

Les virus émergents et techniques de détection

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Endémie : Persistance d'une maladie infectieuse au sein d'une population ou d'une région.

↳ Exemple: Hépatite A en Thaïlande

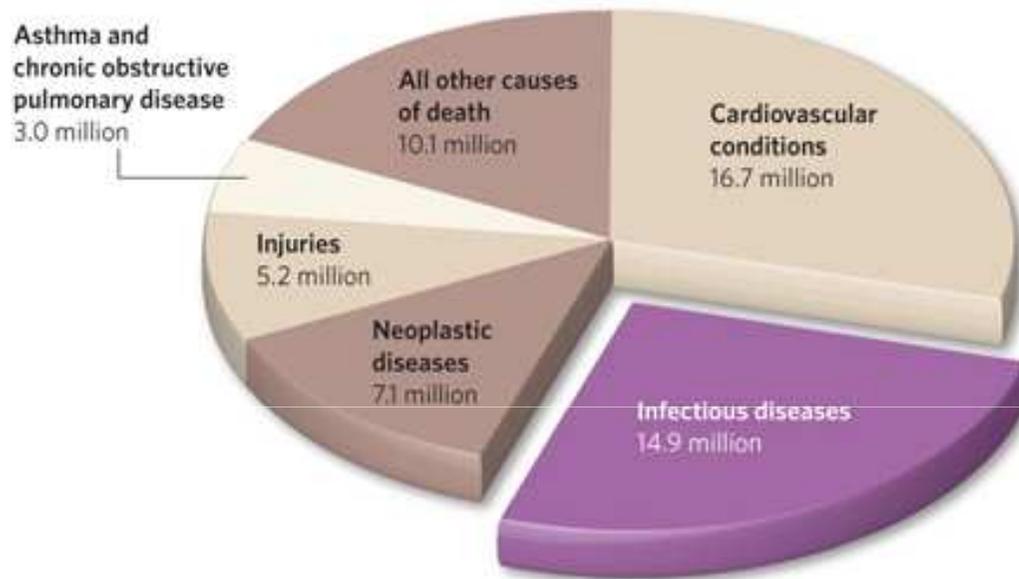
Epidémie : Développement et propagation rapide d'une maladie contagieuse, le plus souvent d'origine infectieuse, dans une population.

↳ Exemple: Epidémie Ebola en Ouganda, rougeole

Pandémie : Epidémie étendue à toute la population d'un continent, voire au monde entier.

↳ Exemple: HIV, Grippe

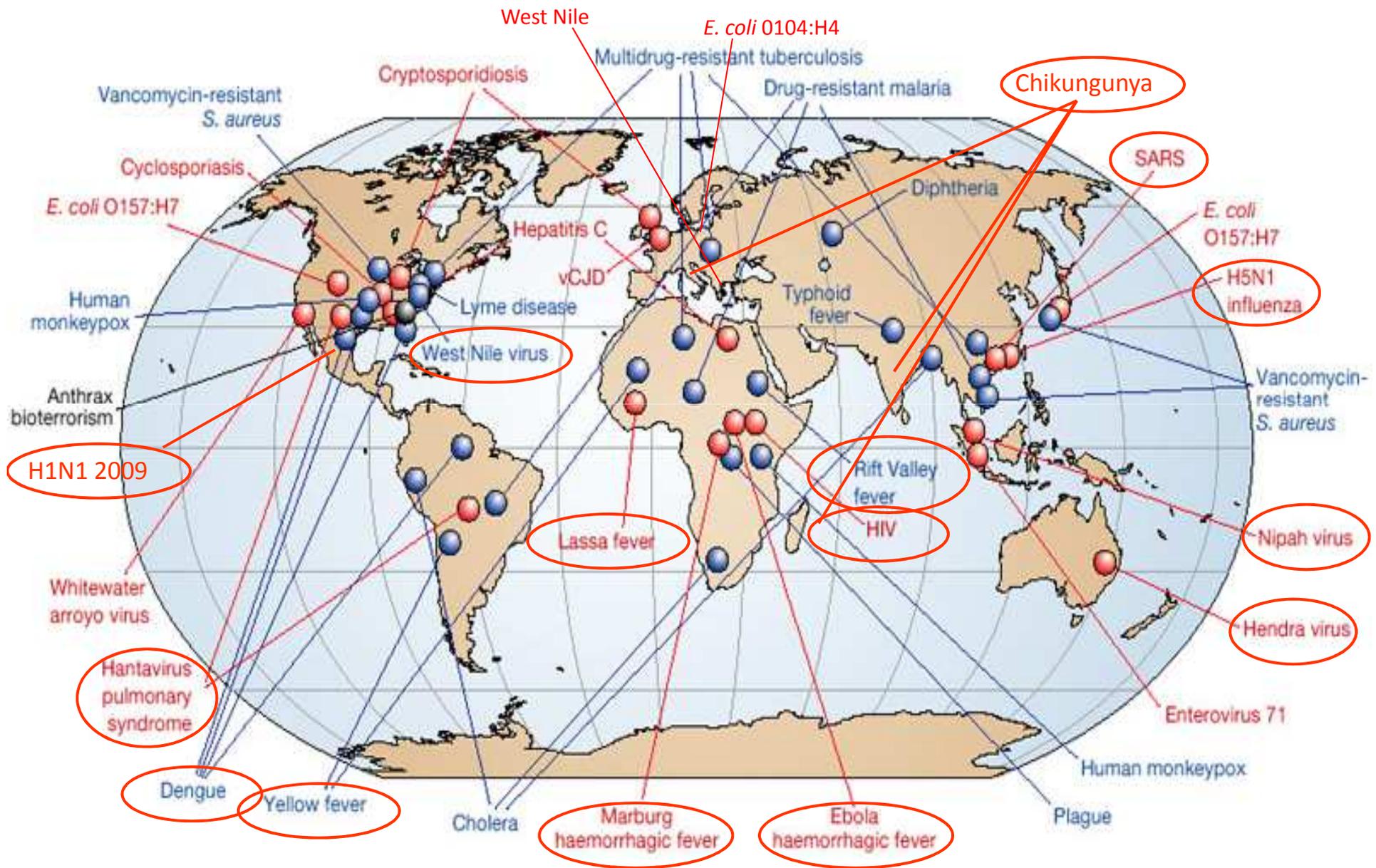
Principales causes de décès dans le monde



Infectious diseases	Annual deaths (millions)
Respiratory infections	3.96
HIV/AIDS	2.77
Diarrhoeal diseases	1.80
Tuberculosis	1.56
Vaccine-preventable childhood diseases	1.12
Malaria	1.27
STDs (other than HIV)	0.18
Meningitis	0.17
Hepatitis B and C	0.16
Tropical parasitic diseases	0.13
Dengue	0.02
Other infectious diseases	1.76

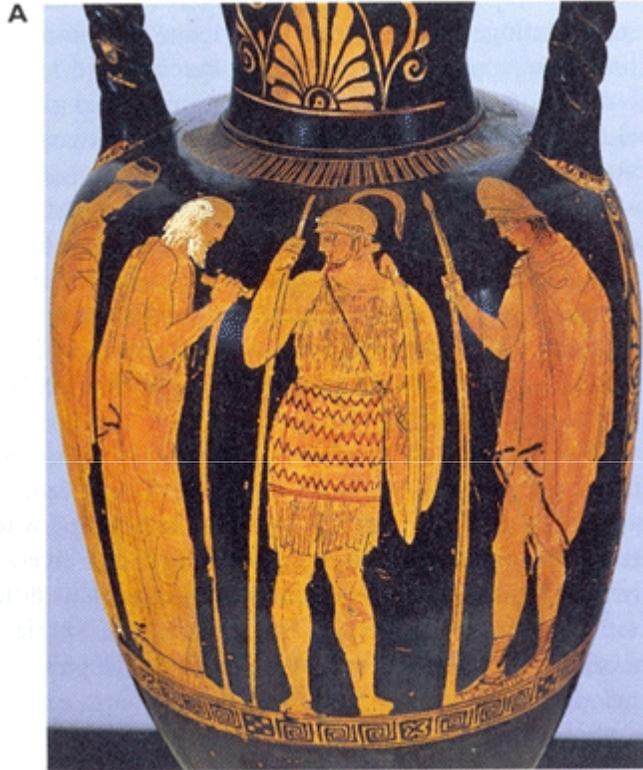
Nature, 430: 242 (2004)

Environ 15 millions des 57 millions de décès annuels (>25 %) sont dus directement aux maladies infectieuses





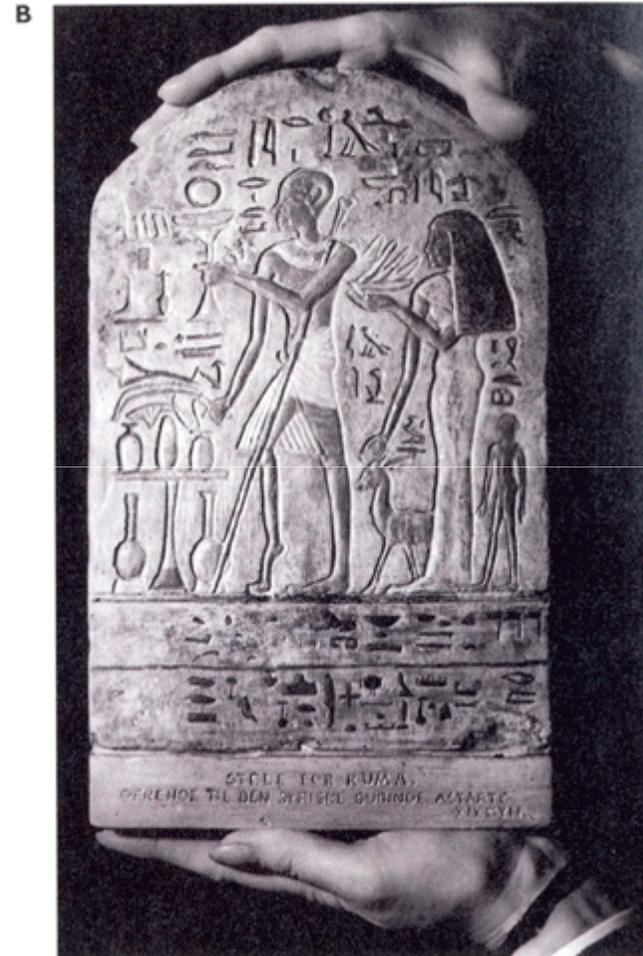
Virus présents depuis toujours



Here this firebrand, rabid Hector, leads the charge.

HOMER, *The Iliad*,
translated by Robert Fagels
(Viking Penguin)

850 av JC

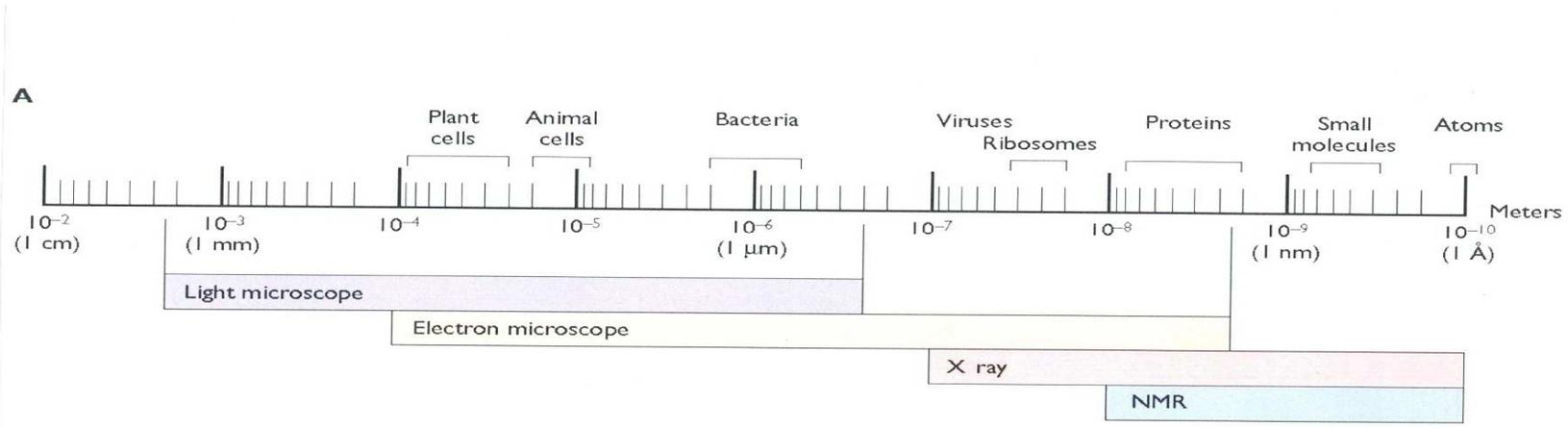


1500 av JC

D'après Principles of Virology, Flint, Vol1, 3rd Ed

Virus et hommes

- Variole: a détruit des civilisations entières et tué > 1 milliard d'êtres humains.
- La pandémie d'influenza de 1918: > 40 mio victimes.
- La pandémie de VIH: > 40 mio victimes.
- Notre ADN est composé de 5-8% de séquences virales.
- Réservoir animal incontrôlable.



❖ Virus : génome de petite taille: de 1'700 à 1'200'000 nucléotides, peu de protéines

- Influenza: 8 gènes (10 protéines)
- Virus herpès: plus de 80 gènes

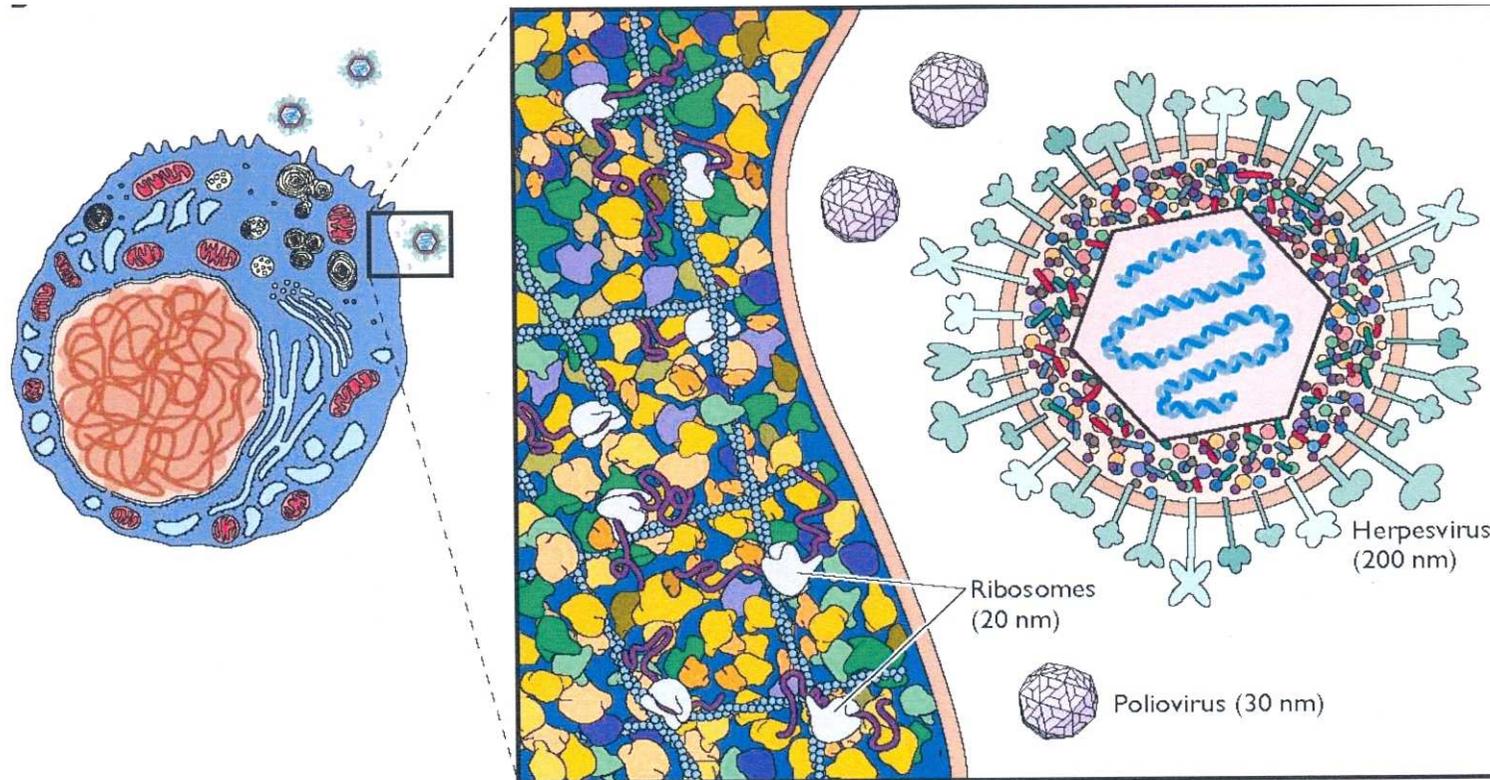
❖ Bactéries: génome de 650'000 à ~13'000'000 nucléotides, 500 à 8000 gènes

❖ Homme: génome = 3 billions de nucléotides ($=3 \times 10^{12}$), 20'000 à 25'000 gènes

Virus: définition et propriétés

- Structure simple.
- Agent infectieux qui a besoin d'une cellule (ribosomes + mitochondries...).
- Le virus se désintègre dans la cellule pour que son génome dirige la synthèse des composants viraux.
- Les composants viraux synthétisés s'assemblent dans la cellule hôte pour former des virions.
- Libération par la cellule et poursuite des cycles d'infection (avec destruction ou non de la cellule).

1. Attachement et reconnaissance d'un récepteur spécifique sur une cellule « permissive »
2. Réplication
3. Libération

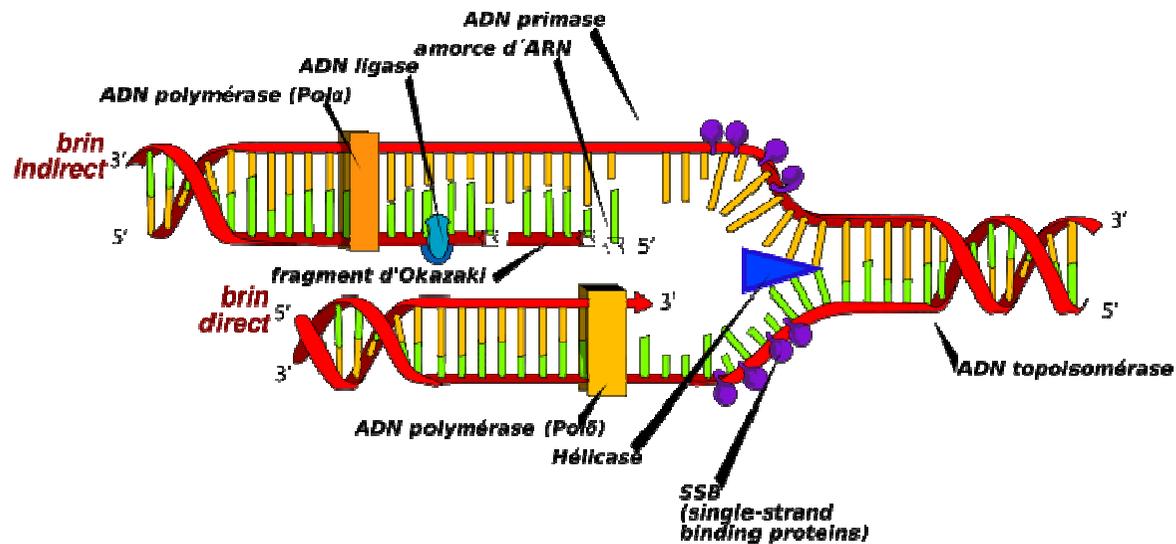


D'après Principles of Virology, Flint, Vol1, 3rd Ed

Réplication du matériel génétique dans une cellule

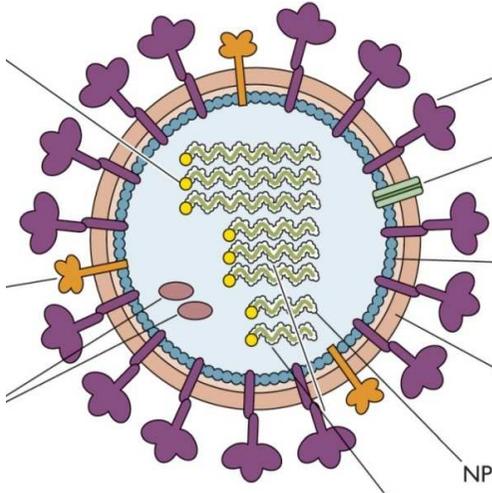
ADN → ADN → ARNm → Protéine

ADN polymérase ADN dépendante

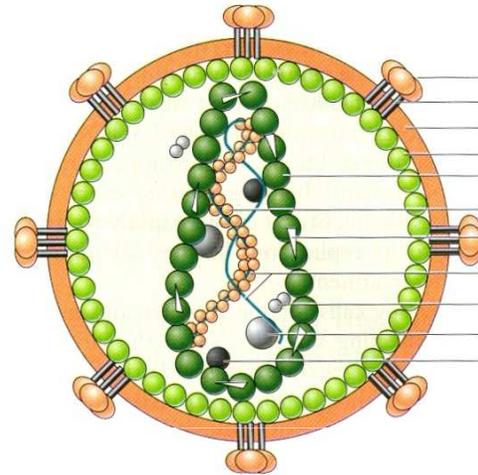


Nature des acides nucléiques

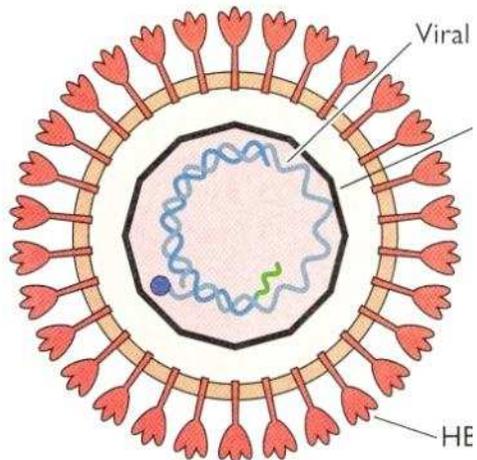
Influenza: ARN- segmenté



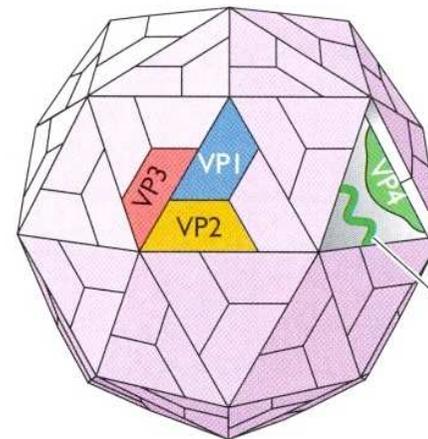
HIV: 2 génomes d'ARN +

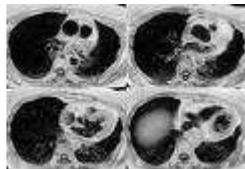
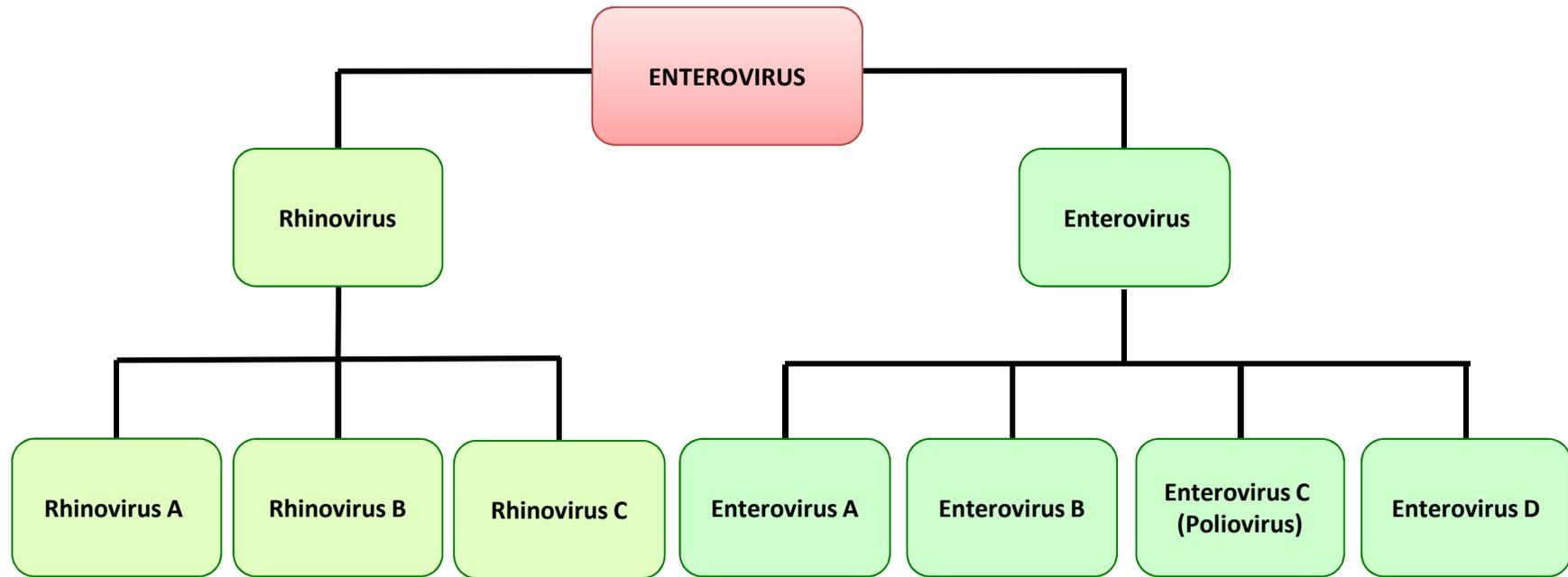
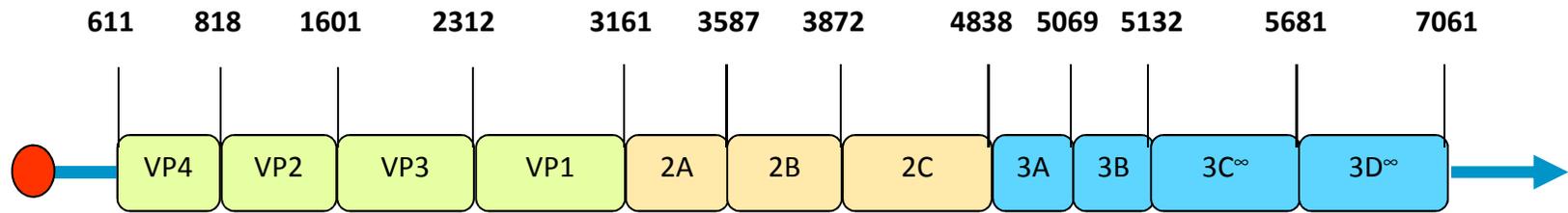


Hépatite B: ADN partiellement double brin circulaire

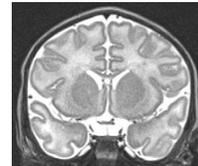


Poliovirus: ARN +

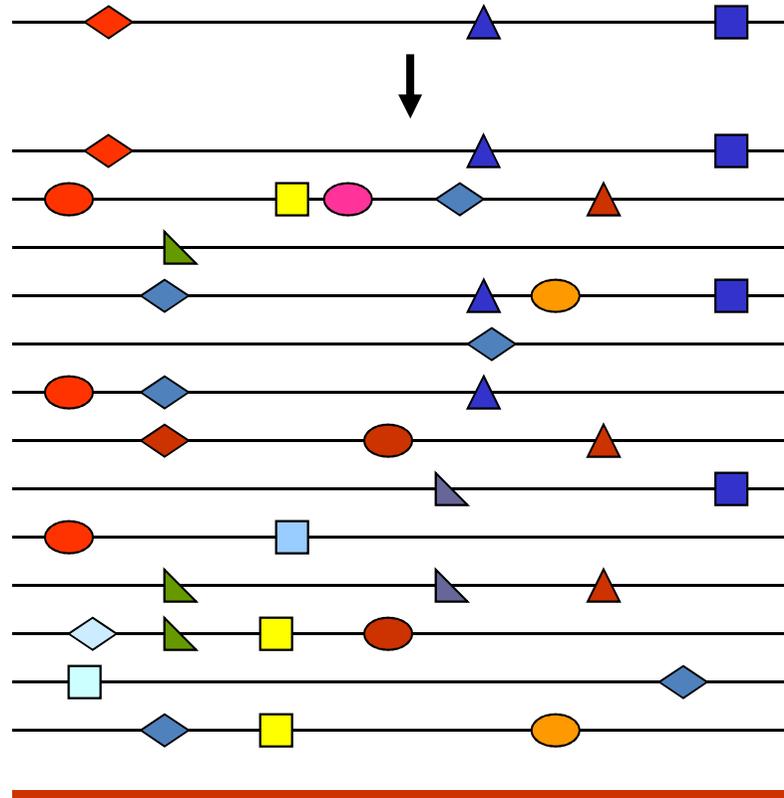




HAND, FOOT AND MOUTH DISEASE



Mutations



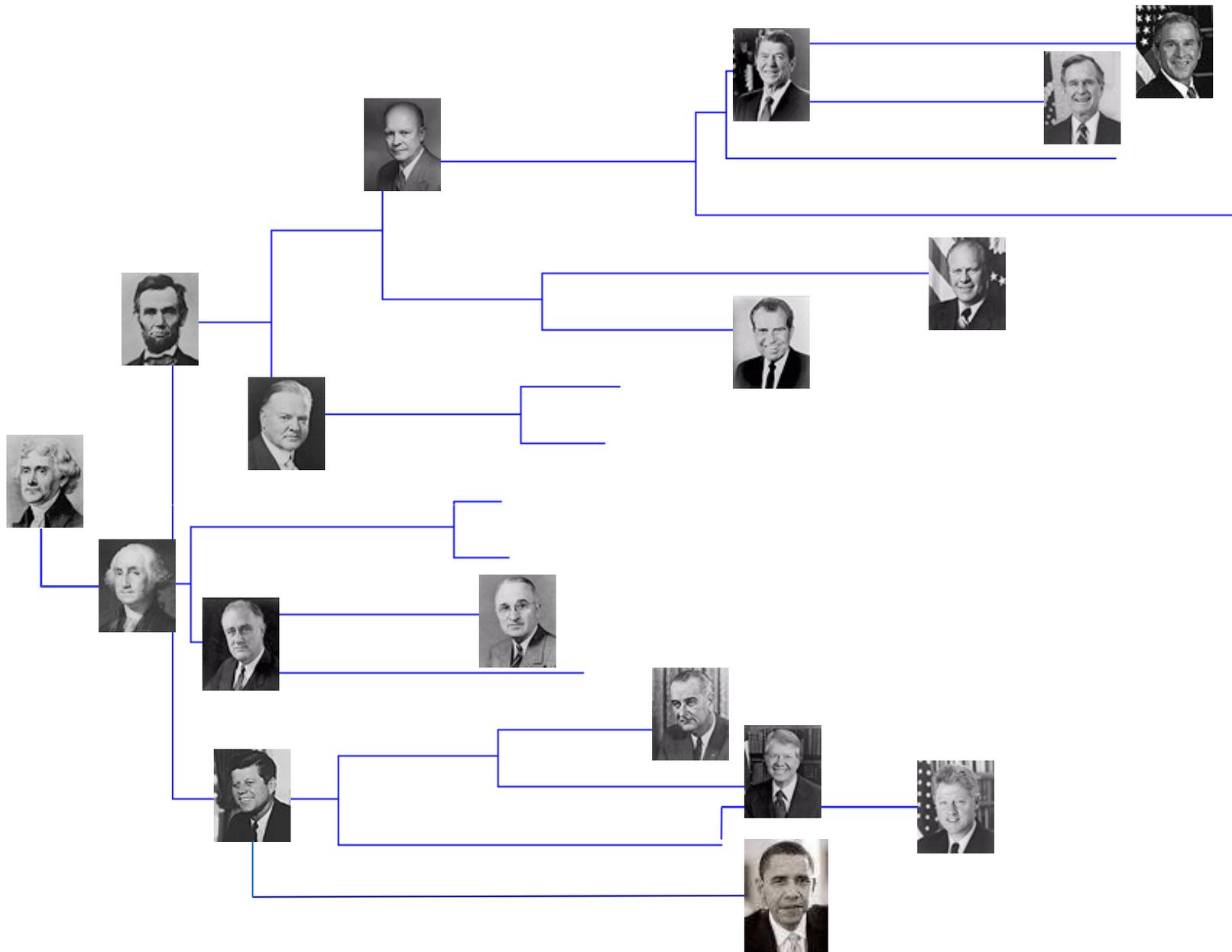
Les mutations conférant un avantage vont être sélectionnées (espèce dominante)

La majorité des mutants ne sont pas viables mais d'autres acquièrent des avantages:

- Meilleure “fitness”
- Echappement à la réponse immune
- Passage de la “barrière des espèces”
- Acquisition de nouveaux traits de virulence
- Meilleure transmissibilité

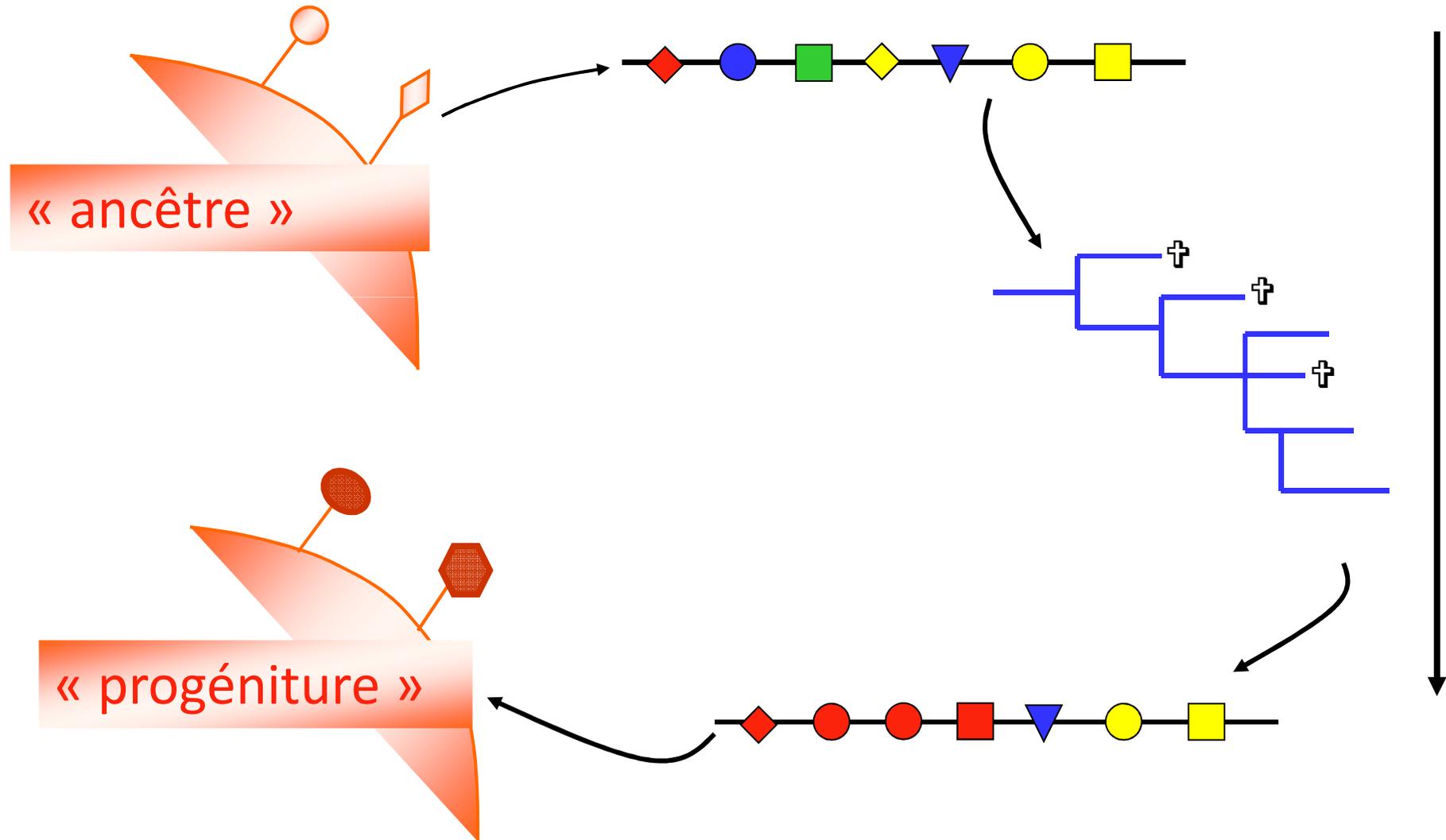
Conséquences potentielles:

- Rend la création de vaccins très difficile (HIV, HCV)
- Les virus deviennent résistants aux traitements (trithérapie HIV)
- Emergence de “nouveaux virus”



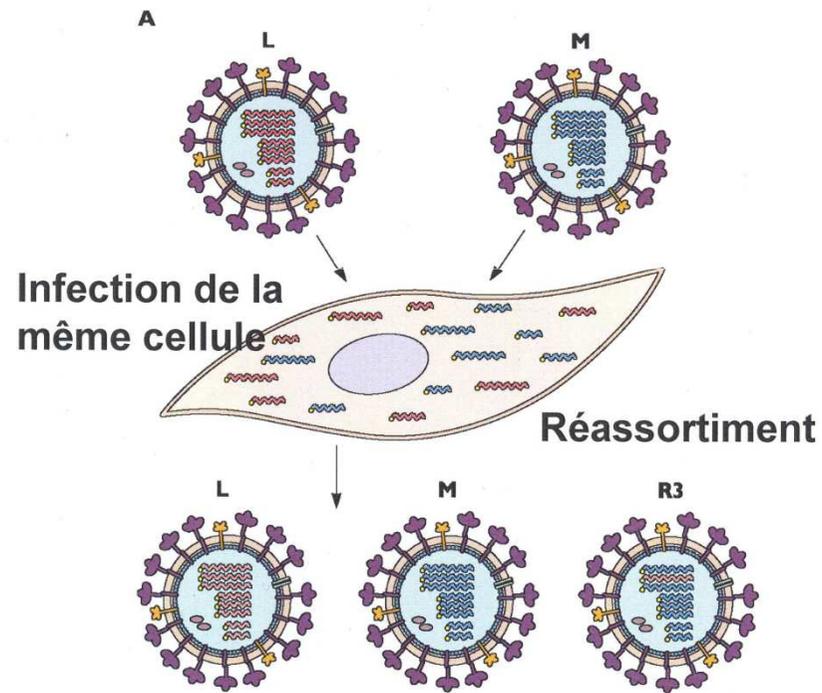
— Unit of genetic distance

Evolution virale



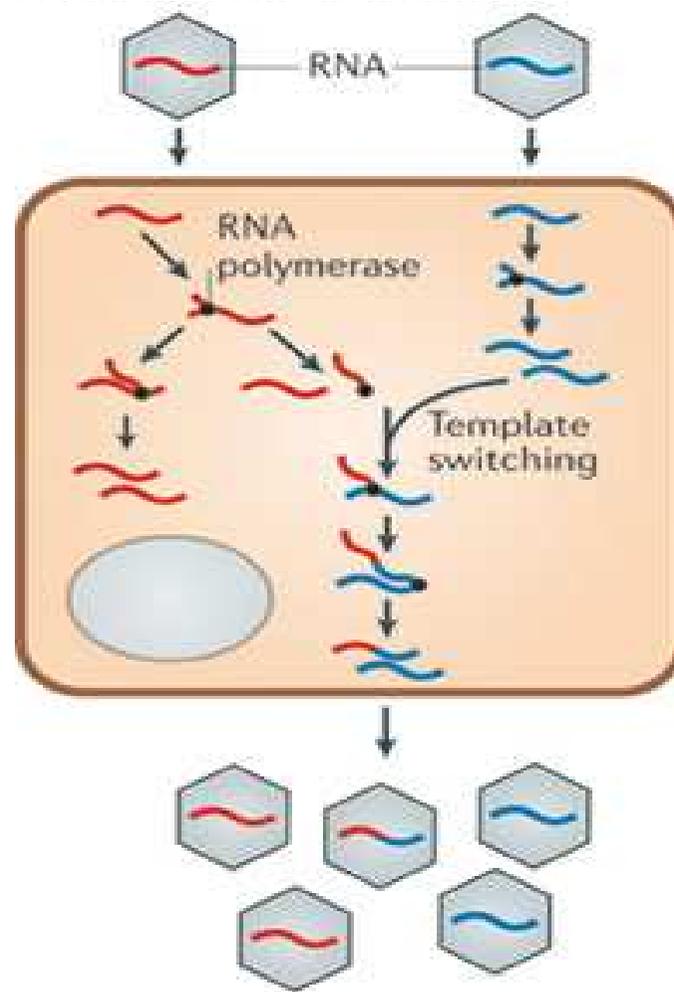
Le réassortiment

Différentes souches de virus influenza

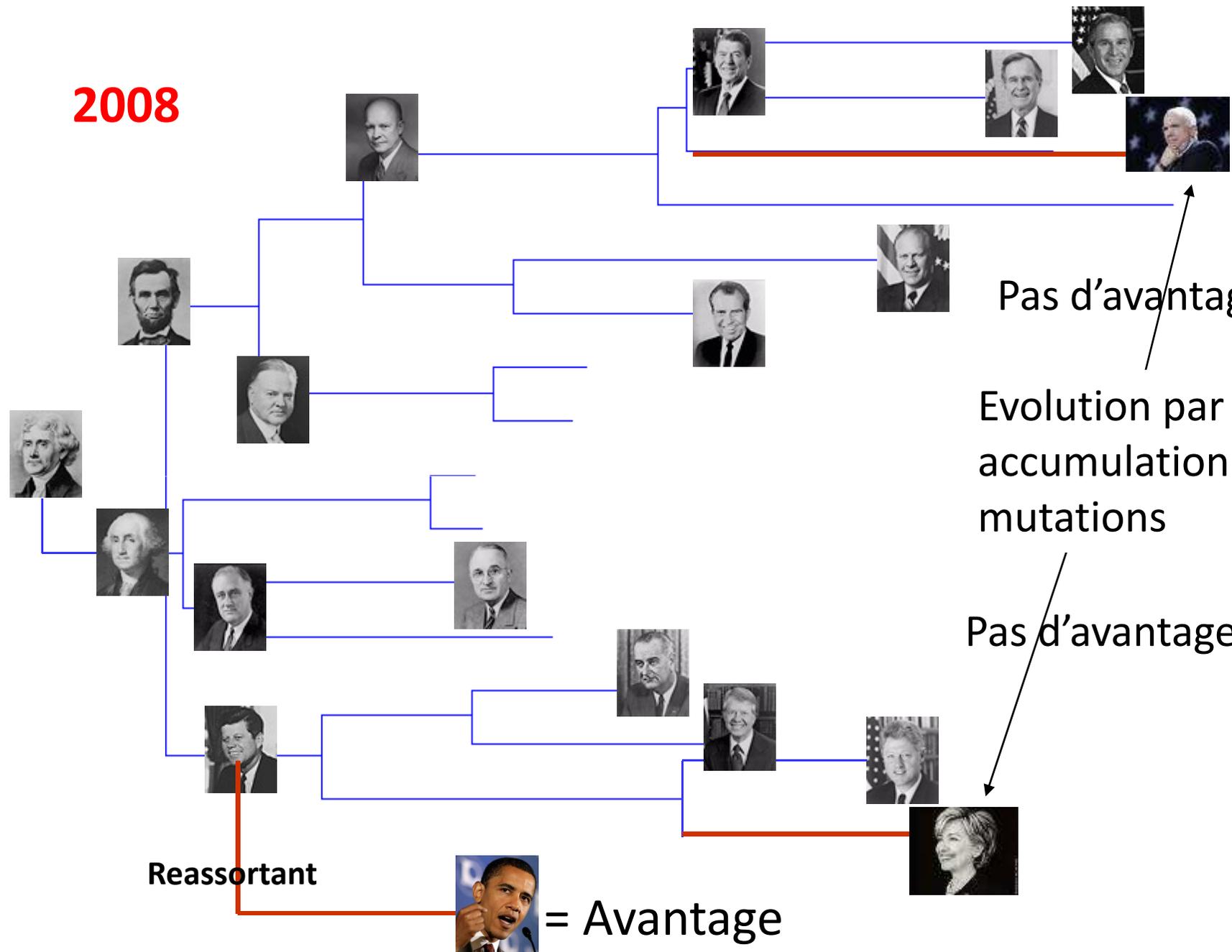


D'après *Principles of Virology, Flint, Vol1, 3rd Ed*

La recombinaison



2008



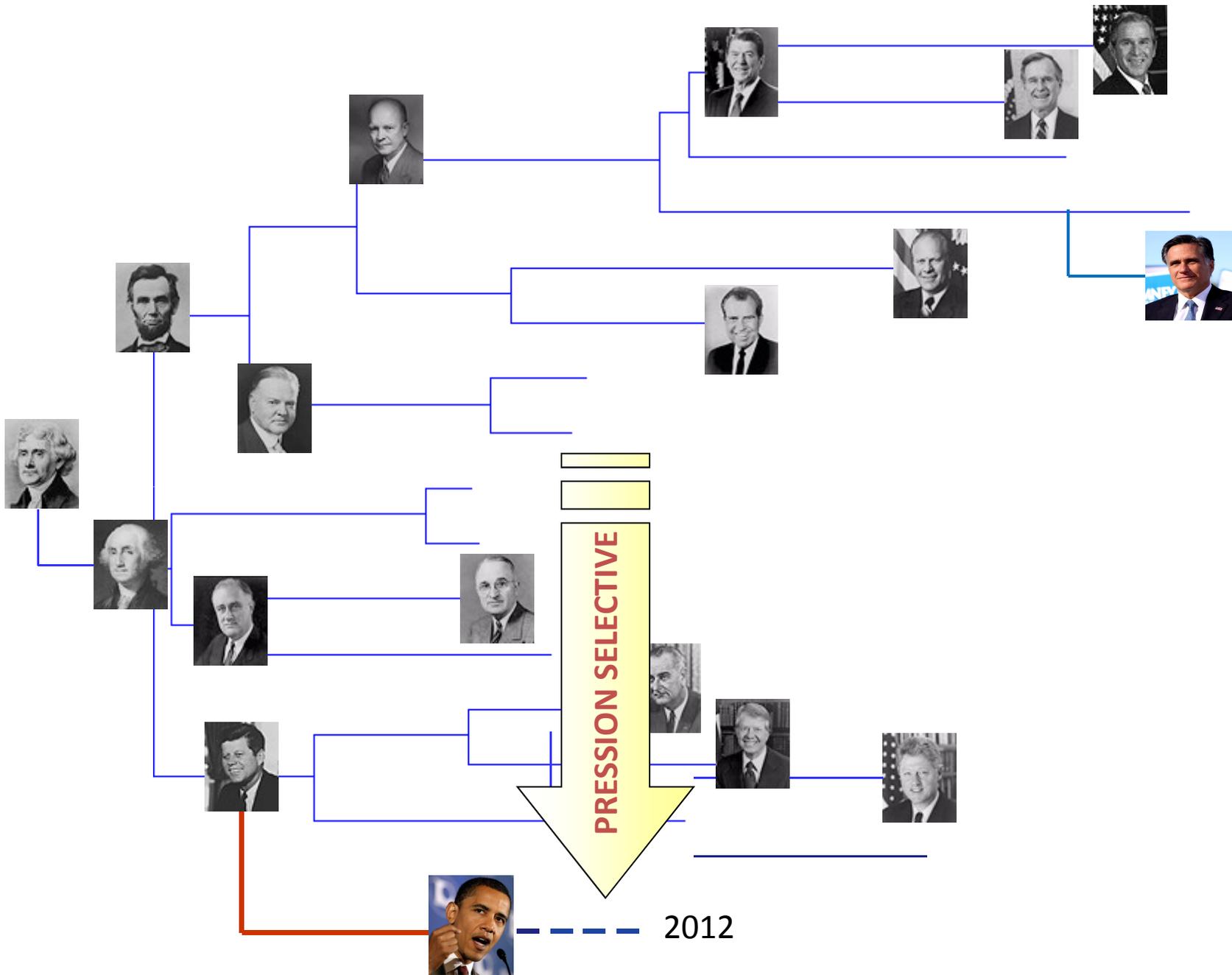
Pas d'avantage

Evolution par accumulation de mutations

Pas d'avantage

Reassortant

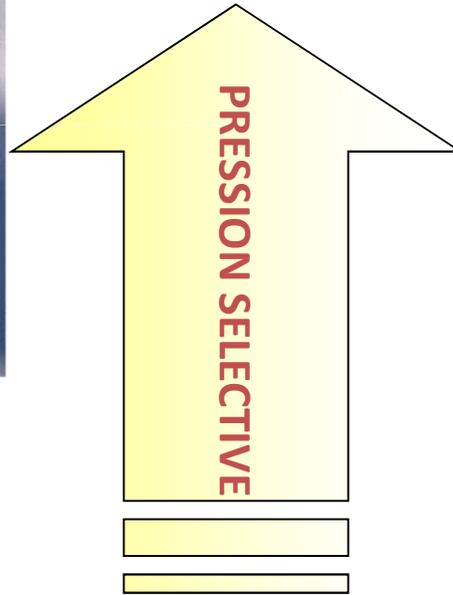
= Avantage



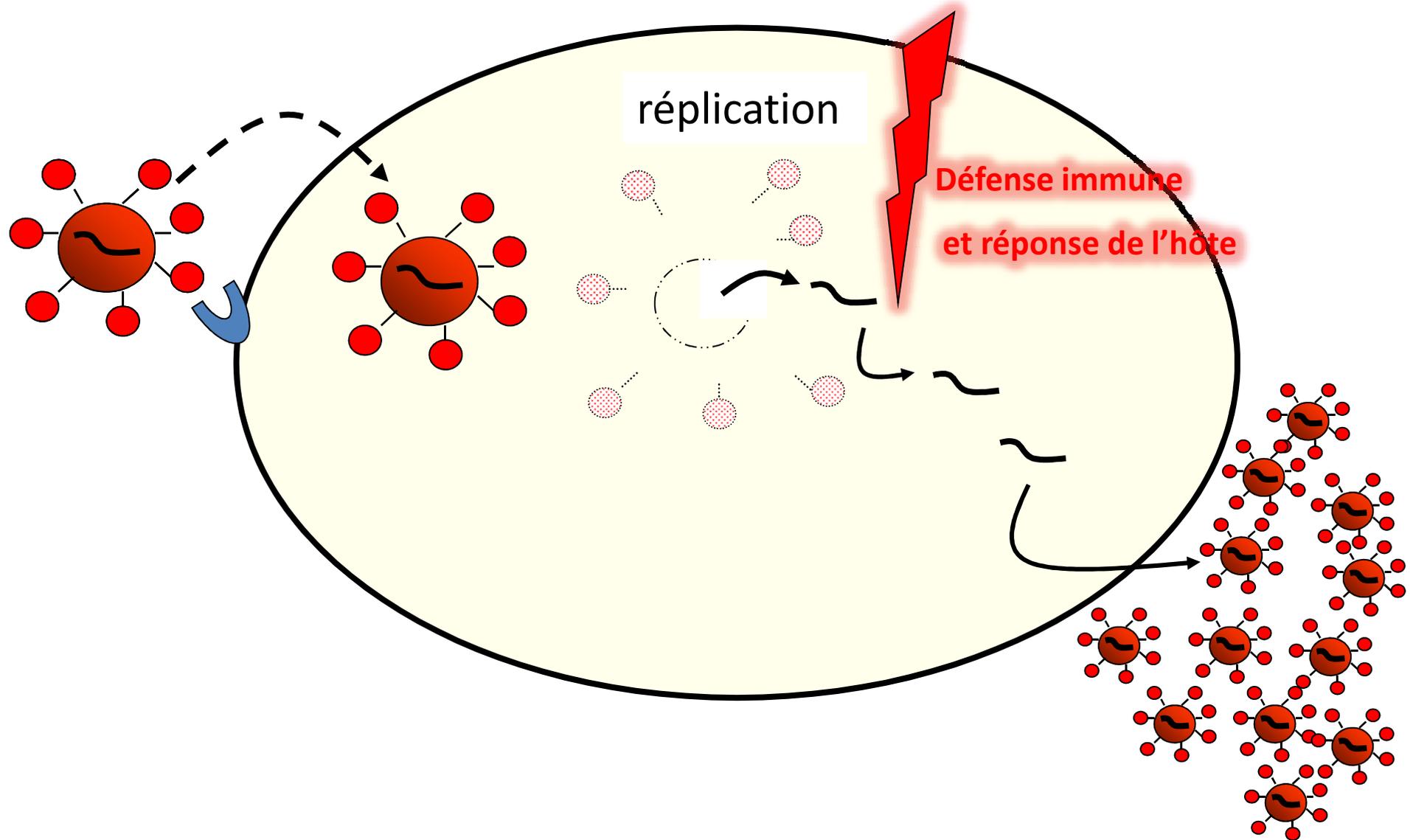
2008



2012

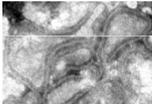
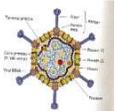
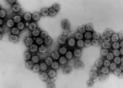


Cycle viral: au niveau de la cellule



Virus respiratoires

- 1^{ère} cause d'infections chez l'homme
- 1^{ère} cause de rhinopharyngites
 - Sinusites
 - Otites
 - Prescription antibiotiques
 - Infections bactériennes secondaires
- "1^{ère}" cause d'exacerbations
 - Asthme
 - COPD (bronchite chronique-emphysème)

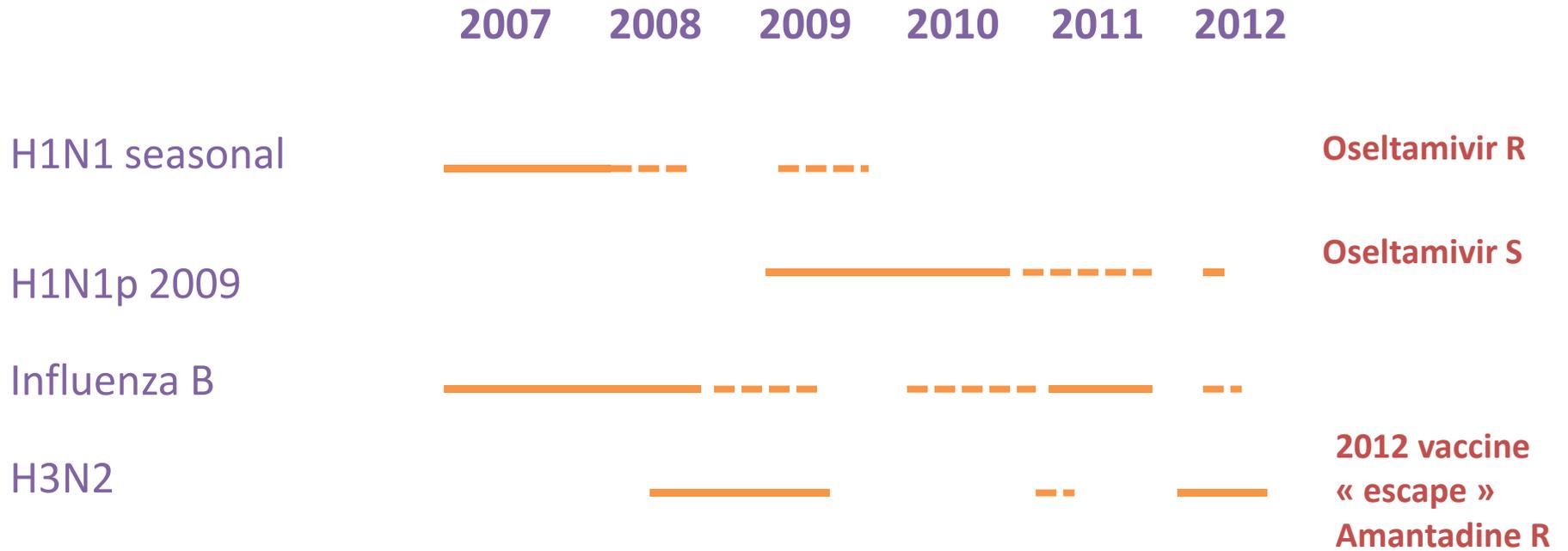
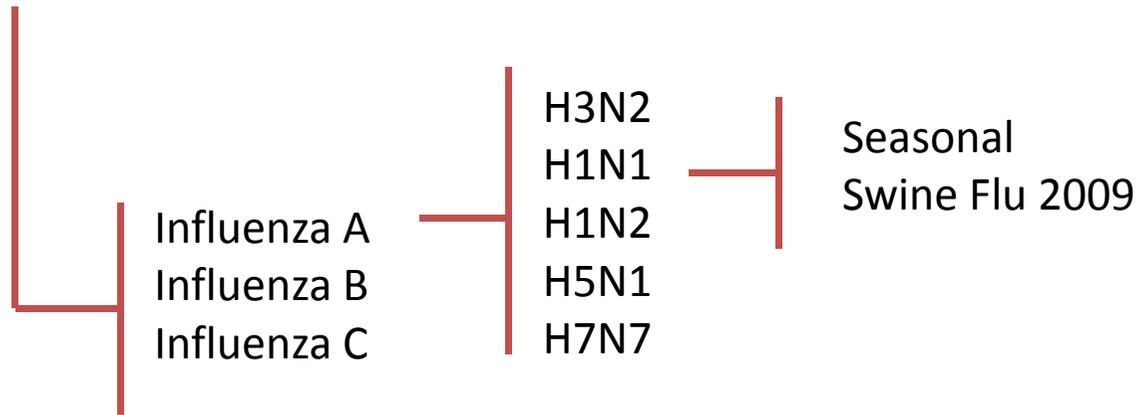
Human	Virus	Species/Sub-Sero-Genotypes	
	Rhinovirus	A, B, C, >140 serotypes	RNA
	Influenza	A (H3N2,H1N1..) ,B ,C	RNA
	RSV	A and B	RNA
	Parainfluenza	Type 1, 2, 3 and 4	RNA
	Metapneumovirus	A1, A2, B1, B2	RNA
	Coronavirus	OC43, E229, HKU1, NL63	RNA
	Enterovirus	>100 serotypes	RNA
	Adenovirus	7 species, > 50 serotypes	DNA
	Bocavirus	4 species	DNA
	Polyomavirus	KI, WU, Merkel...	DNA

Immunité

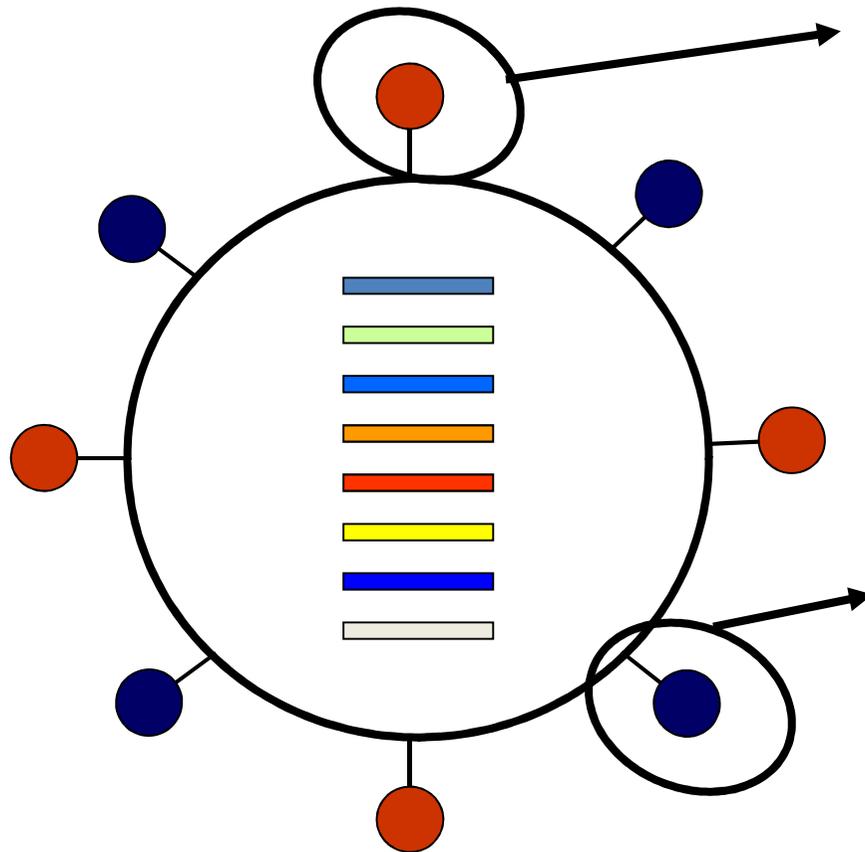
Protection immune limitée:

- Variabilité des sérotypes.
- Réponse immune non protectrice.
- Réponse immune de courte durée (?).
- Evolution des antigènes viraux (influenza).
- Réponse humorale vs. Cellulaire (?).
- Absence de vaccin « universel ».
 - But: immunité muqueuse
- Réinfections fréquentes.

Influenza



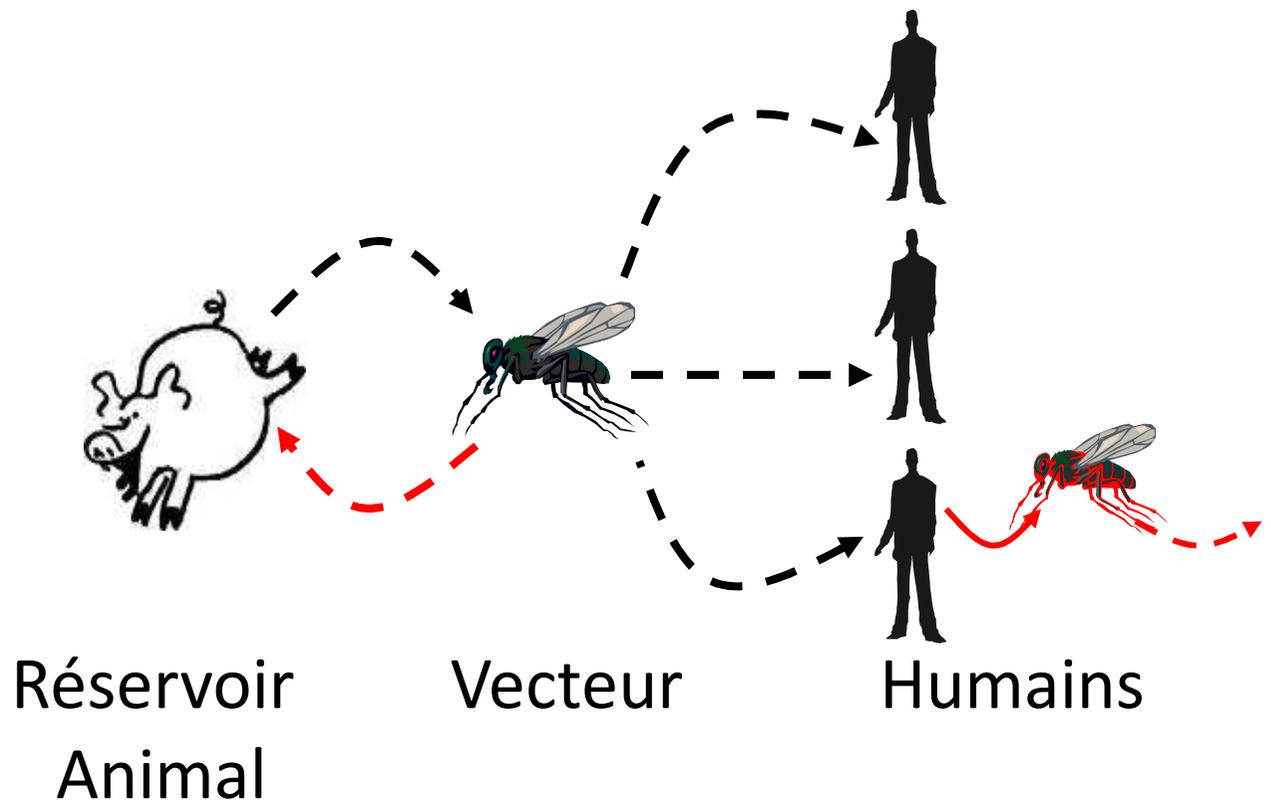
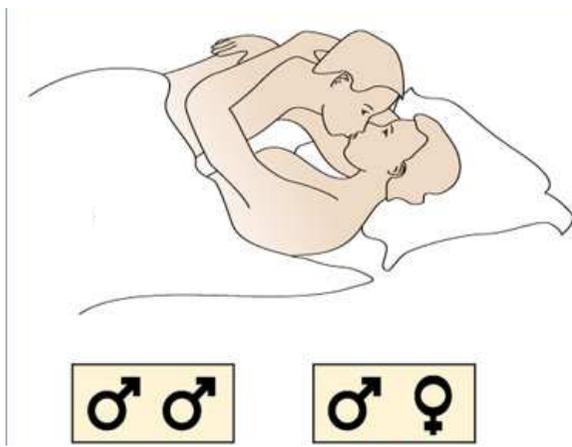
Virus Influenza



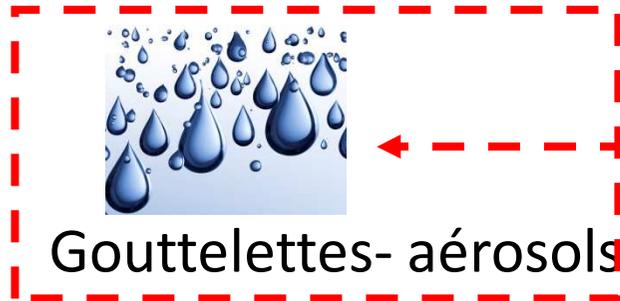
- **Hemagglutinine:**
- Adaptation à l'hôte
- Tropisme
- Transmission
- Réponse immune

- **Neuraminidase (NI):**
- Résistance antivirale

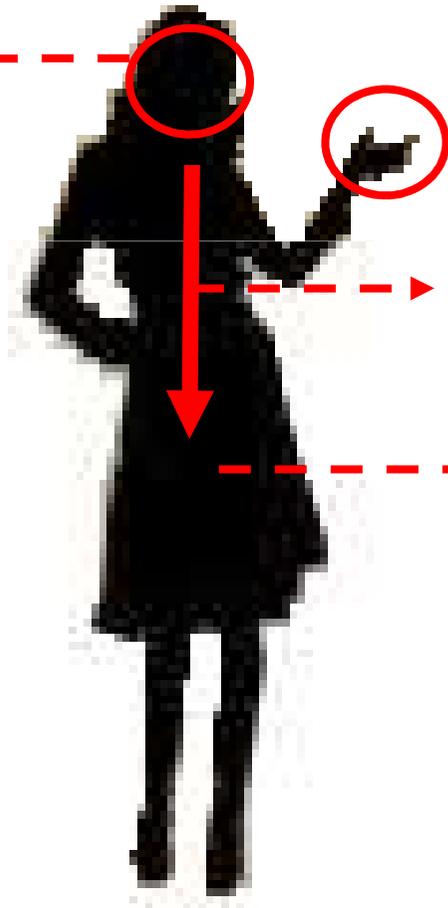
Transmission



Transmission virale entre humains



Le plus efficace?

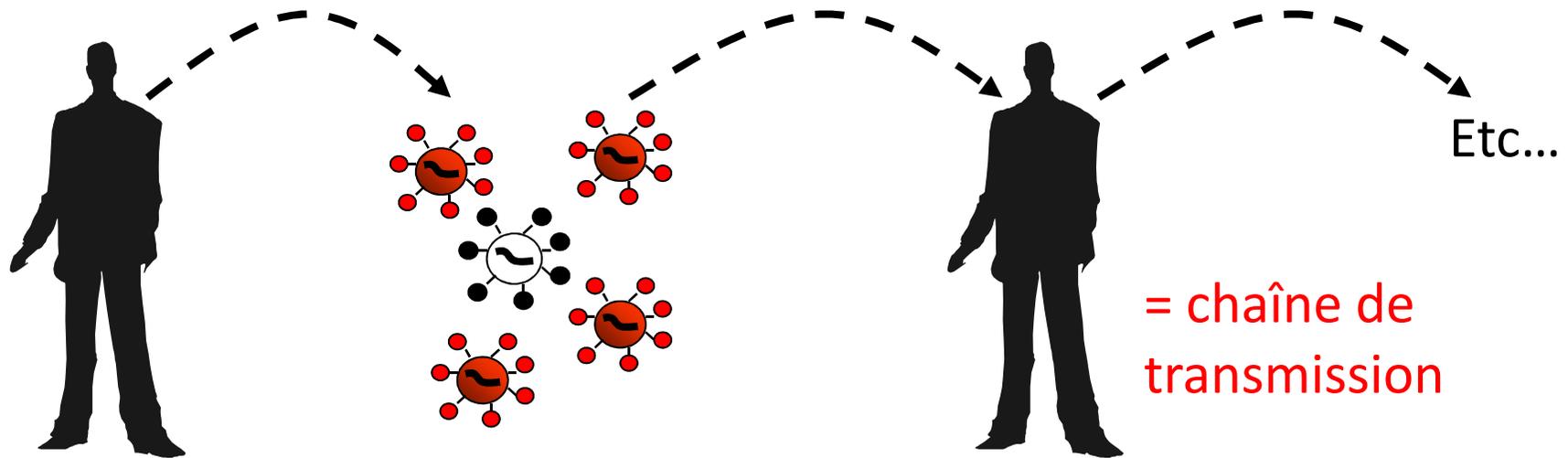


Contact

Verticale: femmes enceintes
ou allaitement

Transmission sexuelle

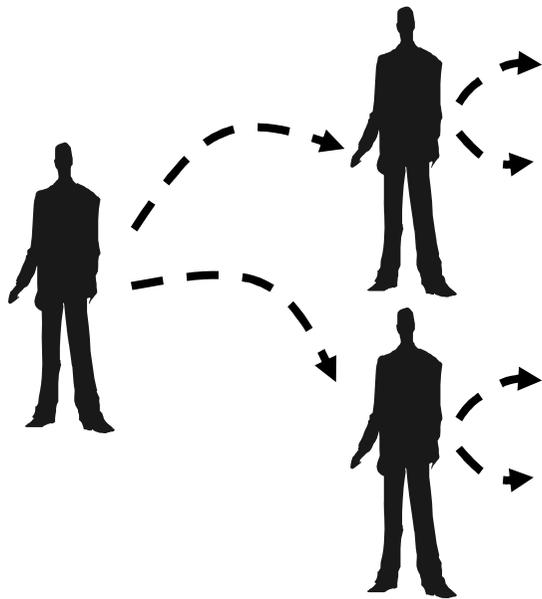
Cycle viral: réservoir et transmission



Pré-requis:

- Production de virus infectieux facilement transmissibles + opportunité de transmission

Transmission virale



« Vaccin = éradication »

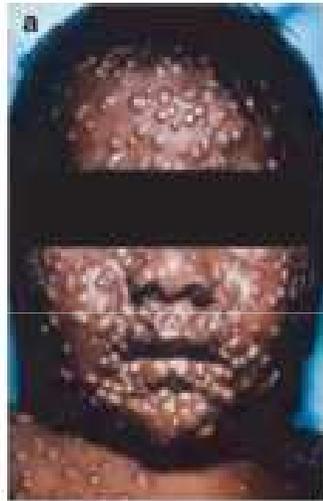
Réservoir = Humains



Réservoir

Barrière d'espèces

Barrière d'espèces



Facteurs influençant l'efficacité de transmission:

- Mode de transmission
- Période de contagiosité
- Immunité de la population

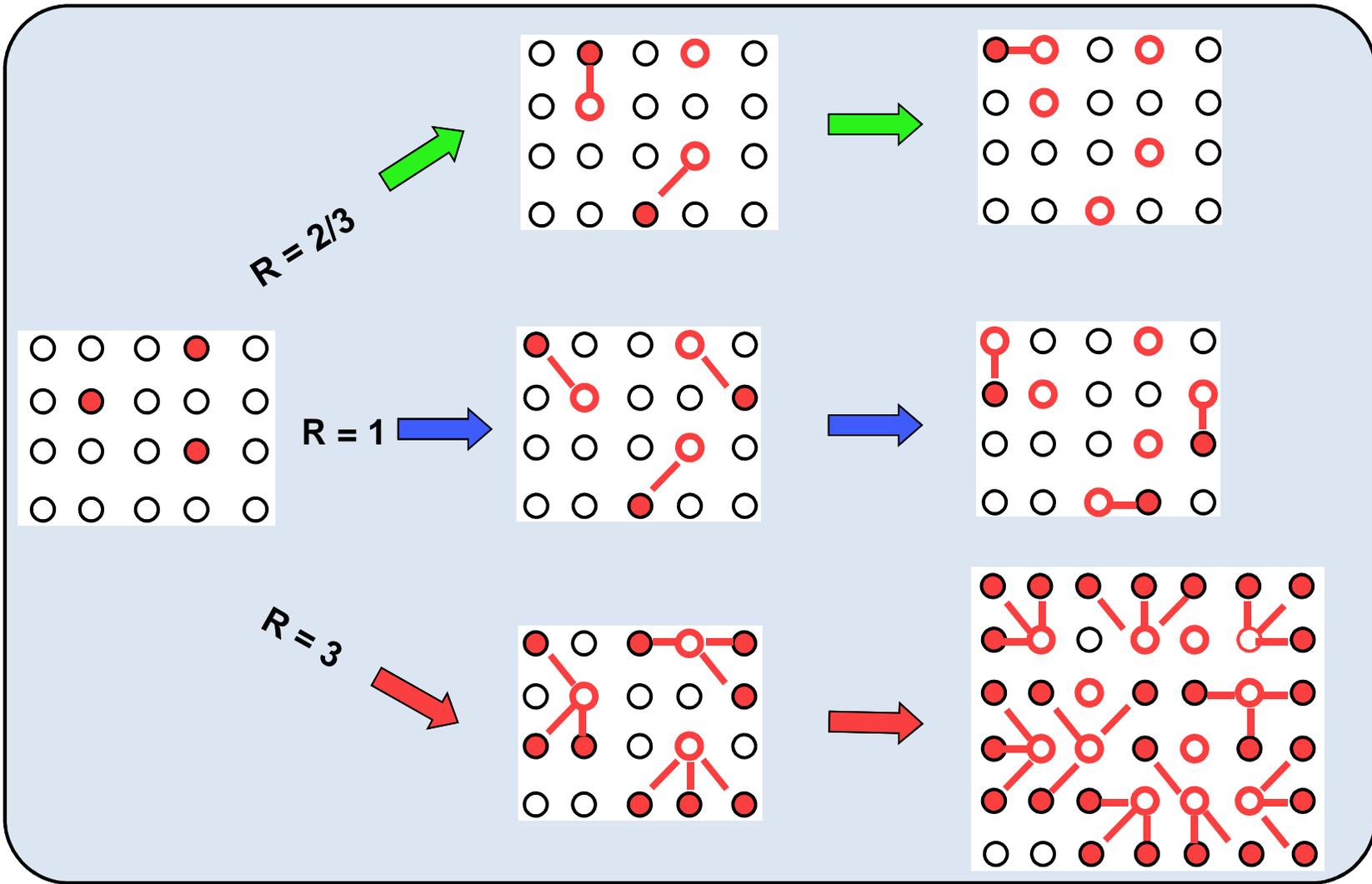


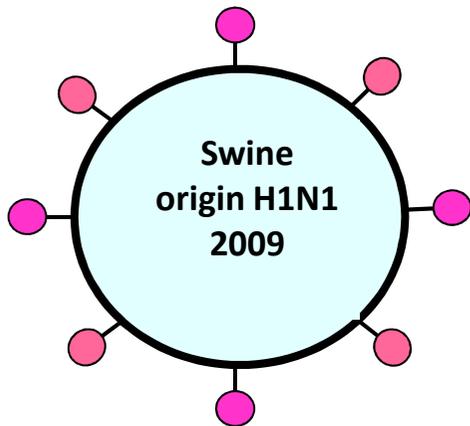
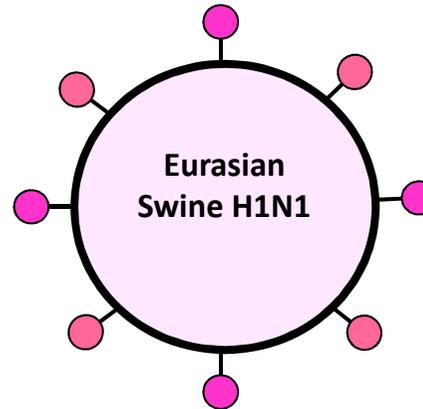
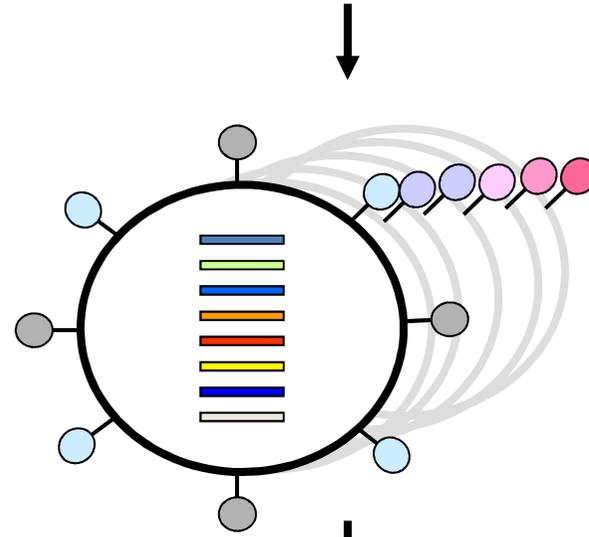
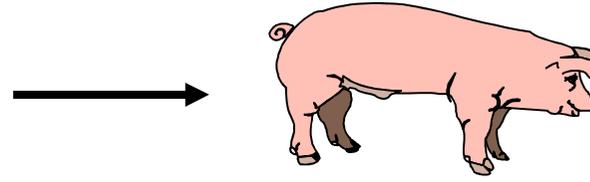
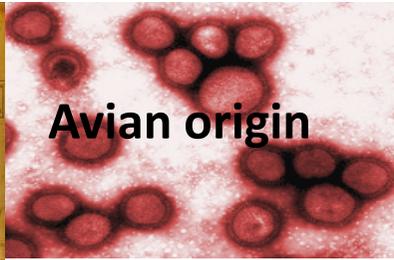
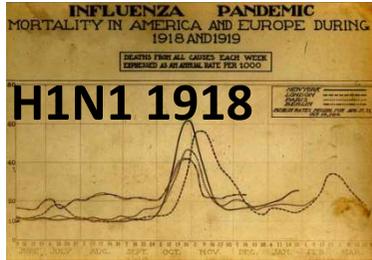
Taux « R » d'efficacité de transmission (nombre moyen d'infections secondaires causées par une personne infectée)

$R < 1$: Diminution du nombre de personnes infectées à chaque « génération » de l'agent

$R = 1$: Seuil

$R > 1$: Epidémie





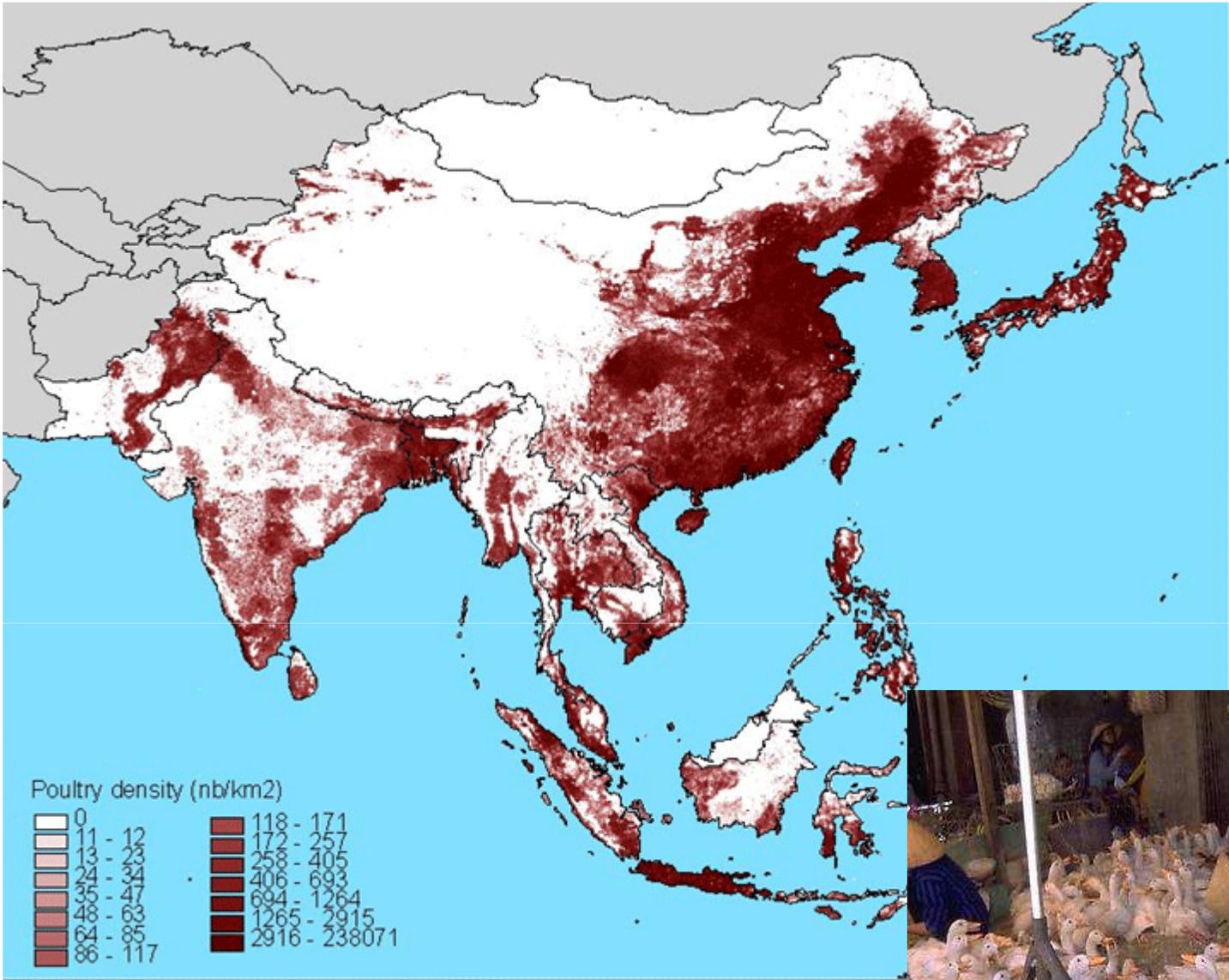
H5N1, pas adapté à l'Homme



Facteurs pouvant expliquer l'émergence de certains virus

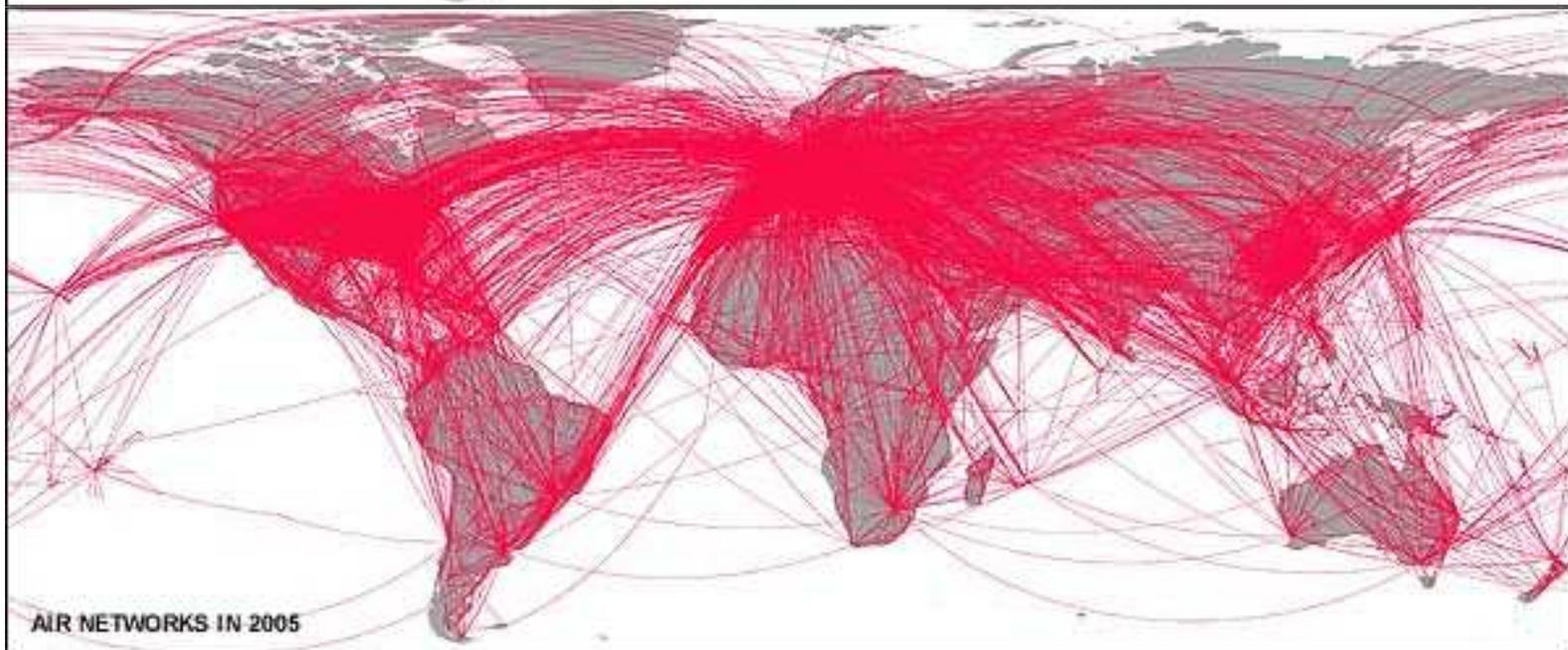
Hong Kong: 1924



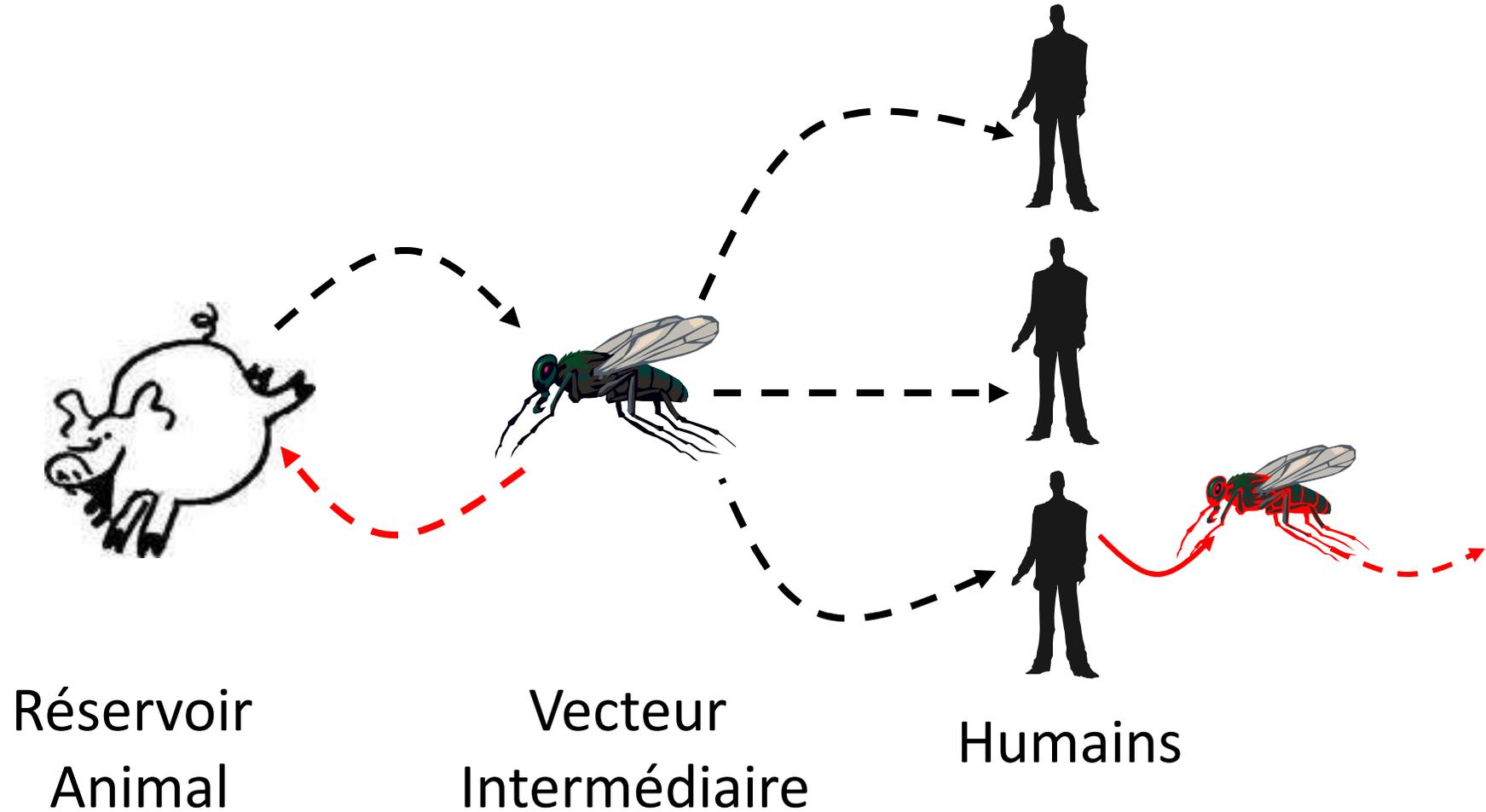


Déforestation, intrusion dans des zones « préservées » jusqu'à aujourd'hui





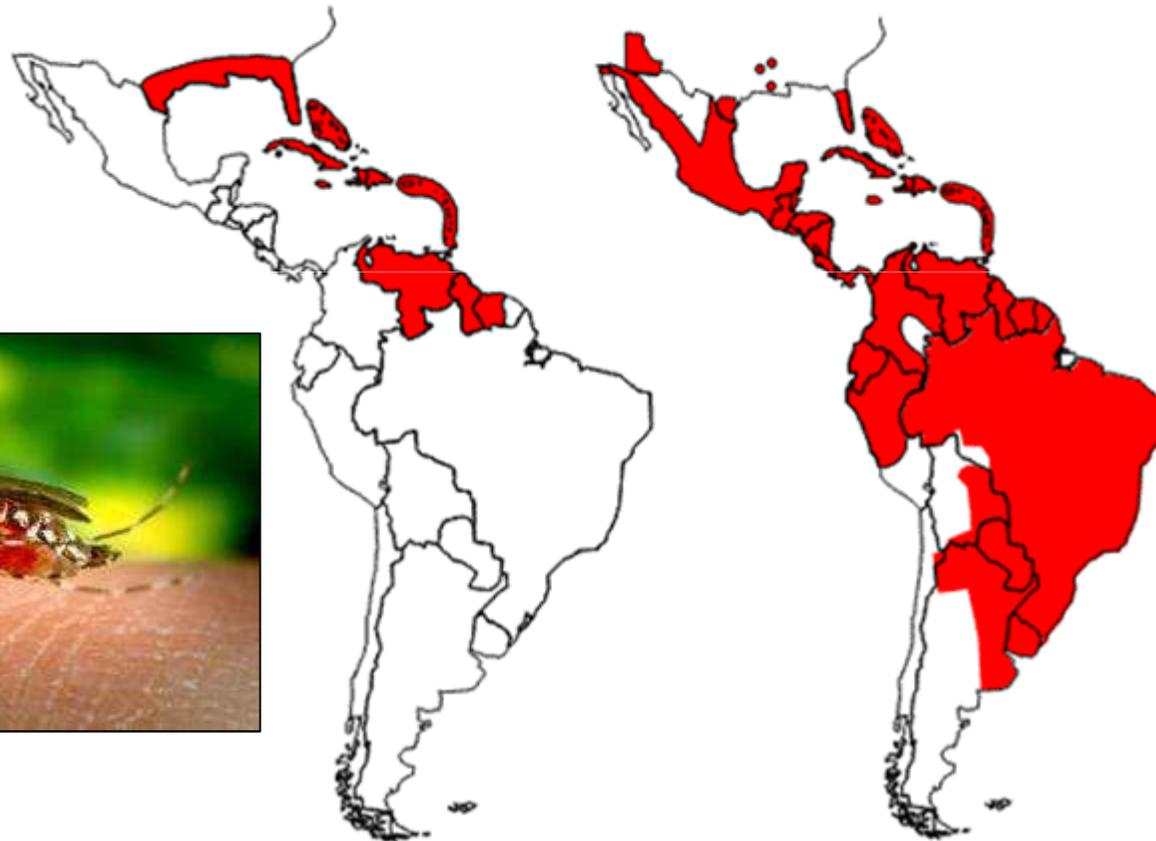
Transmission par un vecteur intermédiaire

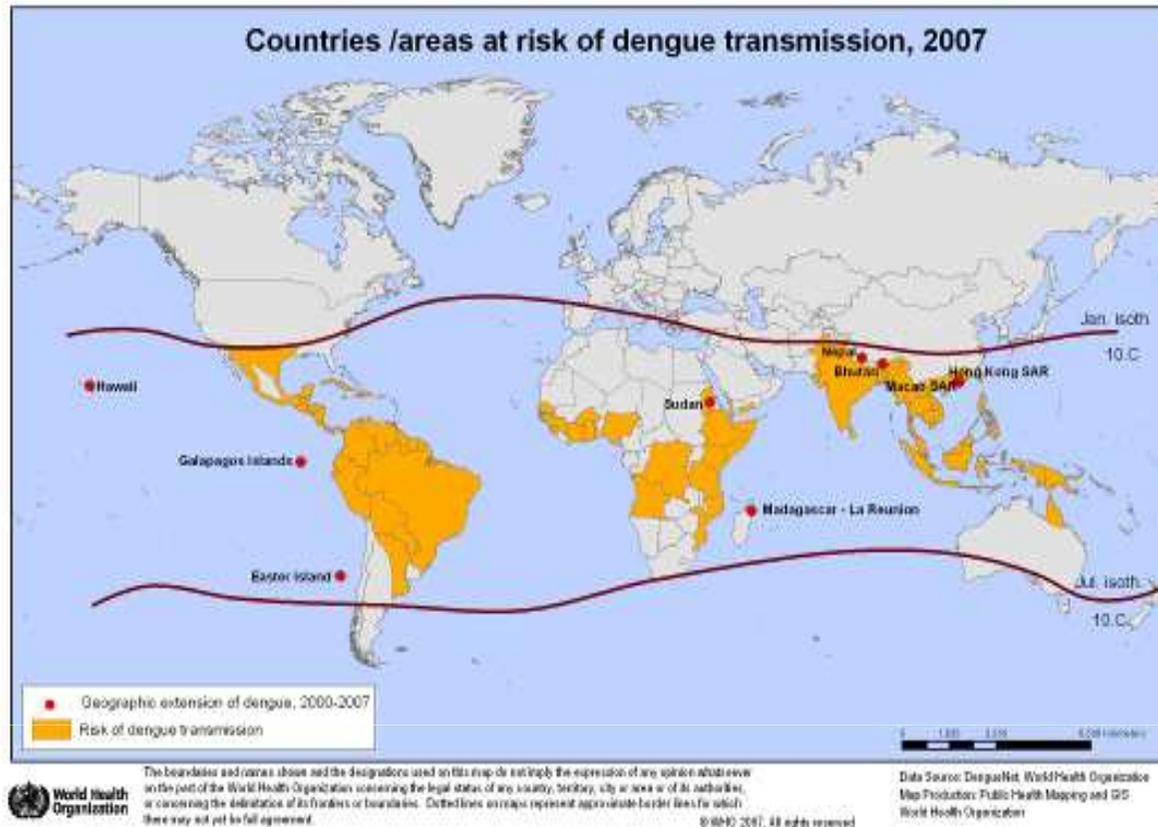


Exemple de distribution d'*A. aegypti*:

1970

2002





L'incidence a progressé de manière spectaculaire dans le monde entier au cours des dernières décennies (en 50 ans, multiplication ~30x).

40% de la population mondiale exposée au risque.

Estimations OMS: chaque année, de 50 à 100 millions de cas dans le monde, 500 000 pers. atteintes de dengue sévère.

Très forte proportion d'enfants, environ 2,5% de mortalité.

Raisons de la propagation de la dengue

Extension de l'aire de distribution géographique

- virus
- vecteurs

- Croissance rapide des populations urbaines
- Changements climatiques
- Moins de campagnes d'éradication des moustiques



Symptômes cliniques:

- Fièvre
- Eruption cutanée
- Arthralgies

Une forme hémorragique existe, mais elle est relativement rare!



Dengue, countries or areas at risk, 2008*



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization



Yellow Fever, countries or areas at risk, 2008

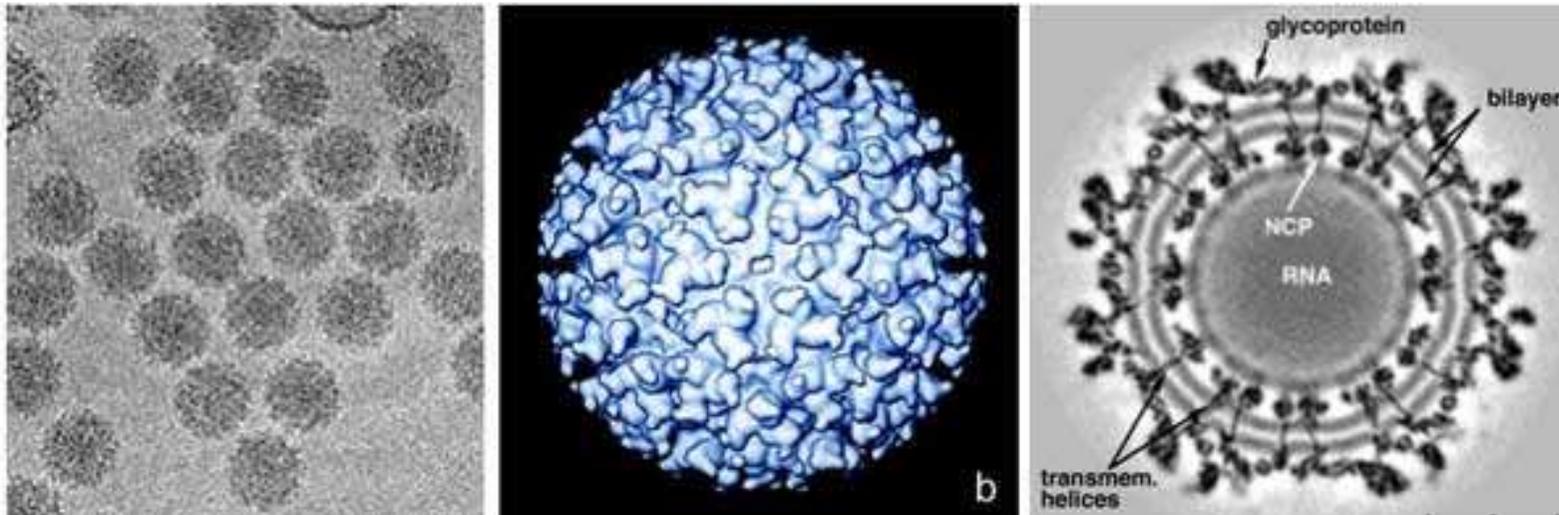


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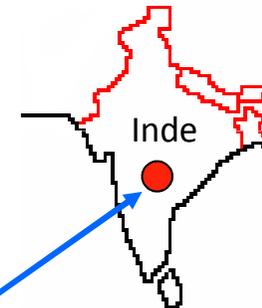
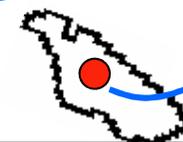
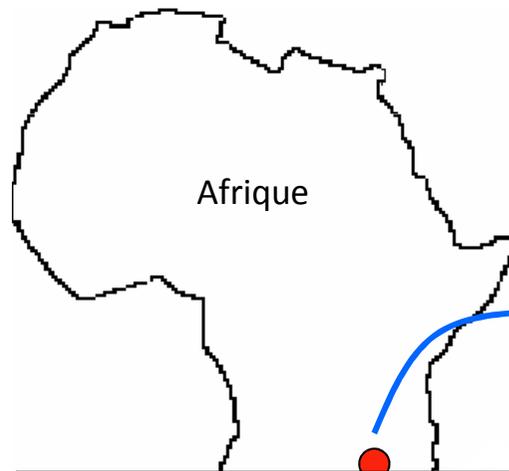
Data Source: World Health Organization/CDC
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization



Chikungunya (arbovirus)



Famille: *Togaviridae*, genre *Alphavirus*
Enveloppé, ARN+
Isolé en Tanzanie la 1ère fois en 1952



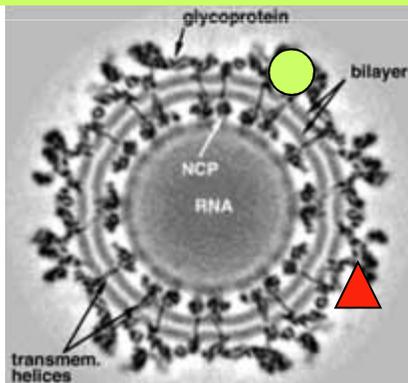
Pays
La Réunion (777'000)
Inde (gouvernement)
Inde (estimation réelle)

Cas (2005-2006)
258'000 cas (38%)
1'4 mio cas
6'5 mio cas

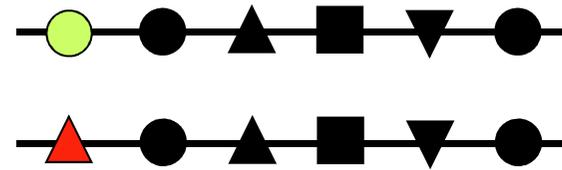
Mortalité/100'000
91.8
91.8
276

Chikungunya: adaptation et mutation GPE1 (A226V)

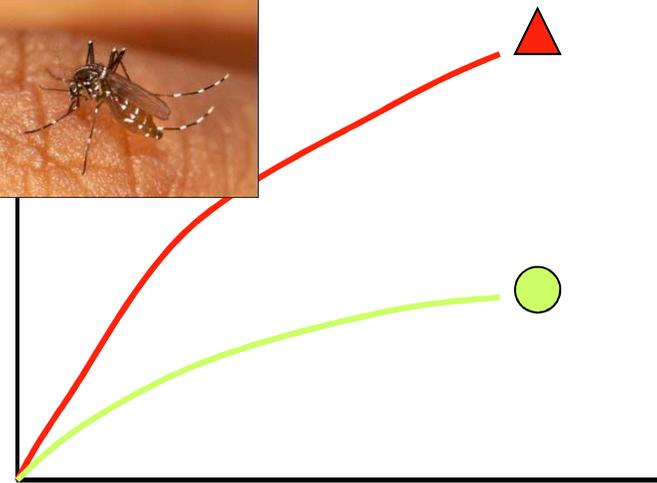
Mars 2005:
100% souches : A226



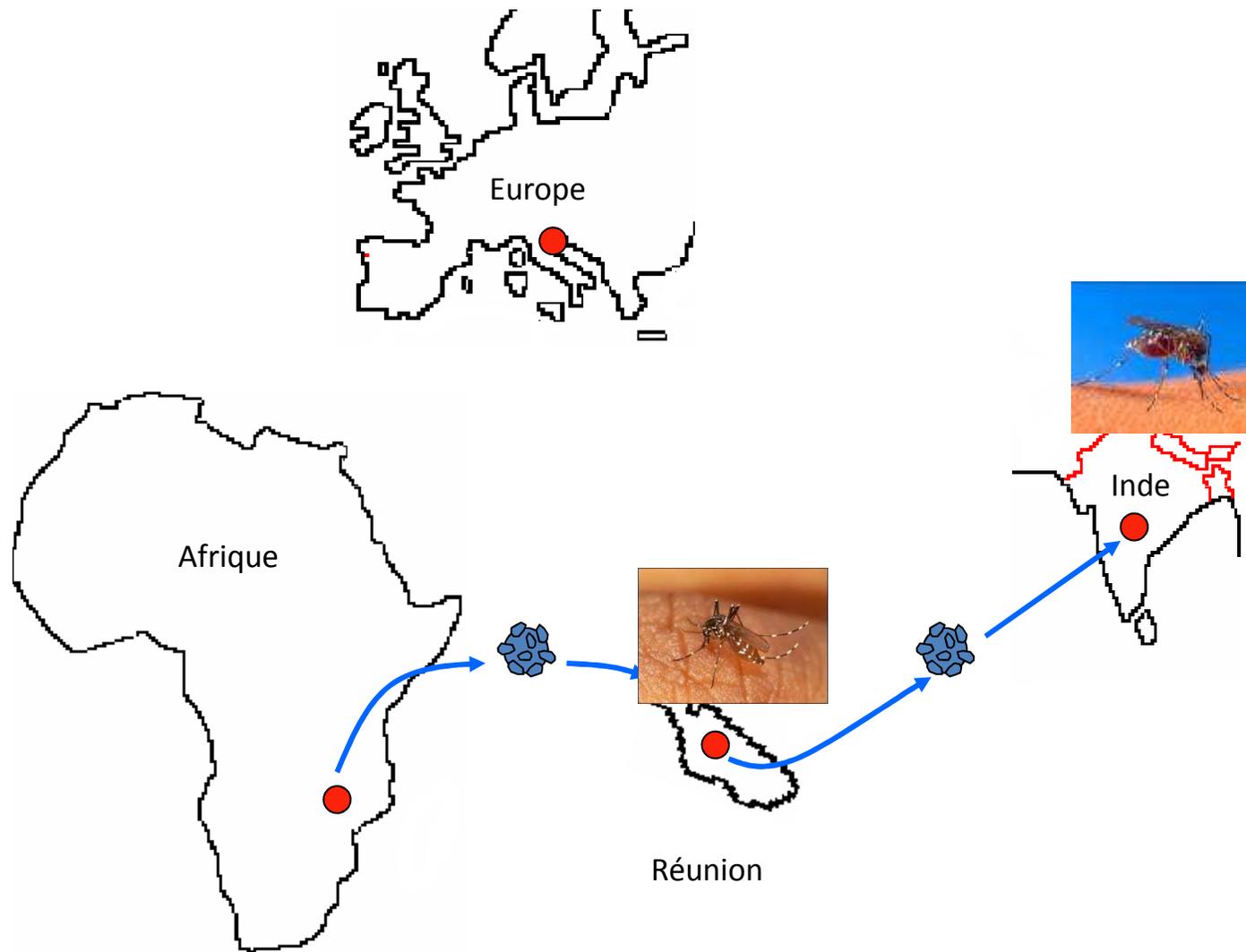
Avril 2006: 90% A226

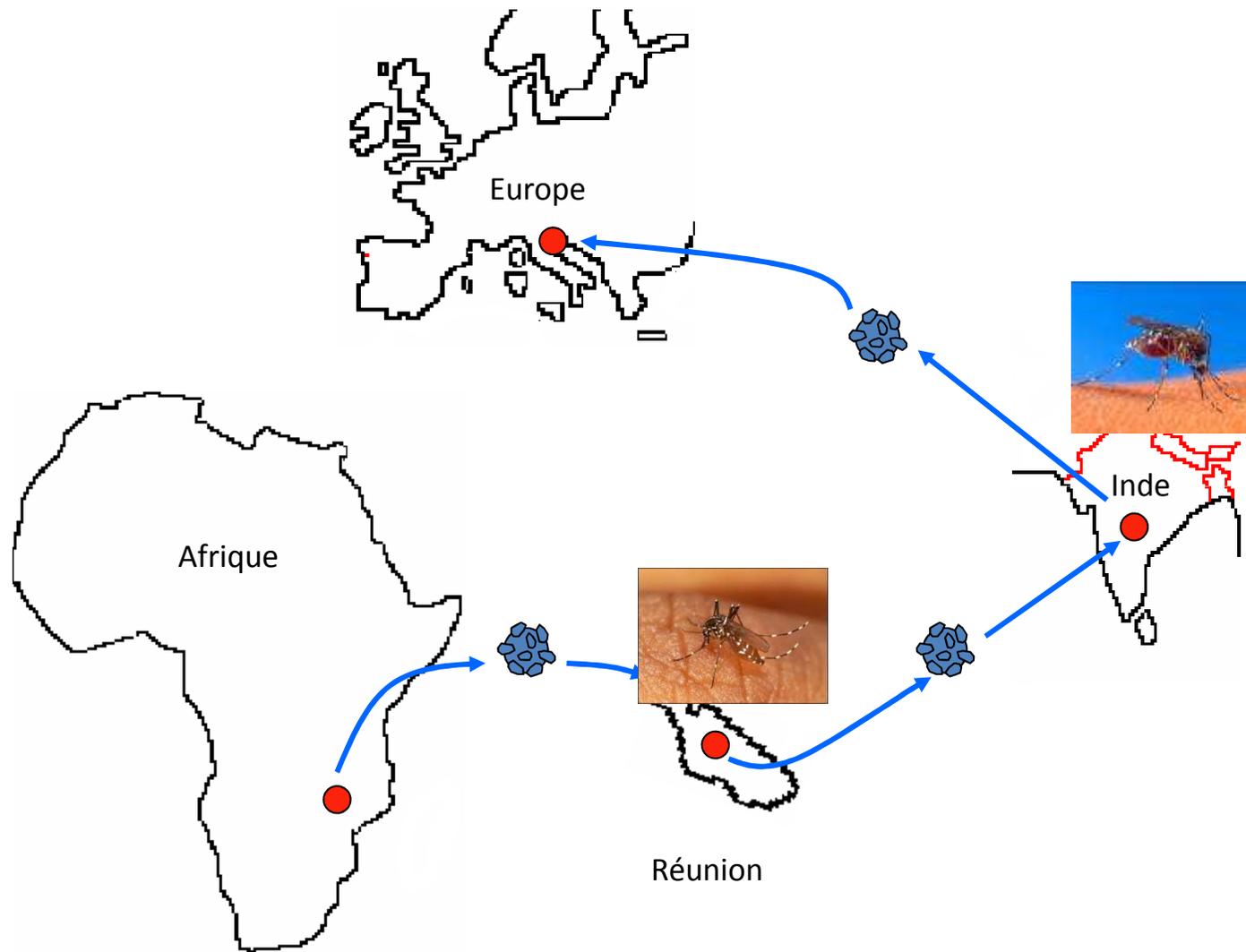


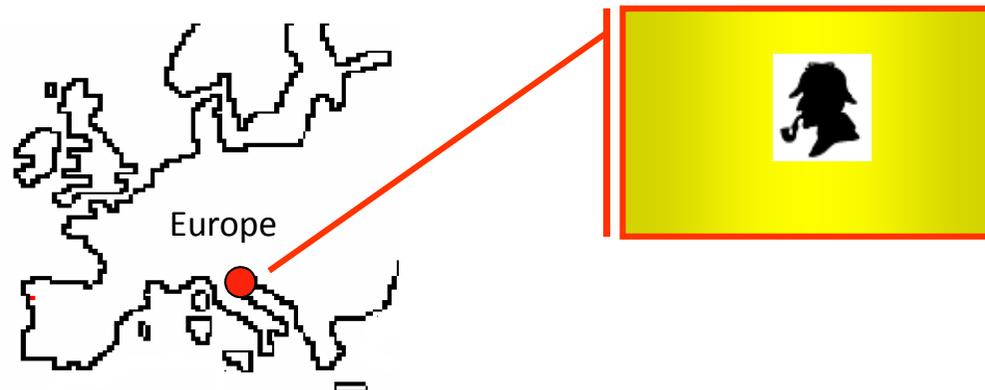
Virémie



Jours







	Number of cases (%)
Fever*	205 (100%)
Joint pain†	199 (97%)
Fatigue	190 (93%)
Skin rash	106 (52%)
Headache	105 (51%)
Muscle pain	94 (46%)
Diarrhoea	48 (23%)
Itching	42 (20%)
Vomiting	40 (19%)
Photophobia	31 (15%)
Conjunctivitis	7 (3%)

*Mandatory in the case definition. †Not mandatory if diagnosis is laboratory confirmed.

Table 2: Distribution of symptoms

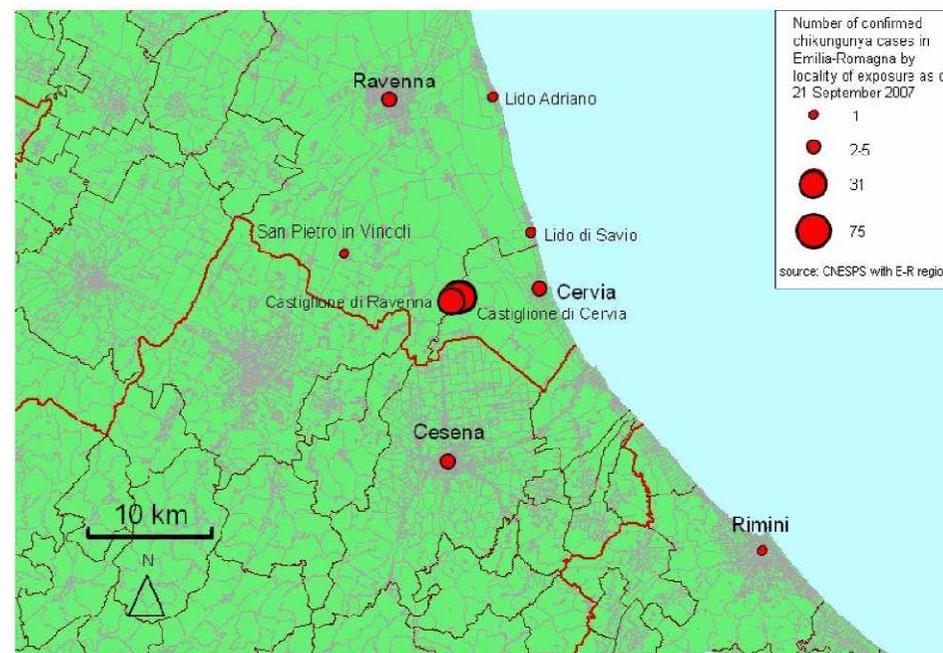


Figure 2. Distribution of confirmed cases of chikungunya fever by locality of exposure, region of Emilia-Romagna, as of 21 September 2007 (n = 125).

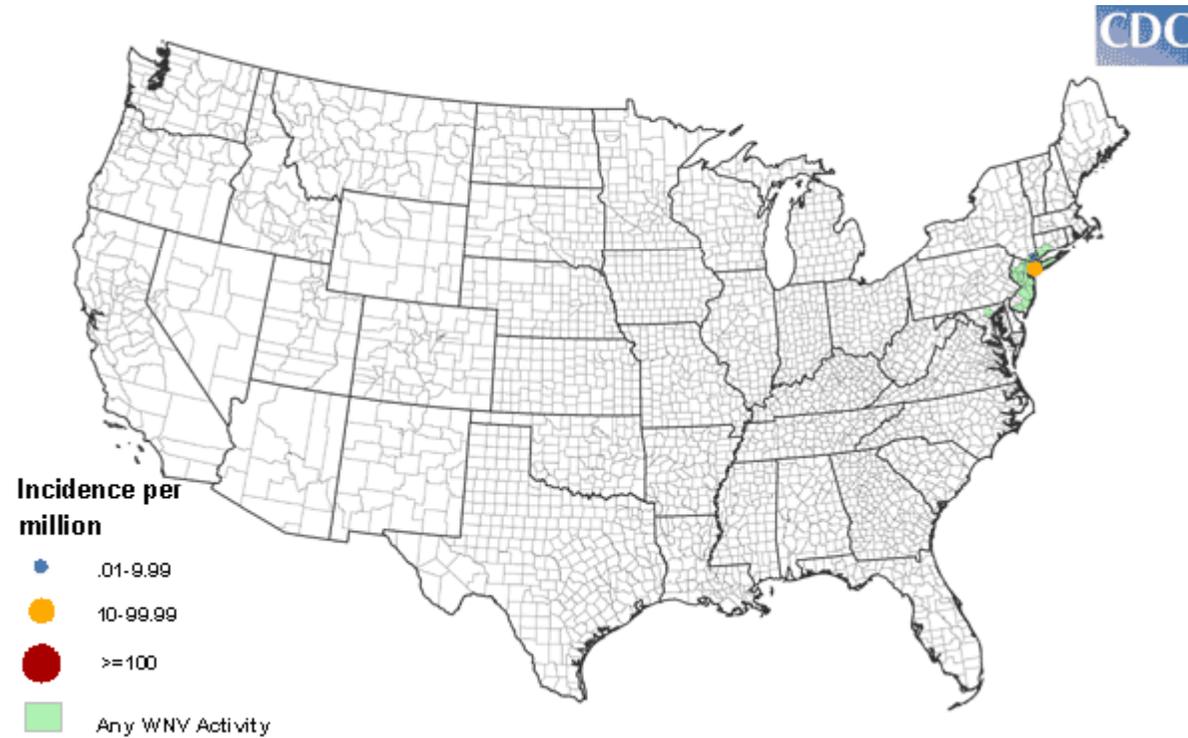
***Aedes albopictus*: Moustique tigre vecteur Chikungunya + Dengue**



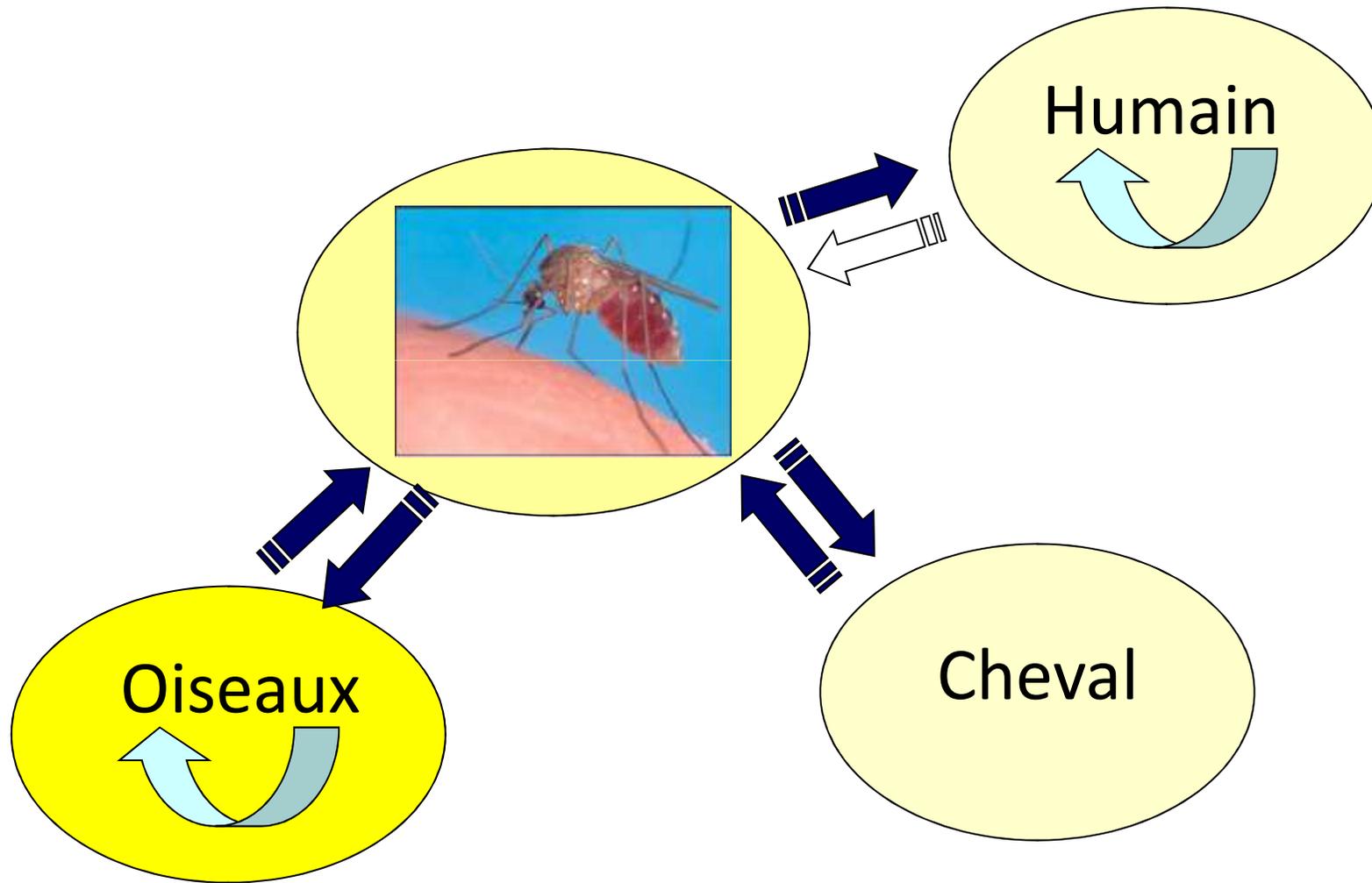
Septembre 2010, Nice, France: 2 cas de Dengue acquises localement, pas d'historique de voyage

2010, Key West, Floride: nombreux cas documentés, vecteur *A. aegypti*

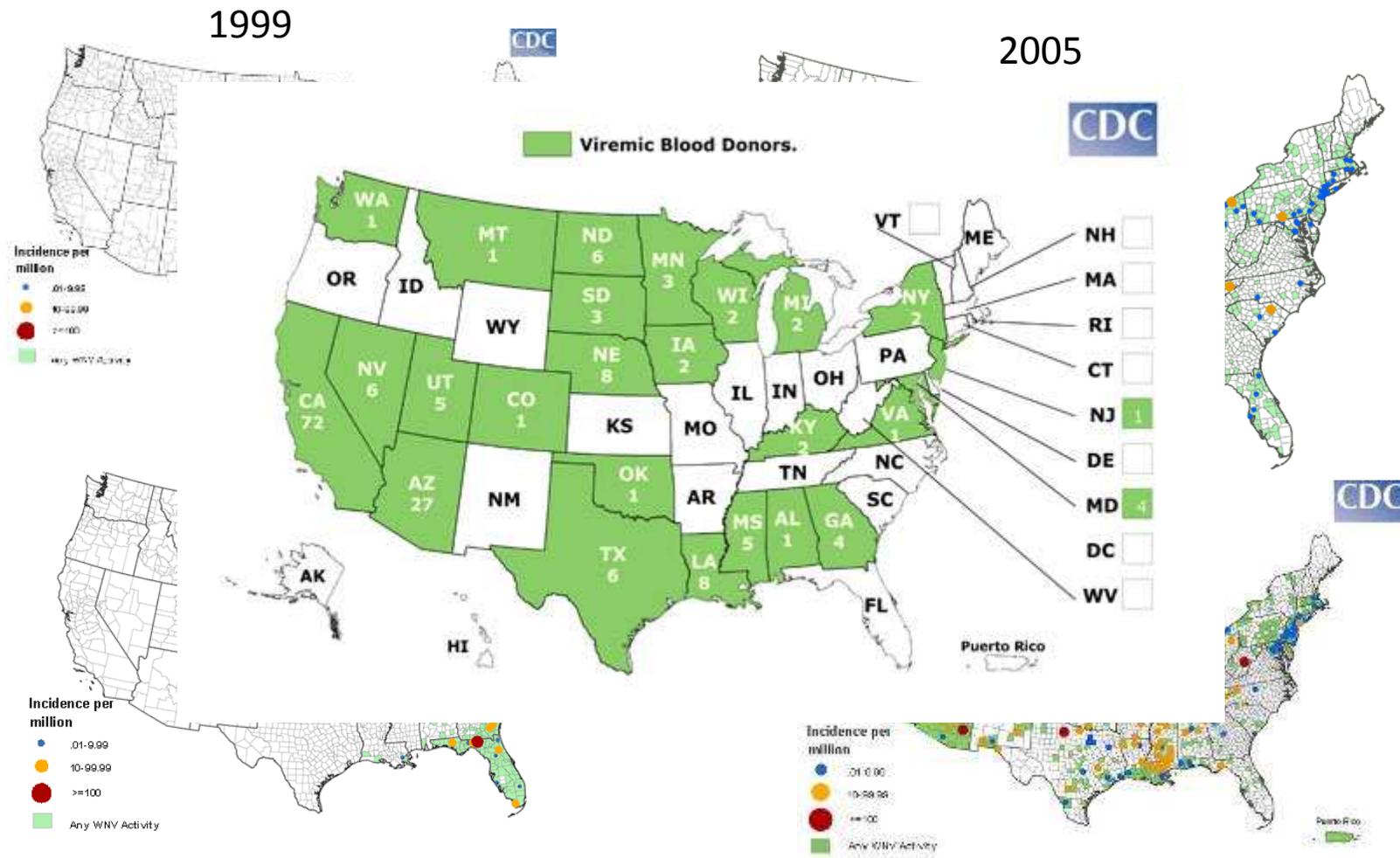
West Nile virus: NYC 1999



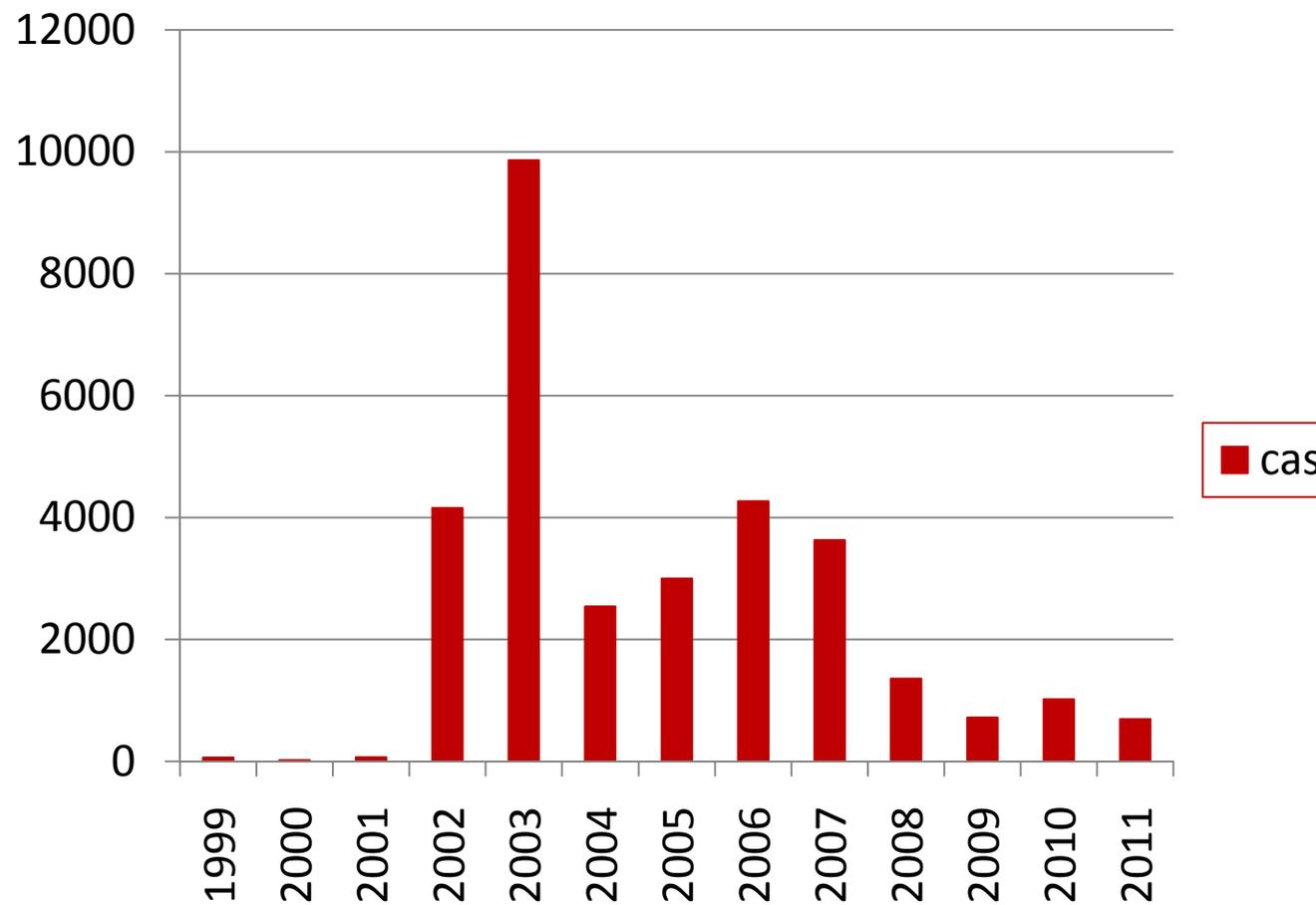
Transmissibilité et réservoir: West Nile



West Nile: USA 2008



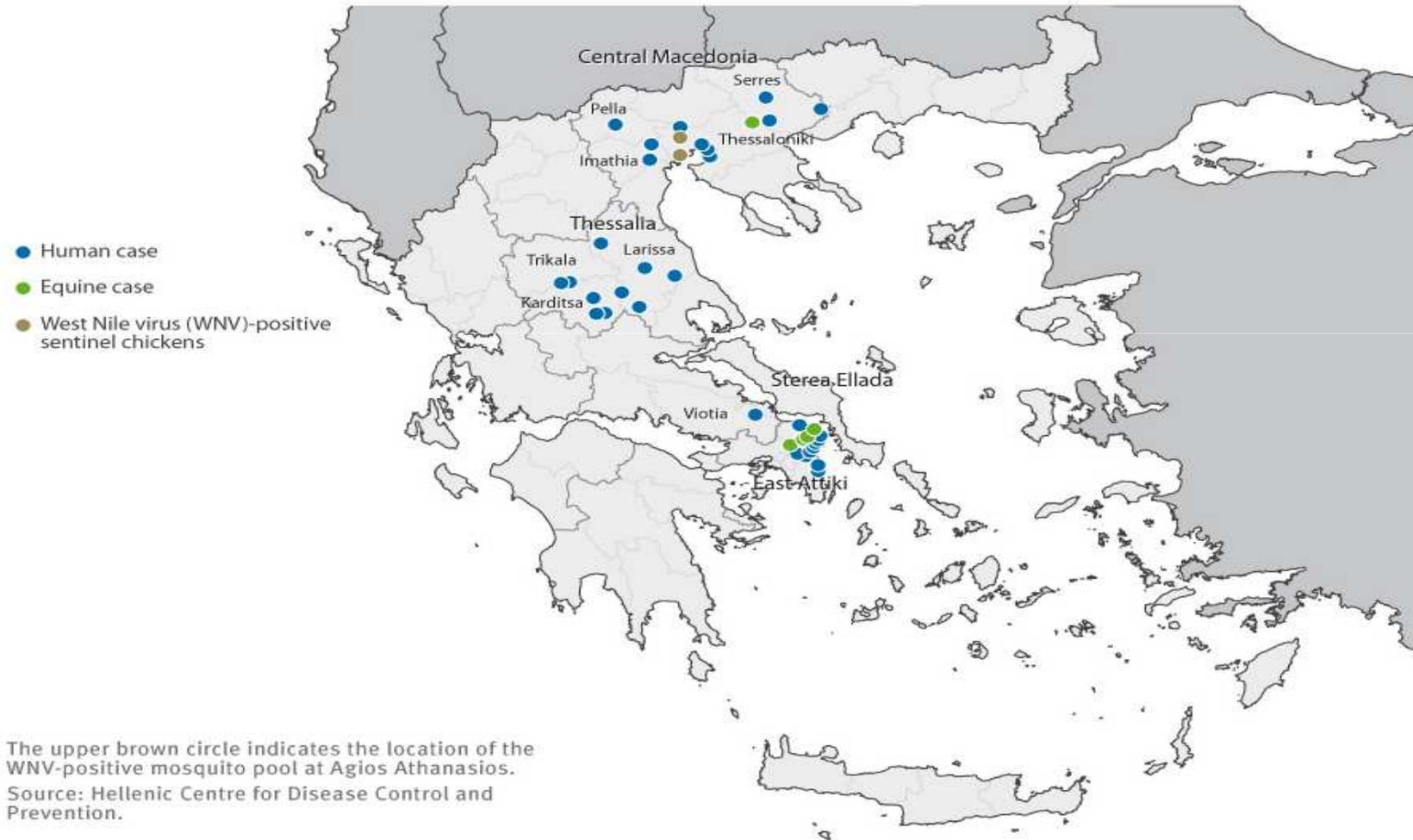
Nombre de cas humains de West Nile aux USA/an



Grèce 2011

FIGURE 2

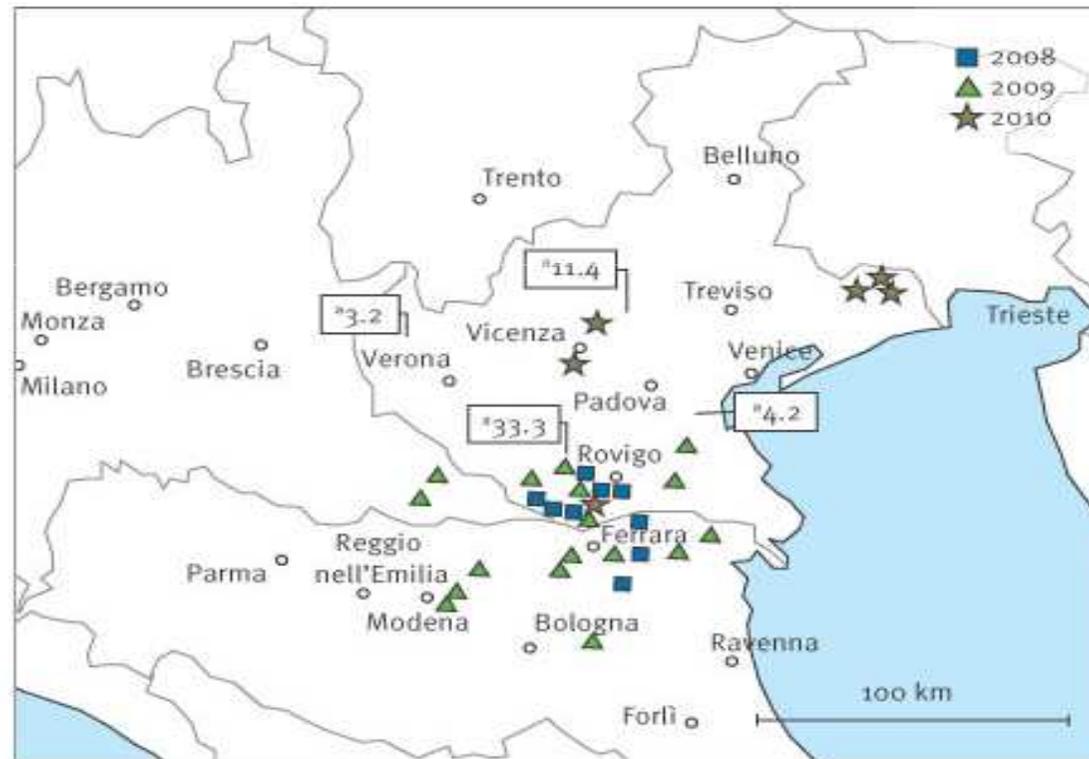
Place of residence of reported cases of West Nile neuroinvasive disease, Greece, 16 July – 21 August 2011 (n=31)



Italie 2008-2010

FIGURE

Map of north-eastern Italy representing autochthonous human cases of West Nile neuroinvasive disease and West Nile fever notified in Italy, 2008–2010 (n=32)

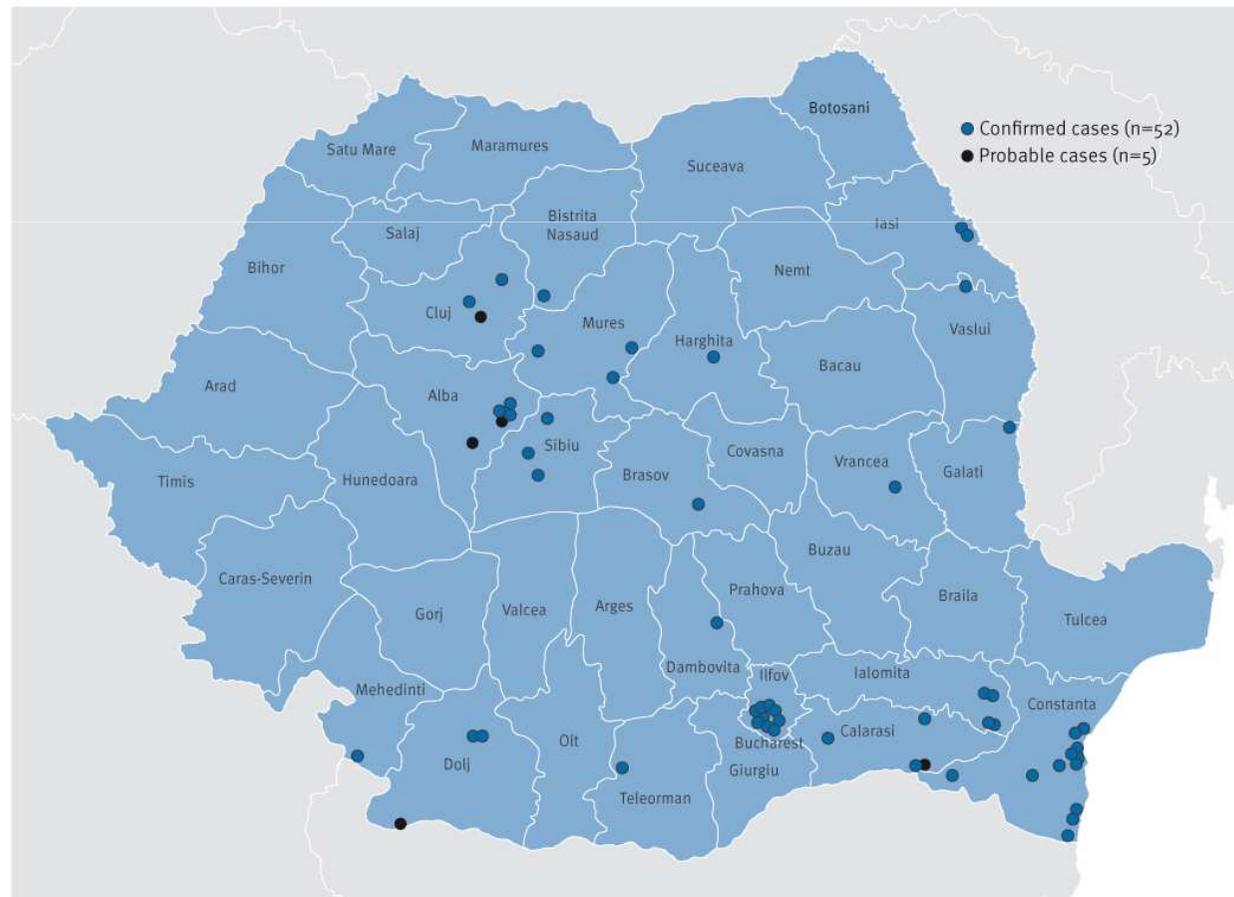


^a West Nile virus IgG antibody prevalence per 1,000 blood donors, determined in 2010 in four blood donor centres in Veneto.

Roumanie juillet-octobre 2010

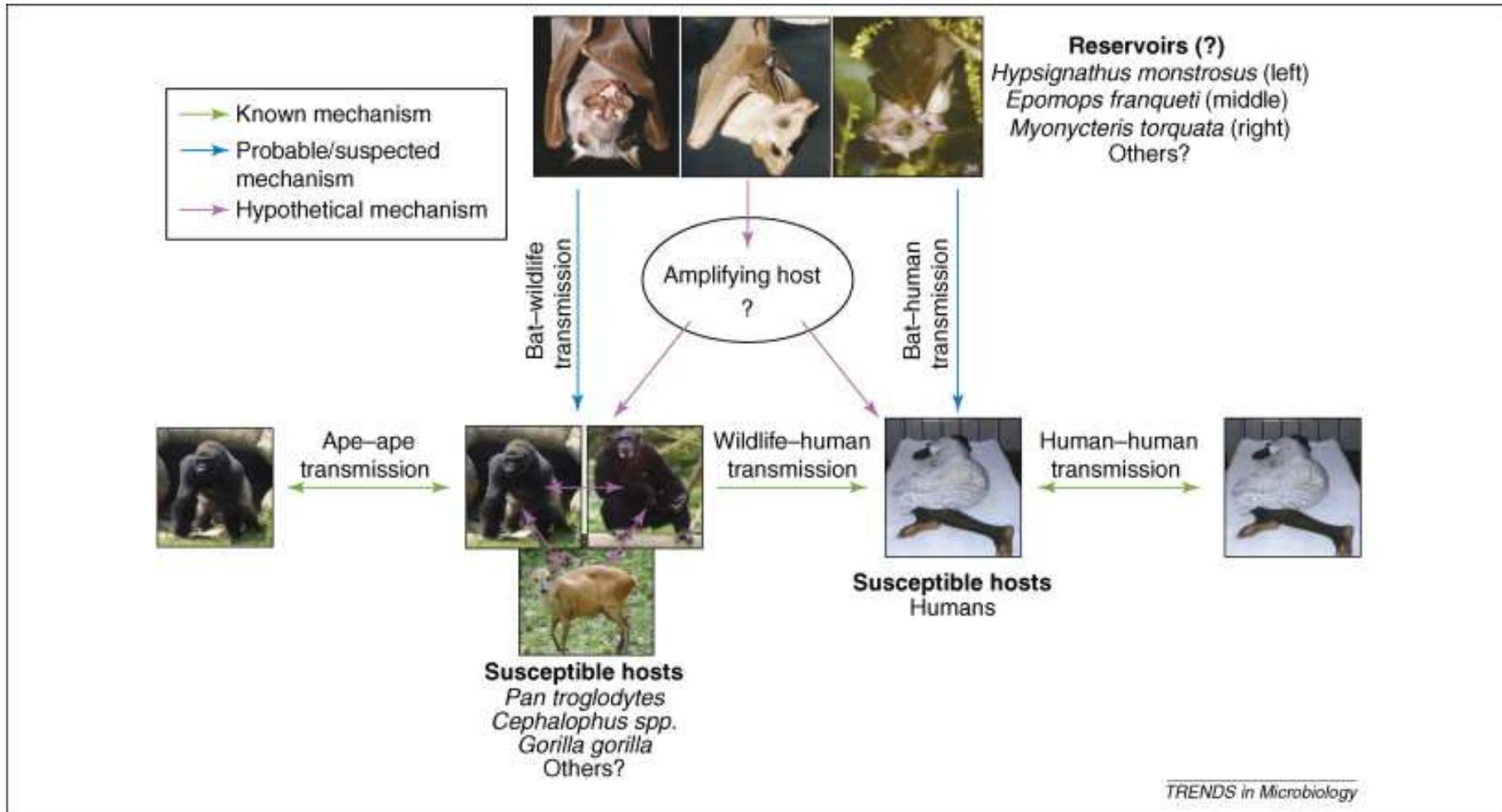
FIGURE 3

Distribution of cases of West Nile virus infection (probable and confirmed) by place of exposure, Romania, July – October 2010 (n=57)

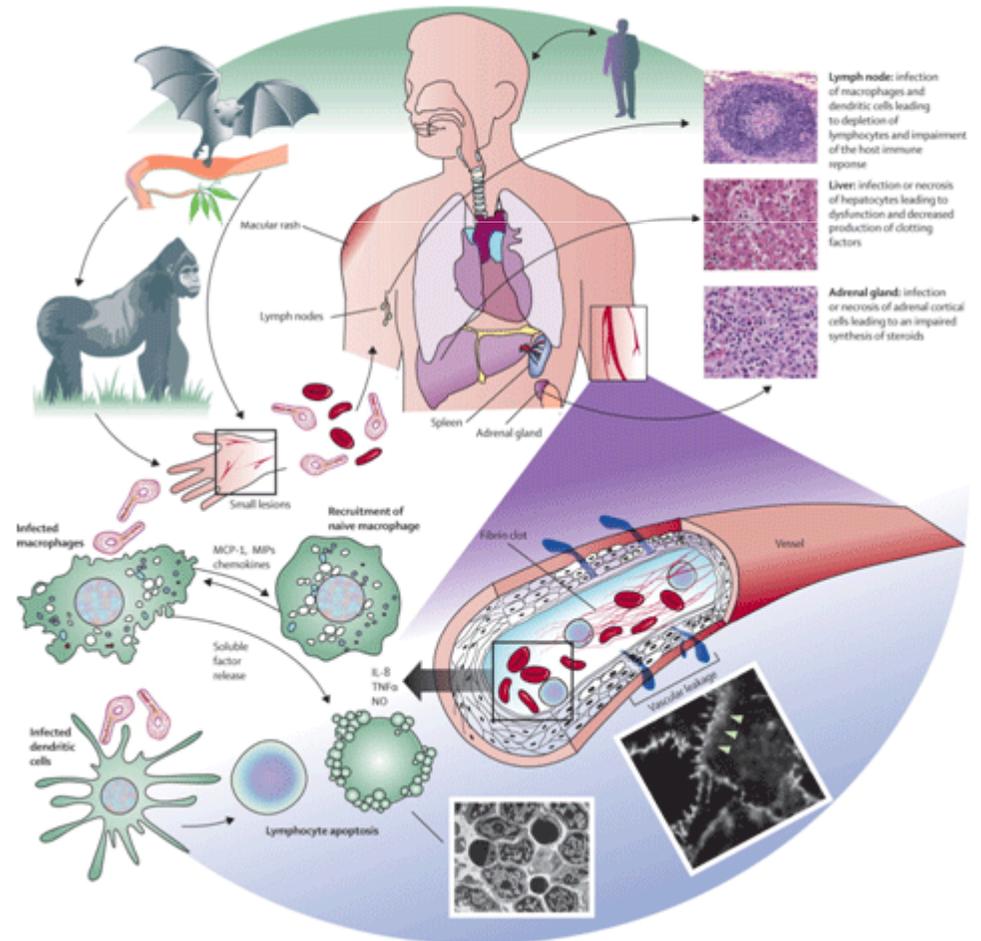


One dot represents one case.

Virus Ebola

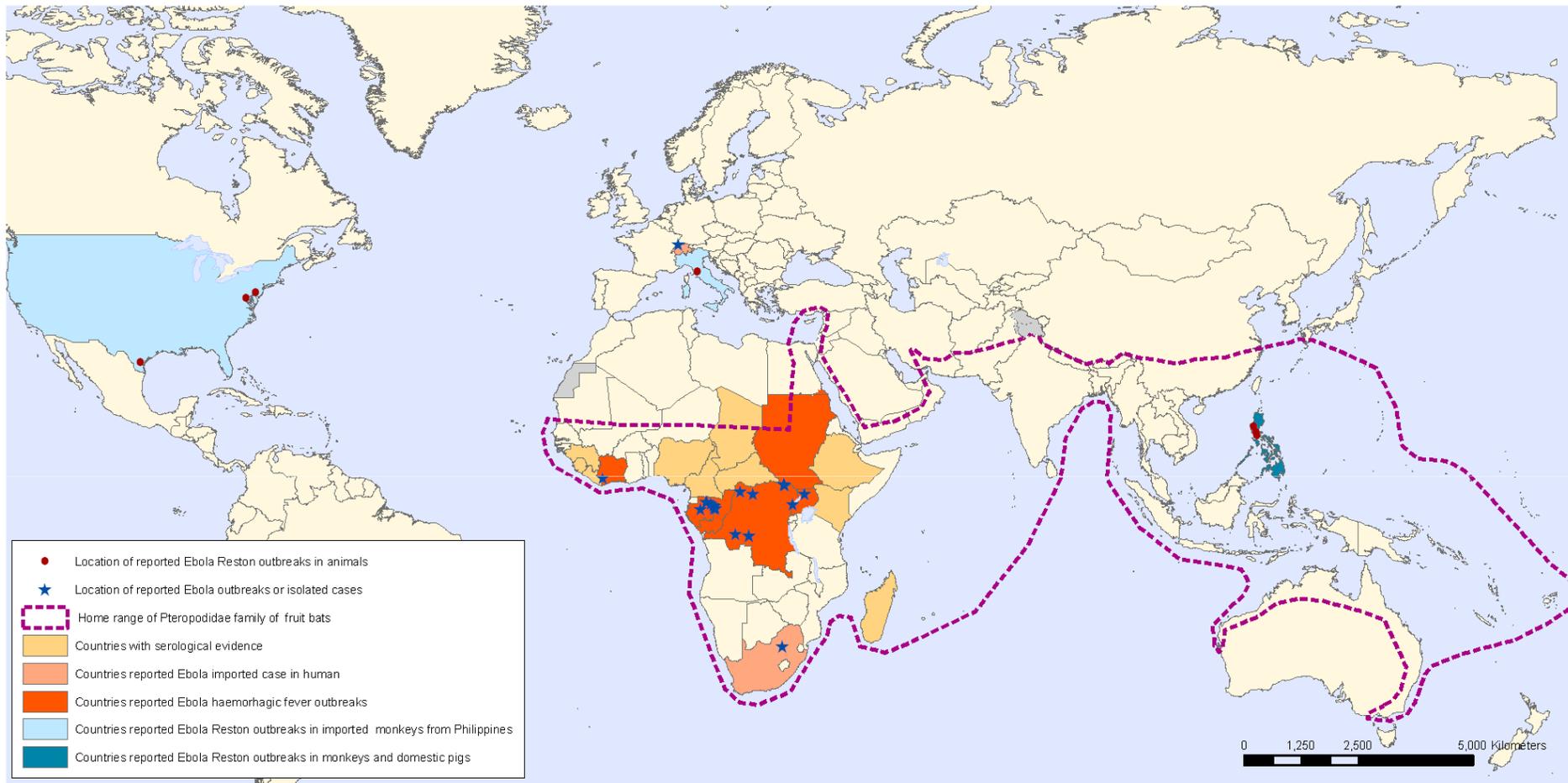


Trends in Microbiology Allison Groseth, Heinz Feldmann and James E. Strong
 Volume 15, Issue 9, September 2007, Pages 408-416



The Lancet, Early Online Publication, 16 November 2010

Geographic distribution of Ebola haemorrhagic fever outbreaks and fruit bats of Pteropodidae Family



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: Global Alert and Response Department
 World Health Organization
 Map Production: Public Health Information
 and Geographic Information Systems (GIS)
 World Health Organization



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Yosemite National Park Hantavirus Infection



- Total de 9 cas confirmés : 3 décès
- 8/9 exposés durant un séjour au Curry Village
- 1/9 exposé probablement durant un séjour au High Sierra Camps (25 km du Curry Village)



Rodents in the United States that Carry Hantavirus



Deer Mouse Habitat
(*Peromyscus maniculatus*)



Sin Nombre Virus



Cotton Rat Habitat
(*Sigmodon hispidus*)



Black Creek Canal virus



Rice Rat Habitat
(*Oryzomys palustris*)



Bayou virus



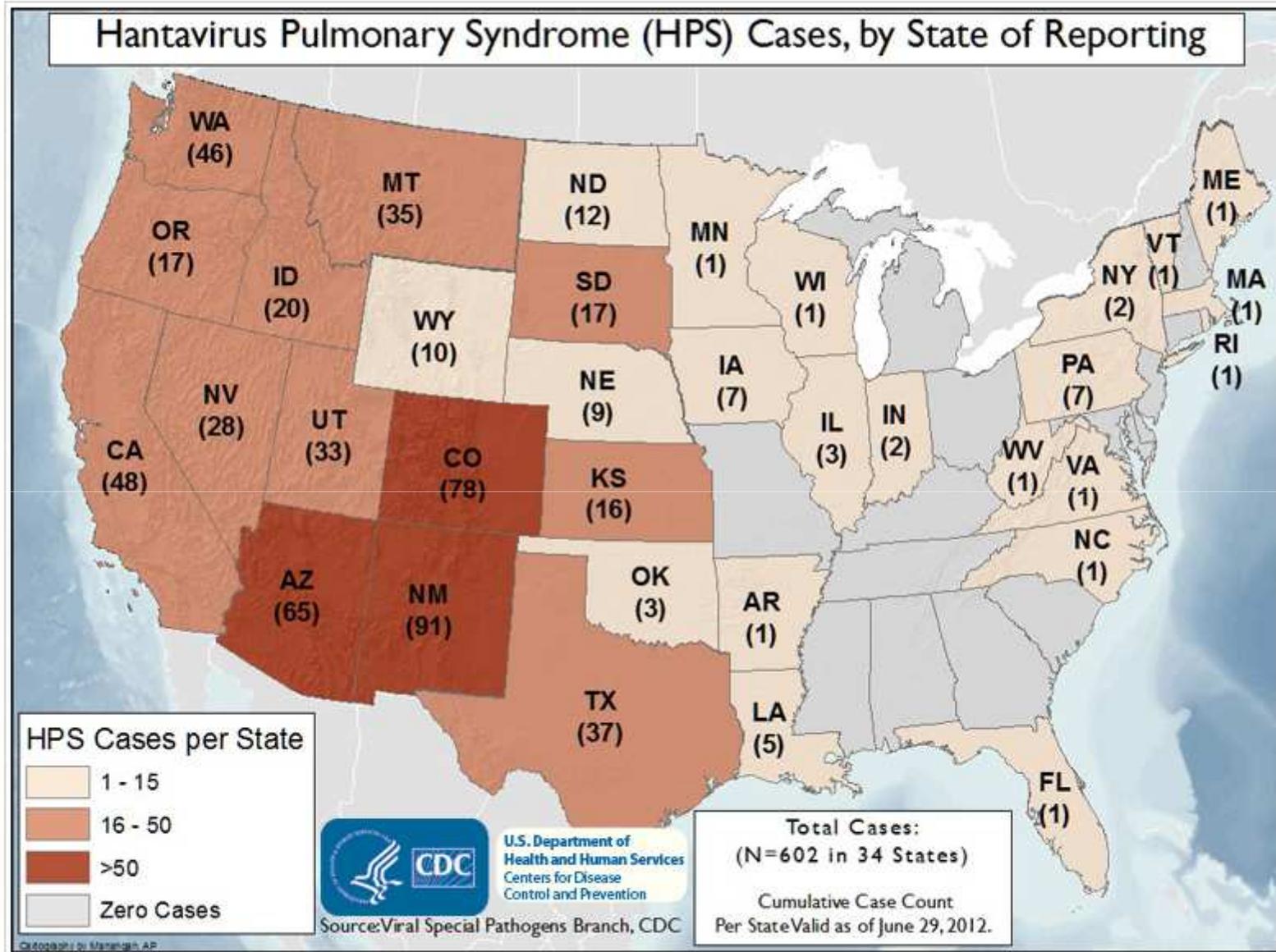
White-footed Mouse Habitat
(*Peromyscus leucopus*)



New York virus



U.S. HPS Cases, by Reporting State



Total Cases: 602 (Cumulative case count per state valid as of June 29, 2012)



Encéphalite à tiques

Peut être évité avec le vaccin FSME.

Pour enfants et adultes.

Aussi pour les voyageurs dans les régions d'endémie



Figure 1 : Tique *Ixodes ricinus* : stades

Larves

adulte femelle

Nymphes

1mm

World-wide

Distribution map of Western and Eastern subtypes of TBE virus



Literature: J. Suß (Hrsg.), 4th Potsdam Symposium on Tick-borne encephalitis (1997), data 2002 from National Health Institutes

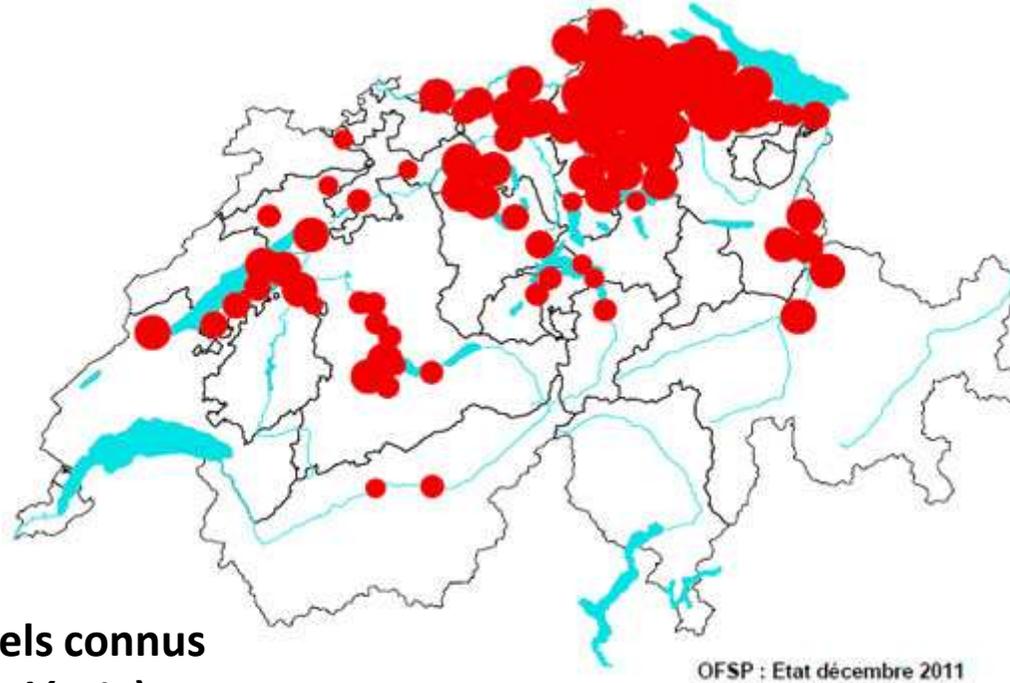
■ Eastern subtypes ■ Western subtype ■ both types

Ixodes ricinus: biotopes à risque

- Zones humides
- Forêts feuillus et mixtes (sous-bois), zones herbeuses (1.5m)
- Jardins: rare
- En général absent à plus de 1'000 m d'altitude
- Risque maximum: printemps et début automne
- Il existe un vaccin contre ce virus



Encéphalite virale à tique (OFSP): décembre 2012



**Foyers naturels connus
(régions d'endémie)**

Encéphalite à tiques	2011	2010	2009
Nombre de cas en Suisse	178	93	116

Rougeole, quelques chiffres (données OMS)

- En 2009 : 220'000 cas déclarés dans le monde
- En 2008 : 164'000 décès dans le monde = 18 par heure
- 95% des décès surviennent dans les pays possédant une mauvaise structure sanitaire
- La vaccination a permis de chuter de 78% le mortalité rougeoleuse entre 2000-2008
- > 83% des enfants dans le monde ont reçu au moins 1 dose de vaccin

Complications

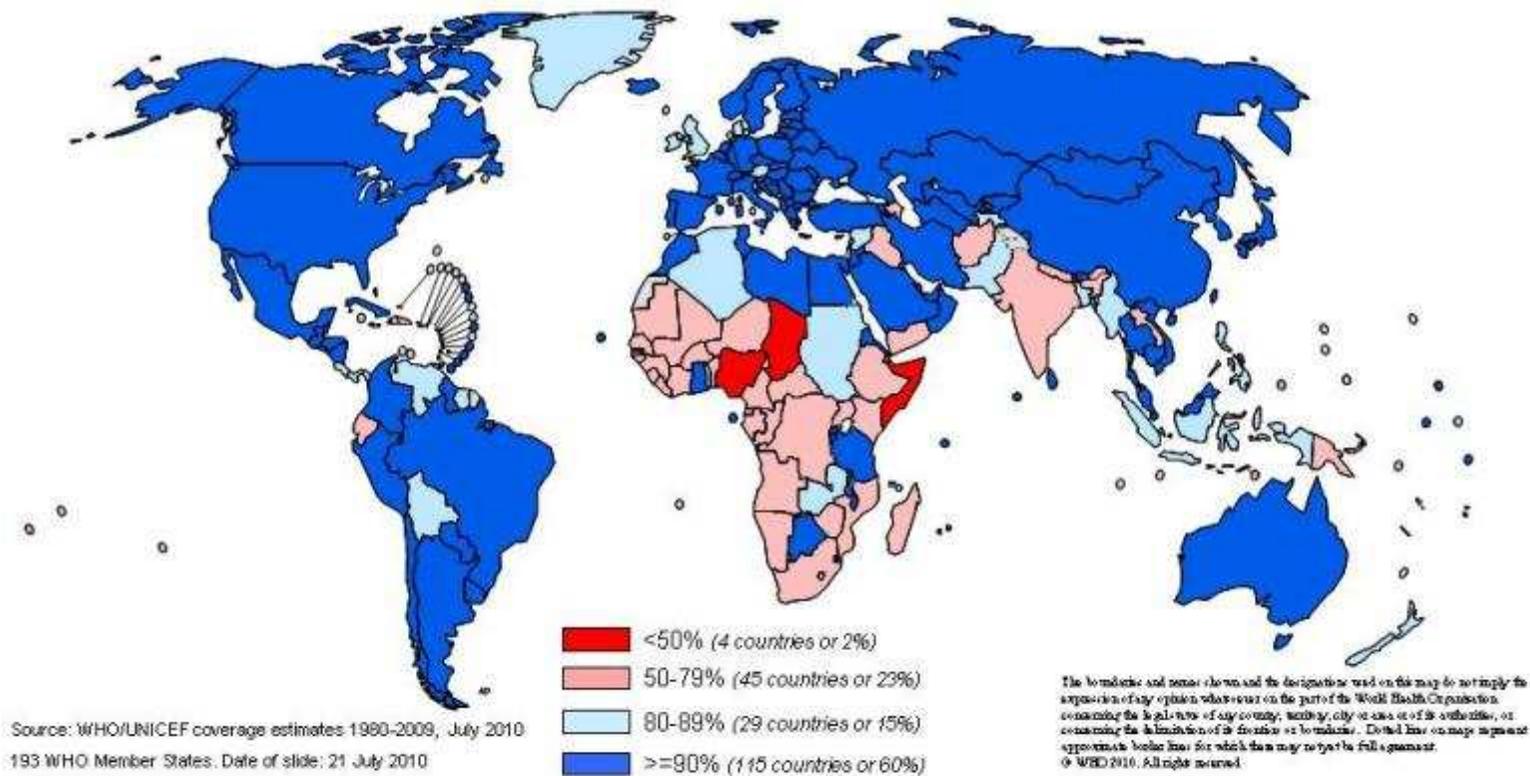
- Otite (7-9%)
- Pneumonie (6%)
- Diarrhée (6%)
- Encéphalite (très rares)

Encéphalomyélopathie (ADEM)(1/1000) → 5-30% †
→ ~30% séquelles

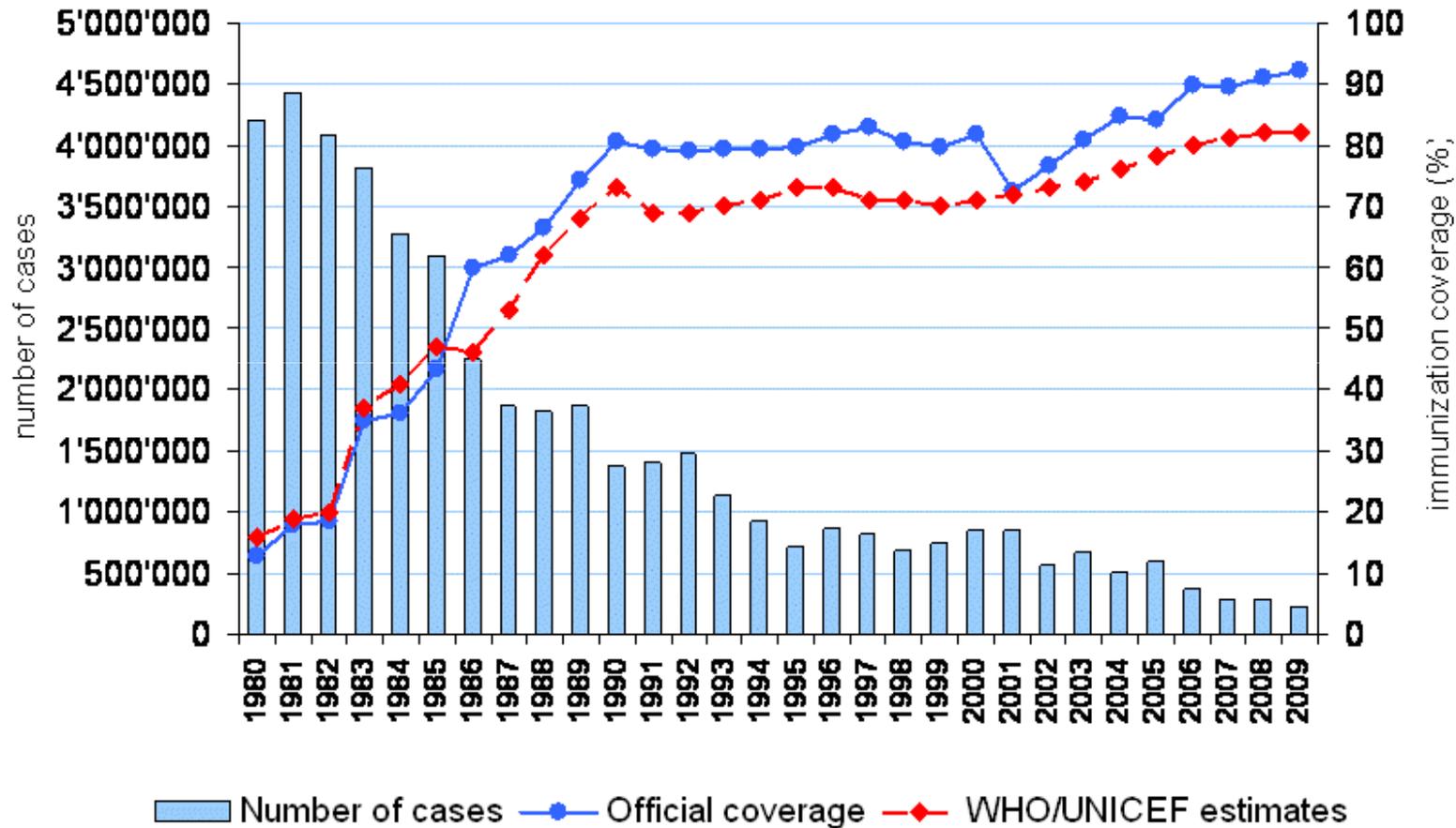
Encéphalite rougeoleuse à corps d'inclusion (MIBE, immunosupprimés)
→ ~100% †

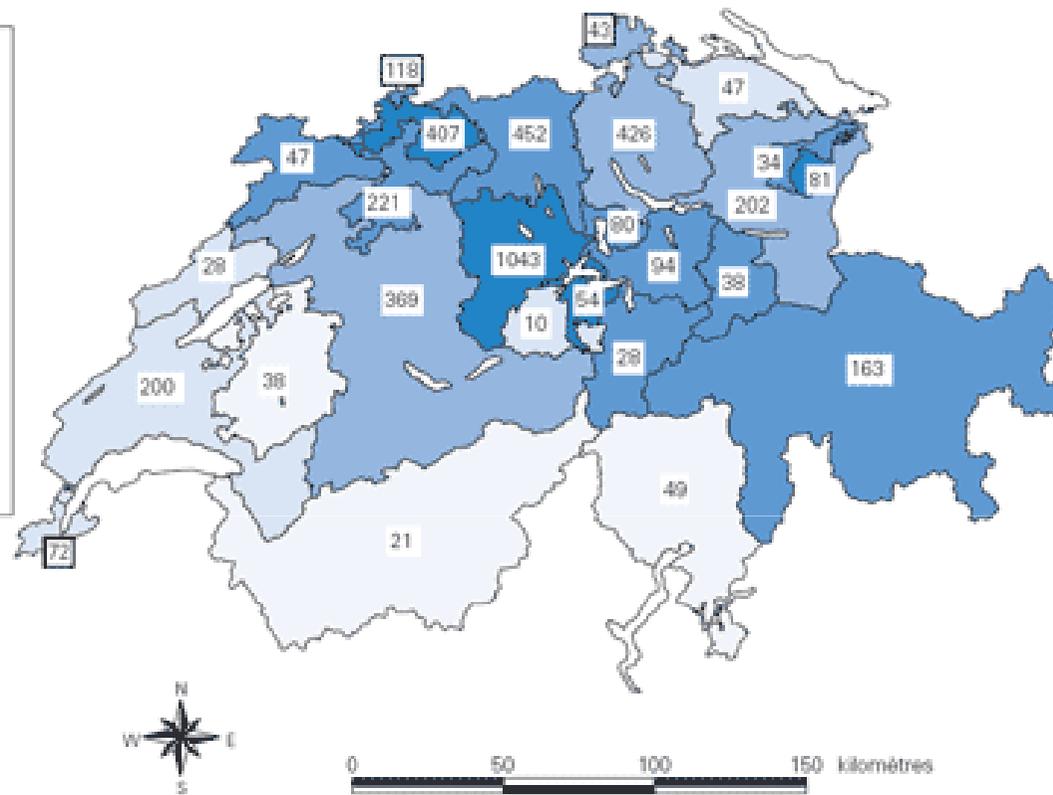
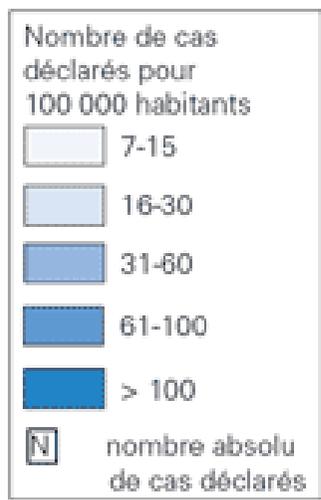
Panencéphalite sclérosante subaiguë (SSPE) (1/100000) → 100% †

Immunization coverage with measles containing vaccines in infants, 2009



Measles global annual reported cases and MCV coverage, 1980-2009





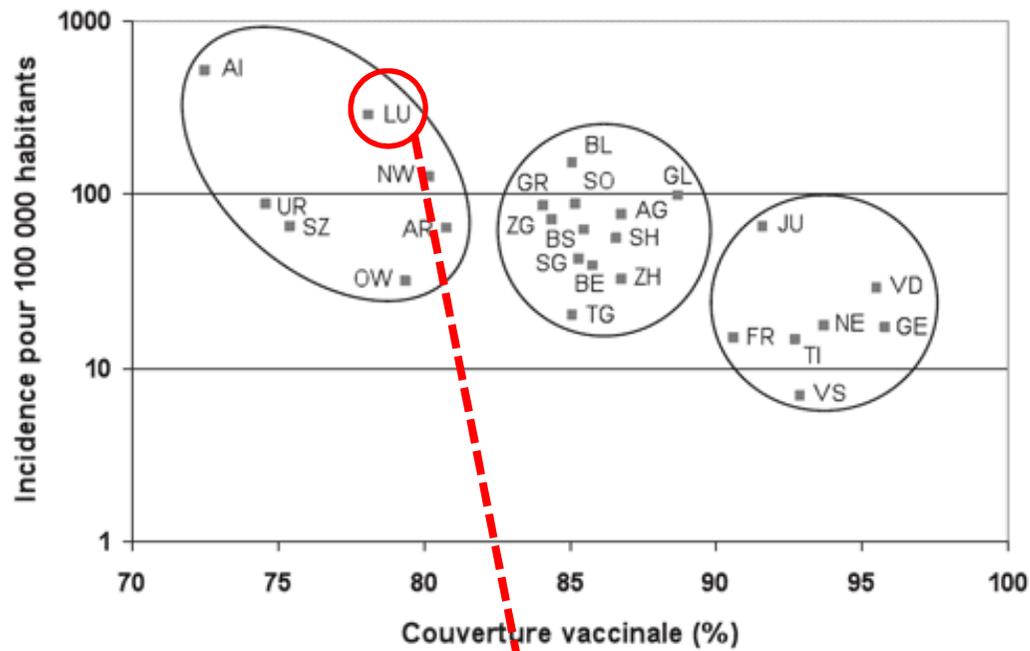
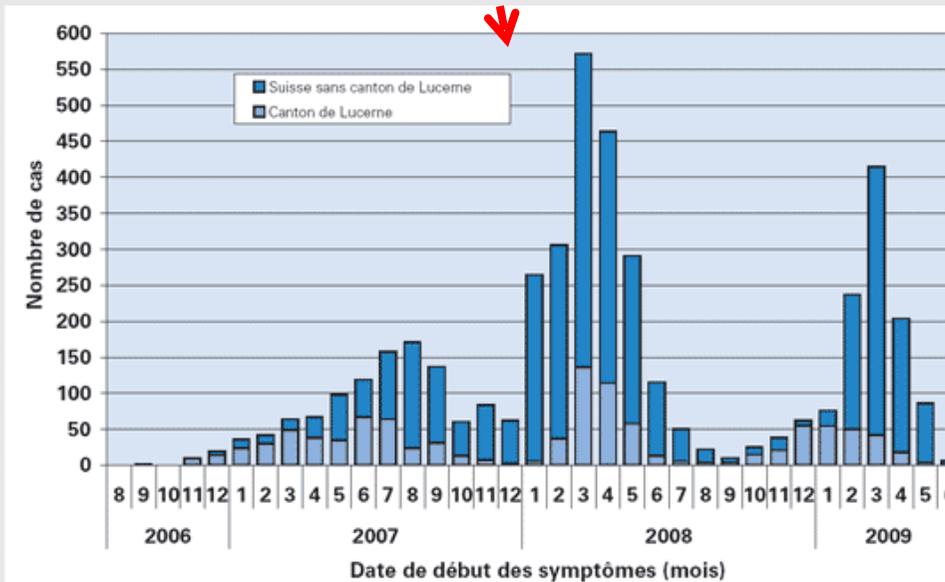


Figure 1: Nombre de cas de rougeole déclarés par mois en Suisse, du 1^{er} août 2006 au 9 juin 2009



Conclusions

Hot Spots for Emerging Diseases

Map shows an analysis of the future likelihood of infectious diseases originating in wildlife that have the potential to infect humans.



Factors in the analysis included population density, proximity to and variety of wildlife, and climate.



West Nile virus A mosquito-borne illness that causes symptoms in about a fifth of those exposed. One in 150 becomes severely ill with encephalitis.

ANIMAL RESERVOIR Various birds, especially robins in the U.S.

FIRST HUMAN CASE West Nile district of Uganda, 1937; first U.S. case was in Queens in 1999.

WHY IT EMERGED International air travel.

SUSCEPTIBLE HOSTS Humans; birds, especially crows; horses.



SARS A severe viral respiratory infection that quickly spread from China to more than two dozen countries. The outbreak was contained, and since 2004 no new cases have been reported.

ANIMAL RESERVOIR Horseshoe bats.

FIRST HUMAN CASE Guangdong Province, China, 2003.

WHY Wildlife markets and trade; global travel.

SUSCEPTIBLE Humans, civets (inset, left).



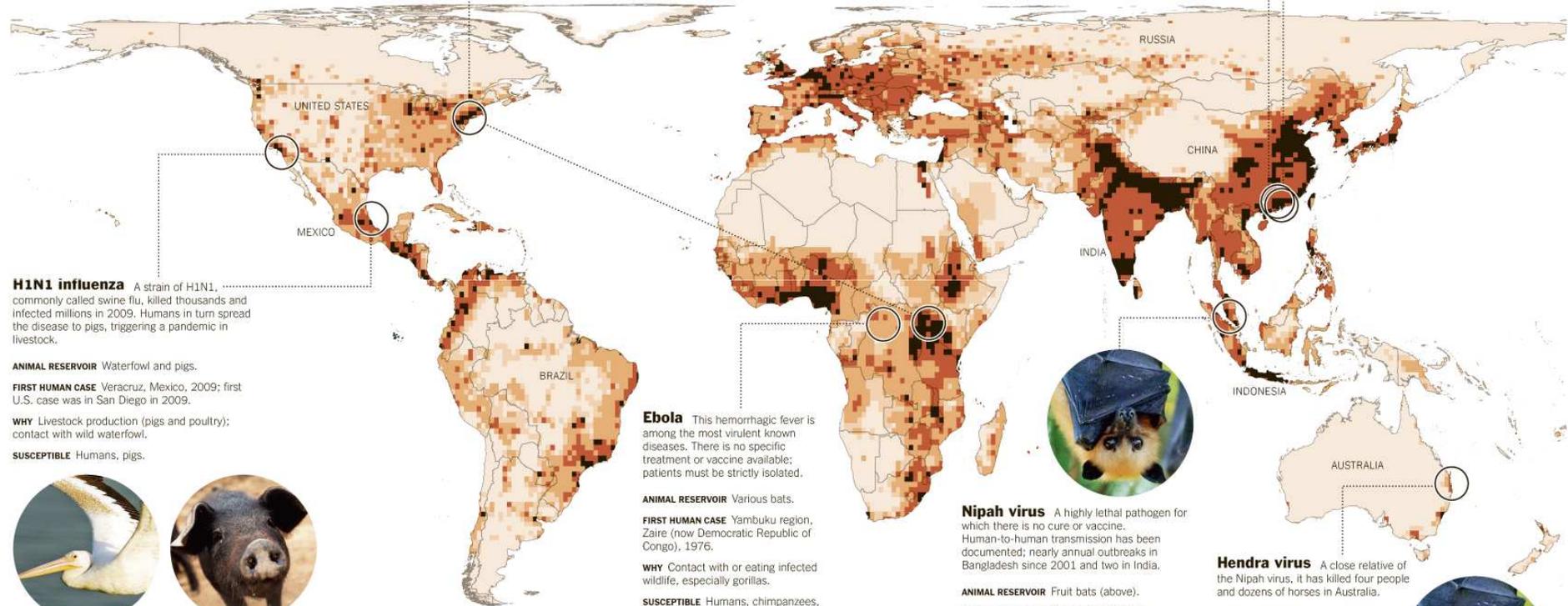
Bird flu A deadly strain of the avian influenza virus called H5N1 has spread to humans via contact with live or dead poultry.

ANIMAL RESERVOIR Wild waterfowl.

FIRST HUMAN CASE Hong Kong, 1997. It re-emerged widely in 2003 and 2004.

WHY Global expansion of intensive poultry farming; contact with infected birds.

SUSCEPTIBLE Humans, poultry, cats.



H1N1 influenza A strain of H1N1, commonly called swine flu, killed thousands and infected millions in 2009. Humans in turn spread the disease to pigs, triggering a pandemic in livestock.

ANIMAL RESERVOIR Waterfowl and pigs.

FIRST HUMAN CASE Veracruz, Mexico, 2009; first U.S. case was in San Diego in 2009.

WHY Livestock production (pigs and poultry); contact with wild waterfowl.

SUSCEPTIBLE Humans, pigs.



Ebola This hemorrhagic fever is among the most virulent known diseases. There is no specific treatment or vaccine available; patients must be strictly isolated.

ANIMAL RESERVOIR Various bats.

FIRST HUMAN CASE Yambuku region, Zaire (now Democratic Republic of Congo), 1976.

WHY Contact with or eating infected wildlife, especially gorillas.

SUSCEPTIBLE Humans, chimpanzees, gorillas, duikers (small African antelopes, below right).



Nipah virus A highly lethal pathogen for which there is no cure or vaccine. Human-to-human transmission has been documented; nearly annual outbreaks in Bangladesh since 2001 and two in India.

ANIMAL RESERVOIR Fruit bats (above).

FIRST HUMAN CASE Sungai Nipah, Negri Sembilan, Malaysia, 1998.

WHY Large-scale livestock production; presence of orchards on pig farms; date palm sap harvest (eating contaminated sap is a significant cause of infection).

SUSCEPTIBLE Humans, pigs, horses, dogs, cats.



Hendra virus A close relative of the Nipah virus, it has killed four people and dozens of horses in Australia.

ANIMAL RESERVOIR Fruit bats.

FIRST HUMAN CASE Hendra, a suburb of Brisbane, Australia, 1994.

WHY Urban encroachment of wild habitats.

SUSCEPTIBLE Humans, horses, dogs.



Prédictions et virus émergents

- West Nile virus
- SARS
- Chickungunya
- Influenza A H1N1d'origine porcine



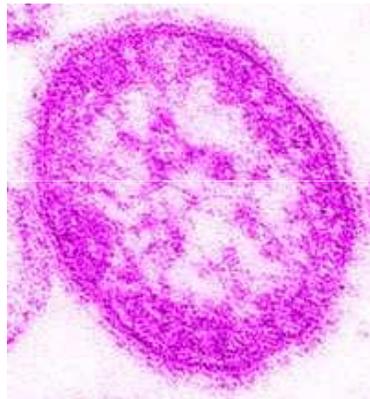
Conclusions: survie d'un virus

- Un virus persistera chez l'humain si les conditions suivantes sont présentes:
 - Réservoir ✓
 - Transmissibilité ✓
 - Population cible non protégée ✓
- Pas de cerveau, pas de stratégie mais une capacité évolutive

Méthodes de Diagnostique

La détection d'une infection virale

Méthodes directes



Détection directe:

- Microscopie électronique
- Détection d'un antigène
- Détection du génome

Méthodes indirectes

Sérologie:

- Dépistages des anticorps

Détection par culture:

- Effet cytopathogène (CPE)

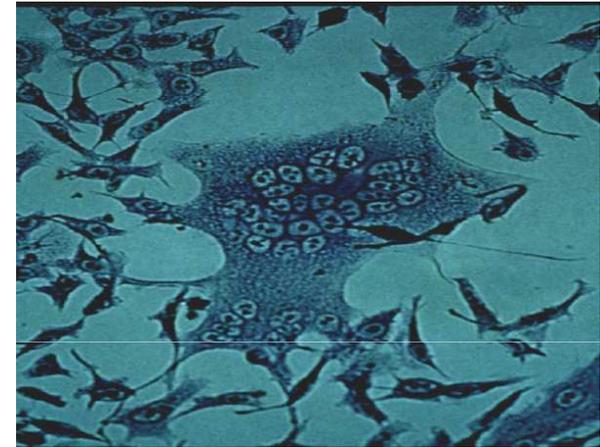
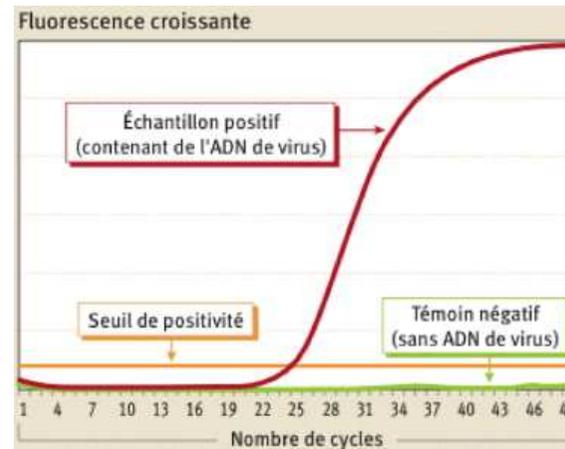
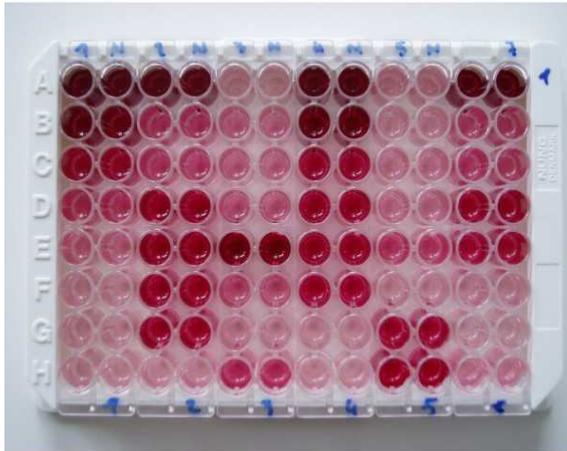
- Caractérisation

Diagnostic Routine

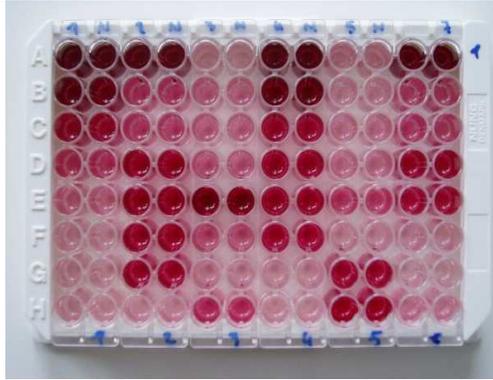
SEROLOGIE (ELISA)

PCR (real-time RT-PCR)

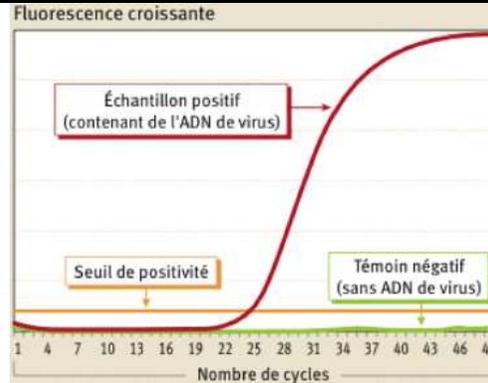
CULTURE (difficile)



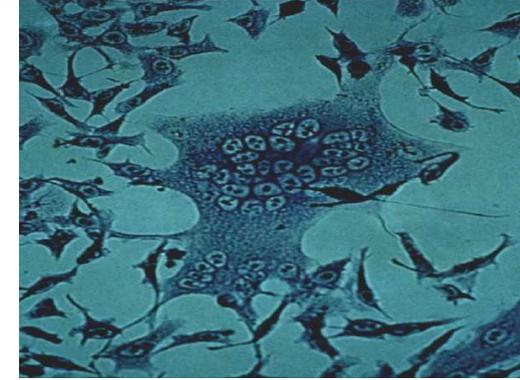
SEROLOGIE (ELISA)



PCR (real-time RT-PCR)



CULTURE (difficile)



Sérum

Plasma / Urine / LCR /
Frottis oropharyngés

Urine/ Frottis oropharyngés /
Lymphocytes sang périph.

Compter 2-6 heures

Compter 3-5 heures

Compter plusieurs jours

2 types d'Ag :

1) provenant de culture de cellules infectées (Vero)

2) provenant vecteur expression (baculovirus) = IgM/IgG contre nucléocapside → Ag de meilleure qualité

Cible généralement le gène de la nucléocapside

Cellules Vero (rein de singe), B95a

Bilan de grossesse (IgG)

Bilan de vaccination (IgG)

Diagnostique (IgM + IgG)
(ex. si rash présent)

Diagnostique
(avant/pendant/après rash)

Génotypage

Diagnostique
Se fait sur des prélèvements obtenus lors des stades prodromiques + éruptifs

Exemple du virus de la Dengue

Sérologies

IgM

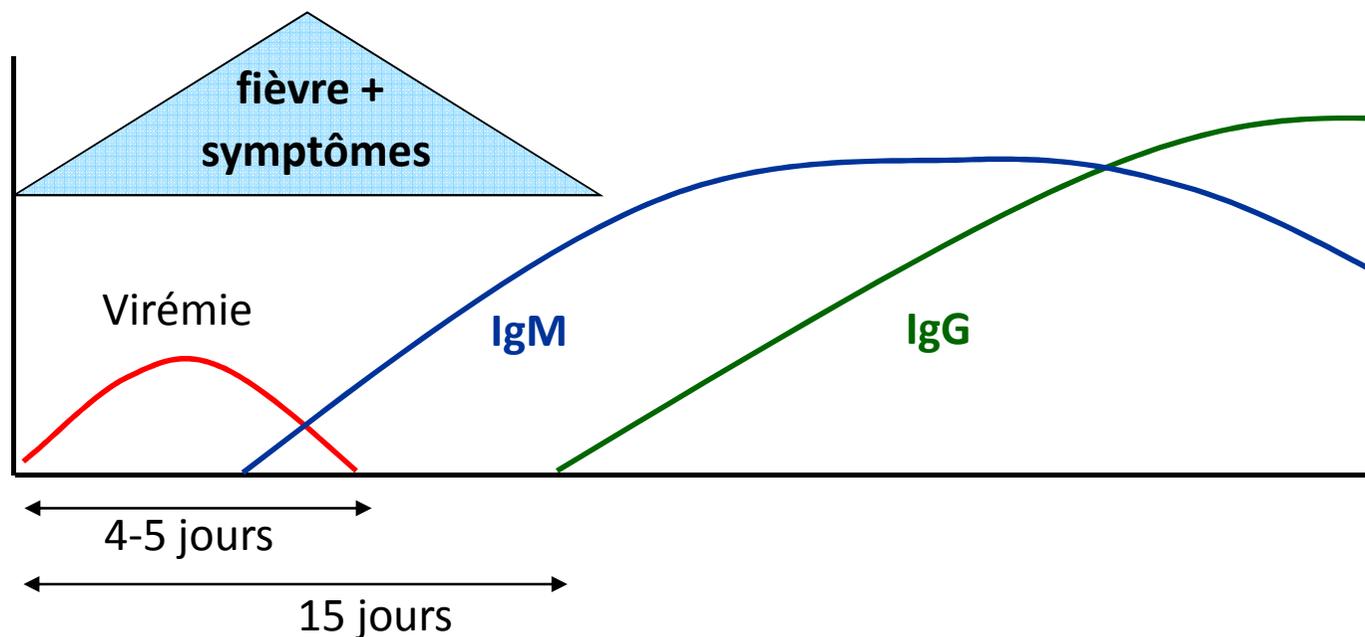
IgG

Relevant pour ce virus

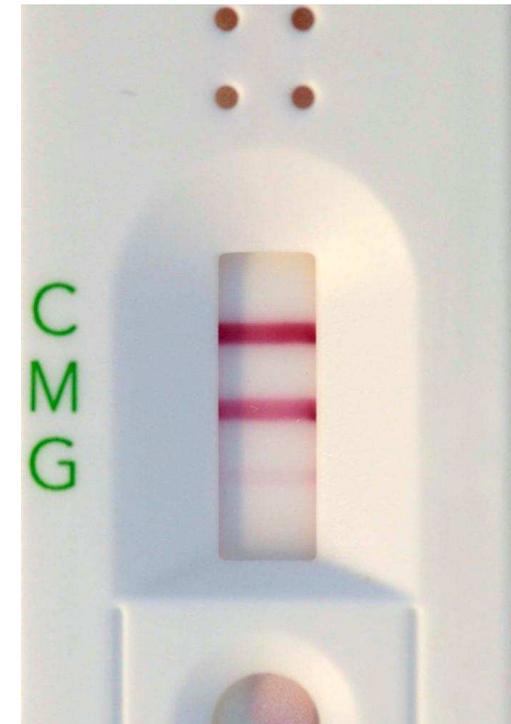
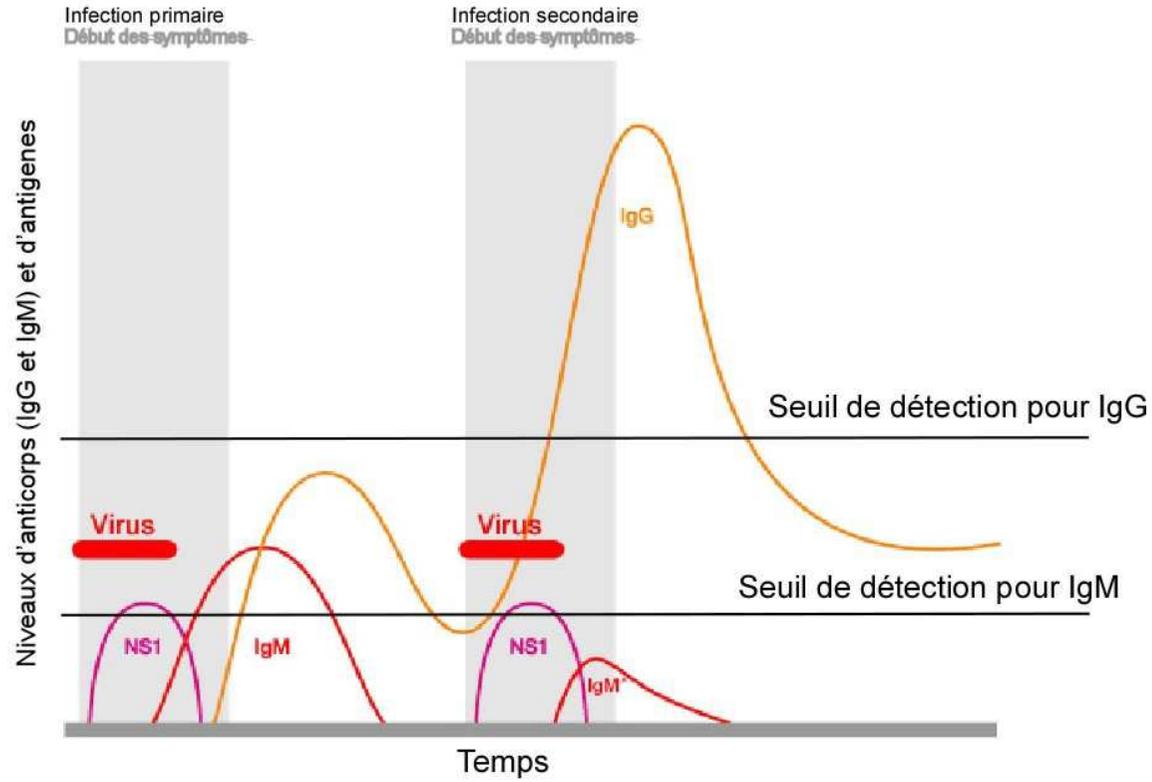
PCR



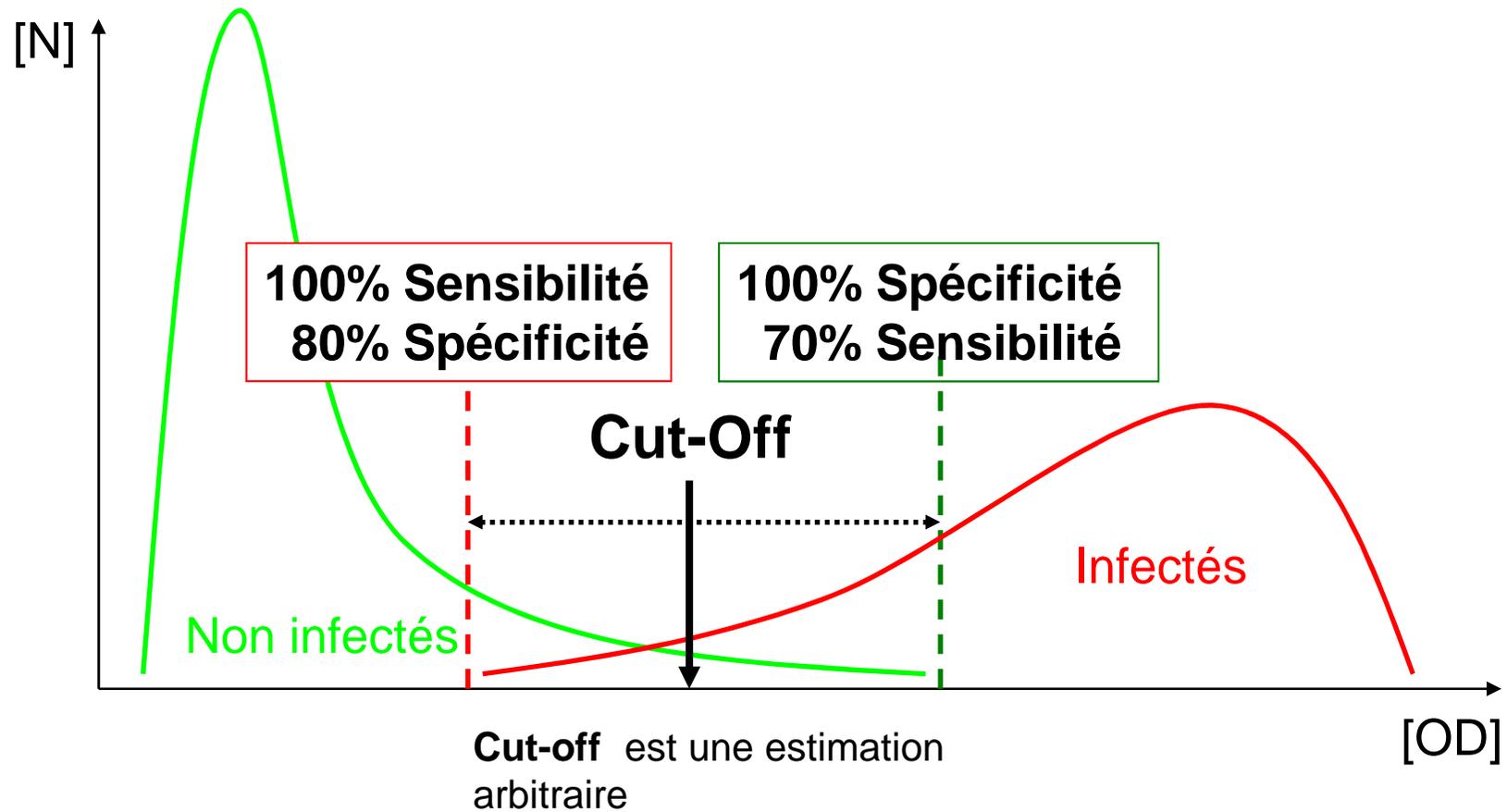
Peu de chance de détecter le virus après 5 jours



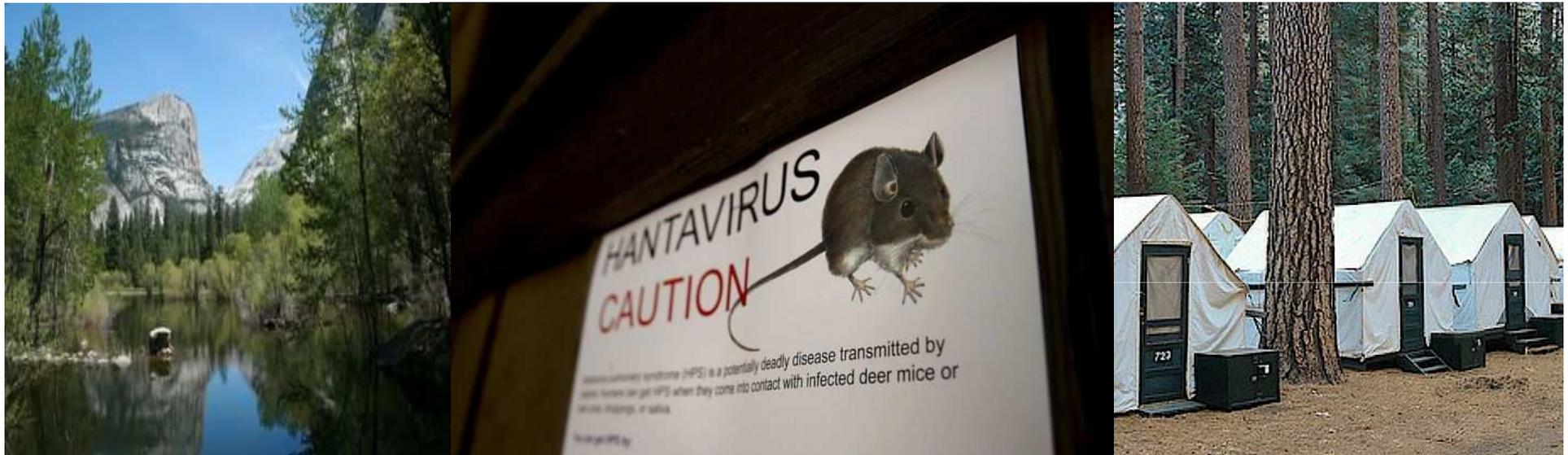
Profil typique de la réponse immunitaire contre le virus de la Dengue



ELISA: Sensibilité / Spécificité



Yosemite National Park Hantavirus Infection



- Total de 9 cas confirmés : 3 décès
- 8/9 exposés durant leur séjour au Curry Village
- 1/9 exposé probablement durant un séjour au High Sierra Camps (25 km du Curry Village)



Characteristics of Some Known Hantaviruses

Hantaviruses	Geographic Region	Reservoir	Pathology	Mortality
Hantaan	Asia	Field mouse	Renal	5-15%
Seoul	Worldwide	Domestic rat	Renal	1%
Puumala	Northern Europe	Bank vole	Renal	1%
Prospect Hill	United States	Meadow vole	No known human disease	N/A
Sin Nombre	North America	Deer mouse	Pulmonary	50%

Comparison of HFRS and HPS

Feature	HFRS	HPS
Major target organ	Kidney	Lung
First phase	Febrile	Febrile "prodrome"
Second phase	Shock	Shock, pulmonary edema
Evolution	Oliguria, diureses, convalescence	Diureses, convalescence
Mortality	1-15%	50%

Early Symptoms



- Fever
- Headaches
- Muscle aches
- Stomach problems
- Dizziness
- Chills

- Late Symptoms**
- Low blood pressure
 - Acute shock
 - Vascular leakage
 - Acute kidney failure

Early Symptoms

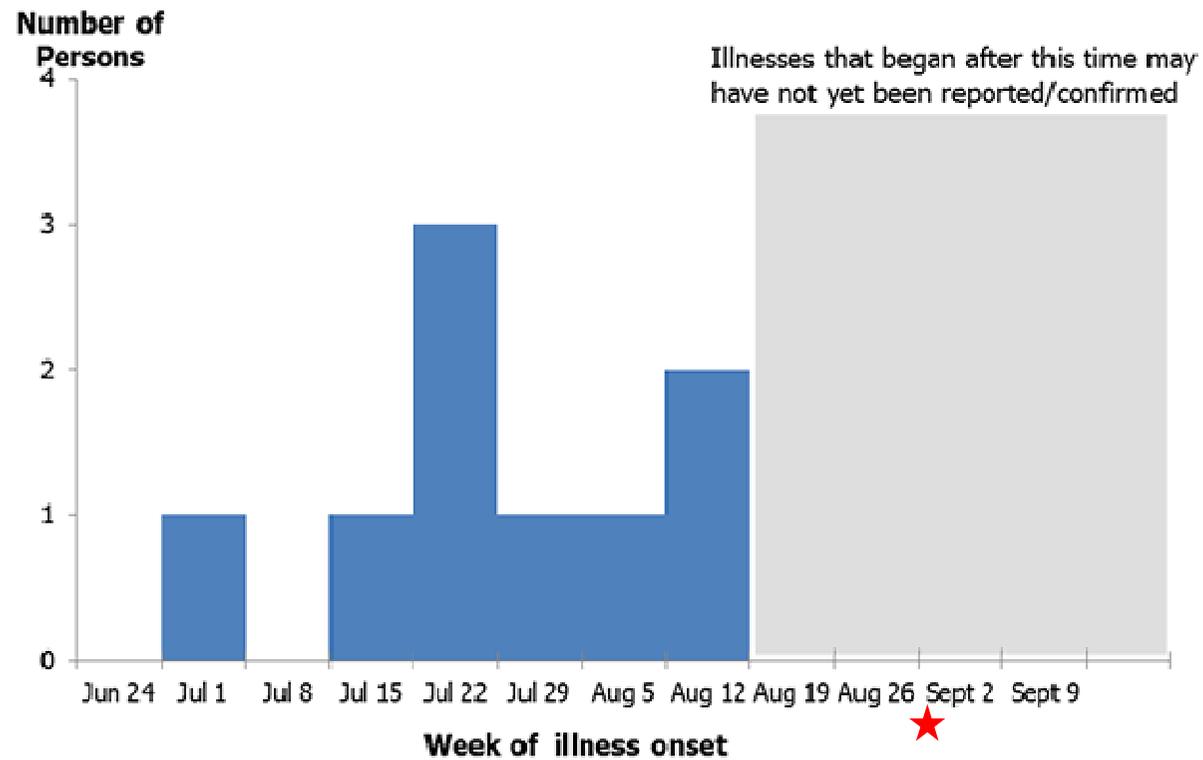


- Fever
- Headaches
- Muscle aches
- Stomach problems
- Dizziness
- Chills

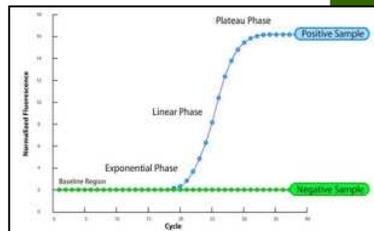
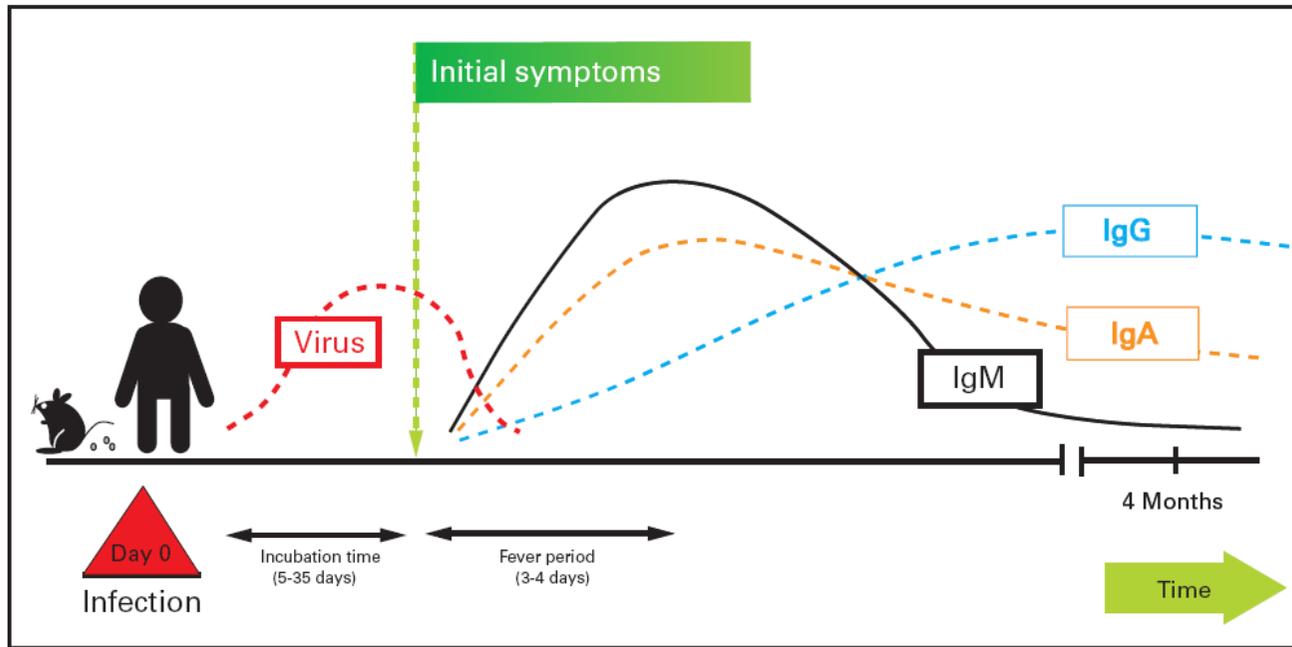
Late Symptoms



- Lungs fill with fluid
- Shortness of breath

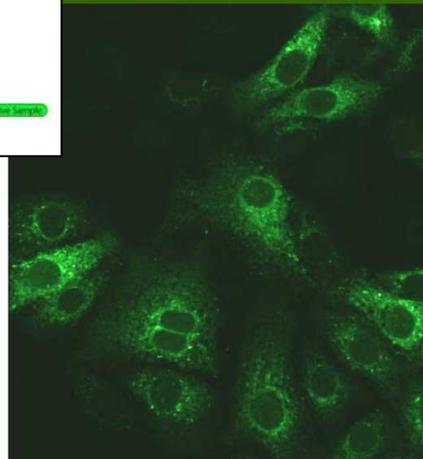


~2 mois entre 1er cas et alerte CDC



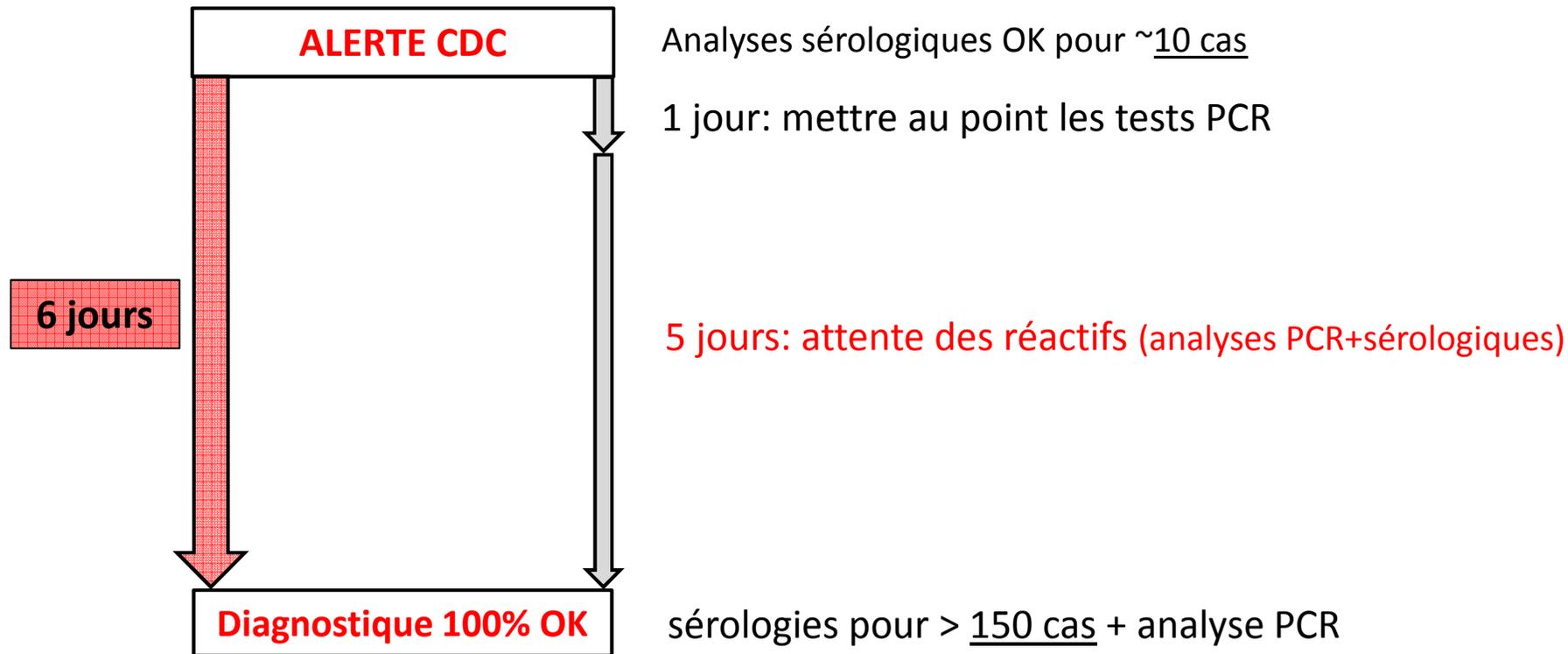
IIFT: Hantavirus Mosaic 1 (IgG or IgM)

- Nested PCR : Pan-hantavirus
- Nested PCR : Sin Nombre Specific
- 2 Real-time PCR : Sin Nombre Specific



EUROIMMUN HANTAVIRUS MOSAIC 1	
Hantaan virus (HTNV)	Sin Nombre virus (SNV)
Puumala virus (PUUV)	Dobrava virus (DOBV)
Seoul virus (SEOV)	Saaremaa virus (SAAV)

Sin Nombre
Dobrava
Puumala
Haantan
Seoul
Saaremaa



2 Biologistes 100% + 1 Technicien de laboratoire

MERCI

