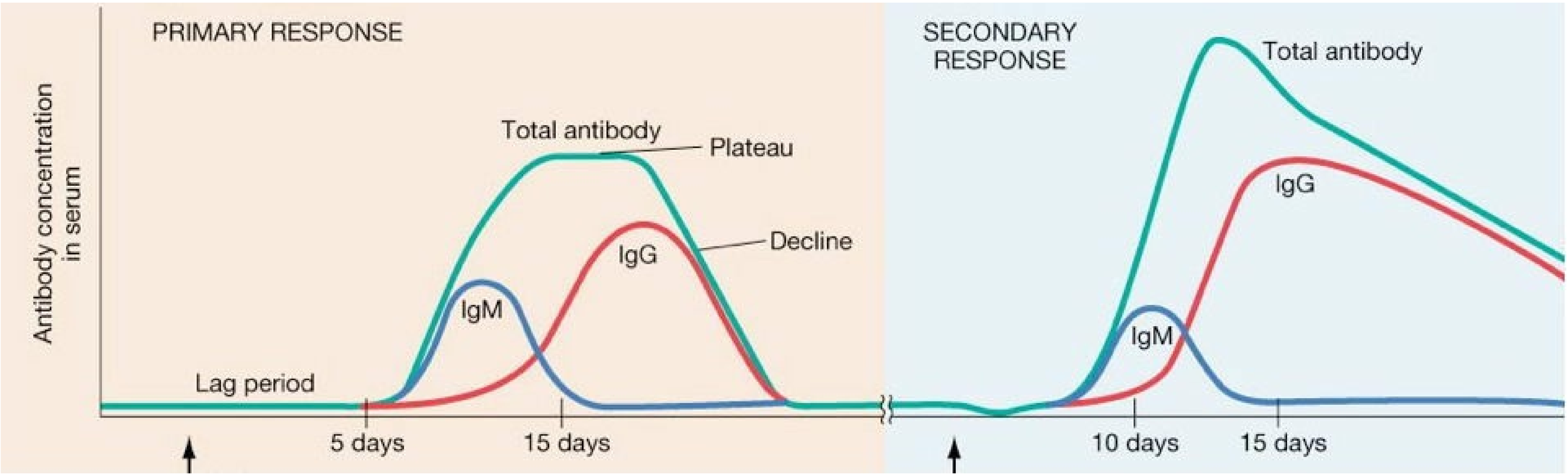
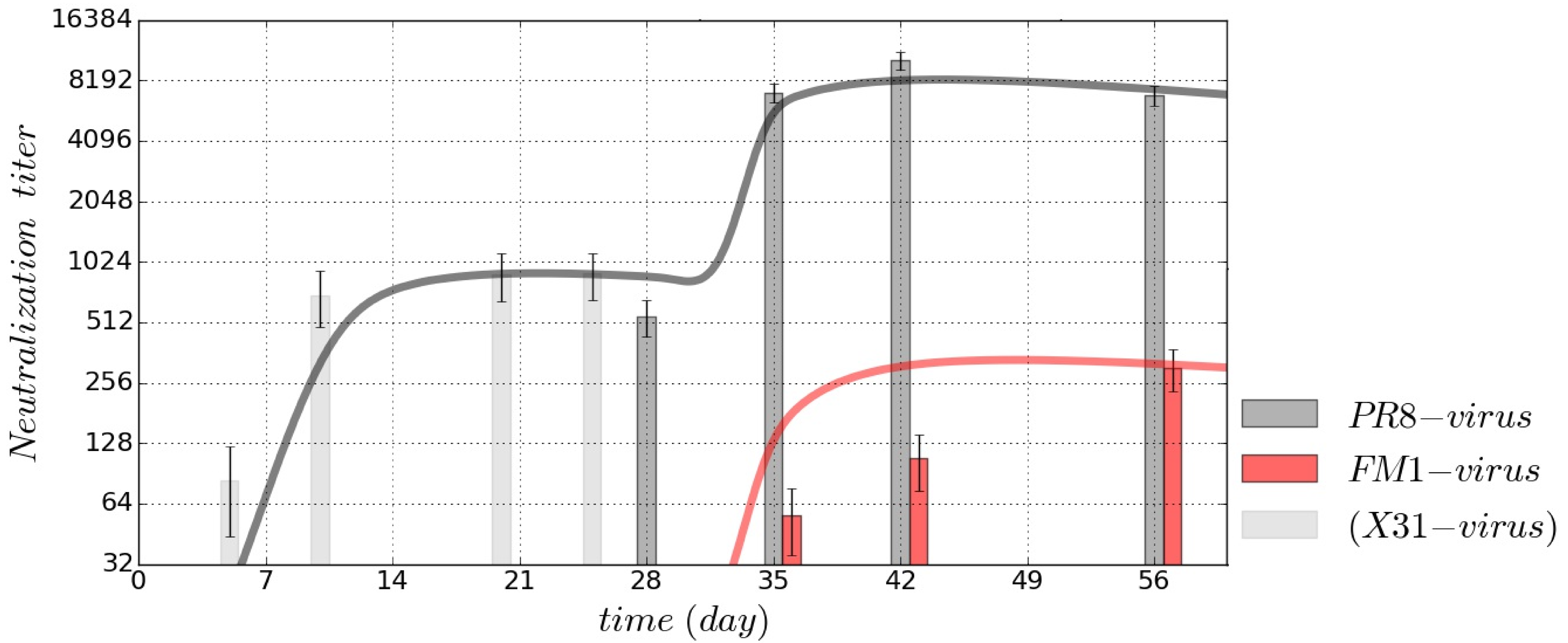
Serology

Serological assays measure circulating antibodies that bind to or neutralize a specific antigen

Antibody response curve

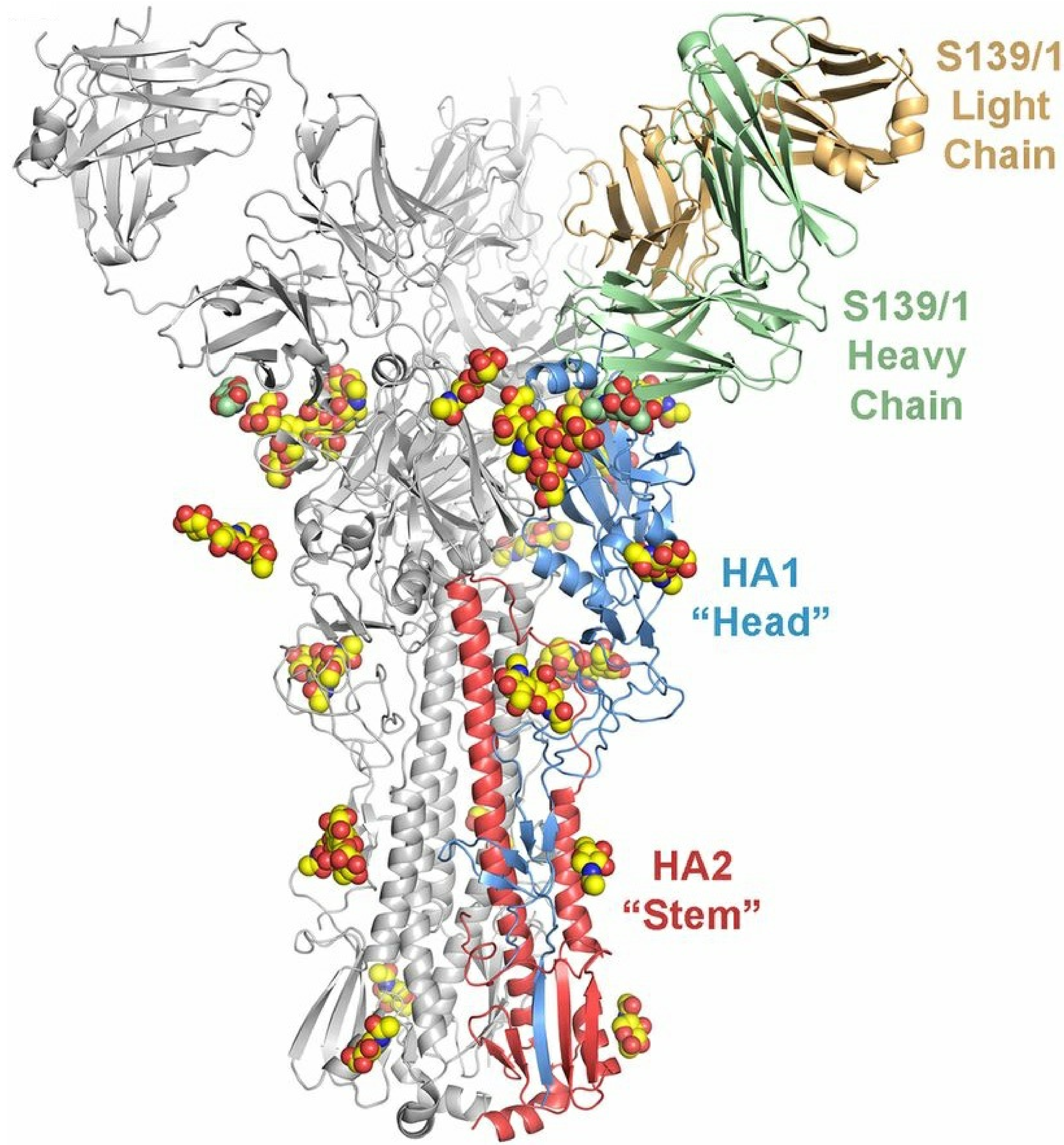


Antibody response curve



Li 2016

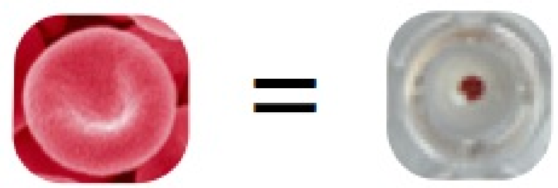
Antibodies bind to virus

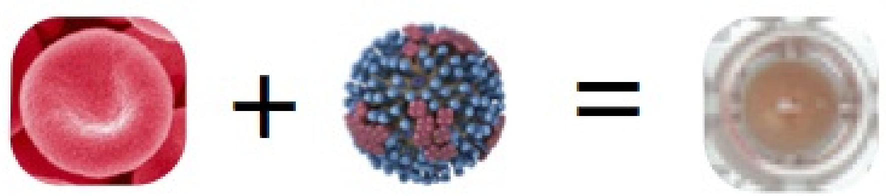


Lee et al. 2012

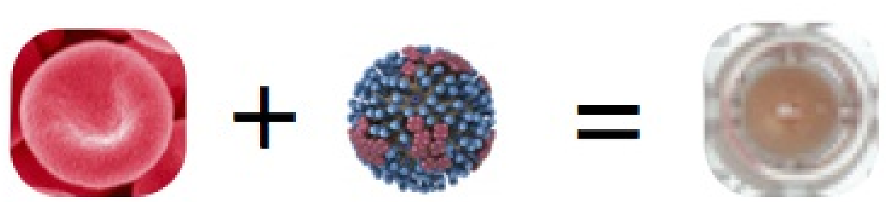
Influenza hemagglutination inhibition (HI) assay

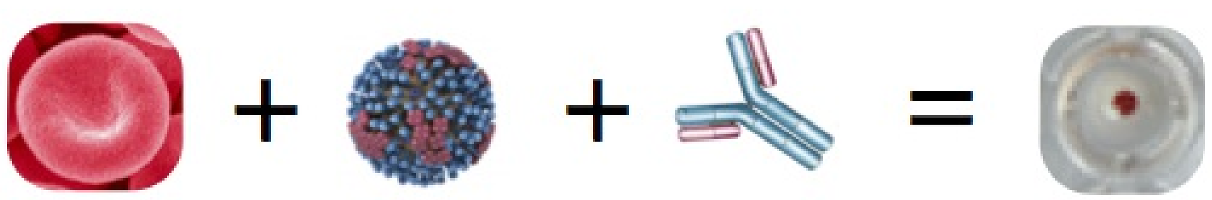
Hemagglutination assay:


Without virus, red blood cell sink to bottom of well

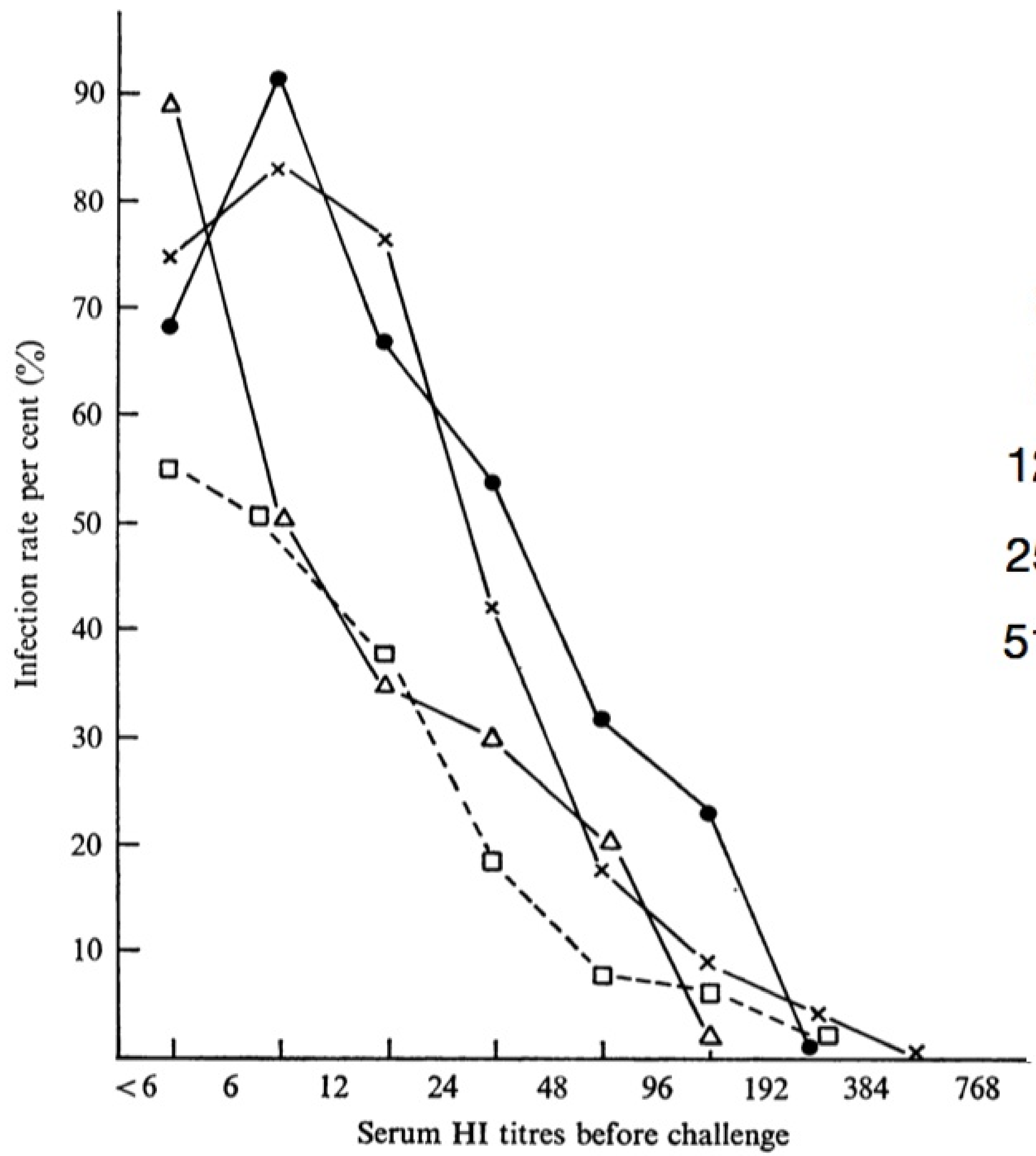

With virus, cells form diffuse lattice

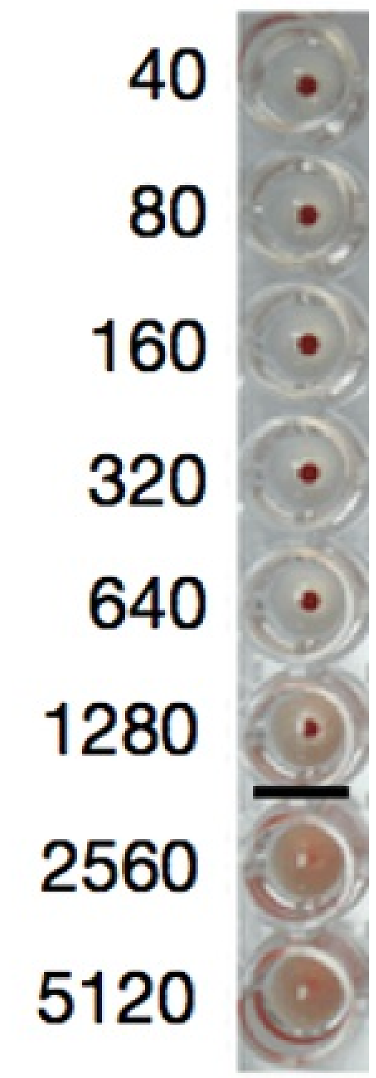
Hemagglutination inhibition assay:


Without antibodies, agglutination of virus to RBC


Antibodies bind viruses, preventing agglutination

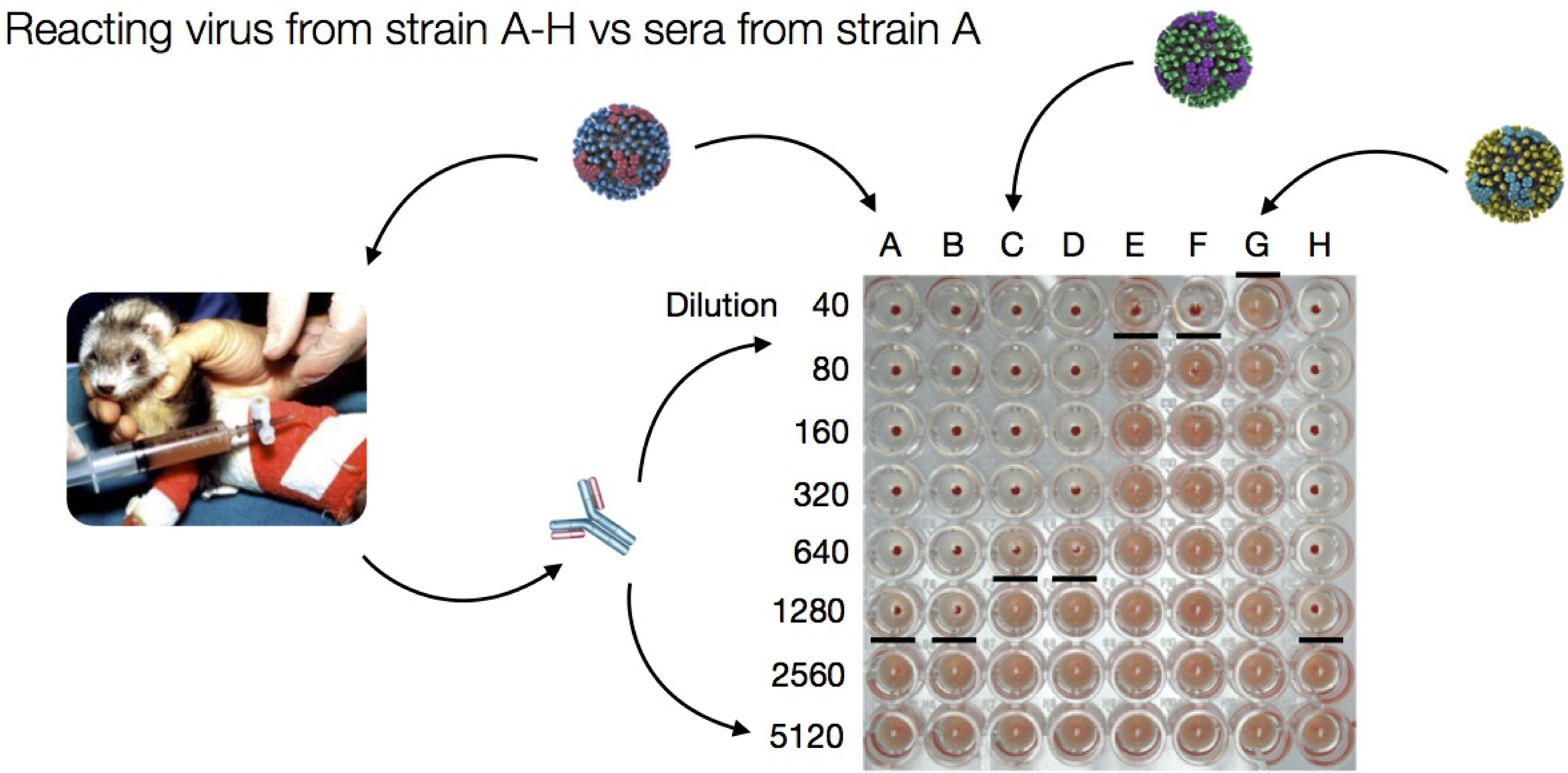
HI titer correlates strongly with protection





Hobson et al. 1972

HI assay can measure cross-reactivity

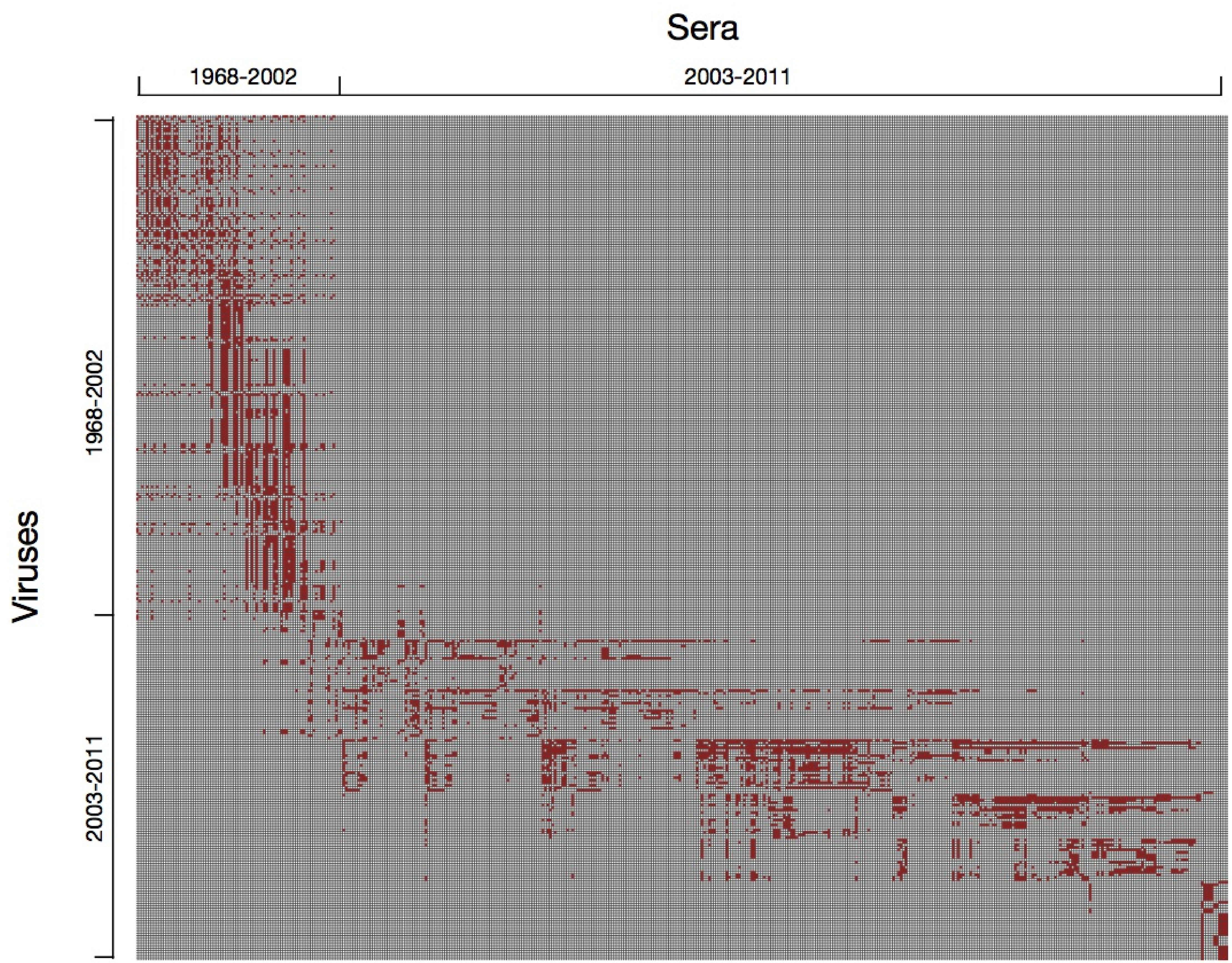


Data presented as pairwise maximum inhibitory titers

Viruses	Collection Date	Passage History	Haemagglutination inhibition titre[1] Post infection ferret sera A/Wis 67/05 F1/06	A/Bris 10/07 F29/08	A/Uru 716/07 F26/08	A/HK 1985/09 F21/09	A/Perth 16/09 F25/09	A/Wis 15/09 F24/09	A/HK 34430/09 F4/10
REFERENCE VIRUSES									
A/Wisconsin/67/2005	2005-08-31	SpfCk3E3/E7	**1280**	1280	1280	40	<	160	40
A/Brisbane/10/2007	2007-02-06	E2/E3	2560	**2560**	2560	80	<	160	160
A/Uruguay/716/2007	2007-06-21	SpfCk1, E3/E3	640	1280	**2560**	<	<	80	40
A/Hong Kong/1985/2009	2009-04-01	MDCK2/SIAT1	40	80	160	**1280**	640	2560	1280
A/Perth/16/2009	2009-07-04	E3/E2	<	<	40	640	**640**	640	640
A/Wisconsin/15/2009	2009-07-06	E2/E3	<	<	40	640	640	**1280**	1280
A/Hong Kong/34430/2009	2009-11-22	MDCK2/SIAT2	<	80	160	5120	640	1280	**1280**
TEST VIRUSES									
A/Hong Kong/1737/2010	2010-03-24	MDCK2/SIAT1	40	80	320	5120	1280	1280	1280
A/Hong Kong/1775/2010	2010-03-28	MDCK2/SIAT1	<	80	160	5120	640	2560	1280
A/Hong Kong/1837/2010	2010-03-30	MDCK2/SIAT1	40	80	160	5120	640	2560	1280
A/Hong Kong/1888/2010	2010-04-19	MDCK2/SIAT1	160	320	320	5120	1280	2560	2560

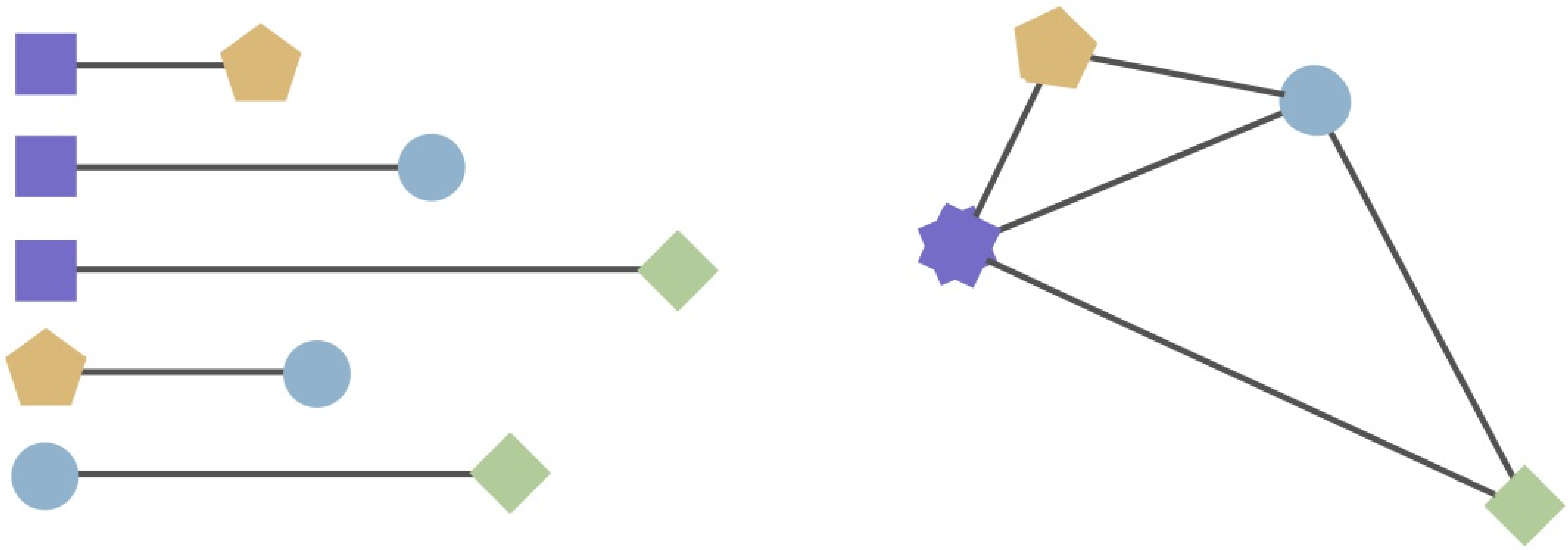
NIMR WHO interim report Sep 2010

Data from many HI assays are hard to summarize



Antigenic cartography

Uses multidimensional scaling (MDS) to position viruses in 2D space such that the distances in this space best fit the HI titers.



Cartography exercise: example

Pairwise titers:

	Serum A	**Serum B**
Virus A	2560	80
Virus B	160	1280

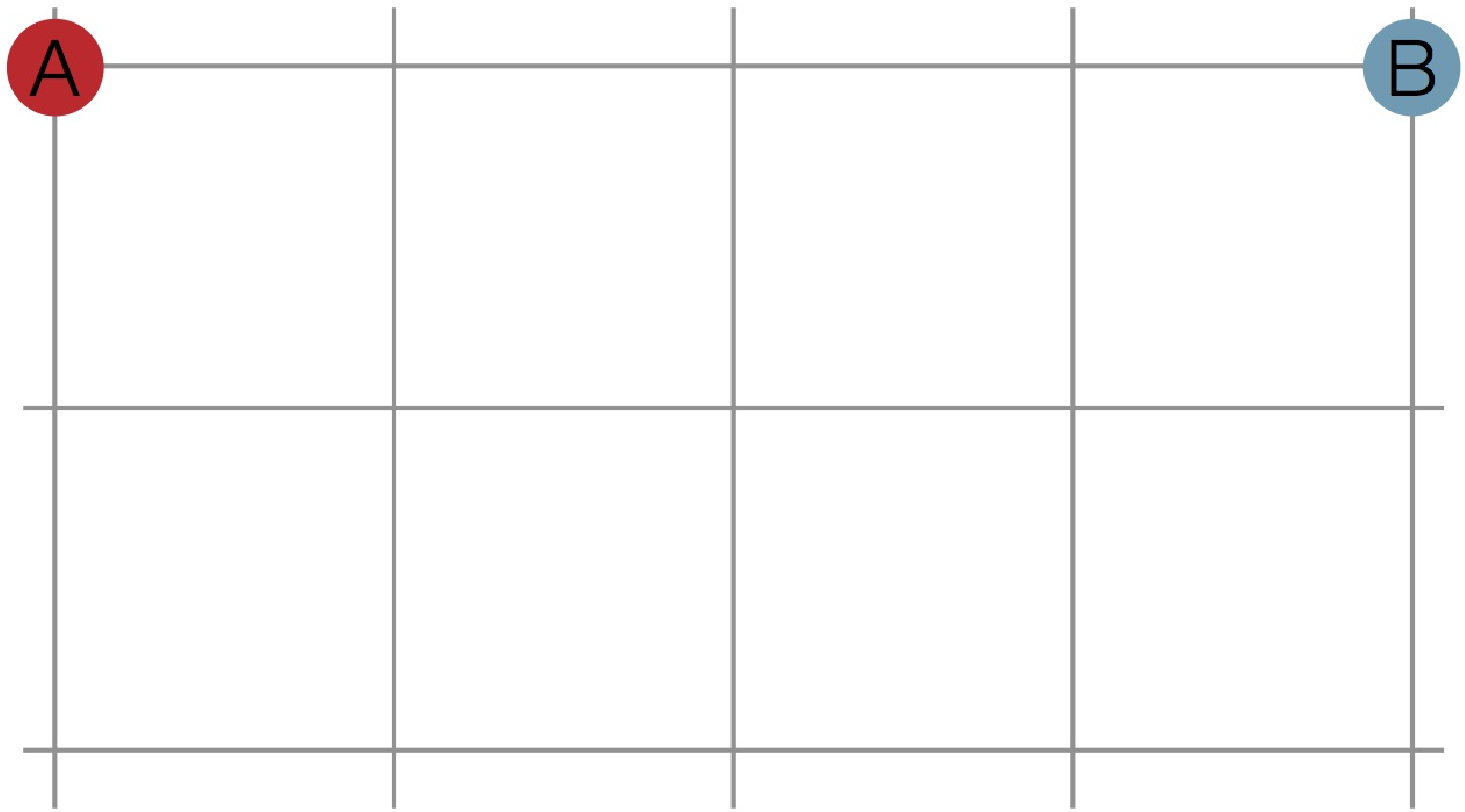
Cartography exercise: example

Convert to distances, based on 2-fold drops in titer from highest titer in a column.

	Serum A	**Serum B**
Virus A	0	4
Virus B	4	0

Cartography exercise: example

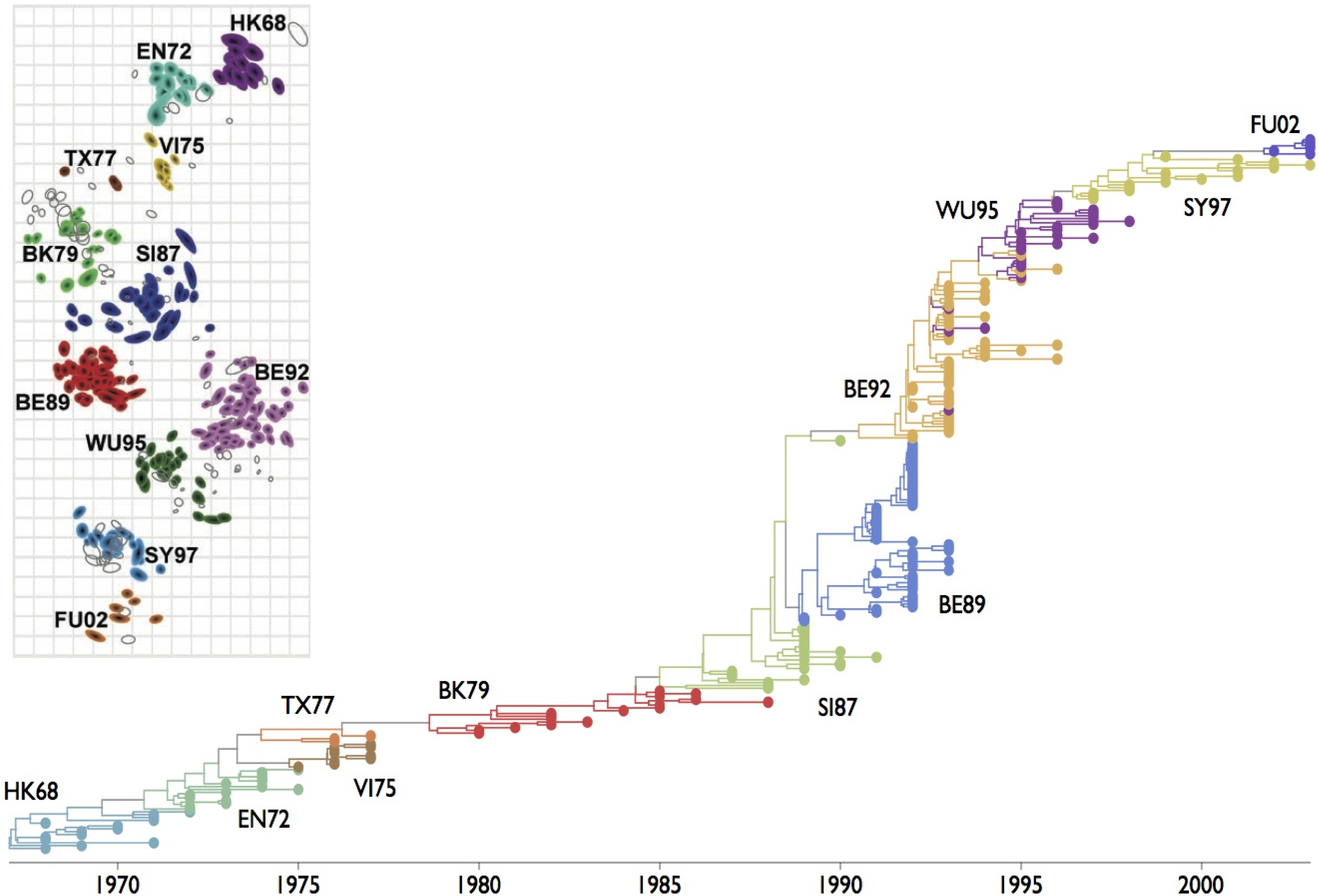
Position elements in 2D space so that distances are recapitulated.



Cartography exercise: data

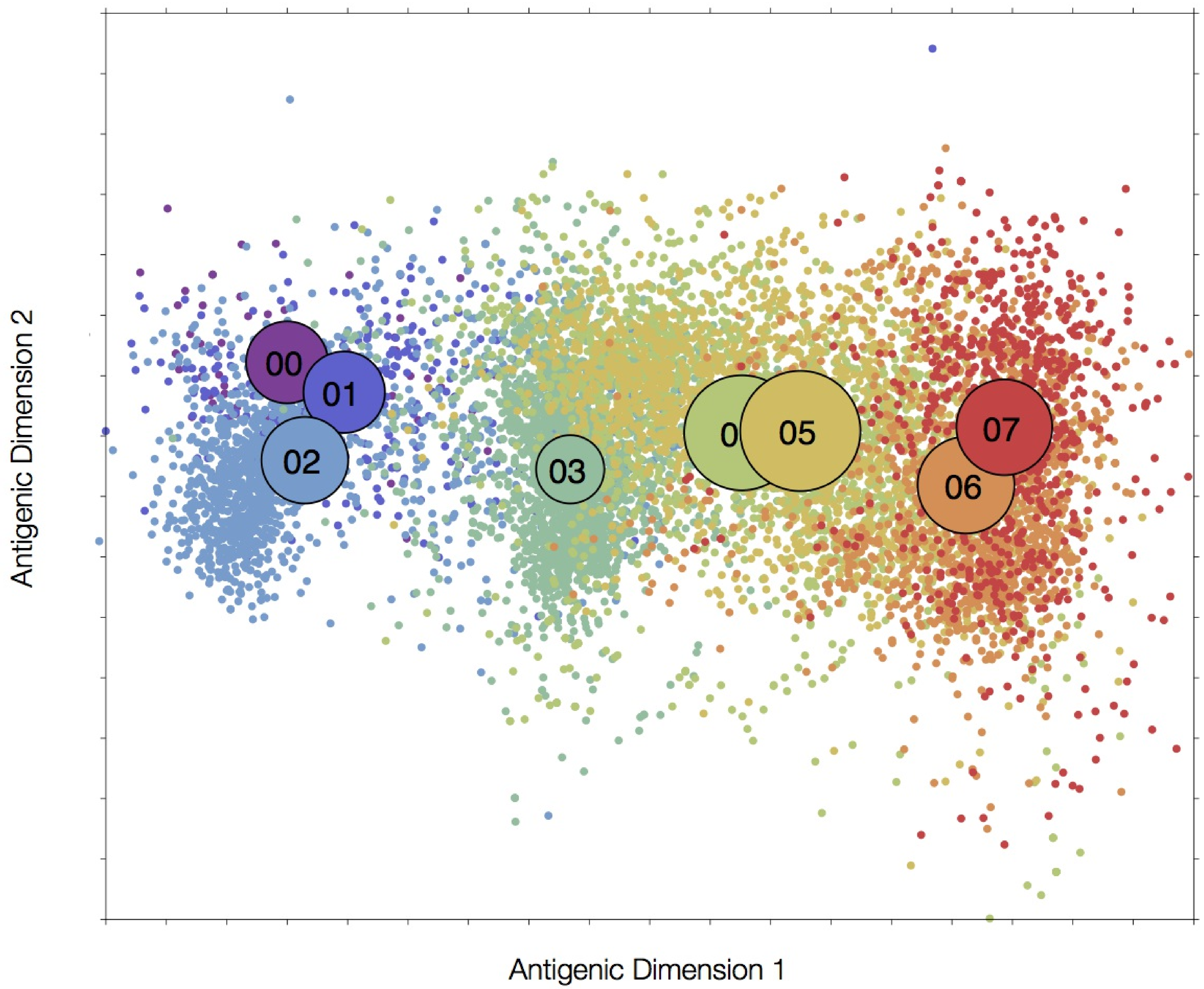
	Serum A	Serum B	Serum C	Serum D
Virus A	2560	80	640	320
Virus B	160	1280	160	80
Virus C	320	40	5120	40
Virus D	320	40	80	2560

Antigenic cartography for H3N2 influenza



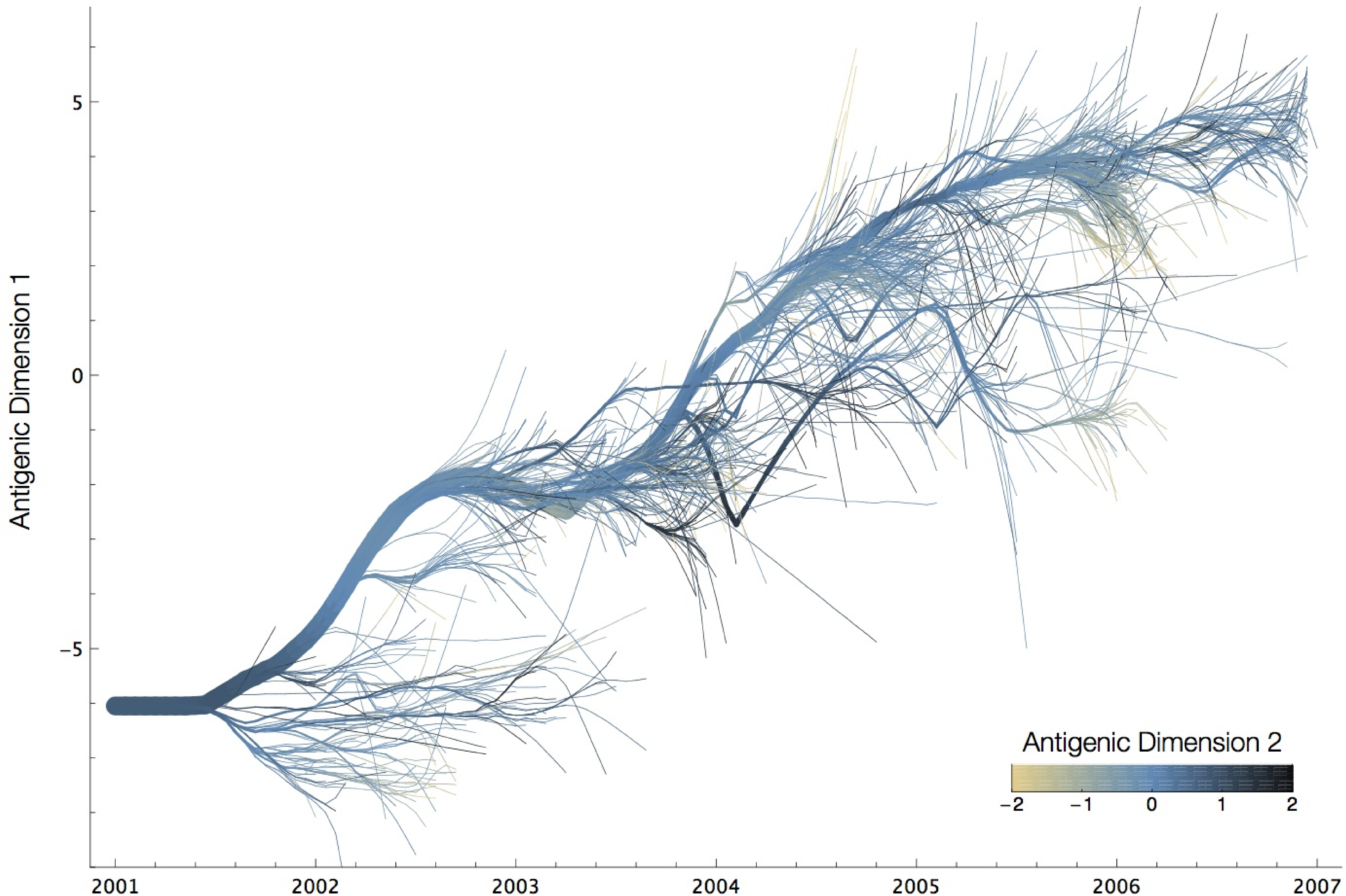
Smith et al 2004

More detailed analysis of H3N2 viruses from 2000 to 2007

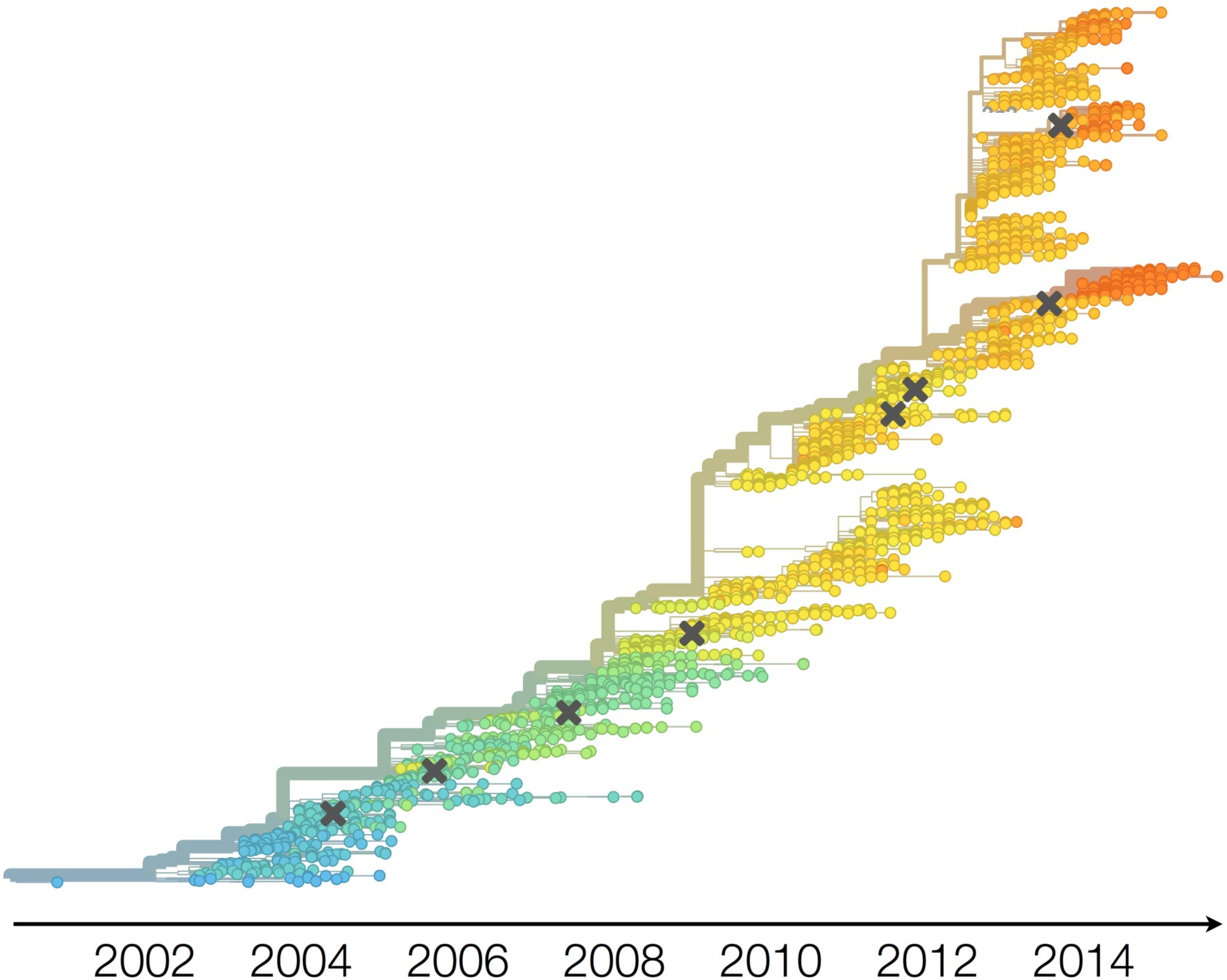


Russell et al 2008

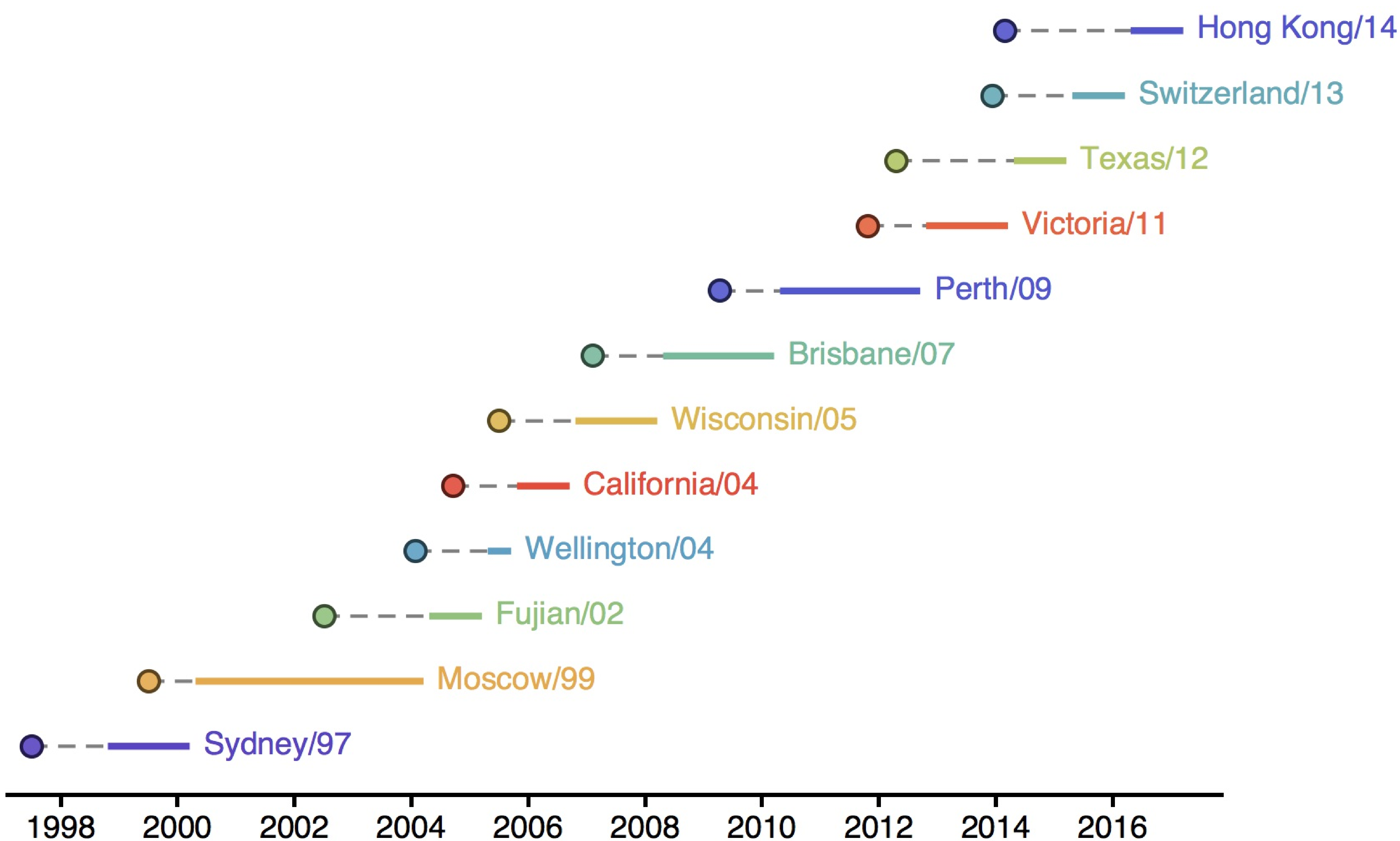
Primitive lineages die out, while advanced lineages persist



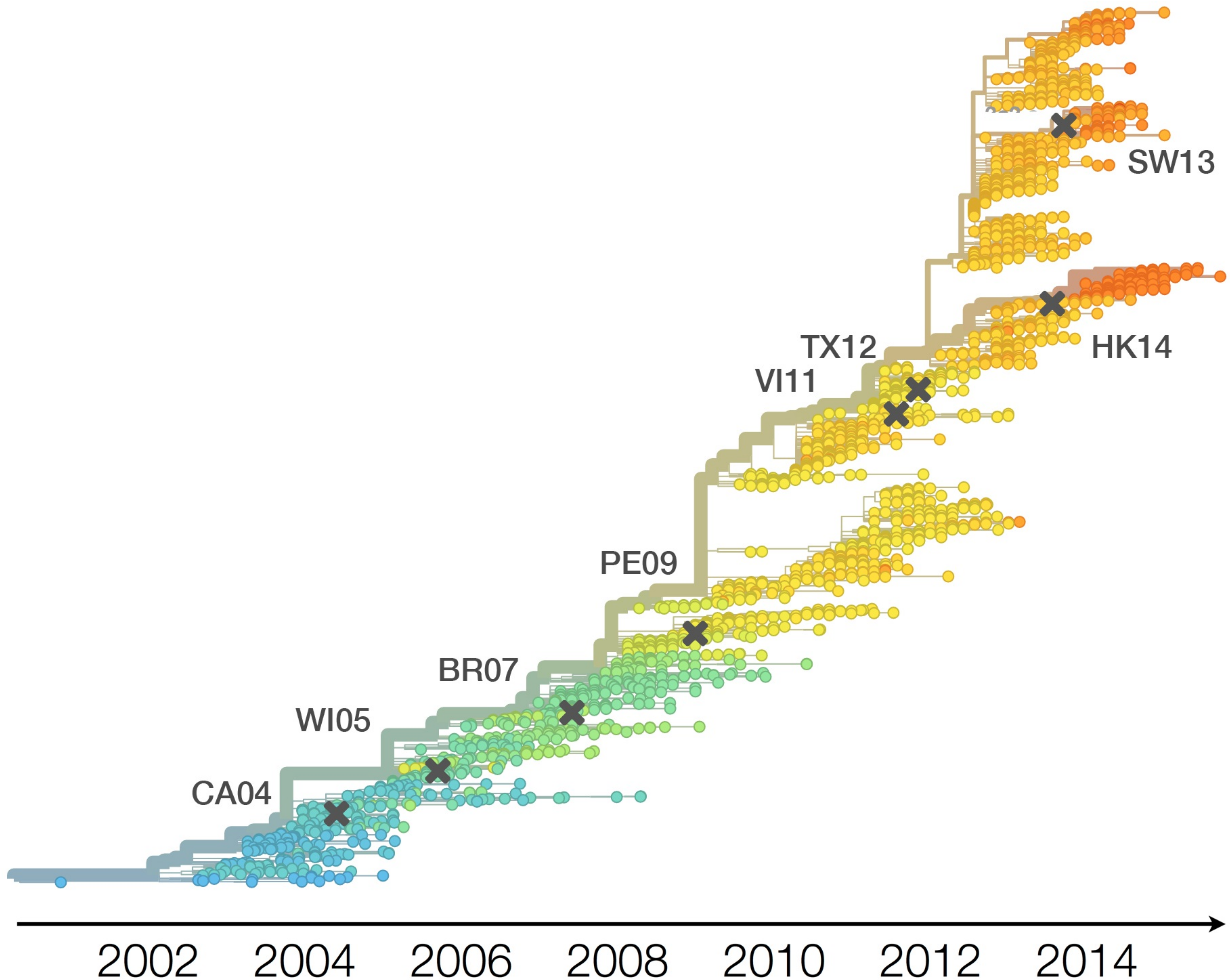
Antigenic evolution leads to clade turnover



The WHO has to keep updating vaccine strain to keep up with ongoing evolution



Vaccine strains map to drift events

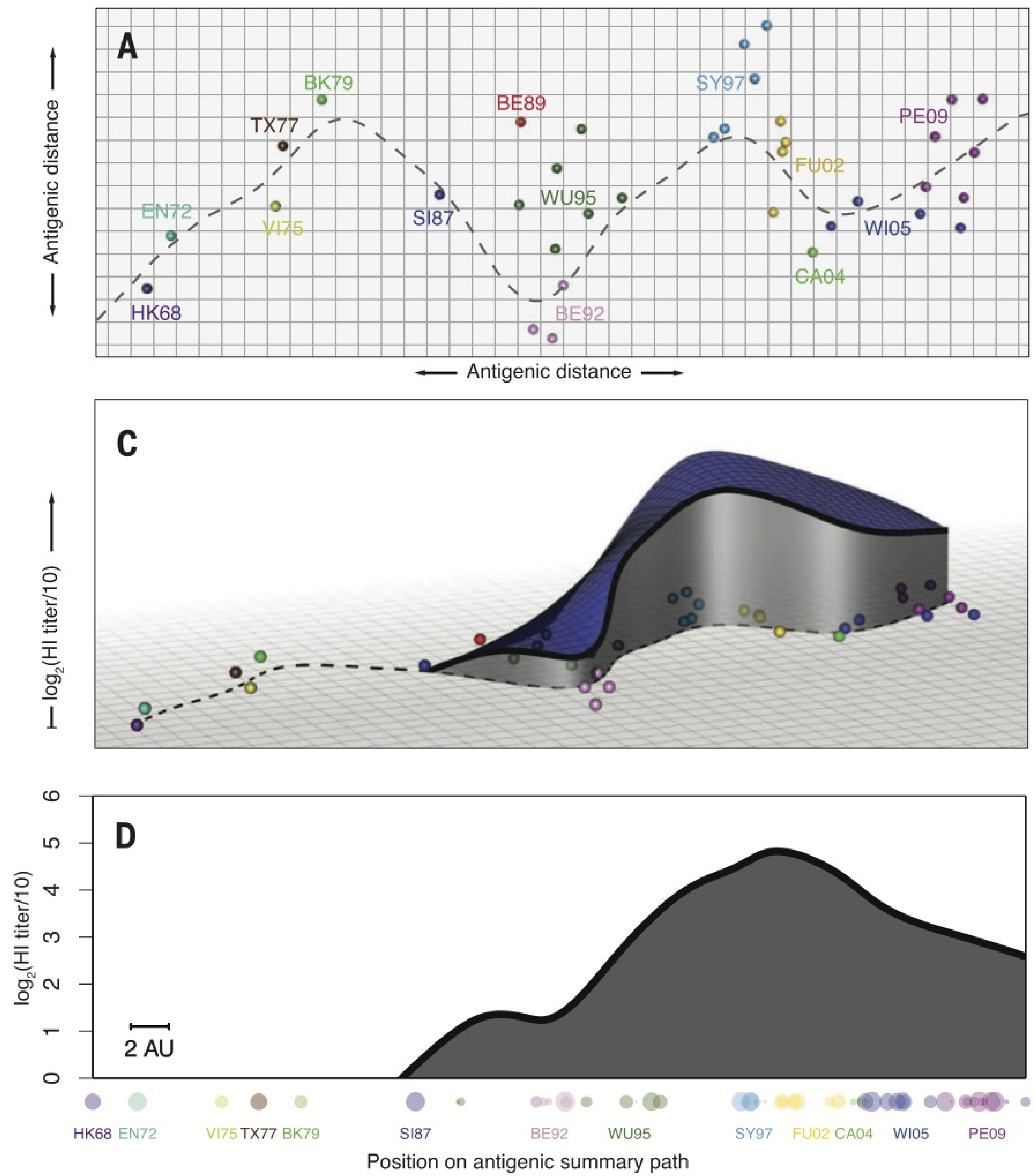


Original antigenic sin

"Humans vaccinated against influenza produce antibodies against the immunizing antigen, but produce antibodies of higher titer against the antigen that was their first childhood experience of influenza, even if that strain happend to be absent from the vaccine."

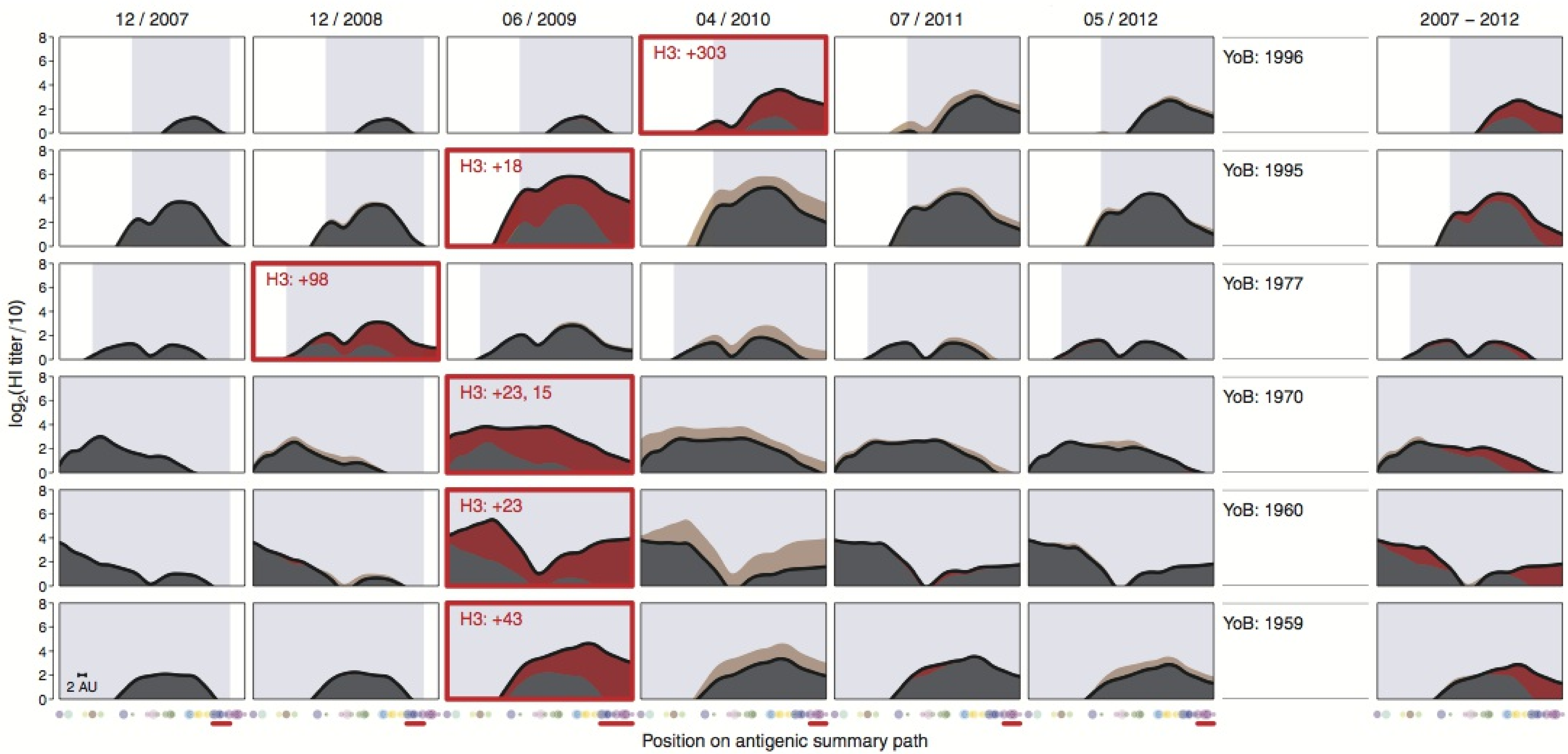
Fazekas de St. Groth and Webster 1966

Plotting human HI titers through time



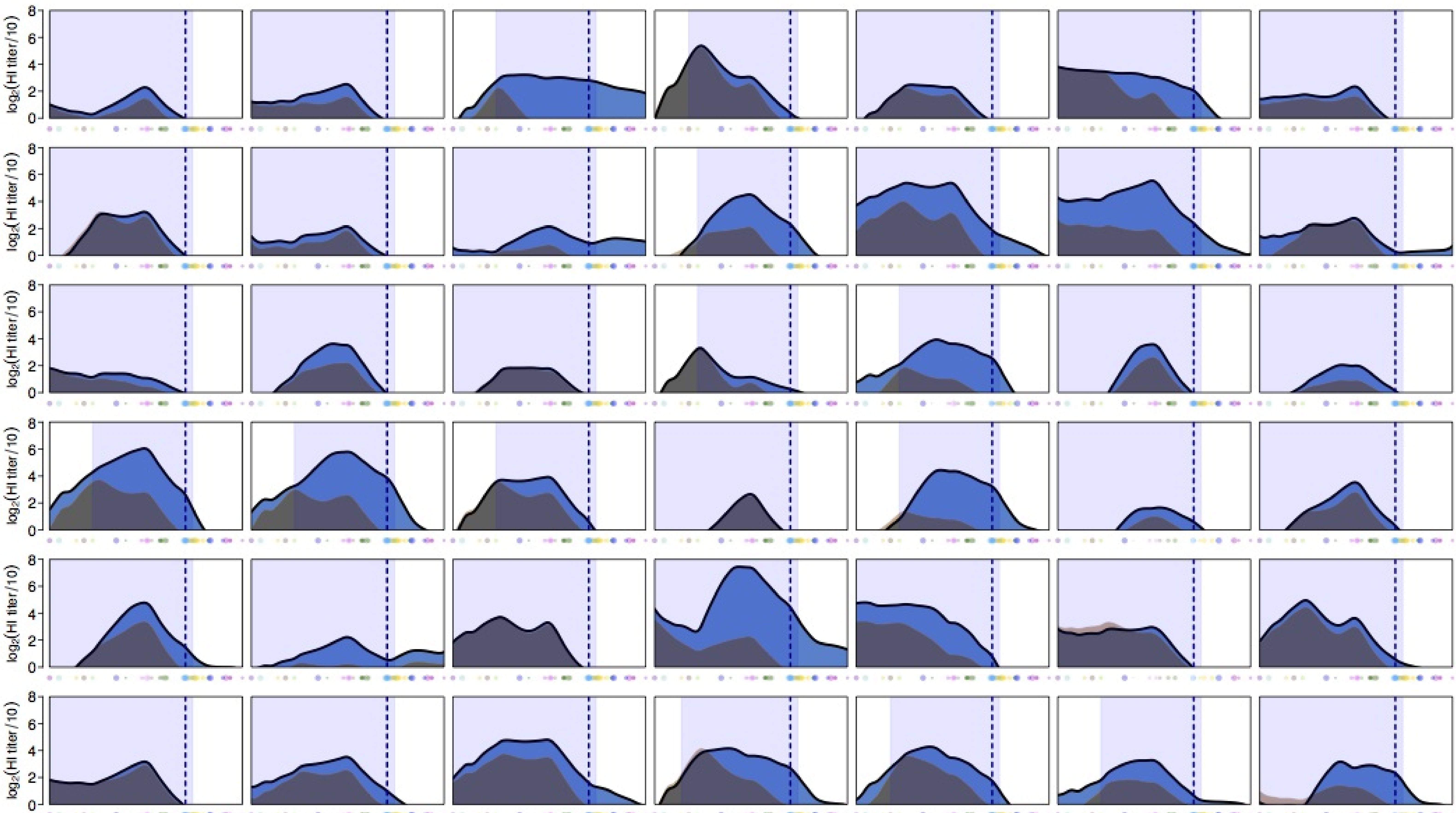
Fonville et al 2014

Infection transiently raises titers



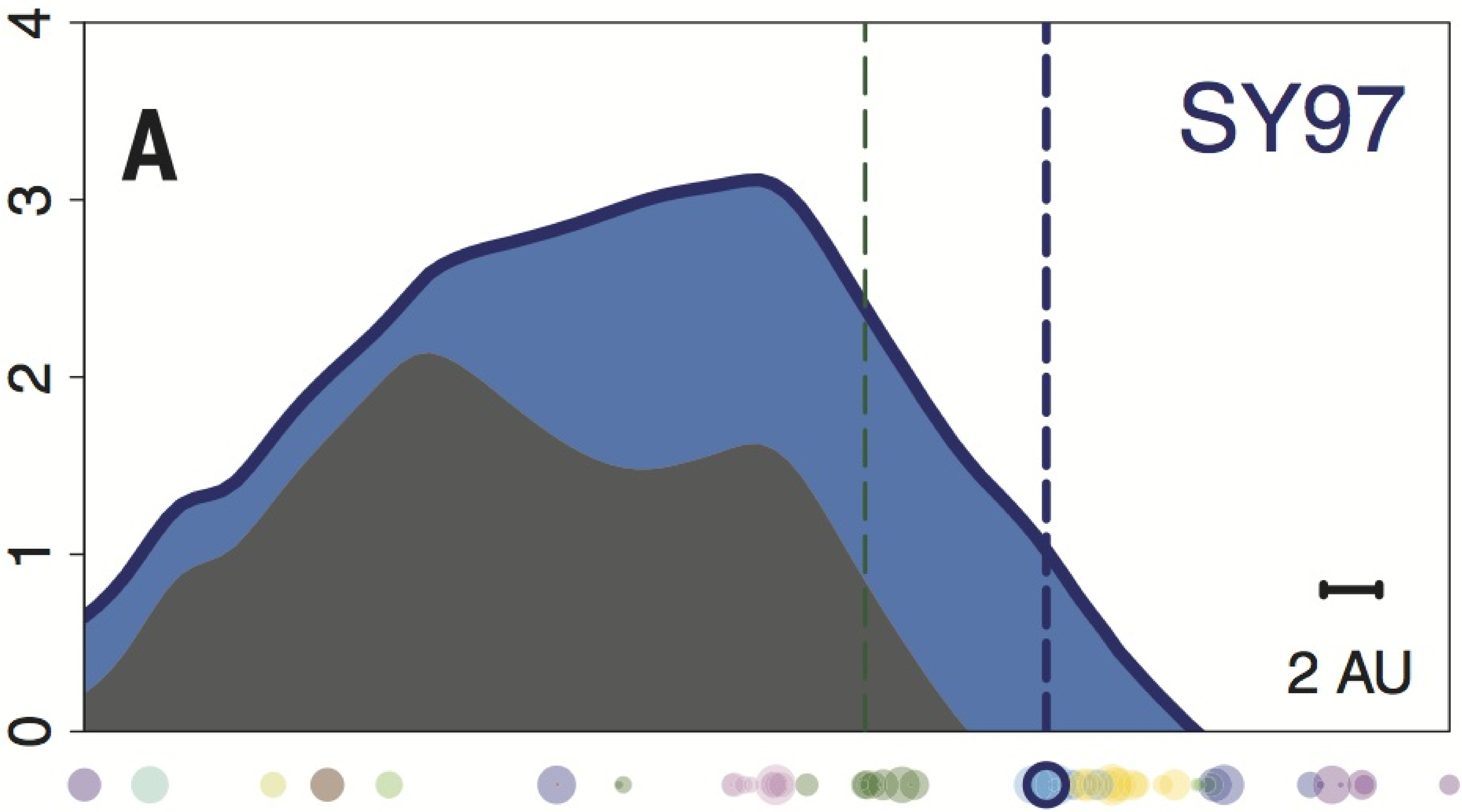
Fonville et al 2014

Vaccination shows a similar effect



Fonville et al 2014

Titers increase more to older viruses, not to antigenically matched viruses



Fonville et al 2014