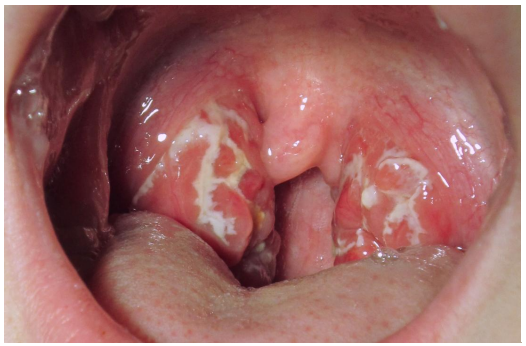
Understanding the relationship between the epidemiology of, and immune response to, Group A *Streptococcus* infection

Rebecca Chisholm

Thank you

Martin Lopez-Garcia, Nagasuma Chandra, Carmen Molina-Paris, Saumyadipta Pyne, and ICTS

Group A *Streptococcus*



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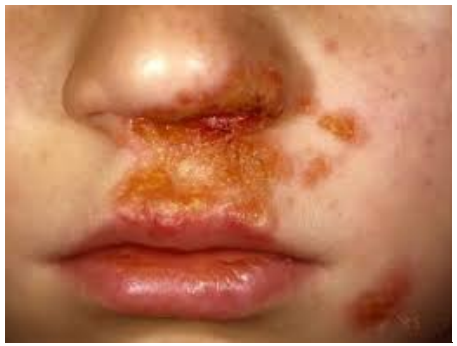
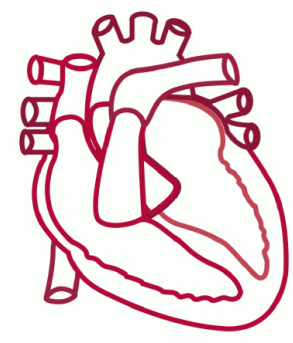
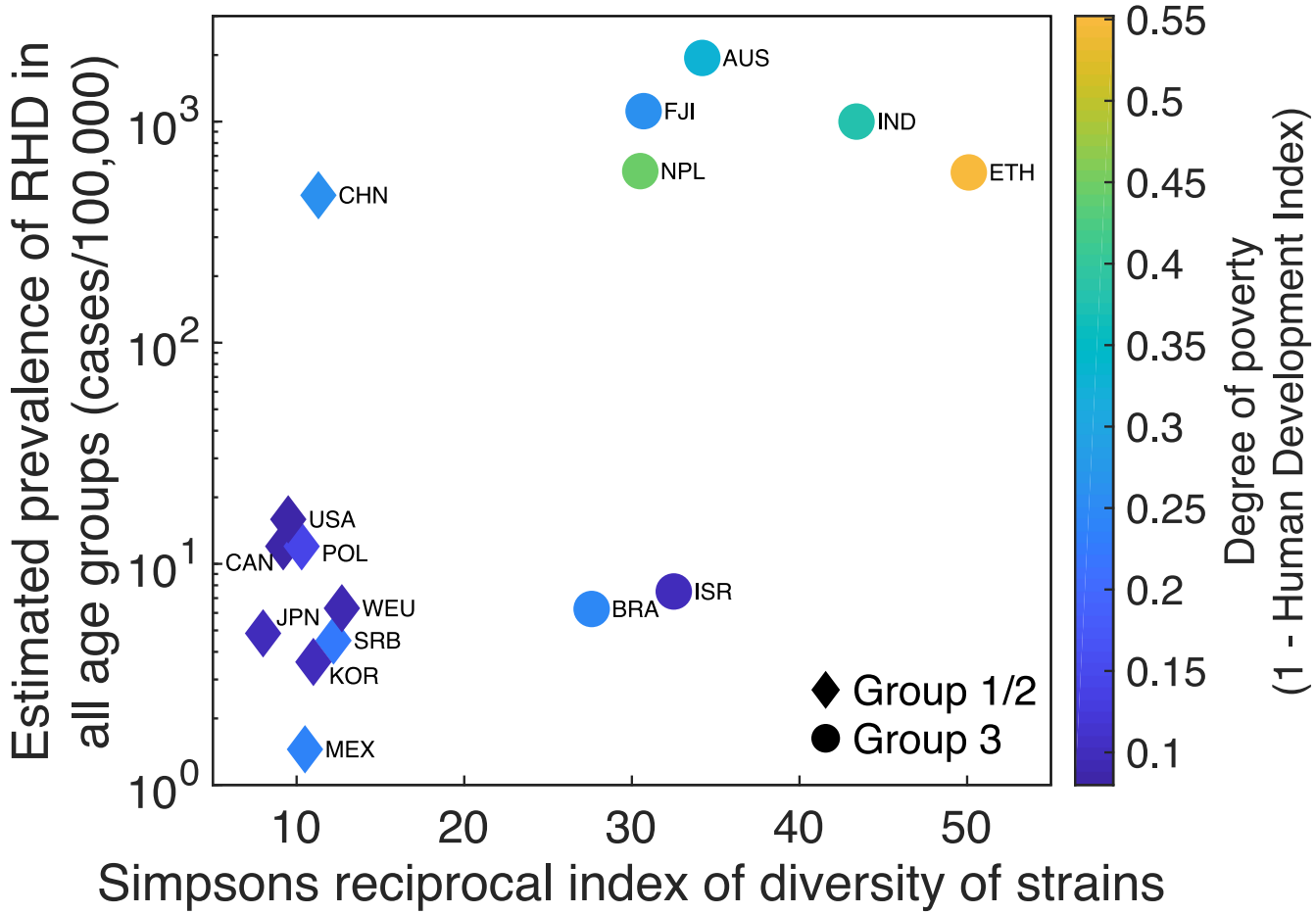




- Obligate human pathogen that mostly causes mild 'strep throat' and skin sores
- These mild infections are generally easily treated with antibiotics
- Untreated, it can lead to fatal and debilitating conditions such as invasive infection, acute rheumatic fever (ARF), and rheumatic heart disease (RHD) which has no cure
- Globally, $\approx 500,000$ deaths per year due to Group A *Strep*

Global epidemiology of Group A *Streptococcus*

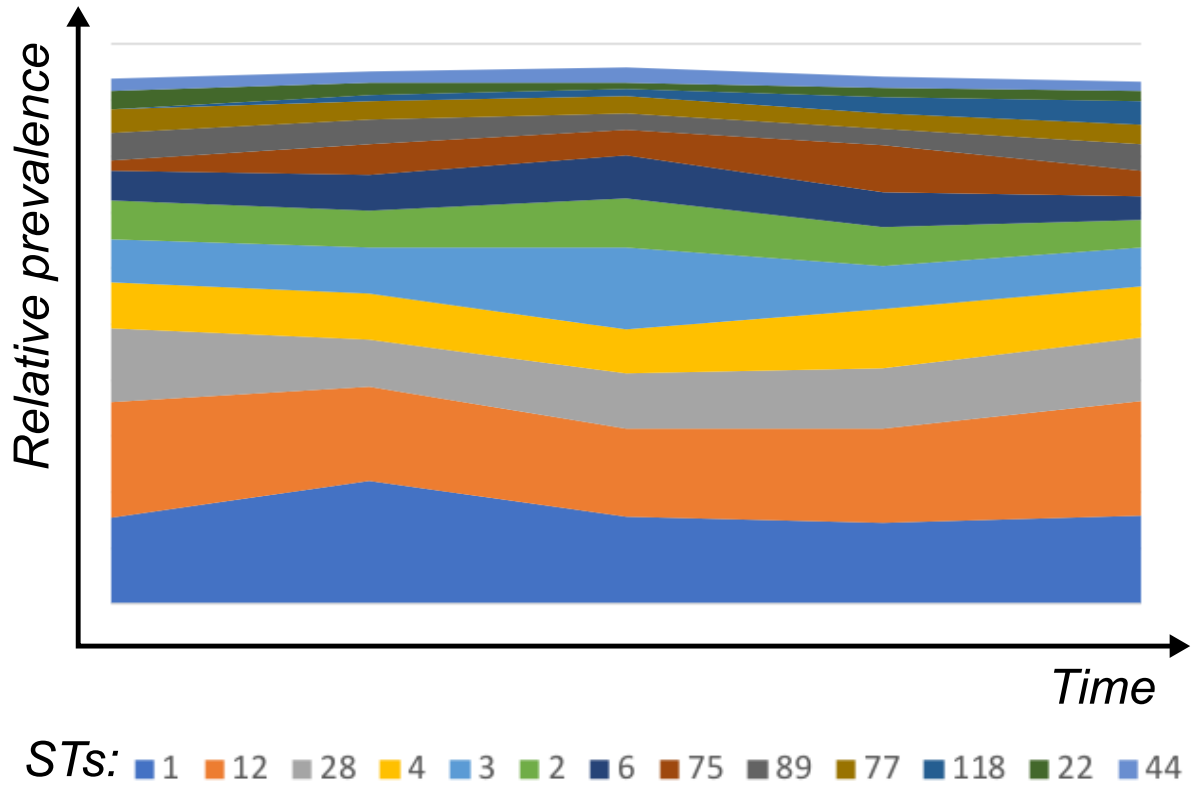
- Highest burden of disease occurs in Indigenous and other disadvantaged population where there is high strain diversity



Smeester et al., 2009, Watkins et al., 2017, Parnaby & Carapetis, 2010, UN Development Program, 2016.

Low-prevalence population: USA

- Group A *Strep* is a major cause of childhood **throat infection**
- Diversity low, RHD uncommon
- Prevalence of STs across 10 sites in US over 5 years:

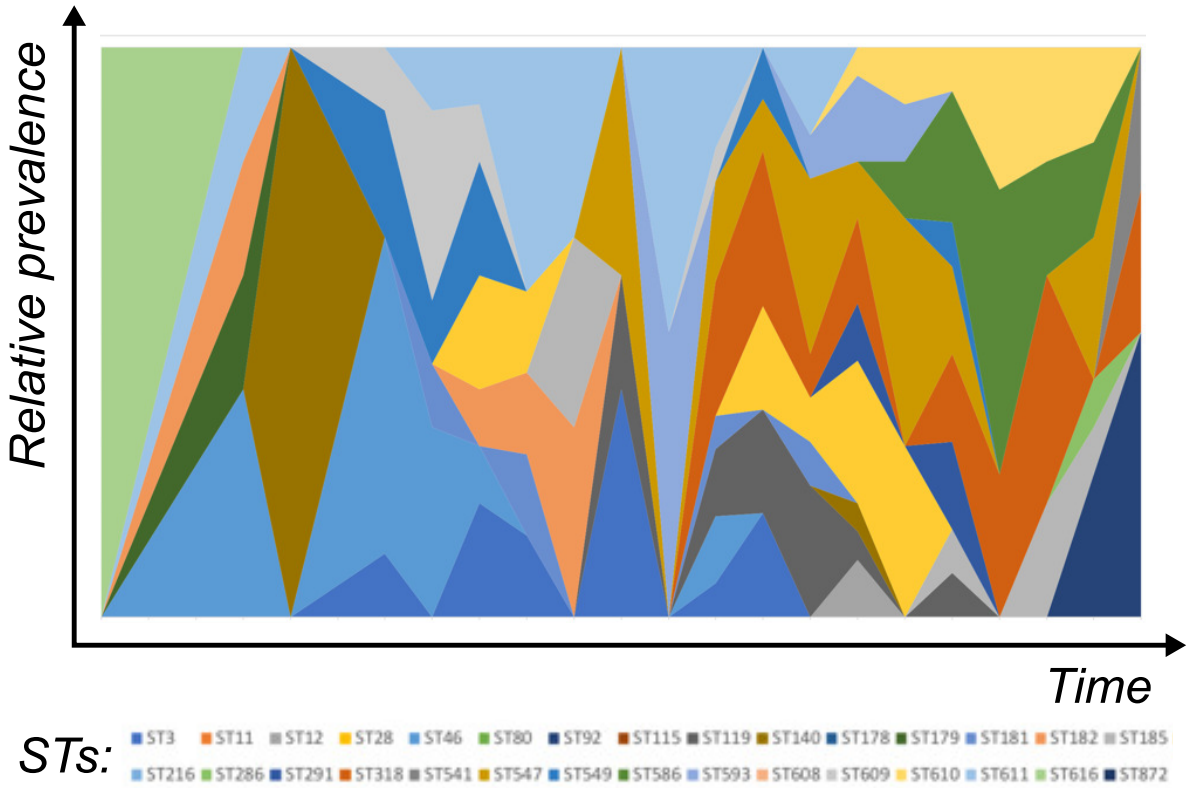


5000 isolates

Data: Shulman et al., CID, 2009

Hyper-endemic population: Indigenous Australians

- Group A *Strep* is a major cause of childhood **skin infection**
- Diversity high, highest prevalence of RHD in the world
- Prevalence of STs in one remote community over 23 months:

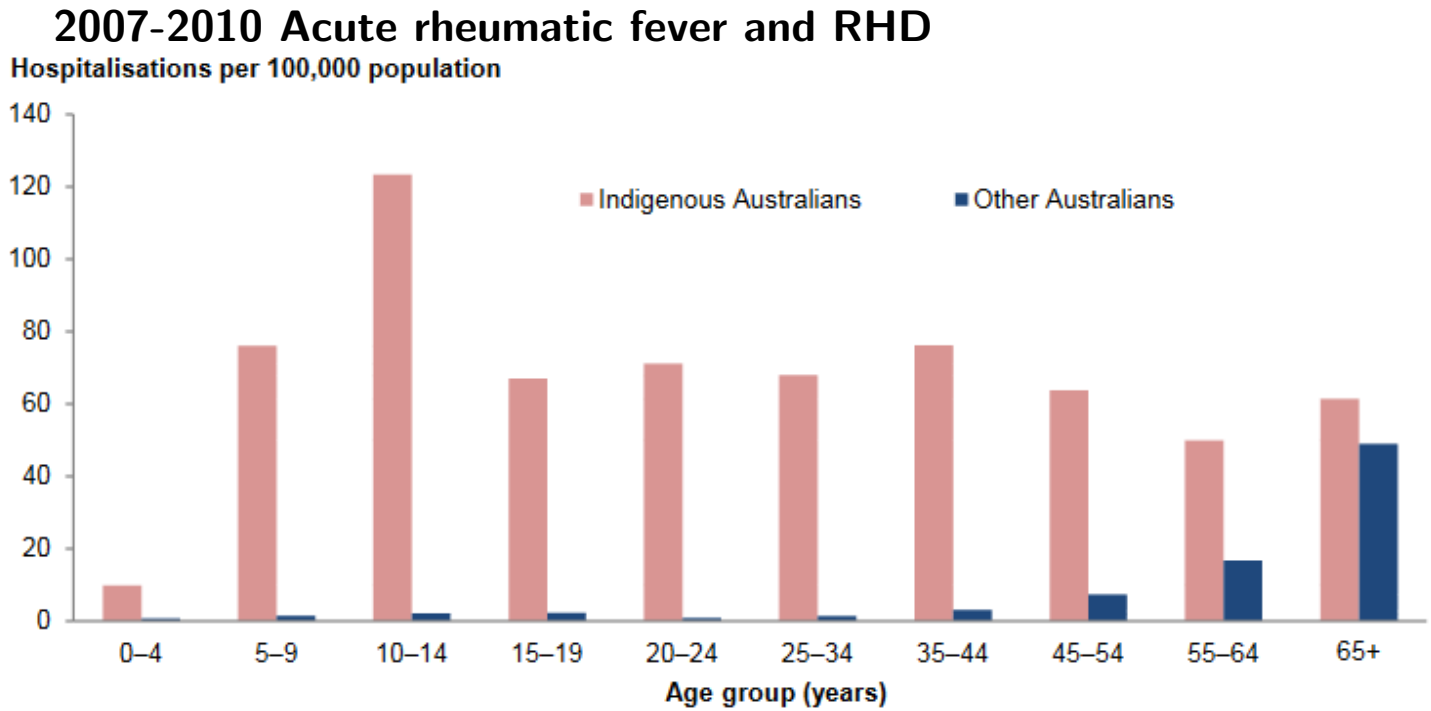


218 isolates

Data: McDonald et al., CID, 2006, figure: Jake Lacey

Group A *Strep* disease in Australia – a preventable injustice

- Disproportionately affects Aboriginal and Torres Strait Islander people — 64 times more likely to develop RHD, 20 times more likely to die from it



Health Policy Analysis 2017, Evaluation of the Commonwealth Rheumatic Fever Strategy – Final report. Commonwealth Department of Health.

Group A *Strep* disease in Australia – a preventable injustice

- *Why is Group A Strep disease so common in Indigenous Australian populations?*
- **Risk factors for infection:** household crowding, poor health, inadequate health hardware in homes, co-infection with scabies, ...
- **Past interventions:** treatment based, short-term success not sustained
- **Future interventions:** general consensus is that they should be focused on primordial factors / primary prevention

Group A *Strep* disease in Australia – a preventable injustice

Ministers
Department of Health

Home | Media centre | The Hon Greg Hunt MP | Senator the Hon Richard Colbeck | The Hon Mark Coulton

$160 million for Indigenous health research

The Liberal National Government will provide $160 million for a national research initiative to improve the health of Aboriginal and Torres Strait Islander people.

- $35 million for the development of a vaccine to eliminate RHD in Australia.
- Realistically, a vaccine is years away
- We need to reduce the burden of Group A *Strep* disease now through non-vaccine interventions. *But, which ones?*

What is the best strategy to reduce the burden of Group A *Strep* disease in Indigenous Australians?

- Screening and treatment: household-focused, school-focused, childcare
- Mass-drug administrations: targeting skin sores, scabies
- Surveillance
- Education delivery: community-wide, region-wide, via health-care professionals
- Housing programs
- Health hardware maintenance programs
- ...

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Developing a Group A *Strep* transmission model

- **Our Aim:** to determine the best combination of non-vaccine interventions needed to achieve effective and sustained control of Group A *Strep* transmission in Aus Indigenous populations

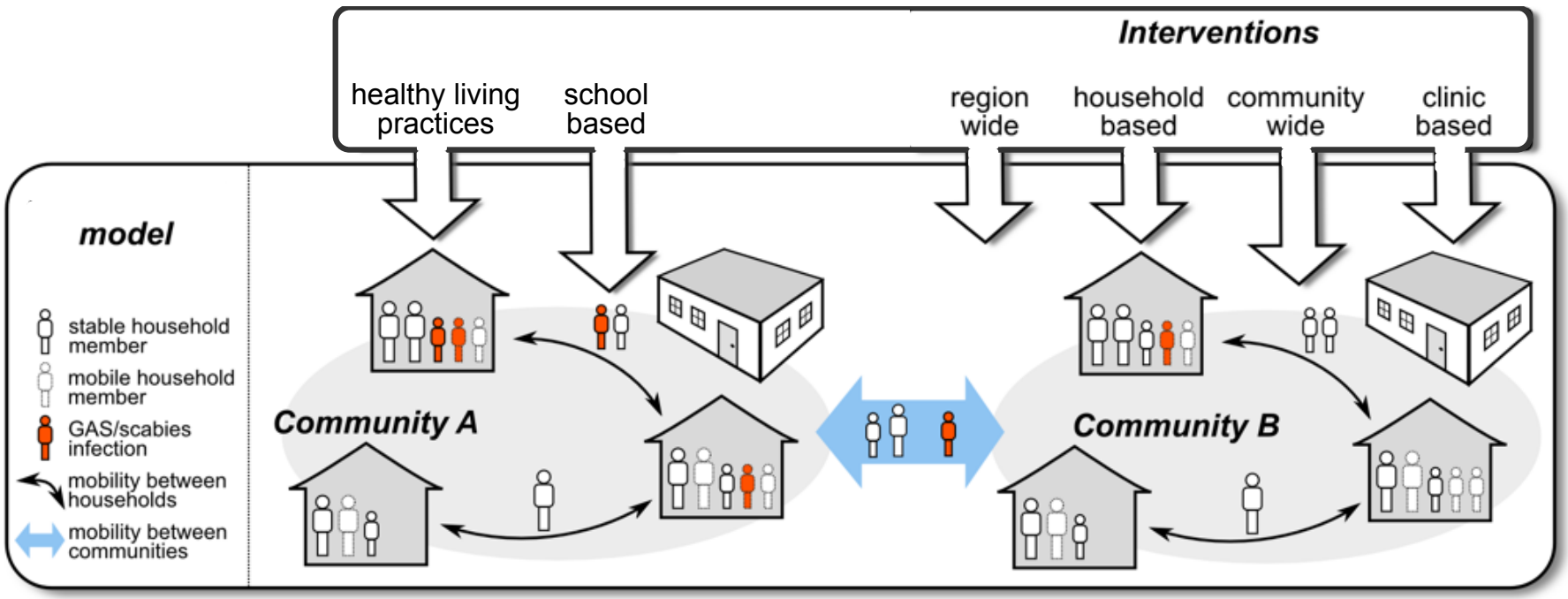


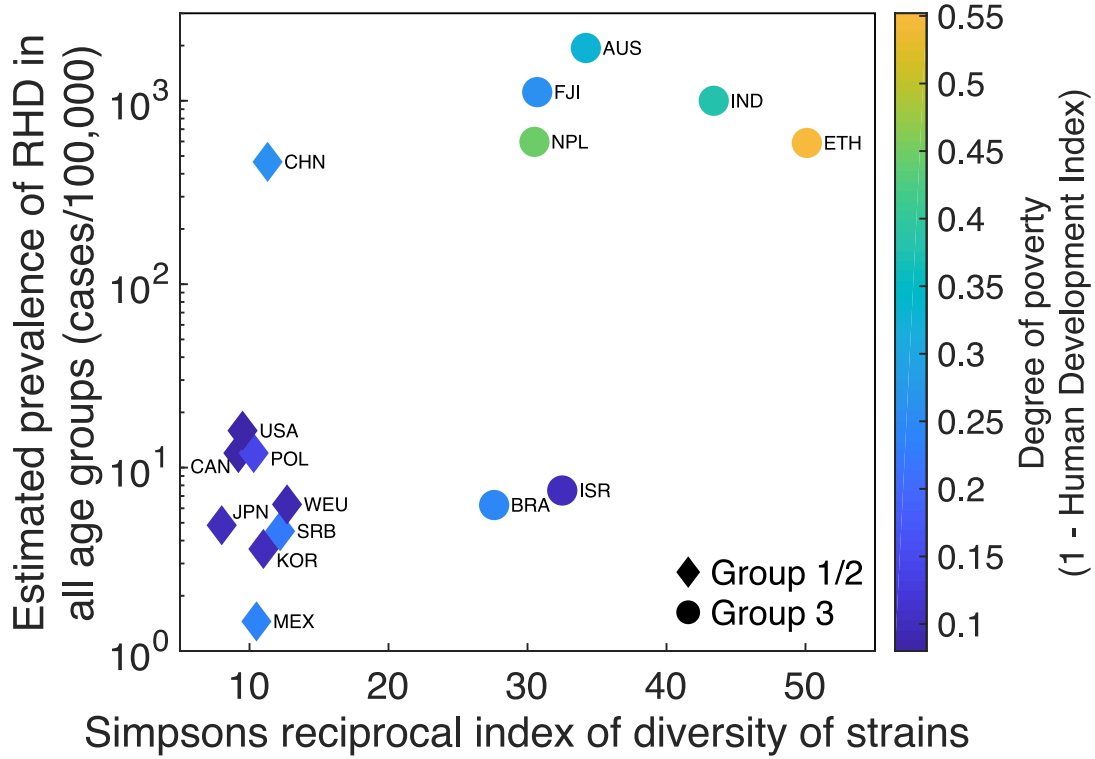
Figure: Nic Geard

Developing a Group A *Strep* transmission model

- **Our Aim:** to determine the best combination of non-vaccine interventions needed to achieve effective and sustained control of Group A *Strep* transmission in Aus Indigenous populations

- **Road block:** An incomplete understanding of the within-host dynamics of Group A *Strep* infection and immunity

Can we translate global epidemiological data into understanding of within-host dynamics?



Method:

1. Build general multi-strain transmission model
2. What within-host conditions lead to these population-level patterns?

Step 1: Build model

Model requirements

Aim:

- *To better understand Group A Strep infection & immunity using population-level observations of prevalence and diversity.*

Model needs to:

- Capture strain diversity $\rightarrow$ multi-strain model
- Capture different combinations of within-host dynamics $\rightarrow$ tune level of co-infection, strain-specific and cross-strain immunity

Relevant work:

- Models of *N. meningitidis* (Gupta et al.) and *S. pneumoniae* (Lipsitch et al.)

Model features

- $n(t)$ strains, functionally identical but potentially prompt unique host immune responses
- SIRS-type infection model, with co-infection

- Discrete-time, agent-based model
- Agents correspond to hosts that have an age, infection status, and immune status
- N hosts
- Host migration, demography

Within-host dynamics

- A co-infection-type model is assumed where
  - Strain displacement is not possible
  - Infected hosts are less susceptible than non-infected hosts

- Flexibility in
  - The level of resistance to co-infection (x)
  - The strength of strain-specific (σ) and cross-protective (ω) immunity conferred by strain clearance
  - The mean duration of immunity ($1/\theta$)

Between-host dynamics of the ABM

- Well-mixed population. Each time step we simulate contacts events between agents so that, on average, hosts make contact with c other hosts per time step
- Transmission may occur if there is contact with an infected host.
- The probability host i is infected by strain j from a contact with a host infected with strain j at time t is:

$$Q_{i,j}(t) = \underbrace{\beta}_{\substack{\text{Base probability} \\ \text{of transmission}}} \times \underbrace{r}_{\substack{\text{Effect of host} \\ i\text{'s current} \\ \text{infections}}} \times \underbrace{s}_{\substack{\text{Effect of host} \\ i\text{'s past} \\ \text{infections}}}$$

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- Susceptibility of host i relative to an uninfected host:

$$r = \left(1 - \frac{\text{number of infections of host } i}{\kappa}\right)^x,$$

where $x > 0$ scales the level of resistance of acquisition of new infections due to the competitive advantage of already established infections, κ is an individual's infection carrying capacity.

Between-host dynamics of the ABM

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- Susceptibility of host i relative to a host without immunity:

$$s = \begin{cases} 1-\sigma, & \text{if host } i \text{ currently has immunity to strain } j, \\ 1-\omega, & \text{if host } i \text{ currently has immunity to strains} \neq j, \\ 1, & \text{if host currently has no immunity,} \end{cases}$$

where σ and ω are the strengths of strain-specific and cross-strain immunity, such that $0 \leq \omega \leq \sigma \leq 1$.

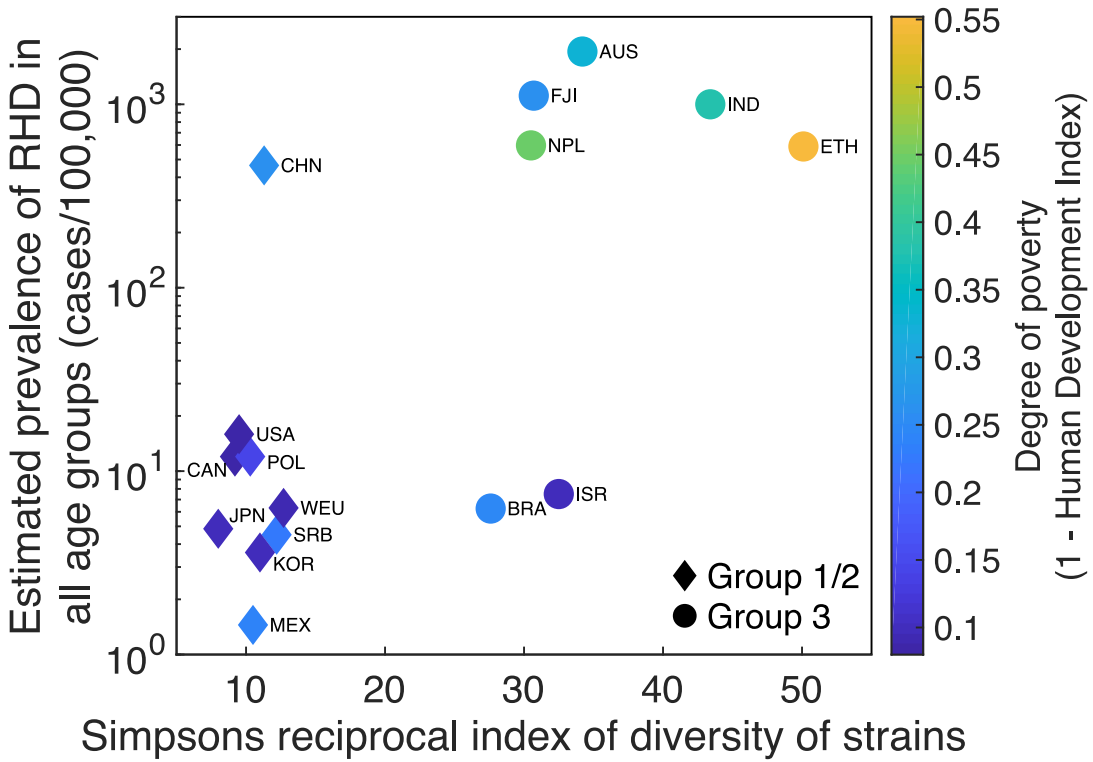
Between-host dynamics of the ABM

- Transmissibility is characterised by the basic reproduction number $\mathcal{R}_0$ defined as

$$\mathcal{R}_0 = \frac{c\beta}{\gamma + d + \alpha},$$

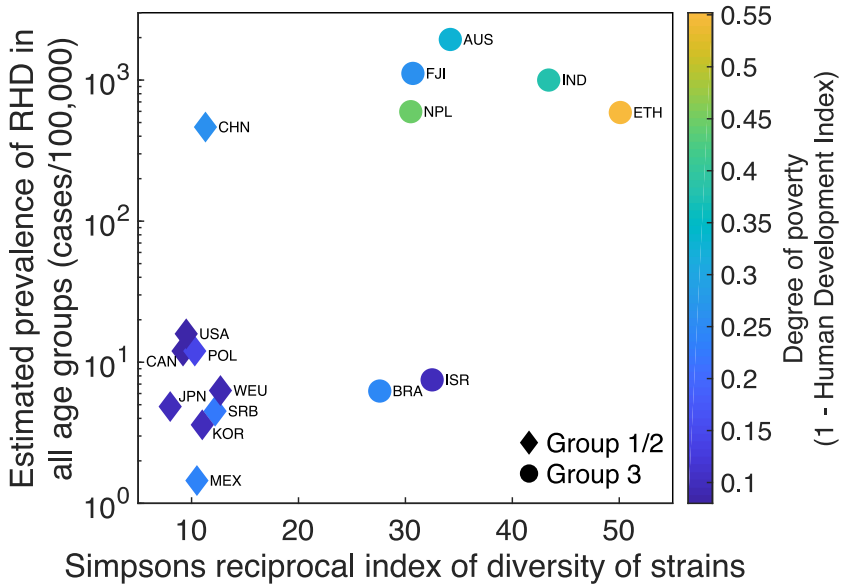
  where d is the per capita birth/death rate, α is the per capita migration rate.
- $\mathcal{R}_0$ is the expected number of secondary cases of infection caused by a primary case of infection in an entirely susceptible population

Step 2: What within-host conditions (x, σ, ω, $1/\theta$) lead to this type of epidemiology?



Measuring prevalence and strain diversity

- The prevalence of infected hosts, $P(t)$, is calculated as the percentage of hosts with one or more infections



- Strain diversity, $D(t)$, is calculated using Simpson's reciprocal index:

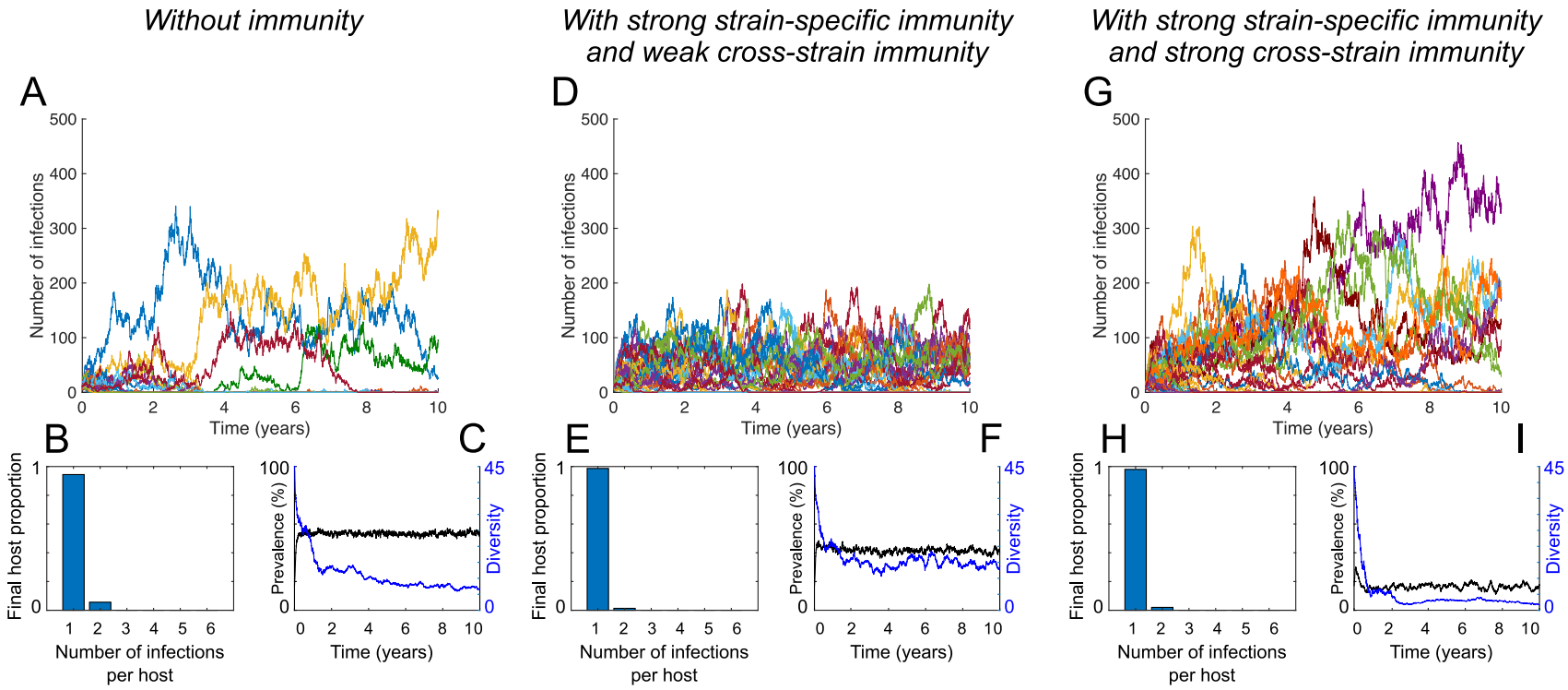
$$D(t) = \frac{M(t)(M(t)-1)}{\sum_j m_j(t)(m_j(t)-1)},$$

where $m_j(t)$ is the total number of infections of strain j in the population at time t, and $M(t) = \sum_j m_j(t)$.

Diversity regimes in the ABM (governed by x, σ, ω)

$$(N, n_{\max}, x, \mathcal{R}_0, 1/\theta) = (2500, 42, 100, 2, 6 \text{ months})$$

- With high resistance to co-infection:

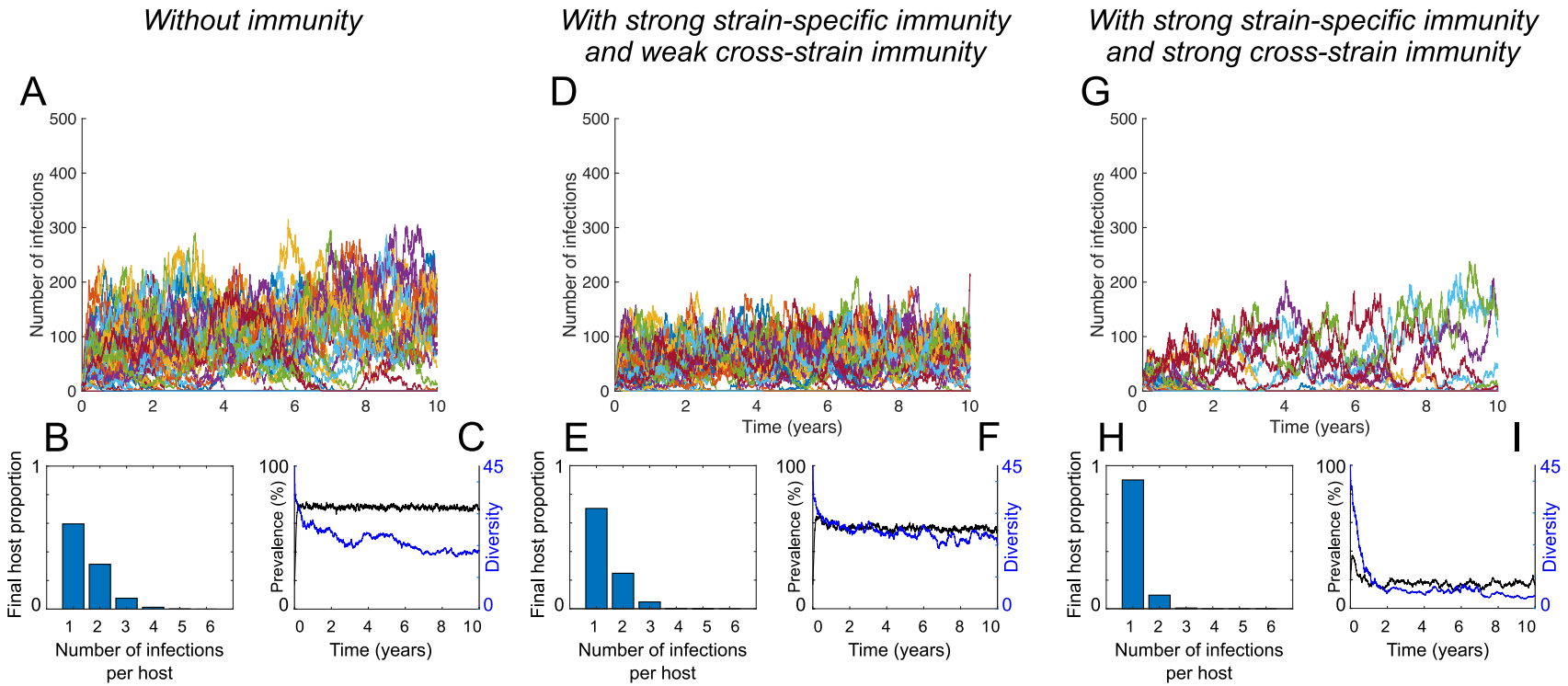


$(\sigma, \omega) = (0, 0)$ $(\sigma, \omega) = (0.5, 0.1)$ $(\sigma, \omega) = (0.5, 0.5)$

Diversity regimes in the ABM (governed by x, σ, ω)

$$(N, n_{\max}, x, \mathcal{R}_0, 1/\theta) = (2500, 42, 10, 2, 6 \text{ months})$$

- With low resistance to co-infection:



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The impact of within-host dynamics on $D(t)$ and $P(t)$

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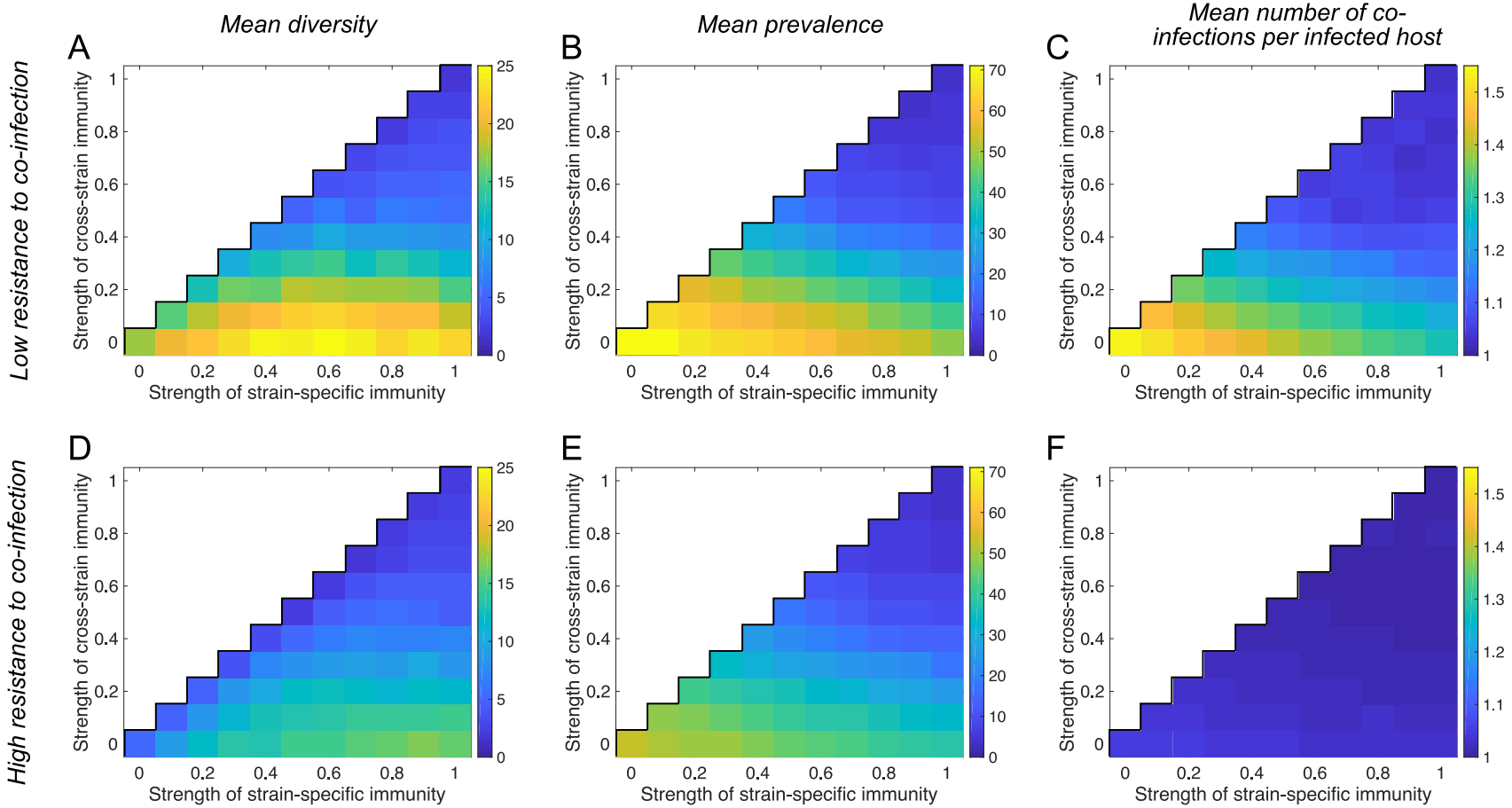

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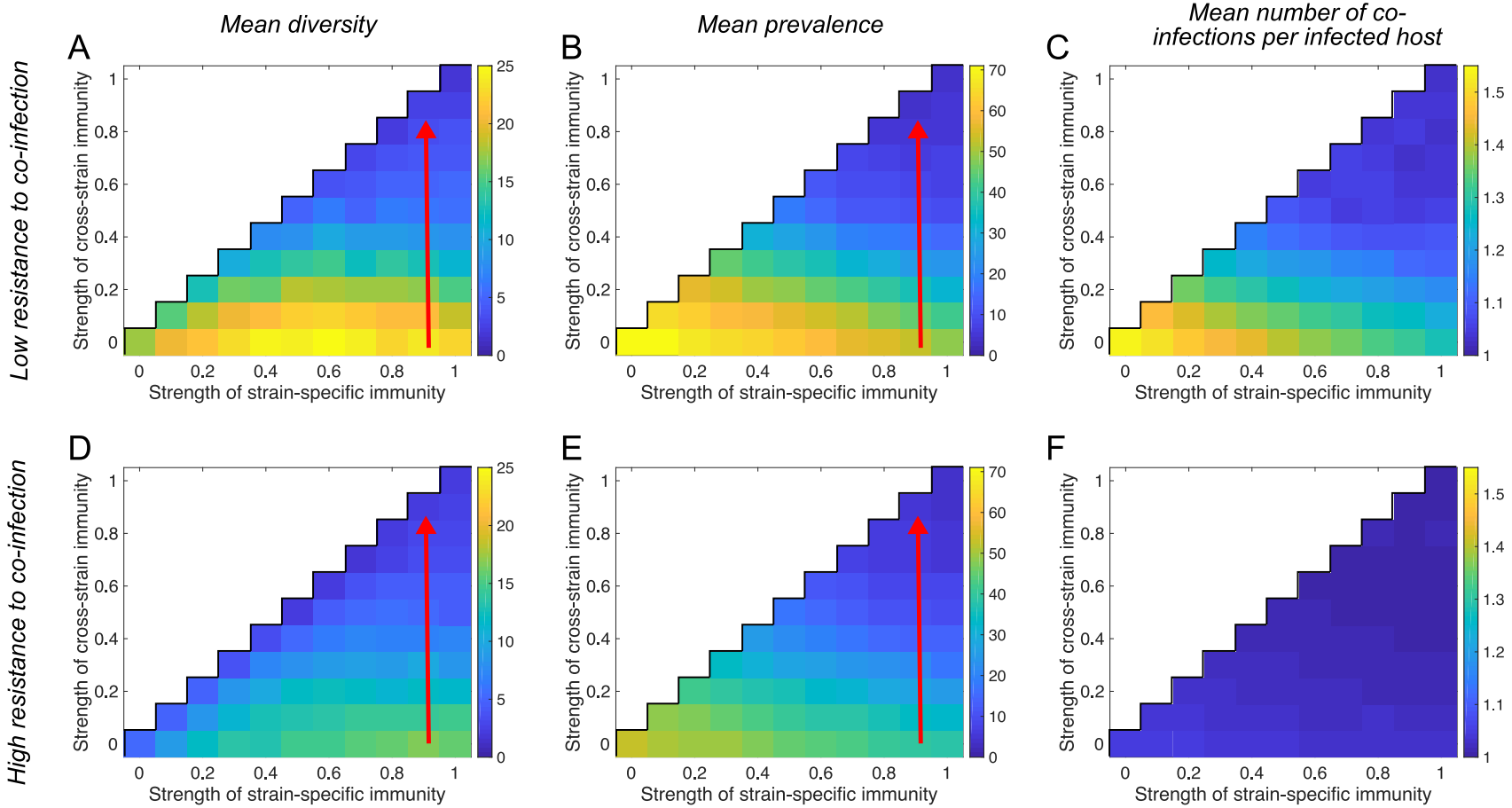

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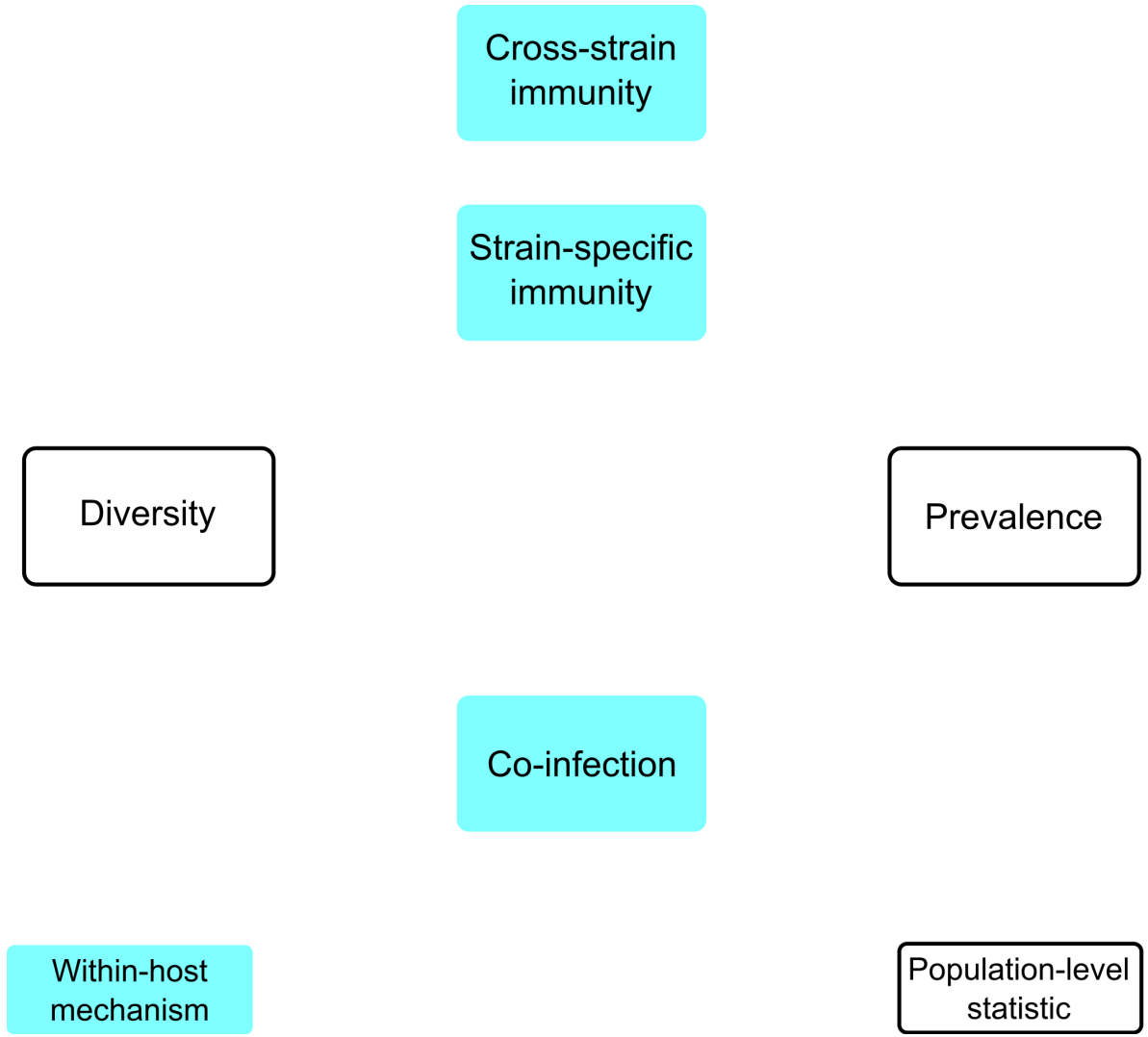

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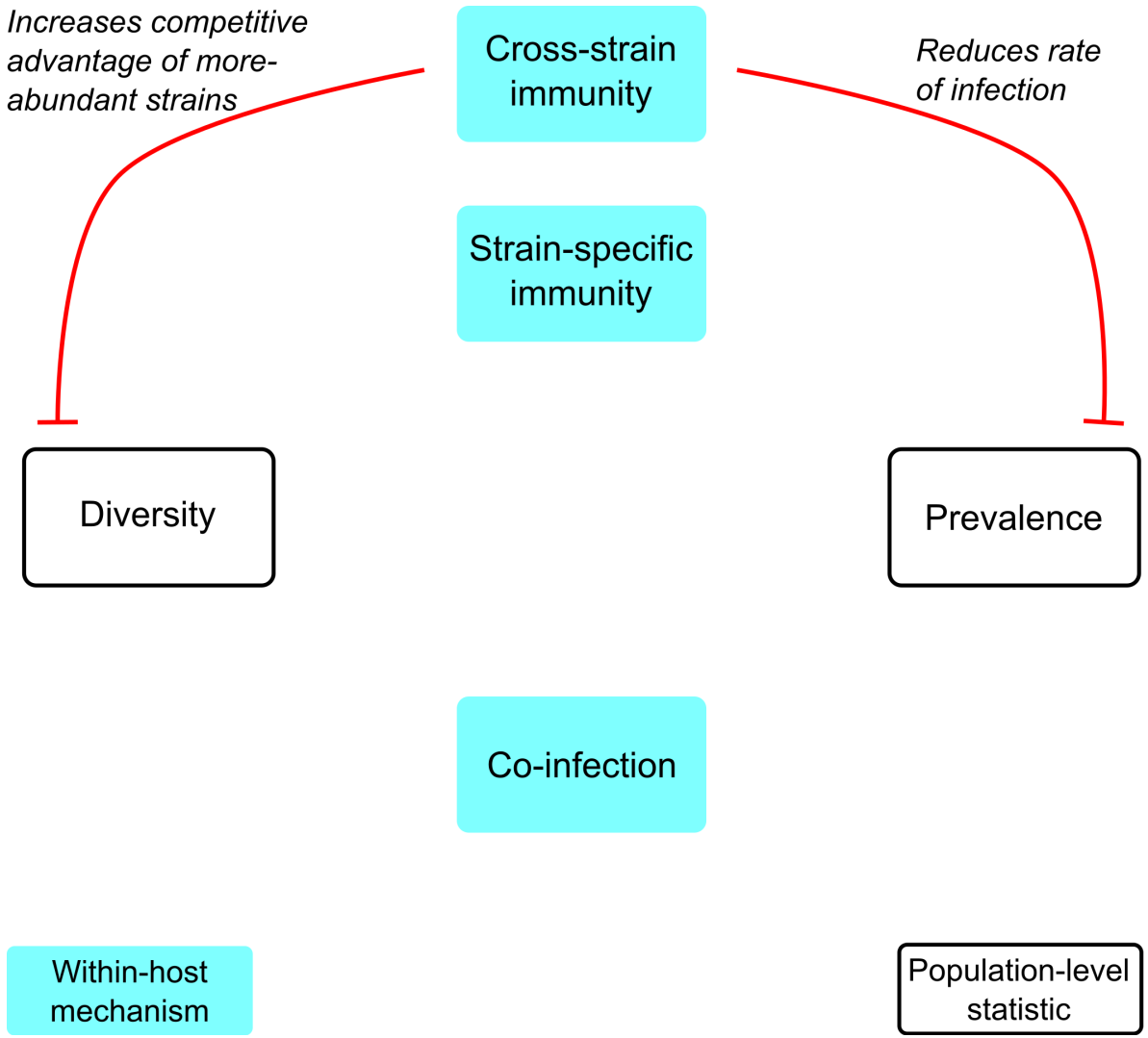

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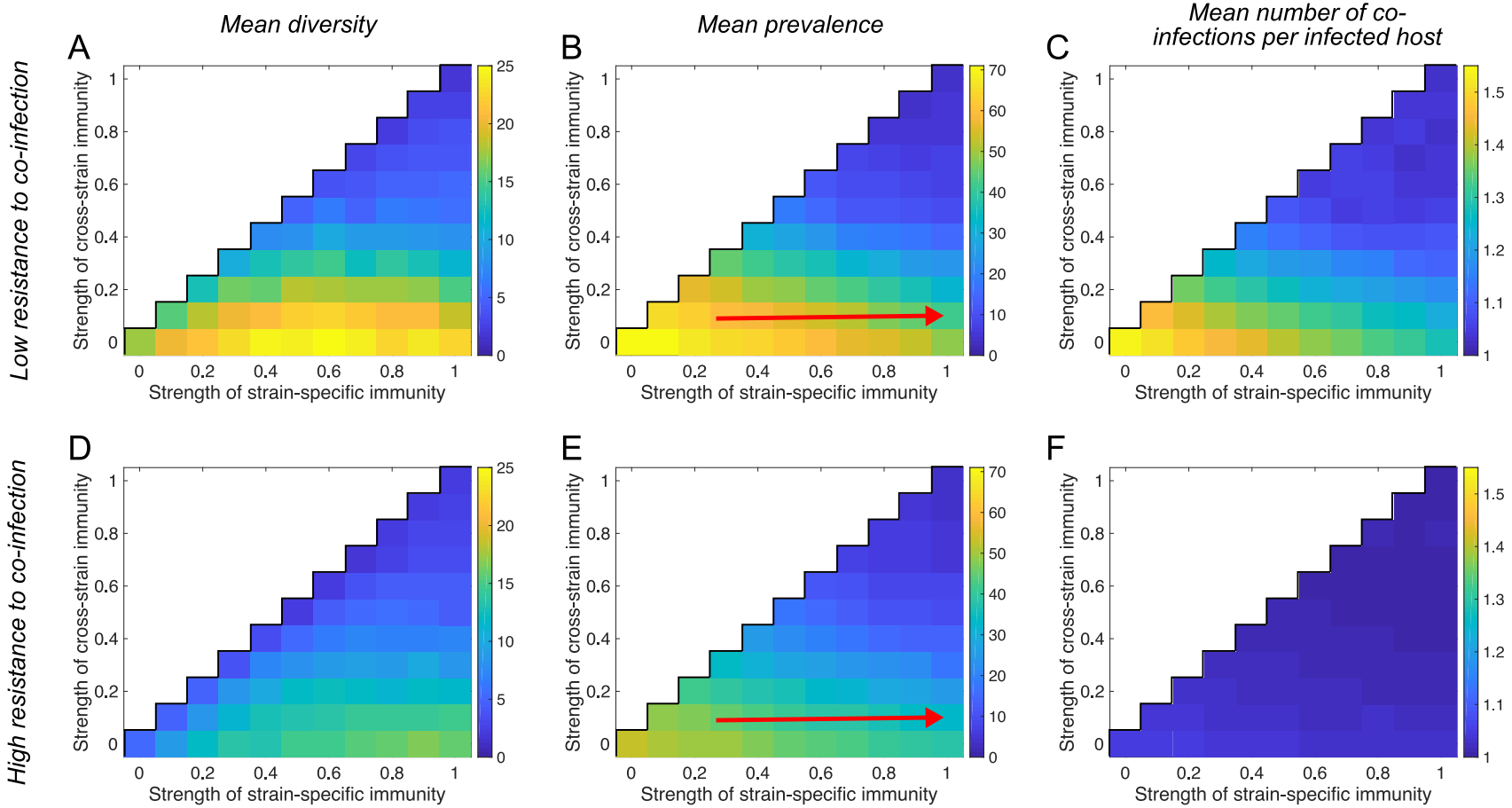

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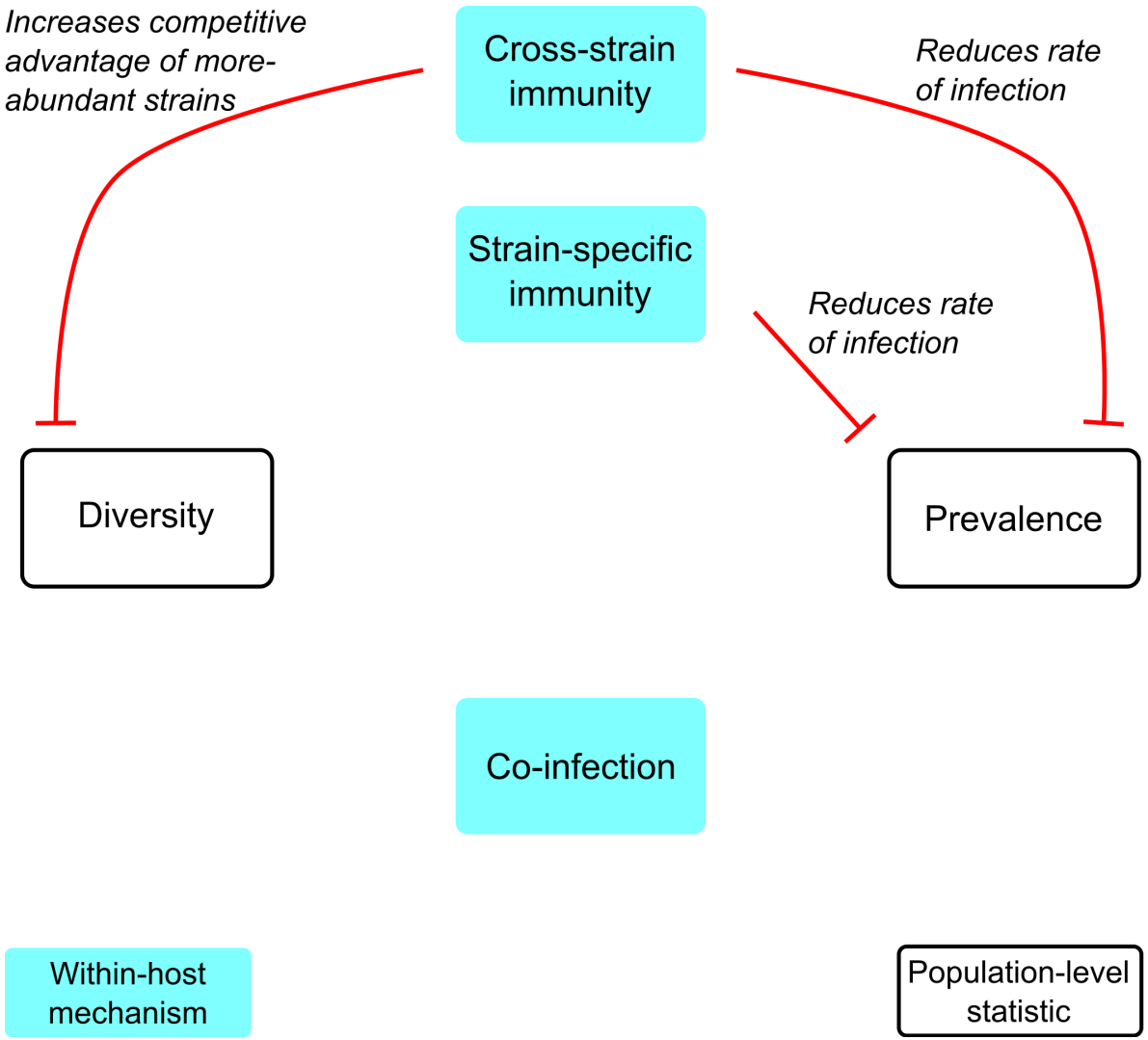

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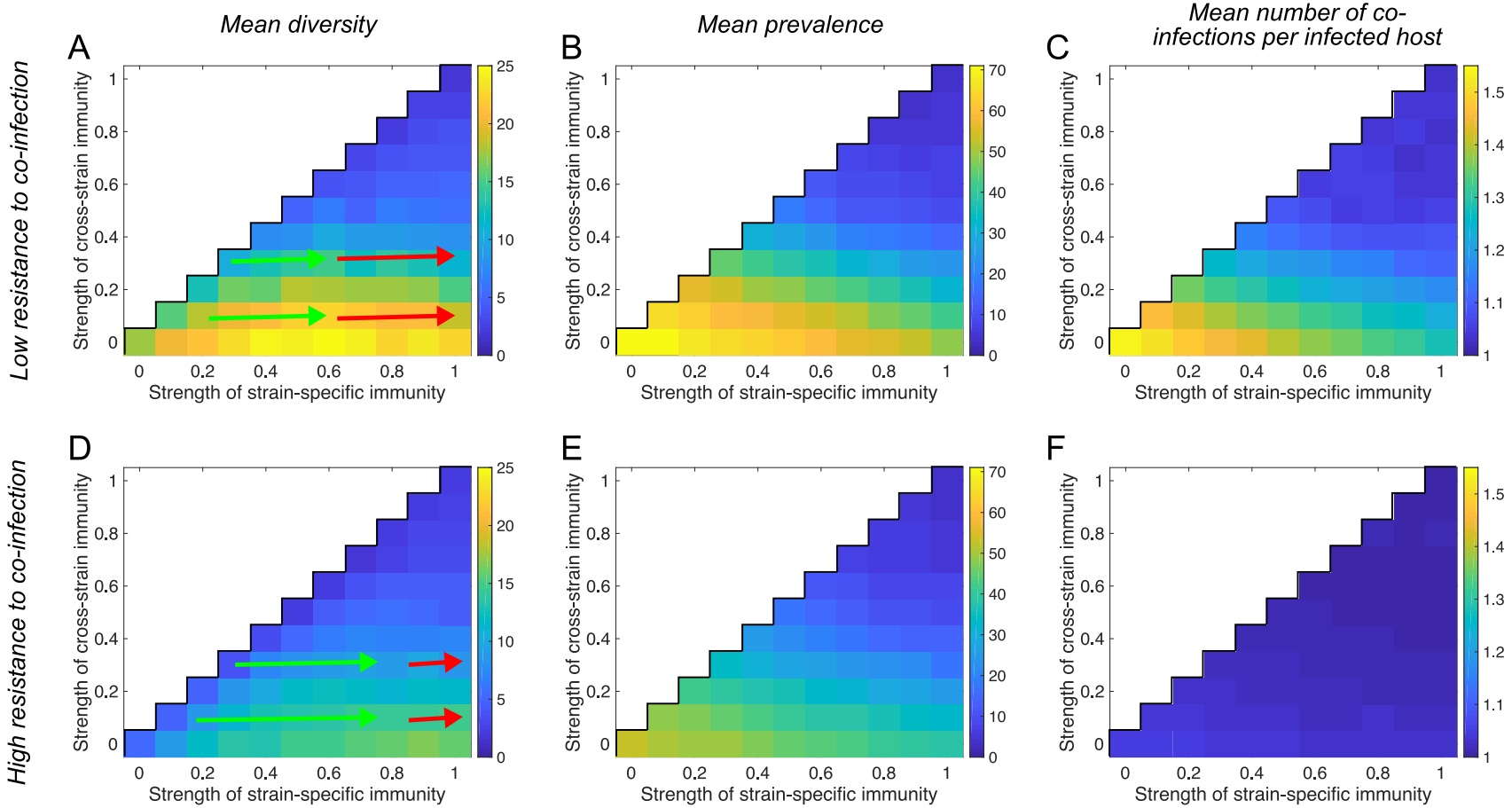

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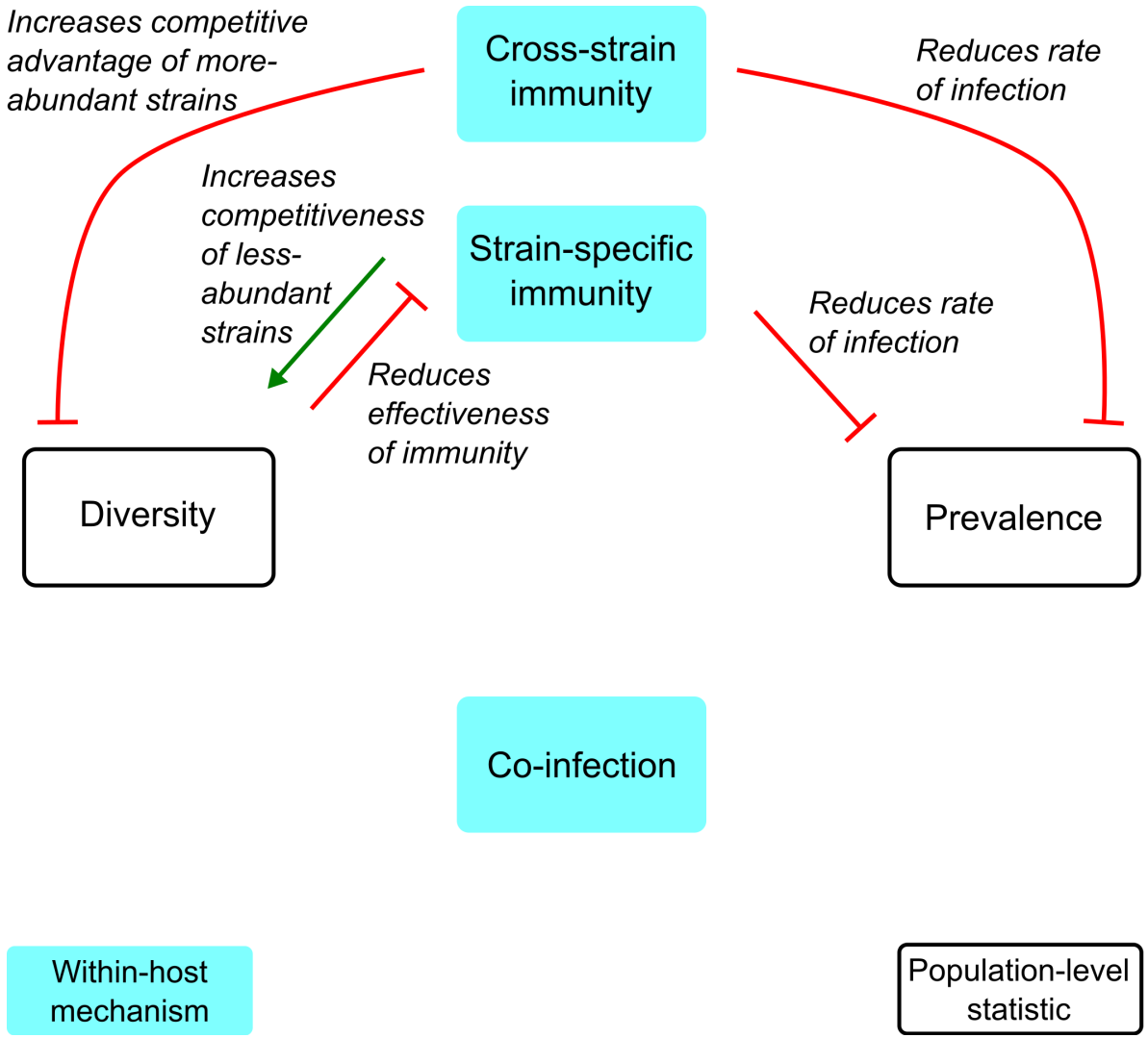

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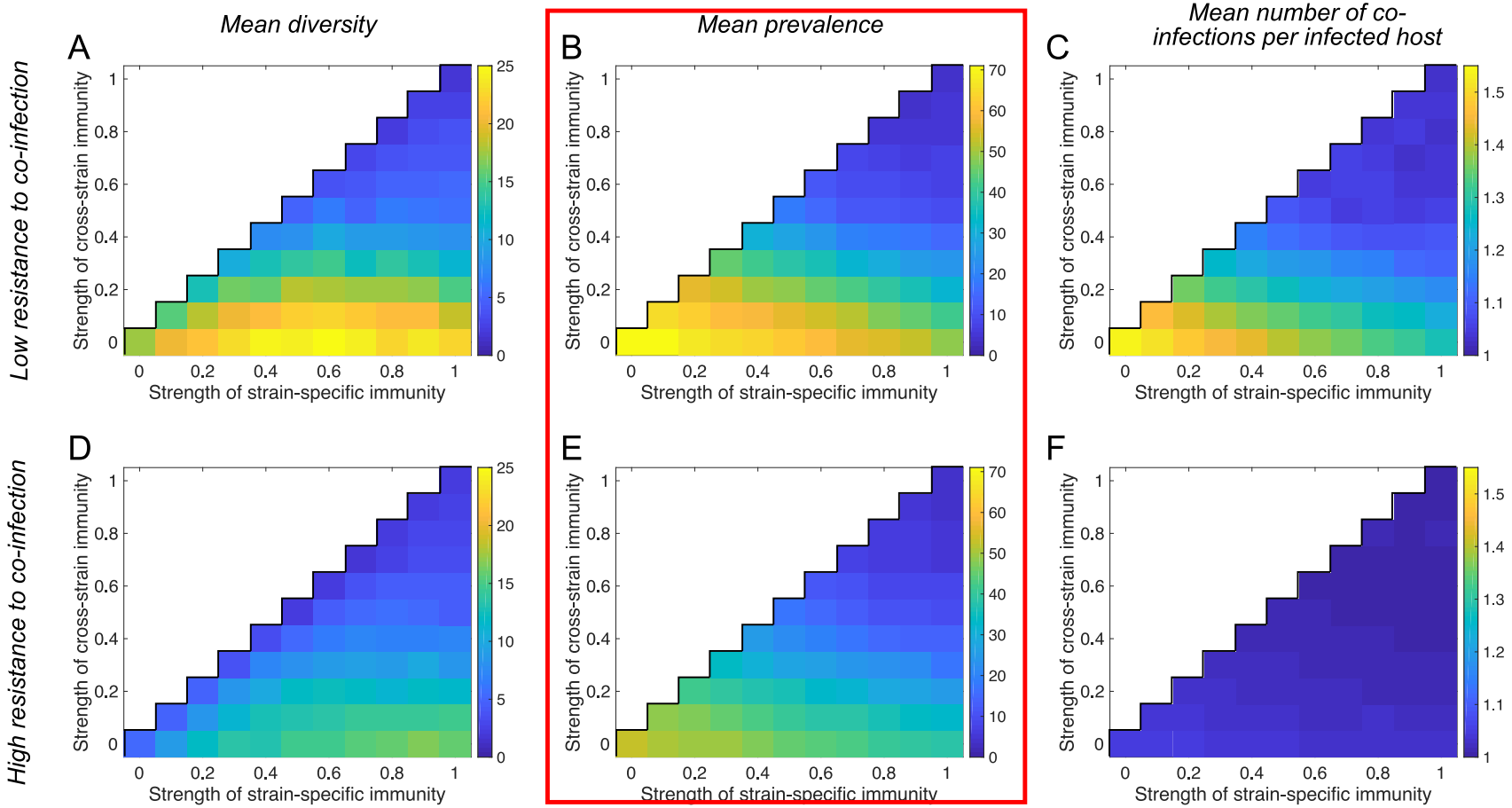

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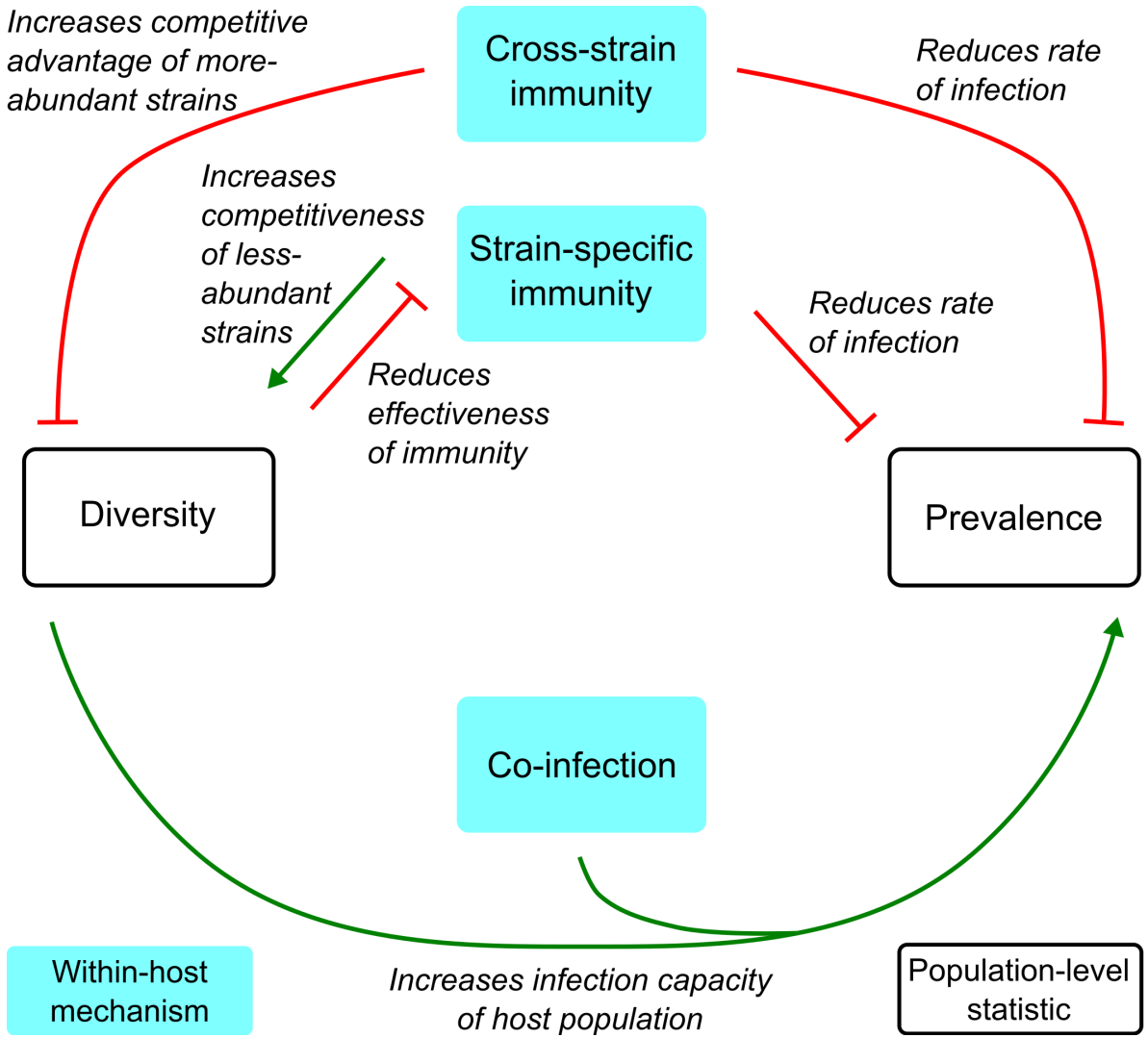

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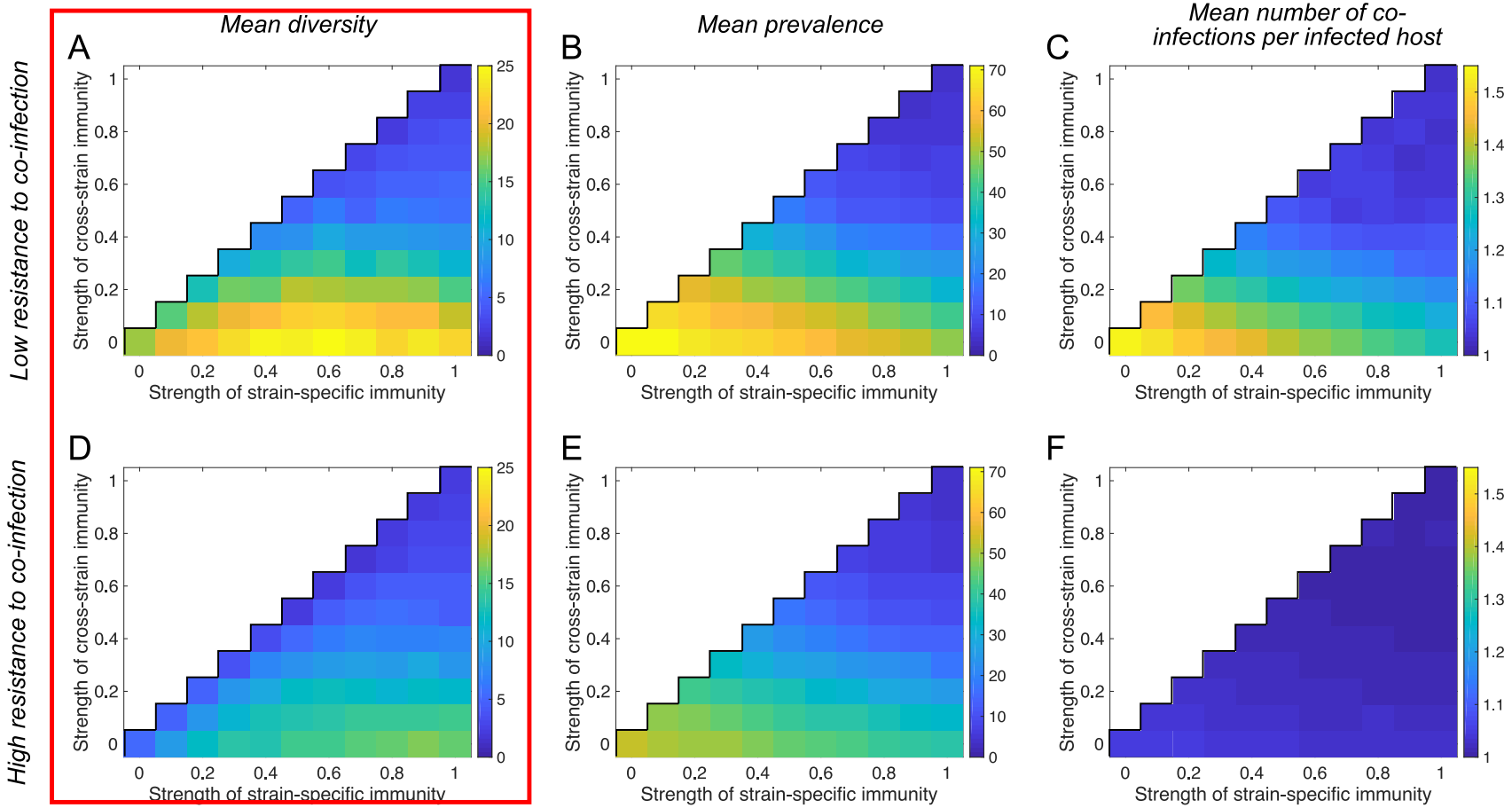

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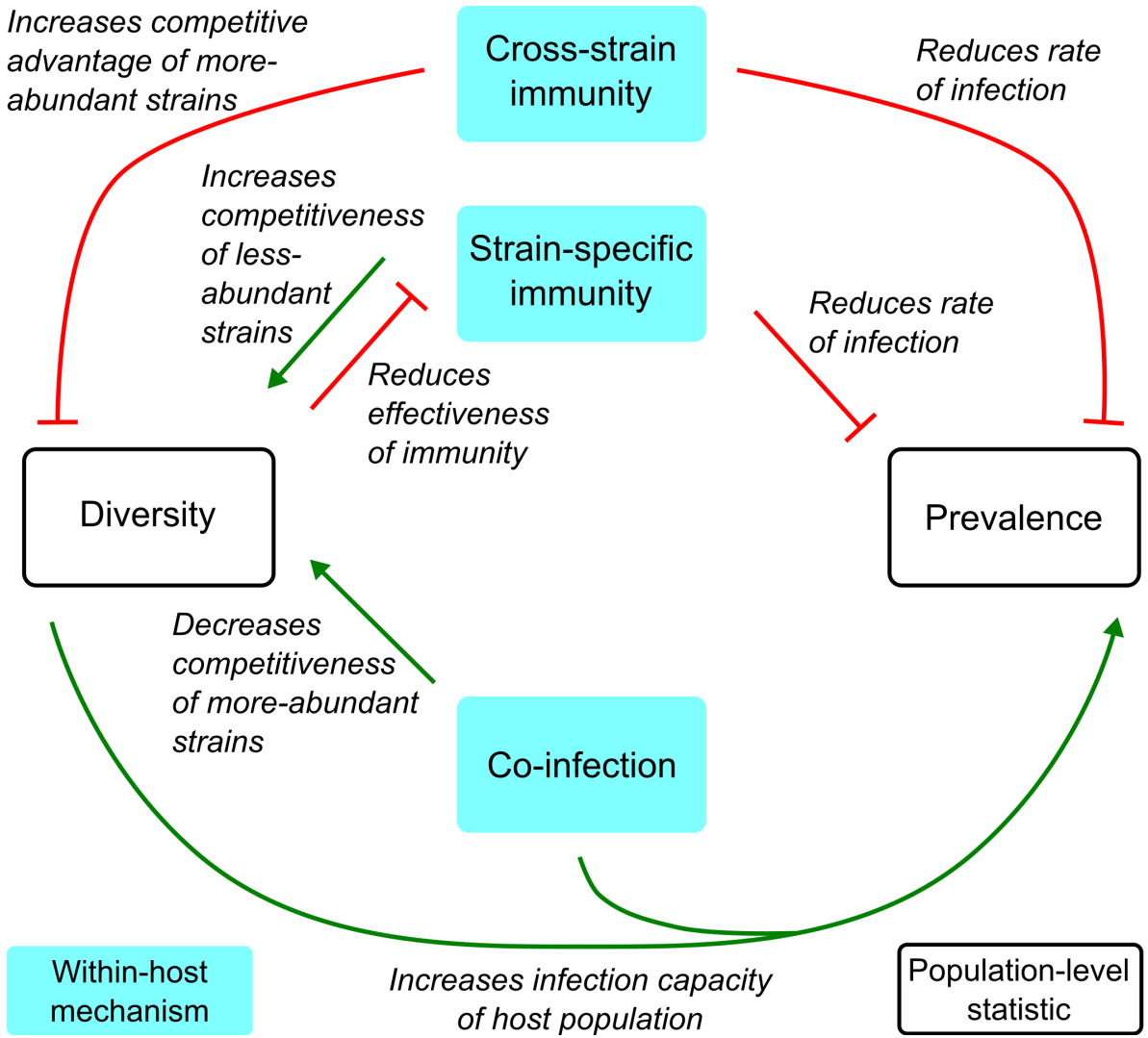

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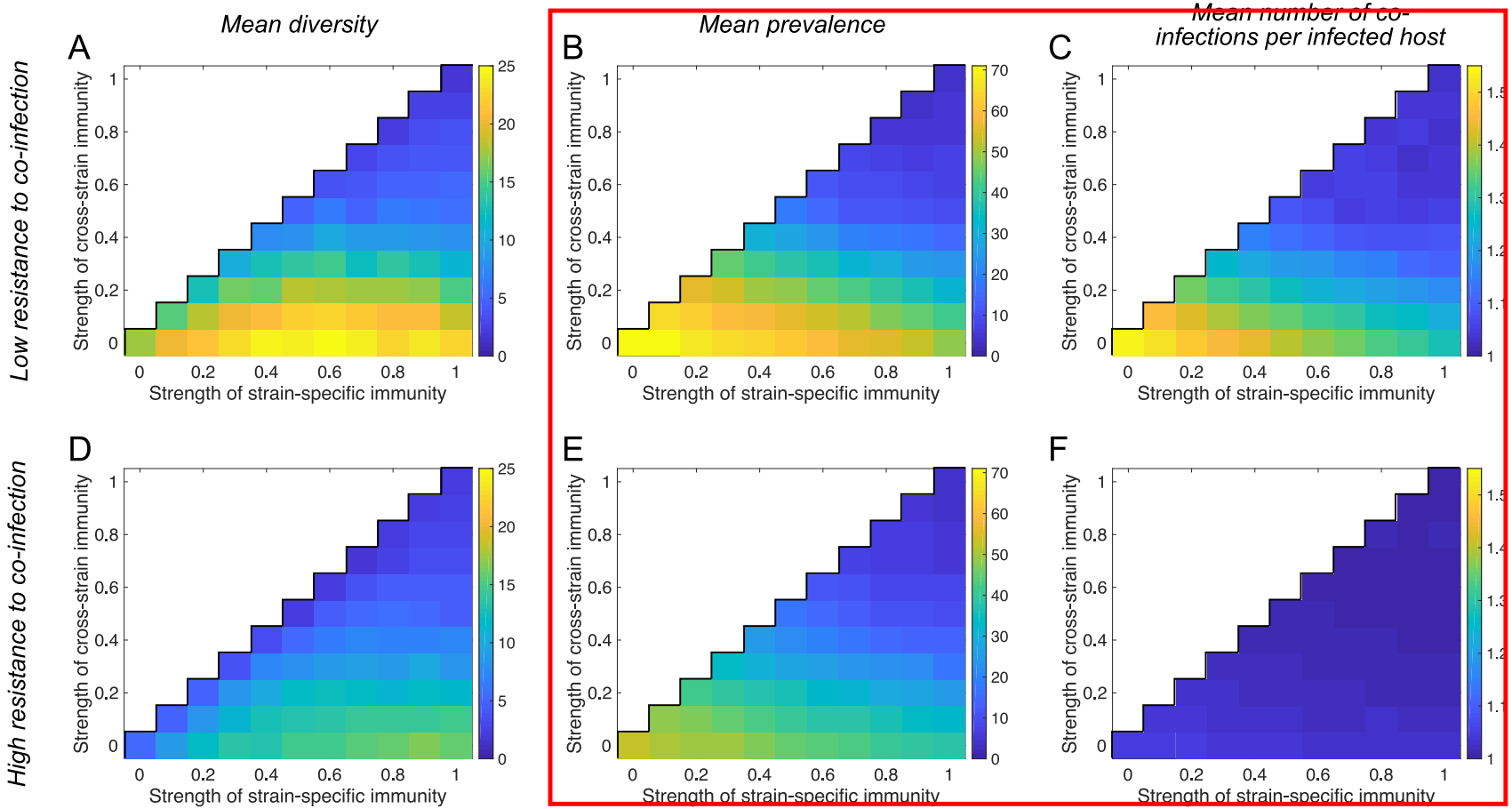

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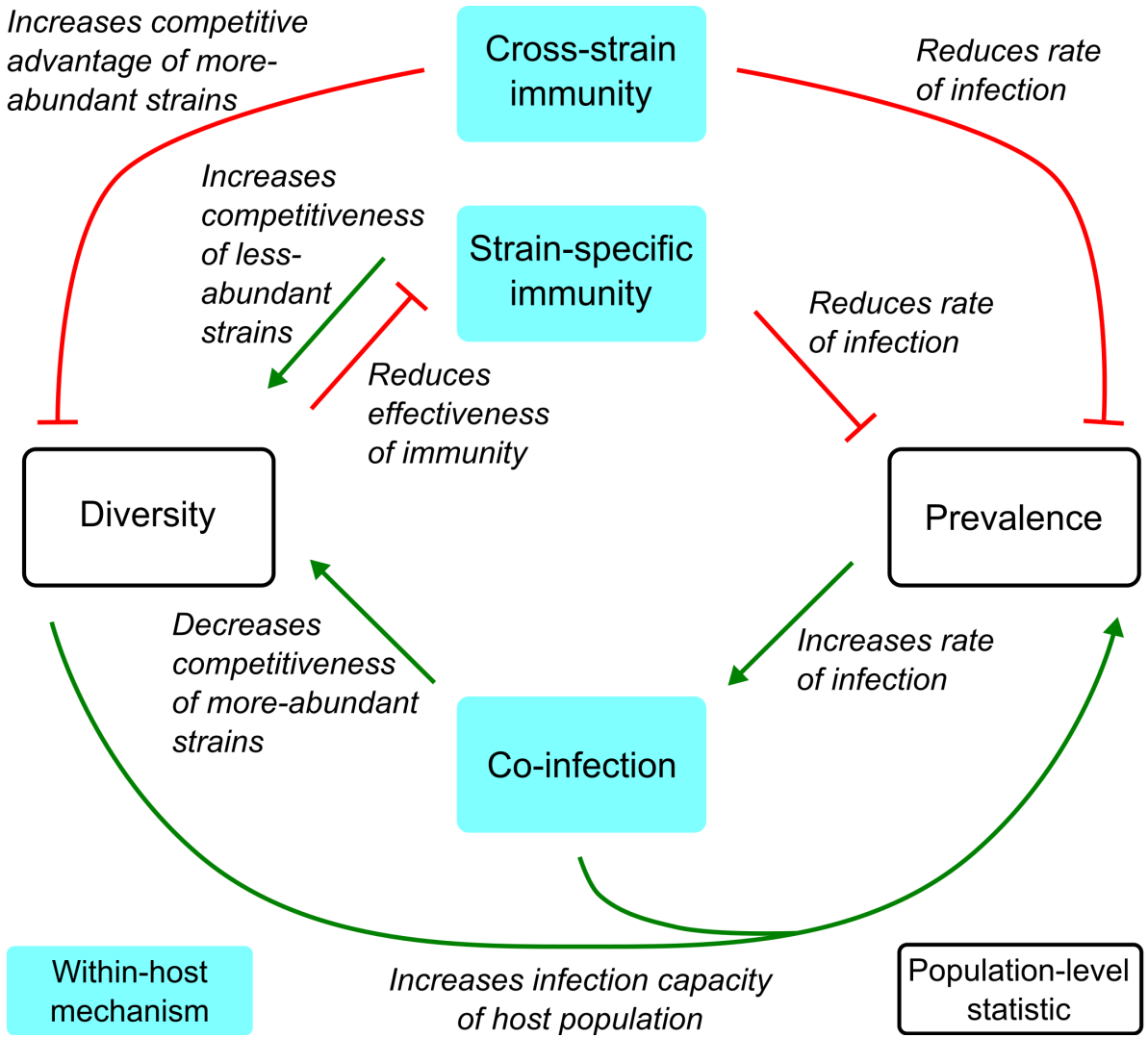
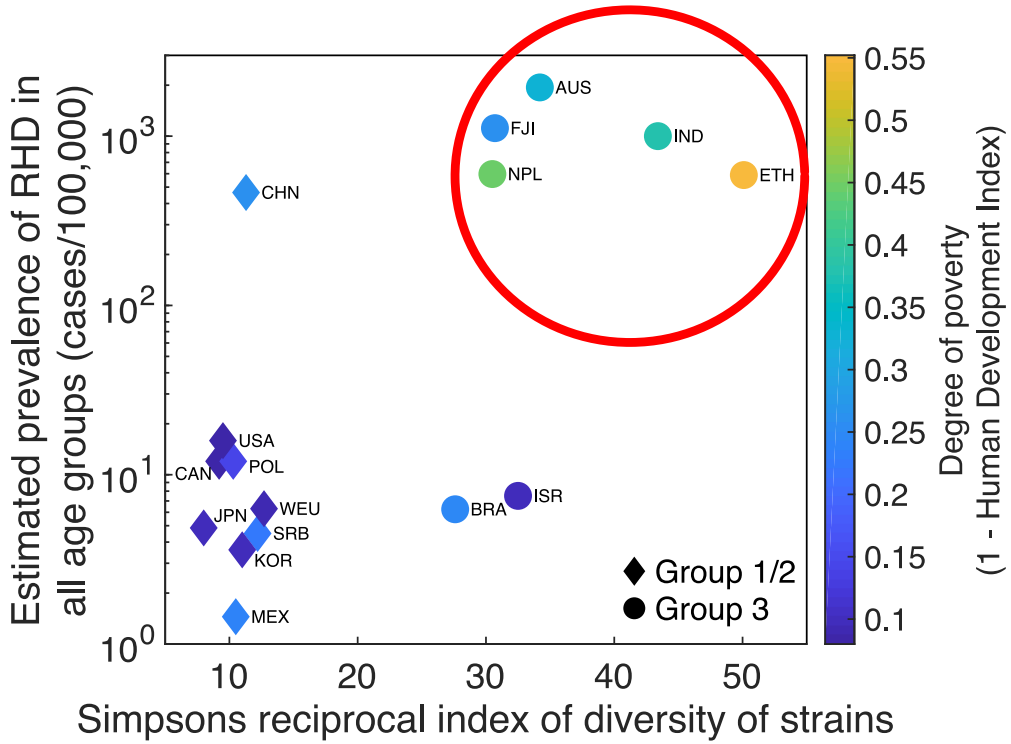


Interaction between within-host dynamics, $D(t)$ and $P(t)$

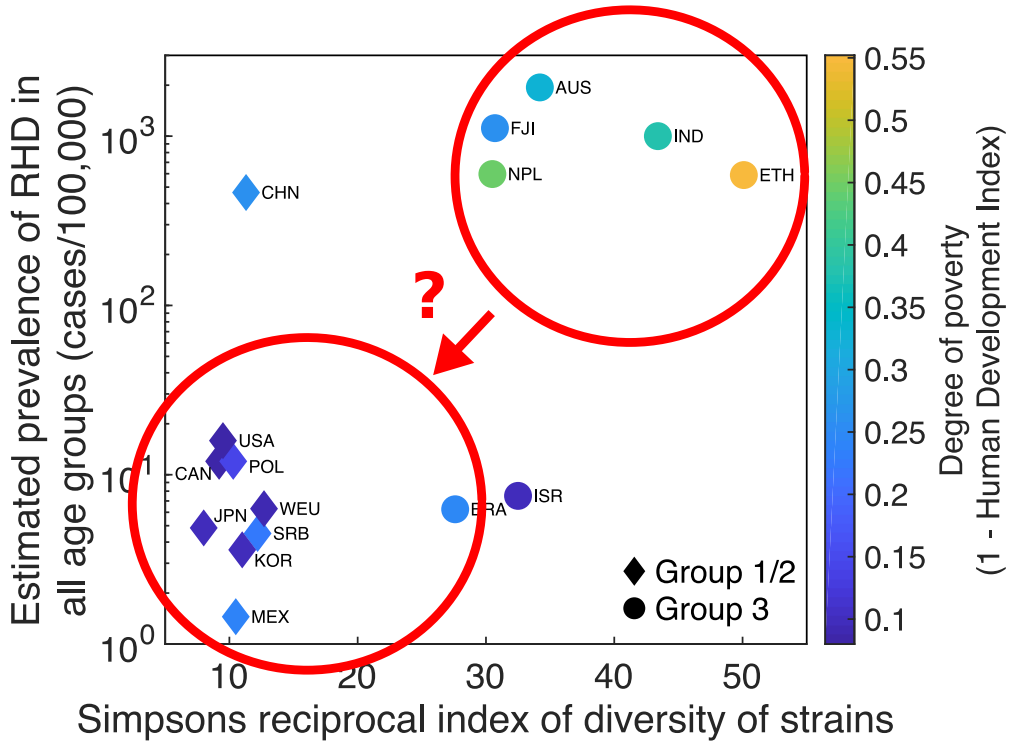


High $D(t)$ and $P(t)$ requires:

- Intermediate-high strength of strain-specific immunity σ
- Low strength or absent cross-strain immunity ω
- There is low resistance to co-infection x

Interaction between within-host dynamics, $D(t)$ and $P(t)$

Little variation between host settings



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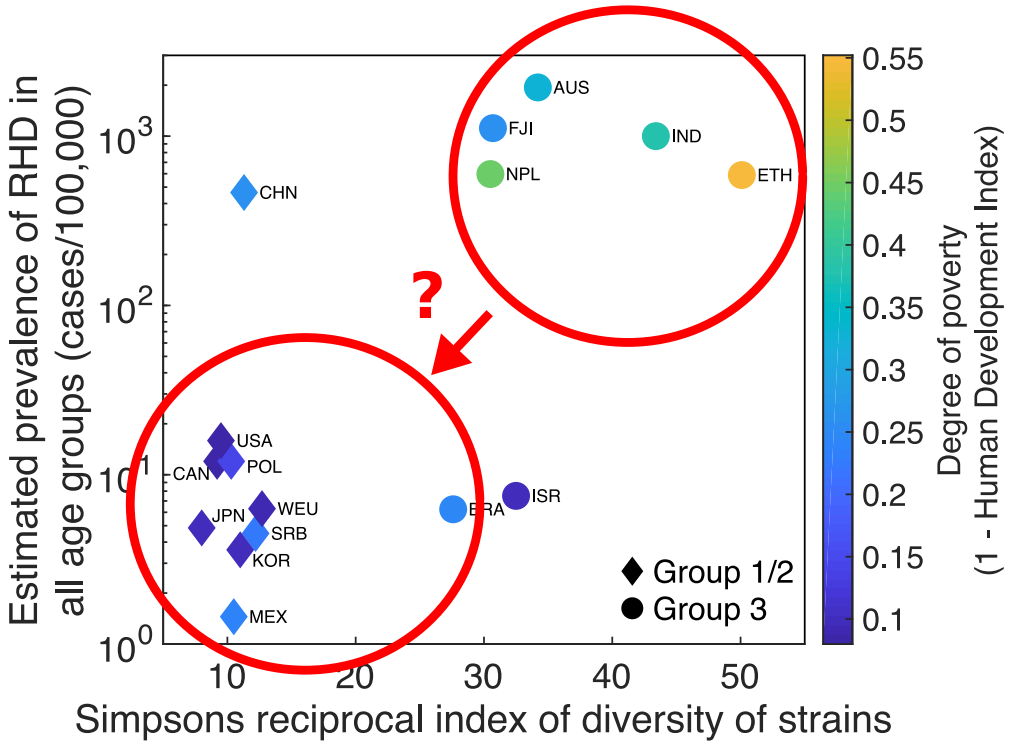


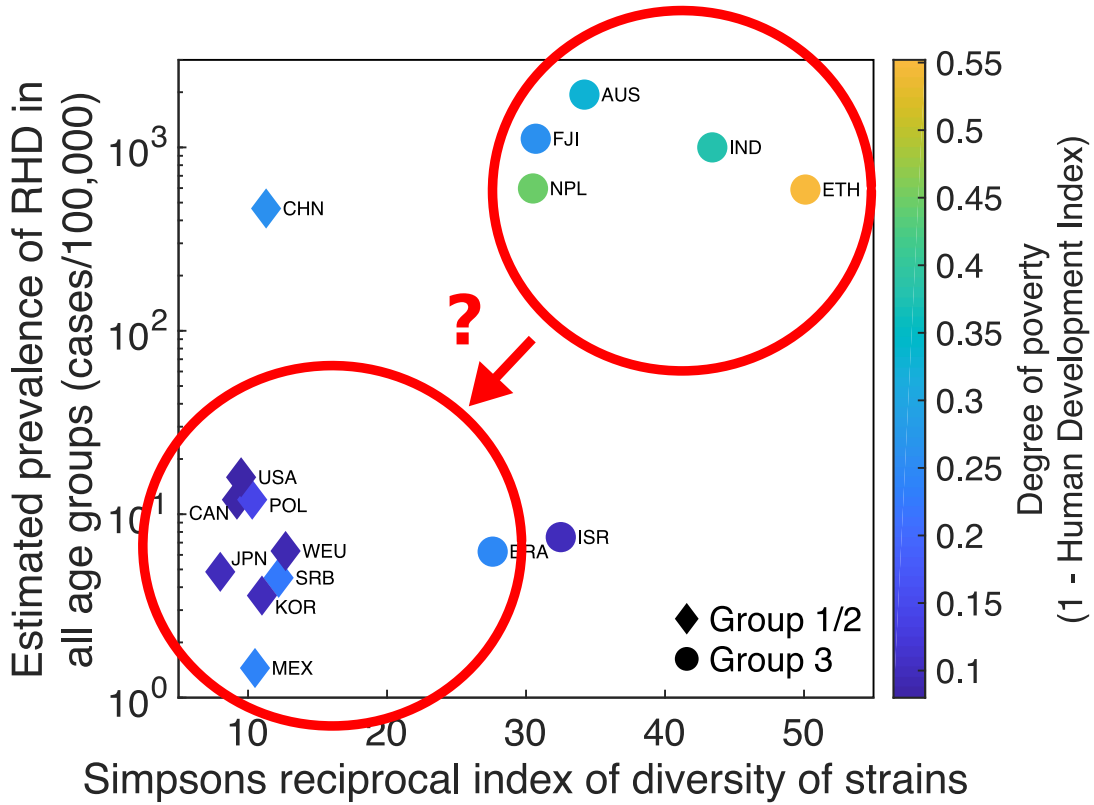
What might vary more? $\mathcal{R}_0$

High $D(t)$ and $P(t)$ requires:

- Intermediate-high strength of strain-specific immunity σ
- Low strength or absent cross-strain immunity ω
- There is low resistance to co-infection x

The impact of between-host dynamics on $D(t)$ and $P(t)$

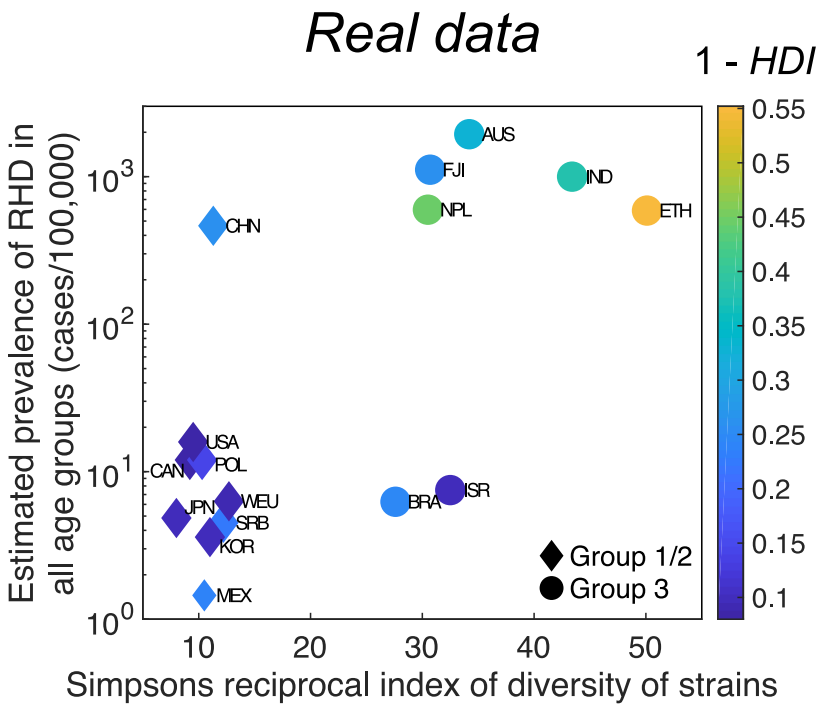
- What within-host conditions must hold so that a reduction in $P(t)$ (due to reduction in $\mathcal{R}_0$) corresponds to a reduction in $D(t)$?

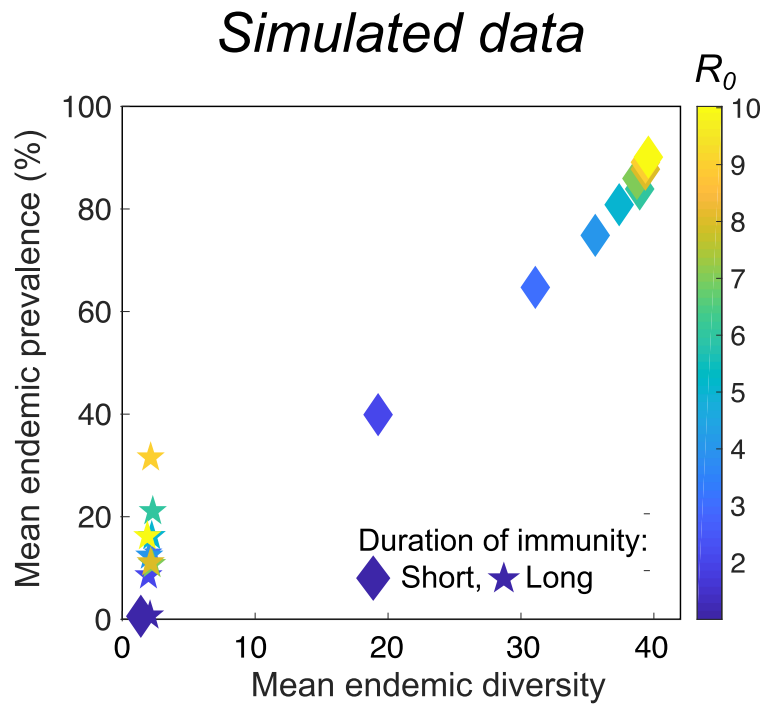


Smeester et al., 2009, Carapetis et al., 2005.

The impact of $\mathcal{R}_0$ on diversity and prevalence

- With low resistance to co-infection and short duration of immunity, we see clustering of points similar to real data:





Hypothesis for the within-host dynamics of Group A *Strep*

- Intermediate-high strength of strain-specific immunity σ
- Low strength or absent cross-strain immunity ω
- There is low resistance to co-infection x
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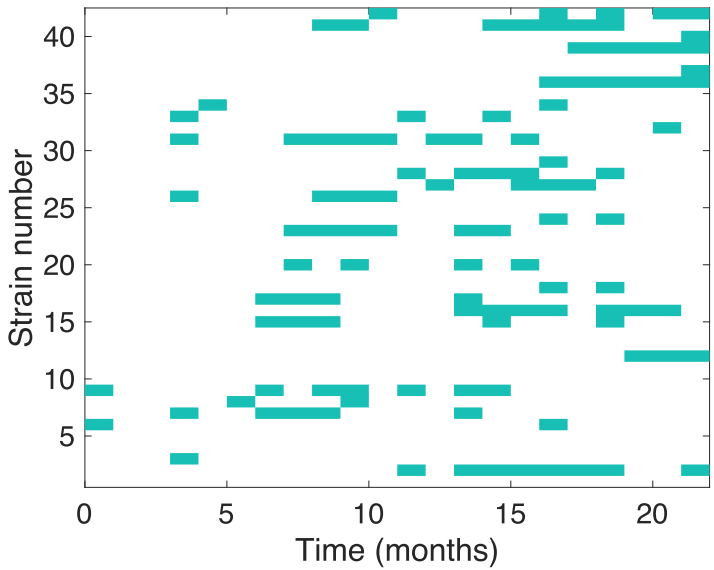
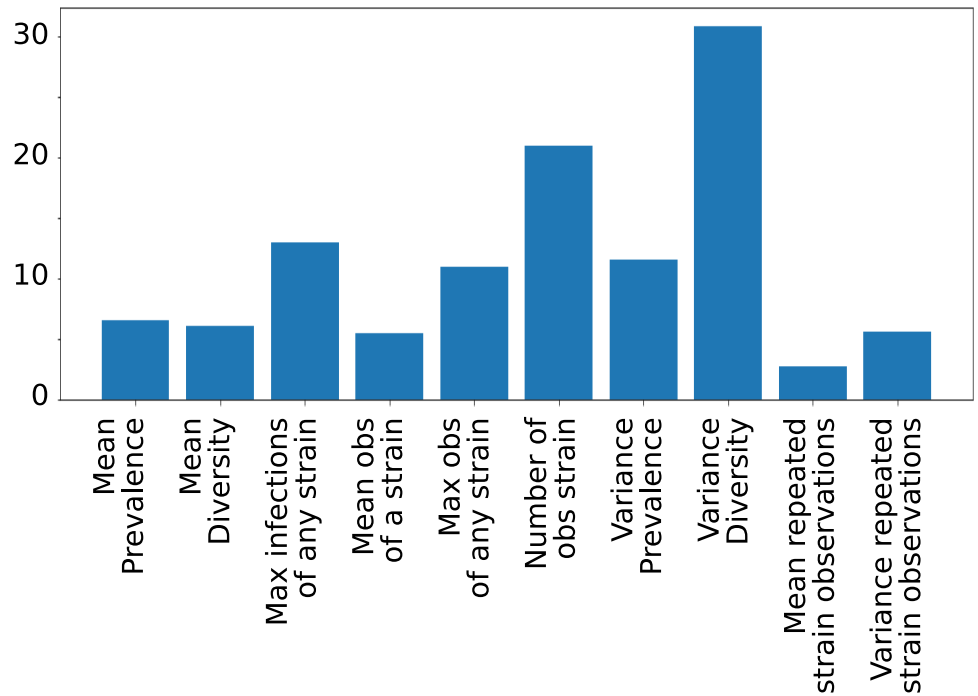
- How short / low / high ?

- Need more summary statistics of transmission dynamics than just $D(t)$ and $P(t)$

Fitting model to longitudinal NT data

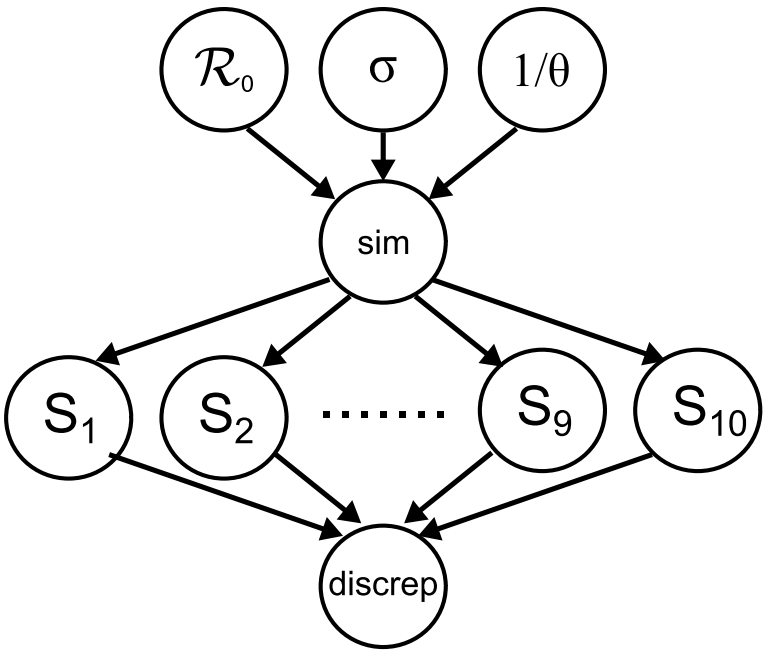
- Hyper-endemic community of approximately 2500 people in Aus NT (McDonald et al., 2008).
- 1-11 strains (emm type) circulate in the community at any one time-point for variable durations





- Can we learn anything more about σ and $1/\theta$? What is $\mathcal{R}_0$?

Fitting model to NT data using BOLFI

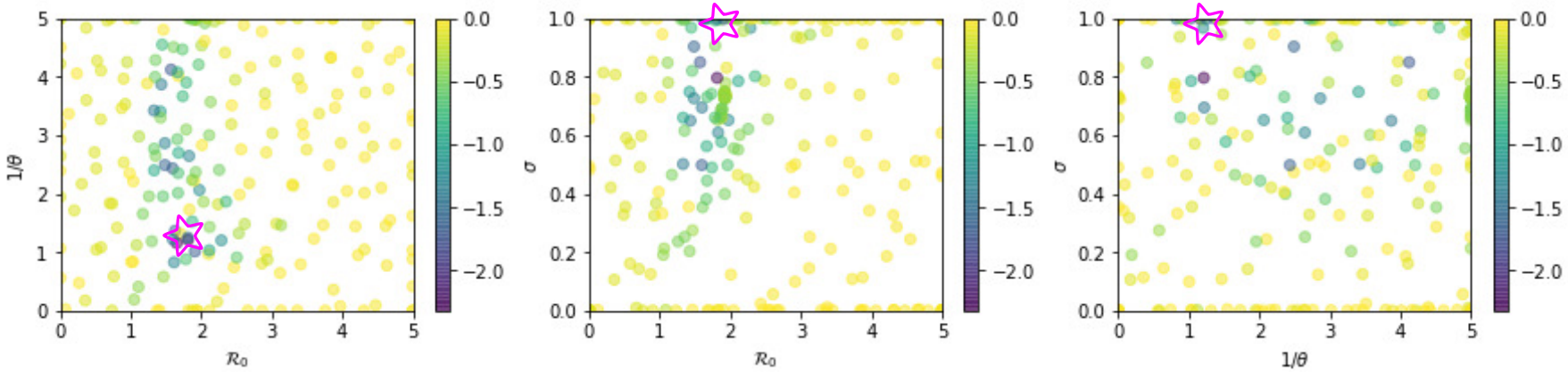


- Bayesian Optimization for Likelihood-Free Inference (BOLFI) framework (Gutmann & Corander, JMLR 17:1–47, 2016)
- Similar to ABC, but more quickly finds favourable regions in the parameter space to sample
- A statistical model is created for the relationship between model parameters and the discrepancy between the observed and simulated data, and its minimum is inferred with Bayesian optimization.

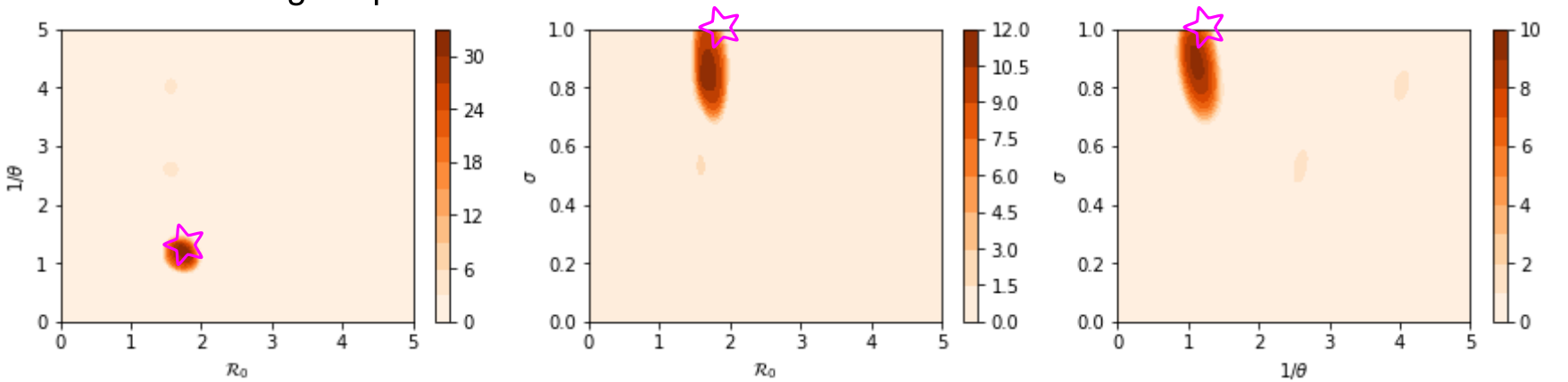
Preliminary results

Fitting to simulated data:

Log discrepancy between model-generated data and observed data



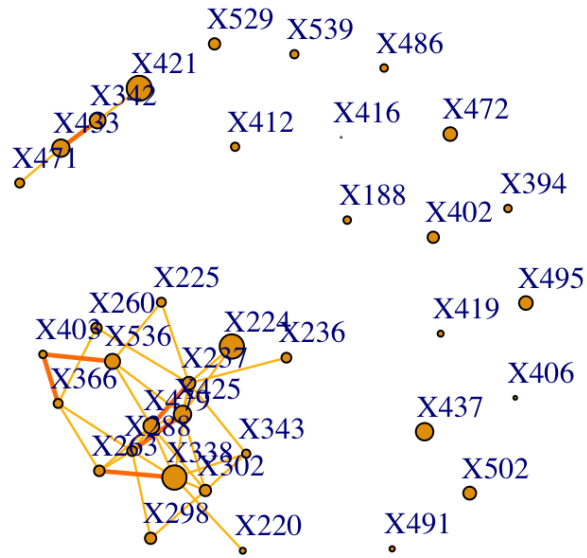
Estimated marginal posterior distributions



Fitting to observed data: in progress ...

Towards modelling the impact of interventions

- Group A *Strep* transmission model now has:
  - More realistic demography (triangle-shaped age distribution)
  - Age-dependent community contact rates, household structure
- Currently working on the "best" way to model short and long-term mobility between households
- Network analysis of WGS data of isolates associated with households in 2 communities



- Related work:
  - Use the model to test hypotheses about the infection requirements for Group A *Strep* sequelae: ARF and APSGN

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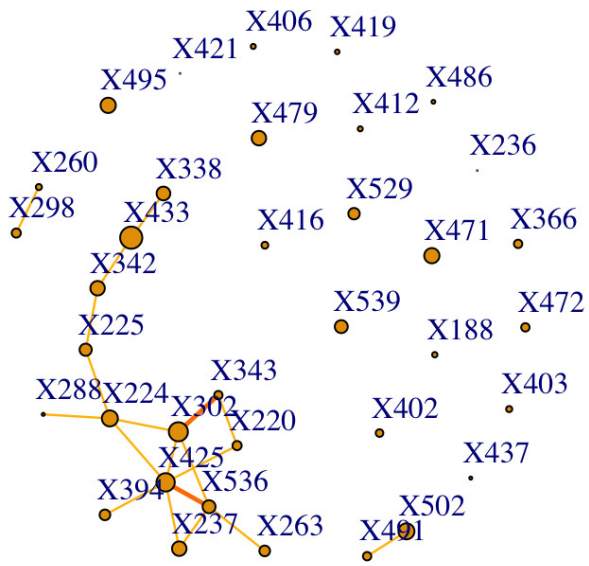

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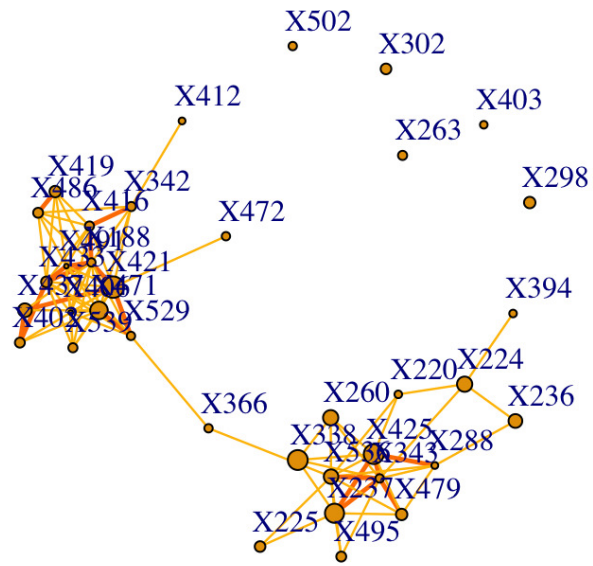

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