

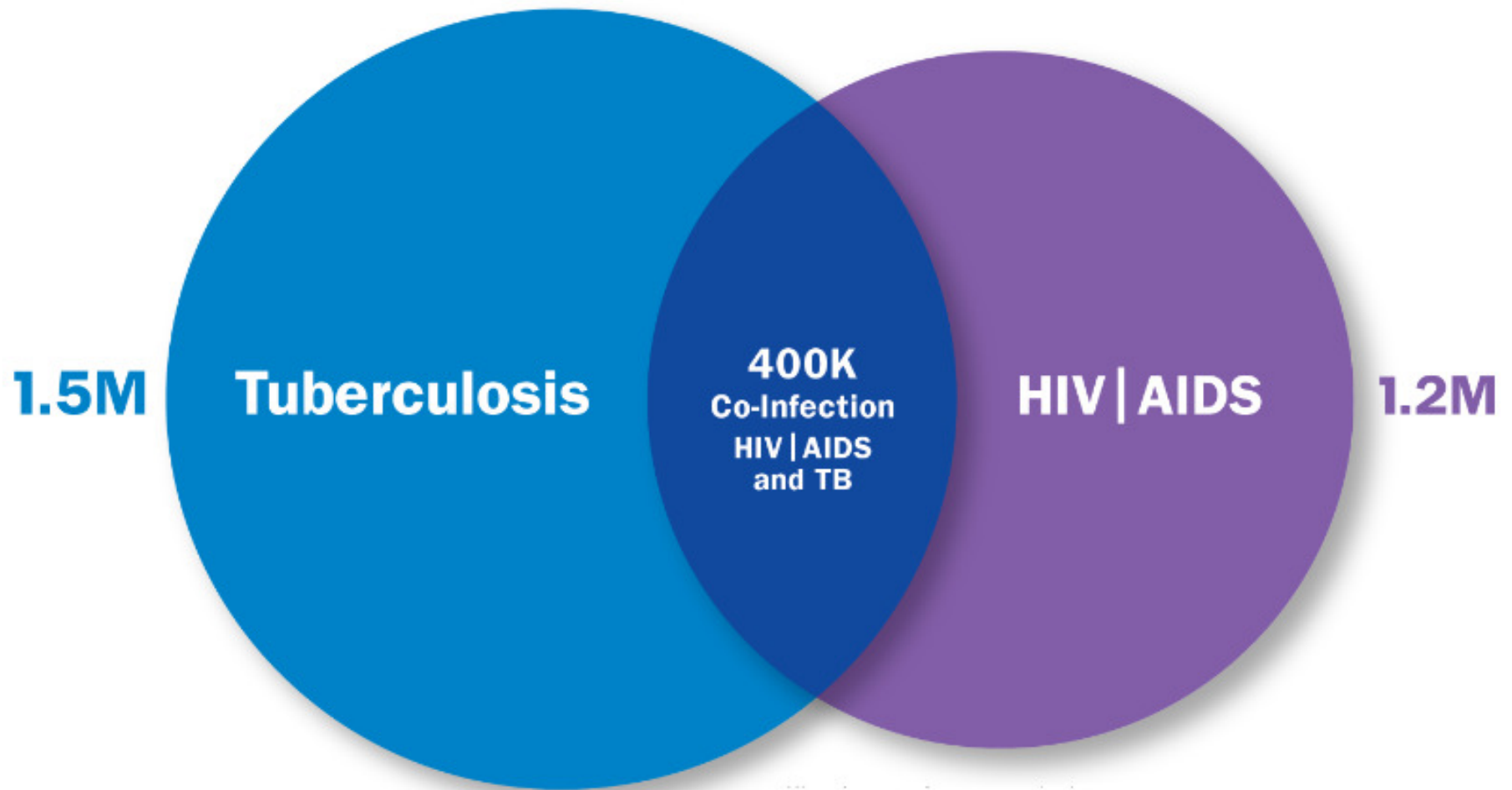


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TB Vaccine Research and Development: Progress, Strategies and Controversies

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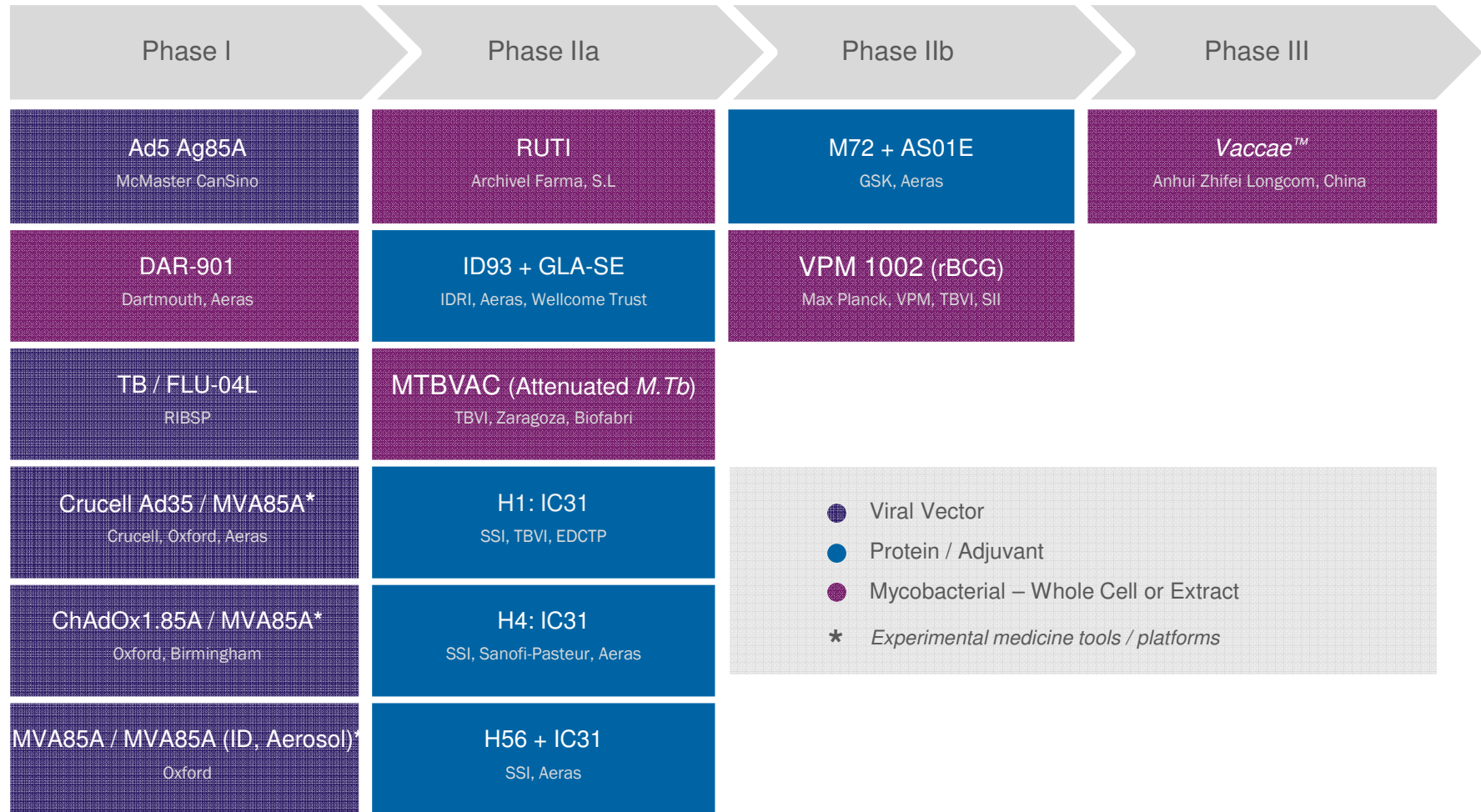
Tuberculosis kills more people than any other single infectious disease in the world.



Outline

- Progress
- Major challenges in TB vaccine R&D efforts
- Controversies in the TB vaccine R&D field

The Global Clinical Pipeline of TB Vaccine Candidates



TB Vaccine Candidates: Summary of Status

Candidate	Description	Status	Comments
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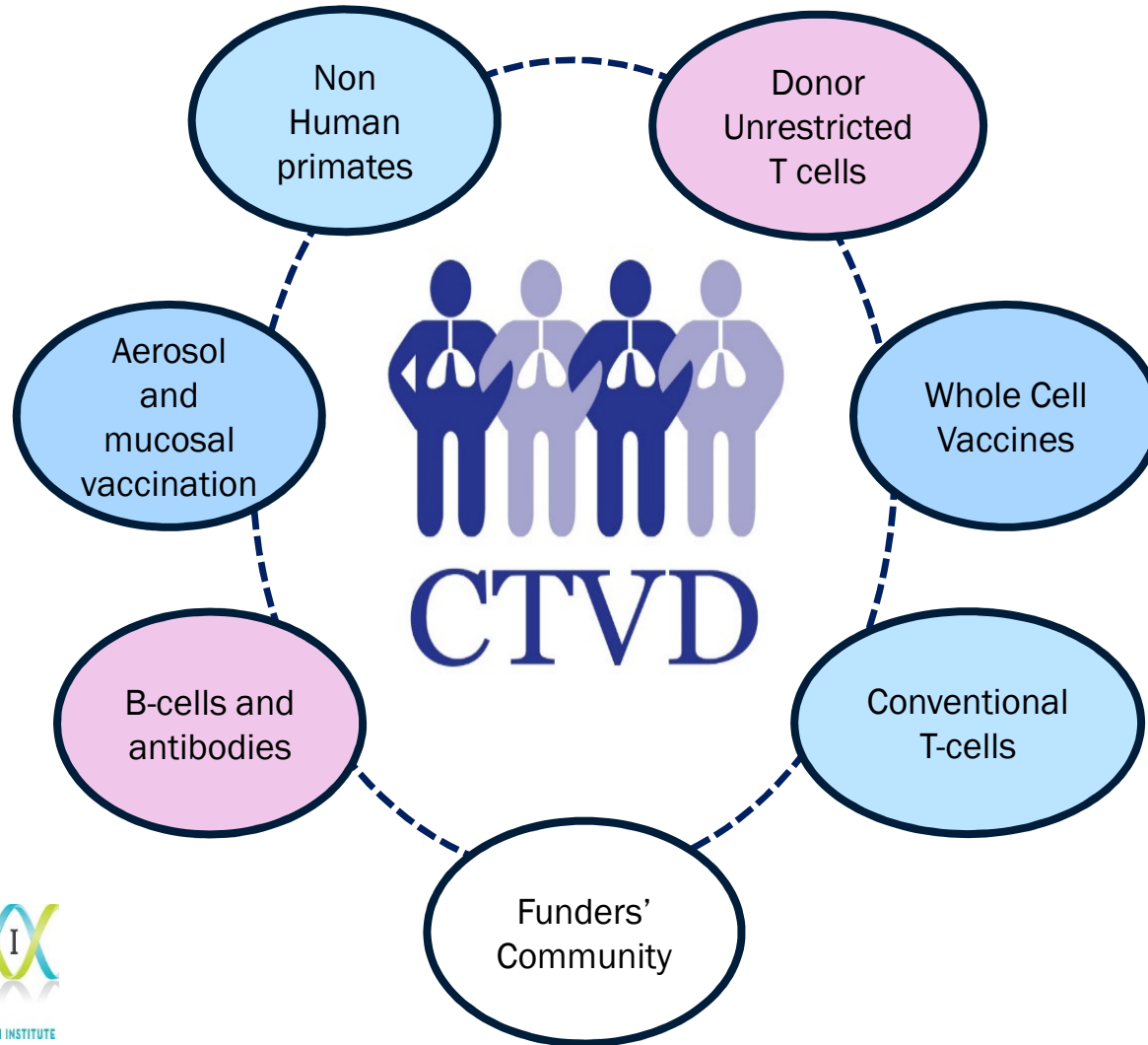
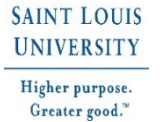
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High-Interest Pre-clinical Candidate: CMV-Vectored TB (Louis Picker, OHSU)

- Live, attenuated, persistent CMV vector
- Also used for HIV vaccine development (IAVI)
- Unique characteristics
 - Stimulates tissue effector memory
 - UL 128-130 deletion stimulates MHC II-restricted CD8+ T-cell responses
- Encouraging results in Rhesus macaque Mtb challenge studies
- Will need to address regulatory hurdles re: safety of live, persistent CMV



TB Vaccine R&D: Challenges

- Mono-focus on CD4+ T-cell responses; lack of immunological diversity
- Lack of immune correlate of protection
- Lack of a reliable, reproducible functional assay
- Lack of a human challenge model
 - Human challenge consortium formed (Harvard, AECOM, Imperial College, Cornell, Rutgers, Aeras)
 - Key issues
 - Develop safe challenge strains (auxotrophs; genetic kill switches)
 - Develop reporter methodology (blood-borne substrates; volatile aromatics)
 - Achieve regulatory guidance/approval

TB Vaccine R&D: Challenges

- Poor predictive power and lack of standardized animal models that reliably predict human clinical outcomes
- Lack of funding*
 - HIV vaccine funding, 2014: \$841 million
 - Malaria vaccine funding, 2014: ~\$170 million
 - Total TB vaccine funding, 2004-2014: ~\$600 million

*From Vaccines and Alternative Approaches: Reducing our Dependence on Antimicrobials. Review on Antimicrobial Resistance, Jim O'Neill, Chair. February 2016

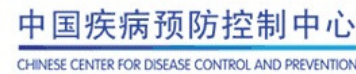
TB Vaccine R&D: Controversies

- Resource allocation balance: experimental vs. vaccine product development
- Role of small animal models (mice, guinea pig, rabbit) in vaccine candidate evaluation
- Target patient population
 - Infant-targeted vaccine (BCG replacement)
 - Adolescent/adult targeted vaccine (prevention of infection and/or disease; reduce transmission)
- Choice of endpoint/indication
 - Prevention of established Mtb infection (feasible/licensable?)
 - Prevention of TB disease (IGRA-'s vs. IGRA+'s)
 - Prevention of recurrent disease (many variables; too high a bar?)
- Infant BCG vaccination – effect of prior sensitization to vaccine development
- Effect of co-factors (e.g., DM, NTM exposure) on vaccine response

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- Ann Ginsberg, Aeras
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- Zhongkai Shi, Aeras
- Nathalie Cadieux, Aeras
- Ravi Anantha, Aeras
- Thomas Scriba, UCT/SATVI

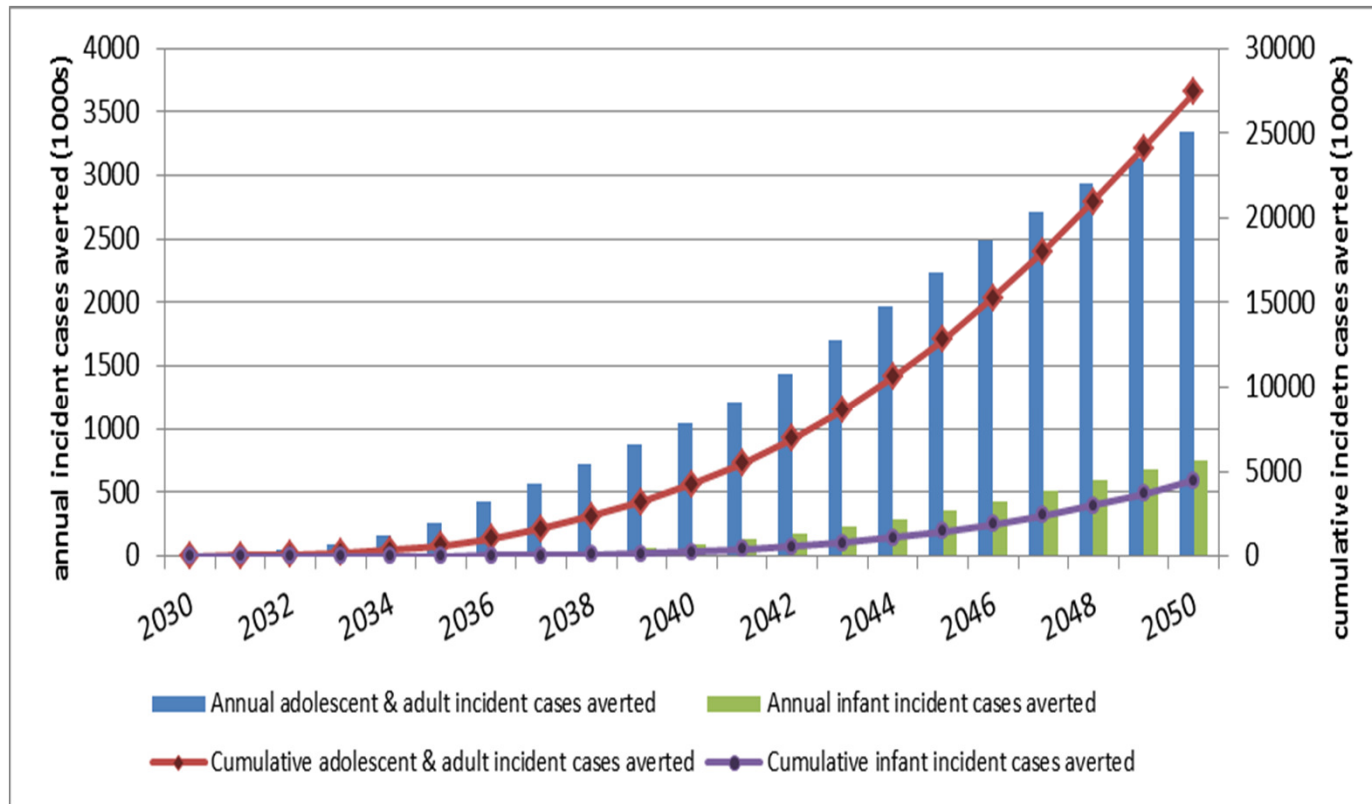
Recent Major Funders and R&D Partners



Thank You.



Potential Worldwide Impact of New TB Vaccines

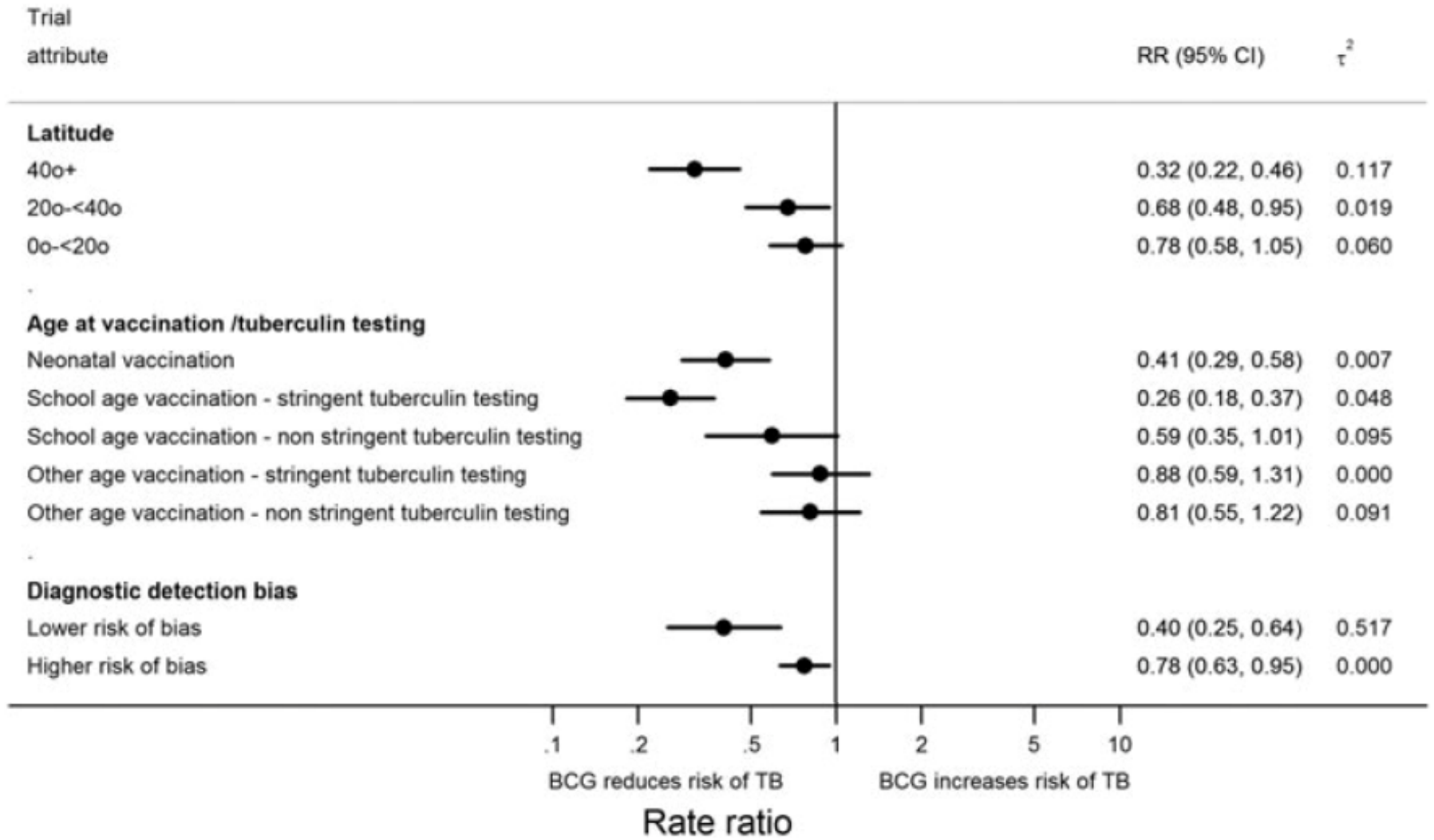


Immunization of infants, adolescents, adults with a 60% efficacious vaccine:
 20% coverage rate for adolescents and adults
 90% coverage rate for infants

Controversies

- **We do not understand immunological protection against *M. tuberculosis***
- **Prior sensitization to mycobacteria (immune priming) clouds the picture**
- **TB diagnosis is critical (detecting the pathogen directly)**
- **How do we choose amongst vaccine candidates for efficacy trials?**

Controversies: BCG protection against pulmonary TB



Mangtani et al., CID 2014