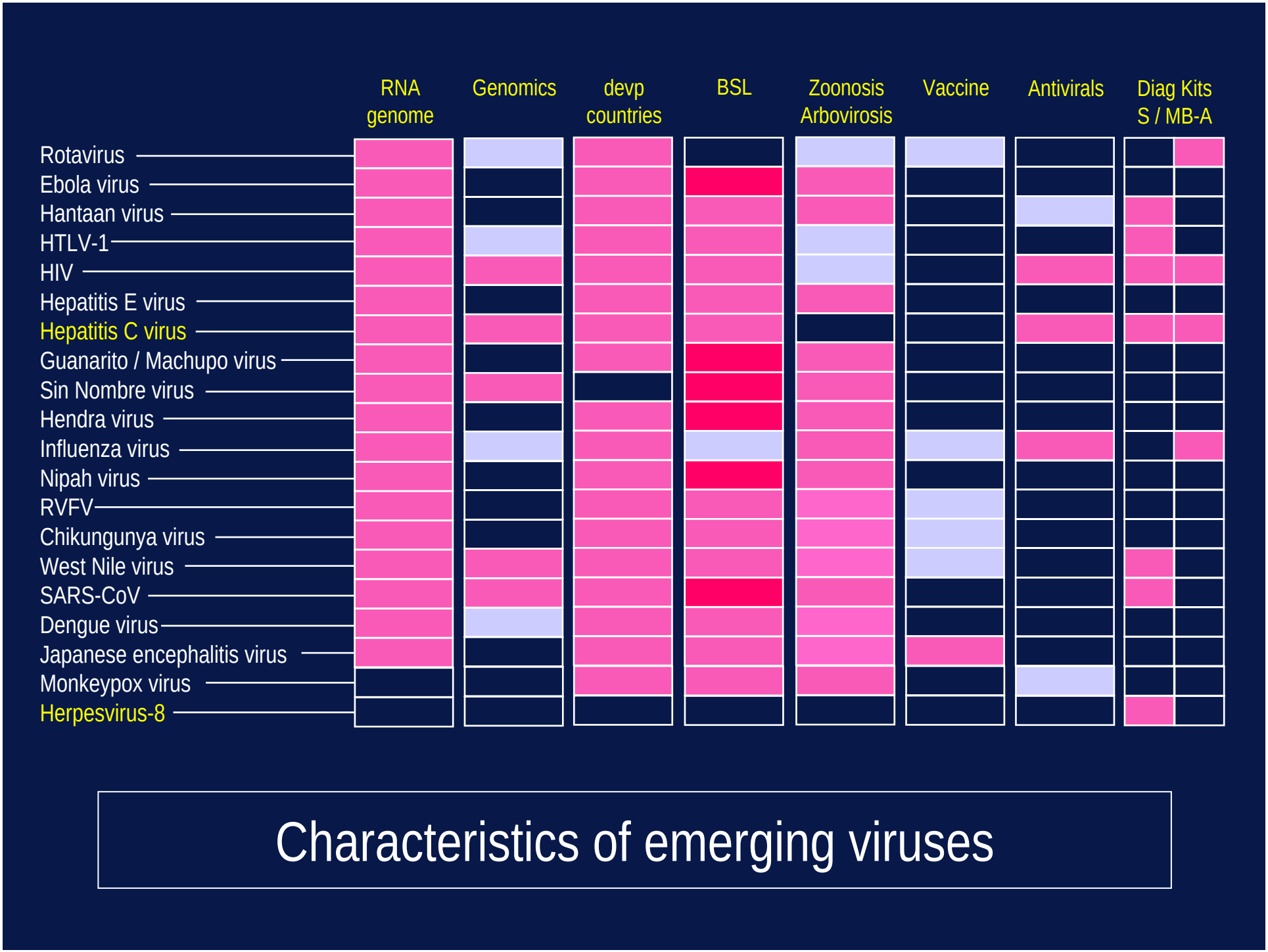
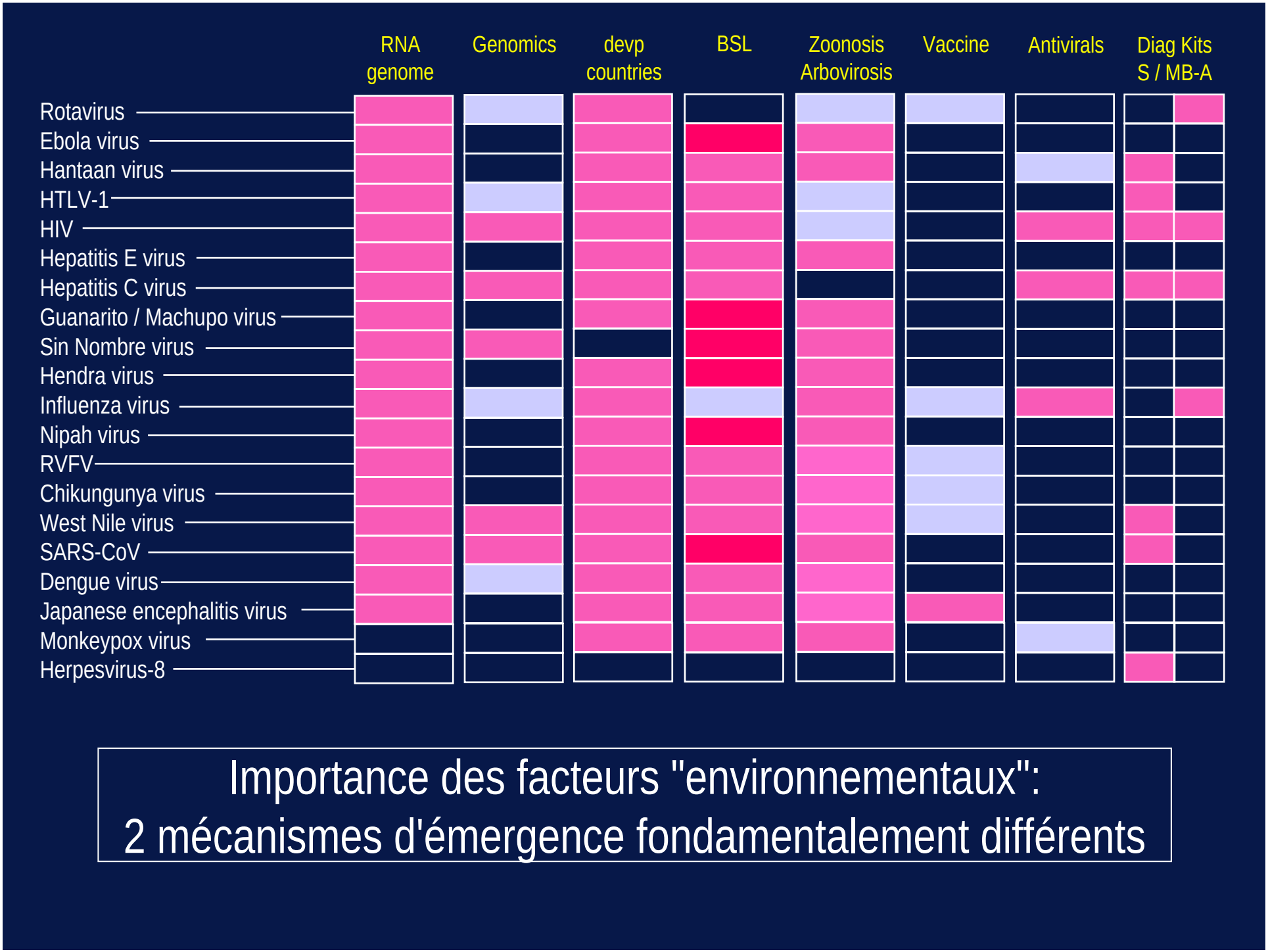
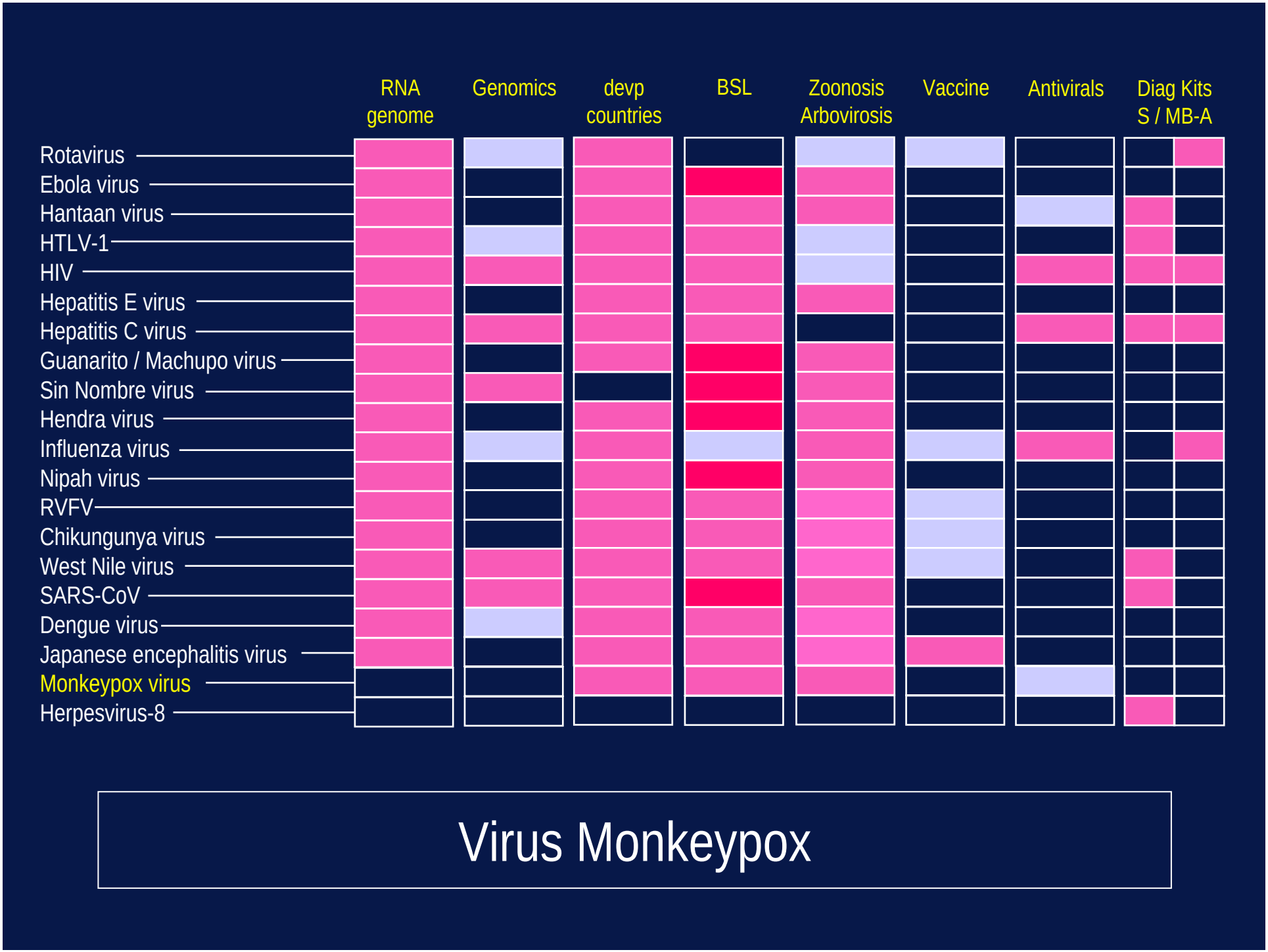
Évolution du virus de la dengue : le cas remarquable du virus de la dengue (sérotype 1) en Polynésie française

Xavier de Lamballerie
University of Marseilles / Institut de Recherche pour le Développement, France


RNA genome
Genomics
devp countries
BSL
Zoonosis Arbovirosis
Vaccine
Antivirals
Diag Kits S / MB-A
Rotavirus
Ebola virus
Hantaan virus
HTLV-1
HIV
Hepatitis E virus
Hepatitis C virus
Guanarito / Machupo virus
Sin Nombre virus
Hendra virus
Influenza virus
Nipah virus
RVFV
Chikungunya virus
West Nile virus
SARS-CoV
Dengue virus
Japanese encephalitis virus
Monkeypox virus
Herpesvirus-8
Characteristics of emerging viruses



Importance des facteurs "environnementaux":
2 mécanismes d'émergence fondamentalement différents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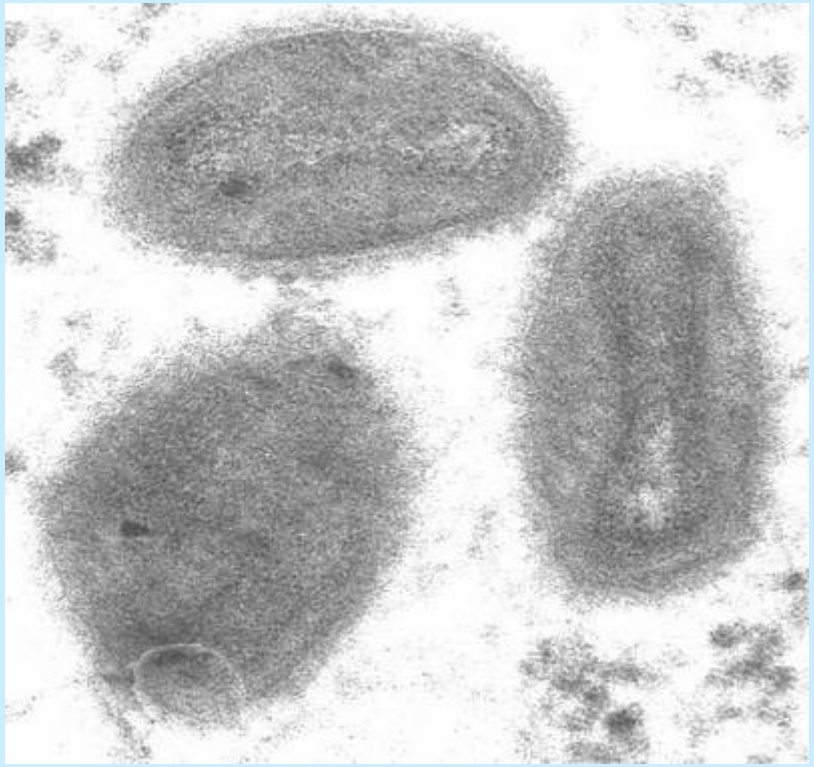
Virus Monkeypox

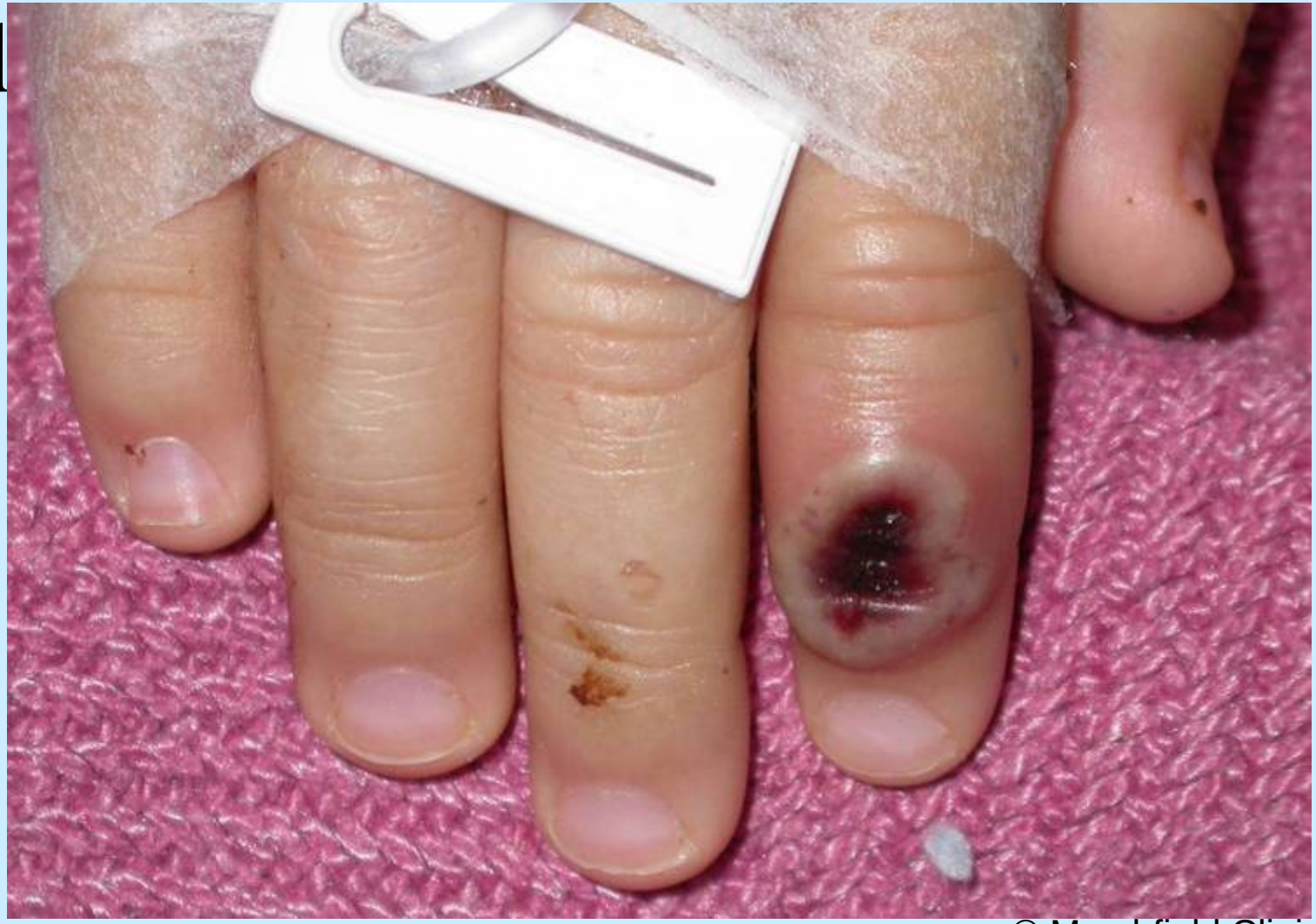

WE'VE GOT A NEW ONE!
NORTH AMERICA
MONKEY POX
WEST NILE VIRUS
MAD COW
SARS
caglecartoons.com

Historique

- 5/11/2003 – 2 chiens de prairie achetés pour la fete des meres
- 5/13 – 1 chien de prairie mords un enfant de 3 ans a la main
- 5/22 – enfant hospitalisé
- 5/24 – tularémie suspectée, puis éliminée
- 5/26 – la mère de l'enfant tombe malade : fièvre et rash
- 5/30 – morphologie d'Orthopoxvirus en ME sur la biospie de la mère
- 6/4 - l'état du Milwaukee rapporte un cas de rash fébrile chez un sujet qui vend des animaux exotiques de compagnie, parmi lesquels des chiens de prairie
- 6/4 - Orthopoxvirus identifié en culture



Primary inoculation site right index finger, 5/27/03. 14 days after prairie dog bites,

11  day

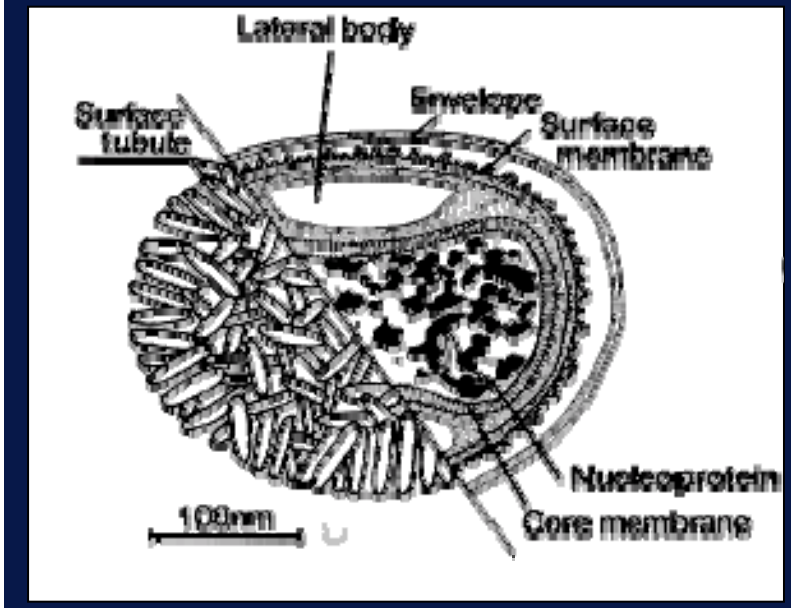
- Real problem (imported Gambian rat)

Innocent bystanders

Virus Monkeypox

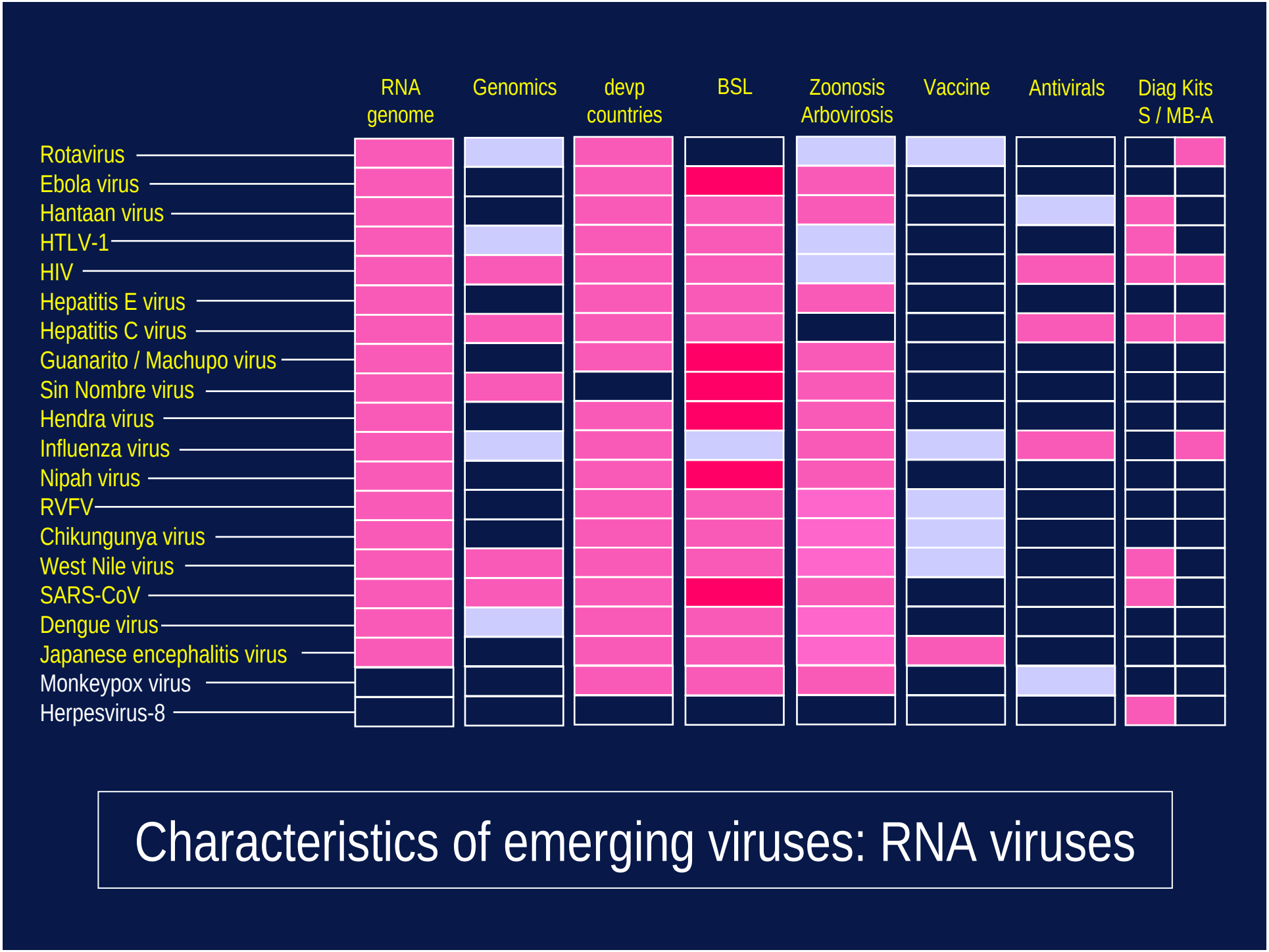
- Virus zoonotique Africain (écureuil, rongeurs divers)
- Capacité d'infection d'un spectre d'hôtes très large incluant des primates (singes, homme)
- Capacité d'évolution ("adaptation") très faible

Causes de l'émergence ?



- Génome viral >150 kb
- Nombre de gènes élevé
- Réplication cytoplasmique "autonome"

Spectre d'hôtes intrinsèquement important, infection de nouveaux hôtes dépendant des opportunités épidémiologiques de dissémination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Characteristics of emerging viruses: RNA viruses

Absent Proofreading Activity of RNA Polymerases & Viral Intra-Host Diversity

Virus de la dengue

- Virus émergent majeur (50-100 millions de cas par an)
- Arbovirus (transmission par les moustiques aedes)
- 4 sérotypes

- Circulation du sérotype 1 en Polynésie Française entre 2001 et 2006:

  2 périodes épidémiques (2001, 2006) séparées par une phase non-épidémique de 4 ans (circulation à bas bruit)

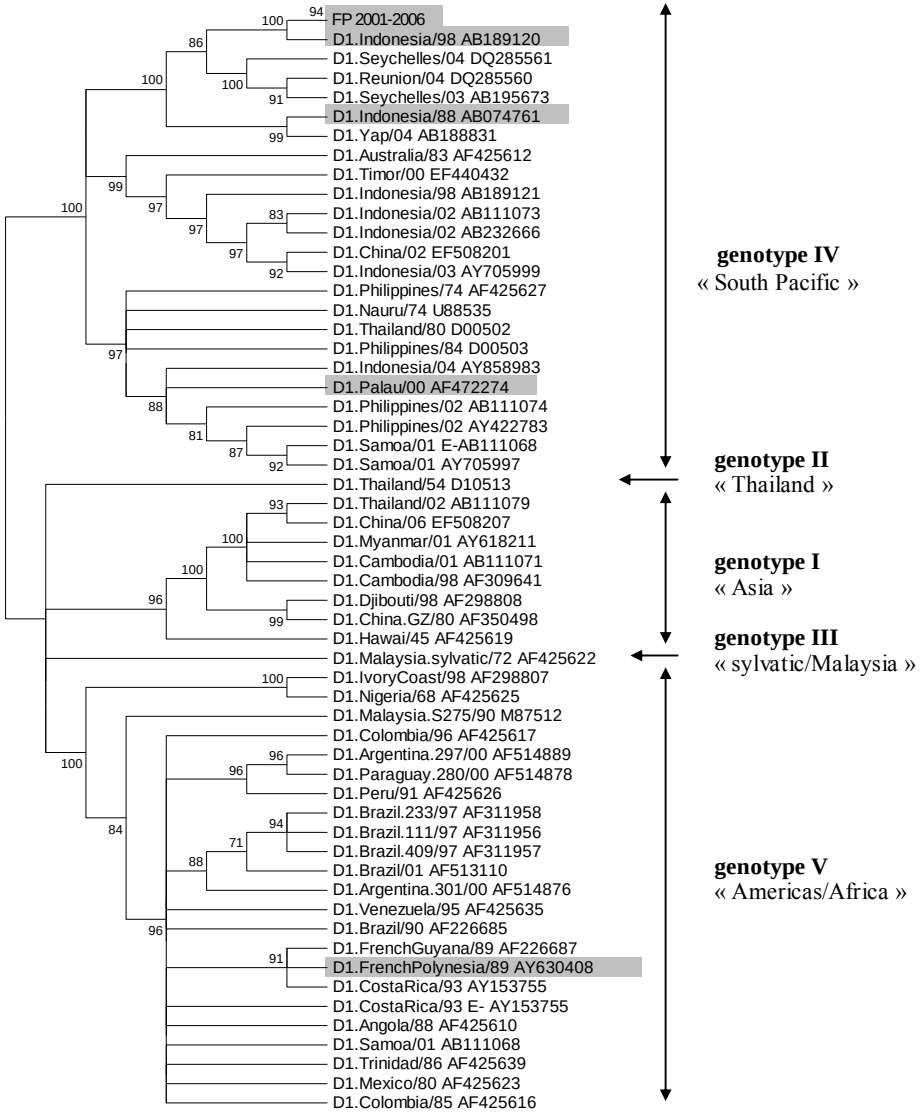


Figure 1a : Phylogenetic tree based on 240 DENV-1 nucleotide sequences of 1759 bp including the E gene (Neighbor-Joining method, Kimura 2 algorithm). The 181 sequences generated in FP are condensed in the branch called « FP 2001-2006 ». Taxon names of GenBank sequences correspond to D1.country/last two digits of year of isolation and GenBank accession number. Numbers on branches represent bootstrap support for each branch.

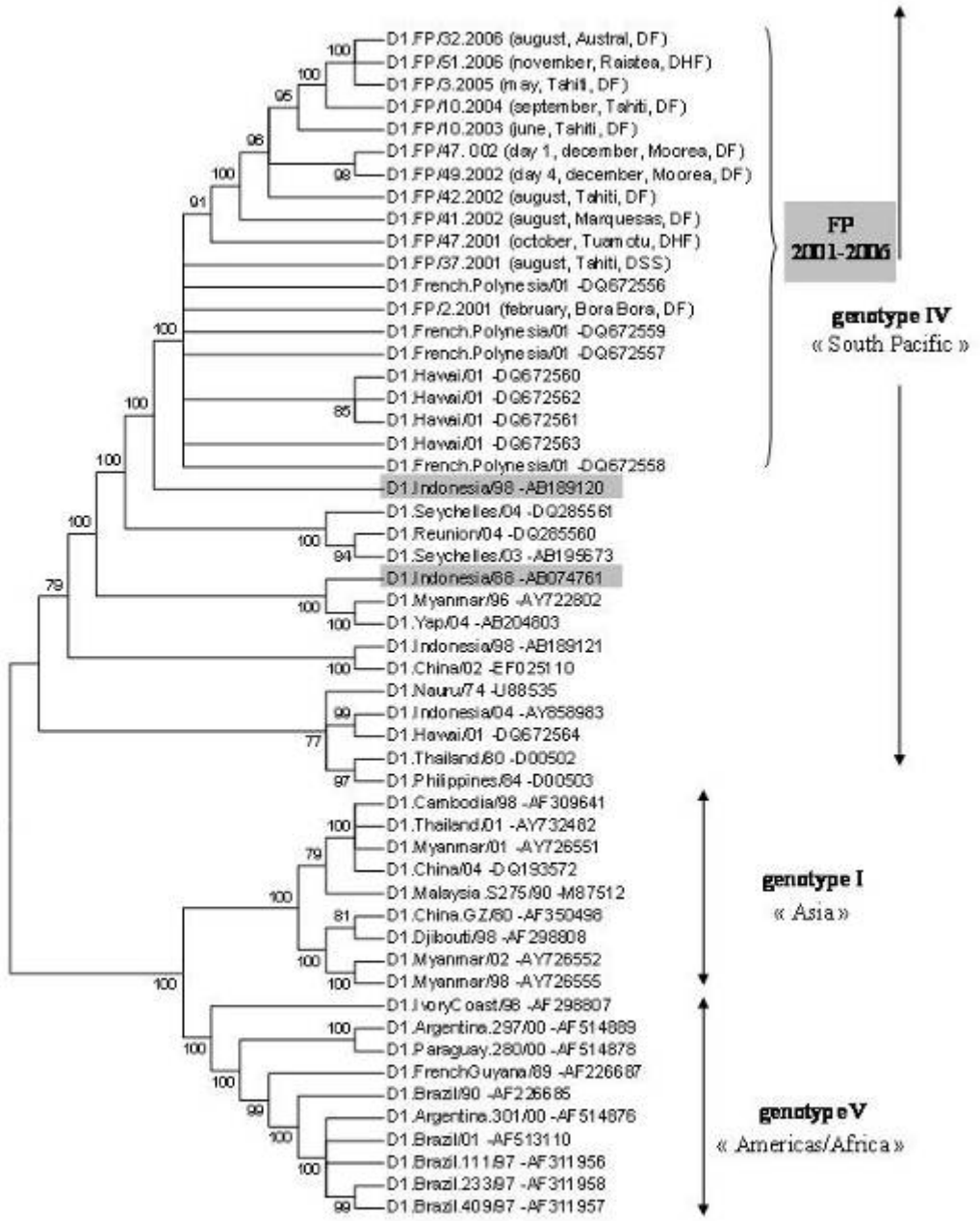


Figure 2: Phylogenetic tree based on 53 sequences of complete coding region of DENV-1 (Neighbor-Joining method, Kimura 2 algorithm). Taxon names of FP sequences correspond to D1 FP/sample number.year (month, geographical origin, clinical presentation). Taxon names of GenBank sequences correspond to D1.country/last two digits of year of isolation and GenBank accession number. Numbers on branches represent bootstrap support for each branch.

Table 6: Analysis of genetic variability in DENV-1 at different levels of evolutionary divergence based on a 758 bp fragment in the E gene

	No. of nt mutations/ No. of nt sites	No. of aa mutations/ No. of aa sites	nt π	aa π	pN	dN	dS	dN/dS
INTER-HOST GROUPS								
Serotype 1	245/758	25/252						
59 sequences	32,3%	9,9%	6,0%	2,2%	10%	0,01	0,223	0,045
Genotype IV	135/758	25/252						
26 sequences	17,8%	9,9%	3,8%	1,7%	19%	0,008	0,138	0,058
FP 2001-2006	47/758	17/252						
181 sequences	6,2%	6,7%	0,3%	0,4%	36%	0,002	0,006	0,333
INTRA-HOST GROUP								
FP 2001-2006	53/758	34/252						
662 clones (17 strains) sequences*	7,0%	13,5%	0,5%	0,9%	63%	0,004	0,007	0,620

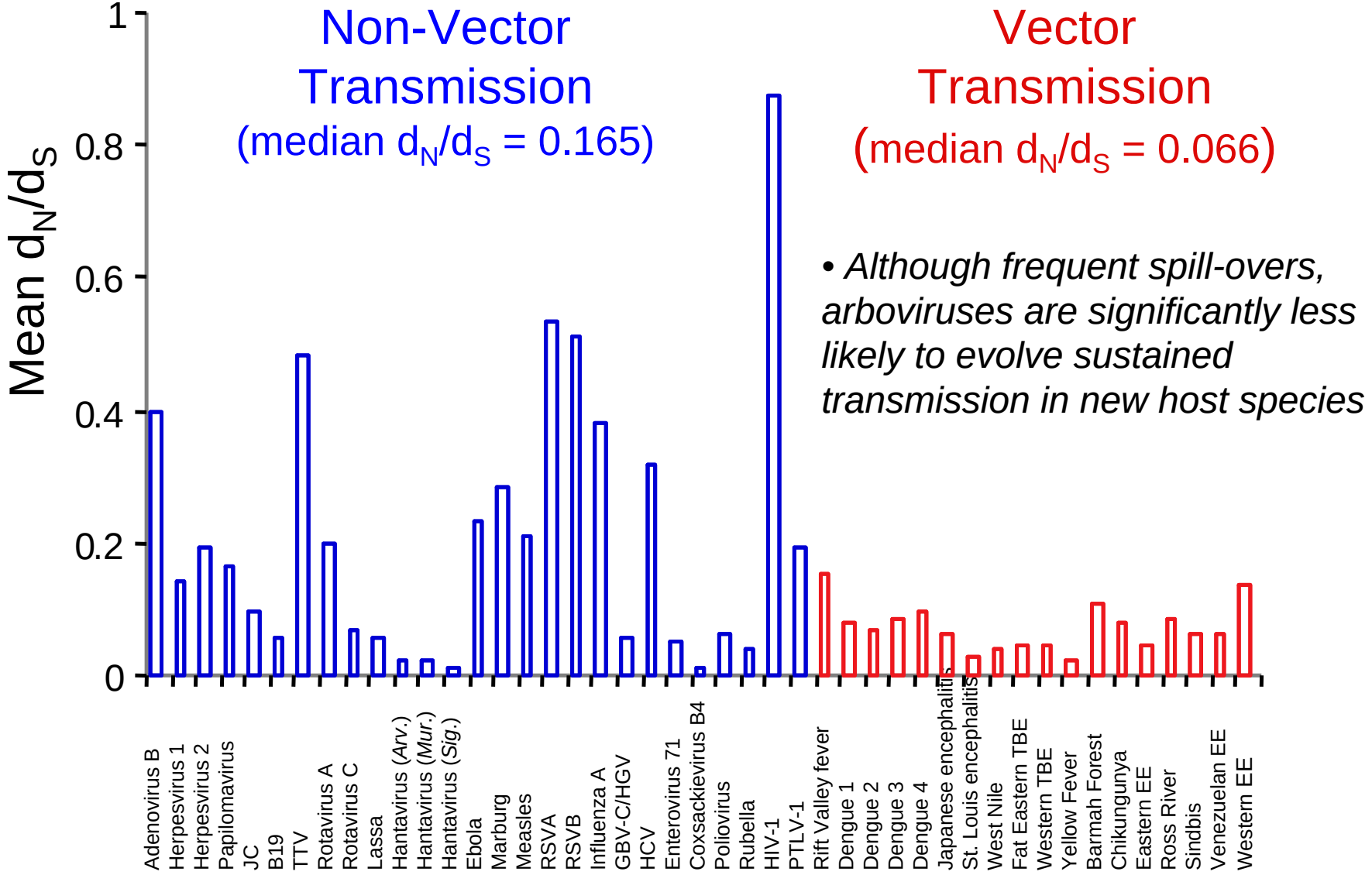
*average of the results obtained for each group of clones

The p-distance method was used to calculate the percentages of sequences divergence (π).

The proportion of mutations that were non synonymous (pN) were computed in each nucleotide alignement.

The mean ratio of non-synonymous (dN) and synonymous (dS) substitutions per site were estimated using the pairwise method of Nei and Gojobori p-distance method.

Strong Selective Constraints in Vector-Borne RNA viruses (Arboviruses)



- *Although frequent spill-overs, arboviruses are significantly less likely to evolve sustained transmission in new host species*

Virus replication
in the vector

Virus replication
in the
vertebrate host

Strong evolutionary constraints :
different temperatures, cell receptors, etc..

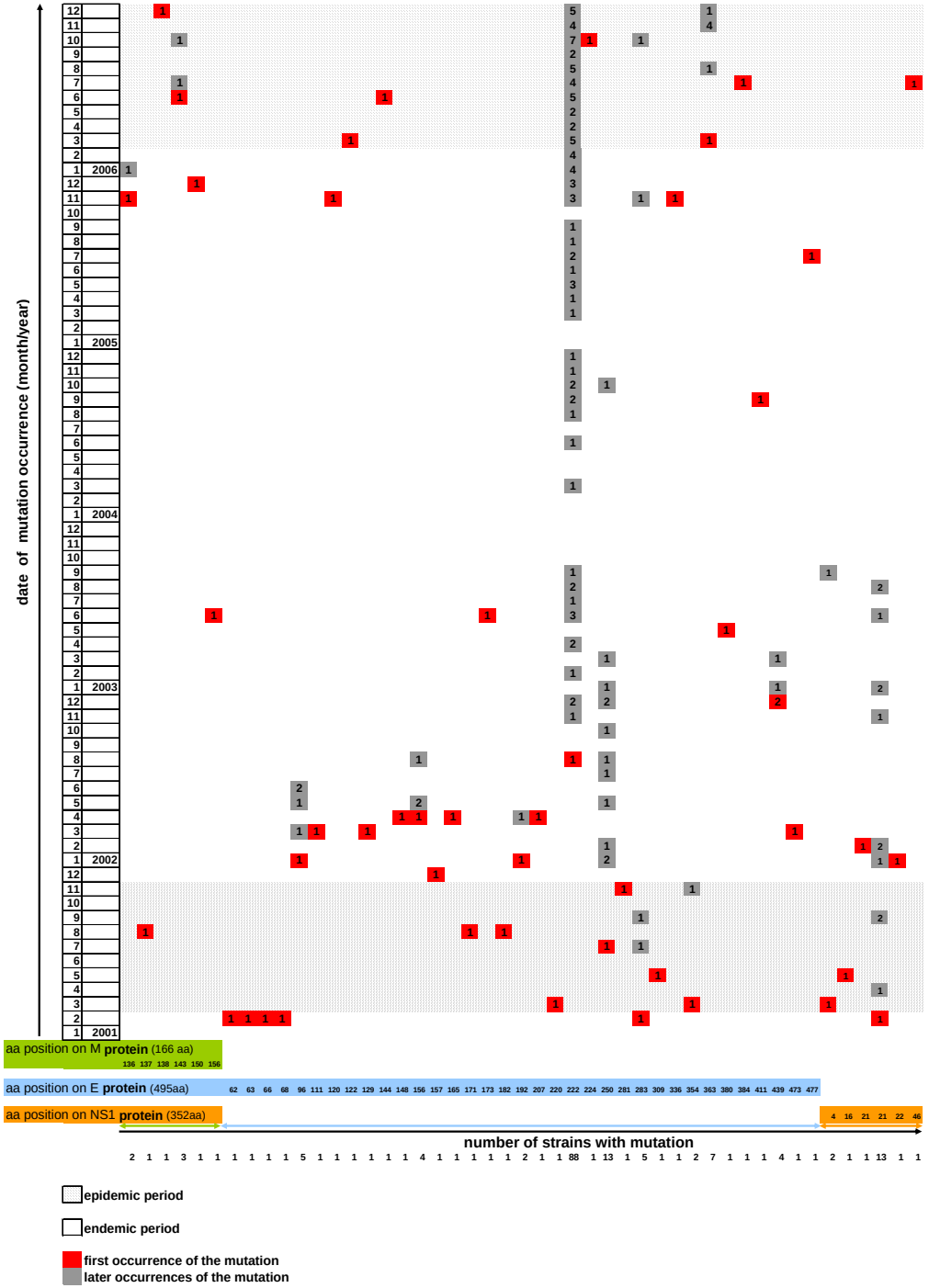

date of mutation occurrence (month/year)
2006
2005
2004
2003
2002
2001
aa position on M protein (166 aa)
aa position on E protein (495aa)
aa position on NS1 protein (352aa)
number of strains with mutation
epidemic period
endemic period
first occurrence of the mutation
later occurrences of the mutation

Table 4: Genetic diversity of DENV-1 at different levels and at different times of viral evolutionary divergence based on a 1759 bp fragment including the E gene.

Dataset [a]	No. of variable nt sites/ No. of nt analysed %	No. of variable aa sites/ No. of aa analysed %	pN	dN/dS
Serotype 1	537/1759	92/586		
59 sequences	30,5%	15,7%	**17%**	**0,042**
Genotype IV	338/1759	47/586		
26 sequences	19,2%	8,0%	**14%**	**0,045**
FP 2001-2006	128/1759	47/586		
181 sequences	7,3%	8,0%	**37%**	**0,091**
FP 2001 epidemic period	34/1759	13/586		
42 sequences [b]	1,9%	2,2%	**38%**	**0,500**
FP 2002-2005 endemic period	78/1759 [c]	27/586 [c]		
93 sequences	4,4%	4,6%	**35%**	**0,100**
FP 2006 epidemic period	28/1759	10/586		
41 sequences	1,6%	1,7%	**36%**	**0,250**

The proportion of non synonymous mutations (pN) corresponded to the number of non synonymous mutations divided by the total number of nucleotide mutations.
The average pairwise distance was calculated among the nucleotide sequences in each dataset (? nt).
The mean ratio of synonymous (dS) and non synonymous mutations per site (dN) were estimated using the pairwise method of Nei and Gojobori.

[a] Sequences in datasets "Serotype 1", "Genotype IV" and "FP 2001-2006" were also used for phylogenetic reconstructions (Figures 1a, 1b, 2).

[b] Five samples collected in February 2001 before the beginning of the 2001 outbreak were excluded from the comparative analysis of DENV-1 evolution during the endemic and epidemic periods (a total of 176 samples collected between March 2001 and December 2006 was analyzed).

[c] Results were significantly higher during the 2002-2005 endemic period than during the 2001 or the 2006 epidemic period ($p<0,01$ with Fisher's exact test).

Conclusion

- Forte pression de sélection négative confirmée
- Présence de variants viraux chez 1 individu donné dès le premier jour de la virémie

- Pattern de variabilité observé probablement le reflet de la diversité générée par la multiplication virale chez le moustique
- Pressions de sélection majeures observées en phase endémique

Les pressions de sélection majeures semblent liées à la multiplication et la survie du virus chez le moustique

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