Mathematical modelling to inform development of new tuberculosis vaccines

TB MAC Annual Meeting

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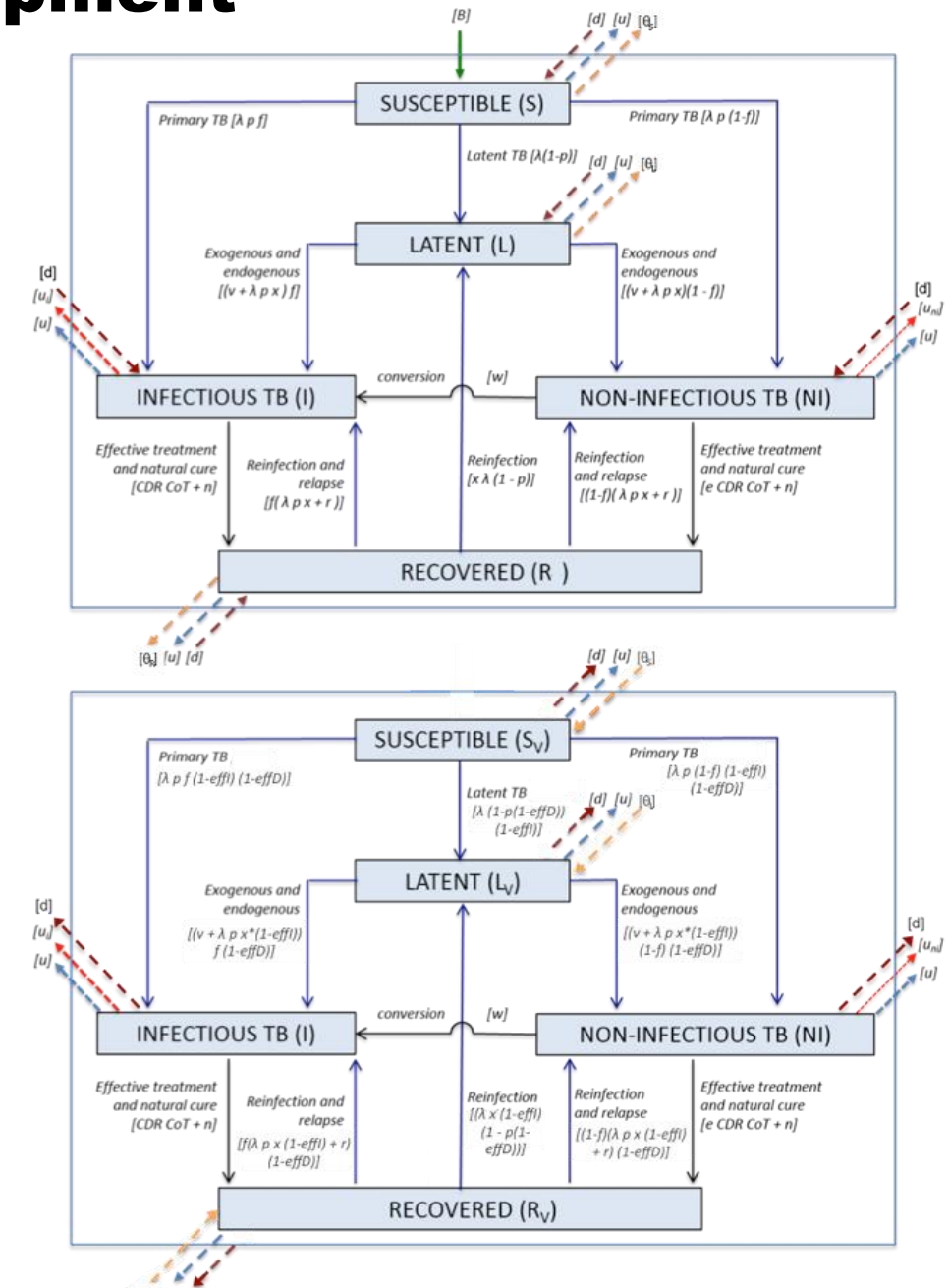
Informing strategic TB vaccine development

- Target product profiles (TPPs) and Preferred Product Characteristics (PPCs) guide strategic development of new TB vaccines to ensure new vaccines are fit for purpose and maximise future epidemiological impact.
- When results become available from efficacy trials, value in estimating potential future epidemiological impact to guide decision making.
- Mathematical modelling as a logical framework
- Summarise the available mathematical modelling evidence to inform TPPs
  - Systematic review (Harris et al. 2016) summarising 23 studies
  - + studies published since publication of the review
  - + unpublished studies exploring the impact of potential new TB vaccine characteristics



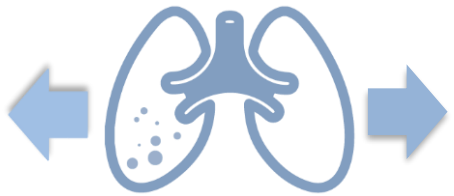
Harris et al. 2016, Liu 2017, Arregui 2017, and Harris et al. submitted

Summary of modelling literature

Vaccine characteristics

- Prevention of infection (POI) versus prevention of disease (POD), effective pre- versus post-infection
  - Globally, over 2050 time horizon, prevention of disease vaccines would provide faster and greater impact than prevention of infection.
  - Literature divided as to whether pre- or post-infection vaccine would provide greatest impact, may depend upon prevalence of infection and balance of new infection vs. reactivation disease in a given setting.

  - In China, India and South Africa, a vaccine efficacious for prevention of disease in post-infection populations would have greater impact over the 2025-2050 timeframe.
  - Vaccines efficacious for prevention of infection or disease in pre-infection populations demonstrated increasing, and useful, impact in higher transmission settings (India > SA > China)
  - In ageing, reactivation settings such as China over 2025-50, vaccines effective against disease post-infection will be essential to maximise impact before 2050.



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- Duration of protection
  - In LMICs over 2025-50 , as little as 5 years protection may be cost effective with appropriate vaccine and delivery.
  - In China/South Africa, duration of protection of at least 5 years ideal to ensure reduction of at least a quarter in 2050 incidence rates. In India 2 years protection may achieve this.

- Vaccine efficacy
  - In LMICs over 2025-50, as low as 20% could be cost effective if delivered to adolescents/adults.

Vaccination population

- Age
  - In LMICs over 2024-50, **adolescent and adult** vaccination would deliver **greater and faster** impact than infant vaccination. Even 20% VE with 5 years protection could be cost effective.
  - To reduce TB in 0-4 year olds, vaccination of adolescents/adults would be more effective than vaccinating neonates.
  - Vaccines suitable for latently infected **older adults** (>60 years) would provide greater impact than adolescent vaccination in ageing, reactivation driven epidemics, such as China.

- HIV status
  - Population-level impact in SA would be substantially **reduced** with a vaccine **contraindicated in HIV** positive populations

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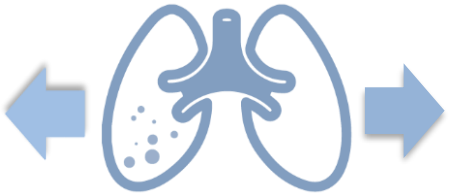

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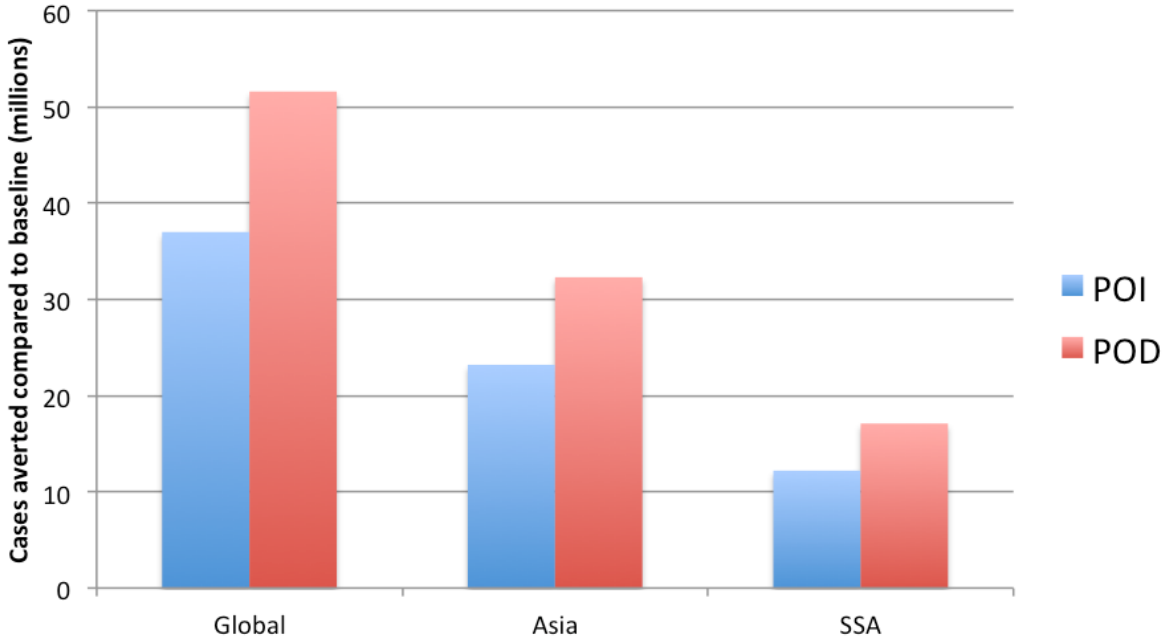
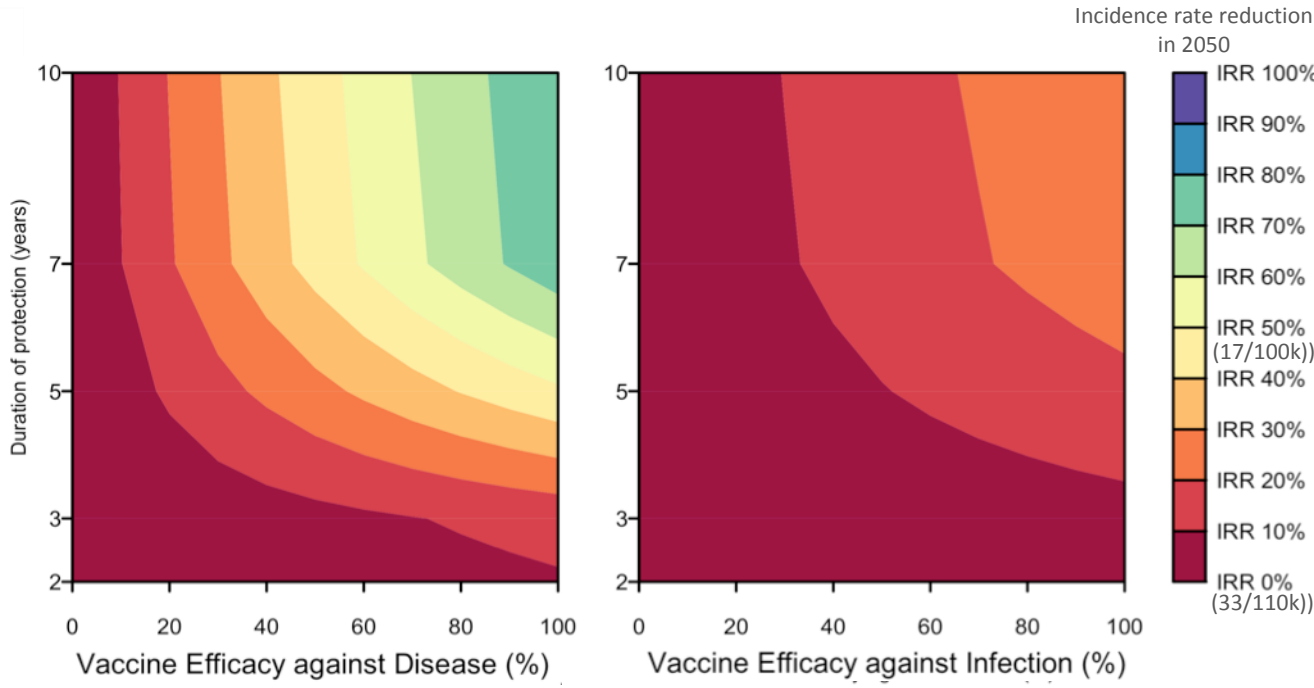
Prevention of infection or disease

- Over 2050 time horizon, prevention of disease vaccines would provide **faster and greater** impact than prevention of infection (Dye 2000, Dye *et al.* 2013, Murray et al. 1998, Harris et al unpublished)
- If completely block new infections from 2015, expected TB incidence of 16.5 per 100,000 per year in 2035 and 8.3 per 100,000 per year in 2050 – need prevention of disease to reach WHO targets (Houben & Dodd, 2016)



Murray et al 1998

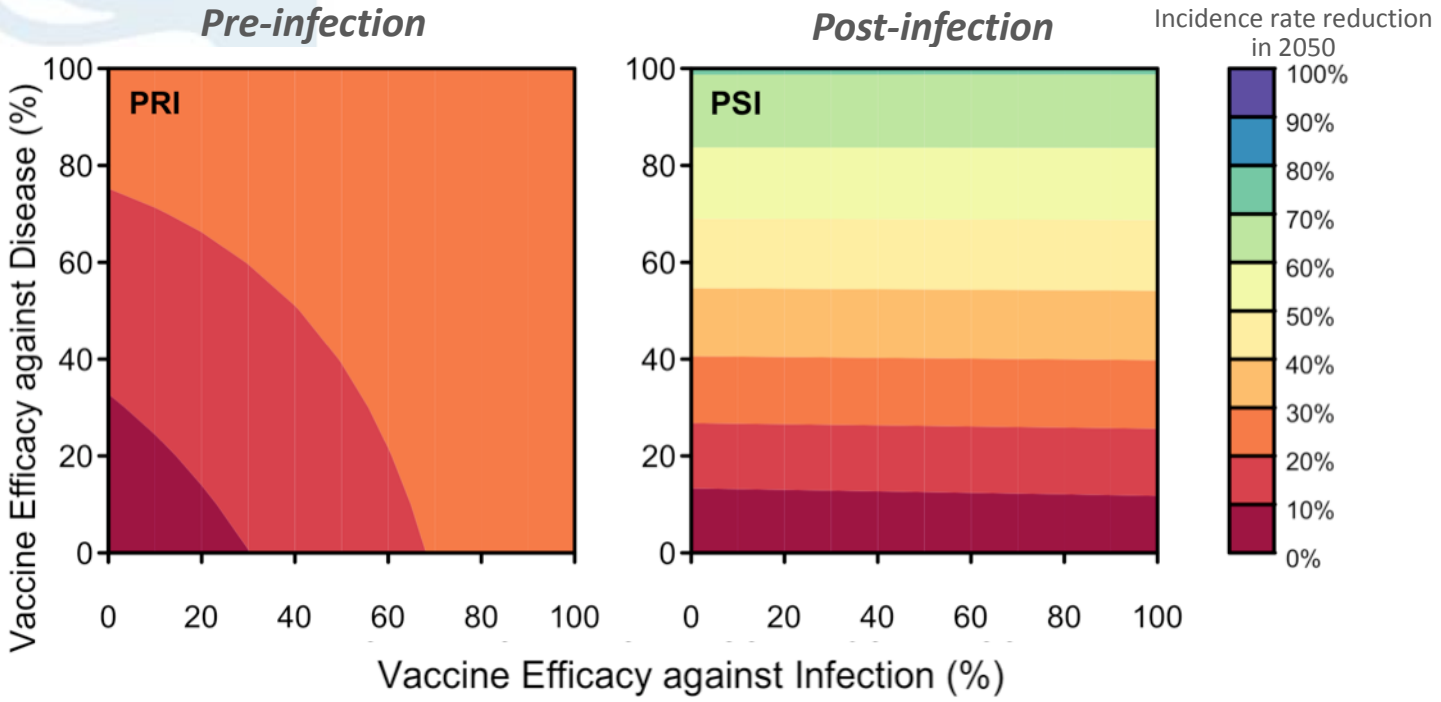


Harris et al unpublished

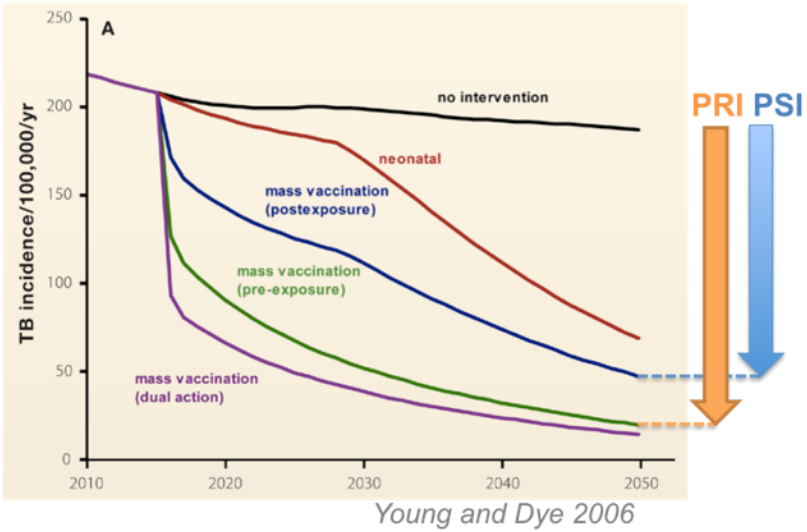
Pre-infection versus post-infection

- Published literature divided as to which would provide greatest impact:

  3 models suggest pre-infection (Young and Dye 2006, Abu-Raddad *et al.* 2009, Dye 2008) and 3 indicate post-infection (Dye *et al.* 2013, Lietman *et al.* 2000, Ziv *et al.* 2004)

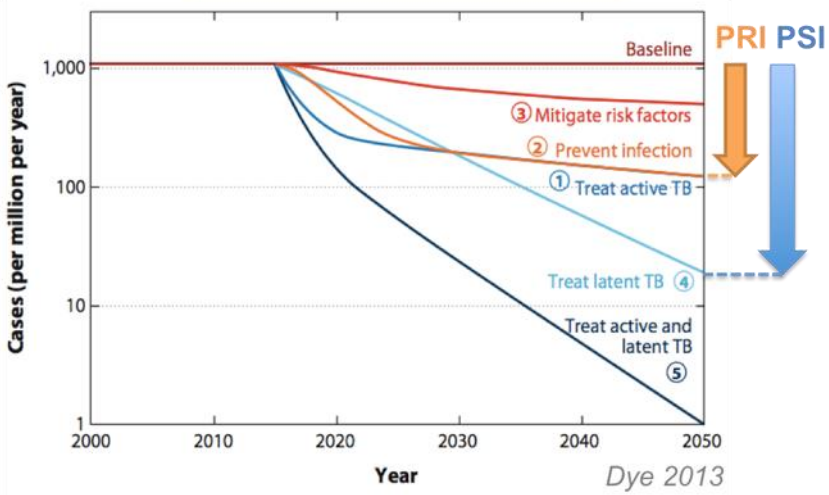


Pre-infection



Young and Dye 2006

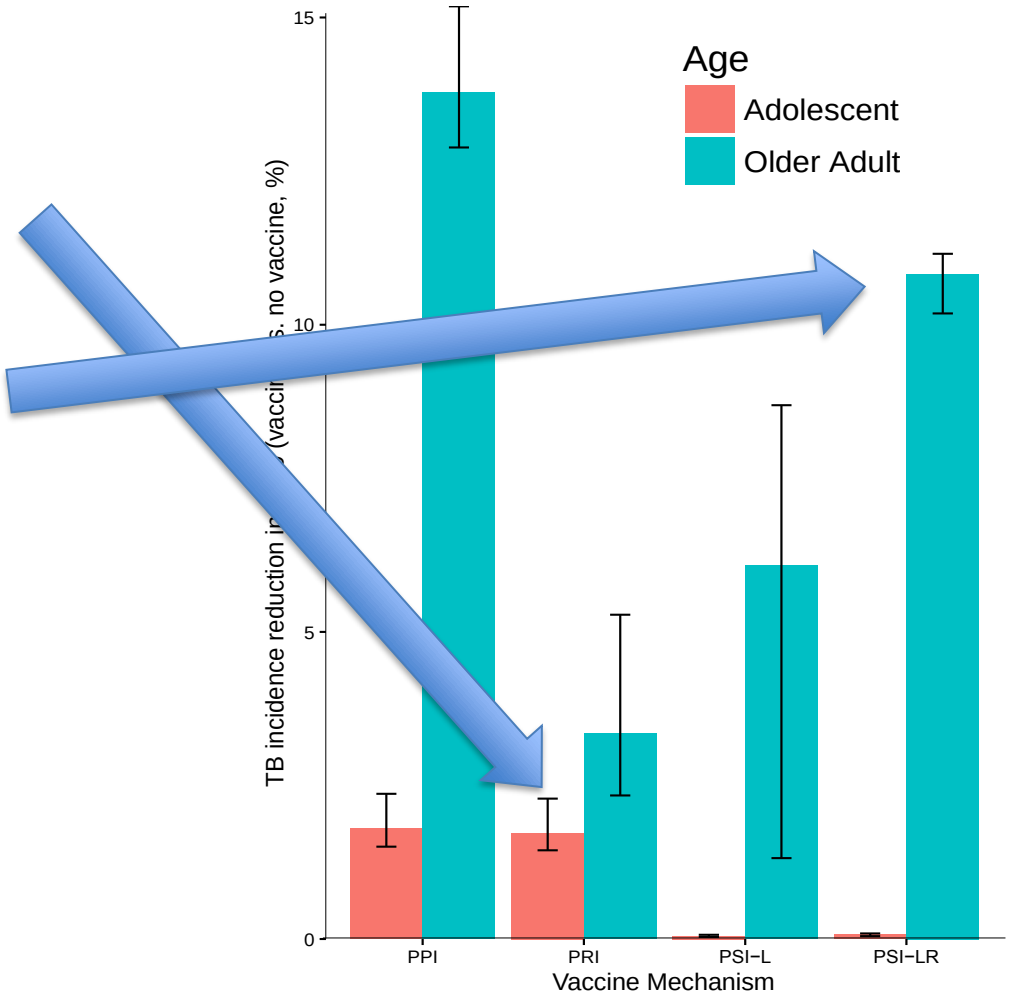
Post-infection



Dye 2013

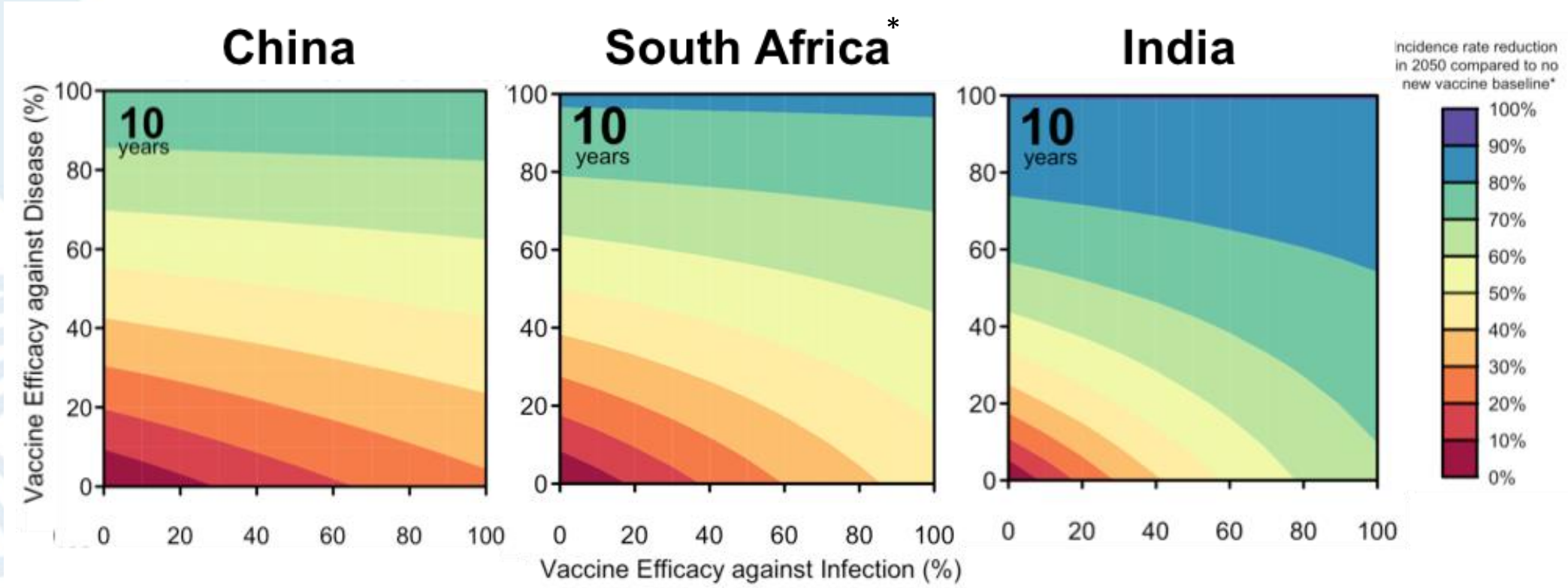
Pre-infection and post-infection

- **In China**, 2025-50:
  - In **adolescents** (low prevalence of infection, mostly new transmission) **pre-infection** vaccines were more effective
  - In **older adults** (high prevalence of infection, mostly reactivation disease) **post-infection** vaccines were more effective (& most effective overall)



Harris et al., submitted

Median incidence rate reduction (%) for pre- and post-infection vaccine with 10 years duration of protection and 10-yearly mass vaccination campaigns compared to no new vaccine baseline in 2050



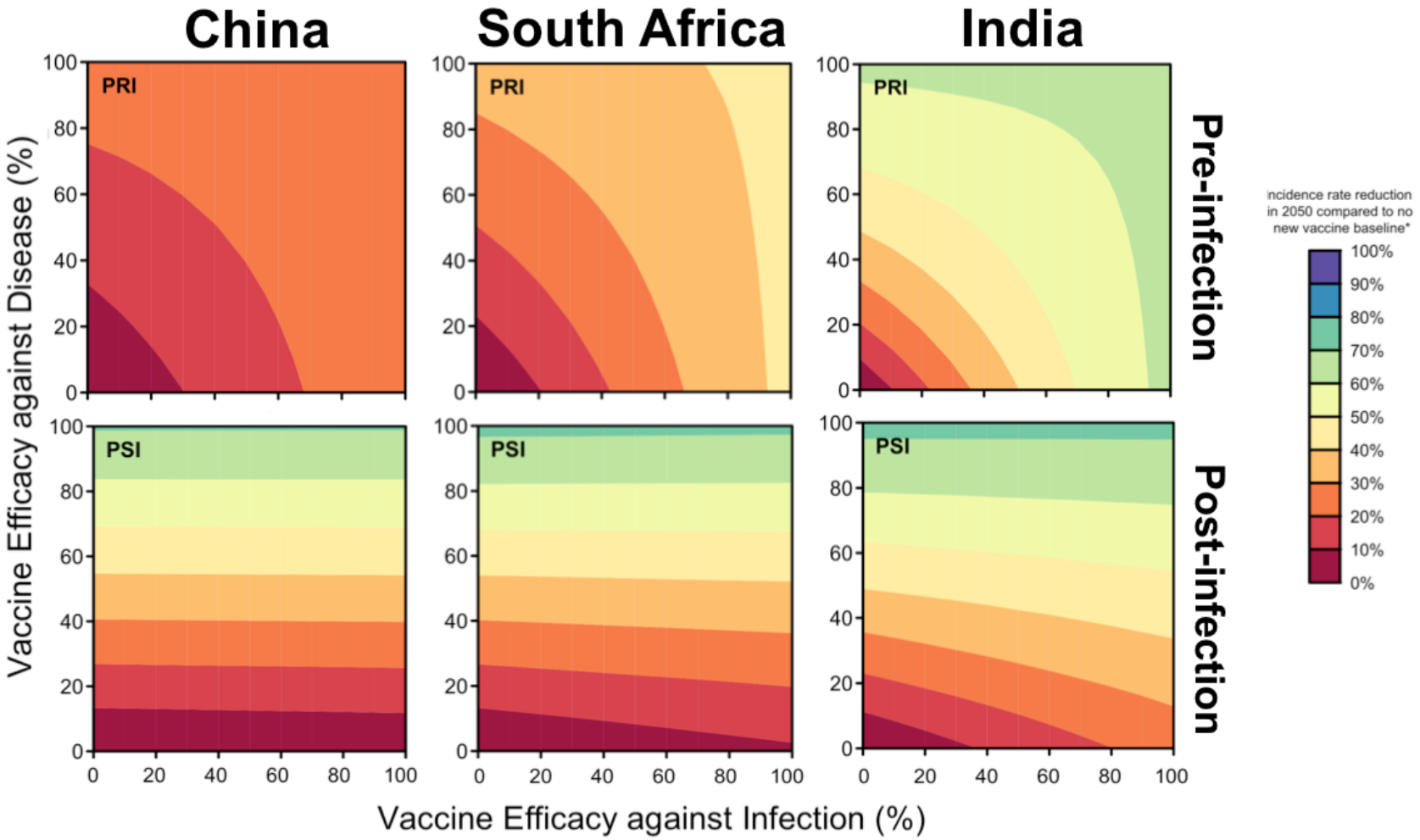
VE against disease provided greatest impact

Relative impact of prevention of infection vs disease varies by setting - importance of prevention of infection increased in higher transmission settings

* Safe and equally effective in HIV positive populations in SA

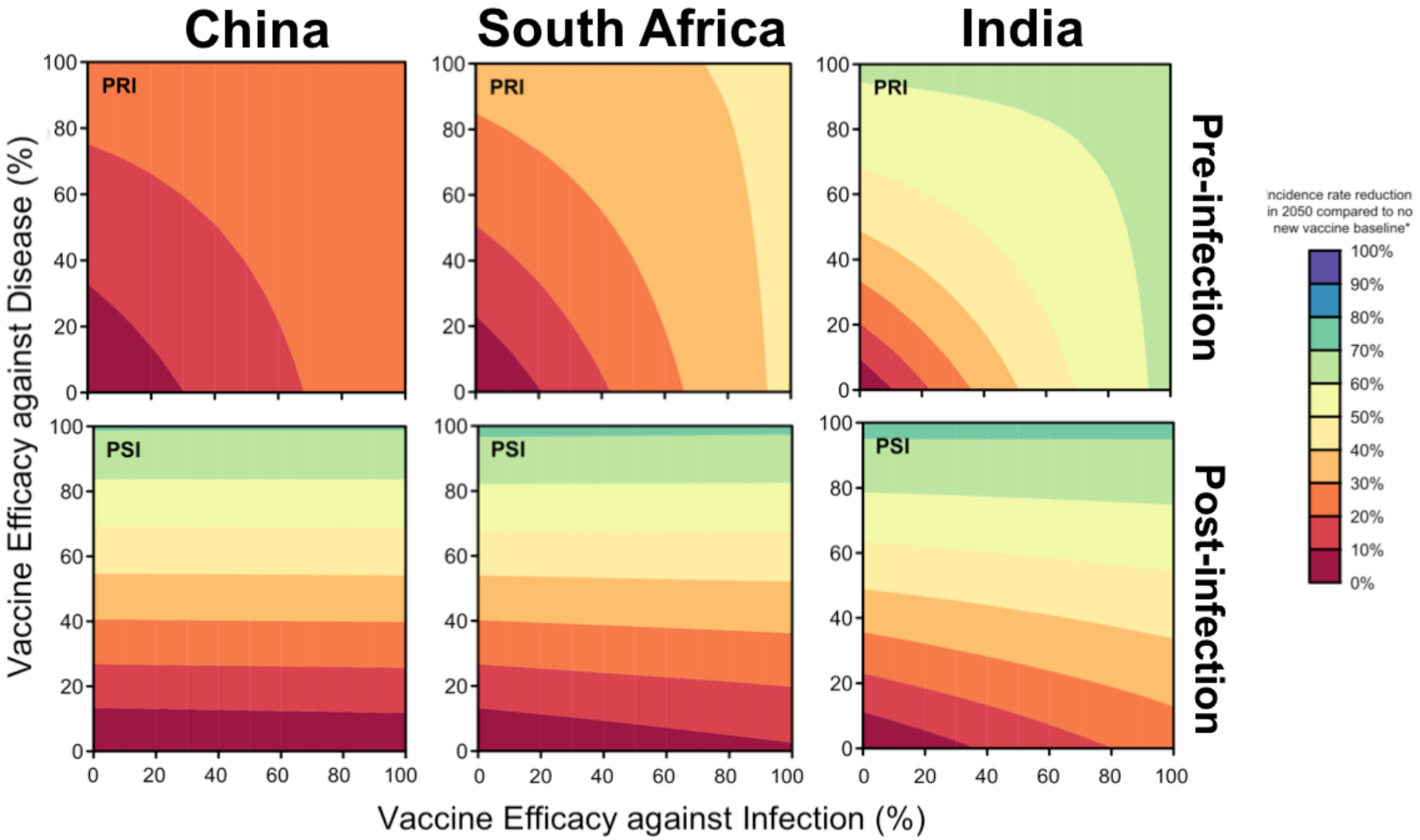
Harris et al unpublished

Vaccine efficacious **post-infection** for **prevention of disease** provides most impact in all 3 settings, will be very important in China.



Harris et al unpublished

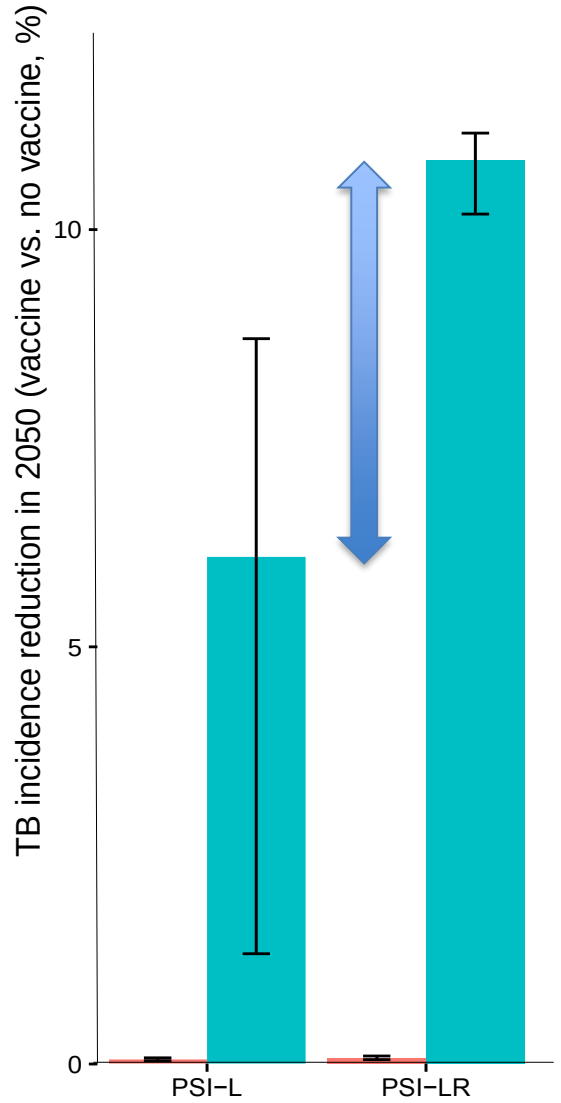
Vaccine efficacious **pre-infection** efficacious against **infection or disease** demonstrated increasing impact in higher transmission settings



Harris et al unpublished

Prevention of reactivation

- No models have specifically explored POR vaccines
- Challenging to fit due to availability of suitable data
- Results of China modelling suggestive that with a post-infection vaccine **POR-like vaccine could provide important additional impact** above protection of those latently infected.



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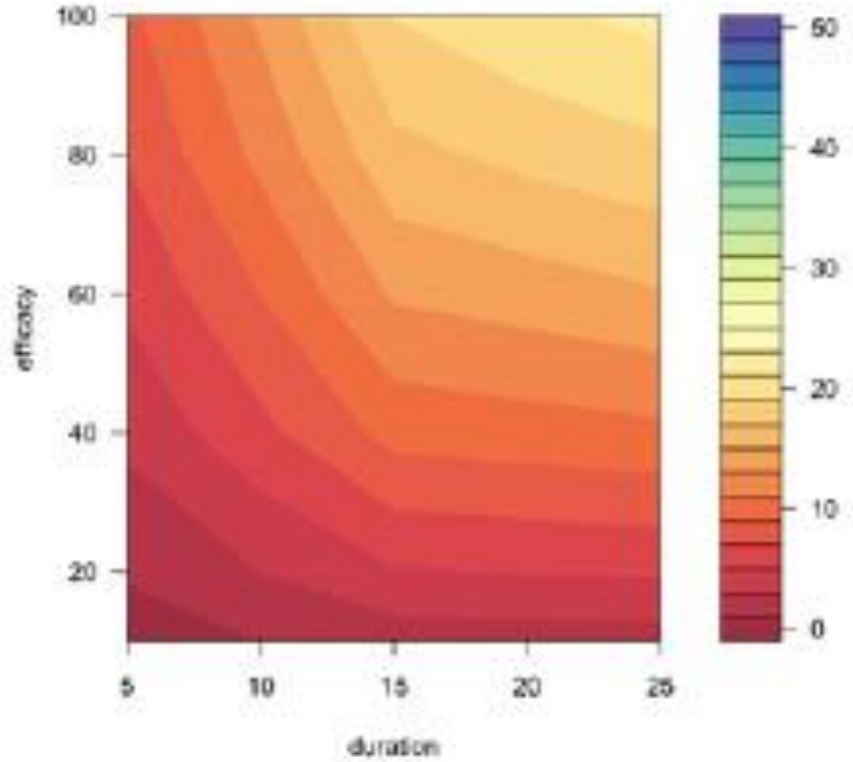
Duration of protection and vaccine efficacy

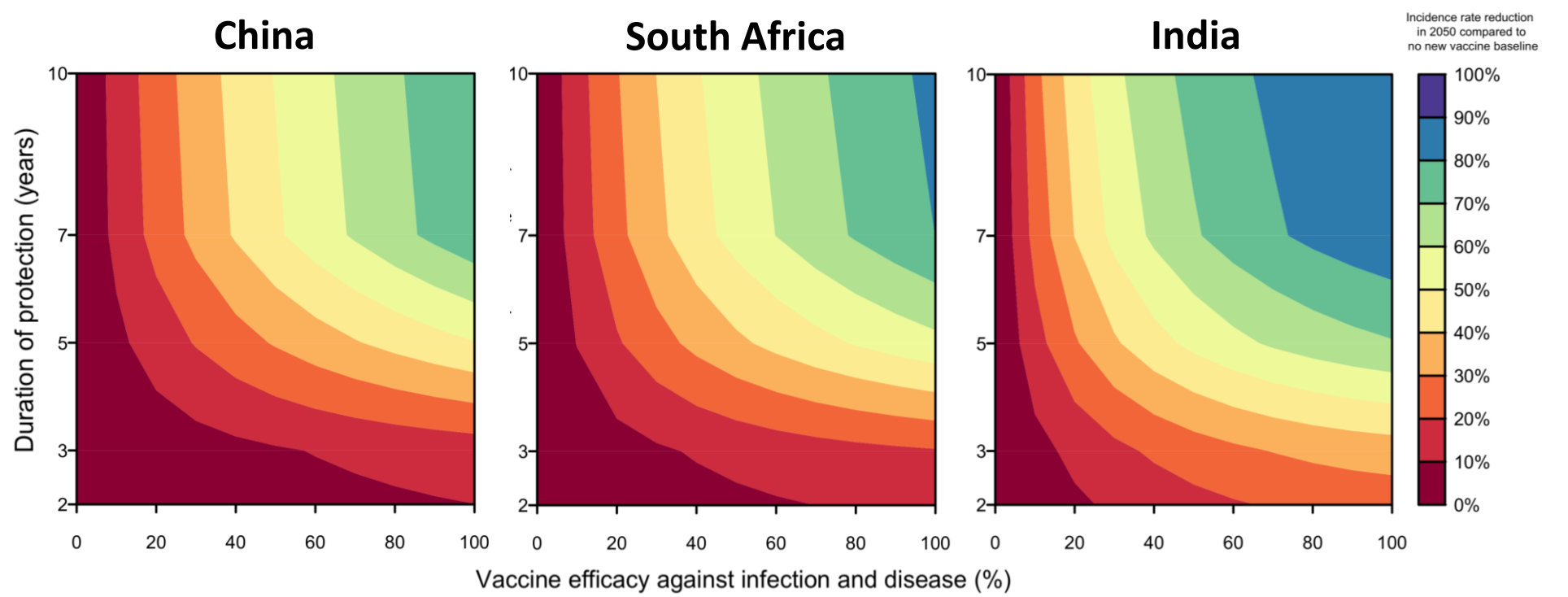
Cost-effective vaccine price (US dollars) of adolescent/adult vaccination in LMICs 2024-50



- As would be expected, all literature supports the benefit of higher efficacy and duration of protection
- As low as 20% VE and 5 years protection could be cost effective if delivered to adolescents/adults

Knight et al., 2014

Duration of protection and vaccine efficacy



- With 10-yearly mass campaigns, duration of protection of at least 5 years ideal to ensure reduction of at least a quarter in 2050 incidence rate.
- In India 2 years protection may achieve this if VE-POI&D is >60%
- If feasible, shorter durations may be compensated for by more frequent mass campaigns

Harris et al., unpublished

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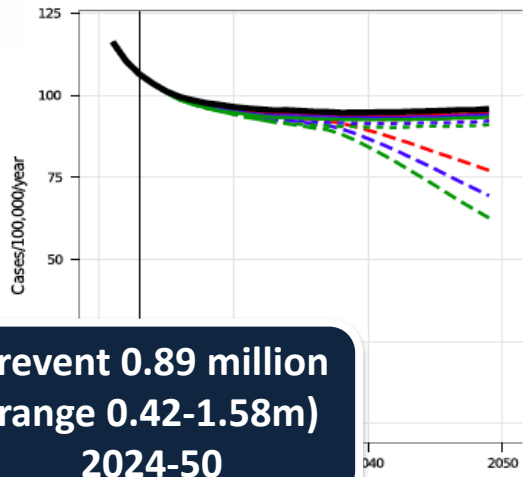
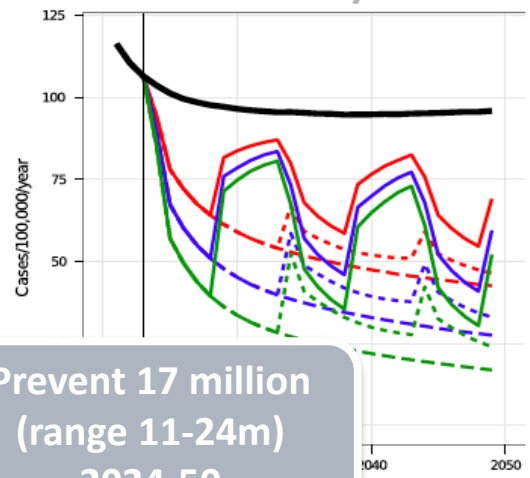
Infant

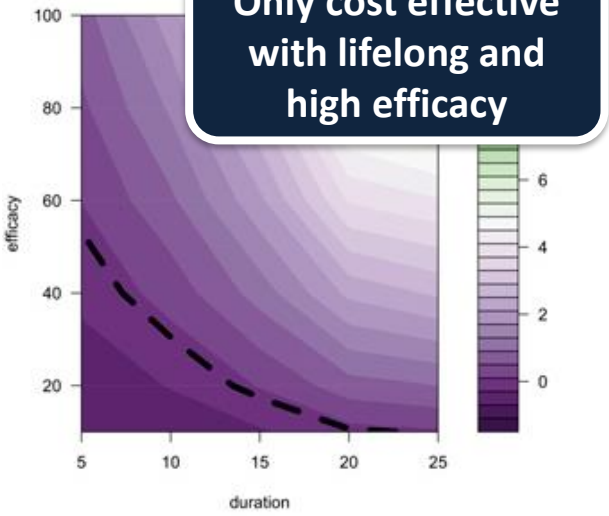


Prevent 0.89 million (range 0.42-1.58m) 2024-50

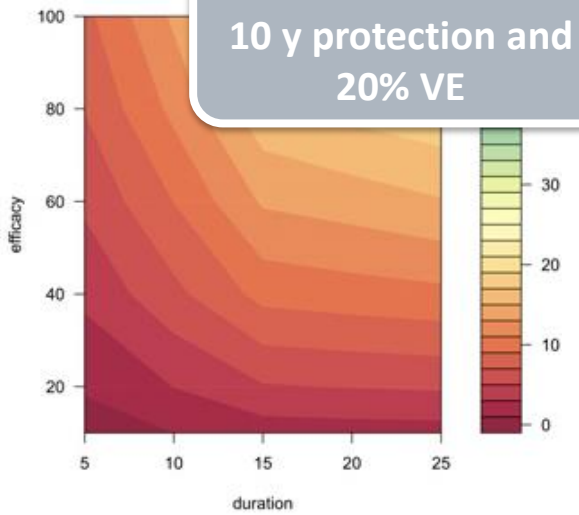
Adolescent/Adult



Prevent 17 million (range 11-24m) 2024-50



Only cost effective with lifelong and high efficacy



Cost effective with 10 y protection and 20% VE

Vaccination age

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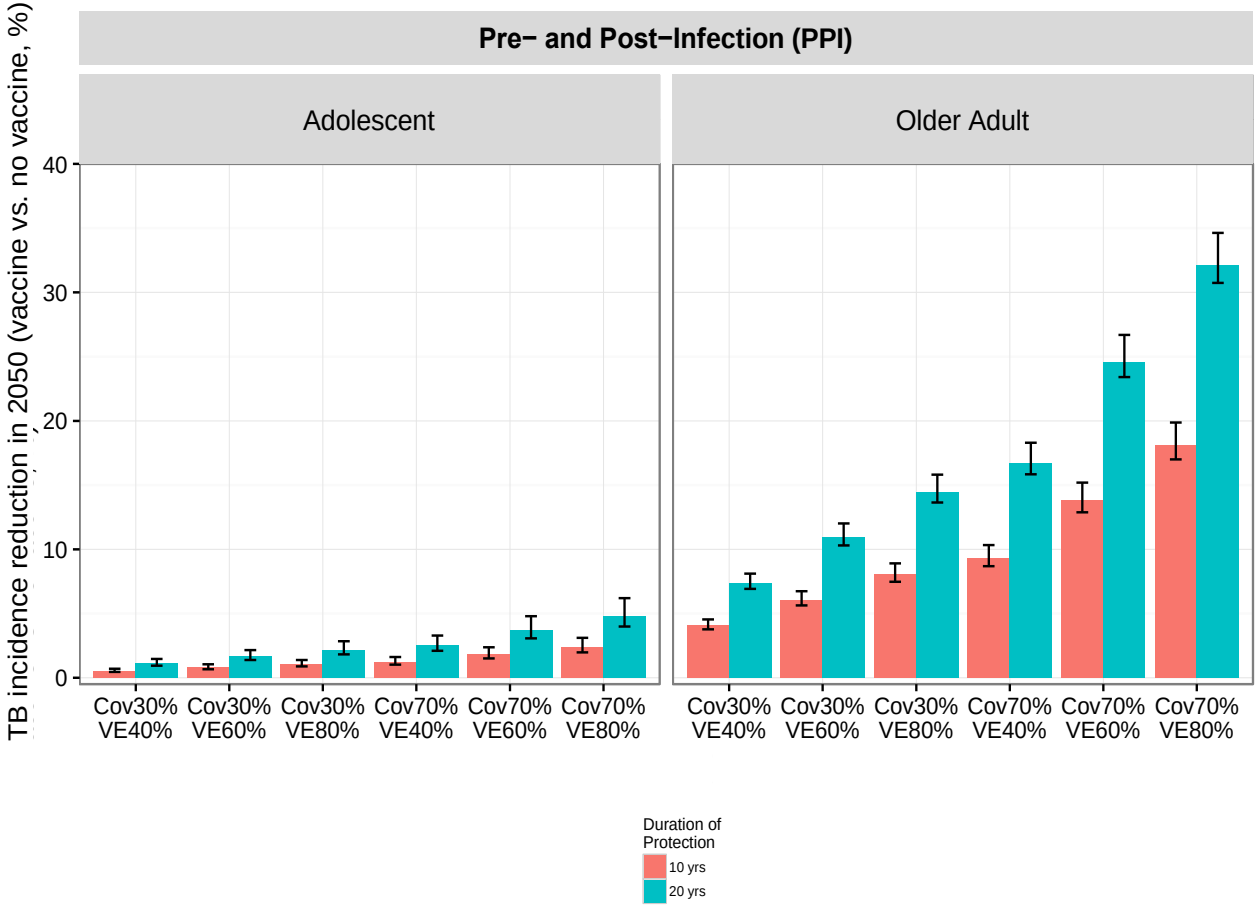
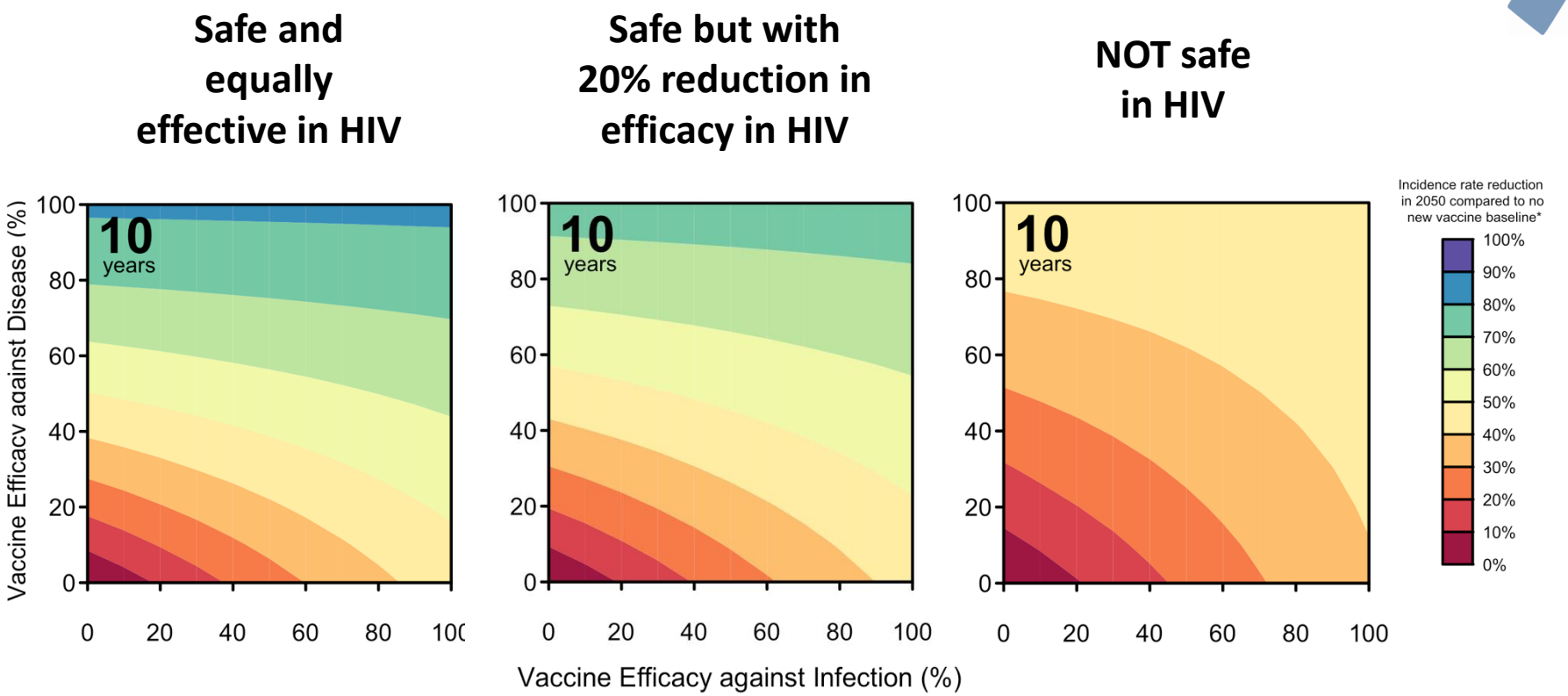


Harris et al. Submitted

Impact of HIV safety and efficacy in South Africa



Depending on vaccine, 10-43% lower 2050 incidence rate reduction if contraindicated in HIV-positive populations

Harris et al. Unpublished

Limitations of vaccine modelling

- Simplification of very complex reality
- Absolute and relative impact of vaccines may be sensitive to assumptions regarding future TB control measures.
- Assumes POI vaccine protects those populations that, if infected, would later progress to disease
- Predicting implementation success using new platforms is challenging
- Generalisability to other settings

Informing PPCs, TPPs and stage gates

Modelling can be used for informing the minimum and ideal profiles in TPPs, preferred product characteristics in PPCs, and to demonstrate the potential impact of vaccines in development as new results come available.

Vaccine characteristic	To achieve 40-49% TB IRR in 2050		
	Shortest duration	Revaccination duration	Annotation
Duration	5 years	10 years	Consult heat maps in appendix for full results. The medians of VE-POI and VE-POD are indicative of the minimum profile considered highly likely to provide the minimum required epidemiological impact (40-49% TB IRR) at the given duration of protection. Ranges should be interpreted with caution, as an interaction exists between these characteristics, therefore the minimums of each range combined would not provide sufficient impact. For example, with 5 years duration a POI-only vaccine is not feasible, but with VE-POD 60%, VE-POI would need to be 100%. With VE-POI 0%, a VE-POD of 80-100% would be required.
Median VE-POD (range)	90% (60-100%)	40% (20-50%)	
Median VE-POI (range)	50% (0-100%)	50% (0-100%)	

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Implications for vaccine development

Recruitment populations

- Post-infection in all settings. Pre-infection should also/instead be recruited in higher transmission settings (India > SA > China). Ideally, if feasible, trials should be powered to assess efficacy in both populations.
- If vaccine safe, HIV-positive populations should be recruited.
- If maximum population-level impact by 2050 is the goal, development of vaccines for adolescents/adults should be prioritized. China - inclusion of older adults in clinical trials (at least 60-64 years).

Endpoints

- In all settings, disease endpoints would be useful for demonstrating future impact.
- However, in higher transmission settings (India & SA) infection endpoints could be used, especially in proof of concept.
  - Ideally both infection & disease endpoints would be measured in PhIII, but evidence of prevention of infection *may* be sufficient.
  - Assumed that POI vaccine can protect those who will progress to disease if infected
- Vaccine efficacy – assess feasibility of designing trials to detect lower vaccine efficacies

Study duration

- Shorter duration vaccines (e.g. 5 years) may be cost-effective. Studies could benefit from extended follow up to 5 years (e.g. immuno subgroup). However, if high efficacy observed, 2 years may be sufficient in India.

Take home

Population-level impact of future vaccines is dependent upon the underlying epidemiology.

One size for vaccine/implementation may not fit all.

The relative impact of vaccines effective against infection and disease, and in uninfected or latently infected populations needs to be considered in the context of the epidemiological setting to inform decision making for development strategy, trial design and implementation.

Acknowledgements

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- Chathika Weerasuriya

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- WHO (Johan Vekemans, Gitte Giersing)
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Thank you

Any questions?

Key References

Systematic review and TB vaccine publications post-review:

- Harris RC, Sumner T, Knight GM, and White RG. Systematic review of mathematical models exploring the epidemiological impact of future TB vaccines. *Hum Vaccin Immunother* 2016; **12**(11): 2813-32. [and references contained within]
- Liu S, Li Y, Bi Y, Huang Q. Mixed vaccination strategy for the control of tuberculosis: A case study in China. *Math Biosci Eng* 2017; **14**(3): 695-708.

Unpublished papers/reports:

- Harris RC, Sumner T, Knight GM, Evans T, Cardenas V, Chen C, and White RG. New TB vaccines – the impact of age targeted vaccination and implications for vaccine development. *Submitted*
- Harris RC, Sumner T, Knight GM, and White RG. Mathematical modelling to accelerate development of new tuberculosis vaccines and inform vaccine characteristics to maximise impact: China case study. Unpublished report
- Harris RC, Sumner T, Knight GM, and White RG. Mathematical modelling to accelerate development of new tuberculosis vaccines and inform vaccine characteristics to maximise impact: India case study. Unpublished report
- Harris RC, Sumner T, Knight GM, and White RG. Mathematical modelling to accelerate development of new tuberculosis vaccines and inform vaccine characteristics to maximise impact: South Africa case study. Unpublished report

If interested in papers or unpublished work/reports, contact: rebecca.harris@lshtm.ac.uk