Evolution of highly pathogenic avian influenza A (H5) virus

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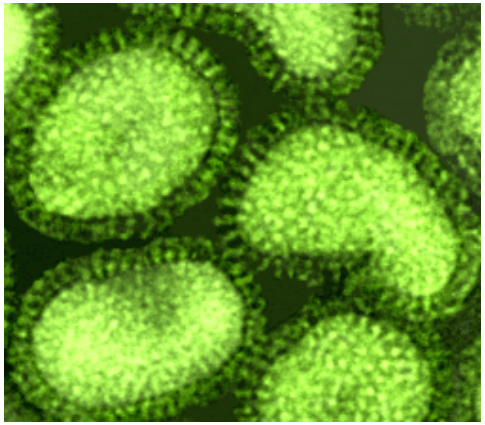
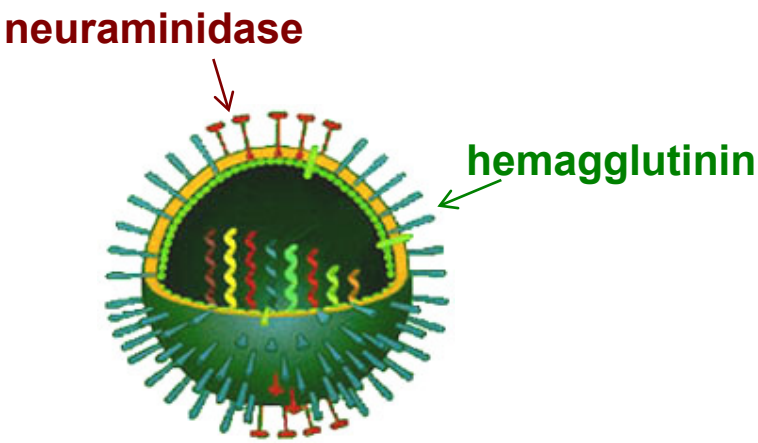
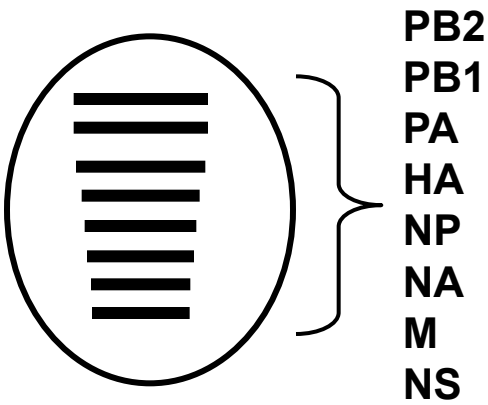
KITP – March 2, 2011

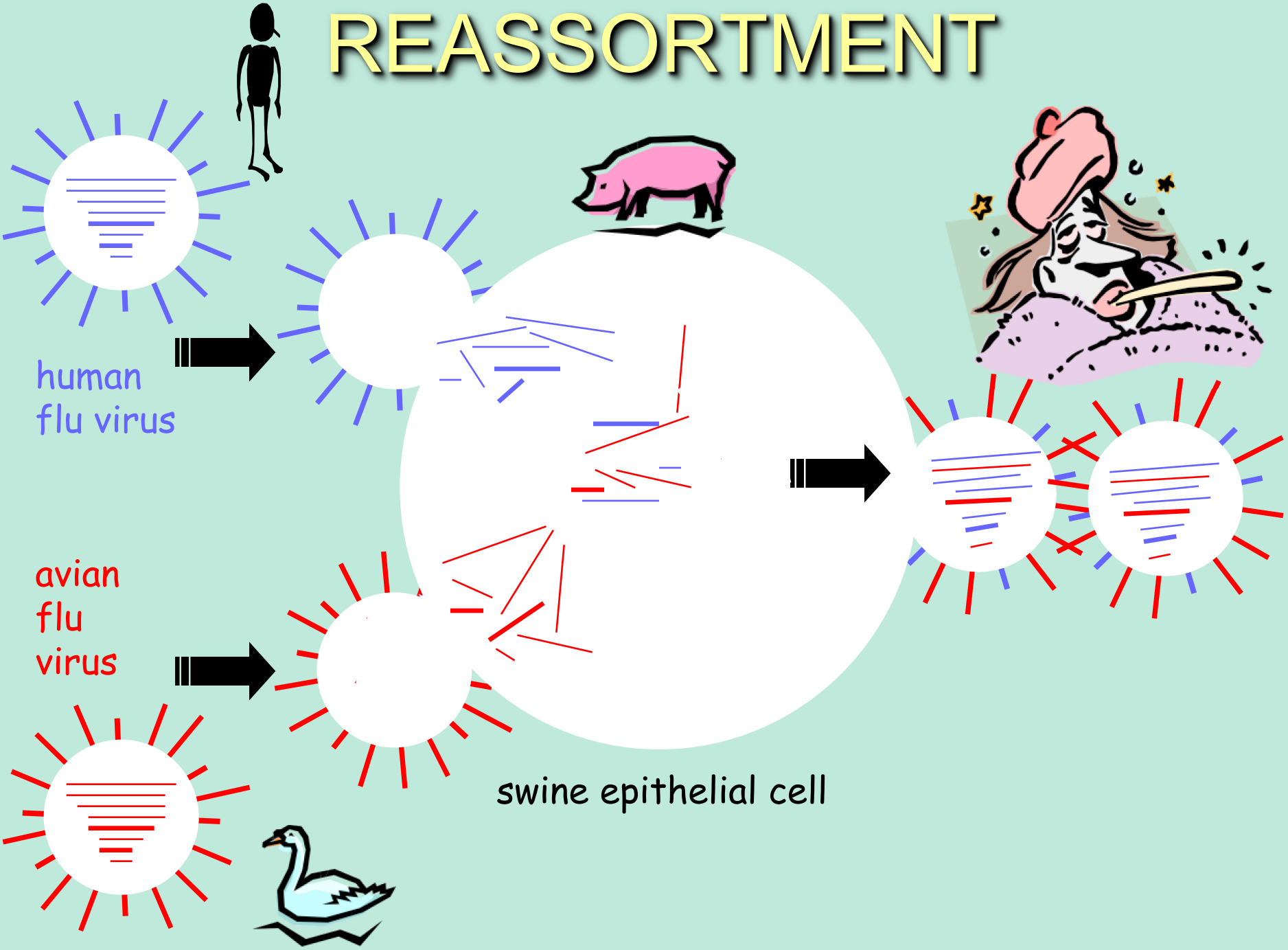


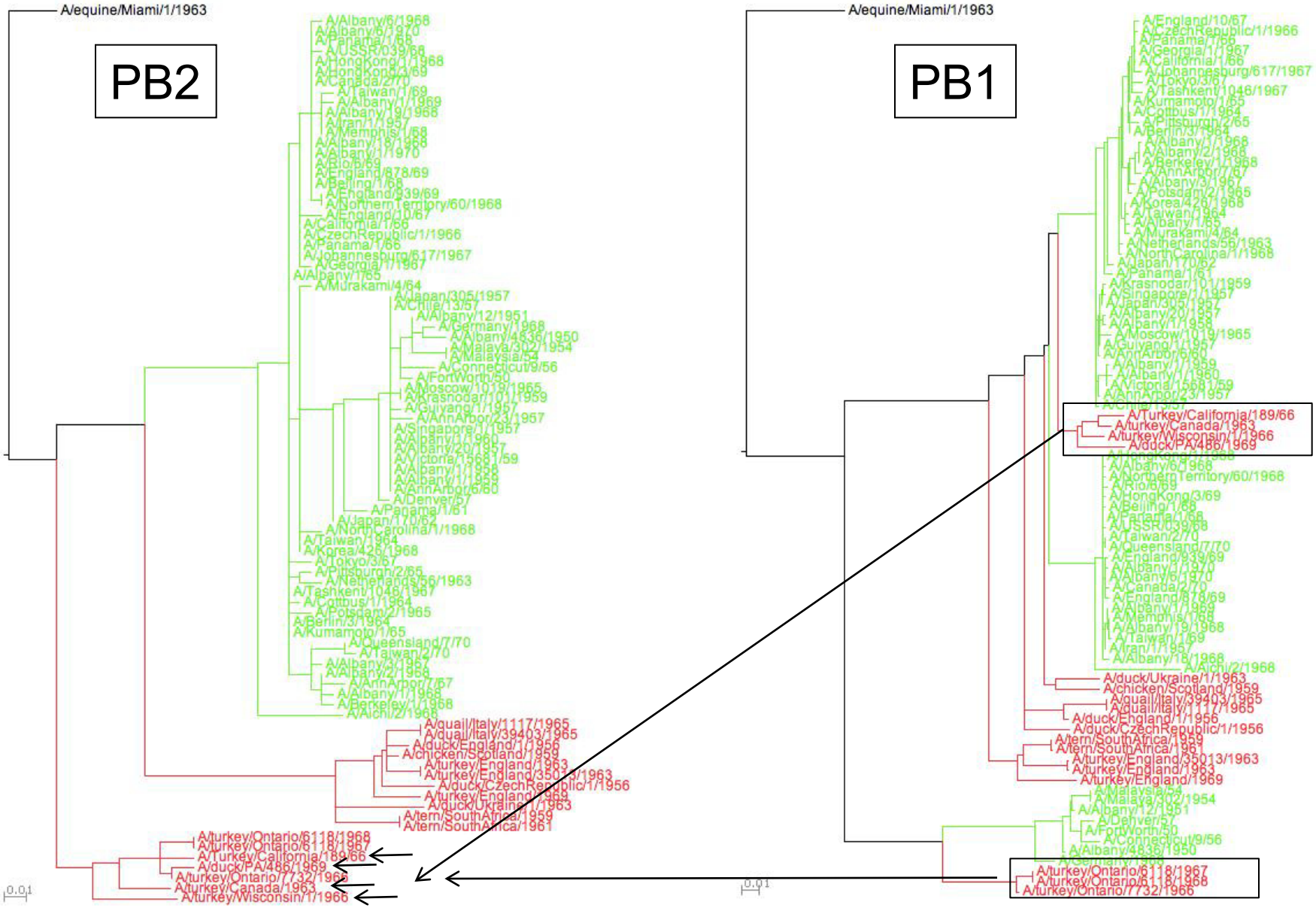
Influenza types A, B and C
RNA virus
Segmented genome





REASSORTMENT




PB2
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A/Albany/6/1968
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A/HongKong/3/69
A/Canada/2/70
A/Taiwan/1/69
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A/Iran/1/1957
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A/Rio/6/69
A/England/878/69
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A/Murakami/4/64
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A/Malaya/302/1954
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A/Connecticut/9/56
A/FortWorth/50
A/Moscow/1019/1965
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A/AnnArbor/23/1957
A/Singapore/1/1957
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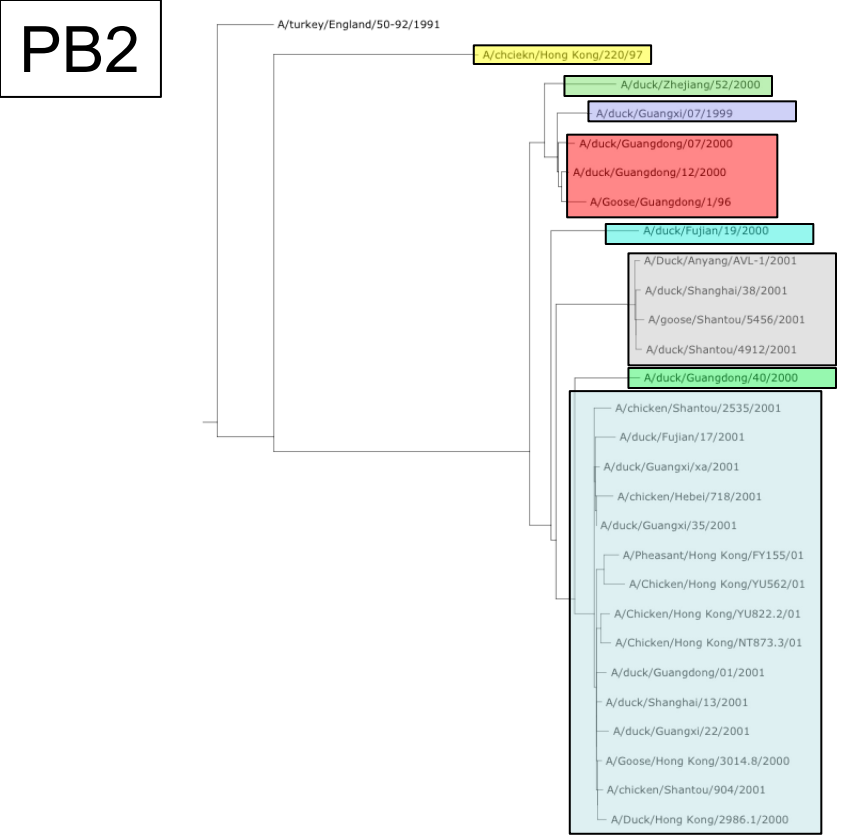
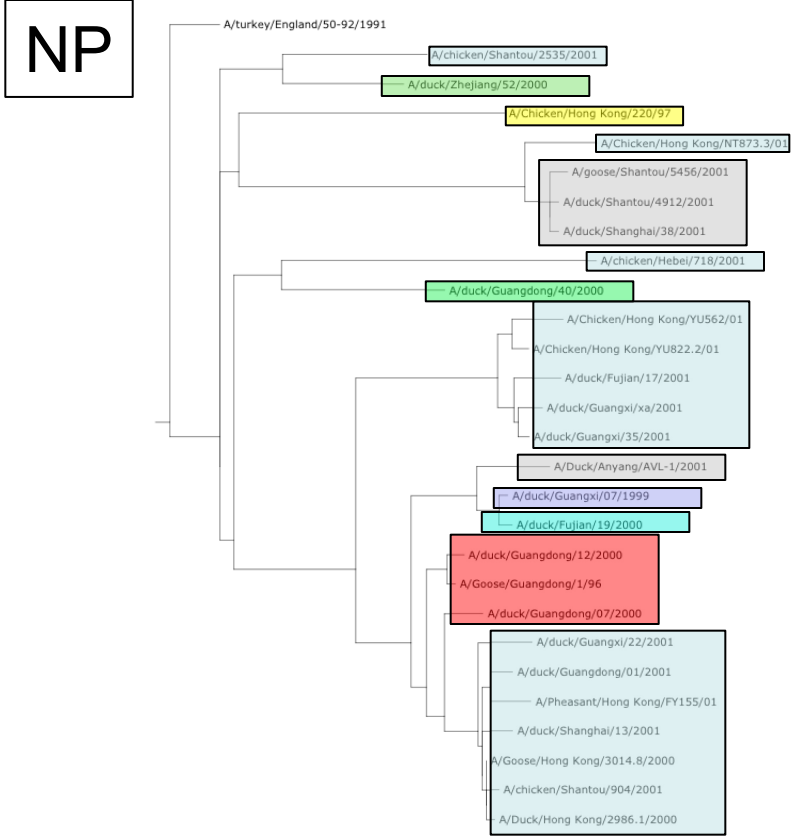
0.01

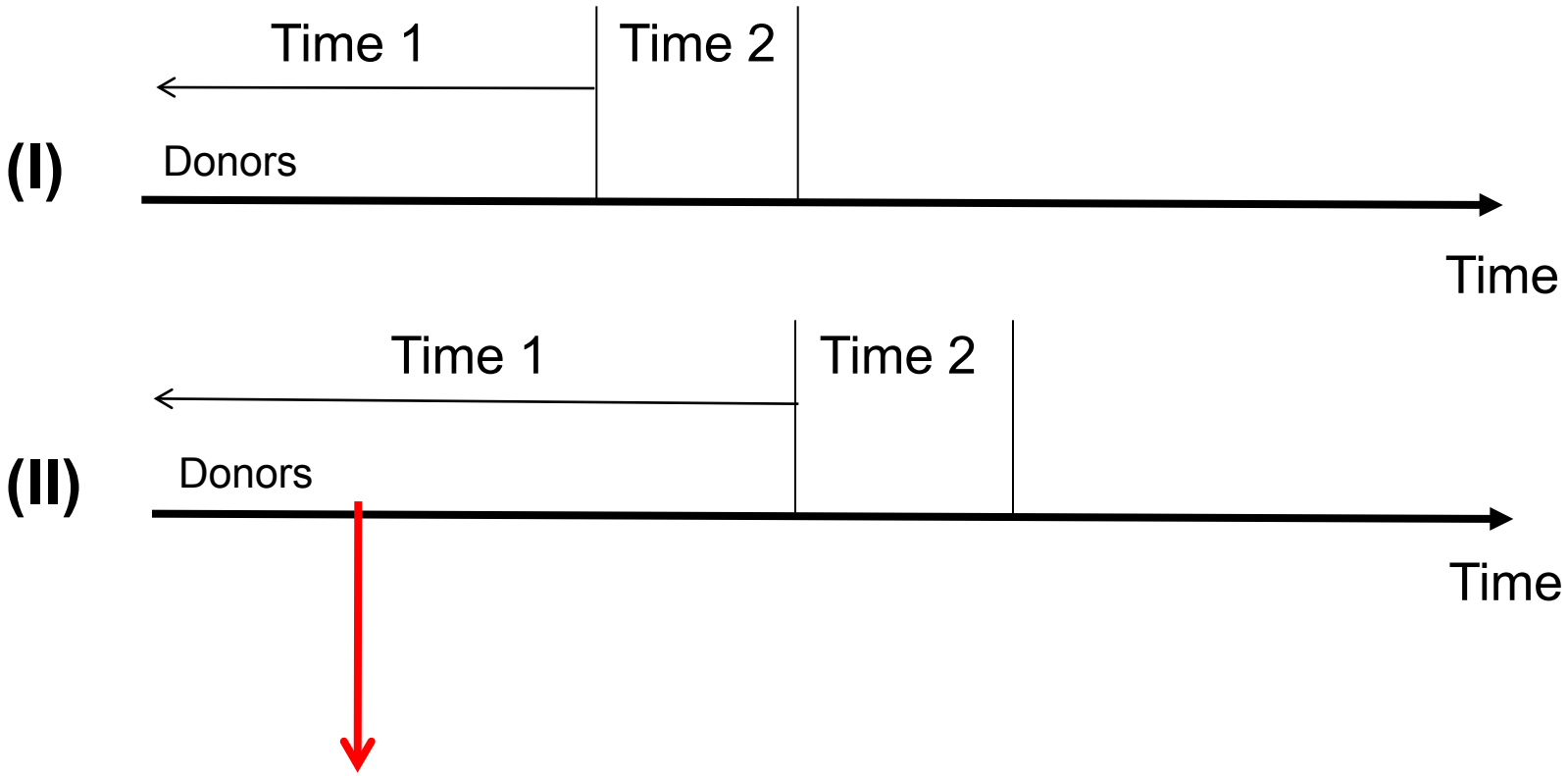
HUMAN AVIAN





Avian influenza A HA sequences, 1996-2001

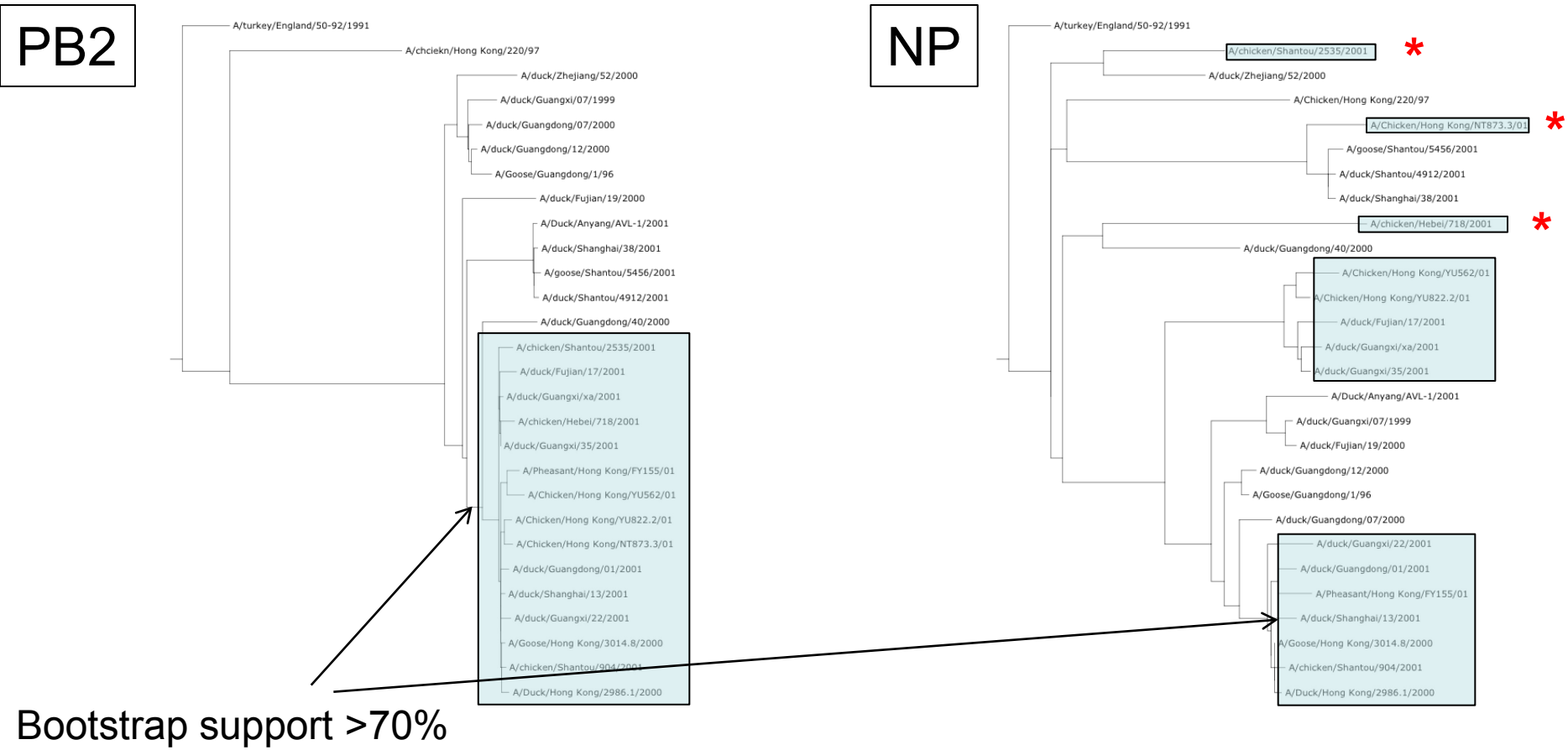
Two-time test for reassortment



Set of single representatives of each unique genotype among “donor” viruses = “reference trees”
Test viruses in Time 2 against reference viruses in Time 1

Macken, Webby and Bruno (2006) J. General Virology

Inference of reference trees



Bootstrap support >70%

Avian influenza A (H5N1) HA sequences, 1996-2001

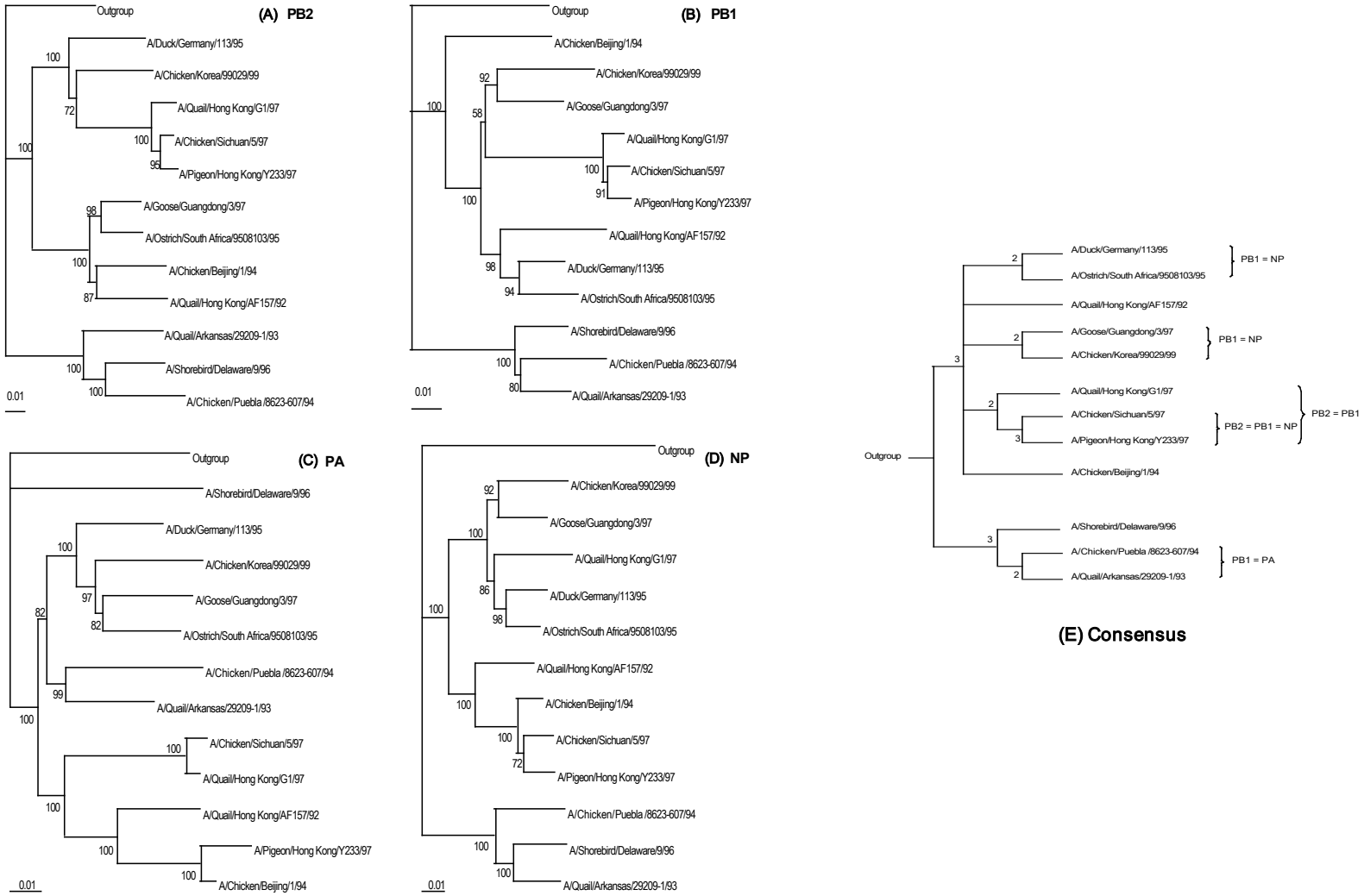
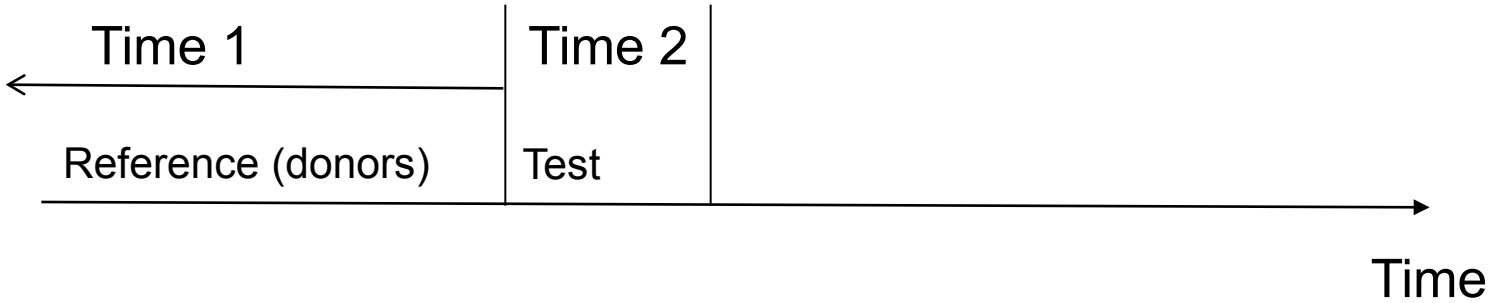


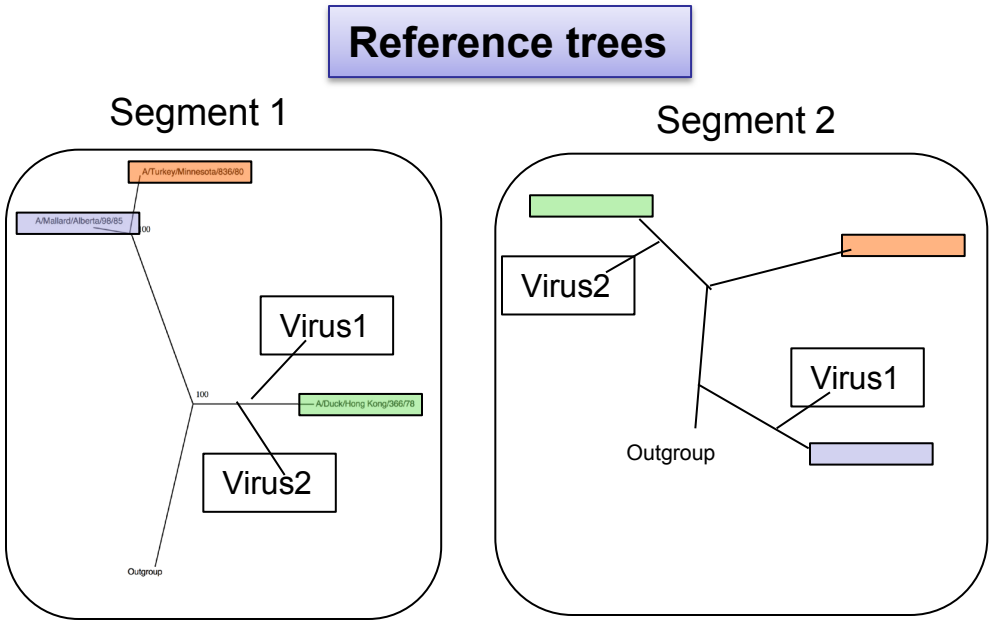
Figure 3

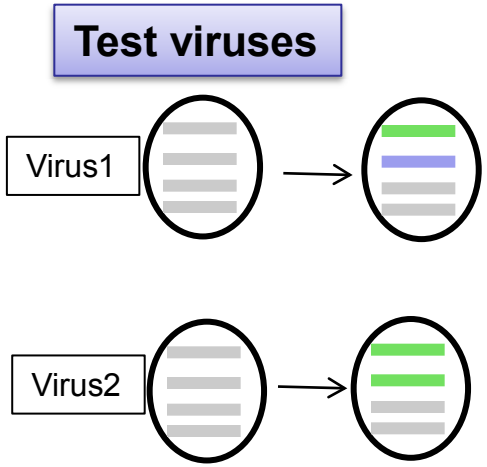
Replication complex – avian influenza A viruses, 1993 - 1999

Two-time test for reassortment

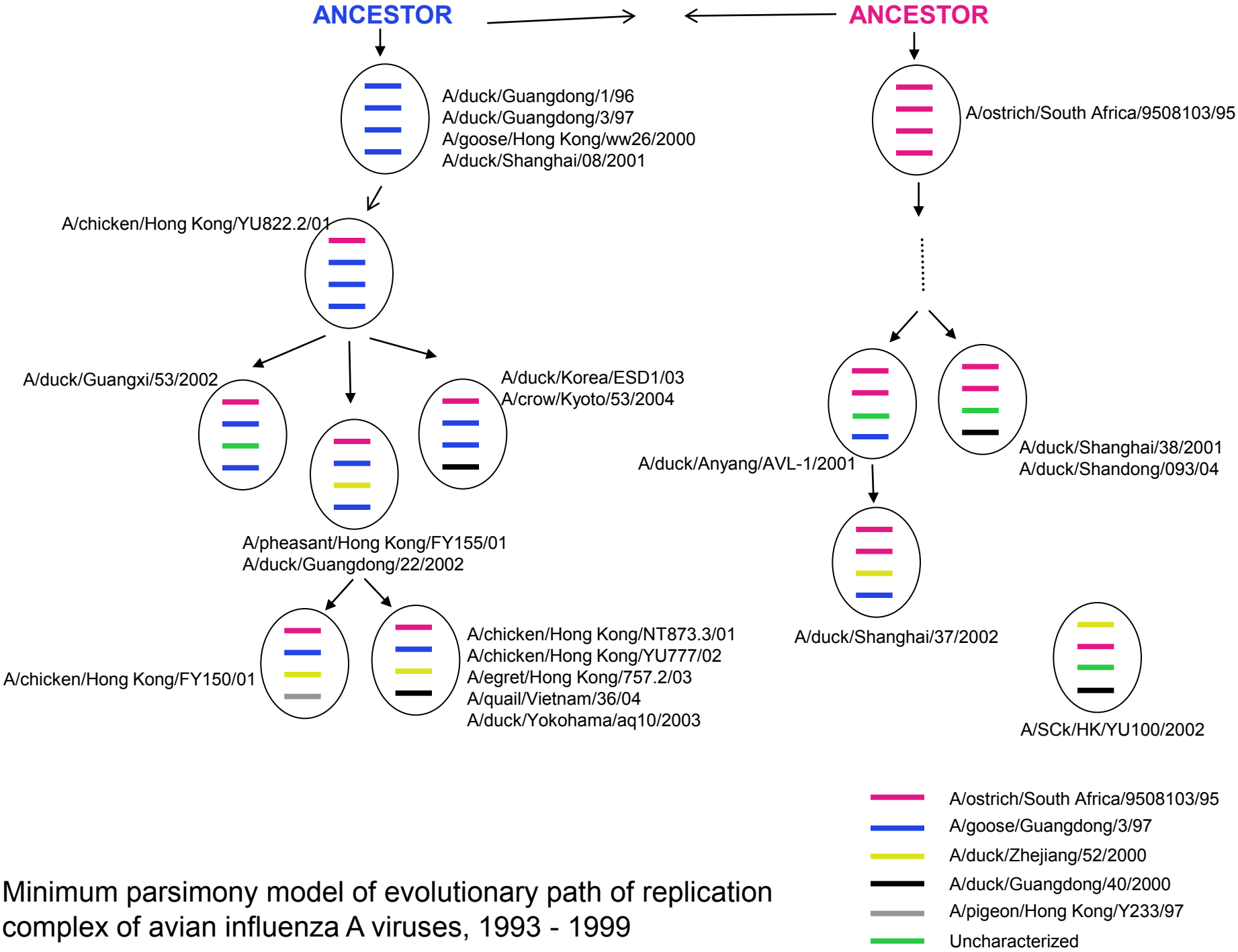
Macken, Webby and Bruno (2006) J. General Virology



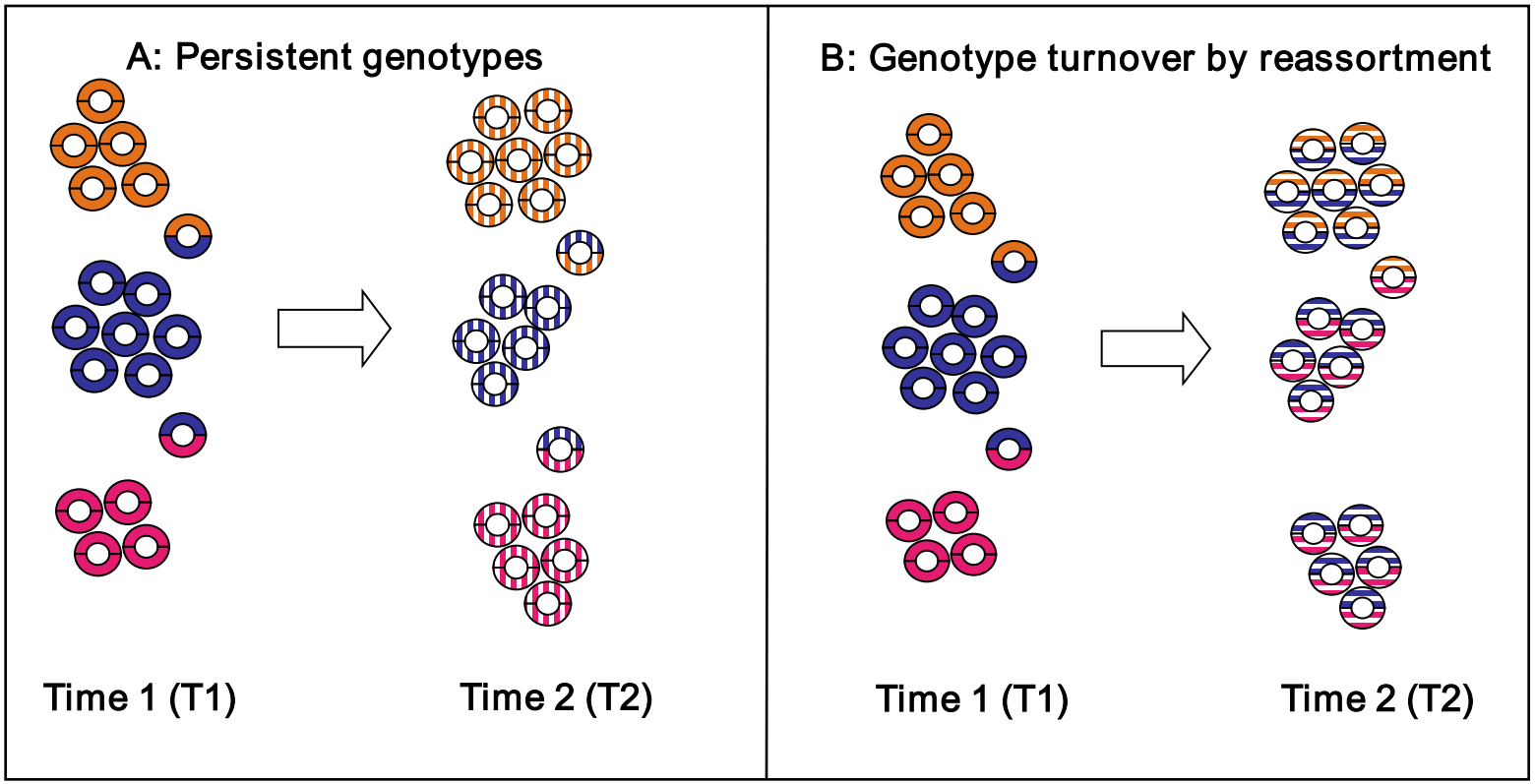




+ reference trees for segments 3 and 4



Minimum parsimony model of evolutionary path of replication complex of avian influenza A viruses, 1993 - 1999


A: Persistent genotypes
Time 1 (T1)
Time 2 (T2)
B: Genotype turnover by reassortment
Time 1 (T1)
Time 2 (T2)

Conclusions

- Segments reassort independently
- New reassortants replace earlier viruses
- Reassortants circulate for apparently short periods of time

How fast is reassortment?

Likelihood function: example

$$\rho^{4(1996-R_{0G})} * \rho^{4(1997-R_{0G})} * \rho^{4(2000-R_{0G})} * \rho^{4(2001-R_{0G})} * \binom{4}{1}\rho^{3(2001-R_{0G})}(1-\rho^{(2001-R_{0G})}) * \binom{4}{2}\rho^{2(2002-R_{0G})}\left[(1-\rho^{(2002-R_{0G})})\right]^2 *$$

$$\binom{4}{2}\rho^{2(2001-R_{0G})}\left[(1-\rho^{(2001-R_{0G})})\right]^2 * \binom{4}{2}\rho^{2(2002-R_{0G})}\left[(1-\rho^{(2002-R_{0G})})\right]^2 * \binom{4}{2}\rho^{2(2003-R_{0G})}\left[(1-\rho^{(2003-R_{0G})})\right]^2 *$$

$$\binom{4}{2}\rho^{2(2004-R_{0G})}\left[(1-\rho^{(2004-R_{0G})})\right]^2 * \binom{4}{3}\rho^{(2001-R_{0G})}\left[(1-\rho^{(2001-R_{0G})})\right]^3 * \binom{4}{3}\rho^{(2001-R_{0G})}\left[(1-\rho^{(2001-R_{0G})})\right]^3 *$$

$$\binom{4}{3}\rho^{(2002-R_{0G})}\left[(1-\rho^{(2002-R_{0G})})\right]^3 * \binom{4}{3}\rho^{(2003-R_{0G})}\left[(1-\rho^{(2003-R_{0G})})\right]^3 * \binom{4}{3}\rho^{(2004-R_{0G})}\left[(1-\rho^{(2004-R_{0G})})\right]^3 *$$

$$\binom{4}{3}\rho^{(2003-R_{0G})}\left[(1-\rho^{(2003-R_{0G})})\right]^3$$

Estimate of rho = 0. 9473

TR =the time in years between creation of a new genotype at C and the first reassortment with a biologically distinct lineage to create a new, viable (i.e. transmissible) genotype

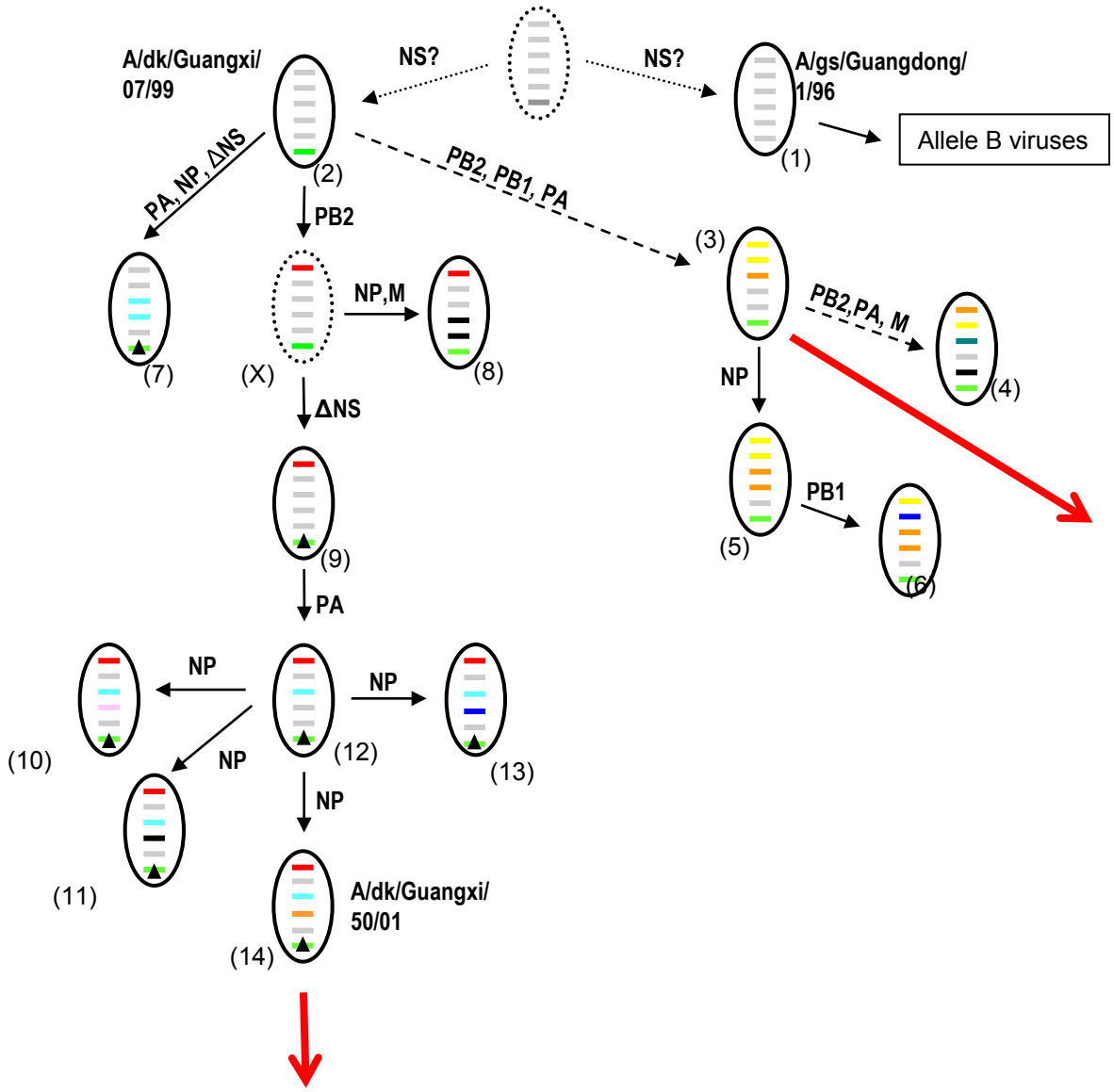
Estimated median value of TR is 3 years and the chance that TR exceeds 7 years is 22 %.

Avian influenza A (H5N1), HP viruses

- 651 viruses HP influenza A (H5N1) viruses from Eurasia
- 1999 – 2008
- six internal genes/8 proteins
- exclude HA and NA (surface proteins) – did not reassort (cladal expansion)
- time intervals: 2000-1, 2003-3, 2004-8

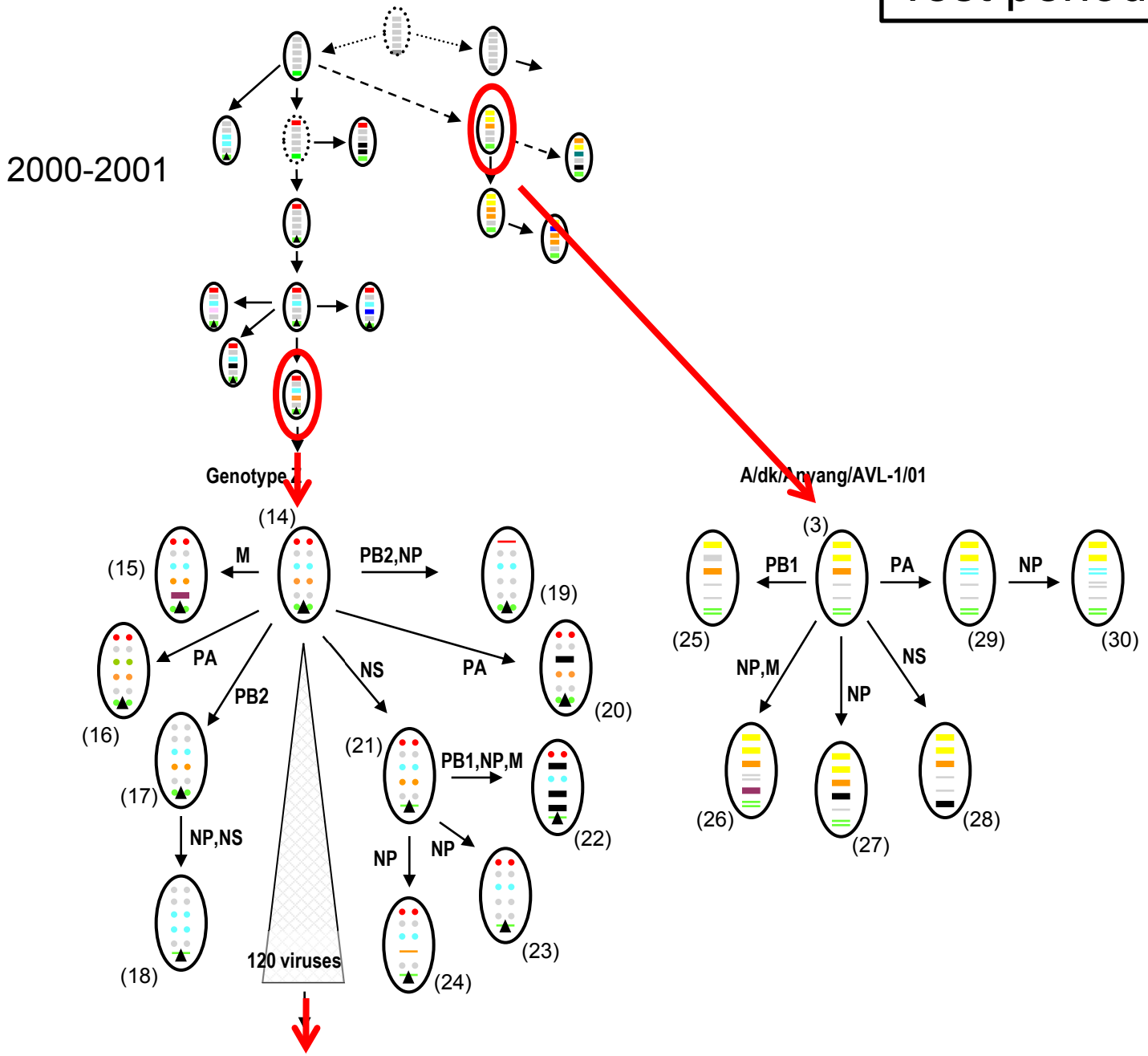
Avian influenza A (H5N1), HP viruses

Test period 2000-1

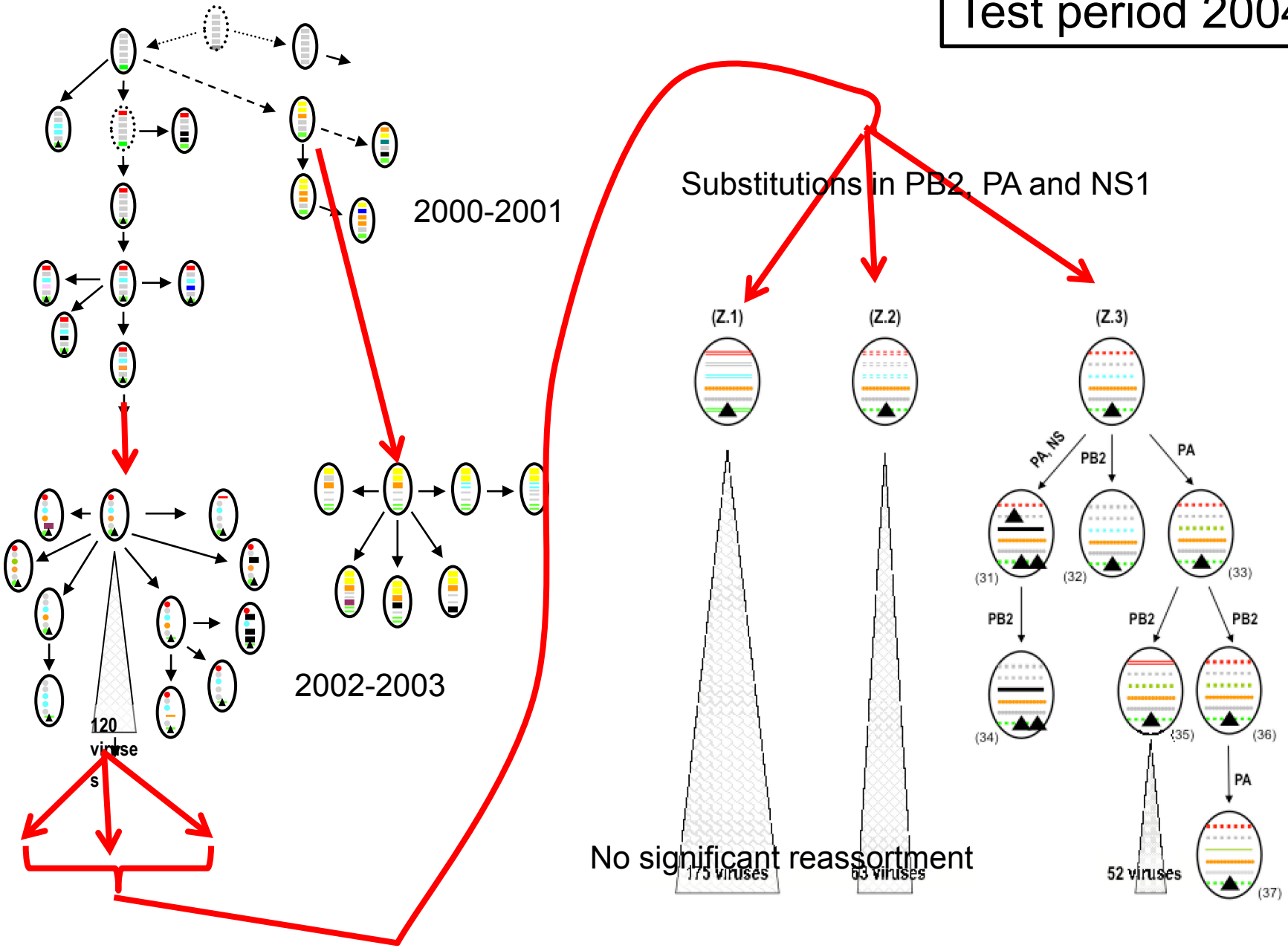


Neumann, Green, Macken (2010) J. General Virology

Test period 2002-3



Test period 2004-8



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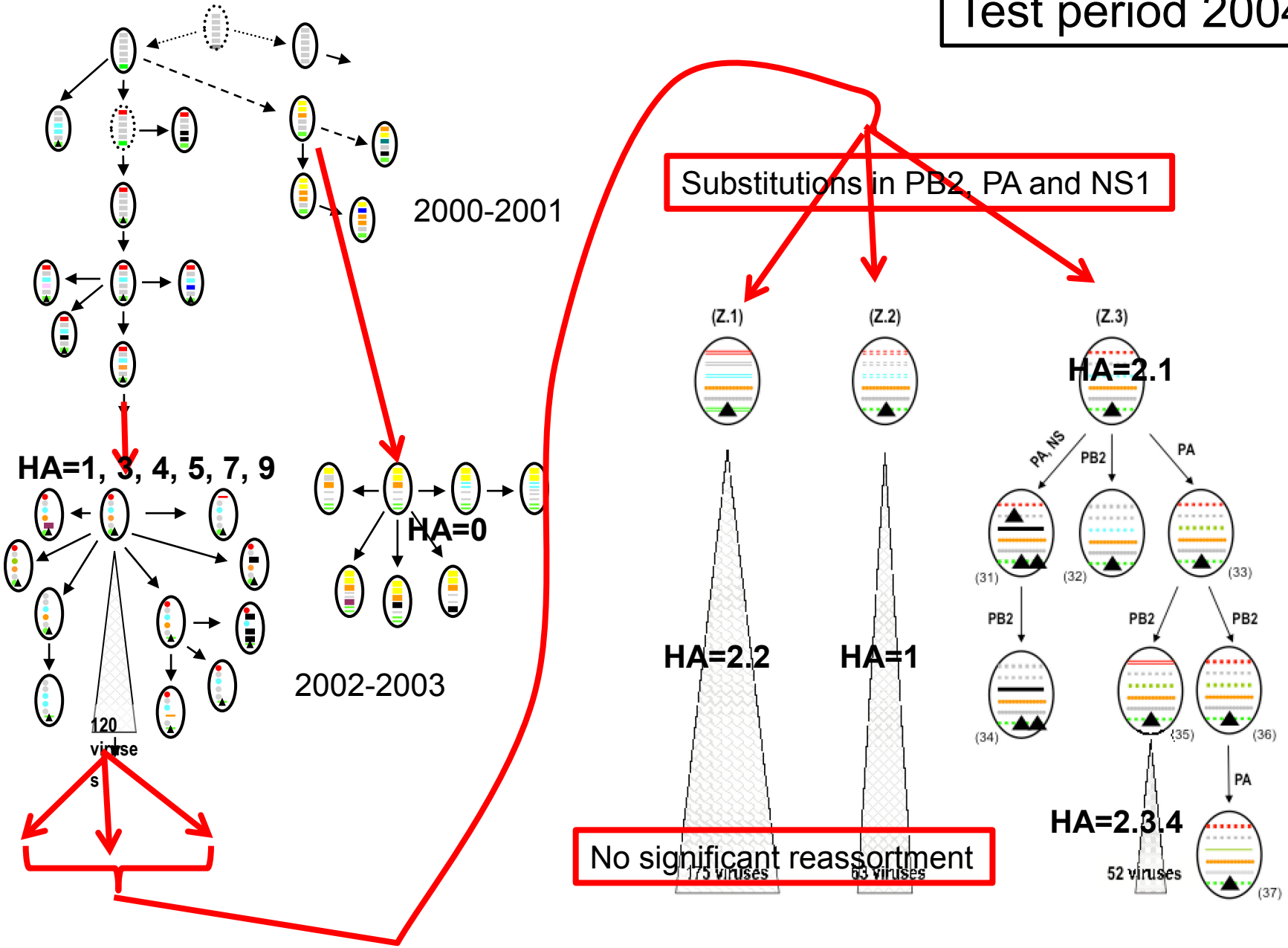
Test period 2004-8

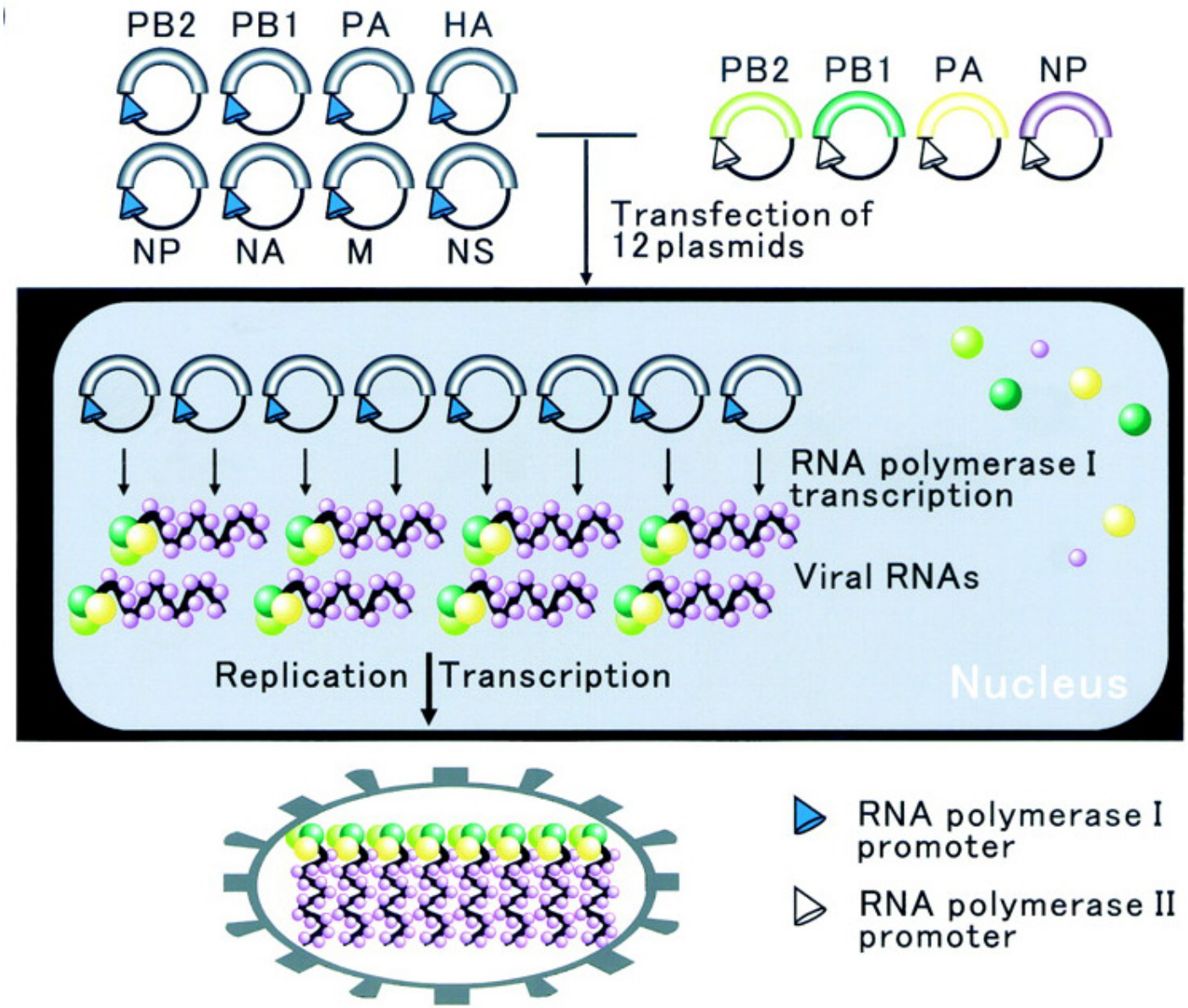


Conclusions

- It is essential to deal with reassortment in a "rigorous" manner for many analyses.
- Reassortment and point mutation both contribute significantly to evolution over a short period of time
- Reassortment creates novel genotypes, many of which are unsuccessful; successful ones replace earlier genotypes
- Point mutation distinguishes apparently "stable" lineages

Many questions

- What factors contribute to "stability" of lineages?
- Interaction of surface and internal proteins?


PB2
PB1
PA
HA
NP
NA
M
NS
PB2
PB1
PA
NP
Transfection of
12 plasmids
RNA polymerase I
transcription
Viral RNAs
Replication
Transcription
Nucleus
RNA polymerase I
promoter
RNA polymerase II
promoter