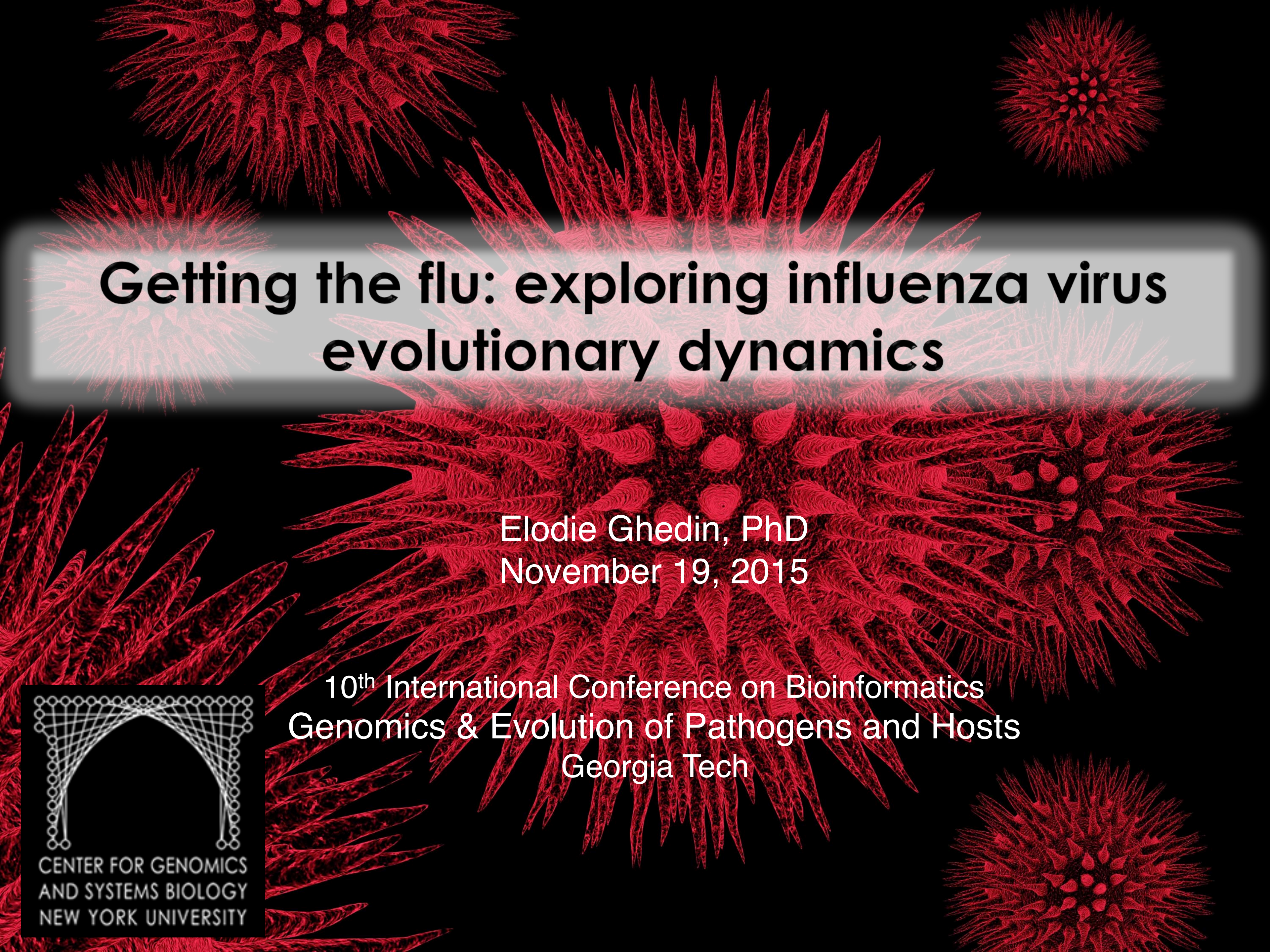
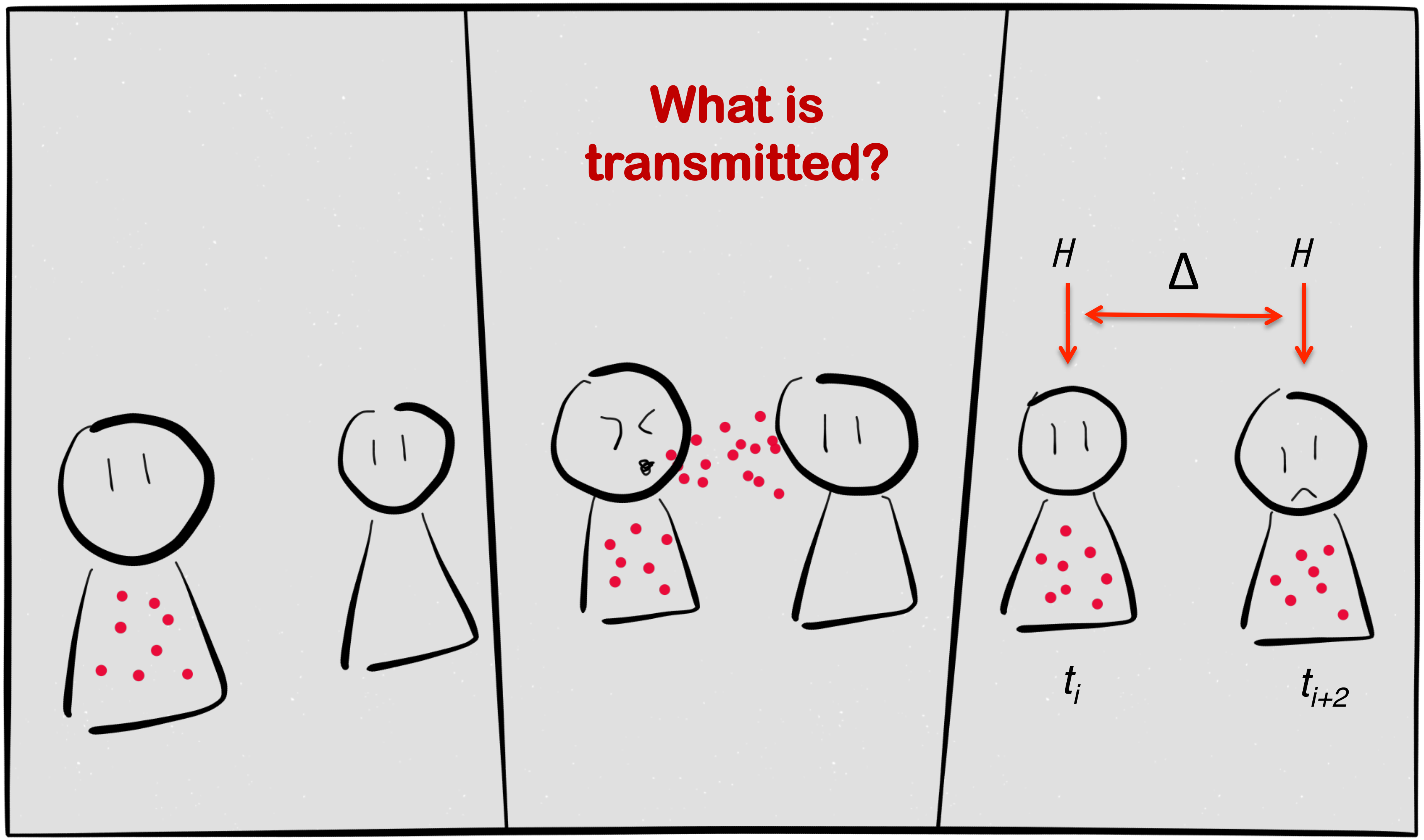


Getting the flu: exploring influenza virus evolutionary dynamics

Elodie Ghedin, PhD
November 19, 2015

10th International Conference on Bioinformatics
Genomics & Evolution of Pathogens and Hosts
Georgia Tech

CENTER FOR GENOMICS
AND SYSTEMS BIOLOGY
NEW YORK UNIVERSITY



What is transmitted?

Forces in play….

Replicative vs transmission capacity

Diversifying vs purifying selection

(High mutation rate vs conservation of function)

Epistatic interactions

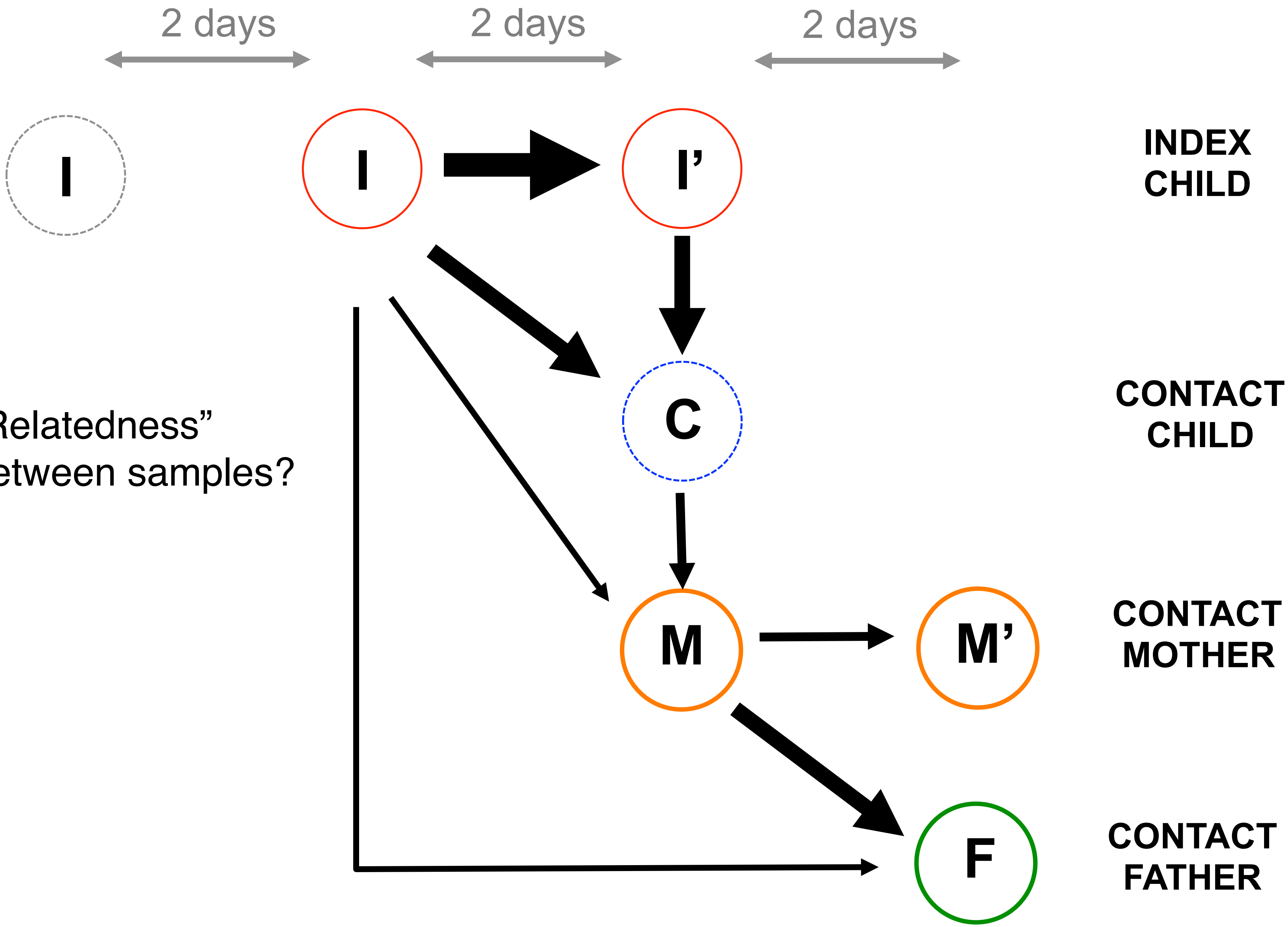
(Effect of gene mutations on another gene)

Household Transmission Study
(during first wave of H1N1 pandemic)

Collaborators:

Leo Poon, Ben Cowling, Malik Peiris

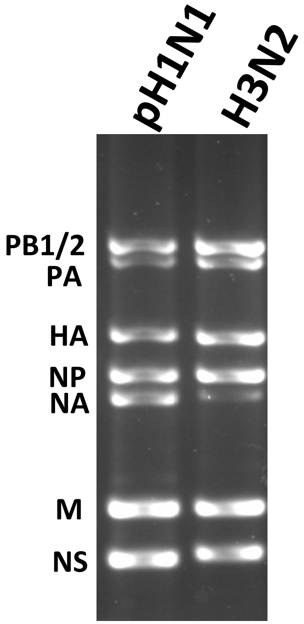
University of Hong Kong



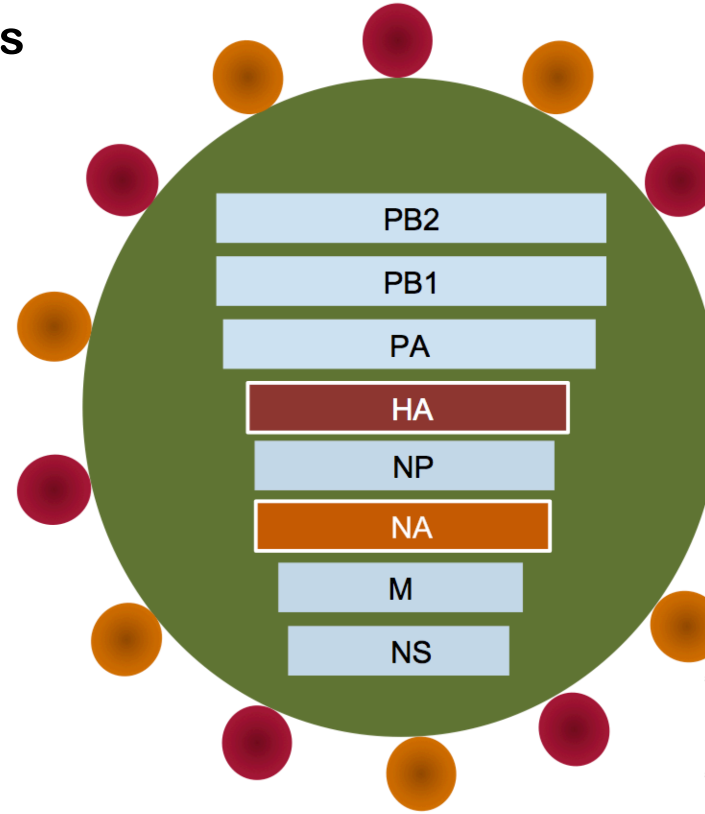
“Relatedness”
between samples?

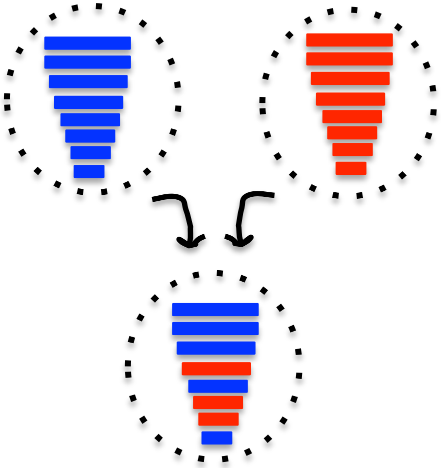
Influenza A Virus

8 (-)RNA segments



Multi-segment
RT-PCR



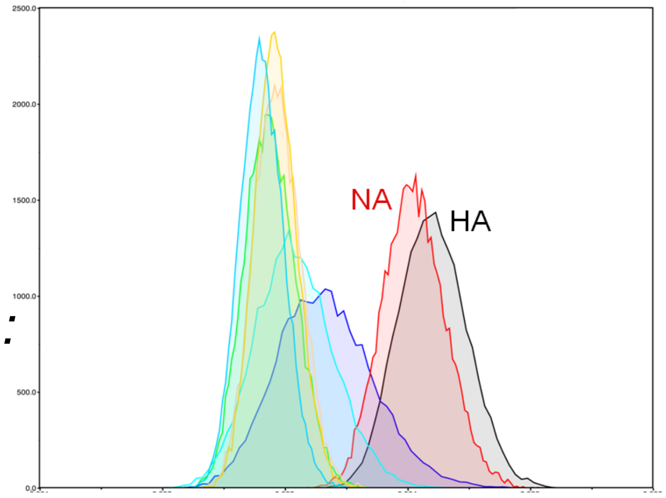


reassortment

- *RNA viruses (RNA-dependent RNA polymerase):*

~0.1 - 1 mutation per genome, per replication

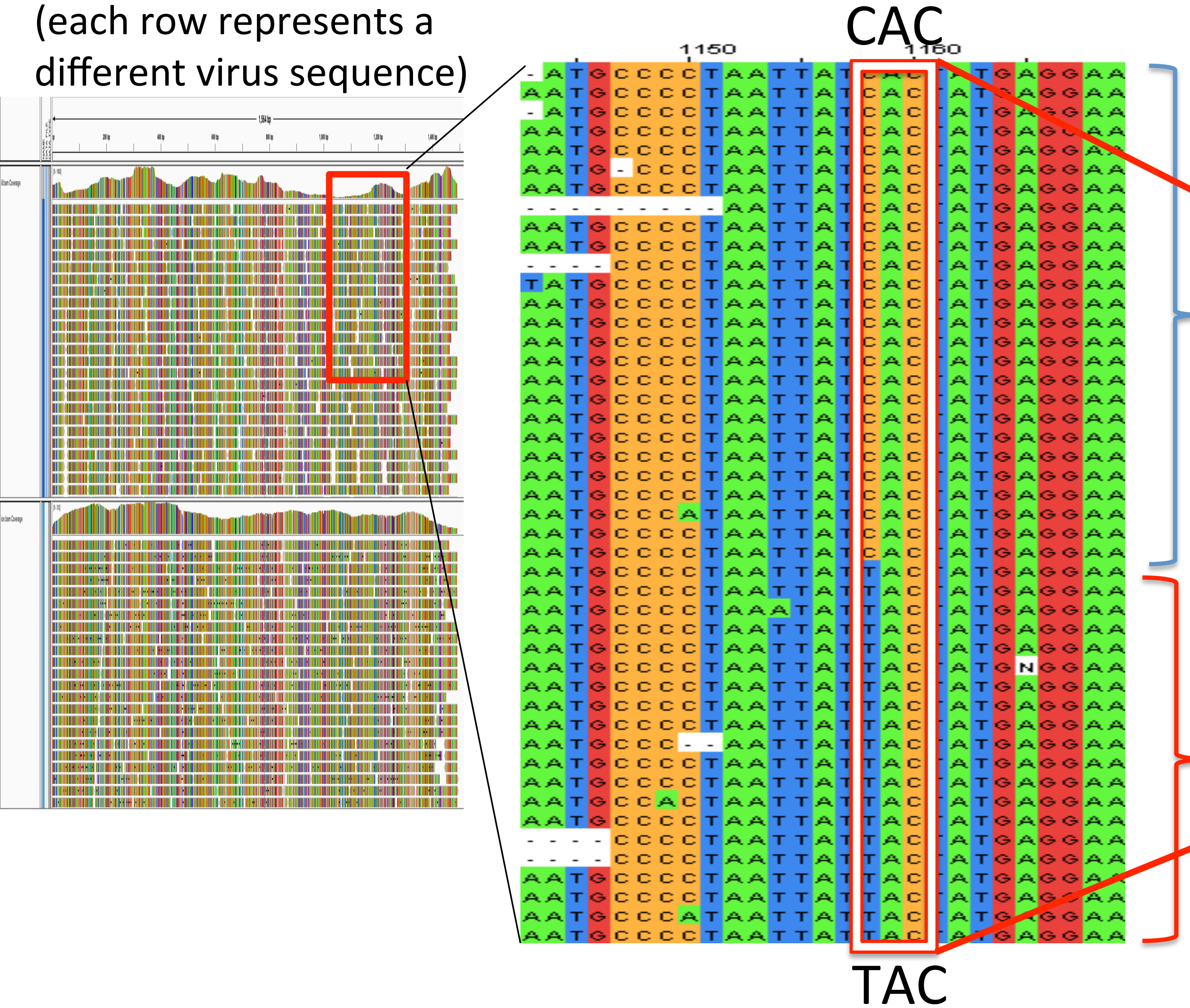
~10^{-3} to 10^{-4} nucleotide substitutions/site/year



Rate of nucleotide substitution per site

Capturing within host virus diversity

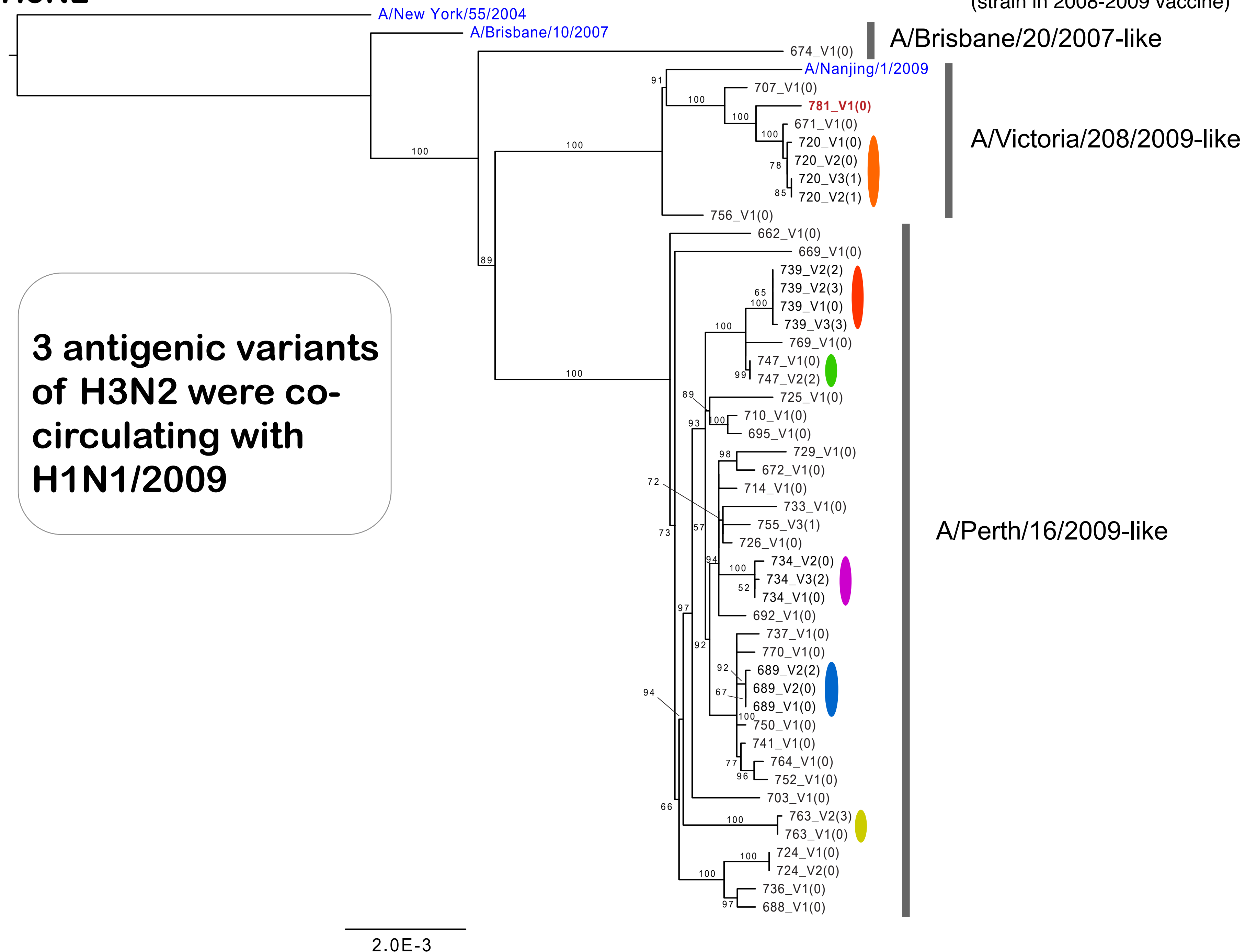
(each row represents a different virus sequence)



NA gene:
drug
sensitive
(CAC codon @
1157)

drug resistance
mutation
(TAC codon @
1157)

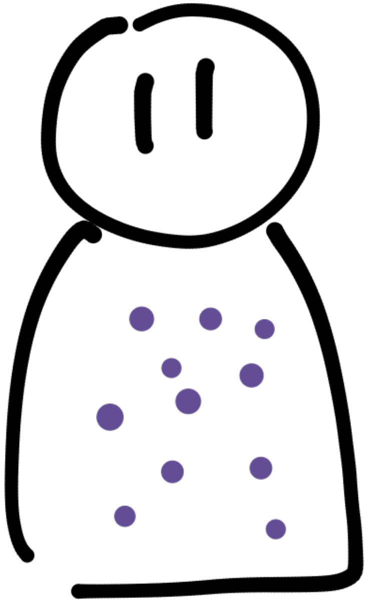
H3N2



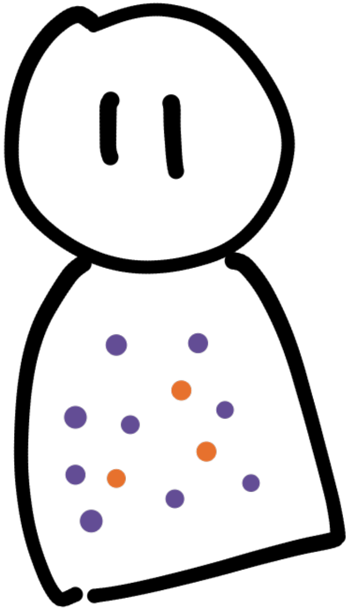
3 antigenic variants of H3N2 were co-circulating with H1N1/2009

Possible Infection States

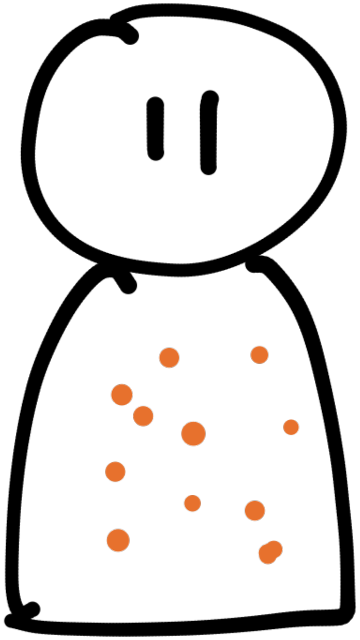
Victoria/208/2009

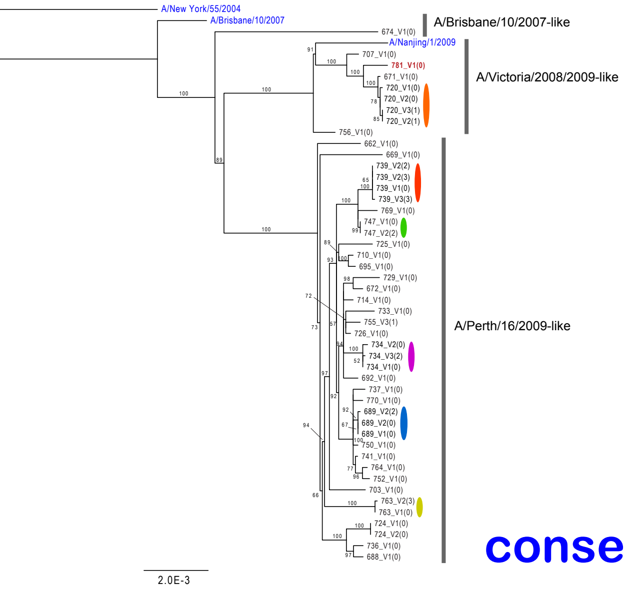


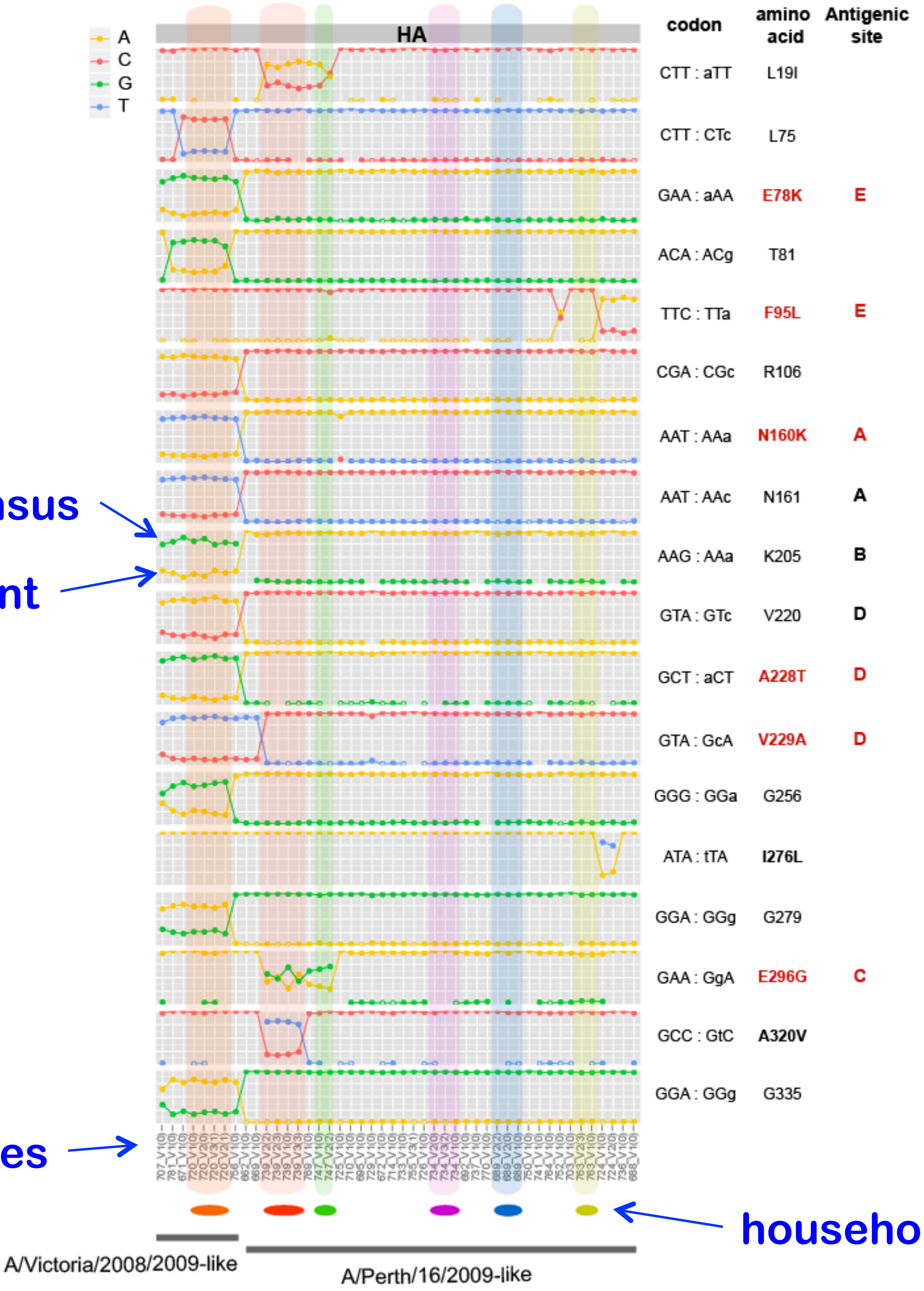
?



Perth/16/2009







consensus

variant

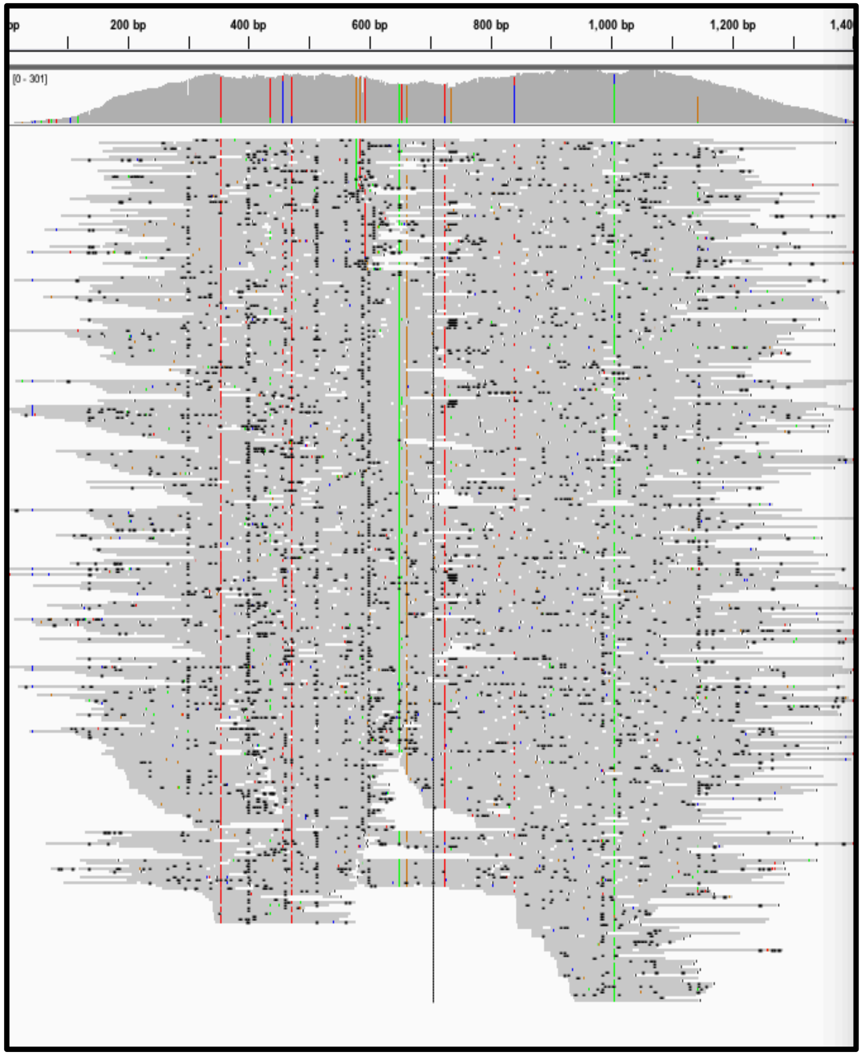
samples

households

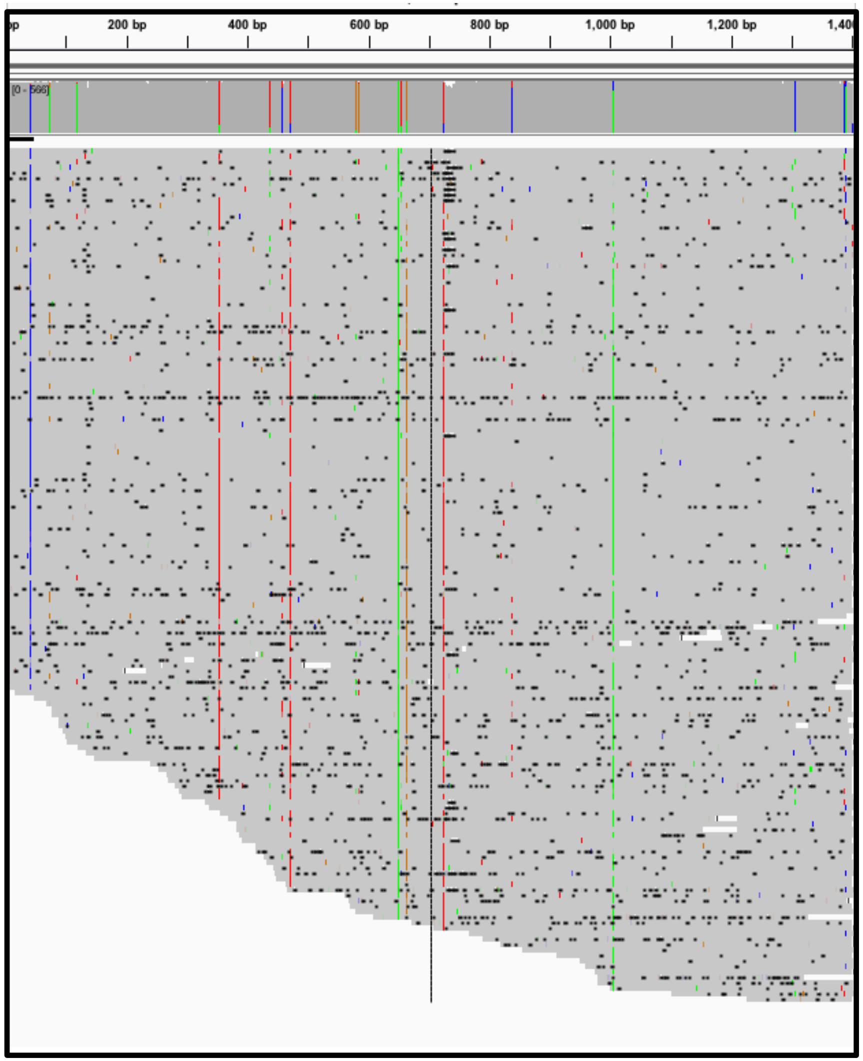
variant nucleotide analysis (SNVs)
across all genes

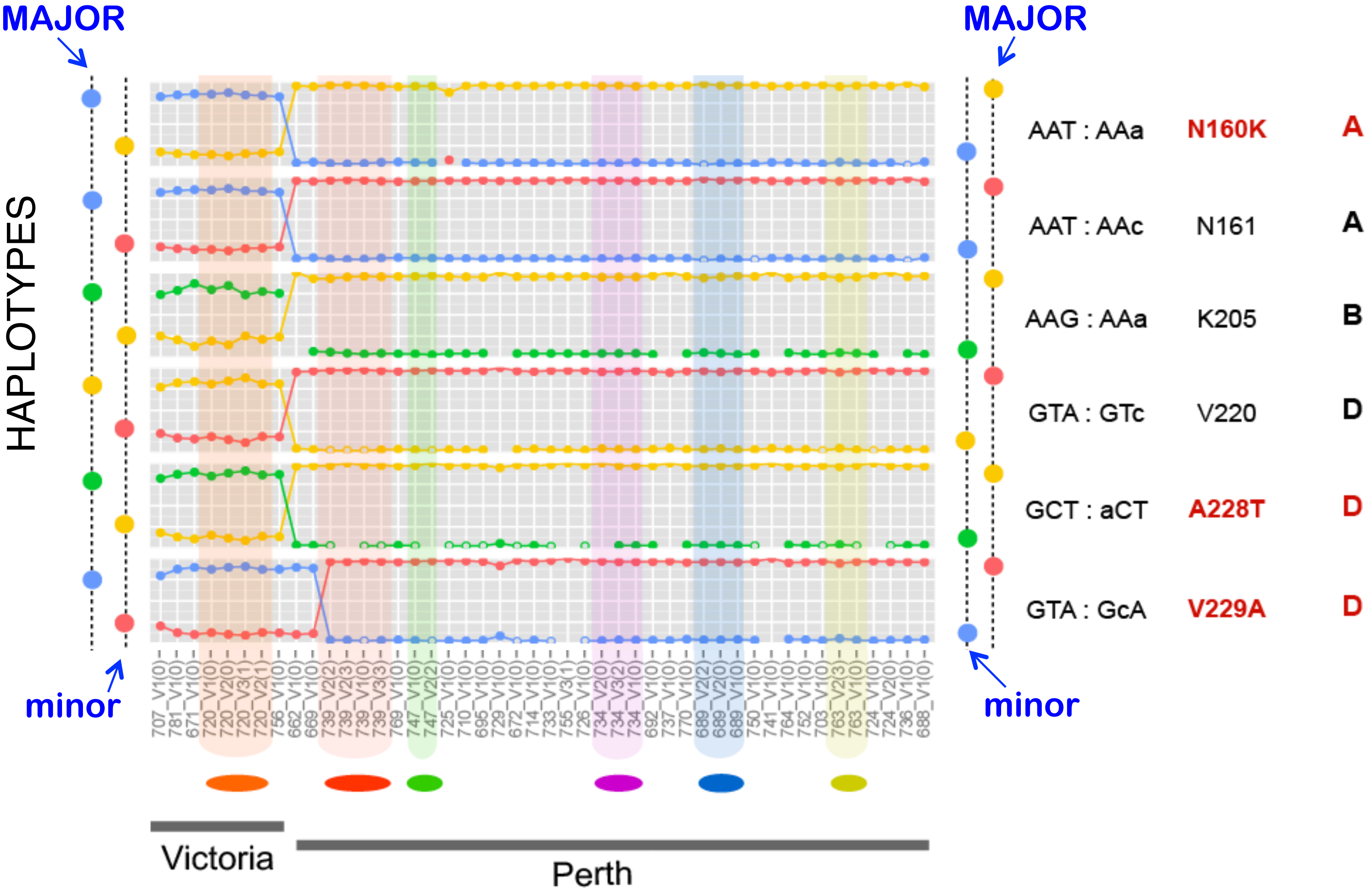
PacBio data to phase SNVs identified from short read data

Short reads (e.g. Ion Torrent, HiSeq)



Single molecule seq (e.g.PacBio, MinION)

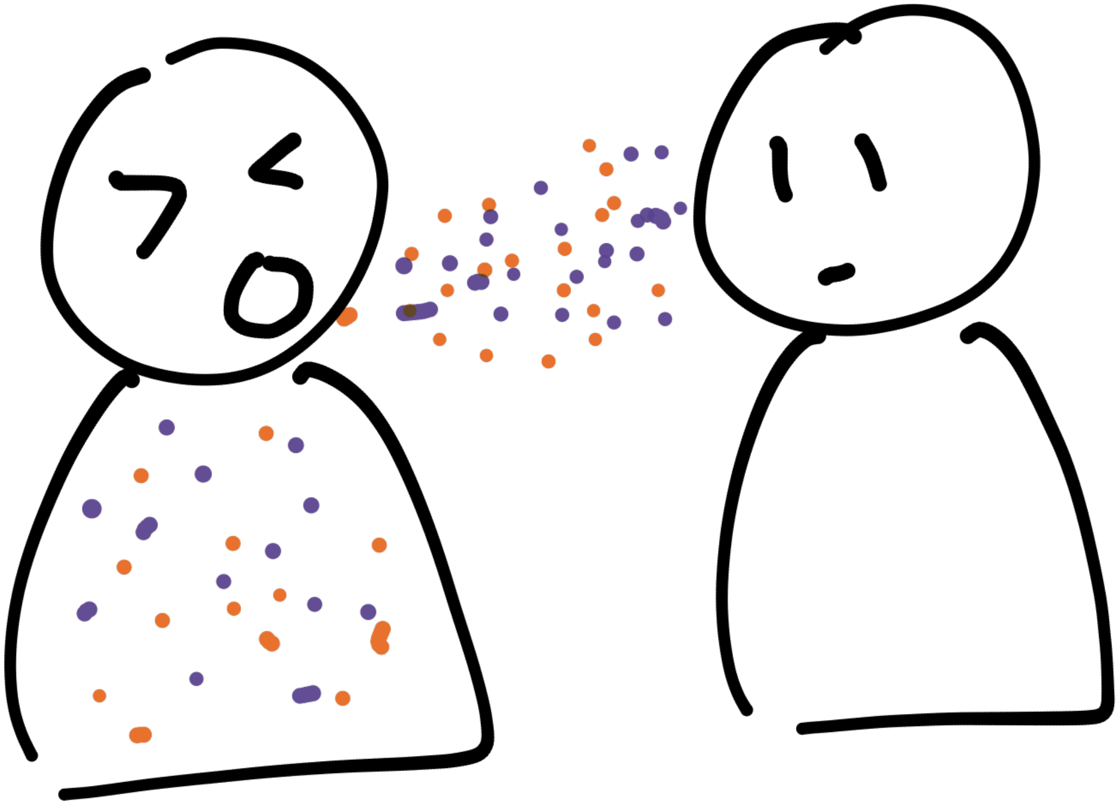




AAT : AAa	N160K	A
AAT : AAc	N161	A
AAG : AAa	K205	B
GTA : GTc	V220	D
GCT : aCT	A228T	D
GTA : GcA	V229A	D

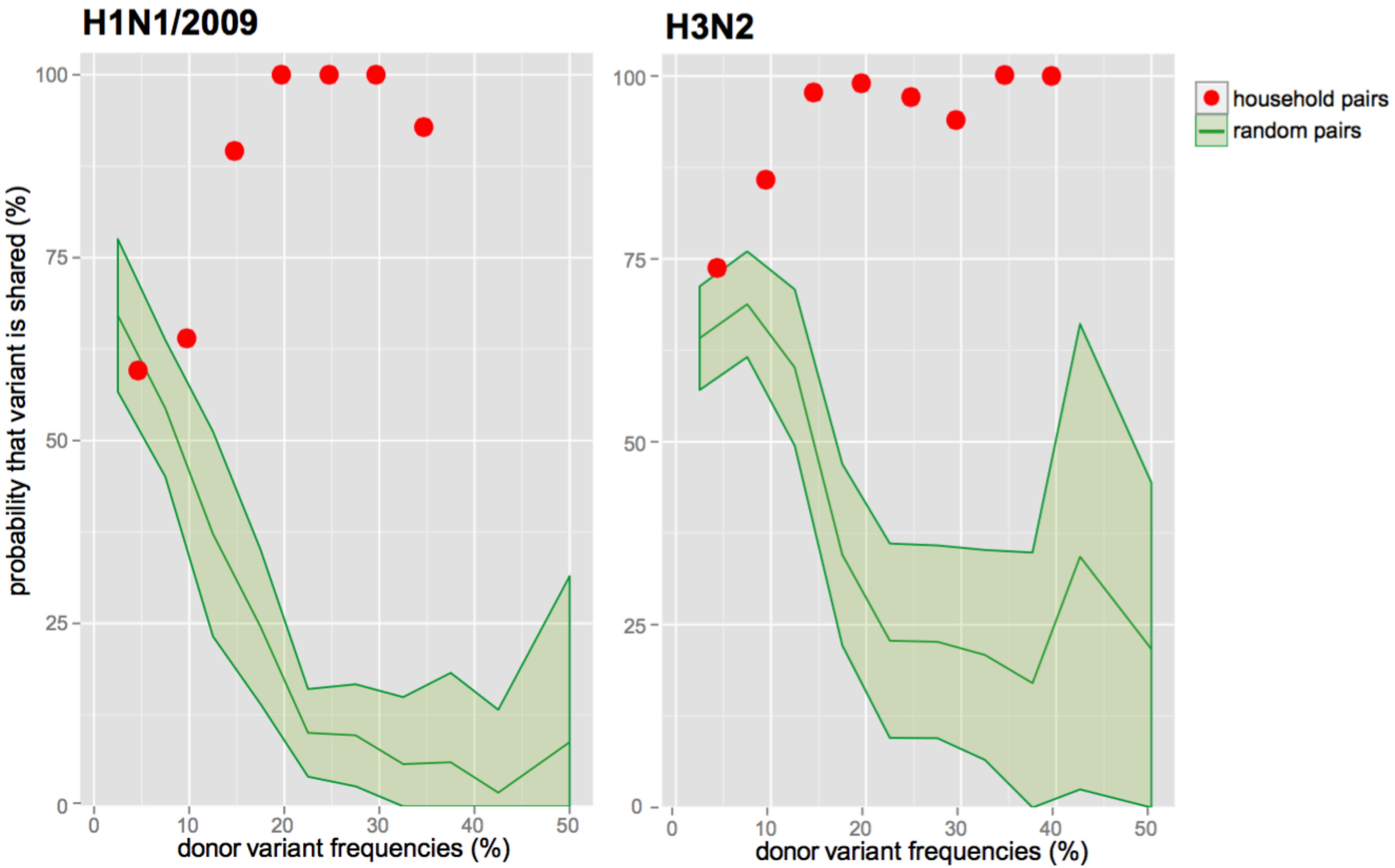
Patients carry and transmit mixed infections of different antigenic strains

What is being transmitted?



Can we quantify transmission?

Estimating transmission probability

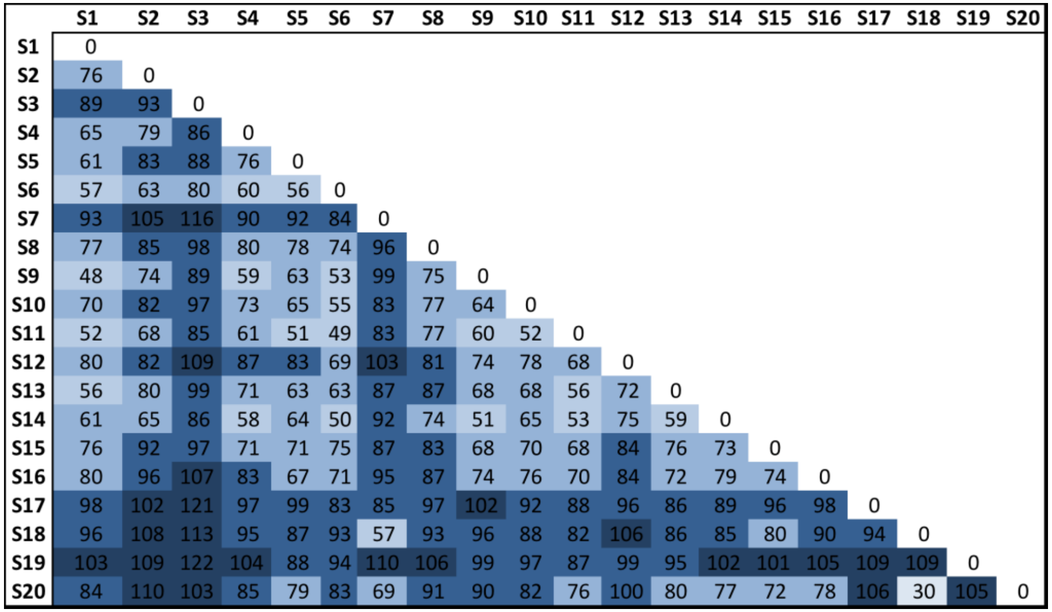


Poon, Song et al. *Nature Genetics* (accepted)

Determining genetic distance between (intra-host) virus populations based on variant nucleotide information

- all-versus-all pairwise comparison at each variant nucleotide position using an L1-norm (Manhattan distance)

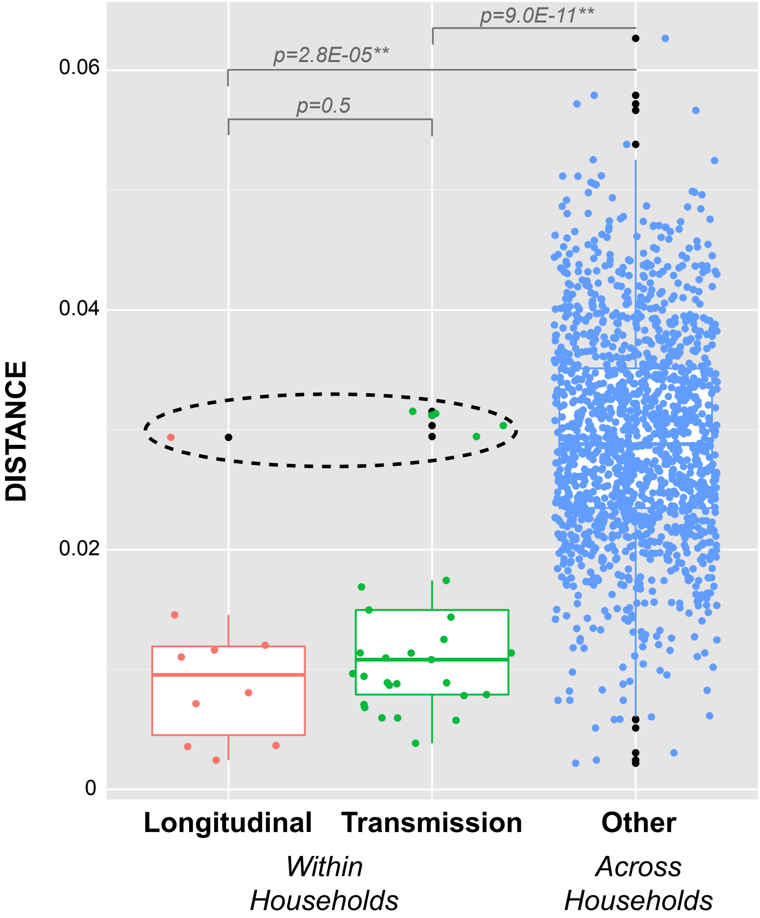
$$d_k(p,q) = \sum_{i=1}^{n} |p_i - q_i|$$



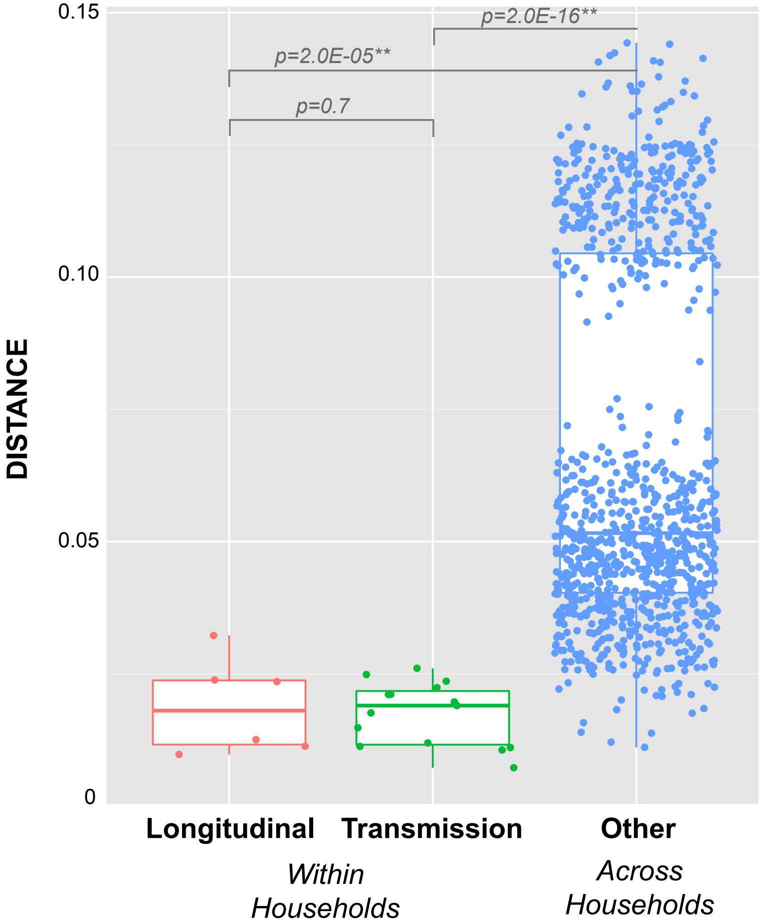
	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14	S15	S16	S17	S18	S19	S20
S1	0																			
S2	76	0																		
S3	89	93	0																	
S4	65	79	86	0																
S5	61	83	88	76	0															
S6	57	63	80	60	56	0														
S7	93	105	116	90	92	84	0													
S8	77	85	98	80	78	74	96	0												
S9	48	74	89	59	63	53	99	75	0											
S10	70	82	97	73	65	55	83	77	64	0										
S11	52	68	85	61	51	49	83	77	60	52	0									
S12	80	82	109	87	83	69	103	81	74	78	68	0								
S13	56	80	99	71	63	63	87	87	68	68	56	72	0							
S14	61	65	86	58	64	50	92	74	51	65	53	75	59	0						
S15	76	92	97	71	71	75	87	83	68	70	68	84	76	73	0					
S16	80	96	107	83	67	71	95	87	74	76	70	84	72	79	74	0				
S17	98	102	121	97	99	83	85	97	102	92	88	96	86	89	96	98	0			
S18	96	108	113	95	87	93	57	93	96	88	82	106	86	85	80	90	94	0		
S19	103	109	122	104	88	94	110	106	99	97	87	99	95	102	101	105	109	109	0	
S20	84	110	103	85	79	83	69	91	90	82	76	100	80	77	72	78	106	30	105	0

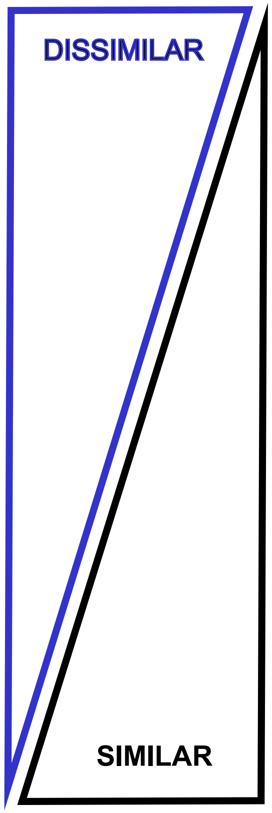
Smaller genetic distance within households than across households

H1N1/2009



H3N2





21 predicted donor/recipient pairs within households

Poon, Song et al. *Nature Genetics* (accepted)

How does host immunity affect virus genetic diversity (and transmission)?

Immunosuppressed

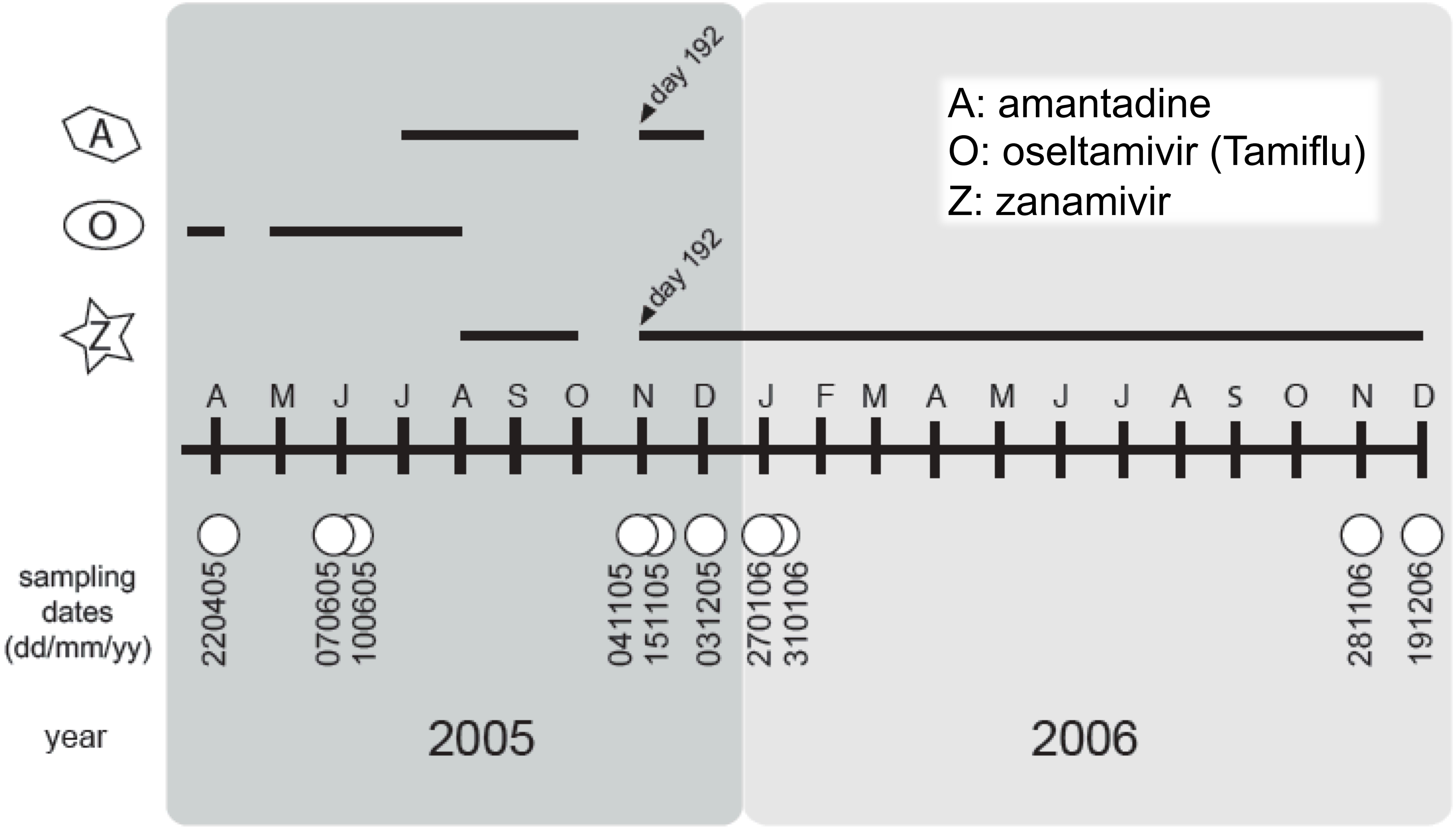
vs

Vaccinated/pre-exposed

Virus shed for 2 years in SCID patient

(Severe Combined Immune Deficiency)

Guy Boivin, CHUL

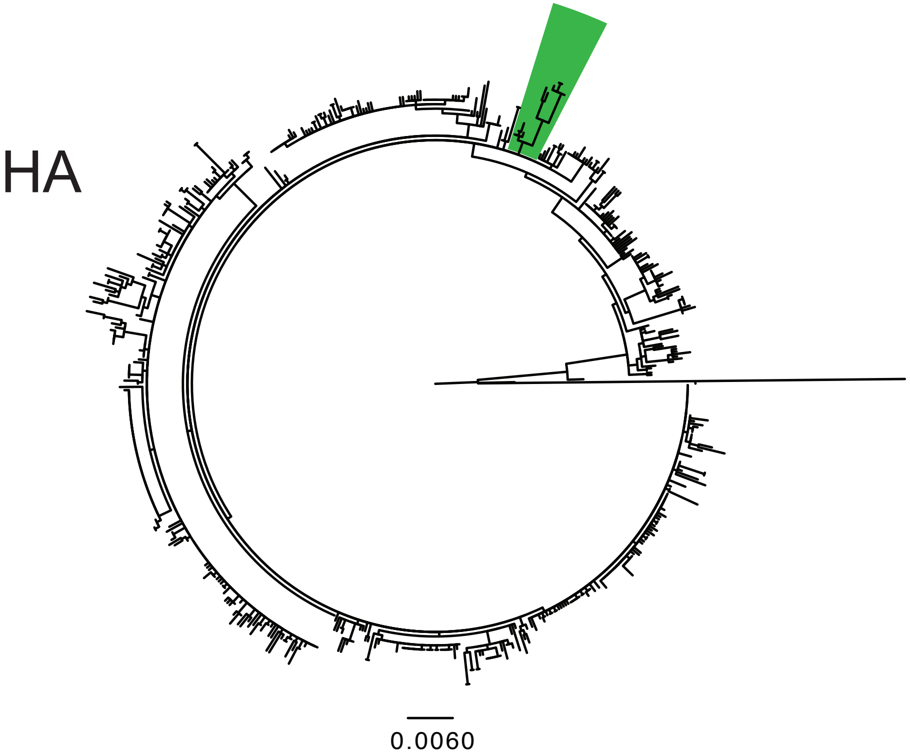


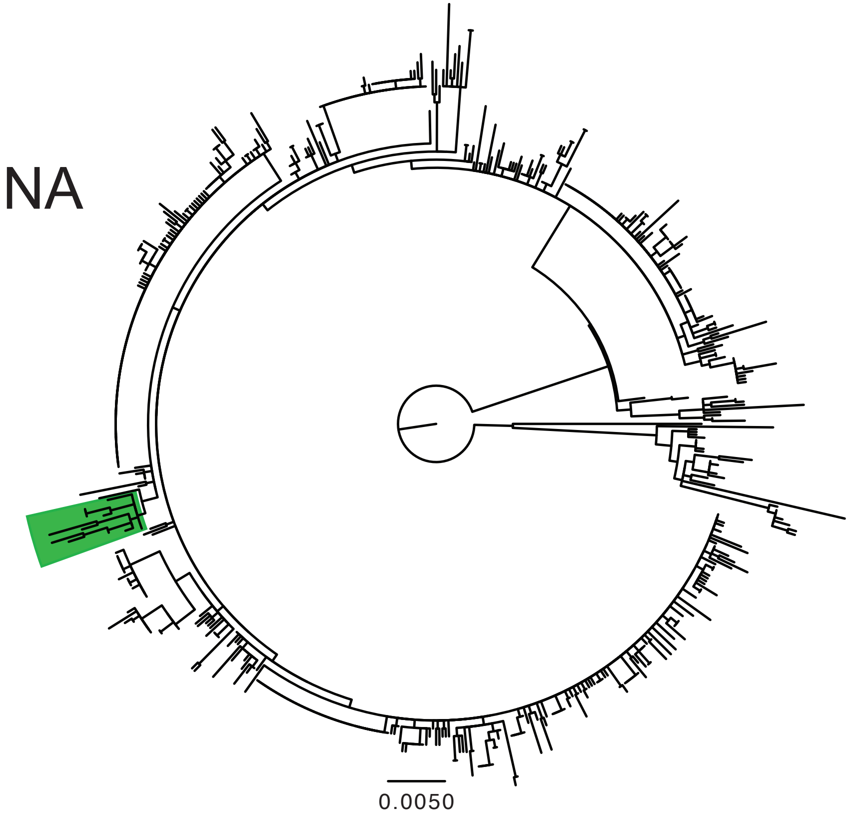
A: amantadine
O: oseltamivir (Tamiflu)
Z: zanamivir

606 days

Rogers et al. (2015) *mBio*

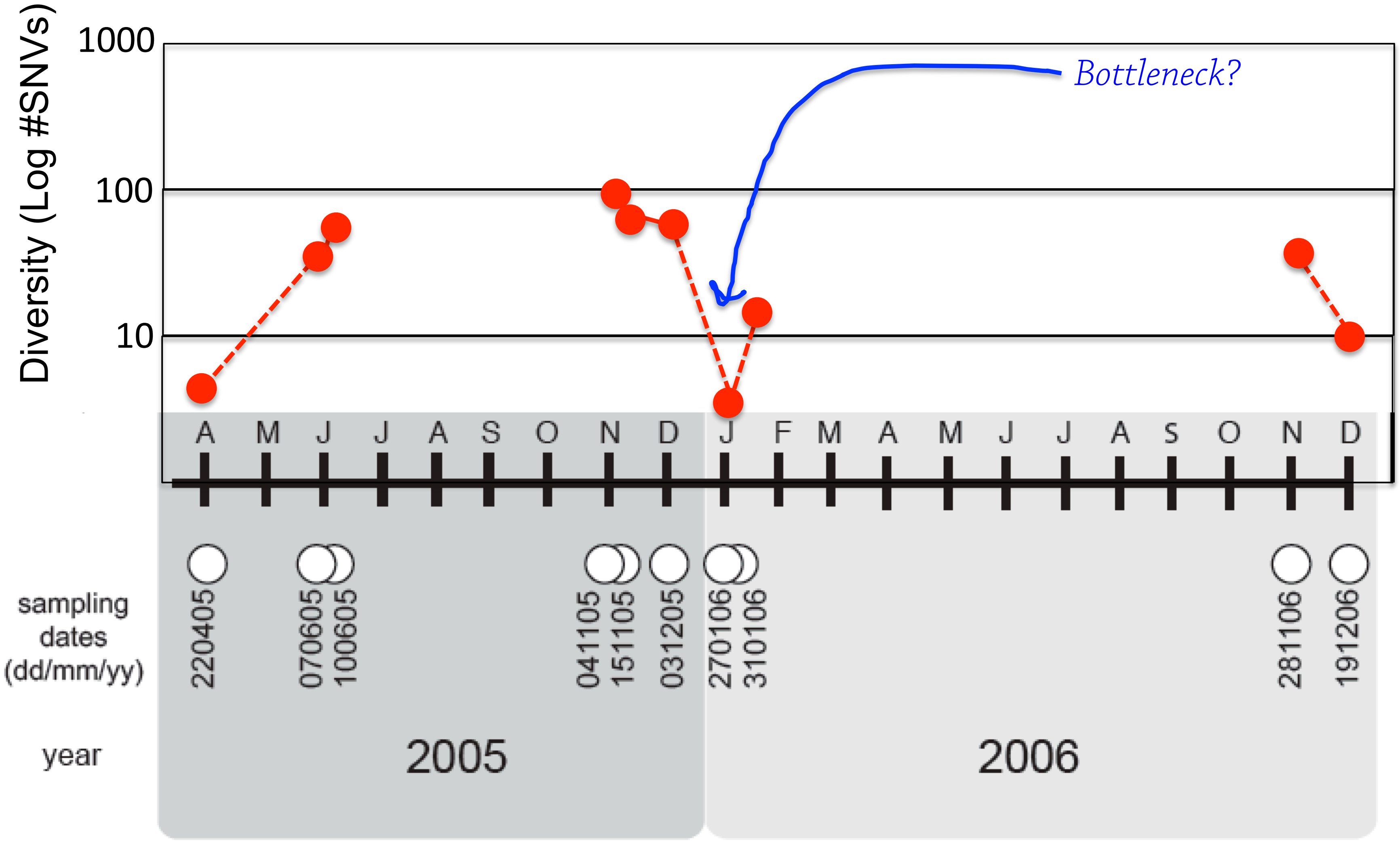
Patient samples always cluster together: no re-infection





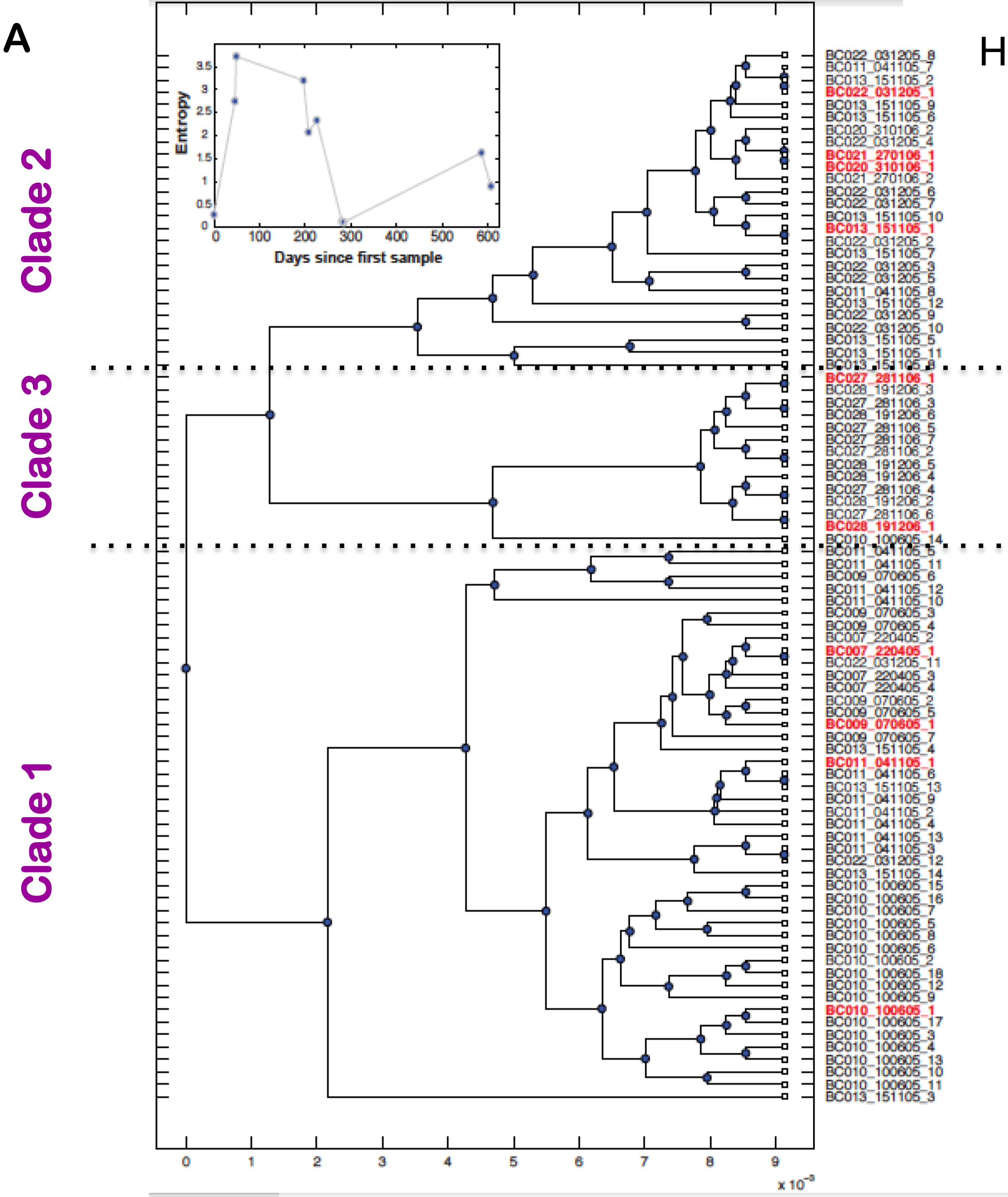
Samples collected in 2005
Background sequences from seasons 2004 to 2007

Genetic diversity of virus population increases over time until bottleneck

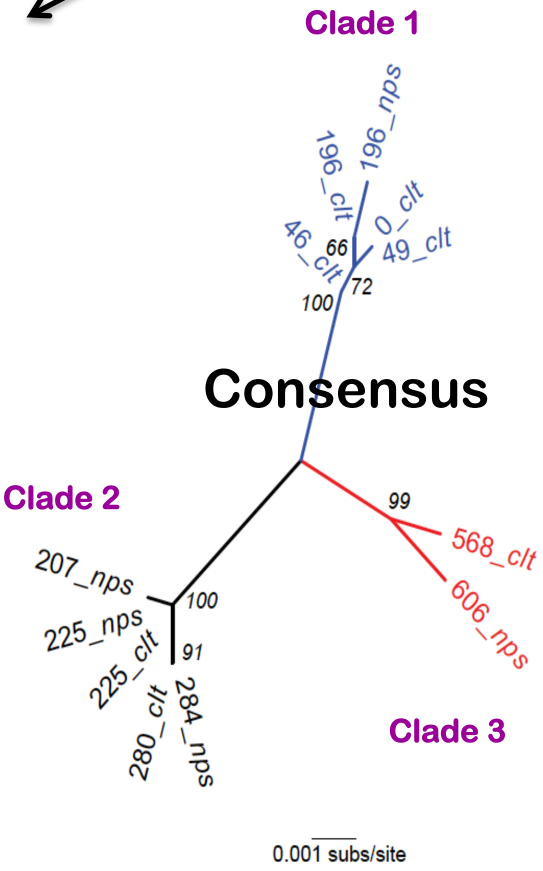


606 days

HA



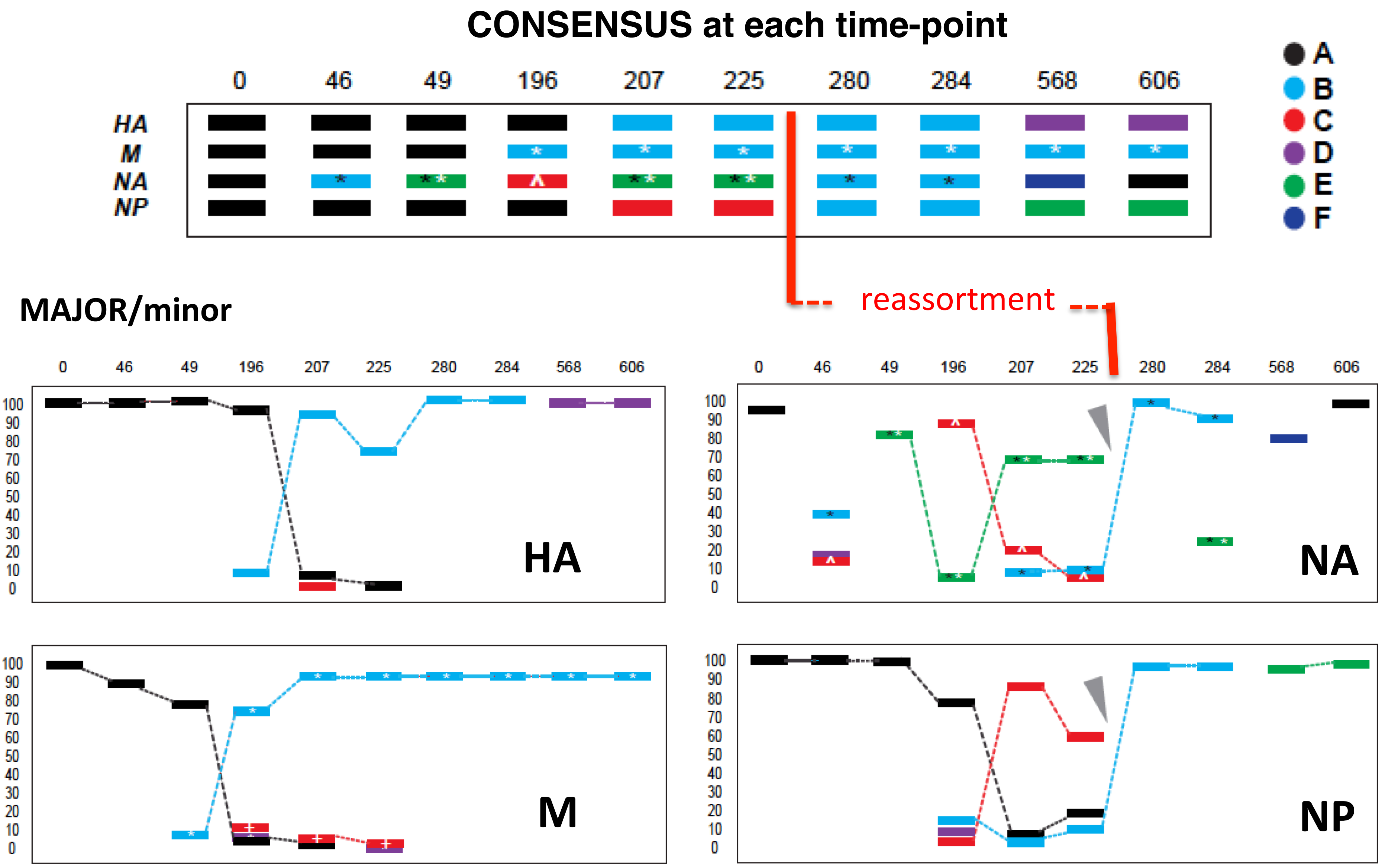
Haplotypes reconstructed by phasing



Red: consensus
Black: variants (haplotypes)

Tracking emergence of minor variant

★
★☆ Drug Resistance mutations
^



CONSENSUS at each time-point

MAJOR/minor

Immunocompromised

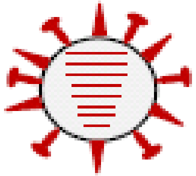
- Reassortment in response to drug pressure
- Emergence of truncated mutants (NS1 and NA)

Vaccinated or pre-infected

- ?

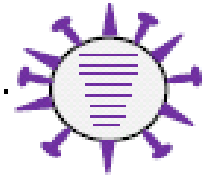
Does pre-immunity have an effect on virus genetic diversity?

PRE-IMMUNIZED



Initial
Infection
A/Denver/1/1957(H1N1)
or
A/Brisbane/59/07(H1N1)
or
A/Texas/36/91 (H1N1)
or
A/PR/34(H1N1)

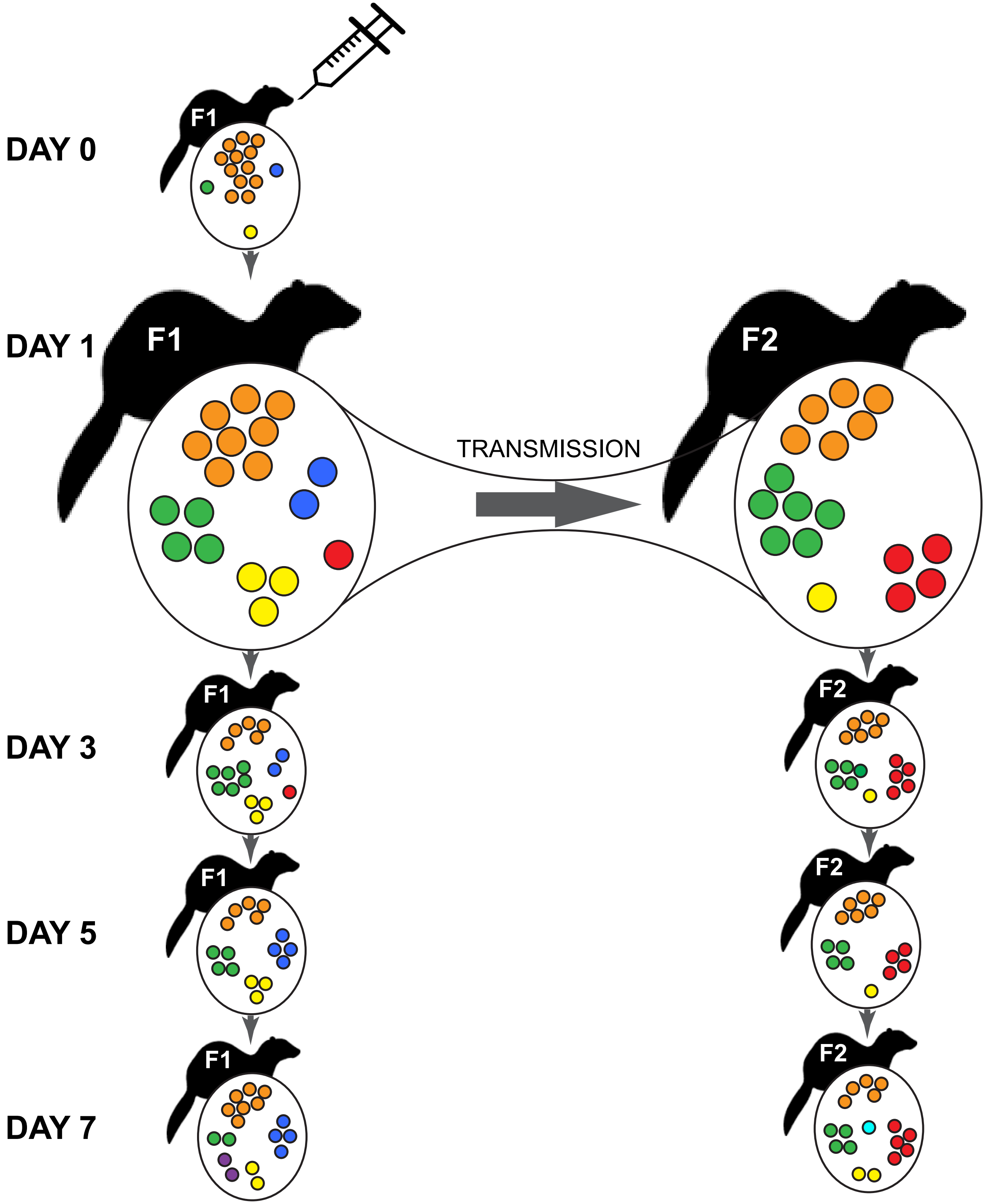
12 weeks →



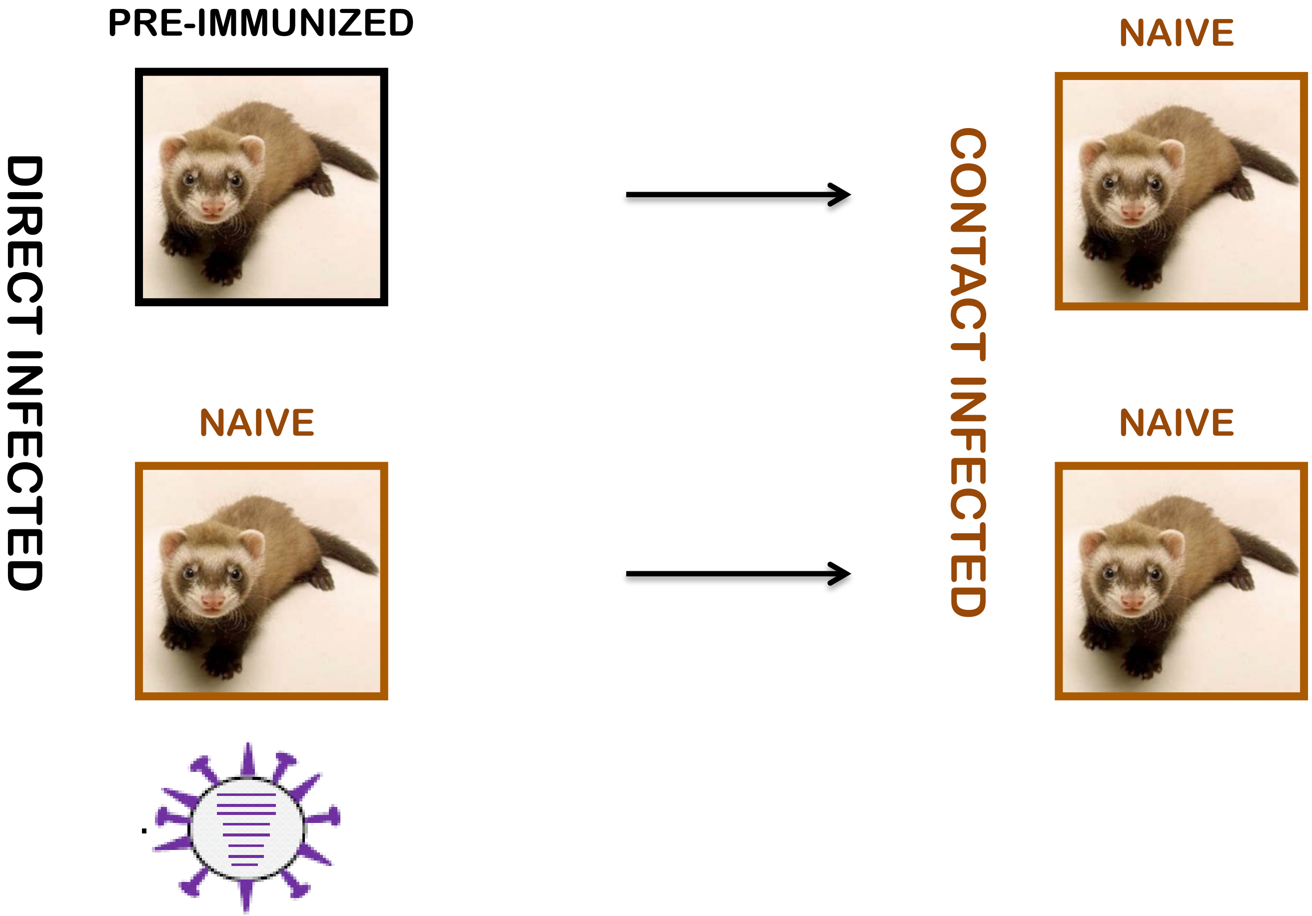
Challenge
Infection
A/California/07/2009(pH1N1)

NAIVE

Challenge
Infection
A/California/07/2009(pH1N1)



DAY 0
F1
DAY 1
F1
TRANSMISSION
F2
DAY 3
F1
F2
DAY 5
F1
F2
DAY 7
F1
F2



DIRECT INFECTED

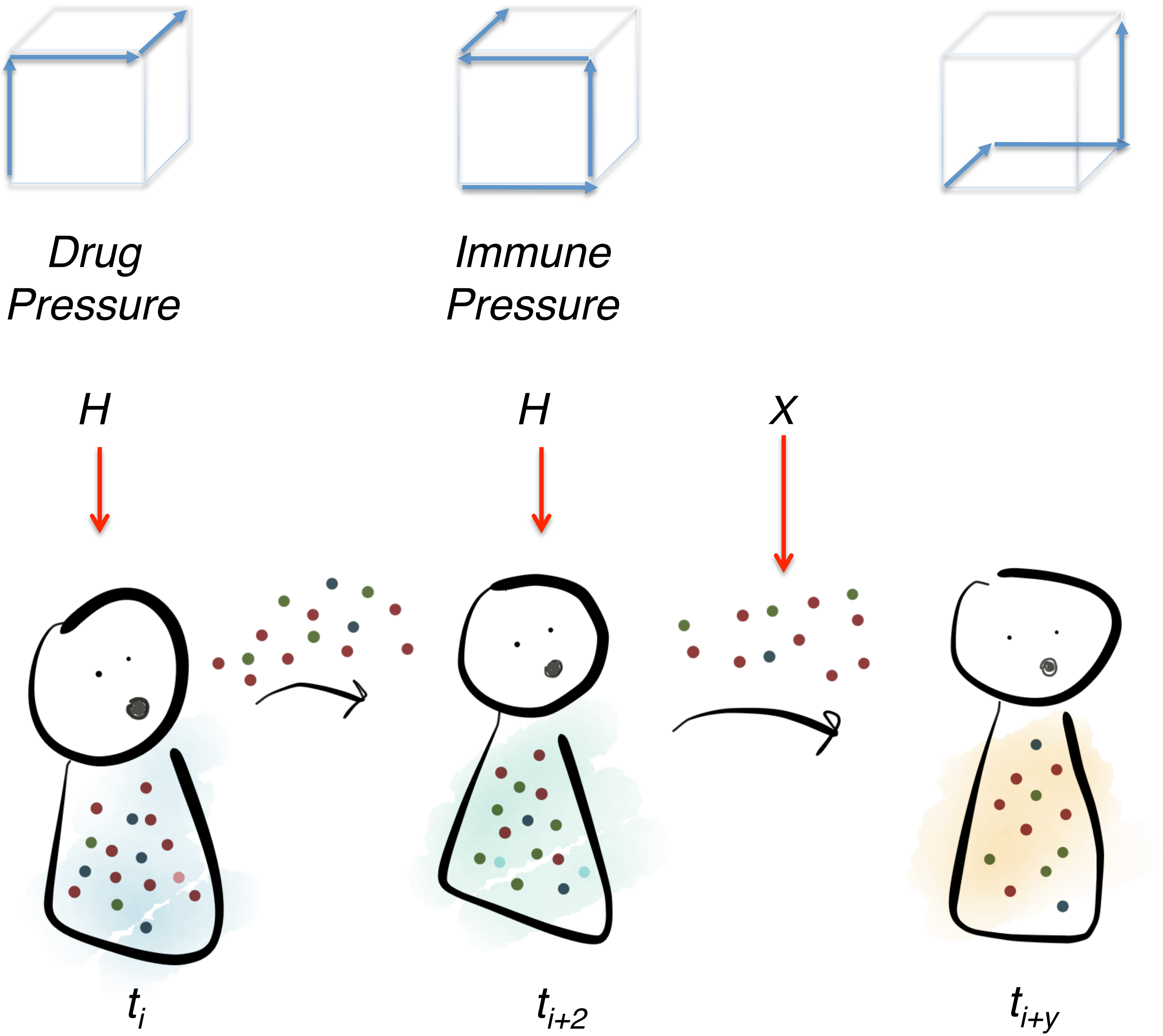
PRE-IMMUNIZED

NAIVE

CONTACT INFECTED

NAIVE

NAIVE


Drug Pressure
Immune Pressure
H
H
X
t_i
t_{i+2}
t_{i+y}

Acknowledgments

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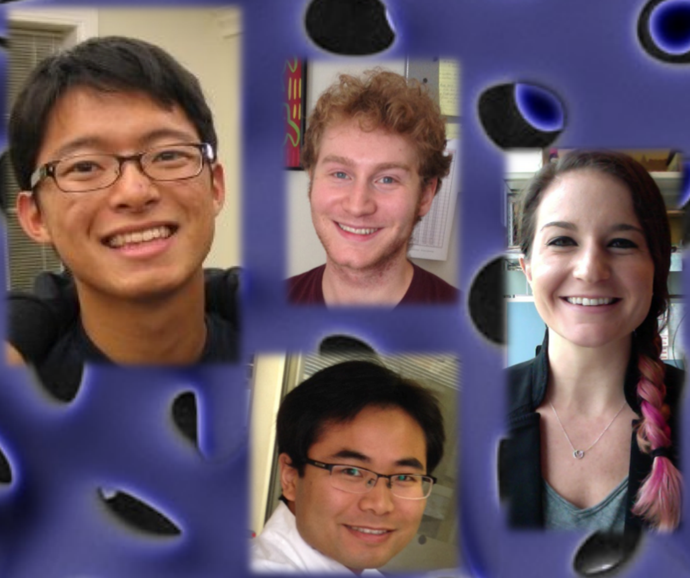

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U. Sydney

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CMU

Roni Rosenfeld

JCVI

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