

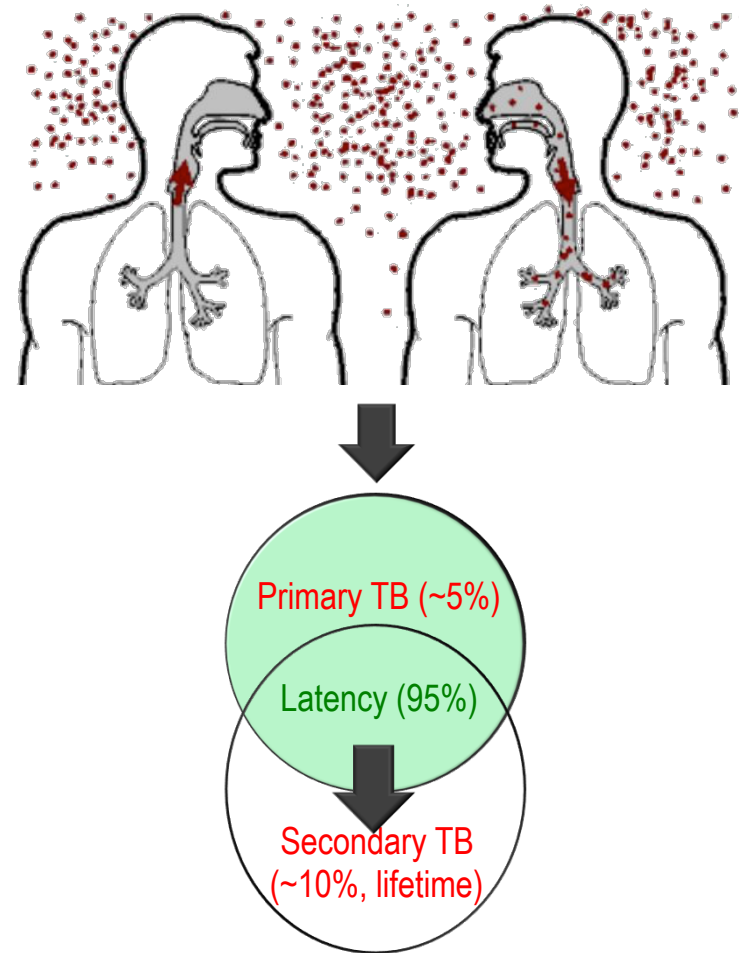
The BCG vaccine: Its manipulation & limitations

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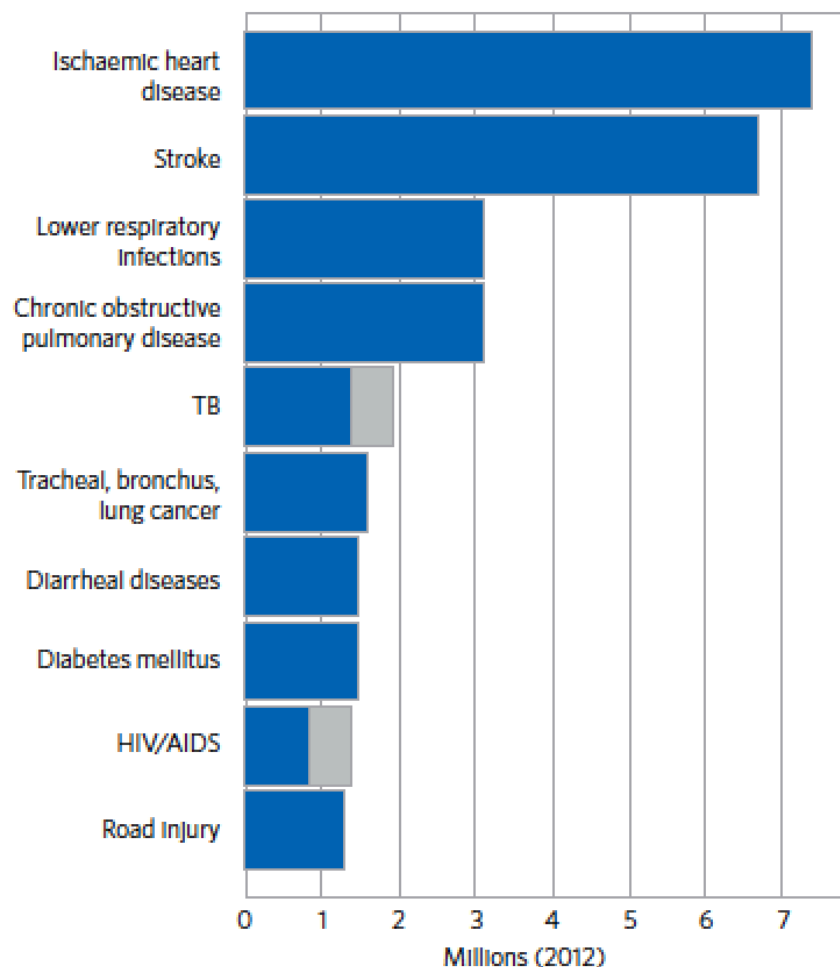
What is Tuberculosis?

- Tuberculosis (TB) is a chronic bacterial (*Mycobacterium tuberculosis*) infection that often affects the lungs
- TB spreads from person to person through the air
- About a third (2+ billion) of the world's population has latent TB
- Infected people have a lifetime risk of falling ill with TB of 10%
- People with compromised immune system (e.g., HIV+, malnutrition) have a much higher chance

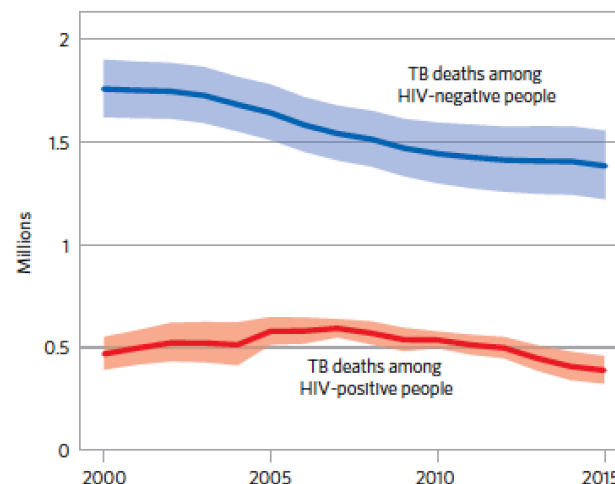


Tuberculosis still is a serious public health issue

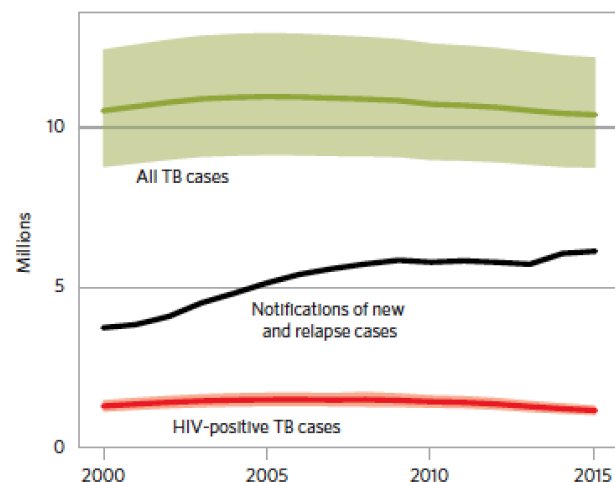
Top causes of death worldwide in 2012.^{a,b,c,d} Deaths from TB among HIV-positive people are shown in grey.^d



TB deaths

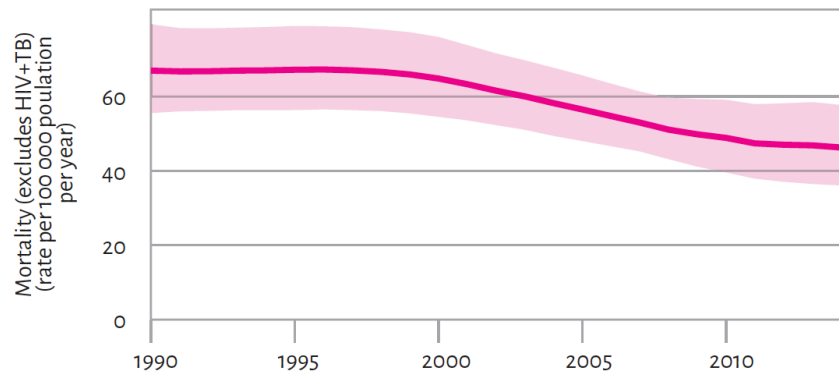


TB incidence

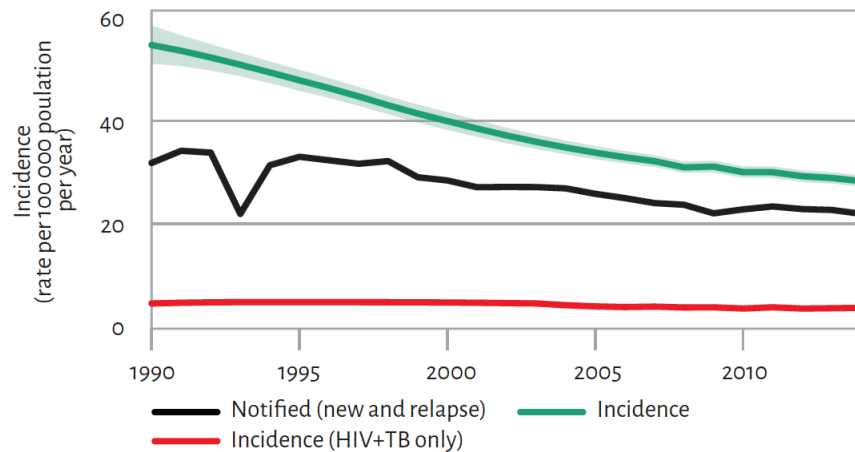
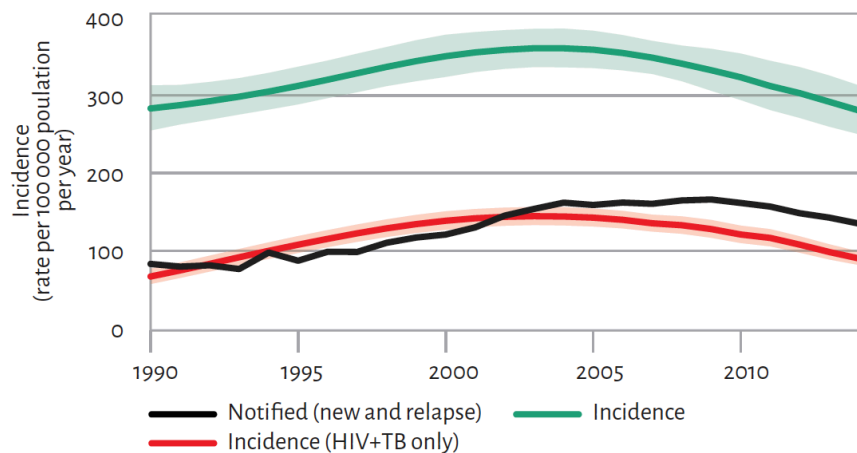
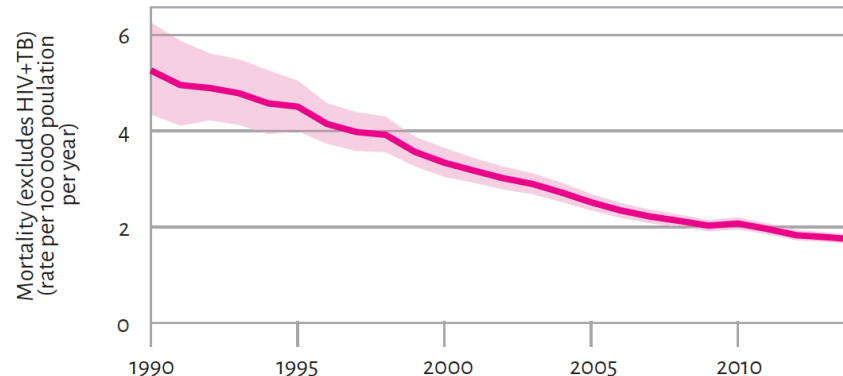


TB incidence in Africa is higher than in Europe

Africa

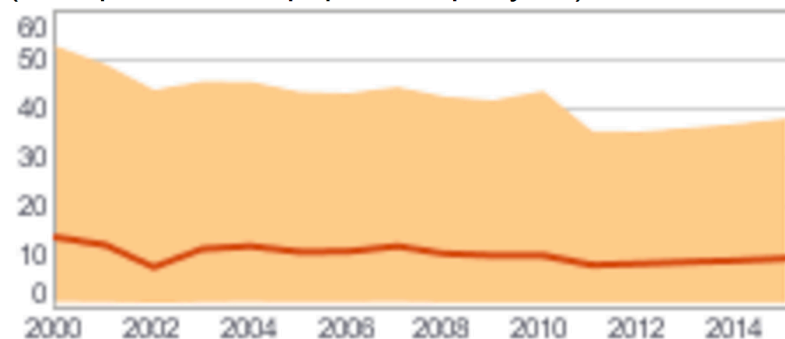


European Union



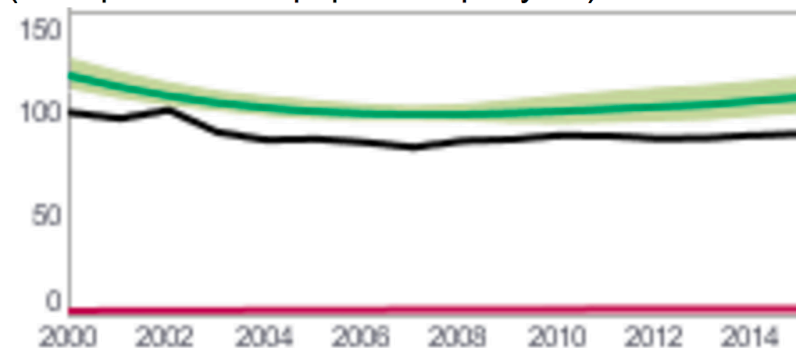
TB incidence in Morocco

(Rate per 100 000 population per year)



— Mortality (excludes HIV+TB)

(Rate per 100 000 population per year)



— Incidence

— Notified (new and relapse)

— Incidence (HIV+TB only)

Multiple mechanisms for a complex disease

- Nutrition & hygiene (e.g. vitamin D)
- HIV co-infection
- Sex (2 males:1 female)
- Age (adults)
- *M. tuberculosis* strain (e.g. Beijing)
- Host genetic background (e.g. NRAMP, VDR, DC-SIGN...)

Toll-Like Receptor Triggering of a Vitamin D–Mediated Human Antimicrobial Response

Philip T. Liu,^{1,2*} Steffen Stenger,^{4*} Huiying Li,³ Linda Wenzel,⁴ Belinda H. Tan,^{1,2} Stephan R. Krutzik,² Maria Teresa Ochoa,² Jürgen Schaubert,² Kent Wu,¹ Christoph Meinken,⁴ Diane L. Kamen,⁴ Manfred Wagner,² Robert Bals,⁸ Andreas Steinmeyer,² Ulrich Zügel,¹⁰ Richard L. Gallo,⁵ David Eisenberg,² Martin Hewison,¹¹ Bruce W. Hollis,¹² John S. Adams,¹¹ Barry R. Bloom,¹³ Robert L. Modlin^{1,2,†}

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PLOS MEDICINE

Research in Translation

Sexual Inequality in Tuberculosis

Olivier Neyrolles^{1,2*}, Lluís Quintana-Murci³

¹Centre National de la Recherche Scientifique, Institut de Pharmacologie et de Biologie Structurale, Toulouse, France, ²Université de Toulouse, Université Paul Sabatier, Institut de Pharmacologie et de Biologie Structurale, Toulouse, France, ³Institut Pasteur, Human Evolutionary Genetics, CNRS, URA3013, Paris, France

Influence of vitamin D deficiency and vitamin D receptor polymorphisms on tuberculosis among Gujarati Asians in west London: a case-control study

Robert J Wilkinson, Martin Llewelyn, Zahra Toossi, Punita Patel, Geoffrey Pasvol, Ajit Lalvani, Dennis Wright, Mohammed Latif, Robert N Davidson

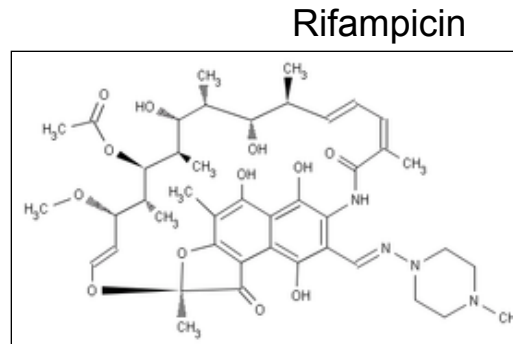
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PLOS MEDICINE

Promoter Variation in the DC-SIGN–Encoding Gene *CD209* Is Associated with Tuberculosis

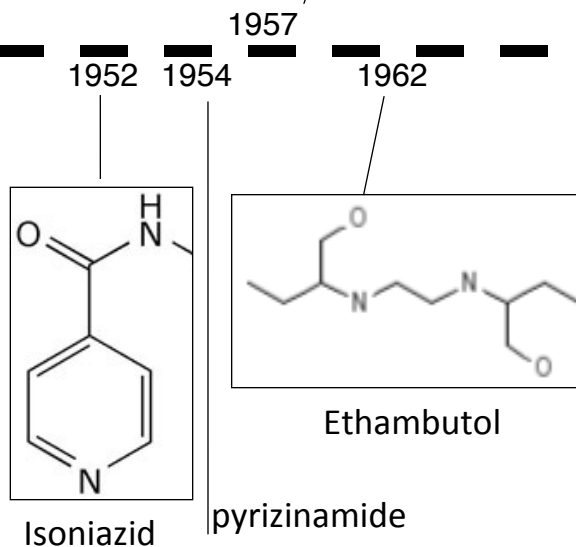
Luis B. Barreiro^{1,2}, Olivier Neyrolles², Chantal L. Babb³, Ludovic Tailleux², Héléne Quach¹, Ken McElreavey⁴, Paul D. van Helden³, Eileen G. Hoal³, Brigitte Gicquel², Lluís Quintana-Murci^{1*}

Therapy for TB: falling behind the times...



Moxifloxacin

1903-1940
1903: Phototherapy
(Nobel prize, N.R. Finsen)

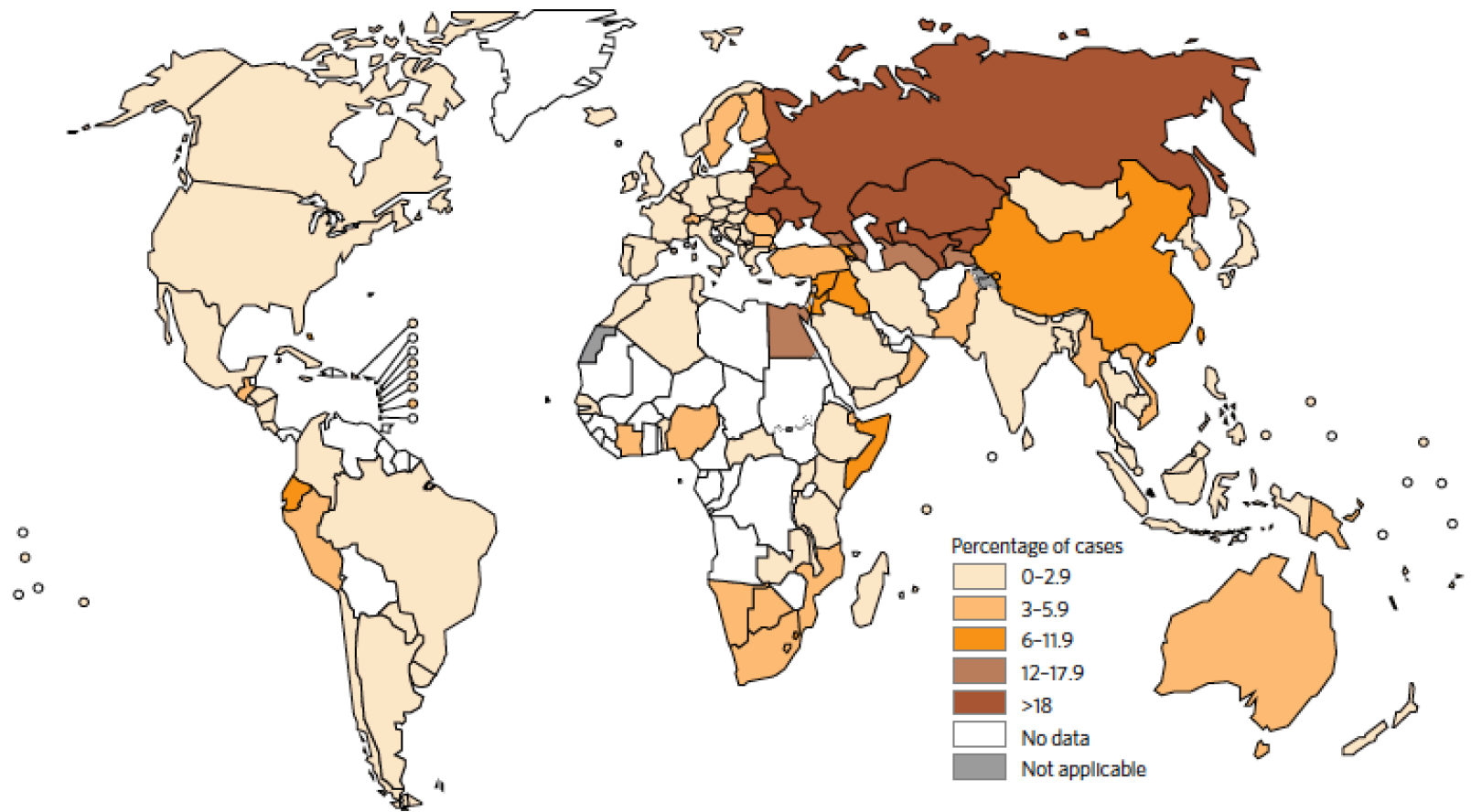


MDR
TB

XDR
TB

The rise of multidrug-resistant TB strains

Percentage of new TB cases with MDR/RR-TB^a



BCG: the only TB vaccine available today!



Albert CALMETTE
(1863-1933)



Camille GUERIN
(1872-1961)

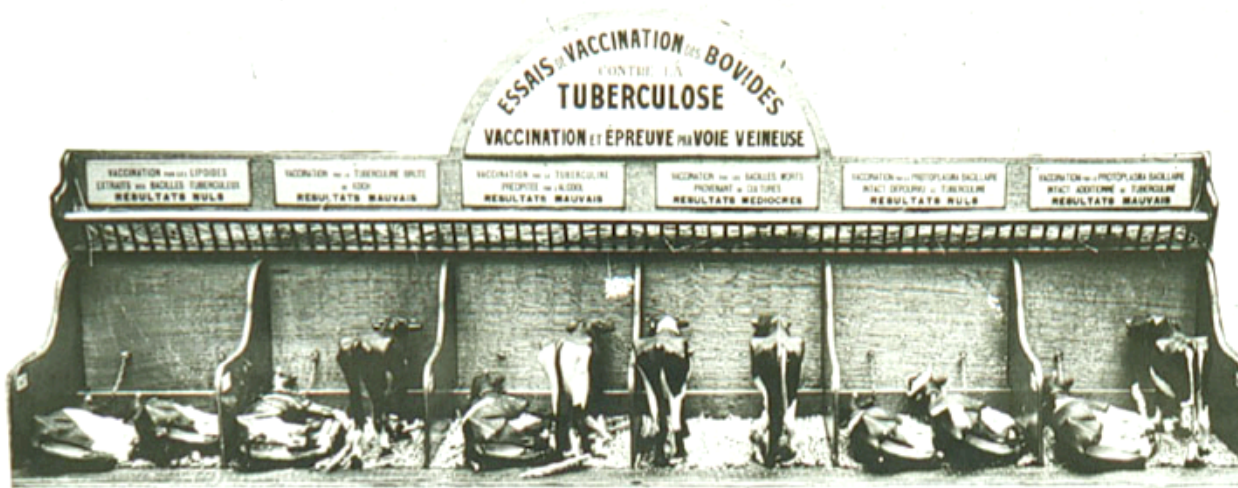
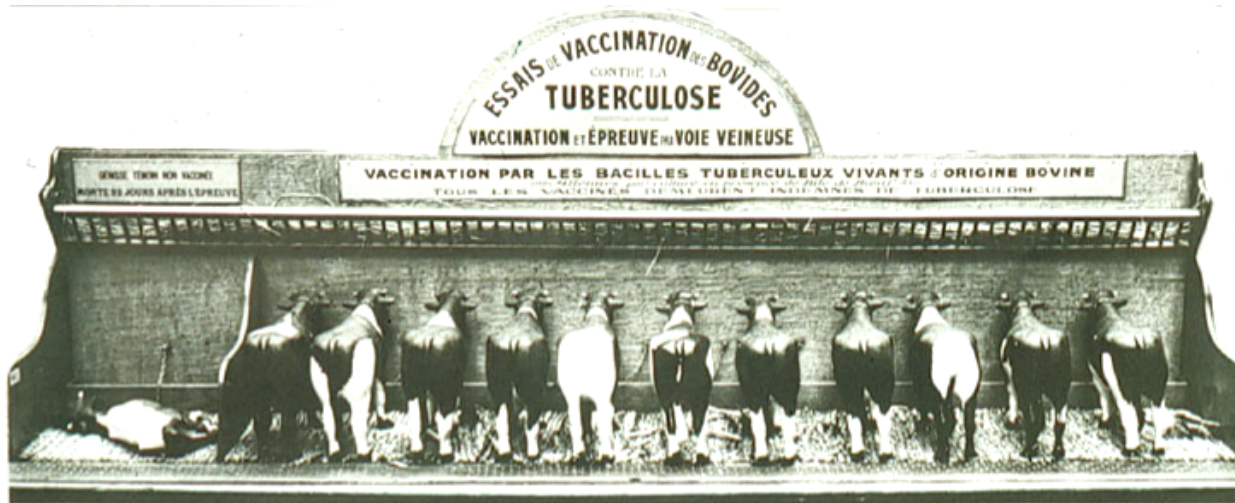
1908: *M. bovis* (« Lait de Nocard ») culture on cooked potatoes and glycerinated ox bile



BCG: the only TB vaccine available today!



BCG: the only TB vaccine available today!



BCG: the only TB vaccine available today!

1921: 231 passages

Safety studies in
animals:

- Cattle
- Horses
- Sheep
- Guinea pigs
- Dogs
- Rabbits
- Rats
- Mice
- Primates
- Chicken
- Pigeons

Recommandation:

Vaccinate young cattle
during their first days of life

BCG: the only TB vaccine available today!

1921: 231 passages

- First vaccination of newborn (days 3, 5, 7)
- 1924-1936: first large-scale multi-centric efficacy trial on 5,183 children in France
- No placebo – Efficacy estimated at 93%, compared to 25% TB-caused death rate in children born in TB families (1st year of life!)



BCG: the only TB vaccine available today!

About 3 billion doses have been given since 1921!

About 115 million doses are given annually to around 80% of children in the world

Not anymore mandatory in France, except in Paris, Provence-Alpes-Côte d'Azur & Guyane (recommendation)



BCG vaccine: its limitations

- Protection rates against TB meningitis & disseminated disease: up to 80%!
- However, BCG offers poor protection against pulmonary tuberculosis in adolescents and adults (0-80% efficacy rate)
- Reasons:
 - method differences among clinical assays
 - genetic differences among sample populations
 - degrees of malnutrition in vaccinated subjects
 - variation in the virulence of *M. tuberculosis* strains
 - effects of environmental mycobacteria exposure on the immune response to BCG

The need for new TB vaccines

- Most successful vaccines today target pathogens against which **humoral immunity** is sufficient to achieve protection & sterile eradication
- Vaccines against pathogens whose control depends on **cellular immunity** is a challenge!

1990
0 vaccine candidate



Today
>12 candidates in clinical trials

The journey towards more efficient TB vaccines: Strategy #1

- Aim = replacing BCG with safer, more immunogenic, inducing longer lasting protection, inducing protection against highly virulent clinical isolates (e.g. Mtb Beijing strains, MDR etc.)
 - To improve BCG:
 - Introduce immunodominant Mtb-specific Ag (e.g. ESAT6)
 - Overexpressing BCG/Mtb Ag (e.g. Ag85)
 - Genetic engineering for superior immune efficacy (e.g. Ag cross-priming)
 - To attenuate Mtb:
 - Deletion of essential metabolic genes (e.g. *panCD*)
 - Deletion of major virulence genes (e.g. *phoP*)

Viable TB vaccines

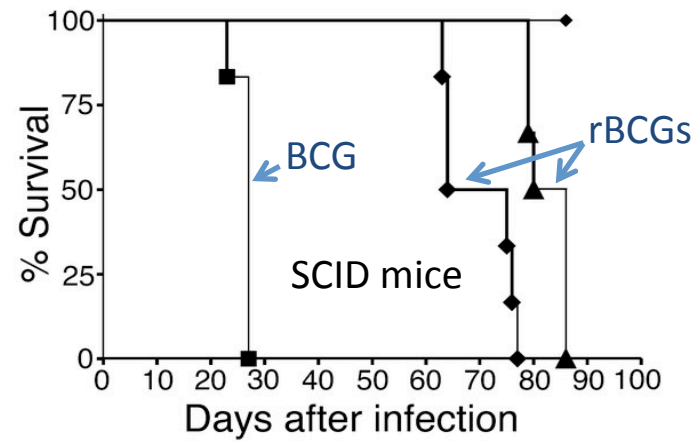
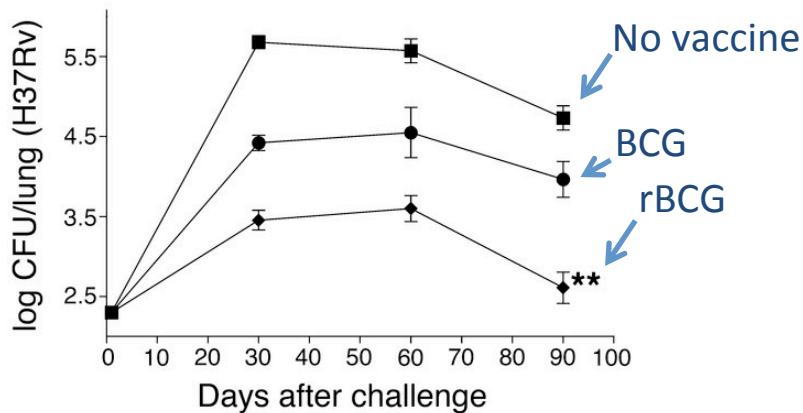
Name	Vaccine	Modification
VPM1002	BCG	Chromosomal integration of listeriolysin encoding gene (perforation of phagosomal membrane); deletion of urease gene (acidification of phagosome)
MTBVAC	<i>Mycobacterium tuberculosis</i>	Deletion of <i>PhoP</i> (transcription factor) and of <i>fadD26</i> (phthiocerol dimycocerosate synthesis)

TB, tuberculosis; BCG, bacille Calmette–Guérin.

Strategy#1: An example of better BCG, the VPM1002



Stefan KAUFMANN
Max Planck Institute
Berlin, Germany



Grode *et al.* 2005 J Clin Invest

Inactivated whole-cell mycobacterial vaccines

Name	Inactivated organism	Goal
DAR-901	Non-tuberculous Mycobacterium	Prevention
Mw	<i>Mycobacterium indicus pranii</i>	Therapy
Vaccae	<i>Mycobacterium vaccae</i>	Therapy
RUTI	<i>Mycobacterium tuberculosis</i>	Therapy

The journey towards more efficient TB vaccines: Strategy #2

- Aim = boosting BCG with sub-unit vaccines
 - Protein/lipid Ag + adjuvant
 - Recombinant viral vectors

Antigens used in subunits for TB vaccines

Vaccine	Antigen	Description
M72	Rv1196	PPE family member
	Rv0125	Peptidase
H1	ESAT-6	Prominent antigen of Mtb encoded in region of difference 1
	Ag85B	Mycolyl transferase
H4	TB10.4	Prominent TB antigen
	Ag85B	Mycolyl transferase
H56	H1 + Rv2660c	Dormancy antigen
ID93	Rv2608	PPE family member
	Rv3619	Virulence factor
	Rv3620	Virulence factor
	Rv1813	Dormancy antigen
Ad5Ag85A	Antigen 85A	Mycolyl transferase
MVA85A	Antigen 85A	Mycolyl transferase
Ad35	Antigen 85A	Mycolyl transferase
	TB10.4	Prominent TB antigen
Ag85B	Antigen 85B	Mycolyl transferase
TB-FLU-04L	Antigen 85A	Mycolyl transferase

TB, tuberculosis; PPE, proline, poline, glutamate residues; Mtb, *Mycobacterium tuberculosis*.

Adjuvants used for TB vaccines

Vaccine	Name	Composition
H1, H4, H56	IC31	Cationic peptide/TLR9 agonist
H1	CAF01	Cationic liposome/immunomodulatory glycolipid
ID93	GLA-SE	Oil in water emulsion/TLR4 agonist
M72	AS01E	Liposome/TLR4 agonist

TB, tuberculosis; TLR, toll-like receptor.

Viral Vectors used for TB vaccines

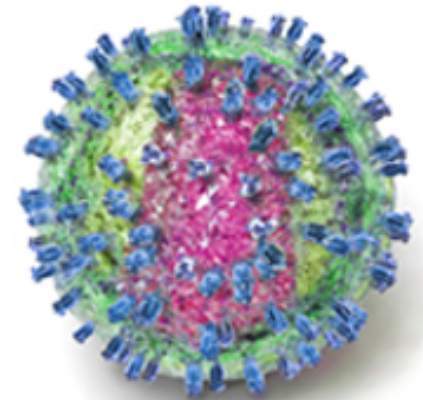
Name	Vector
MVA	Modified vaccinia Ankara virus
Ad5	Adenovirus 5
Ad35	Adenovirus 35
ChAd	Chimpanzee adenovirus
FLU	Replication-deficient influenza virus (H1N1)

TB, tuberculosis.

Strategy#2: An example of a viral vector-carried a mycobacterial antigen, MVA-Ag85A



Helen MCSHANE
University of Oxford, UK

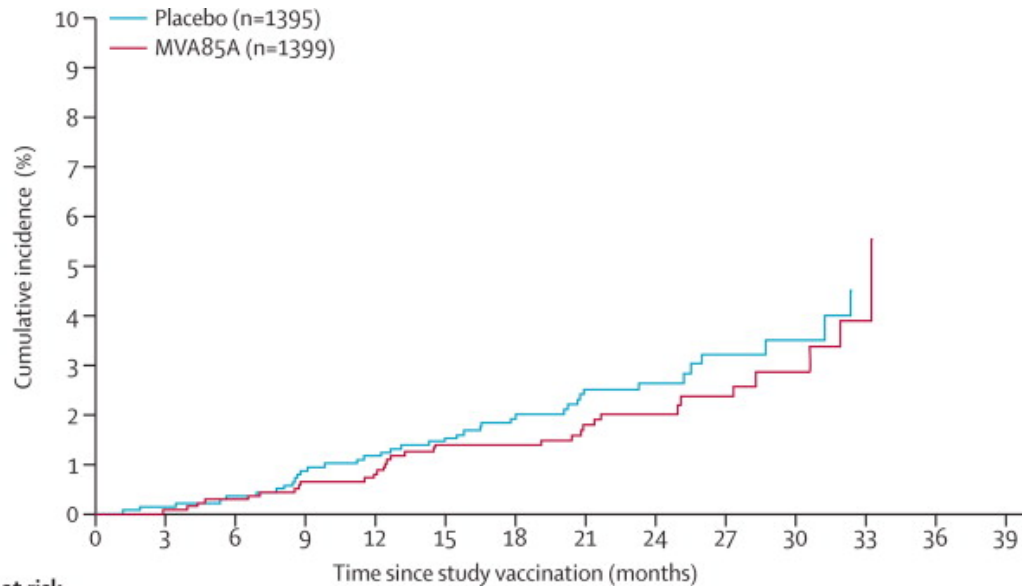


Tameris *et al.* 2013 Lancet

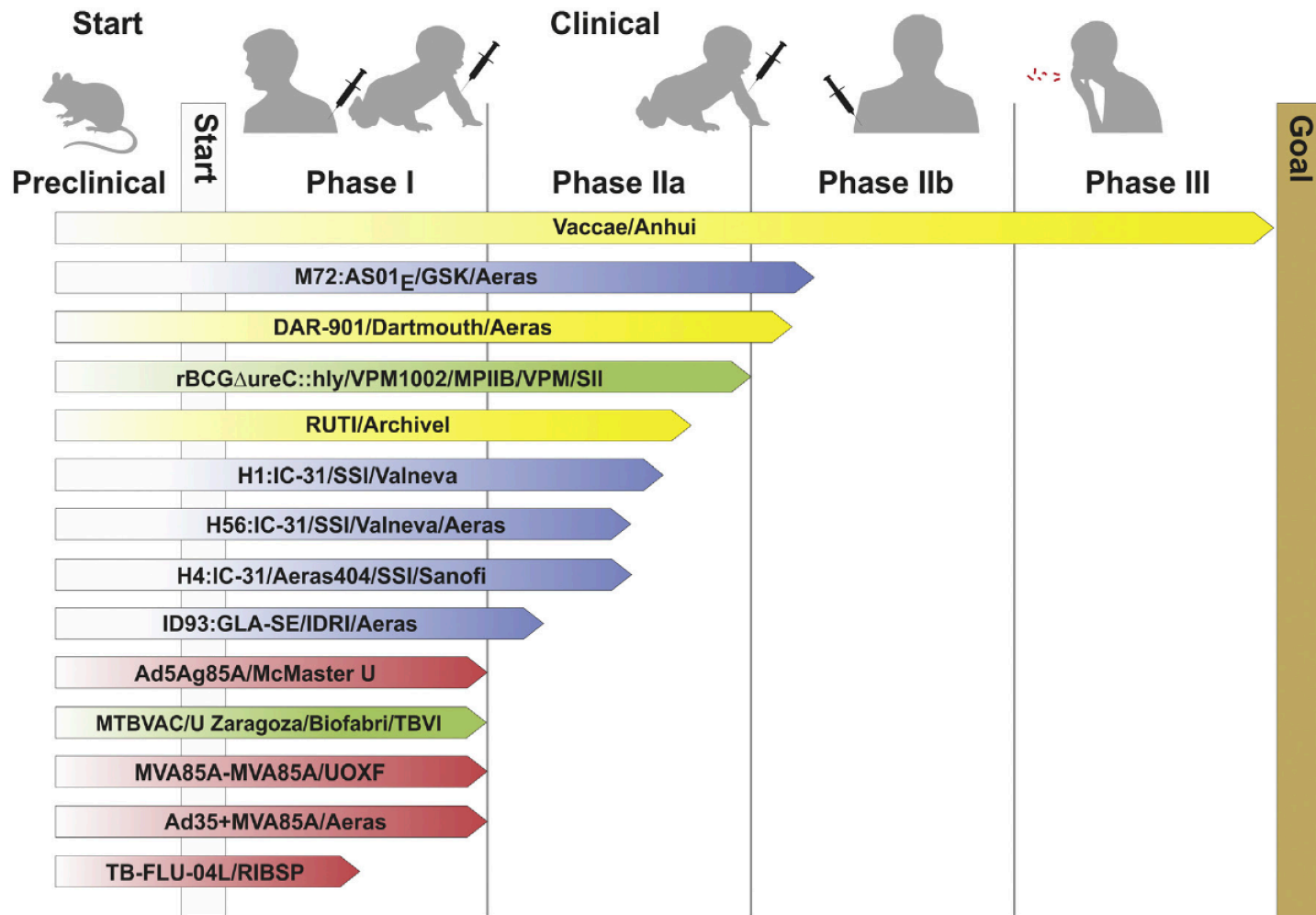
Phase IIb trial

Efficacy = 0!

McShane *et al.* 2004 Nat Med



Present Pipeline of major TB vaccines in clinical trials



Future Perspectives

- Despite limitations, BCG vaccine is not easy to replace because it is safe and offers multiple advantages
- The improvement of BCG remains the best alternative for the rational design of a TB vaccine
- Identification of novel mycobacterial epitopes & antigens can be applied to enhance BCG:
 - e.g. infection stage-specific epitopes
 - Lipid antigens
- Further improvement of the immune stimulatory capacity → making a multi-valent BCG vaccine
 - novel adjuvants for mucosal delivery/T cell homing



Thank you!



Questions?

