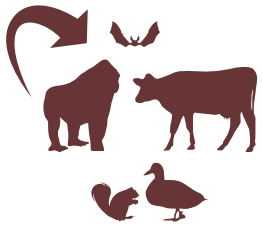
Pathogen emergence in populations with heterogeneous immune competence

Jamie Lloyd-Smith

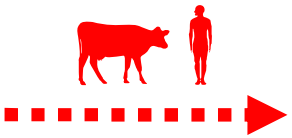
Dept of Ecology & Evolutionary Biology
University of California, Los Angeles

RAPIDD, Fogarty International Center, NIH

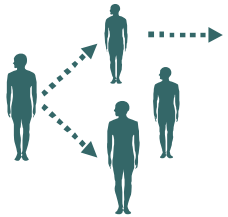
Emergence of zoonotic pathogens



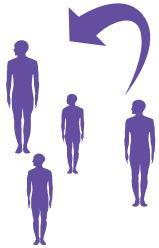
Circulation in reservoir



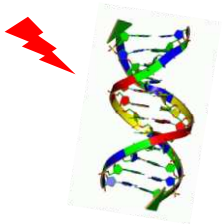
Cross-species spillover



Stuttering chains (R_0<1)



Epidemics and persistence (R_0 > 1)



Pathogen evolution

Basic dynamics apply to other ‘disease introduction’ problems

Community ⇢ Hospital

Common Emergence of Amantadine- and Rimantadine-Resistant Influenza A Viruses in Symptomatic Immunocompromised Adults

Recovery of Drug-Resistant Influenza Virus from Immunocompromised Patients: A Case Series

Prolonged Excretion of Amantadine-Resistant Influenza A Virus Quasi Species after Cessation of Antiviral Therapy in an Immunocompromised Patient

An outbreak of multidrug-resistant tuberculosis among hospitalized patients with the acquired immunodeficiency syndrome.

The impact of HIV-1 on the malaria parasite biomass in adults in sub-Saharan Africa contributes to the emergence of antimalarial drug resistance

Persistent Rotavirus Infection in Mice with Severe Combined Immunodeficiency

PROLONGED INFLUENZA A INFECTION RESPONSIVE TO RIMANTADINE THERAPY IN A HUMAN IMMUNODEFICIENCY VIRUS-INFECTED CHILD

Persistent Infection Promotes Cross-Species Transmissibility of Mouse Hepatitis Virus

Immune competence and pathogen emergence

Many factors affect the host immune response to a given pathogen:

Host factors: genetics, age, sex, condition

Epidemiological history: vaccination, previous exposure, co-infections (incl. HIV)

Environmental influences: nutrition, stress, pollutants, drugs

Compromised immunity known to cause **individual-level effects**:

greater susceptibility to infection
disseminated infection and death
higher pathogen loads
chronic infection

Chronic infections linked with development of drug resistance.

Today's talk

Compromised immunity known to cause **individual-level effects.**

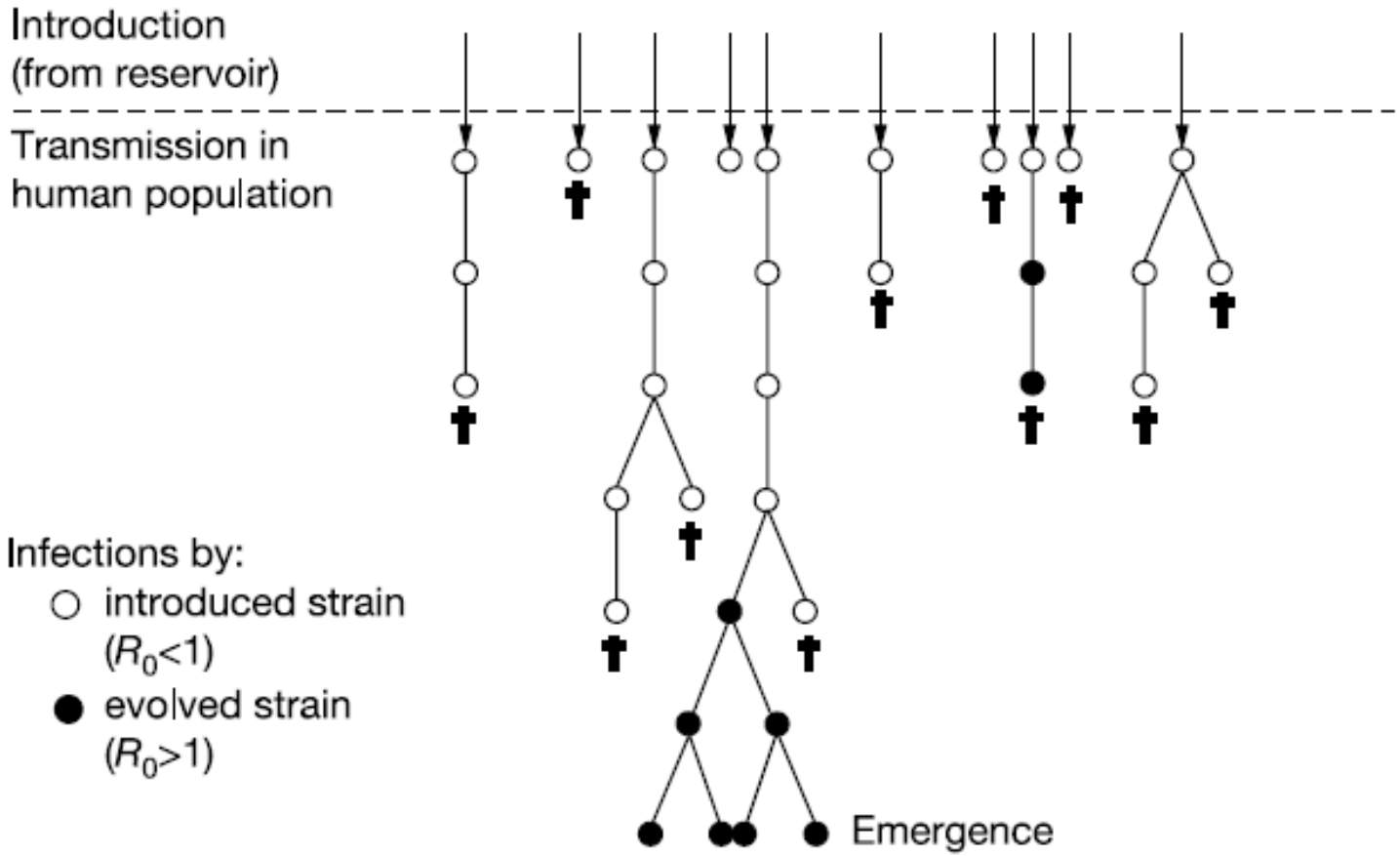
What are the **population-level effects** of immunocompromised groups on *de novo* emergence of pathogen strains?

Outline

- Background: evolutionary emergence and branching processes
- Simple model for heterogenous immune competence
  - probability of disease invasion (without evolution)
  - probability of emergence of a novel strain (via evolution)
- Illustrative example: HIV prevalence and emergence risk

Modelling pathogen emergence

For a pathogen with $R_0<1$ in a new environment, can adaptation increase R_0 and rescue the pathogen from extinction?



Antia et al (2003) *Nature*

Previous models of evolutionary emergence

Antia et al, 2003: Probability of emergence increases as R_0 of initial strain approaches 1, mutation rate increases, or evolutionary path is shorter/simpler .

Andre & Day, 2005: If you allow for evolution within hosts, then duration of infection can be as important as R_0.

Yates et al, 2006: Heterogeneity in host susceptibility or infectiousness alone has little effect on emergence.

Reluga et al, 2007: Continued contact with reservoir population can promote emergence.

Alexander & Day, 2010(??): Considering contact rate distributions and more complex evolutionary trajectories leads to subtleties…

Previous models of evolutionary emergence

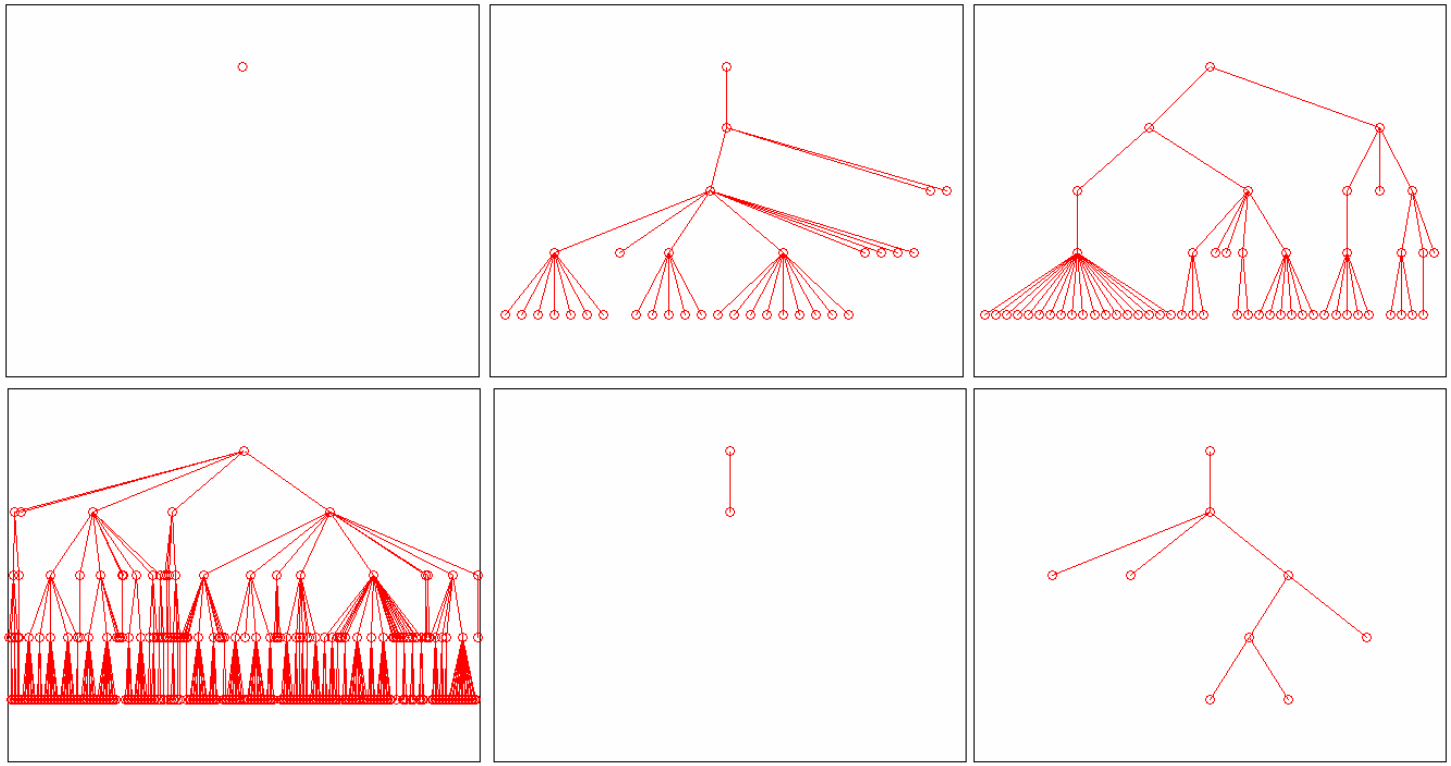
Antia et al, 2003: Probability of emergence increases as R_0 of initial strain approaches 1, mutation rate increases, or evolutionary path is shorter/simpler .

Andre & Day, 2005: If you allow for evolution within hosts, then duration of infection can be as important as R_0.

Yates et al, 2006: Heterogeneity in host susceptibility or infectiousness alone has little effect on emergence.

Present goal: analyze disease emergence in a population with heterogeneous immunocompetence so that parameters may co-vary, with both within- and between-host evolution.

Branching process: a stochastic model for disease invasion into a large population.



Offspring distribution: $\Pr(Z=j) = p_j$

Define probability generating function for Z: $f(s) = \sum_{j=0}^{\infty} p_j s^j$

Then q = Pr(extinction) is solution to $q = f(q)$.

Simple model for heterogeneity in immune competence

Divide population into two groups, healthy and immunocompromised, which mix at random.

Consider different epidemiological effects of immune compromise:

NO EFFECT (0), S↑, I↑ , I↓, S↑I↑, S↑I↓

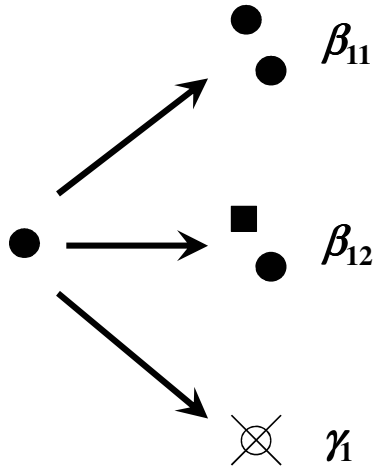
(assume 10-fold changes)

Infectiousness can vary via either the rate or duration of transmission.

Assume that epidemiological and evolutionary parameters are independent.

Model 1: heterogeneous immune competence, but no evolution

Multi-type birth-and-death process



β_{ij} = rate at which individual in group *i* infects new cases in group *j*

γ_i = recovery rate of individuals in group *i*

Probability generating functions:

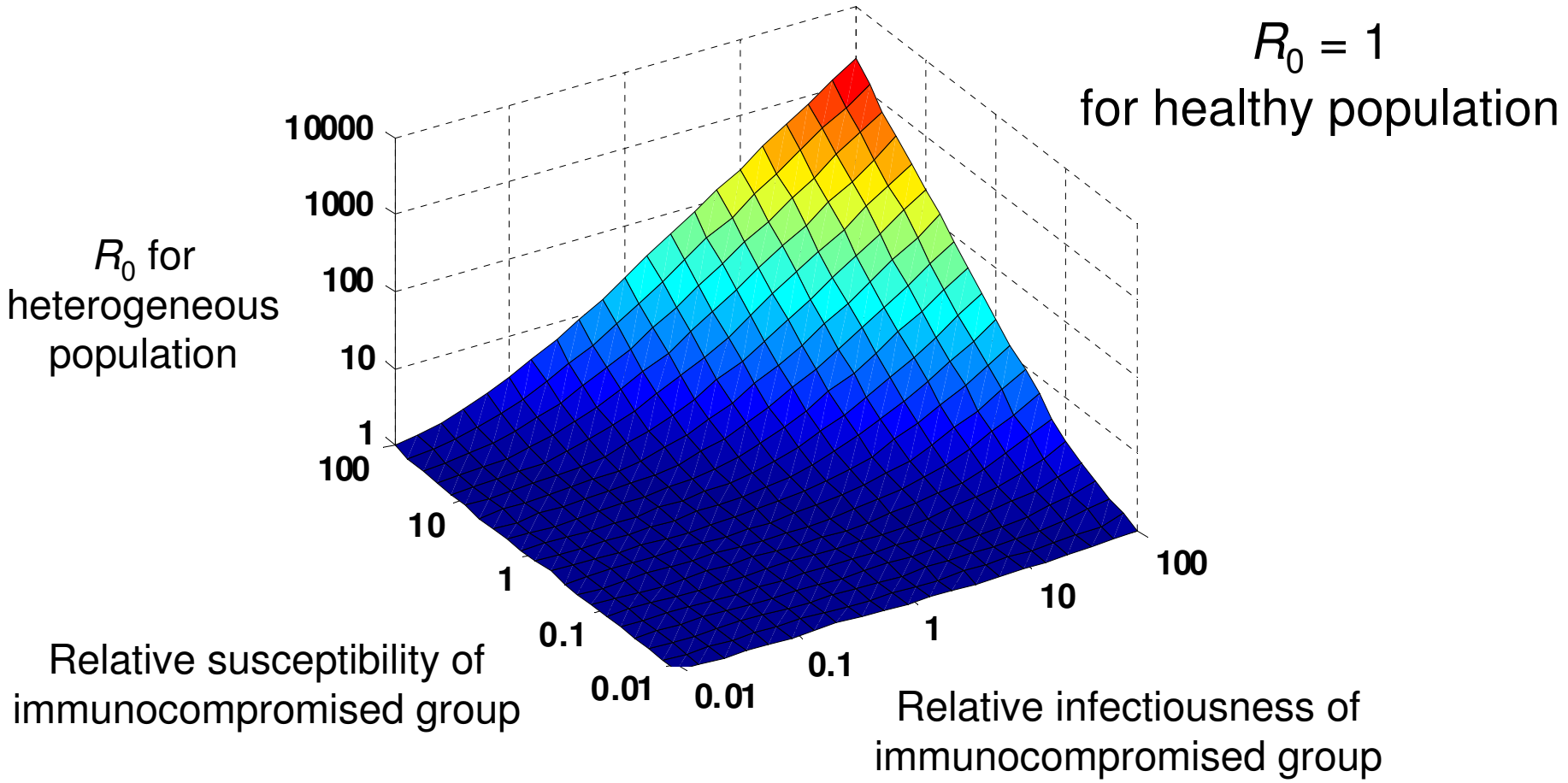
$$f_1(s) = \frac{1}{\gamma_1 + \beta_{11} + \beta_{12}}\left(\gamma_1 + \beta_{11}s_1^2 + \beta_{12}s_1 s_2\right)$$

$$f_2(s) = \frac{1}{\gamma_2 + \beta_{21} + \beta_{22}}\left(\gamma_2 + \beta_{21}s_2 s_1 + \beta_{22}s_2^2\right)$$

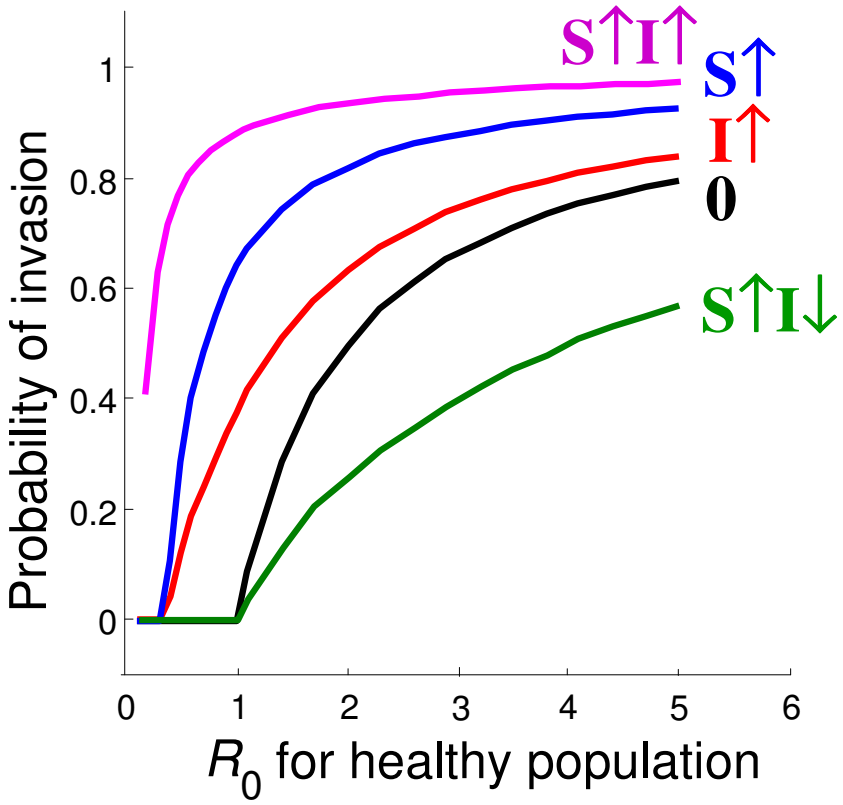
Solve for $\boldsymbol{q}$ such that $\boldsymbol{f}(\boldsymbol{q})=\boldsymbol{q}$.

Then $1-q_i$ is probability of invasion following introduction of a single case of type i.

R_0 for the heterogeneous population „ R_0 for a healthy population



Pathogen invasion

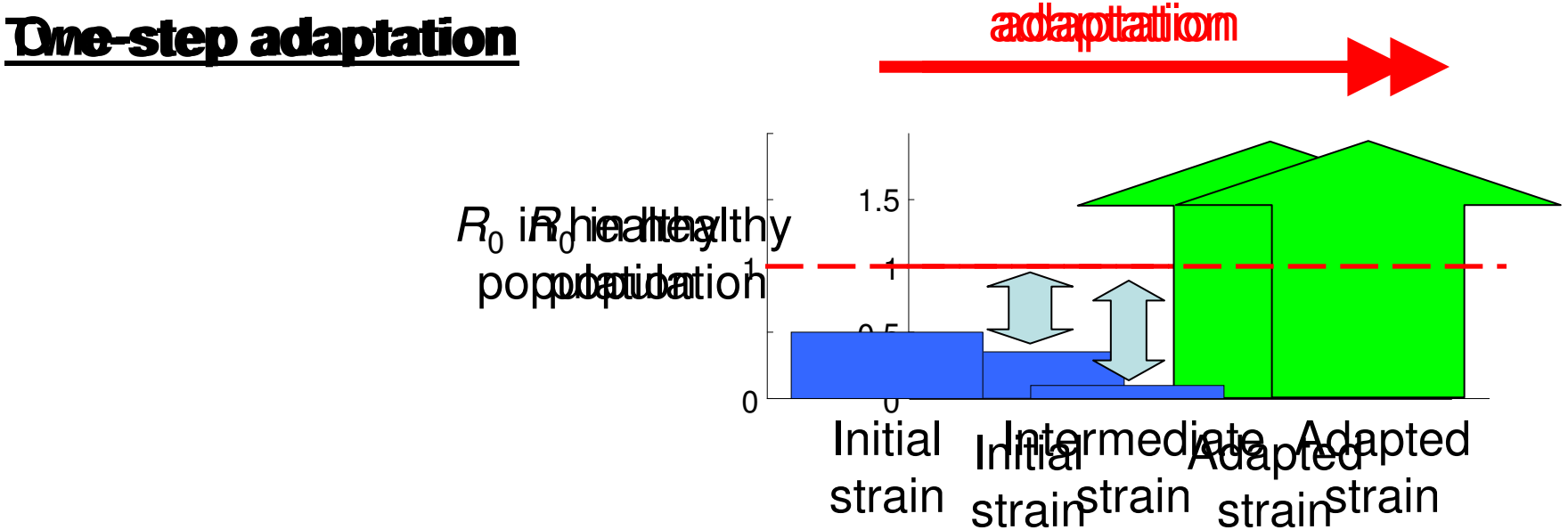


- Immune compromised group with **I↑** or **S↑** can make invasion possible for an otherwise non-adapted pathogen.
- Increase in both (**S↑I↑**) greatly amplifies this effect.

Incorporating pathogen evolution

Pathogen is structured into strains representing stages of adaptation to a novel host species.

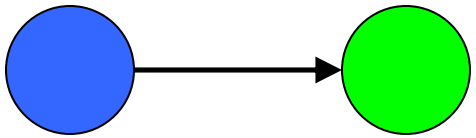
These are described by a pathogen fitness landscape.



Steps in the fitness landscape arise through two basic mechanisms:

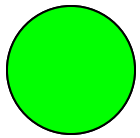
Between-host evolution

population bottleneck in transmission causes founder effect



Within-host evolution

mutation arises during infection and goes to fixation within host



Model assumes:

Occurs with fixed probability per transmission event.

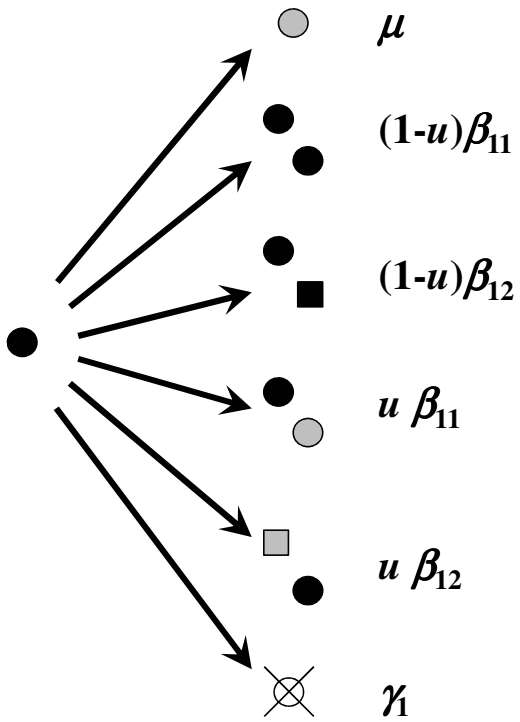
Occurs at a constant rate within each infected host.

Total probability of an event depends on the length of the transmission chain.

Total probability depends on the cumulative duration of infection, summed over all hosts.

Model 2: heterogeneous immune competence, including evolution

Extended multi-type birth-and-death process



β_{ij} = rate at which individual in group *i* infects new cases in group *j*

γ_i = recovery rate of individuals in group *i*

μ = rate of within-host evolution

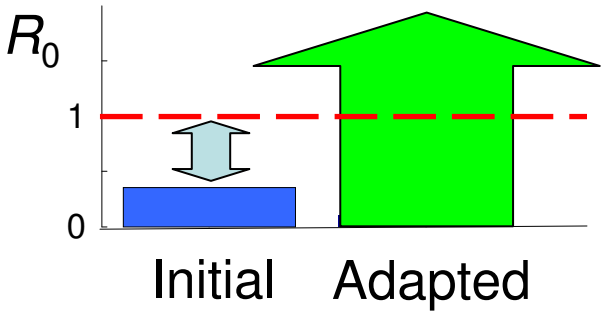
u = probability of between-host evolution

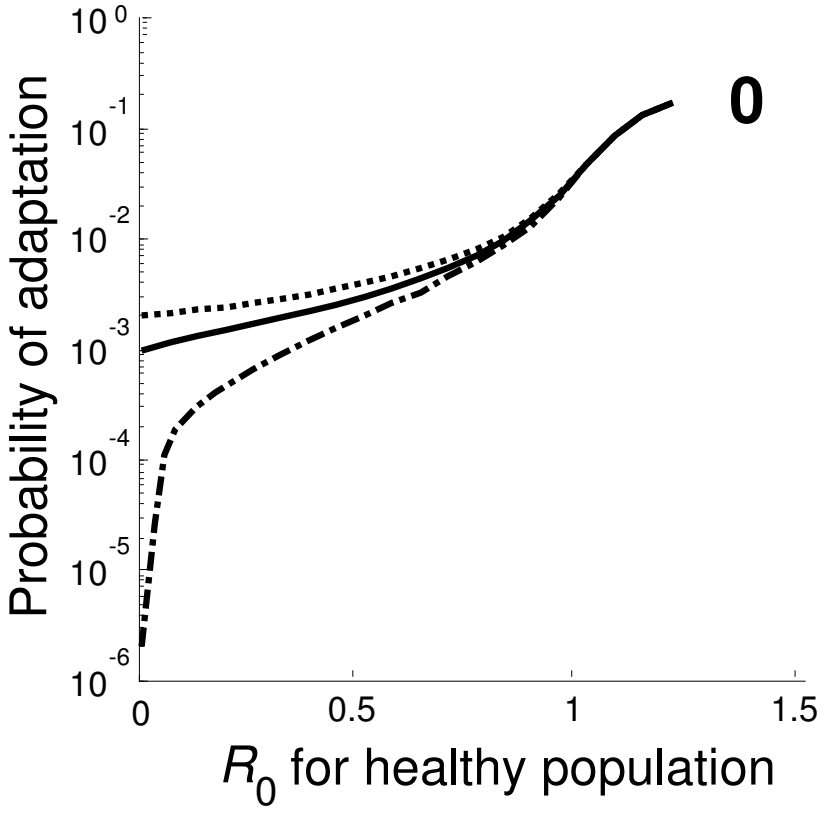
Probability generating functions look like:

$$f_1^{(1)}(s) = (1-u)\left[\frac{\chi_{11}^{(1)}}{\theta_1^{(1)}}\left(q_1^{(1)}\right)^2 + \frac{\chi_{12}^{(1)}}{\theta_1^{(1)}}\left(s_1^{(1)}s_2^{(1)}\right)\right] + u\left[\frac{\chi_{11}^{(1)}}{\theta_1^{(1)}}\left(s_1^{(1)}s_1^{(2)}\right) + \frac{\chi_{12}^{(1)}}{\theta_1^{(1)}}\left(s_1^{(1)}s_2^{(2)}\right)\right] + \frac{\mu}{\theta_1^{(1)}}s_1^{(2)} + \frac{\gamma_1^{(1)}}{\theta_1^{(1)}}$$

Pathogen evolution: probability of adaptation

One-step adaptation





Three scenarios with **equal total probability of adaptation**, per host:

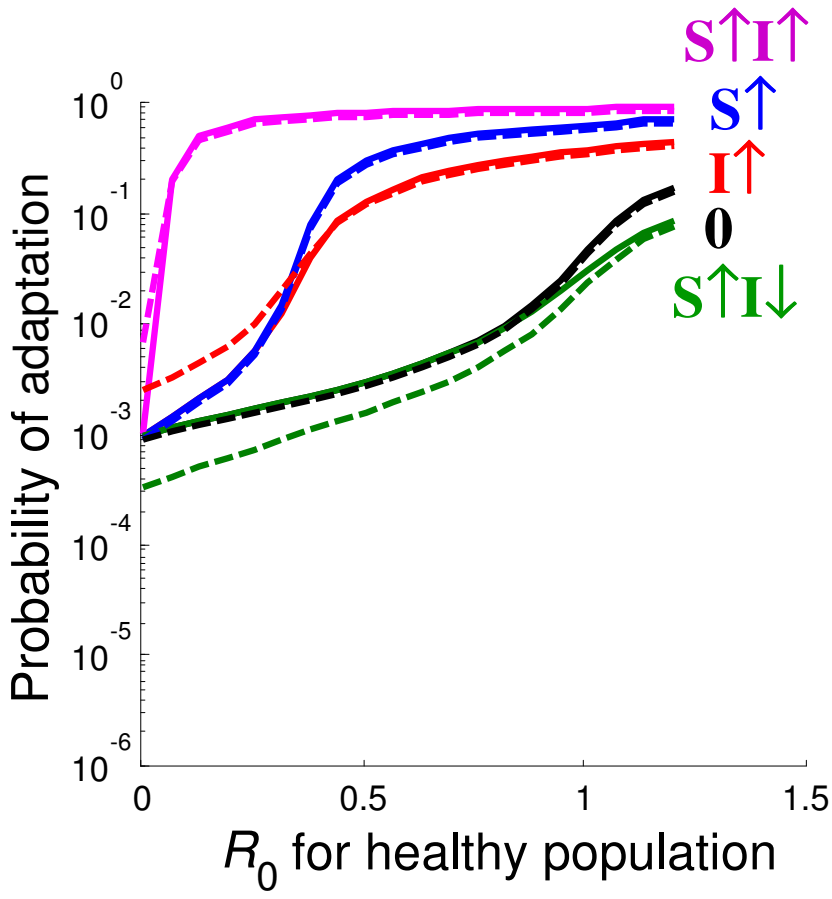
..... **WITHIN >> between**

——— **within = between**

– · – · · **within << BETWEEN**

Pathogen evolution: probability of adaptation

Assuming P(within) = P(between) = 1×10^{-3}

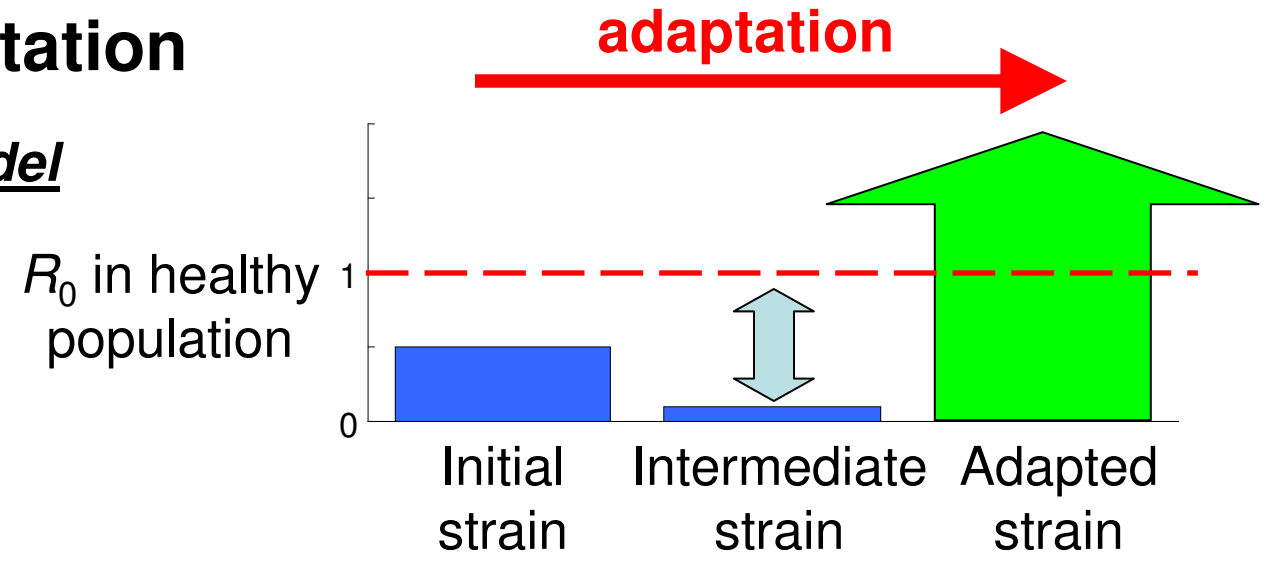


Solid lines: infectiousness varies by transmission rate

Dashed lines: infectiousness varies by duration

Two-step adaptation

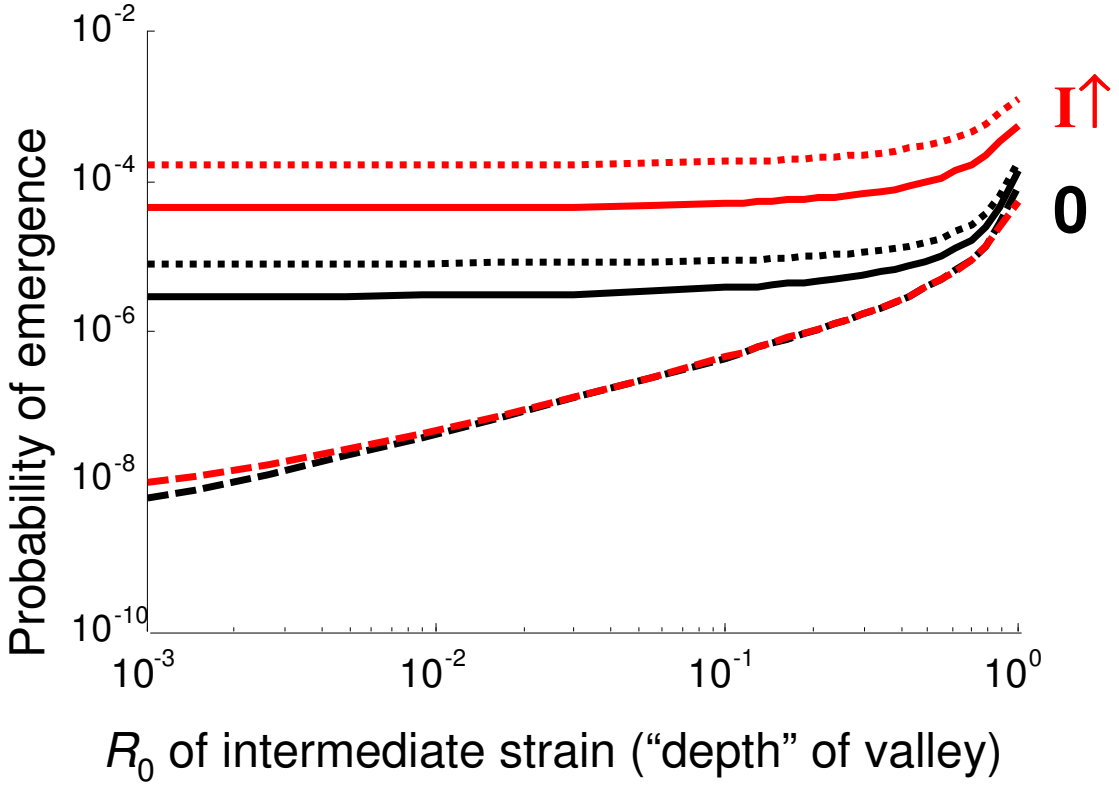
Fitness valley model



WITHIN >> between

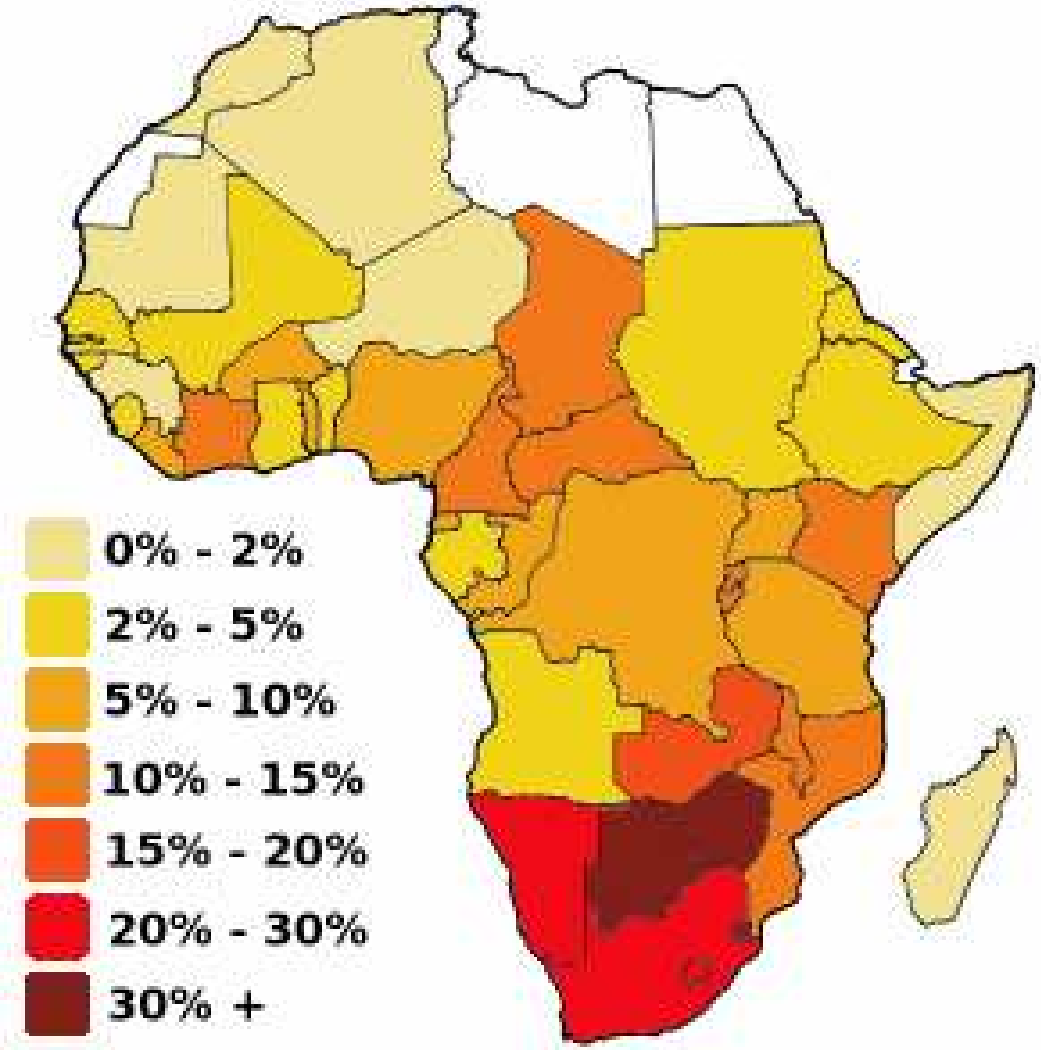
within = between

within << BETWEEN



HIV in Africa: a changing immune landscape

HIV prevalence in adult populations



How might this influence disease emergence?

HIV and acute respiratory infections

Studies from Chris Hari-Baragwanath Hospital in Soweto, South Africa

Bacterial respiratory tract infections (Madhi et al, 2000, *Clin Inf Dis*):

Organism	HIV-1$^+$ children	HIV-1$^-$ children	RR; 95% CI	*P*
Streptococcus pneumoniae	1233	29	42.9; 20.7–90.2	<.00001
Haemophilus influenzae type b	569	27	21.4; 9.4–48.4	<.00001
Staphylococcus aureus	337	3	49.0; 15.4–156.0	<.00001
Escherichia coli	474	10	97.9; 11.4–838.2	<.00001
Salmonella species	95	7	13.4; 2.2–78.1	.02
Mycobacterium tuberculosis	1470	65	22.5; 13.2–37.6	<.00001

Viral respiratory tract infections (Madhi et al, 2000, *J. Ped.*):

	HIV-infected/ 100 000	HIV-uninfected/ 100 000	Relative risk, 95% CI
RSV	1,444	309	1.92, 1.29-2.83
Influenza A/B	1,268	148	8.03, 5.05-12.76
Parainfluenza 1-3	893	106	8.46, 4.95-10.47
Adenovirus	481	32	15.07, 6.62-34.33

HIV and acute respiratory infections

TABLE VI

Reports of Persistence of Respiratory Viral Infection in Immunocompromised Children

Virus	Duration Reported (days)		Reference
	Immunocompromised	Immunocompetent	
Respiratory syncytial virus	0–37	—	6
	4–47	1–20	7
	40–112	1–21	12
	1–199	1–21	13
	8–58	3–18	14
	63	—	15
Parainfluenza 3	20–235	1–26	12
	≥80	—	16
	91	—	17
Influenza A	10–36	3–10	14

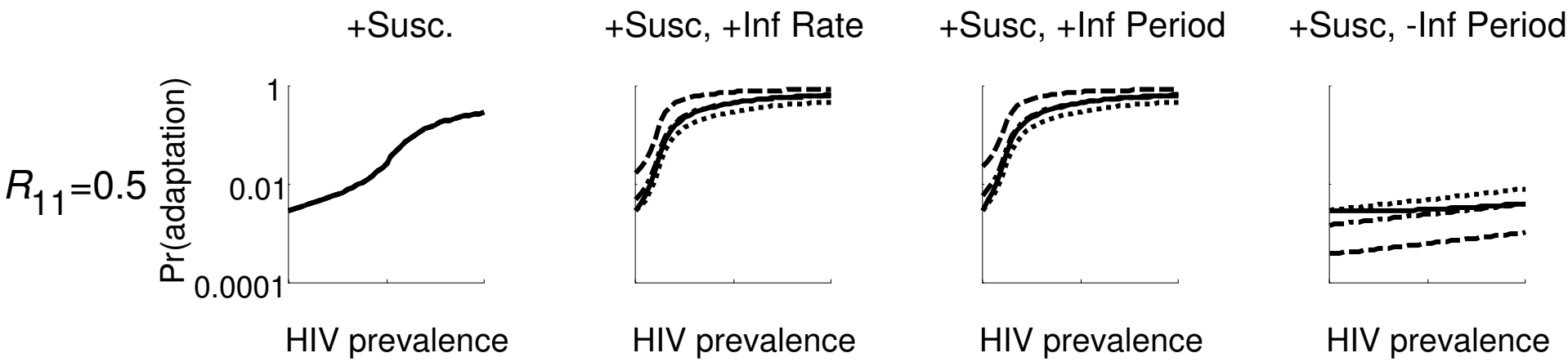
Couch et al, 1997

Parasite genus	Influence of HIV-1 co-infection on:			
	Susceptibility	**Transmission rate**	**Infectious period**	**Treatment efficacy**
Plasmodium	Increased.	Increased (via higher parasite densities).	Increased (via recurrent parasitemia).	Decreased (high treatment failure and inc'd recrudescence in HIV patients with reduced $CD4^+$ count).
Leishmania	Possibly increased.	Increased via higher parasite burdens, new routes of transmission.	Possibly increased due to delayed diagnosis.	Decreased (high treatment failure and frequent relapses)
Trypanosoma	No evidence for effect.	No evidence for *T. brucei*; increased for *T. cruzi* (via higher parasitemia in chronic phase)	No evidence for effect.	Decreased for *T. brucei* (greater risk of relapse); no evidence for *T. cruzi*.
Schistosoma	Increased susceptibility to re-infection.	Decreased (via lower egg excretion).	Possibly increased due to milder symptoms.	No effect observed in humans.
Strongyloides	Possibly increased.	No evidence for effect (no effect of $CD4^+$ count on fecal shedding of larvae).	Possibly increased due to milder symptoms.	No evidence of decrease.

Parasite genus	Influence of HIV-1 co-infection on:			
	Susceptibility	**Transmission rate**	**Infectious period**	**Treatment efficacy**
Plasmodium	Increased.	Increased (via higher parasite densities).	Increased (via recurrent parasitemia).	Decreased (high treatment failure and inc'd recrudescence in HIV patients with reduced $CD4^+$ count).
Leishmania	Possibly increased.	Increased via higher parasite burdens, new routes of transmission.	Possibly increased due to delayed diagnosis.	Decreased (high treatment failure and frequent relapses)
Trypanosoma	No evidence for effect.	No evidence for *T. brucei*; increased for *T. cruzi* (via higher parasitemia in chronic phase)	No evidence for effect.	Decreased for *T. brucei* (greater risk of relapse); no evidence for *T. cruzi*.
Schistosoma	Increased susceptibility to re-infection.	Decreased (via lower egg excretion).	Possibly increased due to milder symptoms.	No effect observed in humans.
Strongyloides	Possibly increased.	No evidence for effect (no effect of $CD4^+$ count on fecal shedding of larvae).	Possibly increased due to milder symptoms.	No evidence of decrease.

General effects of HIV prevalence

Very simple model with three groups: healthy, moderate, severe.



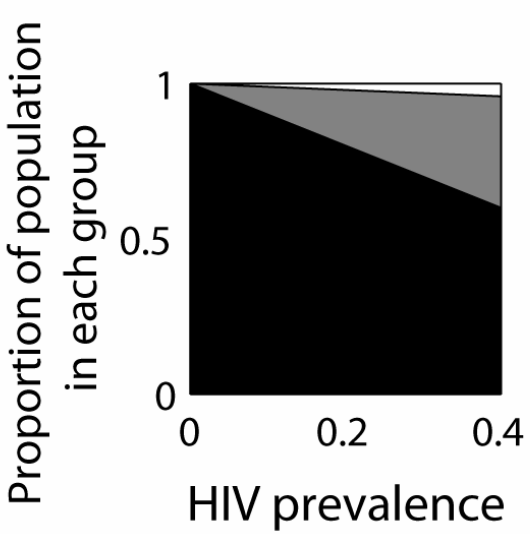
Substantial increase in emergence risk when index case is immunocompromised (+S,+IR or +IP)

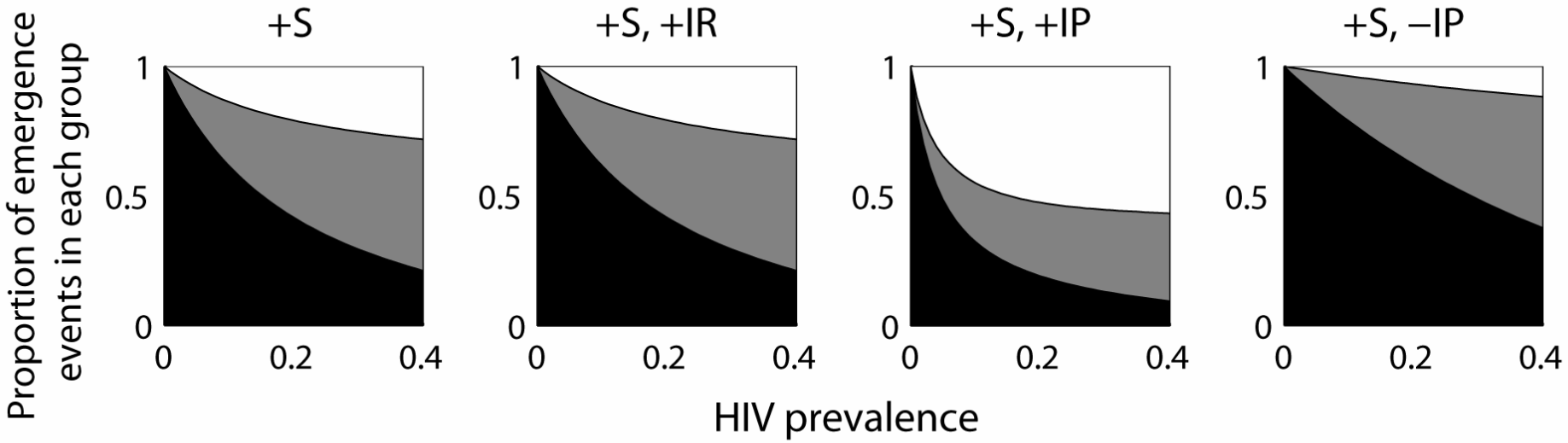
Community benefit to targeted prophylaxis or prevention

Surveillance for strain emergence

Where will novel pathogen strains emerge?

e.g. pathogen with R_0=0.1,
in HIV-affected population.





Targeted surveillance worthwhile, particularly when susceptibility and infectivity are both increased for HIV co-infected hosts.

Summary

Invasion

- An immunocompromised group can provide a toe-hold for emergence of an unadapted pathogen, especially if both susceptibility and infectiousness are increased.

Adaptation

- Within-host evolution is crucial at low R_0, and when pathogen must cross fitness valleys to adapt.
- Prolonged duration of infection has greater influence on emergence than faster rate of transmission.

Policy

- Guidance for targeted prevention or surveillance
- Treat HIV cases protect their contacts

  e.g. Cotrimoxazole prophylaxis given to HIV-1 patients in Uganda led to reduced malaria and diarrhea incidence in their HIV-negative family members (Mermin et al 2005)

Future directions & open questions

- Explicit model for antibiotic treatment
- More realistic representation of evolutionary processes
  - Link to within-host dynamics
  - Data-driven parameter values, fitness landscapes, etc.
- Do fitness landscapes vary as a function of immune status?
- Immune system is highly complex, and "immune competence" is certainly not a one-dimensional space
  - What are relevant indices of immune status?
  - Is it ever sensible to generalize across host-pathogen systems?
    Across causes of immune compromise?
- Could the greater risk of drug resistance in immunocompromised hosts be due simply to increased drug exposure?
  Controlled epi studies? Experimental work?

Acknowledgements

Ideas and insights

Bryan Grenfell, Mary Poss, Andrew Read, Peter Hudson, and many others at Penn State.

Wayne Getz (UC Berkeley)

Sebastian Schreiber (UC Davis)

Funding

CIDD Fellowship, NIH-RAPIDD

Reference (for some of the material)

Lloyd-Smith, Poss, Grenfell (2008) *Parasitology* 135: 795-806.

Additional material

Model assumptions

Epidemiological model

Susceptible pool is large compared to outbreak size.

Number of cases caused by each individual (offspring distribution) is geometrically distributed.

Type of index case is determined by group size weighted by susceptibility.

$$\Pr(\text{index case in group } i) = \frac{(\text{Size of group } i) \times (\text{Susc. of group } i)}{\Sigma_j (\text{Size of group } j) \times (\text{Susc. of group } j)}.$$

Evolution model

Parameters describing relative susc. and inf. don't depend on pathogen strain.

Evolutionary and epidemiological parameters are independent of one another.

Model equations: 1 group, 1 strain

q = Probability that outbreak carried by a single case will go extinct.

β = Transmission rate

γ = Recovery rate

Define $\phi = \beta + \gamma$, then:

$$q = \frac{\beta}{\phi} q^2 + \frac{\gamma}{\phi}$$

where because of the large-population assumption, we assume:

1. $\Pr(\text{2 chains go extinct}) = [\Pr(\text{1 chain goes extinct})]^2$
2. q is independent of time.

Model equations: 1 group, 2 strains

$q^{(i)}$ = Probability that outbreak of strain i carried by a single case will go extinct.

$\beta^{(i)}$ = Transmission rate for strain i

$\gamma^{(i)}$ = Recovery rate for strain i

μ = Rate of within-host evolution

u = Probability of between-host transmission

Define $\phi^{(i)} = \beta^{(i)} + \mu + \gamma^{(i)}$, then:

$$q^{(1)} = \frac{\beta^{(1)}}{\phi^{(1)}}\left[(1-u)\left(q^{(1)}\right)^2 + u\left(q^{(1)}q^{(2)}\right)\right] + \frac{\mu}{\phi^{(1)}}q^{(2)} + \frac{\gamma^{(1)}}{\phi^{(1)}}$$

$$q^{(2)} = \frac{\beta^{(2)}}{\phi^{(2)}}\left(q^{(2)}\right)^2 + \frac{\gamma^{(2)}}{\phi^{(2)}}$$

Model equations: 2 groups, 2 strains

$q_j^{(i)}$ = Probability that outbreak of strain i carried by a single case in group j will go extinct.

$\beta_{jk}^{(i)}$ = Transmission rate from group j to group k for strain i

$\gamma_j^{(i)}$ = Recovery rate for case of strain i in group j

μ = within-host evolutionrate; u = prob. of between-host evolution

Define, $\phi_j^{(i)} = \sum_k \beta_{jk}^{(i)} + \gamma^{(i)} + \mu$, then:

$$q_1^{(1)} = (1-u)\left[\frac{\beta_{11}^{(1)}}{\phi_1^{(1)}}\left(q_1^{(1)}\right)^2 + \frac{\beta_{12}^{(1)}}{\phi_1^{(1)}}\left(q_1^{(1)}q_2^{(1)}\right)\right] + u\left[\frac{\beta_{11}^{(1)}}{\phi_1^{(1)}}\left(q_1^{(1)}q_1^{(2)}\right) + \frac{\beta_{12}^{(1)}}{\phi_1^{(1)}}\left(q_1^{(1)}q_2^{(2)}\right)\right] + \frac{\mu}{\phi_1^{(1)}}q_1^{(2)} + \frac{\gamma_1^{(1)}}{\phi_1^{(1)}}$$

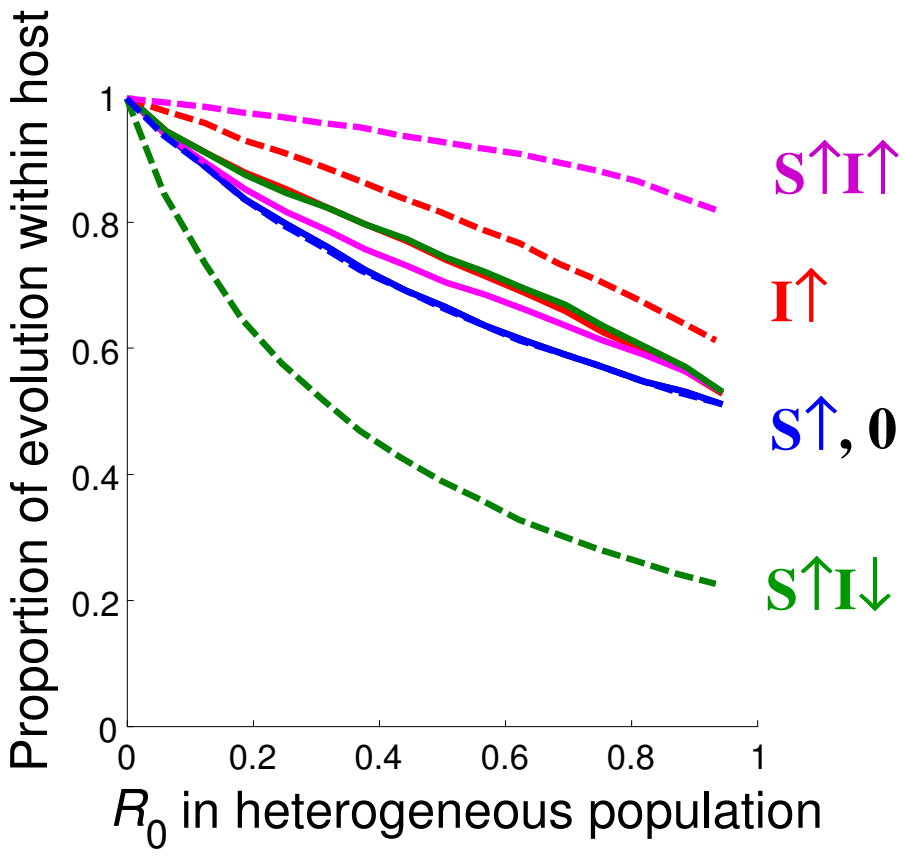
$$q_2^{(1)} = (1-u)\left[\frac{\beta_{21}^{(1)}}{\phi_2^{(1)}}\left(q_1^{(1)}q_2^{(1)}\right) + \frac{\beta_{22}^{(1)}}{\phi_2^{(1)}}\left(q_2^{(1)}\right)^2\right] + u\left[\frac{\beta_{21}^{(1)}}{\phi_2^{(1)}}\left(q_1^{(2)}q_2^{(1)}\right) + \frac{\beta_{22}^{(1)}}{\phi_2^{(1)}}\left(q_2^{(1)}q_2^{(2)}\right)\right] + \frac{\mu}{\phi_2^{(1)}}q_2^{(2)} + \frac{\gamma_2^{(1)}}{\phi_2^{(1)}}$$

$$q_1^{(2)} = \frac{\beta_{11}^{(2)}}{\phi_1^{(2)}}\left(q_1^{(2)}\right)^2 + \frac{\beta_{12}^{(2)}}{\phi_1^{(2)}}\left(q_1^{(2)}q_2^{(2)}\right) + \frac{\gamma_1^{(2)}}{\phi_1^{(2)}}$$

$$q_2^{(2)} = \frac{\beta_{21}^{(2)}}{\phi_2^{(2)}}\left(q_1^{(2)}q_2^{(2)}\right) + \frac{\beta_{22}^{(2)}}{\phi_2^{(2)}}\left(q_2^{(2)}\right)^2 + \frac{\gamma_2^{(2)}}{\phi_2^{(2)}}$$

Where does adaptation occur?

Assuming P(within) = P(between) = 1×10^{-3}



Solid lines: infectiousness varies in transmission rate

Dashed lines: infectiousness varies in duration

Pathogen evolution

Can distinguish between mechanisms of evolution by considering total 'opportunity' for each to work.

- Total infectious duration
- Total number of transmission events

Andre & Day (2005) showed P(adaptation) ~ $\mu L + u B$

Generalize to multi-group setting, can extract:

- proportion of transmission due to within vs between
- likelihood that 'adapted pathogen' will emerge in one group or the other.

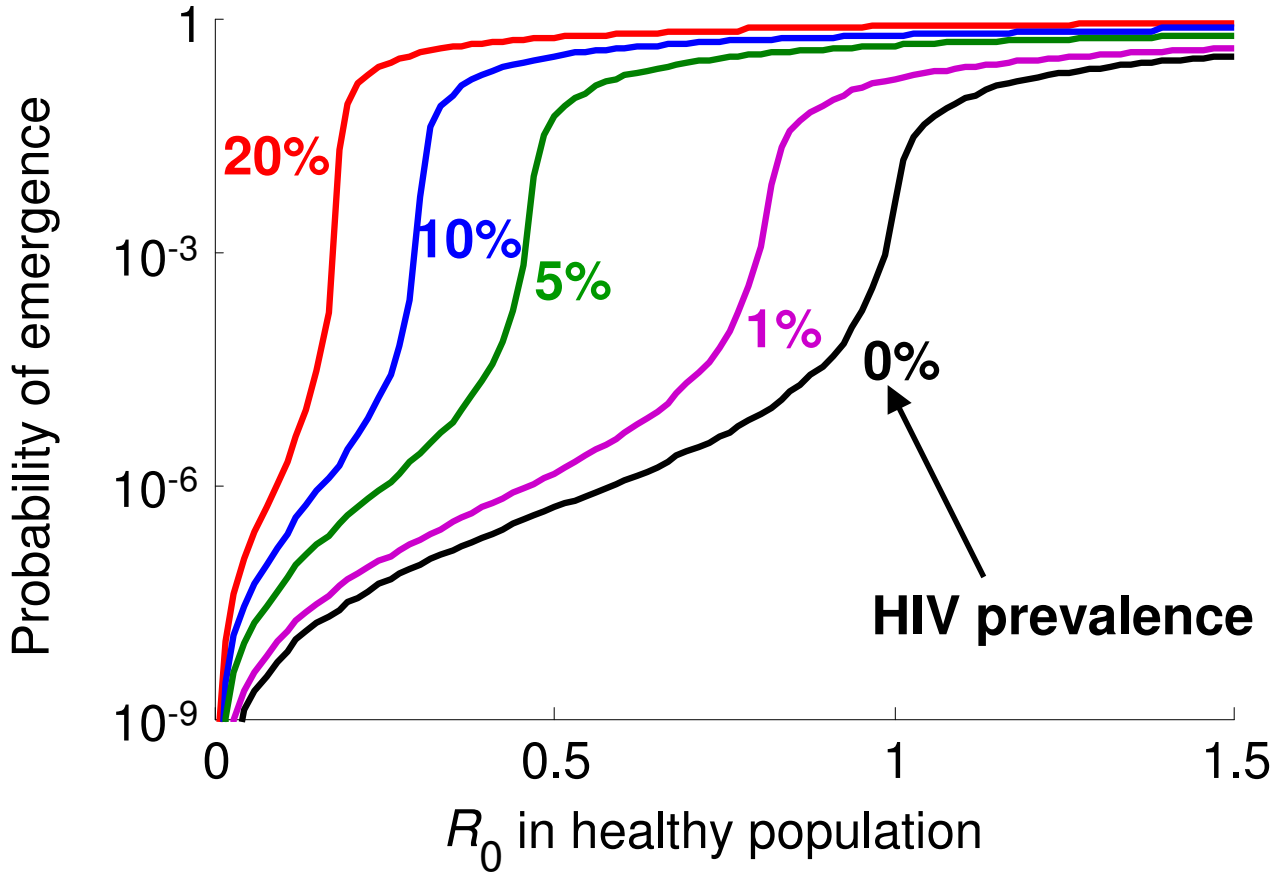
Illustration: HIV prevalence and influenza emergence

Assuming:

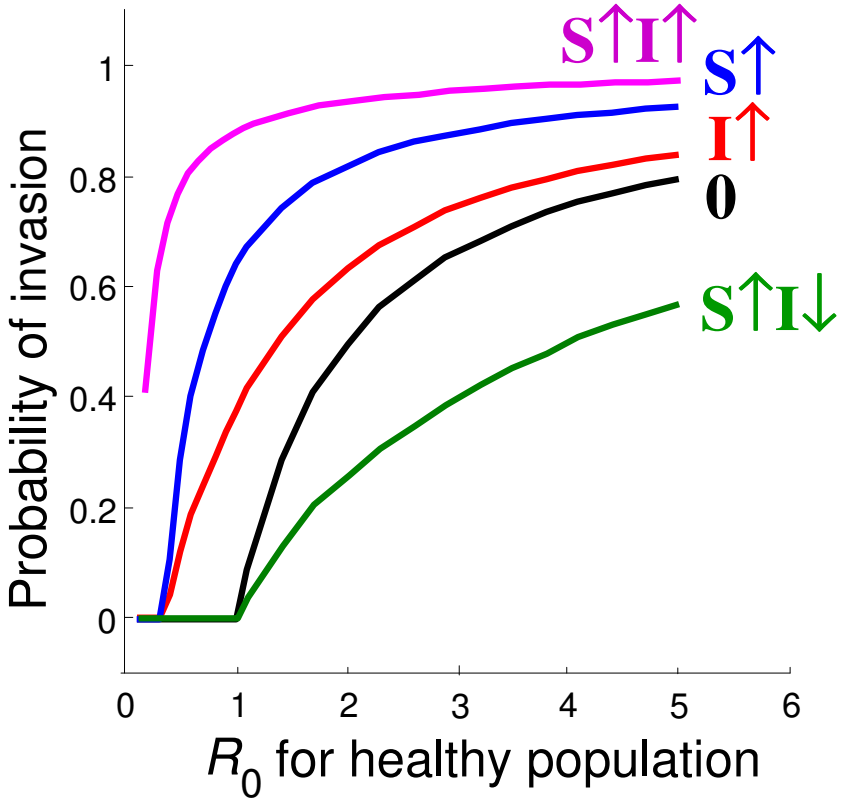
Susceptibility is 8× higher in HIV+ group, and infections last 3× longer.

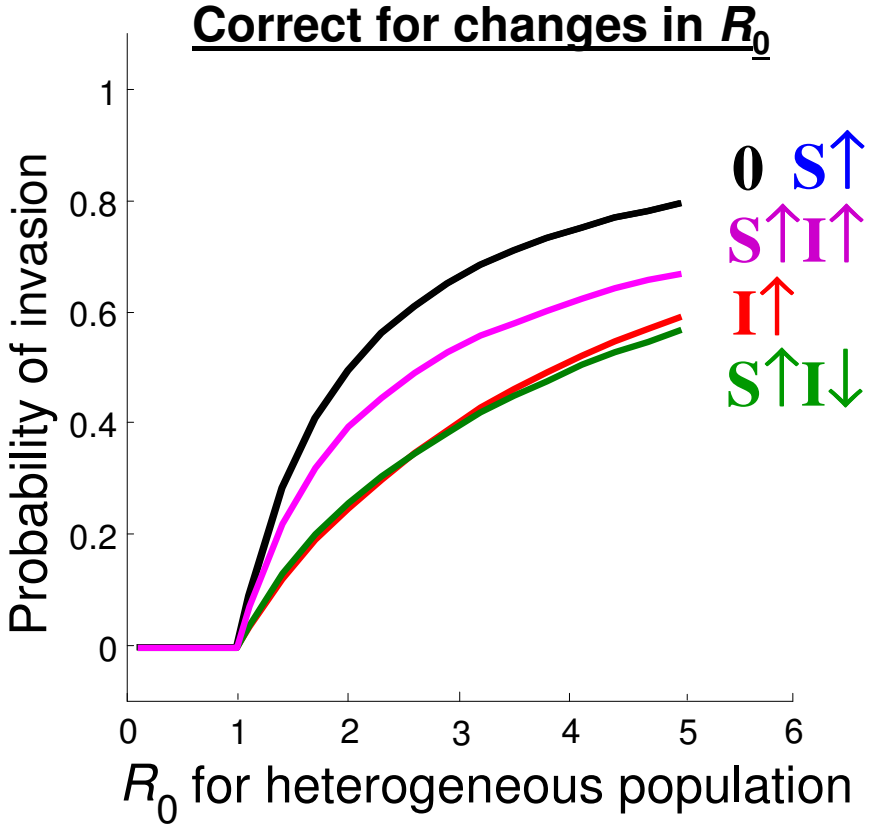
P(within) >> P(between)

Two-step jackpot adaptation $R_0 = 2$ for adapted strain



Pathogen invasion

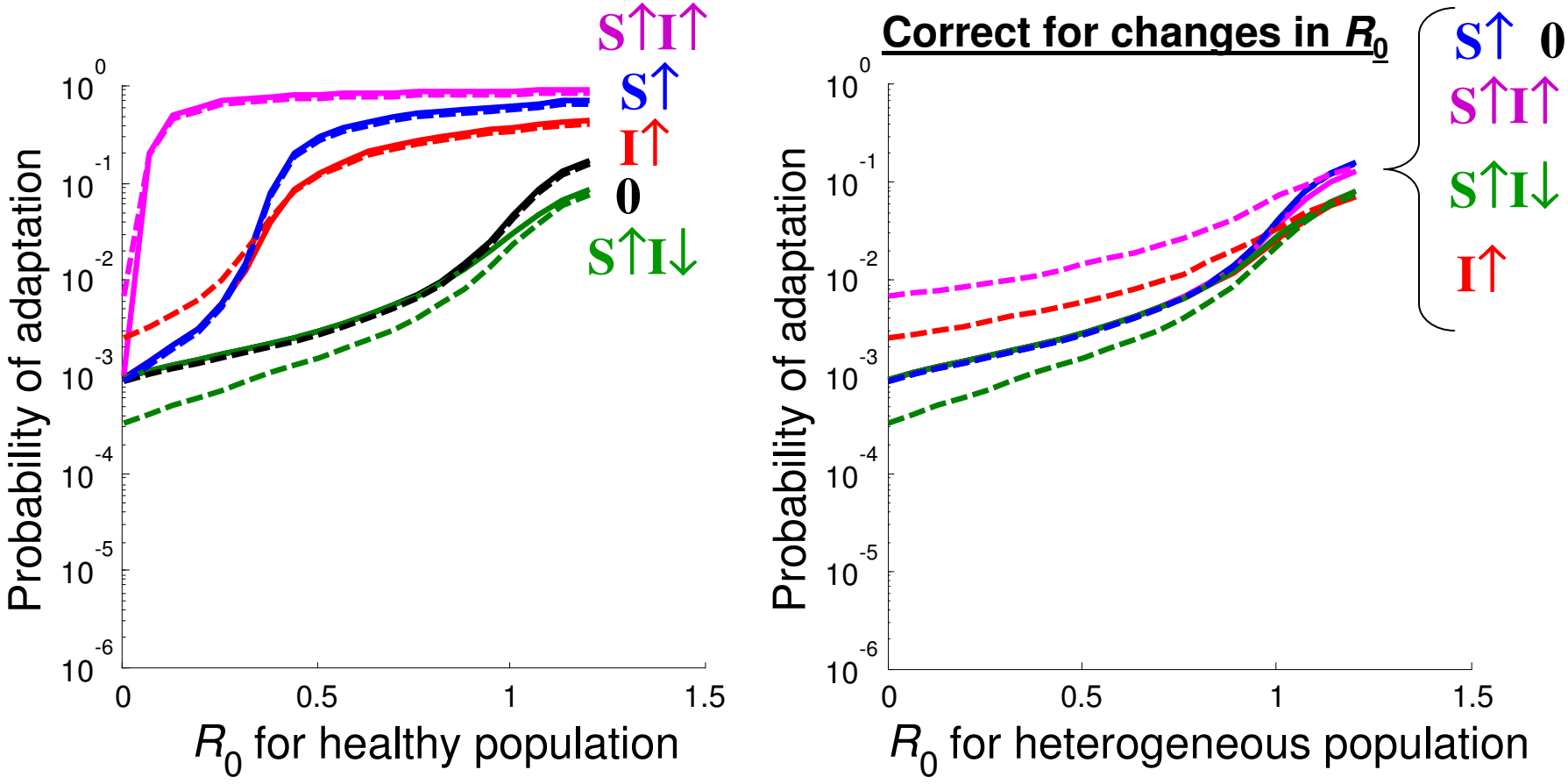




- Immune compromised group with **I↑** or **S↑** can make invasion possible for an otherwise non-adapted pathogen.
- Positive covariation (**S↑I↑**) amplifies this effect.

Pathogen evolution: probability of adaptation

Assuming P(within) = P(between) = 1×10^{-3}



Solid lines: infectiousness varies by transmission rate

Dashed lines: infectiousness varies by duration