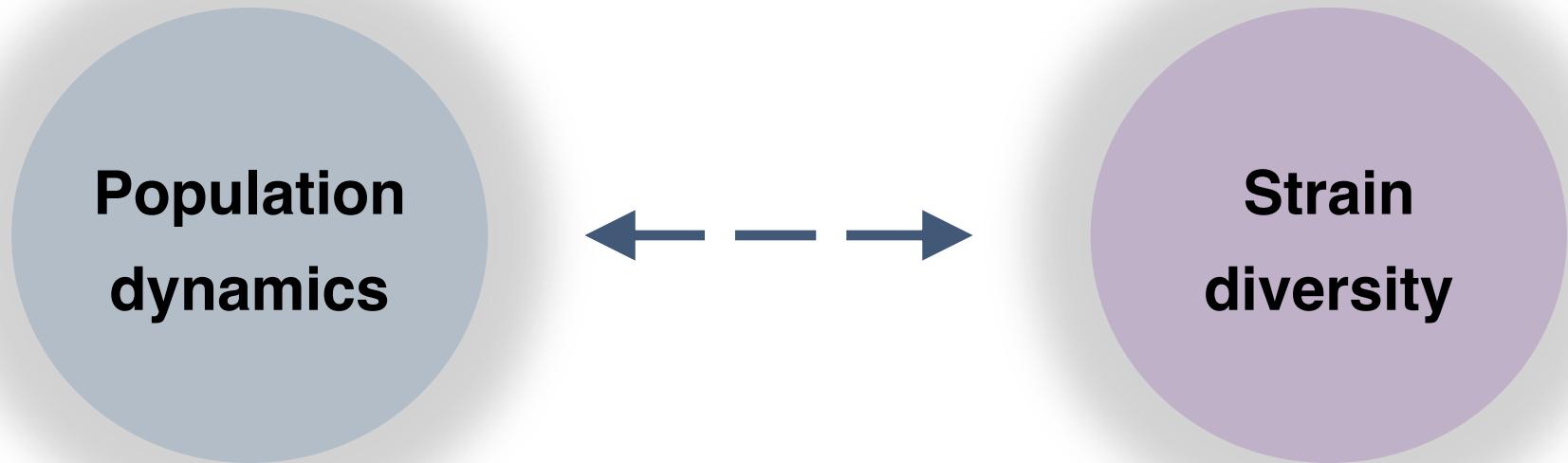


Pathogen diversity and negative frequency-dependent selection: consequences for intervention

Pamela P. Martinez

Center for communicable disease dynamics
Harvard T.H. Chan – School of Public Health

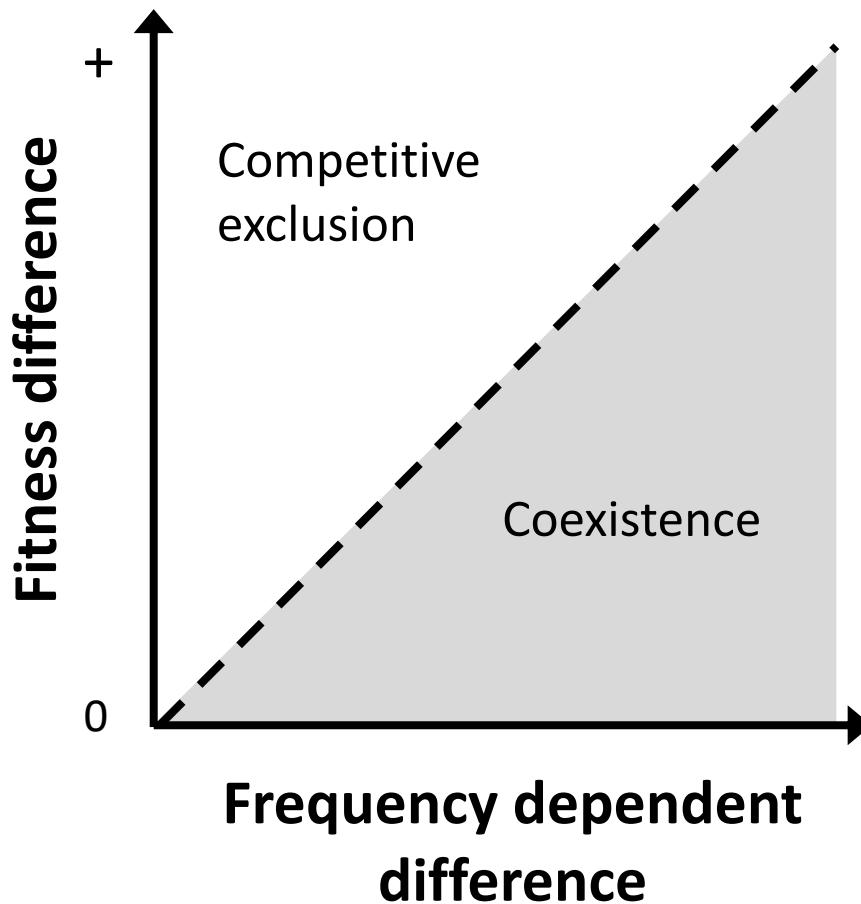
Motivation



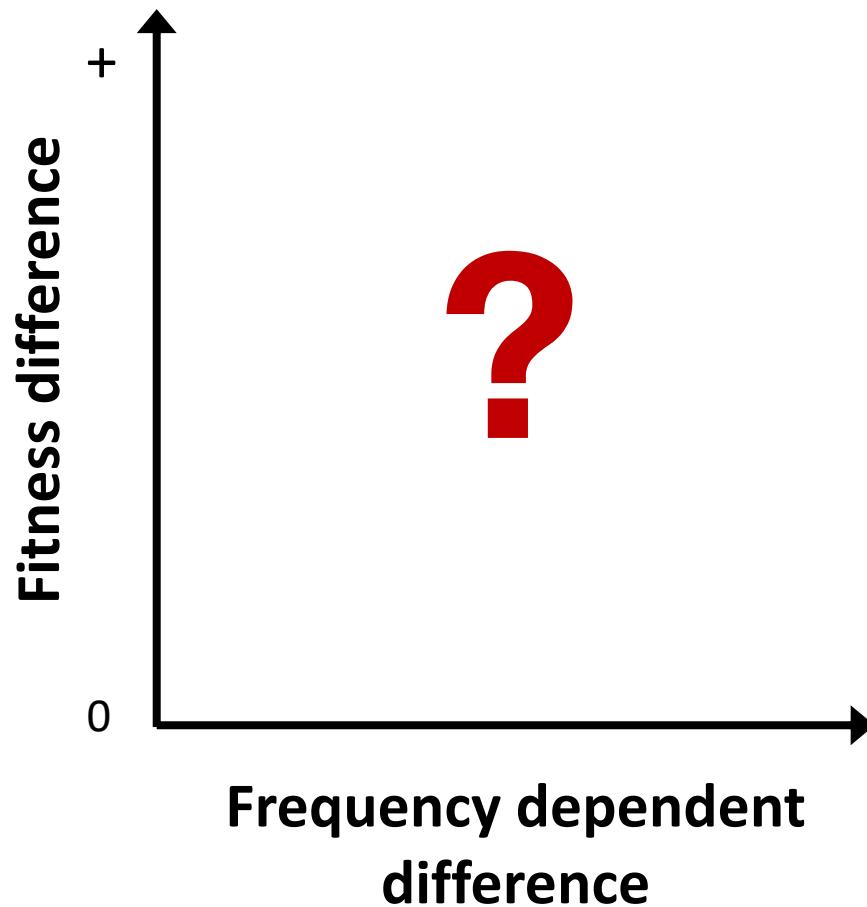
How pathogen populations respond to intervention

When/why intervention can cause irreversible changes in these populations

Species diversity



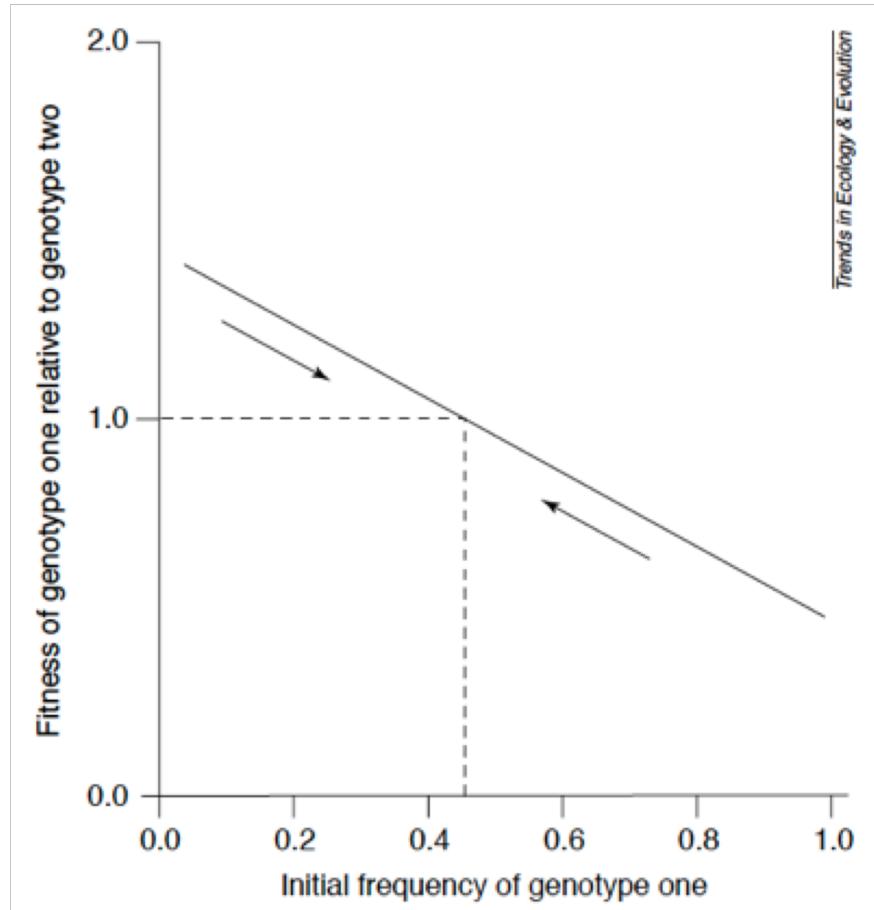
Strain diversity



Frequency dependent selection

Advantage of the rare,
disadvantage of the common

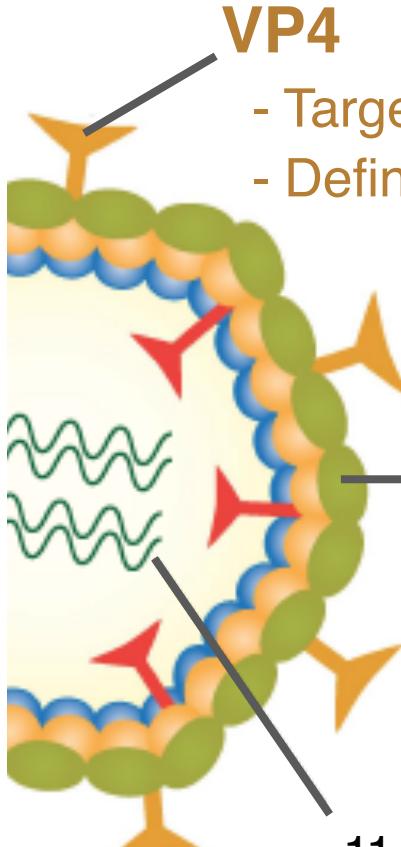
*The fitness of an individual is a function
of past frequencies of alleles it carries*



Part I:

Rotavirus antigenic diversity

Rotavirus



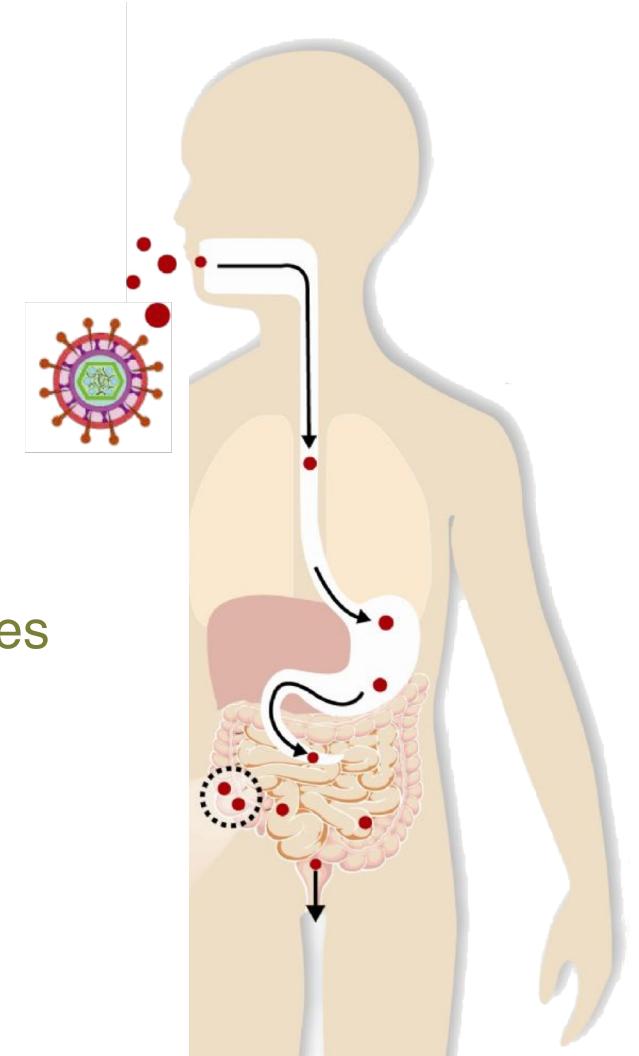
VP4

- Target of neutralization antibodies
- Defines **P serotype**

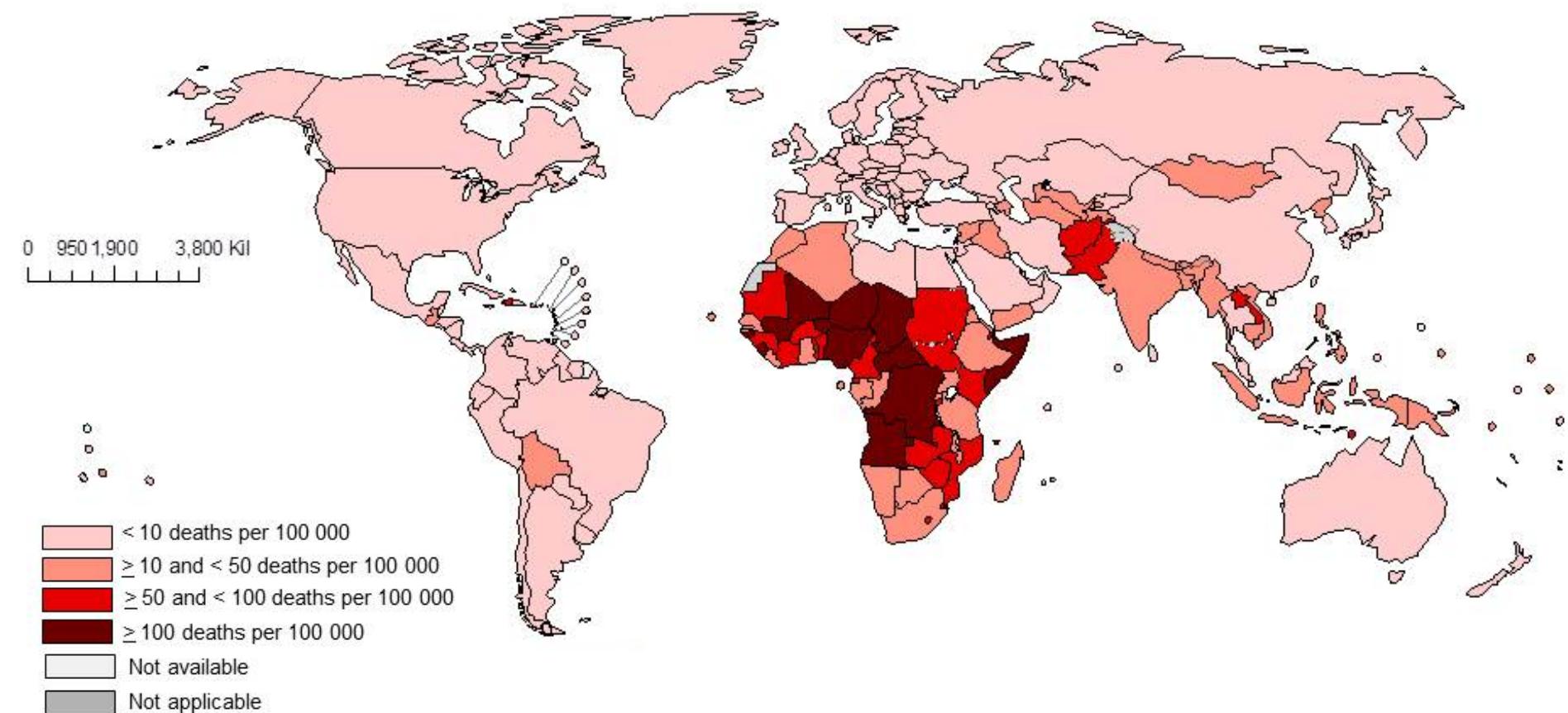
VP7

- Target of neutralization antibodies
- Defines **G serotype**

11 genomic segments of double-stranded RNA

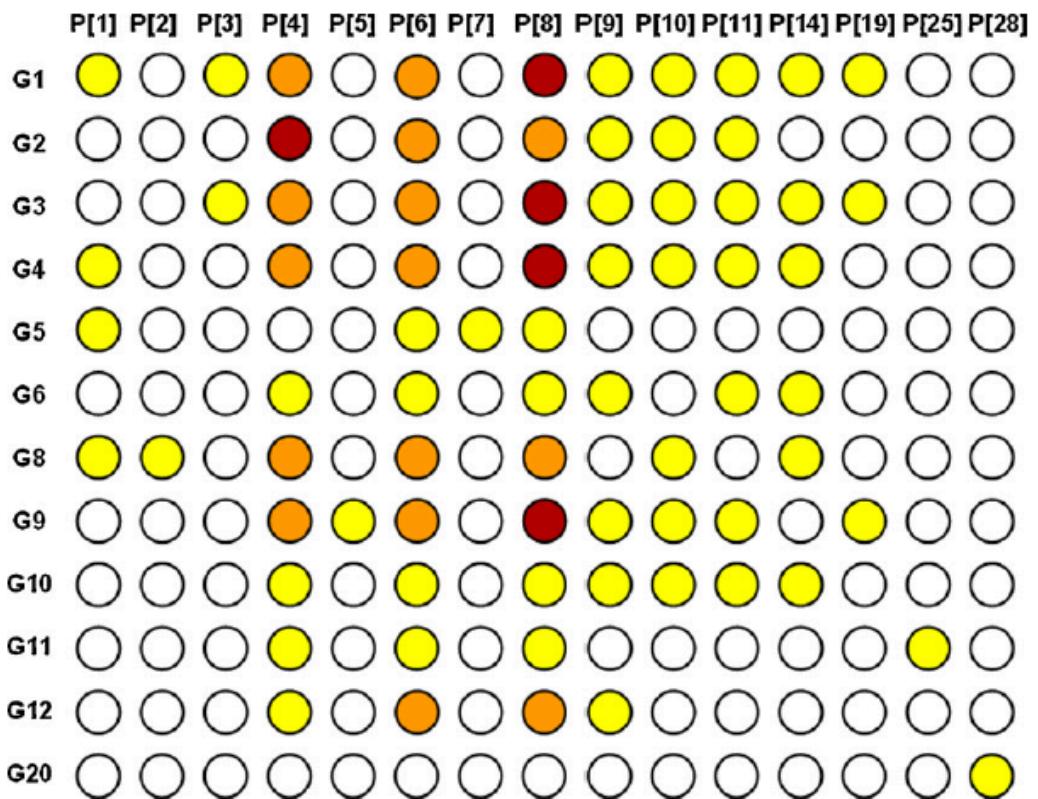
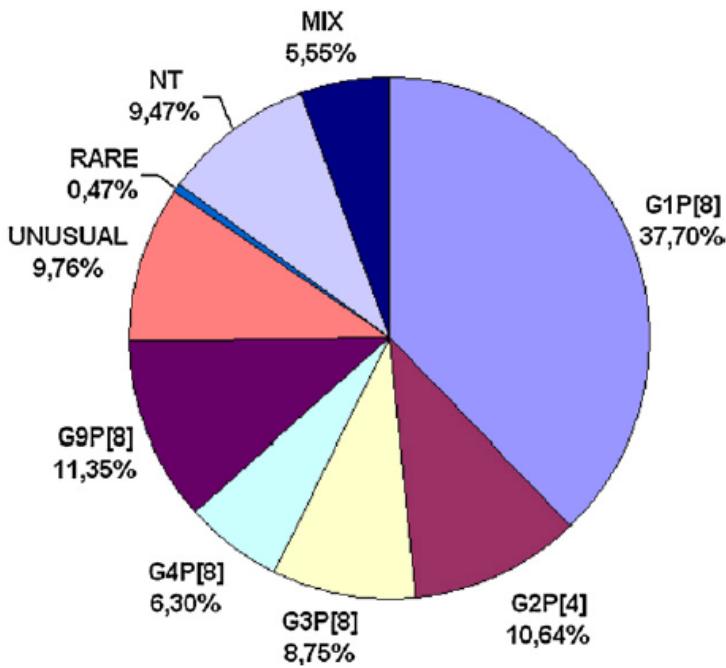


Rotavirus

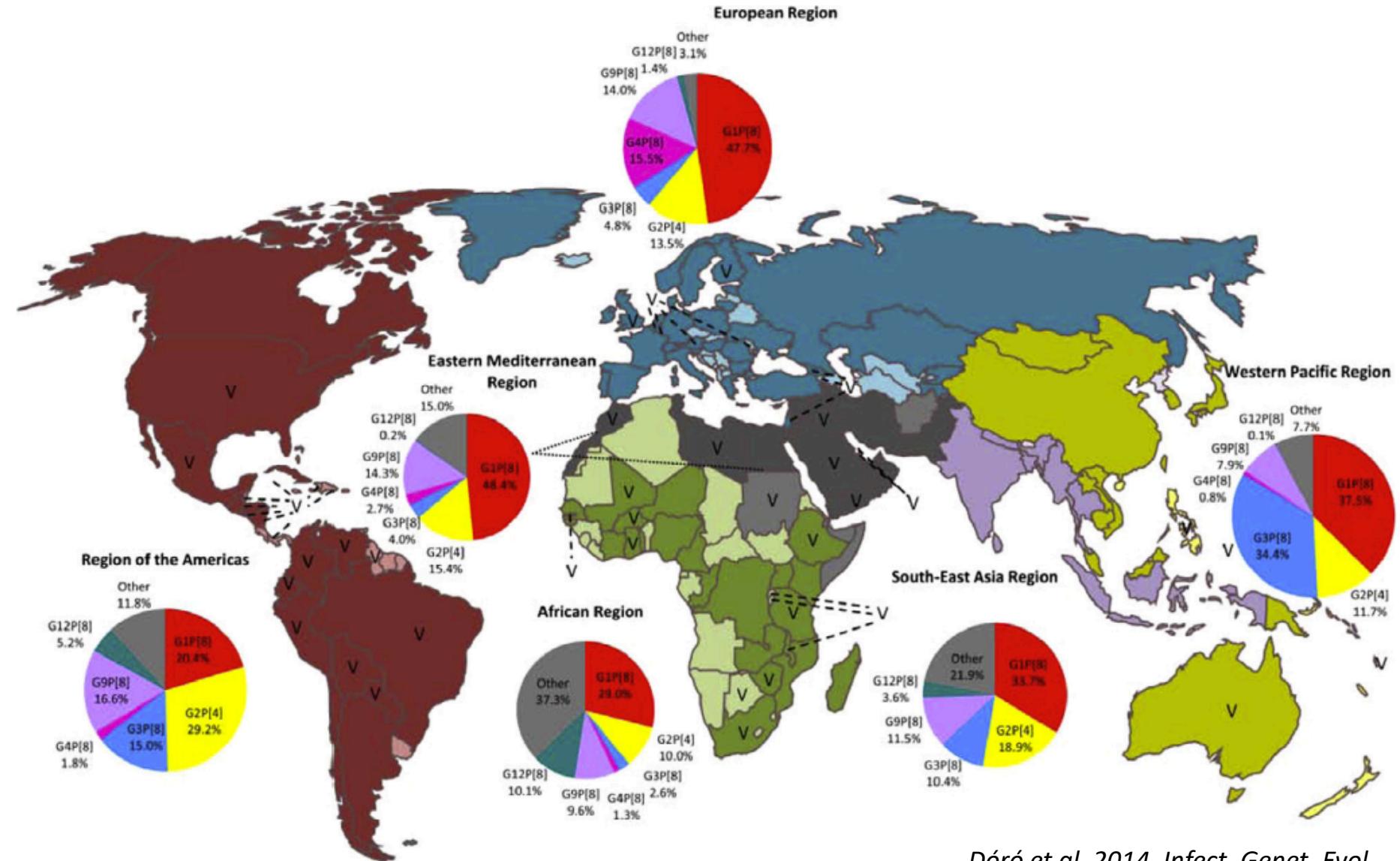


Strain diversity

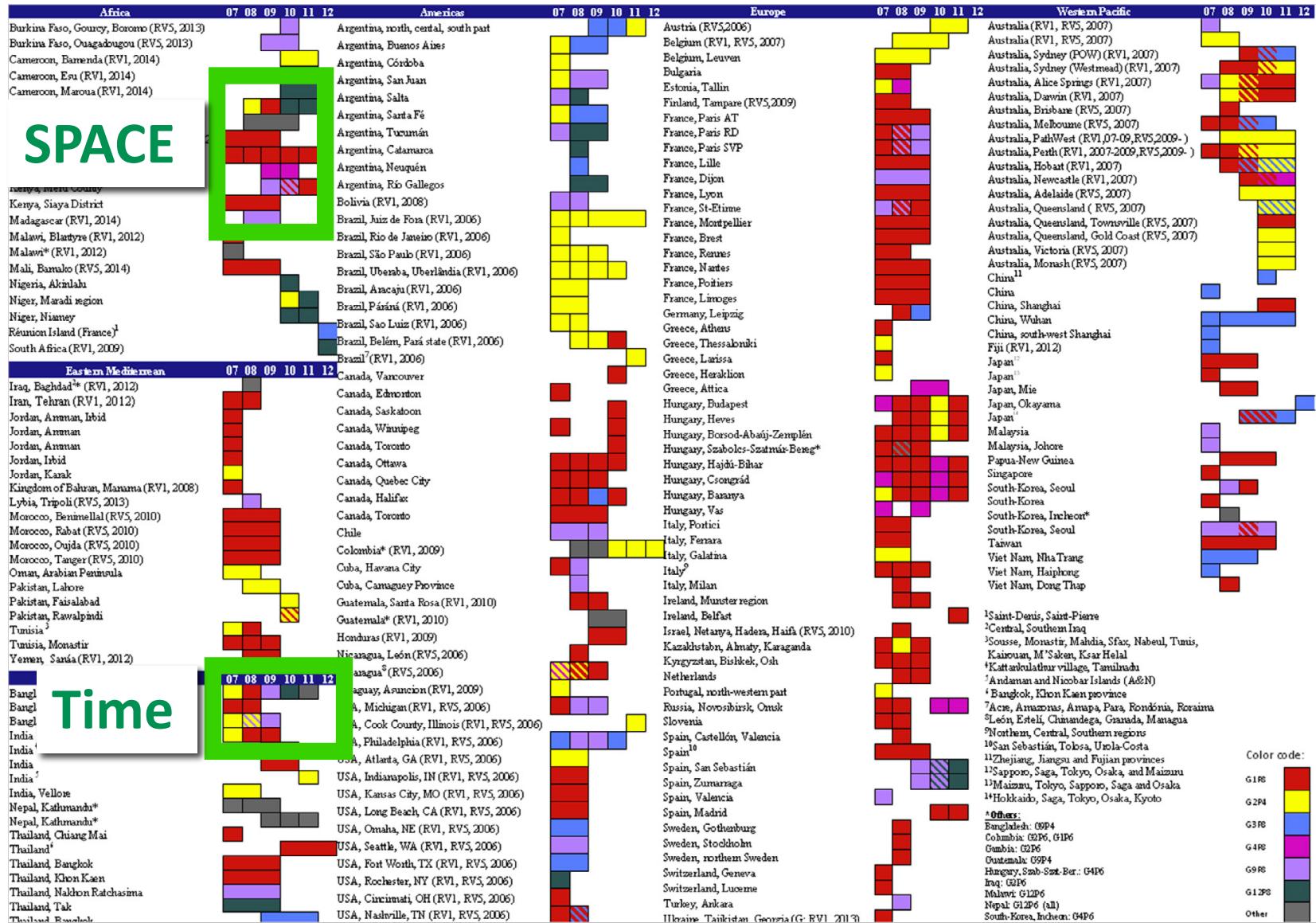
Global pattern



Strain diversity

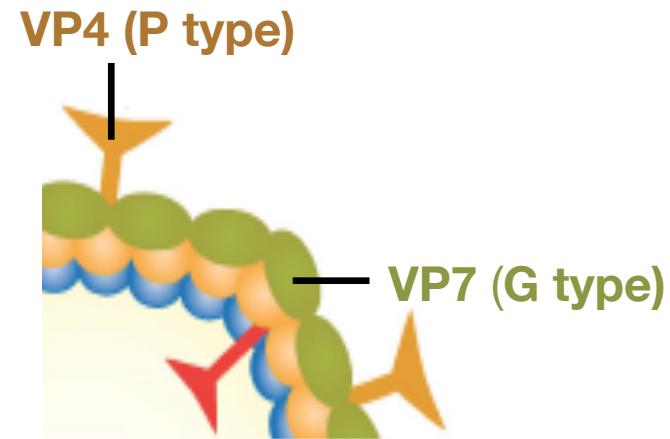
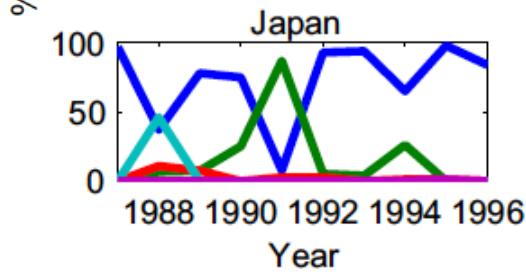
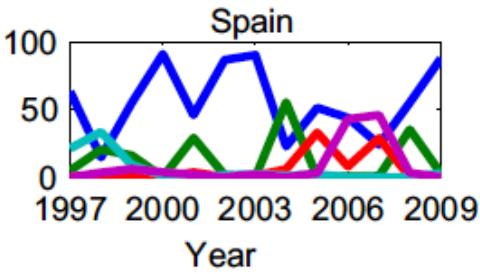
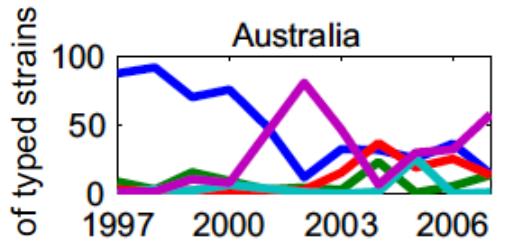
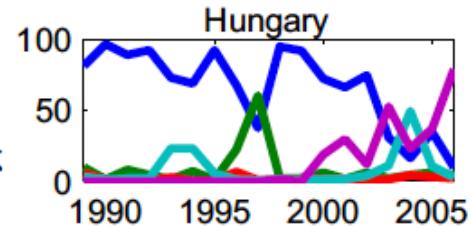
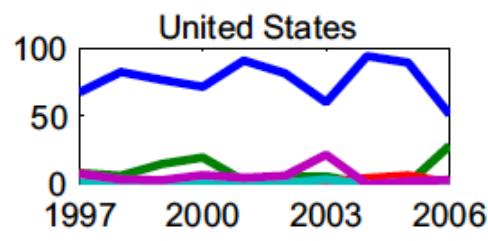
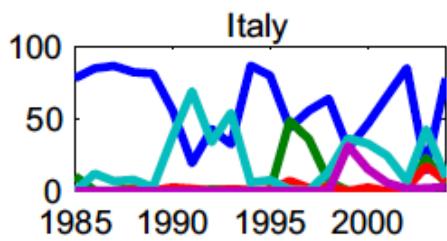


Strain diversity



Strain diversity

— G1 — G2 — G3 — G4 — G9



Strain diversity

Diversity

Process behind



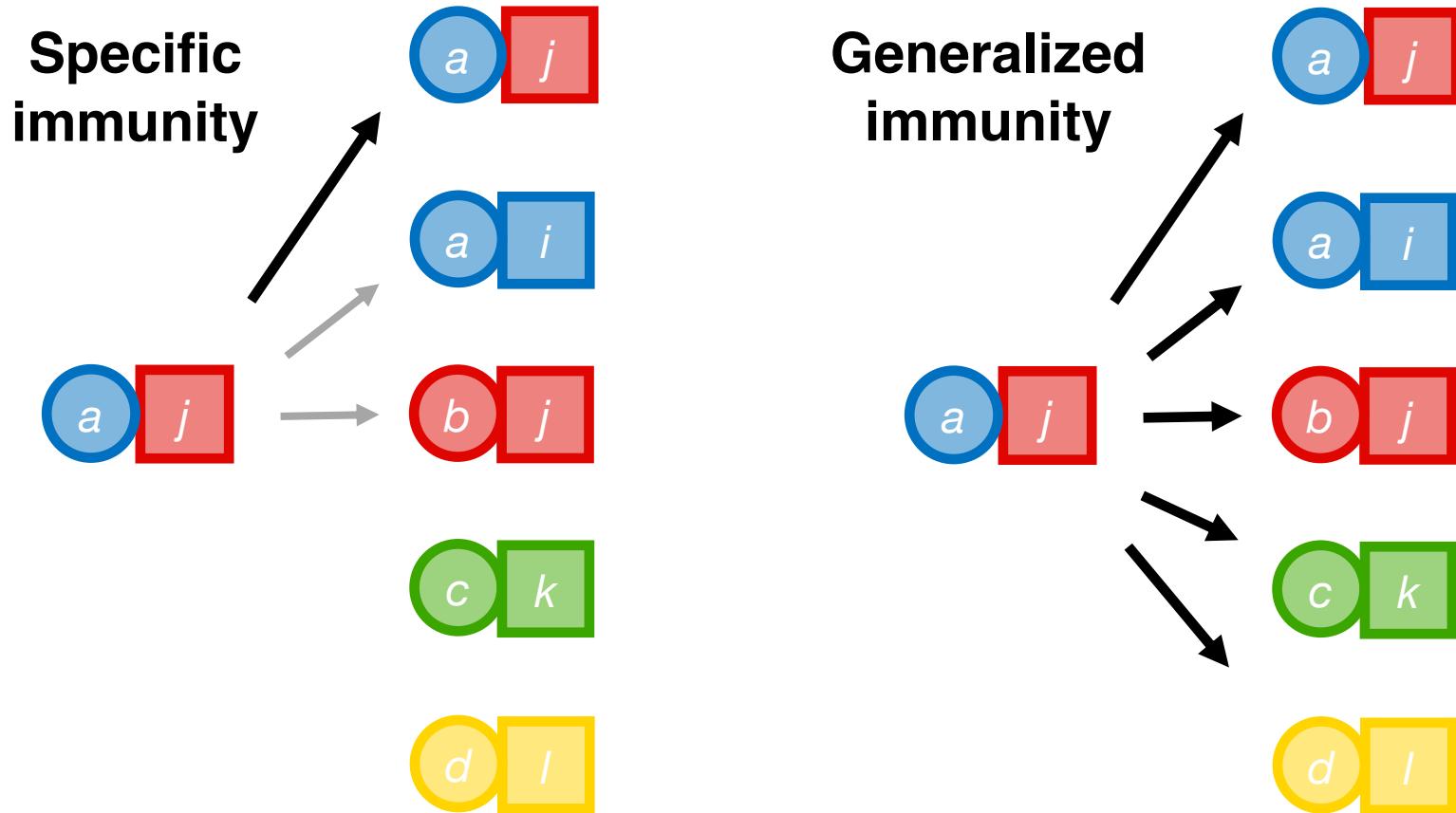
Competition for host

Mediated by



Cross immunity

Acquired immunity

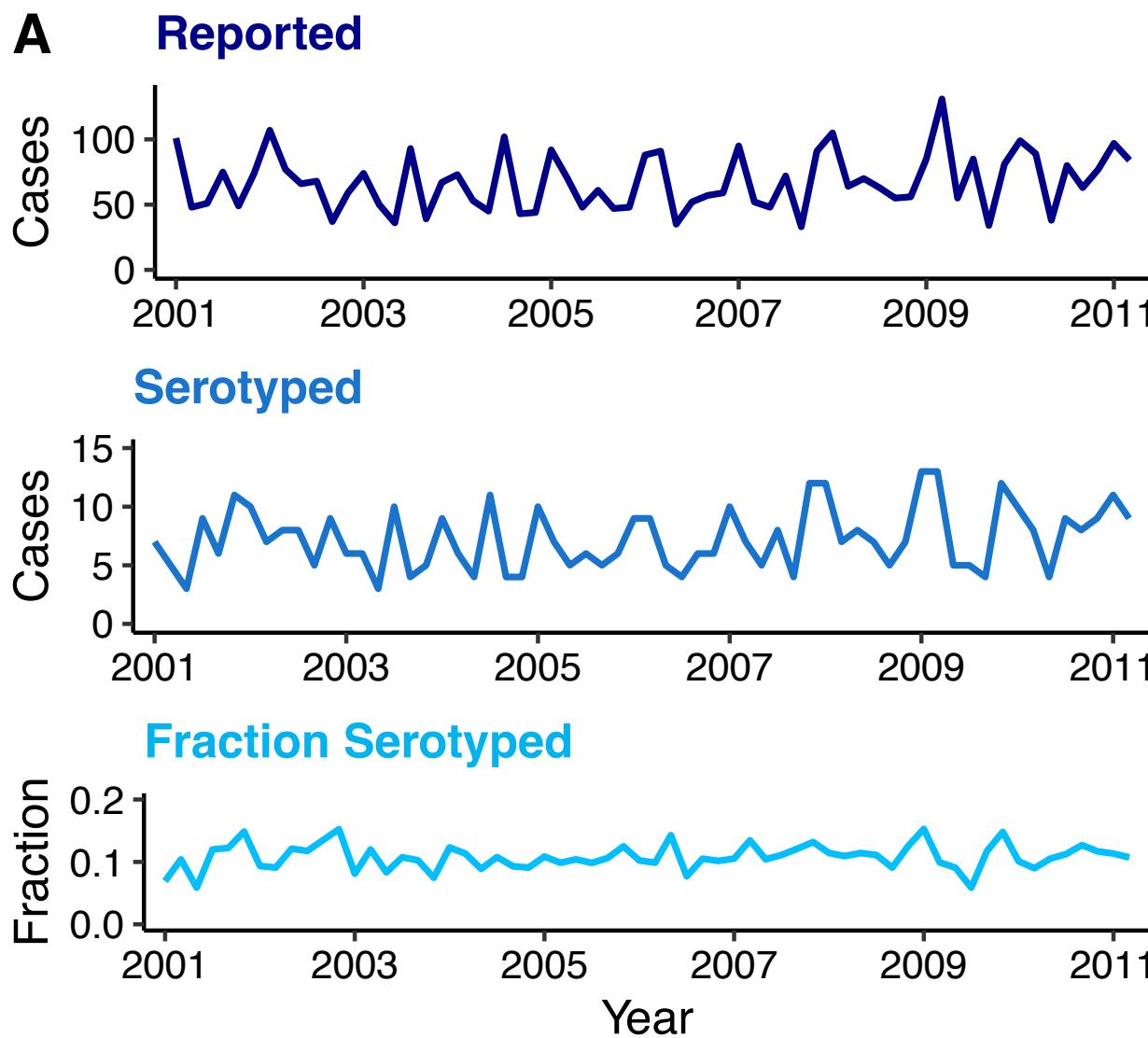


***Impact of specific and generalized
immunity on rotavirus antigenic diversity***

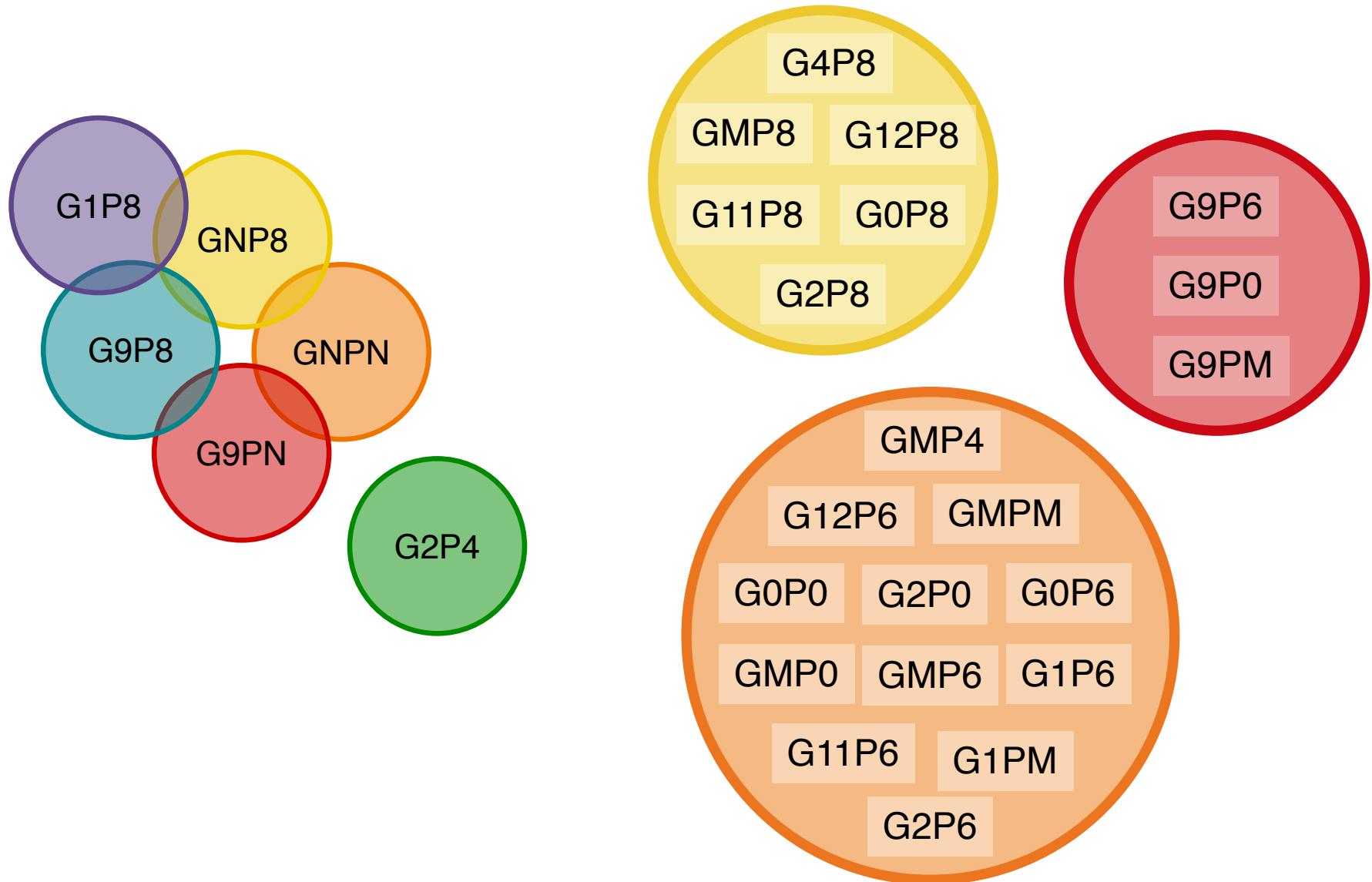
Dhaka - Bangladesh



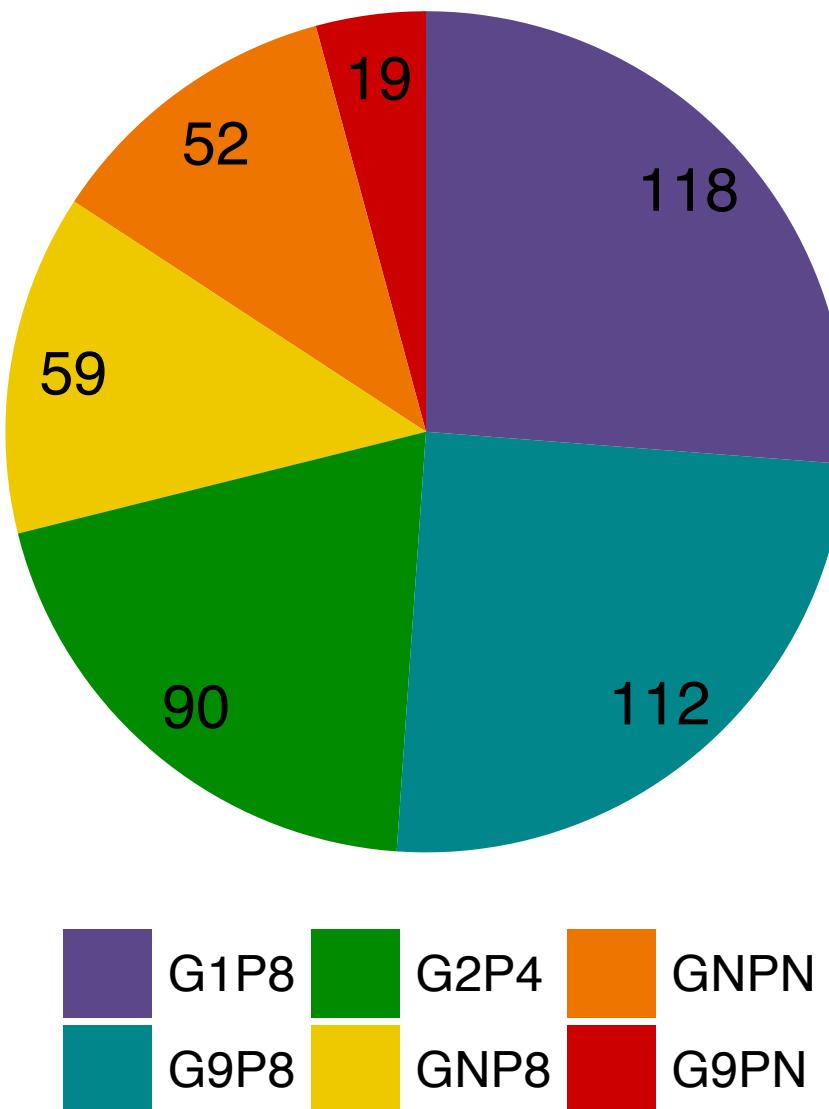
Incidence data



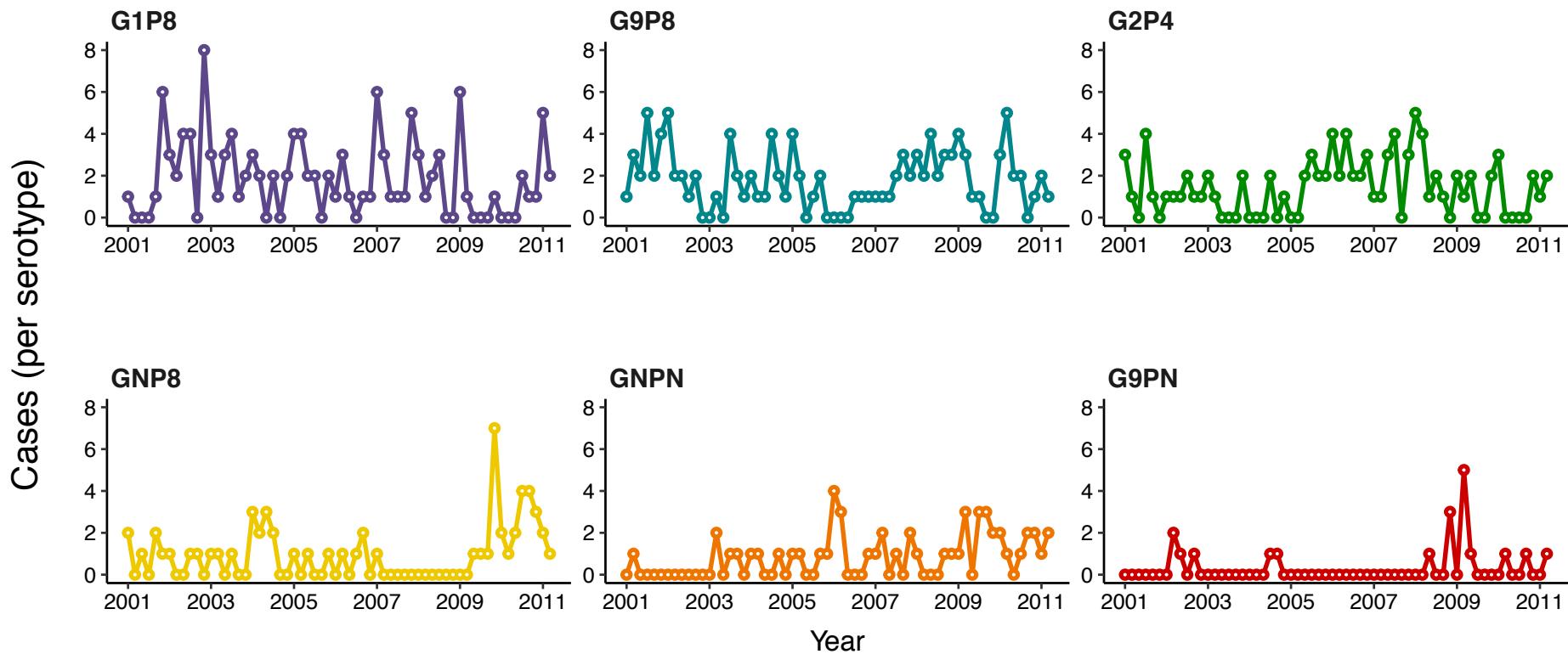
Serotype data



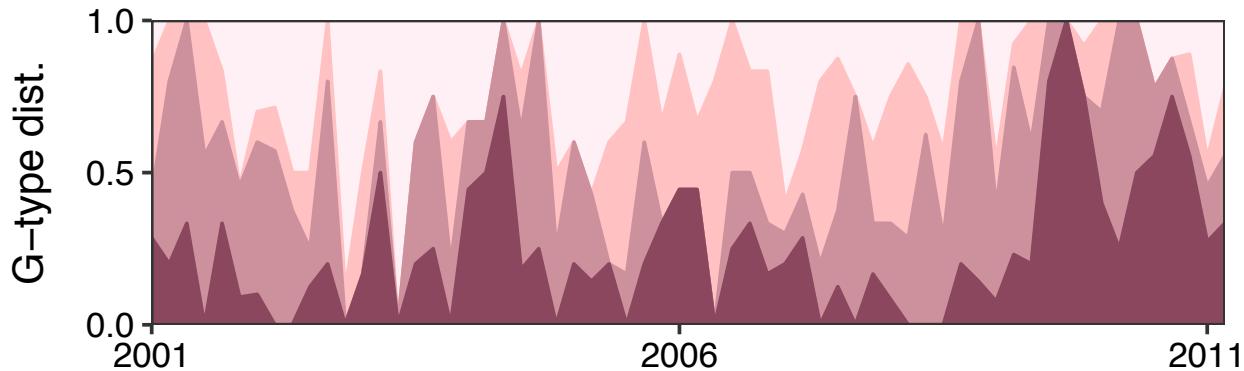
Serotype data



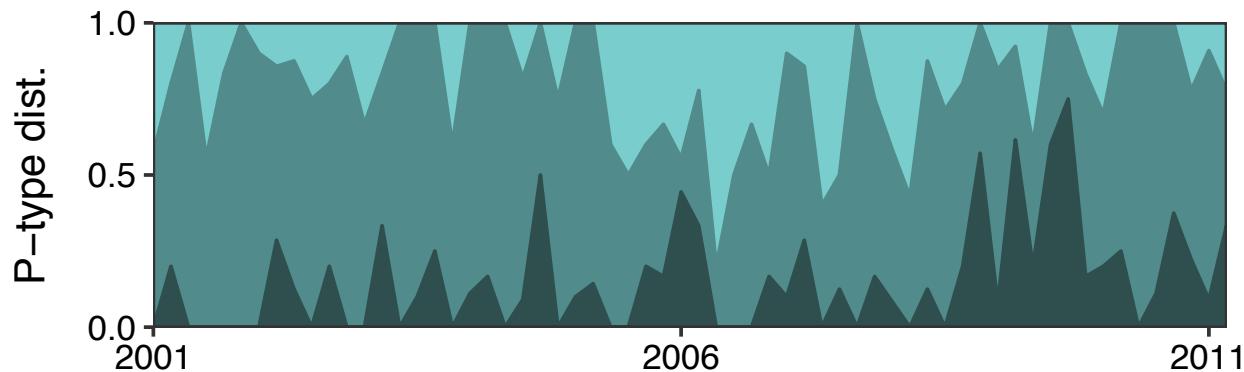
Serotype data



Serotype data



G1 G2 G9 GN



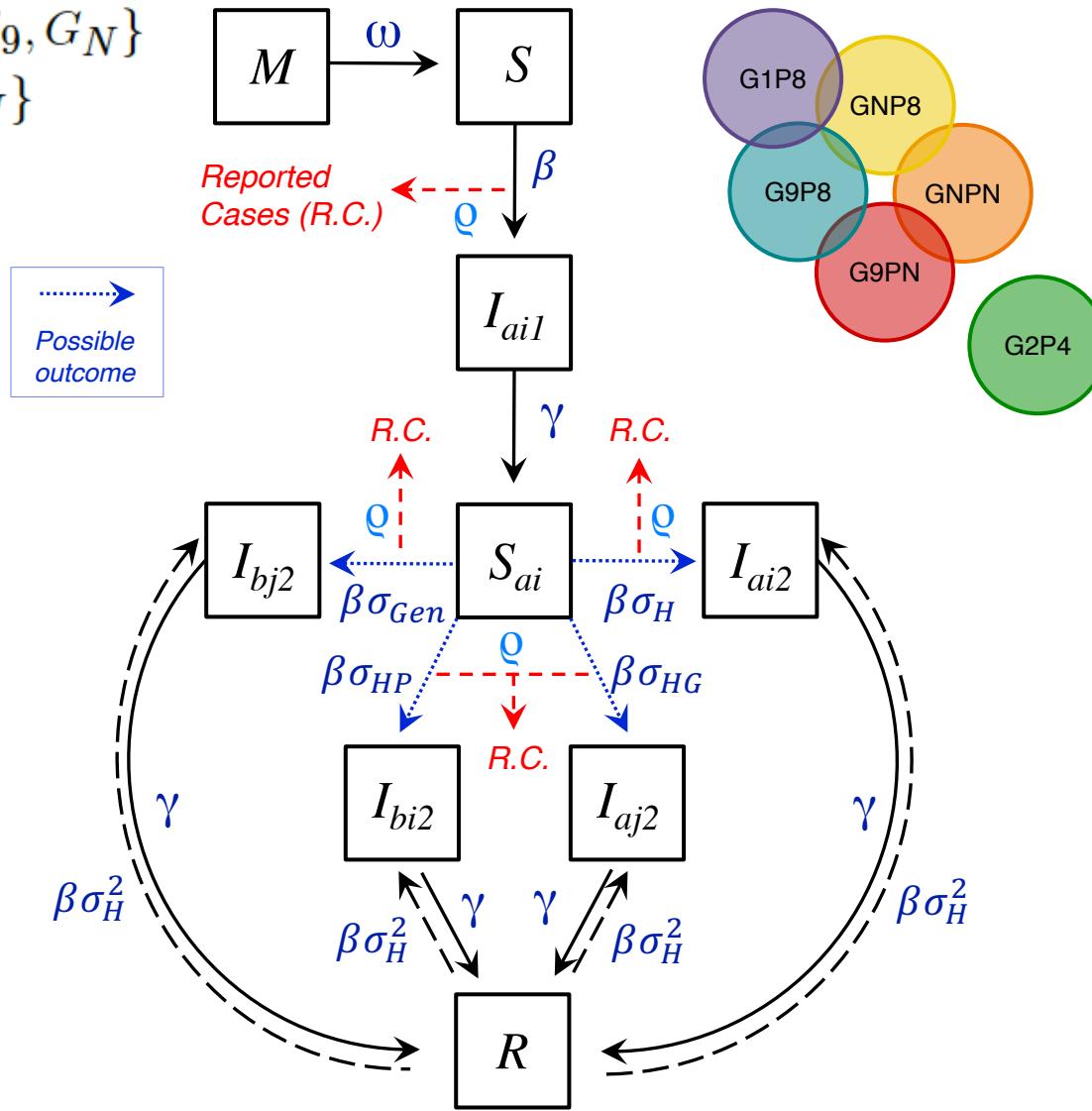
P4 P8 PN

What is the relative importance of specific and generalized immunity in the diversity pattern observed in rotavirus data for Dhaka, Bangladesh?

Transmission model

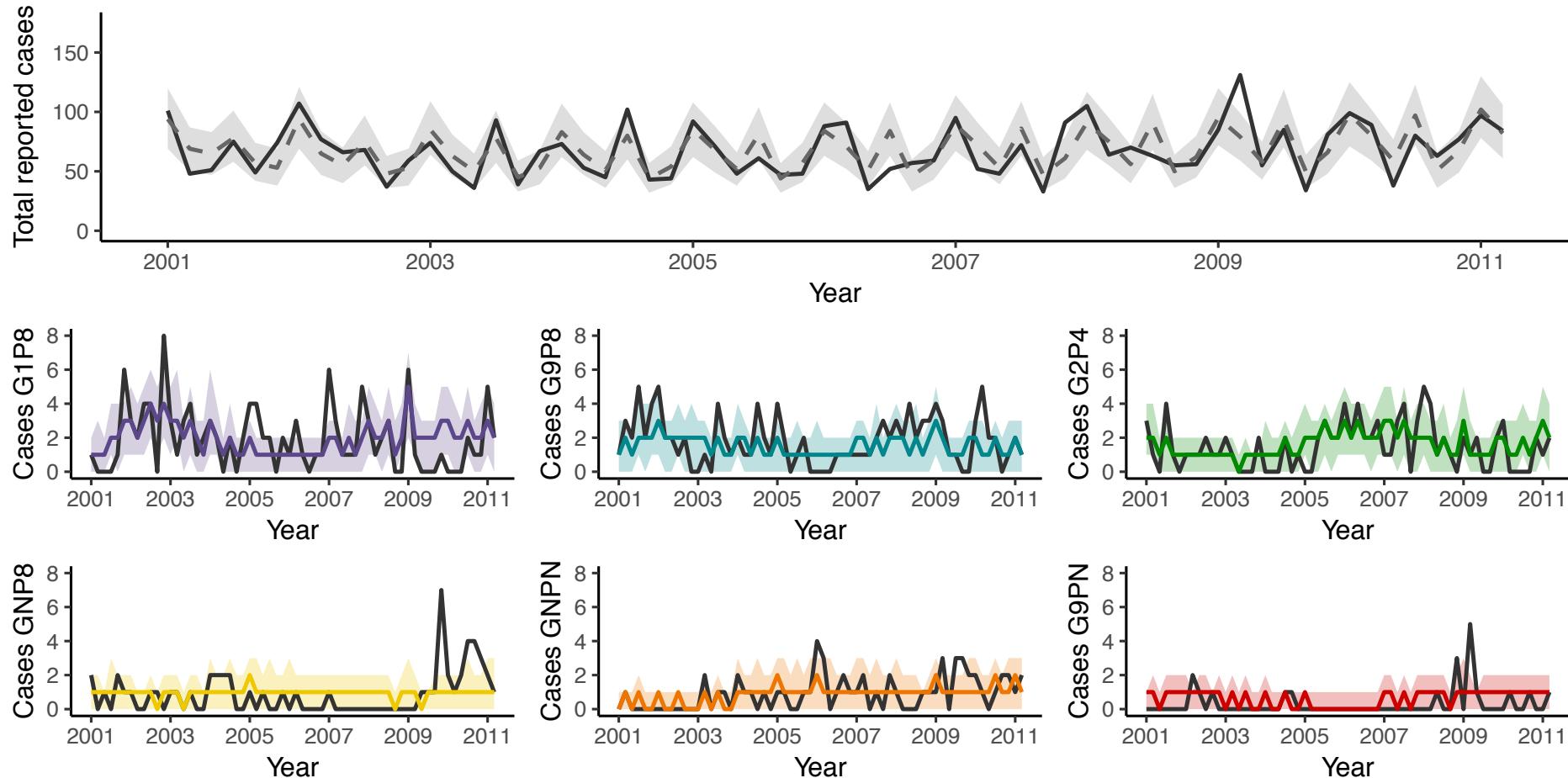
$$a \in \{G_1, G_2, G_9, G_N\}$$

$$i \in \{P_4, P_8, P_N\}$$



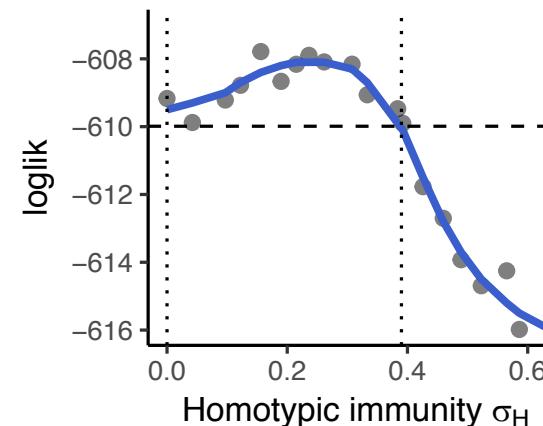
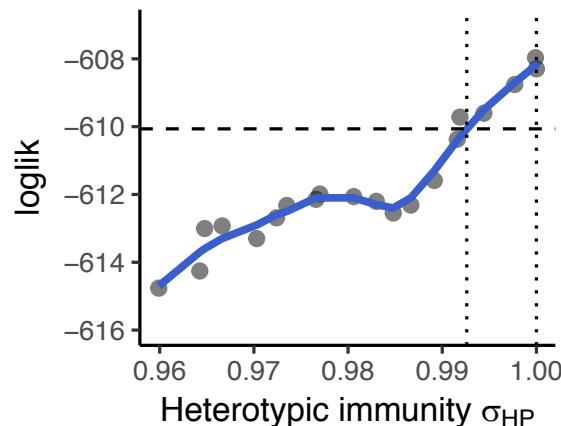
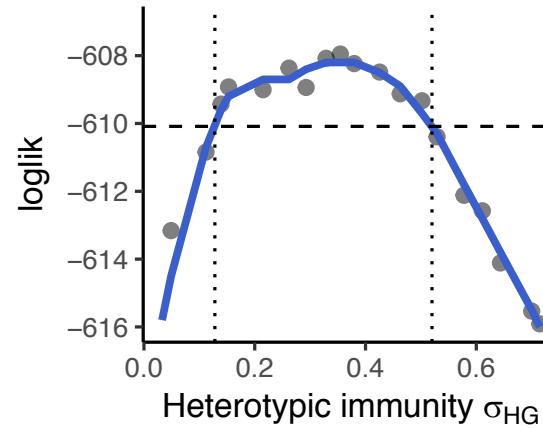
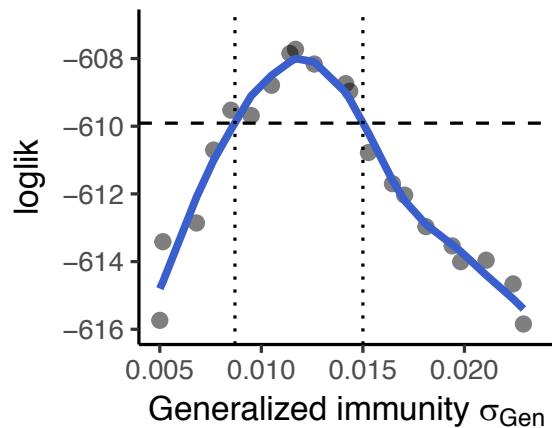
Results

Best model (based on MLE)

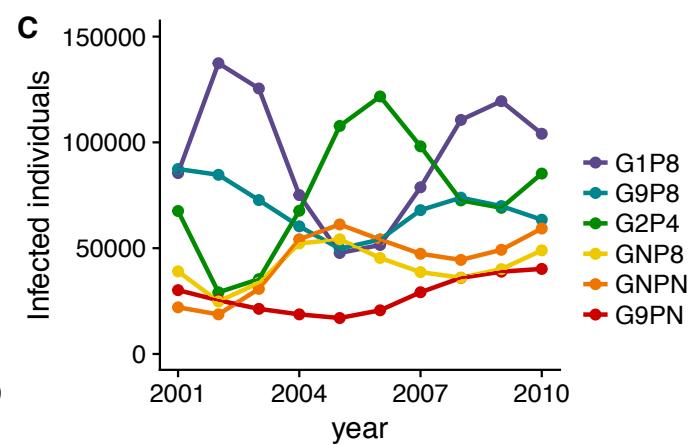
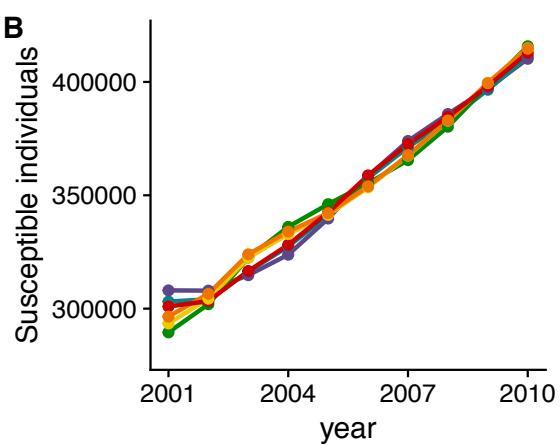
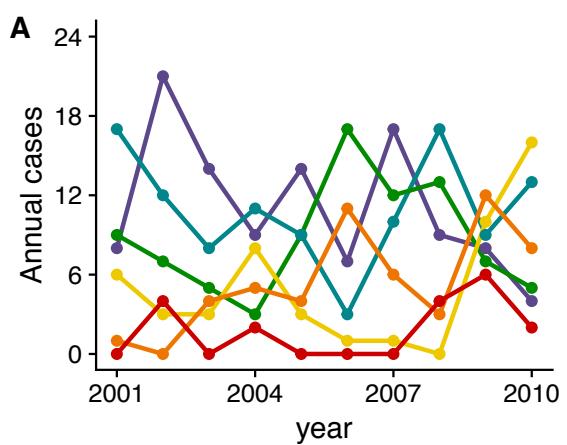


Likelihood profiles

$$\frac{dI_{ai2}}{dt} = \beta \left[\underbrace{\sigma_{Gen} \left(\sum_{\substack{b \neq a \\ j \neq i}} S_{bj} + \sigma_{HG} \sum_{j \neq i} S_{aj} + \sigma_{HP} \sum_{b \neq a} S_{bi} + \sigma_H S_{ai} + \sigma_H^2 R \right)}_{\text{red}} \right] \frac{I_{ai}}{P} - (\gamma + \mu) I_{ai2}$$



Inter-annual variation



Conclusions

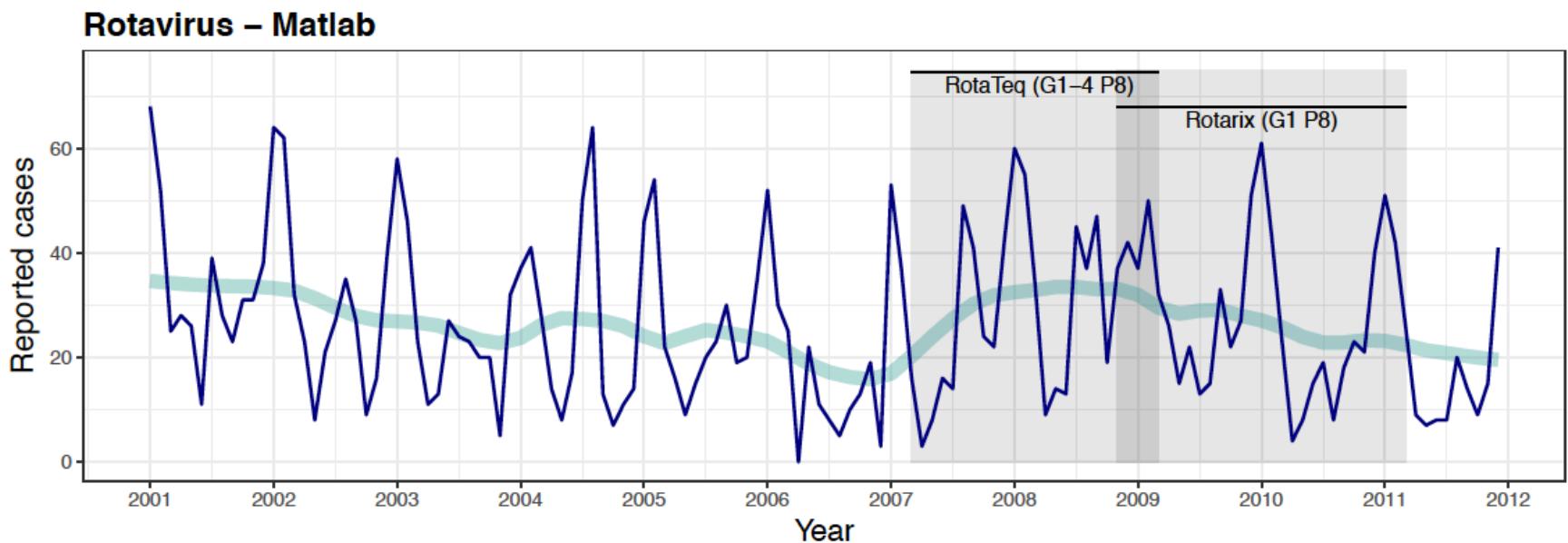
Specific versus generalized immune response

VP7 (G-types) → *Stronger specific immune response*

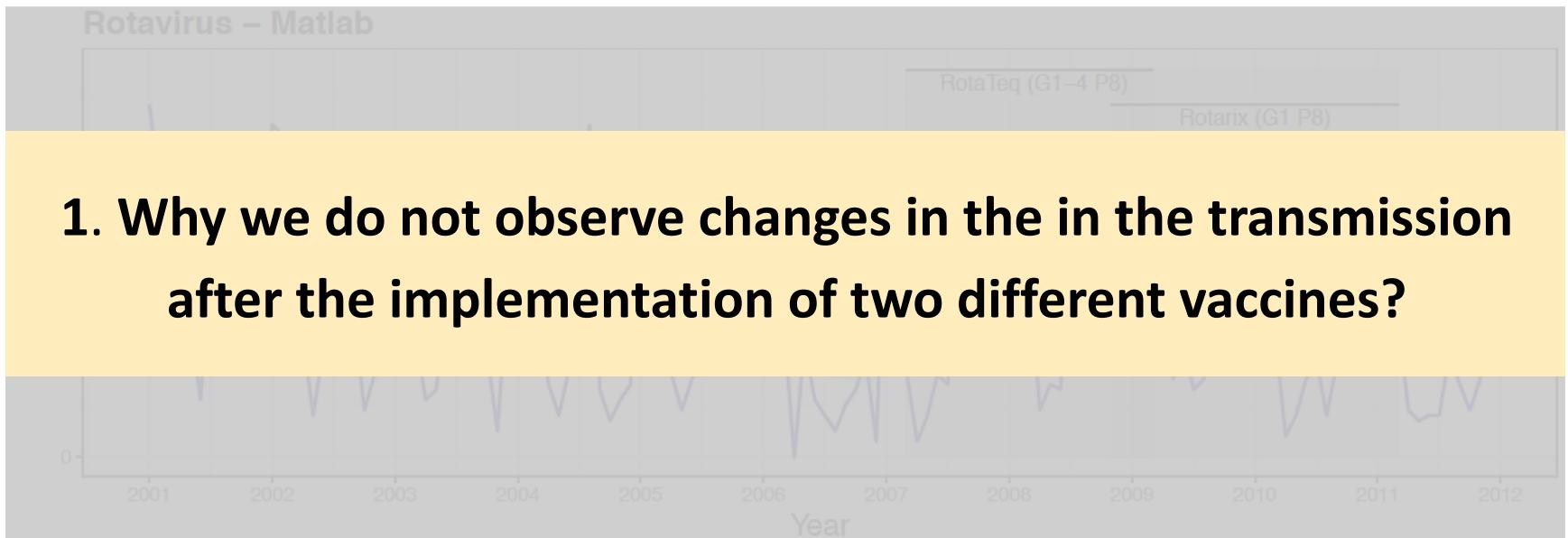
VP4 (P-types) → *A more generalized immune response*

**Questions on things I don't
understand/are confused about**

Questions on things I don't understand/are confused about



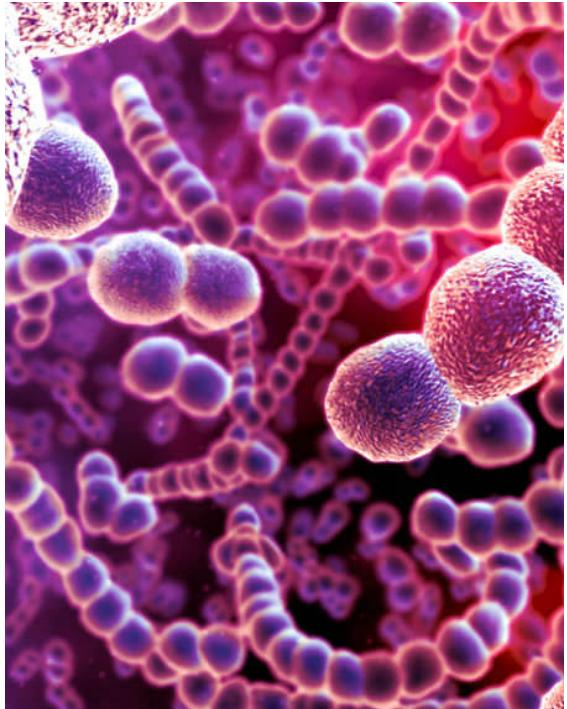
Questions on things I don't understand/are confused about



Part II:

More than just antigens

Streptococcus pneumoniae



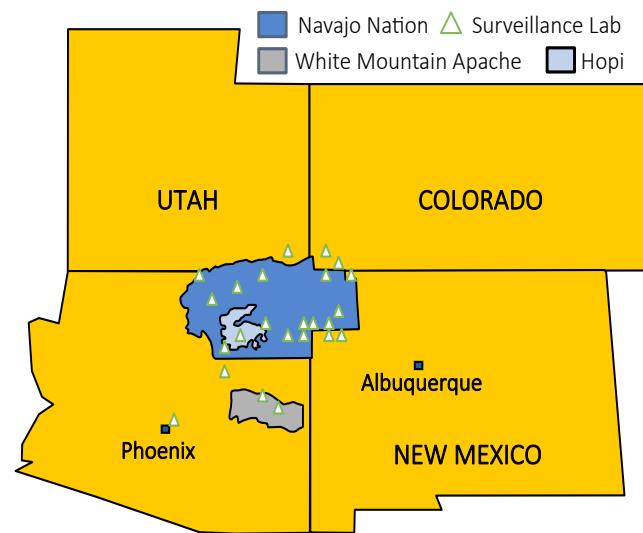
Invasive Pneumococcal Disease (IPD) and Pneumococcal Conjugate Vaccines (PCV)

- *S. pneumoniae* is a leading cause of invasive and non-invasive disease.
- Colonizer of the upper respiratory tract.
- There are more than 90 serotypes defined by capsular polysaccharide.
- Serotype: virulence determinant & vaccine target
- In the U.S., vaccine PCV-7 was introduced in 2000 and vaccine PCV-13 in 2010.

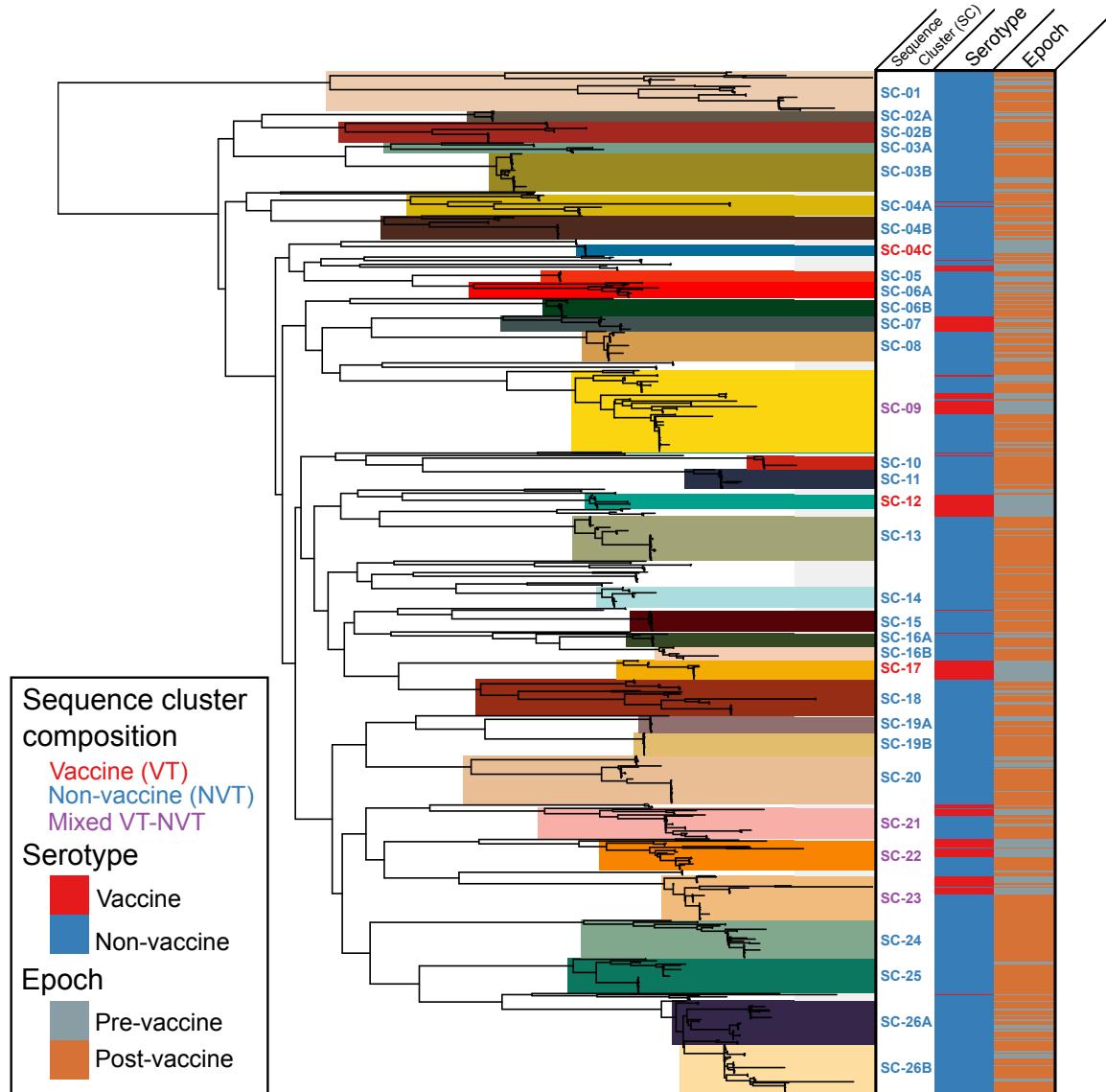
Streptococcus pneumoniae

Data from Navajo/White Mountain Apache (N/WMA) Native Americans

- Pre-PCV7, rates of Invasive Pneumococcal Disease among N/WMA were 7 times greater than the general US population.
- 50% of cases involved PCV-7 vaccine serotypes
- Carriage prevalence was ~60%.
- Introduction of vaccine did not change carriage prevalence.

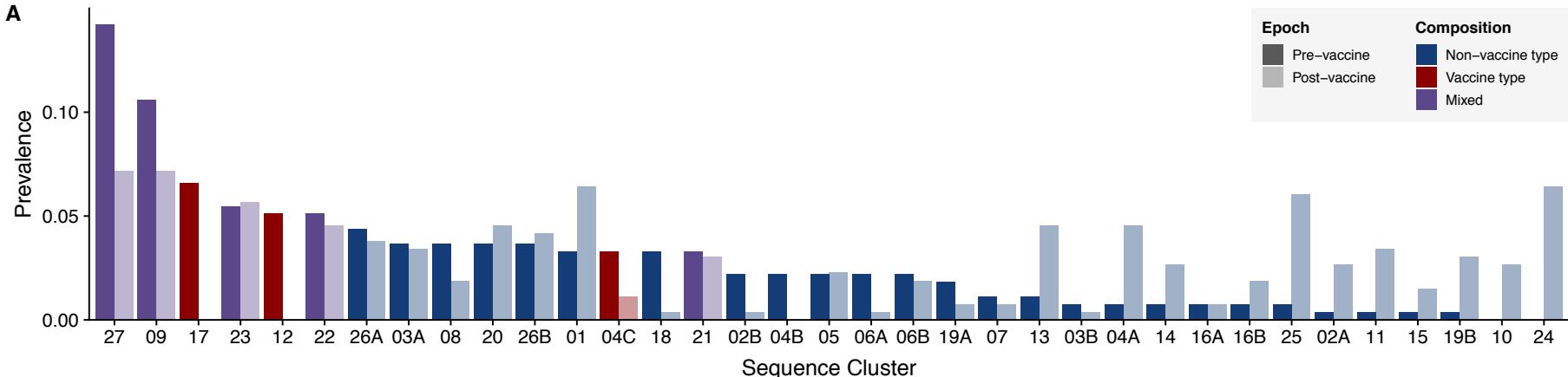


Streptococcus pneumoniae

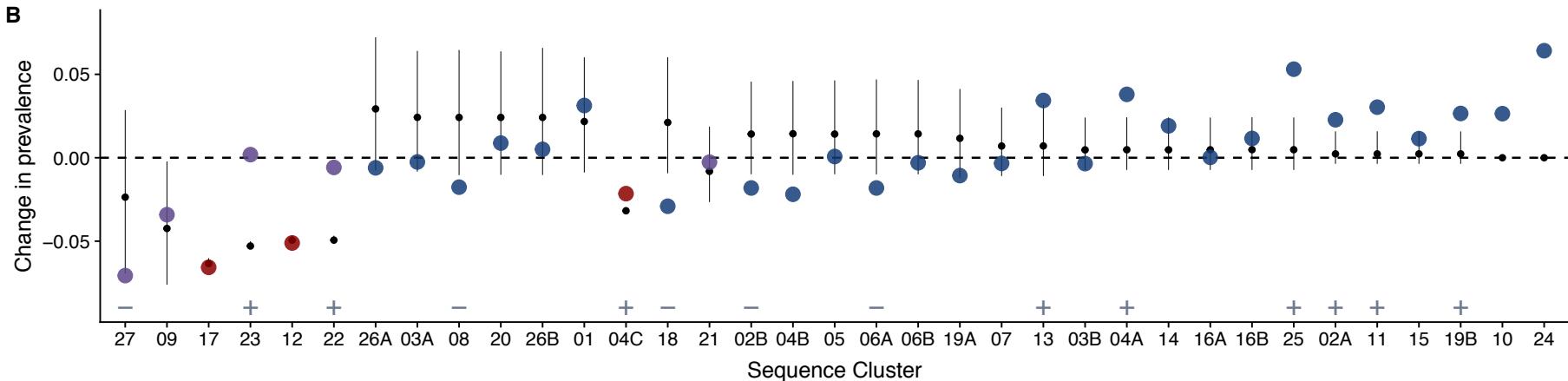


SC prevalence: pre– and post– vaccine

A



B



What are the genotypes that would compensate the perturbation caused by the removal of the vaccine isolates?

Genotypes and presence/absence of genes

	<i>Locus 1</i>	<i>Locus 2</i>	<i>...</i>		<i>Locus L</i>			
<i>Genotype 1</i>	0	1	1	0	0	1	1	0
<i>Genotype 2</i>	1	1	0	1	0	0	1	1
<i>Genotype 3</i>	0	1	0	0	0	1	0	1
	:			:				
<i>Genotype n</i>	0	0	1	0	1	0	1	1

Replicator equation

$$\frac{dx_i}{dt} = x_i(\omega_i - \phi), \quad \phi = \sum_{j=1}^n x_j \omega_j$$

x_i = Frequency of each i^{th} genotype or sequence cluster

ω_i = Fitness of each i^{th} genotype or sequence cluster

ϕ = Average population fitness

Fitness function

$$\omega_i = \sum_{l=1}^L k_{i,l} (e_l - f_l)$$

ω_i = Fitness of each genotype i

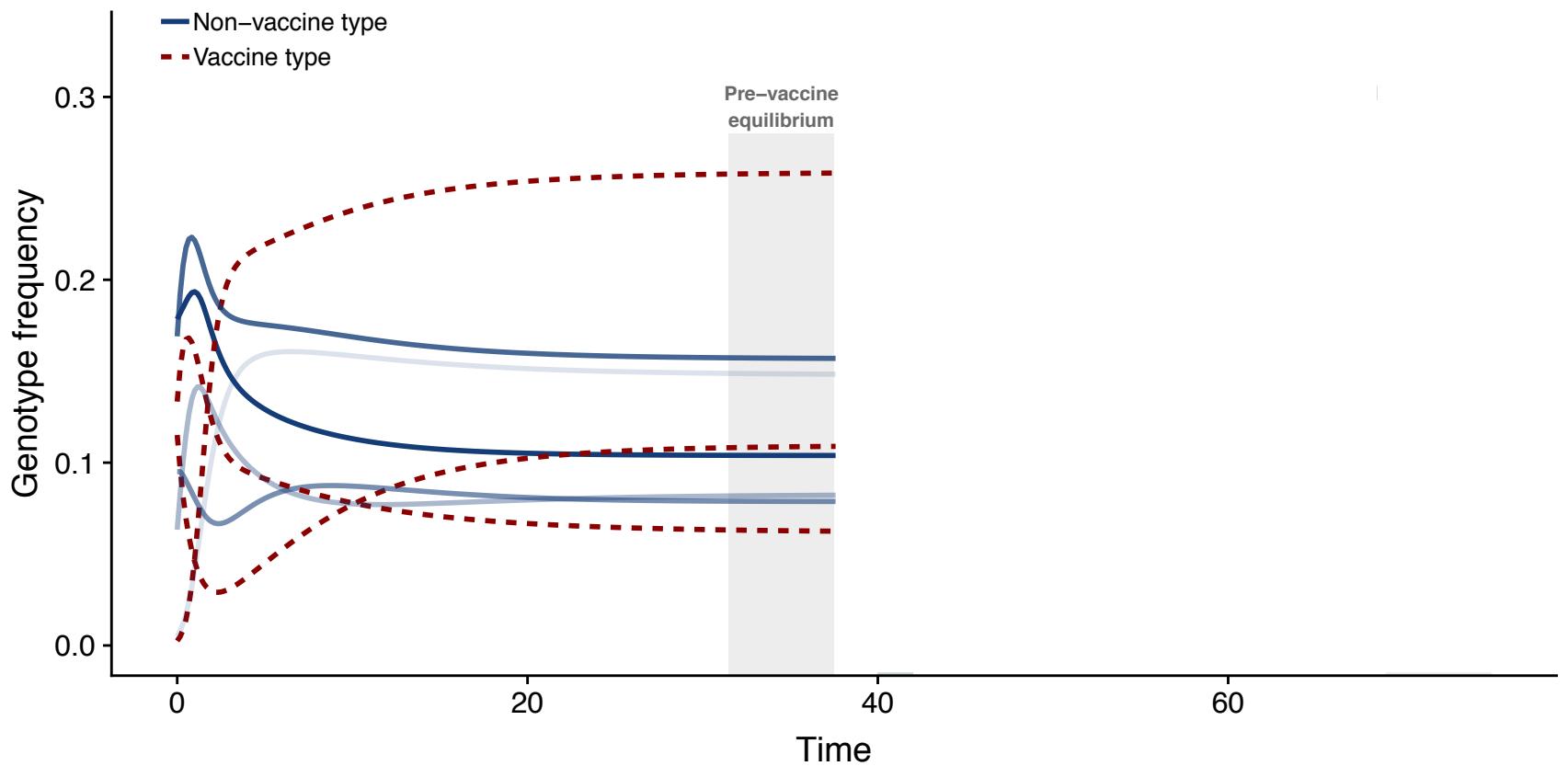
$k_{i,l}$ = Absence (0) or presence (1) of the loci l in genotype i

e_l = Pre-vaccine frequency of each loci l

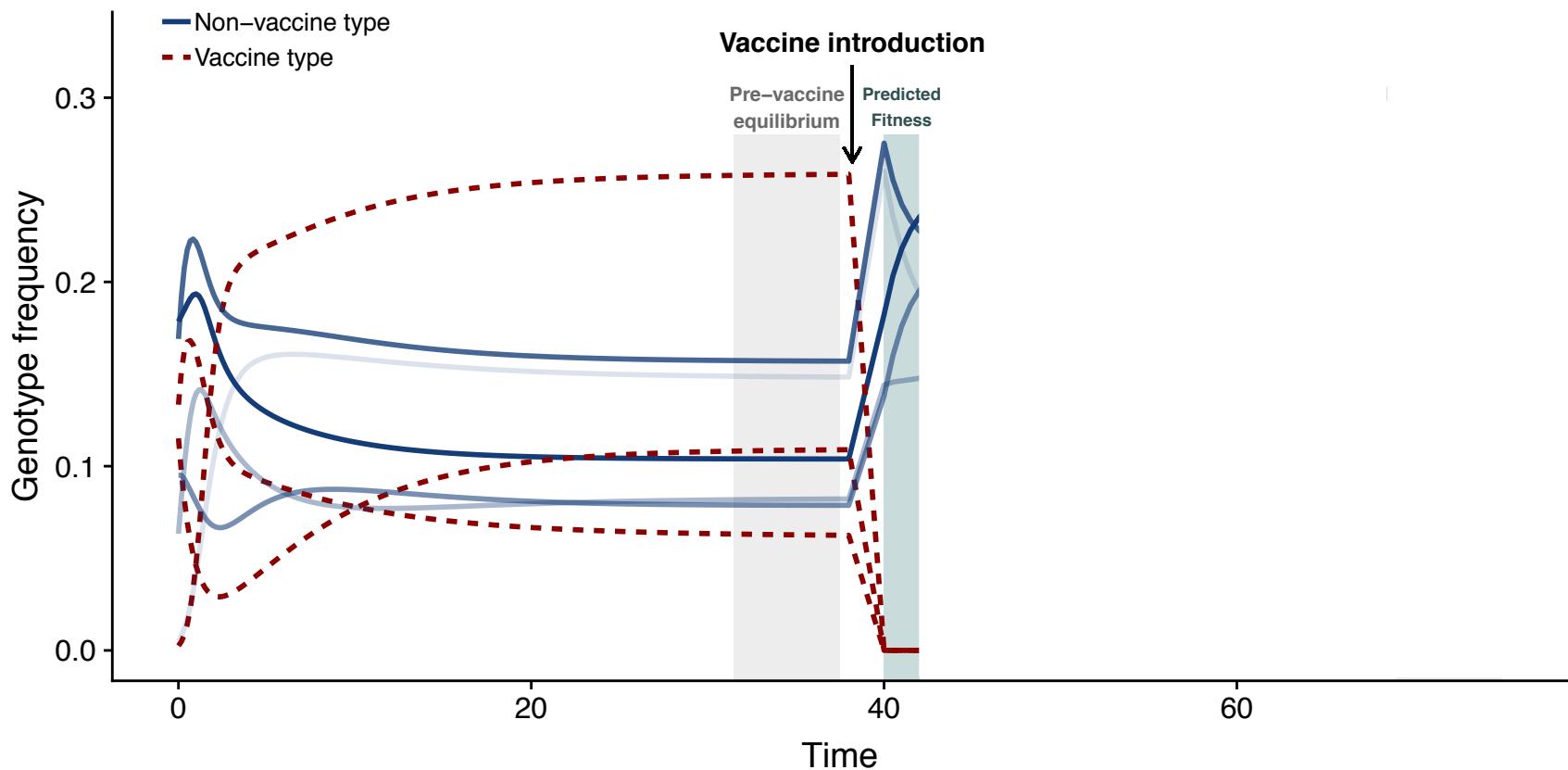
f_l = Post-vaccine frequency of each loci l

Results

Population dynamics

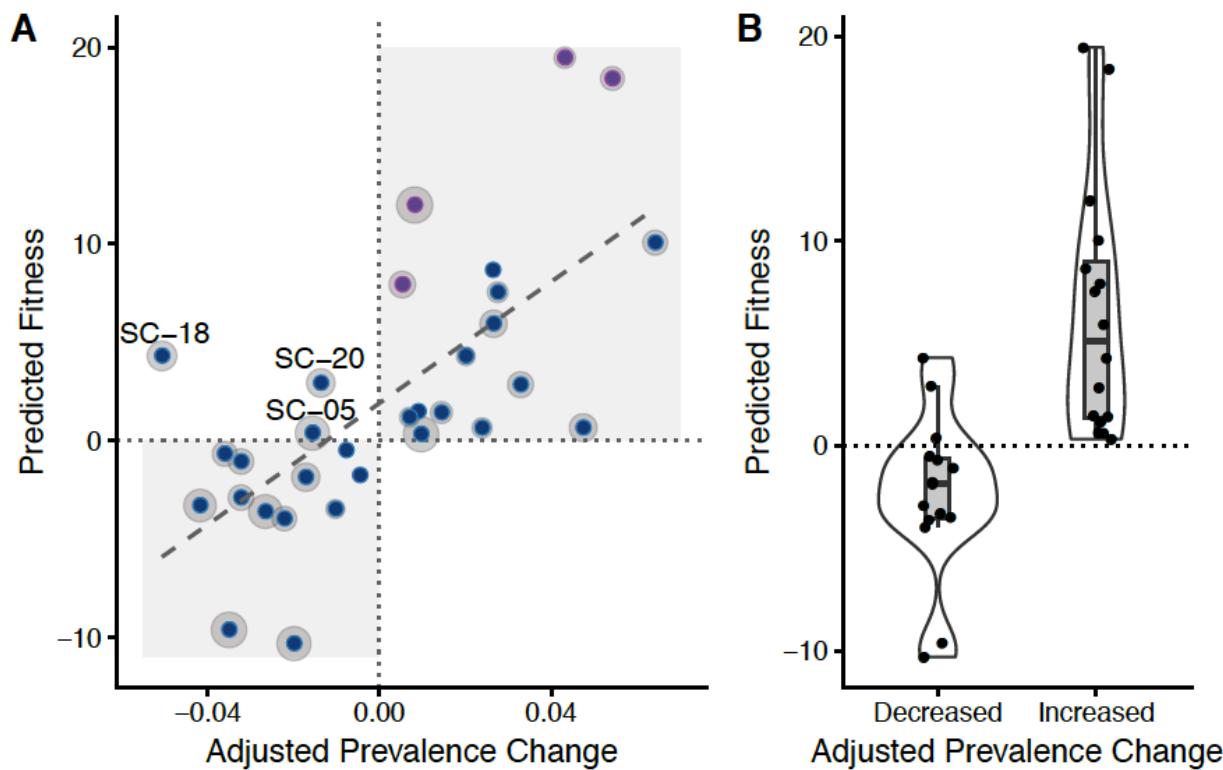


Population dynamics

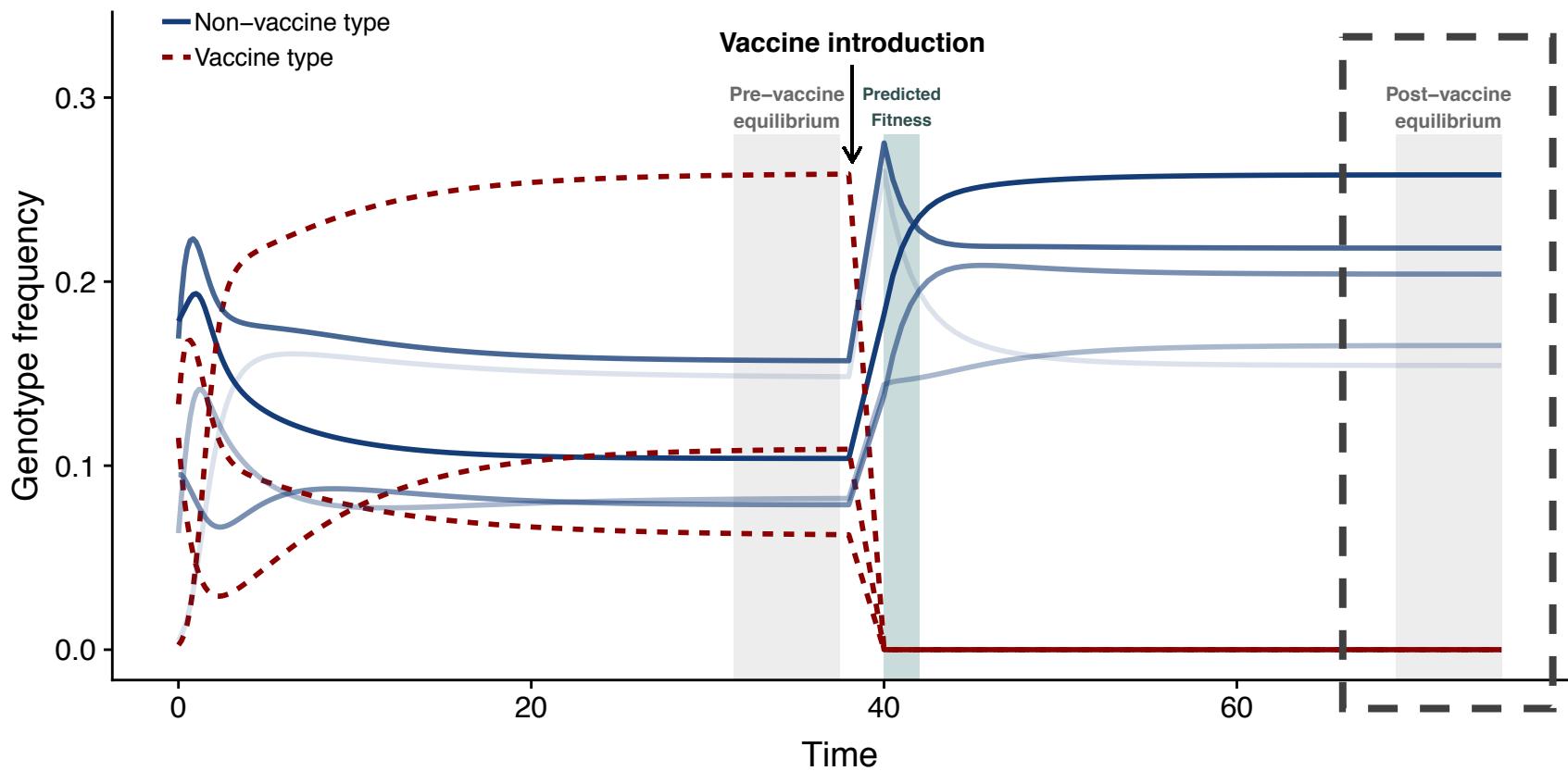


Population dynamics

Predicted Fitness

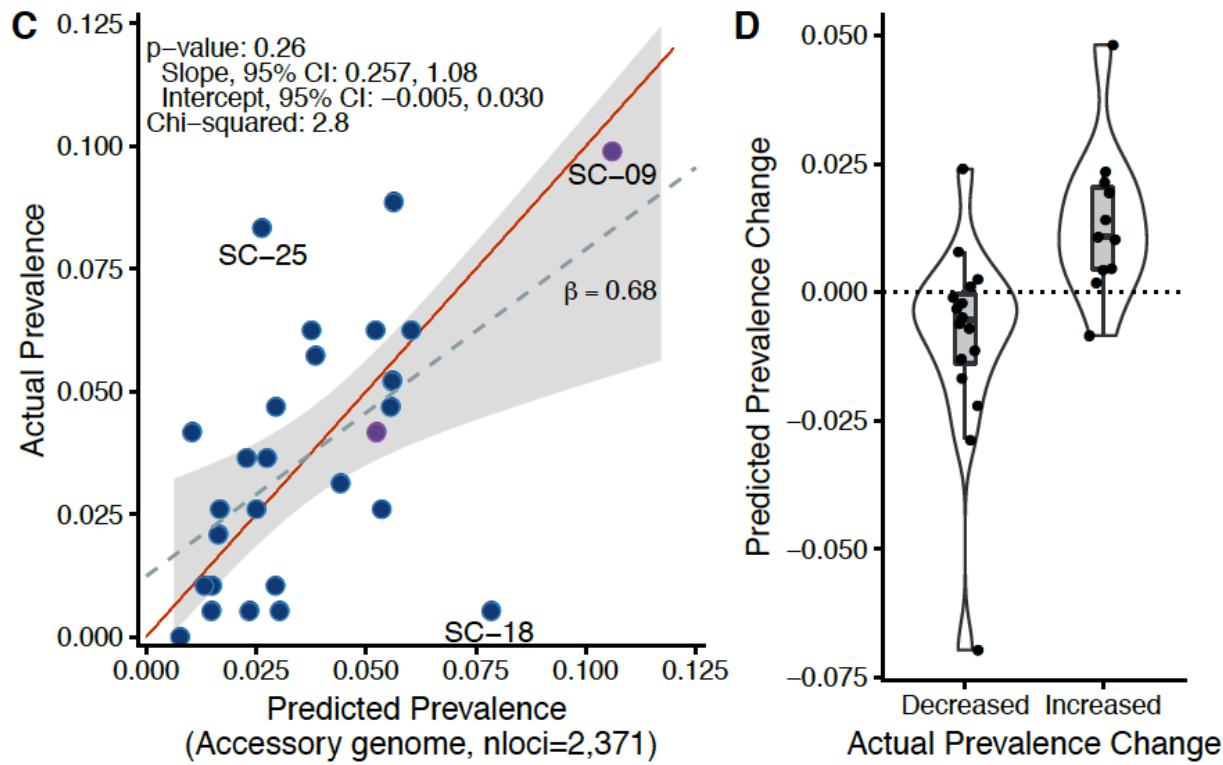


Population dynamics



Population dynamics

Post-vaccine Equilibrium Frequencies



Conclusions

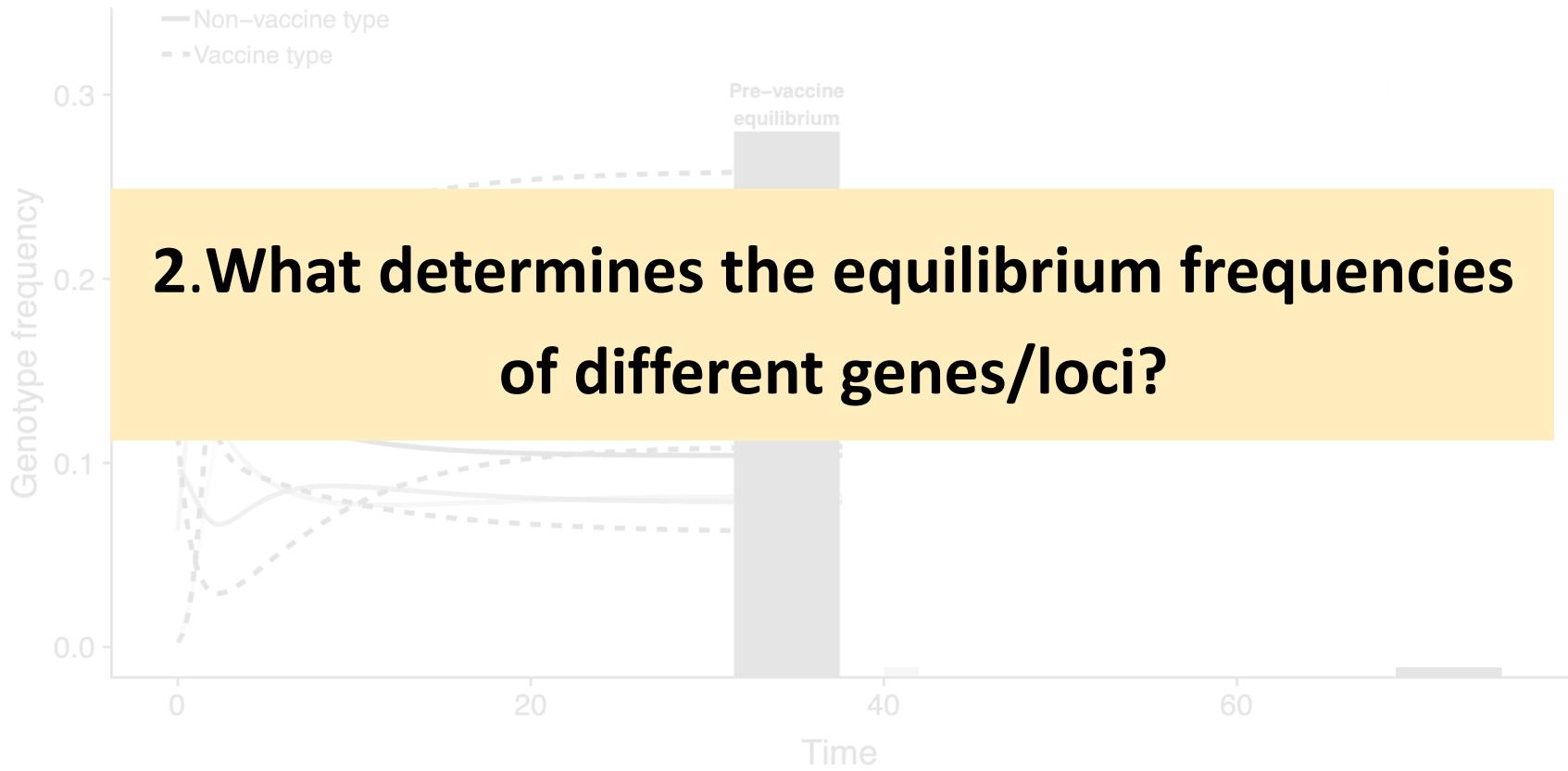
Prediction of post– vaccine prevalence

Predicted fitness → Direction of prevalence change

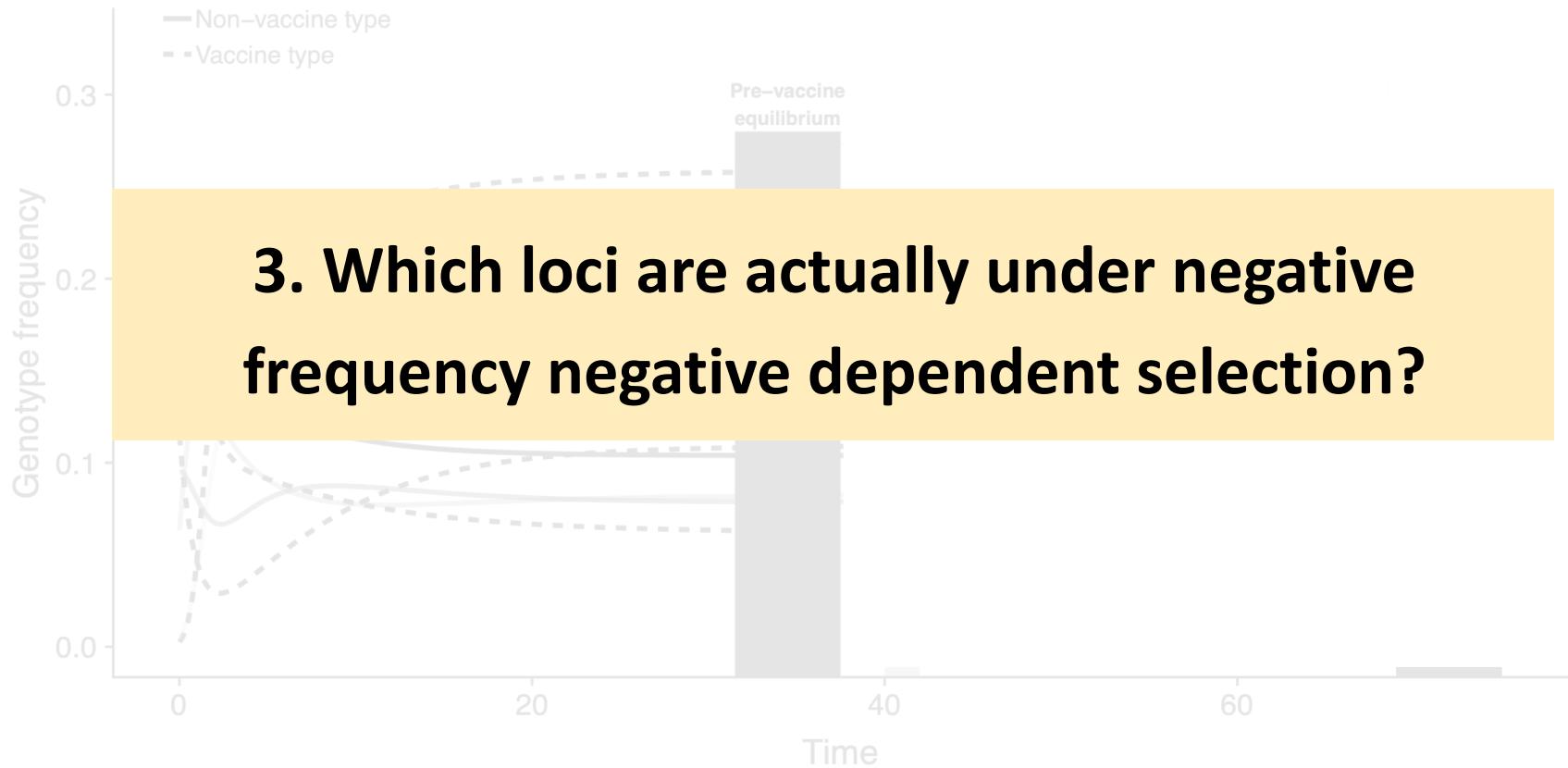
Post–vaccine equilibrium → Accurately predicts direction and magnitude of the observed post – intervention frequencies.

**Questions on things I don't
understand/are confused about**

Questions on things I don't understand/are confused about



Questions on things I don't understand/are confused about



Questions on things I don't understand/are confused about

1. Why we do not observe changes in the transmission after the implementation of two different vaccines?
2. What determines the equilibrium frequencies of different genes/loci?
3. Which loci are actually under negative frequency dependent selection?

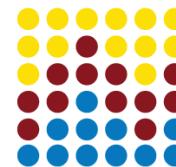
Acknowledgments

Rotavirus project:

Mercedes Pascual (University of Chicago)
Aaron King (University of Michigan)
Mohammad Yunus (Bangladesh – iccdr,b)

Streptococcus pneumoniae project:

Marc Lipsitch (Harvard)
Taj Azarian (University of Central Florida)
Bill Hanage (Harvard)



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Funded by the National Institutes of Health