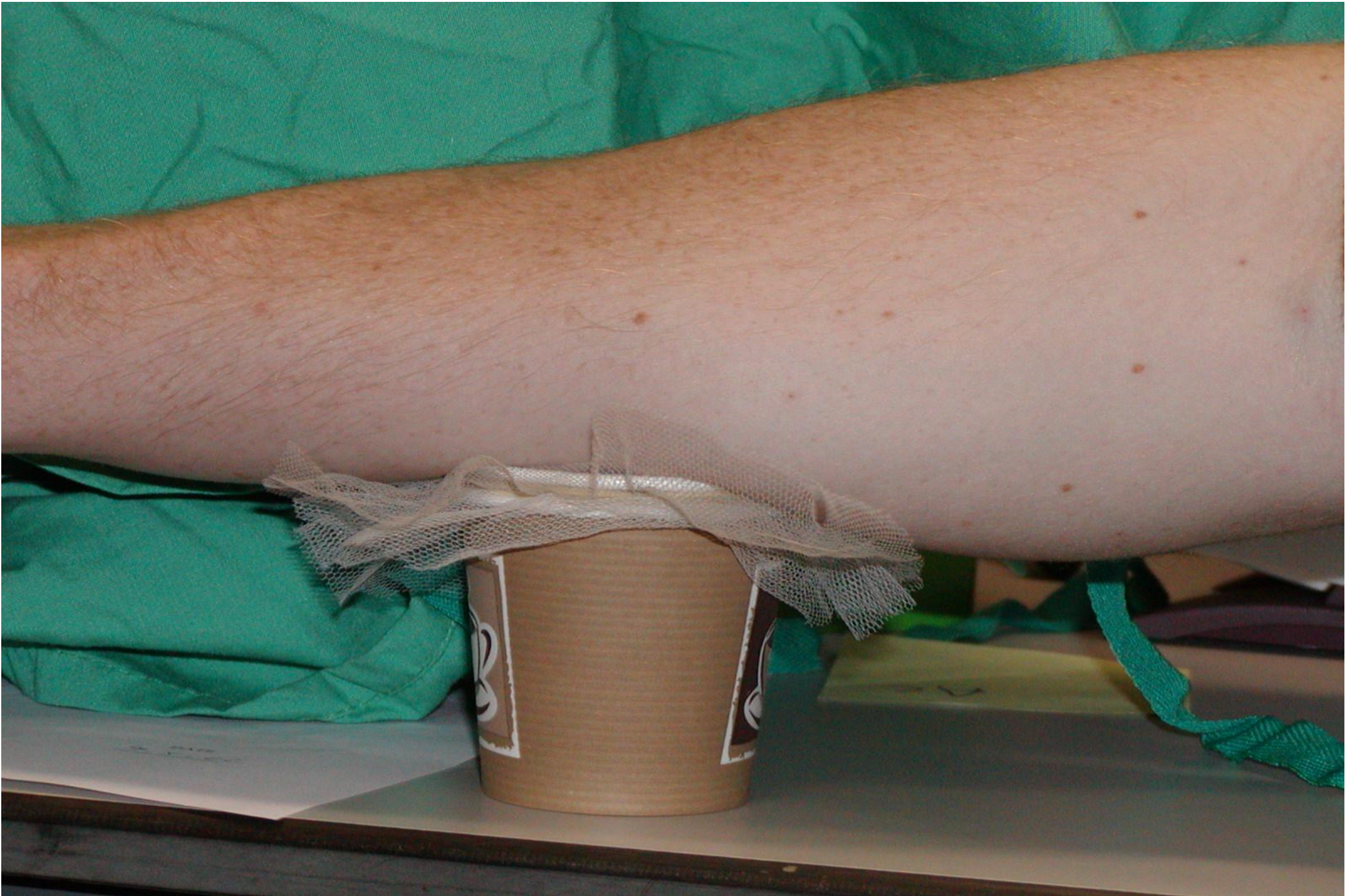
A Complex Life Cycle



Mosquito Stage

Liver Stage

Blood Stage





The NEW ENGLAND JOURNAL of MEDICINE

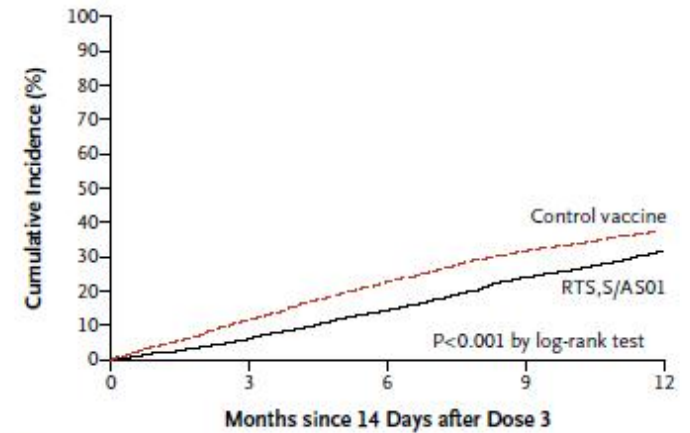
ORIGINAL ARTICLE

A Phase 3 Trial of RTS,S/AS01 Malaria Vaccine in African Infants

The RTS,S Clinical Trials Partnership

- **31% efficacy against malaria in 6-12 week old infants**

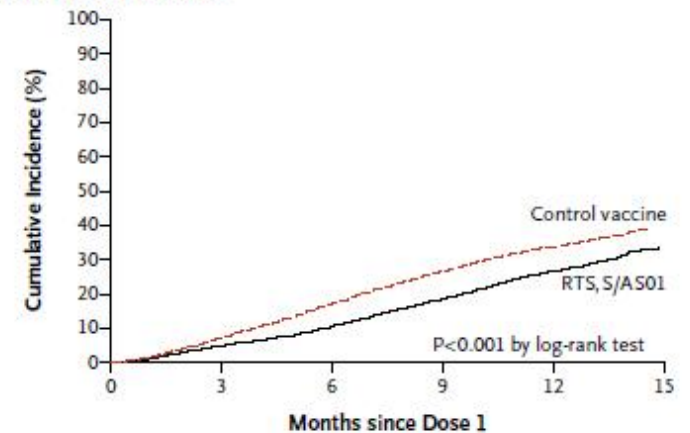
A Per-Protocol Population



No. at Risk

RTS,S/AS01	3995	3692	3309	2845	1272
Control vaccine	2008	1747	1501	1294	600

B Intention-to-Treat Population



No. at Risk

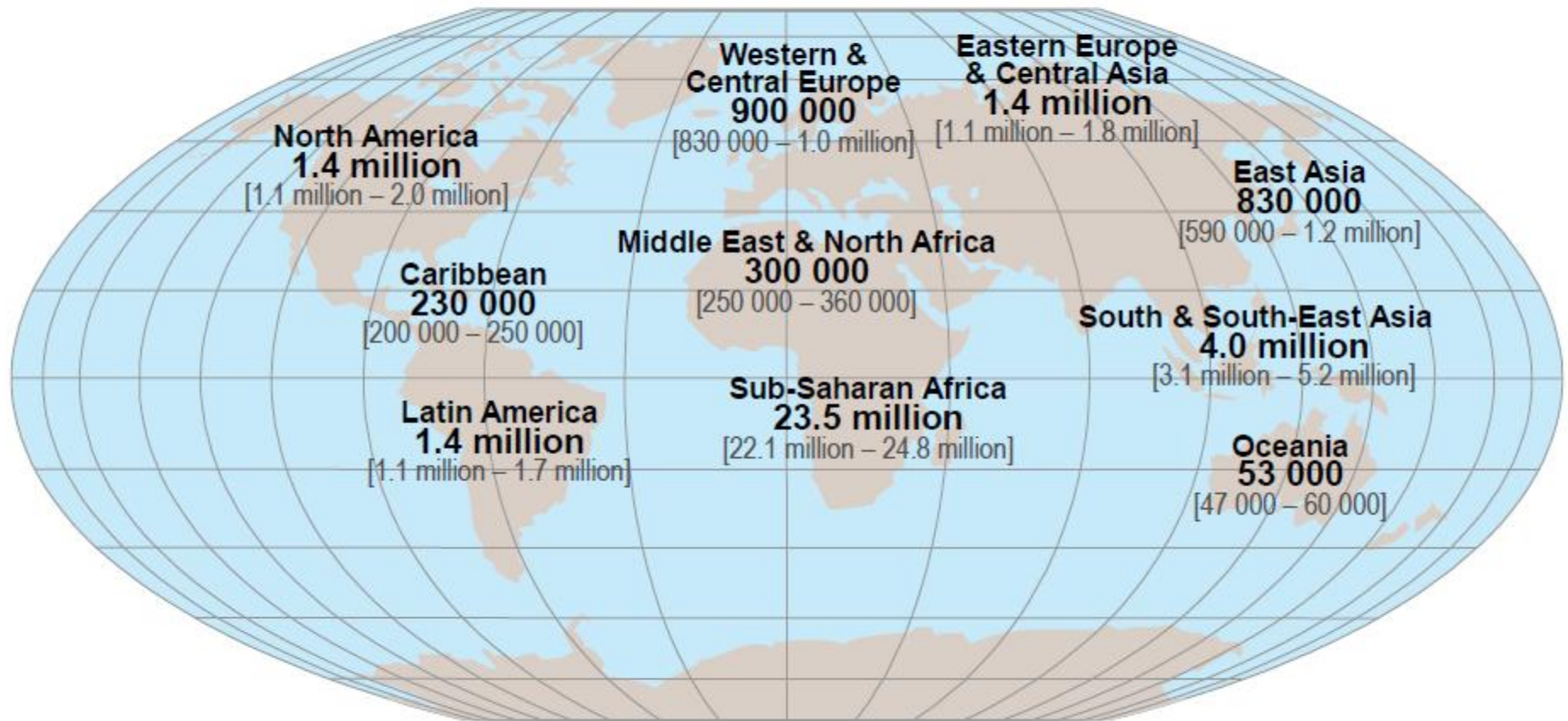
RTS,S/AS01	4358	4015	3709	3322	2884	1152
Control vaccine	2179	1985	1737	1510	1325	535



HIV/AIDS



Adults and children estimated to be living with HIV | 2011



Total: 34.0 million [31.4 million – 35.9 million]



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

DECEMBER 3, 2009

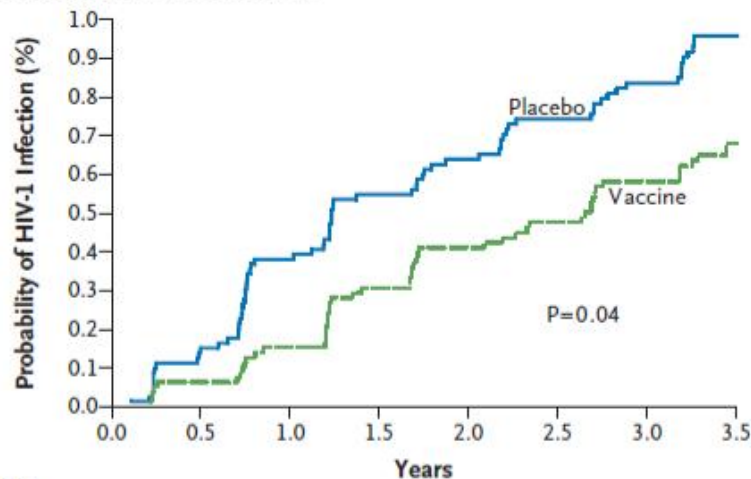
VOL. 361 NO. 23

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

Supachai Rerks-Ngarm, M.D., Punnee Pitisuttithum, M.D., D.T.M.H., Sorachai Nitayaphan, M.D., Ph.D., Jaranit Kaewkungwal, Ph.D., Joseph Chiu, M.D., Robert Paris, M.D., Nakorn Prem Sri, M.D., Chawetsan Namwat, M.D., Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Benenson, M.D., Sanjay Gurunathan, M.D., Jim Tartaglia, Ph.D., John G. McNeil, M.D., Donald P. Francis, M.D., D.Sc., Donald Stablein, Ph.D., Deborah L. Bix, M.D., Supamit Chunsuttiwat, M.D., Chirasak Khamboonruang, M.D., Prasert Thongcharoen, M.D., Ph.D., Merlin L. Robb, M.D., Nelson L. Michael, M.D., Ph.D., Prayura Kunasol, M.D., and Jerome H. Kim, M.D., for the MOPH-TAVEG Investigators*

- **31% efficacy against HIV-1 acquisition.**

C Modified Intention-to-Treat Analysis



No. at Risk					
Placebo	8198	7775	7643	7441	7325
Vaccine	8197	7797	7665	7471	7347
Cumulative No. of Infections					
Placebo		30	50	65	74
Vaccine		12	32	45	51



Tuberculosis



CONSUMPTION IN EARLY STAGES CAN BE CURED

Take your case in time to a good physician or to a dispensary and you may be cured—DO NOT WAIT.
Consumption is “caught” mainly through the spit of consumptives.

Friends of Consumption—Dampness, Dirt, Darkness, Drink.

Enemies of Consumption—Sun, Air, Good Food, Cleanliness.

If you have tuberculosis do not give it to others by spitting; even if you have not, set a good example by refraining from a habit always dirty and often dangerous.

The Committee on the Prevention of Tuberculosis

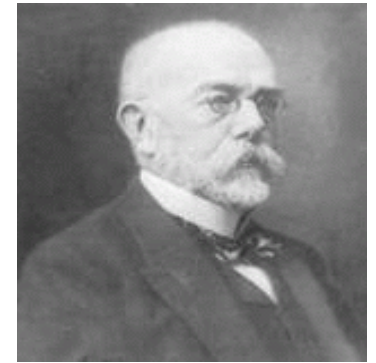
Of the Charity Organization Society

(By Courtesy of Siegel Cooper Co.)

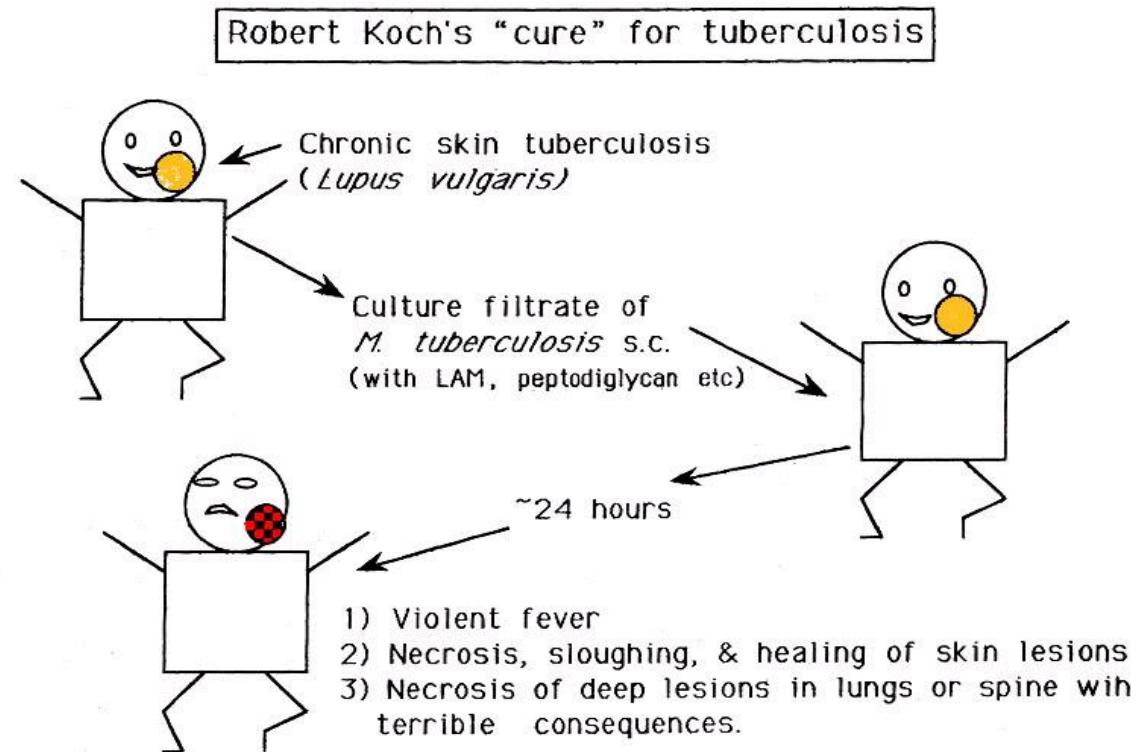




Robert Koch

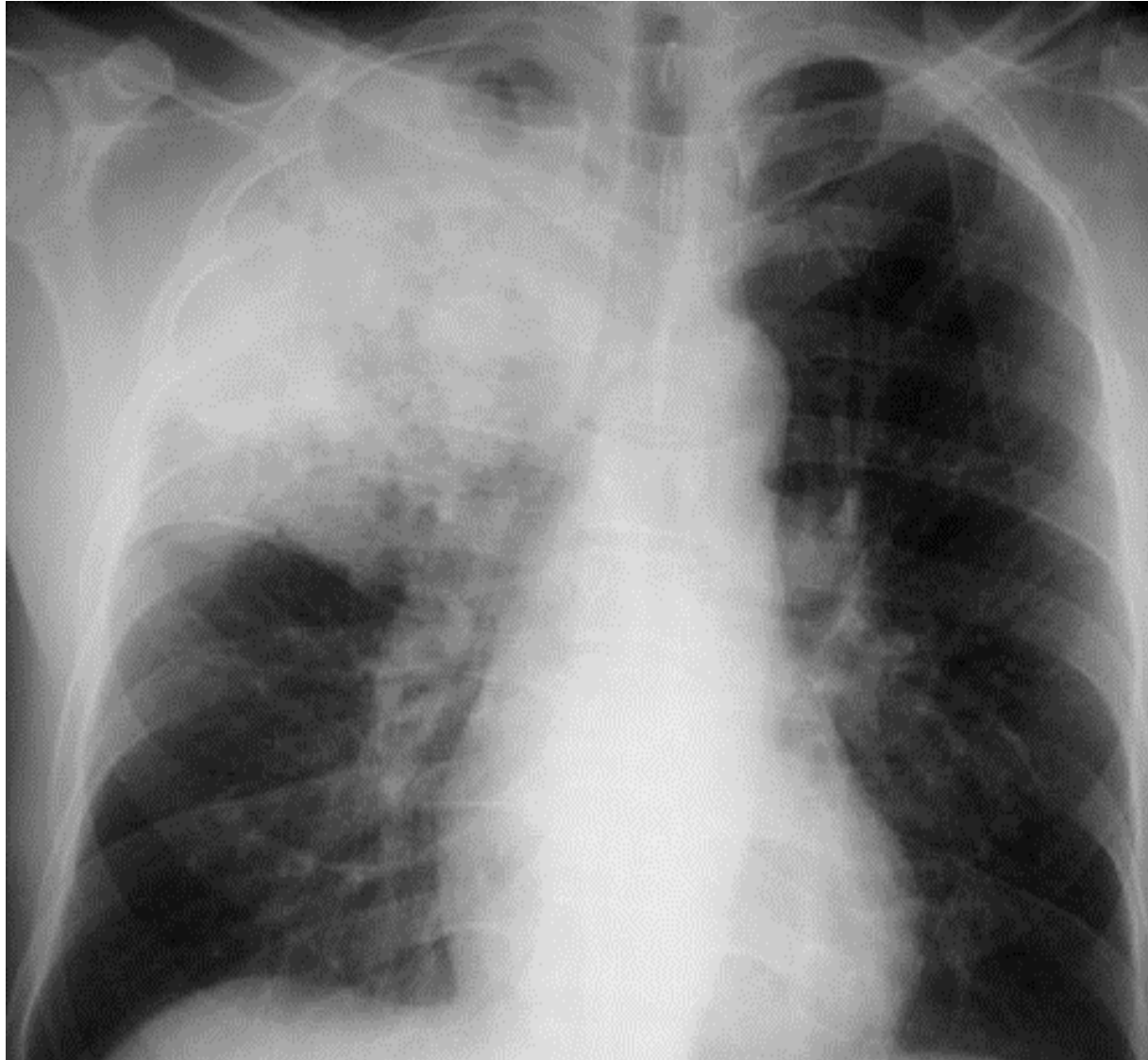


- 1882: Die aetiologie der Tuberculose
- 1890: 'The remedy'





RUL Tuberculosis



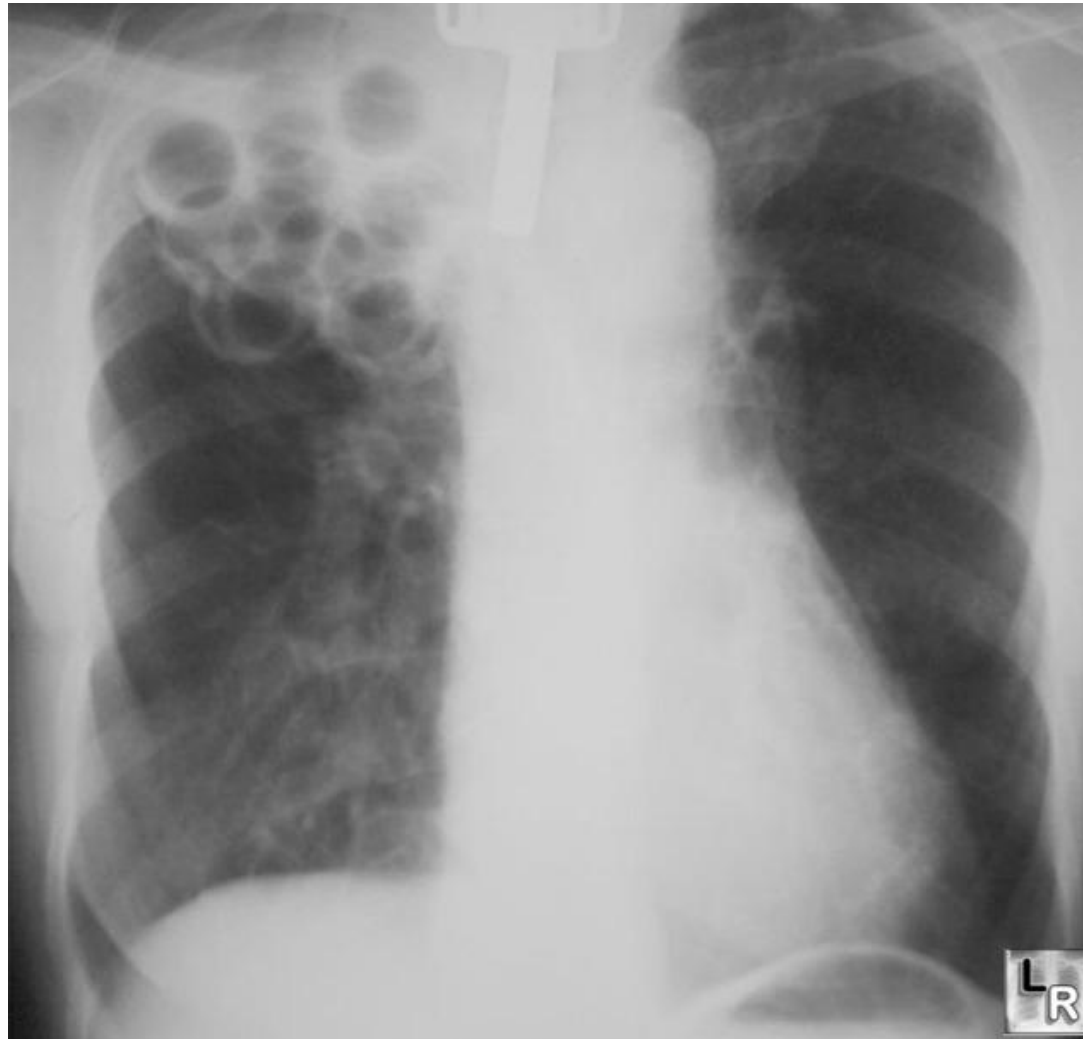


Disseminated (miliary) pulmonary TB





Plombage



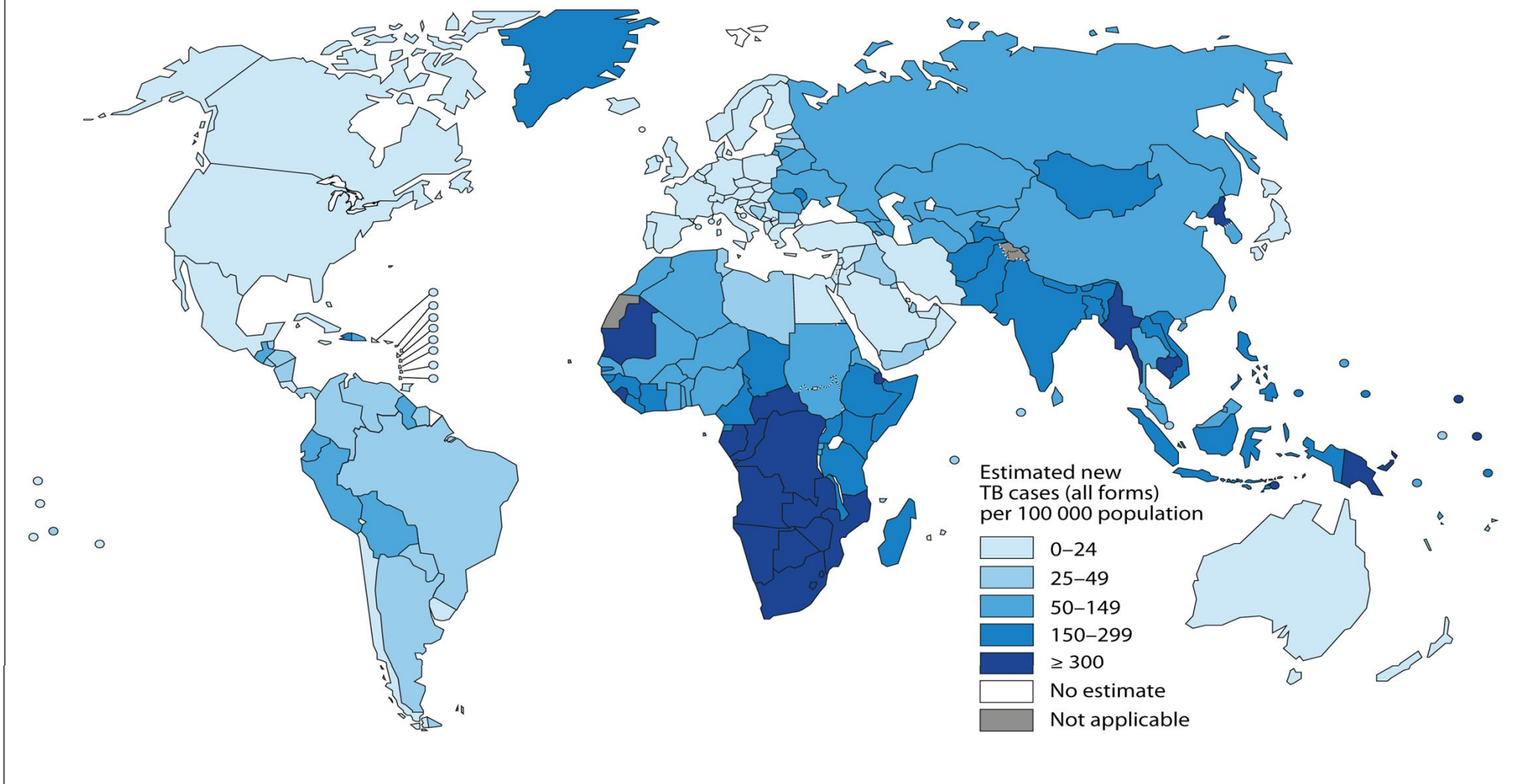


Epidemiology of TB in 21st Century

- In 2011
 - 8.7 million new cases
 - 1.4 million deaths
- Resistance
 - MDR-TB
 - XDR-TB
 - TDR-TB
- Overlap with HIV epidemic
- Burden of latent infection



Estimated tuberculosis (TB) incidence rates, 2011



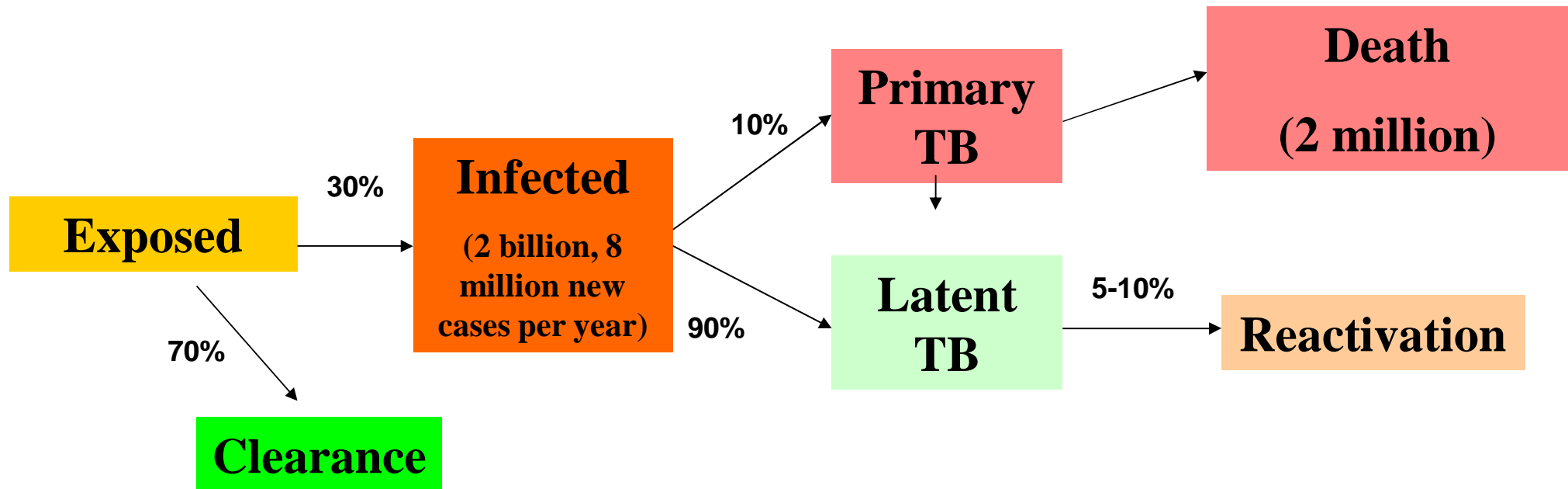
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Source: *Global Tuberculosis Report 2012*. WHO, 2012.





Tuberculosis in humans





Bacille Calmette-Guerin

- Live attenuated *Mycobacterium bovis*
- First used in 1921 (per os)
- 2 big trials in 1950s:
 - UK (Copenhagen strain, highly effective)
 - US (Tice strain, no effect)



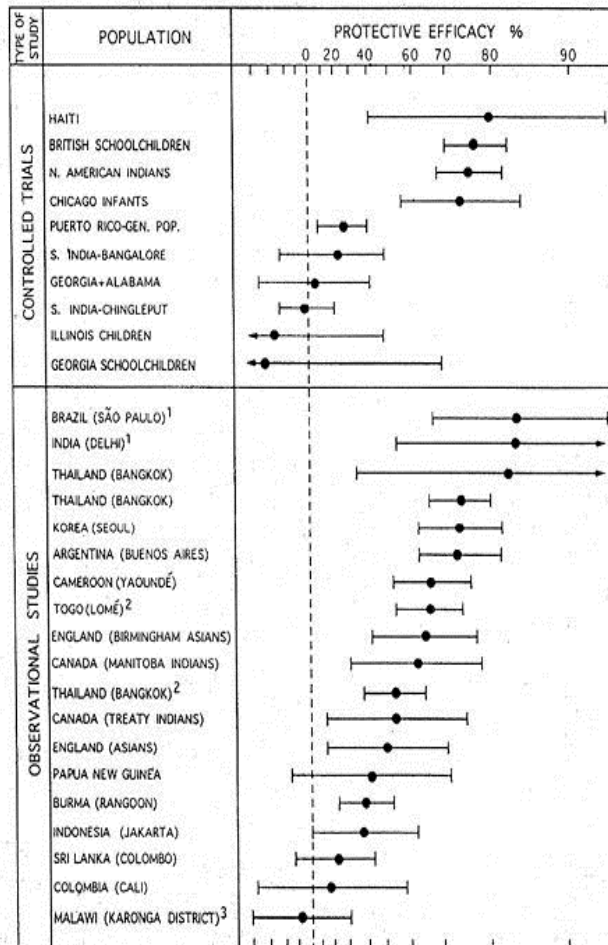


Efficacy of BCG

- Good
 - Disseminated TB and TB meningitis
 - Leprosy
- Bad
 - Lung disease – at any age
 - Boosting (Rodrigues et al, Lancet 2005)



BCG Protective Efficacy – Meta analysis



- 70 trials; spanning 46 years

- Efficacy of 0% - 80%

- Average reduction in incidence of 50%

- Latitude has major influence on efficacy

- Some trials showing durability of protection



Why doesn't BCG work?

- Different strains of BCG
- Nutrition
- Exposure to environmental mycobacteria
 - Masking (Black et al, 2002)
 - Blocking (Brandt et al, 2002)



Other problems with BCG

- Safety in immuno-suppressed
- Contra-indicated in HIV-infected adults
- Risk of disseminated BCG disease in HIV-infected infants
- Change of WHO policy
- Relative balance of risks



Potential vaccine types

- Whole organism
 - Improved BCG
 - Attenuated *M.tb*

- Subunit – choice of vector and antigen
 - DNA
 - Protein/adjuvant
 - Recombinant virus/bacteria



Design of an improved vaccine against TB

- Include BCG in new regime
- Needs to induce cellular immune response
- 3 possible strategies:
 - Enhance BCG with a subunit vaccine
 - Protein + adjuvant
 - Viral vector
 - Replace BCG with improved BCG / attenuated *M. tb*
 - Enhance an improved BCG



MVA85A

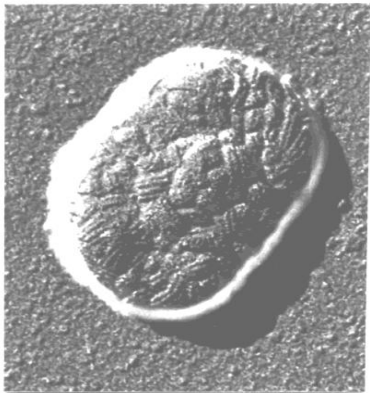
Modified vaccinia Ankara (MVA)

Poxvirus

No replication in mammalian tissues

Good T cell enhancing vector

Excellent safety record



M.tb antigen 85A

Mycolyl transferase

Major target antigen

Protective in small animals

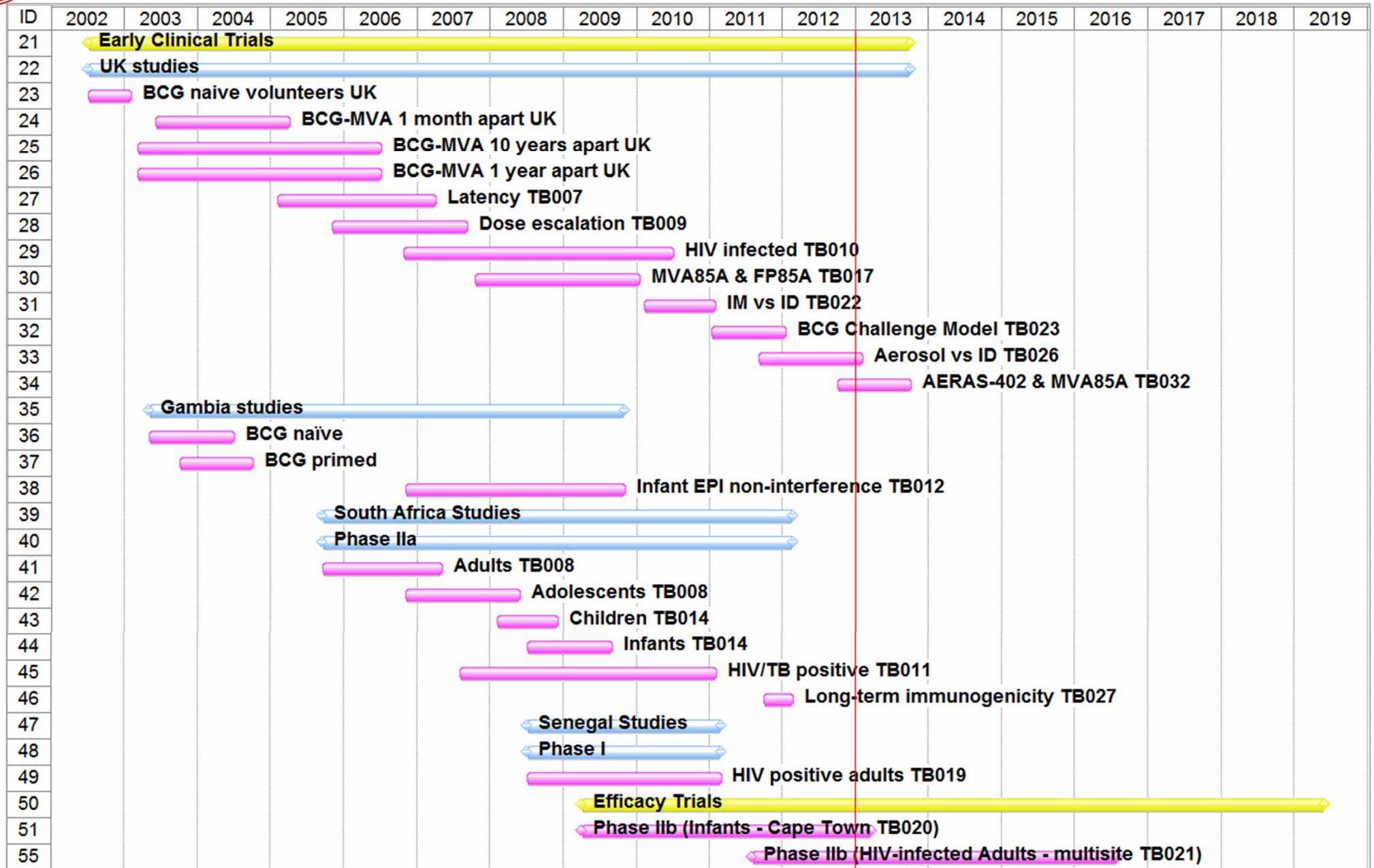
In all environmental
mycobacteria

Doesn't interfere with new
diagnostic tests

BCG - MVA85A regimen



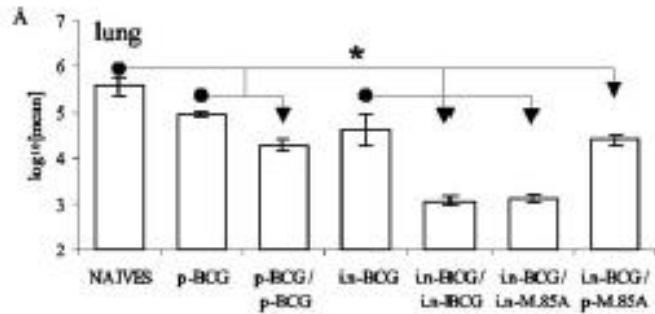
Summary of clinical trials with MVA85A since 2002





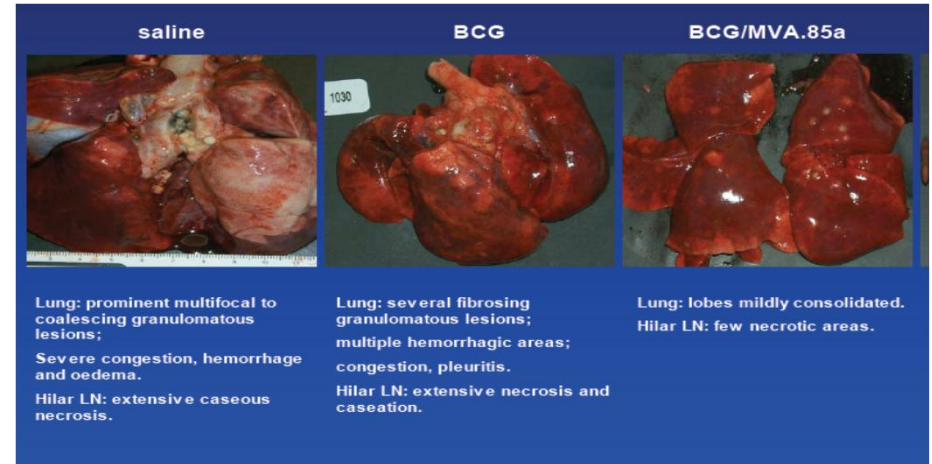
MVA85A can improve BCG induced protection in preclinical animal models

MICE



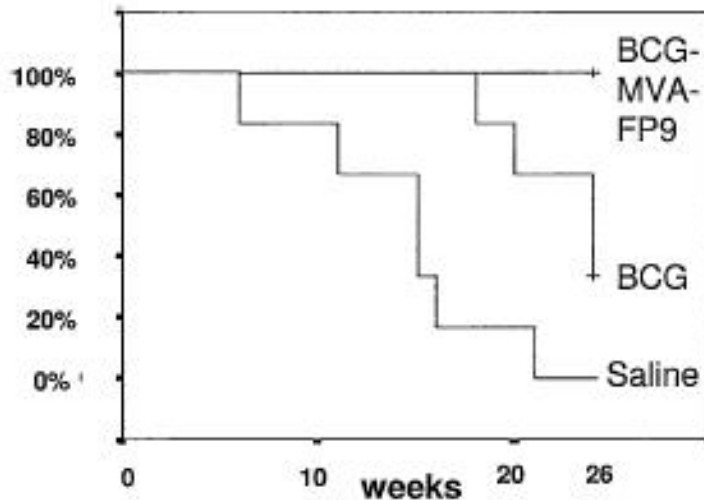
Goonetilleke et al, JI 2003

NHP



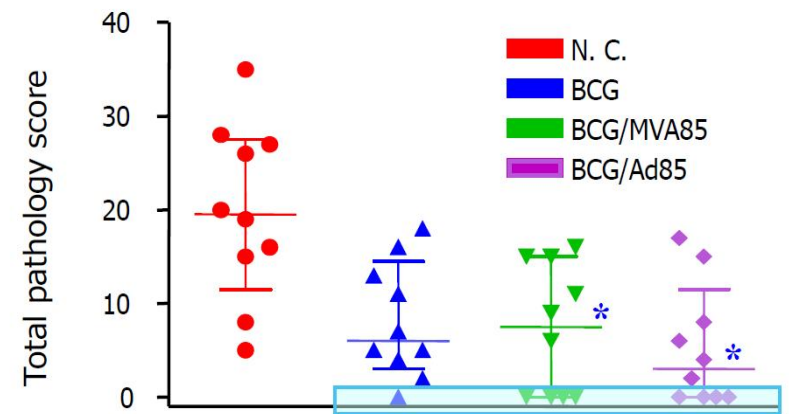
Verreck et al, PLoS ONE 2009

GUINEA PIGS



Williams et al, I&I 2005

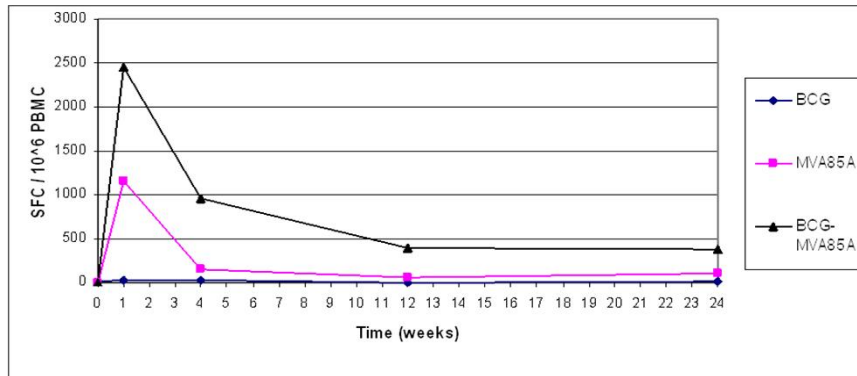
CATTLE



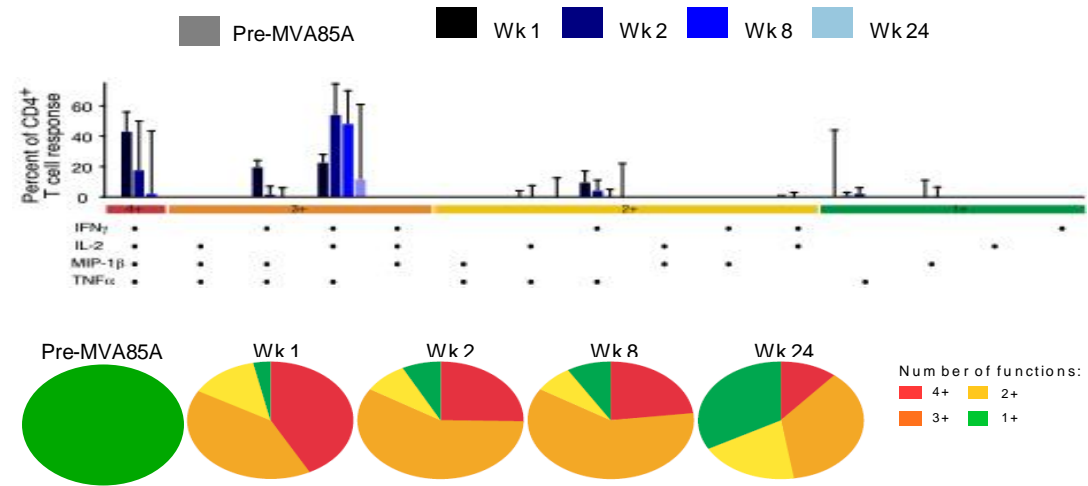
Vordermeier M et al, I&I 2009



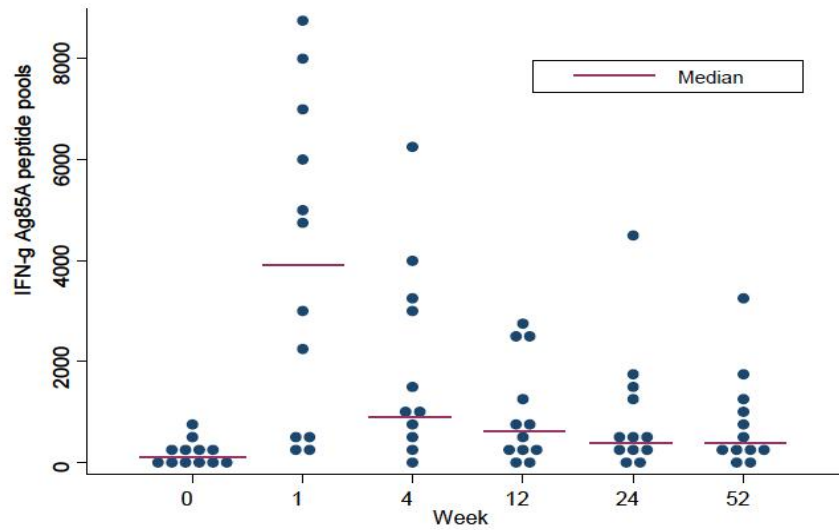
MVA85A is highly immunogenic in UK trials



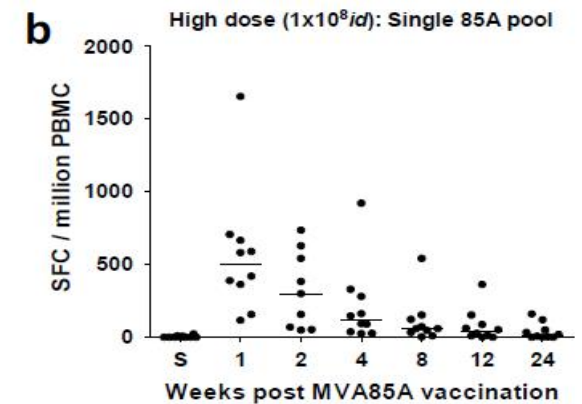
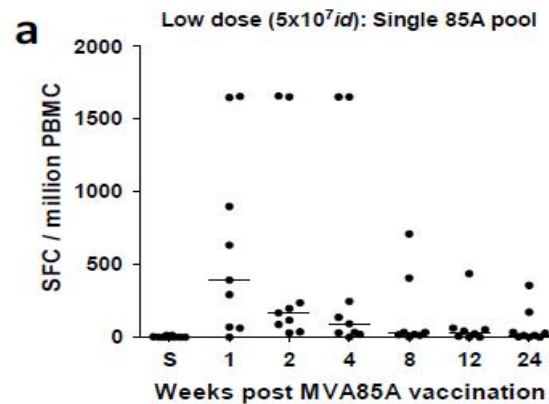
McShane H et al, NM 2004



Beveridge N et al, EJI 2007



Sander C et al, AJRCCM 2009



Minassian A et al, BMJ Open 2011





Infant Phase IIb efficacy trial

- Objectives:
 - Safety
 - Immunogenicity
 - Efficacy (against disease & infection)
 - Immune correlates
- Design:
 - BCG vaccinated infants in Worcester, South Africa
 - Randomised at 18-26 weeks to receive either:
 - MVA85A (1×10^8 pfu)
 - placebo (Candin)
 - Sample size = 2784 (1392/arm)
 - Cumulative TB incidence of 3%
 - 90% power to detect 60% improvement over BCG alone
- Status
 - Fully enrolled
 - 2 DSMB reviews
 - Due to unblind in Q1 2013





Progress

- 14 vaccines evaluated in clinical trials
- Two vaccines being evaluated in efficacy trials
- No immunopathology or other safety issues identified in any clinical trials to date



Challenges

- No immunological correlate
- No validated animal models
- Difficulty with end-points
- Finite capacity to do efficacy testing



Jenner's vaccine challenge study: 1796





Acknowledgements



**WIV-ISP, Brussels,
Belgium**





Funders and partners

wellcometrust

AERAS

FDA U.S. Food and Drug Administration
Protecting and Promoting Your Health

Oxford Emergent Tuberculosis Consortium

European Commission



Study participants