Viroses respiratoires émergentes : H7N9, MERS-CoV

Bruno Lina
Hospices Civils de Lyon, CNR des virus influenza (Sud), F69677, Bron
VirPatH, EMR 4610, Université de Lyon, F69372, Lyon

Liens d'intérêts :
Argene-BioMérieux, AstraZeneca, BioCryst, BMS, GSK, Novartis, Roche, Sanofi-Pasteur, SP-MSD, Conseil scientifique du GEIG, membre de ESWI

Liens d'interets 2009-2013

- **Argene-BioMérieux** (UR grant 2009-2013)

- **BioCryst** (DMC 2009-2012)

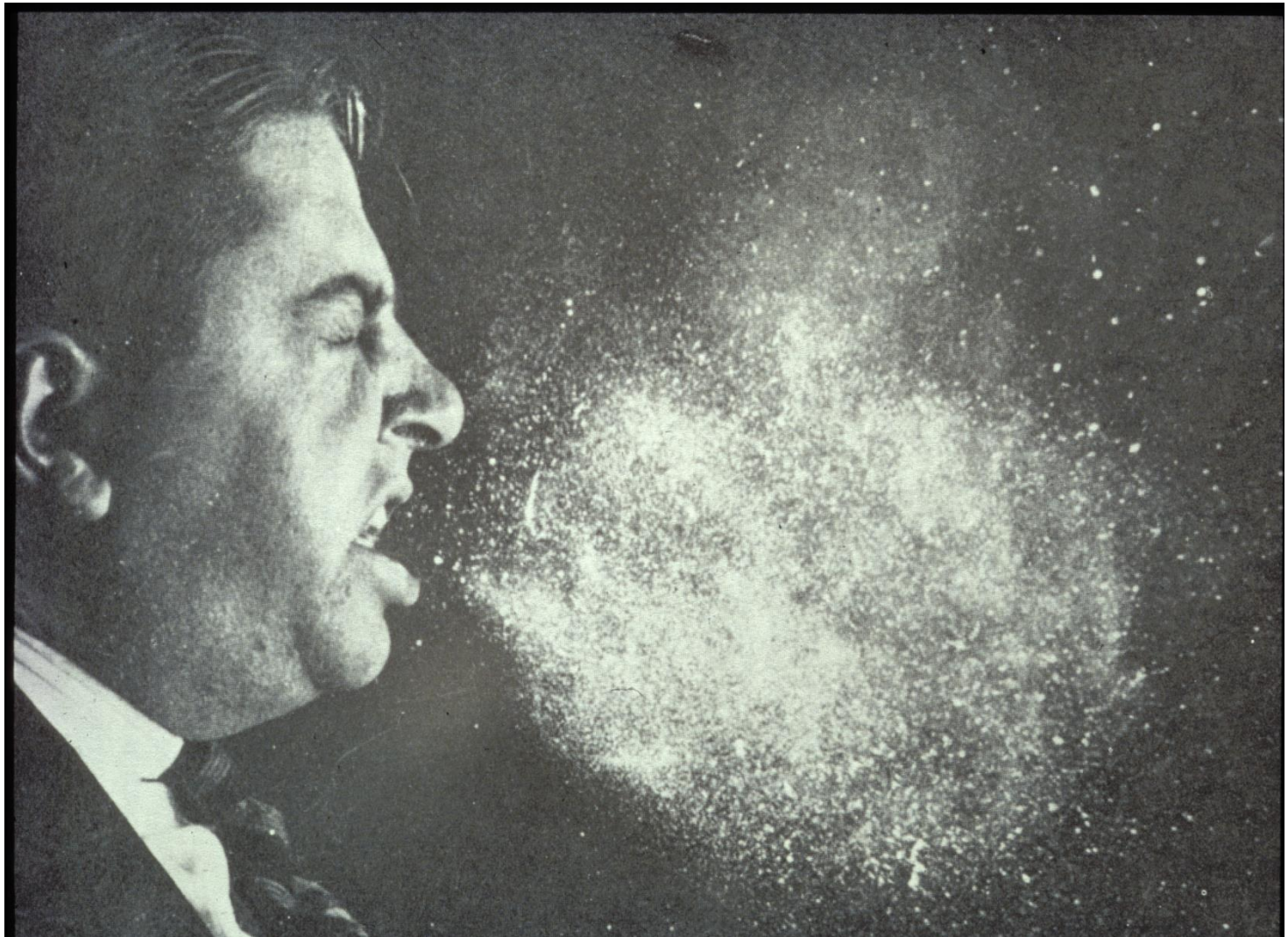
- **GSK** (advisory group 2009)
- **Novartis** (advisory group 2009)
- **Roche** (advisory group 2009-2011, UR grant 2009-2012, Essai Clinique 2009-2011)

- **Sanofi-Pasteur** (2009-2011 études clinique)

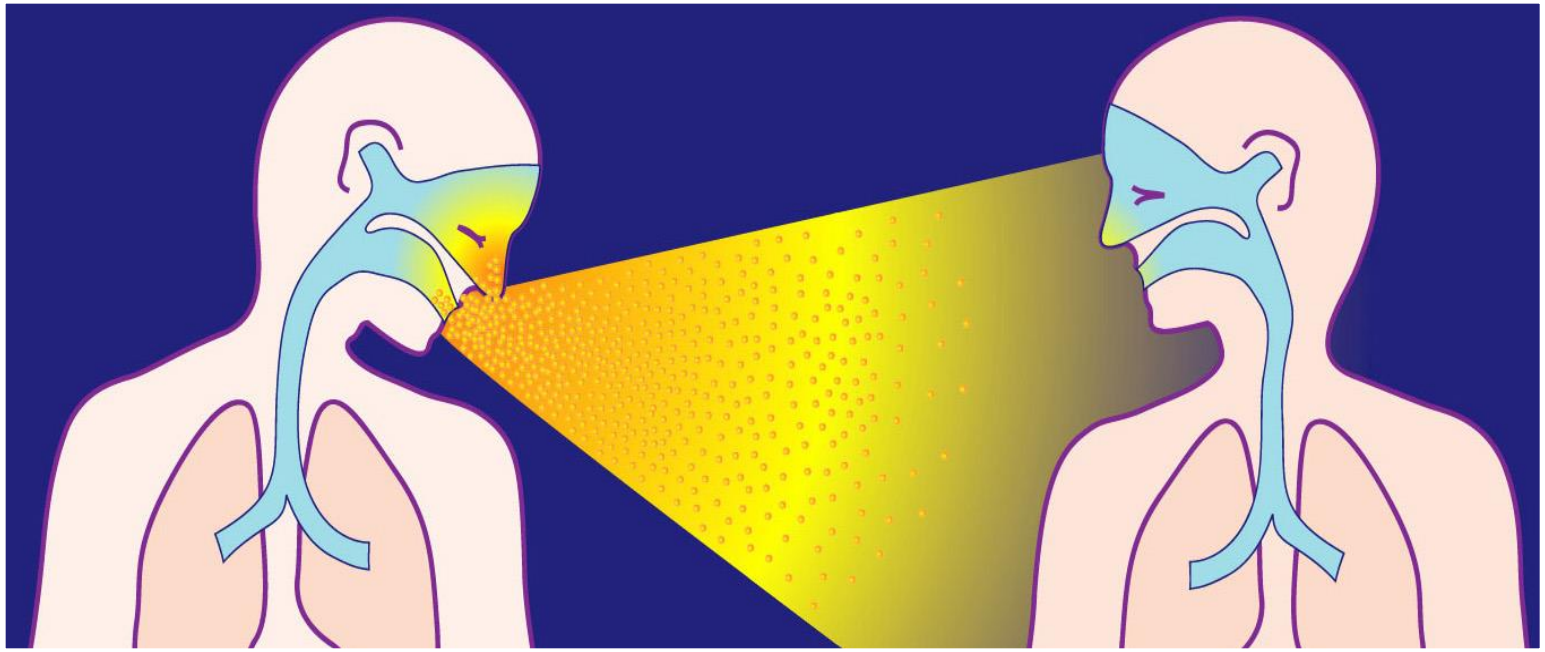
- **Conseil scientifique du GEIG** (2009-2012)
- **Membre du Board ESWI** (2010-2013)

Acteur #1 : le virus

Acteur #2 : le vecteur

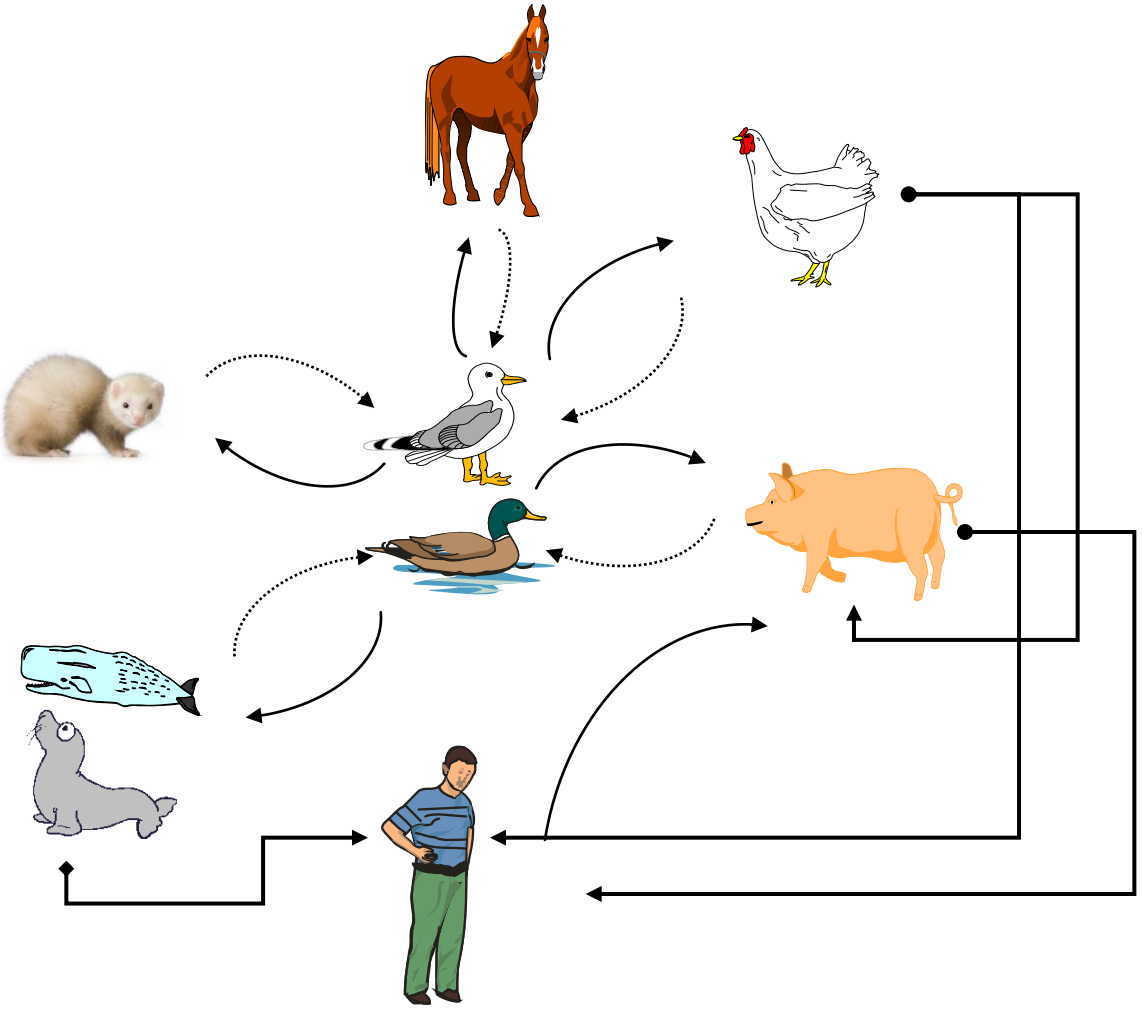


La grippe: une infection virale à transmission aérienne



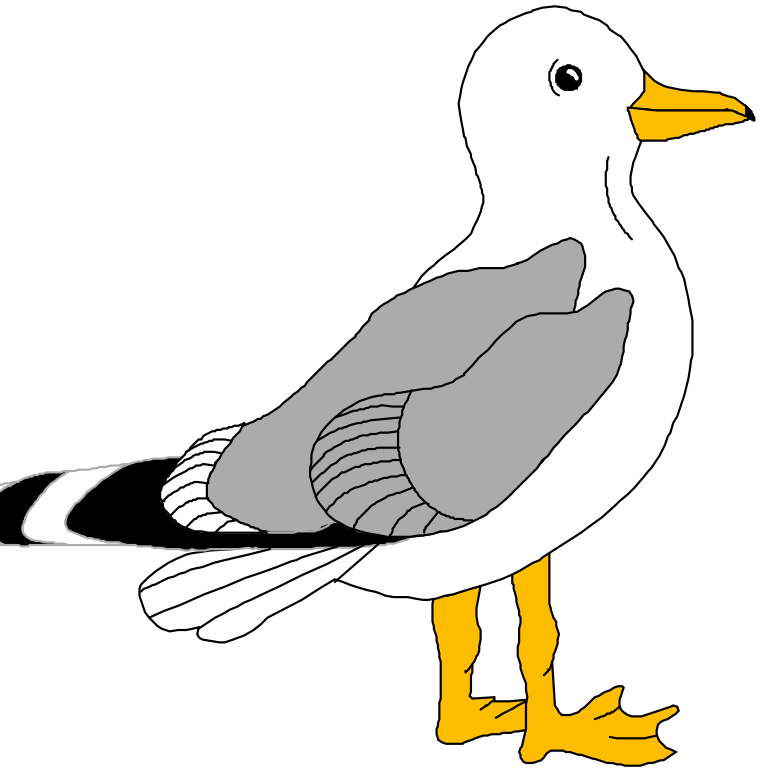
Le virus se propage par le biais des gouttelettes de salive et des petites particules en suspension dans l'air projetées par la toux ou les éternuements. Le virus pénètre dans l'organisme via le nez, la bouche et les yeux

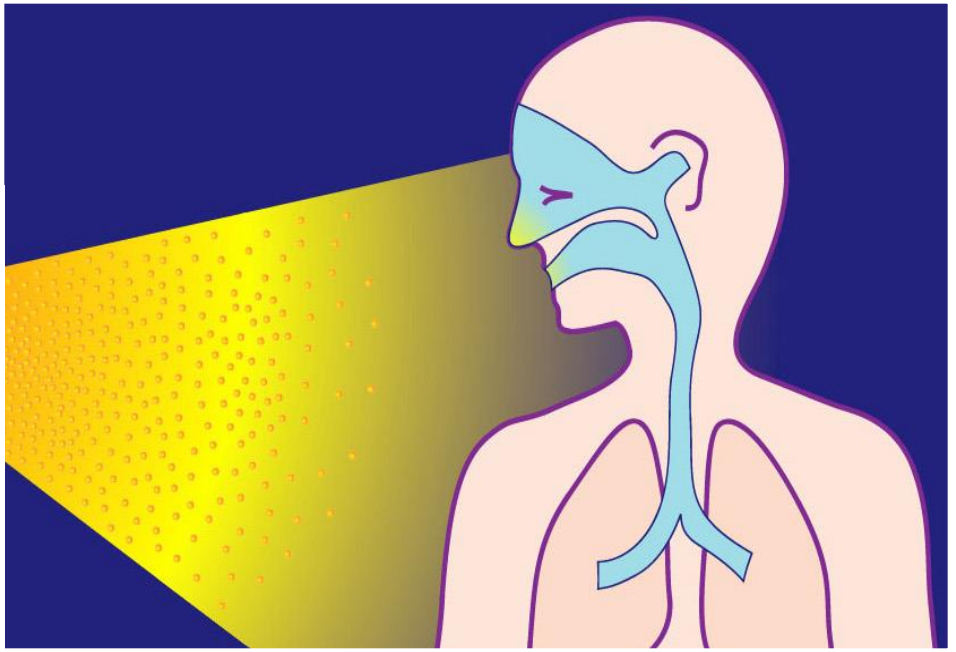
Acteurs #3 : les vecteurs animaux*

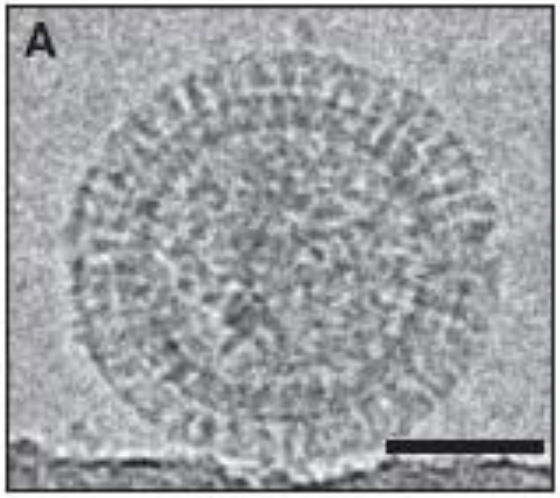


* Uniquement pour les pandémies

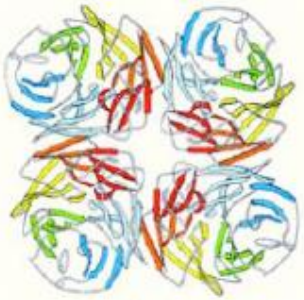
La grippe aviaire: une infection impossible





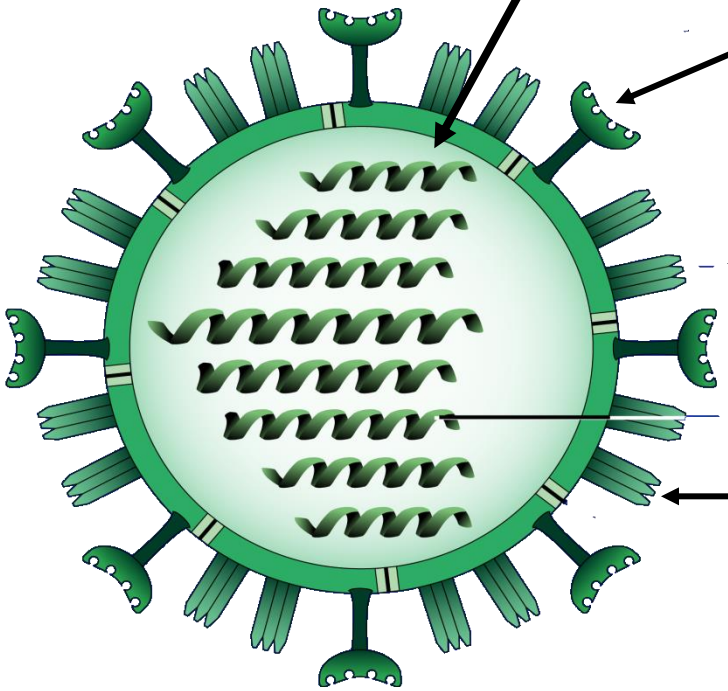


Genome segmenté

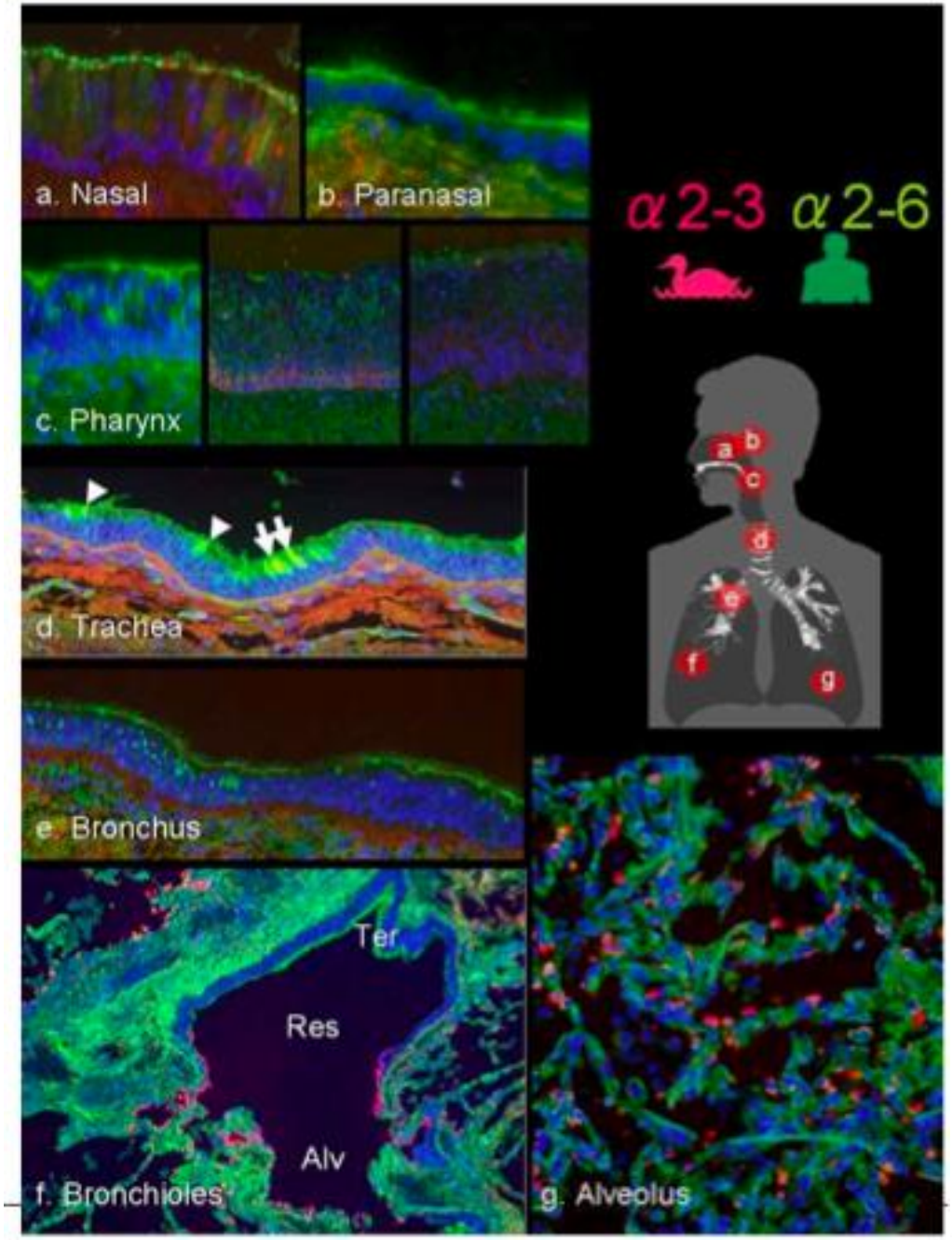


Neuraminidase (N)

Haemagglutinin (H)

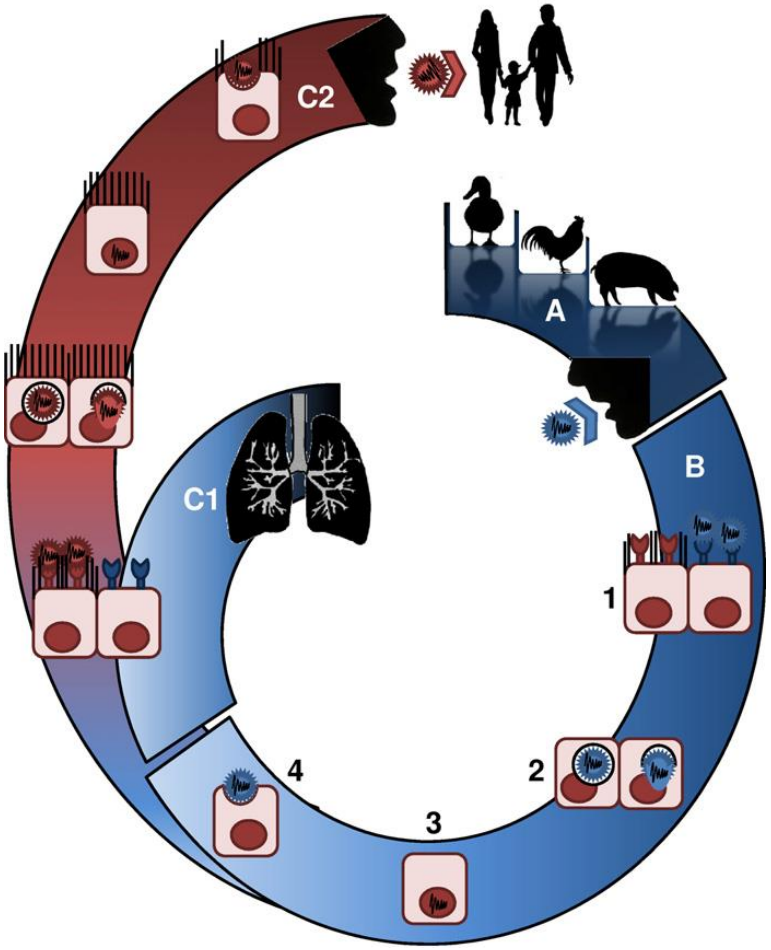


Distribution des récepteurs α 2-6 et α 2-3 dans l'arbre respiratoire humain



- Shynia, Nature 2006

Les étapes du franchissement



Influenza pandemics in the XXth century (1)

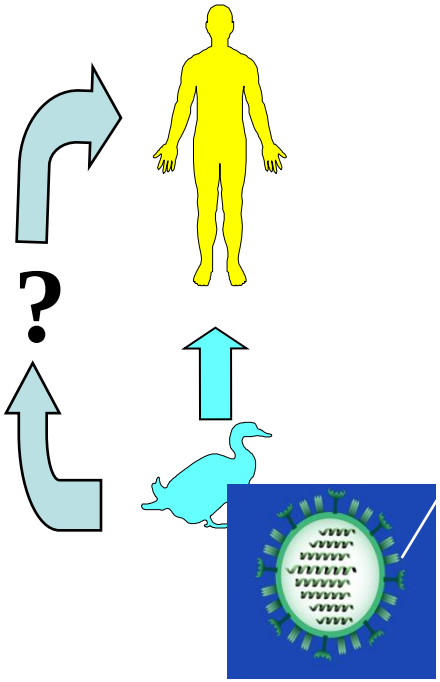
Adaptation par mutation

1918: “Spanish Flu”

40-50 million

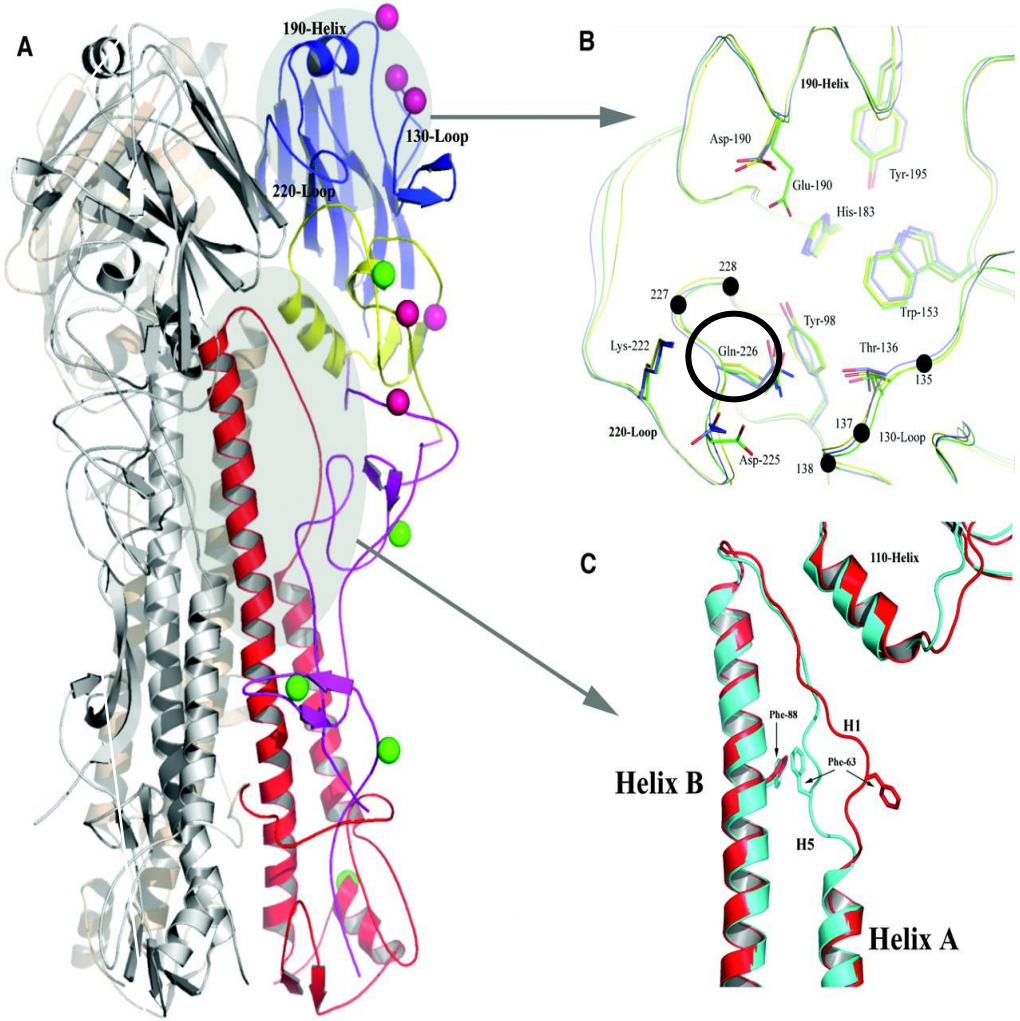
H1N1

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

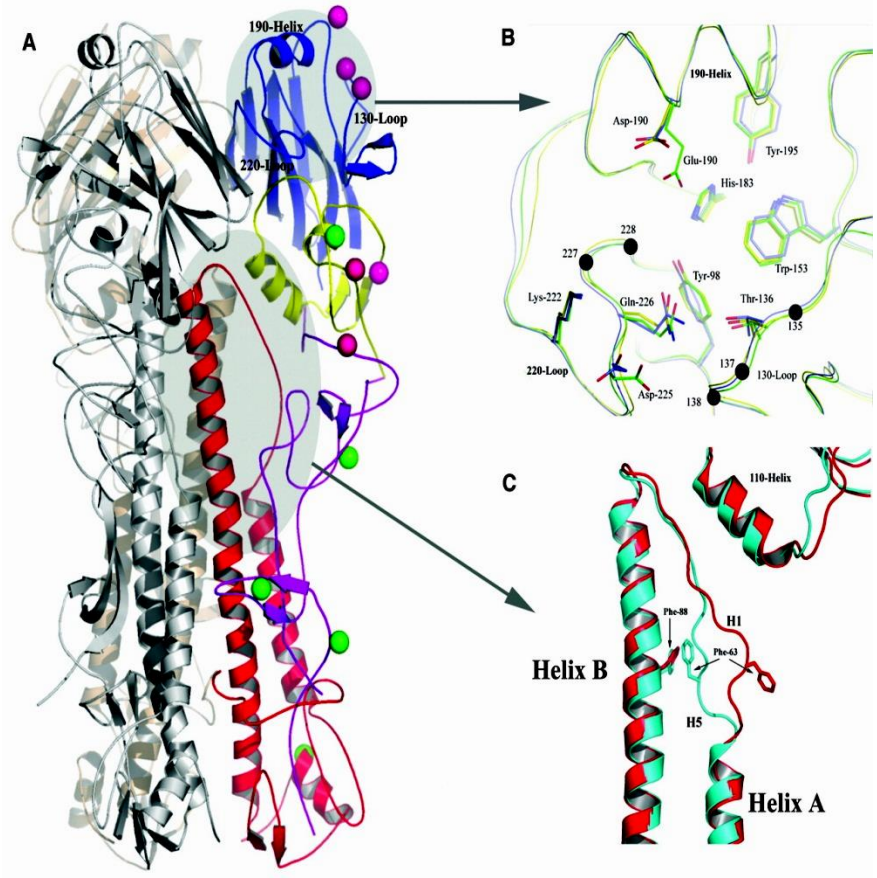


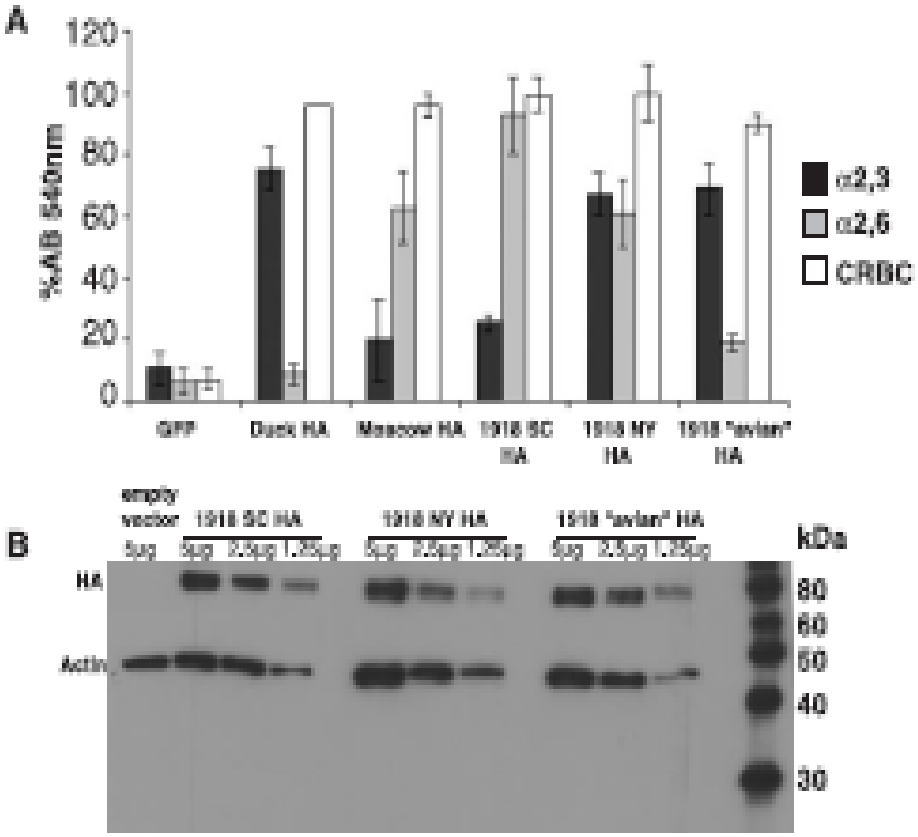
A H_1N_1

D'après Taubenberger



Bascule de l'attachement de H1N1 en 1918





D'après Taubenberger

Influenza pandemics in the XXth century (2)

Adaptation par réassortiment

1957: “Asian Flu”

1-4 million

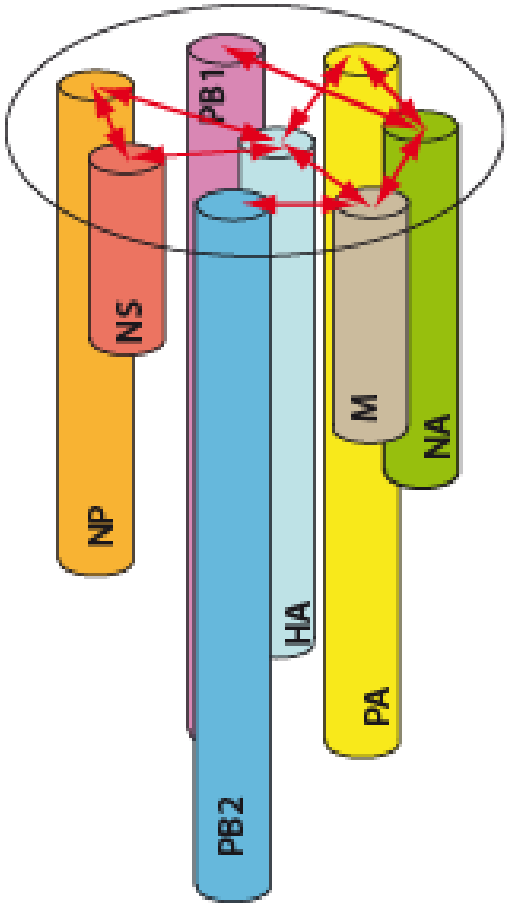
H2N2

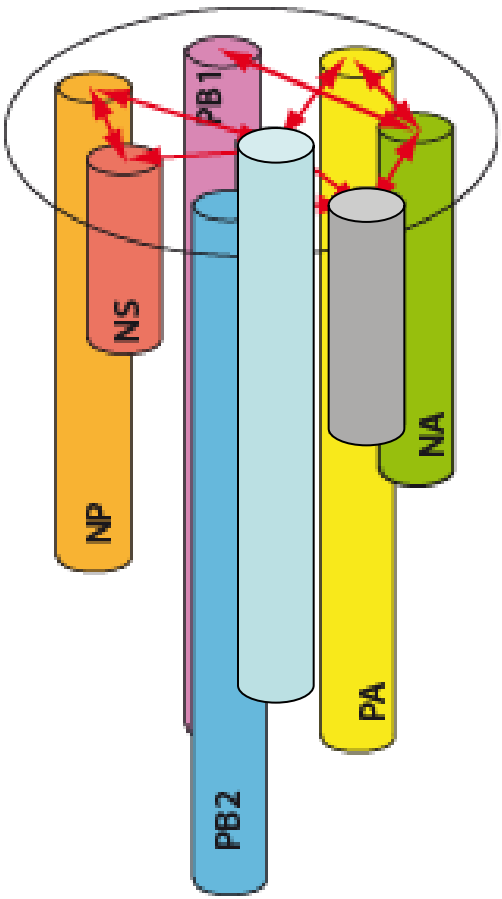
1968: “Hong Kong Flu”

1 million

H3N2

Réassortiment génétique : introduction de plusieurs gènes

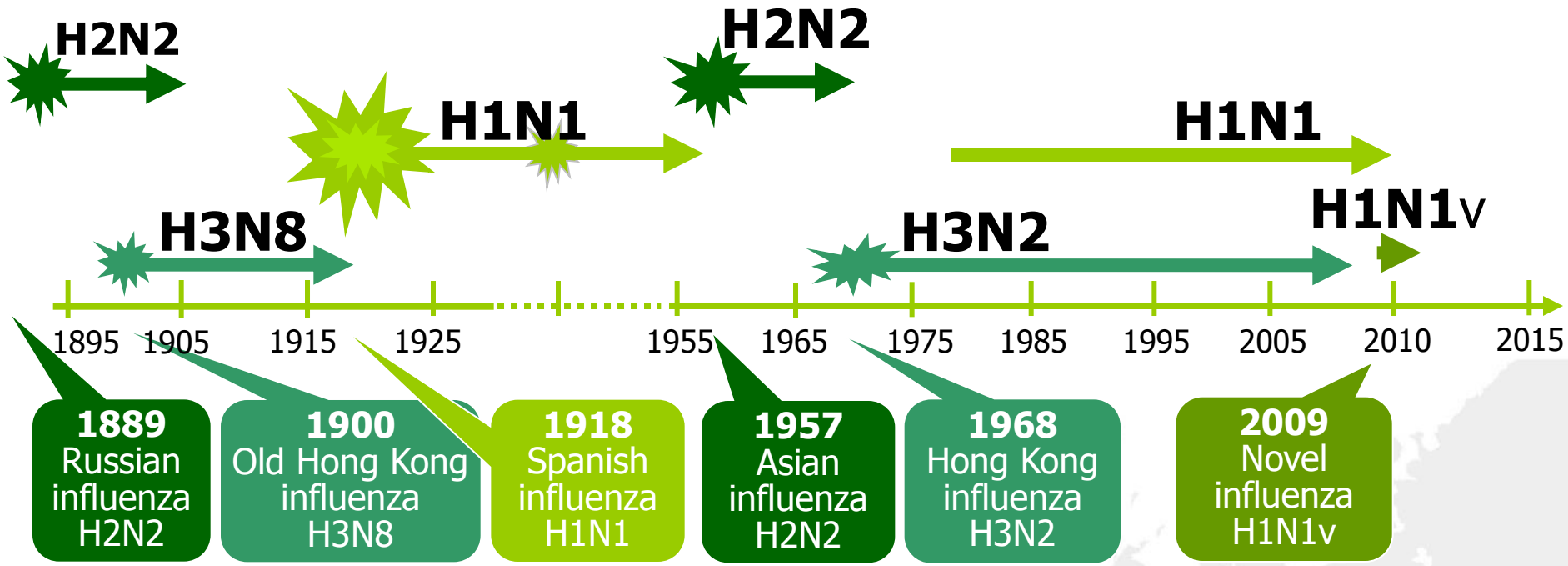




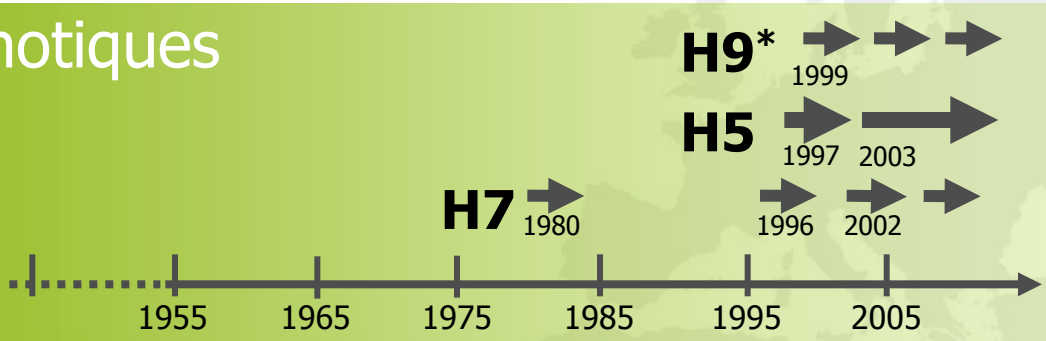
Emilie FOURNIER (Strasbourg) ; Dr Daniel THOMAS (Rennes) ; Dr Vincent MOULES (Lyon)

Pandemies influenza

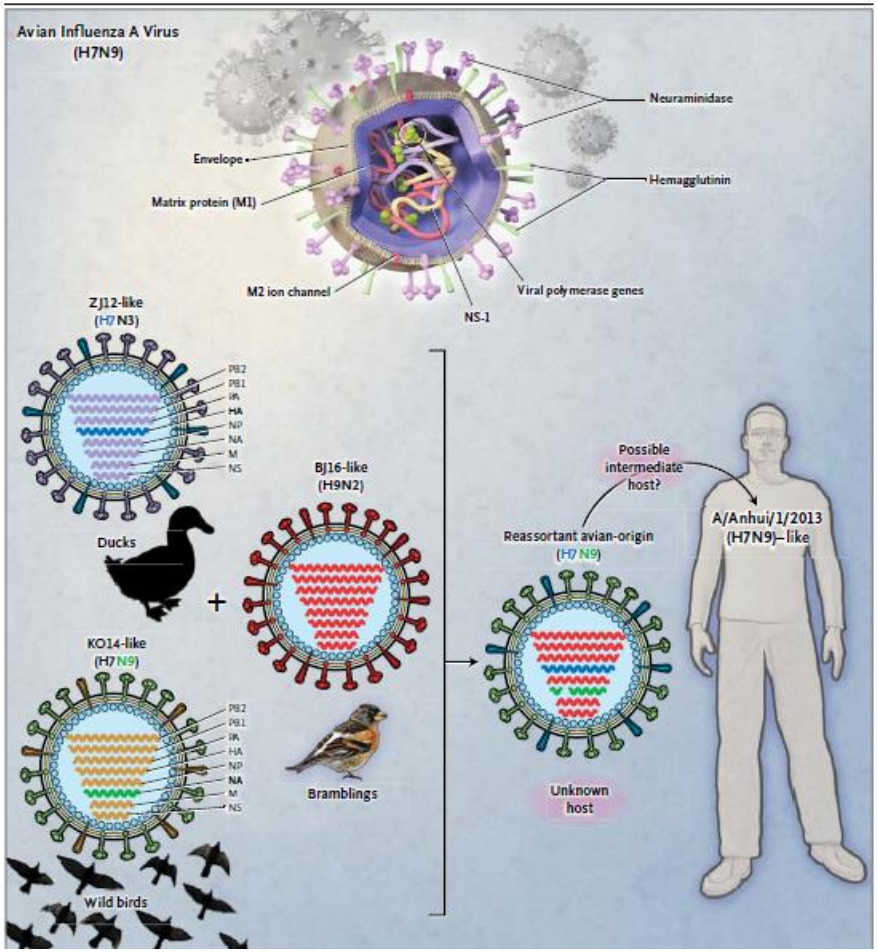
Pandemies influenza du passé
(sous-types précoces déduits par sérologie)



Alertes influenza zoonotiques (exemples)



Alerte H7N9


Avian Influenza A Virus
(H7N9)
Neuraminidase
Envelope
Hemagglutinin
Matrix protein (M1)
M2 ion channel
NS-1
Viral polymerase genes
ZJ12-like
(H7N3)
PB2
PB1
PA
HA
NP
NA
M
NS
Ducks
BJ16-like
(H9N2)
KO14-like
(H7N9)
Bramblings
Wild birds
Reassortant avian-origin
(H7N9)
Possible
intermediate
host?
Unknown
host
A/Anhui/1/2013
(H7N9)–like

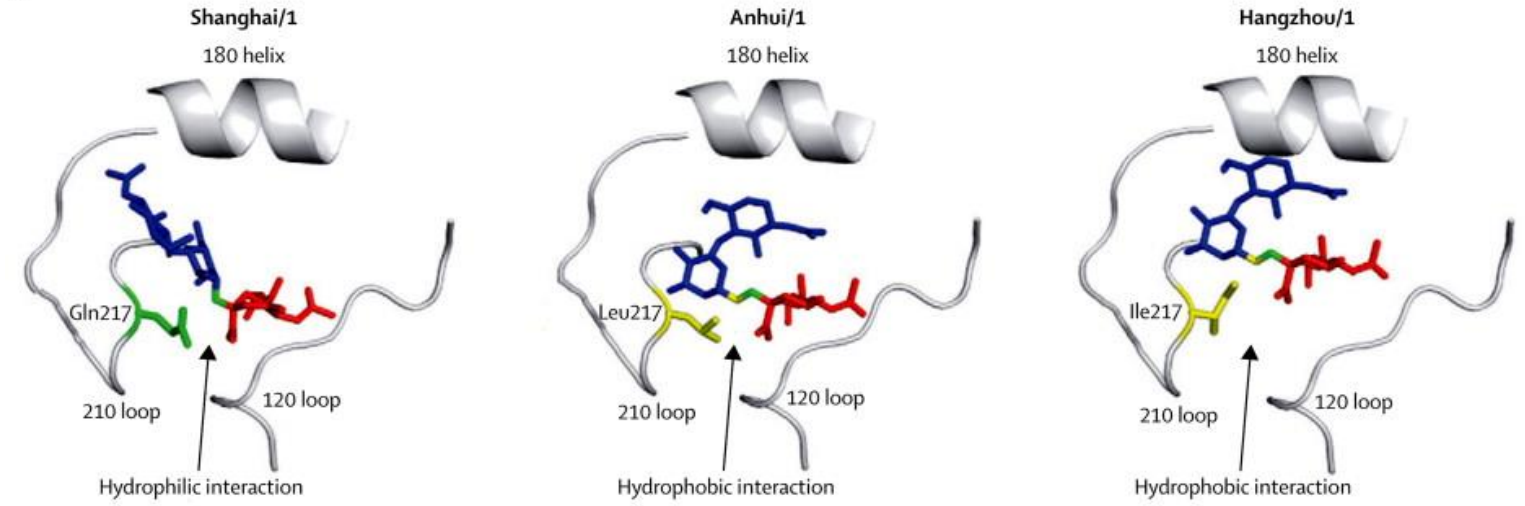
Analyse faite par le CNR le 4 avril 2013

Tableau 1 : Analyse des pourcentages d'homologie des virus A(H7N9) et des virus parentaux putatifs

Influenza strain name	Viral sub-type	Viral genes							
		PB2	PB1	PA	HA	NP	NA	M	NS
A/Shanghai/1/2013	**H7N9**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
A/Shanghai/2/2013	**H7N9**	**99**	**99**	**99**	**99**	**97**	**99**	**99**	**99**
A/Anhui/1/2013	**H7N9**	**99**	**99**	**99**	**99**	**97**	**99**	**99**	**99**
A/brambling/Beijing/16/2012	H9N2	99	98	99	NA	97	NA	97	98
A/chicken/Zhejiang/329/2011	H9N2	98	98	96	NA	98	NA	98	96
A/chicken/Jiangsu/Q3/2010	H9N2	98	98	98	NA	98	NA	98	96
A/duck/Zhejiang/12/2011	H7N3	NA	NA	NA	96	NA	NA	NA	NA
A/wild bird feces/Korea/HDR22/2006	H7N7	NA	NA	NA	95	NA	NA	NA	NA
A/duck/Shiga/B149/2007	H7N7	NA	NA	NA	95	NA	NA	NA	NA
A/duck/Shimane/137/2006	H7N3	NA	NA	NA	94	NA	NA	NA	NA
A/duck/Mongolia/867/2002	H7N1	NA	NA	NA	94	NA	NA	NA	NA
A/mallard/Czech Republic/13438-29K/2010	H11N9	NA	NA	NA	NA	NA	96	NA	NA
A/Baikal Teal/Hongze/14/2005	H11N9	NA	NA	NA	NA	NA	96	NA	NA
A/wild bird/Korea/A14/11	H7N9	NA	NA	NA	NA	NA	96	NA	NA
A/sharp-tailed sandpiper/Australia/10/2004	H11N9	NA	NA	NA	NA	NA	96	NA	NA
A/duck/Hokkaido/W245/2004	H11N9	NA	NA	NA	NA	NA	96	NA	NA
A/duck/Tsukuba/239/2005	H11N9	NA	NA	NA	NA	NA	95	NA	NA
A/sharp-tailed sandpiper/Australia/6/2004	H11N9	NA	NA	NA	NA	NA	95	NA	NA

Table: Percentage of identity between A/Shanghai/1/2013 (H7N9) strain and other avian influenza strains (NA: non applicable)

A



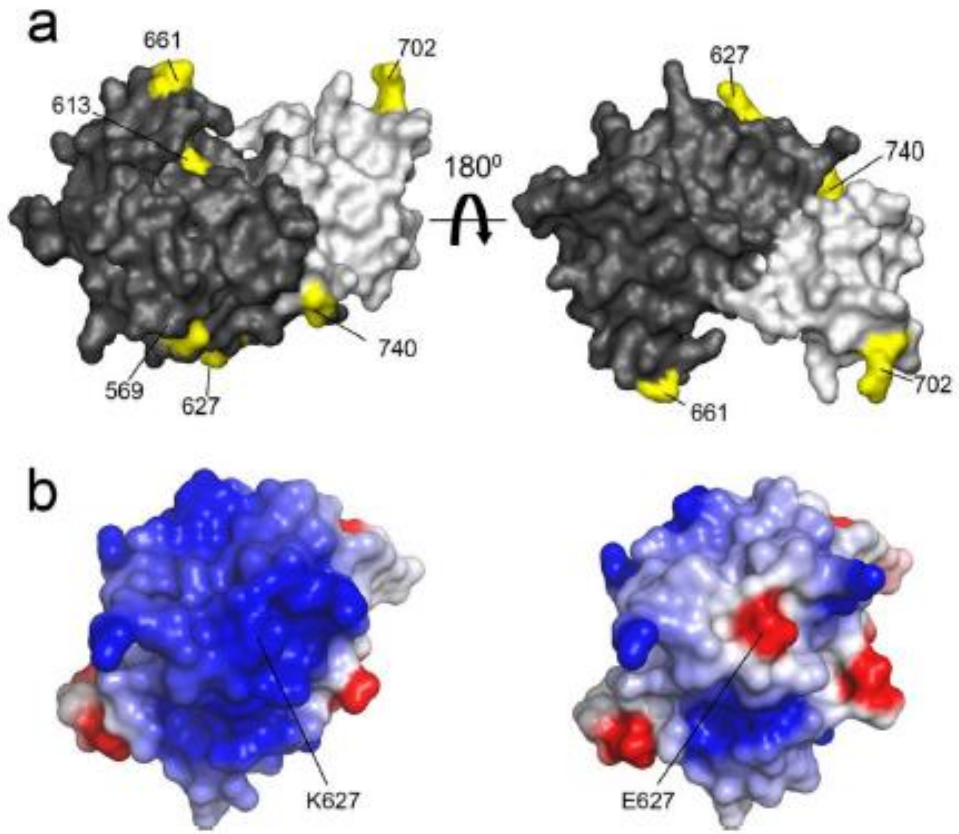
B

	HA1												HA2		
	128	163	165	170	177	193	212	217	267	274	280	317	392	437	523
A/duck/Zhejiang/2/2011(H7N3)	Ala	Lys	Asp	Ile	Gly	Ile	Pro	Gln	Asp	His	Val	Thr	Thr	Asn	Ala
A/duck/Zhejiang/10/2011(H7N3)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
A/duck/Zhejiang/12/2011(H7N3)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
A/Anhui/1/2013(H7N9)	.	Arg	Ser	Val	Val	Val	.	Leu	Asn	.	Ile	Ile	Asn	Asp	Val
A/Shanghai/2/2013(H7N9)	.	Arg	Ser	Val	Val	Val	.	Leu	Asn	.	Ile	Ile	Asn	Asp	Val
A/Hangzhou/1/2013(H7N9)	.	Arg	Ser	Val	Val	Val	.	Ile	Asn	.	Ile	Ile	Asn	Asp	Val
A/Shanghai/1/2013(H7N9)	Ser	Arg	Asn	Val	.	Val	Thr	.	.	Tyr	Ile	Ile	.	Asp	.

C

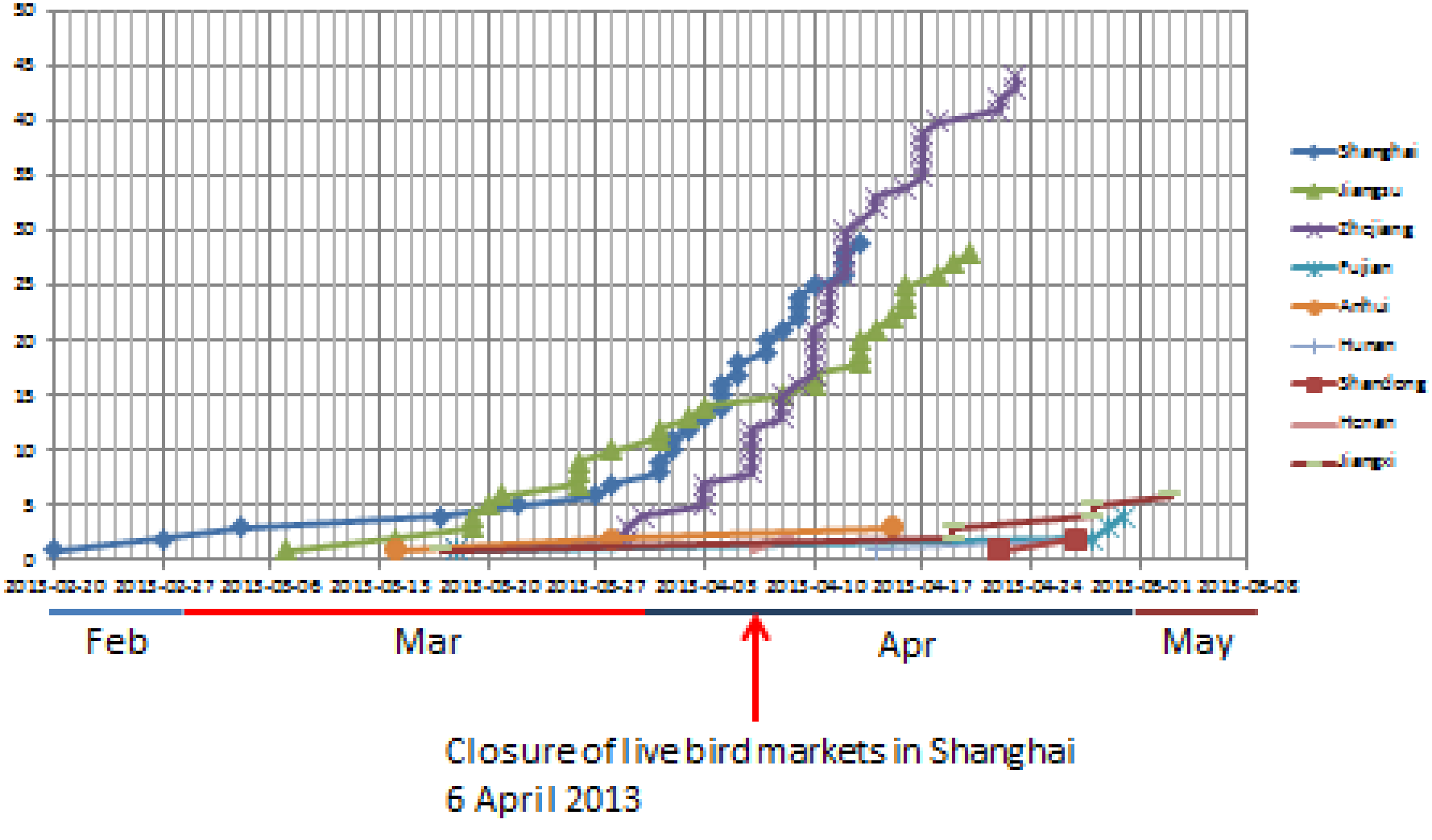
					Deletion												
	22	26	27	40	69		~		73	81	84	111	117	294	401	415
A/wildbird/Korea/A9/2011(H7N9)	Ile	Ile	Thr	Ser	Gln	Ile	Ser	Asn	Thr	Ala	Gly	Lys	Ile	Arg	Thr	Asp
A/wildbird/Korea/A14/2011(H7N9)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Gly
A/wildbird/Korea/A3/2011(H7N9)	.	.	.	.	.	.	.	.	.	Ser	.	.	.	.	.	Gly
A/spot-billed duck/447/2011(H7N9)	.	.	.	.	.	.	.	.	.	Ser	.	.	.	.	.	Gly
A/Anhui/1/2013(H7N9)	Val	.	Ala	Gly	-	-	-	-	-	Thr	Asn	Glu	Val	.	Ala	Ala
A/Shanghai/2/2013(H7N9)	Val	Met	Ala	Gly	-	-	-	-	-	Thr	Asn	Glu	Val	.	Ala	Ala
A/Hangzhou/1/2013(H7N9)	Val	.	Ala	Gly	-	-	-	-	-	Thr	Asn	Glu	Val	.	Ala	Ala
A/Shanghai/1/2013(H7N9)	Val	.	Ala	.	-	-	-	-	-	Thr	Asn	Glu	Val	Lys	Ala	Ala

Adaptation de PB2 (polymérase)

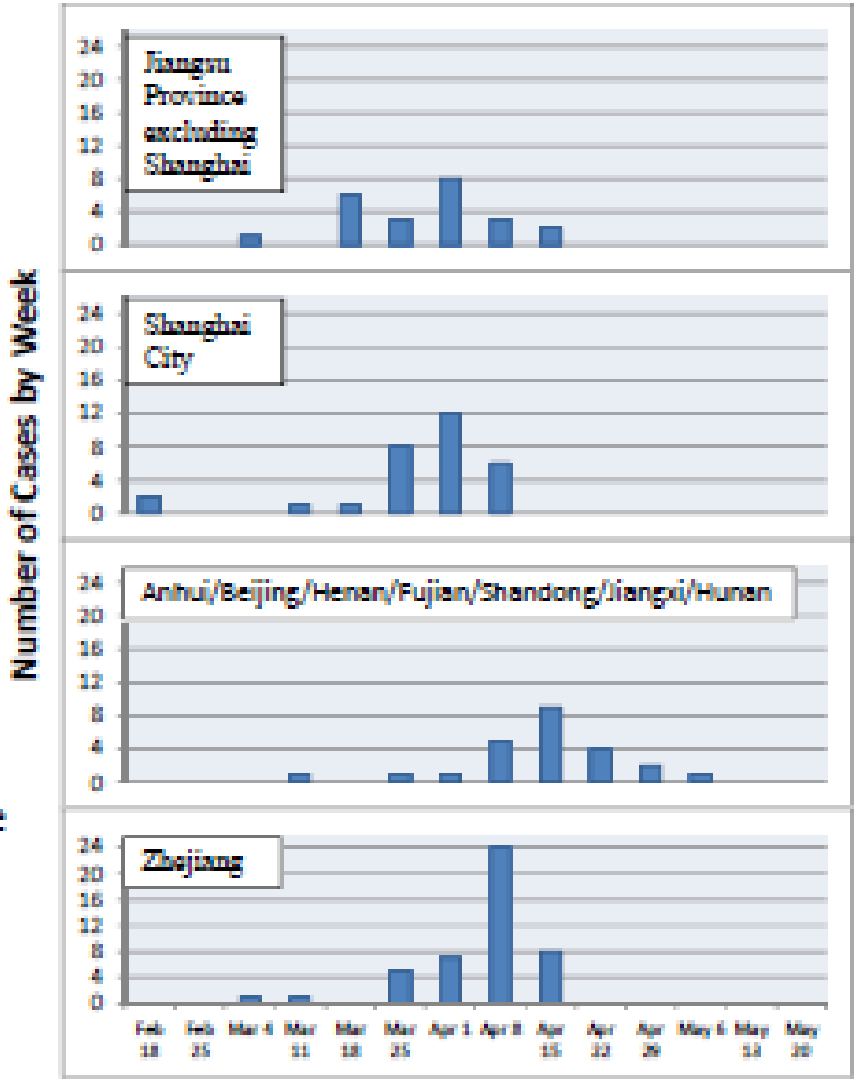


Cases of H7N9 in China by province

(data taken from South China Morning Post)



Cases of H7N9 Influenza in China by Province/City (6/10/13)*



*4 cases from Jiangsu, 4 cases from Shanghai, 1 case from Beijing, 1 case From Jiangxi and 1 case from Henan are missing date of onset. Case hospitalized in Taiwan is not shown.

Total cases = 133

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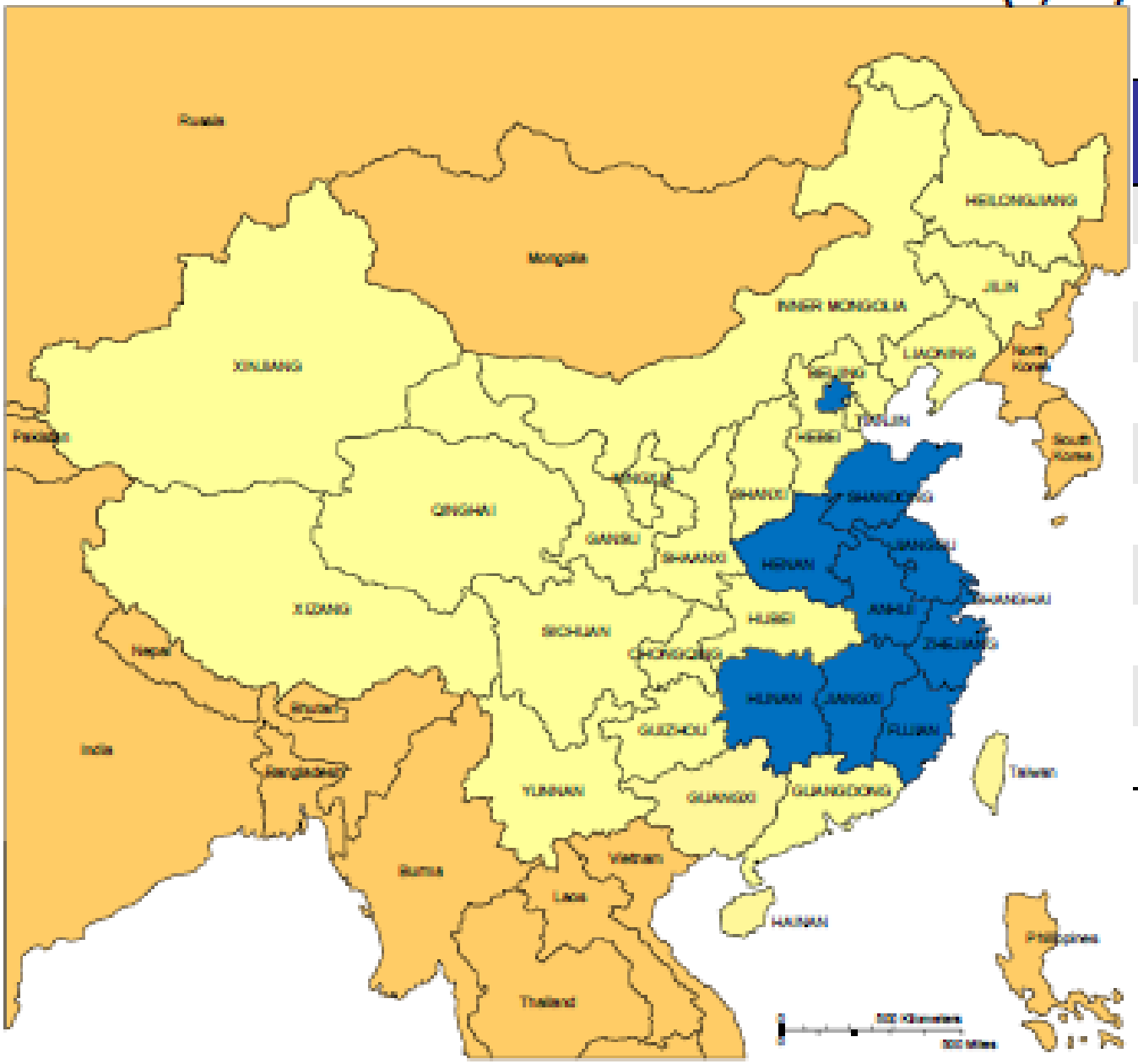
Location of H7N9 Influenza in China (6/10/13)*



*133 total cases/39 deaths

Province/ City	Number of Cases
Anhui	4
Beijing	3
Fujian	5
Henan	4
Hunan	2
Jiangsu[α]	27
Jiangxi	6
Shandong	2
Shanghai	34
Zhejiang	46

α- includes a case hospitalized in Taiwan

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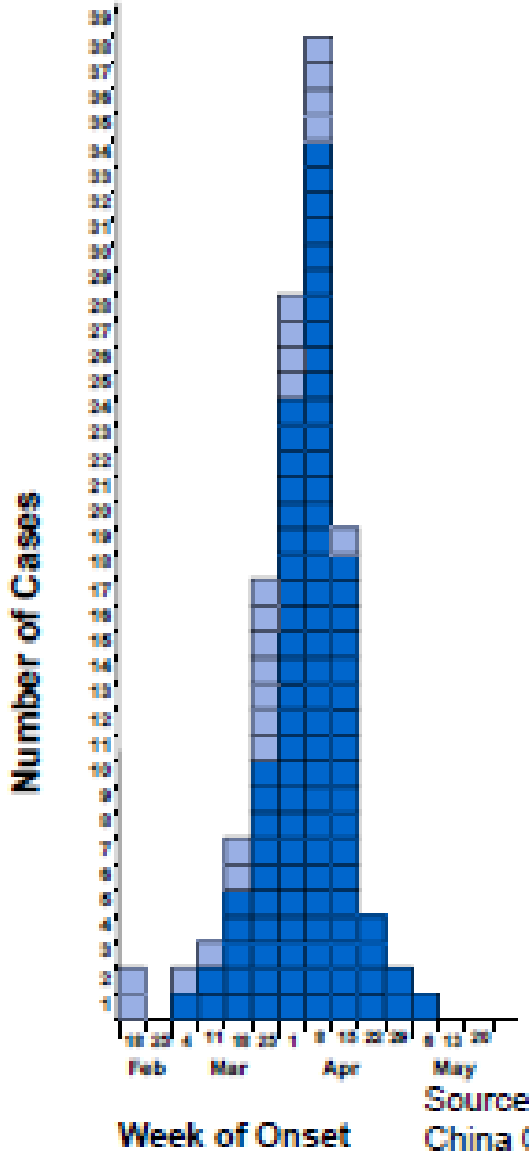
Map of cases of H7N9 in China
Red= fatal
Blue= severe
Yellow= recovered

Cases of H7N9 Influenza in China by Week of Onset (6/11/13)*



*133 total cases/39 deaths;
date of onset missing for 10 cases

Cases Deceased

Cases Alive

Note: total cases includes an asymptomatically infected child in Beijing

Source: Provincial CDC (China), National China CDC, WHO, and news reports

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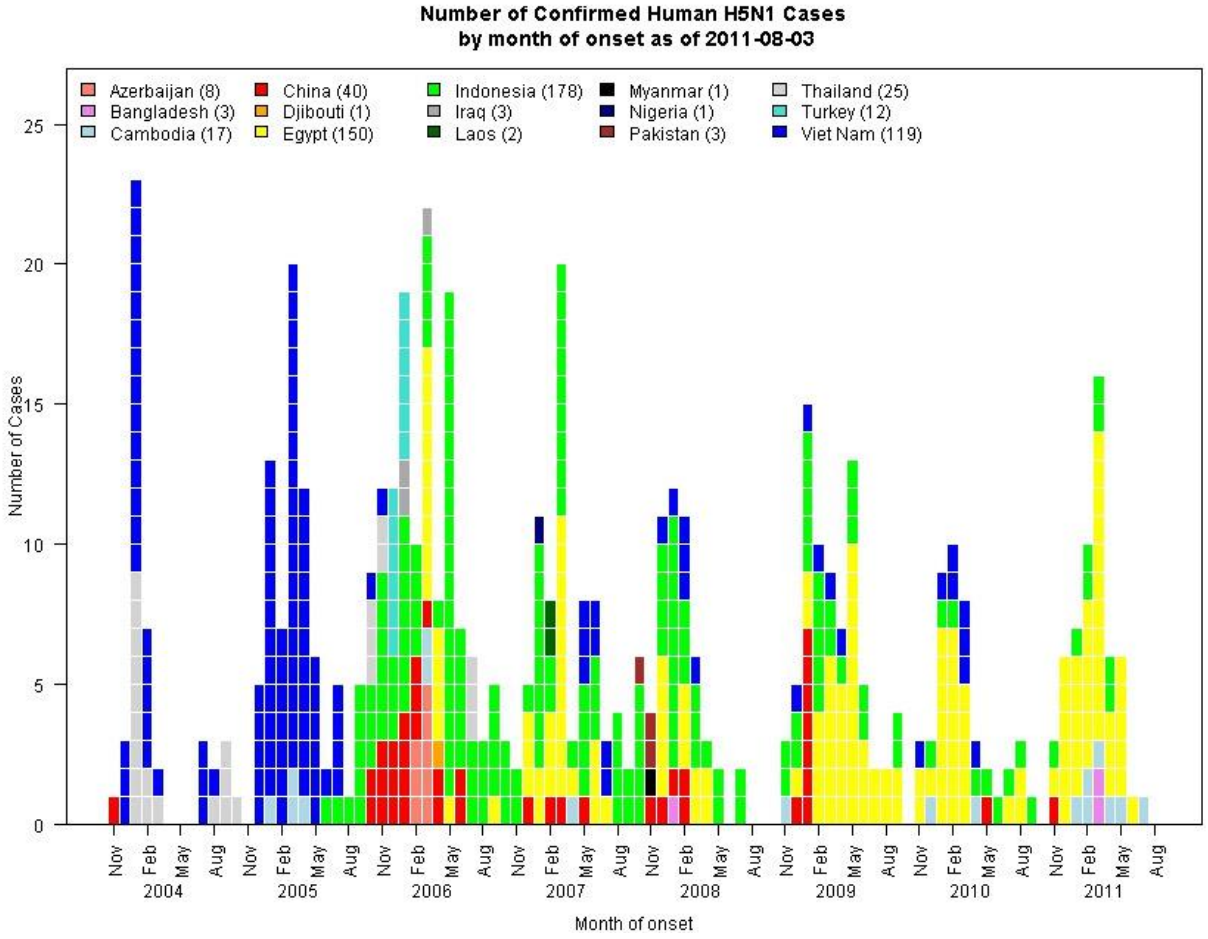
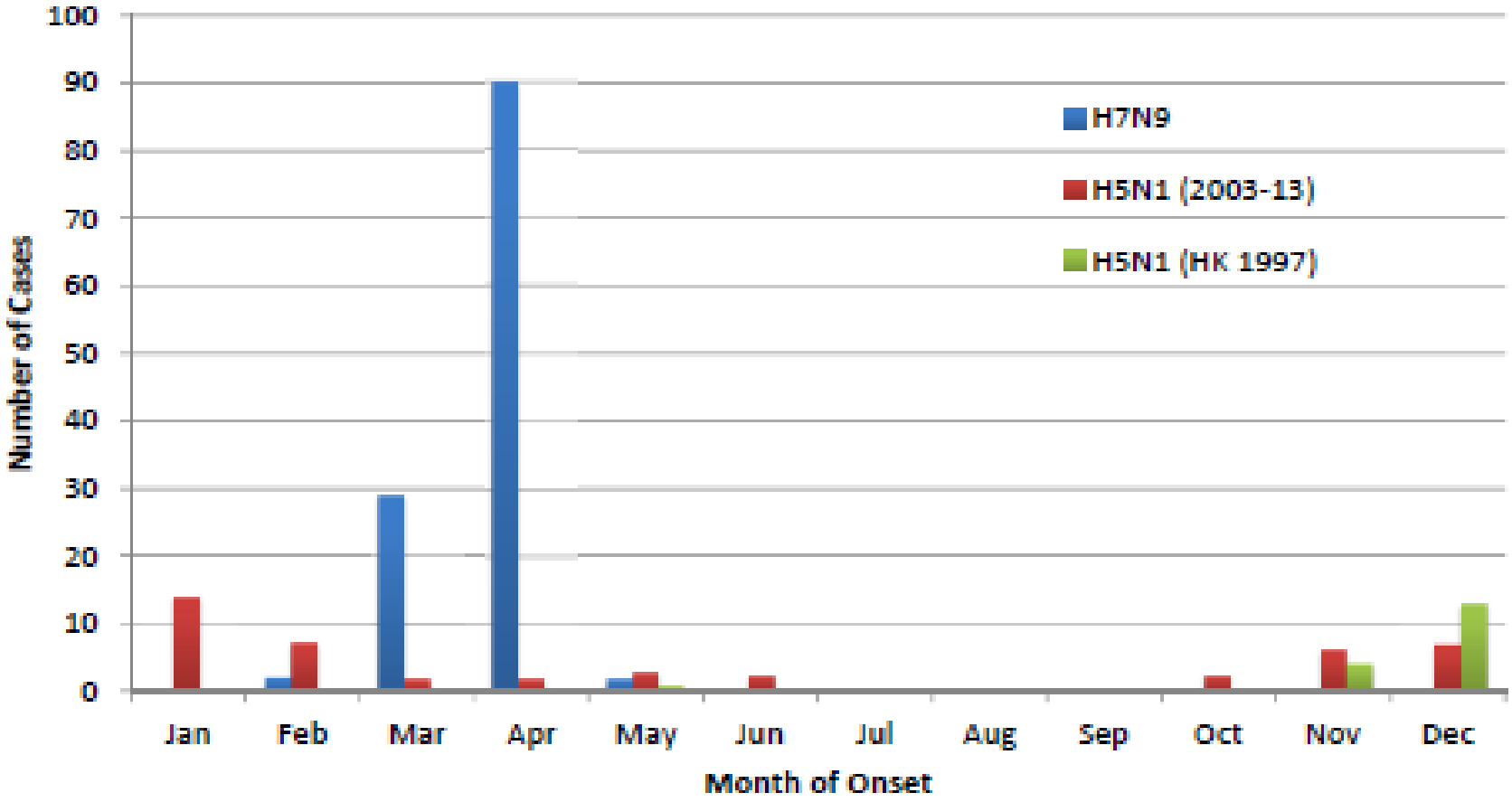
Distribution of the death recorded for H5N1



Cases of H7N9 and H5N1 Influenza in China by Month of Onset (6/10/13)



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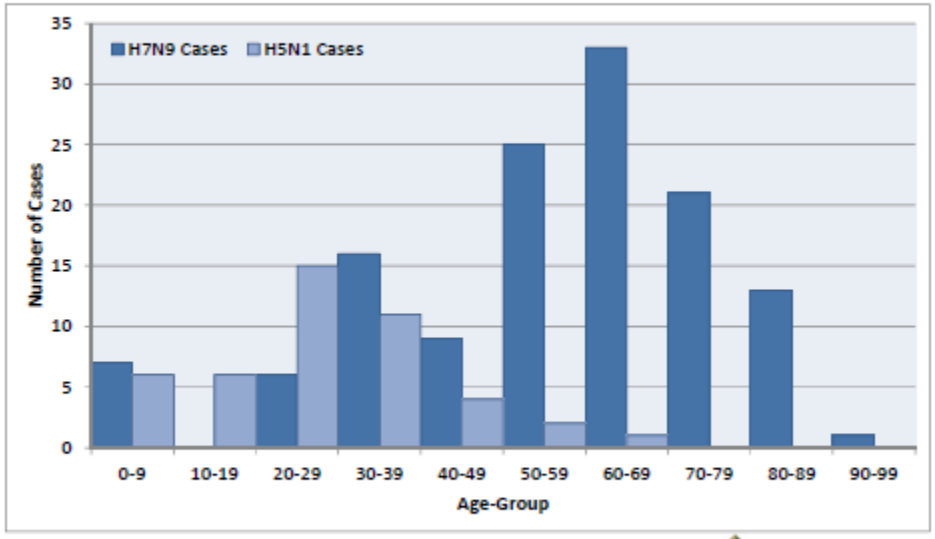
Cases of H7N9 and H5N1 Influenza in China by Age-Group (6/10/13)*



*Total cases = 133

Note: ages of 2 cases are unknown

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H7N9

Virus attachement **OK**

Virus fusion **OK**

Virus réplication **OK**

Virus release **OK**

Immune response **OK**

Virulence **OK**

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 α2,6 binding in H5 subtype	[194]
		N182K	Increases α2,6 binding and decreases α2,3 binding in H5 subtype	[194,195]
		E190D	Increases α2,6 binding in H1 subtype	[86,196]
		Q192R	Increases α2,6 binding and decreases α2,3 binding in H5 subtype	[195]
		D222G	Increases α2,3 binding in H1 subtype	[75,197]
		Q222L	Increases α2,6 binding and decreases α2,3 binding in H5 subtype	[194]
		S223N	Increases α2,6 binding and decreases α2,3 binding in H5 subtype	[194]
		G224S	Increases α2,6 binding and decreases α2,3 binding in H5 subtype	[194]
		G225D	Decreases α2,3 binding in H1 and H9 subtypes	[81,86,196]
		Q226L	Increases α2,6 binding and decreases α2,3 binding in H2, H3, H4, H5 and H9 subtypes	[81,86,198,199]
		S227N	Increases α2,6 binding and decreases α2,3 binding in H5 subtype	[200,201]
		G228S	Decreases α2,3 binding in H3 subtype Increases α2,6 binding in H2 and H5 subtypes	[86,198,201]
		L129V + A134V	Increases α2,6 binding possibly in H5 subtype	[202]
		G139R + N182K	Increases α2,6 binding in H5 subtype	[194]
		Q192R + S223N	Increases α2,6 binding and decreases α2,3 binding in H5 subtype	[194]
		Q222L + G224S	Increases α2,6 binding and decreases α2,3 binding in H5 subtype	[194]
		S227N + NST158 – 150NNA	Increases α2,6 binding in H5 subtype	[203]
		N158S + Q226L + N248D	Increases α2,6 binding and decreases α2,3 binding in H5 subtype	[194,204]
		N182K + Q222L + G224S	Increases α2,6 binding and decreases α2,3 binding in H5 subtype	[194]
		Q192R + Q222L + G224S	Increases α2,6 binding and decreases α2,3 binding in H5 subtype	[194]
		Q222L + S223N + G224S	Increases α2,6 binding and decreases α2,3 binding in H5 subtype	[194]
		NST158-150NNA + K193R + Q226L + G228S	Increases α2,6 binding and decreases α2,3 binding in H5 subtype	[205]
		N182K + Q222L + S223N + G224S	Increases α2,6 binding and decreases α2,3 binding in H5 subtype	[194]
		Q192R + Q222L + S223N + G224S	Increases α2,6 binding and decreases α2,3 binding in H5 subtype	[194]
		N182K + Q192R + Q222L + S223N + G224S	Increases α2,6 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 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-α1, and shifting nuclear import dependency from importin-α3 to importin-α7 in human and other mammalian cells	[112]
Virus release	NA	I275V	Increases α2,6 substrate specificity in N2 subtype	[133]
Viral escape from host immune responses	HA	Antigenic shift	Escapes pre-existing humoral immunity	[134]
	NS1	D92E	Confers HPAIV H5N1 resistance to IFN-α, IFN-γ and TNF-α (unknown mechanism)	[139]
		P42S	Prevents double-stranded RNA-mediated activation of NF-κB and IRF-3 pathways during HPAIV H5N1 infection	[140]
		L103F + I106M	Allows binding of HPAIV H5N1 NS1 protein and CPSF30 resulting in decreased INF-β mRNA production	[141]
		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]

MERS-CoV

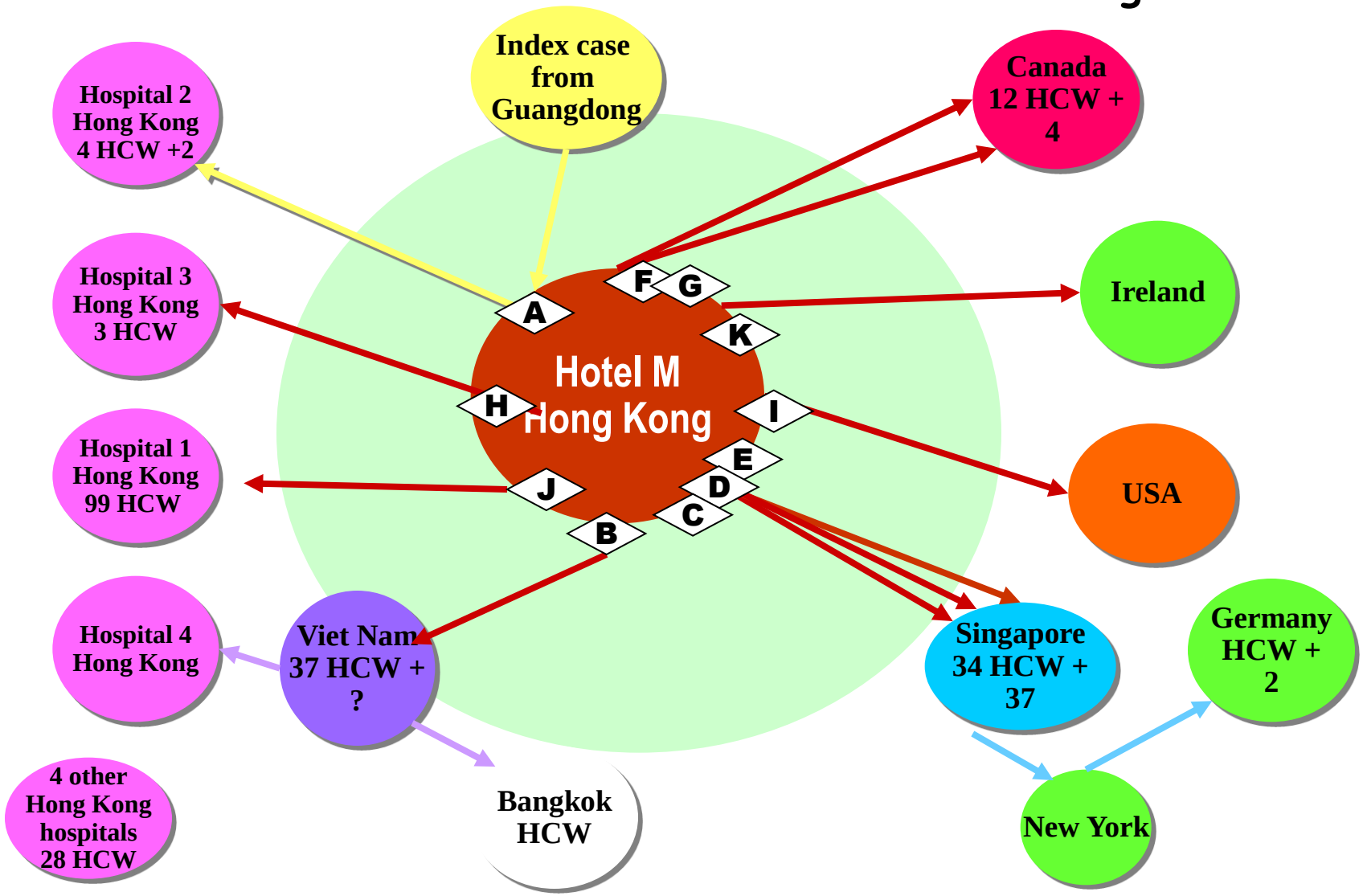
nCoV

CoV-EMC

hCoV

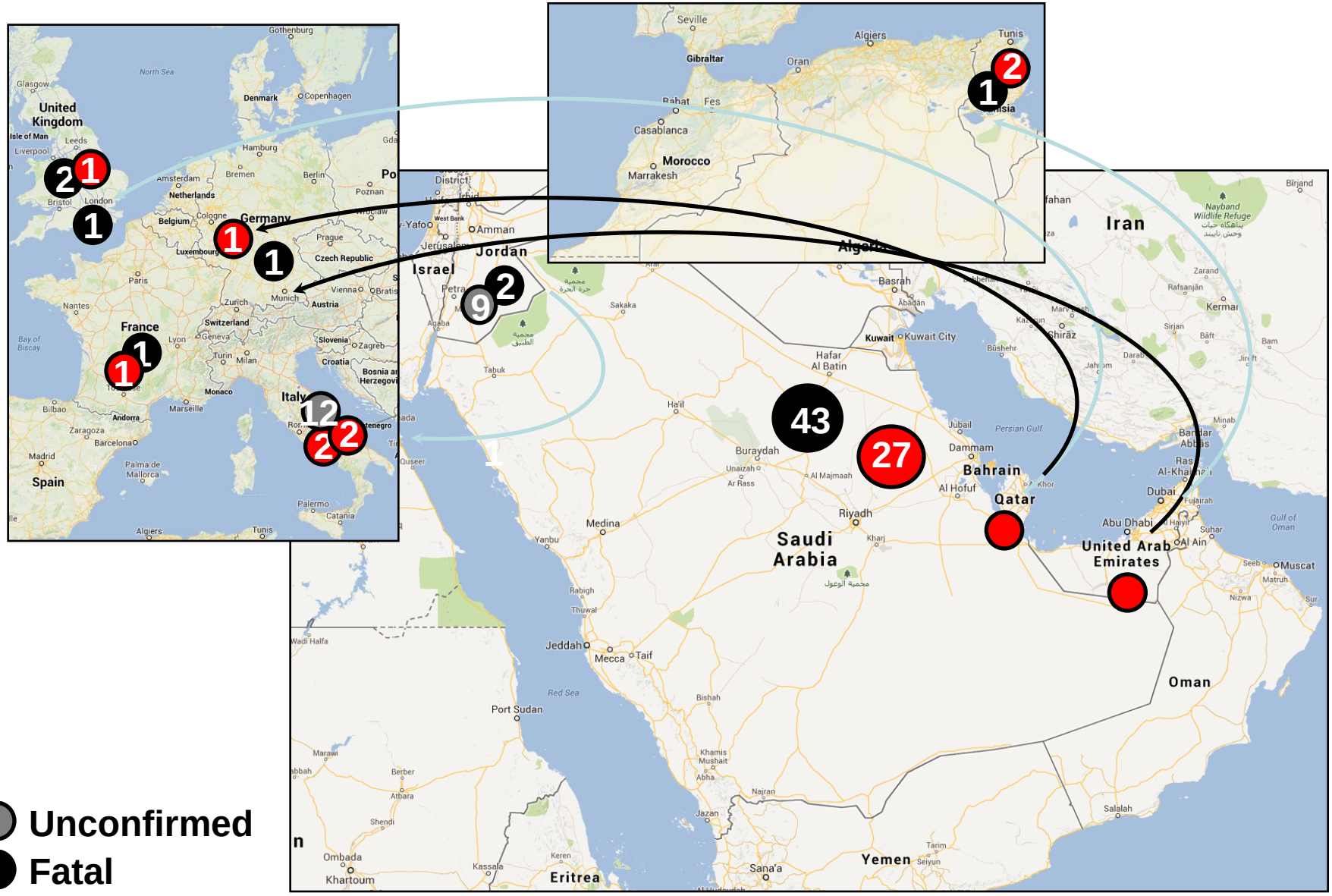
Hôtel M. à Hong Kong , février 2003

219 soignants
30 non-soignants



Emergence of MERS-CoV

- 58 confirmed cases, 33 deceased, 57% CFR -



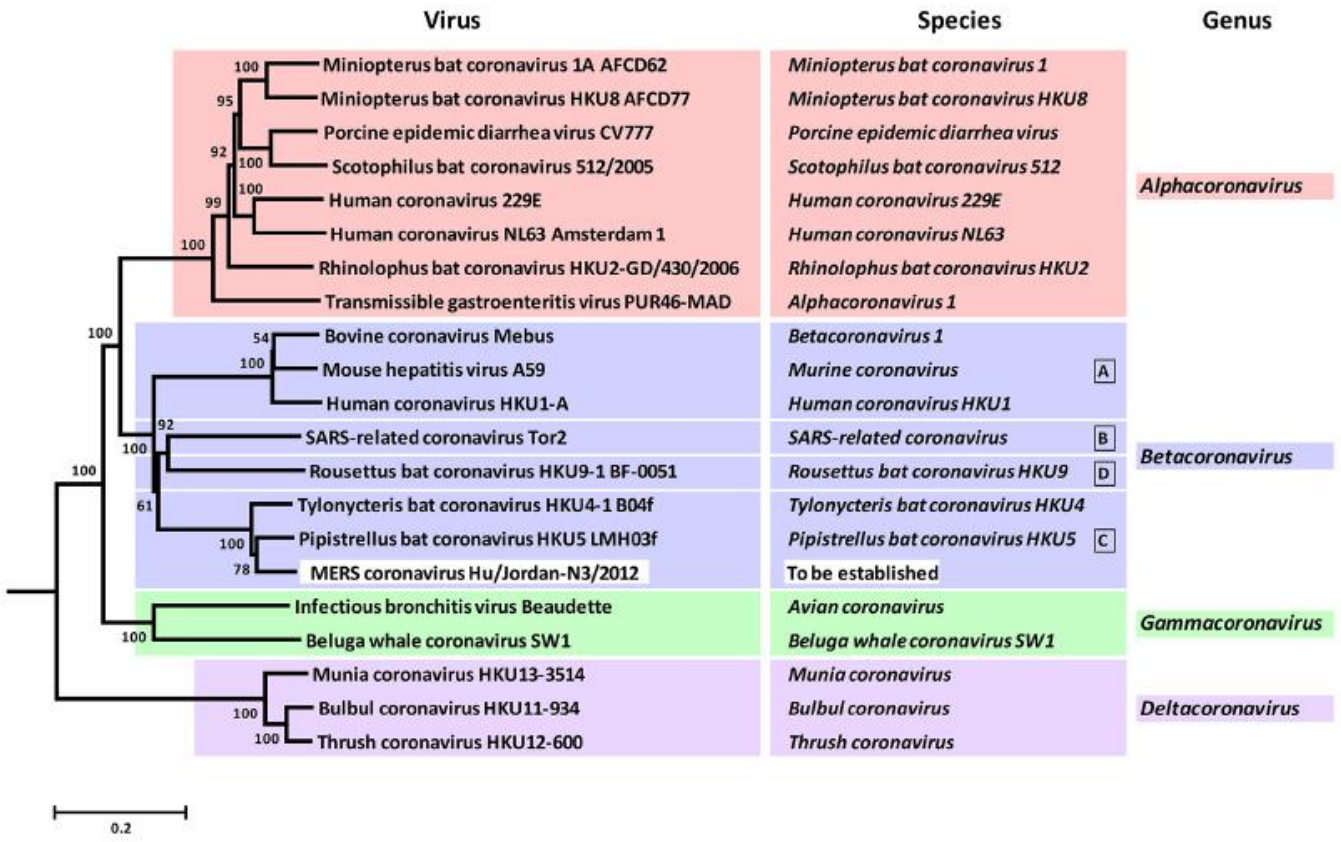
Jordanian initial cluster (1)

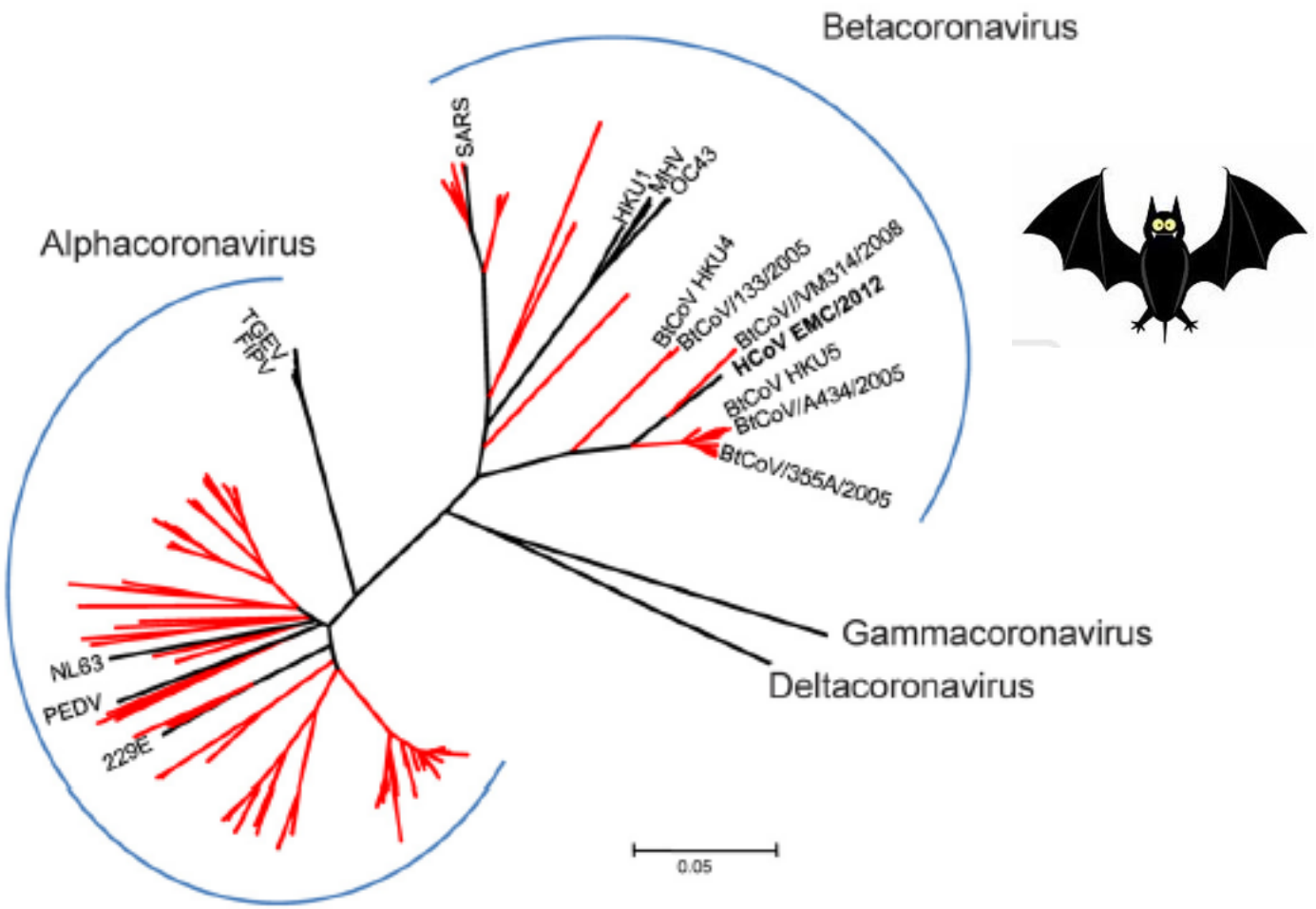
- The first hospital cluster involved 2 confirmed and 11 probable cases in April 2012. They were not identified as such until about 7 months later,
- Of the 13 confirmed and probable cases, 10 were in healthcare workers (HCWs)
- Investigators found that the illnesses came in two waves or phases: four with onset between Mar 21 and Apr 2, and nine with onset between Apr 11 and 26.
- Only three patients were women.
- But the median age was only 33, as compared to 56 years for the Saudi case cluster.
- The first (index) case in the cluster was in a 25-year-old university student who got sick on Mar 21 but was not hospitalized until Apr 4.

Jordanian initial cluster (2)

- The index patient, who died on Apr 25, had no travel history and no reported contact with animals in the 10 days before his first symptoms.
- Oddly, however, the second and third patients got sick before the first case-patient was hospitalized, leaving it unclear how the second patient became infected.
- To prevent "stigmatization of patients, " the HCWs didn't use any personal protective equipment except gloves when caring for them.
-
- The apparent incubation period for the illness was no more than 10 days.
- Overall, the findings "suggest that although person-to-person infection is possible, there is no evidence at present of sustained person-to-person transmission of MERS CoV

Classification phylogénétique du MERS CoV

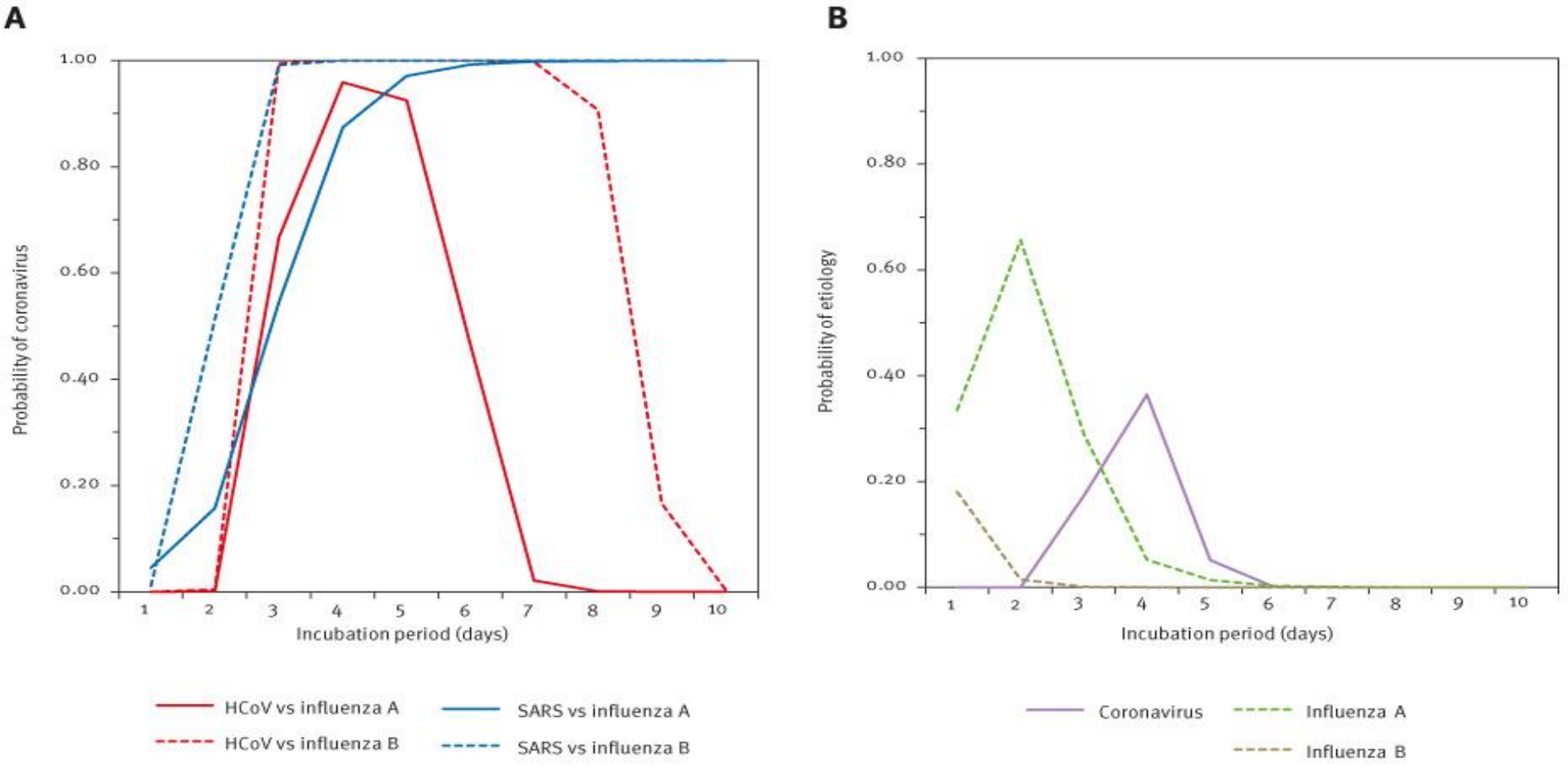




Bat coronavirus	Host	Location	Accession number
BtCoV/VM314/2008	*Pipistrellus* bat	Netherlands	GQ259977
BtCoV/133/2005	*Tylonycteris* bat	China	DQ648794.1
BtCoV/ 355A/2005	*Pipistrellus* bat	China	DQ648809.1
BtCoV/A434/2005	*Pipistrellus* bat	China	DQ648819.1
HKU4	*Pipistrellus* bat	China (HK)	DQ249214.1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

Figure

Probability of coronavirus infection given the incubation period of a case



A. The probability of coronavirus infection given the incubation period, when comparing between coronavirus infection and influenza virus infection as possible diagnoses. We use 50% probability for each of the two viruses (i.e. coronavirus versus influenza virus) for a conservative argument to avoid an underestimation of the risk of novel coronavirus. Since known coronaviruses are classified into severe acute respiratory syndrome (SARS)-associated virus and non-SARS viruses, and because influenza viruses are crudely classified as type A and B viruses, there are four possible combinations for comparison. HCoV stands for human coronavirus infection other than severe acute respiratory syndrome (SARS).

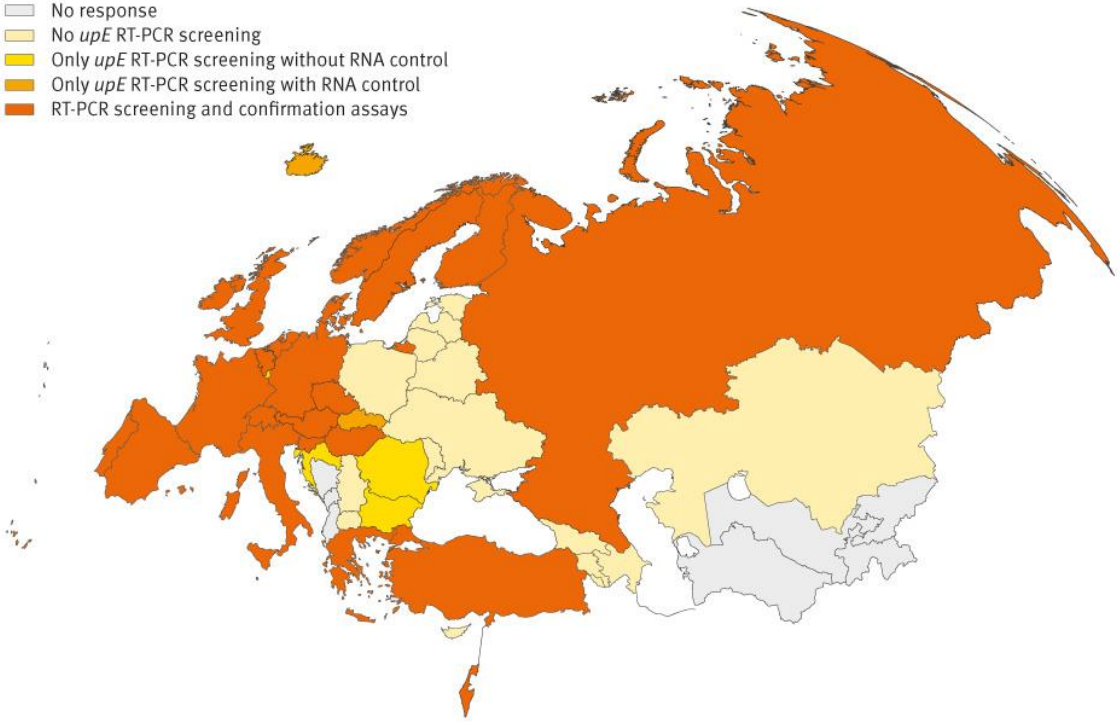
SITUATION des CAS POSSIBLES à NCoV au 17 MAI 2013 - 14H

date de Signalement	N° de signalement	Ville	HDM	Date prélèvement 1	Statut prélèvements	Résultat attendu le	Résultat	Date et heure du résutat	Commentaire	Statut
16/05/2013	77	Rennes	**CHU Rennes.** Femme 62 ans résidente Abu Dabi. Arrivée en France dans sa famille le 03/05/2013. DDS le 09/05/2013 : Toux, Notion de fièvre, dyspnée. ATCD de BPCO. Ag LP1 et Pneumo Neg. CRP 25 et GB=16000. Pas de foyer à la RXT. Hospit le 16/05 en pneumo CHU Rennes. Chambre seule avec précautions renforcées en Maladies Inf. depuis 10h00 le 16/05.	16/05/2013	Reçu CNR (Paris)	17/05/2013 AM				En cours
16/05/2013	82	Le Havre	**CH Le Havre.** Femme 53 ans. Retour d'Arabie Saoudite le 11-05-2013, le 15-05-2013 présente dyspnée, fièvre 39°6C, oppression thoracique, adénopathies cervicales mais pharynx inspecté normale, auscultation OK, RXT Normale mais de mauvaise qualité. sans ATCD, ne parle pas français (-> famille). Biologie en faveur d'une étiologie non bactérienne. Transférée au CH du Havre pour isolement.	17/05/2013	envoyé CNR Paris				2ème prélèvement à discuter	En cours
17/05/2013	83	Chambery	**CH Chambery.** Homme 48 ans, retour EAU (Dubaï) où il a passé 5 jours du 12 au 16/05/2013. DDS le 15/05/2013. Fièvre 38,7°, toux , signes respi bilatéraux, SaO2 = 89% à l'admission. ATCD asthmatiques. En isolement depuis hier soir. Prélèvements réalisés et adressés au CNR le 17/05 en matinée.	16/05/2013	Reçu CNR (Lyon)	17/05/2013 AM				En cours
17/05/2013	85	Strasbourg	**CHU Strasbourg**. Femme 85 ans. Séjour en Arabie Saoudite du 18/04/2013 au 28/04/2013. DDS le 06/05 : consulte son médecin traitant pour un syndrome grippal franc (fièvre>38°, toux,gène respiratoire, arthromyalgies). Mise sous Ceftriaxone devant des ATCD cardiaques. Pas d'amélioration dans les jours suivants, Aggravation de son état le 14/05. Hospitalisation au CHU de Strasbourg le 16/05 via le SAU. Isolée d'emblée en Maladies Inf. Etat de santé préoccupant, CRP=150, Infection diffuse à la RXT.	17/05/2013	envoyé CNR Paris				2ème prélèvement à discuter	En cours

Capacité diagnostique en Europe

FIGURE

Countries in the World Health Organization (WHO) European Region and Lichtenstein indicating the available capacity for screening and confirmation of novel coronovirus infection, 28 November 2012



The map indicates the level of screening and confirmation tests available in the 47 responding countries, including 46 WHO European Region Member States, 27 EU Member States and three EEA countries, of which two are also Member States of WHO European Region.

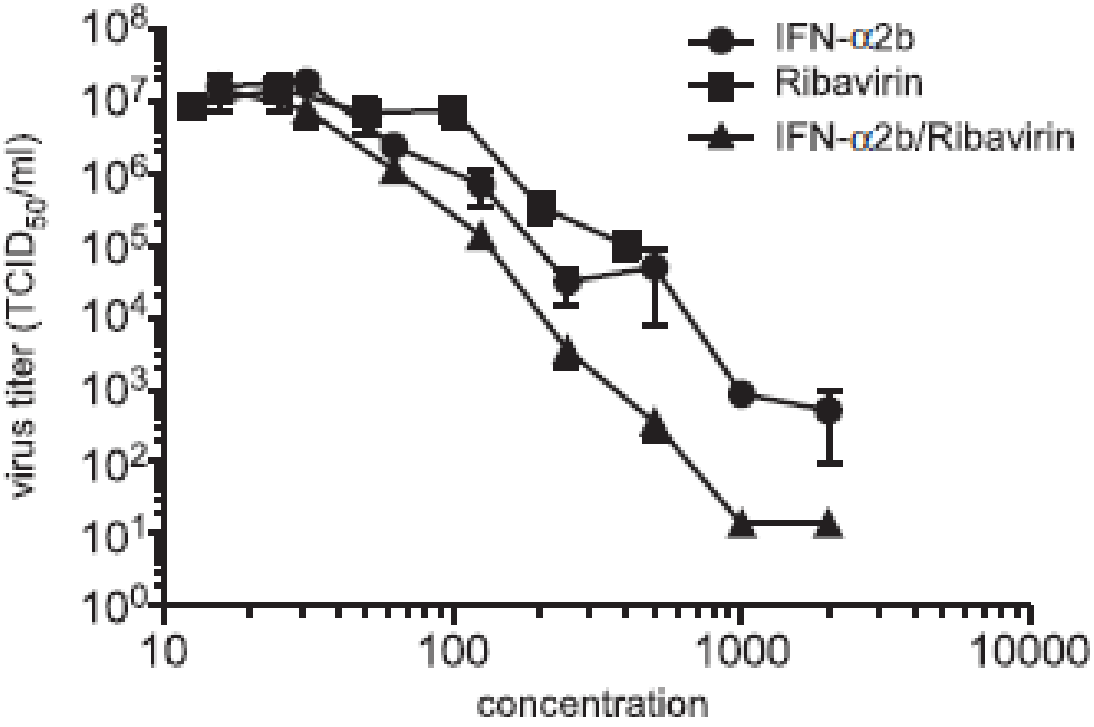
Au total

- Des analogies avec le SRAS
- Les transmissions nosocomiales sont une réalité
- Les prélèvements des VAI meilleurs que ceux des VAS
- Les selles potentiellement contaminées
- Le taux de léthalité est élevé (33/58)
- La source infectieuse est inconie (chauve-souris?)

- La période du pèlerinage va être délicate a gérer
- Actuellement beaucoup d'incertitudes…
- Pas de traitement, mais des pistes

Inhibition of novel β coronavirus replication by a combination of interferon-α2b and ribavirin

Darryl Falzarano[1], Emmie de Wit[1], Cynthia Martellaro[1], Julie Callison[1], Vincent J. Munster[2] & Heinz Feldmann[1,3]



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• Vincent Munster	NIAID, Hamilton, MT (USA)