The Evolution of Antiviral Resistance

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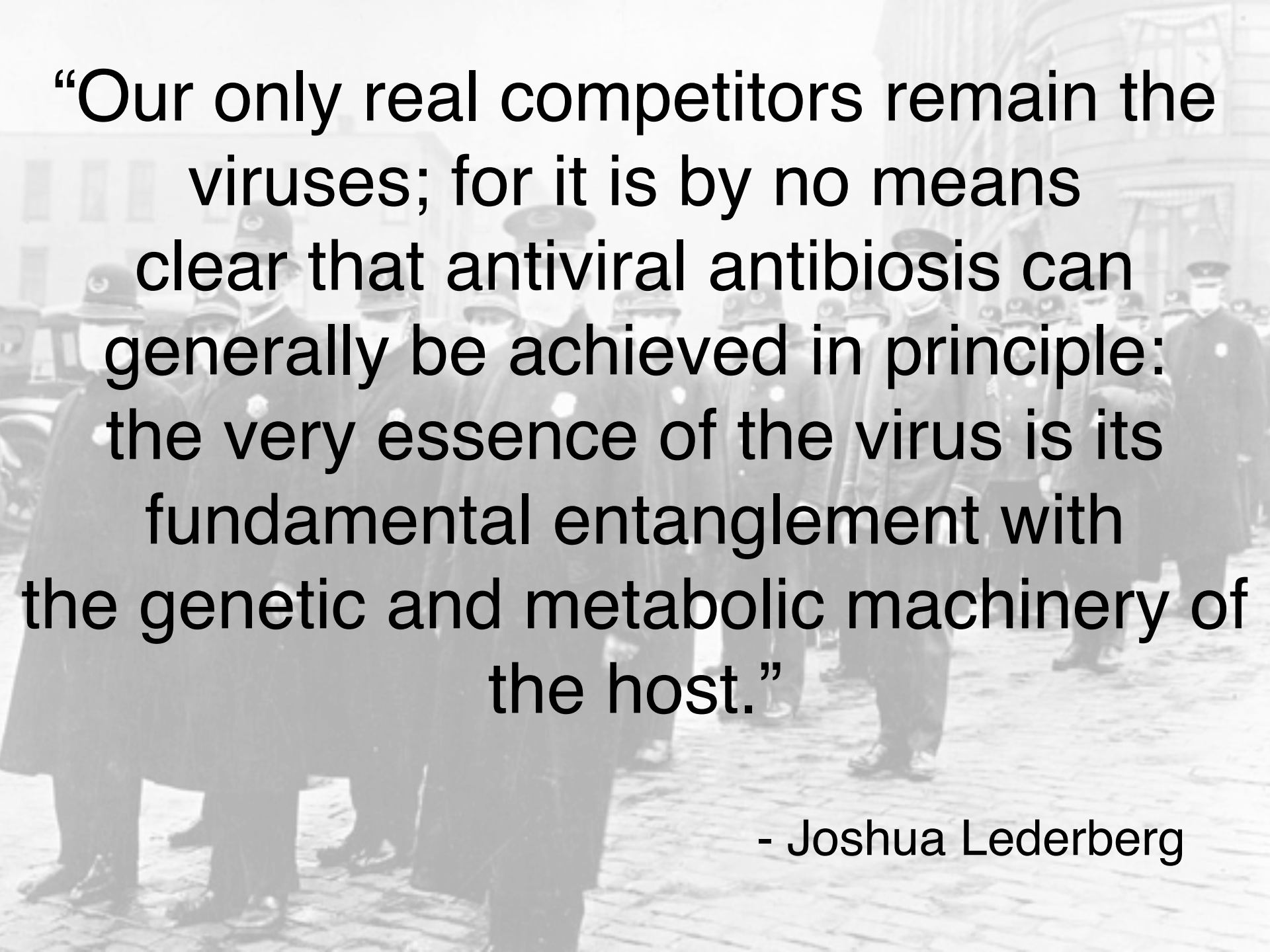
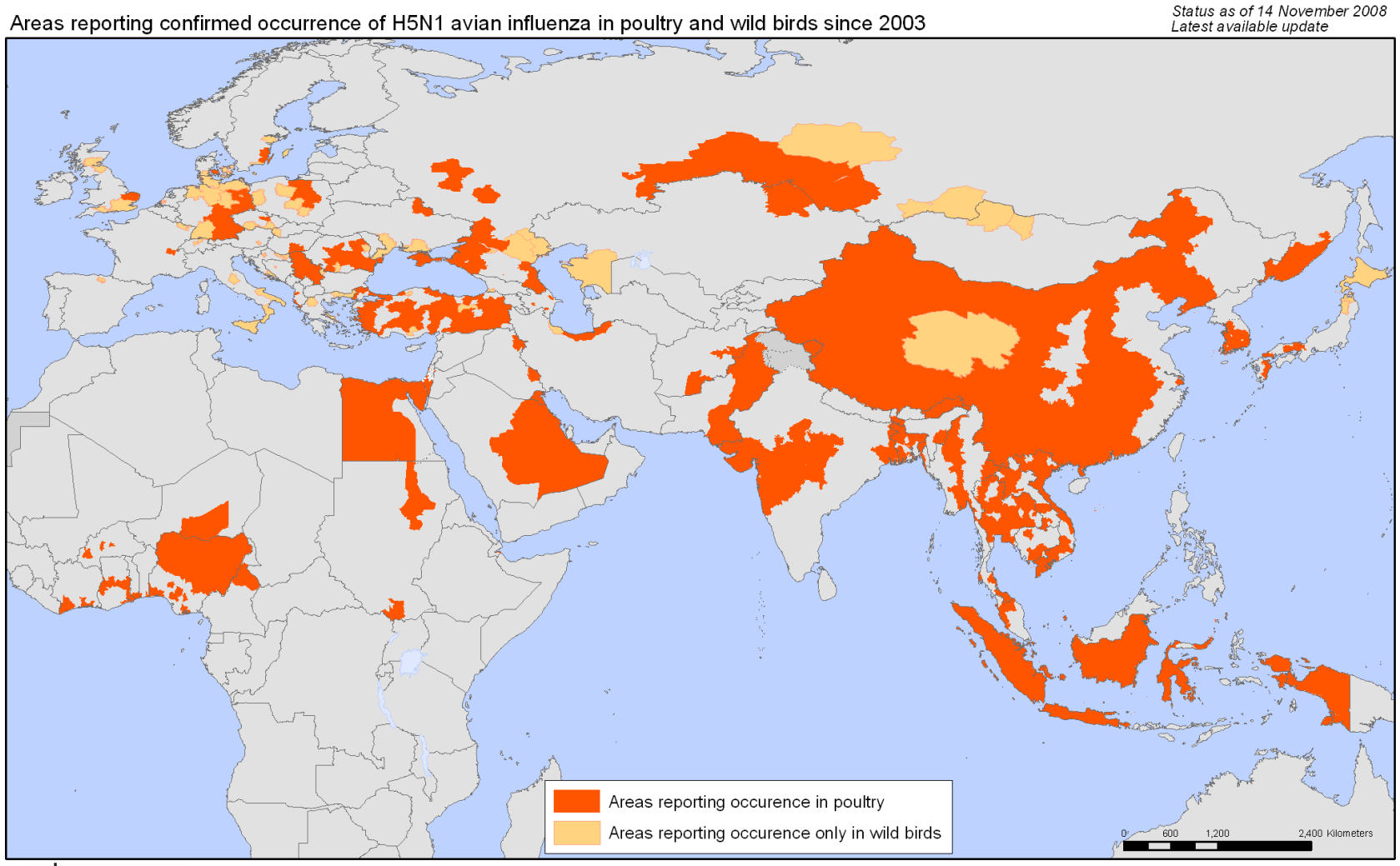


"Our only real competitors remain the viruses; for it is by no means clear that antiviral antibiosis can generally be achieved in principle: the very essence of the virus is its fundamental entanglement with the genetic and metabolic machinery of the host."

- Joshua Lederberg

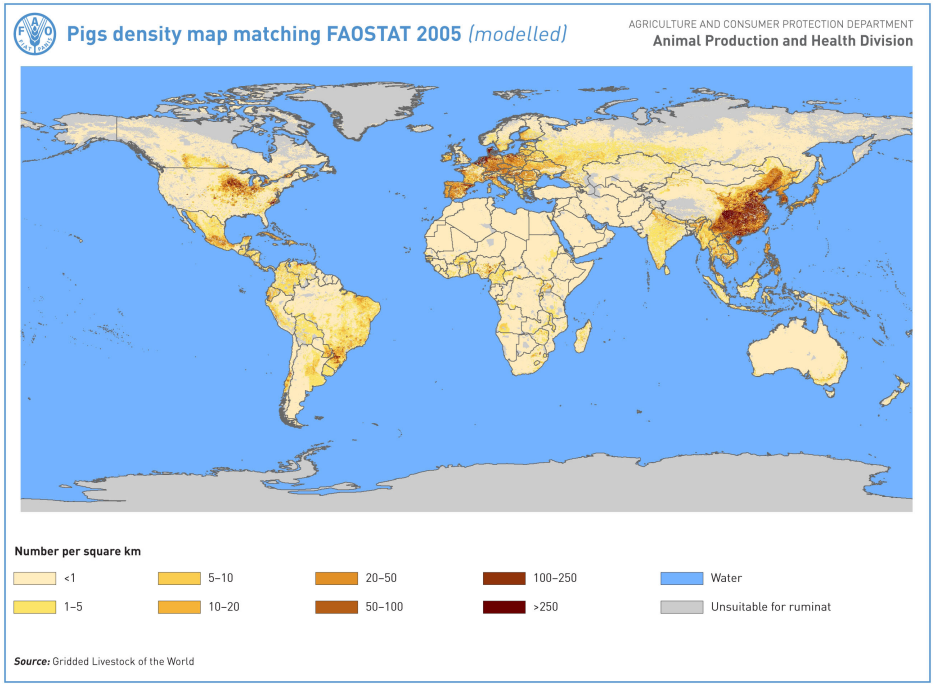
In 2009, we were caught off guard



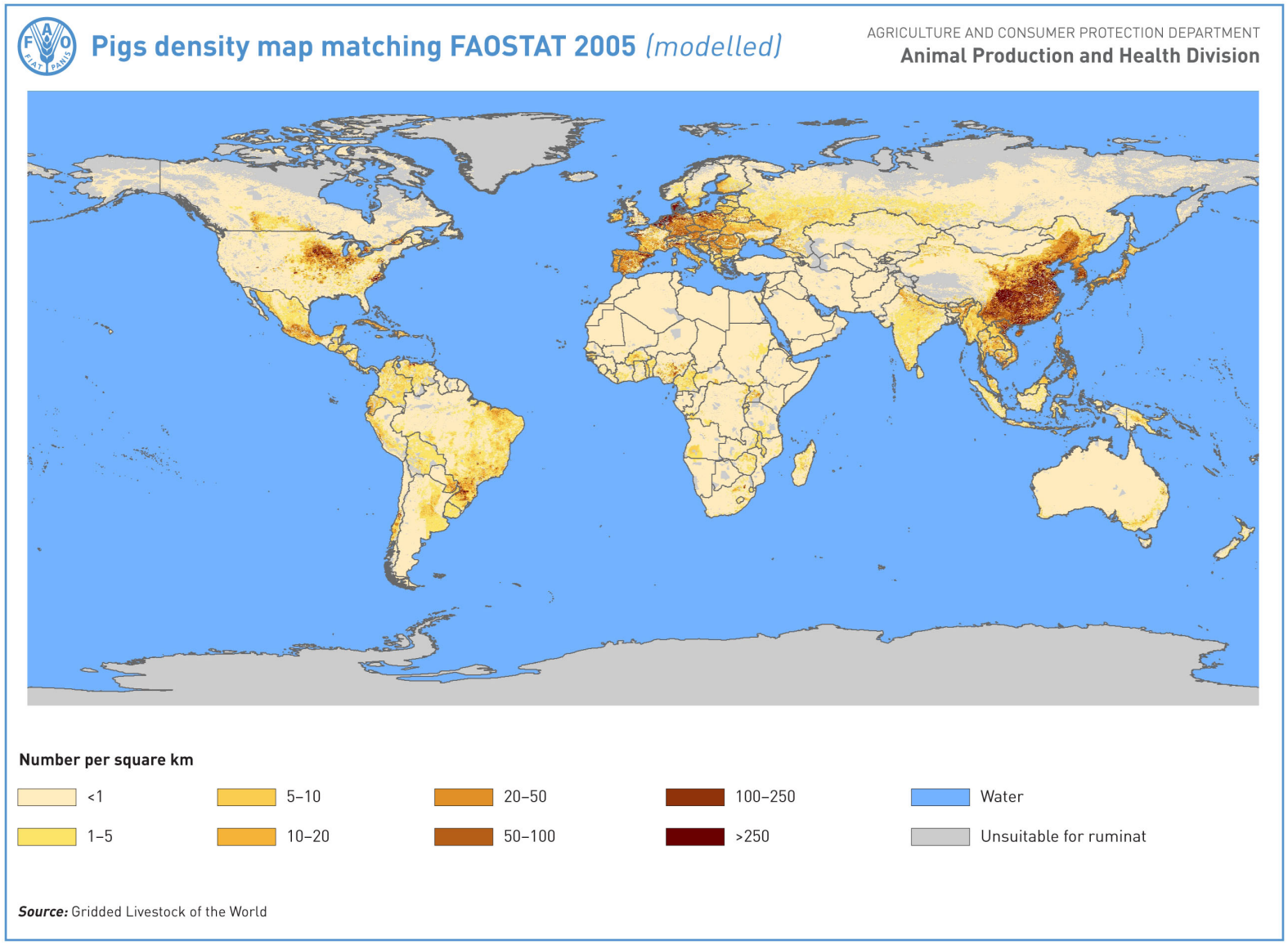
Why?

Air travel

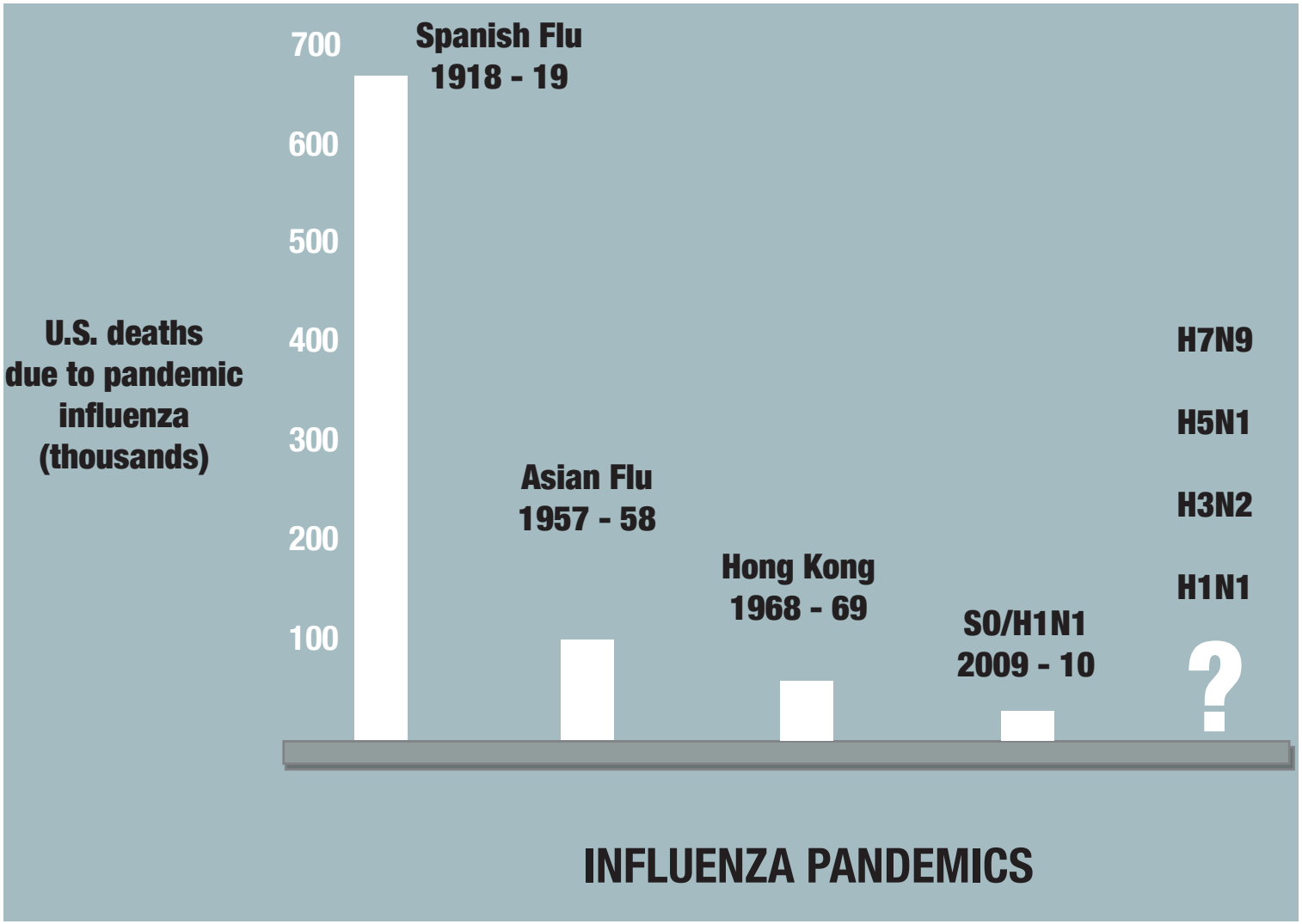
Density of pig farms



Pigs are an evolutionary intermediary



The next pandemic is right around the corner



The next pandemic and antiviral resistance

The next pandemic and antiviral resistance

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ARTICLE

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Influenza A(H7N9) virus gains neuraminidase inhibitor resistance without loss of *in vivo* virulence or transmissibility

Detection of Molecular Markers of Antiviral Resistance in Influenza A (H5N1) Viruses Using a Pyrosequencing Method[∇]

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Where are we going?

1. Biology of antiviral resistance
2. Emerging patterns of antiviral resistance
3. Modeling the evolution of resistance
4. Modeling results
5. Conclusions

Influenza: Basic Biology

RNA Virus
- flu A: 8 segments, 11 genes

3 main genera
- A,B,C

Subtypes determined by envelope glycoproteins
- H's (16, 3 human) and N's (9, 2 human)

Causes recurrent, seasonal epidemics in temperate regions.

Pigs: an evolutionary intermediary?

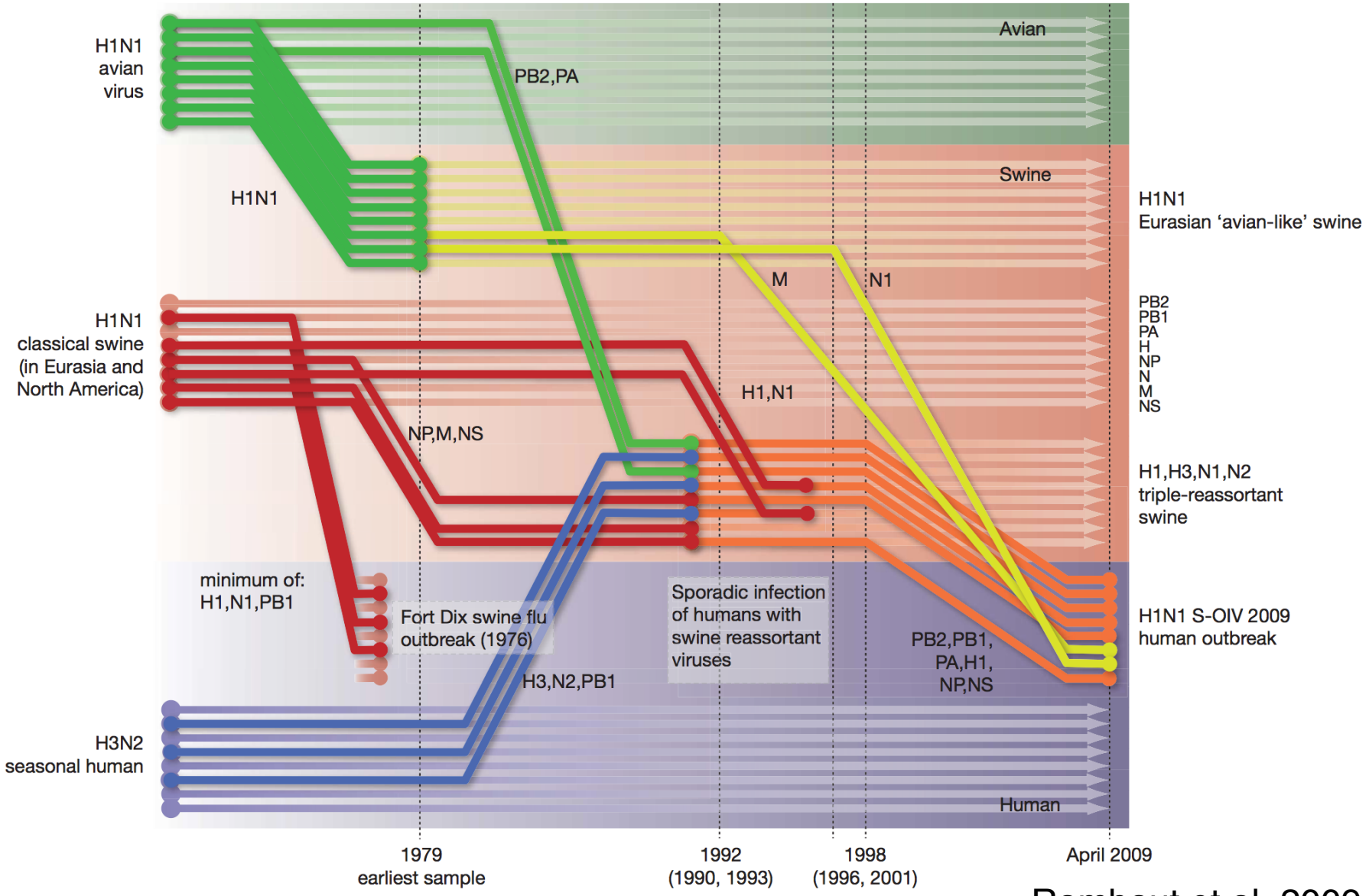
NeuAc-2,3Gal

NeuAc-2,3 & 2,6 Gal

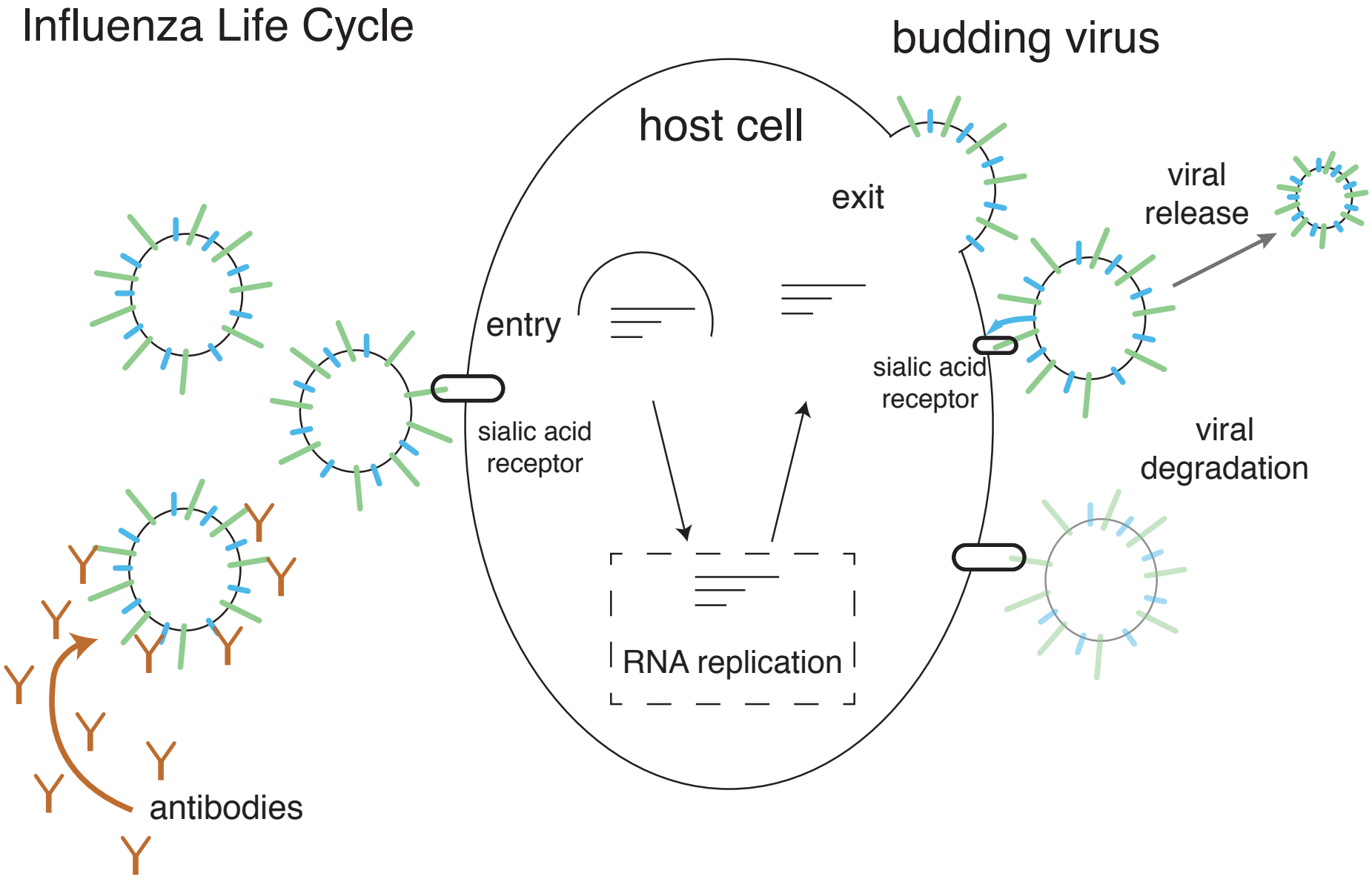
NeuAc-2,6Gal

Zhou et al. 1999

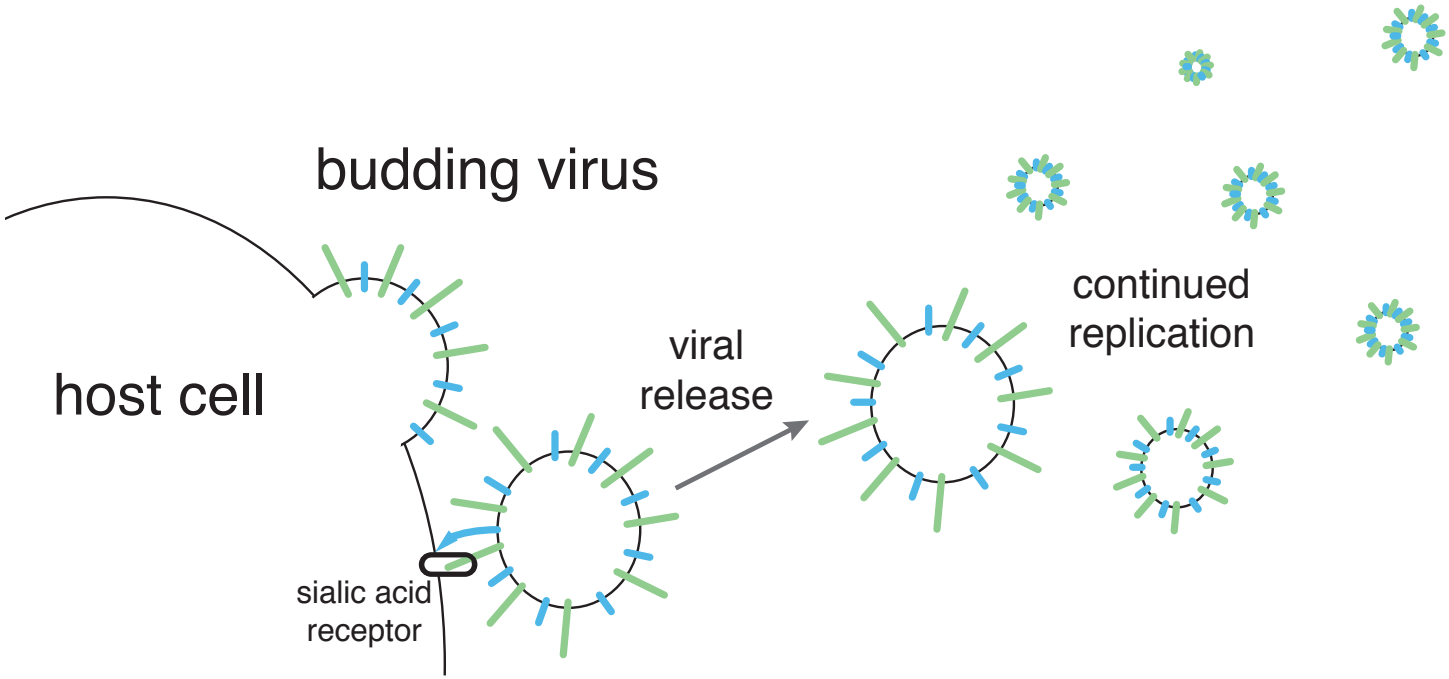
The emergence of H1N1



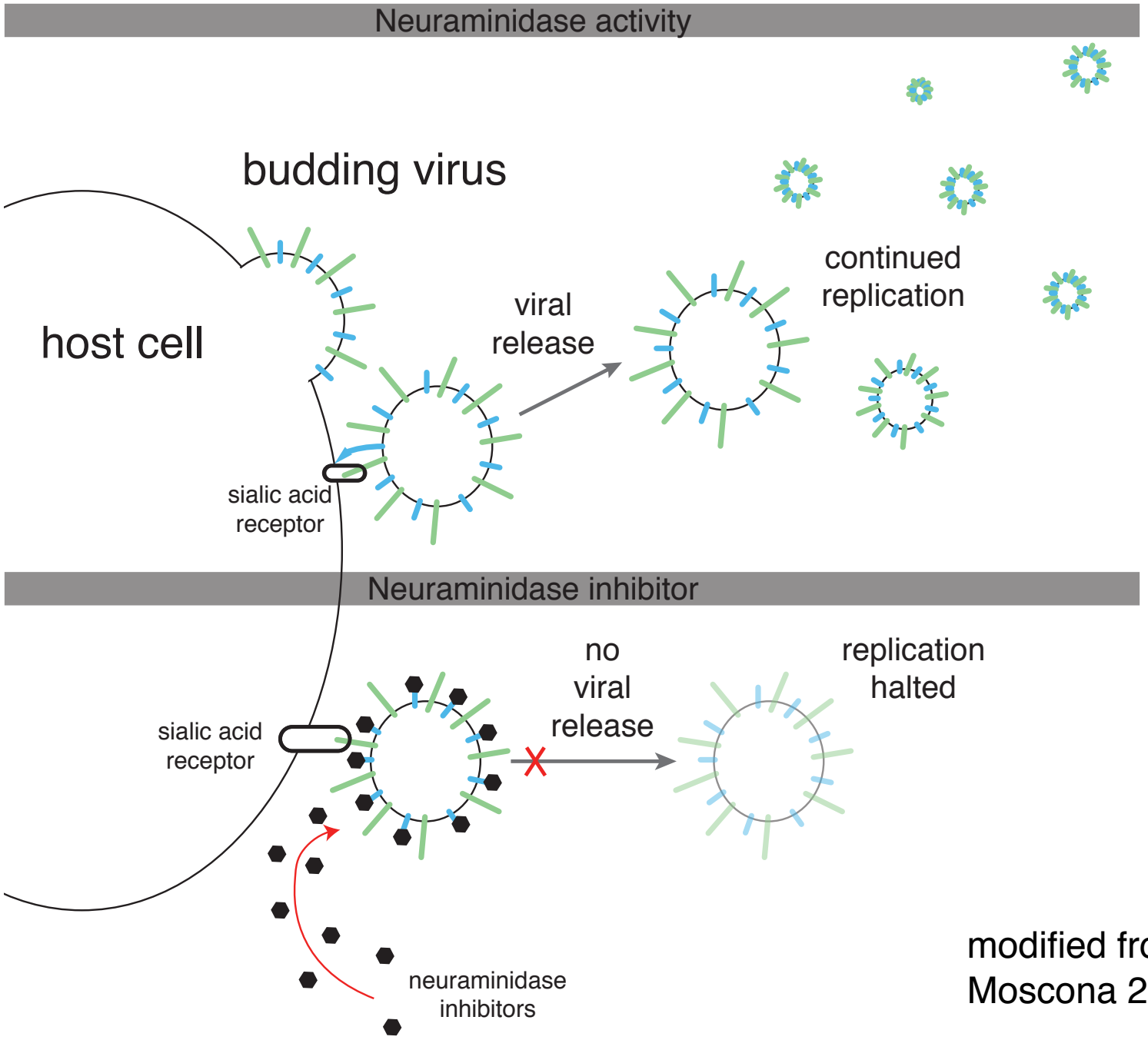
Rambaut et al. 2009


Influenza Life Cycle
budding virus
host cell
exit
viral
release
entry
sialic acid
receptor
sialic acid
receptor
viral
degradation
RNA replication
antibodies

Neuraminidase activity



modified from
Moscona 2005



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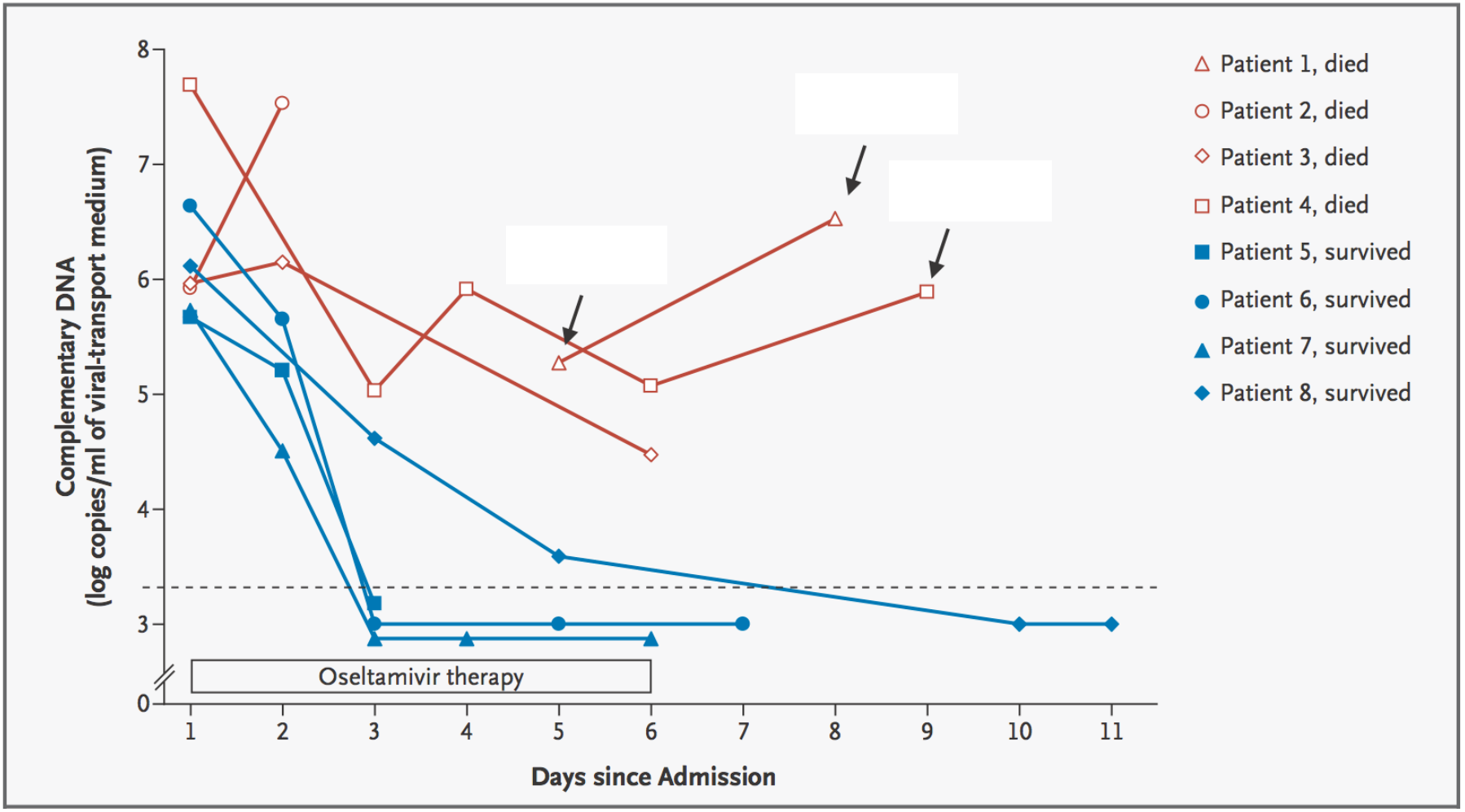
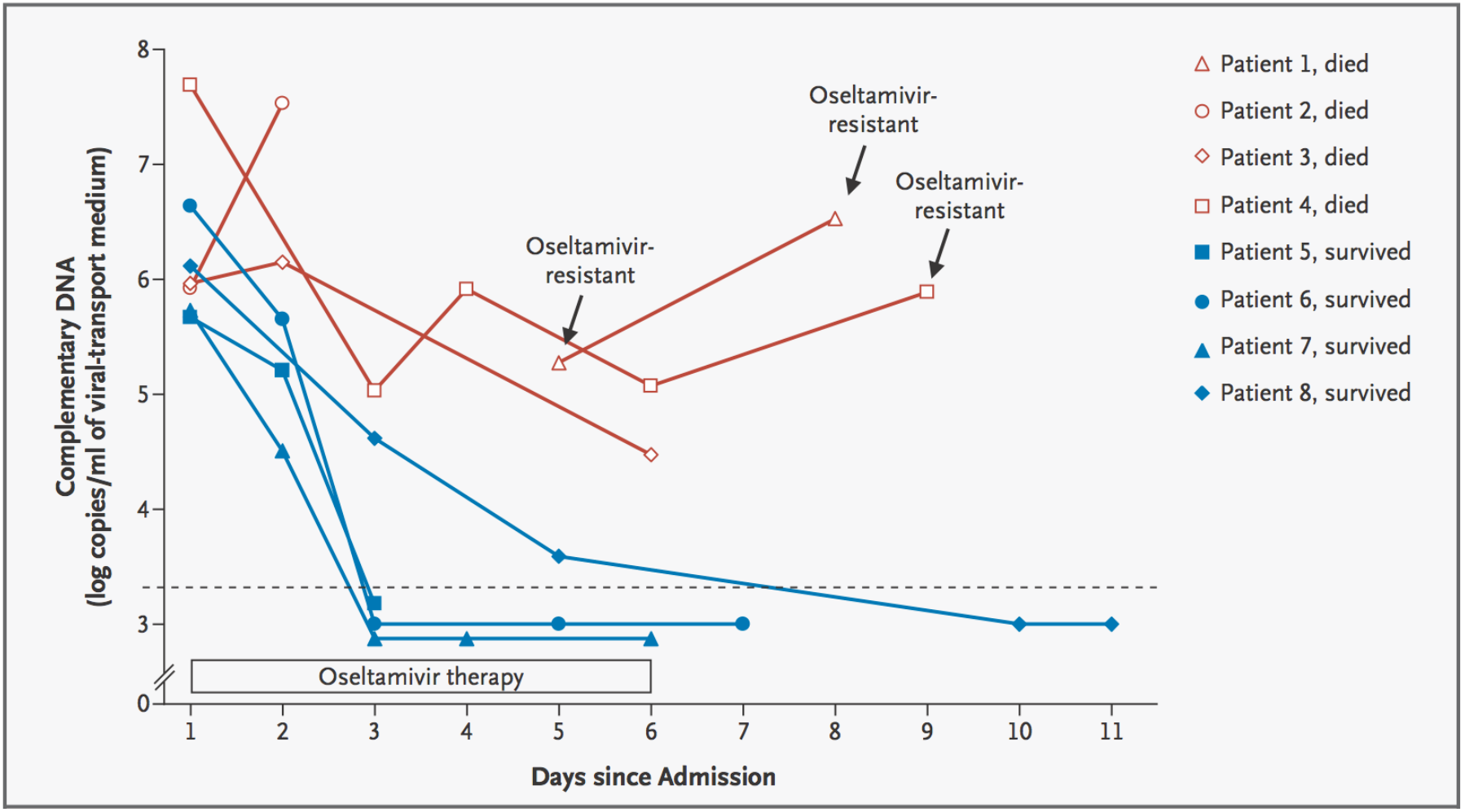
Neuraminidase inhibitors



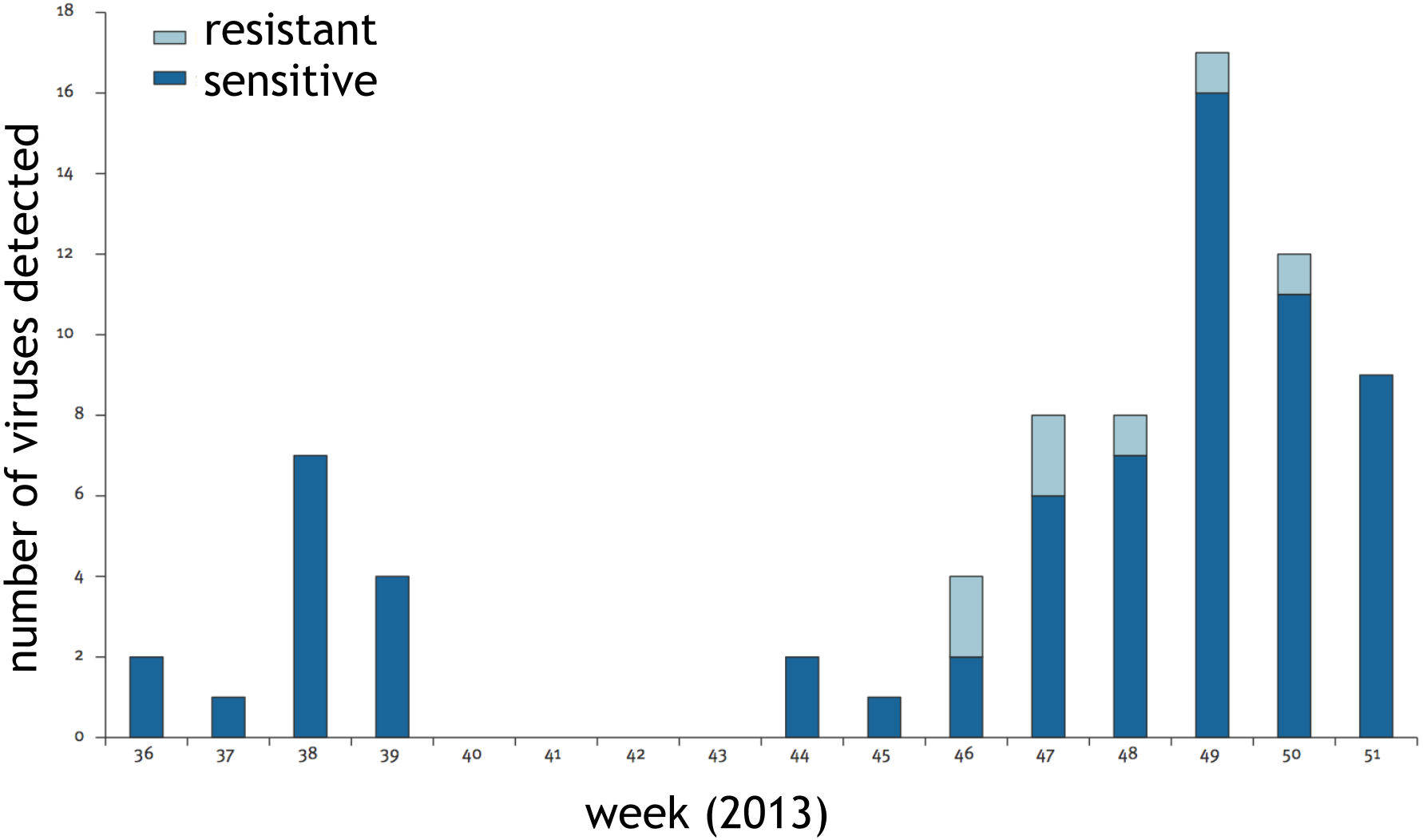
de Jong et al. 2005

Neuraminidase inhibitors



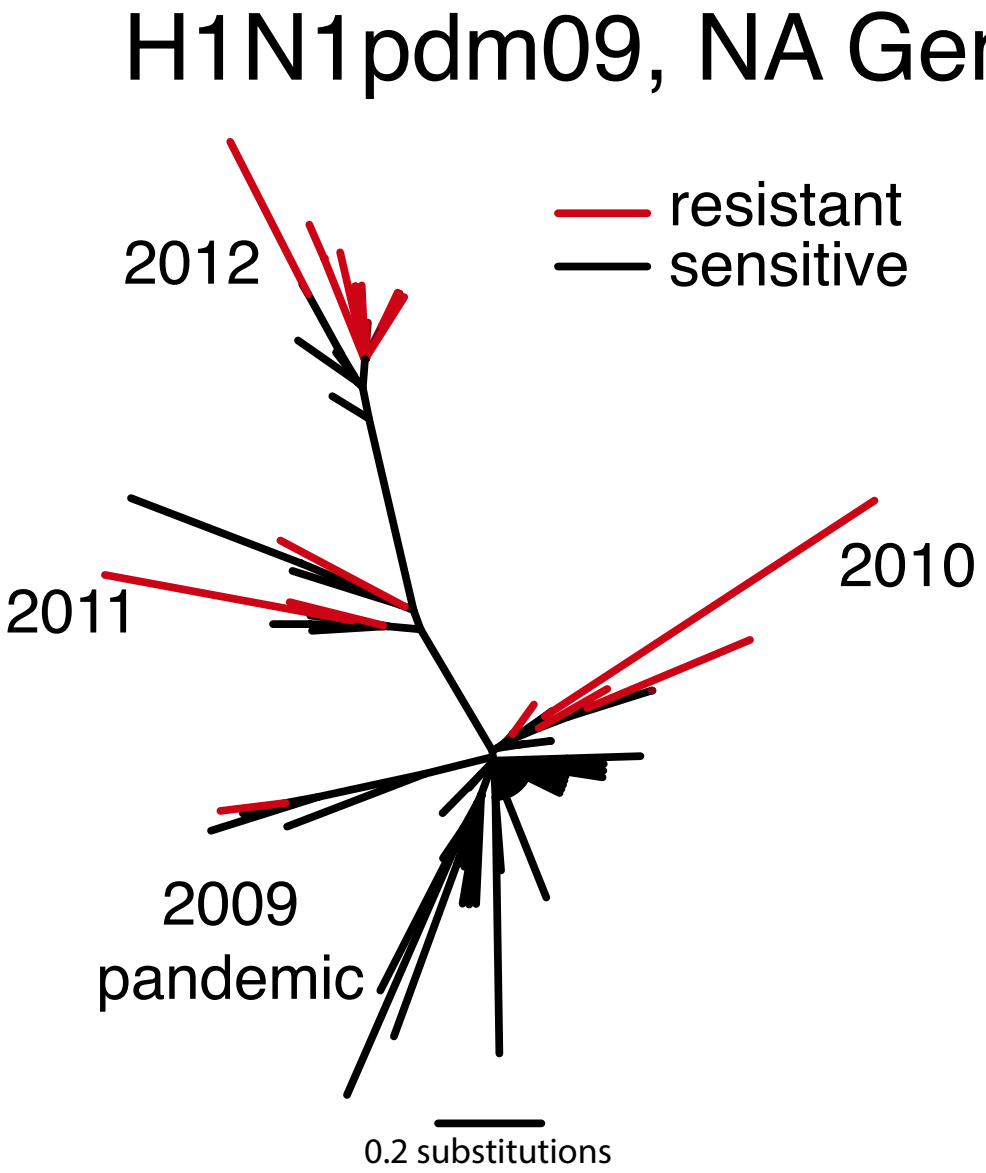
de Jong et al. 2005

Community spread of antiviral resistance

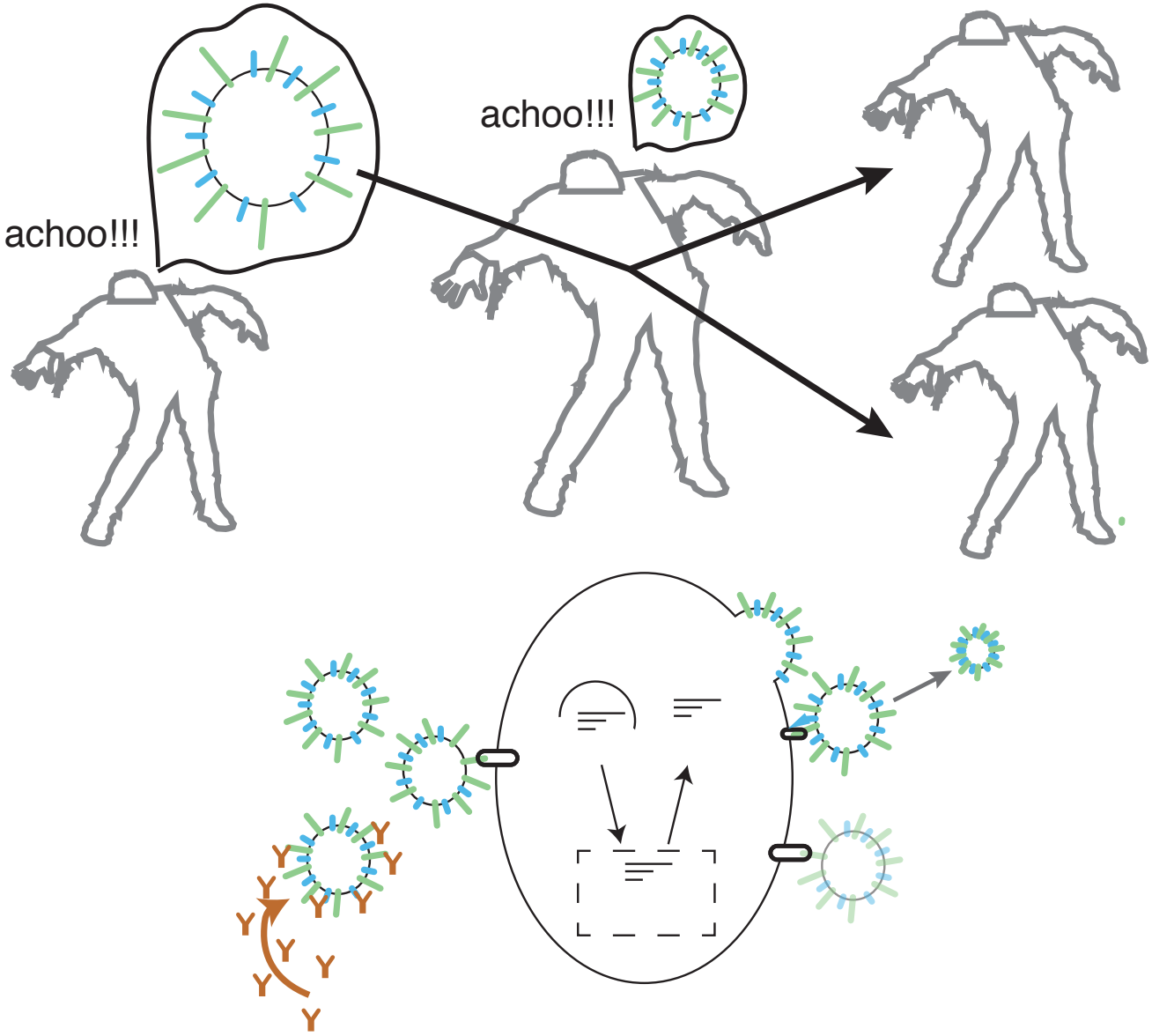


Takashita et al. 2014

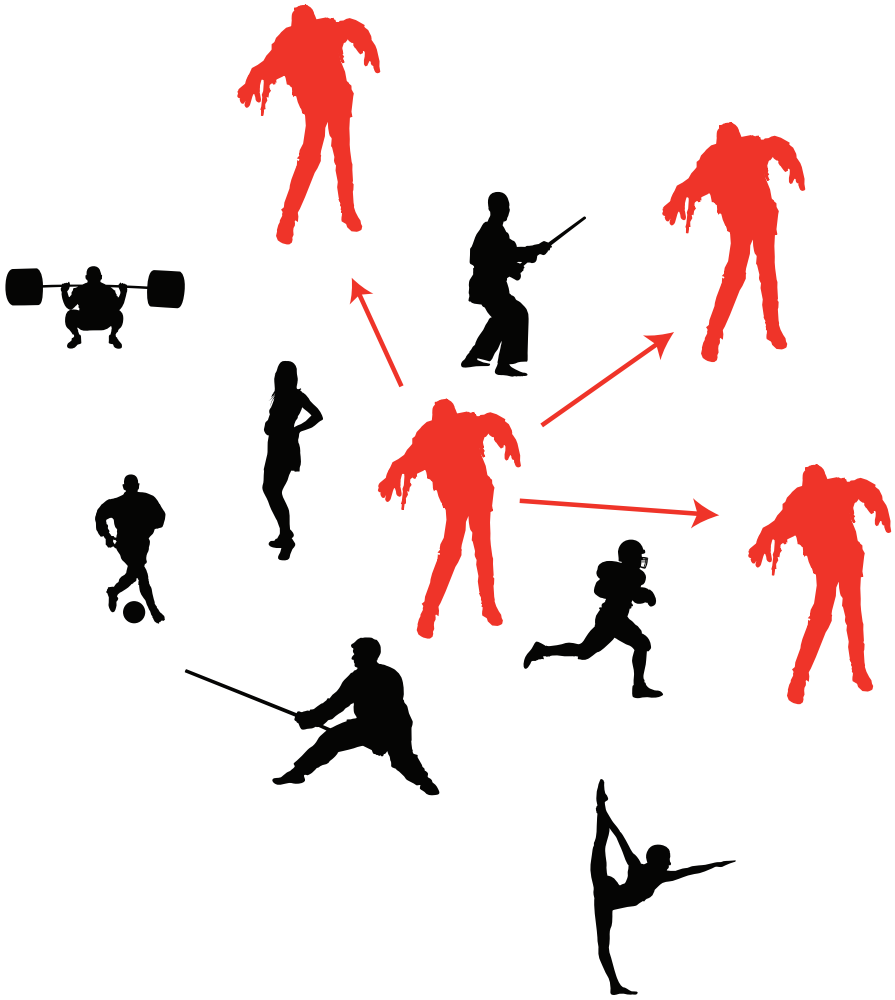
Antiviral resistance phylogenetic pattern



Modeling the evolution of resistance

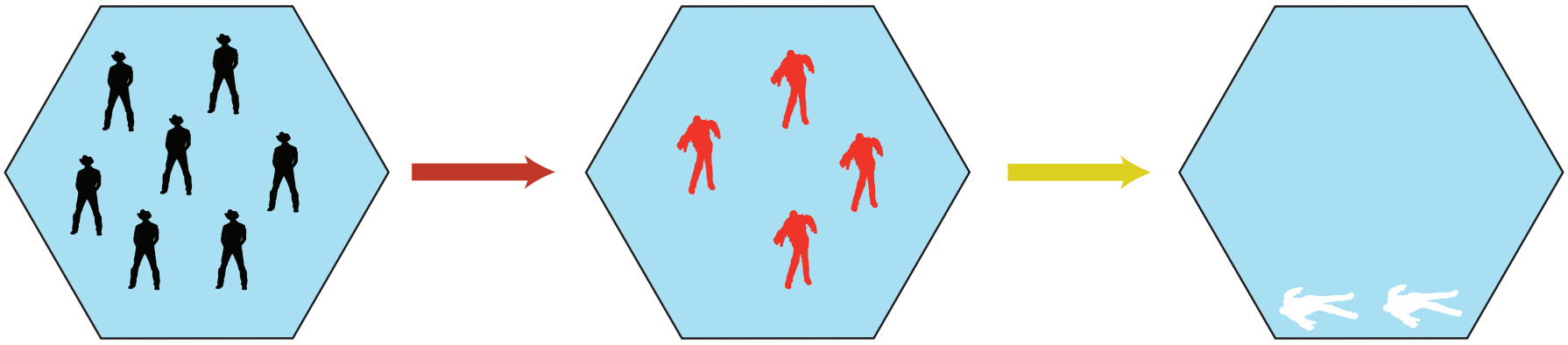


R0: the basic reproductive number



R0 =
Expected number of secondary cases

R0 and the SIR model



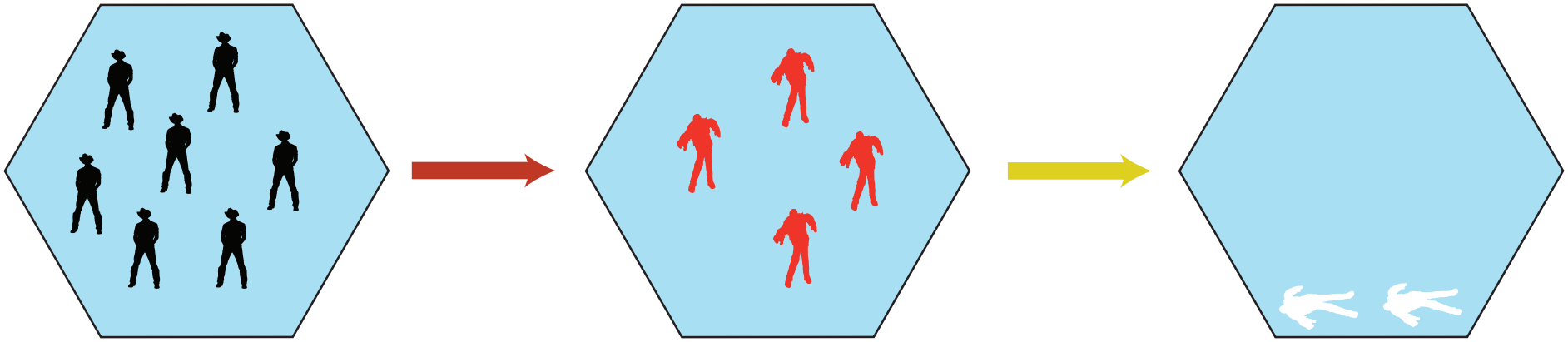
Susceptible (S)

Infected (I)

Removed (R)

Recovery or Death

R0 and the SIR model



Susceptible (S)

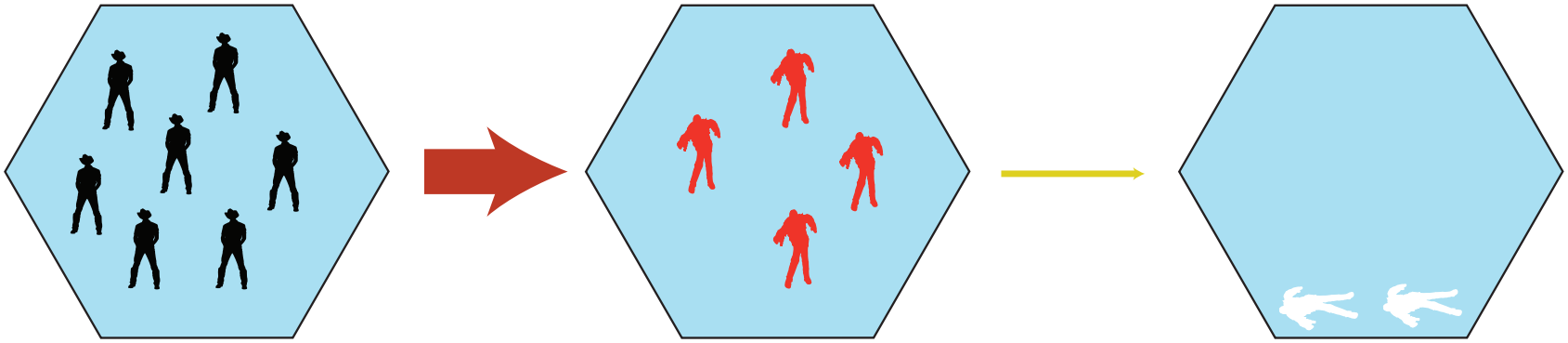
Infected (I)

Removed (R)

Recovery or Death

$$R0 = \frac{\text{Infection Rate}}{\text{Recovery +Mortality}} = \frac{\rightarrow}{\rightarrow}$$

R0 and the SIR model



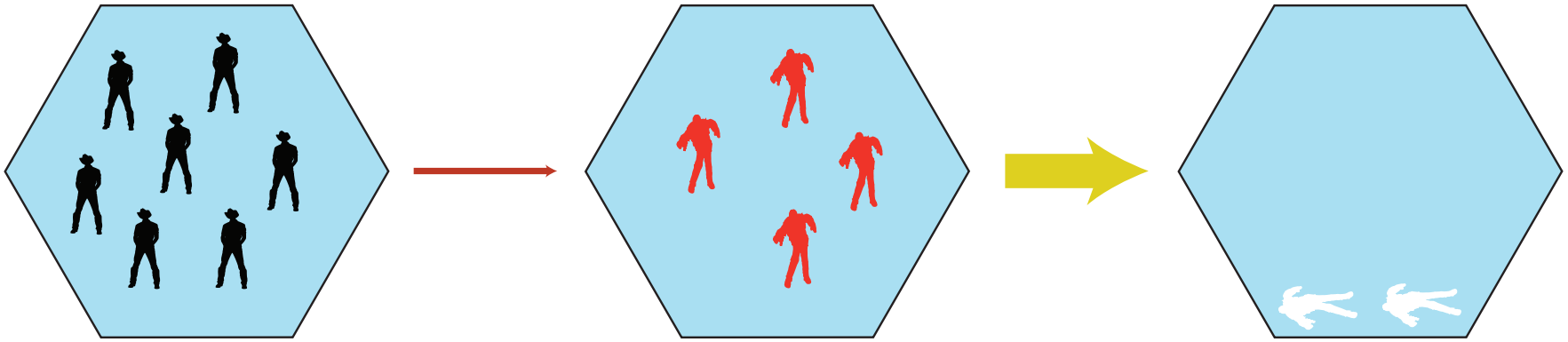
Susceptible (S)

Infected (I)

Removed (R)
Recovery or Death

$$R0 = \frac{\text{Infection Rate}}{\text{Recovery + Mortality}} = \frac{\rightarrow}{\rightarrow} = \text{We're Zombies}$$

R0 and the SIR model



Susceptible (S)

Infected (I)

Removed (R)
Recovery or Death

$$R0 = \frac{\text{Infection Rate}}{\text{Recovery + Mortality}} = \frac{\rightarrow}{\rightarrow} = \text{We're Fine}$$

The players

Four types of host

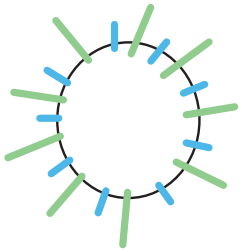
strong immune response

strong immune response
treated with antivirals

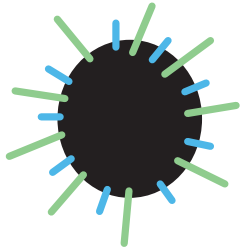
weak immune response

weak immune response
treated with antivirals

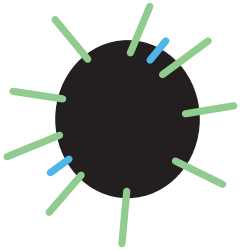
Three types of virus



sensitive to antivirals

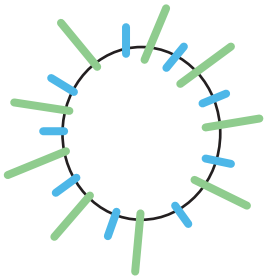


resistant to antivirals
no cost to resistance

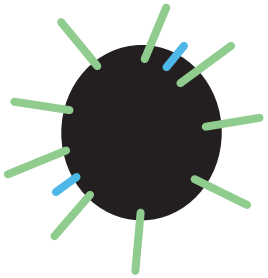


resistant to antivirals
cost to resistance

The cost of antiviral resistance



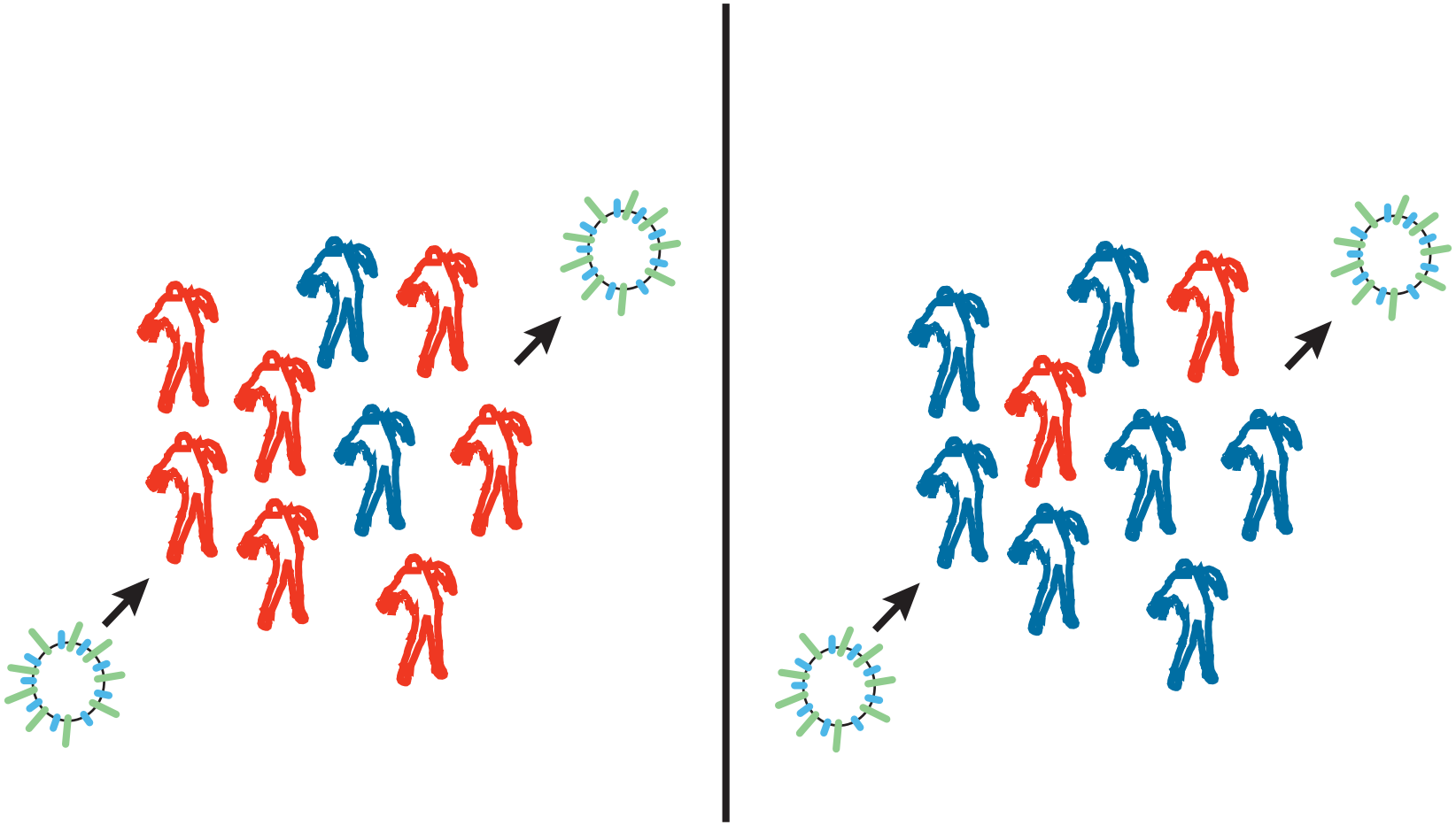
sensitive to antivirals



resistant to antivirals
cost to resistance

Bloom et al. 2010
Butler et al. 2014

Evolution of the viral surface proteins

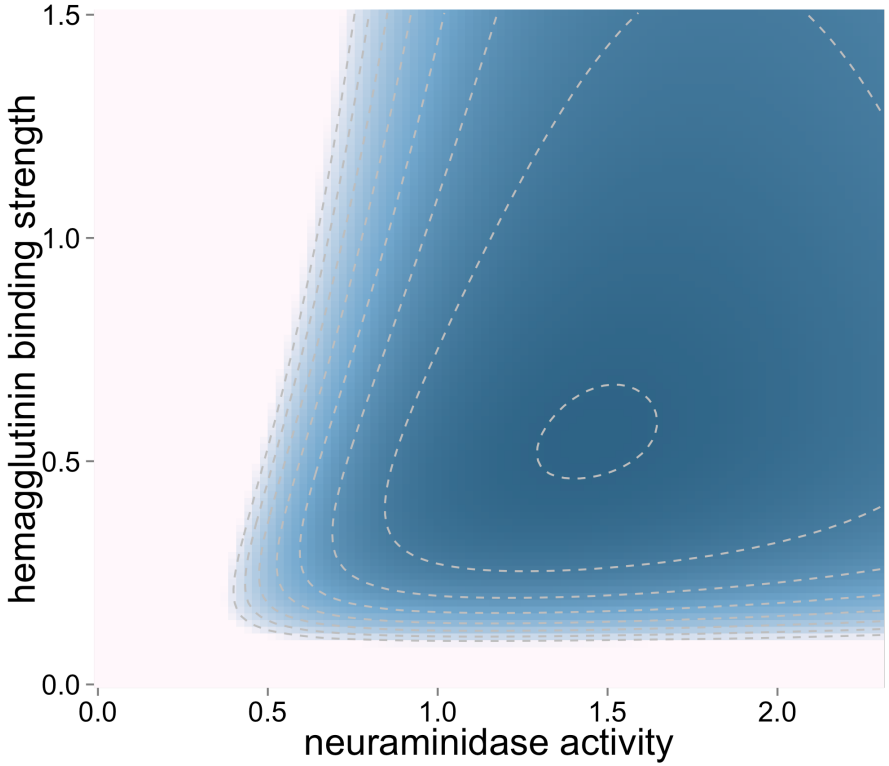


higher average immunity

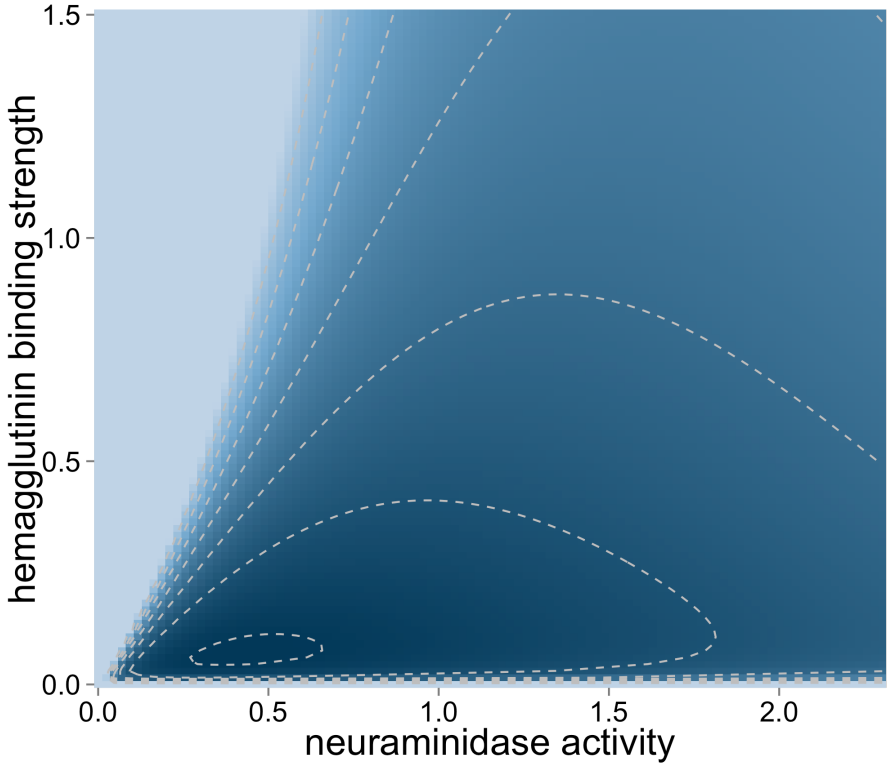
lower average immunity

Evolution of the viral surface proteins

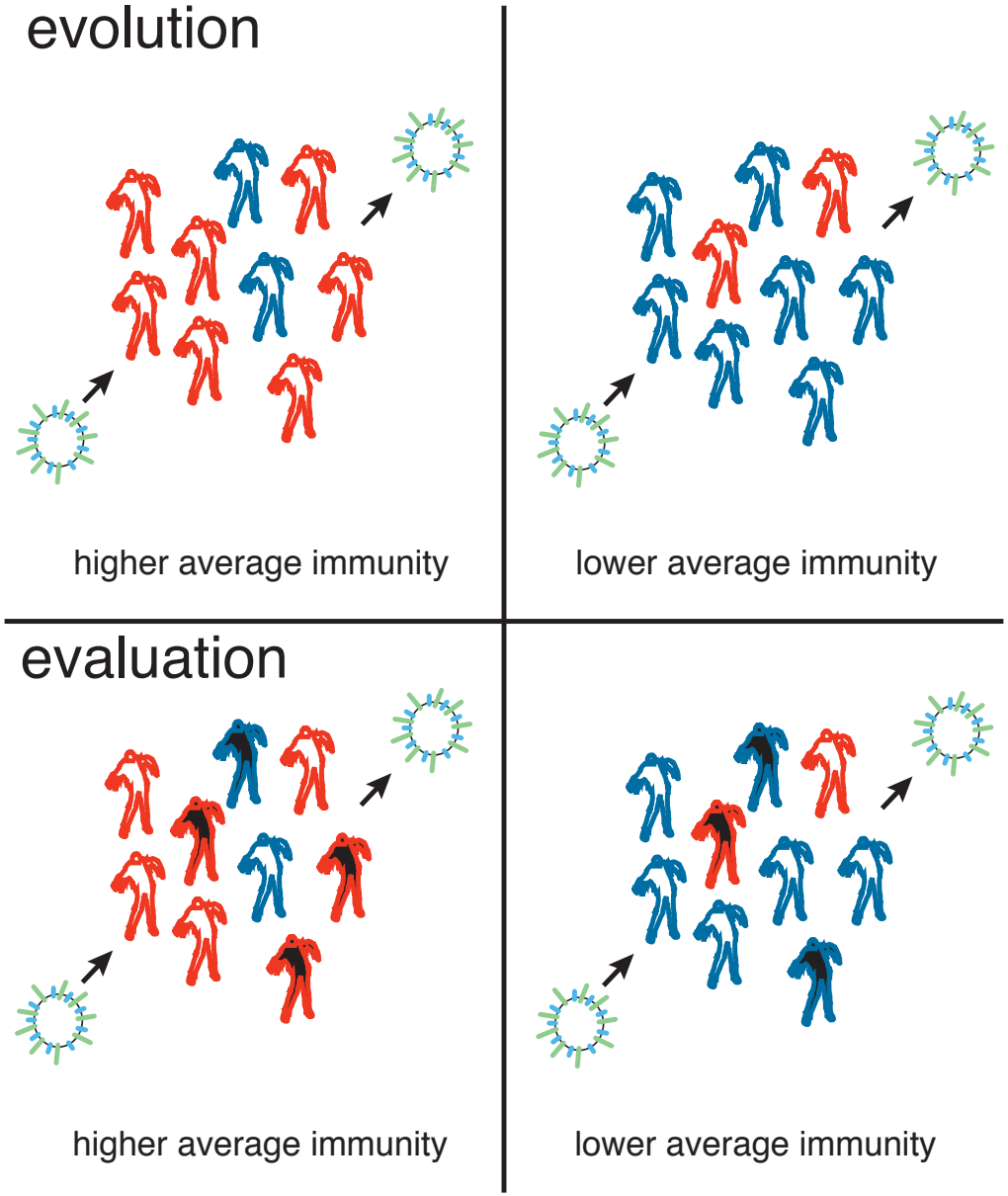
high immune host



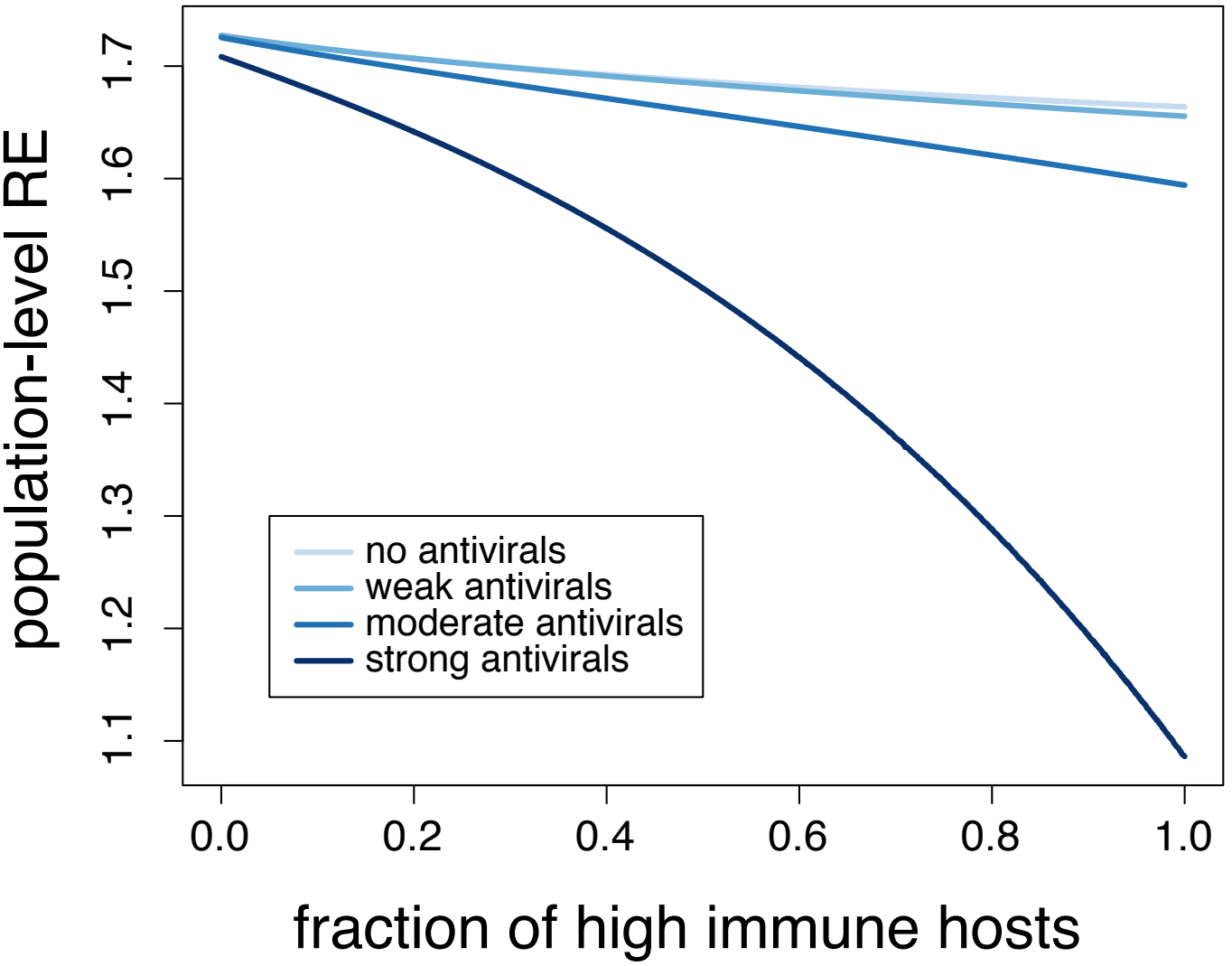
low immune host



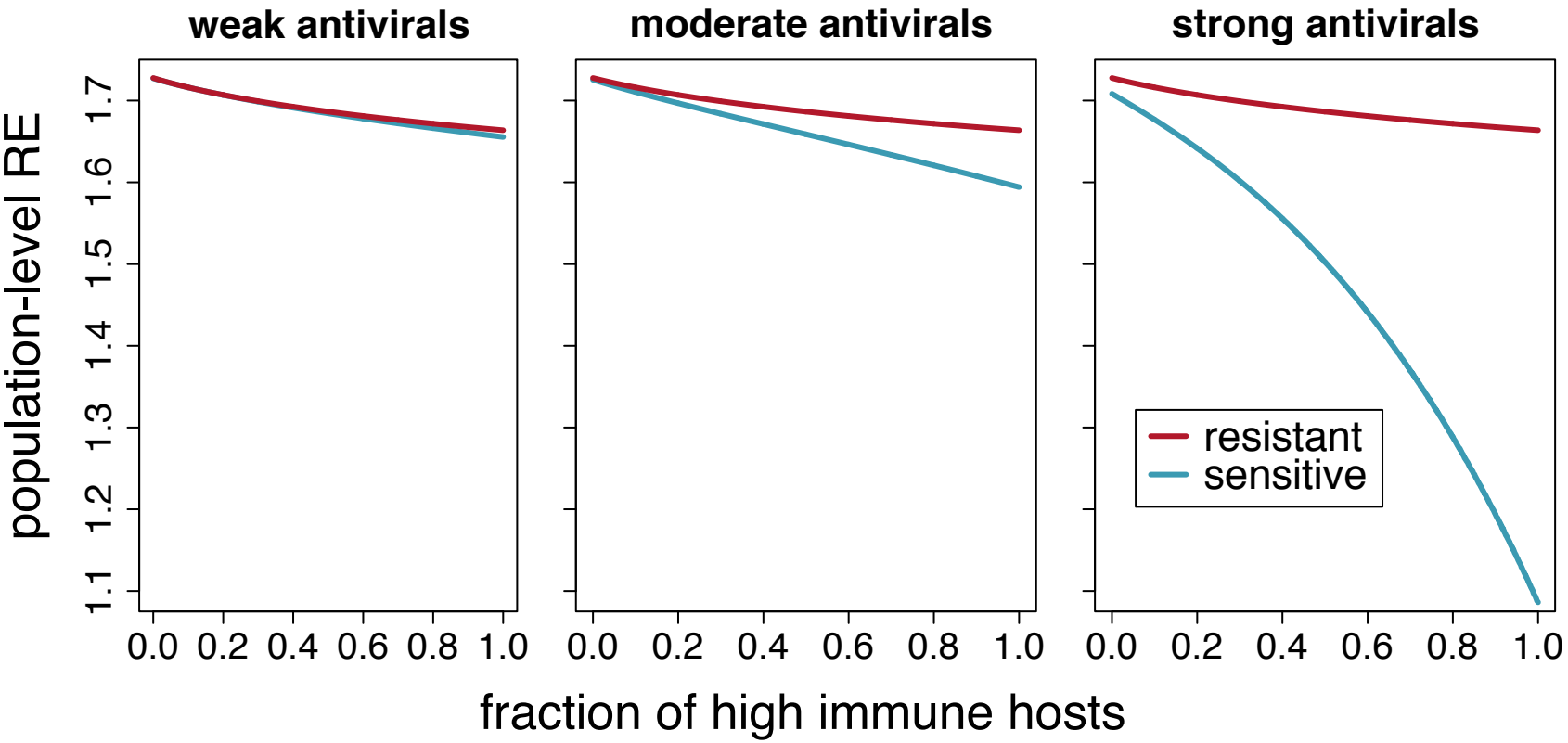
Calculating viral fitness



The effect of antivirals



The evolution of resistance (no cost)



Why consider no cost to resistance?

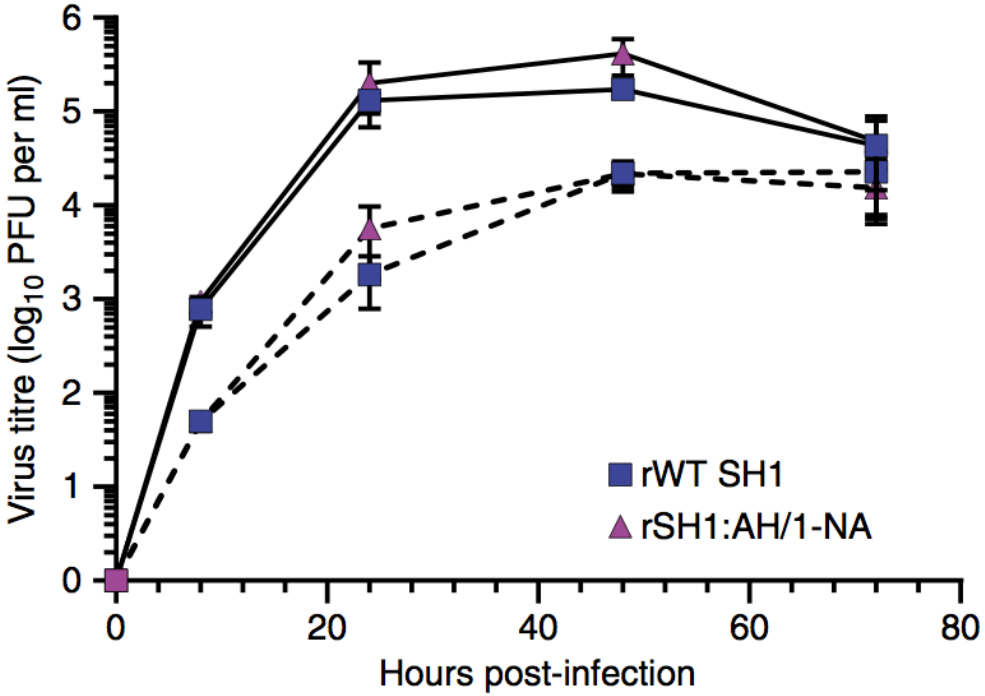
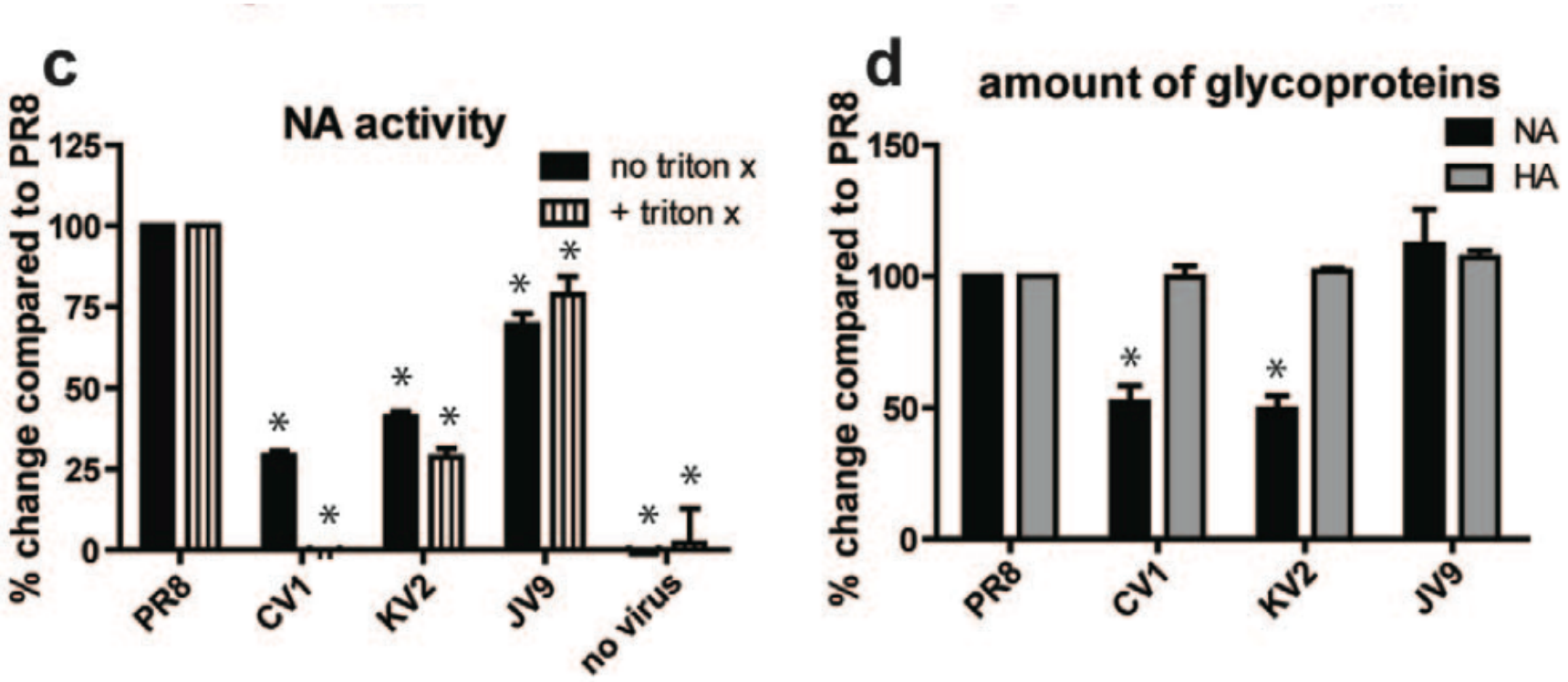


Figure 1 | Oseltamivir resistance does not affect viral replication in human tracheobronchial epithelial cells. Differentiated human tracheobronchial epithelial cells were infected with rSH/1 (squares) or rSH/1:AH/1-NA (triangles) viruses, at an MOI of 0.01, at either 33 °C (dashed line) or 37 °C (solid line). At 8, 24, 48 and 72 h post infection, cells were washed with PBS/BSA and the concentration of virus in each wash sample was determined by standard plaque assay on MDCK cells. The hTBE growth curves were performed in triplicate. Error bars represent s.d.

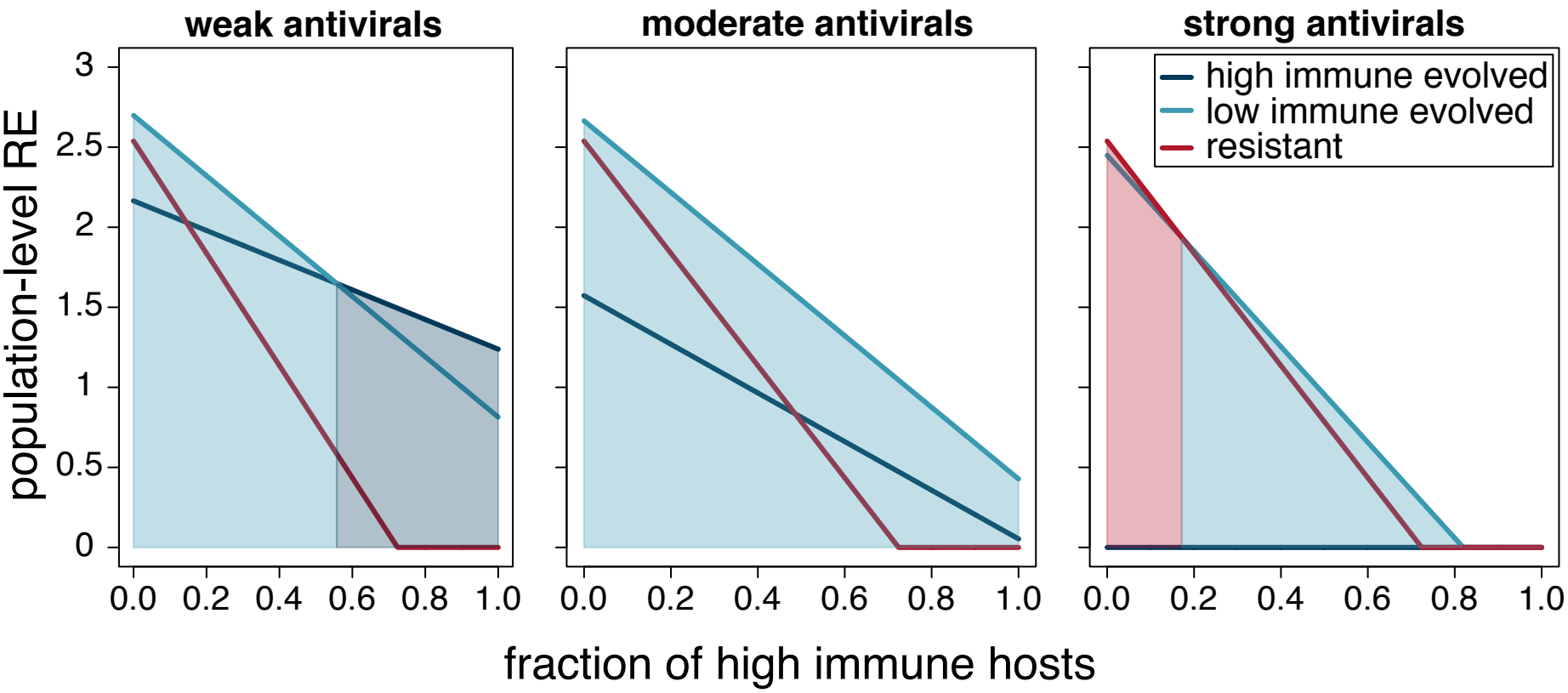
Hai et al. 2013

Compensatory change 1: Hemagglutinin

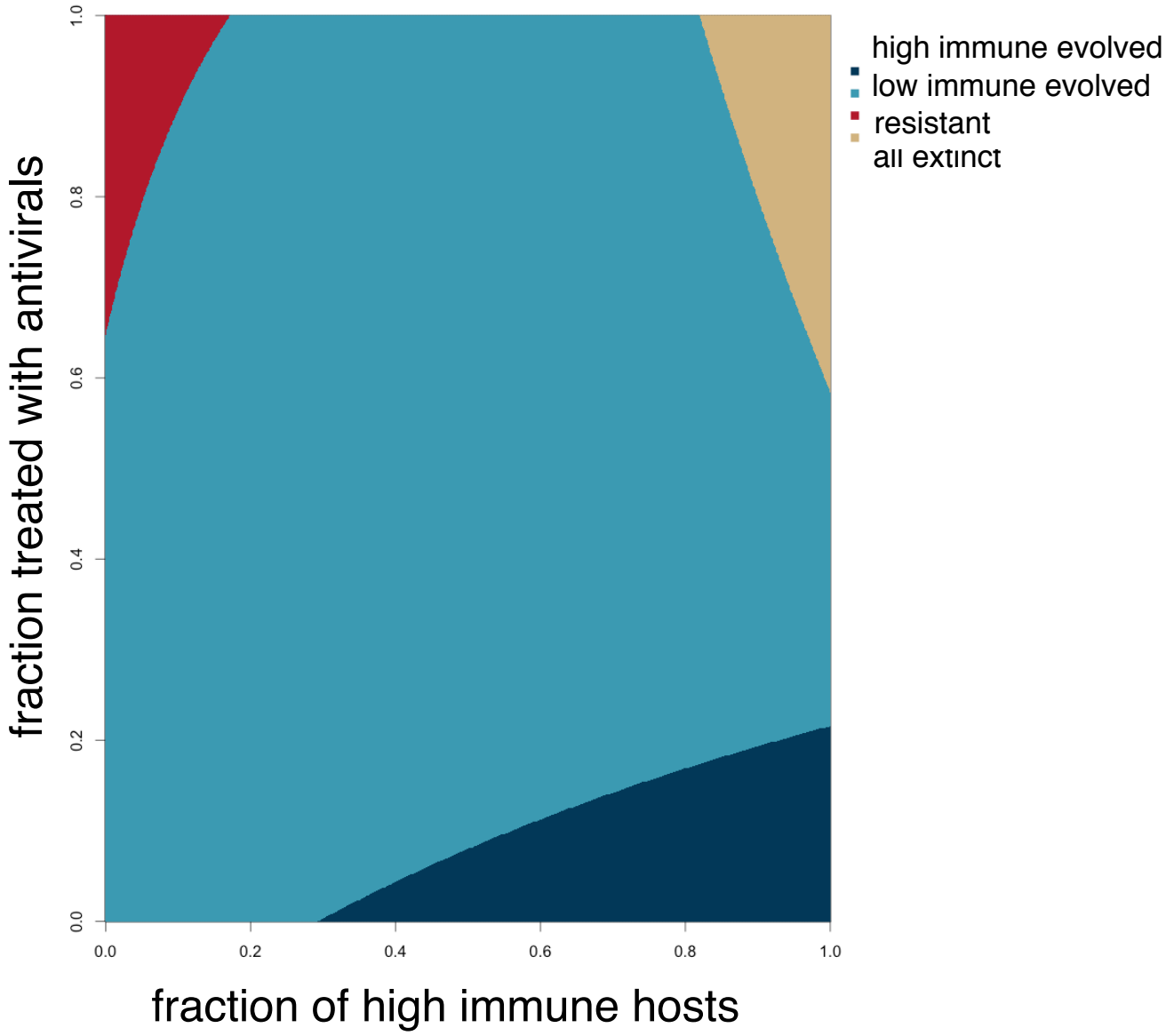


Hensley et al. 2011

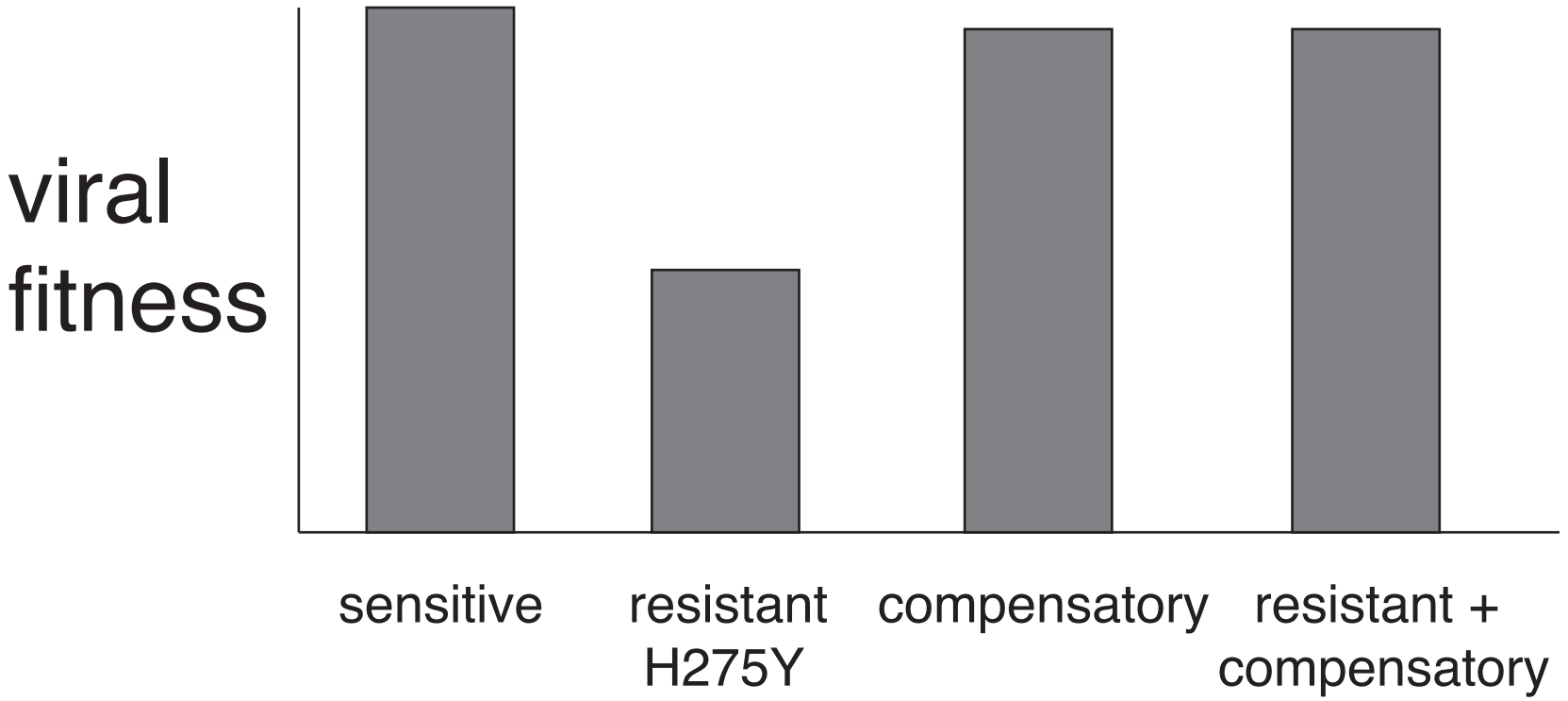
Compensatory change 1: Hemagglutinin



Compensatory change 1: Hemagglutinin

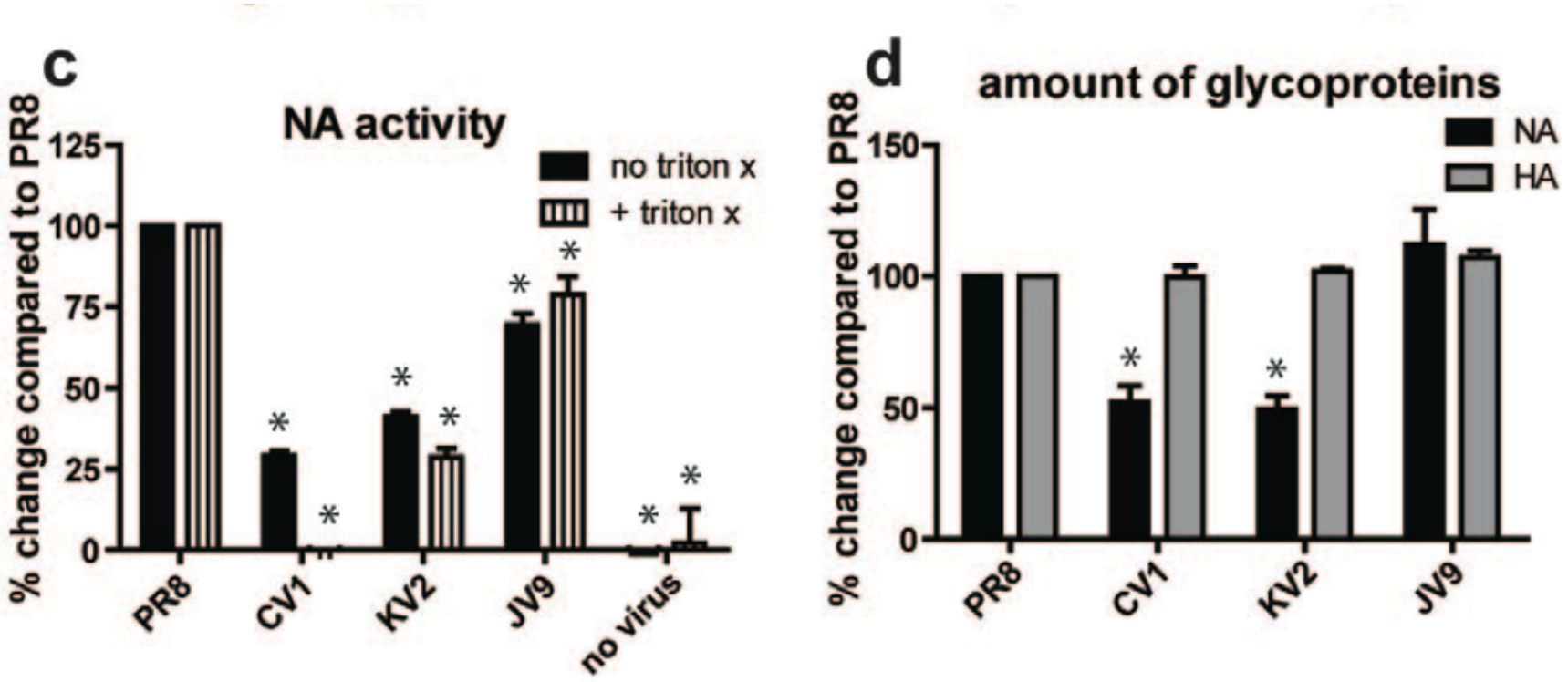


Compensatory change 2: Neuraminidase



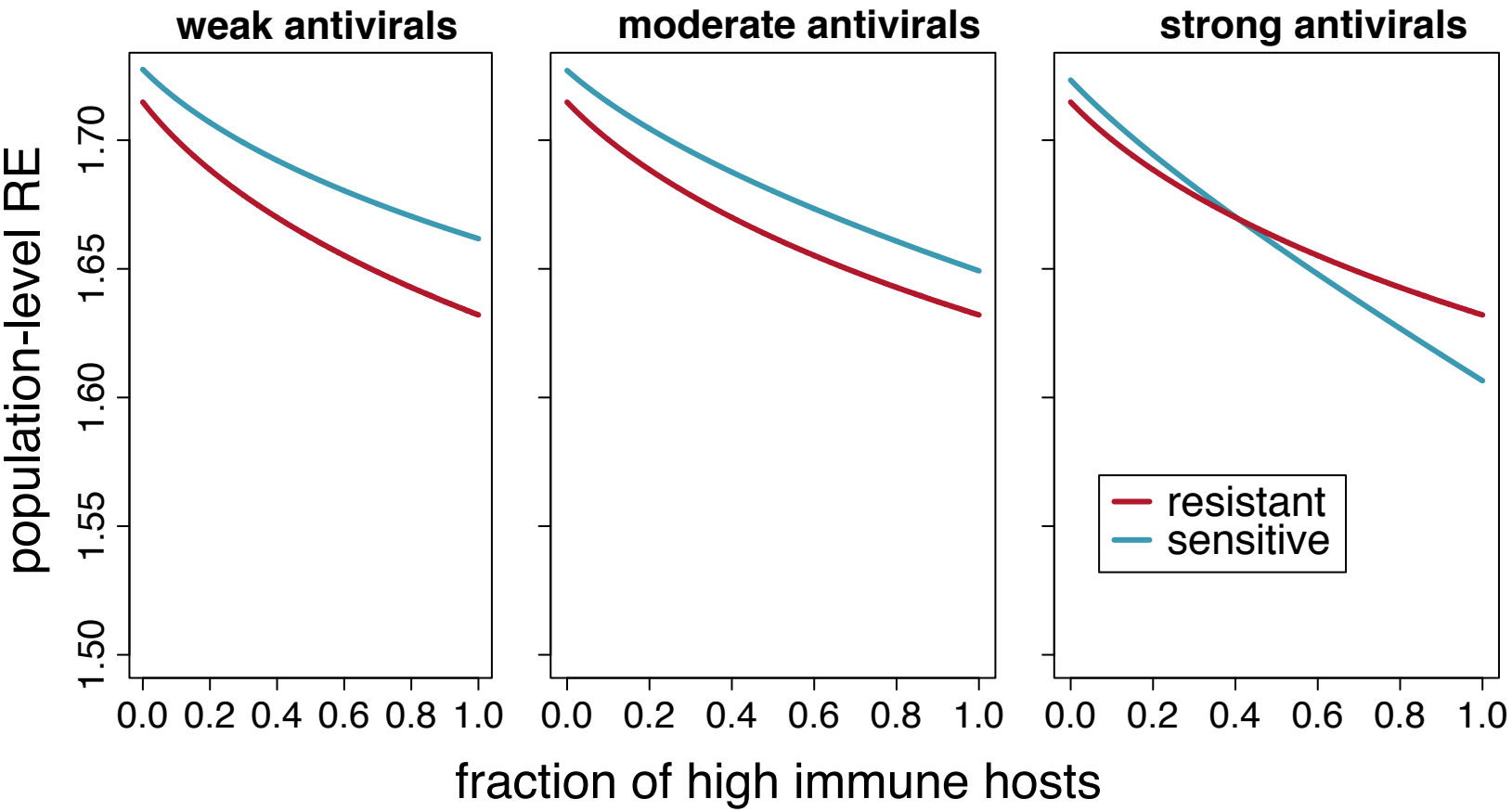
modified from
Butler et al. 2014

Compensatory change 2: Neuraminidase



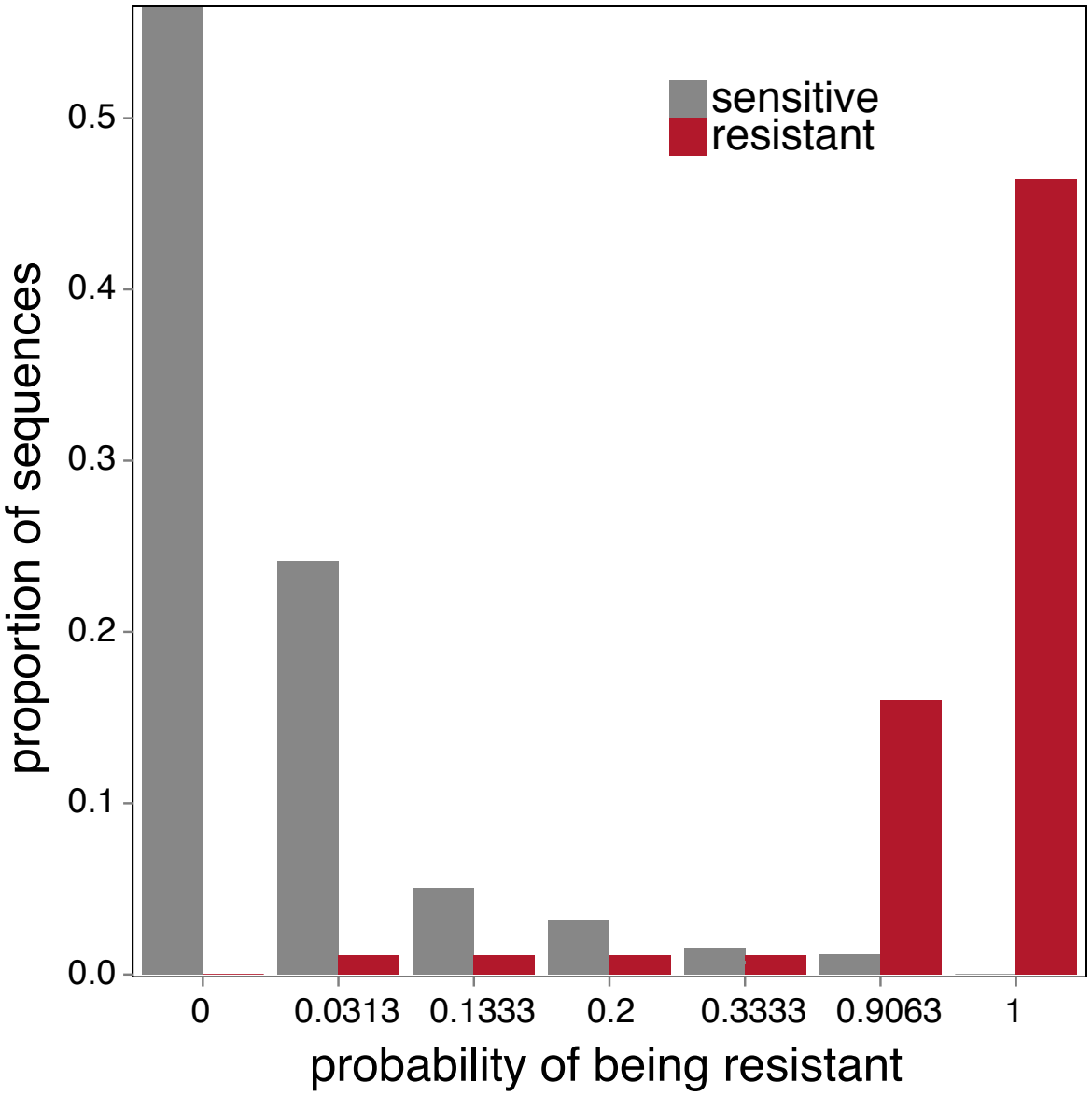
Hensley et al. 2011

Compensatory change 2: Neuraminidase



Variation in resistance mutations

Variation in resistance mutations



Conclusions

Questions?

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