



Maladies
infectieuses



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Les virus respiratoires émergents font de la résistance

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Liens d'interet

President du conseil scientifique du Global Influenza Initiative

Président du conseil scientifique du comité scientifique indépendant du Global Influenza Hospital Surveillance Network

Président du conseil scientifique d'Immuniser-Lyon

Président du Comité scientifique AuRA pour le COVID-19

Membre du conseil Scientifique COVID-19

Aucune de ces activités n'est rémunérée

Les histoires d'introduction des coronavirus

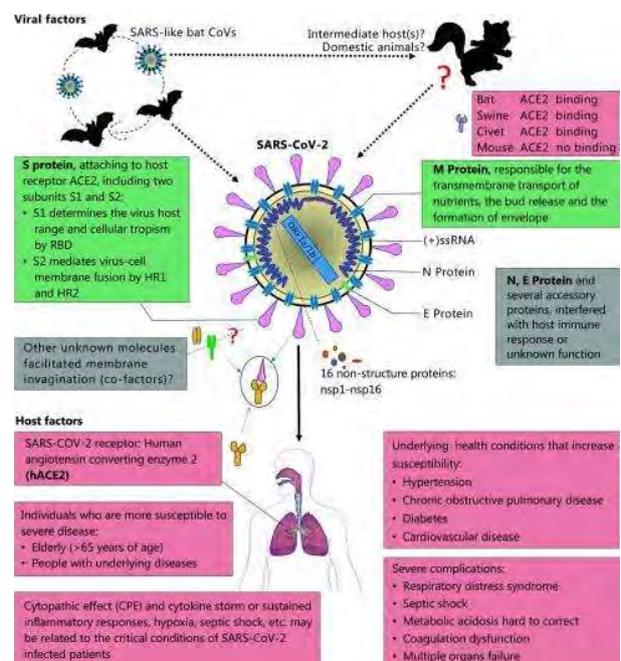
Coronavirus humain (HCoV)	Origine possible (hypothèse)	Hôte intermédiaire identifié	Date d'émergence (détermination ou MRCA)	Circulation chez l'humain
HCoV-229E <i>Alphacoronavirus</i>		 Camelidae, <i>Alpaca</i> sp.	Début XIX ^e siècle	Ubiquitaire, saisonnier
HCoV-NL63 <i>Alphacoronavirus</i>		?	XIII ^e siècle	Ubiquitaire, saisonnier
HCoV-OC43 <i>Betacoronavirus</i> Clade A	 ?	 Bovidae	Fin XIX ^e siècle	Ubiquitaire, saisonnier
HCoV-HKU1 <i>Betacoronavirus</i> Clade A	 ?	 ?	?	Ubiquitaire, saisonnier
SARS-CoV <i>Betacoronavirus</i> Clade B		 <i>Paguma larva</i> 'a (civette)	2002	Pandémie décembre 2002 – juillet 2003 Arrêt de la circulation
MERS-CoV <i>Betacoronavirus</i> Clade C		 <i>Camelus dromedarius</i>	2012	Circulation péninsule arabique. Risque pandémique lié aux voyages

Les récepteurs utilisés par les différents coronavirus humains

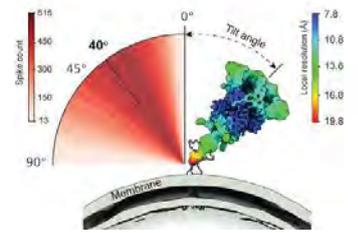
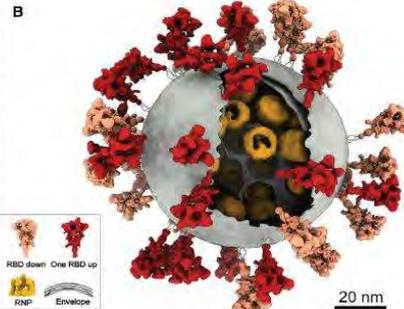
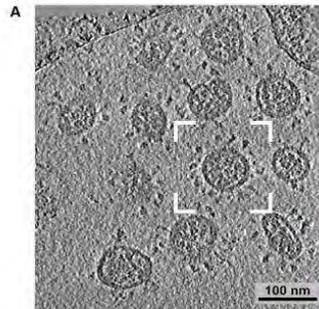
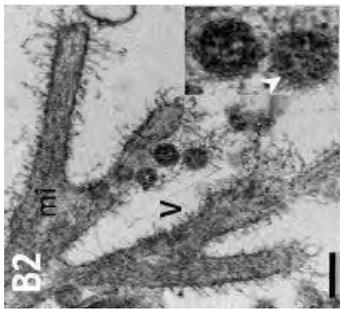
Coronavirus humains (HCoV)	Année d'identification du virus	Récepteur cellulaire identifié	Site de liaison au récepteur sur la protéine S (résidus)
HCoV-229E	1966	<i>Aminopeptidase N</i> (hAPN)	407- 547
HCoV-OC43	1967	<i>N-acetyl-9-O-acetyl neuraminic acid</i> (NEU 5,9 AC2)	Non connu
SARS-CoV	2003	<i>Angiotensin converting enzyme 2</i> (ACE2)	303 - 537
HCoV-NL63	2004	<i>Angiotensin converting enzyme 2</i> (ACE2)	476 - 616
HCoV-HKU1	2005	Non connu	Non connu
MERS-CoV	2012	<i>Dipeptidyl peptidase 4</i> (DPP4)	358 - 588

The path to humans

A WHO team is on its way to China to decipher the early events and the missing link



Le Virus



Pizzorno MA et al, 2020, Yao H et al, 2020

Phylogénie genome entier des précurseurs de SARS-CoV-2



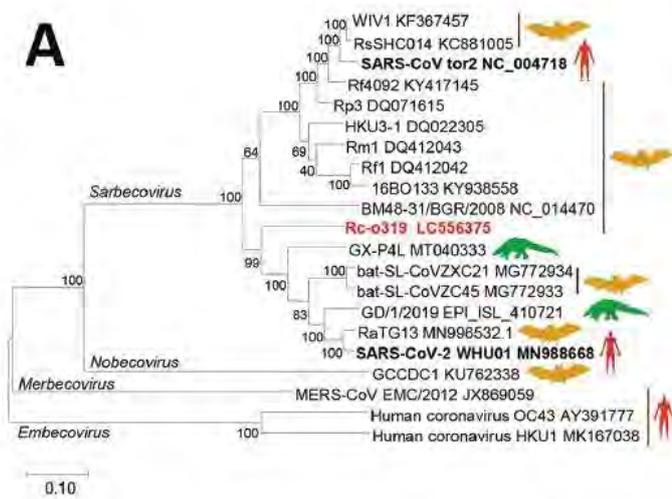
- **New nearest bat precursor from Yunnan 2019 (high identity in Orf1ab, greatest difference in Spike protein, recombination or mixed viruses in metagenomic sample, not yet peer-reviewed)**
- **Nearest pangolin precursors from Guangdong (Southern China)**
- **Previous closest bat precursor also from Yunnan (Southern China) but sample from 2013**

Light Orange ... previous bat CoVs
 Orange ... previous closest bat precursor (Yunnan 2013)
 Red ... new bat CoVs (Yunnan 2019)
 Light blue ... hCoV-19 2019-2020
 Green ... pangolin CoV (Southern China 2019)
 Blue ... SARS CoV

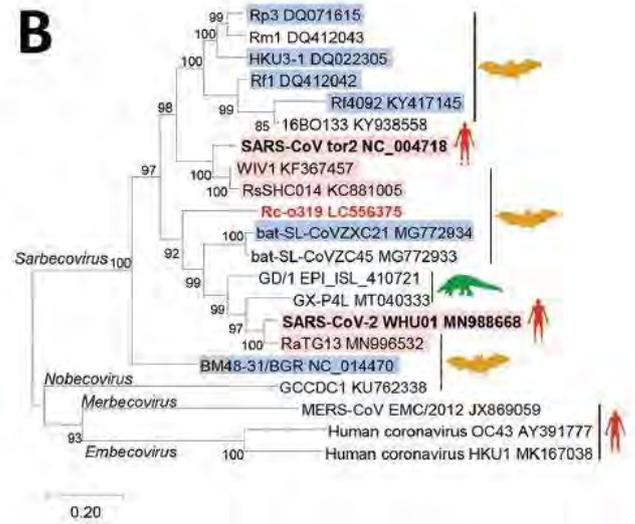
We gratefully acknowledge the Authors from Originating and Submitting laboratories of sequence data on which the analysis is based.



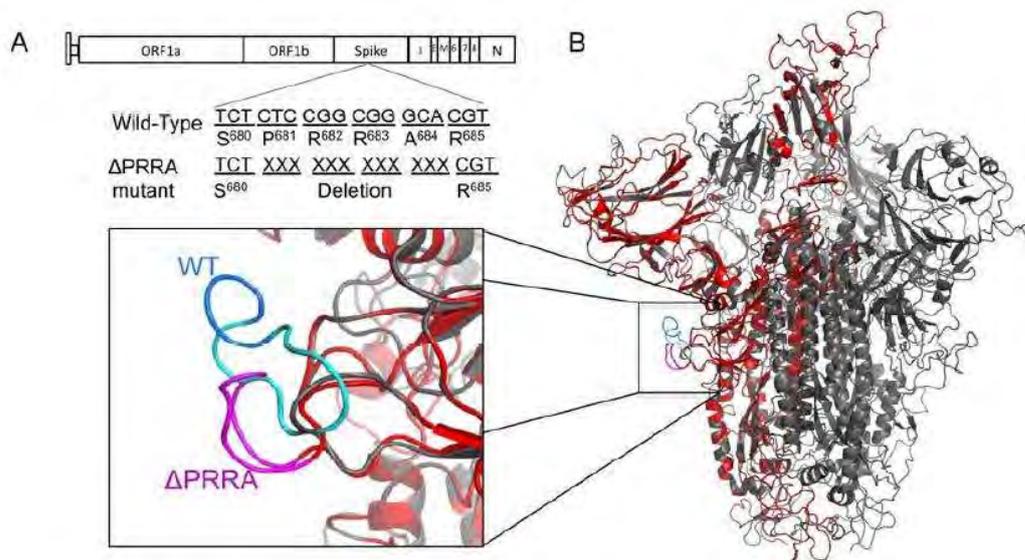
Which viruses were precursors?



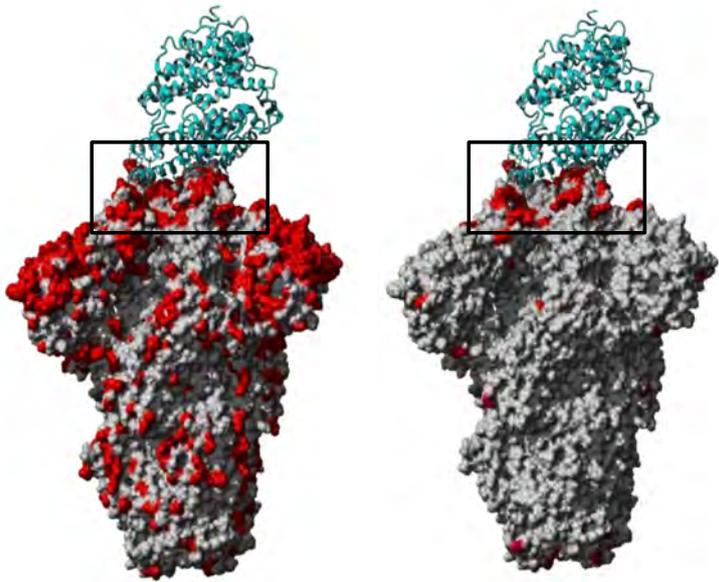
Murakami S et al, EID 2020



The furin cleavage site: adaptation step to its new host?



Site d'attachement au récepteur cellulaire : différences entre le SARS, le précurseur chez la chauve-souris (RaTG13) et le SARS-CoV-2



Cyan ... ACE2 human host receptor
Gray ... CoV spike glycoprotein
Red ... mutations between either SARS (left side) or bat precursor RaTG13 (right side) vs human outbreak WIV04 CoV

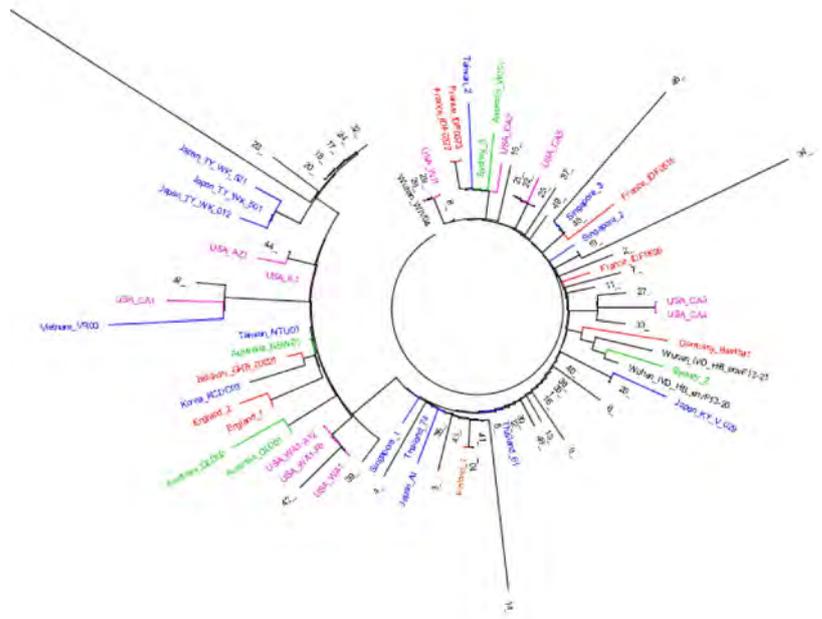
SARS vs SARS-CoV-2

RaTG13 vs SARS-CoV-2

- Surface proteins are 76% and 98% identical, respectively
- Antigenic surface highly divergent compared to SARS
- Bat precursor differences in receptor binding interface indicative of changes that allowed host switch

Le virus (émergence)

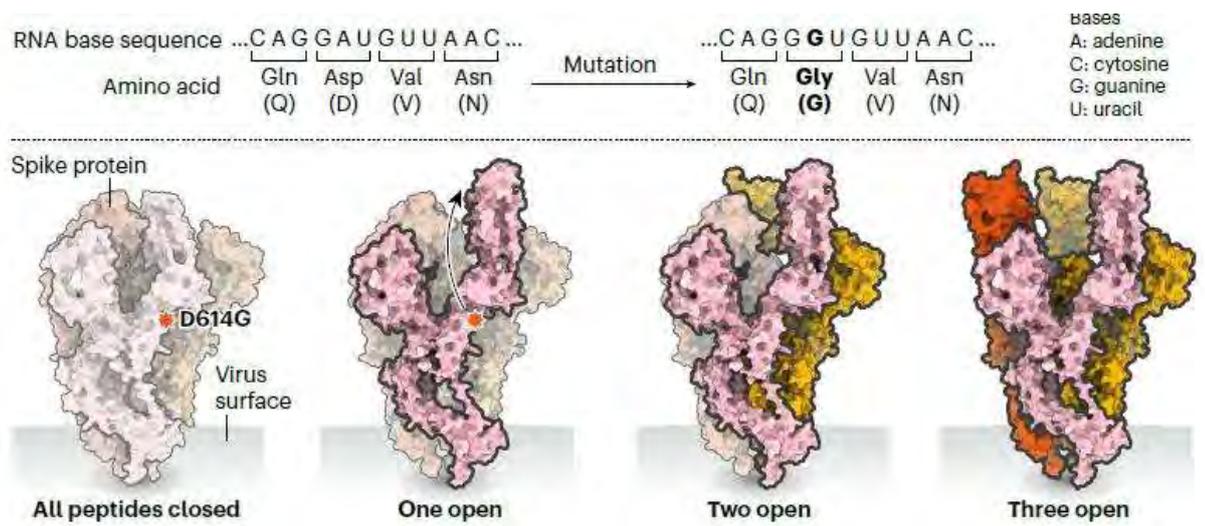
- 11-2-2020



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Impact de la substitution D614G : le début de l'évolution

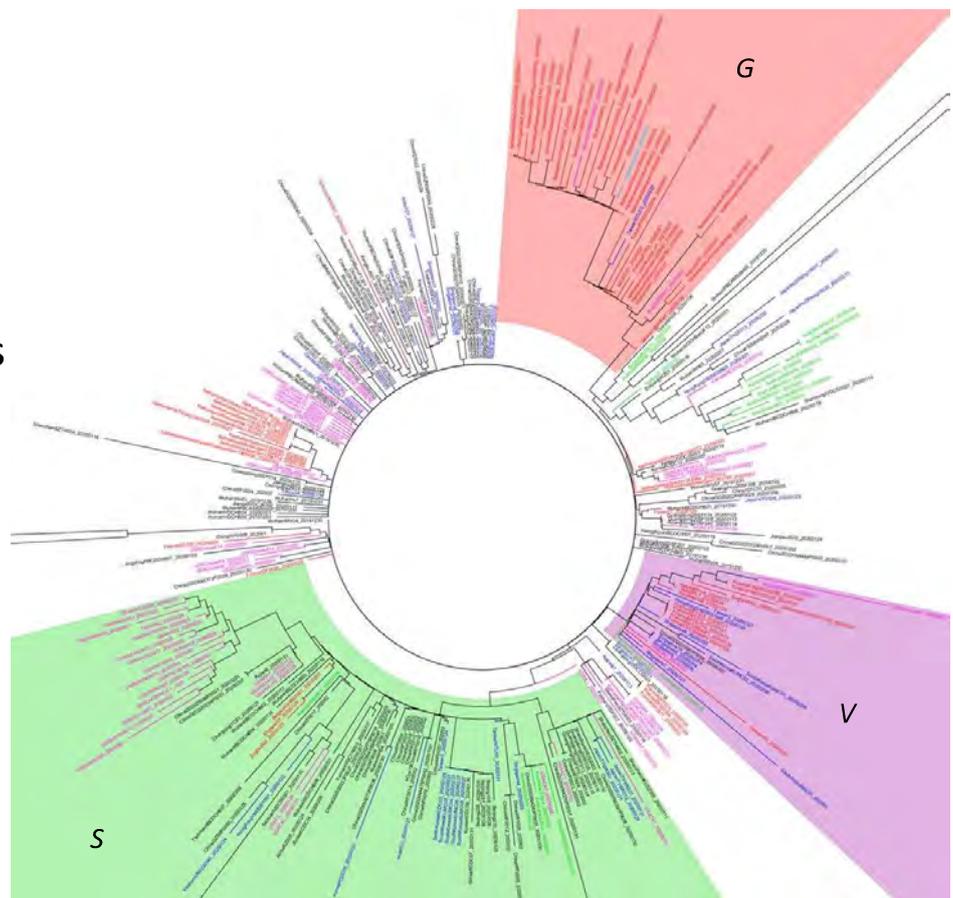


De Callaway E, Nature, 2020; 585:174-

Le virus (diffusion)

- 10-3-20

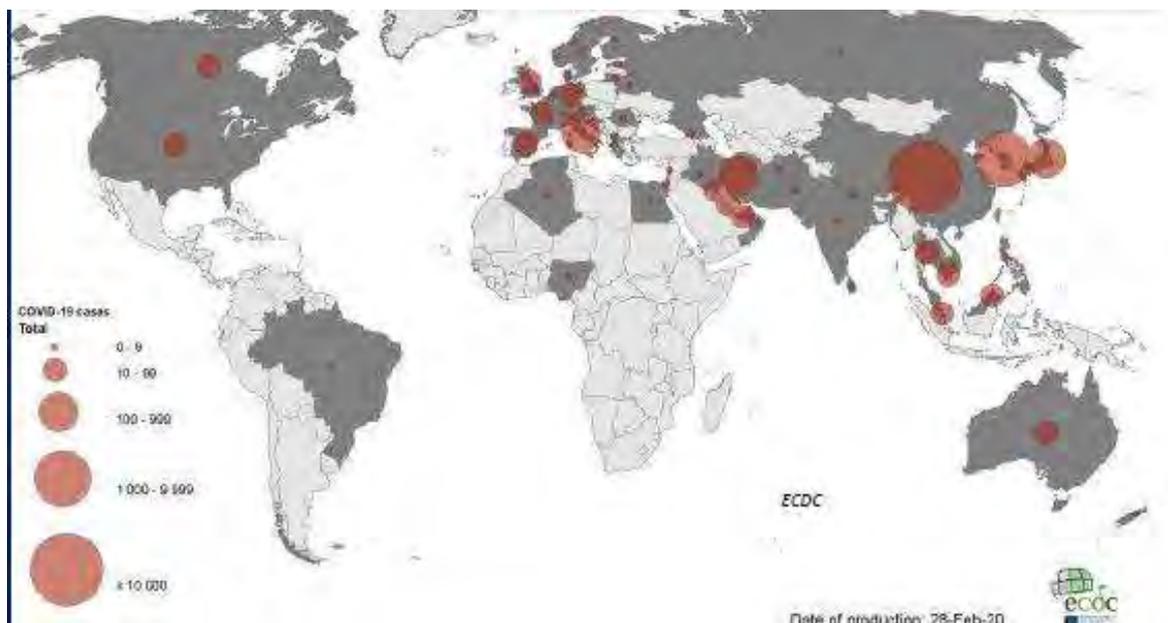
Description des clades



We gratefully acknowledge the Authors from Originating and Submitting laboratories of sequence data on which the analysis is based.



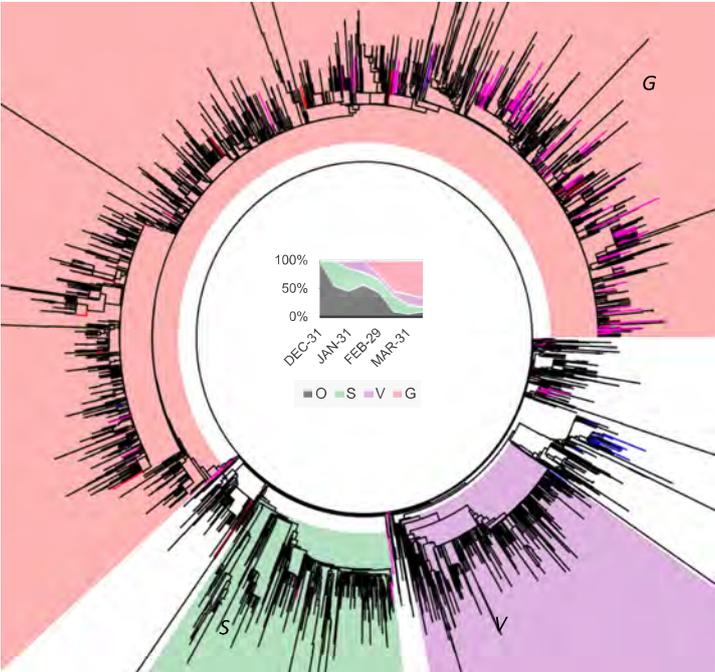
Diffusion phase (late February - early March 2020)



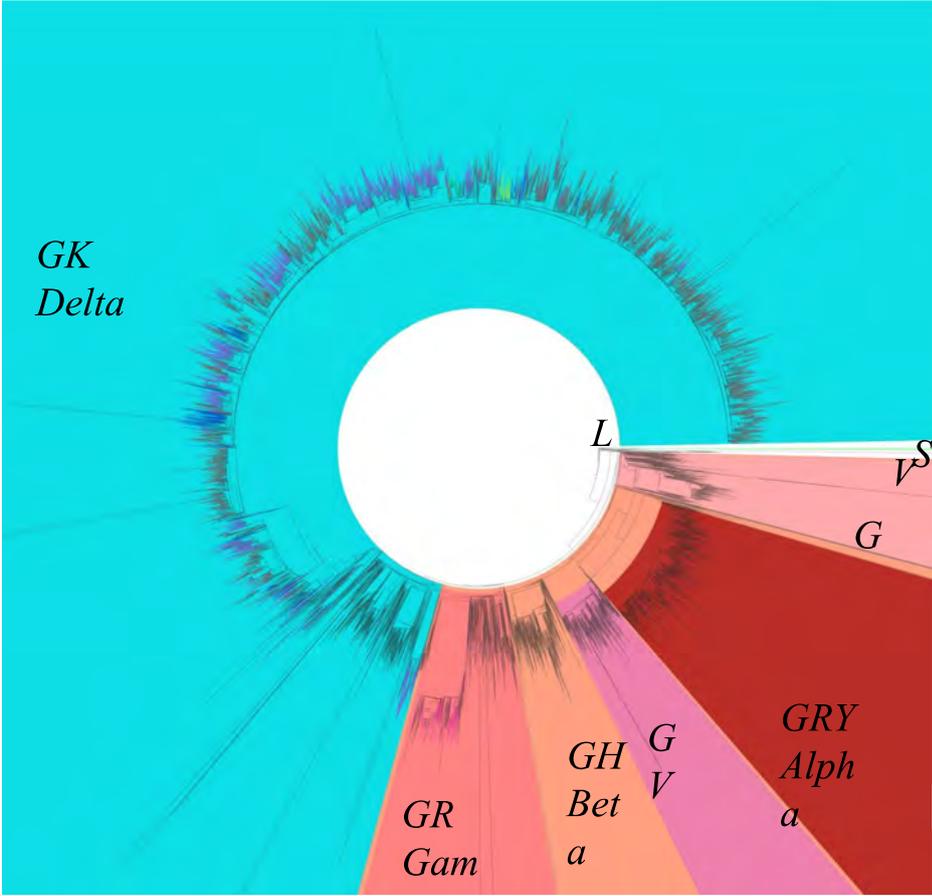
Extension phase (April-May 2020)

- 30-4-20
 - Larger clades were named based on marker variants:
 - S ... ORF8-L84S
 - G ... S-D614G
 - V ... NS3-G251V

We gratefully acknowledge the Authors from Originating and Submitting laboratories of sequence data on which the analysis is based



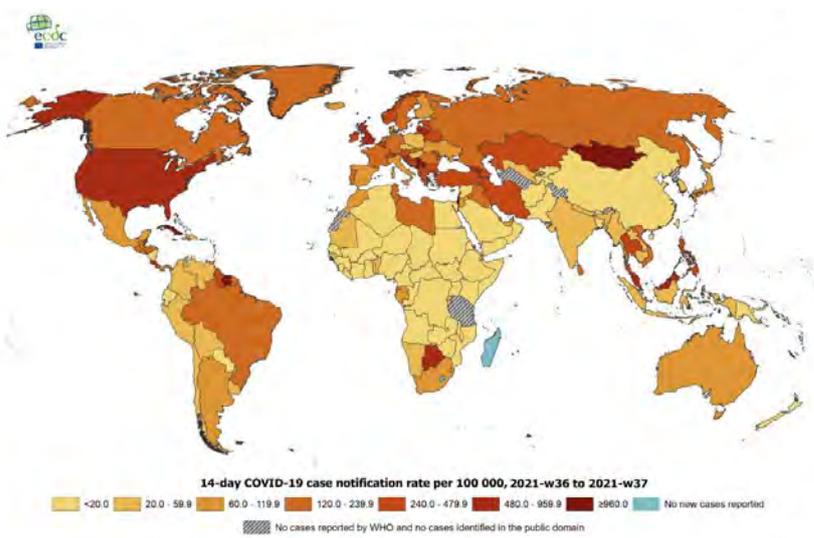
Sampled genome tree derived from all outbreak sequences 2021-10-01



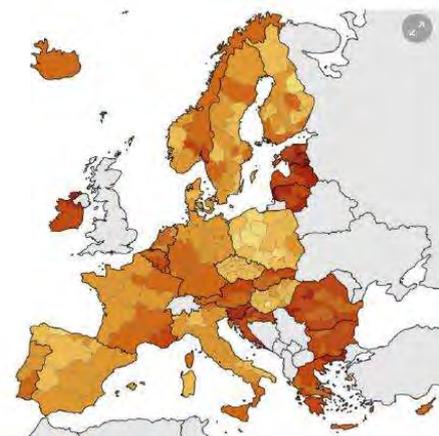
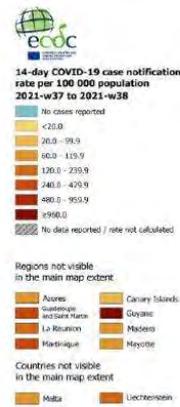
Neighbor-Joining tree with fasttree visualized in ete3.



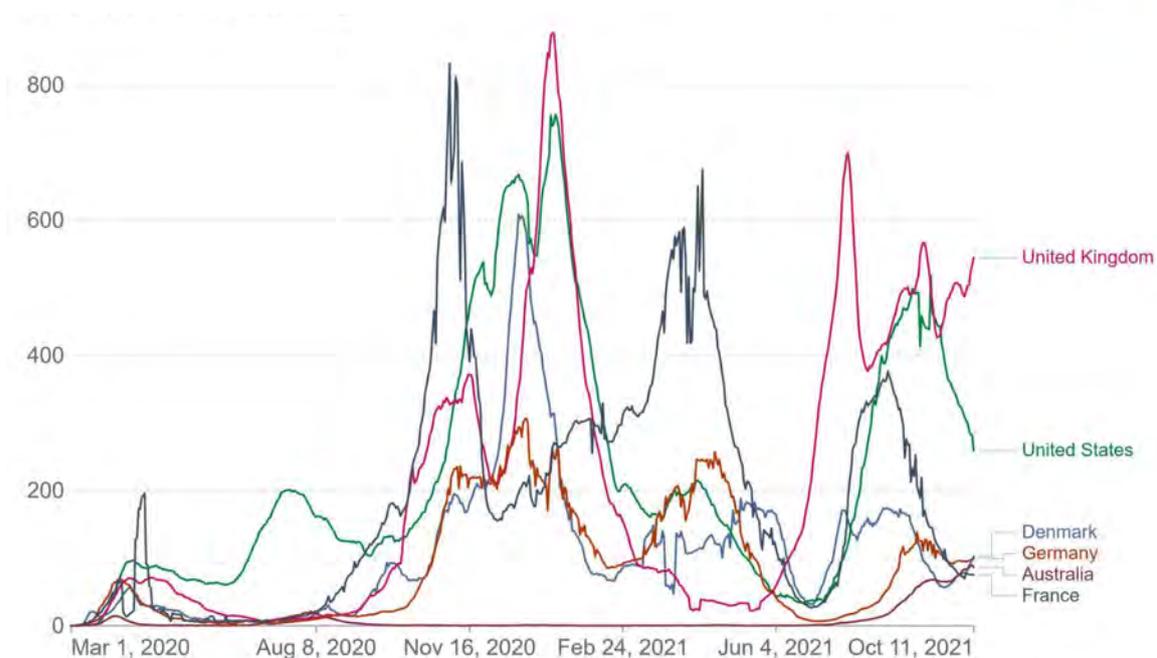
Situation internationale au 5 oct 2021



Administrative boundaries: © EuroGisGraphics © UN-FAO © Turbide. The boundaries and names shown on this map do not imply official endorsement or acceptance by the European Union. Date of production: 22/09/2021



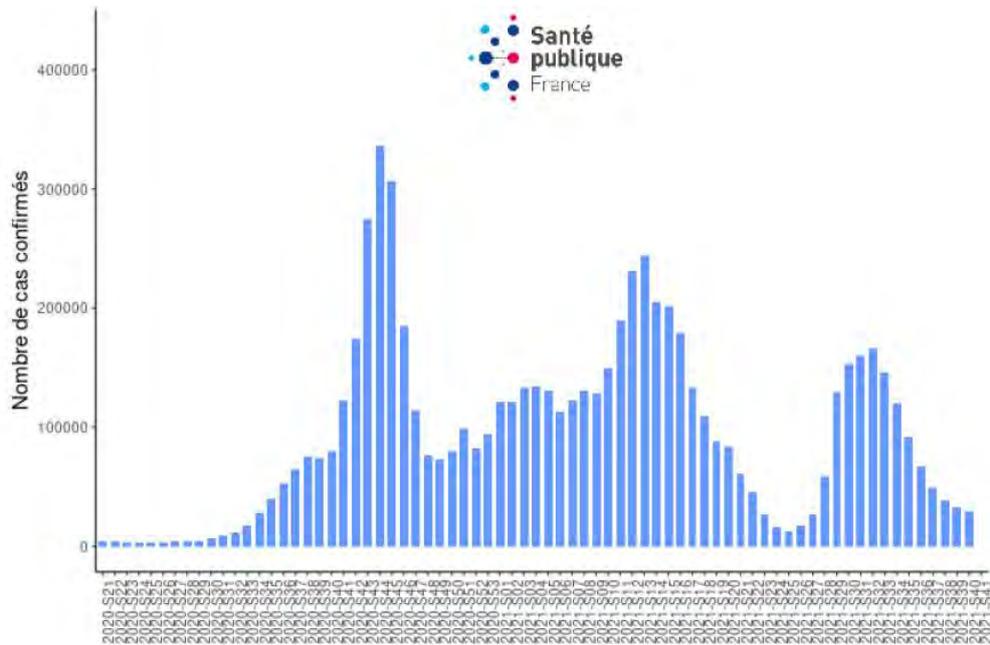
Situation actuelle (12 oct 2021)



Source: Johns Hopkins University CSSE COVID-19 Data

CC BY

En France

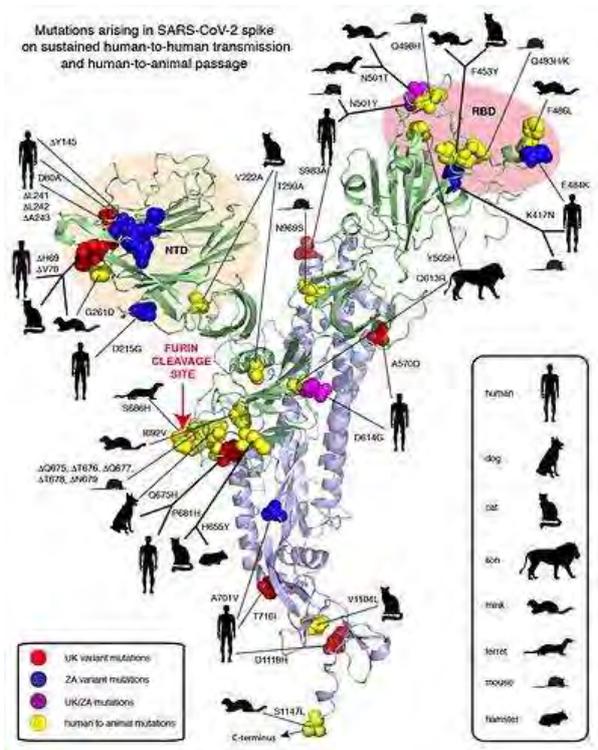


Classement des variants circulant en France métropolitaine

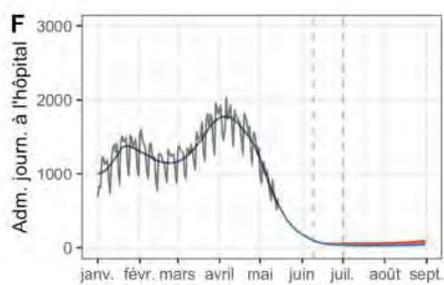
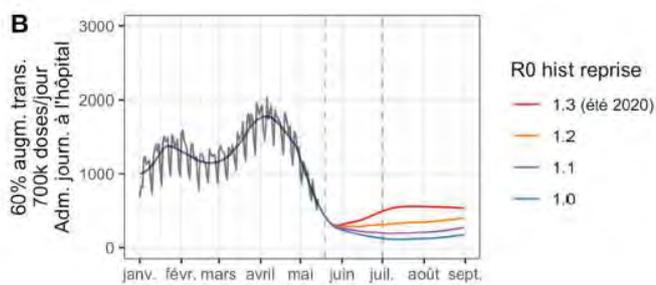
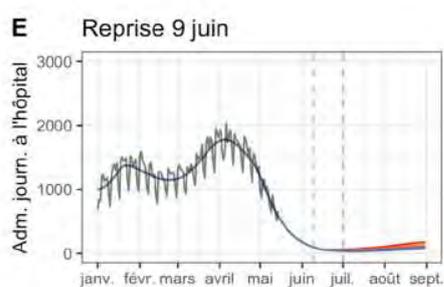
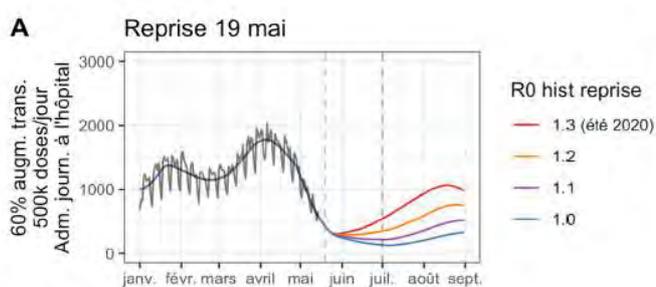
Variants préoccupants (VOC)	Variants à suivre (VOI)	Variants en cours d'évaluation (VUM)
20I (V1, B.1.1.7 +/- E484K/Q, Q.*, Alpha) 0,1% des séquences (Flash #22)	21G (C.37, Lambda) Non détecté depuis Flash #16 (20/07)	20A (B.1.620) Non détecté lors de Flash #22
20H (V2, B.1.351/ B.1.351.*, Beta) Non détecté depuis Flash #19 (10/08)	21H (B.1.621/B.1.621.1, Mu) 0,1% des séquences (Flash #22)	20B (B.1.1.318) <0,1% des séquences (Flash #22)
20J (V3, P.1/P.1.*, Gamma) <0,1% des séquences (Flash #22)		20D (C.36.3) Non détecté depuis Flash #19 (10/08)
21A (B.1.617.2/AY.*, Delta) 99,6% des séquences (Flash #22)		20D (C.1.2) Jamais détecté lors d'enquêtes Flash

Mutations arising in SARS-CoV-2 spike on sustained human-to-human transmission and human-to-animal passage

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Que disait la modélisation de l'évolution épidémique à 3 mois fin mai?



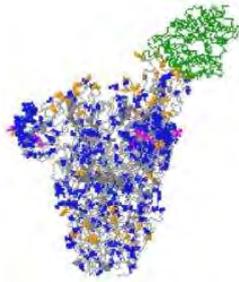
Données Simon Cauchemez

Pourquoi est-ce le moins bon scénario qui a été observé?

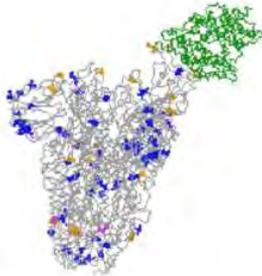
- Relâchement précoce des mesures de contrôle
 - Mais étagé
 - Mais décliné régionalement
 - Mais vaccination bien enclenchée
- Apparition d'un nouvel acteur, le variant Delta
 - R_0 estimé entre 5 et 6
 - Discussions sur les possibles impacts sur l'immunité collective et individuelle

Les mutations sur la protéine Spike

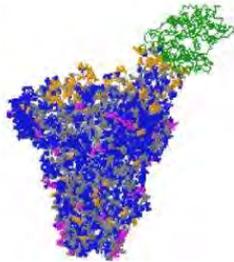
**K417T V445A N501Y E484K Y449H
T478K Y449S S494P F490S G485V**
in GR & GRY clade (B.1.1.1 & B.1.1.7)



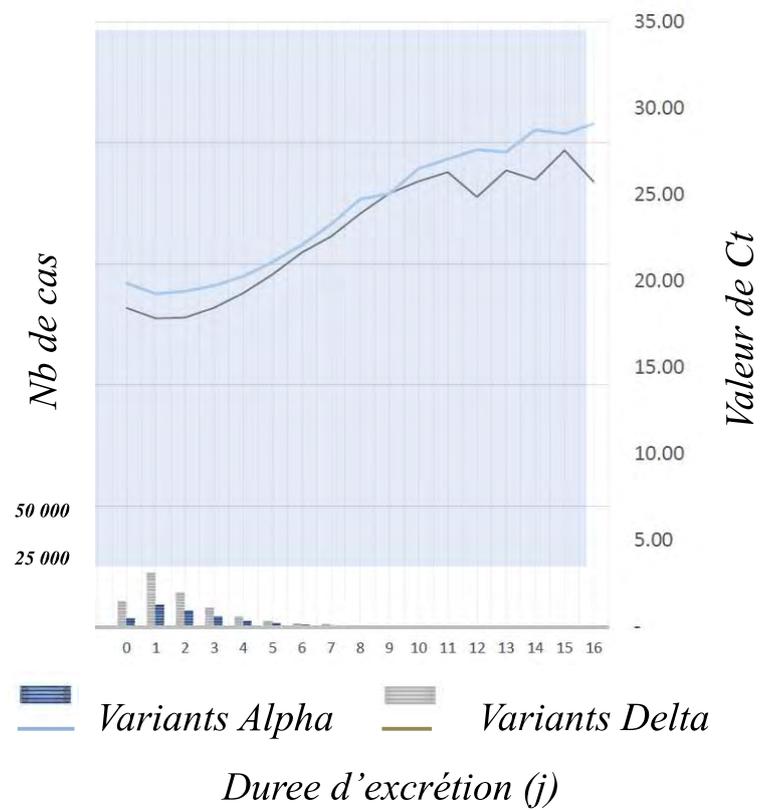
E484K T478K N501Y
in nonG clade (A, B & B.2)



**K458R G496V E484Q V445F V445A S494L
K458M F456L G446V S477N F490L G476S
N501T T478R G446A N501Y P499R E484K
E484V N437S G485R Q493L T478K S494P
E484G K417N N501I Q493E N439K S477G
A475V Q493P F490S S477I K417T R403K
L455F V445I G485S G446S E484D G446R**
in G, GK & GV clades (B.1, B.1.617.2, AY.* &
B.1.177)



L'excrétion virale du Delta



Obermeyer et al,

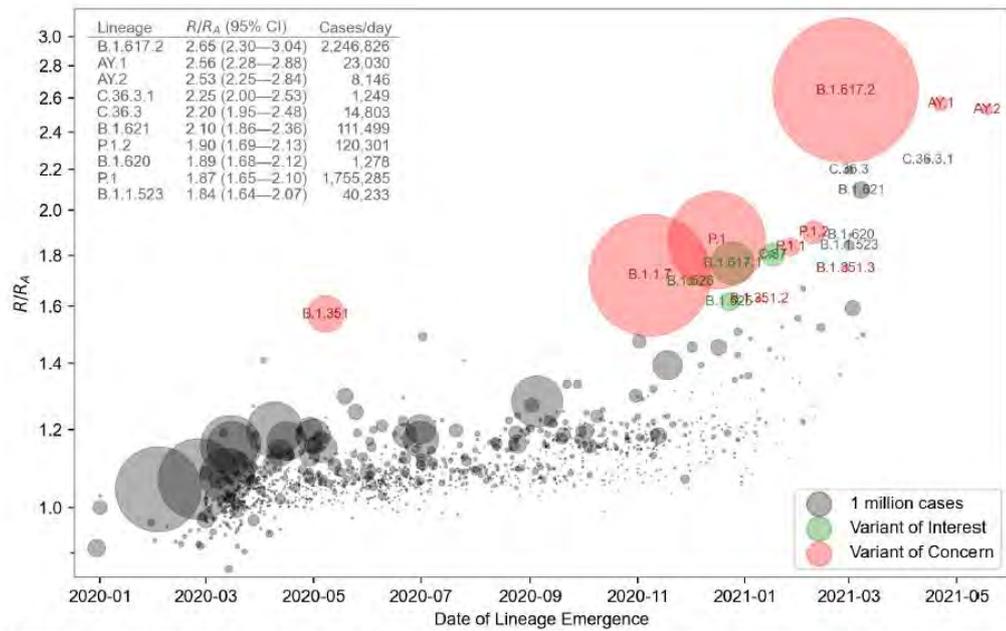
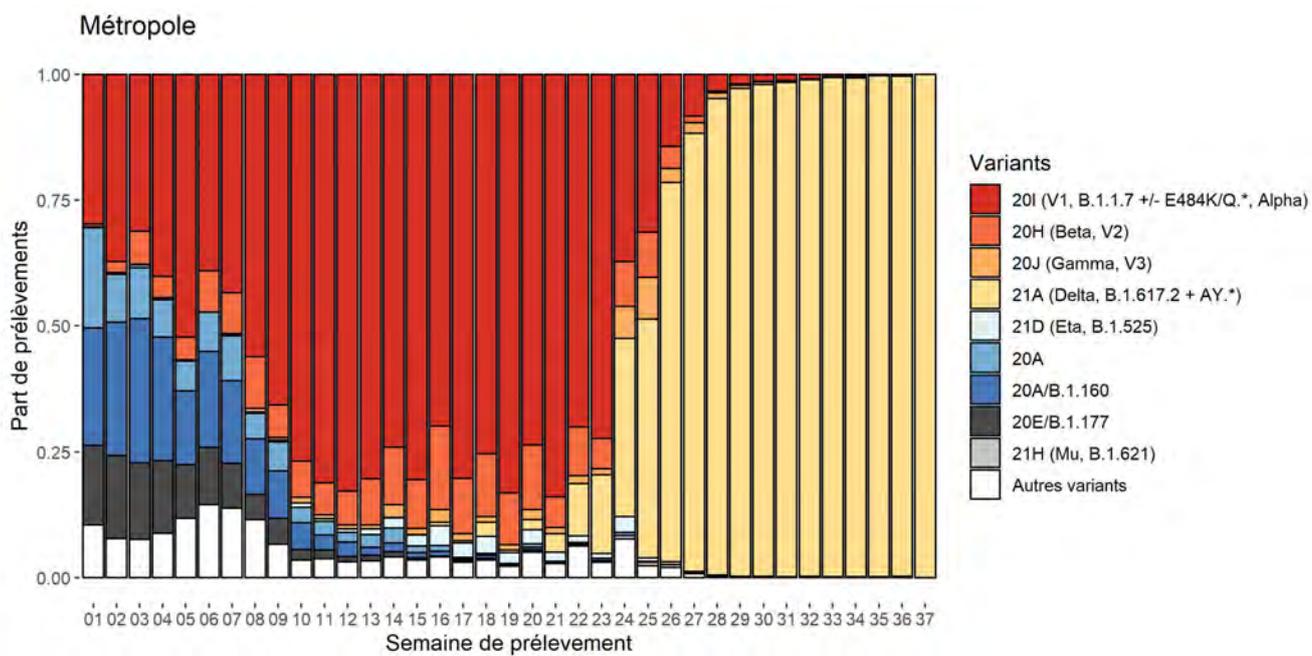
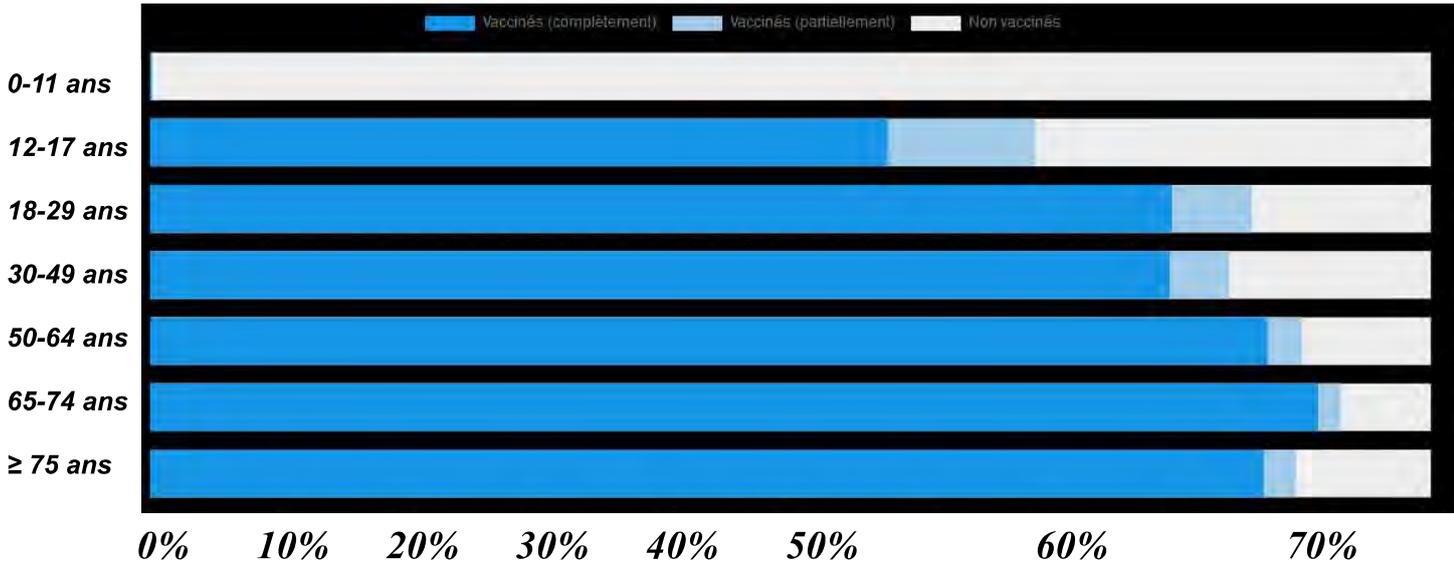


Figure 2. Growth rate versus date of lineage emergence. Circle size is proportional to cumulative case count inferred from lineage proportion estimates and confirmed case counts. Inset table lists the 10 most transmissible lineages inferred by the model. R/R_A : the fold increase in effective reproductive number over the Wuhan (A) lineage, assuming a fixed generation time of 5.5 days.

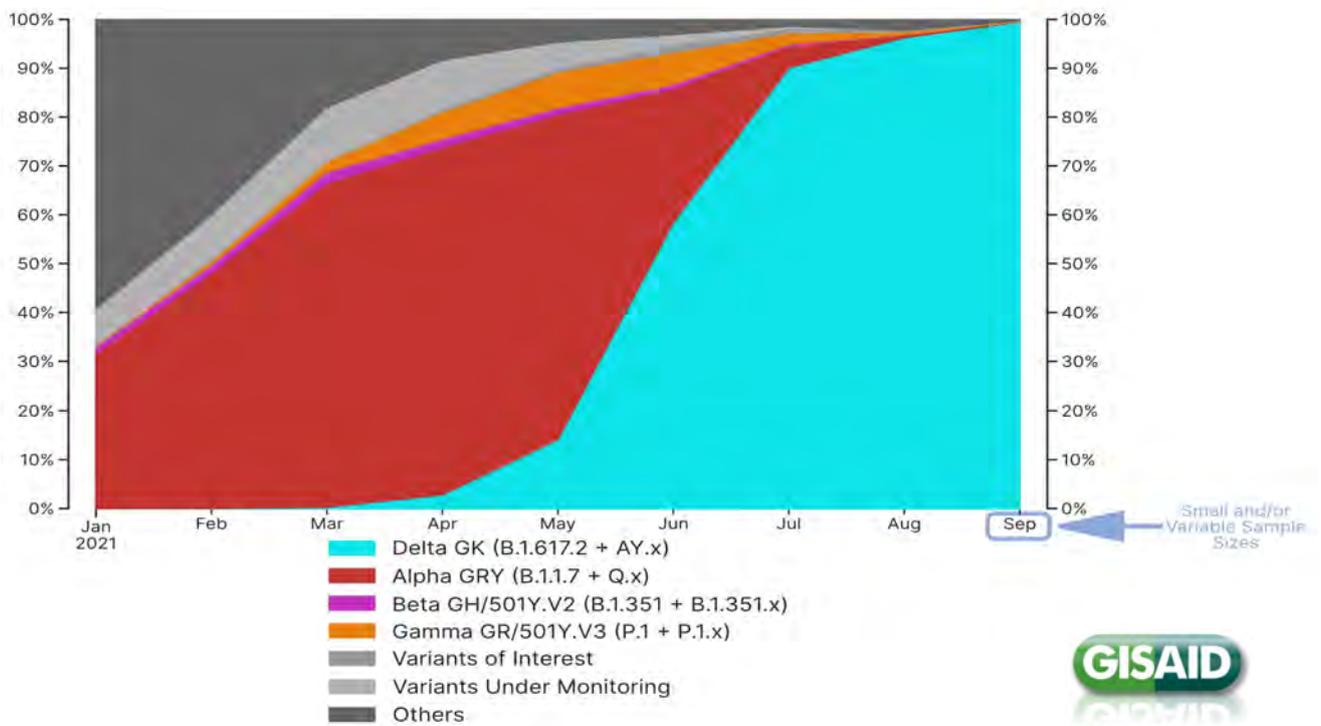
Evolution des proportions de variants en France



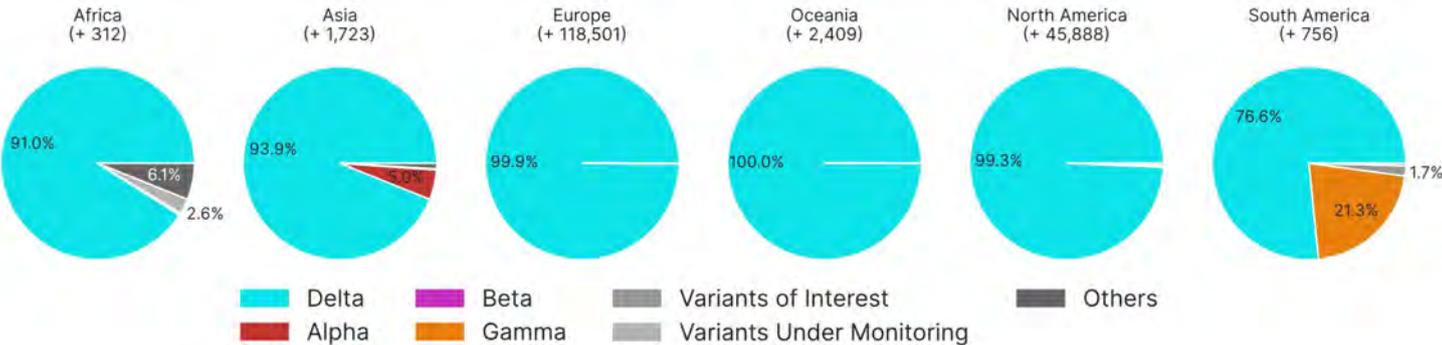
Taux de vaccination par tranche d'âge



L'évolution de la distribution des variants circulant au niveau mondial



Circulation des variants par zone géographique



See <https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/> for variant information and definitions



by BII/GIS, A*STAR Singapore

Les questions actuelles

- La vaccination va-t-elle être suffisante

- Nouvelle souche vaccinale
- Nouveau schéma vaccinal

Oui	Non

- Comment va évoluer l'épidémie

- Nouveau variant
- Persistance ou non du virus
- Quid des autres virus respiratoires

Bien	Mal

- Faut-il alléger les mesures de contrôle

- Maintien de toutes les mesures de contrôle
- Renforcement de la vaccination

Oui	Non

Synthèse

- Les Coronavirus sont des virus zoonotiques à potentiel pandémique
- Ce beta-coronavirus a émergé fin 2019 dans la province Hubei (calendrier exact?)
- Le chemin de cette émergence n'est pas encore élucidé (hôte intermédiaire)
- Le passage chez les mustélidés est une hypothèse, mais aurait pu induire des modifications initiales plus importantes
- Le virus a présenté d'emblée des caractéristiques de parfaite adaptation à l'homme (récepteur ACE2)
- Son évolution a commencé, à la marge (D614G), et peut continuer ou se stabiliser
- Une évolution antigénique est possible du fait de l'immunité collective grandissante (accumulation de variants mineurs notamment sur le RBD)
- La connaissance accumulée sur la biologie du SARS-CoV-2 apporte des informations intéressantes sur les coronavirus en général

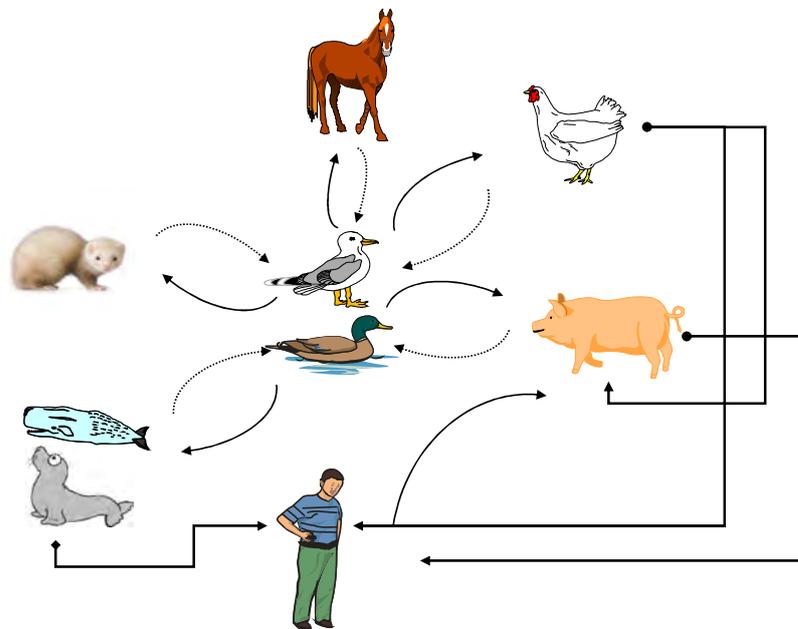


influenzavirus emergents

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VirPath, EMR 4610, Université de Lyon, F69372, Lyon

*Acteurs #3 : les vecteurs animaux**



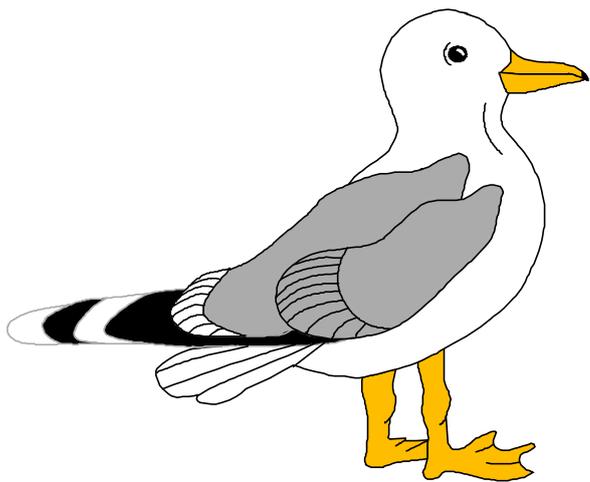
** Uniquement pour les pandémies*

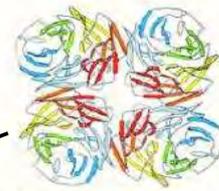
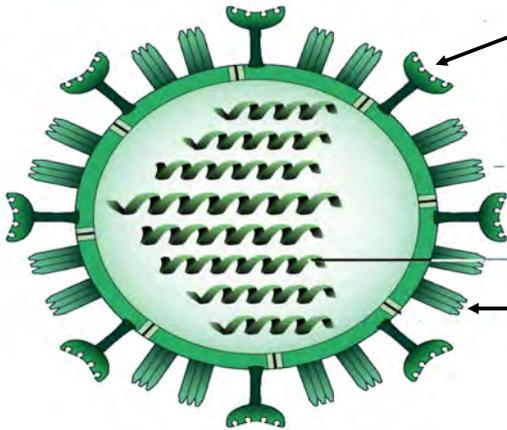
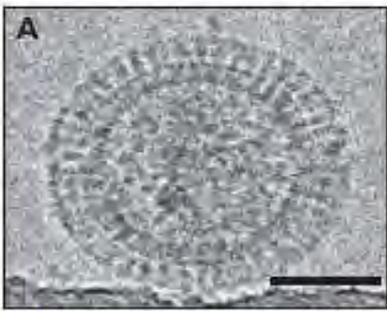
H1				
H2				
H3				
H4				
H5				
H6				
H7				
H8				
H9				
H10				
H11				
H12				
H13				
H14				
H15				
H16				

N1				
N2				
N3				
N4				
N5				
N6				
N7				
N8				
N9				

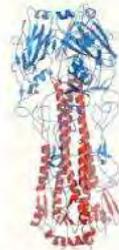
Les hôtes des différents sous-types de virus influenza A

La grippe aviaire: une infection impossible



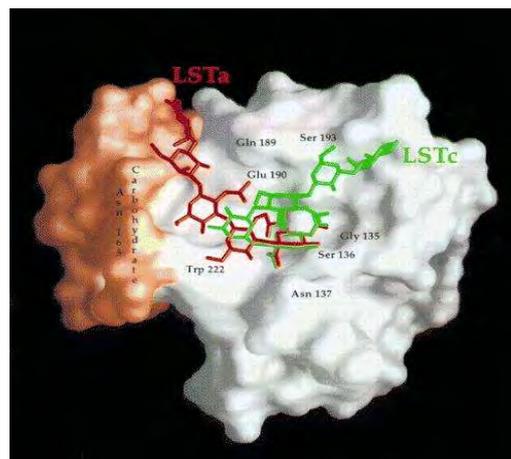
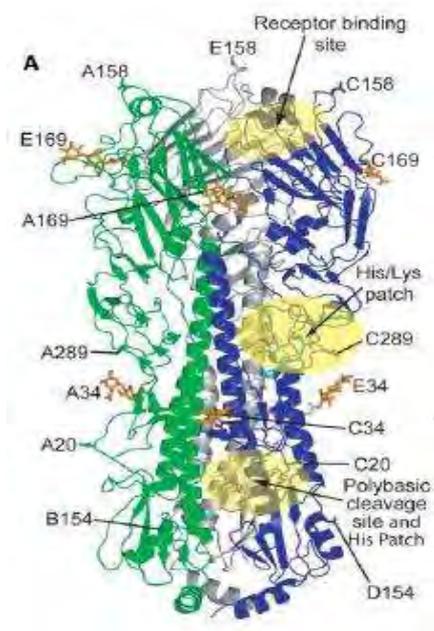


Neuraminidase (N)



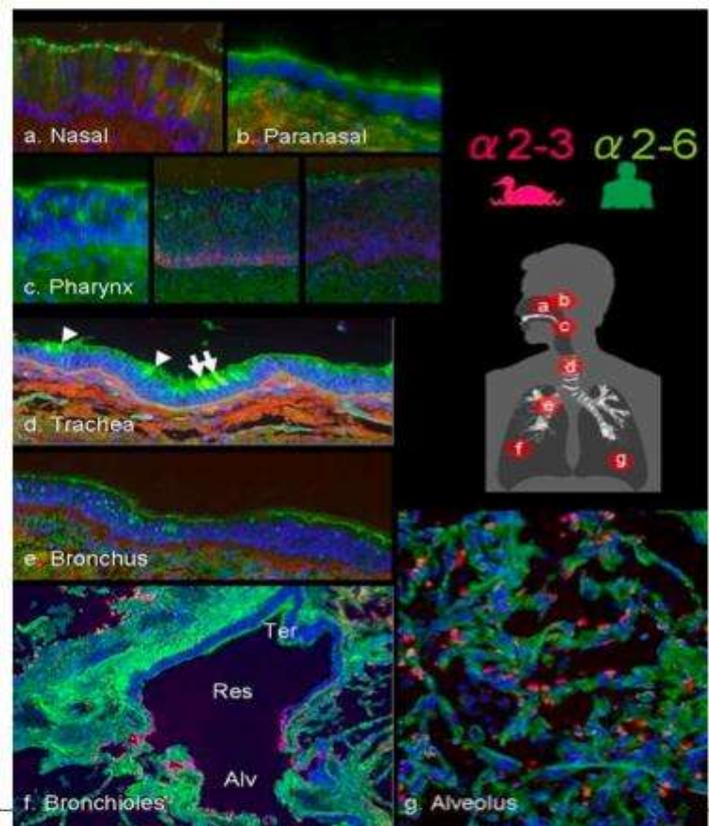
Haemagglutinin (H)

Variations sur le RBS : $\alpha 2,3$ et $\alpha 2,6$



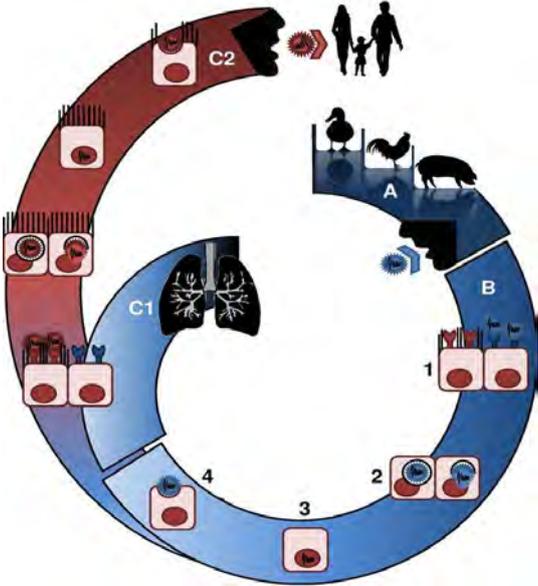
D'après Skehel & Wiley, 2000

Distribution des récepteurs α 2-6 et α 2-3 dans l'arbre respiratoire humain



- Shynia, Nature 2006

Les étapes du franchissement



Les (nombreux) facteurs limitants

MAIS...

Table 2
Known mutations and associated mechanisms of adaptation of zoonotic influenza viruses to human hosts via the crossing of virus-cell interaction barriers.

Virus-cell interaction barrier	Protein	Mutation	Adaptive mechanism	Ref.		
Virus attachment	HA	N154S	Increases α 2,6 binding in H5 subtype	[194]		
		N182K	Increases α 2,6 binding and decreases α 2,3 binding in H5 subtype	[194,195]		
		E190D	Increases α 2,6 binding in H1 subtype	[86,196]		
		Q192R	Increases α 2,6 binding and decreases α 2,3 binding in H5 subtype	[195]		
		Q222G	Increases α 2,3 binding in H1 subtype	[75,197]		
		Q222L	Increases α 2,6 binding and decreases α 2,3 binding in H5 subtype	[194]		
		S223N	Increases α 2,6 binding and decreases α 2,3 binding in H5 subtype	[194]		
		G224S	Increases α 2,6 binding and decreases α 2,3 binding in H5 subtype	[194]		
		G225D	Decreases α 2,3 binding in H1 and H9 subtypes	[81,86,196]		
		Q226L	Increases α 2,6 binding and decreases α 2,3 binding in H2, H3, H4, H5 and H9 subtypes	[81,86,198,199]		
		S227N	Increases α 2,6 binding and decreases α 2,3 binding in H5 subtype	[200,201]		
		G228S	Decreases α 2,3 binding in H3 subtype	[86,198,201]		
		L129V + A134V	Increases α 2,6 binding in H2 and H5 subtypes	[202]		
		G139R + N182K	Increases α 2,6 binding possibly in H5 subtype	[194]		
		Q192R + S223N	Increases α 2,6 binding and decreases α 2,3 binding in H5 subtype	[194]		
		Q222L + G224S	Increases α 2,6 binding and decreases α 2,3 binding in H5 subtype	[194]		
		S227N + N211S + I50NNA	Increases α 2,6 binding in H5 subtype	[203]		
		N158S + Q226L + N248D	Increases α 2,6 binding and decreases α 2,3 binding in H5 subtype	[194,204]		
		N182K + Q222L + G224S	Increases α 2,6 binding and decreases α 2,3 binding in H5 subtype	[194]		
		Q222L + S223N + G224S	Increases α 2,6 binding and decreases α 2,3 binding in H5 subtype	[194]		
		Q222L + S223N + G224S	Increases α 2,6 binding and decreases α 2,3 binding in H5 subtype	[194]		
		NST158 + I50NNA + K193R + Q226L + G228S	Increases α 2,6 binding and decreases α 2,3 binding in H5 subtype	[205]		
		N182K + Q222L + S223N + G224S	Increases α 2,6 binding and decreases α 2,3 binding in H5 subtype	[194]		
		Q192R + Q222L + S223N + G224S	Increases α 2,6 binding and decreases α 2,3 binding in H5 subtype	[194]		
		N182K + Q192R + Q222L + S223N + G224S	Increases α 2,6 binding in H5 subtype	[194]		
		Virus-cell fusion	HA	Single R cleaved site	Allows cleavage by extracellular host proteases restricted to respiratory tract in humans	[92]
				Multi-basic cleaved site	Allows cleavage by ubiquitous intracellular host proteases present in various tissues in humans	[92]
Viral replication	PB1 + PB2	Unknown	Increases polymerase activity of HPAIV H5N1 in human cells (unknown mechanism)	[126]		
		PB2	E158G	Increases polymerase activity of HPAIV H5N1 in human cells (unknown mechanism)	[121]	
	T271A		Increases polymerase activity of LPAIV H3N2 in human cells (unknown mechanism)	[124]		
	Q591 K		Increases polymerase activity of HPAIV H5N1 activity in human cells (unknown mechanism)	[120]		
	E627 K		Increases polymerase activity by increasing PB2 and NP binding in human cells	[118]		
	D253N + Q291 K		Increases polymerase activity of LPAIV H9N2 in human cells (unknown mechanism)	[122]		
	G590S + Q591R		Increases polymerase activity of 2009 pandemic H1N1 virus in human cells (unknown mechanism)	[123]		
	PA		T552S	Increases polymerase activity of avian influenza viruses in mammalian cells and increases pathogenicity in mice (unknown mechanism)	[125]	
			NP + PB2	N319K + D701 N	Increases polymerase activity by increasing binding of vRNP to importin- α 1, and shifting nuclear import dependency from importin- α 3 to importin- α 7 in human and other mammalian cells	[112]
	Virus release	HA		I275V	Increases α 2,6 substrate specificity in N2 subtype	[133]
Antigenic shift			Escapes pre-existing humoral immunity	[134]		
D92E			Confers HPAIV H5N1 resistance to IFN- α , IFN- γ and TNF- α (unknown mechanism)	[139]		
I42S			Prevents double-stranded RNA-mediated activation of NF- κ B and IRF-3 pathways during HPAIV H5N1 infection	[140]		
L103F + I106M			Allows binding of HPAIV H5N1 NS1 protein and CPSF30 resulting in decreased IFN- β mRNA production	[141]		
Viral escape from host immune responses	NS1	PDZ domain ligand in C-terminus	Disruption of protein-protein interactions, including impairment of IFN-stimulated signaling, disruption of tight junctions, and reduction of apoptosis	[142-145]		
		PB1-F2	N66S	Unknown mechanism associated with apoptosis pathway regulation	[150]	

Les pandémies du 20e et 21e siècles



1918: "Spanish Flu"

H1N1

40-50 million



1957: "Asian Flu"

H2N2

1-4 million



1968: "Hong Kong Flu"

H3N2

1 million

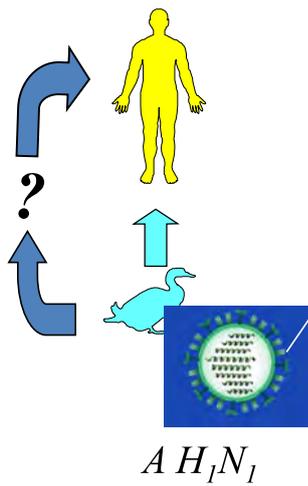


2009: "Swine Flu"

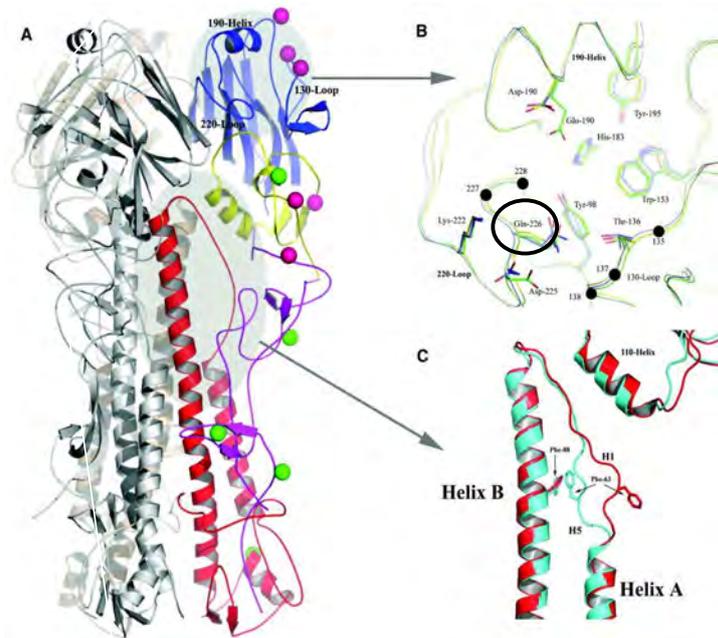
H1N1

0.7 million

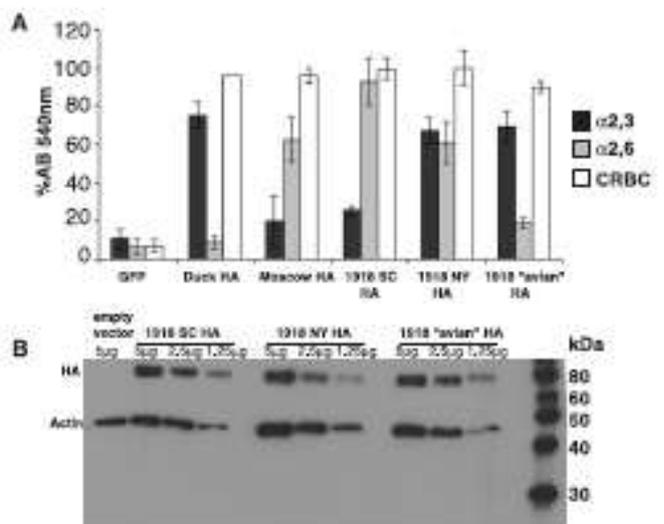
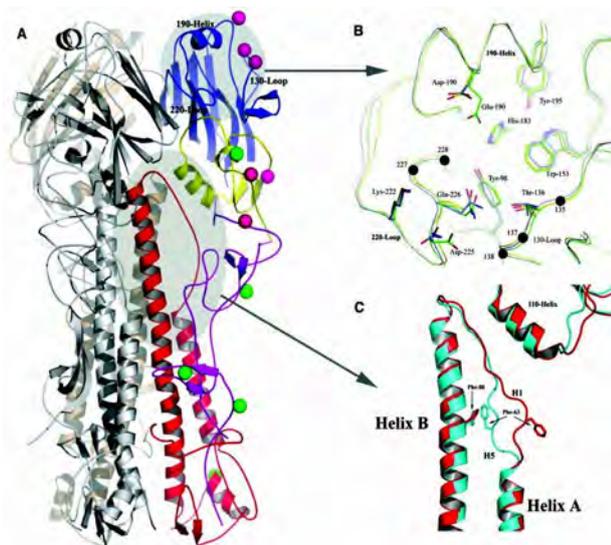
Mécanisme théorique de l'émergence du virus A H1N1 : mutation du RBS



D'après Taubenberger



Bascule de l'attachement de H1N1 en 1918

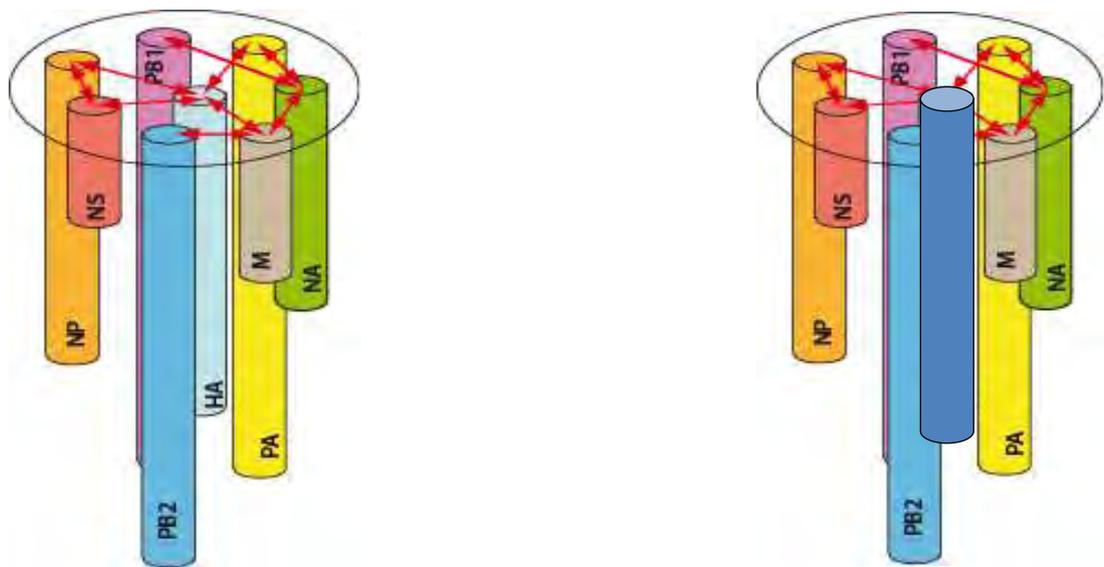


D'après Taubenberger

**Les deux modes d'adaptation des virus
influenza :
réassortiments et mutations**

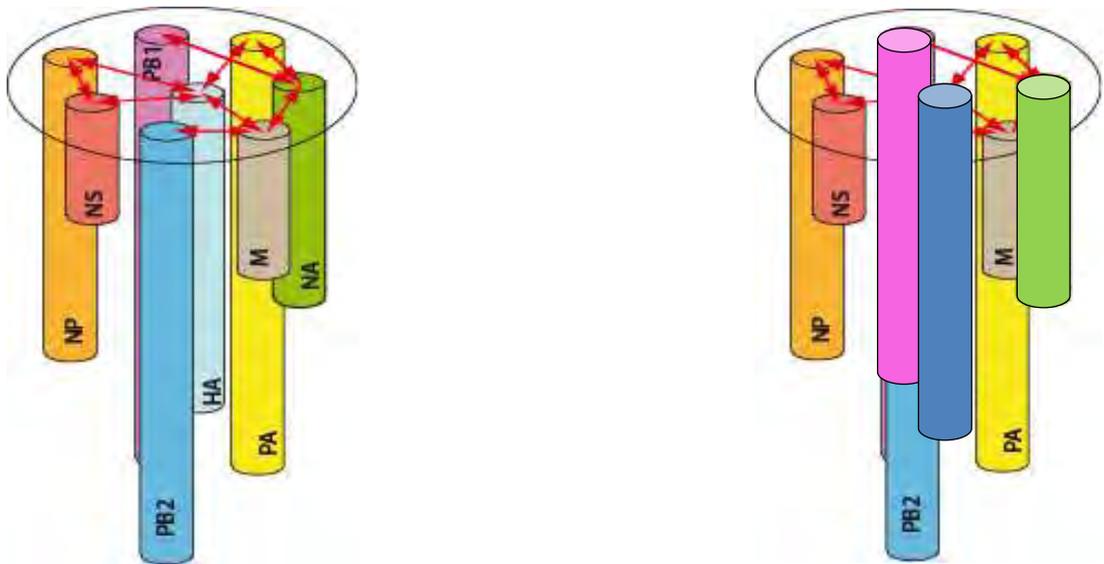


Réassortiment génétique : échanges de gènes entre virus



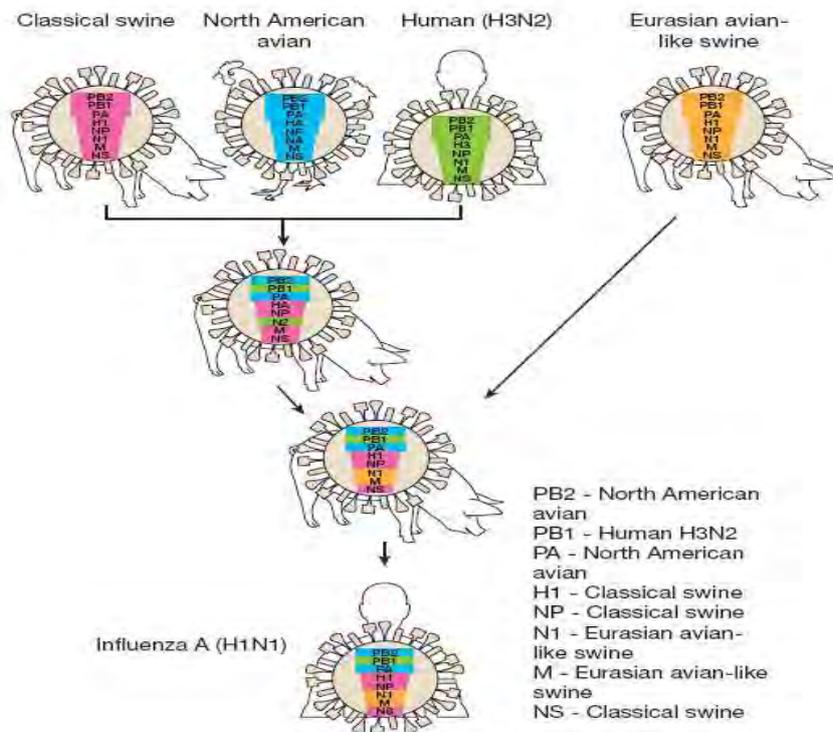
Emilie FOURNIER (Strasbourg) ; Dr Daniel THOMAS (Rennes) ; Dr Vincent MOULES (Lyon)

Réassortiment génétique en 1957 : introduction des gènes Ha/PB1/Na



Emilie FOURNIER (Strasbourg) ; Dr Daniel THOMAS (Rennes) ; Dr Vincent MOULES (Lyon)

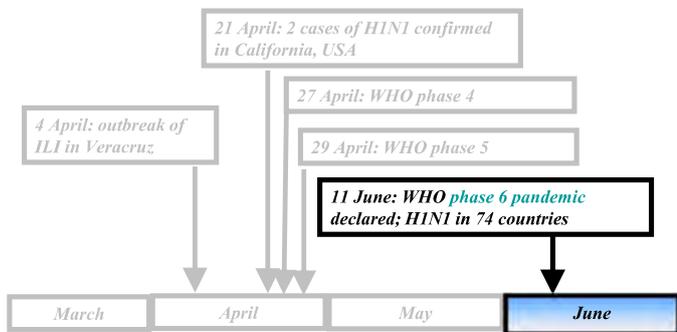
**Birth and spread of a pandemic virus in the
pandemic preparedness world:
example of H1N1**



The Timeline of a Pandemic : early phases



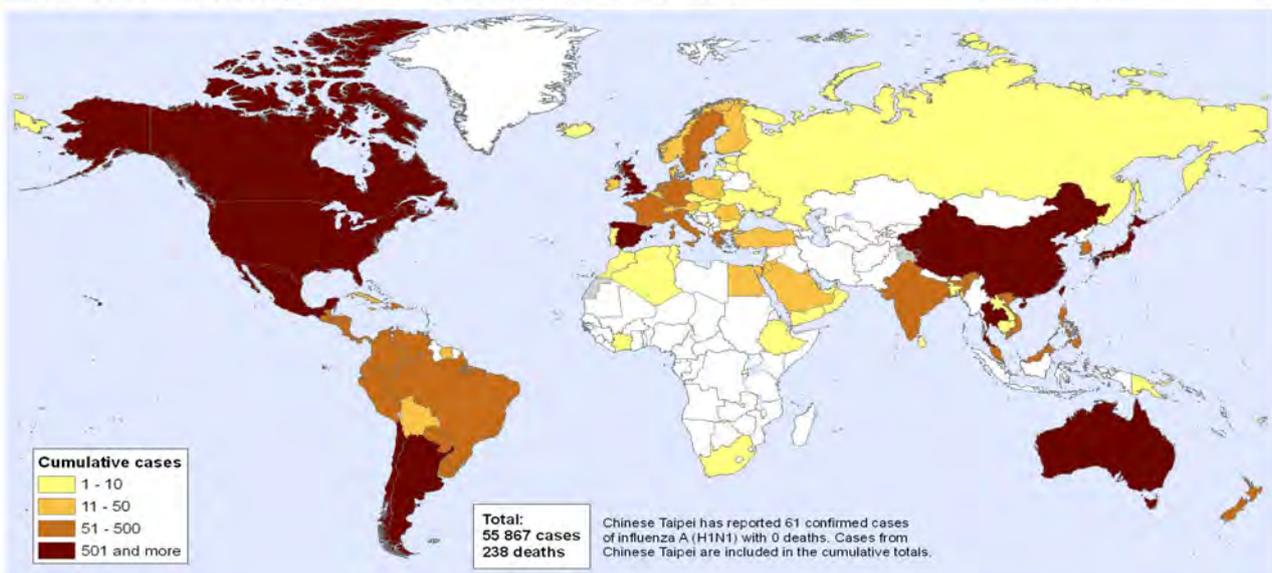
Pandemic H1N1 2009 Timeline



It took 6 week to reach 3 continents as compared to 3 months in 1957

**New Influenza A (H1N1),
Number of laboratory confirmed cases as reported to WHO**

**Status as of 24 June 2009
06:00 GMT**



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

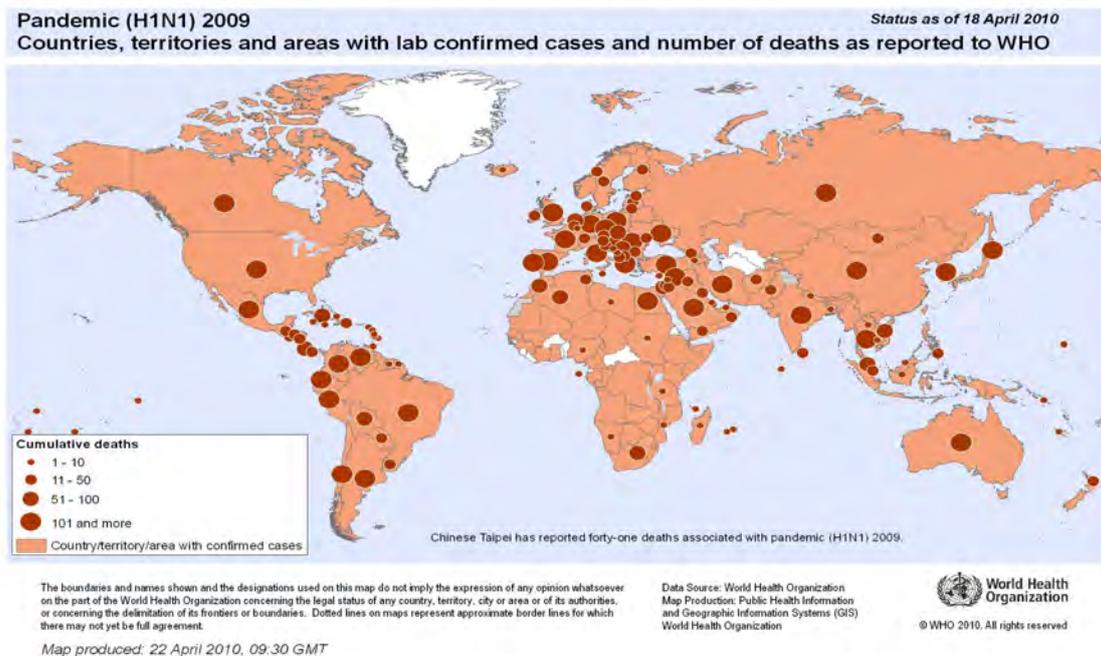


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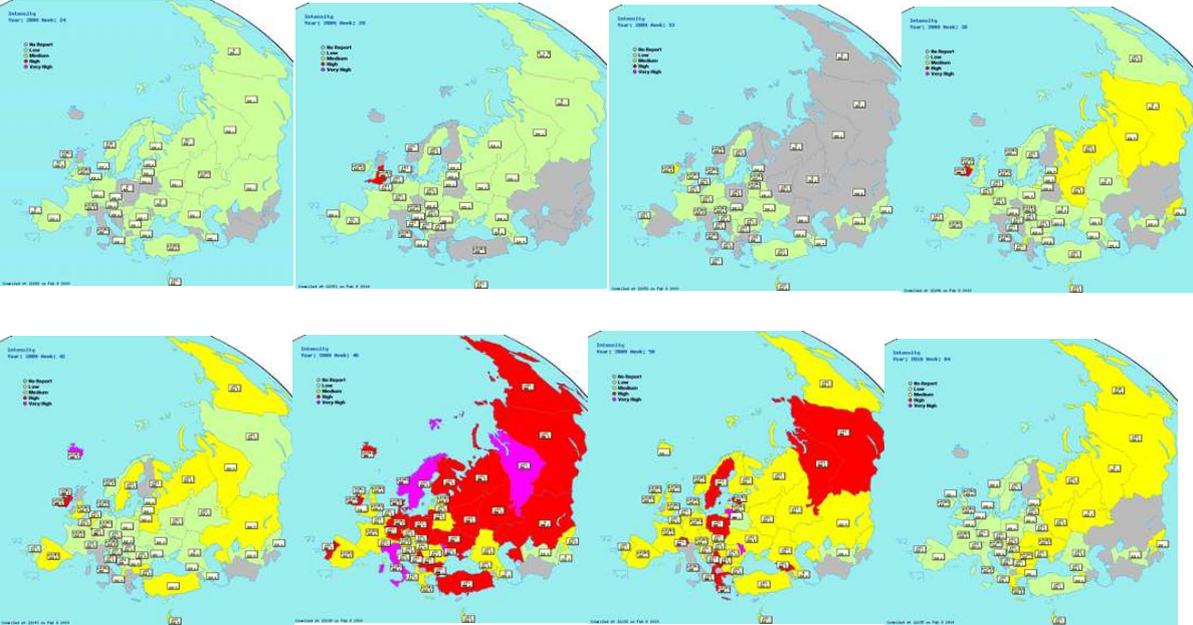
Map produced: 24 June 2009 10:00 GMT



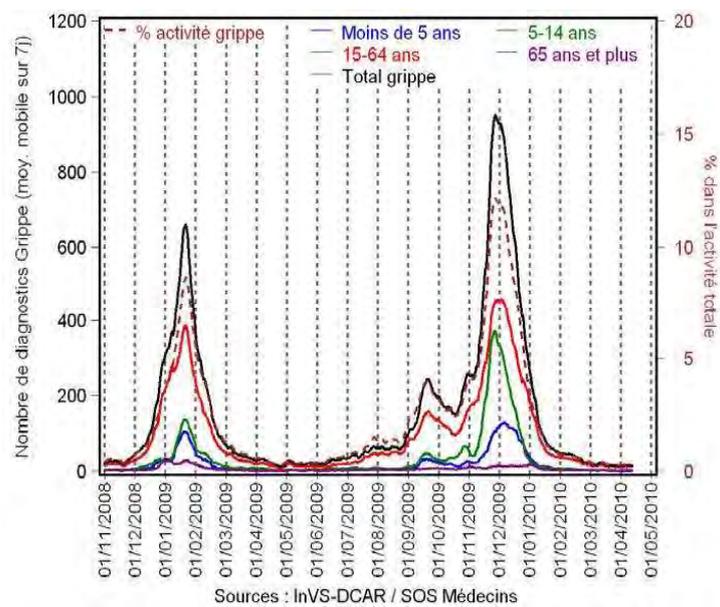
Total spread and death recorded



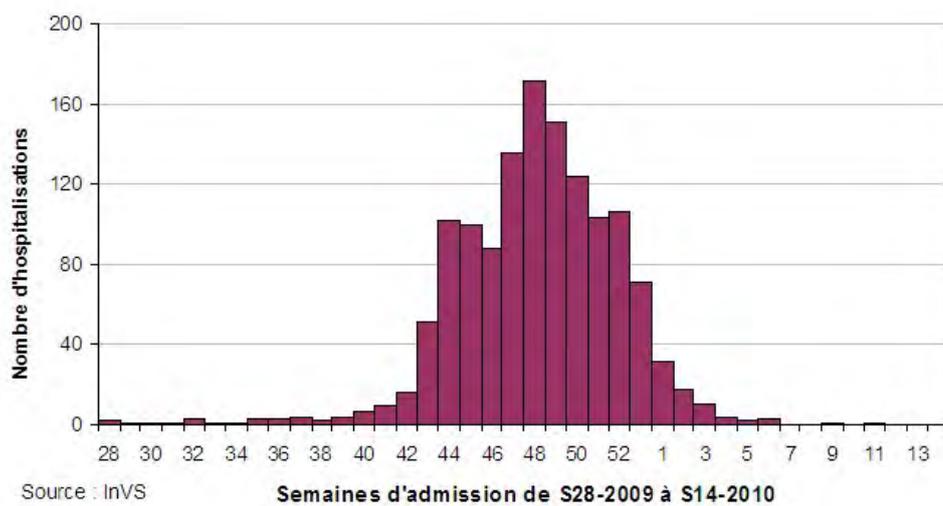
European status between oct-dec 2009



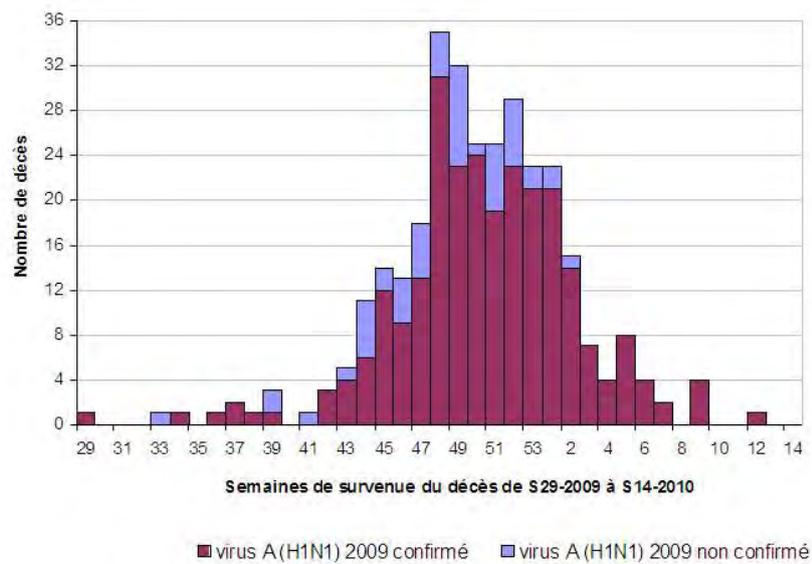
Impact in France



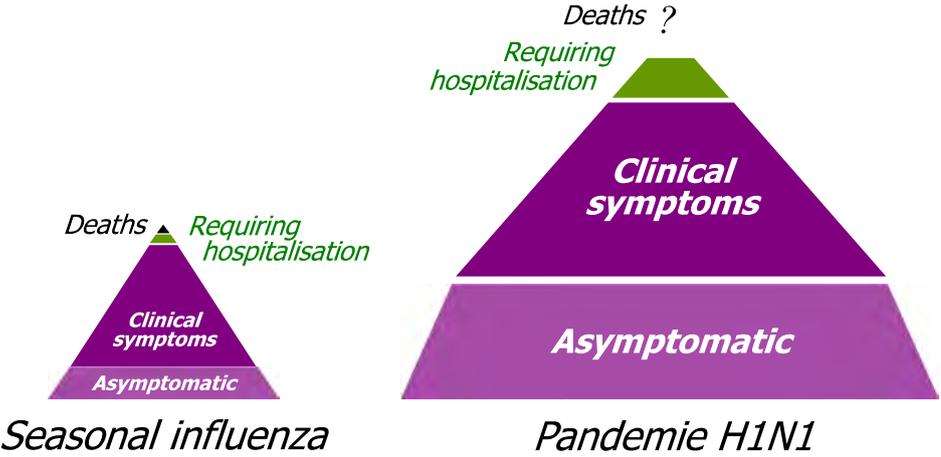
Severe cases



deaths



Comparison of the impact observed with the predictions: “minor” pandemic



Impact of influenza pandemics: the H1N1 Mexican flu



Figure 2: Estimated age-adjusted respiratory and cardiovascular mortality rate associated with 2009 pandemic influenza A H1N1 per 100 000 individuals by country

	Average life expectancy at birth (years) ¹¹	YLL due to pandemic influenza A H1N1 respiratory mortality	YLL if age distribution of deaths was similar to seasonal influenza*
Africa	53	2 278 800 (1 194 500-4 196 500)	556 100
Americas	76	1 050 600 (567 600-1 965 100)	361 800
Eastern Mediterranean	65	862 500 (446 100-1 645 900)	219 200
Europe	75	927 600 (506 800-1 756 400)	360 900
Southeast Asia	65	2 725 300 (1 407 900-5 243 400)	738 700
Western Pacific	75	1 862 200 (1 015 800-3 445 500)	605 000
Global	68	9 707 000 (5 138 700-18 252 800)	2 841 700

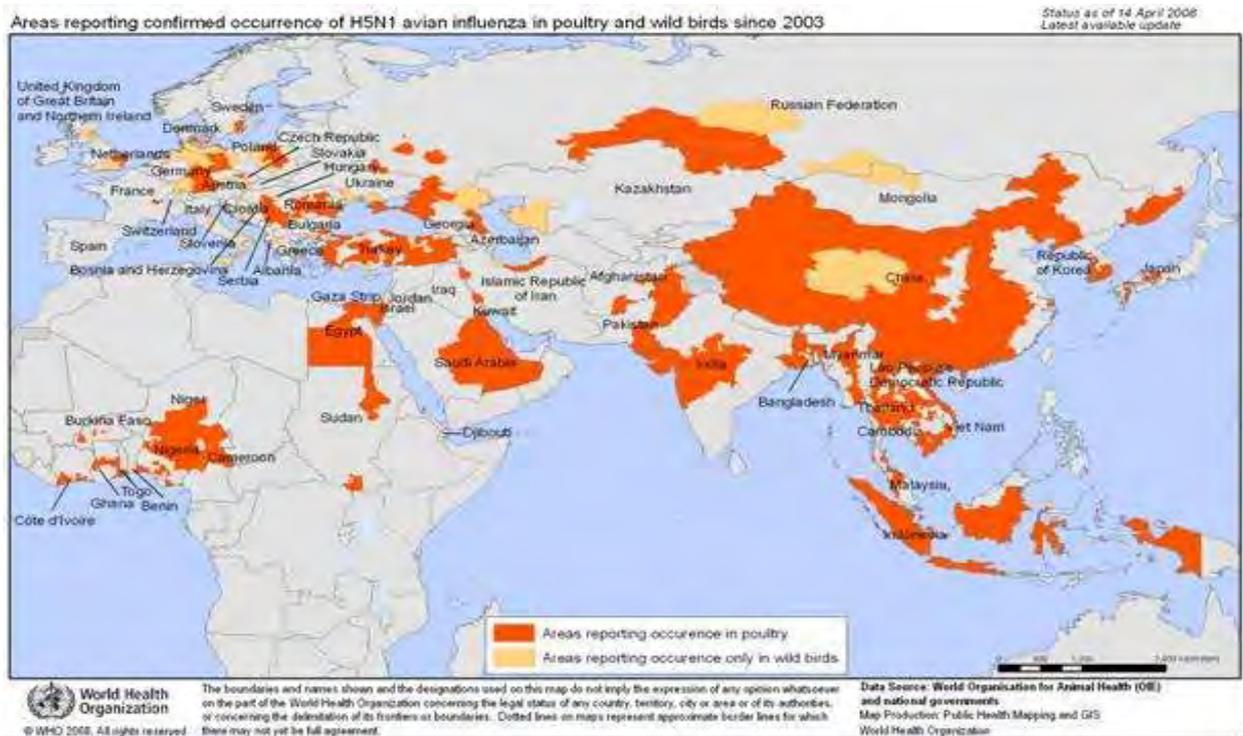
Data are total of medians (range), unless otherwise indicated. YLL=years of life lost. * Number of 2009 pandemic influenza A H1N1 deaths is redistributed across age groups to approximate the typical age distribution of seasonal influenza deaths in developed countries where estimates were available (90% for people aged >64 years, 9% for age 18-64 years, and 1% for age 0-17 years).

Table 4: YLL because of deaths associated with 2009 pandemic influenza A H1N1 during the first 12 months of virus circulation and YLL that would be lost with a seasonal influenza age distribution of deaths

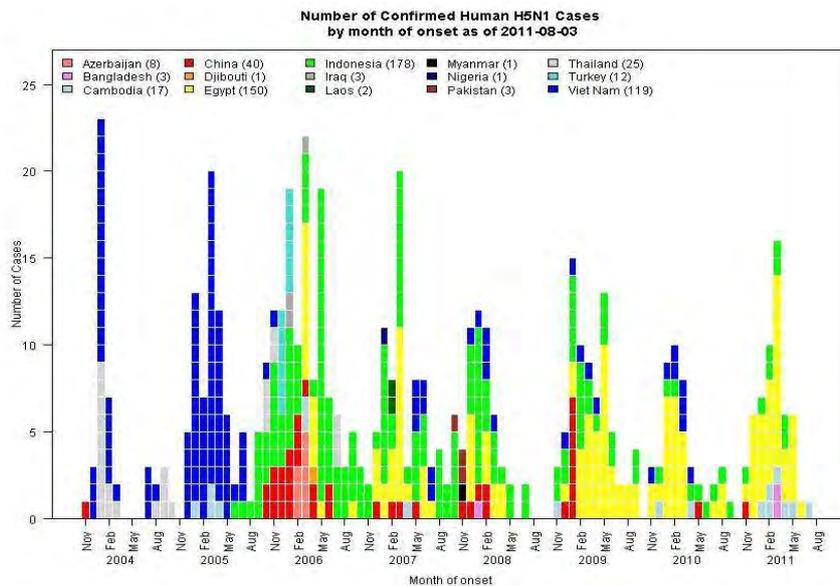
Dawood et al, Lancet (2012)

Alerte N° 1 : H5N1

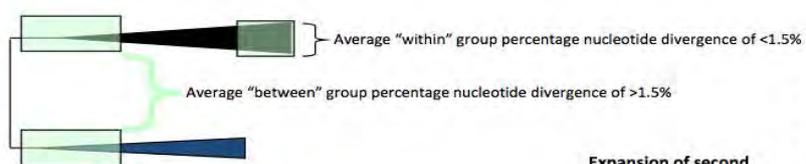
H5N1 (grippe aviaire)



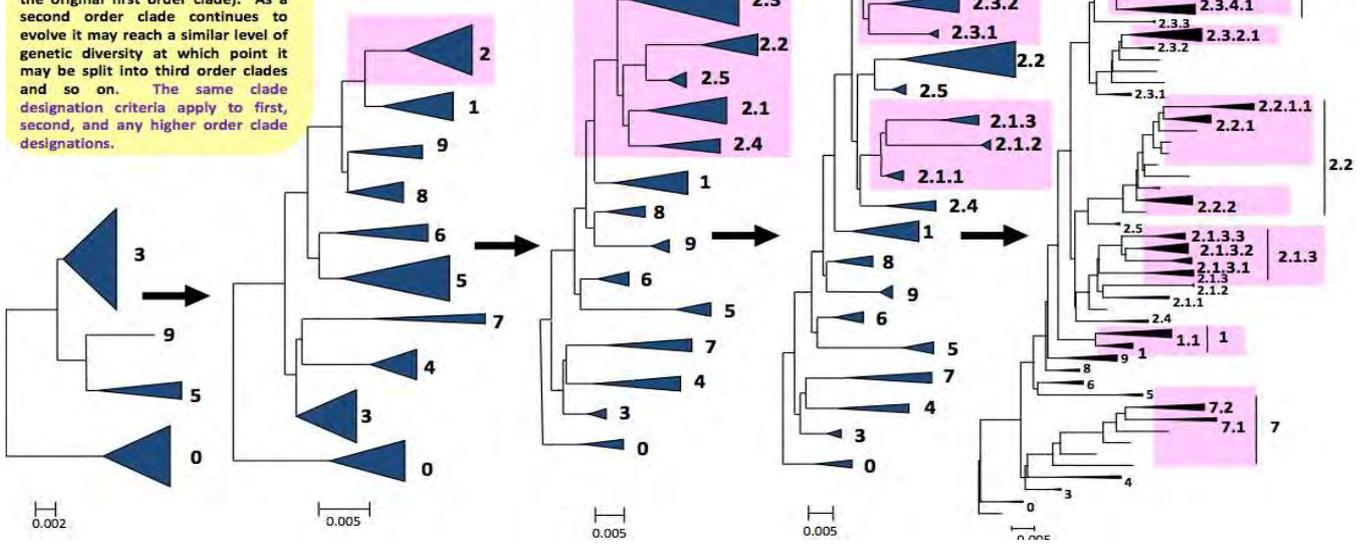
Distribution of the death recorded



Evolution of the Asian H5 Hemagglutinin



When discrete monophyletic groups begin to appear within a specific clade and those groups meet the nucleotide divergence criteria (as well as having bootstrap values >60), they are split into second order clades (but still considered part of the original first order clade). As a second order clade continues to evolve it may reach a similar level of genetic diversity at which point it may be split into third order clades and so on. The same clade designation criteria apply to first, second, and any higher order clade designations.

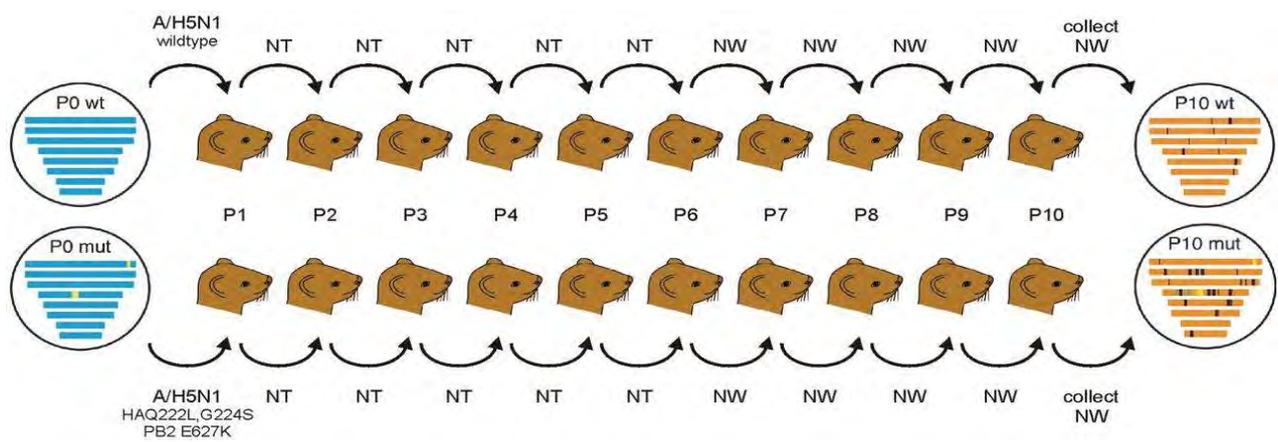


Expansion of first, second and third order clades into additional second, third and fourth order clades

Expansion of second order clades into additional third order clades

Expansion of clade 2 into five second order clades

Pas de transmission inter-humaine, mais...



Herfst et al, Science, 2012

Alerte N° 2 : H5N8

Alerte N° 3 : H7N9

Alerte N° 4 : H10N7

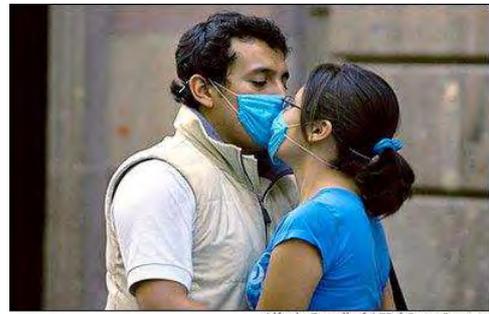
Alerte N° 5 : H5N8 (France)

Alerte N° 6 : H1N2v (France)

Gestion de la situation des virus influenza zoonotiques

C'est un défi :

- Expliquer l'incertitude
- Expliquer que c'est évolutif
- Expliquer qu'on peut changer de braquet
- Expliquer qu'il faut envisager le pire en espérant le meilleur



Worst case scenario durant une pandémie:

Exemples imaginés :

- Les fournisseurs d'accès Internet ne peuvent pas fournir suffisamment de trafic internet
- L'importation de marchandises en provenance de pays endémiques est impossible
- Les petites entreprises sous-traitantes sont aussi confrontées à l'absentéisme dû au personnel malade, ou au personnel s'occupant des enfants en raison de la fermeture de l'école. Impact sur les grandes entreprises
- Les centrales au charbon en Allemagne ne peuvent plus produire d'électricité en raison du manque d'extraction de charbon. Pénurie d'électricité en Allemagne
- La mortalité est 2 à 5 fois plus élevée en Afrique du Nord qu'en Europe. Migration massive vers l'Europe qui fermera ses frontières
- Le traitement antiviral n'est plus disponible en Suisse. Les suisses vont en Italie où les antiviraux sont disponibles en vente libre. Le nord de l'Italie fait face à une pénurie de médicaments
- La nourriture n'est pas livrée à Londres. Les 8 Millions d'habitants demandent de l'aide et fuient Londres pour rejoindre d'autres villes.
- Un nouveau produit « naturel » censé être actif contre la grippe a été livré aux gens par internet. On observe une intoxication massive qui entraîne une augmentation des taux d'hospitalisation.

Similitudes et différences entre les émergences Influenza et Coronavirus

- Réservoir
- Adaptation au nouvel hôte
- Mécanisme d'émergence

- Système de surveillance

- Fréquence
- Immunité croisée
- Impact

- Quelle réponse globale a apporter?