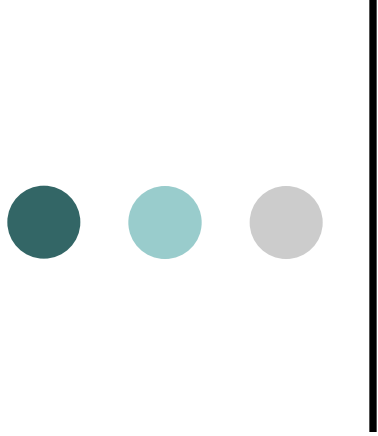


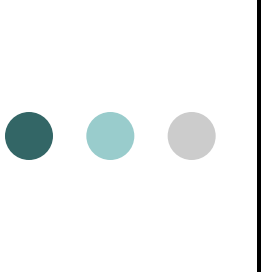


Pandemik H1N1 virusunun moleküler epidemiyolojisi

Doç. Dr. Kenan Midilli

İ.Ü. Cerrahpaşa Tıp fakültesi

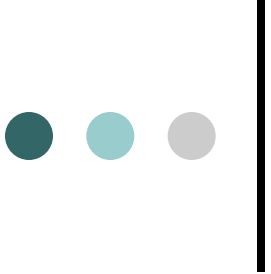
Tıbbi Mikrobiyoloji Anabilim Dalı



- HA → 16 H

- NA → 9 N

Tüm H ve N tipleri kuşlarda bulunur →
Tüm INFv'lerinin kuş kaynaklı olduğu
hipotezi

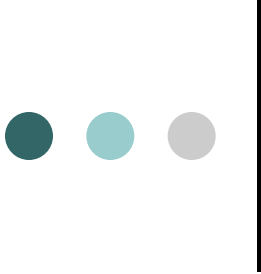


- 1918 → H1N1

- 1957 → H2N2

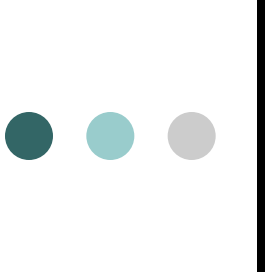
- 1968 → H3N2

- 1977 → H1N1'in tekrar ortaya çıkışı



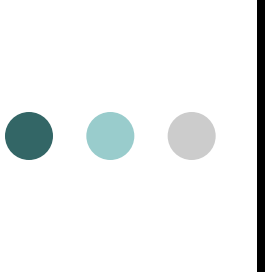
İnfluenza viruslarının evrimi:

- **Antijenik “drift” (sürüklenme):**
Mevsimsel kökenlerdeki minör antijenik değişiklikler
- **Antijenik “shift” (kayma):**
Pandemilerden sorumlu majör antijenik değişiklikler
- **Rekombinasyon???** Nadir



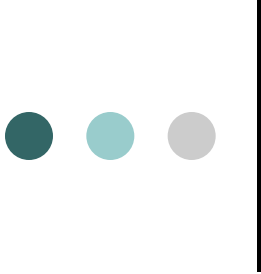
Pandemik H1N1

- Klasik domuz
- Avrasya domuz
- Kuzey Amerika üçlü reasorte domuz



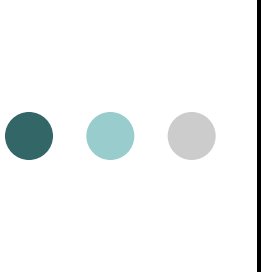
Avrupa ve Asya'da

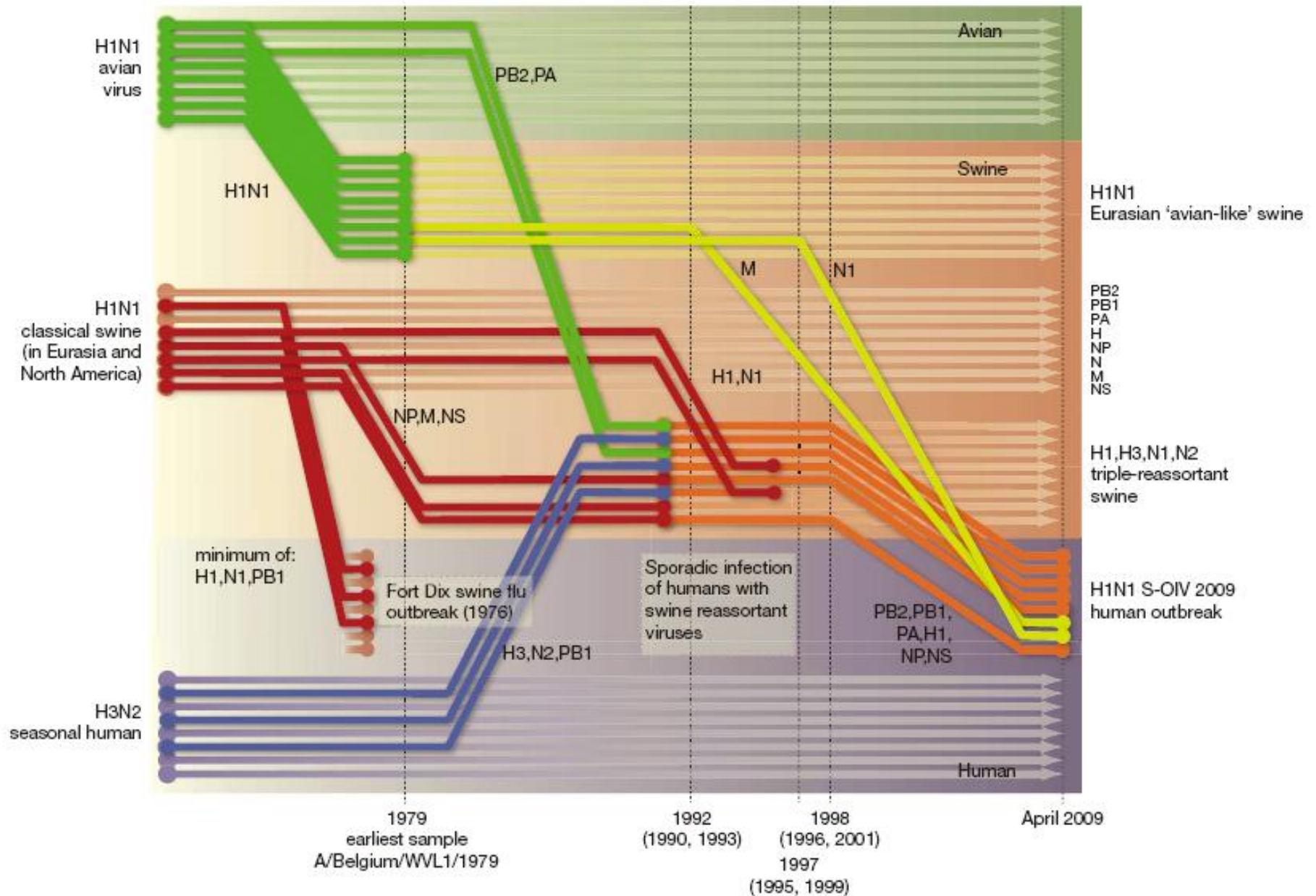
- 1970'lerin sonunda kuş kökenli domuz virusları → Avrasya kuş-benzeri domuz virusları



Domuzlarda

- Klasik domuz cH1N1 (1930'lar)-halen tüm dünyada dolaşımda
- 1998'de insan H3N2+klasik domuz kökenli ikili reasorte H3N2 (HA, NA ve PBP1 insan virusu kaynaklı)
- Daha sonra üçlü reasorte H3N2 (HA, NA ve PBP1 *insan* virusu; M, NS ve M klasik domuz; PA ve PB2 iki kuş virusu kaynaklı)
- Daha sonra H3N2 ve cH1N1 arası reasortmanlarla H3N2, rH1N1, H1N2 ve H3N1domuzlarda endemik
- Daha sonra insan benzeri domuz H1 virüsleri

- 
- PA ve PB2 kuş
 - NS, NP ve M klasik domuz
 - PB1 insan
- TRIG (üçlü reasorte internal gen kaseti) Farklı HA ve NA'ları kabul ediyor



Novel H1N1

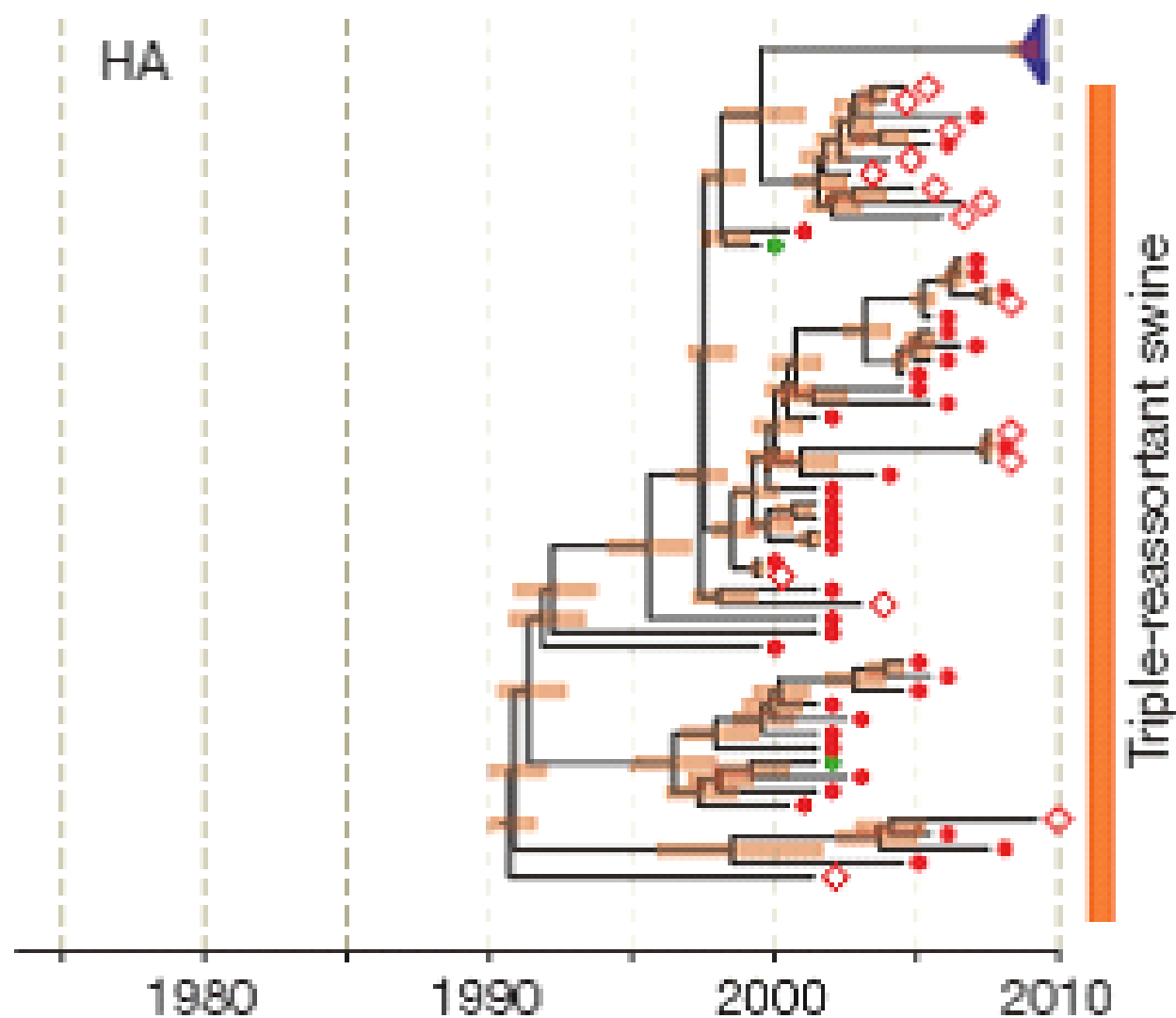
Polymerase basic 2	PB2	
Polymerase basic 1	PB1	
Polymerase acidic	PA	
Hemagglutinin	HA	
Nucleoprotein	NP	
Neuraminidase	NA	
Matrix protein	MA	
Nonstructural protein	NS	

Gene Segment	Host and Year of Introduction
PB2, PA	 ~1998 
PB1	 ~1968  ~1998 
HA, NP, NS	 ~1918 
NA, MA	 ~1979 

Triple reassortant

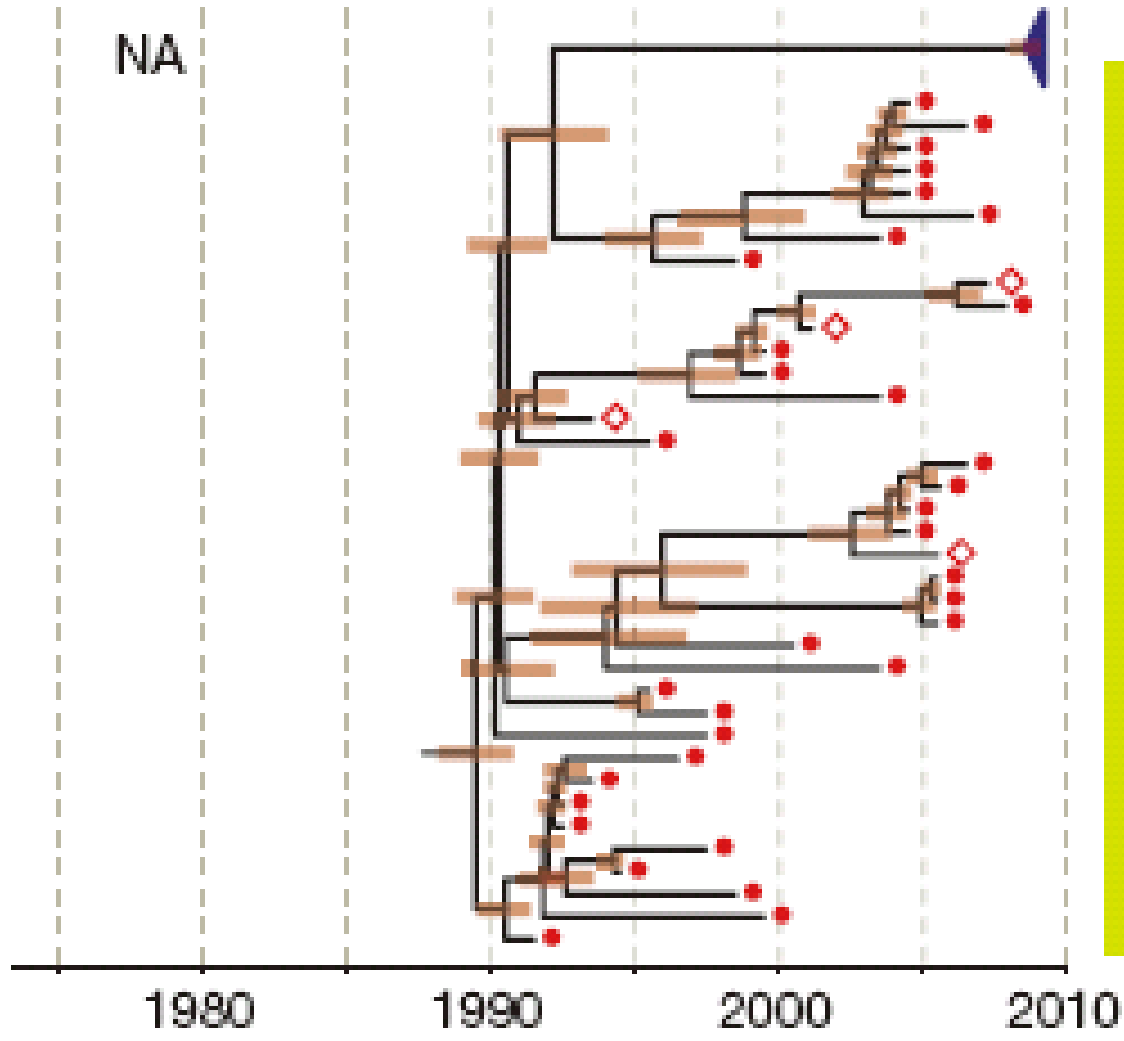
Classical swine

Eurasian swine





NA



Eurasian 'avian-like' swine

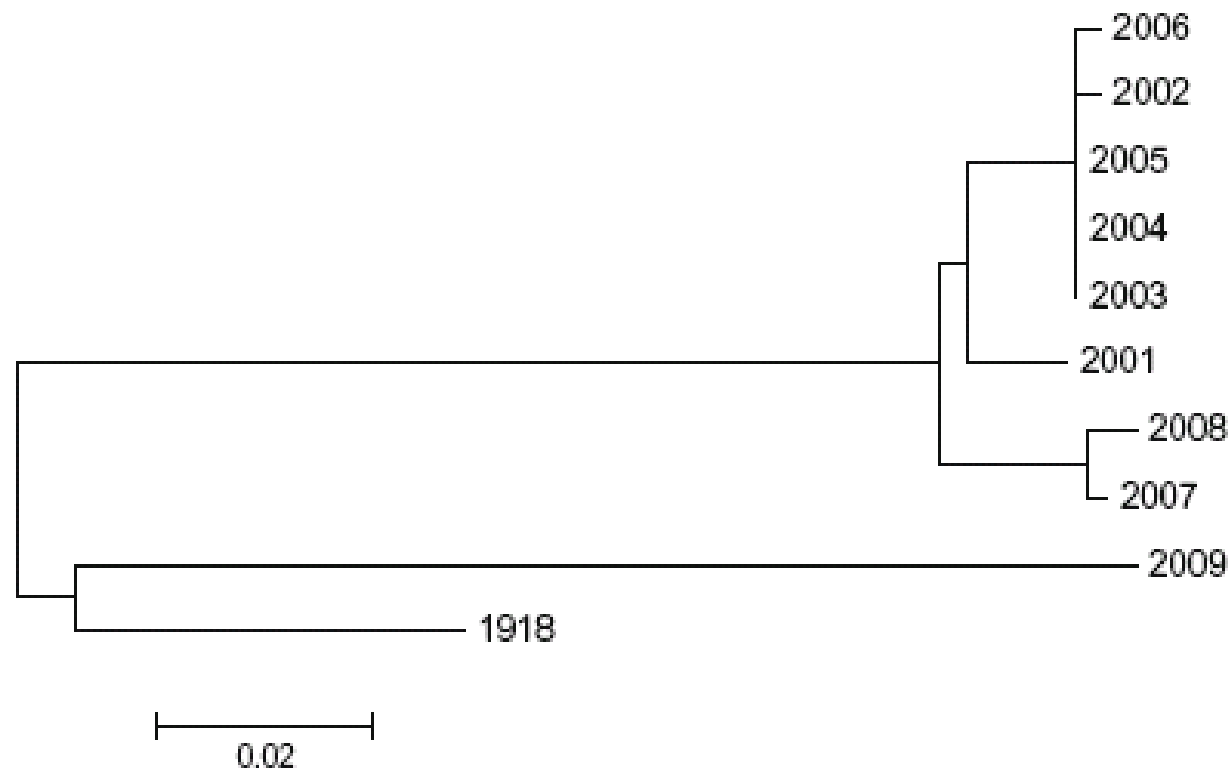
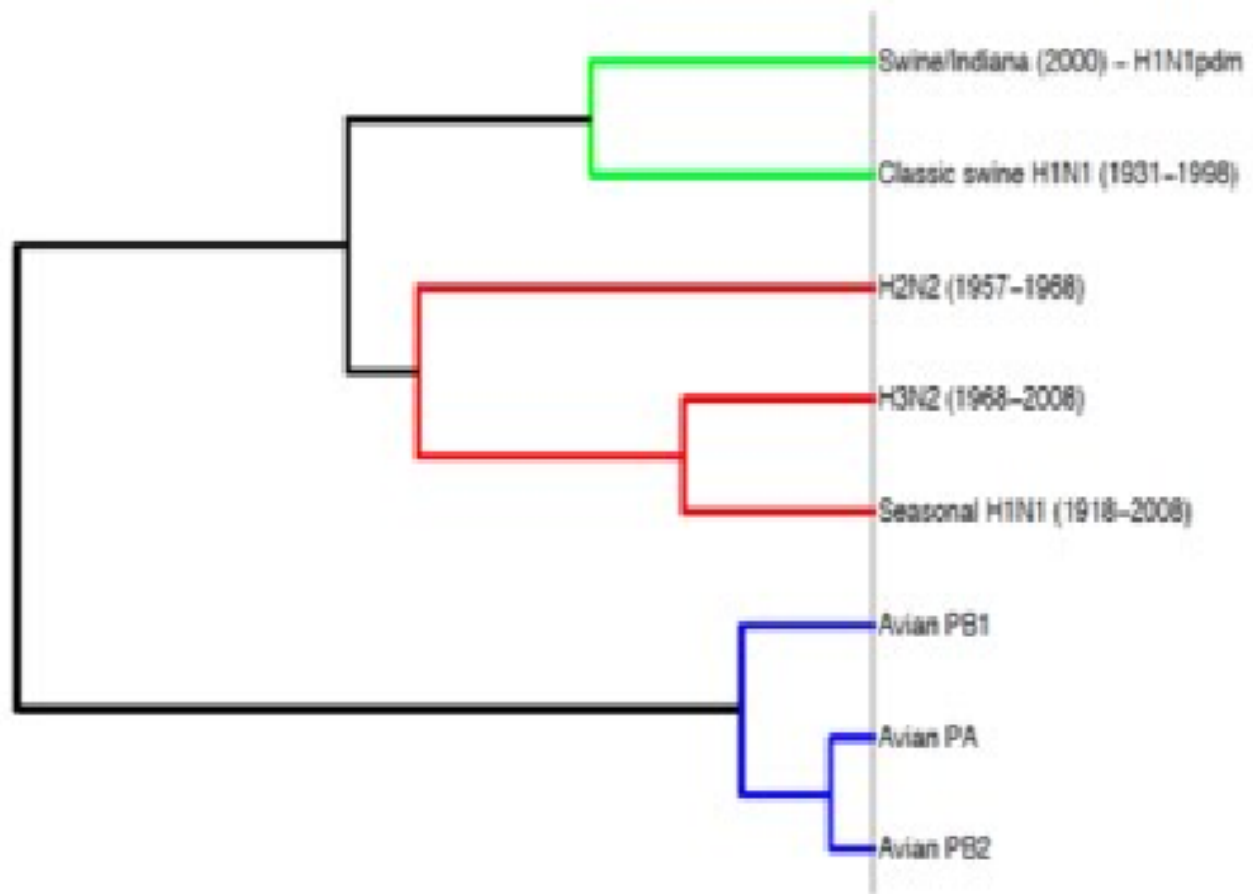
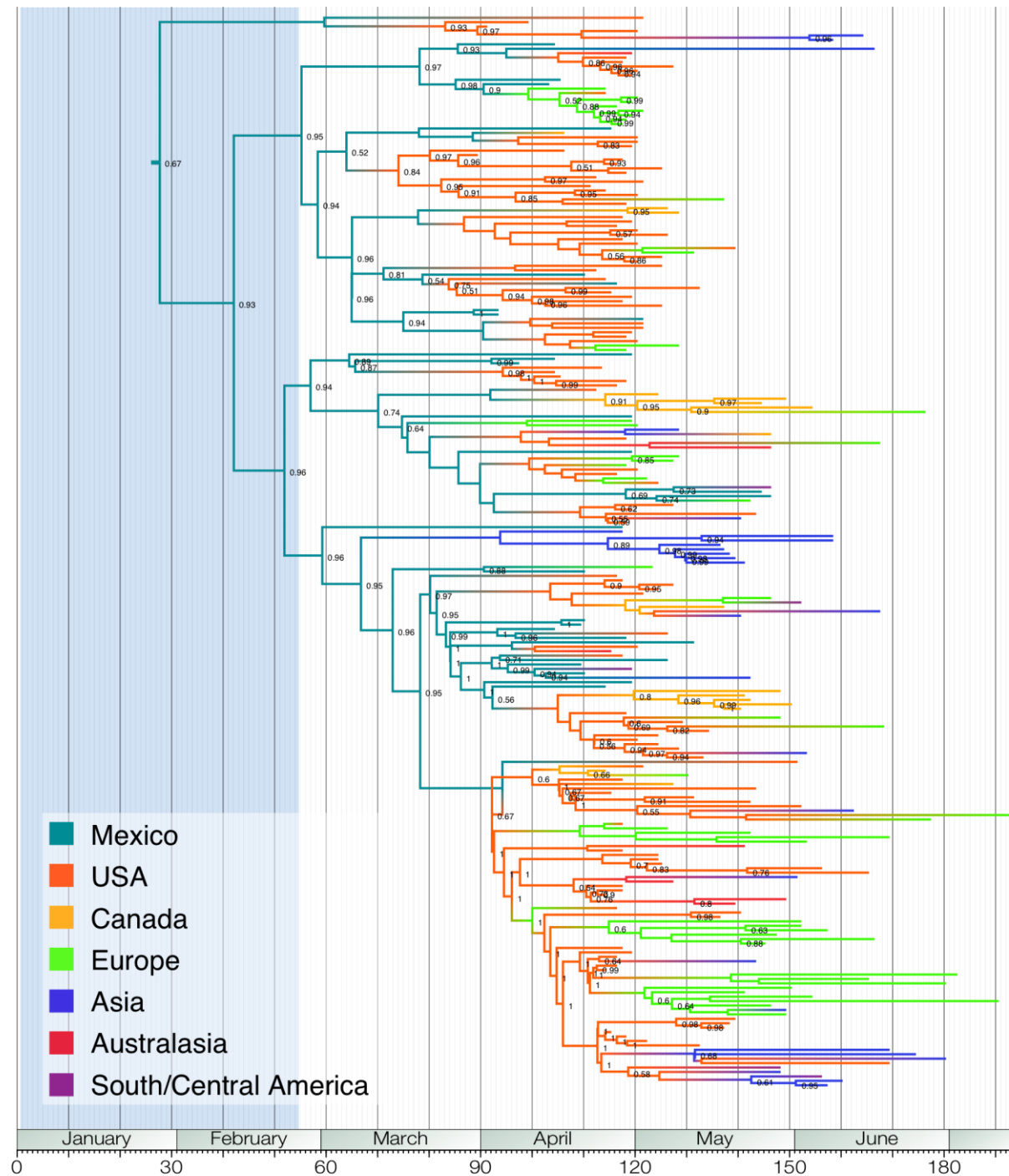


Fig. 1. Phylogenetic tree constructed by the Neighbour Joining Method of NA protein sequences collected during 2001–2009 in the USA.





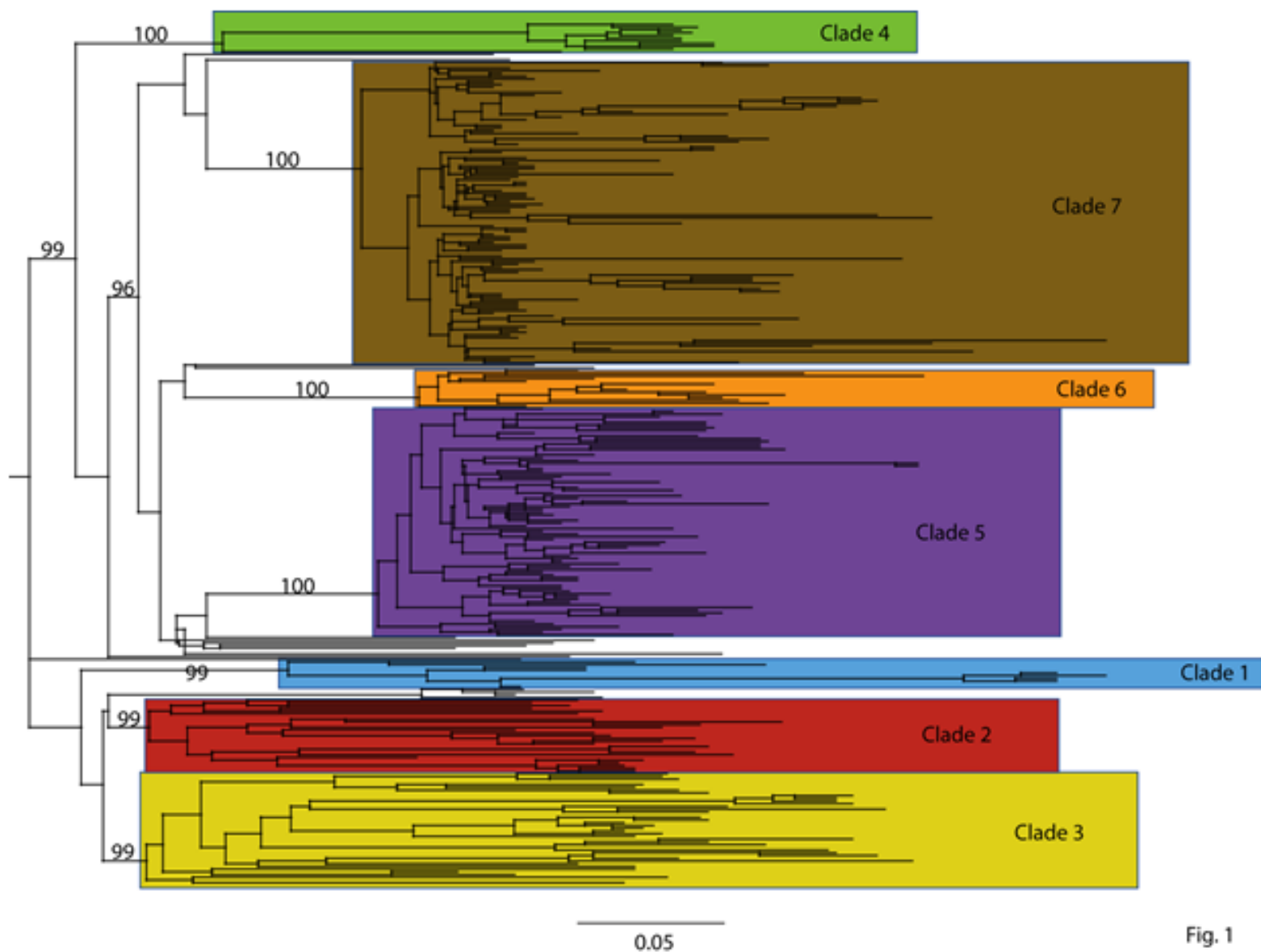
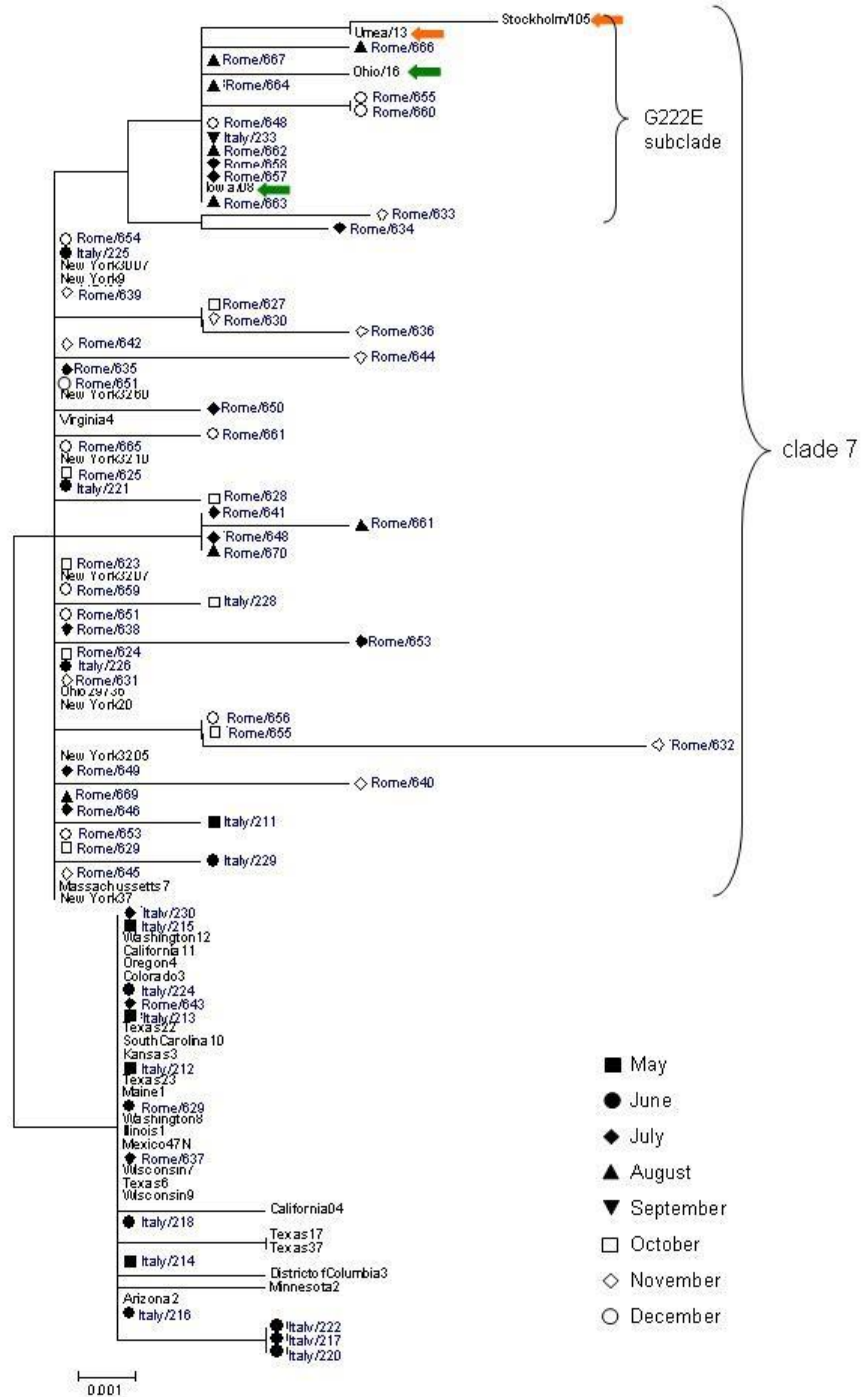


Fig. 1. Maximum Clade Credibility (MCC) tree of the concatenated coding regions of 290 H1N1pdm isolates sampled globally between April 1 – July 9, 2009. Bayesian posterior probability (BPP) values > 90% are included for key nodes. The tree is automatically rooted through the assumption of a strict

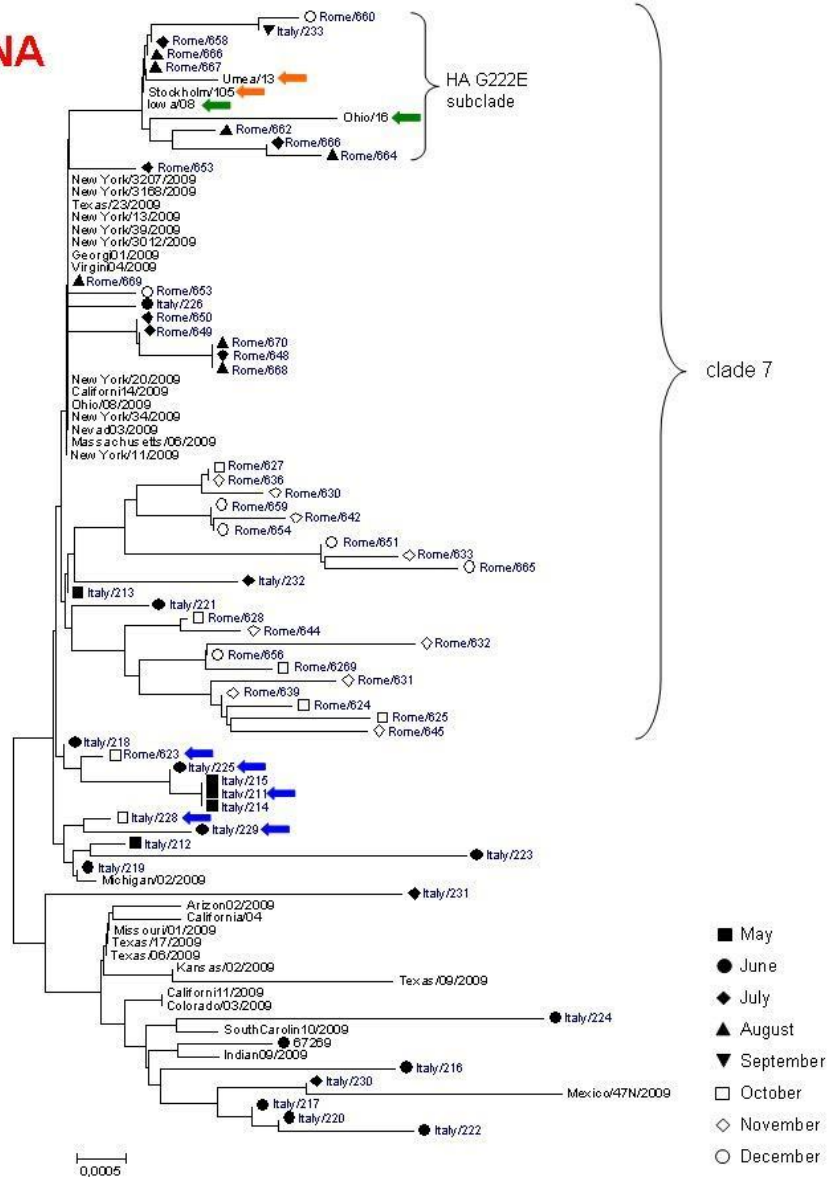


HA



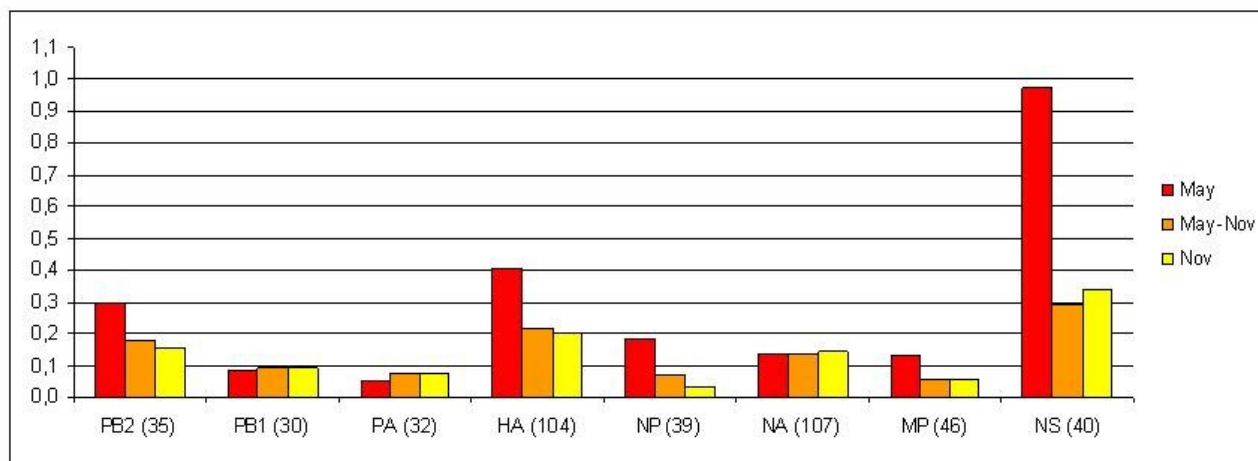


NA

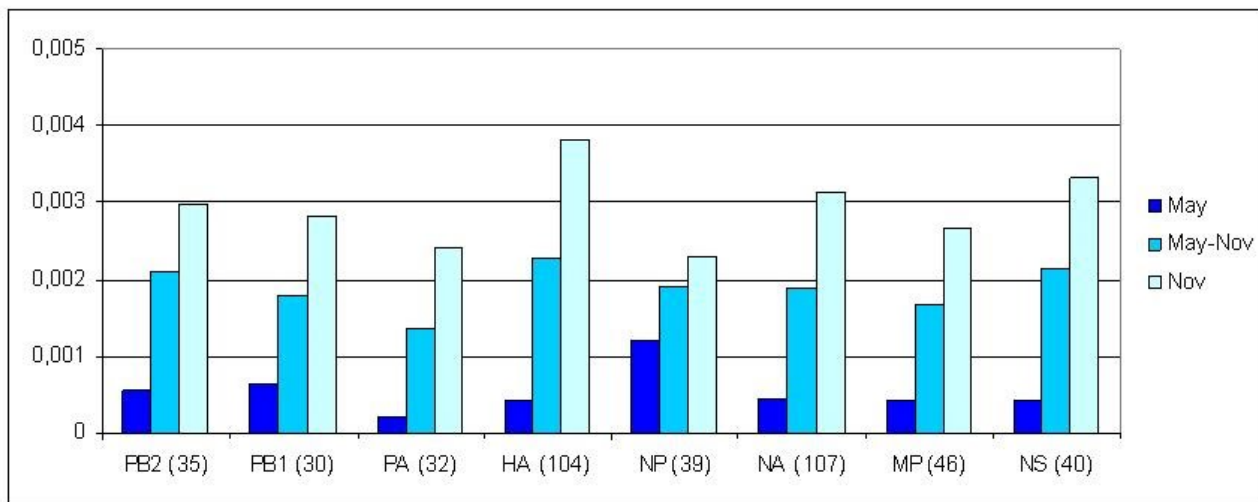


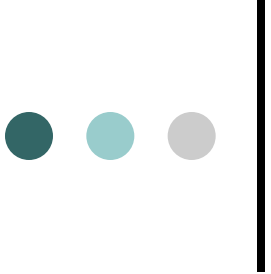
I

A



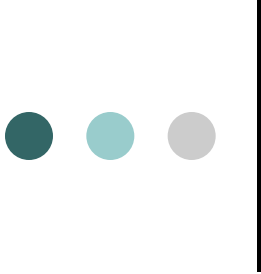
B





H1N1 pdm'in kökenleri?

- Domuzlarda saptanmadan kaldı
- Labortauvar kaynaklı?



HA D190 ve D225 değişiklikleri

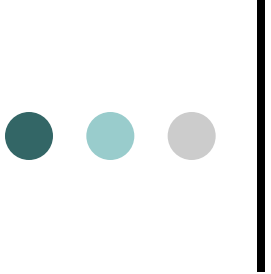
- Bu pozisyonlarda D→G değişiklikleri

Dual reseptör bağlanma kapasitesine yol
açıyor

Bu tarz değişiklikler – Ağır/fatal seyirli olgular
arasında ilişki

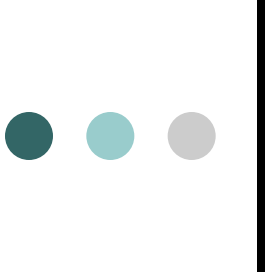
?? pozitif seleksiyon

HA1 ve Ha2 kesilme bölgesinde bazik aa
sayısı:



PB1-F2

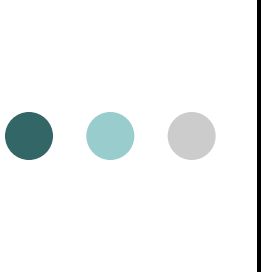
- PB1 den alternati (+1) ORF üzerinden sentezlenen 90 aa protein
- Apoptoz indükleyicisi
- Bazı viruslarda hiç yoktur ya da güdüktür
- H1N1 pdm'de güdük

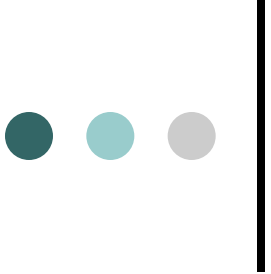


- PB1

L13P ve S678N → farelerde artmış
replikasyon

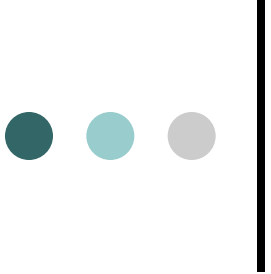
H1N1'de yok

- 
- PB2 627K (lizin) → glutamik asit varlığı
 - PB2 D701N (aspartam)
 - 33'C'de üreme → Virulans Artışı



NA değişiklikleri

- His274Tiro → Oseltamivir direnci



Güncel sorular

- H1N1 pdm nasıl bir evrim gösterecek
- HPAI H5N1'in izlenmesi
- Yeni ortaya çıkacak virusların hızla tanımlanması; tiplendirilmesi; saptama ve izlemeye yönelik standartların geliştirilmesi ve tüm dünyada uygulanması
- Sürveyansların genişletilmesi
- Direnç gelişim trendinin izlenmesi