AERAS

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Update on Tuberculosis Vaccines - 2014

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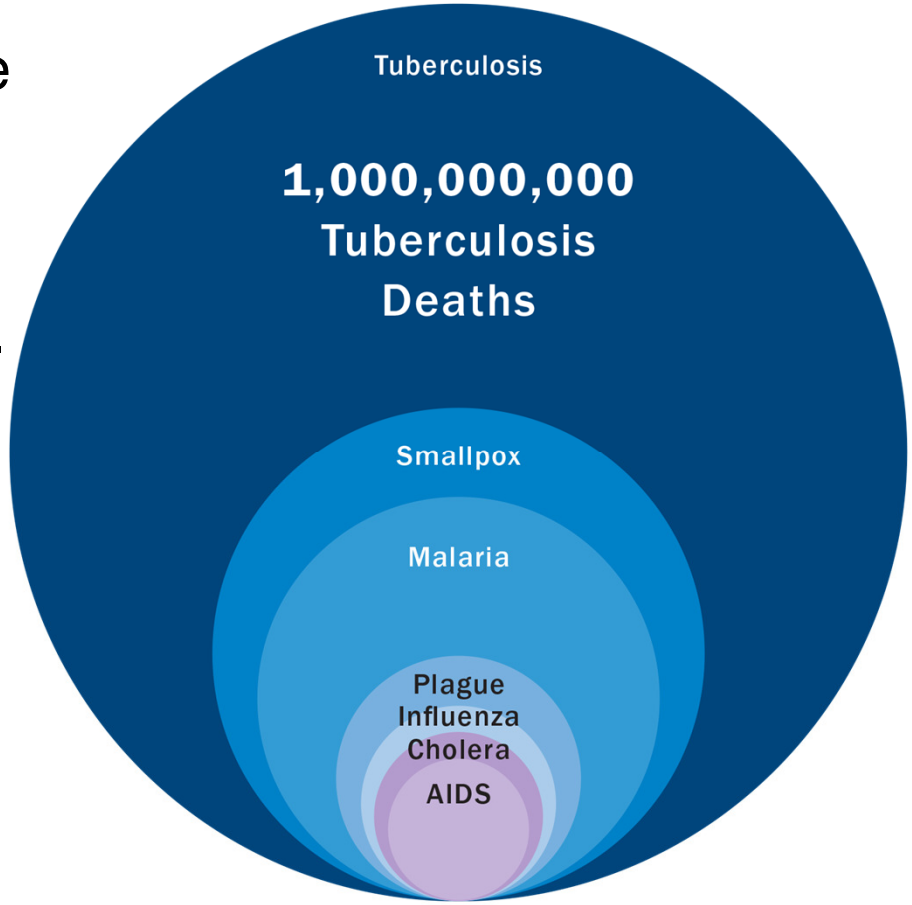
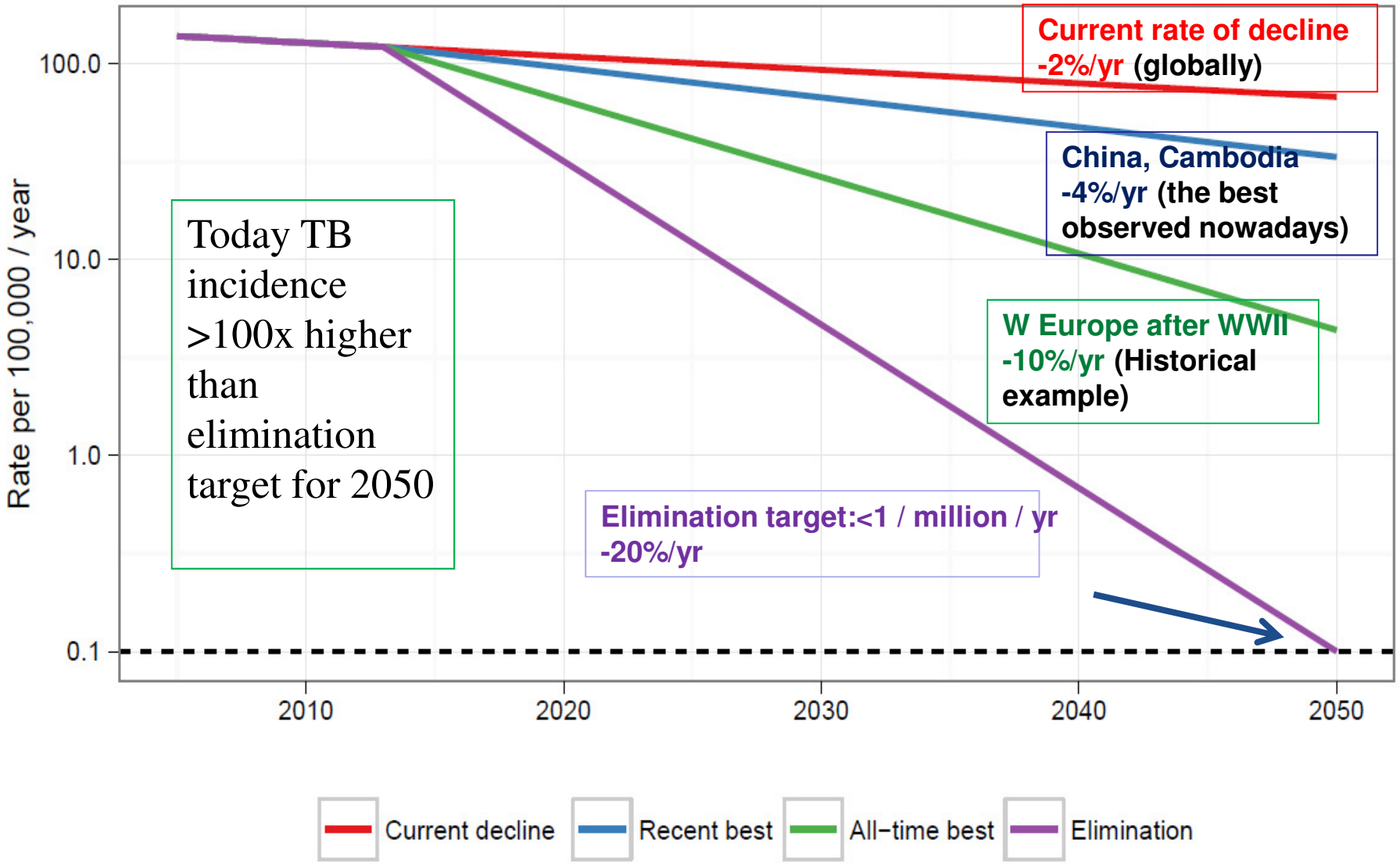
TB is Mother Nature's number one killer over the past centuries

- TB is spread through the air like a common cold
- Nearly 8.5 million people become sick with TB each year.
- TB kills 1 in 4 people infected with HIV.
- 530,000 annual cases among children aged under 15
- 410,000 women killed annually by the disease

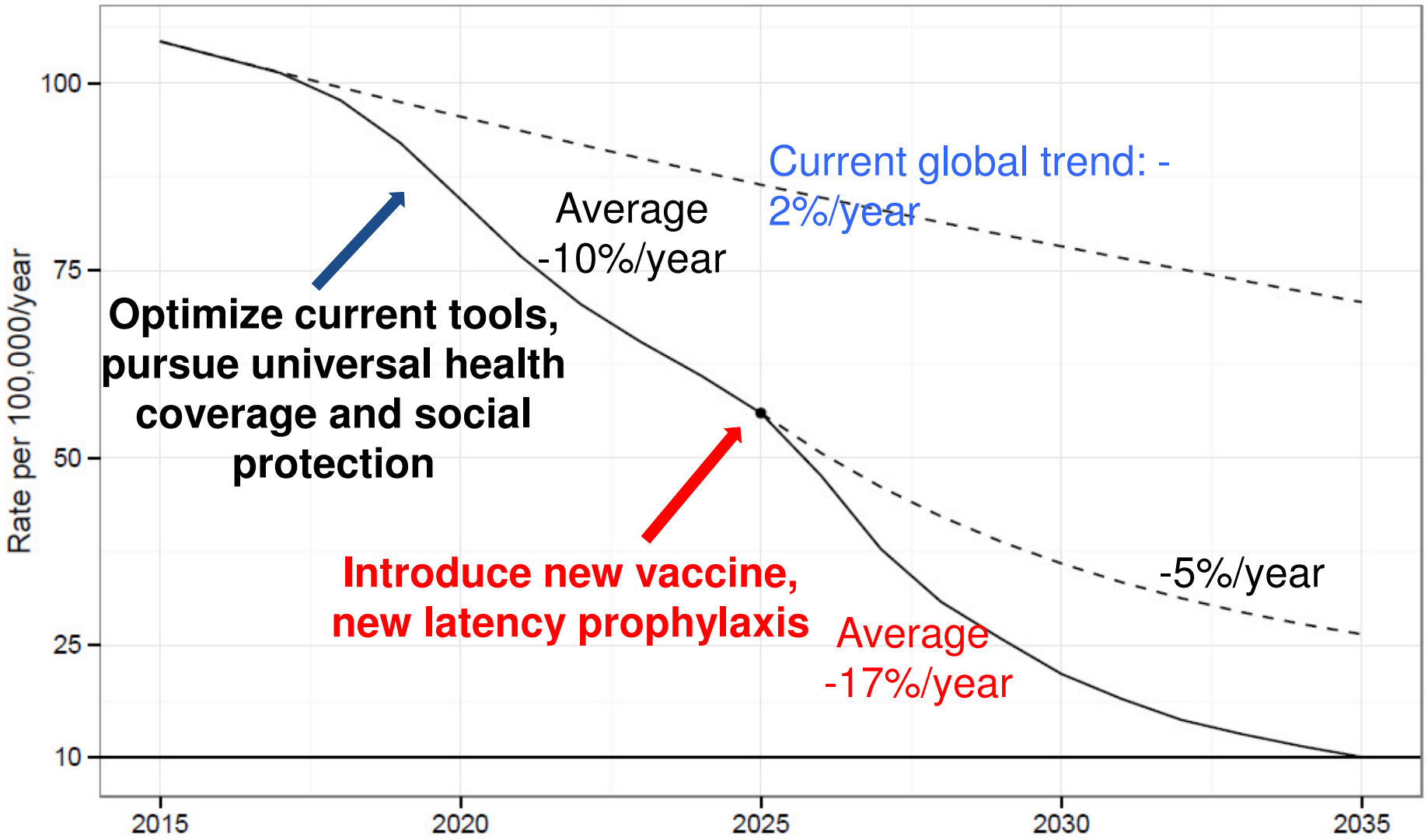


Source: Nature/ World Tuberculosis Report, 2013

TB will not be eliminated by 2050



Projected acceleration of TB incidence decline to target levels



GLOBAL TB PROGRAMME

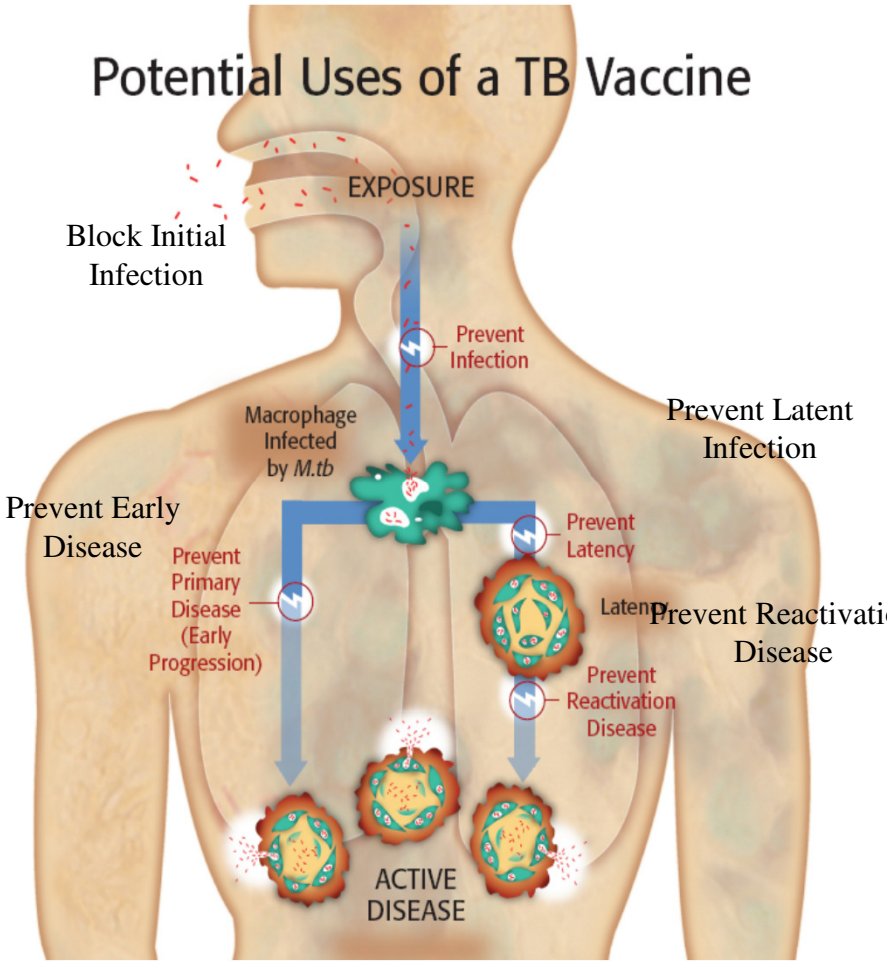
World Health Organization

Strategies for TB Vaccine Development

- **Pre-infection:** to prevent infection
- Either initial infection or establishment of the granuloma

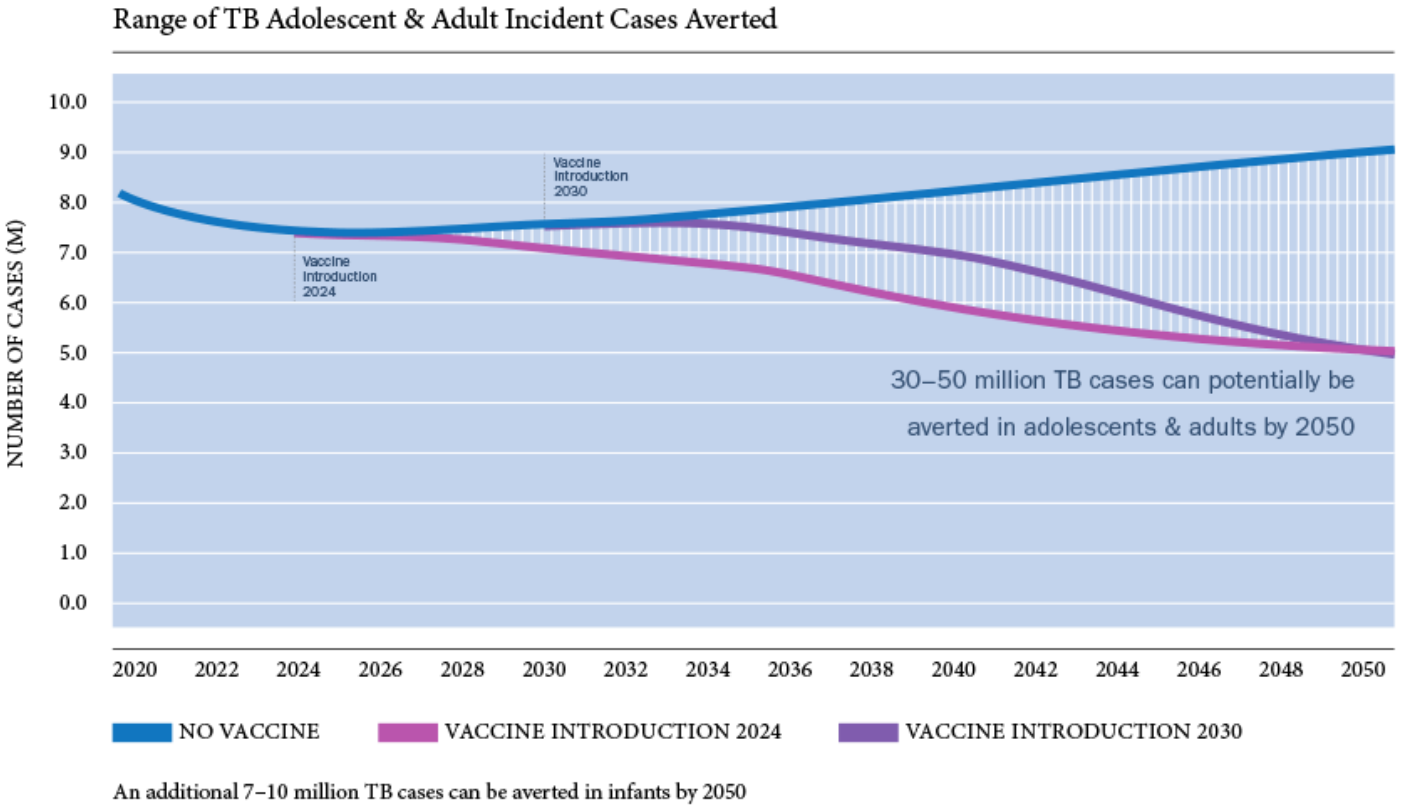
–Post-infection: to prevent disease
– *after initial infection (most animal data to date)*
– reactivation from latency (minimal animal data)

– **Immunotherapeutic:** treatment
  - Shorten the course of chemotherapy for active TB
  - Decrease relapse or reinfection rates (*may correlate to latency*)



Public Health Impact

A new vaccine that could prevent adolescents and adults from developing and transmitting TB would be the single most cost-effective tool in mitigating the epidemic.

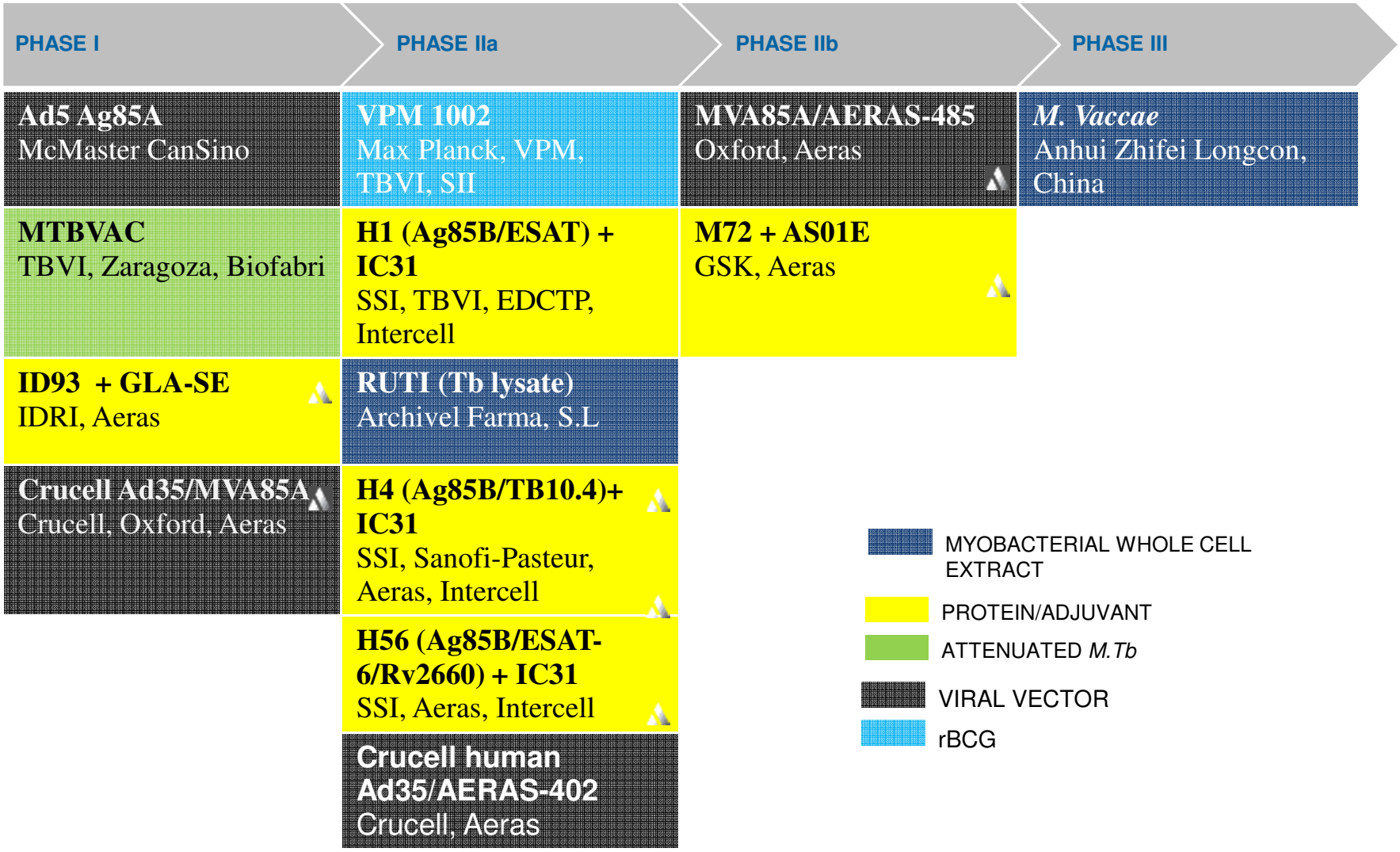


A 60% efficacious adolescent and adult vaccine, delivered to 20% of the target population, could potentially avert 30 - 50 million incident cases of TB by 2050.

Achievements to date- 2014

- One Phase 2b trial in 2800 infants successfully completed, although no efficacy was seen using a viral vectored, single antigen construct in infants boosted at age 4-6 mo.
- Recent NHP studies have shown the ability of novel constructs, such as CMV, to protect in a highly stringent model that resembles human tuberculosis
- Increased diversity of candidates in the clinic, as compared to none in 2000, to use as tools for testing speific hypotheses
- Improvement in diagnostics (Xpert, IGRA tests) for clinical trial implementation
- Correlate of risk studies are underway

The Global Pipeline of TB Vaccine Candidates



TB Vaccines in 2014- An Innovation Strategy
(“life without a correlate of immunity”)

- Advance candidates in clinic using portfolio management, innovative trial designs, and improved animal (NHP) models
- Select and evaluate candidates that may work through antibody mediated mechanisms, and use improved animal models
- Develop and test CD1-restricted glycolipids through a trans-Atlantic consortium
- Focus on novel methods of delivery of vaccines to induce mucosal (pulmonary) immunity
- Encourage novel preclinical approaches (e.g., RNA, electroporated DNA, combinations)
- Evaluate new approaches to selecting antigens that are not dependent on the gamma-interferon/TH1 hypothesis
- Develop strains for human challenge trials

Approaches to studies in human populations to explore likelihood of technical success at lower cost

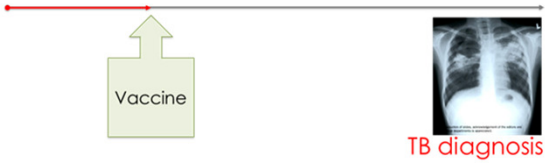
- Small intensive immunologic studies in Phase 1 in endemic area (when feasible) to see if novel animal data can be reproduced in humans
  - Phase 1 trials are to measure safety, assess immune response, generate human samples for investigation, head to head comparisons

1. RCT: compare vaccines' efficacy in preventing Mtb infection

Example:

1. *BCG vs Hyvac4 vs placebo to start at SATVI; n=990 total*
2. *Ongoing adaptive trial setting, allowing future testing of other candidates*

2. RCT: compare vaccines' efficacy in preventing recurrent TB disease



Examples:

1. *H56 vs placebo planned at multiple sites by Aeras; n~800 total*
2. *ID-93 vs placebo planned at SATVI; n=800 total*

Incidence of recurrent TB disease at least 5% in 1st year

- Consider prevention of TB disease trials in other high risk populations, e.g., prisoners, health care workers, household contacts of adults with lung TB
- Every efficacy trial must have adequate sample collection for describing correlates of risk

In both Prevention of Infection and Prevention of recurrence studies samples collected for both correlates of infection and/or correlates of risk

Important missing tools for TB Vaccine development

- Measure of exposure to the organism
- True measure of infection (using TST and IGRA now)
- Measure of burden of TB during latency (can we decrease bacterial burden?)
- True measure of cure (sterilization)
- A validated small and large animal model, especially to evaluate transmission

Most importantly, a correlate of vaccine-induced protection

Thank You.

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