Эволюция вирусов
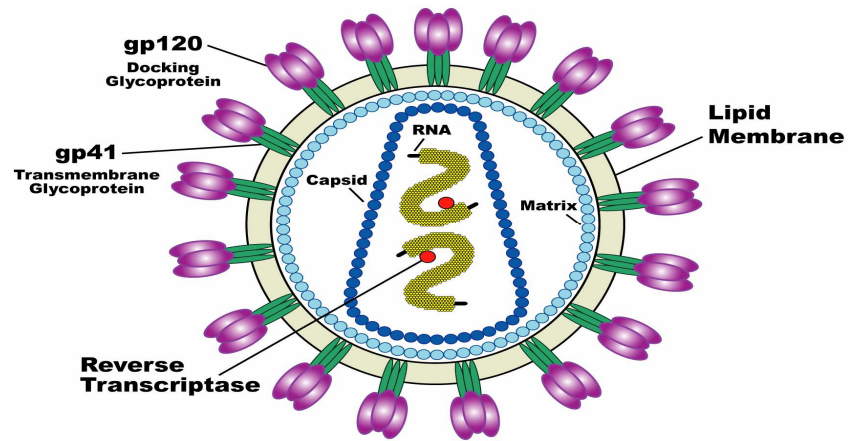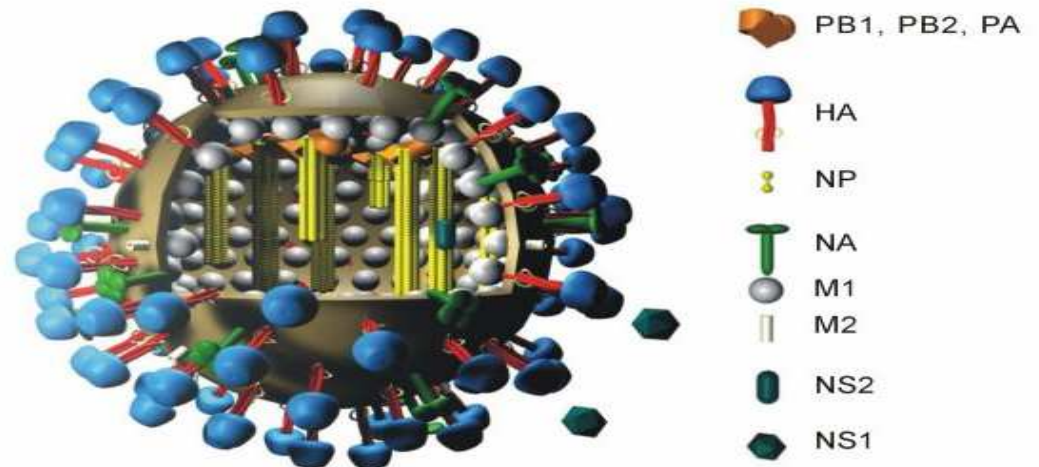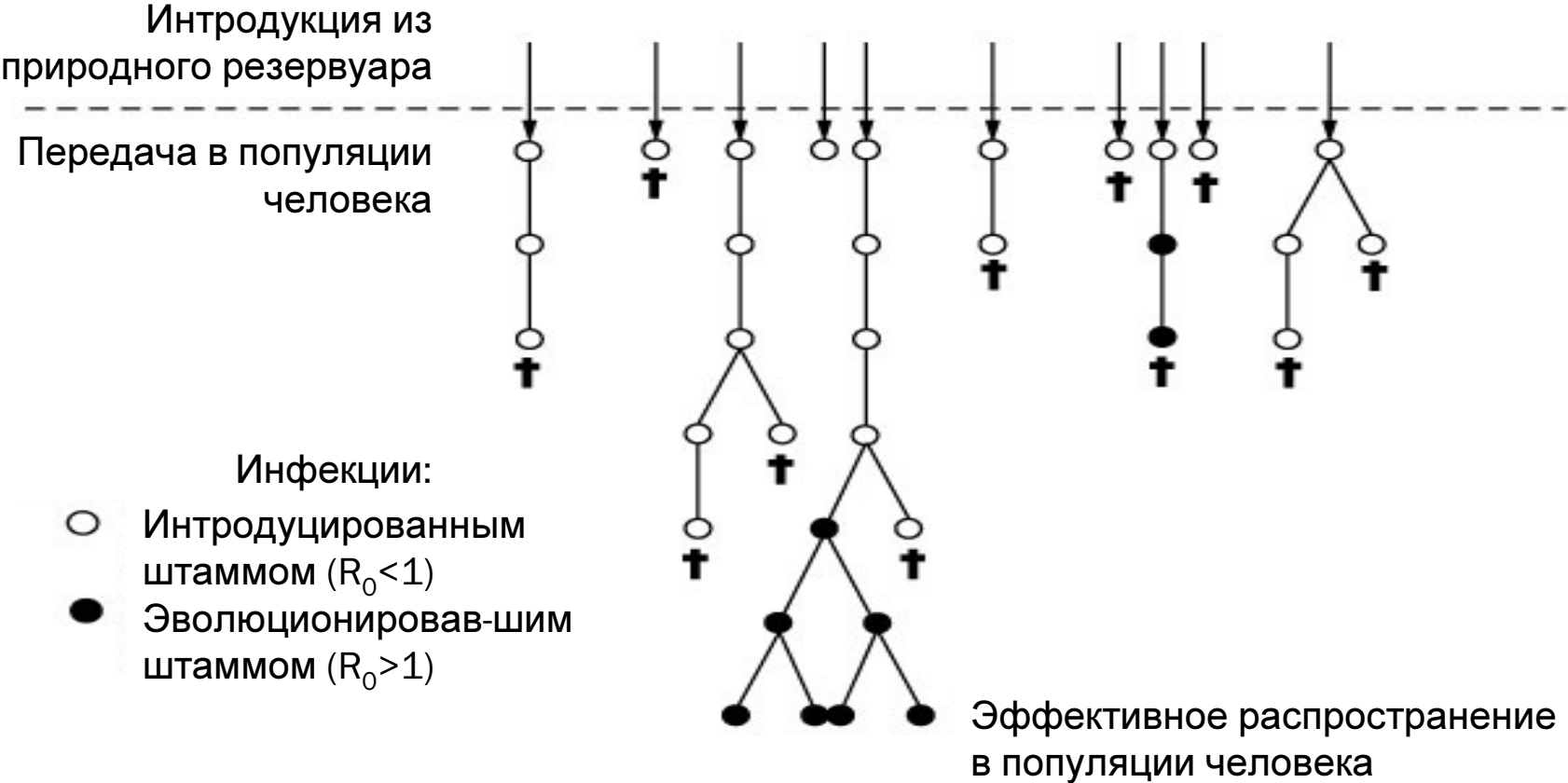
- ВИЧ-1

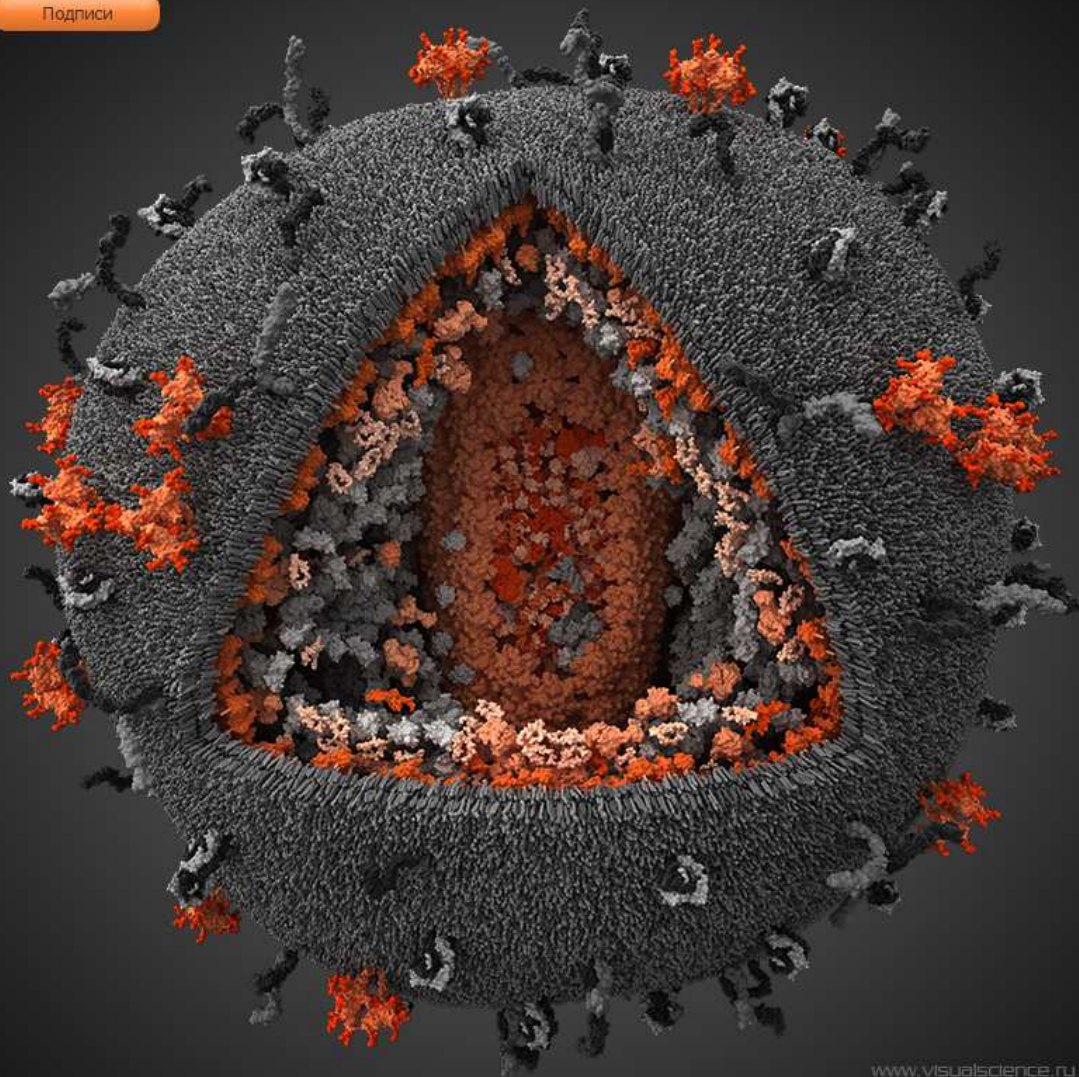- грипп A

Возникновение инфекционного заболевания

Интродукция из
природного резервуара

Передача в популяции
человека

Инфекции:

○ Интродуцированным
штаммом ($R_0 < 1$)

● Эволюциониров-шим
штаммом ($R_0 > 1$)

Эффективное распространение
в популяции человека

Подписи

ВИЧ-1

Adult HIV prevalence %
- 15 - 50
- 5 - 15
- 1 - 5
- 0.5 - 1.0
- 0.1 - 0.5
- 0.0 - 0.1
- No data
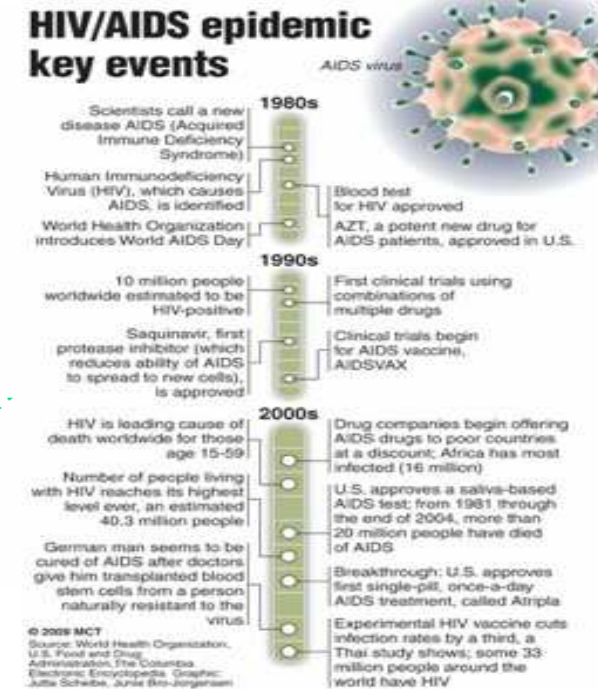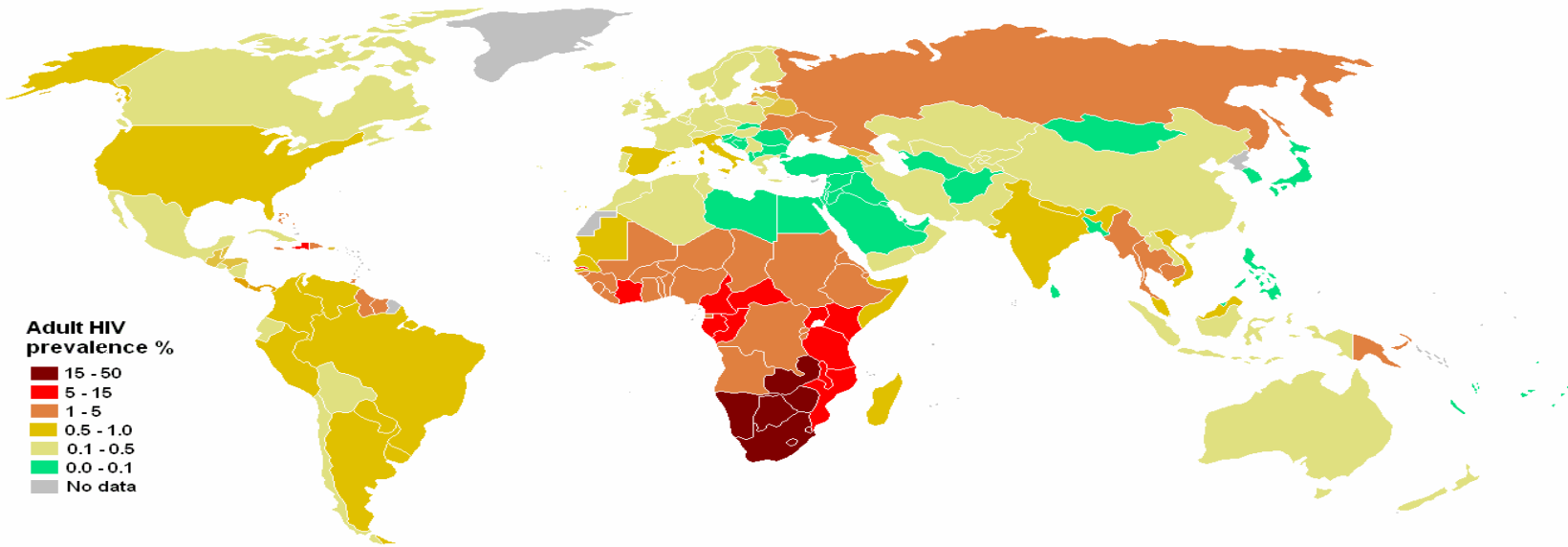
http://en.wikipedia.org/wiki/AIDS_pandemic
http://www.jameslogancourier.org/index.php?itemid=5436

a)

- HIV-1/U455: Human
- HIV-1/LAI: Human
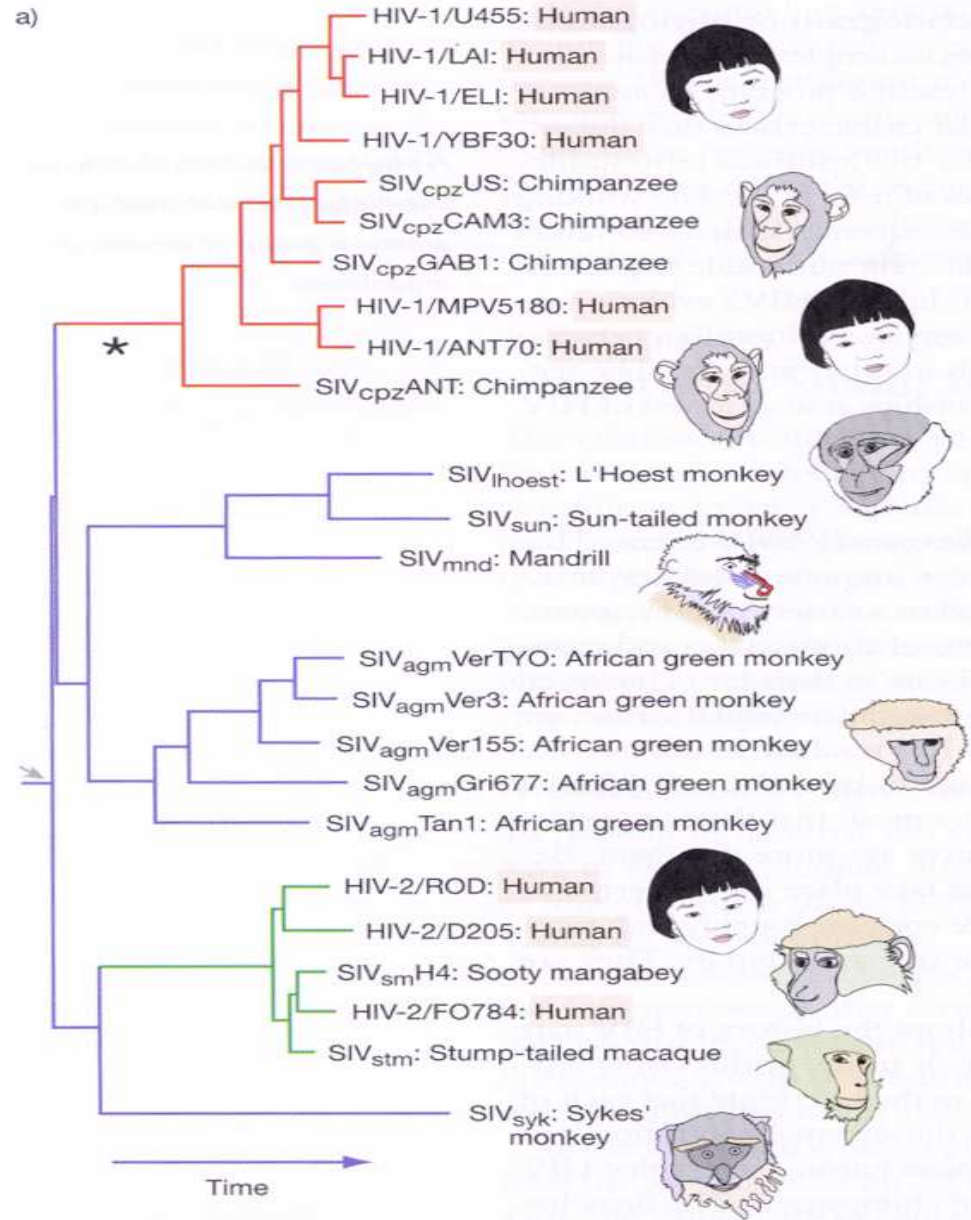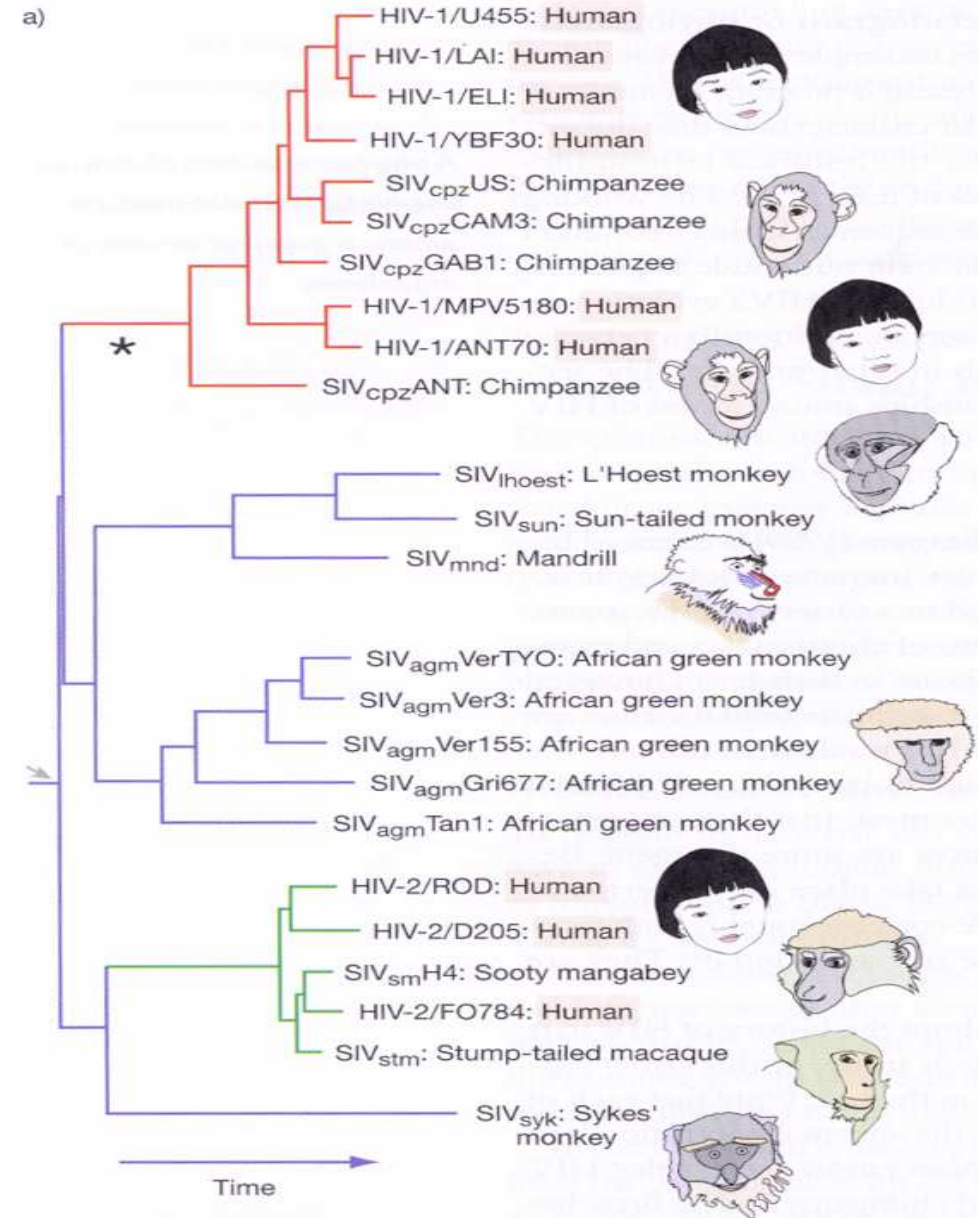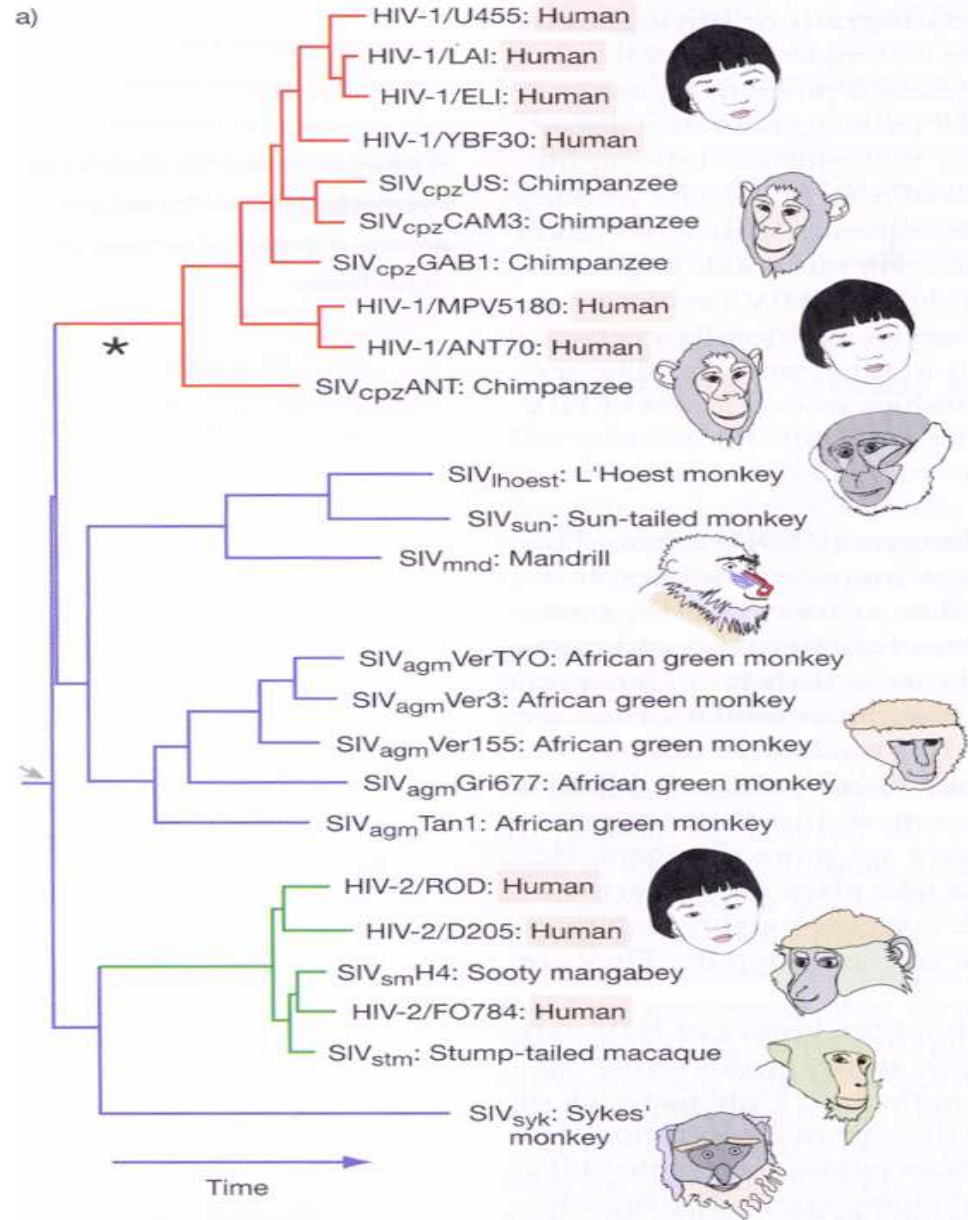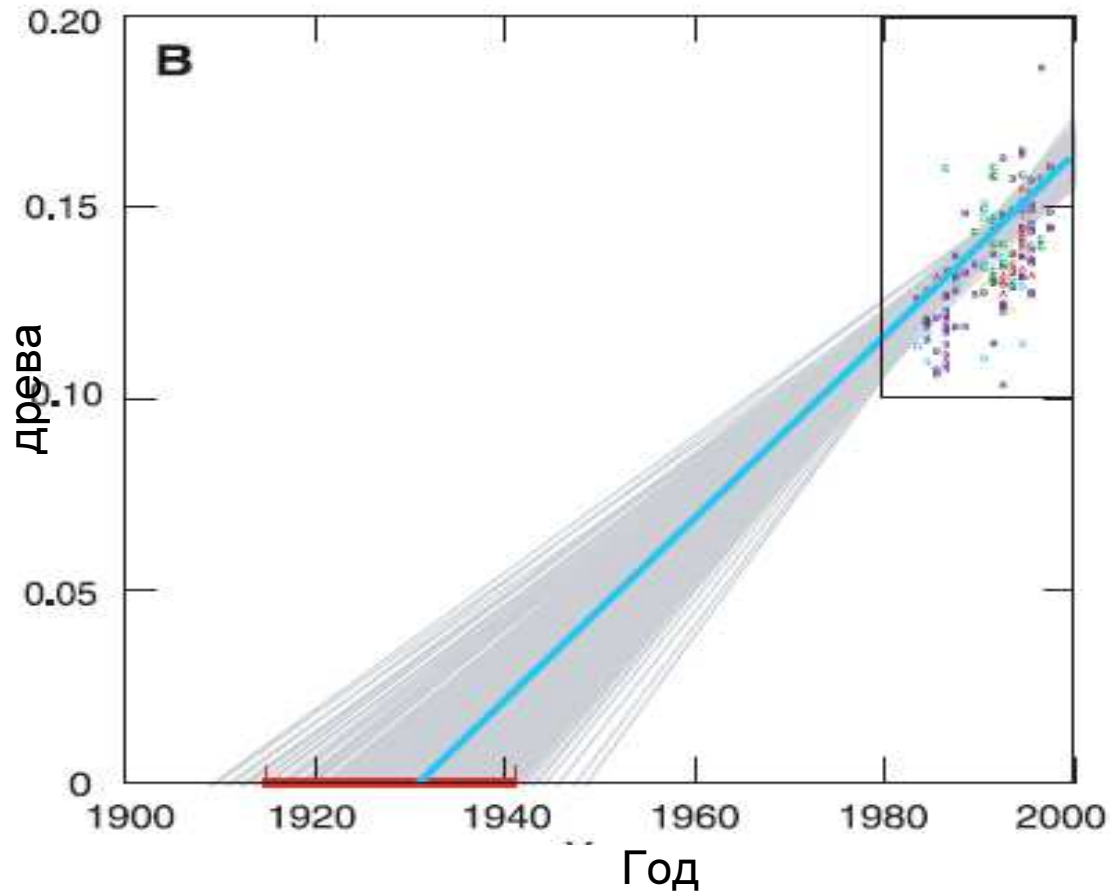- HIV-1/ELI: Human
- HIV-1/YBF30: Human
- SIV$_{cpz}$US: Chimpanzee
- SIV$_{cpz}$CAM3: Chimpanzee
- SIV$_{cpz}$GAB1: Chimpanzee
- HIV-1/MPV5180: Human
- HIV-1/ANT70: Human
- SIV$_{cpz}$ANT: Chimpanzee
- SIV$_{lhoest}$: L'Hoest monkey
- SIV$_{sun}$: Sun-tailed monkey
- SIV$_{mnd}$: Mandrill
- SIV$_{agm}$VerTYO: African green monkey
- SIV$_{agm}$Ver3: African green monkey
- SIV$_{agm}$Ver155: African green monkey
- SIV$_{agm}$Gri677: African green monkey
- SIV$_{agm}$Tan1: African green monkey
- HIV-2/ROD: Human
- HIV-2/D205: Human
- SIV$_{sm}$H4: Sooty mangabey
- HIV-2/FO784: Human
- SIV$_{stm}$: Stump-tailed macaque
- SIV$_{syk}$: Sykes' monkey

*

Time

a)

Selection Pressure for HIV-1 Protease
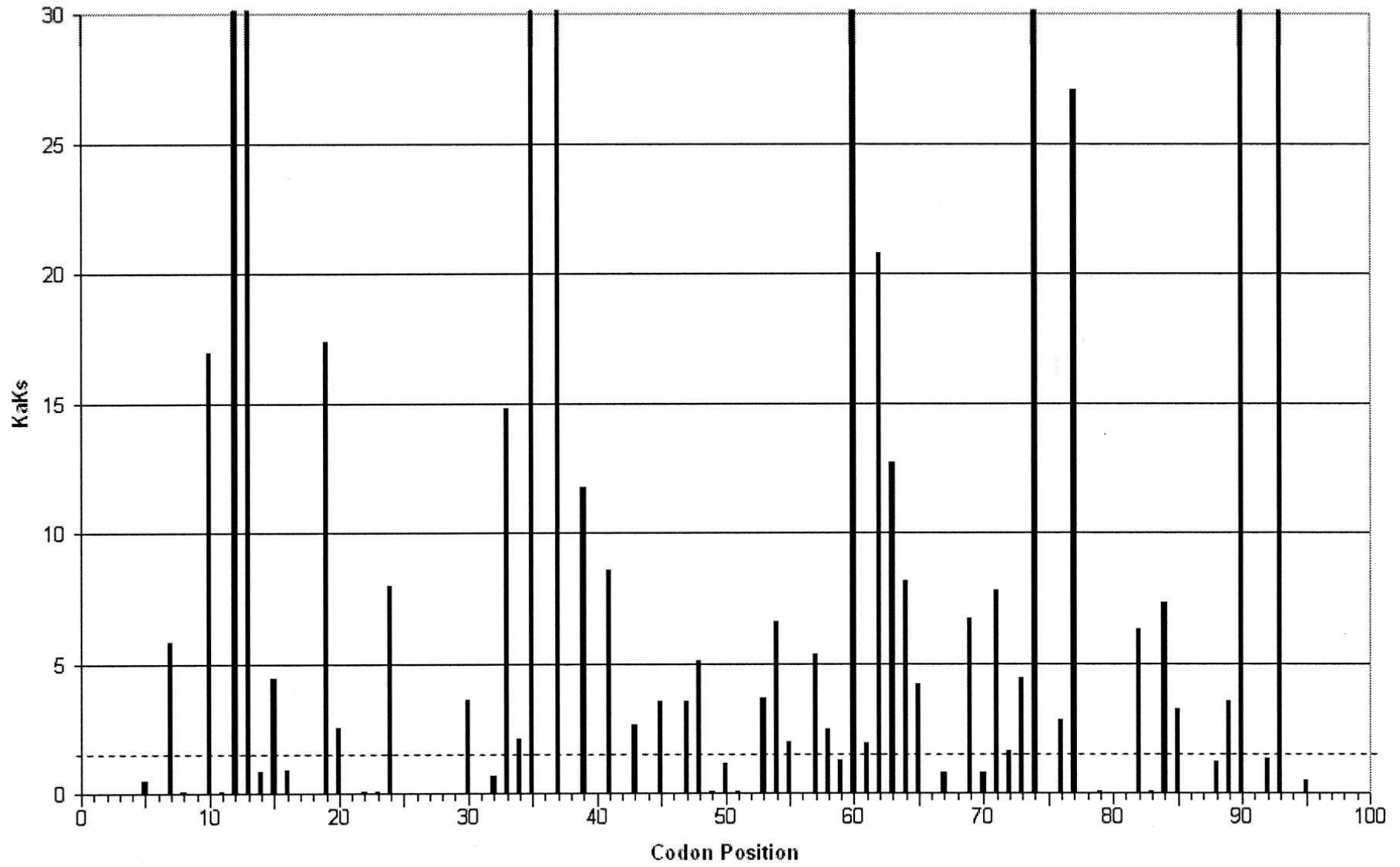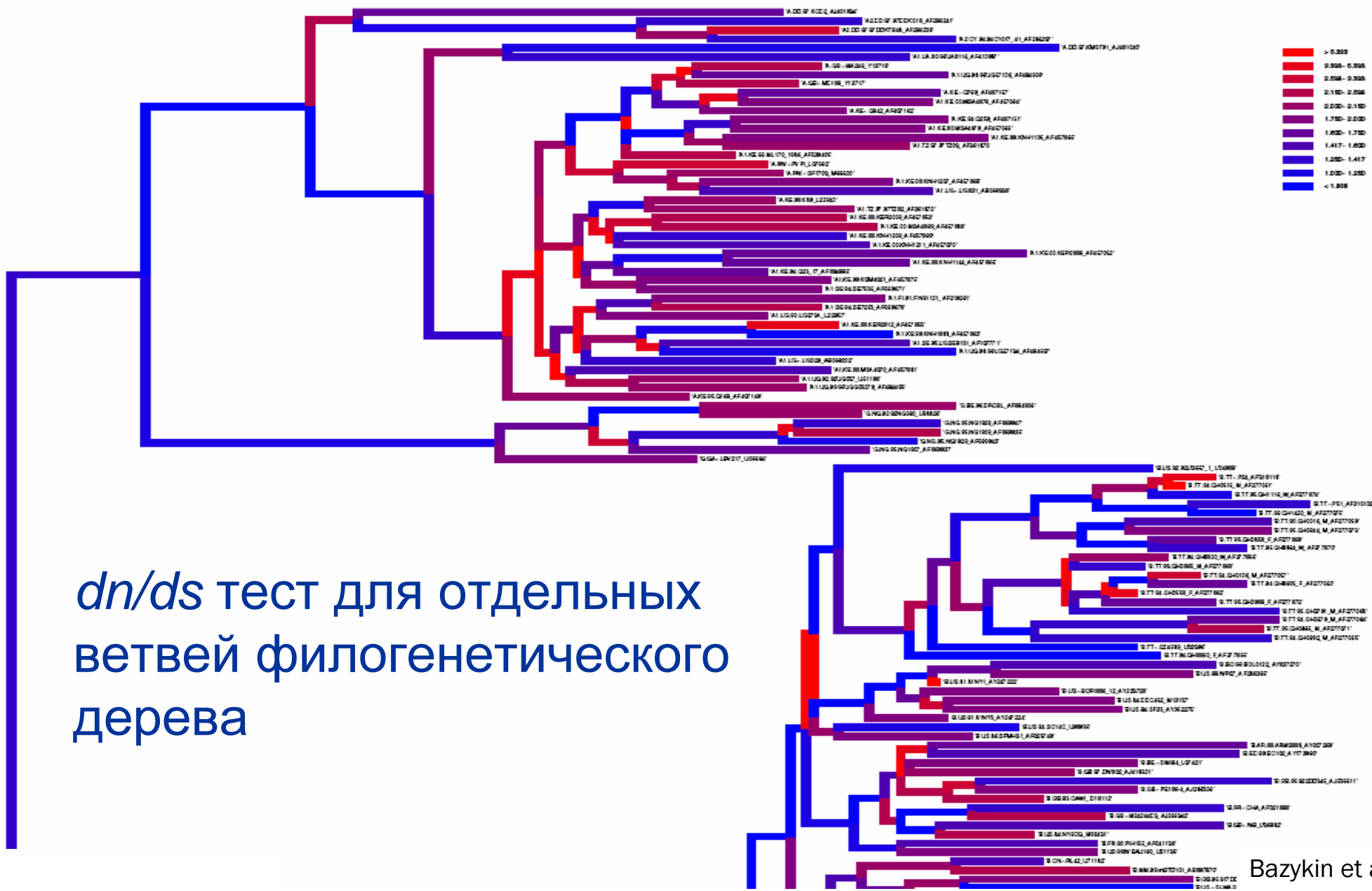
dn/ds тест для отдельных ветвей филогенетического дерева
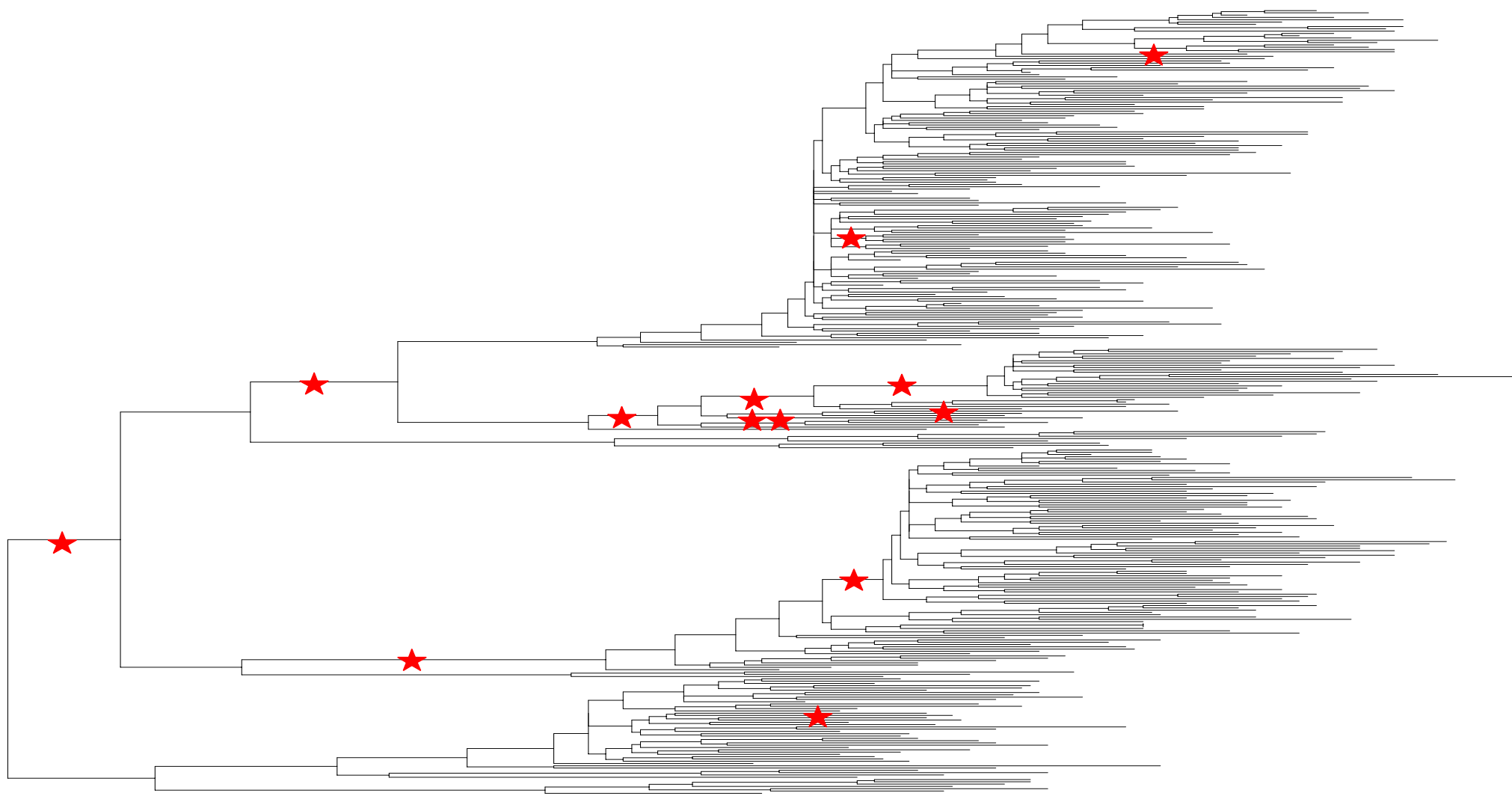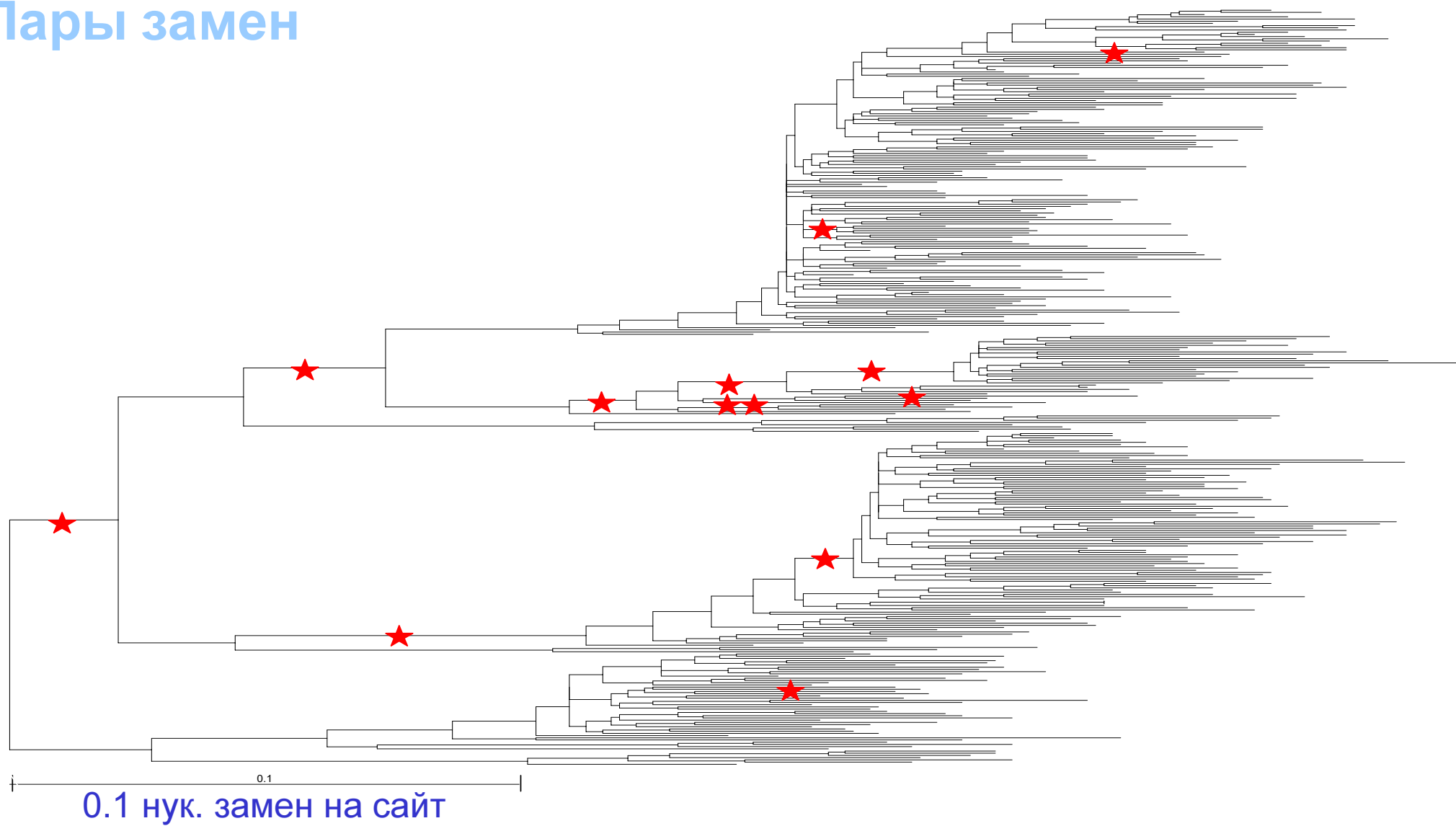
Bazykin et al. *PNAS* 2006

0.1

0.1 нук. замен на сайт

Bazykin et al. *PNAS* 2006

0.1

0.1 нук. замен на сайт
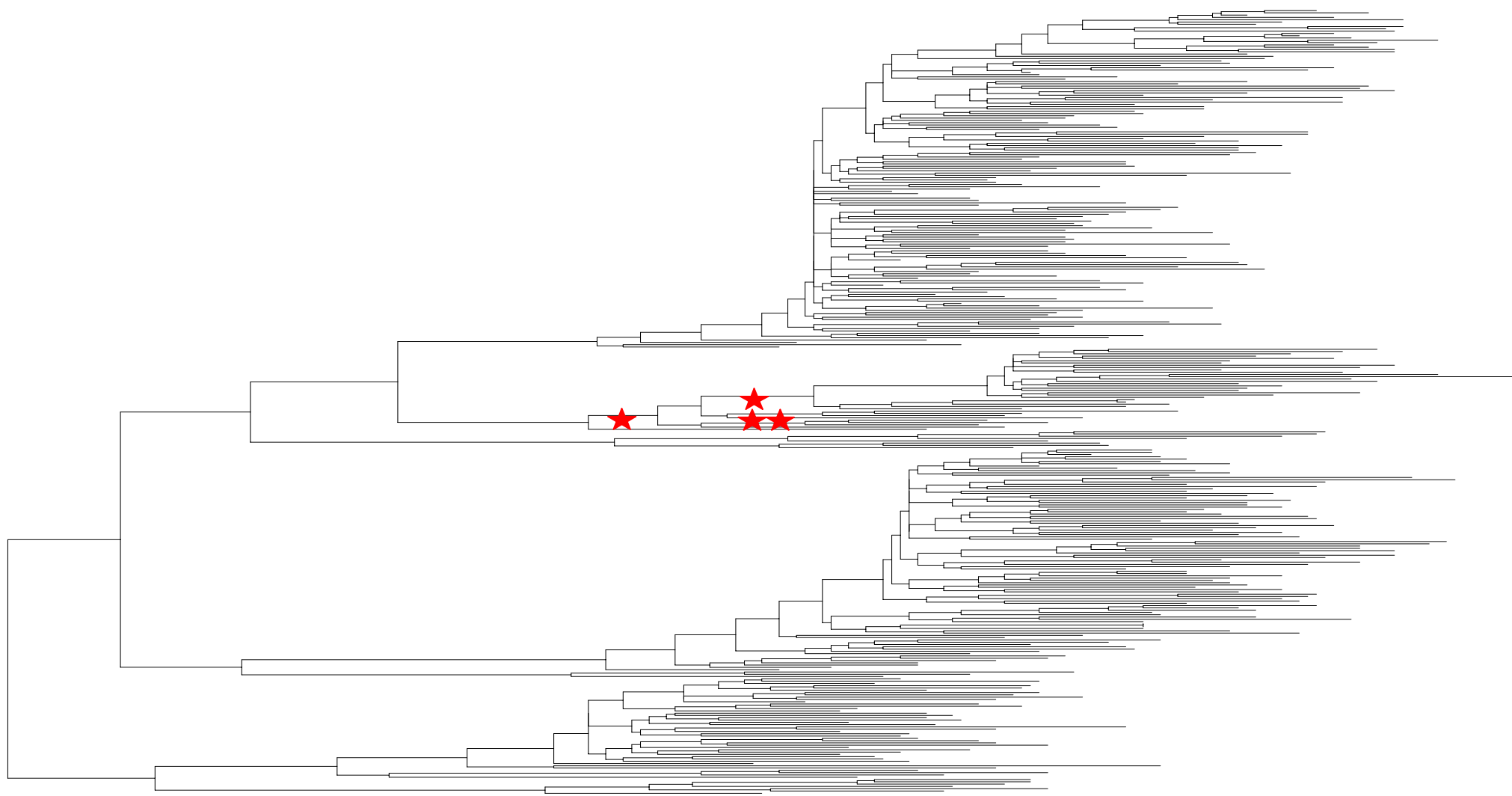
Bazykin et al. *PNAS* 2006

Пары замен

0.1

0.1 нук. замен на сайт

Bazykin et al. *PNAS* 2006

Пары замен

0.1 нук. замен на сайт

0.1

Bazykin et al. *PNAS* 2006

Расстояние между заменами в паре

0.1 нук. замен на сайт

Bazykin et al. *PNAS* 2006

Расстояние между заменами в паре

несинонимичные　　　　синонимичные

Mean distance between successive substitutions

Substitutions on tree　　　　Substitutions on tree
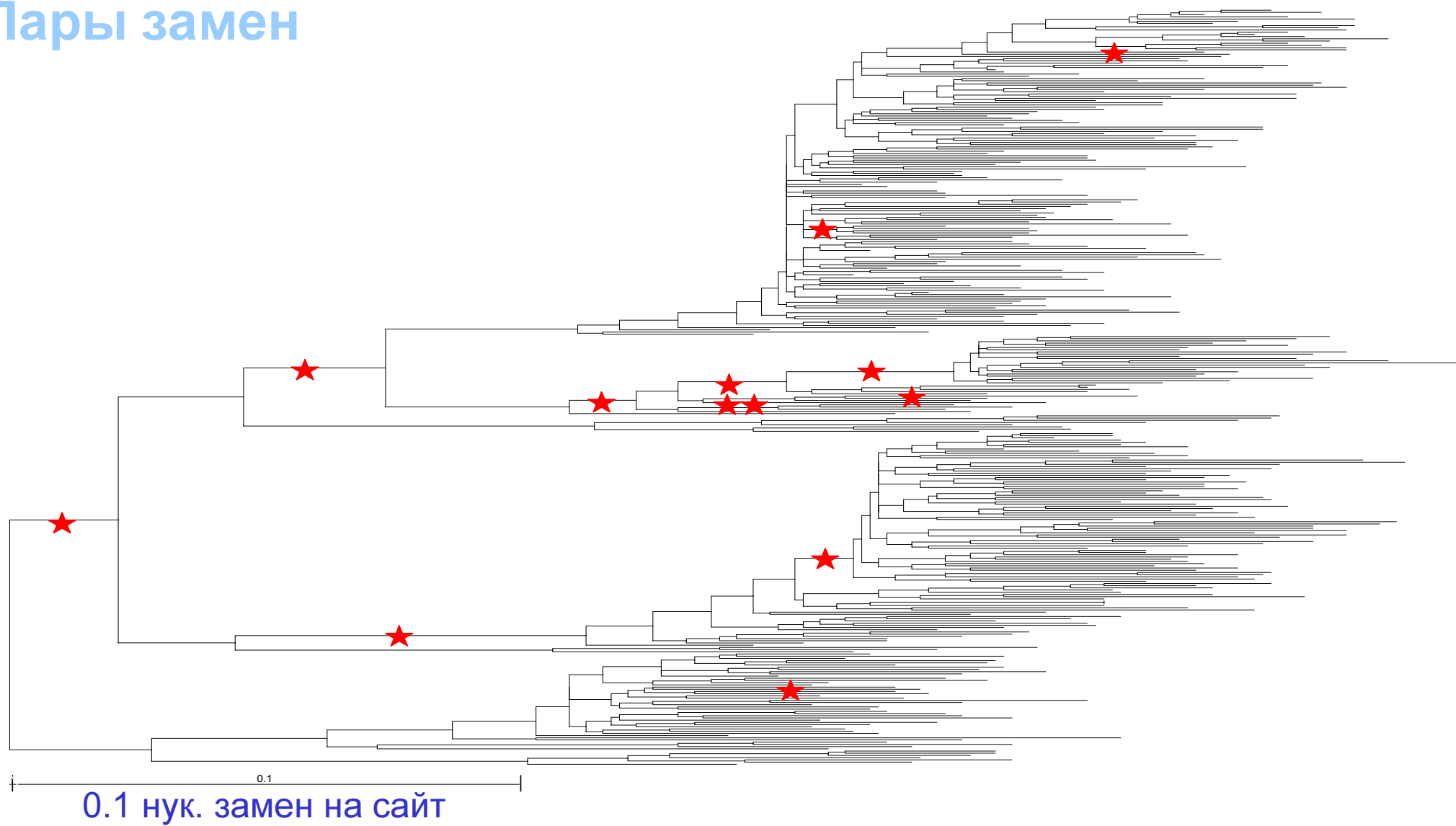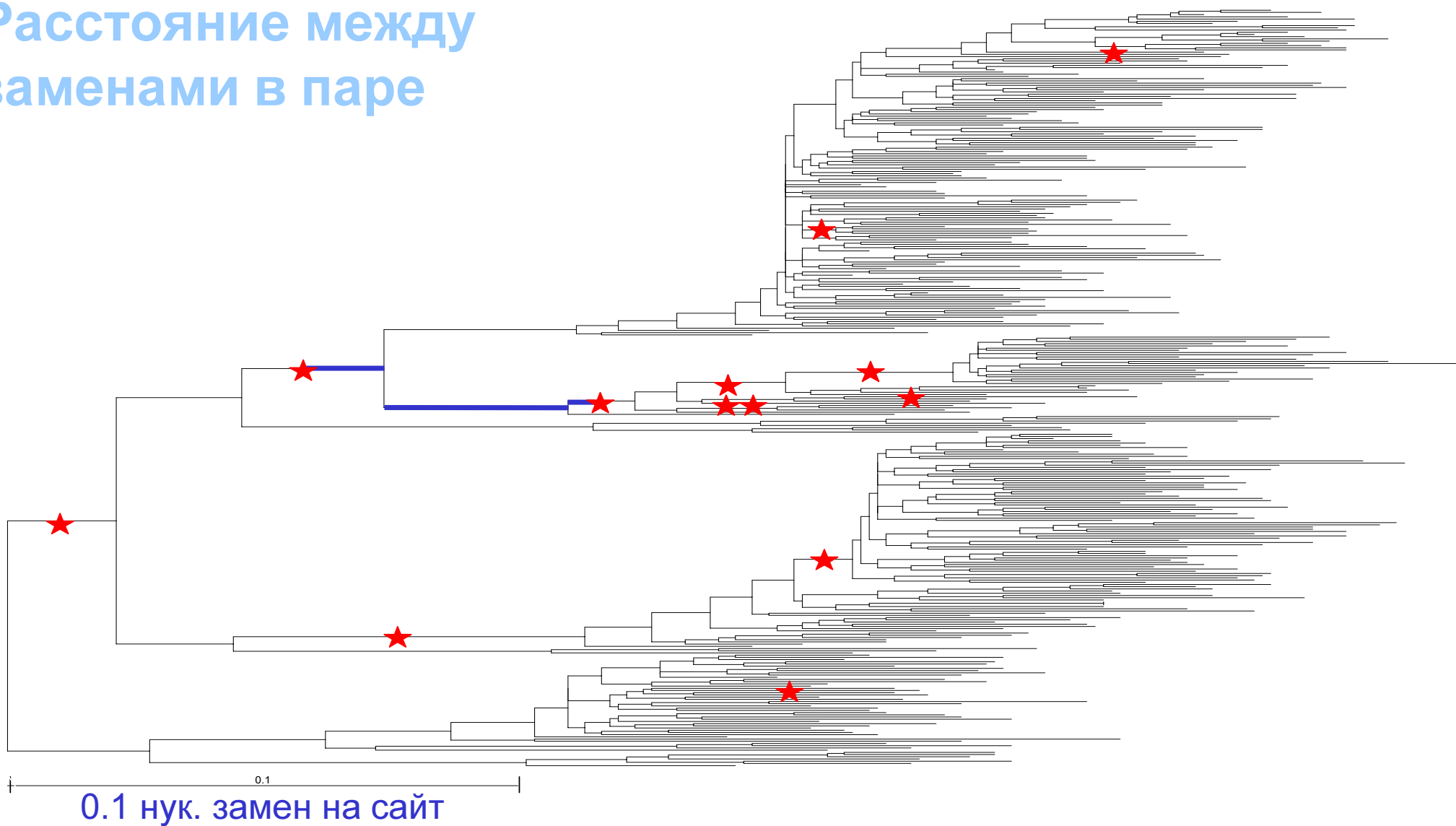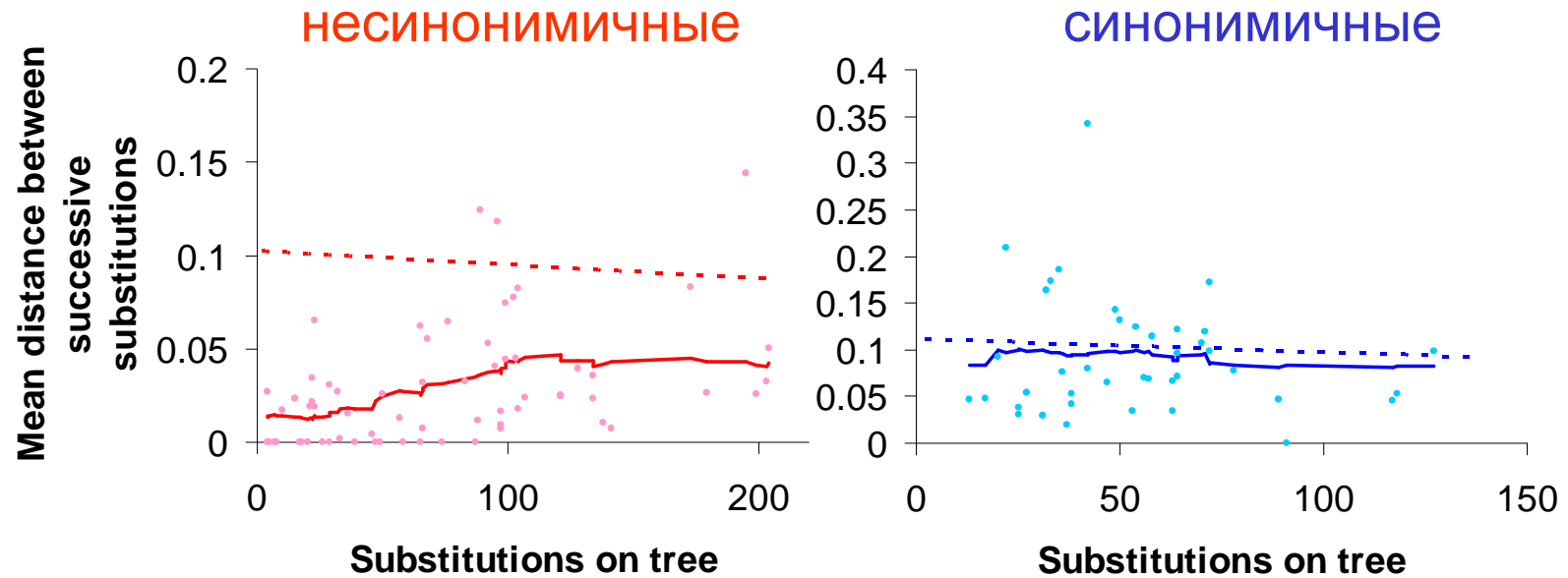
- ▶ расстояние между последовательными синонимичными заменами приблизительно соответствует ожиданию

- ▶ последовательные несинонимичные замены идут «очередями»
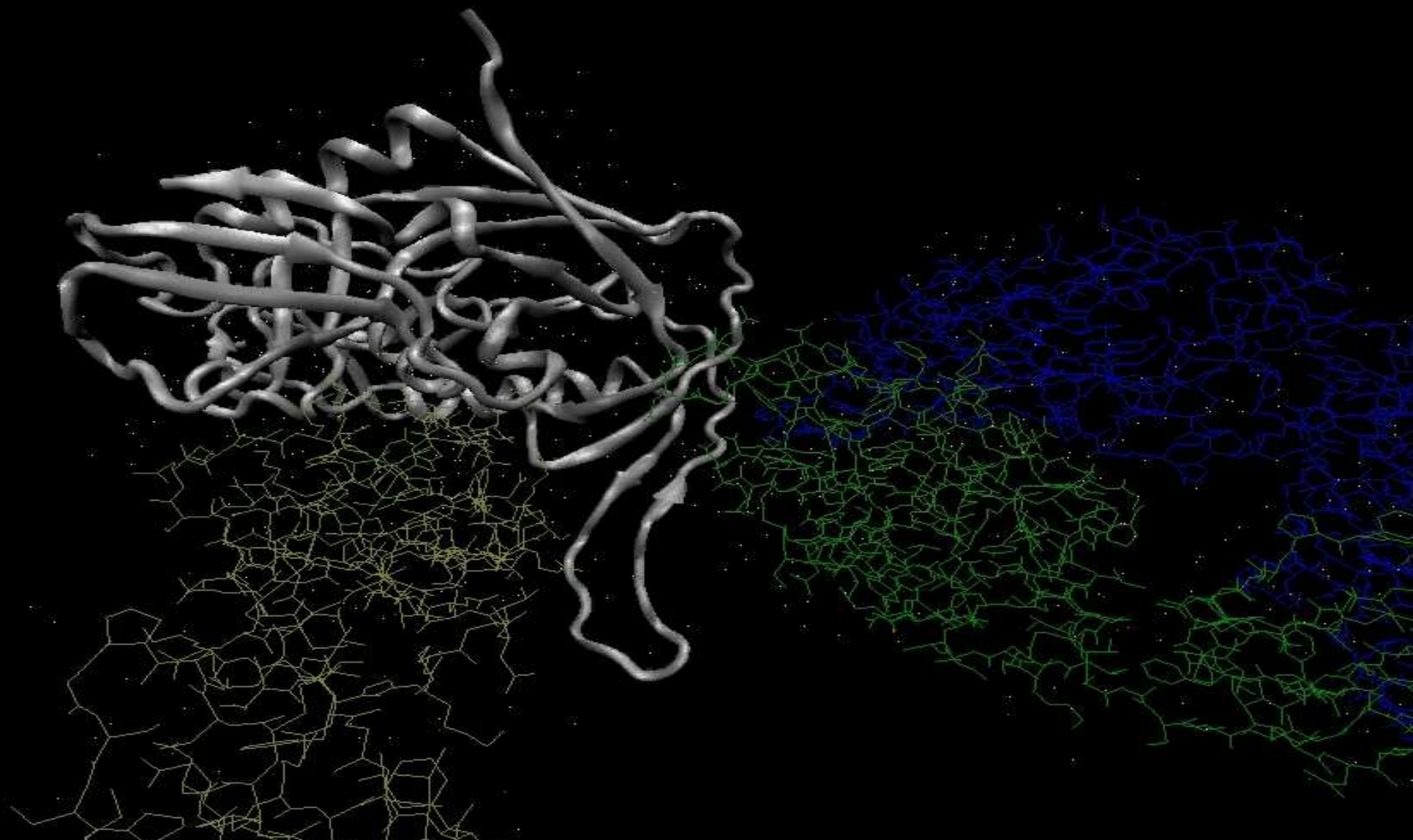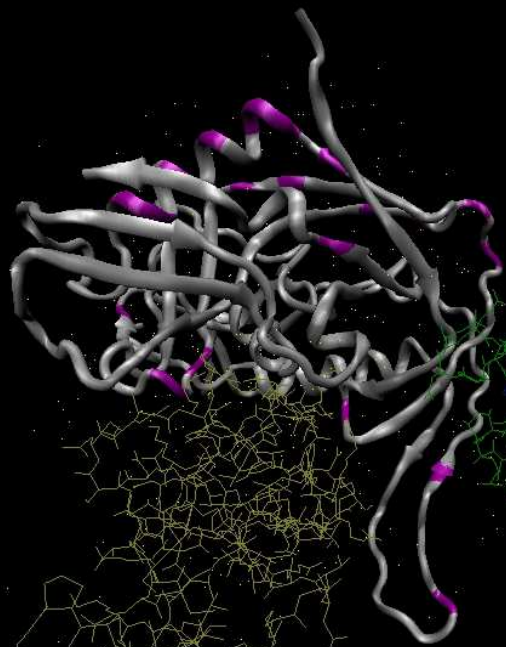
Сайты под
положительным
отбором
*(Yamaguchi-Kabata and
Gojobori, 2000)*
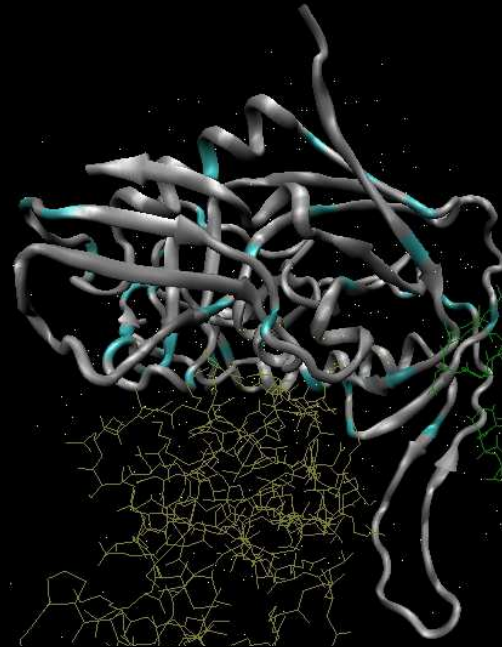
Консервативные
сайты под
эпизодическим
положительным
отбором

В популяциях человека, в которых чаще встречается определенный вариант HLA, чаще встречается и мутация ВИЧ, «защищающая» вирус
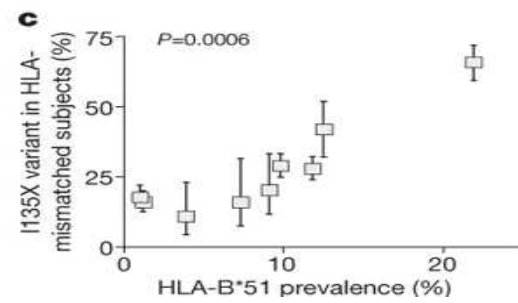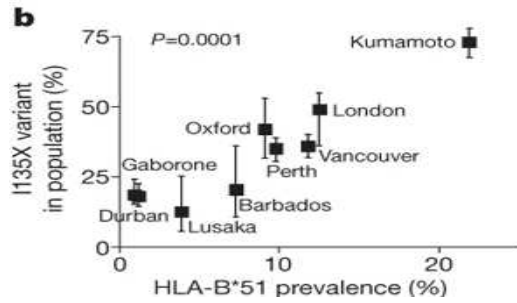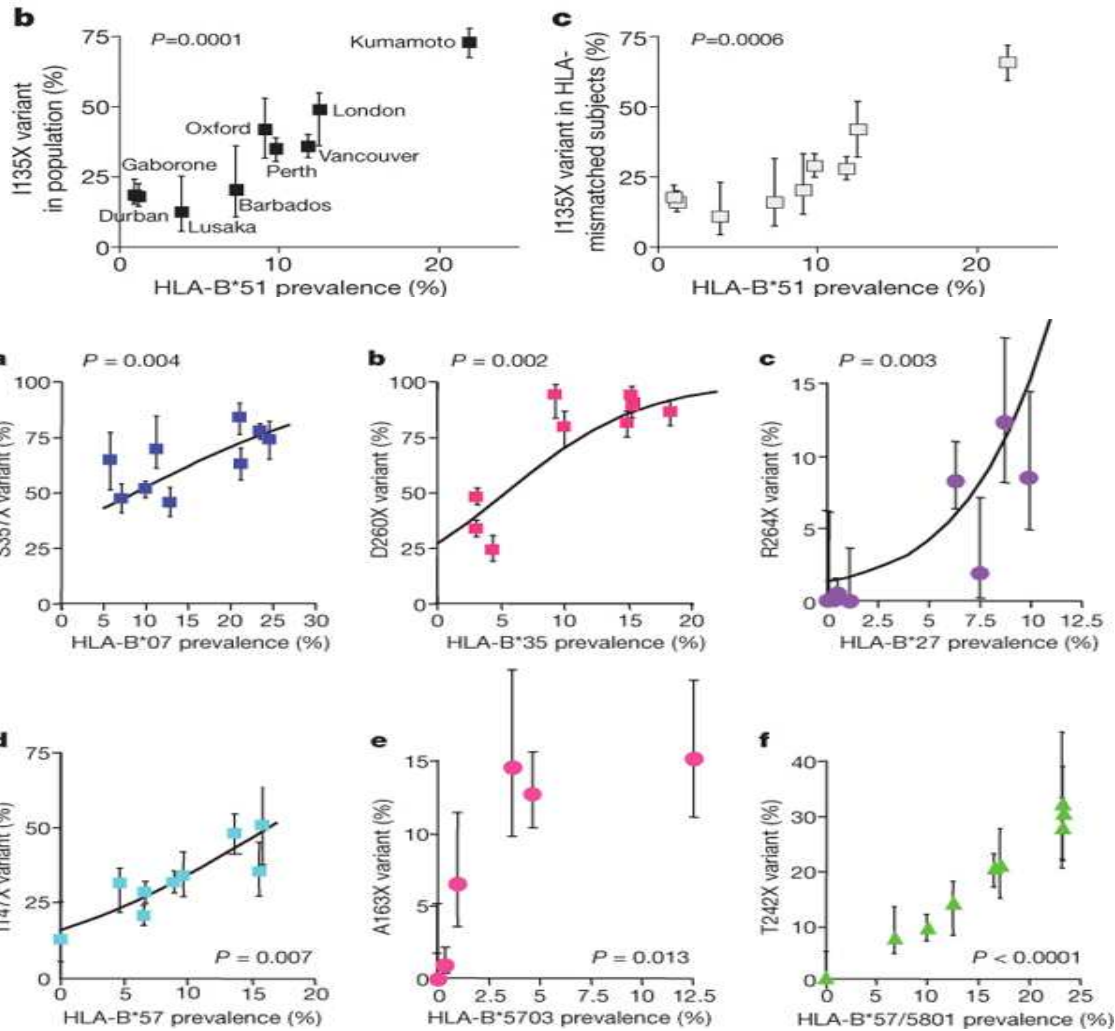
Мутация CCRV-Δ32

Rambaut et al. *Nat Rev Gen* 2004
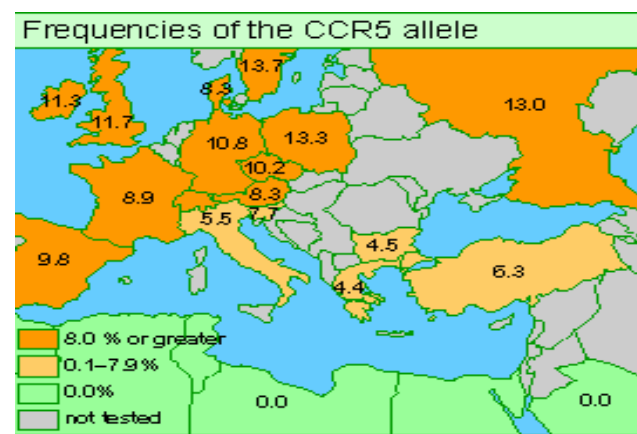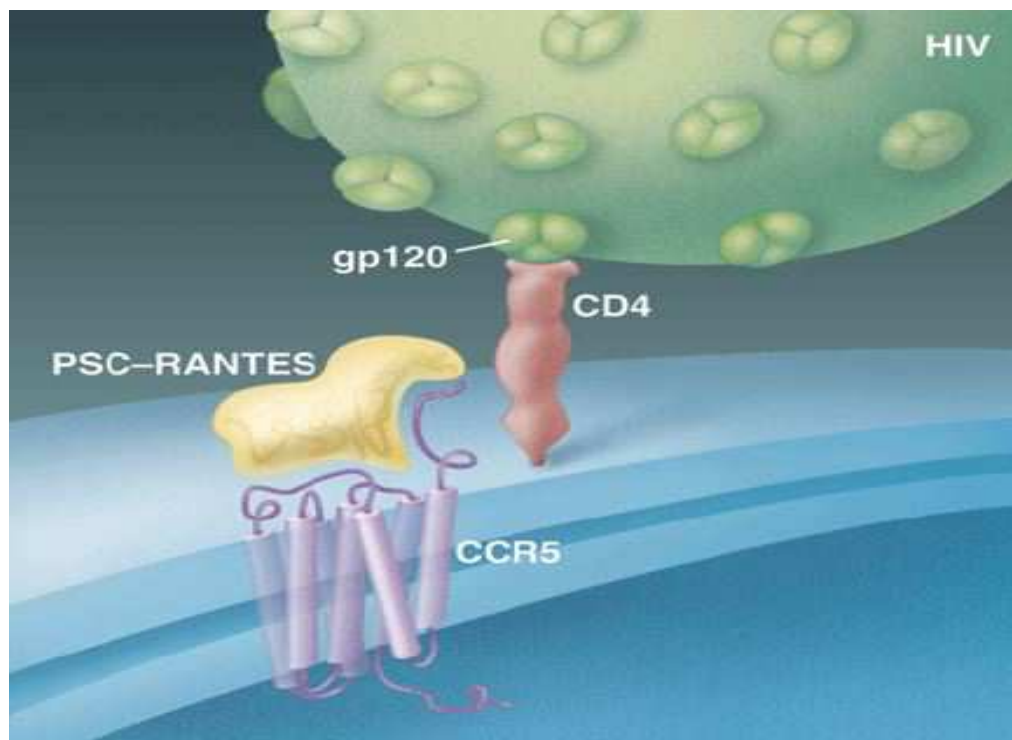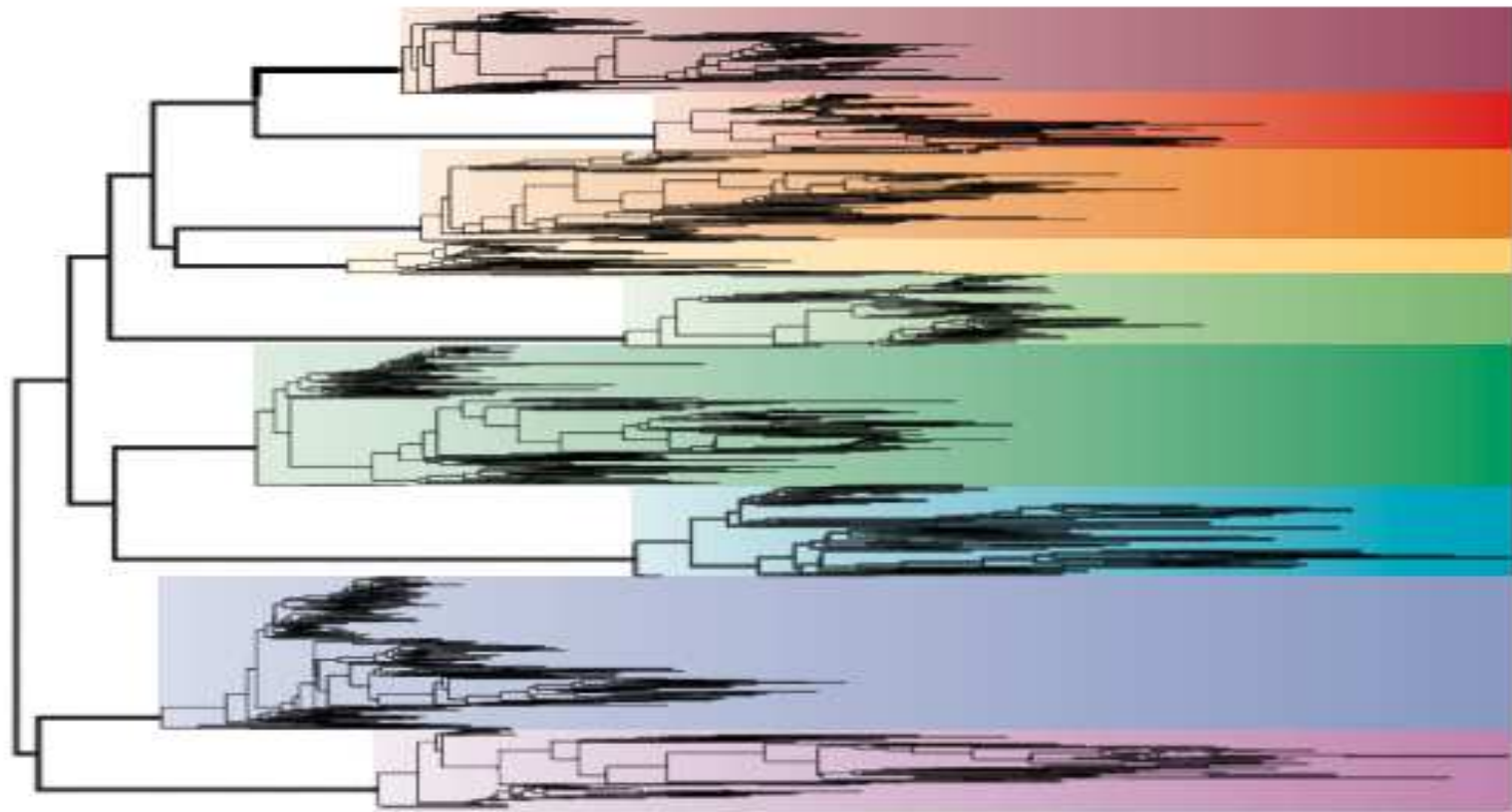
Эволюция ВИЧ внутри пациента

генетическое разнообразие
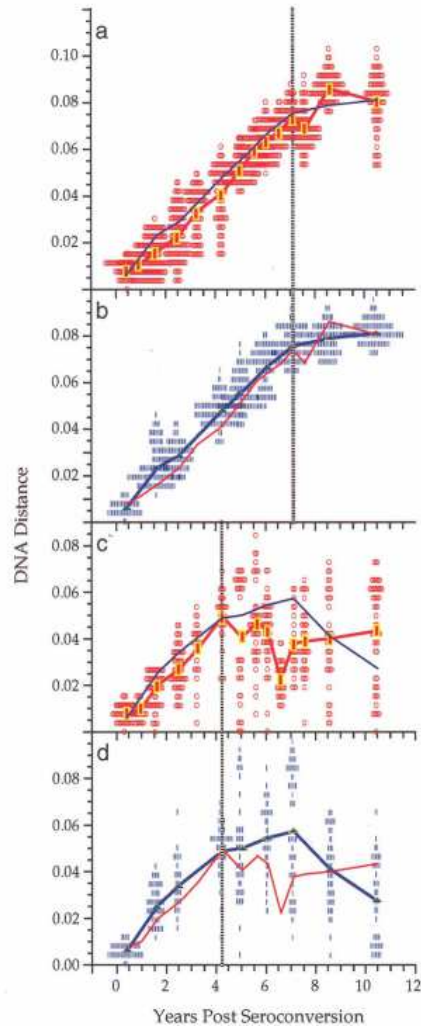
пациент 1
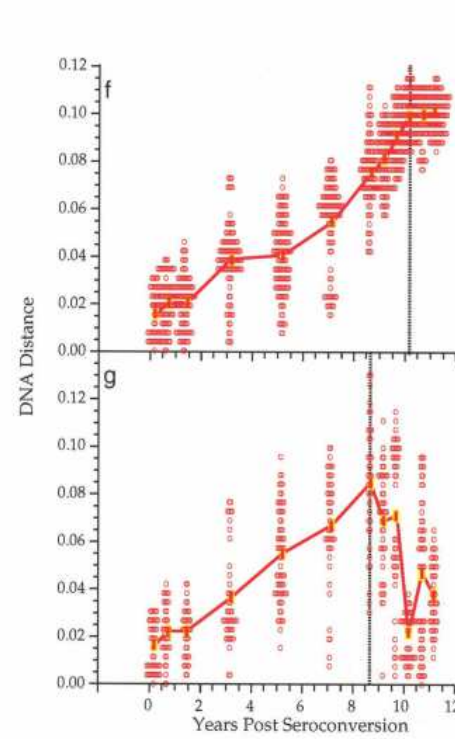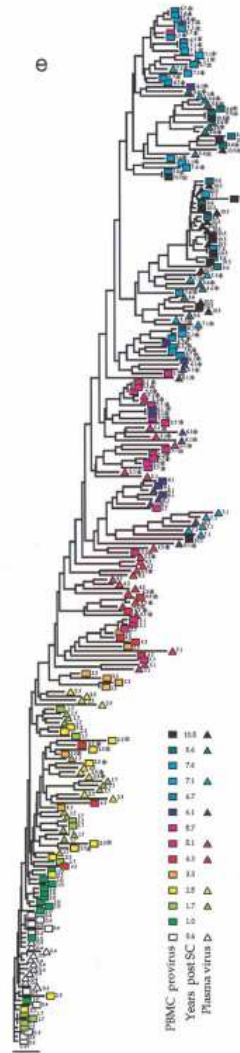
пациент 2
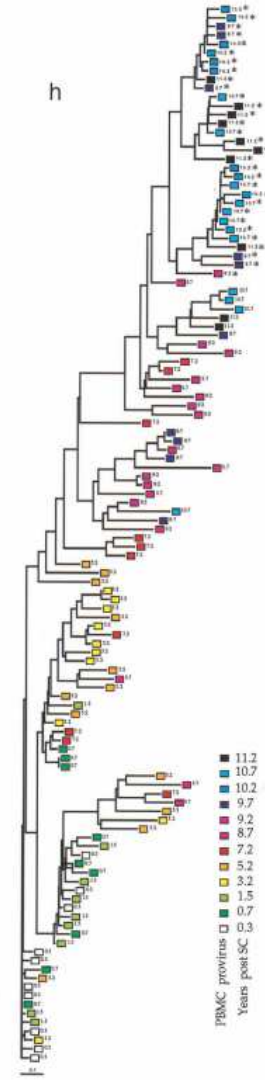
Shankarappa et al. *J Virol* 1999

Стратегии борьбы
с лекарственной устойчивостью

Infecting virion

Integration

Provirus

Nucleus

B
c
a

Reverse transcription

a   b   c
A   B   C

Progeny production
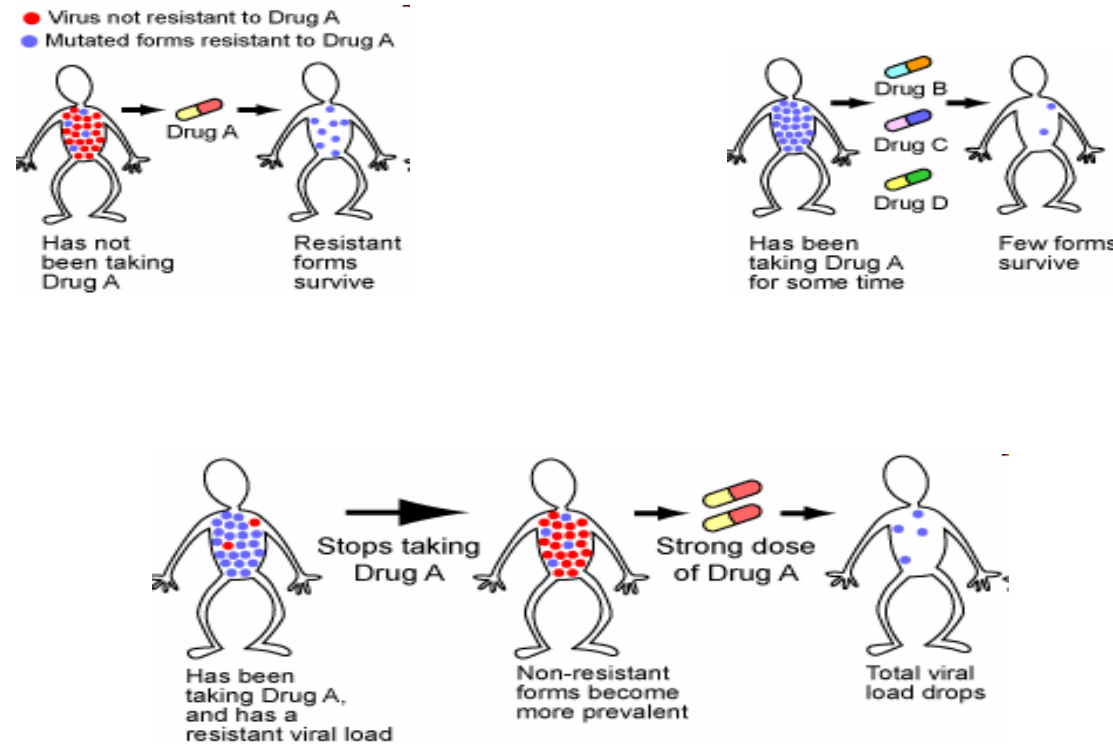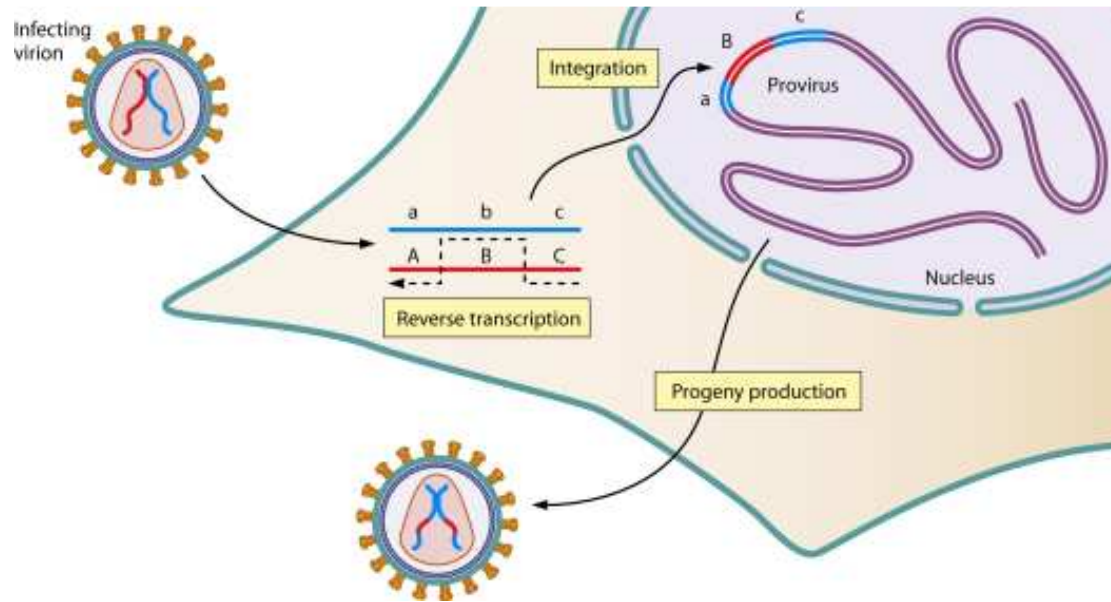
Onafuwa-Nuga and Telesnitsky
Microbiol Mol Biol Rev. 2009

Drug A resistance mutation

Double resistance recombinants

Recombination

Drug B resistance mutation
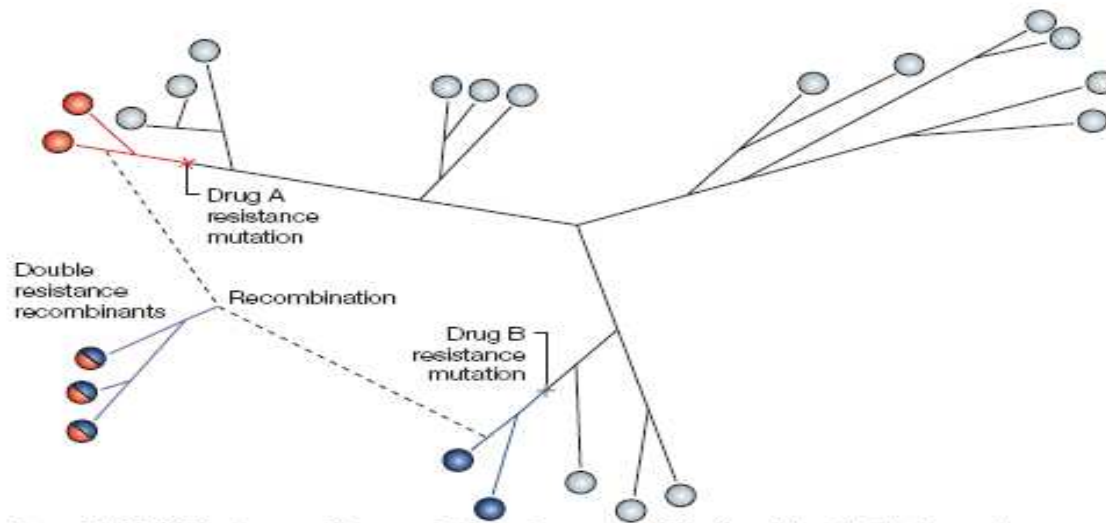
Figure 5 | **Multiple drug resistance induced by recombination.** Hypothetical example showing how recombination will be an important mechanism to generate drug resistance in HIV. In this figure, two different HIV strains that are resistant to drug A (in red) and drug B (in blue) recombine to produce a new strain that is resistant to both drugs.

Rambaut et al. *Nat Rev Gen* 2004

Катастрофа ошибок

(A) Before application of mutagen

Point of Error Catastrophe

(B) After application of mutagen

Mutation rate/replication

Seq. 1	TCC TTC CAG ACC TAA	
Seq. 2	TCC TTA CAG ACC TAA	

Seq. 1	TCC TTC CAG ACC TAA	
Seq. 2	TCA TTA CAG ACT TAG	
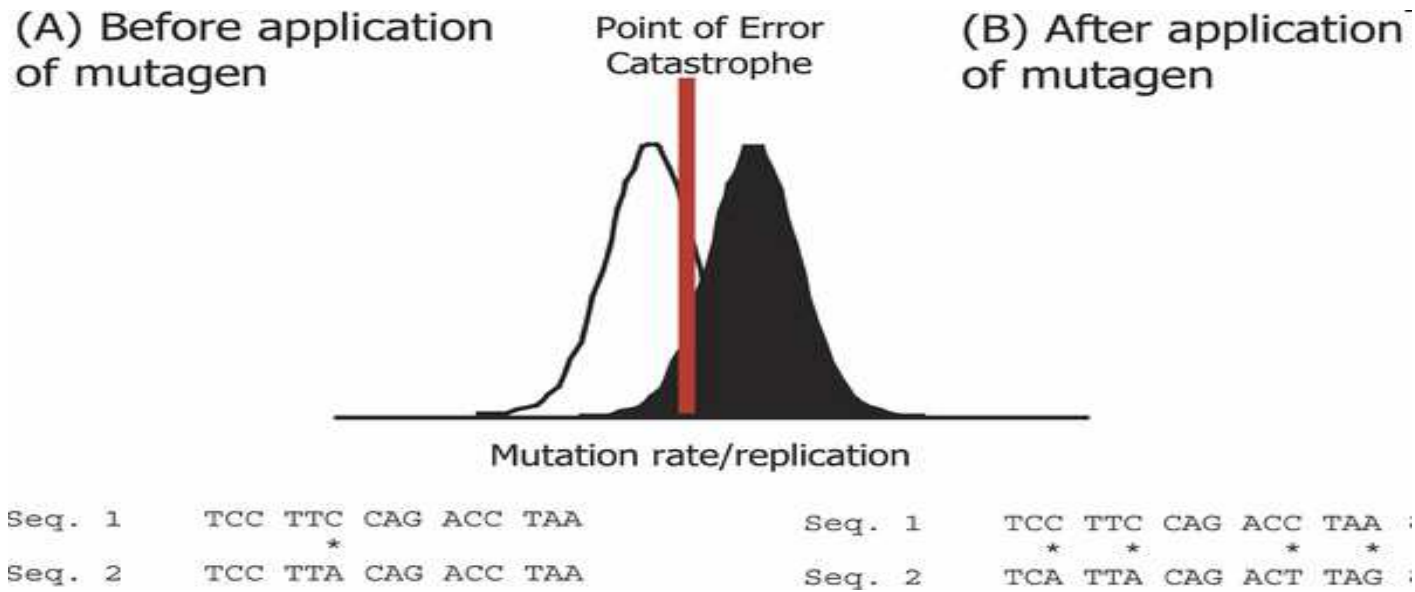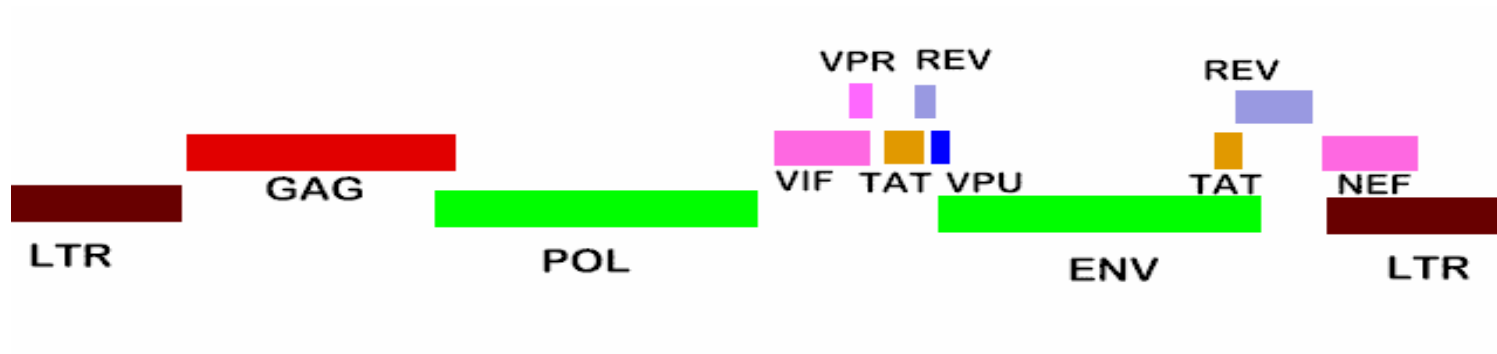
APOBEC3G:
оружие массового деаминирования

цитозин   урацил
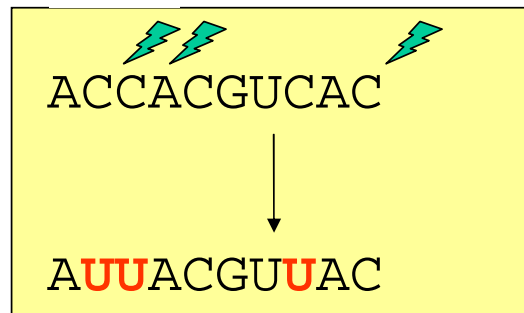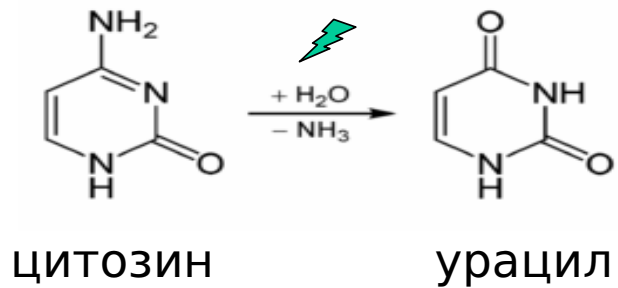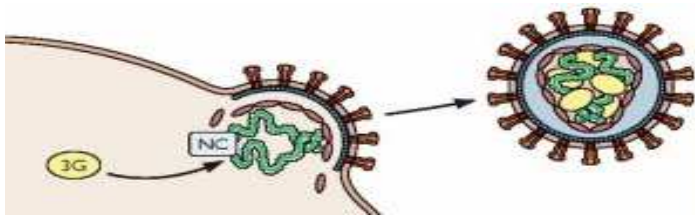
vif: ответ на APOBEC3G
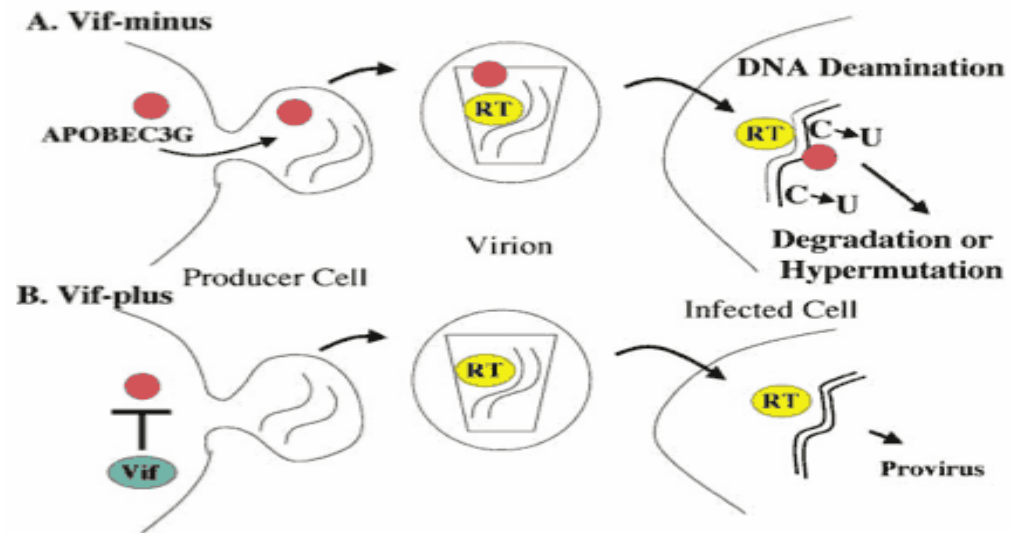
33 mya
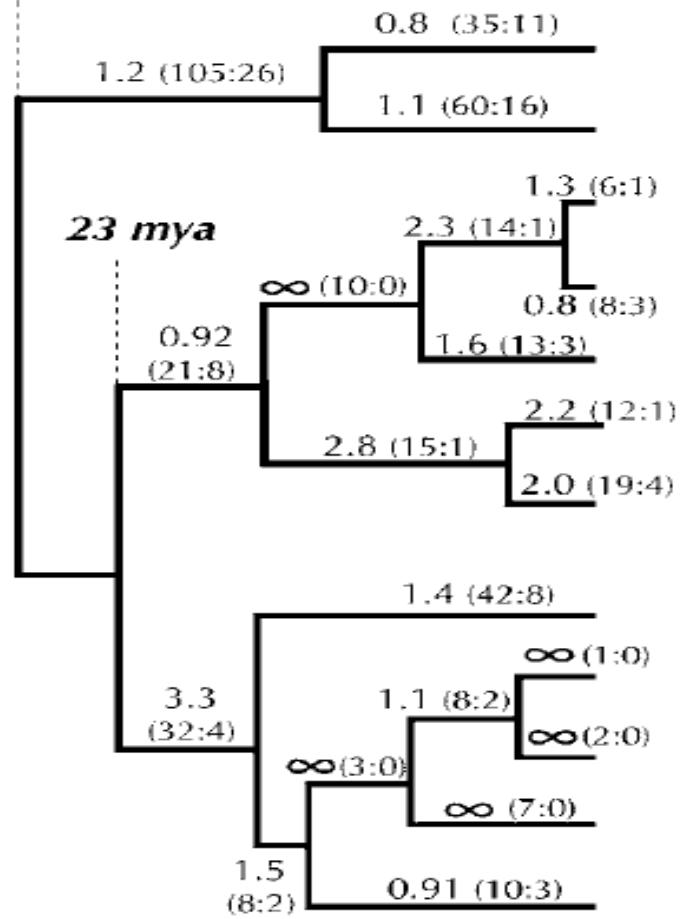
0.8 (35:11) — *Lagothrix lagotricha* - woolly monkey

1.2 (105:26)

1.1 (60:16) — *Saguinus labiatus* - tamarin

New World Monkeys

23 mya

1.3 (6:1) — *Macaca nigra* - celebes crested macaque

2.3 (14:1)

∞ (10:0)

0.8 (8:3) — *Macaca fascicularis* - crab eating macaque

0.92 (21:8)

1.6 (13:3) — *Papio anubis** - baboon

2.2 (12:1) — *Erythrocebus patas** - patas monkey

2.8 (15:1)

2.0 (19:4) — *Chlorocebus aethiops** - African green monkey

Old World Monkeys

1.4 (42:8) — *Pongo pygmaeus* - orangutan

3.3 (32:4)

∞ (1:0) — *Pan troglodytes** - chimpanzee

1.1 (8:2)

∞ (2:0) — *Pan paniscus* - bonobo

∞ (3:0)

∞ (7:0) — *Homo sapiens** - human

1.5 (8:2)

0.91 (10:3) — *Gorilla gorilla* - gorilla

Hominids

Грипп А

visualscience.ru

AN INFLUENZA VIRUS

Antigenic sites

Hemagglutinin

Neuraminidase

M2 ion channel

Ribonucleoprotein

www.cdc.gov
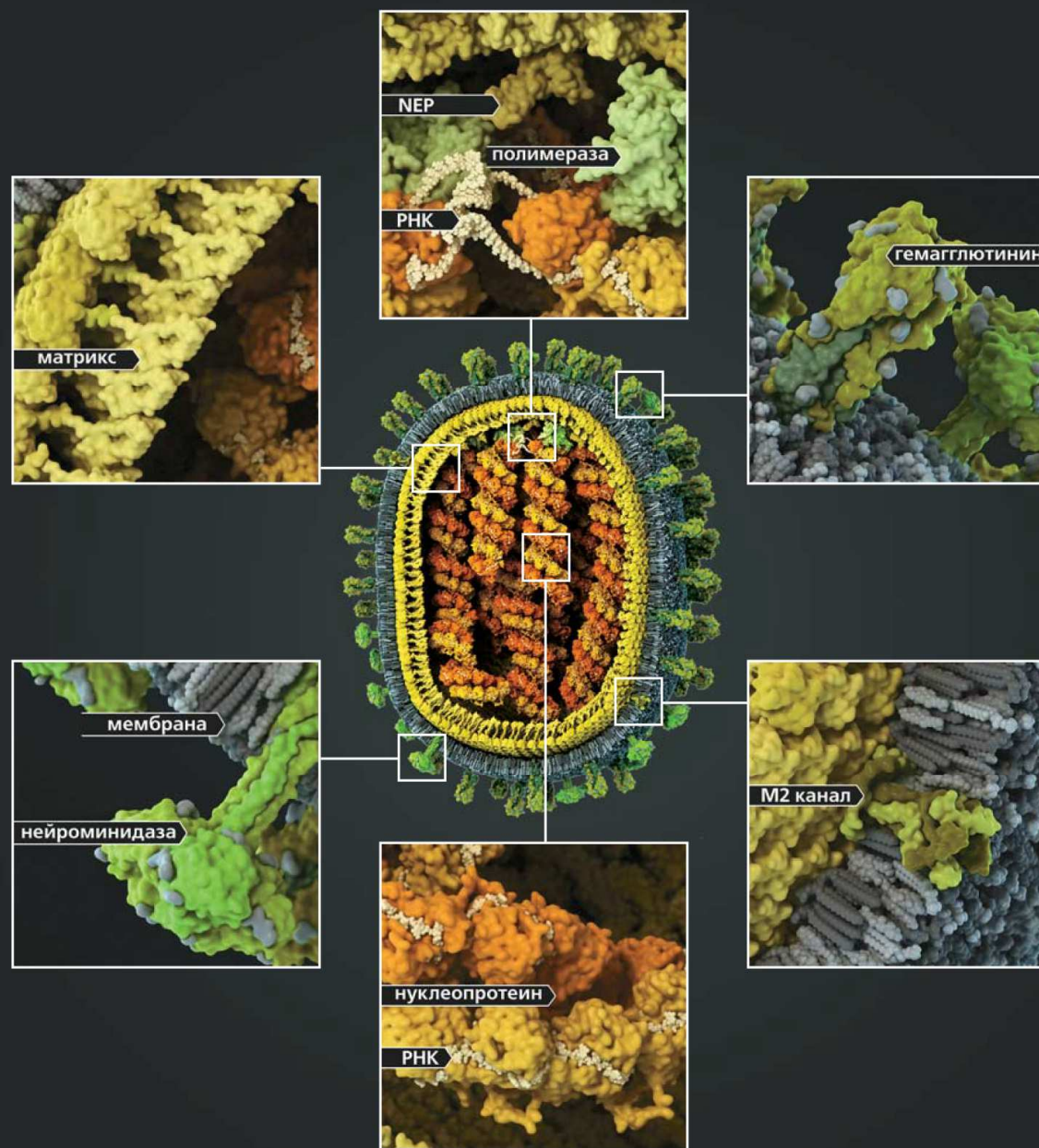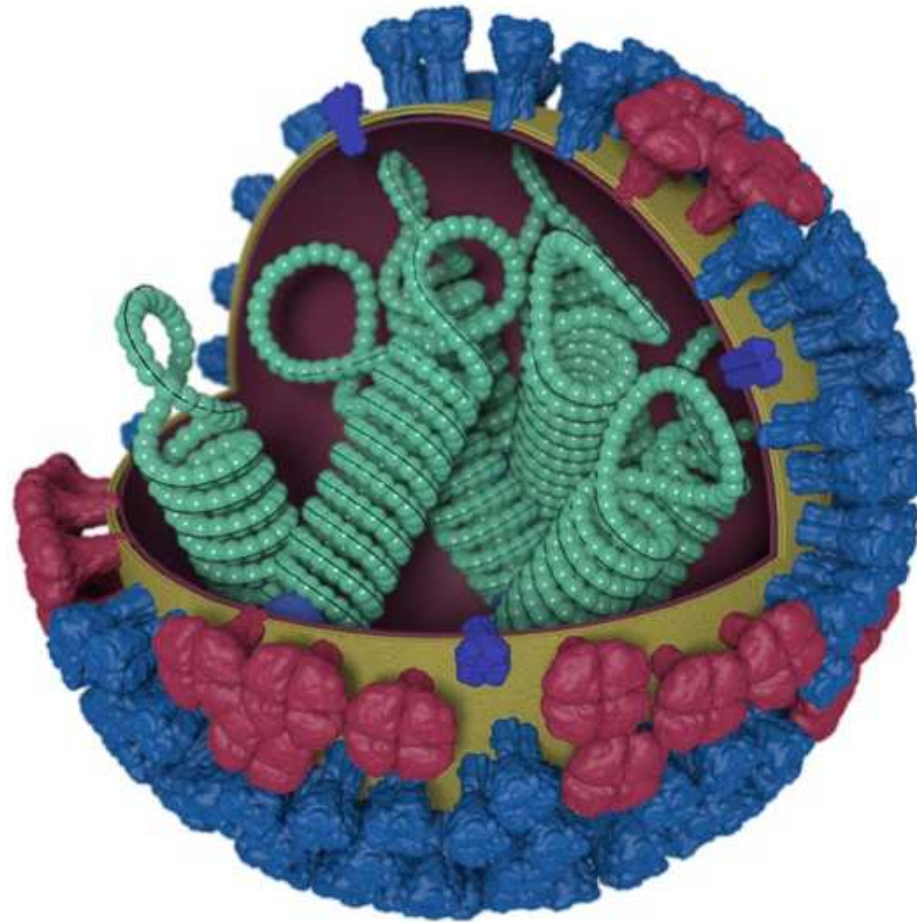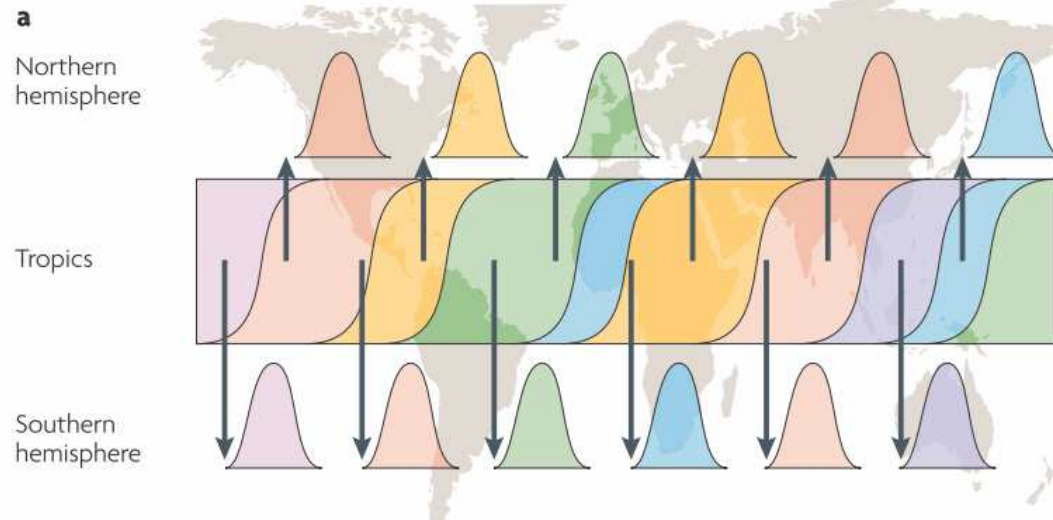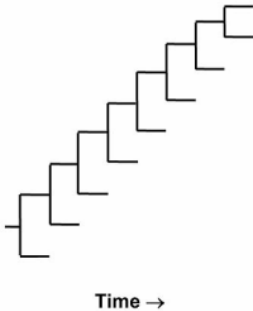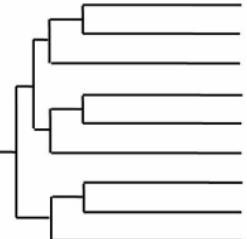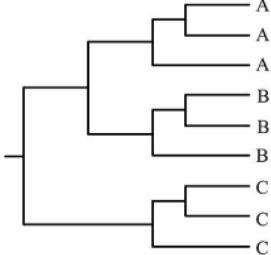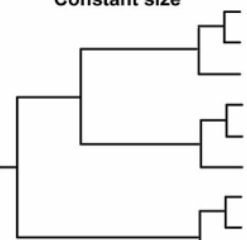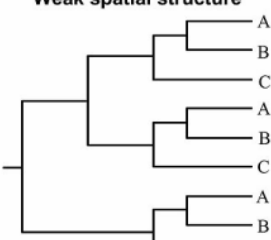
Pybys and Rambaut *Nat Rev Genet* 2009

Unifying the Epidemiological and Evolutionary Dynamics of Pathogens

Bryan T. Grenfell,[1]* Oliver G. Pybus,[2] Julia R. Gog,[1] James L. N. Wood,[3] Janet M. Daly,[3] Jenny A. Mumford,[3] Edward C. Holmes[2]

	Continual Immune Selection	Weak or Absent Immune Selection	
		Tree shape controlled by non-selective population dynamic processes	
		Population size dynamics	Spatial dynamics
Idealized Phylogeny Shapes	Time →	**Exponential growth** / **Constant size**	**Strong spatial structure** (A A A B B B C C C) / **Weak spatial structure** (A B C A B C A B C)
Examples	Human influenza A virus intra-host HIV	inter-host HIV inter-host HCV	Measles, rabies inter-host HIV
Tree Inferences	Detection of antigenic escape mutations	Estimation of population growth rates	Estimation of population migration rates

A   Structured Host
     Population

B   Unstructured Host
     Population

Legend (map):
- *P. t. verus*
- *P. t. vellerosus*
- *P. t. troglodytes*
- *P. t. schweinfurthii*

NIGERIA
CAMEROON
CENTRAL AFRICAN REPUBLIC
Bioko Island
EQUATORIAL GUINEA
GABON
REPUBLIC OF CONGO

Phylogenetic tree labels:
- 99 — SIVcpzMB66
- SIVcpzMB248
- SIVcpzMB245
- SIVcpzLB7
- SIVcpzMB192
- SIVcpzMB23
- SIVcpzMB317
- 100 — HIV-1 M/A
- HIV-1 M/B
- 98 — HIV-1 N
- HIV-1 N
- 100 — SIVcpzEK519
- SIVcpzEK516
- SIVcpzEK502
- SIVcpzEK505
- 97 — SIVcpzCAM3
- SIVcpzCAM5
- SIVcpzUS
- SIVcpzGAB2
- 96 — SIVcpzGAB1
- SIVcpzCAM13
- 100 — SIVcpzDP25
- SIVcpzDP206
- 100 — SIVcpzMT115
- SIVcpzMT145
- 100 — HIV-1 O
- HIV-1 O
- 100 — SIVcpzTAN1
- 99 — SIVcpzTAN2
- 100 — SIVcpzTAN3
- SIVcpzANT

0.1

A
Exponential Growth

B
Constant Population Size
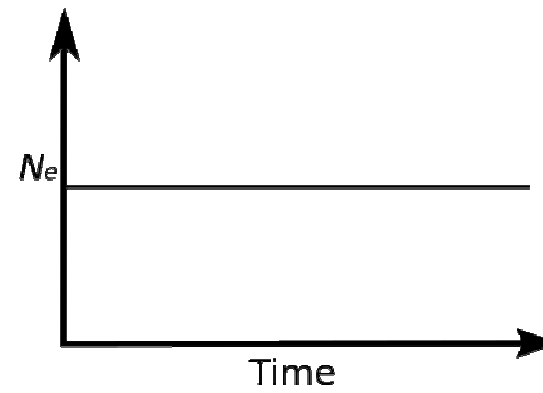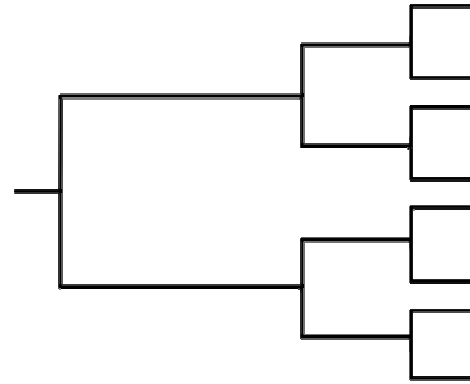
Pandemic Potential of a Strain of Influenza A (H1N1): Early Findings

Christophe Fraser,[1]* Christl A. Donnelly,[1]* Simon Cauchemez,[1] William P. Hanage,[1]
Maria D. Van Kerkhove,[1] T. Déirdre Hollingsworth,[1] Jamie Griffin,[1] Rebecca F. Baggaley,[1]
Helen E. Jenkins,[1] Emily J. Lyons,[1] Thibaut Jombart,[1] Wes R. Hinsley,[1] Nicholas C. Grassly,[1]
Francois Balloux,[1] Azra C. Ghani,[1] Neil M. Ferguson[1]†;

those over 60 years of age (*3*), and this could result in an underestimate of overall morbidity. Right censoring of mortality data, which occurs when additional deaths subsequently arise among cases already included in surveillance data, can also bias estimates of the true case fatality ratio (*4*). Finally, suspected deaths may not all have been caused by infection with the novel virus. These uncertainties necessarily affect any estimate

Fig. 4. (A) Time course of the Mexican epidemic with **(B)** the posterior estimates (median and 95% CrI) of the reproduction number over time obtained under Poisson and negative binomial models from the analysis of confirmed cases. The estimate of the negative binomial dispersion parameter k is for a low-to-moderate overdispersion, but this is enough to greatly increase the uncertainty in $R(t)$.
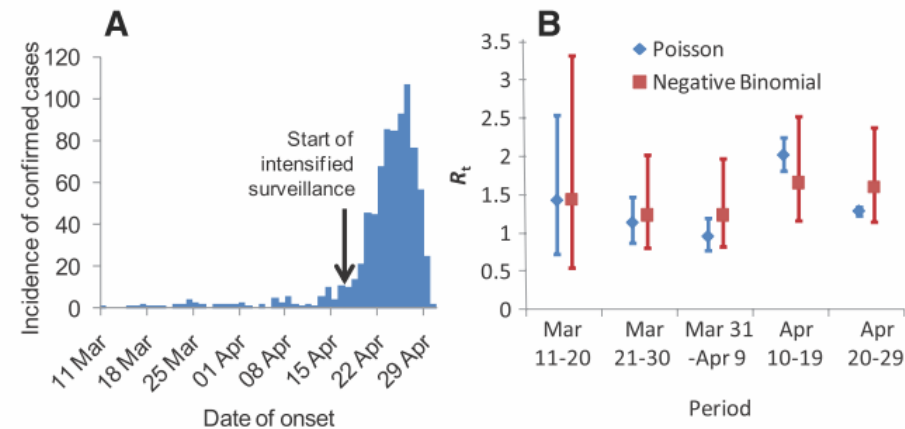
Phylogenies reveal new interpretation of speciation and the Red Queen

Chris Venditti[1], Andrew Meade[1] & Mark Pagel[1,2]
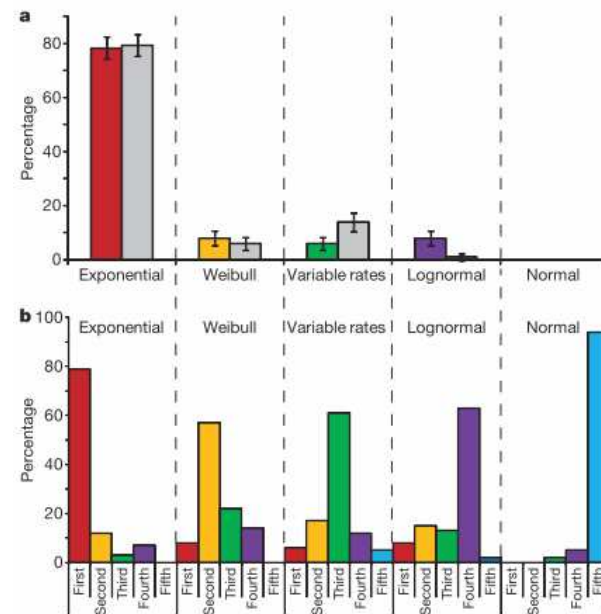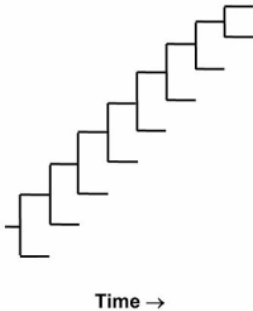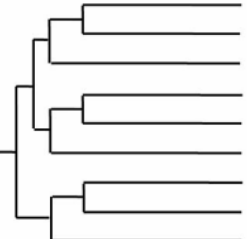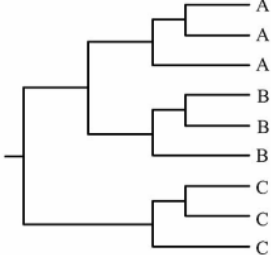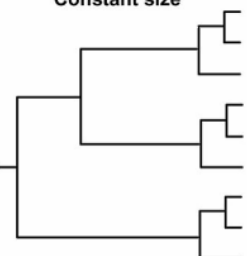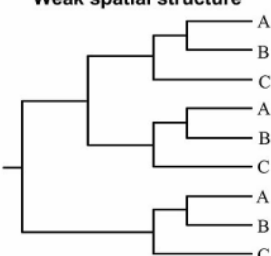
Figure 1 | Performance of the five models. We fitted the statistical models in two ways. In one, we implemented a Bayesian reversible-jump[27] Markov chain that moved among the five statistical models estimating their parameters while simultaneously jumping among trees in the posterior sample (Supplementary Information). Allowed to run for many iterations, the proportion of time the chain spends in each model measures its posterior probability of describing those data. In the second method, we fitted each model separately in its own Markov chain that estimated the parameters of the statistical model while moving among trees, recording the harmonic mean of the likelihoods (based on samples from chains that were run for

Selection
(Imbalanced tree)

No Selection
(Balanced tree)

Time Sampled

http://en.wikipedia.org/wiki/Viral_phylodynamics

Unifying the Epidemiological and Evolutionary Dynamics of Pathogens

Bryan T. Grenfell,[1]* Oliver G. Pybus,[2] Julia R. Gog,[1] James L. N. Wood,[3] Janet M. Daly,[3] Jenny A. Mumford,[3] Edward C. Holmes[2]

Idealized Phylogeny Shapes	Continual Immune Selection	Weak or Absent Immune Selection — Tree shape controlled by non-selective population dynamic processes	
		Population size dynamics	Spatial dynamics
	(Time →)	Exponential growth / Constant size	Strong spatial structure (A A A B B B C C C) / Weak spatial structure (A B C A B C A B C)
Examples	Human influenza A virus intra-host HIV	inter-host HIV inter-host HCV	Measles, rabies inter-host HIV
Tree Inferences	Detection of antigenic escape mutations	Estimation of population growth rates	Estimation of population migration rates

время →

Эволюционное древо ВИЧ
для пациента
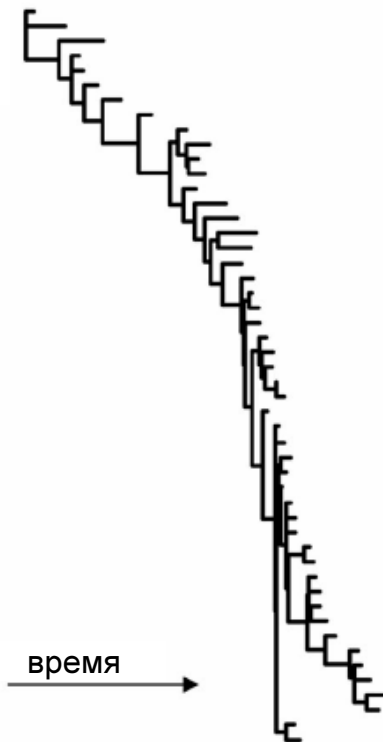
время →

Эволюционное древо гриппа
для человечества

Grenfell et al. *Science* 2004

H1N1

2008/09
2007/08

2006/07

2005/06

Брисбейн

2004/05

Фуджи

H3N2

2003/04
2002/03

2002/03

2001/02

Сидней

1999/00

1997/98

1996/97

1995/96

Вухан

1994/95

1992/93, 1993/94

Chorioallantoic membrane inoculation — Herpes simplex virus / Poxvirus / Rous sarcoma virus

Amniotic cavity
Shell
Albumin
Allantoic cavity
Yolk sac

Shell membrane
Air sac
Amniotic inoculation — Influenza virus / Mumps virus
Yolk sac inoculation — Herpes simplex virus
Allantoic inoculation — Influenza virus / Mumps virus / Newcastle disease virus / Avian adenovirus
Chorioallantoic membrane

2015 pandemic capacity
Million doses; cumulative

6 months (14-week production)

12 months (40-week production)
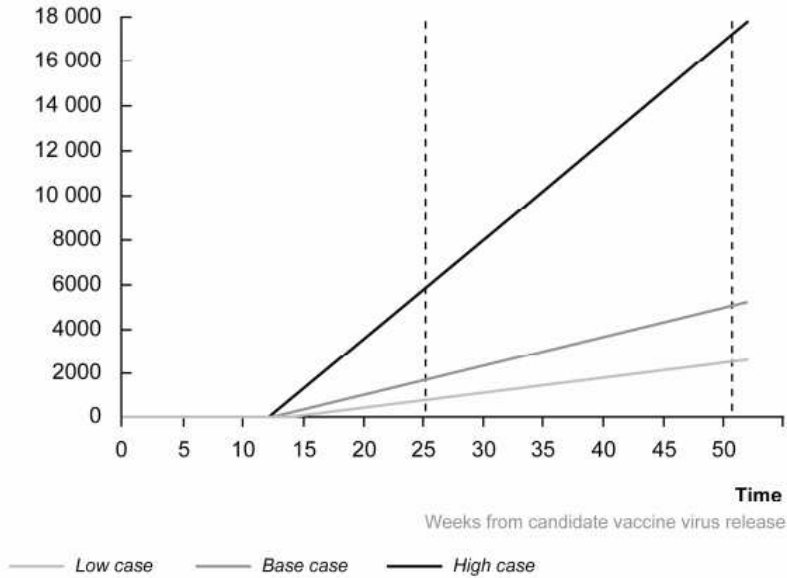
Available vaccine supply
% of world population[1]

	6 months (14-week production)	12 months (40-week production)
	42.4%	121.0%
	12.6%	35.9%
	6.3%	18.0%

Low case — Base case — High case

Weeks from candidate vaccine virus release

Time
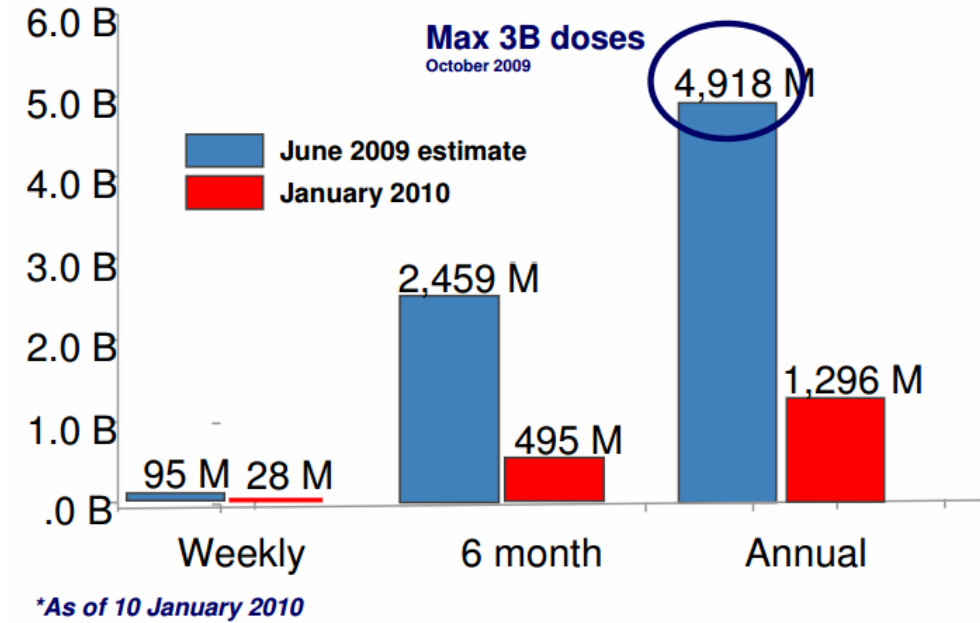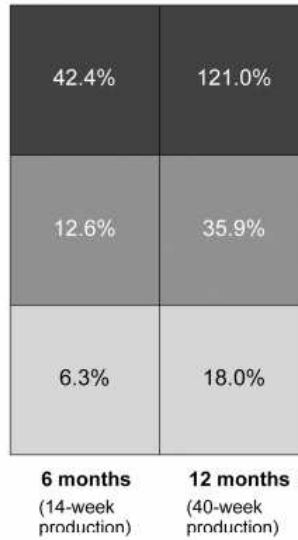
[1] Percentage of the population that could be vaccinated with two doses of vaccine, as per the target of the Global Pandemic Influenza Action Plan to Increase Vaccine Supply, given the estimated vaccine supply. World population in 2015, 7.3 billion.

WHO 10

Max 3B doses
October 2009

4,918 M

June 2009 estimate
January 2010

2,459 M
495 M

95 M   28 M

1,296 M

Weekly   6 month   Annual

*As of 10 January 2010

http://www.who.int/influenza_vaccines_plan/resources/mpk_b.pdf

Previous Season's Vaccine Virus — A
Circulating Virus 1 ("like" virus) — B
Circulating Virus 2 (low reactor) — C

Columns: 1:10, 1:20, 1:40, 1:80, 1:160, 1:320, 1:640, 1:1280, 1:2560, 1:5120, 1:10240, 1:20480
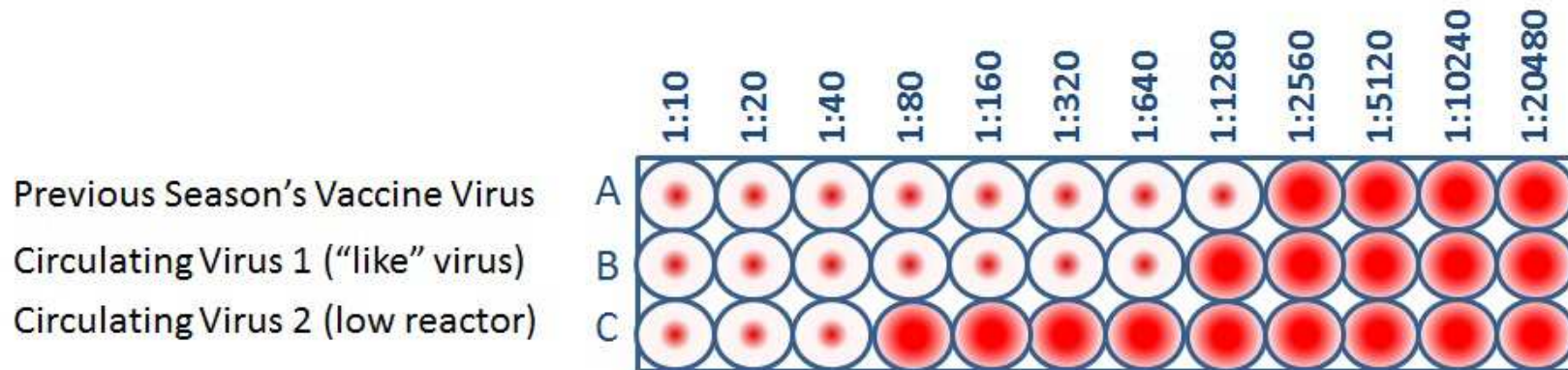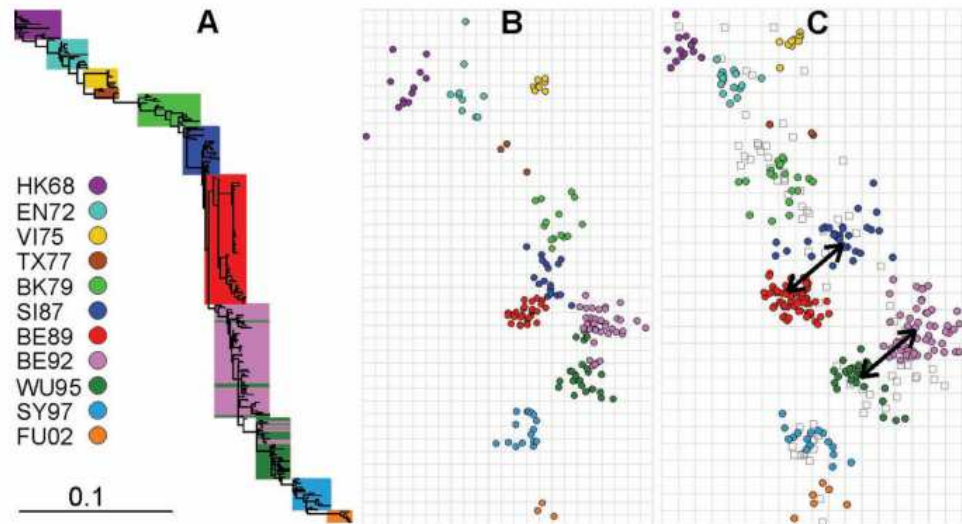
Fig. 2. Comparison of antigenic and genetic evolution of influenza A virus. (**A**) Phylogenetic tree of the HA1 nucleotide sequences, color-coded based on antigenic clusters of Fig. 1. Multiple trees were built using a reversible site-dependent nucleotide ML method (37). There was good consensus among trees, and the tree with ML is shown. (**B**) Genetic map of the HA1 amino acid sequences, color-coded according to the antigenic clusters of Fig. 1. The vertical and horizontal axes represent genetic distance, in this case the number of amino acid substitutions between strains; the spacing between grid lines is 2.5–amino acid substitutions. The orientation of the map was chosen to match the orientation of the antigenic map in Fig. 1. (**C**) The same antigenic map of influenza A virus strains as shown in Fig. 1, except for a rigid-body rotation and translation of the pre-TX77 clusters (fig. S2) to match the genetic map and except that virus strains are represented by colored circles and antisera by open squares. Arrows indicate the two cluster transitions for which the amino acid substitution N145K is the only cluster-difference substitution (Table 1, fig. S1).

Smith et al. *Nature* 2004

Steinbrueck and McHardy *Nuc Acids Res* 2010
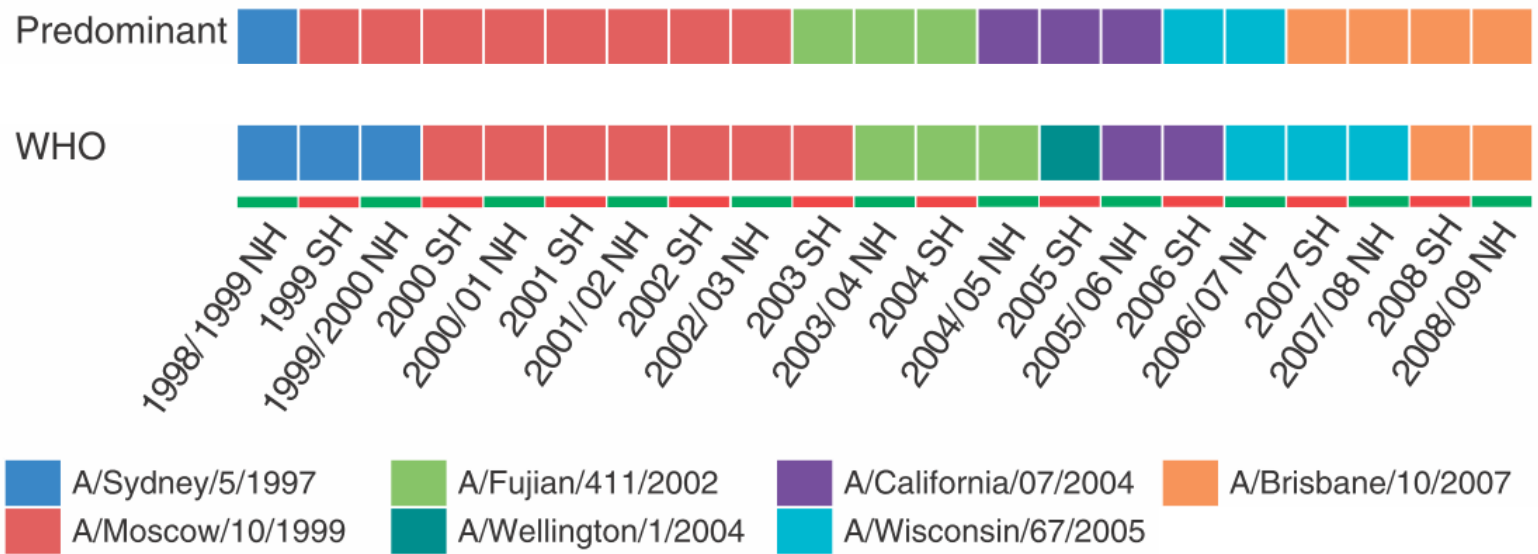
All of the 2015-2016 influenza vaccine is made to protect against the following three viruses:
•an A/California/7/2009 (H1N1)pdm09-like virus
•an A/Switzerland/9715293/2013 (H3N2)-like virus
•a B/Phuket/3073/2013-like virus. (This is a B/Yamagata lineage virus)

http://www.cdc.gov/flu/about/season/flu-season-2015-2016.htm

Influenza Positive Tests Reported to CDC by U.S. Public Health Laboratories, National Summary, 2015-16 Season

Legend:
☐ A (subtyping not performed)
☐ A (H1N1)pdm09
■ A (H3N2)
■ H3N2v
■ B (lineage not performed)
☐ B (Victoria Lineage)
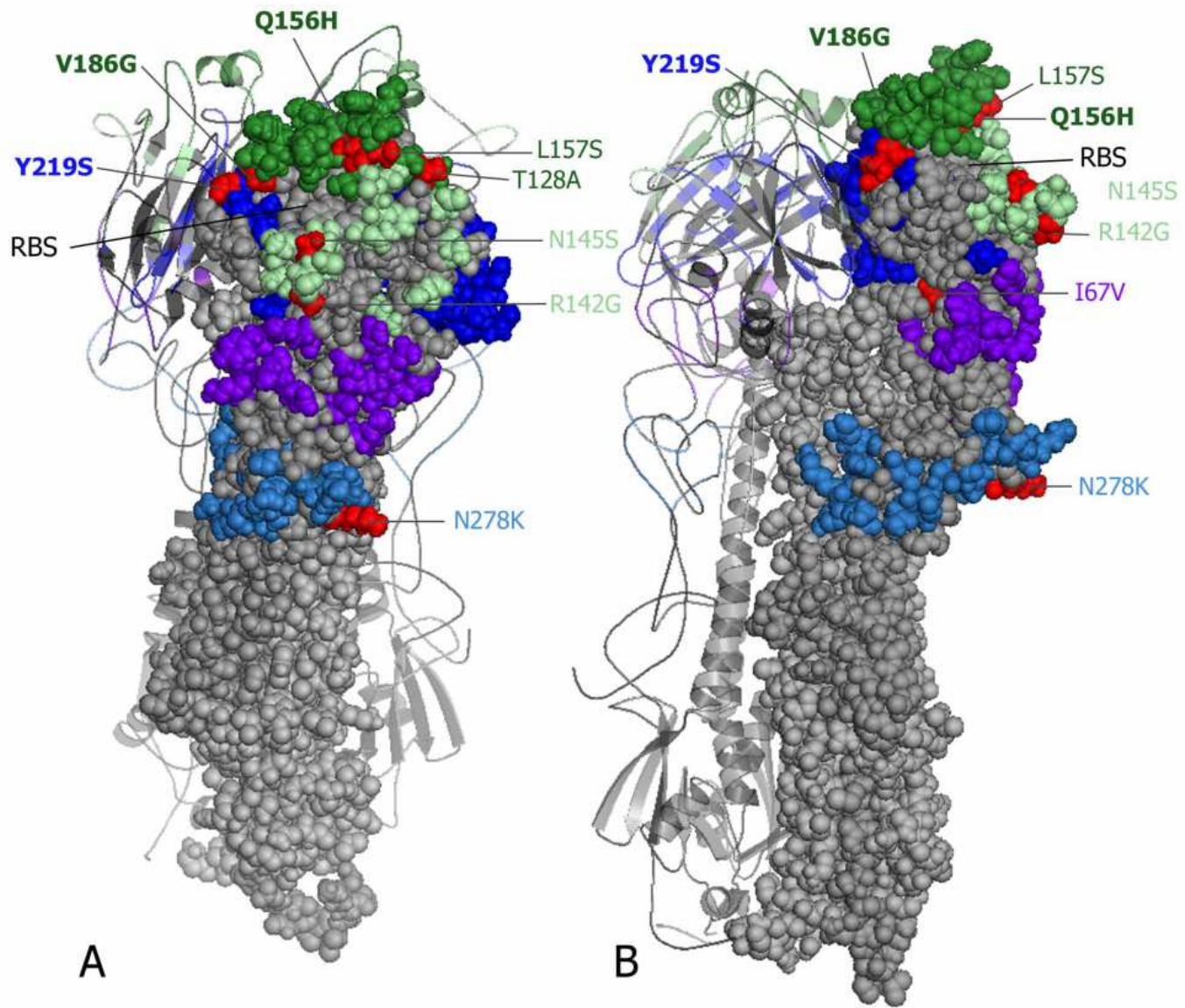■ B (Yamagata Lineage)

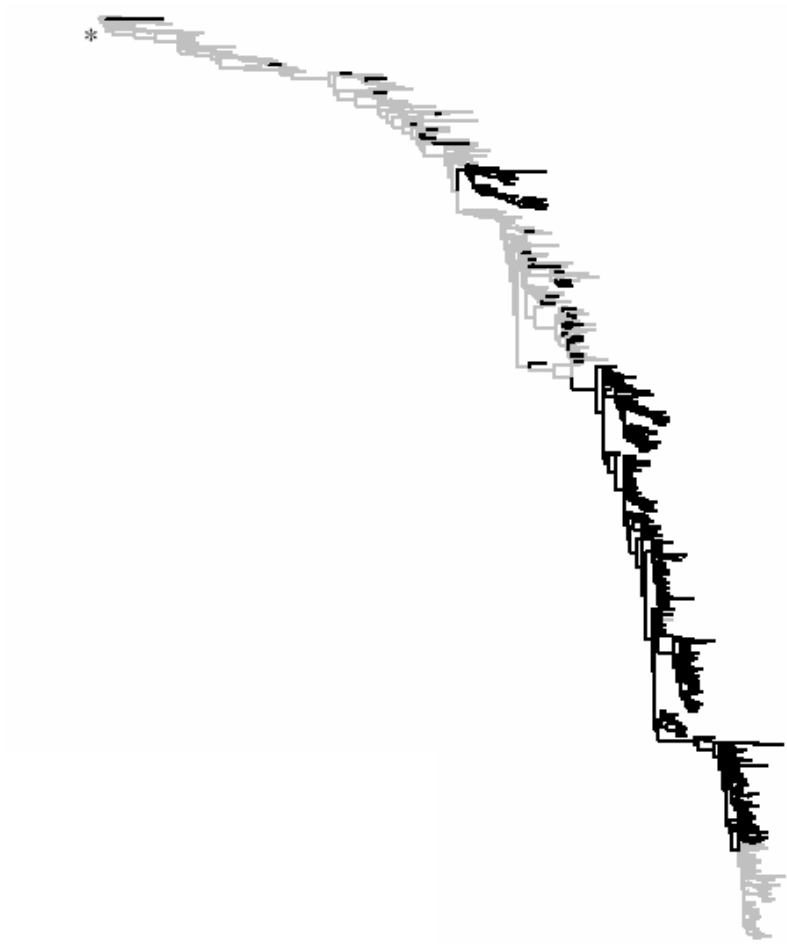http://www.cdc.gov/flu/weekly/
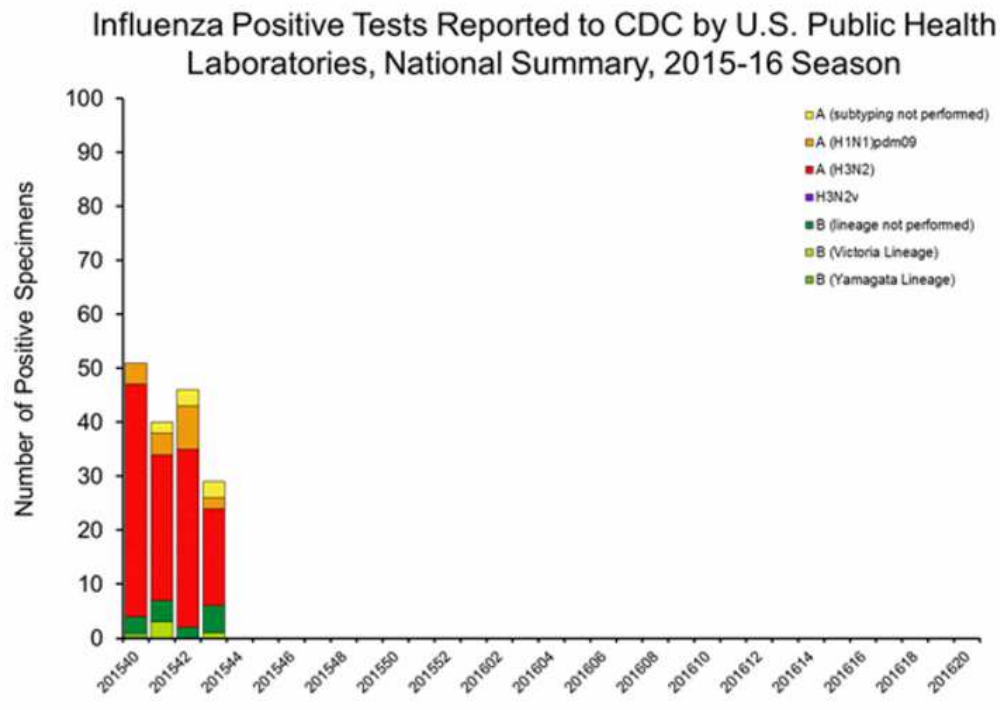
Influenza A Virus [233]
•**A (H1N1)pdm09 [14]:** All 14 (100%) influenza A (H1N1)pdm09 viruses were antigenically characterized as A/California/7/2009-like, the influenza A (H1N1) component of the 2015-2016 Northern Hemisphere.
•**A (H3N2) [219]:** All 219 H3N2 viruses were genetically sequenced and all viruses belonged to genetic groups for which a majority of viruses antigenically characterized were similar to A/Switzerland/9715293/2013, the influenza A (H3N2) component of the 2015-2016 Northern Hemisphere vaccine.

> •A subset of 95 H3N2 viruses also were antigenically characterized; 94 of 95 (99%) H3N2 viruses were A/Switzerland/9715293/2013-like by HI testing or neutralization testing.

Influenza B Virus [71]: Forty-four (62%) of the influenza B viruses characterized belonged to B/Yamagata/16/88 lineage and the remaining 27 (38%) influenza B viruses characterized belonged to B/Victoria/02/87 lineage.

Sergey
Kryazhimskiy
(Harvard U.)

Kryazhimskiy et al. *Proc. R. Soc. B* 2008
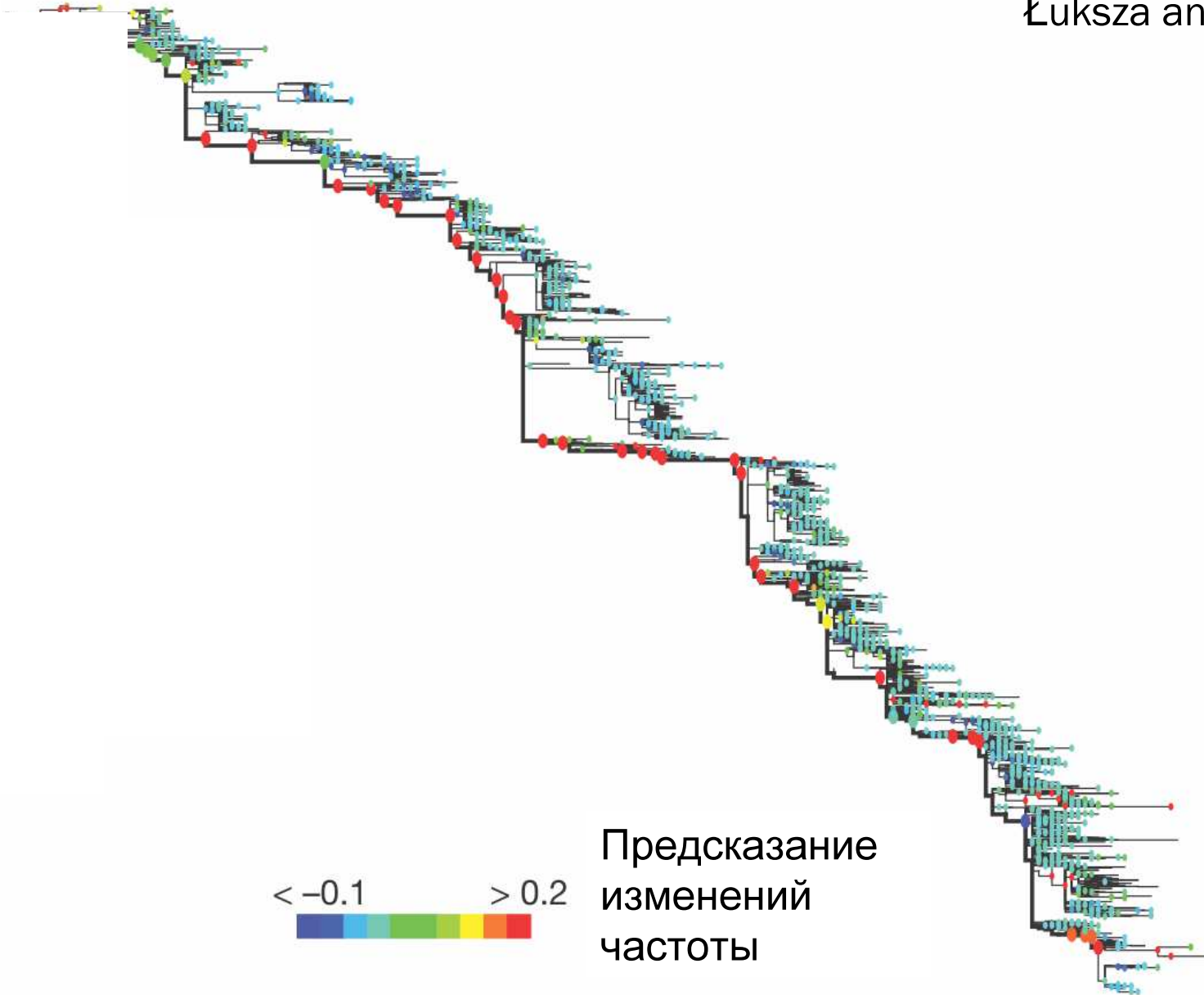
Łuksza and Lässig *Nature* 2014

< −0.1   > 0.2

Предсказание изменений частоты

nextflu.org
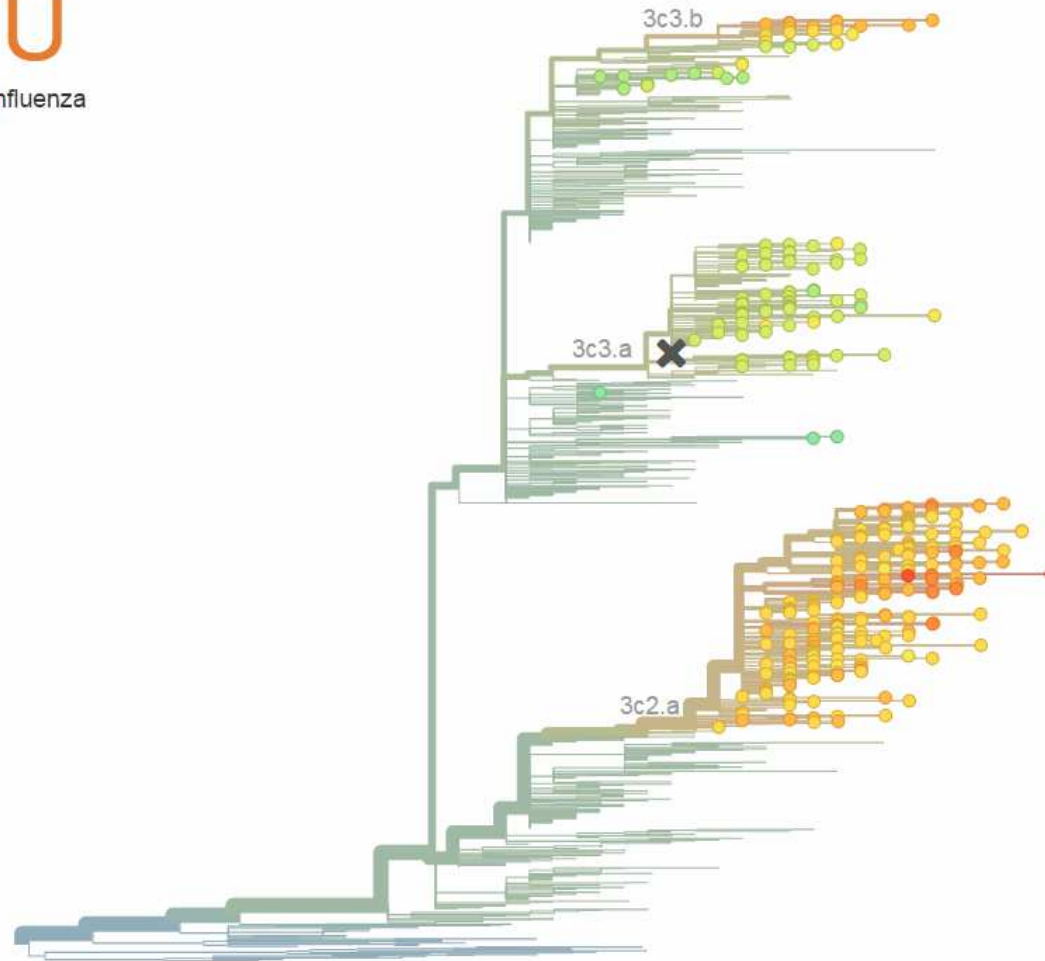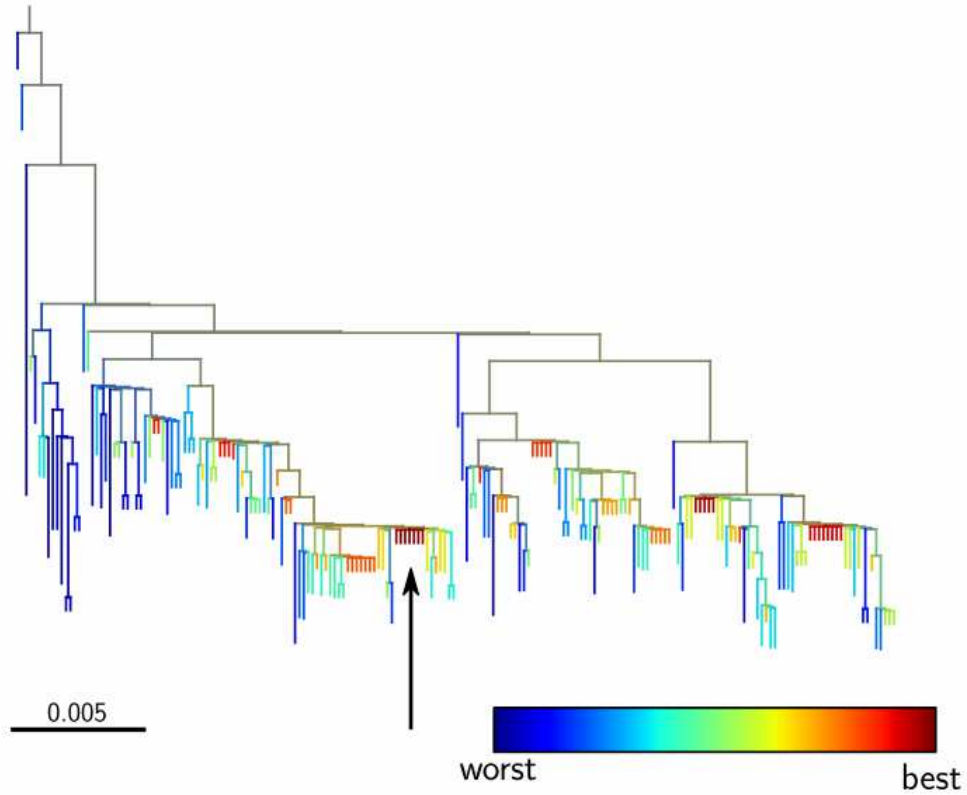
A until Feb 2007

B until Feb 2007 + season 2007/2008 (grey)

0.005

0.005

worst

best

Neher et al. *eLife* 2014
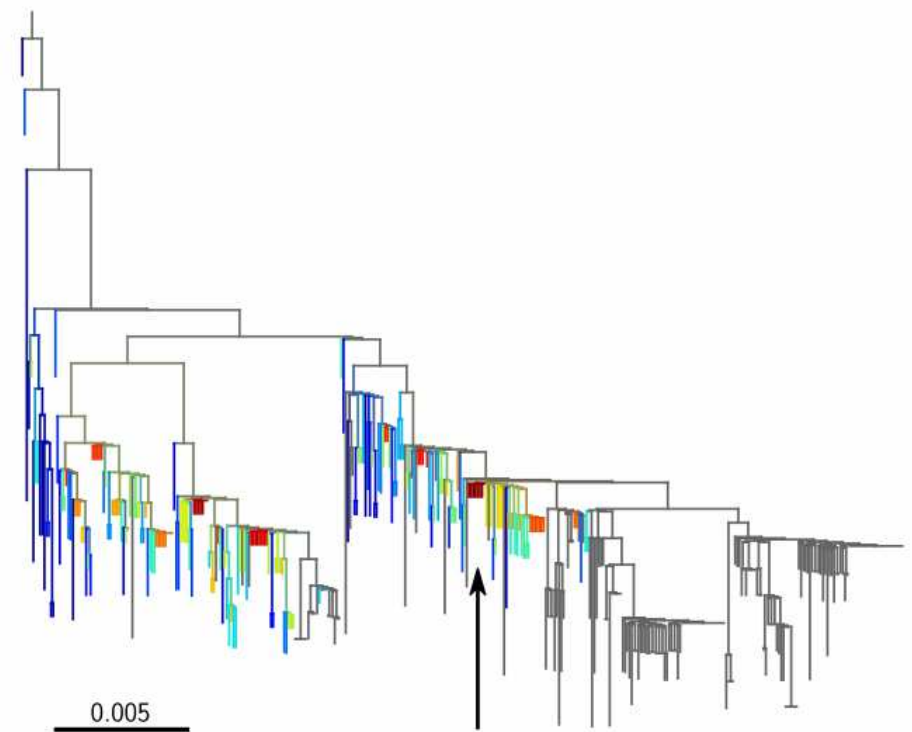
ТАРАН ⟶ БАРАН ⟶ БАРОН

ТАРОН

Gong et al. *eLife* 2013
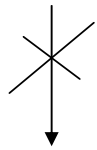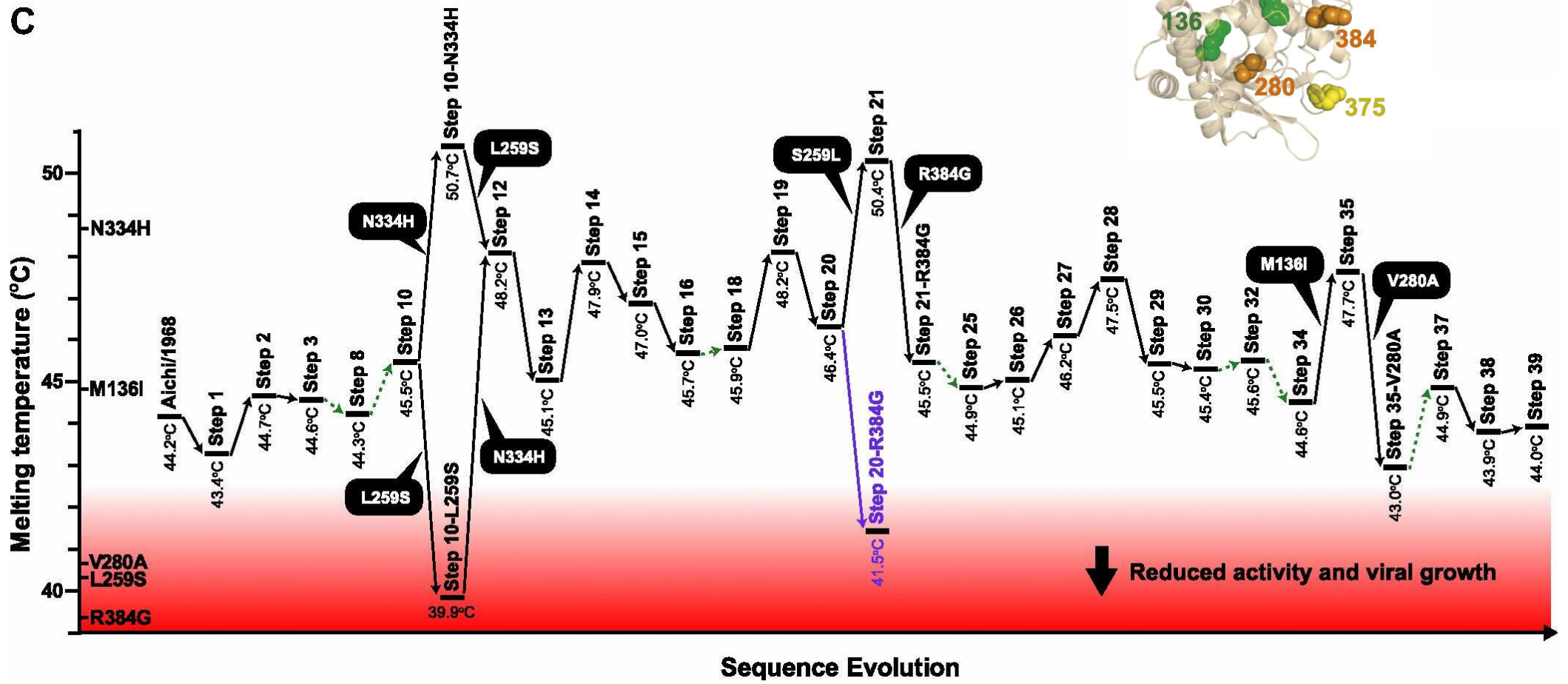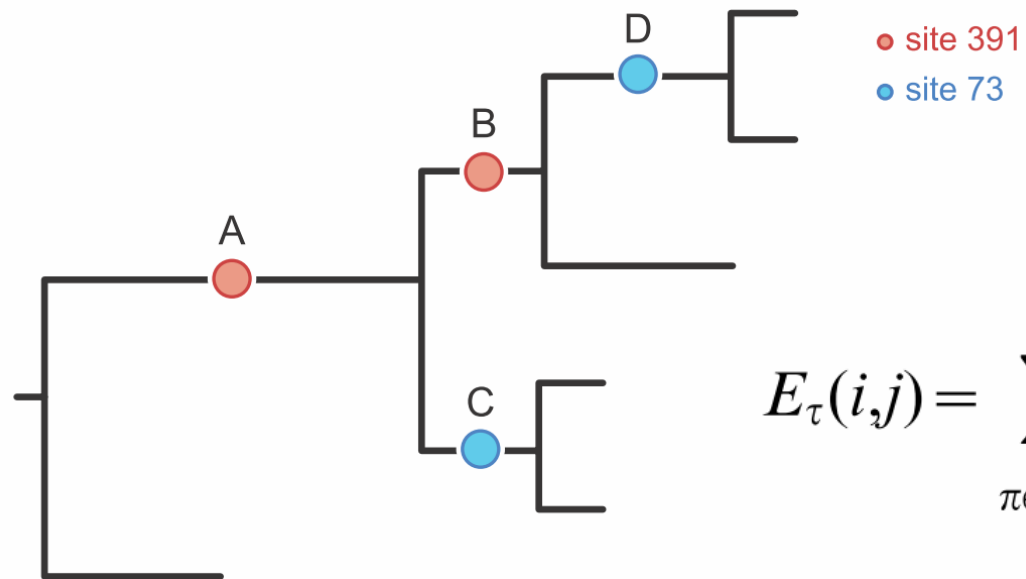
$$E_\tau(i,j) = \sum_{\pi \in S_{ij}^{(1)}} \exp\{-t_\pi/\tau\}.$$

Kryazhimskiy et al. 2011 *PLOS Genetics*

HA ● site 391
       ● site 73
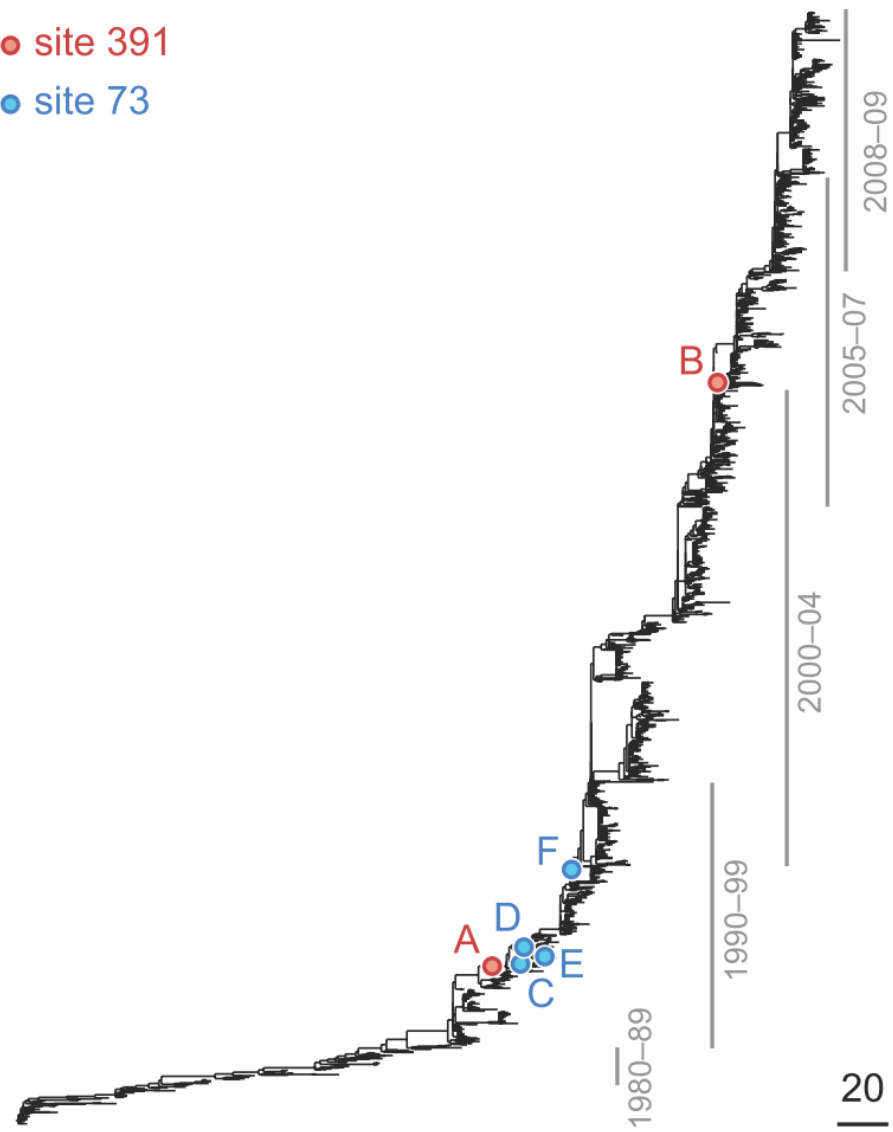
A B C D E F

1980–89 1990–99 2000–04 2005–07 2008–09

20

Kryazhimskiy et al. 2011 *PLOS Genetics*

N1-274

H1-222   N1-275

N1-430

2008

2004–07

2000–03

1990–99

1977–89

40

Neverov et al. 2014

NA
- site 344
- site 275

2008–09

2005–07

2000–04

1990–99

1980–89

20
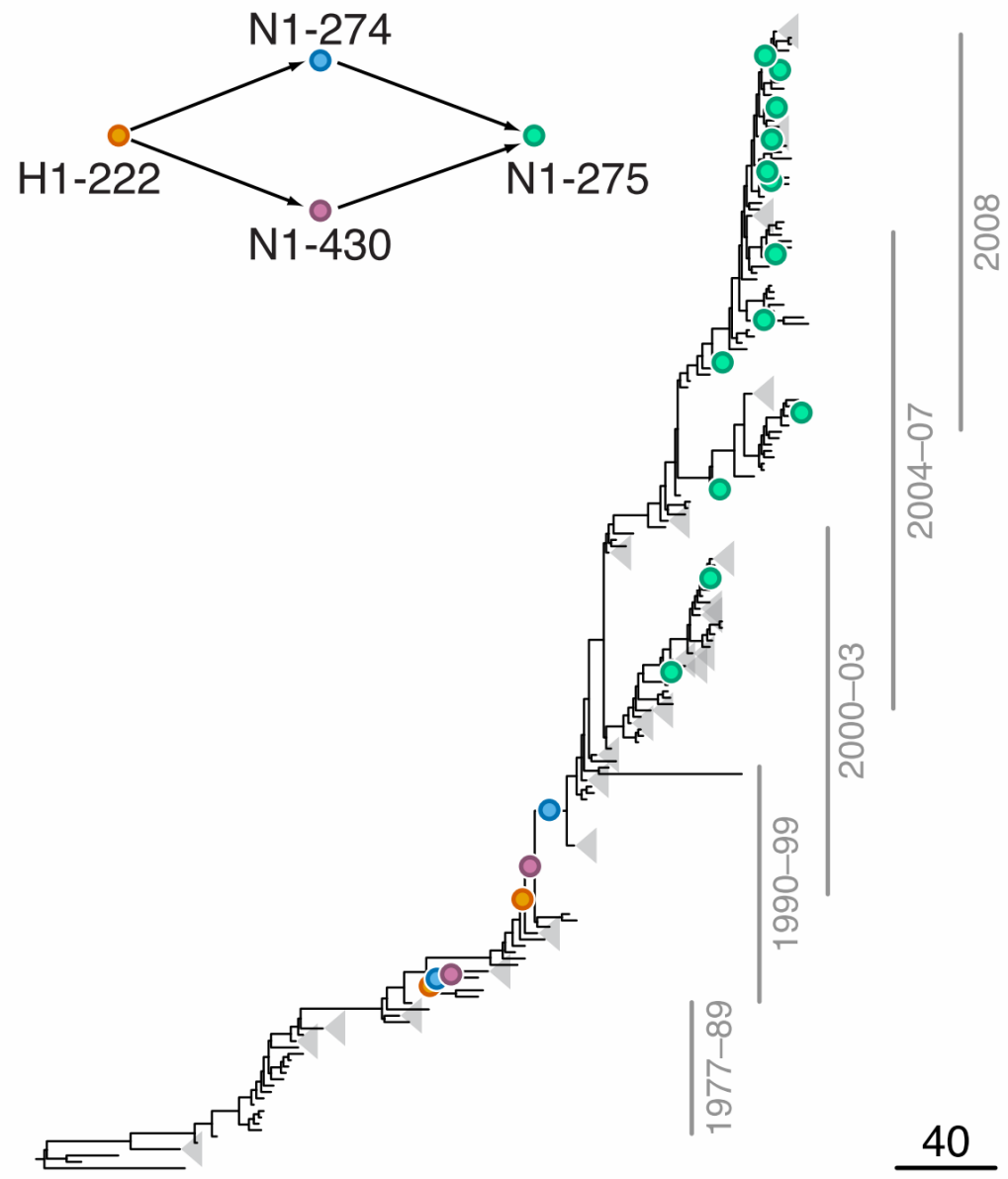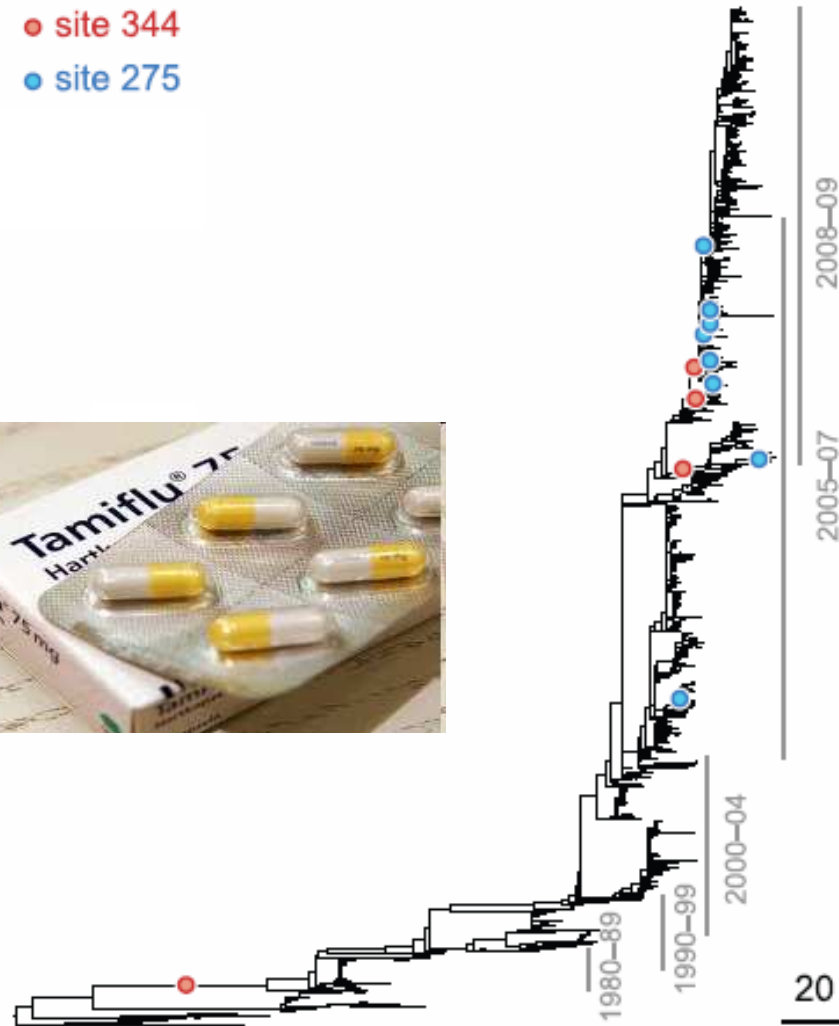
Kryazhimskiy et al. 2011 *PLOS Genetics*

Возникновение инфекционного заболевания

Интродукция из природного резервуара

Передача в популяции человека

Инфекции:
- ○ Интродуцир. штаммом ($R_0 < 1$)
- ● Эволюционир. штаммом ($R_0 > 1$)

Эффективное распространение в популяции человека

captive animals

humans

H1
H3

H1

H1
H3

H1
H2
H3

H3

H3

H4, H9

H5-H7
H9

H10

H3
H7*

H7

H5-H7
H9, H10

H4

H1 - H11, H13

H1

H1 - H16

H3
H4
H7
H10

H17, H18

H1
H13

wild animals

Short et al. 2015

A

110
58
318
47
18

B

Non-adapted   Adapted

Virus attachment to mammalian upper respiratory tract

Relative Fusogenicity (% of maximum)

100

5.0   pH   6.0

5.0   pH   6.0

Acid stability
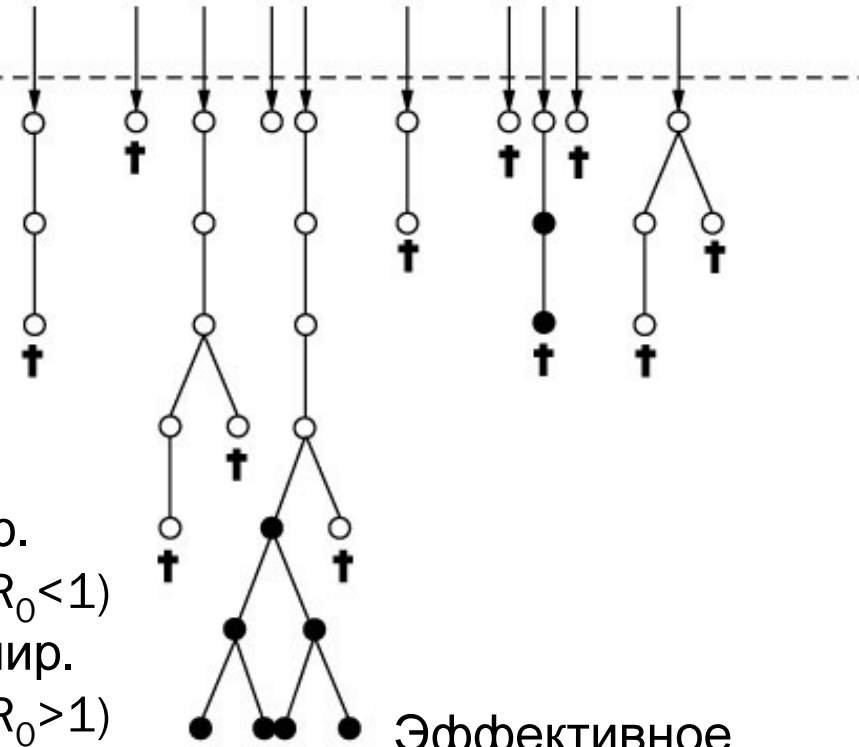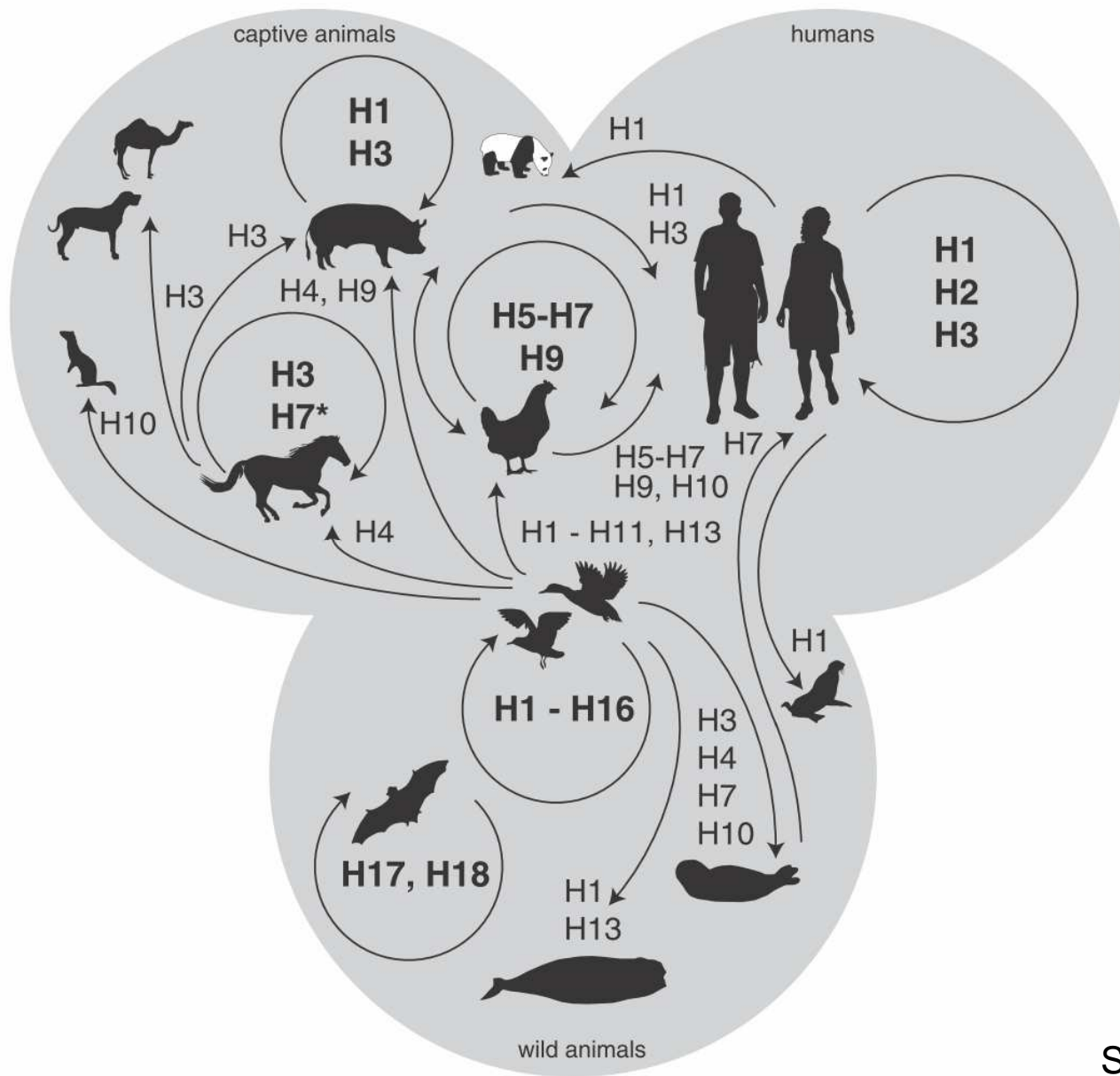
Short et al. 2015
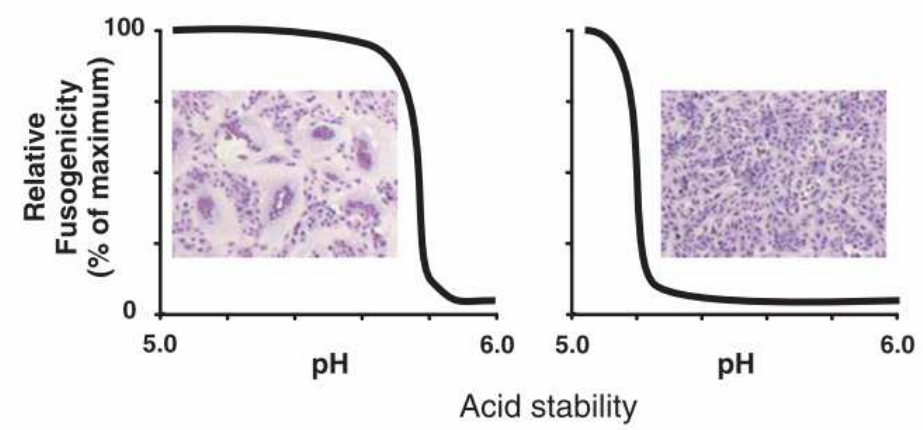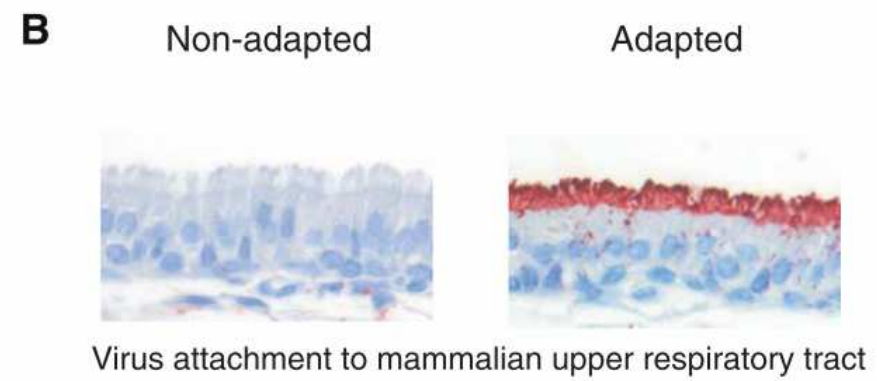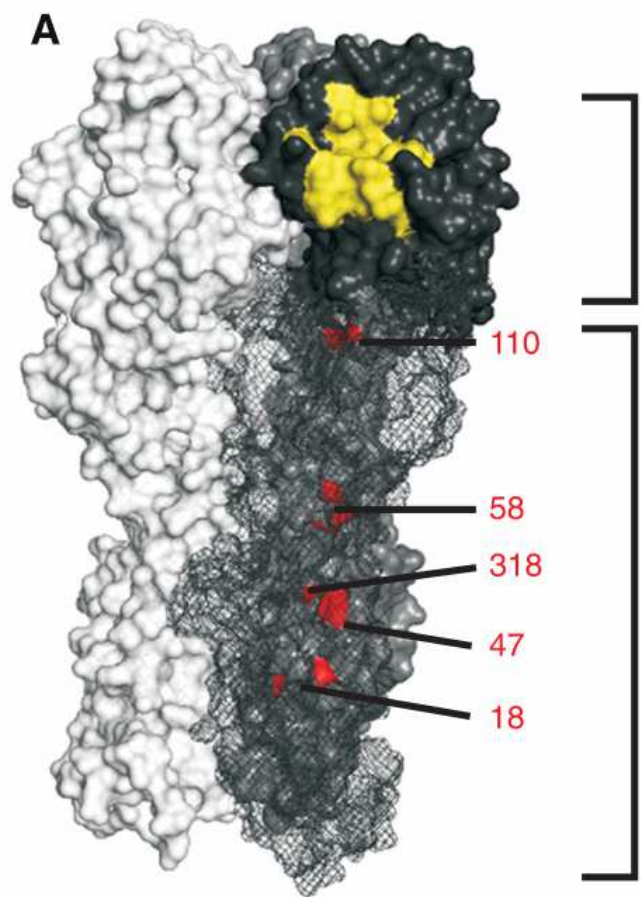
Организация генома

Реассортация

Influenza A virus subtypes in the human population

Palese *Nat Med* 2004

Nature 459:1122 2009

A(H1N1)v =

A(H1)v =

A(H1N1)v =

=

A(H1N1)v +

A(H1N1)v +

+

A(H1)v =

A(H1N1)v =

A(H1)v +

A(H1N1)v =

+

A(H1N1)v +

A(H1)v +

A(H1N1)v +

A(H1)v +

A(H1N1)v +

A(H1)v =

+

Liechtenstein

Luxembourg

Malta
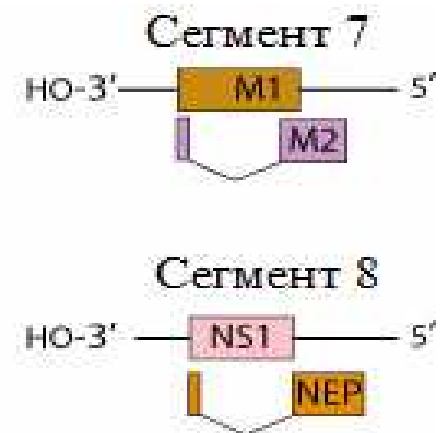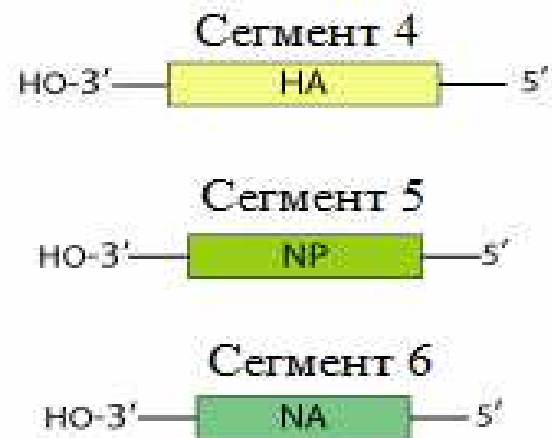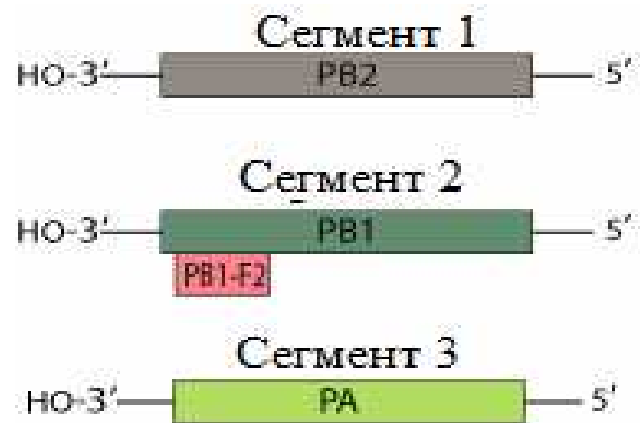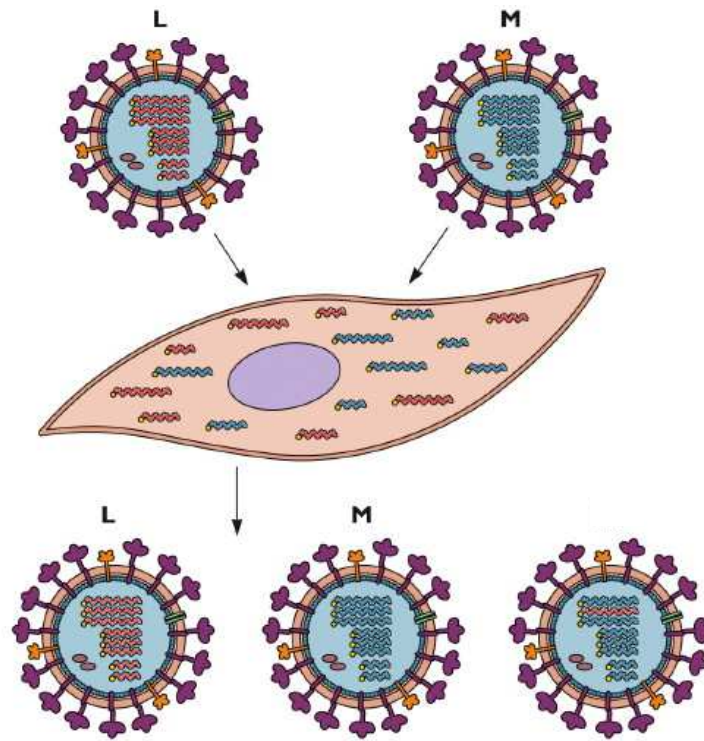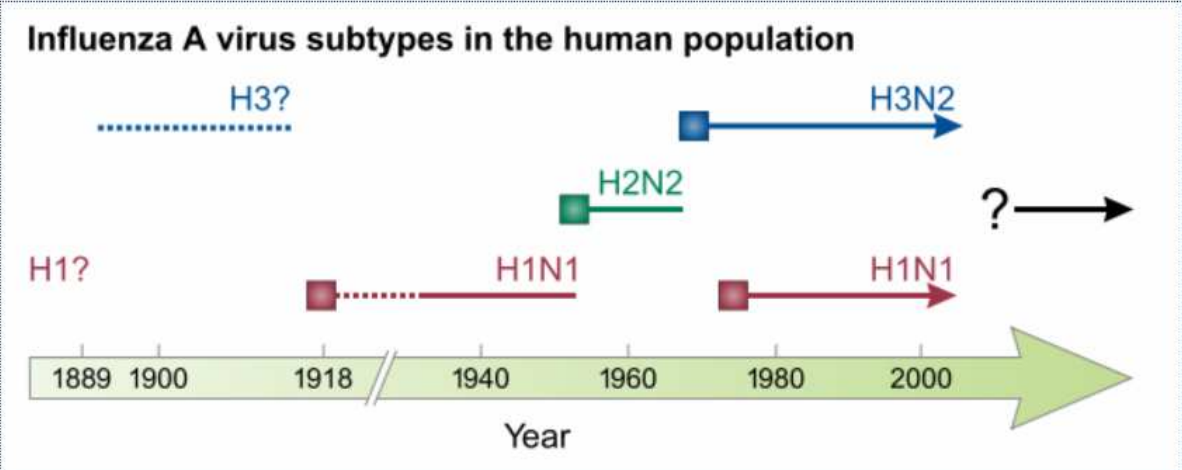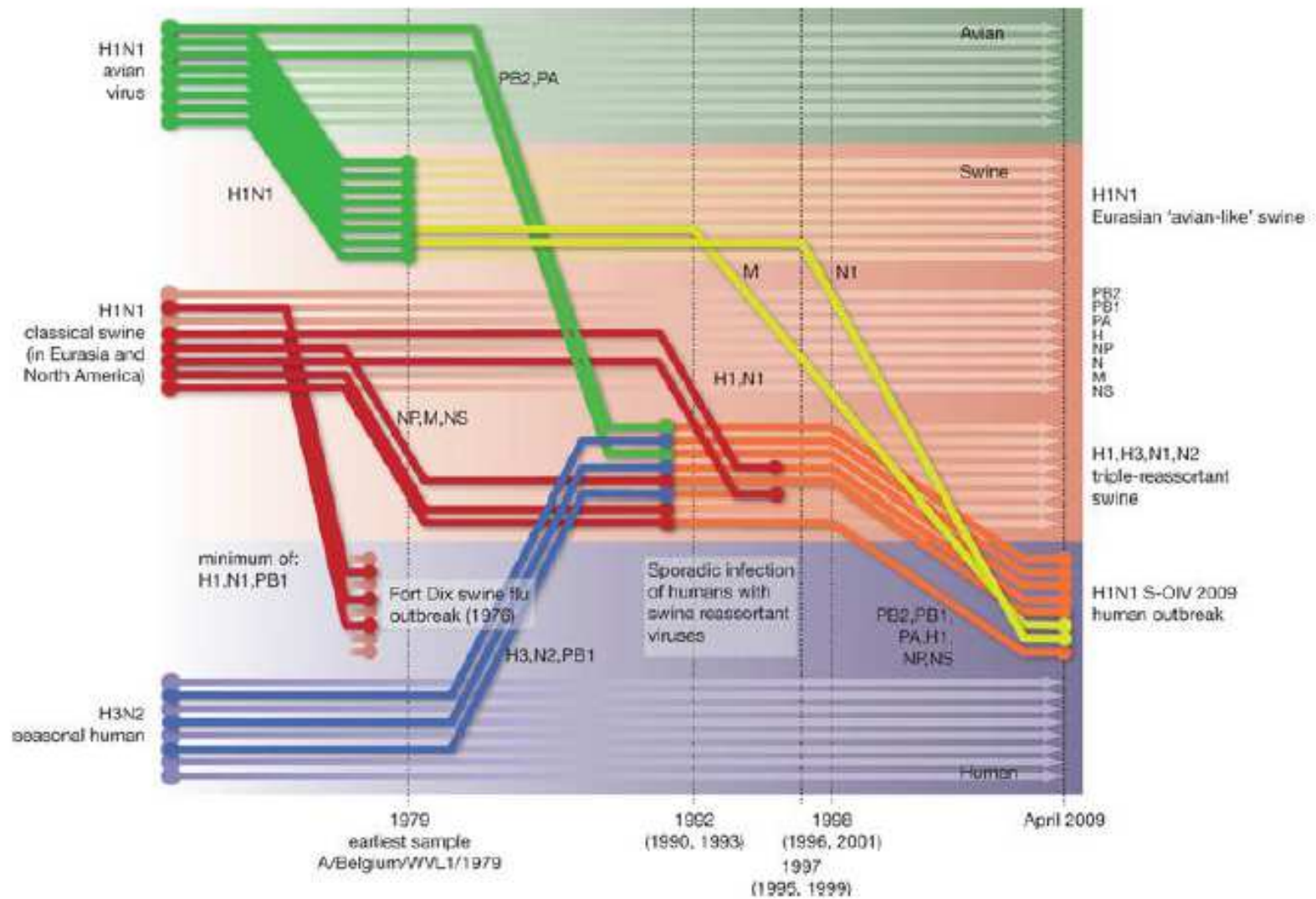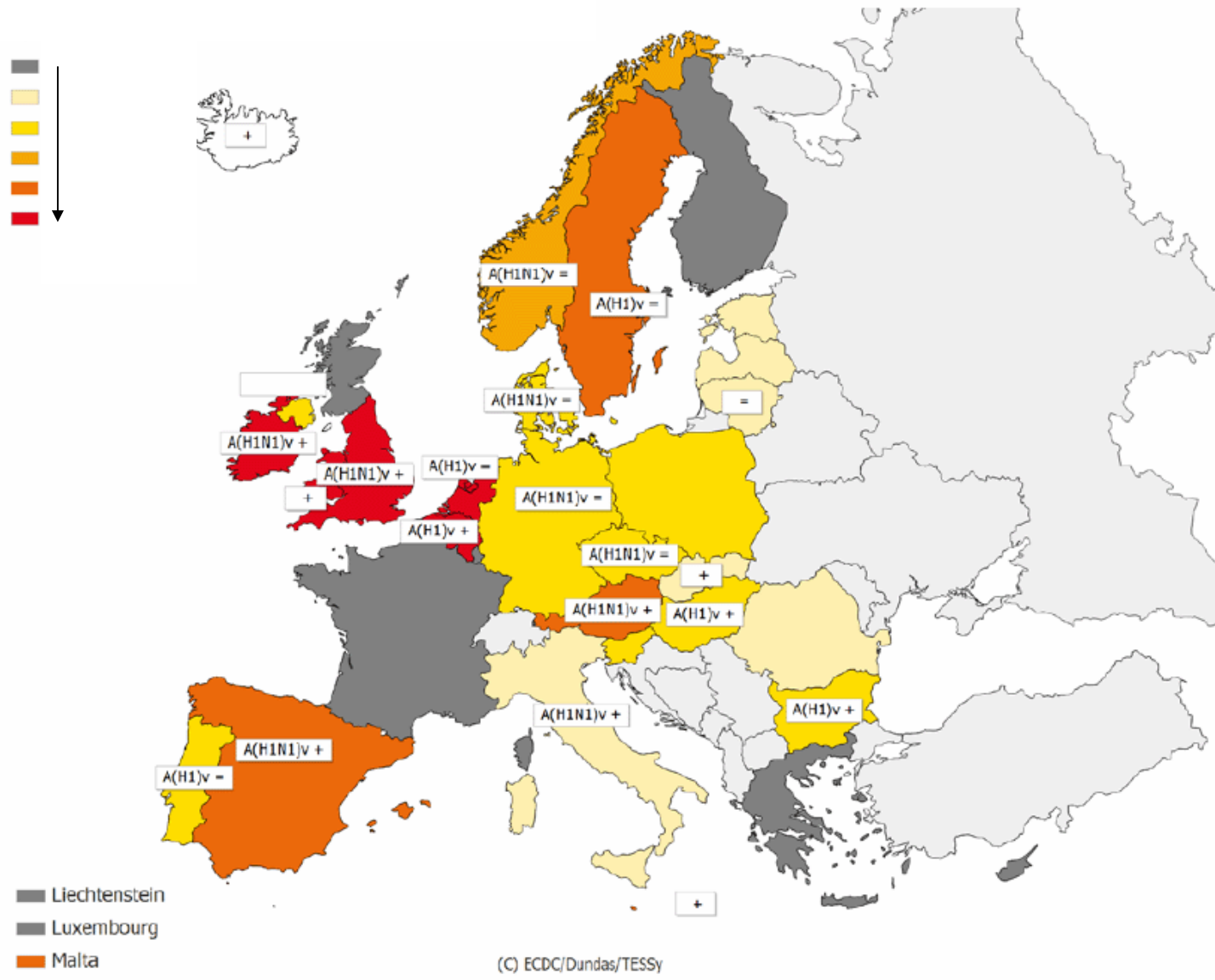
(C) ECDC/Dundas/TESSy

Table 3: Antiviral resistance by influenza virus type and subtype, weeks 40/2008–41/2009

Virus type and subtype	Resistance to neuraminidase inhibitors				Resistance to M2 inhibitors	
	Oseltamivir		Zanamivir		Isolates tested	Resistant n (%)
	Isolates tested	Resistant n (%)	Isolates tested	Resistant n (%)		
A(H3N2)	647	0	606	0	703	703 (100%)
A(H1N1)	284	279 (98%)	284	0	131	2 (<1%)
A(H1N1)v	599	0	487	0	110	110 (100%)
B	117	0	113	0		

A(H1N1)v +
A(H1N1)v +
A(H1)v −
+
A(H1)v +
A(H1N1)v −
A(H1N1)v +
A(H1N1)v =
A(H1N1)v =
+
A(H1N1)v +
A(H1)v +
A(H1)v +
A(H1N1)v +
=
A(H1)v −
A(H1N1)v +
+

Liechtenstein
Luxembourg
Malta

(C) ECDC/Dundas/TESSy

NA   HA

Neverov et al. 2014 *PLOS Genetics*

0.1

A/2009
A/California/VRDL333/2009
A/California/VRDL265/2009
A/Managua/2867.01/2010
A/Managua/4855.03/2010
A/Managua/511.03/2010
A/Managua/3209.01/2010
A/Managua/38-11/2011
A/Managua/4076.04/2010
A/Managua/5664.02/2010
A/Managua/1422.03/2010
A/Managua/1181.03/2010
A/Managua/5099.03/2010
A/San_Salvador/WRAIR3537T/2010
A/Managua/194.01/2010
A/Managua/3345.02/2010
A/Managua/3192.01/2010
A/Managua/4456.02/2010
A/Managua/4203.02/2010
A/Managua/3659.02/2010
A/Managua/58-11/2011
A/Managua/5806.01/2010
A/Managua/90.01/2010
A/Managua/5898.02/2010
A/Managua/5871.02/2010
A/South_Carolina/NHRC0001/2011
A/New_York/20343/2010
A/New_York/6630/2009
A/Sydney/DD2-01/2010
A/California/NHRC0004/2011
A/California/NHRC0003/2011
A/Managua/3424.01/2010
A/Mexico_City/WRAIR3569N/2010
A/Mexico_City/WRAIR3569T/2010
A/Mexico_City/WRAIR3579N/2010
A/Mexico_City/WRAIR3579T/2010
A/District_of_Columbia/WRAIR1753P/2010
A/Moscow/WRAIR4307N/2011
A/Mexico_City/WRAIR3578N/2010
A/Bogota/WRAIR3457N/2010
A/Mexico_City/WRAIR3568N/2010
A/Mexico_City/WRAIR3570T/2010
A/Mexico_City/WRAIR3571N/2010
A/Illinois/NHRC0002/2011
A/Managua/2492.04/2010
A/California/NHRC0001/2011
A/California/NHRC0002/2011
A/Santo_Domingo/WRAIR3514T/2010
A/Santo_Domingo/WRAIR3516N/2010
A/California/VRDL362/2009
A/District_of_Columbia/WRAIR0300/2010
A/Sydney/DD2-02/2010
A/California/VRDL335/2009
A/Thailand/CU-1101/2008
A/Thailand/CU-1102/2008
A/2008-2010
A/New_York/3279/2009
A/New_York/3280/2009
A/Australia/46/2009
A/Australia/19/2009
55A/Australia/30/2009
A/California/VRDL384/2009
A/Nanjing/1/2009
A/Thailand/CU-B4/2009
A/New_York/3519/2009
A/California/VRDL338/2009
A/California/VRDL363/2009
A/New_York/20342/2010
A/Thailand/CU-B657/2009
A/2007-2009
A/Thailand/CU-1103/2008
A/Thailand/CU231/2006

Neverov et al. 2014 *PLOS Genetics*

Influenza A virus subtypes in the human population
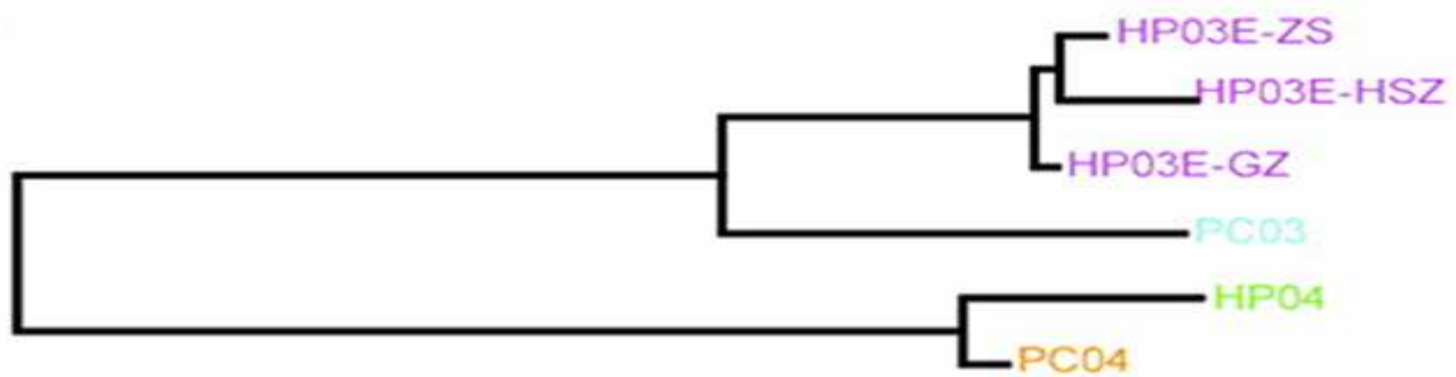
Ron Fouchier and Ab Osterhaus.

DIRK-JAN VISSER/REDUX/EYEVINE; ARIE KIEVIT/HOLLANDSE HOOGTE/EYEVINE

HP03E-ZS

HP03E-HSZ

HP03E-GZ

PC03

HP04

PC04

0.0001