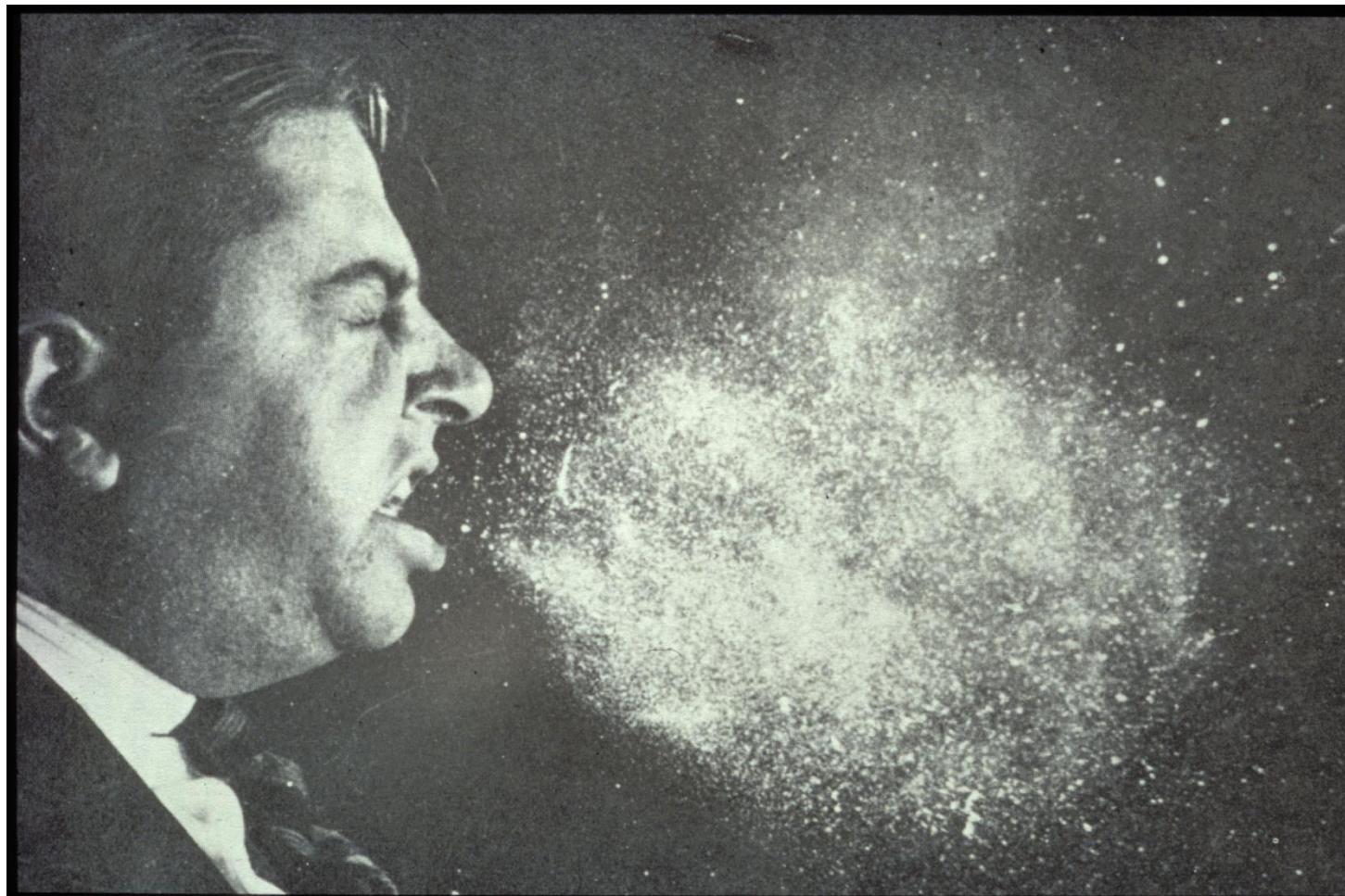


Emergence et diffusion des virus respiratoires à potentiel pandémique

Bruno Lina

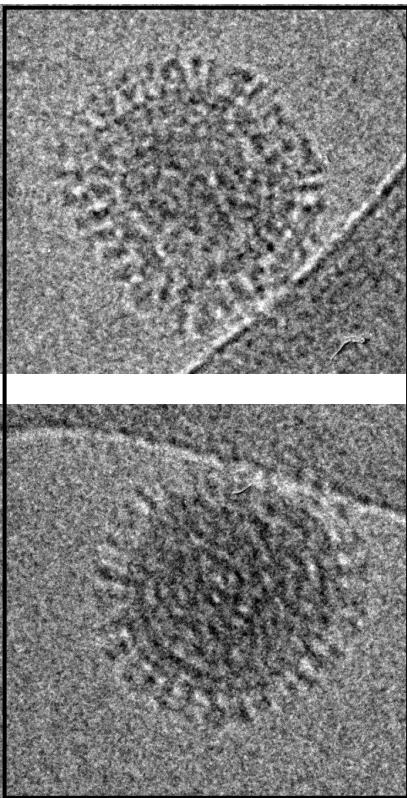
Lab Virology, IAI, Nat Ref Centre for respiratory viruses, Hospices Civils de Lyon, F69004, Lyon
Virpath, CIRI, Université de Lyon, F69372, Lyon

Une transmission respiratoire

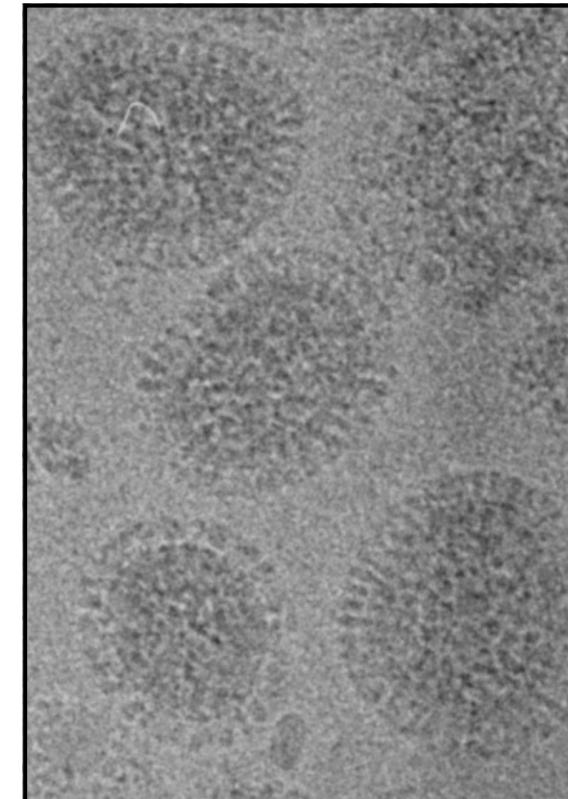


Acteur # 1 : les Influenzavirus

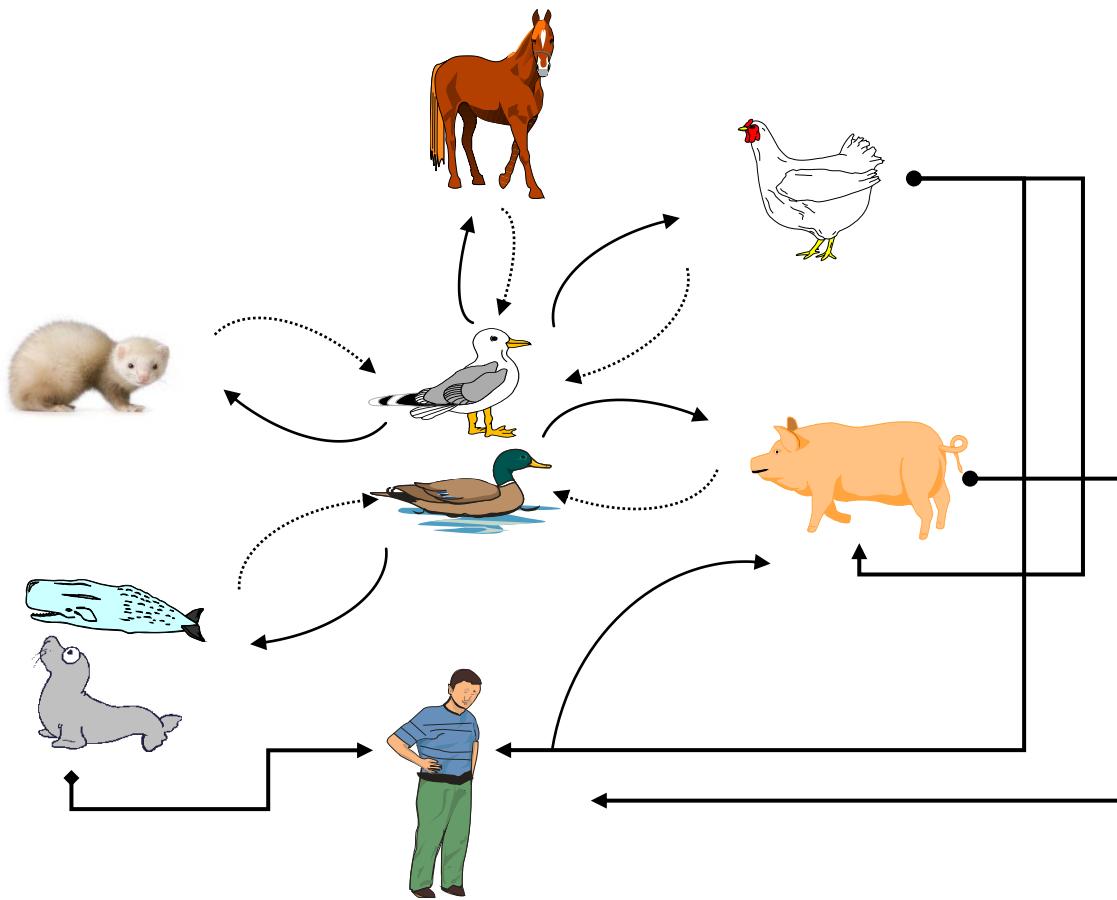
H1N1 A/NewCaledonia/20/99



H3N2 A/California/07/04



*Les vecteurs animaux**



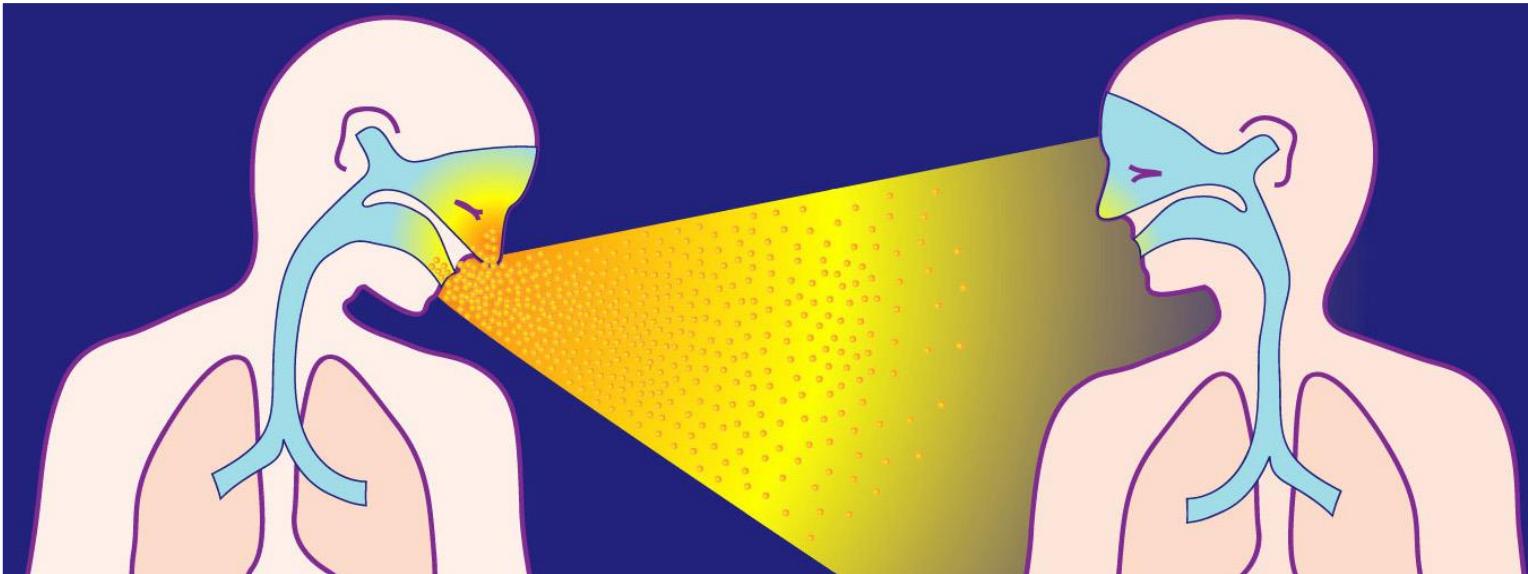
* Uniquement pour les pandémies

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

<i>N1</i>				
<i>N2</i>				
<i>N3</i>				
<i>N4</i>				
<i>N5</i>				
<i>N6</i>				
<i>N7</i>				
<i>N8</i>				
<i>N9</i>				

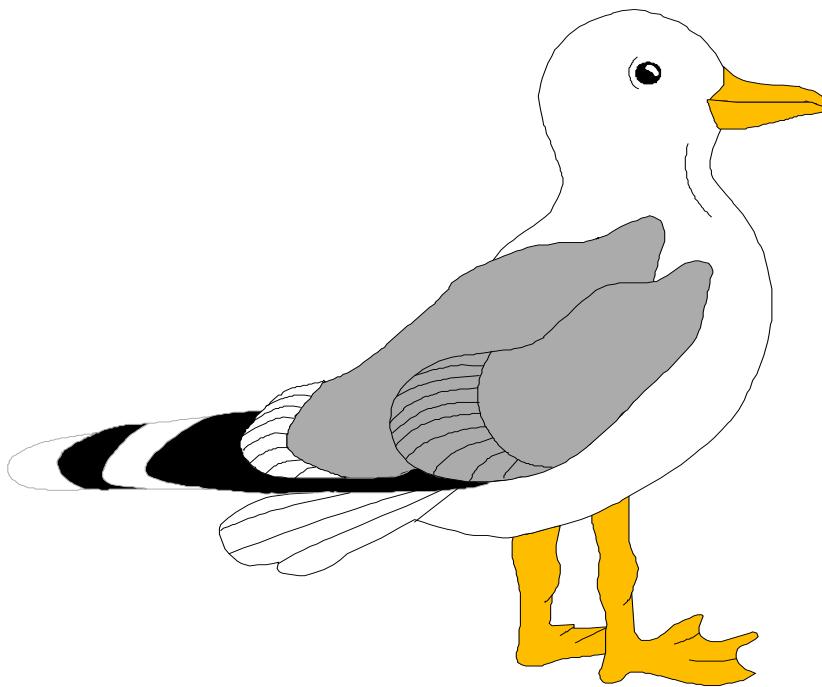
Les hôtes des différents sous-types de virus influenza A

La grippe: une infection virale à transmission aérienne

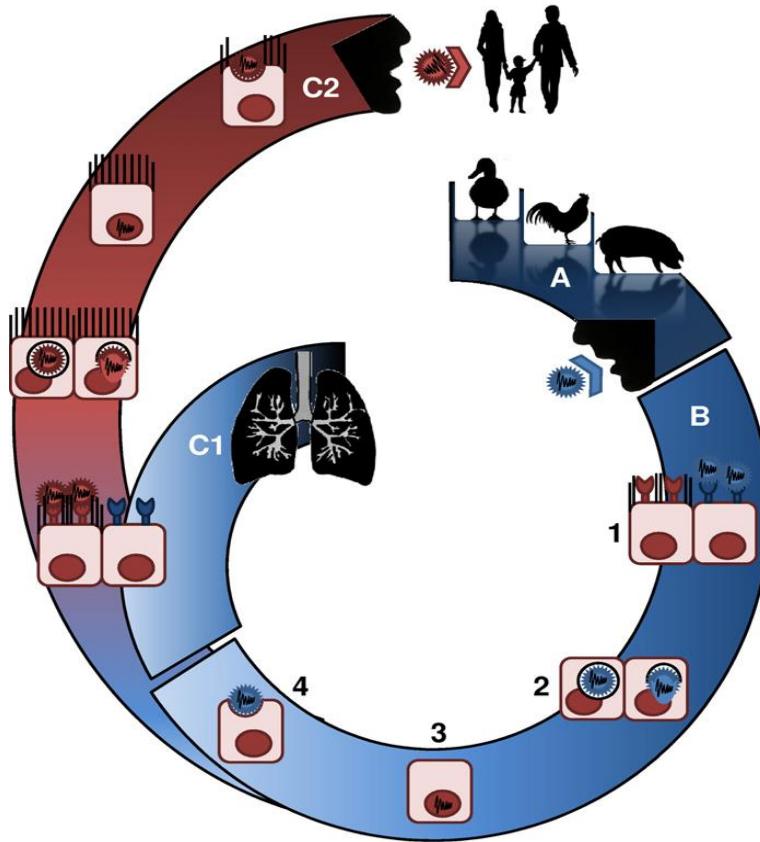


Le virus se propage par le biais des gouttelettes de salive et des petites particules en suspension dans l'air projetées par la toux ou les éternuements. Le virus pénètre dans l'organisme via le nez, la bouche et les yeux

La grippe aviaire: une infection impossible



Les étapes du franchissement



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

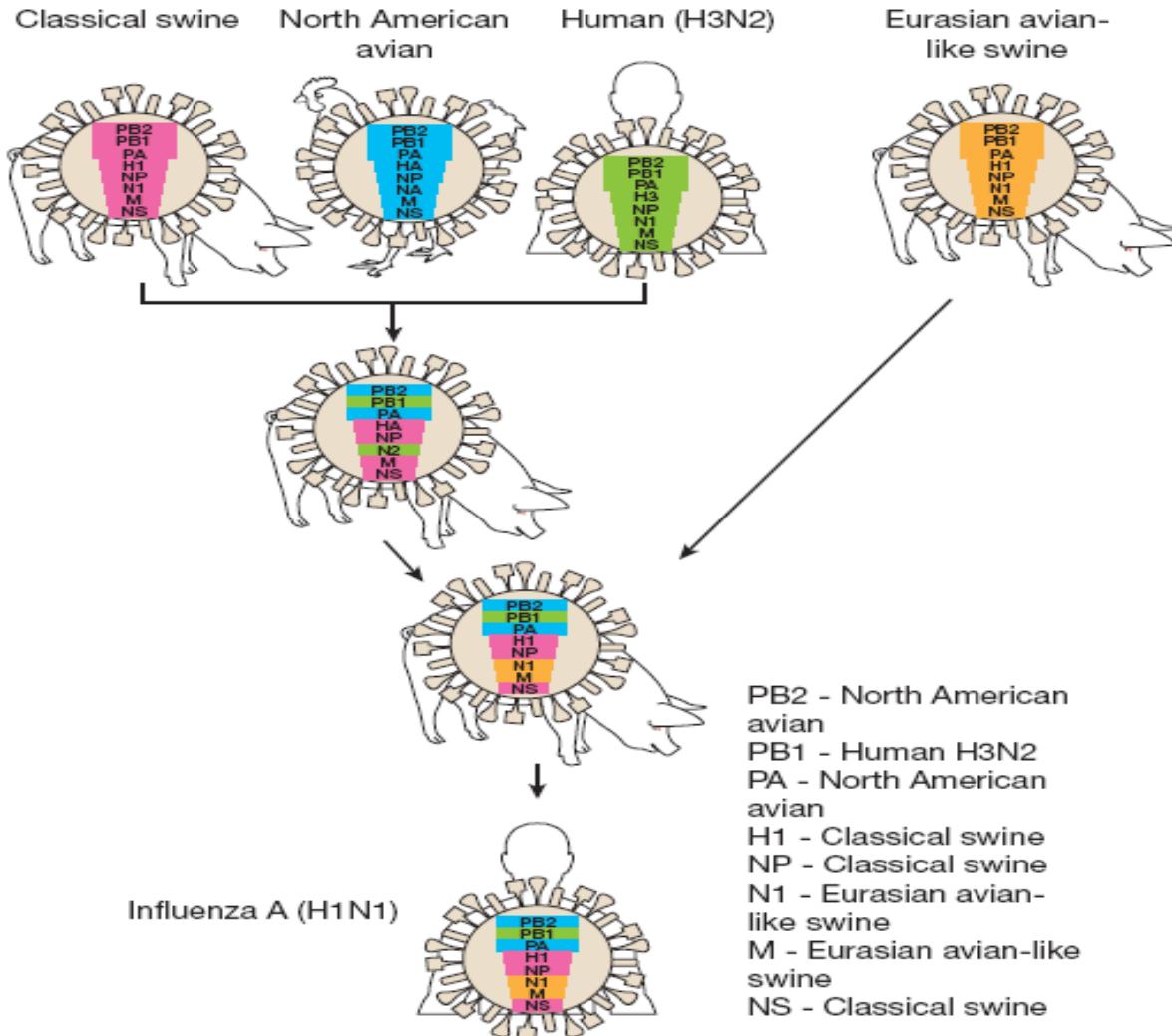
1 million



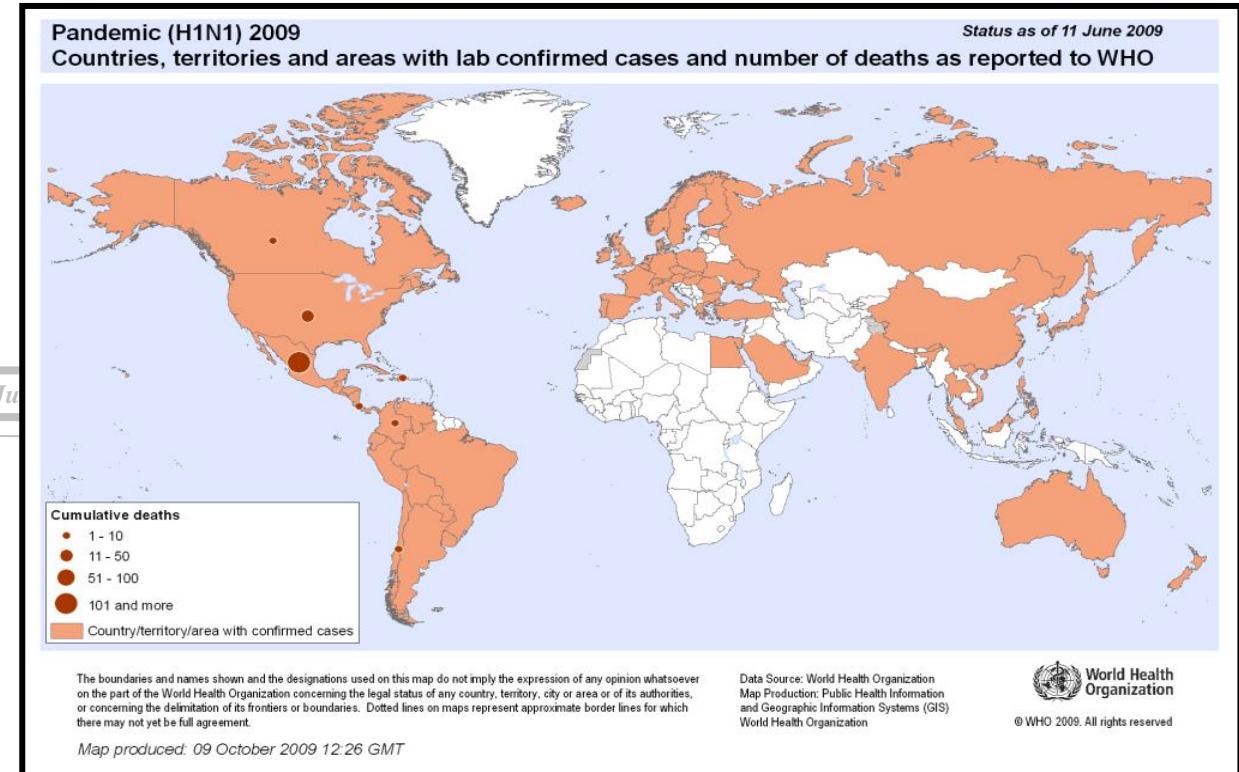
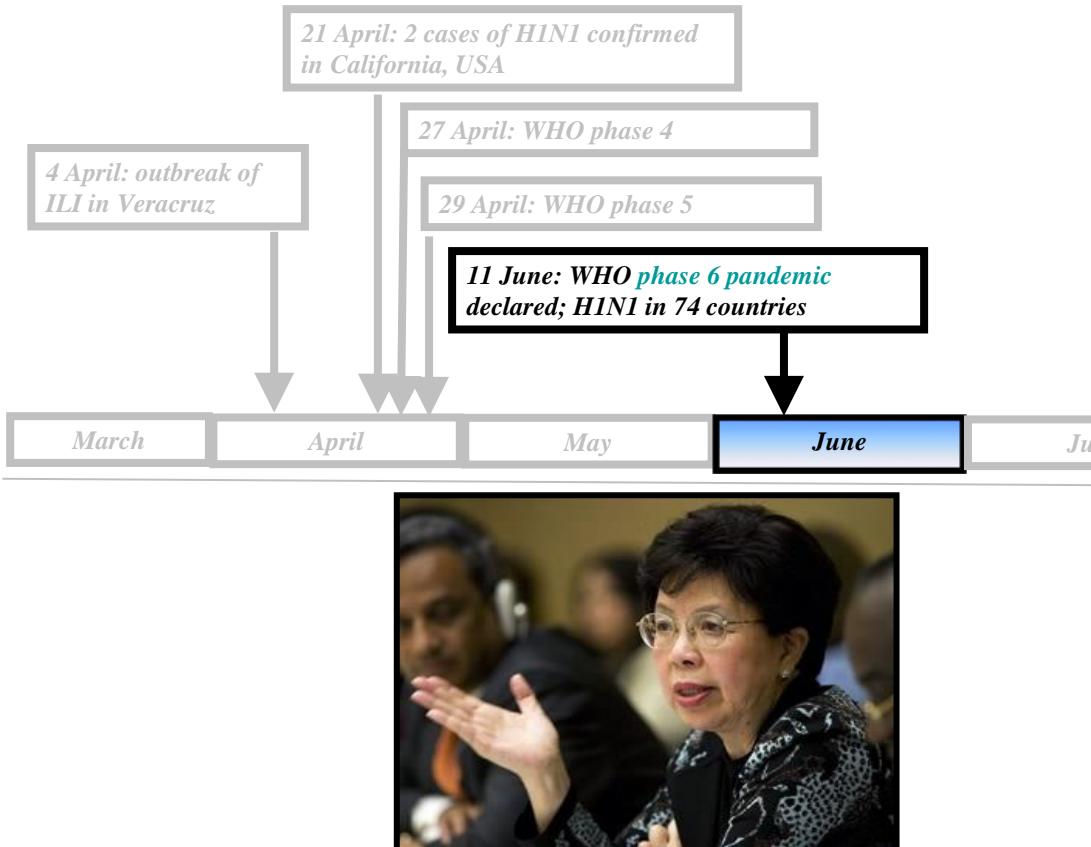
2009: "Swine Flu"

H1N1

0.7 million



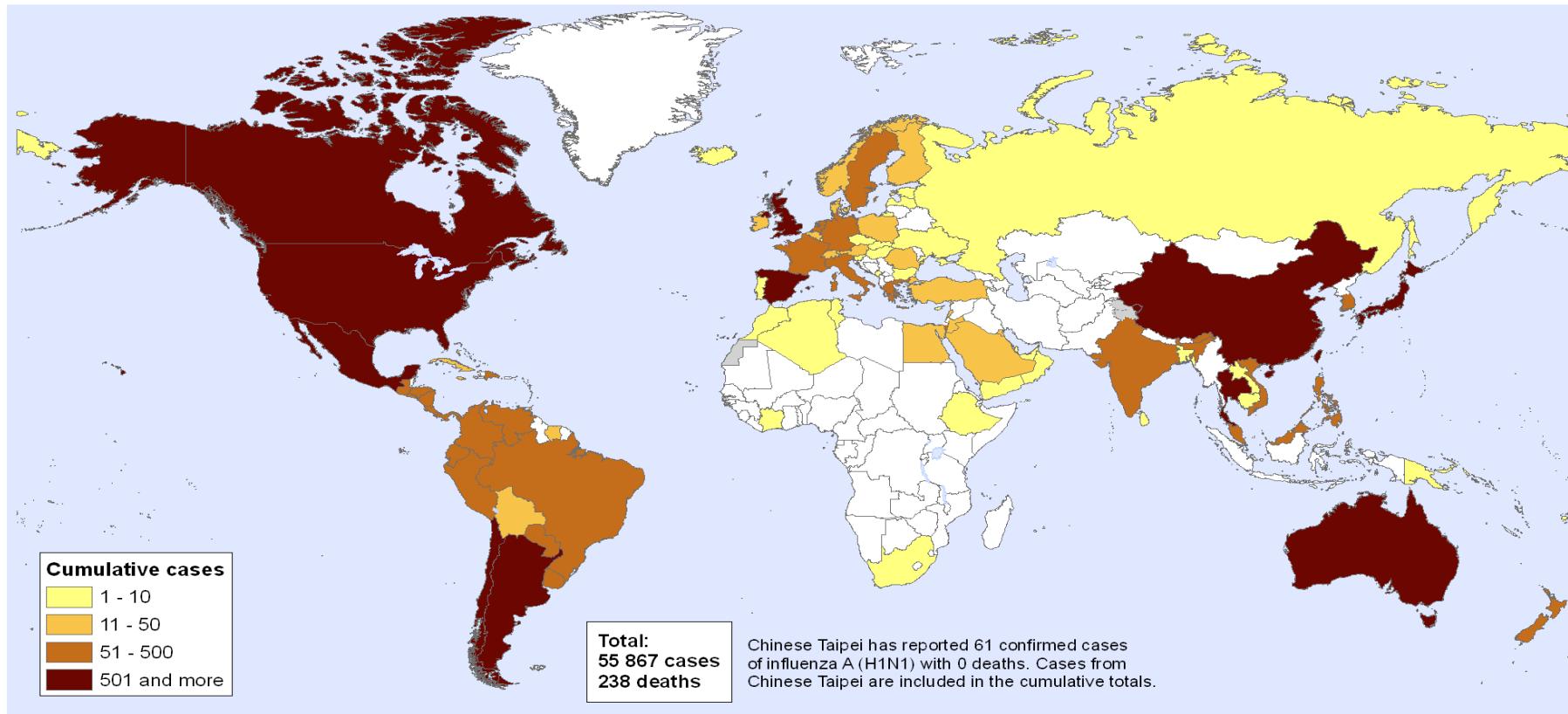
Pandemic H1N1 2009 Timeline



It took 6 weeks 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.

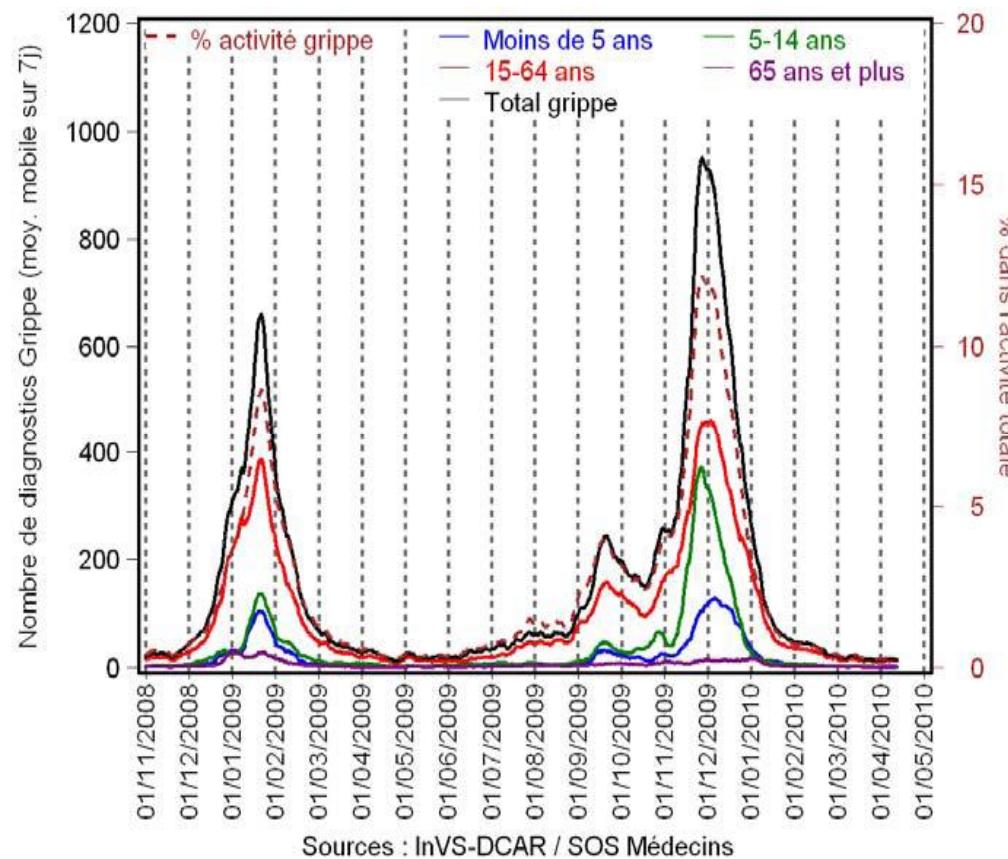
Map produced: 24 June 2009 10:00 GMT

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

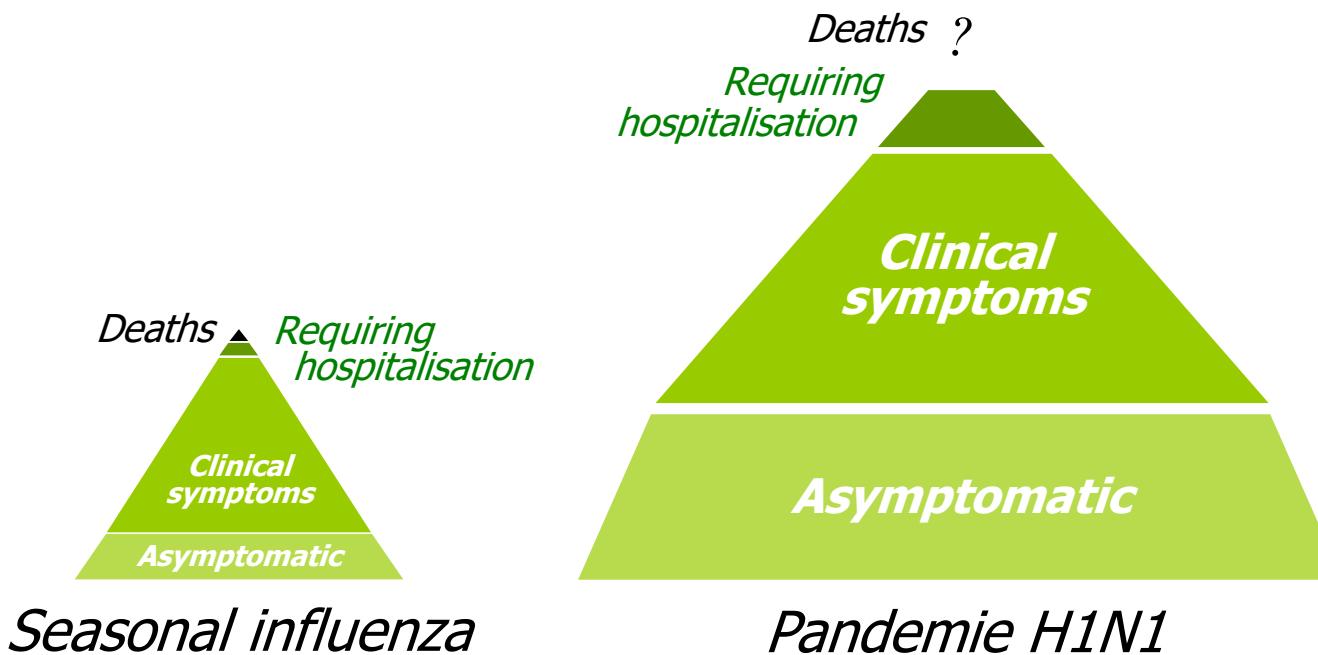


© WHO 2009. All rights reserved

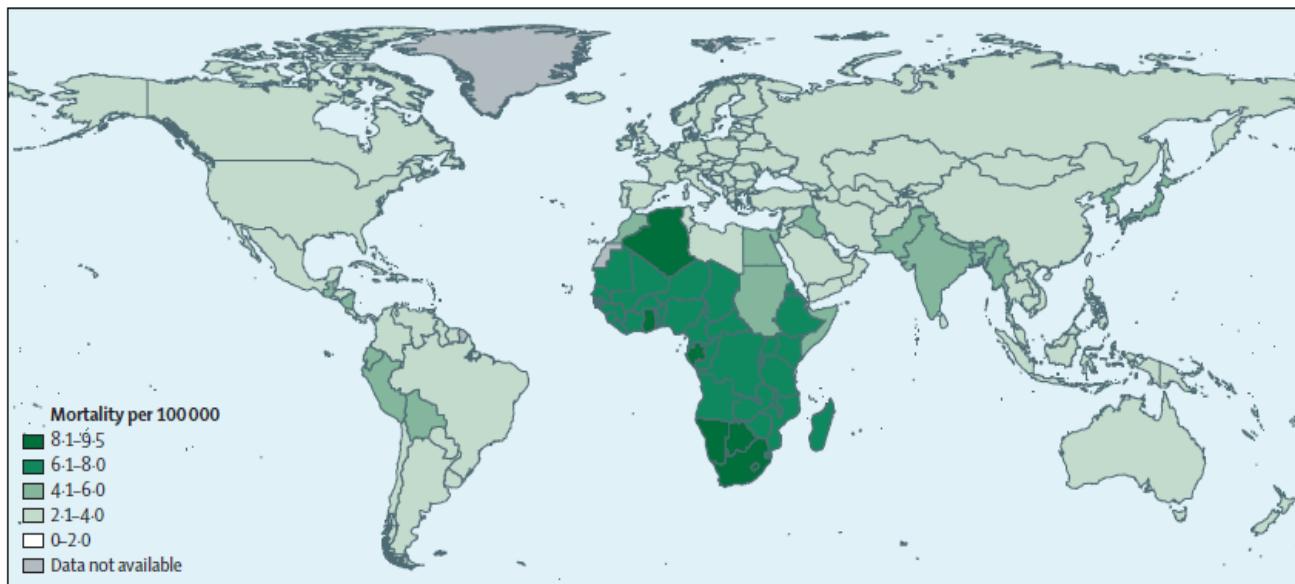
Impact en France



Comparison de l'impact observé avec les prévisions : une pandémie modérée



Impact de la pandémie influenza H1N1pdm09 :



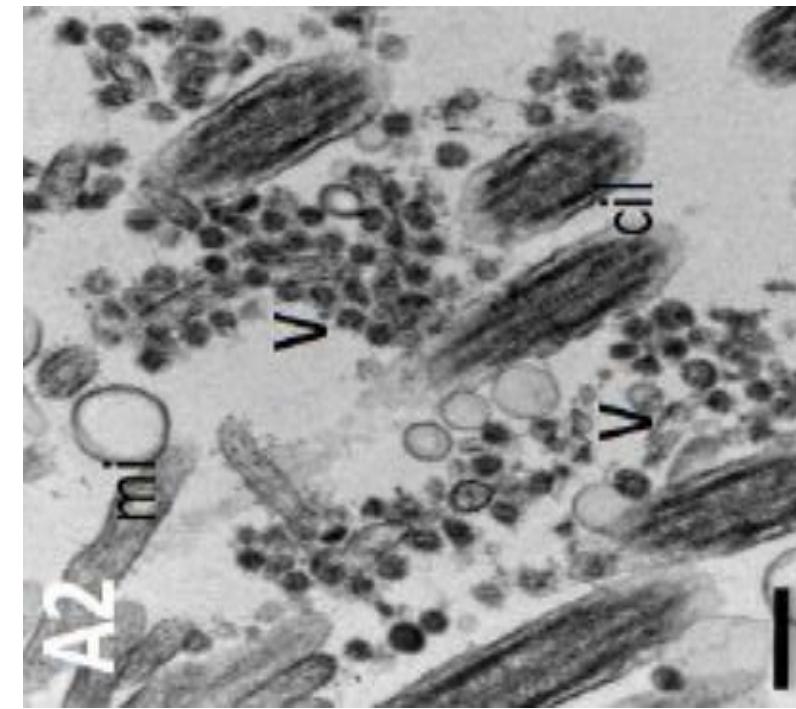
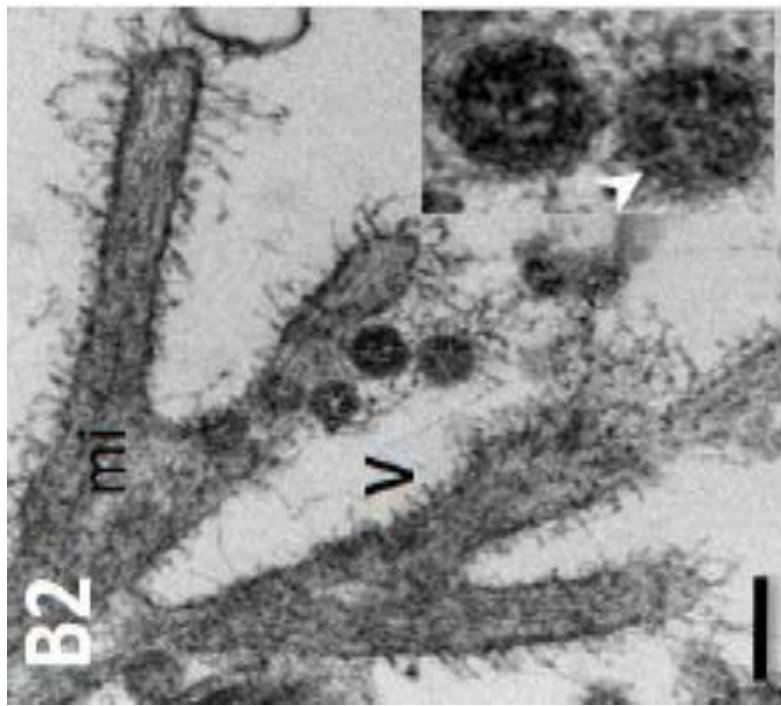
	Average life expectancy at birth (years) ³²	YLL due to pandemic influenza A H1N1 respiratory mortality	YLL if age distribution of deaths was similar to seasonal influenza*
Africa	53	2 278 800 (1 194 500–4 196 500)	556 100
Americas	76	1 050 600 (567 600–1 965 100)	361 800
Eastern Mediterranean	65	862 500 (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).

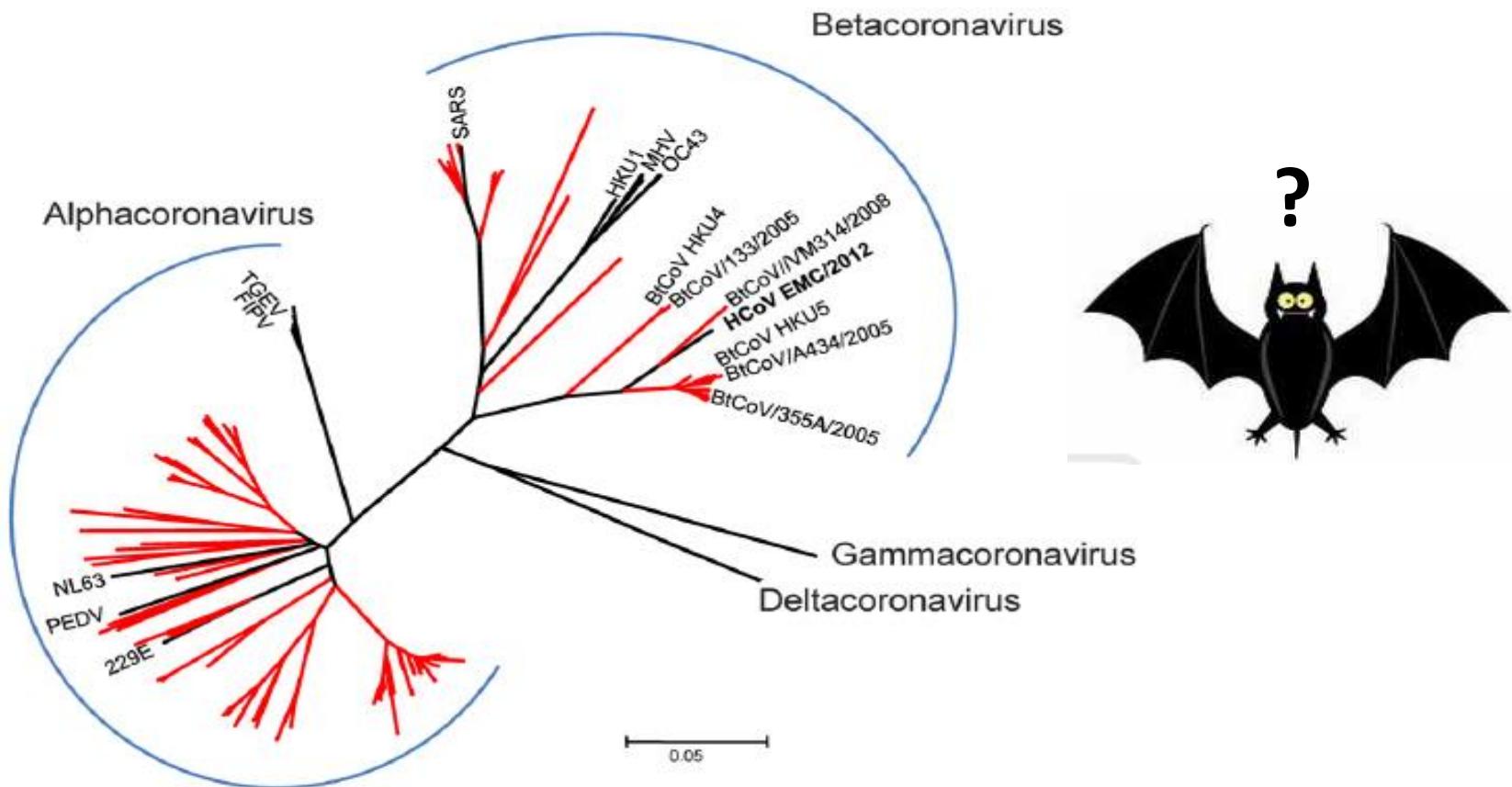
Table 4: YLL because of deaths associated with 2009 pandemic influenza A H1N1 during the first 12 months of virus circulation and YLL that would be lost with a seasonal influenza age distribution of deaths

Dawood et al, Lancet (2012)

Acteur # 2 : les Coronavirus



Le SARS CoV

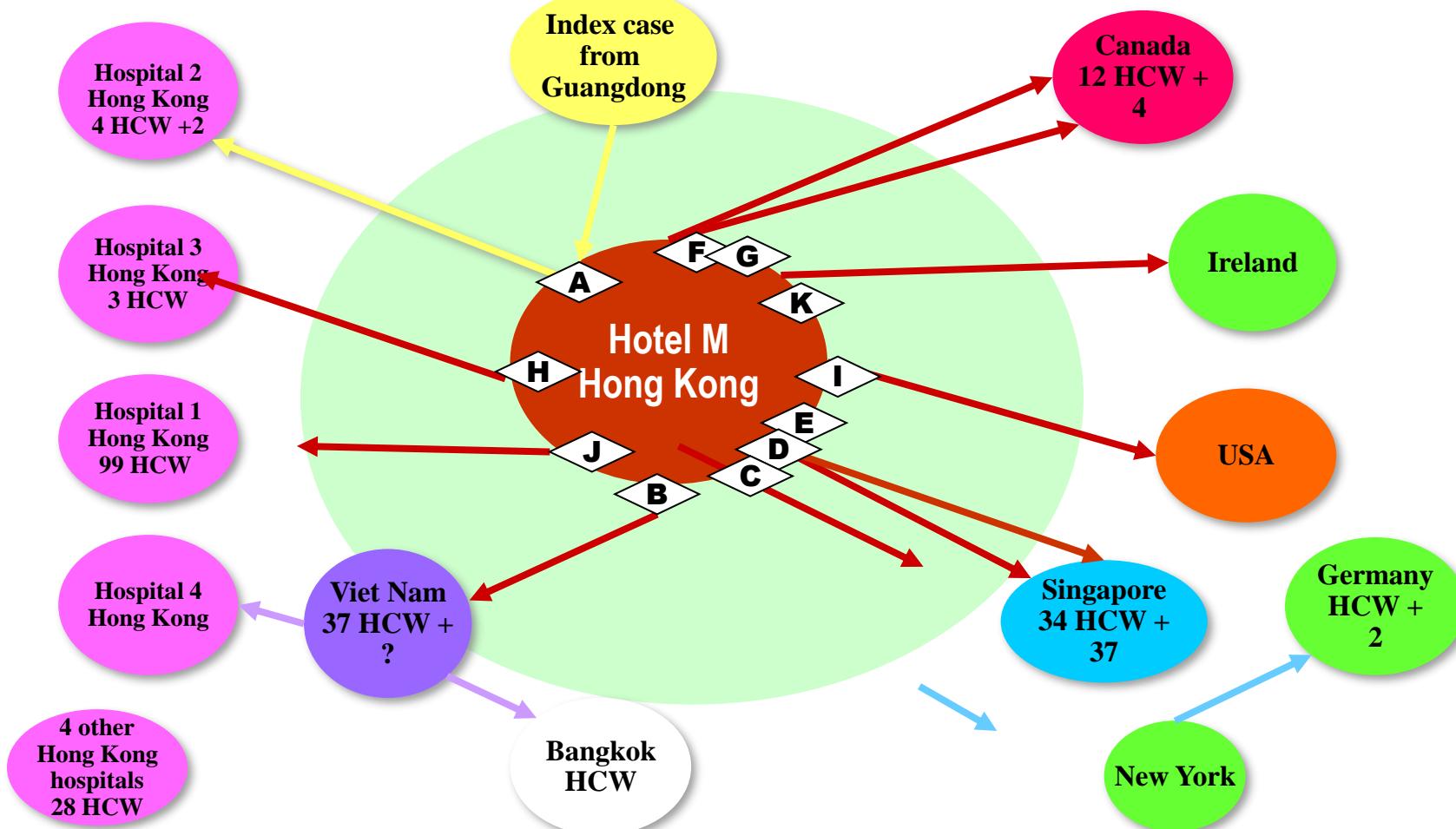


Bat coronavirus	Host	Location	Accession number
BtCoV/VM314/2008	<i>Pipistrellus</i> bat	Netherlands	GQ259977
BtCoV/133/2005	<i>Tylonycteris</i> bat	China	DQ648794.1
BtCoV/ 355A/2005	<i>Pipistrellus</i> bat	China	DQ648809.1
BtCoV/A434/2005	<i>Pipistrellus</i> bat	China	DQ648819.1
HKU4	<i>Pipistrellus</i> bat	China (HK)	DQ249214.1
HKU5	<i>Tylonycteris</i> bat	China (HK)	DQ249217.1

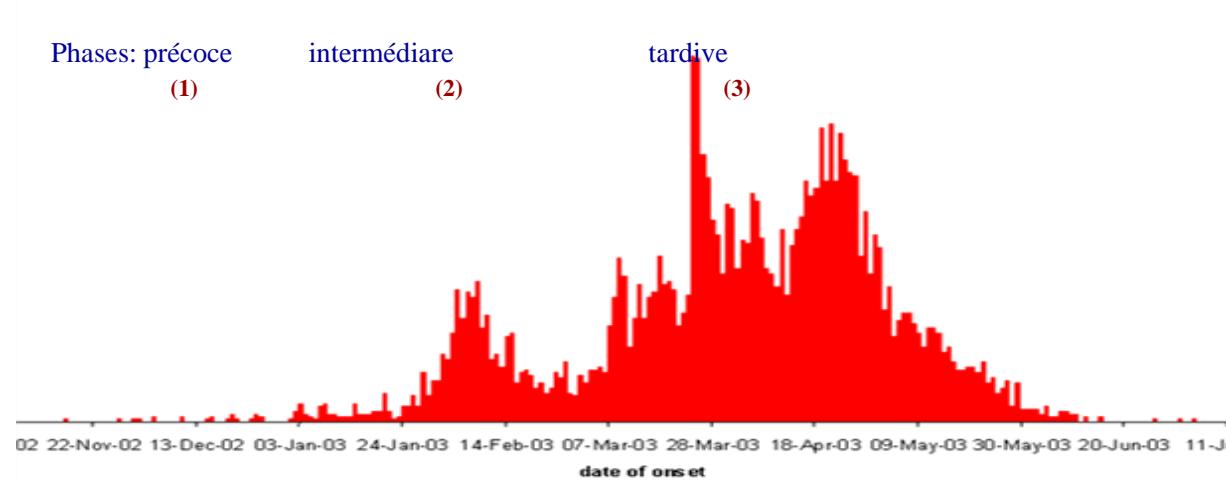
Renee W. Y. Chan and Leo L. M. Poon
 2013. The Emergence of Human Coronavirus EMC: How
 Scared Should We Be? . mBio 4(2): .
 doi:10.1128/mBio.00191-13.

Hôtel M. à Hong Kong , février 2003

219 soignants
30 non-soignants



Novembre 2002-Janvier 2003 : dans la province de Guangdong quelques cas de pneumonies atypiques progressant vers une détresse respiratoire

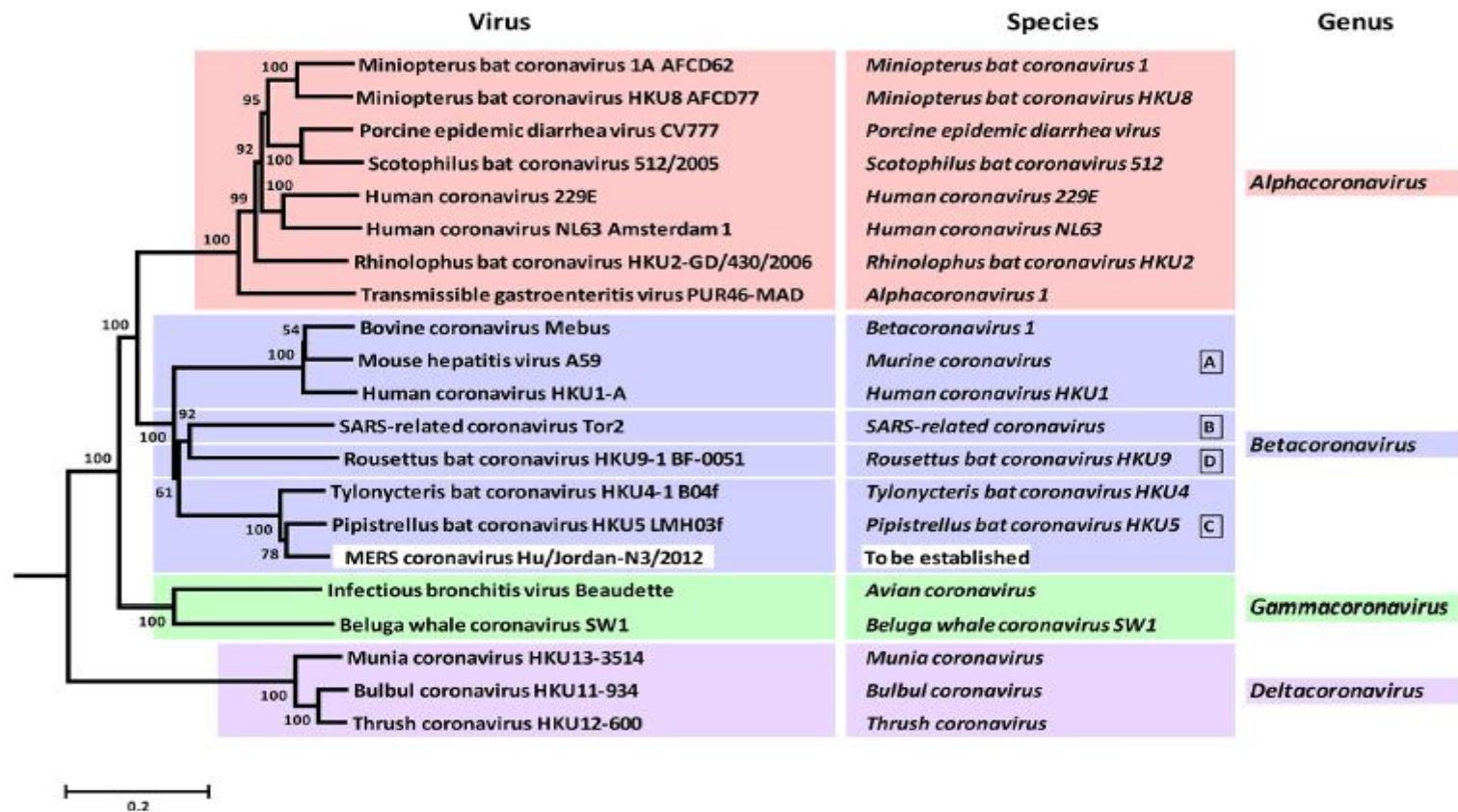


- **Janvier-Février 2003:** épidémies nosocomiales (2)
- **Février 2003:** épisode de l'hôtel M. à Hong Kong (3)
 - diffusion mondiale en China (5327), à Hong Kong (1755), Taiwan (686), Singapour (206), au Vietnam (63), au Canada (250) et en Europe (37)
- **Mars 2003 :**
 - mise en place des stratégies pour contenir l'épidémie
 - identification du SARS-CoV
- **Juillet 2003** : Notification par l'OMS de la fin de l'épidémie :

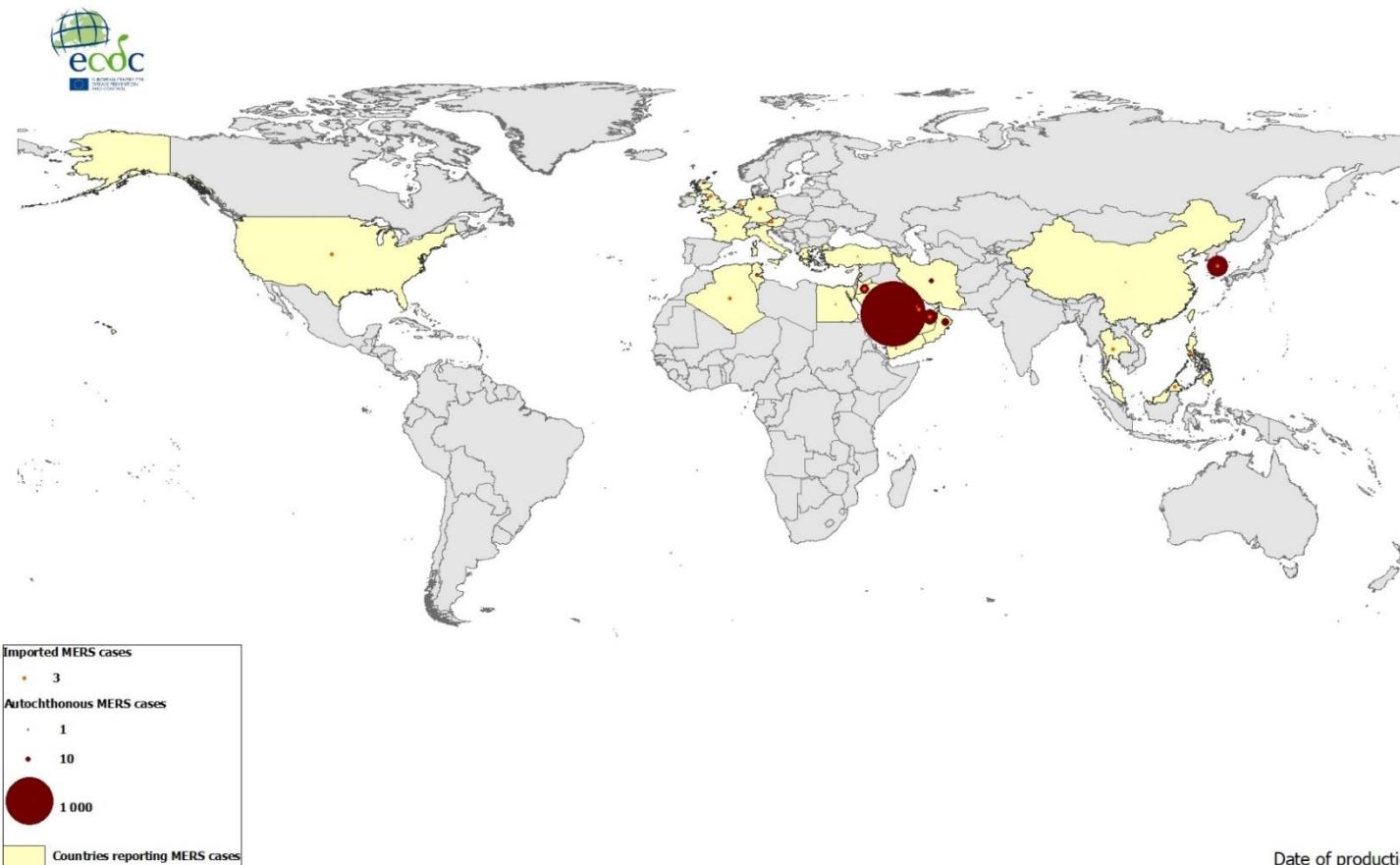
8460 cas probables et 808 décès

Le Mers CoV

Identification du MERS-CoV (2012) et hypothèses sur le réservoir

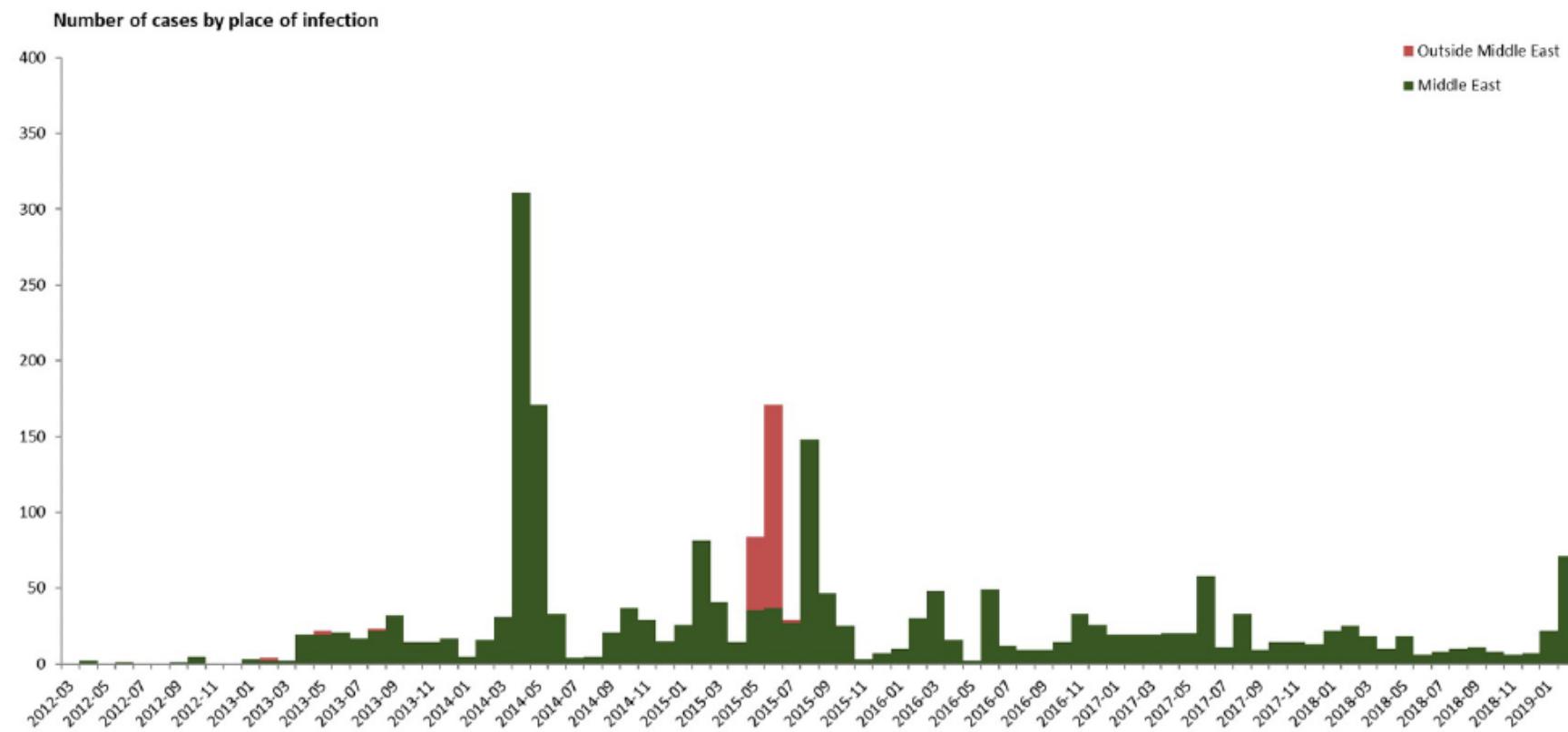


Geographical distribution of confirmed MERS-CoV cases by reporting country,
April 2012–7 March 2019

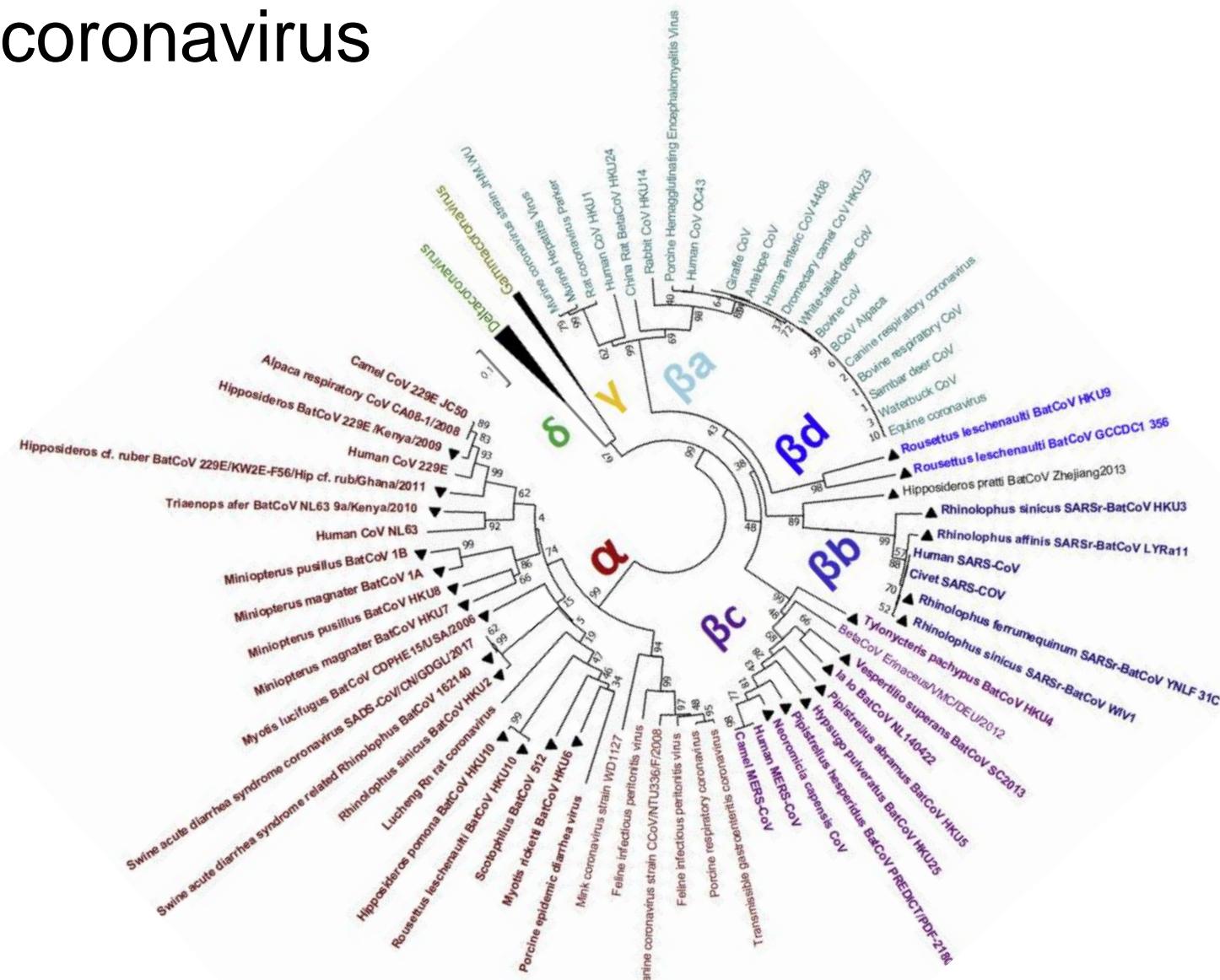


Distribution of confirmed cases of MERS-CoV by place of infection and month of onset, from March 2012 and as of 07 March 2019

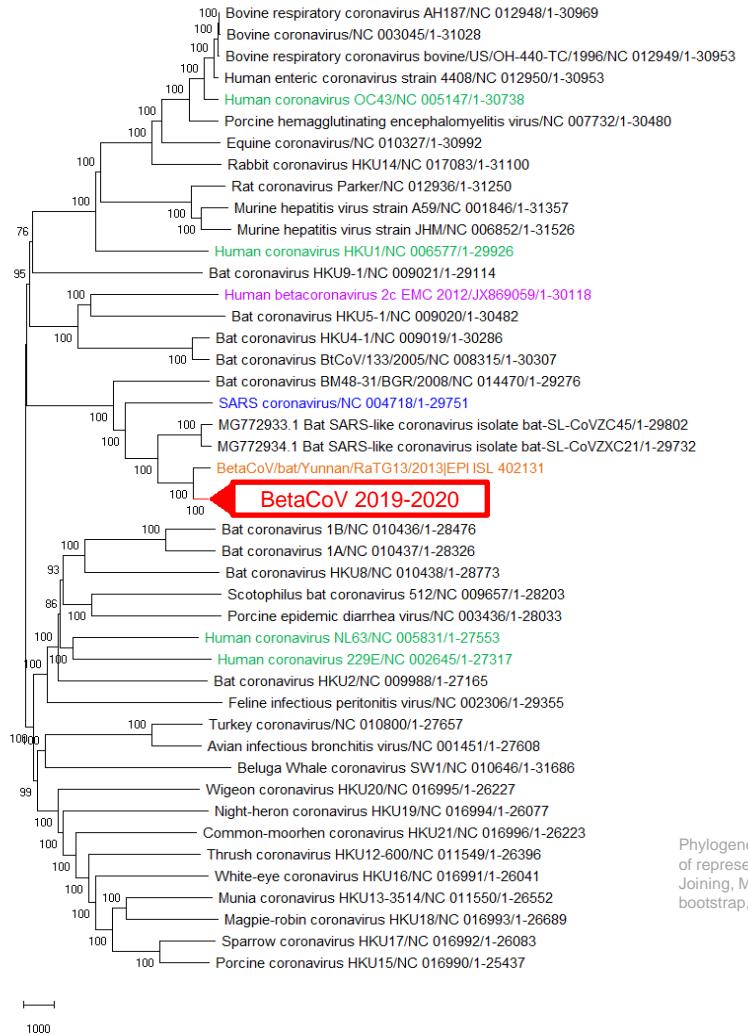
ECDC



La phylogénie des coronavirus



Le SARS CoV-2



Full genome tree all CoV families

- New nearest bat precursor shared by Zhengli Shi's lab included (RaTG13/EPI_ISL_402131)**

Genome identity to BetaCoV:

- 96% **RaTG13** (nearest bat precursor)
- 88% ZC45/ZXC21 bat precursor
- 80% **SARS**

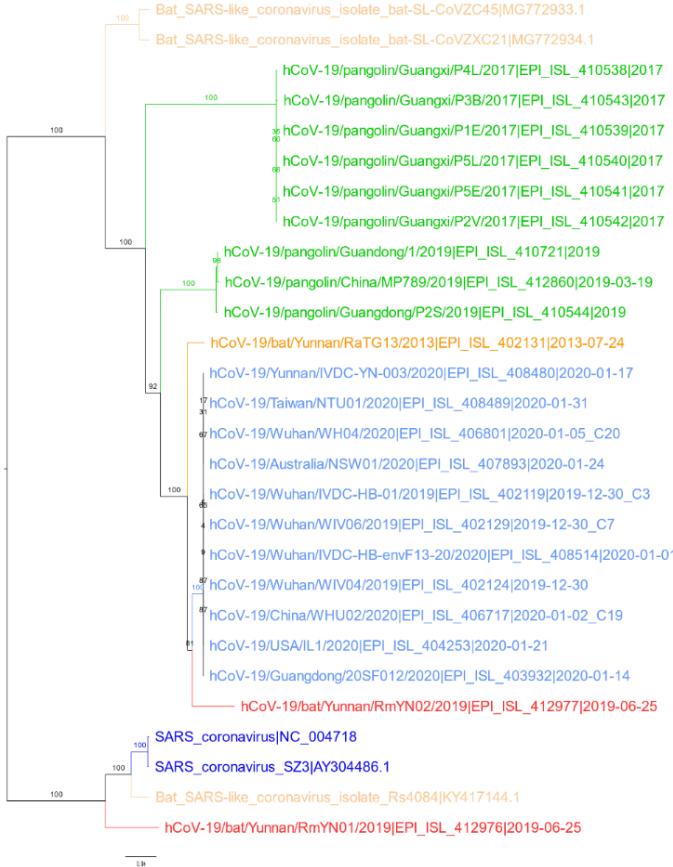
Orange ... bat RaTG13
 Red ... BetaCoV 2019-2020
 Blue ... SARS CoV
 Purple ... MERS CoV
 Green ... common cold CoV

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

Phylogenetic tree of Wuhan CoV full genome sequences in context of representatives of all CoV families (whole genome Neighbor Joining, Maximum Composite Likelihood, uniform rates, 500 bootstrap, MegaX)

GISAID
 by BII, A*STAR Singapore

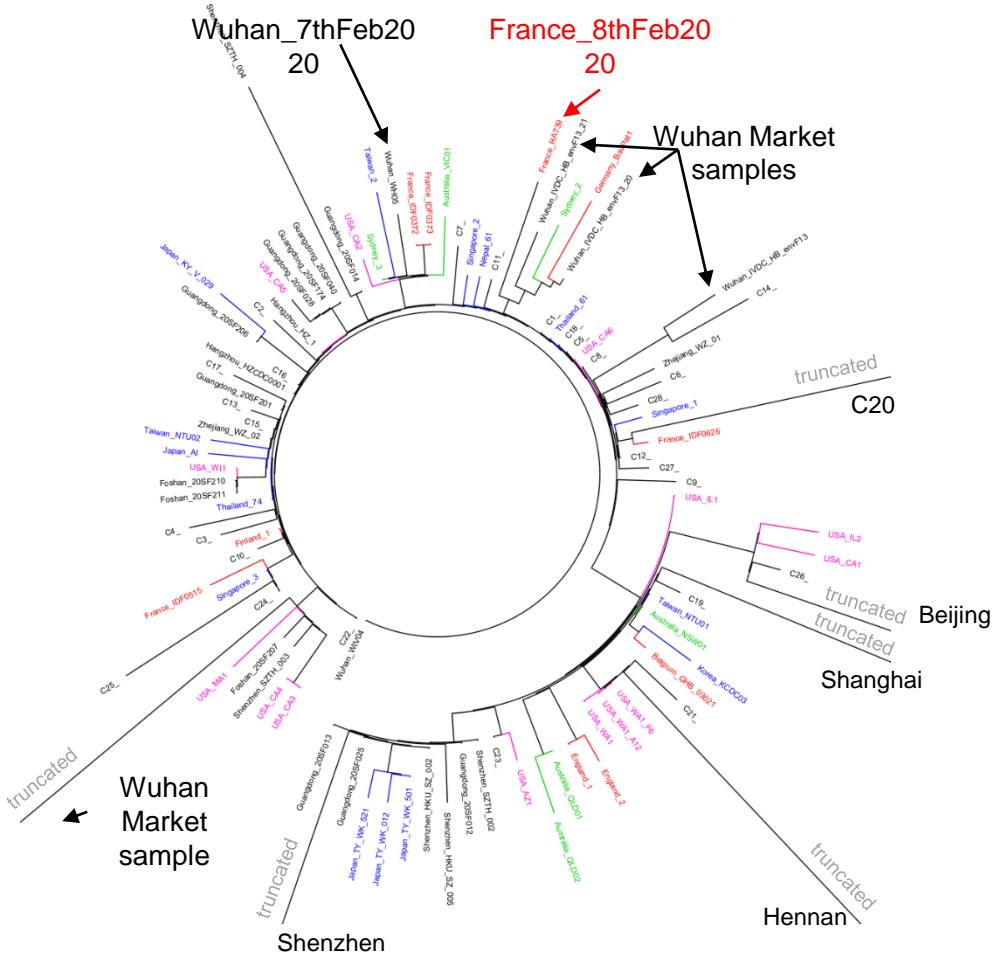
Phylogénie genome entier des précurseurs de SARS-CoV-2



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

- 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

Black ... China (Wuhan cases listed as C#)
 Blue ... Asia (not China)
 Green ... Oceania
 Magenta ... North America
 Red ... Europe

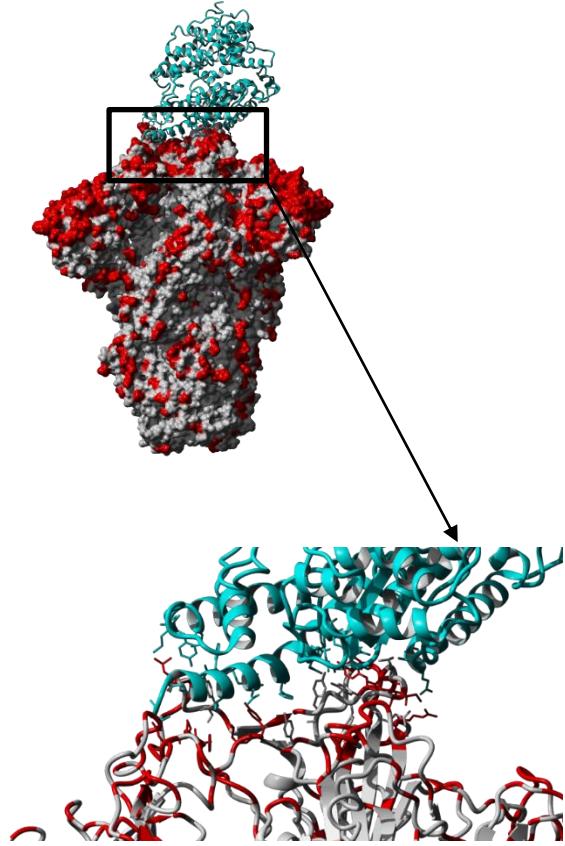


Phylogenetic tree created with RAXML-NG (Maximum Likelihood tree search, 10 randomized parsimony starting trees, GTR model, Gamma distributed rates, 500 bootstrap) and visualized in FigTree

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



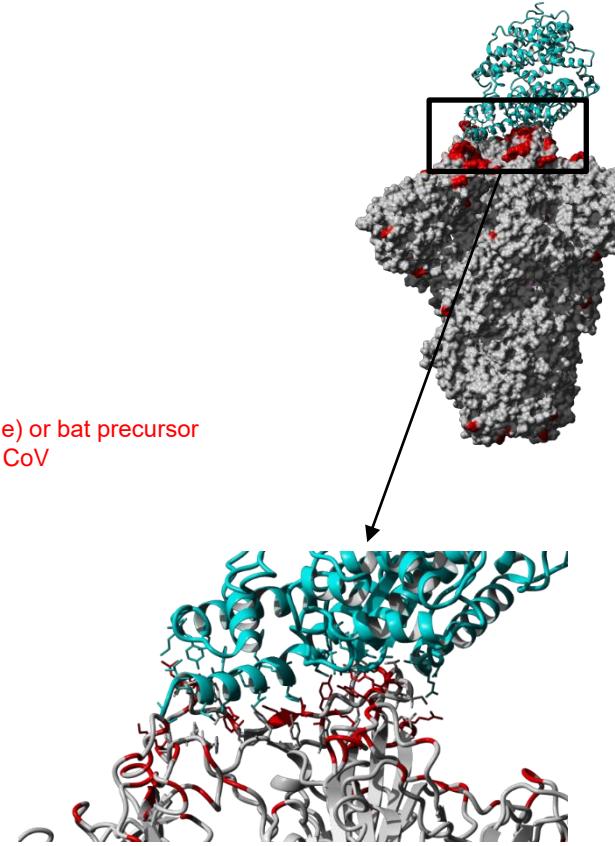
Host receptor binding site differences between SARS, bat precursor (RaTG13) and human outbreak BetaCoV



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

Additional Analysis for RaTG13 sequence from Zhengli Shi's lab

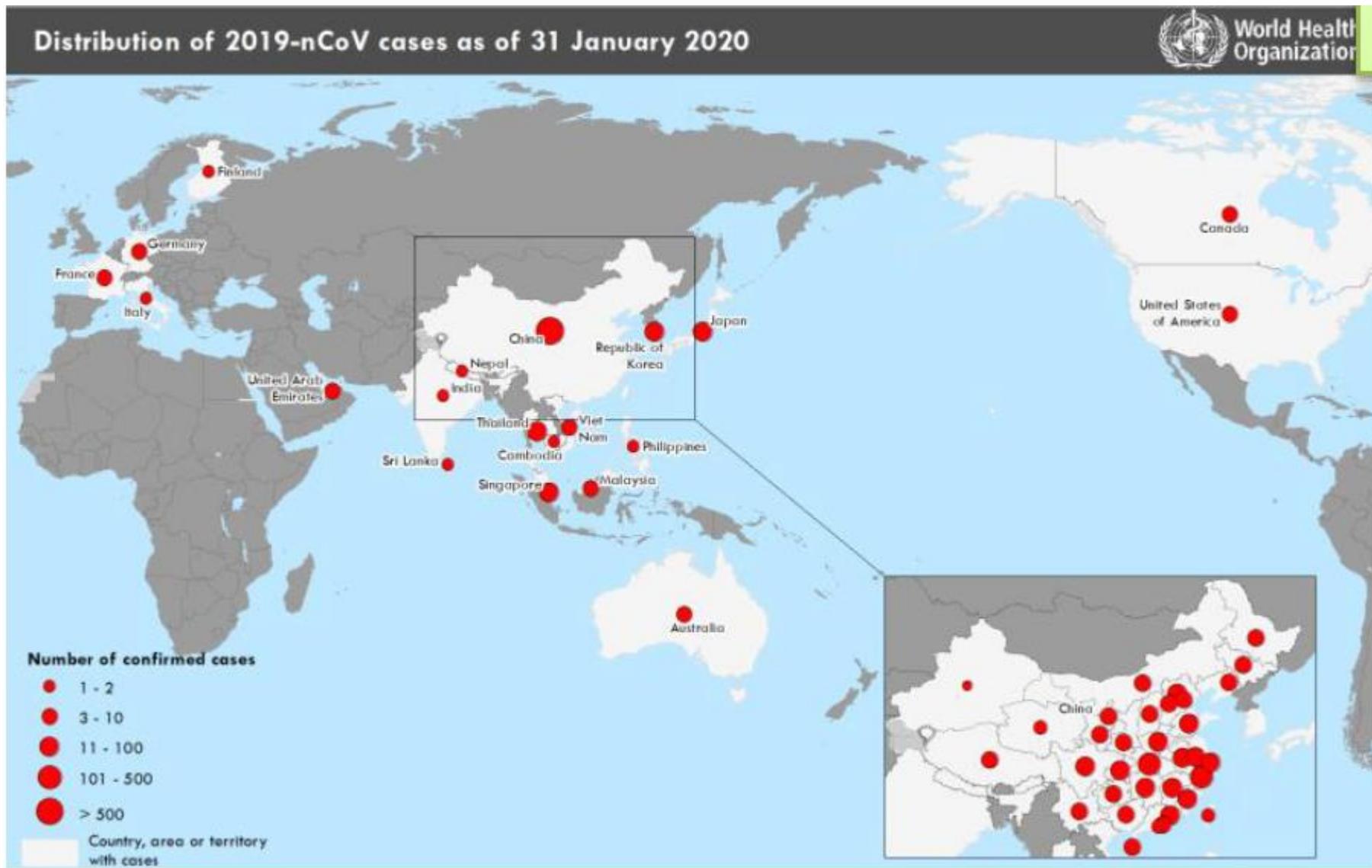
CAS Key Laboratory of Special Pathogens,
Wuhan Institute of Virology



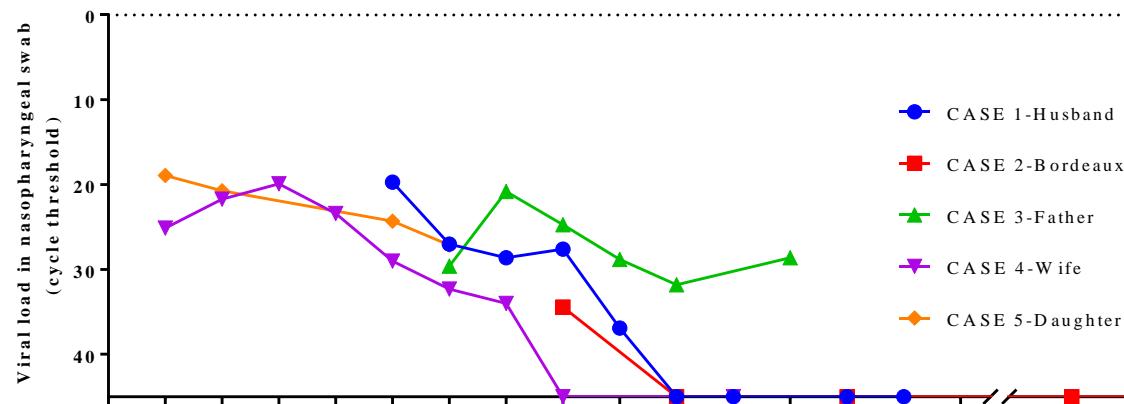
Le 23 janvier 2020



Le 31 janvier 2020



Biologie des premiers patients en France



	Day after onset	1*	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	//	20
Blood	case #1						nd	-	-	-	-	-	nd	nd	-	-			
	case #2								nd	nd	-	nd	nd	nd	nd	nd	nd	//	
	case #3							+	+	+	nd	nd	nd	+					
	case #4						nd	//											
	case #5						nd	-	-	-	nd	//							
Stools	case #1							nd	-	-	nd	nd	-	-	nd	nd	-		
	case #2								nd	nd	-	nd	nd	nd	nd	nd	nd	//	
	case #3								nd	-	nd	-	nd	-					
	case #4						nd	+	+	nd	nd	+	nd						
	case #5						nd	nd	+	nd	+								
Conjunctiva	case #1							nd	nd	-	-	nd	-	nd	nd	-	-		
	case #3								nd	nd	-	nd	-	nd	nd				
	case #4						nd	nd	-	-	nd	-	nd						
	case #5						nd	nd	-	nd	-	nd							
Pleural fluid	case #3								nd	nd	nd	nd	nd	nd	+				

* symptom onset

nd: not determined

Situation au 19 février 2020

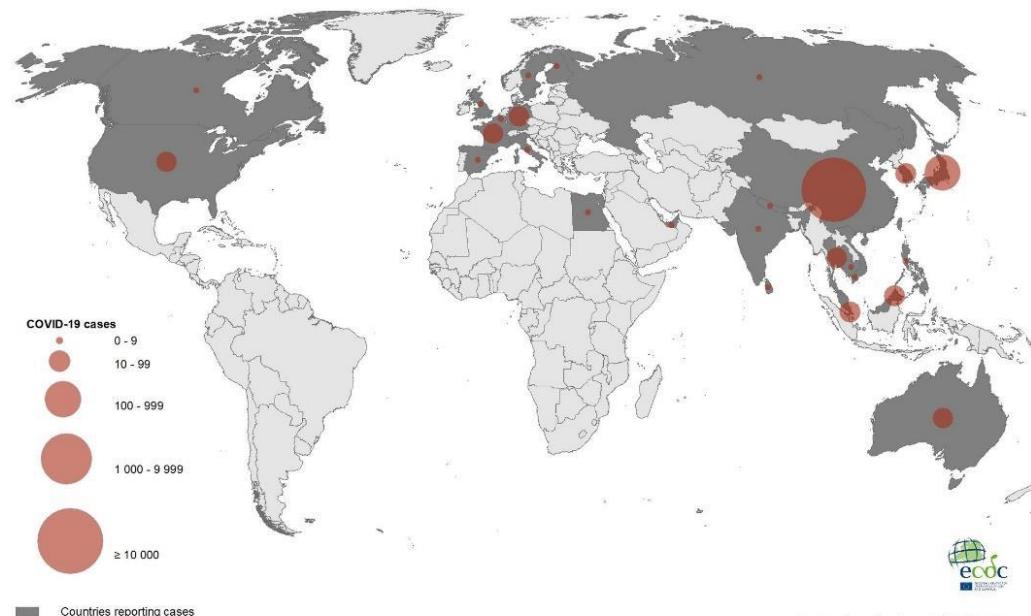
BILAN EPIDÉMIOLOGIQUE

Cas totaux : 75 192 cas dans le monde, 920 hors Chine.

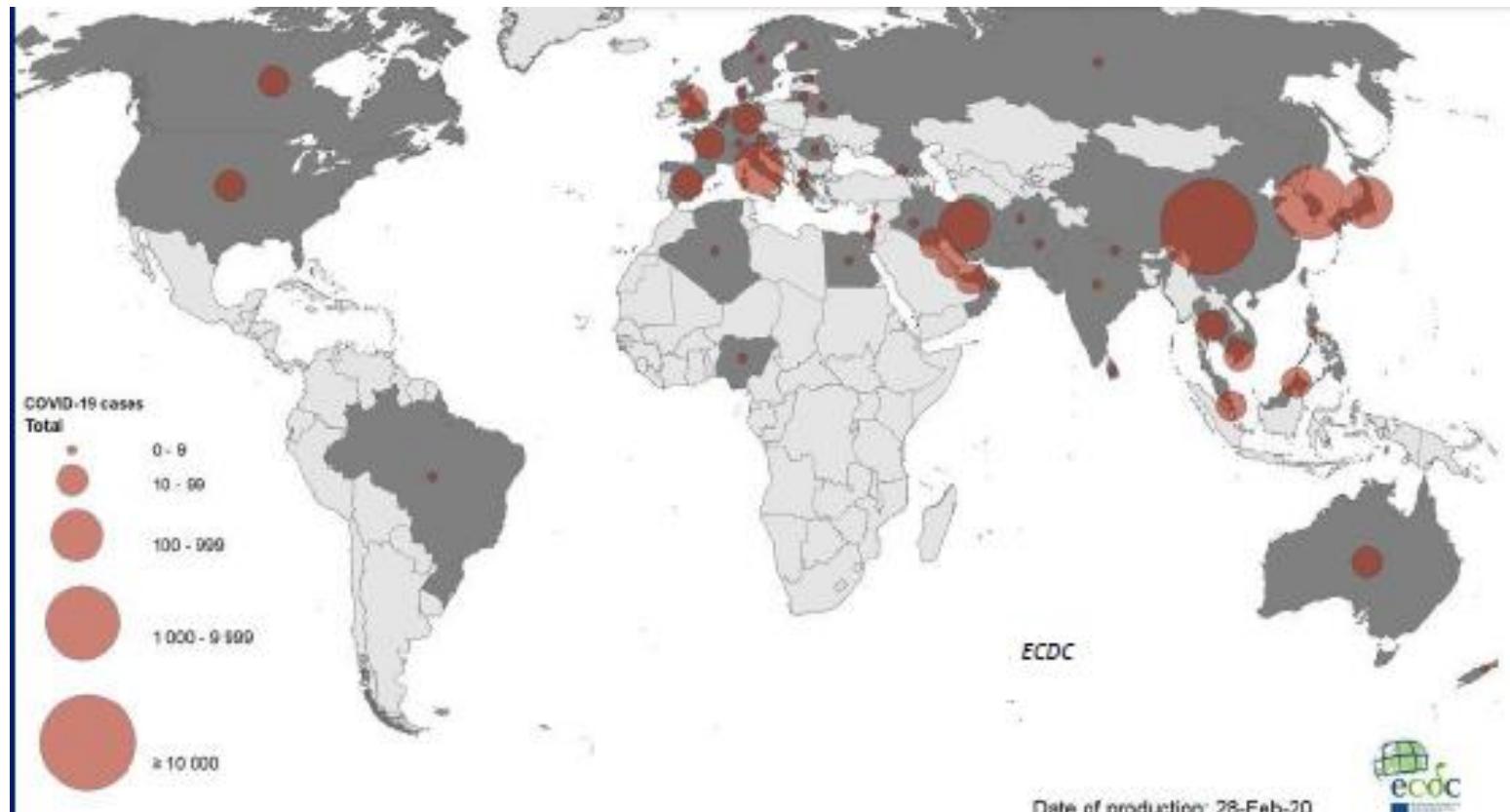
3 cas français confirmés sur le bateau de croisière Diamond Princess (Japon).

Pays touchés : Chine, Hong Kong, Macao, Japon, Singapour, Thaïlande, Corée du Sud, Australie, États-Unis, Malaisie, Allemagne, Taïwan, Vietnam, France (12), Emirats Arabes Unis, Australie, Canada, Inde, Philippines, Italie, Royaume-Uni, Russie, Cambodge, Népal, Sri Lanka, Belgique, Finlande, Espagne, Suède, Egypte et **Iran (information à confirmer)**.

Décès : 1 873 : 1 868 en Chine, 1 à Hong-Kong, 1 aux Philippines, 1 au Japon, 1 à Taiwan et 1 en France.



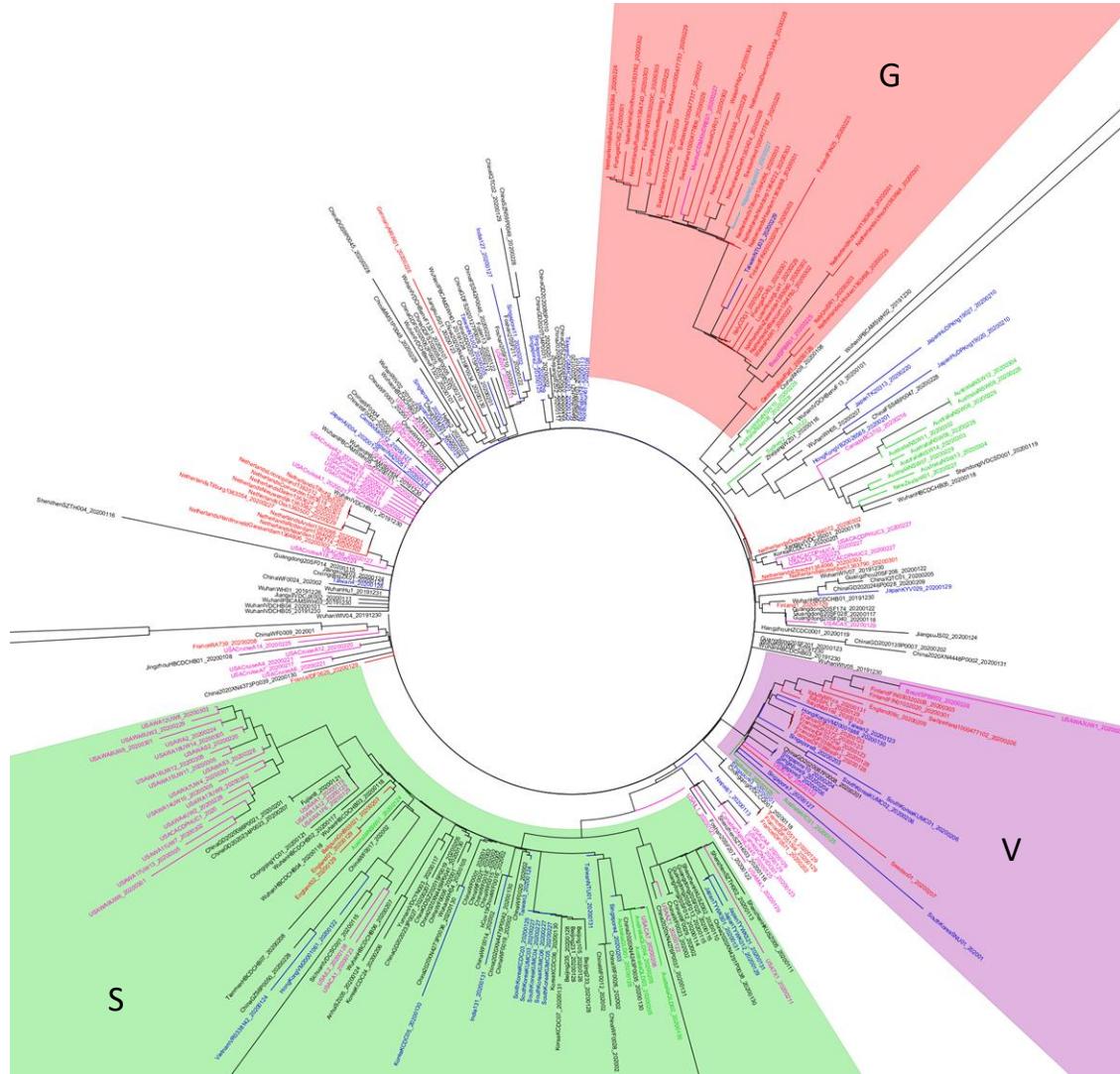
Situation au 28 février 2020



Le virus (diffusion) 10-3-20

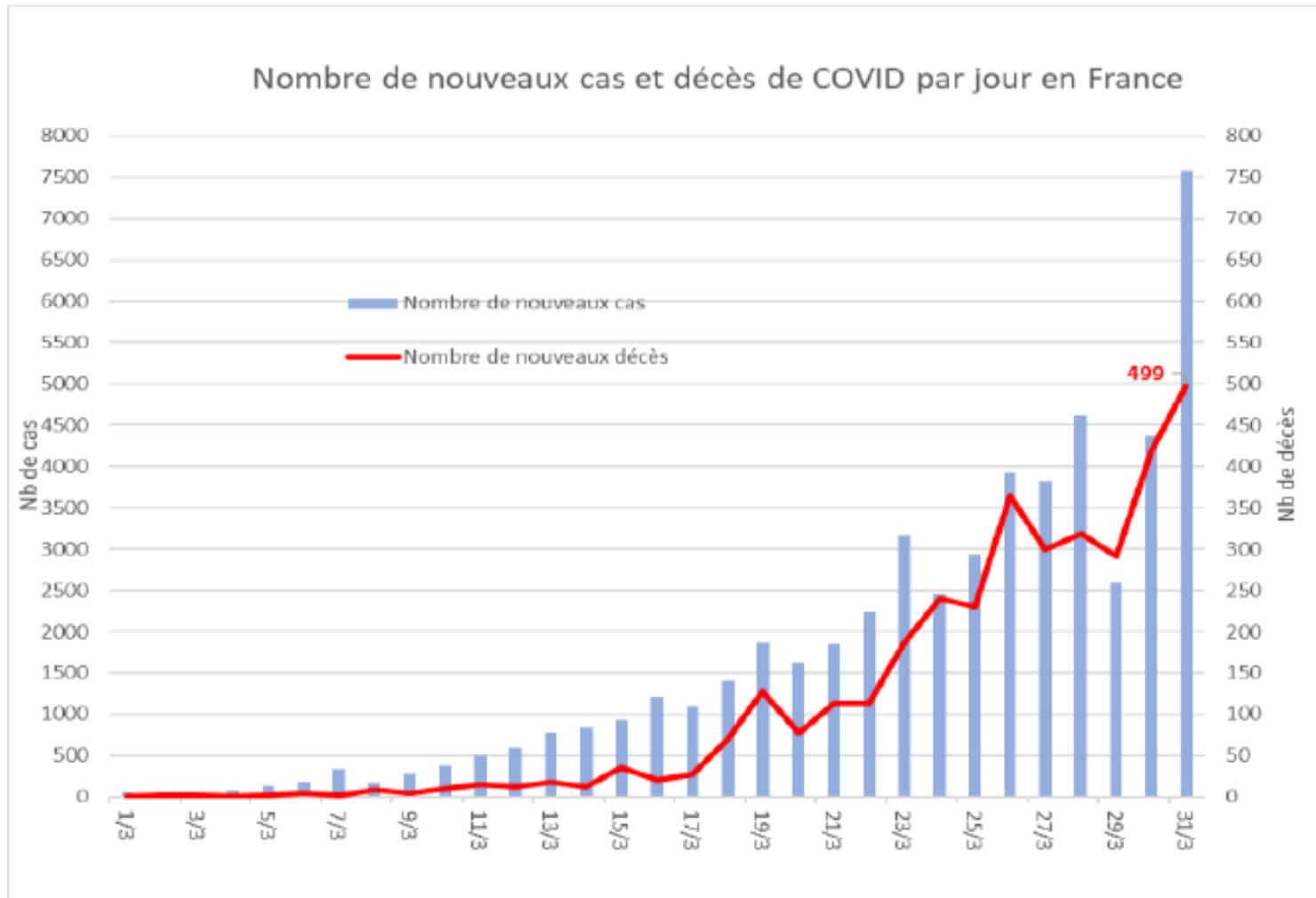
Apparition des génogroupes

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

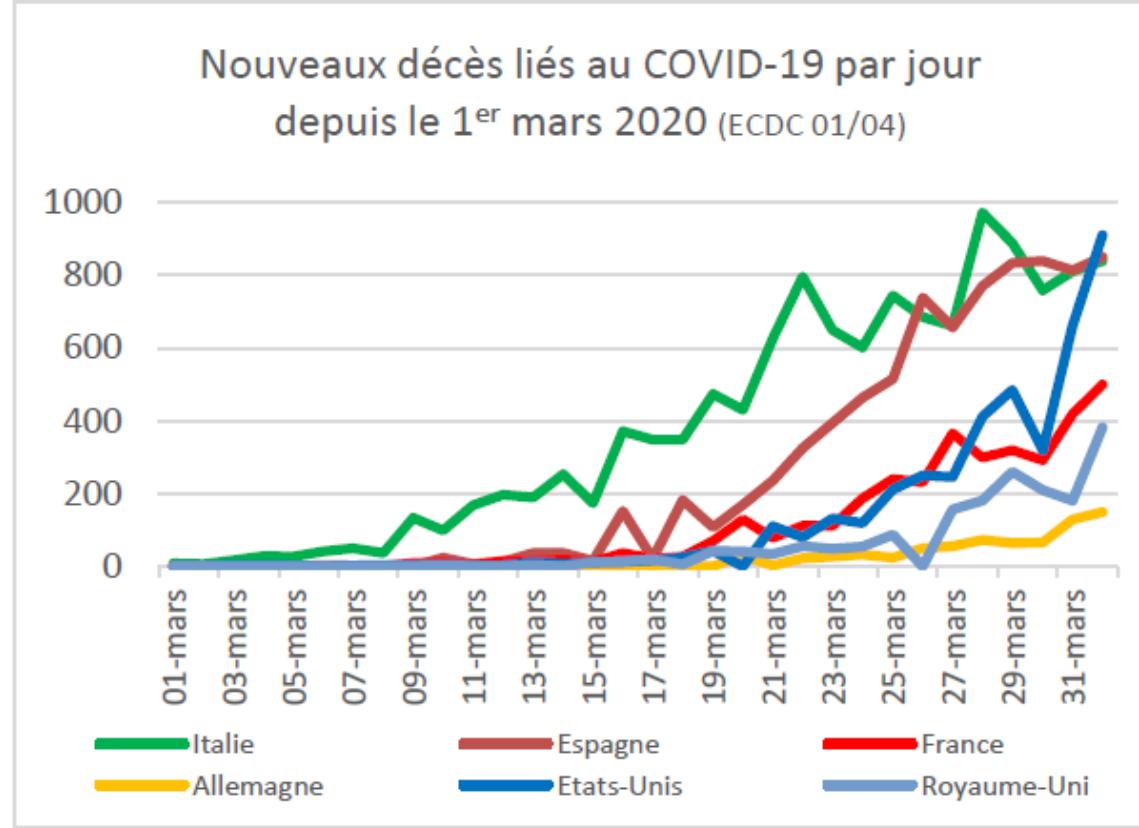
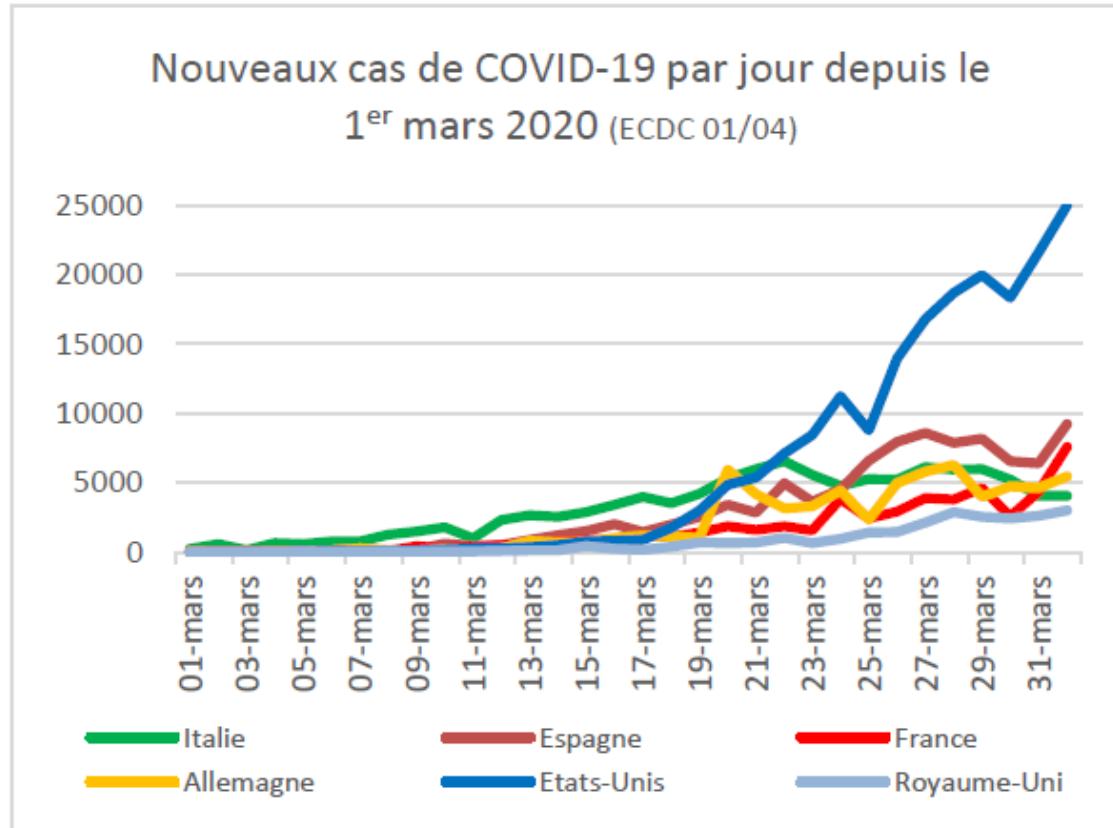


Diffusion fin mars en France

Carte incidence cumulée région pour 100000 hab – Source SpF



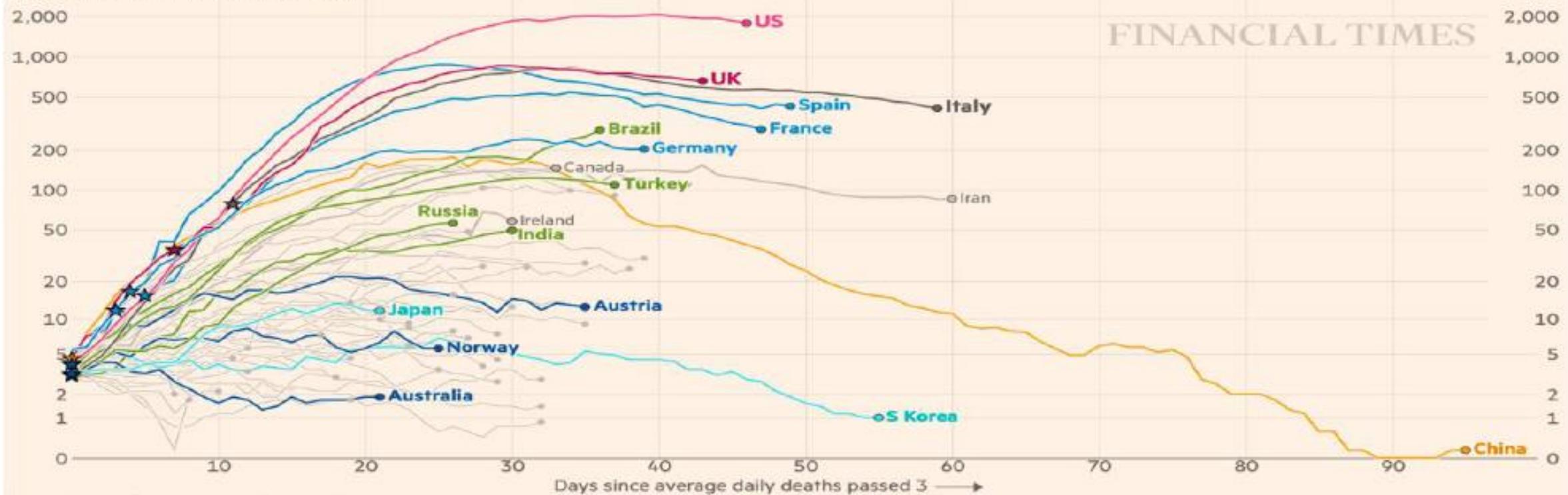
Diffusion fin mars en Europe



Bilan impact international (mortalité) au 28 avril 2020

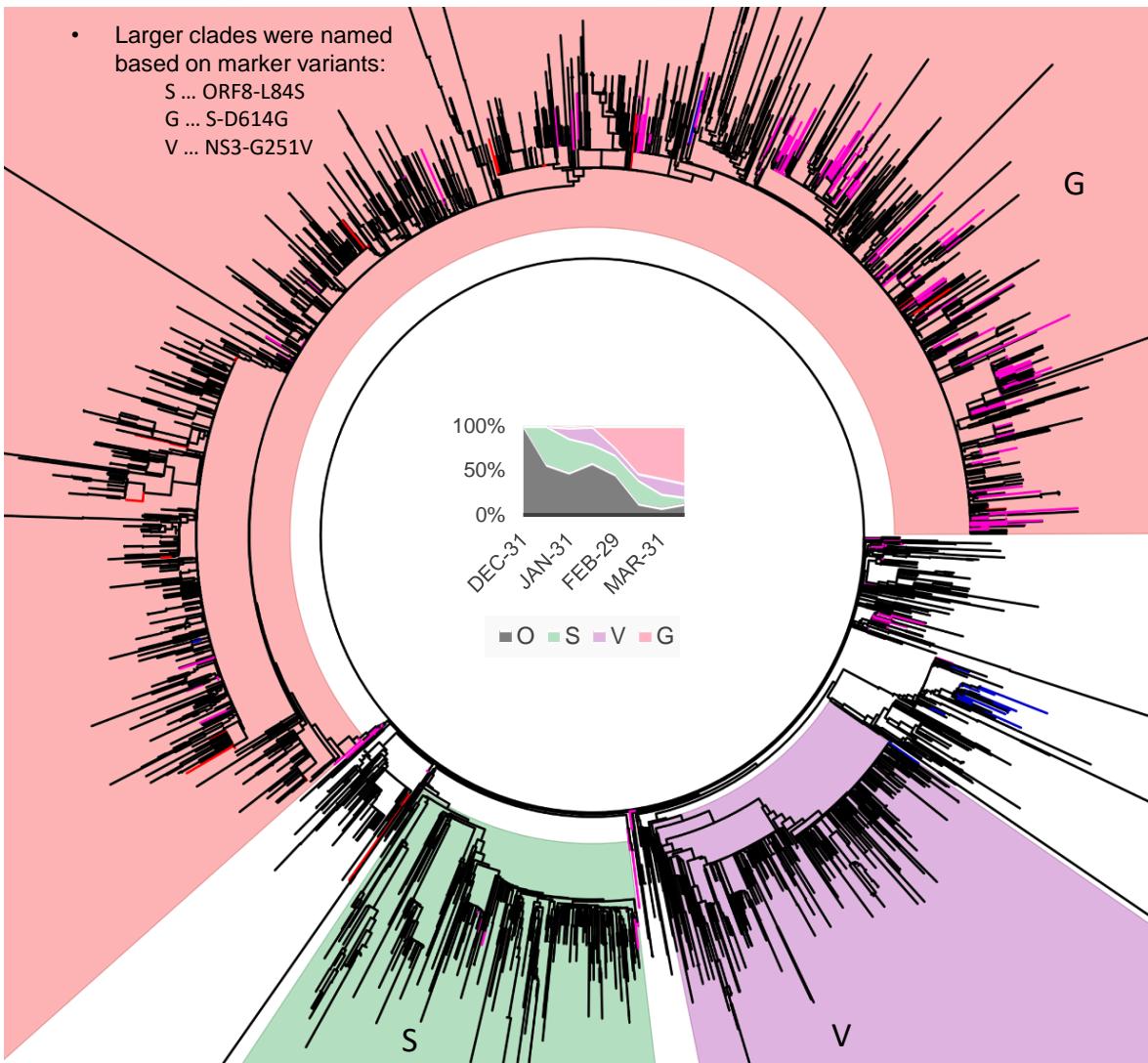
Daily death tolls are now at their peak or falling in many western countries

Daily deaths with coronavirus (7-day rolling average), by number of days since 3 daily deaths first recorded
Stars represent national lockdowns ★



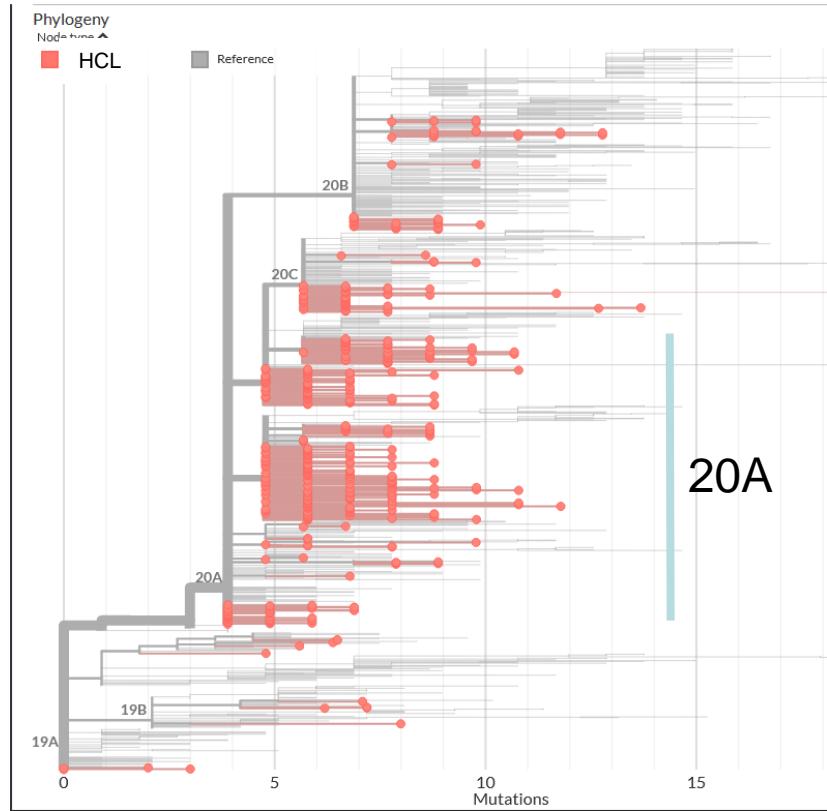
- 30-4-20

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



SURVEILLANCE DES VIRUS EN FRANCE (DONNÉES GÉNOME ENTIER)

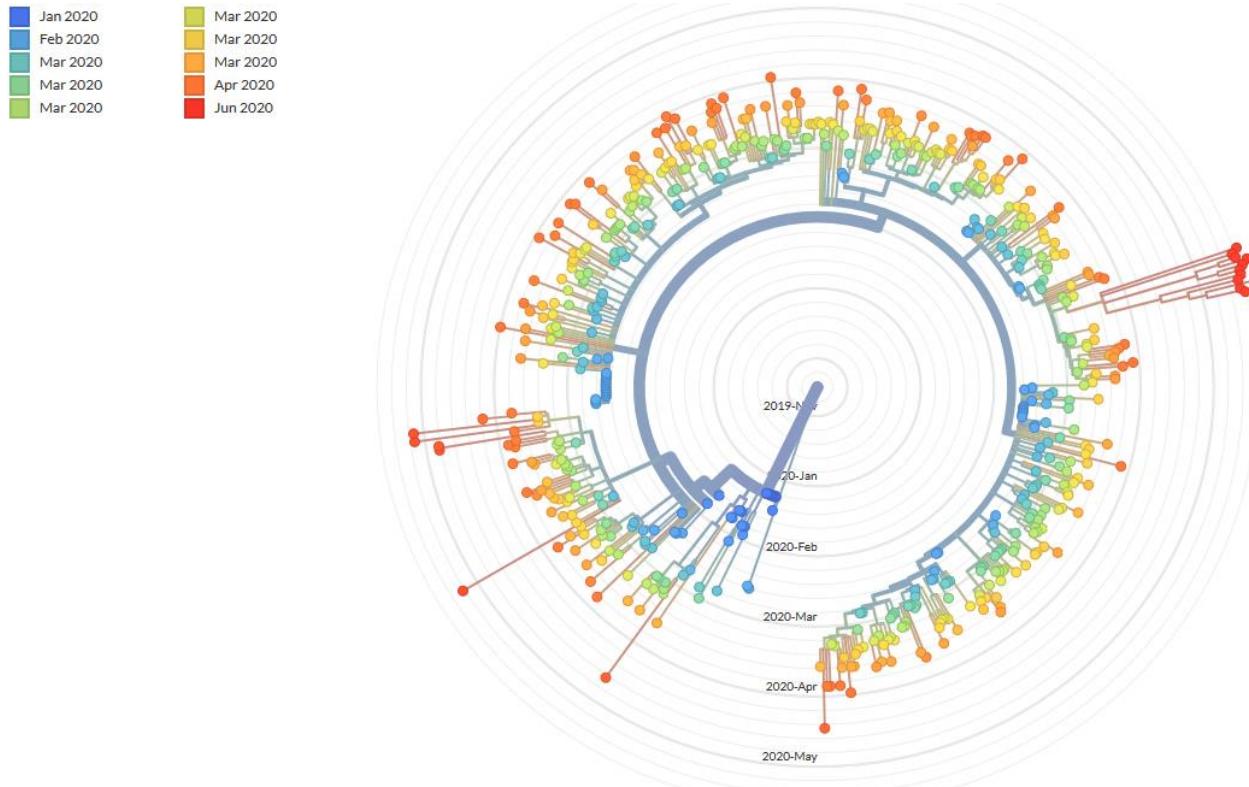
458 SNPs



- Most of these sequences are from Nextstrain clades 20A / Pangolin Lineage B.1
- 0-14 nucleotide substitutions from the inferred ancestor
- 458 positions with SNPs (1.5% of the genome)

<https://clades.nextstrain.org/tree>

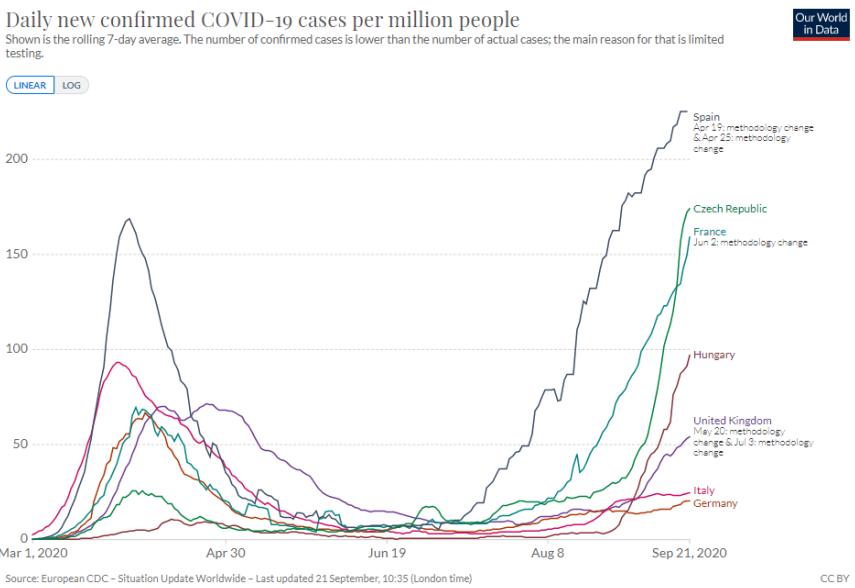
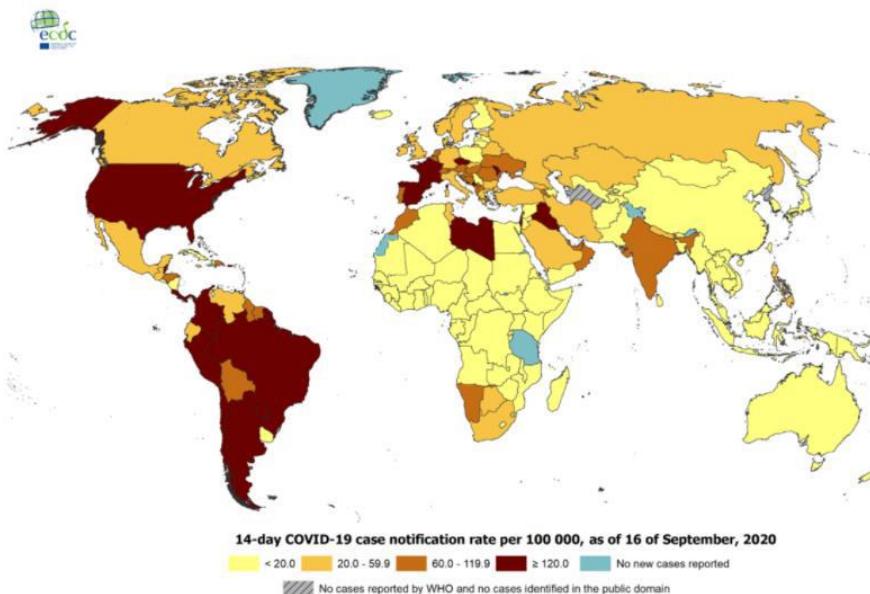
LES VIRUS EN FRANCE



- Josset L, Reigue H, Lina B

IMPACT INTERNATIONAL MI SEPTEMBRE 2020

(données ECDC)



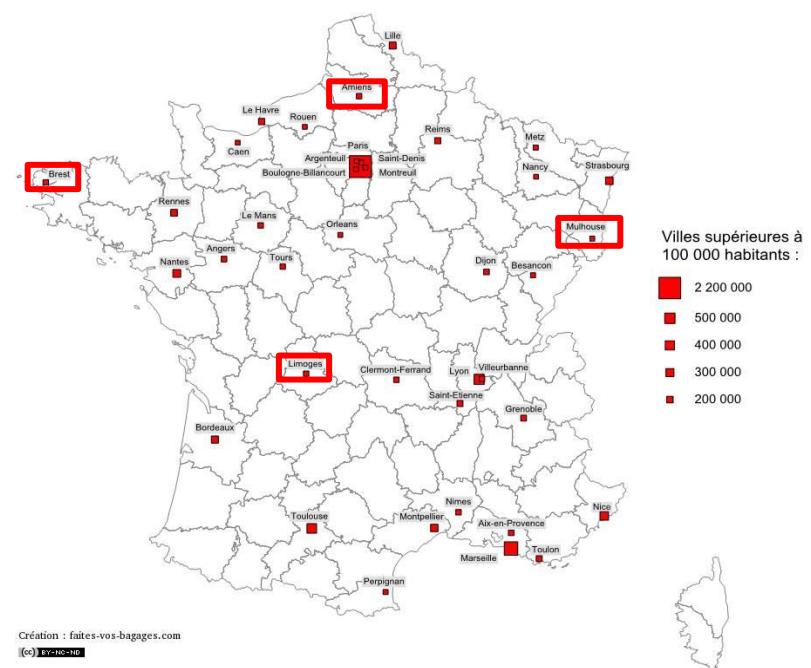
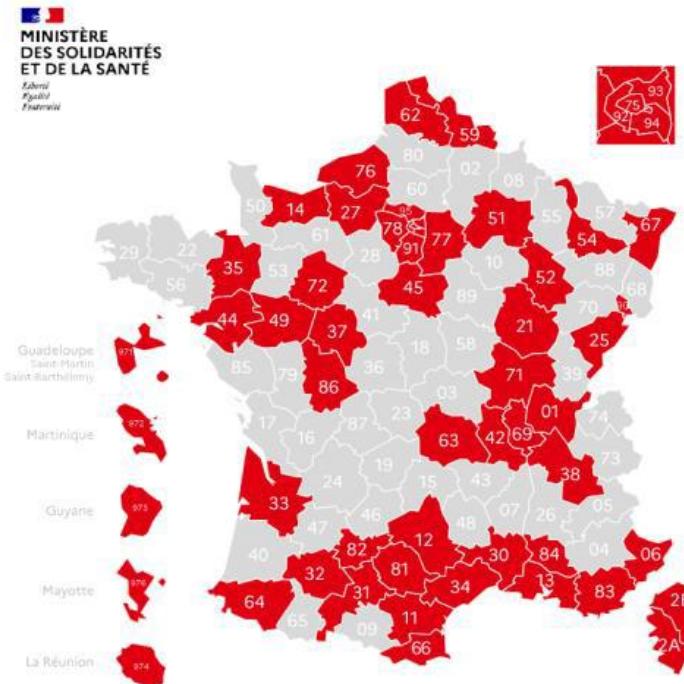
DONNÉES FRANCE ENTIÈRE (SPF) MI SEPTEMBRE

44



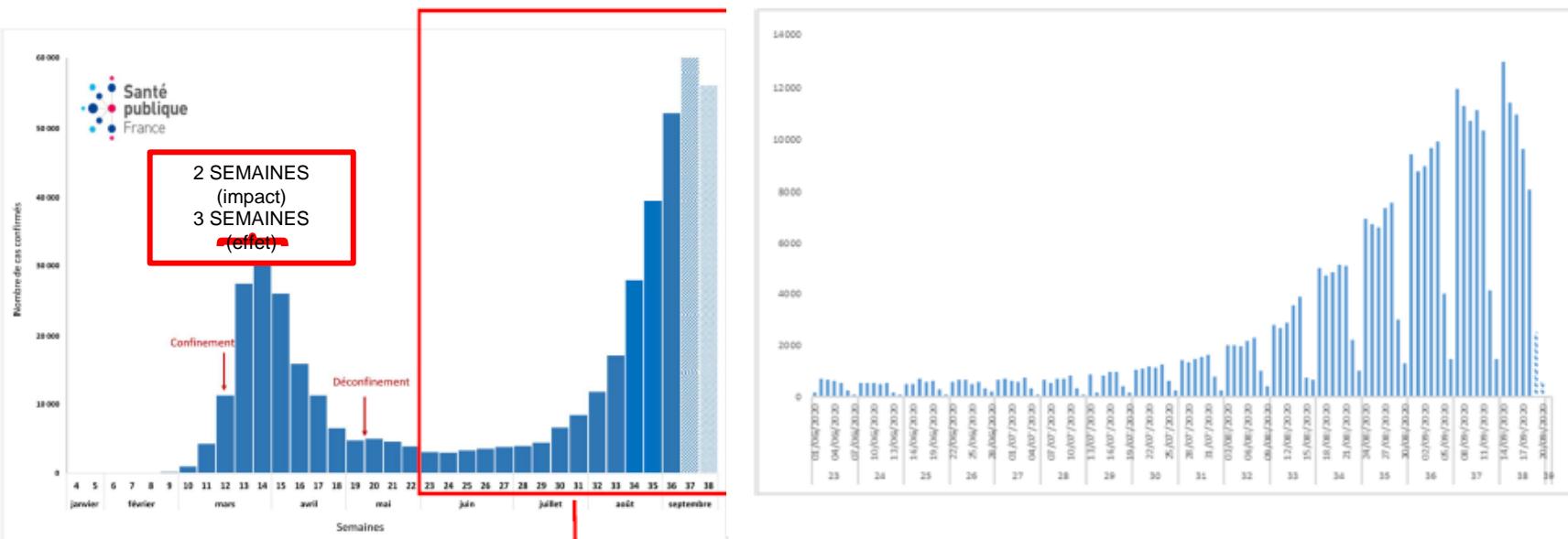
DONNÉES FRANCE ENTIÈRE (SPF) MI SEPTEMBRE

Impact sur les métropoles



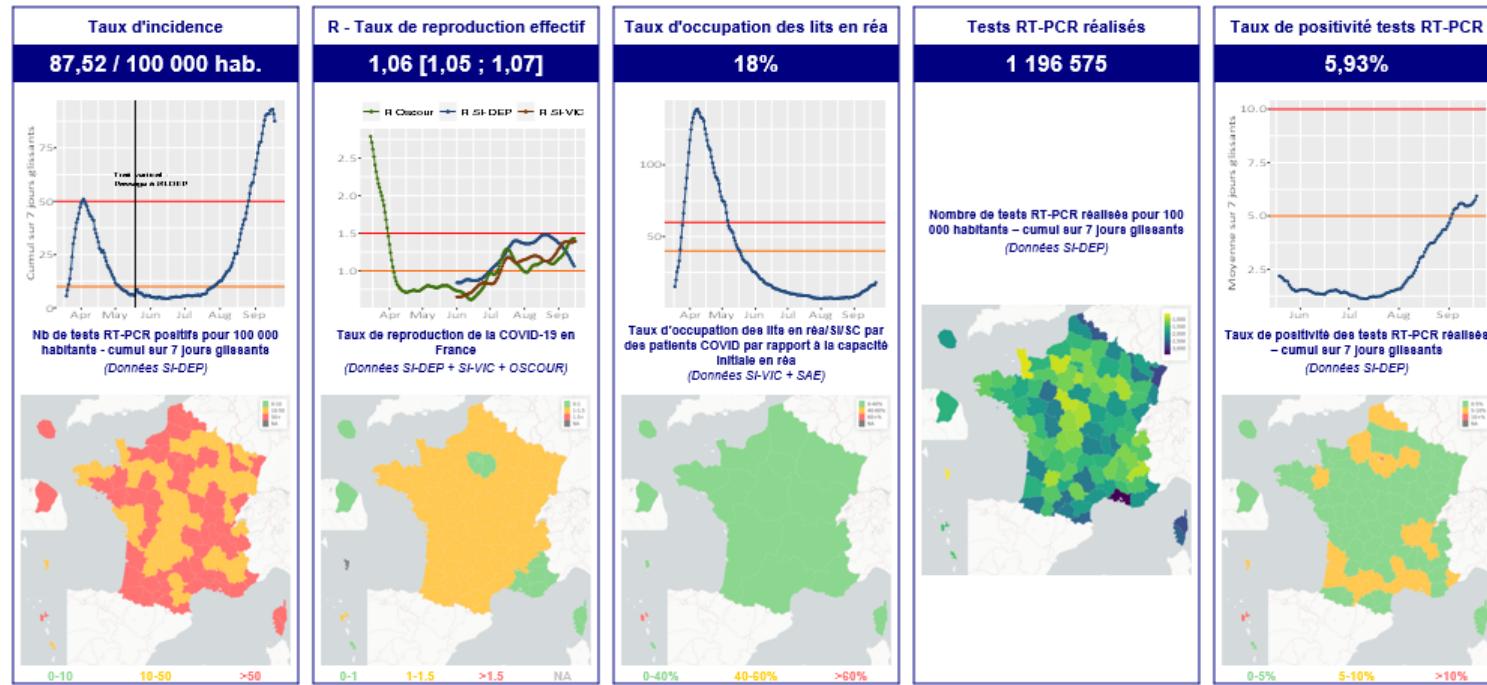
DONNÉES SIDEP CAS CONFIRMÉS MI SEPTEMBRE

Situation comparée Mars / Septembre 2020

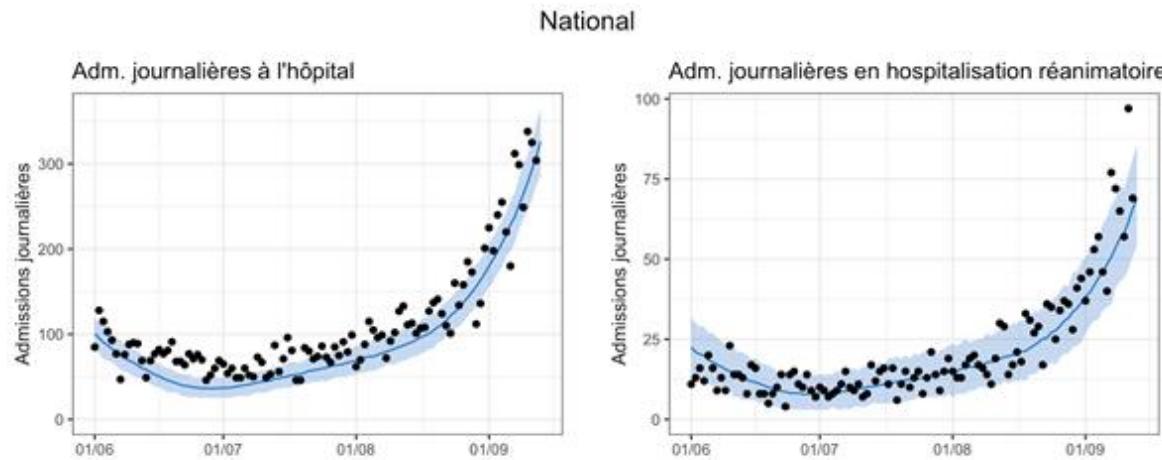


DONNÉES FRANCE ENTIÈRE (SPF)

Les différents indicateurs (Reff ???)



DYNAMIQUE DES HOSPITALISATIONS EN FRANCE



Impossible de ne pas évoquer un départ de 2^e vague épidémique
(sémantique)

Données S Cauchemez, Institut Pasteur

Conclusions

Il y a toujours du neuf et de l'imprévu avec les virus respiratoires

Les données de surveillance de l'épidémie actuelle seront utiles pour le futur

Les nouvelles techniques sont une aide au diagnostic (séquence)

La question du vaccin et des antiviraux est vraiment d'actualité



MERCI

Respiratory virus National Reference Center (NRC) :

NGS team

Antonin Bal (PhD Student)

Grégory Destras (PhD Student)

Grégory Quéromès (PhD Student)

Hadrien Regue (Bioinformatician)

Gwendolyne Burfin (technician)

Solenne Brun (technician)

Pr Florence Morfin
Dr Alexandre Gaymard
Dr Emilie Frobert
Dr Martine Valette
Pr Bruno Lina

Public resources for SARS-CoV-2 genome analysis :

- [GISaid](#)
- [NextStrain](#)
- [COV-GLUE](#)

Virpath lab (Université de Lyon)

Dr Olivier Terrier

Dr Manuel Rosa-Calatrava

Mario Andres Pizzorno (Post-Doc)

Claire Nicolas de Lamballerie (Post-Doc)

Aurelien Traversier (technician)

HCL
HOSPICES CIVILS
DE LYON