H5N1 : Diagnostic et surveillance

Bruno LINA

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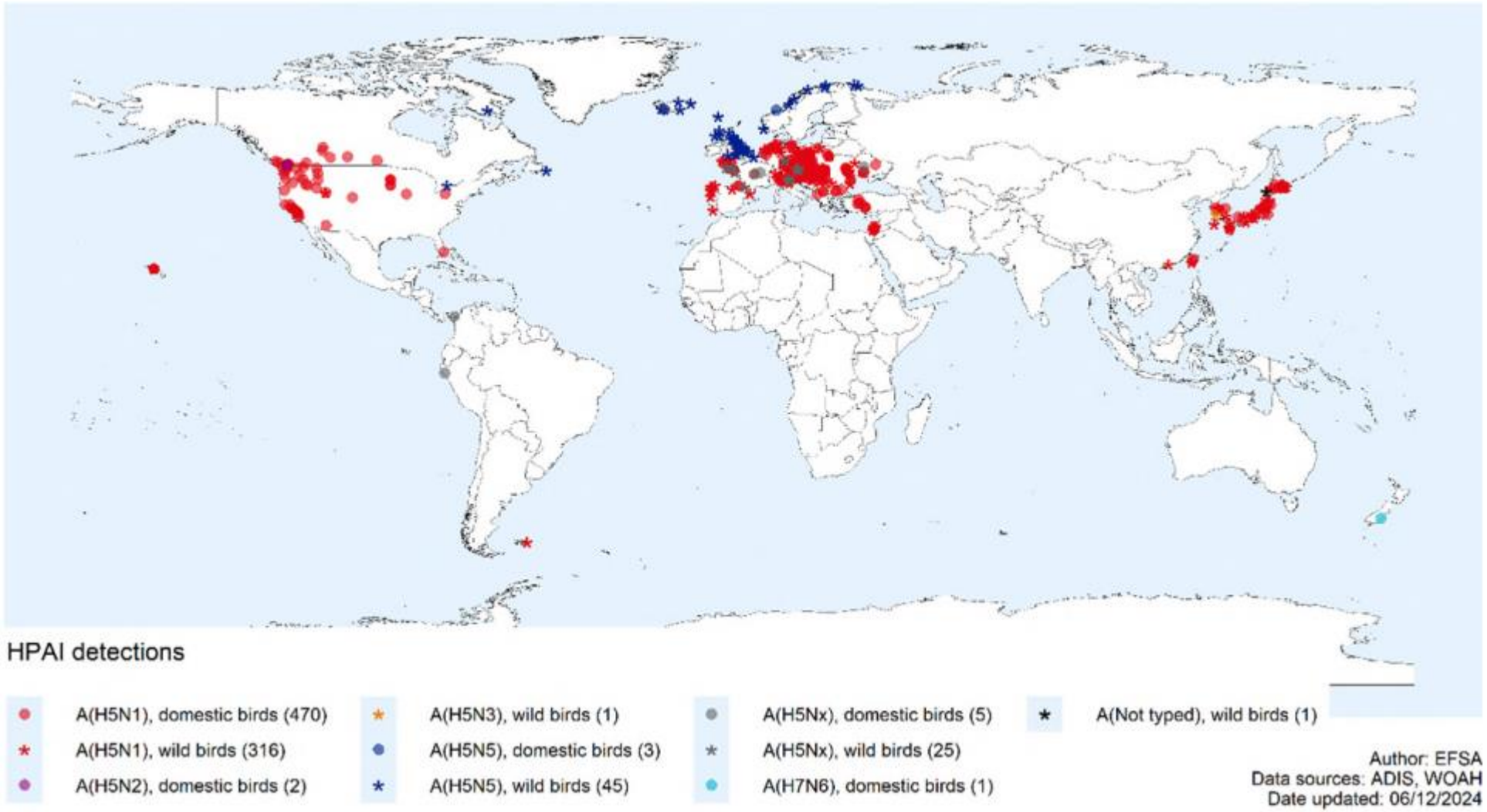
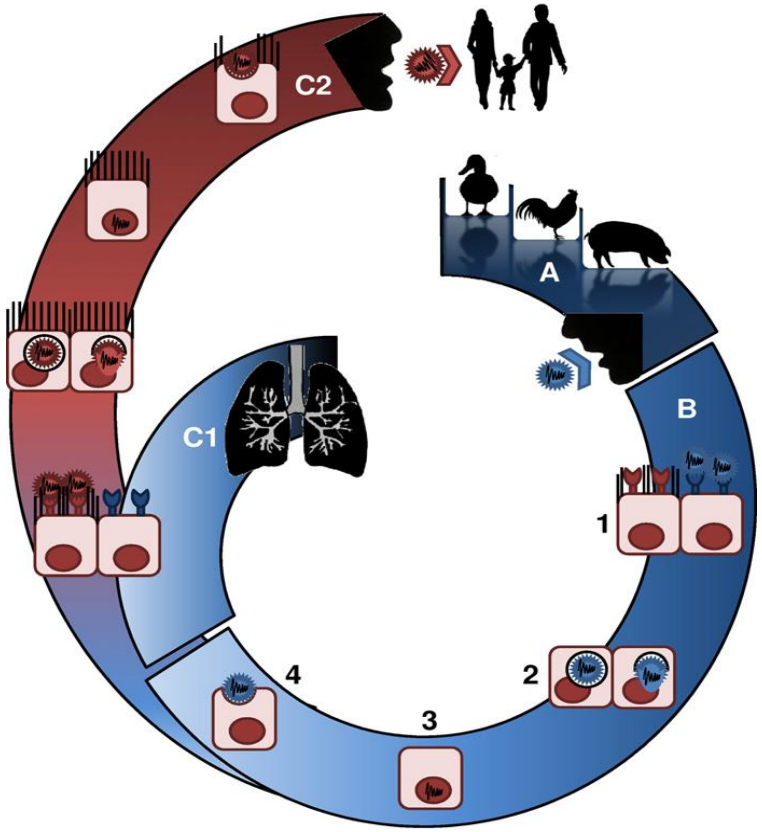
Détection chez les oiseaux jan 25

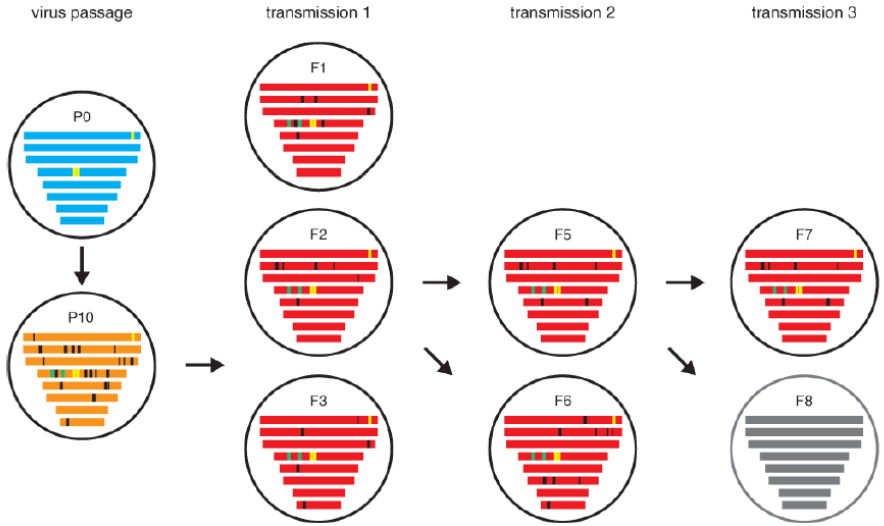


Etat des lieux du risque : le franchissement de la barriere d’espèce

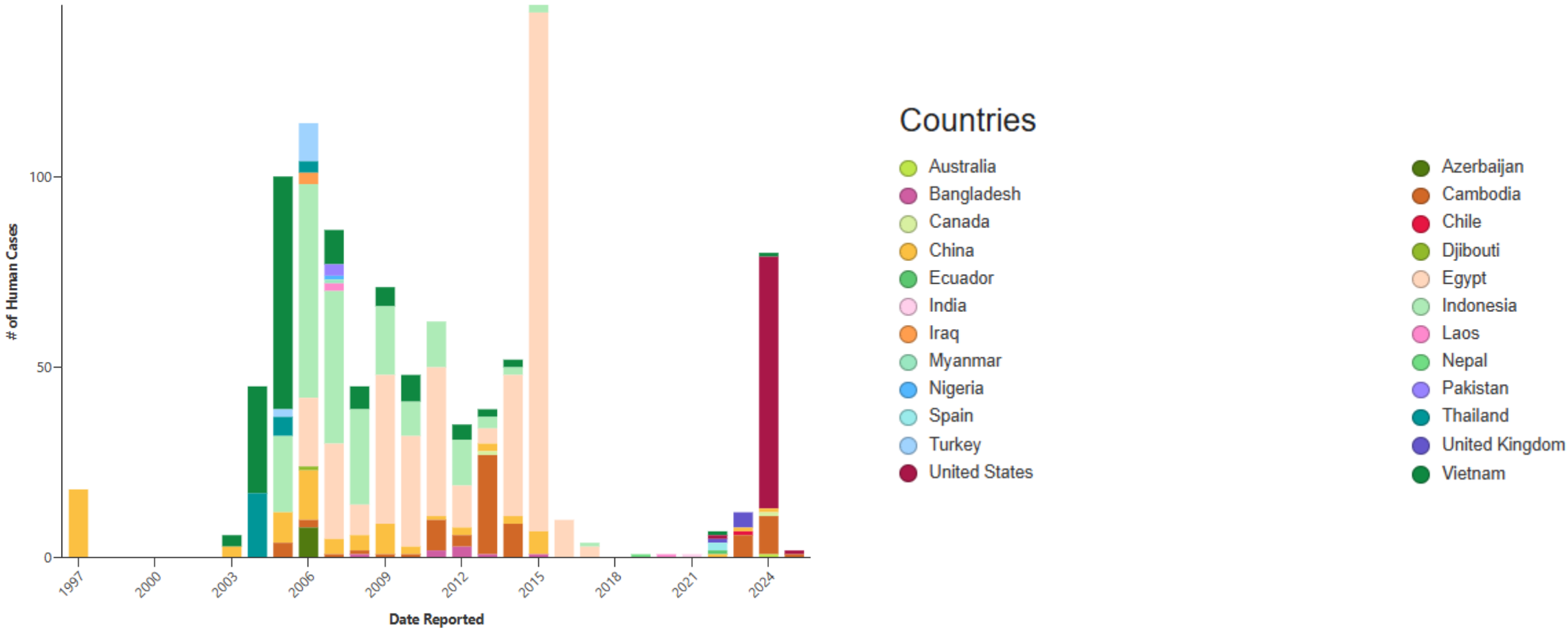


Etude conduite par Herst S et al en 2012.
La transmission aérienne du H5N1 nécessite au minimum la présence combinée des mutations HA Q222L,G224S et PB2 E627K

Science. 2012 June 22; 336(6088): 1534–1541.

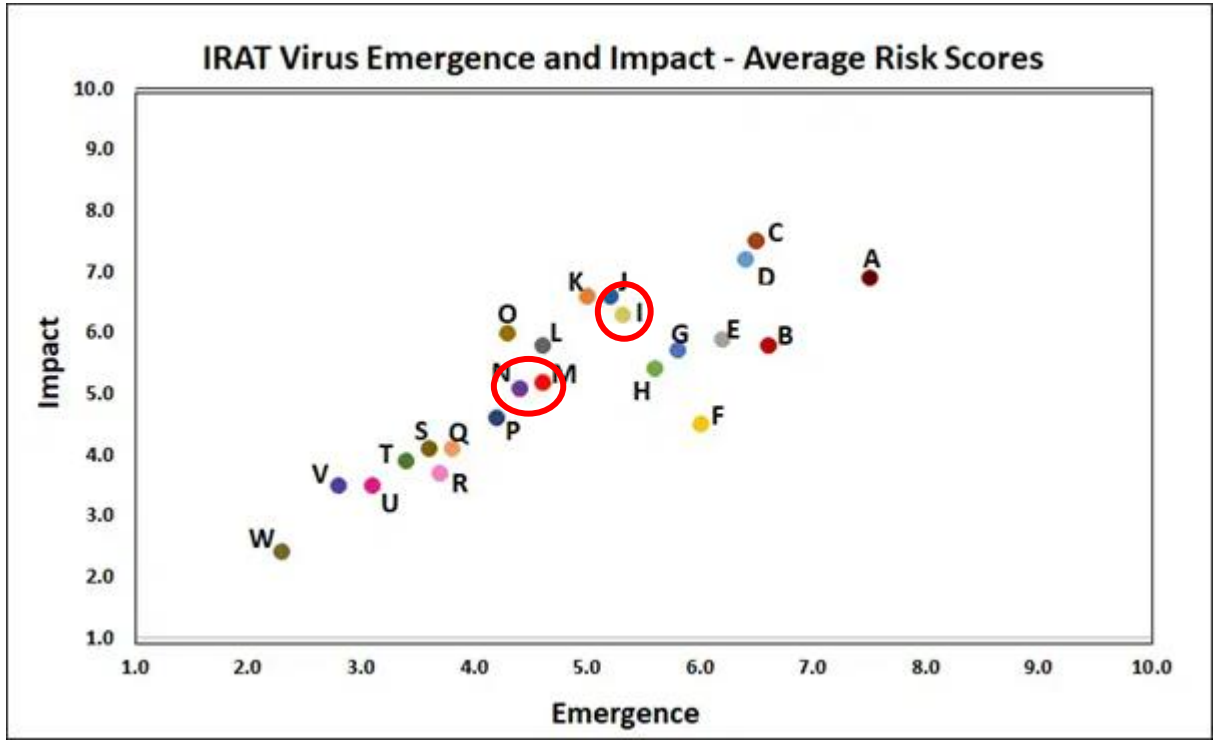


Past Reported Global Human Cases with Highly Pathogenic Avian Influenza A(H5N1) (HPAI H5N1) by Country, 1997-2025

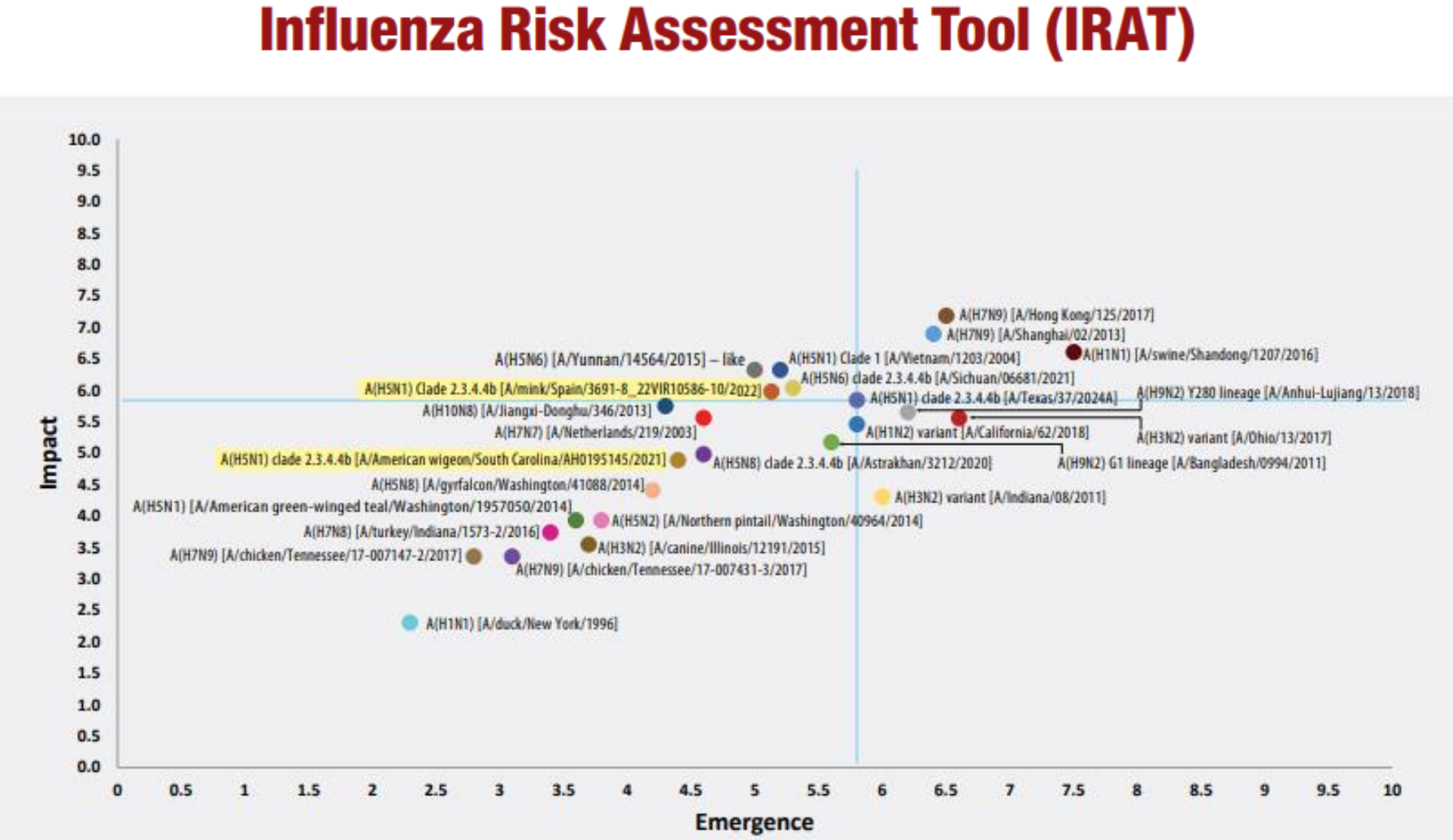


Niveau de risque estimé (CDC atlanta) 2023

Dot	Influenza Virus	Emergence Score	Impact Score	Risk Assessment Year
A	A(H1N1) [A/swine/Shandong/1207/2016]	7.5	6.9	Jul-20
B	A(H3N2) variant [A/Ohio/13/2017]	6.6	5.8	Jul-19
C	A(H7N9)[A/Hong Kong/125/2017]	6.5	7.5	May-17
D	A(H7N9) [A/Shanghai/02/2013]	6.4	7.2	Apr-16
E	A(H9N2) Y280 lineage [A/Anhui-Lujiang/13/2018]	6.2	5.9	Jul-19
F	A(H3N2) variant [A/Indiana/08/2011]	6	4.5	Dec-12
G	A(H1N2) variant [A/California/62/2018	5.8	5.7	Jul-19
H	A(H9N2) G1 lineage [A/Bangladesh/0994/2011]	5.6	5.4	Feb-14
I	A(H5N6) clade 2.3 4 4b [A/Sichuan/06681/2021]	5.3	6.3	Oct-21
J	A(H5N1) Clade 1 [A/Vietnam/1203/2004]	5.2	6.6	Nov-11
K	A(H5N6) [A/Yunnan/14564/2015] - like	5	6.6	Apr-16
L	A(H7N7) [A/Netherlands/219/2003]	4.6	5.8	Jun-12
M	A(H5N8) clade 2.3 4 4b [A/Astrakhan/3212/2020]	4.6	5.2	Mar-21
N	A(H5N1) clade 2.3 4 4b [A/American wigeon/South Carolina/AH0195145/2021]	4.4	5.1	Mar-22

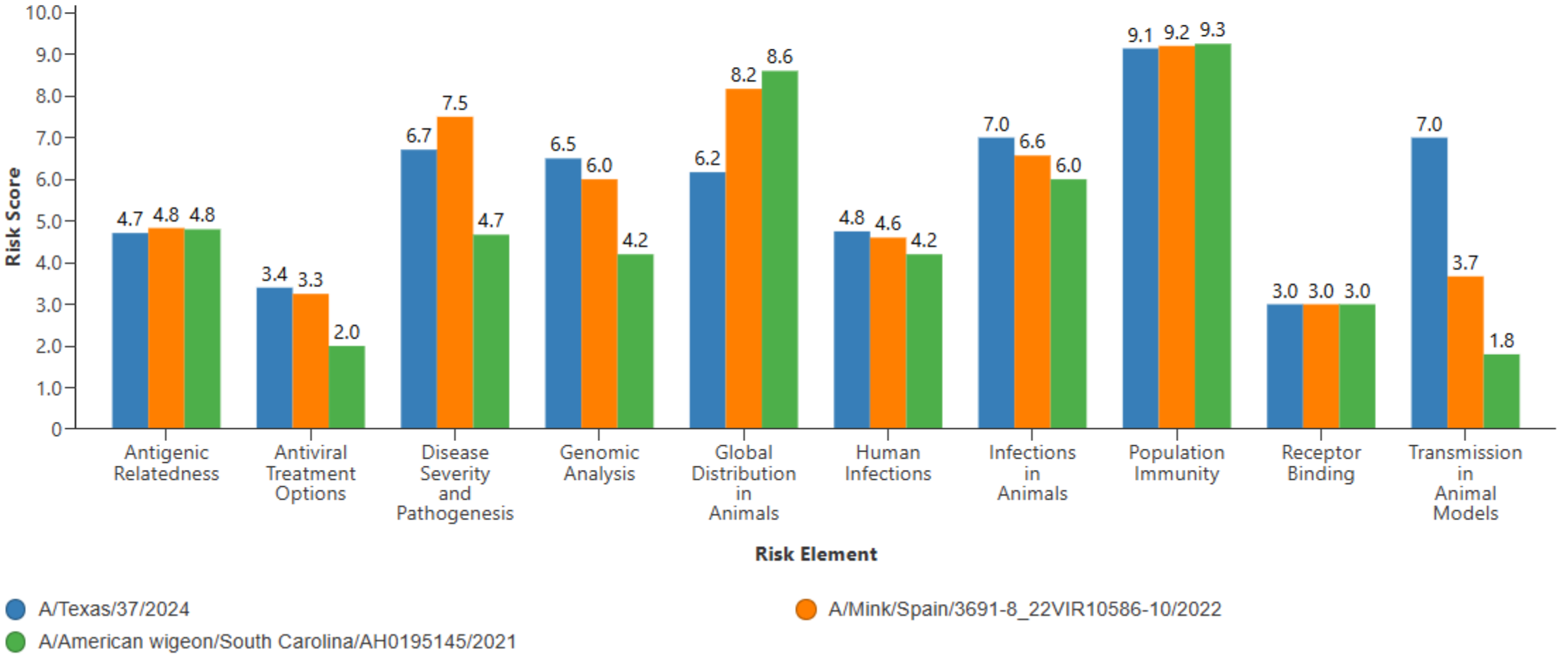


Niveau de risque estimé (CDC atlanta) juin 2024

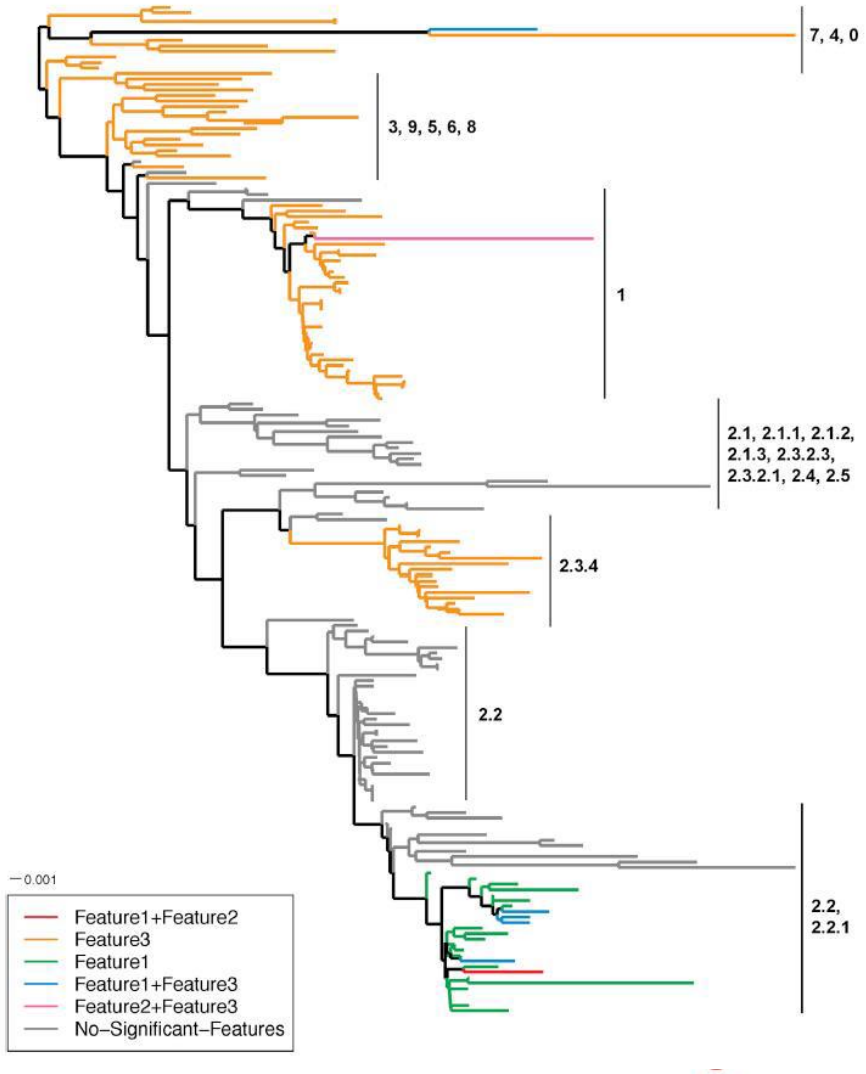


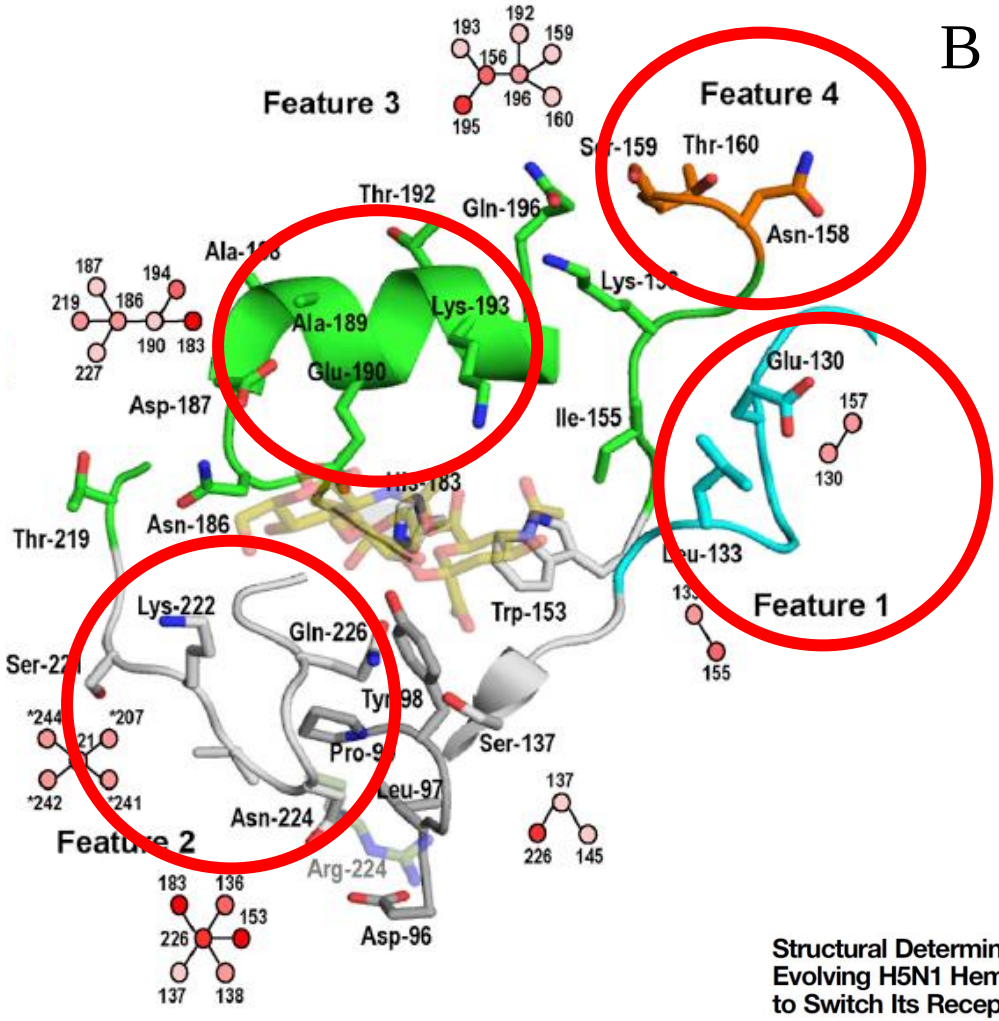
Virus comparison by risk element score

H5N1 Clade 2.3.4.4b Virus Comparison by Risk Element Score



Zones clef de l’adaptation des RBS pour H5 (suivi des clades 2.3.4*)





Structural Determinants for Naturally Evolving H5N1 Hemagglutinin to Switch Its Receptor Specificity

Kannan Tharakaraman,[1] Rahul Raman,[1] Karthik Viswanathan,[1] Nathan W. Stebbins,[1] Akila Jayaraman,[1] Arvind Krishnan,[1] V. Sasisekharan,[1] and Ram Sasisekharan[1,*]
[1]Department of Biological Engineering, Koch Institute of Integrative Cancer Research, Infectious Diseases Interdisciplinary Research Group, Singapore-MIT Alliance for Research and Technology, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge,

Situation HA en 2024, cas BC (clade 2.3.4.4b – D.1.1 late)

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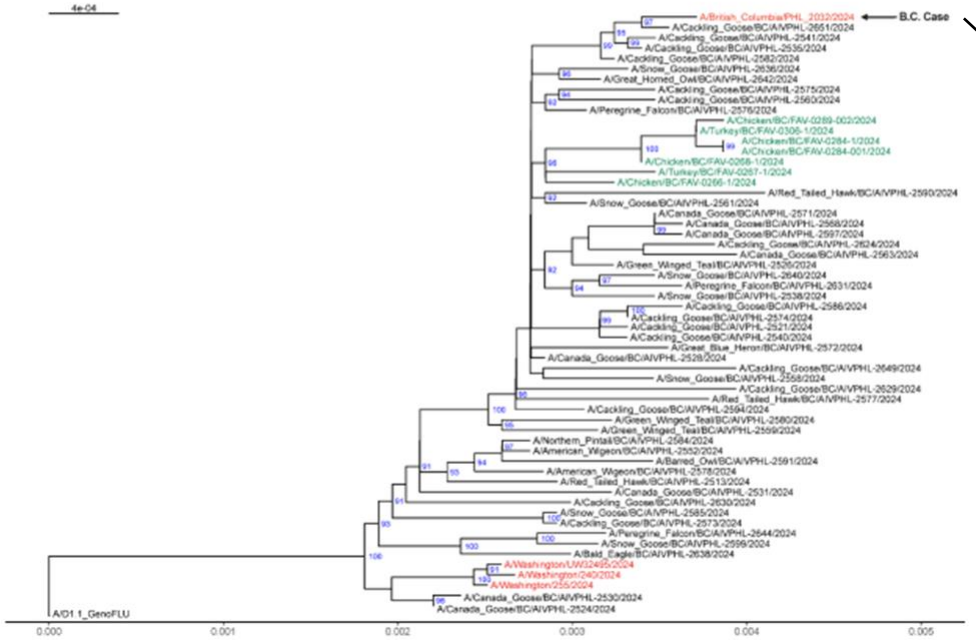
CORRESPONDENCE

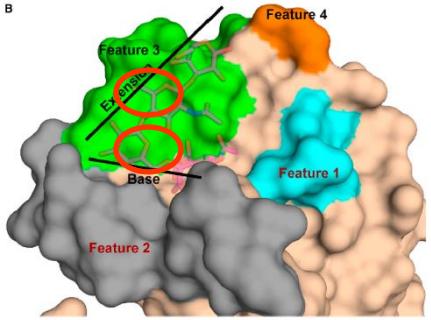
Critical Illness in an Adolescent with Influenza A(H5N1) Virus Infection

Published December 31, 2024 | DOI: 10.1056/NEJMc2415890 | Copyright © 2024

REPRINTS

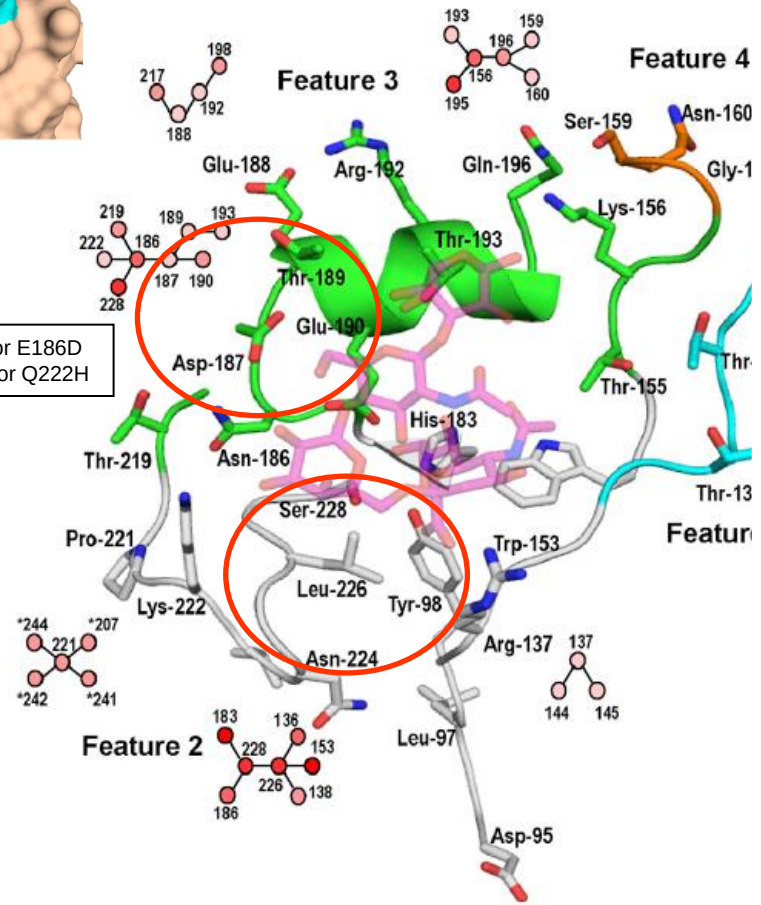
Supplementary Figure 2. Concatenated whole genome phylogeny of HPAI A(H5N1) clade 2.3.4.4b, genotype D1.1 viruses from human cases identified in British Columbia, Canada and Washington state, United states (red), contextualized by B.C wild bird (black) and poultry (green) detections collected between September 23rd and November 8th, 2024. Bootstrap values over 90% are displayed on the nodes. Scale bar is substitutions per site.



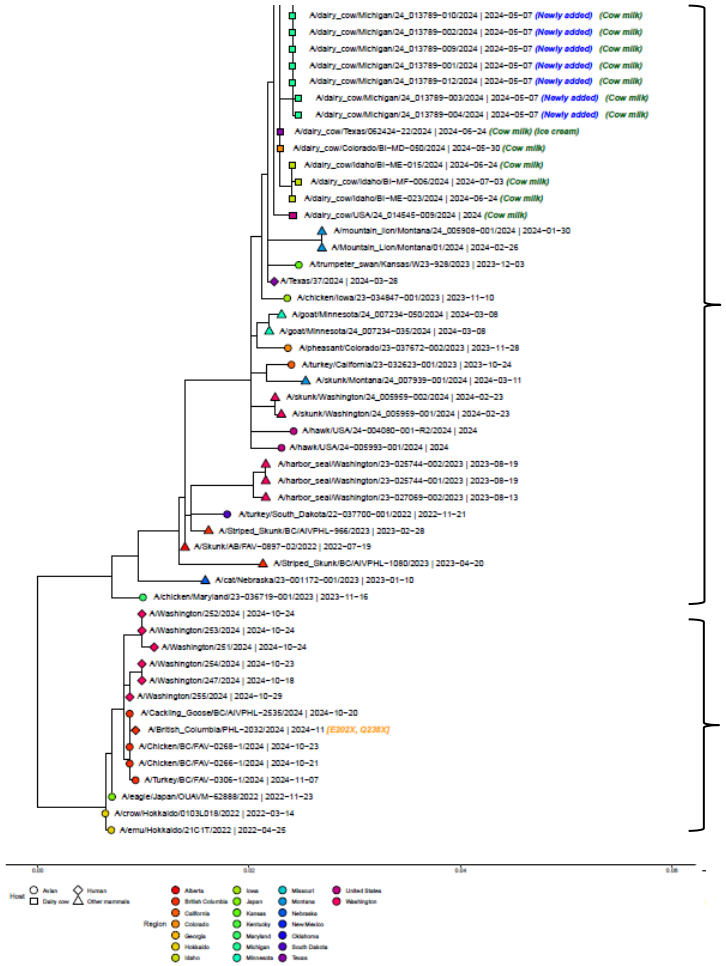


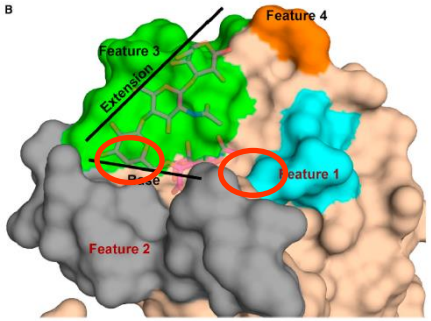
3

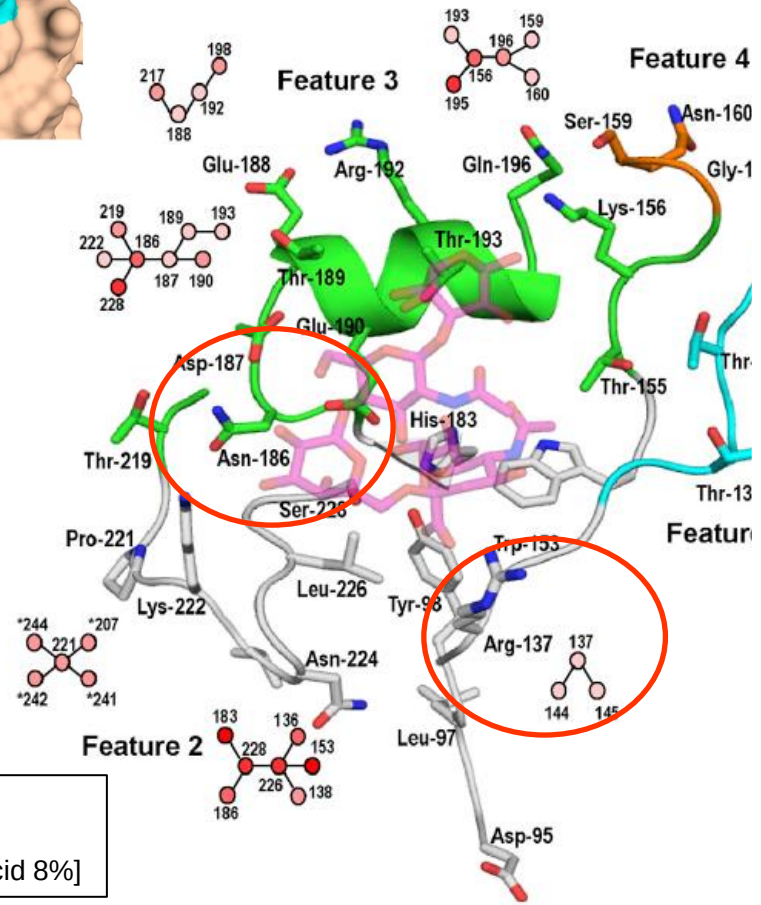
E186 (E190) — 28% allele frequency for E186D
Q222 (Q226) — 35% allele frequency for Q222H



Situation HA en 2024, cas L (clade 2.3.4.4b – D.1.1 early)

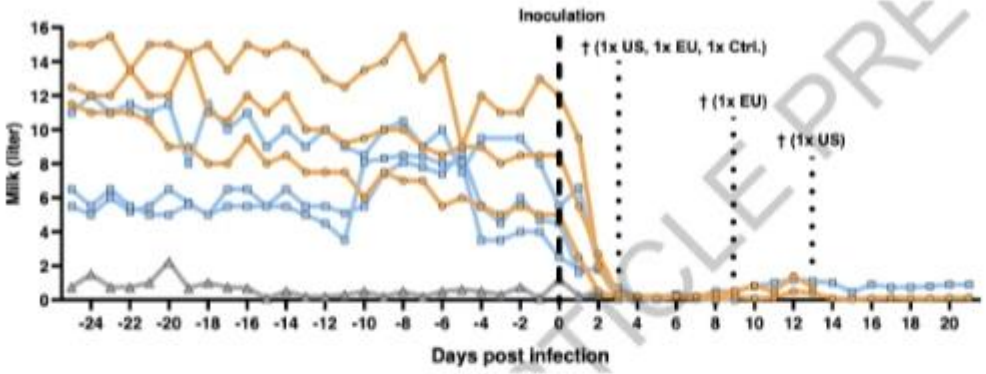


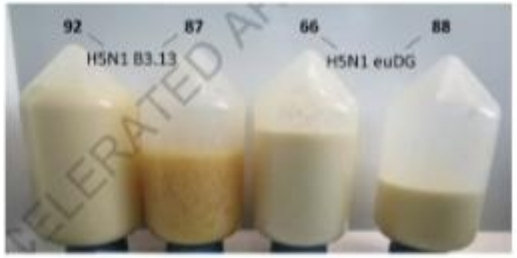


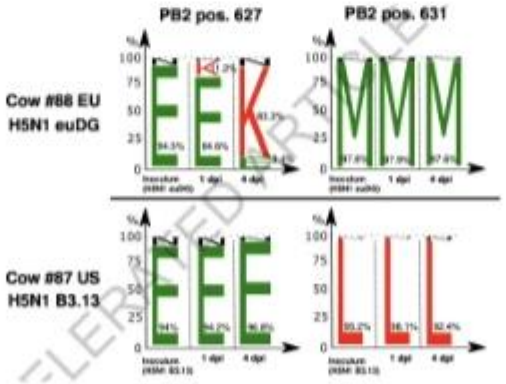


A134A/V [Alanine 88%, Valine 12%];
N182N/K [Asparagine 65%, Lysine 35%];
E186E/D [Glutamic acid 92%, Aspartic Acid 8%]

Dans le lait (B3.13, europe)







Autres facteurs d'adaptation : le rôle des protéines internes

Selected host-adaptive mutations with known effects on polymerase activity and/or host range restriction.

Gene	Origin/Subtype	Mutation	Effect
PB2	Avian various subtypes	E627K	Overcomes restriction of replication of avian IAVs in mammalian cells [36]
	Avian H5N1	D701N	Increased polymerase activity in mammalian cells, increased lethality in mice [40,41]
	Human pandemic H1N1	G590S, G/Q591R	Confers efficient viral replication to pandemic H1N1 viruses in human and pig cells [32,47]
		T588I	Enhanced polymerase activity and viral replication in mammalian cells [48]
	Avian H7N9 and H5N1	Q591K, K526R	Increases the efficiency of viral replication of avian viruses in mammalian cells [32,85,86]
	Human pandemic H1N1, avian H5N1 (clade 2.3.4.4b)	T271A	Enhanced polymerase activity of IAV in mammalian cells and in mice [49]; precursor for the acquisition of a mutation at position 226 of HA that confers recognition of an α2,6-linked SA receptor [50]
	Human pandemic H1N1	E158G	Enhanced polymerase activity in human cells, increased morbidity and mortality in mice [87]
PB1	Avian H9N2	K577E	Increased replication in mammalian cell culture, increased pathogenicity in mice [74]
	Avian H3N8	S524G	Increased replication in mammalian cell culture, increased replication in guinea pigs and ferrets, and increased airborne transmission in ferrets [75]
	Human pandemic H1N1	S216G	Enhanced viral epidemiological fitness by increasing the frequency of adaptive mutations [76]
PA	Avian H5N1	E18G, S388R, A448E	Increased polymerase activity in human cell culture, increased replication in mice [55]
	Human pandemic H1N1	T85I, G186S, L336M	Increased polymerase activity in mammalian cells [57]
		T552S	Increased polymerase activity in human cell culture, increased pathogenicity in mice [64]
	Low-pathogenicity avian H5N2	T97I, E349G	Enhanced polymerase activity in mammalian cells [65]
NP	Avian viruses	F313V/Y	Evasion of BTN3A3 susceptibility (avian-specific host factor) [80]
		Y52H/Q/N	Evasion of NP-313F susceptibility to BTN3A3 [80] (BTN3A3-resistant genotype NP-313V/Y and/or 52H/Q/N)
	Avian H7N7	N319K	Increased efficiency of vRNP nuclear transport in human cells [43]

Virus aux USA

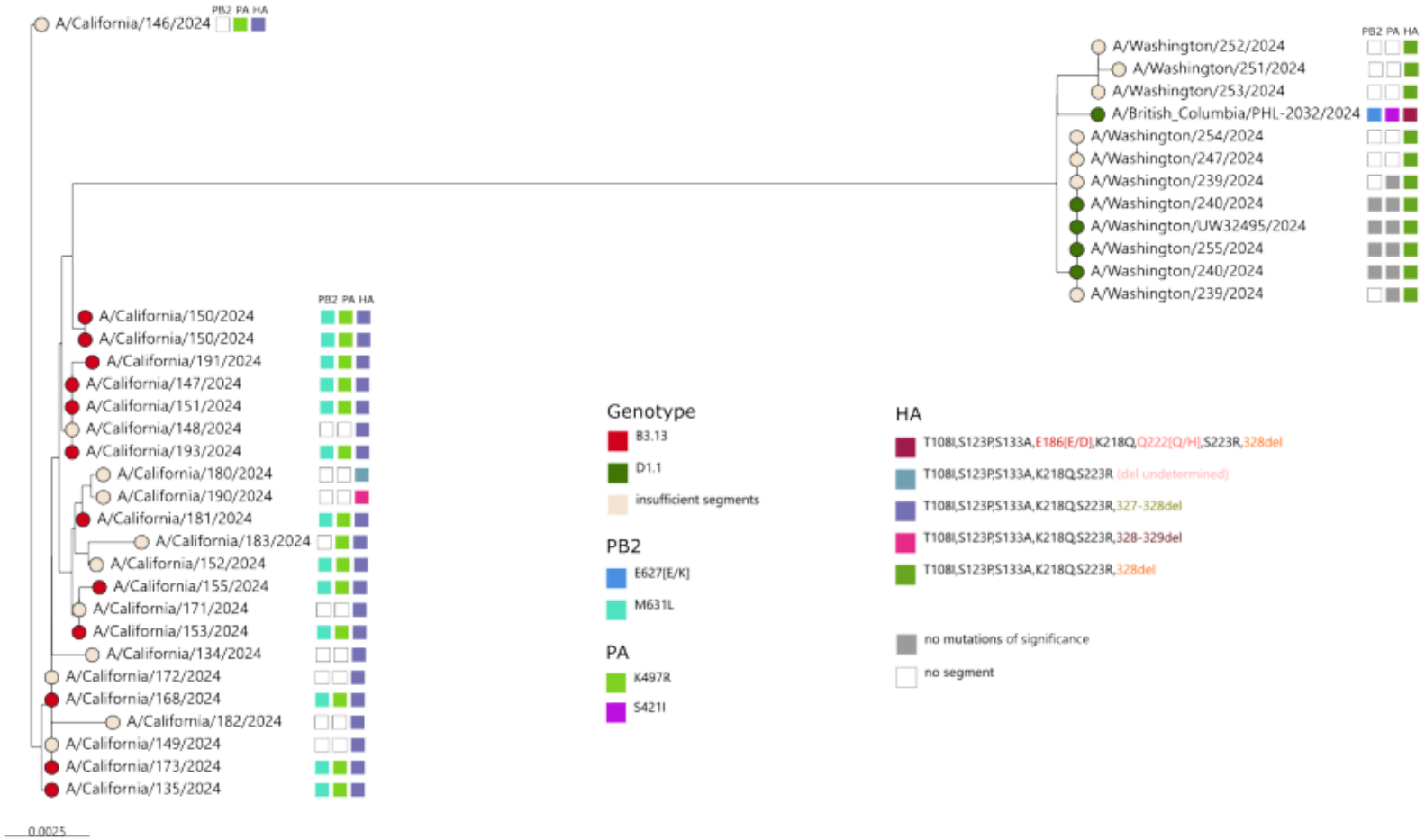


Figure 8: Phylogenetic tree of the HA segment annotated with mutation analysis findings from all available segments

Manifestations cliniques

- Les symptoms de la grippe aviaire peuvent apparaitre rapidement, et peuvent être:
  - Température élevée, frissons
  - myalgies
  - cephalées
  - Toux avec essoufflement
- D’autres symptoms peuvent être observés:
  - Conjonctivite (plus frequent pour H7, mais décrit pour H5N1 B3.13)
  - Diarrhée
  - Nausées, vomissement
  - Fatigue
  - Douleur abdominales
  - Douleur thoracique
  - Saignements du nez et des gencives
  - convulsions (more frequent in H5 infected cases)
- Le délai d’incubation est de 3 à 5 jours après exposition

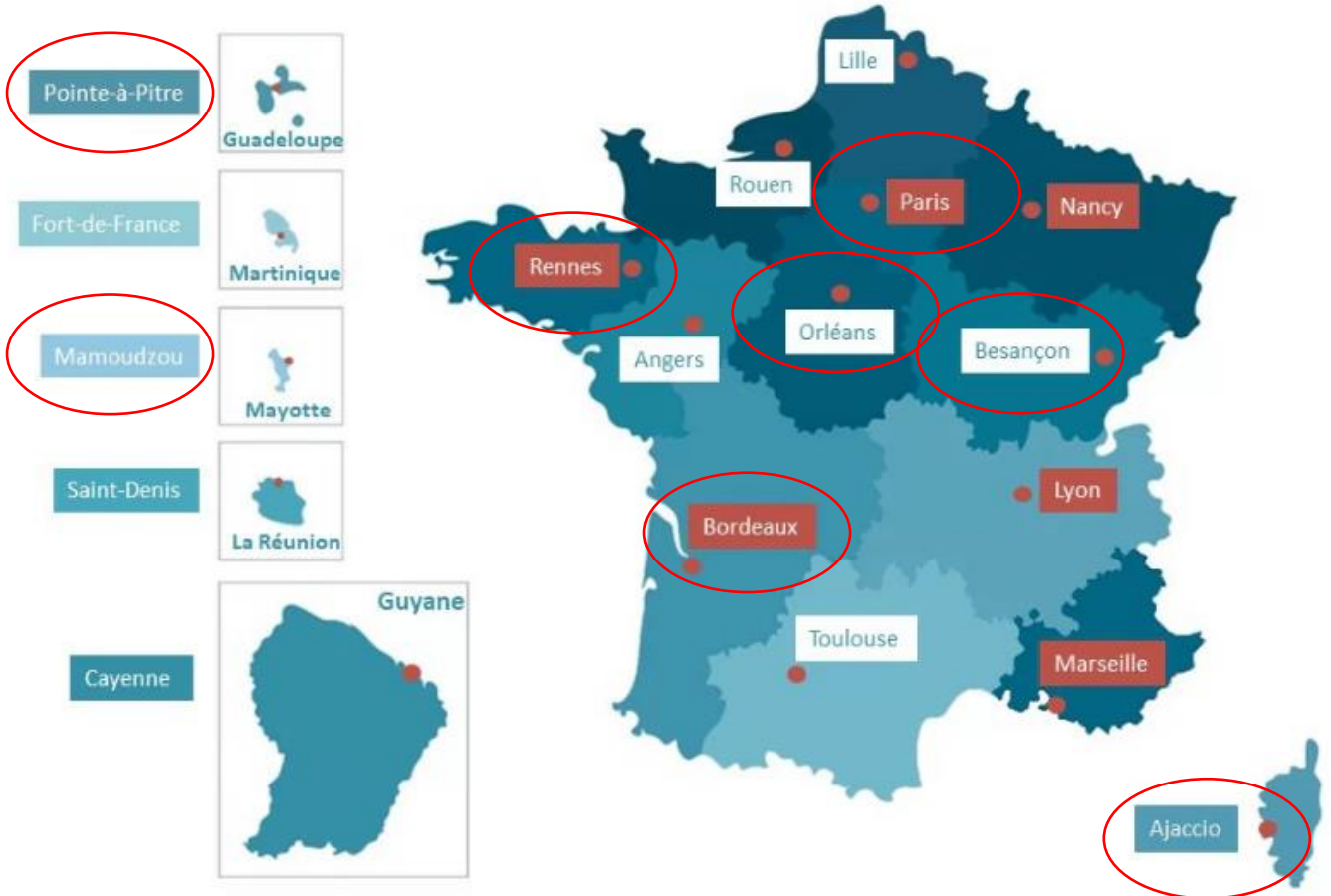
Prise en charge diagnostique cas suspect

- Faire le diagnostic avec des prélèvements adaptés
  - Combiner prélèvements VAS et VAI avec des écouvillons non inactivants (culture a prévoir)
  - Faire une écouvillon conjonctival si tableau de conjonctivite aigue
- Organiser le diagnostic biologique
  - Ne pas utiliser les TROD (cible NP)
  - Le diagnostic de criblage « influenza de type A » est possible avec la plupart des tests PCR grippe humaine
  - Faire le sous-typage H1, H3 et H5 si possible
  - Prévoir des charges virales dans les différents secteurs
  - Prévoir la culture virale (BSL-3 en CNR)
  - Prévoir le séquençage sur échantillon primaire (minimun Ha, Na, PB2)
  - Prévoir des échantillons itératifs (suivi charge et séquence)
  - Si asymptomatique, coupler avec transcriptomique et serologie
  - Organiser un suivi sérologique H5

Reco HCSP et COREB

LABO H5 (CNR + ESR), janvier 2025

- Capacités diagnostiques :
  - CNR Lyon, Paris, Felix Guyon, Guyane (IPG)
  - Labos ESR



Hopital	Date contact	Date demande contrôle
Henri Mondor		
CHU Rouen	18/12/2024	18/12/2024
CHRU Nancy	19/12/2024	19/12/2024
AMU	19/12/2024	20/12/2024
Pitié	19/12/2024	06/01/2025
Purpan	19/12/2024	19/12/2024
Bichat	19/12/2024	19/12/2024
CHU Lille	19/12/2024	19/12/2024
CHU Angers	19/12/2024	19/12/2024
CHU Martinique	20/12/2024	20/12/2024

PCR labos hospitaliers et de ville

Centre National de Référence Virus des Infections Respiratoires (dont la grippe et le SARS-CoV-2)

- Travail CNR ANSM

(note du 7 janvier 2025)

3 nouvelles réponses

- positive (Elitech)
- incomplete (Eurobio, PE REVVITY)

7 janvier 2025
Note sur la capacité de détection des virus H5Nx
par les dispositifs de PCR détectant la grippe disponibles en France

Fabricant	Nom du réactif	Référence
Cepheid	Xpert Xpress Flu/RSV	XPRSFLU/RSV-CE-10
	Xpert Xpress CoV-2/Flu/RSV plus	XP3COV2/FLU/RSV-10
BioMerieux SA	Influenza A/B R-GENE®	71-040
	SC2/FLUA/FLUB/RSV R-GENE®	424433
BioFire Diagnostics, LLC.	FilmArray Pneumonia Panel plus	RFIT-ASY-0142 (6-pack kit) RFIT-ASY-0143 (30-pack kit)
	BioFire Respiratory Panel 2.1 plus (RP2.1plus)	RP2.1plus: 423740 (30-pack kit)
	BioFire SpotFire Respiratory/Sore Throat (R/ST) Panel	R/ST Panel: 423485 (30-pack kit)
Altona Diagnostics	AltoStar Inflenza S&T	AS0161543
QUIAGEN, GmbH	QIAstat-Dx Respiratory SARSCoV-2 v2	691214
	QIAstat- Dx® SARS-CoV-2/FluA/B/RSV Panel	691216
Luminex Molecular Diagnostics, Inc.	NxTAG® Respiratory Pathogen Panel (NxTAG RPP)	I051C0449
SEEGENE Inc	AllplexTM RV Master Assay	RV10307X, RV10363Z
	AllplexTM SARS-CoV-2/FluA/FluB/RSV Assay	RV10259X, RV10349Z
	AllplexTMRespiratory panel 1	RP9801X, RP9702Y, RP10179Z
	AllplexTM Respiratory panel 1A	RP9702X, RP9702Y, RP10231Z
Roche Molecular Systems, Inc.	cobas® SARS-CoV-2 & Influenza A/B v2	10033401190
	cobas Influenza A/B & RSV / cobas SARS-CoV-2 & Influenza A/B	08160104190 / 09211101190
GenMark Diagnostics, Inc	cobas® eplex respiratory pathogen panel 2	9556486001
Abbott Molecular Inc	Alinity m Resp-4-Plex AMP Kit	09N79-090
Becton Dickinson and Company	BD Respiratory Viral Panel for BD MAX™	445215
SD BIOSENSOR	STANDARD™ M10 Flu/RSV/SARS-CoV-2	11FLU10A / M10-CVFR-01
Hologic	Assays Panther Fusion Flu A B RSV	AW-16162-001
	Panther Fusion SARS-CoV-2 Flu A B RSV	AW-29624-001

Prise en charge cas suspect

- Organiser le suivi
  - charges virales itératives (contexte clinique)
  - Séquençage itératifs
  - sérologie H5
- Traitement symptomatique
  - Antipyrétiques
  - Oxygénothérapie si nécessaire
  - Corticothérapie (?)
- Traitement antiviral (le plus tôt possible, mais pas de restriction de délai de mise en œuvre)
  - Inhibiteurs de la neuraminidase (Oseltamivir)
  - Association possible avec Favipiravir ou Baloxavir-Marboxyl

Reco HCSP et COREB

Clinical Data for Patients from 3 Indonesian Clusters of H5N1 in 2005

Table 1. Clinical Data for Patients from Three Indonesian Clusters of H5N1 Virus Infection in 2005.*

Patient No.	Age	Sex	Chronic Conditions	Day of Illness at Hospital Admission	Symptoms and Signs	Findings on Admission						Maximum Temperature	Mechanical Ventilation	Oseltamivir Treatment	Corticosteroid Therapy	Time from Onset to Death or Discharge	Outcome
						Temperature	Respiratory Rate	Total White-Cell Count	Absolute Lymphocyte Count	Platelet Count	Chest Radiography						
	yr					*°C*	*breaths/min*	*per cubic millimeter*				*°C*				*days*	
1A	8	F	None	7	Fever, 7 days; cough, headache, nausea, vomiting	38	40	1780	445	185,000	Bilateral infiltrates	39.2	Yes (on hospital day 2, illness day 8)	No	Yes	22	Death
1B	1	F	None	7	Fever, 7 days; cough, 2 days; rhinorrhea and diarrhea, 3 days; dyspnea, 1 day	38.8	25	4200	NA	221,000	Bilateral infiltrates	38.8	Yes (on hospital day 2, illness day 11)	No	Yes	8	Death
1C	38	M	History of cigarette smoking	7	Fever, cough, shortness of breath, difficulty breathing, abdominal pain	39.3	34	2310	NA	146,000	Bilateral infiltrates	40.0	Yes (on admission, illness day 7)	No	Yes	11	Death
2A	37	F	None	7	Fever, 7 days; rhinorrhea, cough, shortness of breath, hypotension	39	42	2980	NA	208,000	Bilateral infiltrates	41.0	Yes (on admission, illness day 7)	Yes (on illness day 10, started on 75 mg twice daily orally for 1 day)	Yes	11	Death
2B	9	M	None	9	Fever, 9 days; sore throat	38.8	34	7600	2356	313,000	Not done	38.8	No	No	No	17	Recovery
3A	21	M	History of cigarette smoking	5	Fever, cough, 5 days	38.3	48	5000	850	145,000	Bilateral infiltrates	38.3	No	Yes (on illness day 7, started on 75 mg twice daily orally for 5 days)	Yes	25	Recovery
3B	5	M	None	5	Fever, rhinorrhea, cough, headache, 5 days	NA	NA	2900	1421	138,000	Not done	NA	No	No	No	14	Recovery
3C	4	M	None	5	Fever, rhinorrhea, cough, 2 days; all symptoms resolved 3 days before admission	37	30	7600	4256	373,000	Mild bilateral interstitial and perihilar infiltrates	37.0	No	Yes (on illness day 5, started on 35 mg twice daily orally for 7 days)	No	17	Recovery

* NA denotes not available.

N Engl J Med 2006; 355:2186-2194

Results of H5N1 Lab Tests from Indonesian Patients in 2005.

Table 2. Results of Laboratory Testing for H5N1 Virus Infection from Patients in Three Indonesian Clusters in 2005.*

Patient No.	Age	Sex	Days after Onset Specimen Collected	Specimen	Rapid Test†	RT-PCR (HA/H5)‡		MN Titer	H5N1 Virus Isolated	H5N1 Case Classification
	yr					INDO	WHO	WHO		
1A	8	F	17	Nasal and throat swabs, serum	N	N, N	N, N	1:320	No	Confirmed
			20	Serum	—	—	—	1:640	—	
1B	1	F	11	Serum	—	—	—	N	—	Probable
1C	38	M	7	Nasal and throat swabs, serum	N, N	P, P	P, N	N	Yes; A/Indo/5/2005 (from throat swab)	Confirmed
			10	Nasal and throat swabs, serum	N, N	N, P	N, P	N	No	
2A	37	F	7	Nasal and throat swabs	N, N	N, P	N, P	N	No	
			10	Nasal and throat swabs, tracheal aspirate, serum	N, N§	N, P, P	N, N, P	1:80	Yes; A/Indo/6/2005 (from tracheal aspirate)	Confirmed
2B	9	M	4	Nasal and throat swabs, serum	N, N	N, P	N, P	N	No	Confirmed
			15	Serum	—	—	—	1:80	—	
3A	21	M	5	Throat swab, serum	N, N	P	P	N	No	Confirmed
			16	Nasal and throat swabs, serum	N, N	N, N	N, N	1:640	No	
			22	—	—	—	—	1:1280	—	
3B	5	M	5	Nasal and throat swabs, serum	N, N	N, N	N, N	1:20	No	
			101	—	—	—	—	1:320	—	Confirmed
3C	4	M	1	Nasal and throat swabs	N, N	N, P	N, P	—	No	Confirmed
			8	Nasal and throat swabs, serum	N, N	N, P	N, P	N	No	

* HA denotes hemagglutinin, MN microneutralization, INDO Indonesian laboratory, WHO World Health Organization H5 Reference Laboratory, N negative, and P positive. A dash indicates that the indicated test was not performed.
† Only nasal- and throat-swab specimens were analyzed by the rapid antigen test.
‡ HA/H5 refers to H5 hemagglutinin-specific primers and probes.
§ Tracheal aspirate from this patient was not analyzed by the rapid antigen test.

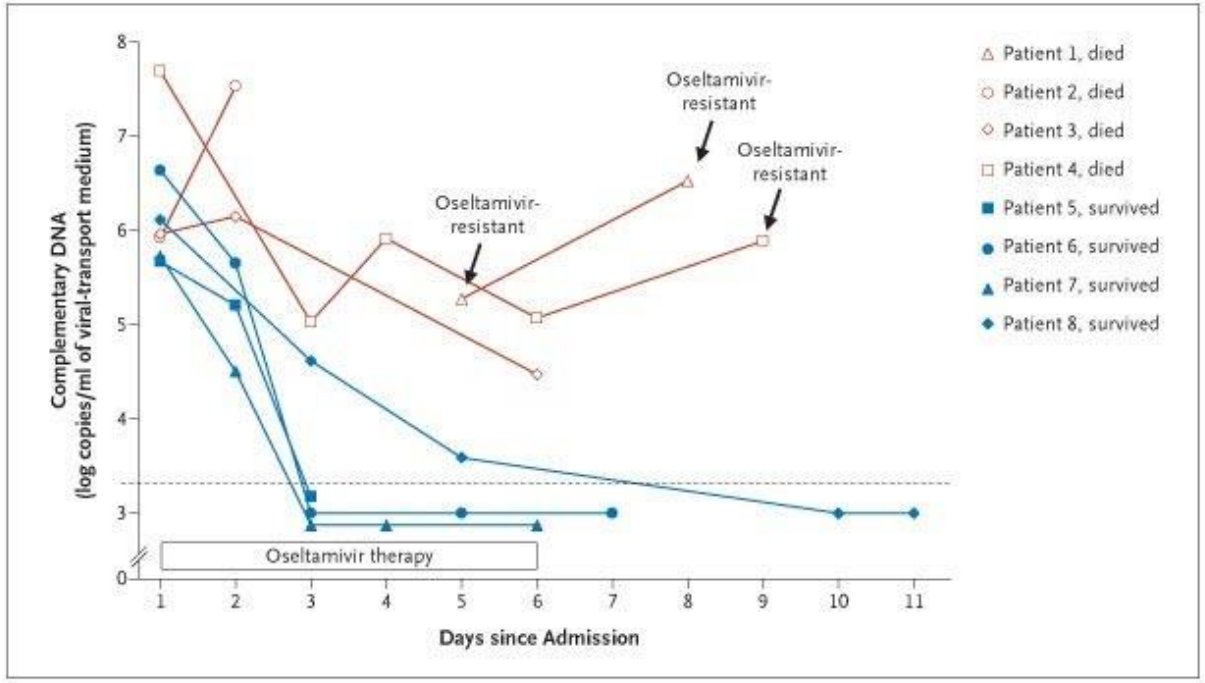
N Engl J Med 2006; 355:2186-2194

Suivi Charges Virales : valeur prédictive de la décroissance et risque d'apparition de résistances

Table 1. Patients' Characteristics and Clinical and Virologic Outcome.

Patient	Age (yr)/ Sex	Admission*		Virus Detectable at End of Treatment†	H274Y in N1 at End of Treatment†	Clinical Outcome
		Date	Day of Illness			
1	13/F	January 2005	2	Yes	Yes	Died on 8th day of illness
2‡	35/F	January 2005	6	NA	NA	Died on 7th day of illness
3	16/F	December 2004	7	Yes	NA	Died on 20th day of illness
4	18/F	January 2005	6	Yes	Yes	Died on 20th day of illness
5	26/F	January 2005	4	NA	NA	Survived
6§	8/F	January 2004	8	No	—	Survived
7§	23/M	February 2004	7	No	—	Survived
8	22/M	February 2004	6	No	—	Survived

* All patients started oseltamivir treatment on the day of admission.
† NA denotes not applicable owing to insufficient follow-up.
‡ Patient 2 was the mother of Patient 1.
§ This patient has been described previously.[2]



N Engl J Med 2005; 353:2667-2672

Synthèse

- Le niveau de circulation des H5Nx est très élevé et différents lignages sont observés
- Ces lignages ont étendu leur spectre d'infection chez les oiseaux et des mammifères
- Ces virus restent faiblement transmissibles aux mammifères en dehors d'expositions massives
- Il existe une situation particulière chez les vaches laitières aux USA (clade B3.13, et D1.1)
- Un portage « silencieux » a été observé (détection sans séroconversion, forme paucisymptomatique)
- Des formes cliniques sont mineures (conjonctivites) ou très symptomatiques sont observées
- Le diagnostic de certitude nécessite un prélèvement sous glottique, ou des conjonctives
- Le suivi est indispensable (charges virales, séquençage, serologie)

MERCI

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