



# Grippe du nouveau-né et de la femme enceinte

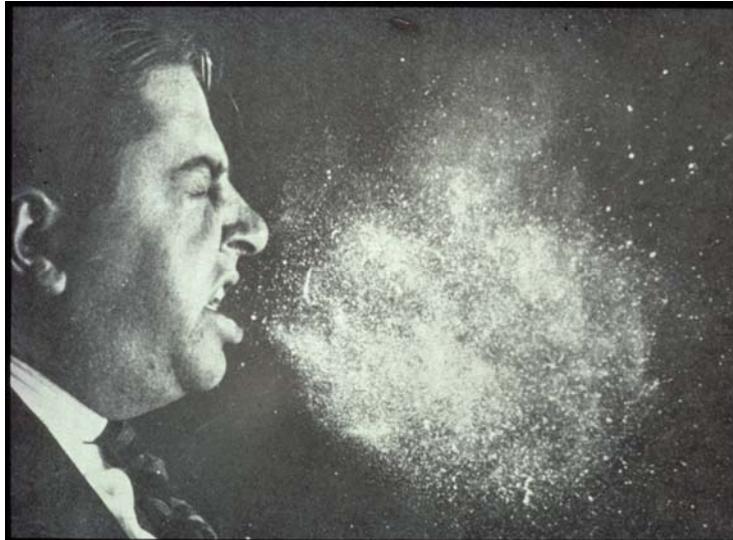
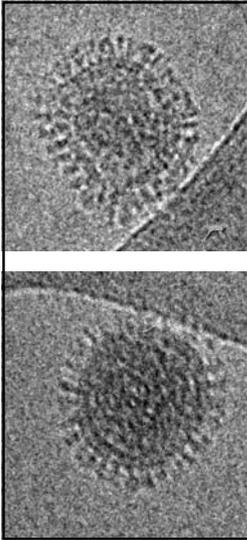
Bruno LINA

CNR des virus respiratoires, HCL,  
Virpath, CIRI, U1111, UMR 5308, ENS, UCBL,  
Lyon, France

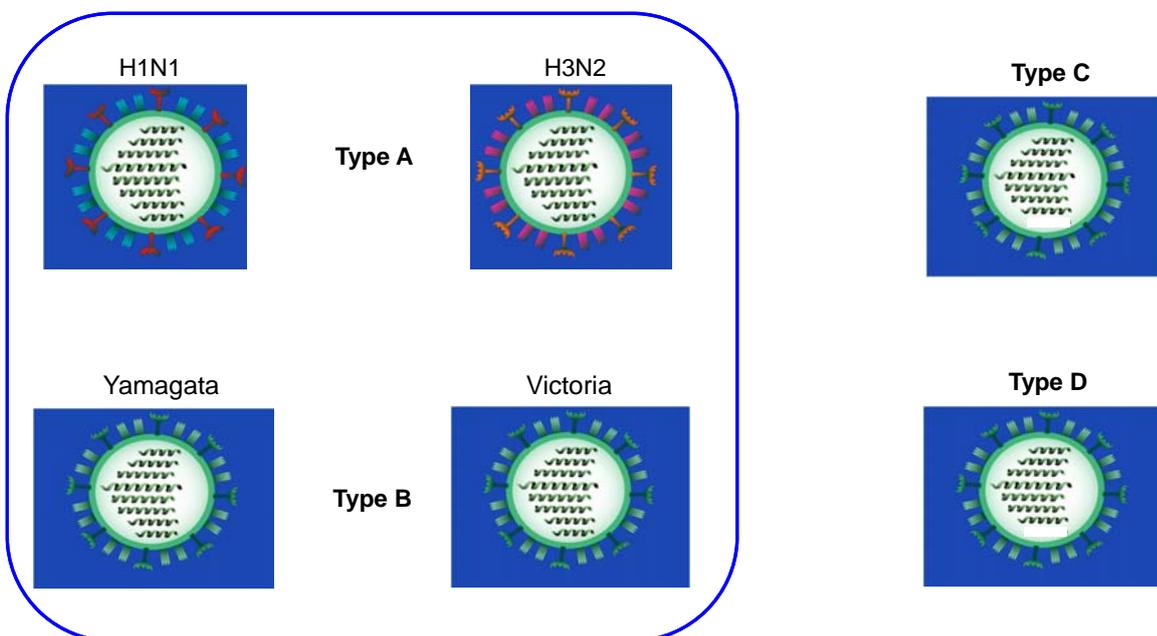
## Liens d'intérêts

- Président du Conseil Scientifique d'Immuniser.Lyon
- Président du Conseil Scientifique du GIHSN de la Fondation for Influenza Epidemiology
- Co-Président du Conseil Scientifique du Global Influenza and RSV Initiative
  
- Aucune de ces activités n'est rémunérée
  
- Un déplacement a un congrès pris en charge par Sanofi-Pasteur

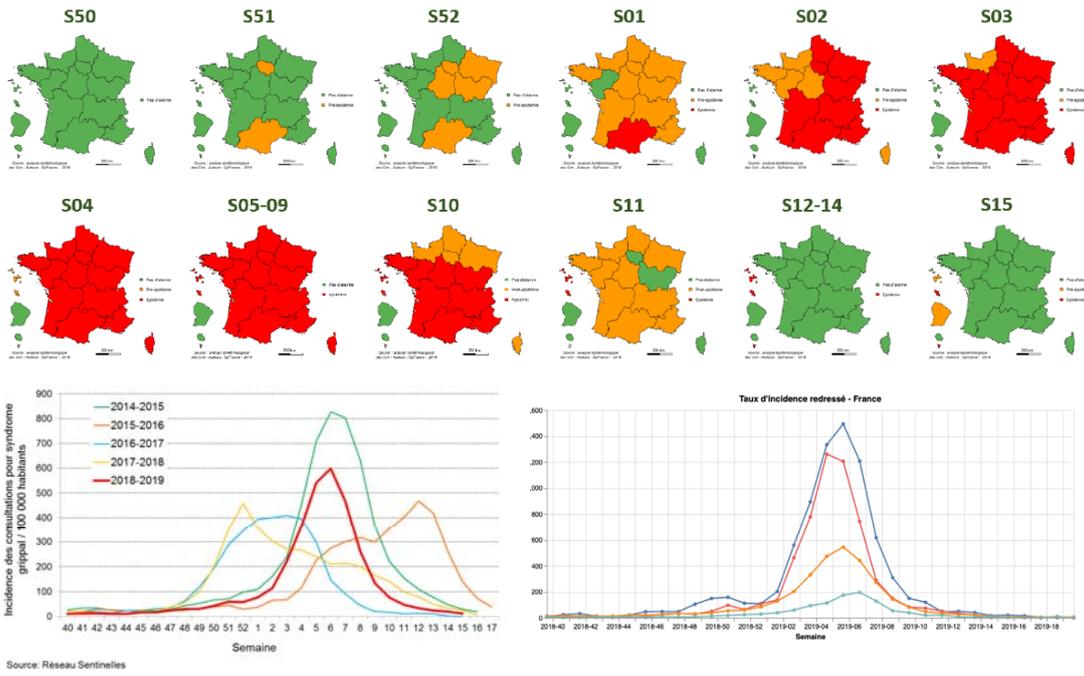
# Les fautifs : le virus et l'hôte



## Types, sub-types & lineages of influenza viruses

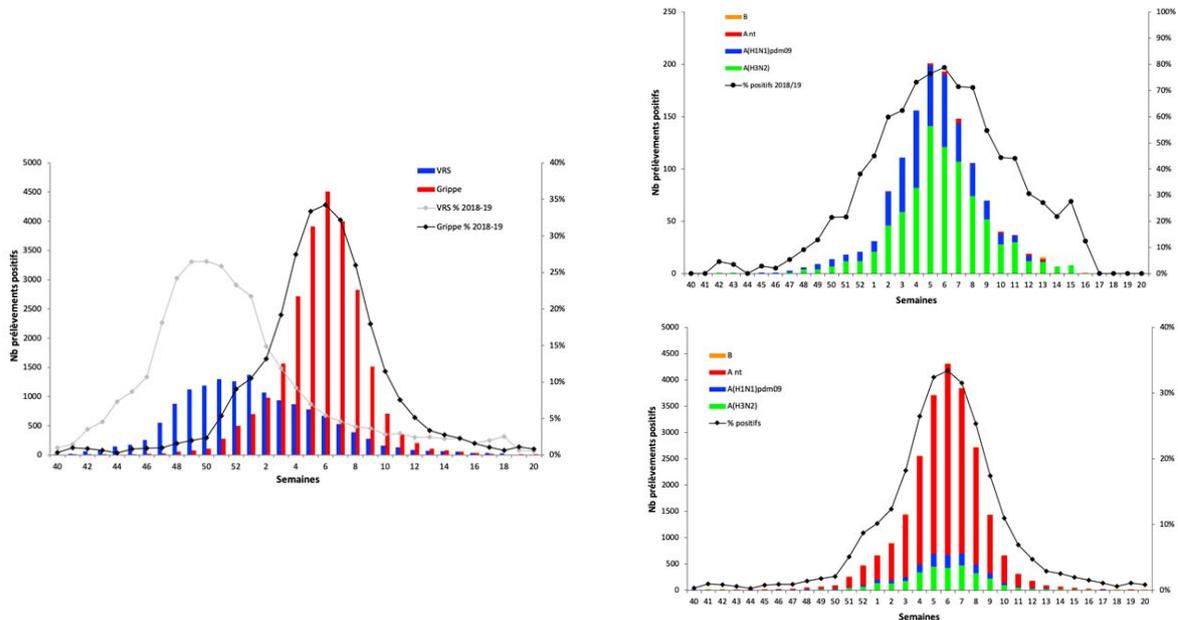


# Impact :2018-19, une épidémie de « courte » durée



Données de Santé Publique France

# Les virus influenza qui ont circulé (France 2018-2019)



# Impact en 2018-19 par groupe d'âge

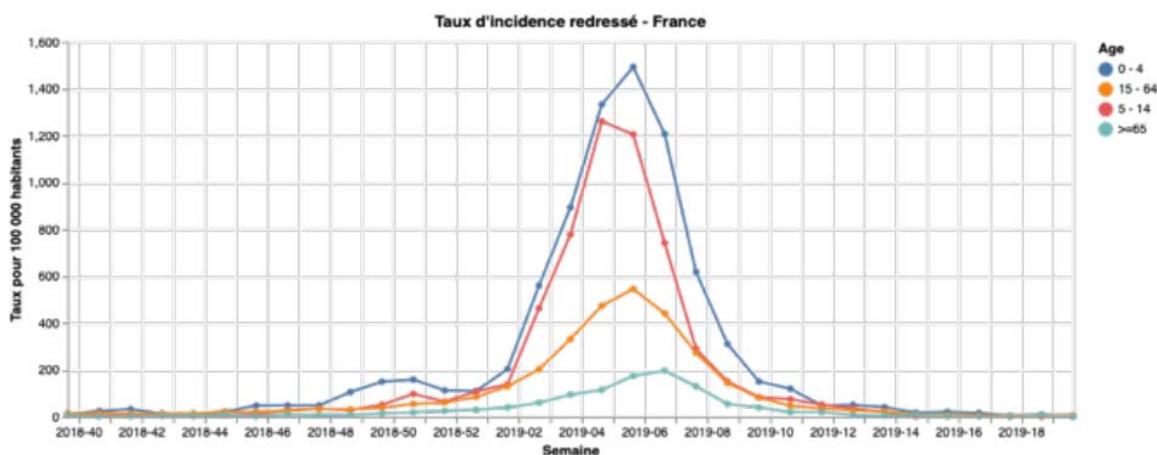
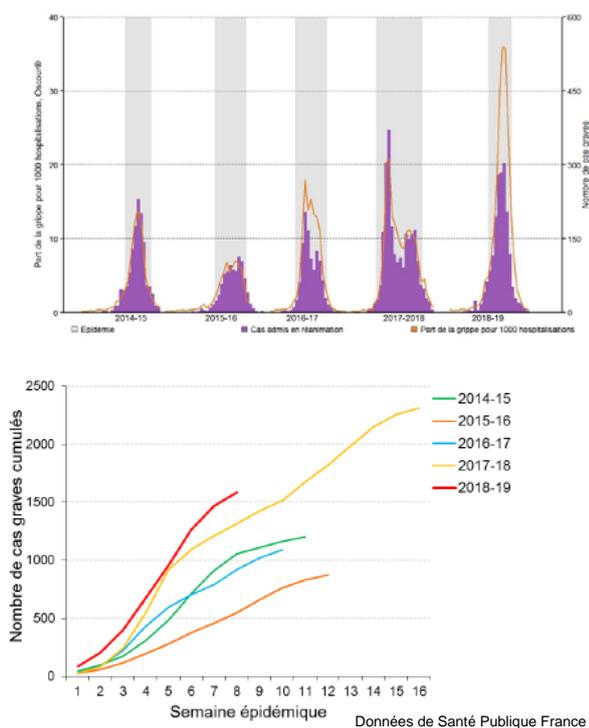


Figure 7 : Syndrome grippaux (Grippe clinique) pour 100 000 habitants par tranches d'âge en France

Données CNR

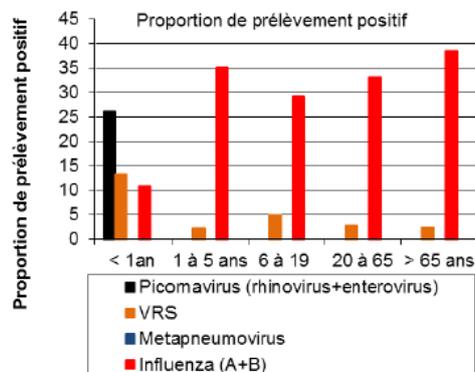
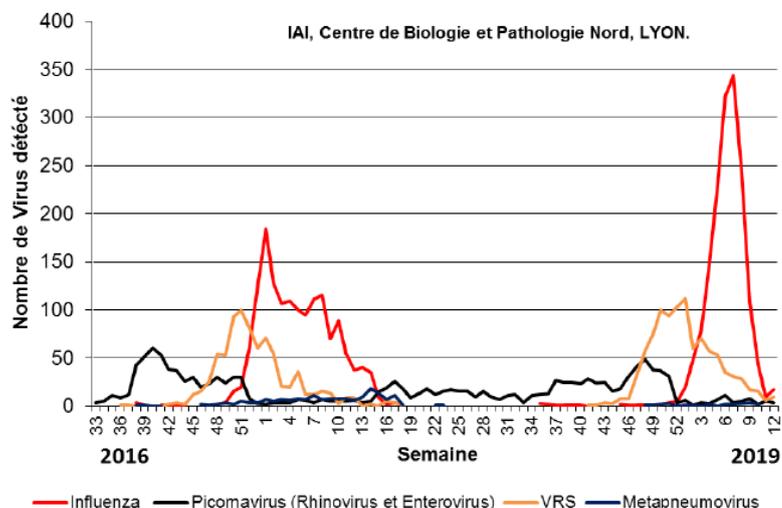
# Impact hospitalier

Statut virologique	Effectif	%
A(H3N2)	546	29
A(H1N1)pdm09	411	22
A non sous-typé	892	48
B	13	1
Co-infectés	1	0
Non confirmés	14	1
Classes d'âge		
0-4 ans	77	4
5-14 ans	45	2
15-64 ans	775	41
65 ans et plus	980	52
Non renseigné	0	0
Sexe		
Sexe ratio M/F - % d'hommes	1.4	58
Facteurs de risque de complication		
Aucun	255	14
Age 65 ans et + sans comorbidité	189	10
Age 65 ans et + avec comorbidité	791	42
Comorbidités seules	547	29
Autres cibles de la vaccination	41	2
Non renseigné	54	3
Statut vaccinal des personnes à risque		
Non Vacciné	748	48
Vacciné	424	27
Non renseigné ou ne sait pas	396	25
Éléments de gravité		
<b>SDRA (Syndrome de détresse respiratoire aigu)</b>		
Pas de Sdra	1023	54
Mineur	144	8
Modéré	258	14
Sévère	421	22
Non renseigné	31	2
<b>Ventilation</b>		
VNI*/Oxygénothérapie à haut débit	738	39
Ventilation invasive	798	43
ECMO/ECCO2R	75	4
<b>Décès parmi les cas admis en réanimation</b>	289	15
<b>Total</b>	<b>1877</b>	<b>100</b>



Données de Santé Publique France

# Epidémiologie des virus respiratoires à Lyon (BEHcl)



## Impact de la grippe chez l'enfant : l'âge compte

**Table 3. Rate of Hospitalizations Attributable to Influenza per 1000 Children, According to Age Group and Study Year.\***

Age Group	2000–2001	2001–2002	2002–2003	2003–2004	2000–2004
0–5 mo of age					
Weighted count	20	37	20	103	180
Rate (95% CI)	2.4 (1.0–3.9)	4.3 (2.2–6.6)	2.3 (0.9–3.8)	7.2 (5.3–9.2)	4.5 (3.4–5.5)
6–23 mo of age					
Weighted count	16	22	10	66	114
Rate (95% CI)	0.6 (0.2–1.2)	0.9 (0.4–1.3)	0.4 (0.1–0.7)	1.5 (1.0–2.1)	0.9 (0.7–1.2)
24–59 mo of age					
Weighted count	11	17	2	50	80
Rate (95% CI)	0.2 (0.1–0.4)	0.3 (0.1–0.6)	0.04 (0.00–0.13)	0.6 (0.3–0.9)	0.3 (0.2–0.5)
0–59 mo of age					
Weighted count	47	76	32	219	374
Rate (95% CI)	0.6 (0.3–0.8)	0.9 (0.6–1.2)	0.4 (0.2–0.6)	1.5 (1.2–1.9)	0.9 (0.8–1.1)

## Tableaux cliniques graves



Figure 3. Chest radiograph showing bilateral diffuse infiltration indicative of acute respiratory distress syndrome.



Figure 4. High-resolution computed tomography scan of the chest, showing areas of airspace consolidation in the left lower lobes and increased bilateral transparency in a 2-year-old child with severe influenza virus infection.

## Etude sur 77 cas de grippe sévère chez l'enfant

Characteristics	Total N = 77 Number (%)	Survivors N = 64 Number (%)	Nonsurvivors N = 13 Number (%)	P-value*
Demographics				
Male	58	49	9	.725
Female	19	15	4	
Age distribution, yr				.045
≤1	19	16	3	
1–3	27	26	1	
3–5	18	14	4	
5–14	13	8	5	

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Microbiologic findings				
Influenza A	64	52	12	.322
Influenza B	13	12	1	.449
Coinfection				
Influenza A/B-virus	9	8	1	>.999
Adenovirus	7	6	1	>.999
Respiratory syncytial virus	1	1	0	>.999
Rhinovirus	1	1	0	>.999
influenza A/B-bacteria	28	26	2	.117

Shi et al. Medicine (2019) 98:35

# Etude sur 77 cas de grippe sévère chez l'enfant

**Table 1**  
Demographics and underlying medical conditions of the children with severe influenza infection who were admitted in the pediatric intensive care unit.

Characteristics	Total N = 77 Number (%)	Survivors N = 64 Number (%)	Nonsurvivors N = 13 Number (%)	P-value*
Demographics				
Male	58	49	9	.725
Female	19	15	4	
Age distribution, yr				
≤1	19	16	3	.045
1-3	27	26	1	
3-5	18	14	4	
5-14	13	8	5	
Underlying comorbid conditions				
Asthma	7	6	1	>.999
Chronic lung disease	1	1	0	>.999
Cardiovascular disease	8	6	2	.616
Renal disease	8	6	2	.616
Prematurity	6	5	1	>.999
Immunocompromized	1	0	1	.169
Malnutrition	4	3	1	.530
Abnormality in airway	3	2	1	.430
Neurologic disorder	5	3	2	.196

\* Pearson Chi-squared test or Fisher exact test when appropriate.

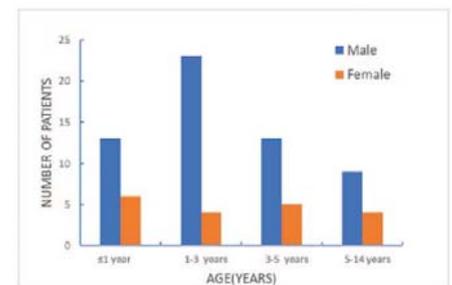


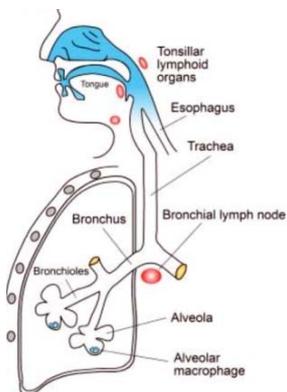
Figure 1. Age distribution of the children with severe influenza virus infection.

Shi et al. Medicine (2019) 98:35

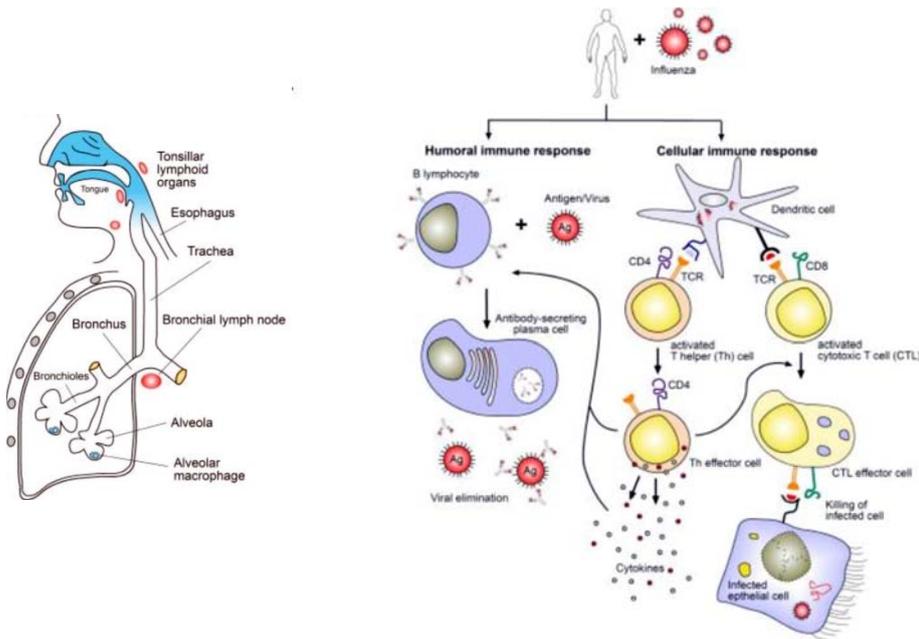
# Comprendre l'infection et les bases de la réponse immunitaire

## Influenza Infection

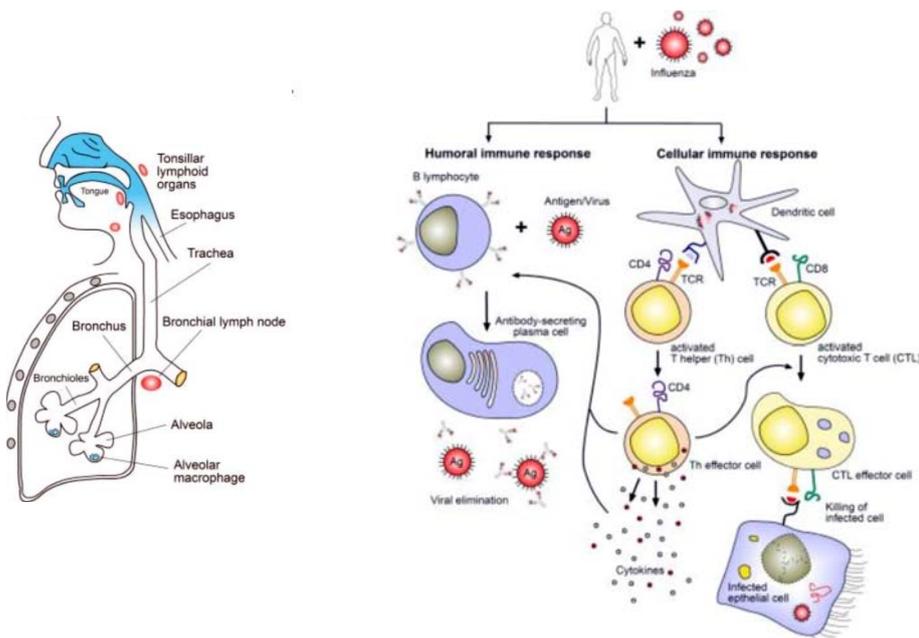
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## Influenza Infection et réponse immunitaire



## Influenza Infection, réponse immunitaire et protection



### Convalescent donors

Hung et al.  
(Clin Infect Disease 2010)  
H1N1 infection

average rate of anti-influenza  
Average GMT IHA titers: 100

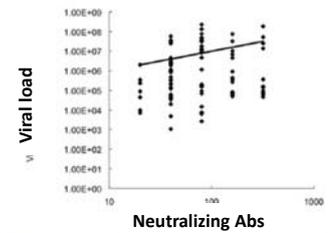
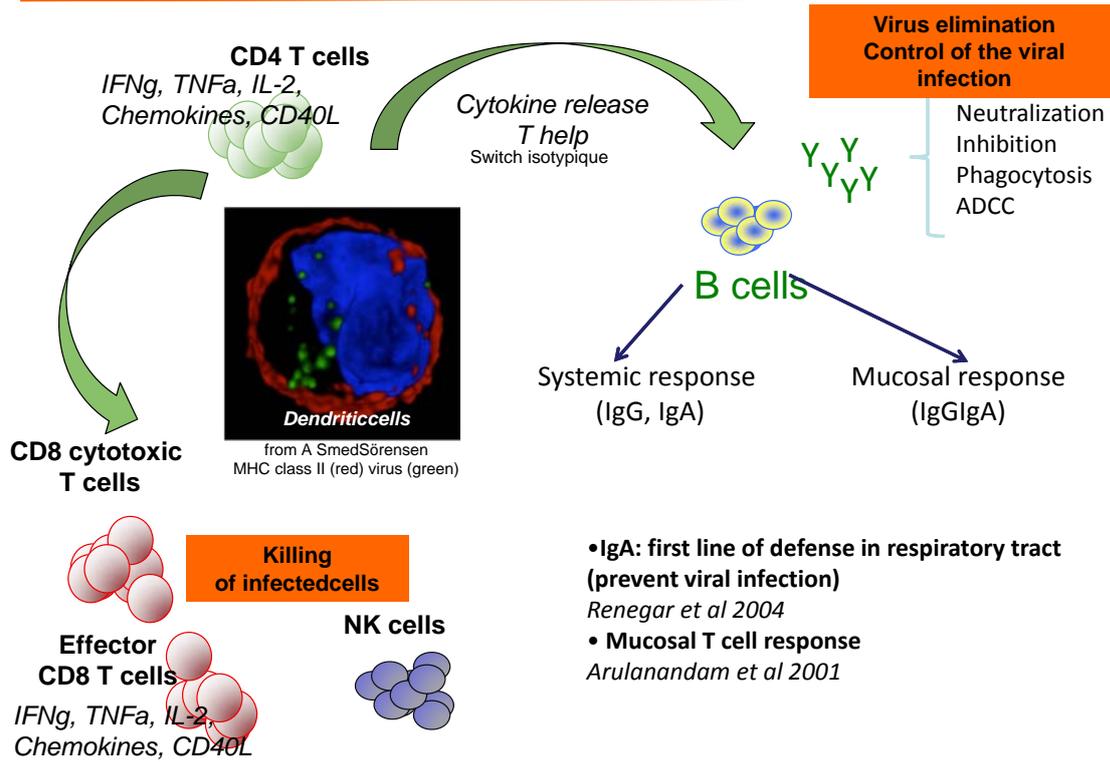
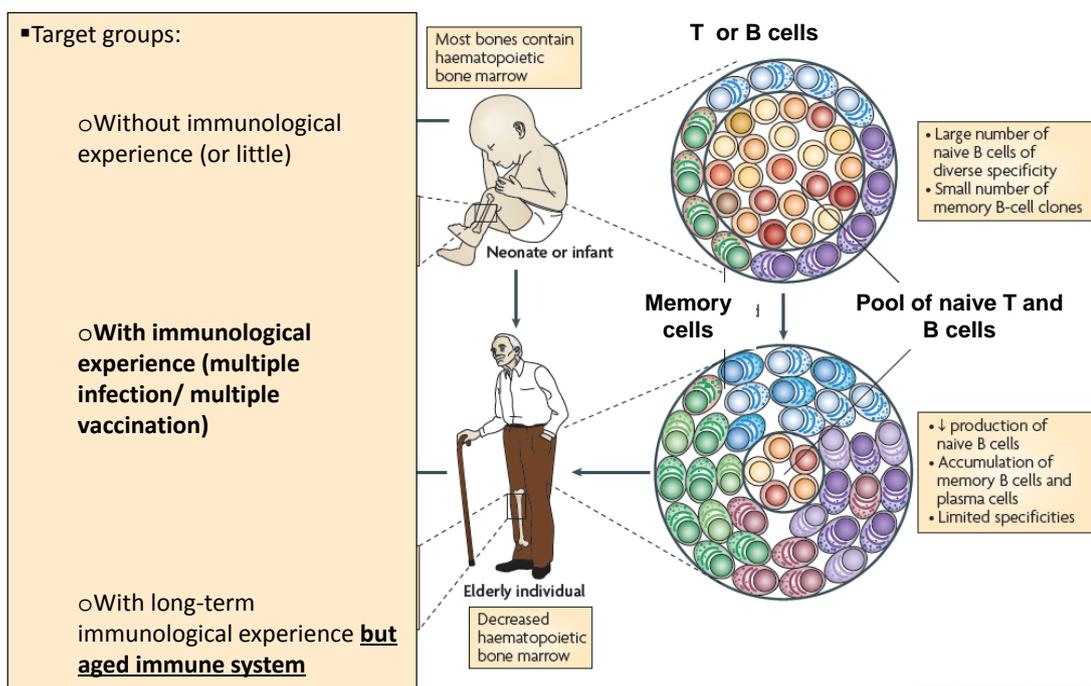


Figure 3. Correlation of viral load with serum neutralizing antibody titer of 87 convalescent donors. Spearman correlation  $\rho$ , 0.238;  $P = .026$ .

## En résumé!



## Infection et vaccination de ceux qui ont un système immunitaire « défaillant »



# Et la femme enceinte?

## Grippe chez la femme enceinte – données de la littérature

**Table 1.** Maternal morbidity in population-based studies.

First author	Year of publication	Study type	Influenza type	Country	No. of women	Hospitalization <sup>a</sup>		Severe cases <sup>b</sup>	
						n	%	n	%
Da Silva (5)	2014	Prospective cohort	2009 influenza A/H1N1	Brazil	163	70	43	18	11
			Seasonal influenza A		34	6	18	2	6
Doyle (6)	2013	Retrospective cohort	2009 influenza A/H1N1	USA	187	163	87	41	22
Dubar (7)	2010	Prospective cohort	2009 influenza A/H1N1	France	315	151	48	40	13
Gérardin (8)	2010	Prospective cohort	2009 influenza A/H1N1	France (La Réunion)	139	84	60	1	1
Jamieson (9)	2009	Prospective cohort	2009 influenza A/H1N1	USA	34	14	41	3	9
Lim (10)	2010	Prospective cohort	2009 influenza A/H1N1	Singapore	211	51	24 <sup>c</sup>	1	0
Malinowski (11)	2011	Retrospective cohort	2009 influenza A/H1N1	Canada	42	5	12	3	7
Naresh (12)	2013	Retrospective cohort	2009 influenza A/H1N1	USA	142	32	23	9	6
Siston (13)	2010	Prospective cohort	2009 influenza A/H1N1	USA	788	509	66	115	15

<sup>a</sup>Hospitalization due to influenza infection.

<sup>b</sup>Severe cases are defined as intensive care unit admission or maternal death.

<sup>c</sup>Only clinical cases are included, mandatory admissions for containment are excluded.

## Grippe chez la femme enceinte – données de la littérature

First author	Year of publication	Study type	Influenza type	Country	No. of pregnant women	Maternal mortality		Length of stay in ICU, days (range)
						n	%	
Anzic investigators (29)	2010	Population-based cohort	2009 influenza A/H1N1	Australia & New Zealand	64	7	11	8 (1–50)
Centers for Disease Control and Prevention (31)	2011	Population-based cohort	2009 influenza A/H1N1	USA	347	75	22	NA
Centers for Disease Control and Prevention (30)	2010	Retrospective cohort	2009 influenza A/H1N1	USA	17	2	12	NA
Dubar <sup>b</sup> (7)	2010	Prospective cohort	2009 influenza A/H1N1	France	40	3	8	10 (2–80)
Ellington (32)	2011	Retrospective cohort	2009 influenza A/H1N1	USA	71	15	21	7 (0–77)
Knight (33)	2010	Population-based cohort	2009 influenza A/H1N1	Australia & New Zealand	59	6	10	10 (1–65)
Louie (35)	2015	Retrospective cohort	Any influenza, mainly influenza A p/ H1N1	USA	57 17	4 4	7 24	6 (1–62) NA
Malinowski <sup>b</sup> (11)	2011	Retrospective cohort	2009 influenza A/H1N1	Canada	3	0	0	7 (1–19)
Maraví-Poma (34)	2011	Prospective cohort	2009 influenza A/H1N1	Spain	50	7	14	NA
Oluyomi-Obi (36)	2010	Prospective/retrospective cohort	2009 influenza A/H1N1	Canada	6	2	33	20 (10–82)

ICU, intensive care unit; NA, not available.

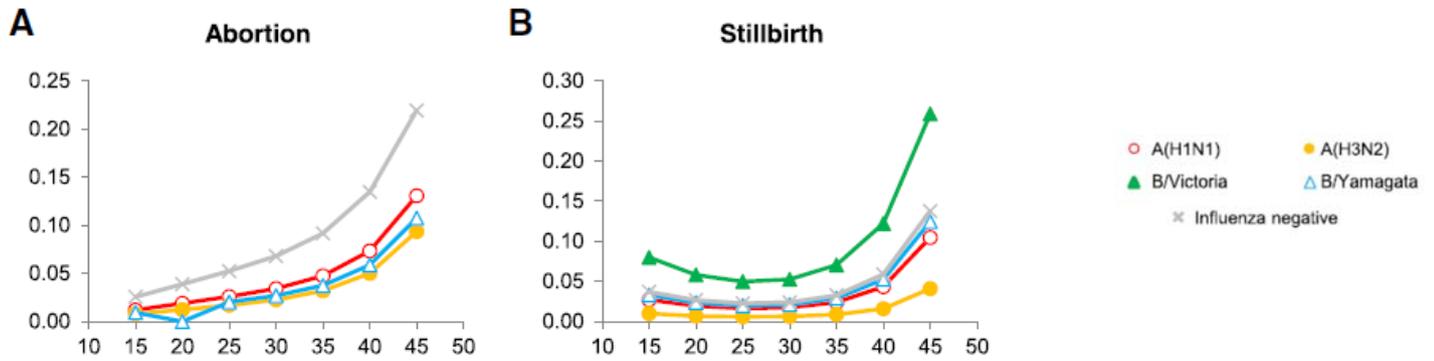
Please cite this article as: Meijer WJ, van Noordwijk AGA, Bruinse HW, Wensing AMJ. Influenza virus infection in pregnancy: a review. Acta Obstet Gynecol Scand 2015; 94: 797–819.

## Grippe chez la femme enceinte – données de la littérature

First author	Year of publication	Study type	Influenza type	Country	Type of patients	No. of pregnancies	Neonate discharged alive		Preterm birth		Small-for-gestational age	
							n	%	n	%	n	%
Da Silva (5)	2014	Prospective cohort	2009 influenza A/H1N1	Brazil	Mixed <sup>a</sup>	163	158	97	38	23	NA	
							34	97	9	26	NA	
Doyle (6)	2013	Retrospective cohort	2009 influenza A/H1N1	USA	Mixed <sup>a</sup>	187	181	95	45	24	NA	
Dubar (7)	2010	Prospective cohort	2009 influenza A/H1N1	France	Mixed <sup>a</sup>	303	300	99	15	5	NA	
Gérardin (8)	2010	Prospective cohort	2009 influenza A/H1N1	France (La Réunion)	Mixed <sup>a</sup>	115	NA		22	19	NA	
Malinowski (11)	2011	Retrospective cohort	2009 influenza A/H1N1	Canada	Mixed <sup>a</sup>	25	24	96	3	12	NA	
Naresh (12)	2013	Retrospective cohort	2009 influenza A/H1N1	USA	Mixed <sup>a</sup>	142	NA		21	15	12	9

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# Risque grippe en fonction de l'âge gestationnel de la femme enceinte



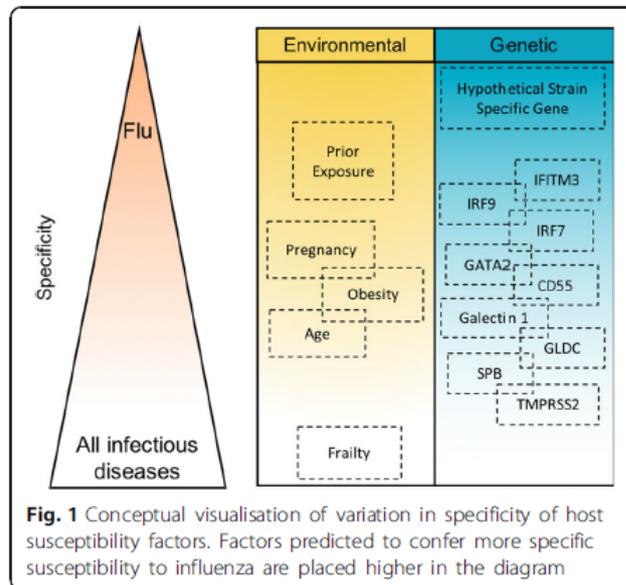
Trushakova et al. *BMC Pregnancy and Childbirth* (2019) 19:72

## Innocuité de la vaccination chez la femme enceinte. Données de la littérature

First author	Year of publication	Study type	Vaccine type	Country	No. of pregnant women (total, vaccinated)	Preterm birth <37 weeks, RR (95% CI)	Small-for-gestational age, RR (95% CI)	Stillbirth, RR (95% CI)
Adedinsewo (71)	2013	Retrospective cohort	Seasonal influenza, inactivated	USA	5422, 916	0.83 (0.60–1.17)	1.07 (0.73–1.58)	NA
Ahrens (72)	2014	Retrospective cohort	Seasonal influenza, trivalent	USA	1619, 637	1.37 (0.84–2.23)	1.03 (0.66–1.62)	NA
Beau (74)	2014	Retrospective cohort	Non-adjuvanted A/H1N1	France	4935, 1645	0.82 (0.64–1.06)	0.36 (0.17–0.78)	0.56 (0.31–1.01)
Chambers (75)	2013	Prospective cohort	Monovalent pH1N1	USA/Canada	1032, 841	3.28 (1.25–8.63)	1.08 (0.46–2.54)	0.97 (0.79–1.20) <sup>a</sup>
Cleary (77)	2014	Retrospective cohort	Inactivated pH1N1, both with and without adjuvant	Ireland	6894, 2996	0.71 (0.58–0.88) <sup>b</sup>	0.98 (0.85–1.13)	0.65 (0.31–1.34)
Dodds (95)	2012	Retrospective cohort	Seasonal influenza	Canada	9647, 1925	0.84 (0.69–1.02)	0.80 (0.65–0.97)	NA
Fell (96)	2012	Retrospective cohort	2009 influenza A/ H1N1	Canada	55 570, 23 340	0.95 (0.88–1.02) <sup>c</sup>	0.90 (0.85–0.96) <sup>d</sup>	0.66 (0.47–0.91)
Håberg (44)	2013	Retrospective cohort	Inactivated, adjuvanted 2009 influenza A/ H1N1	Norway	113 331, 25 976	1.00 (0.93–1.09)	NA	0.88 (0.66–1.17)

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En résumé, pour comprendre le risque grippe en général



## Conclusion

- La grippe du nouveau né n'est pas anodine, même si l'incidence est basse
- Les co-infections sont un facteur de gravité (notamment les co-infections virales)
- La femme enceinte est à risque de faire des formes graves
- L'infection impacte l'issue de la grossesse
- la prévention par la vaccination de la mère permet la protection durant le grossesse et après l'accouchement



## Remerciements



- CNR & VIRPATH-CIRI :
  - Vanessa Escuret
  - Jean Sebastien Casalegno
  - Laurence Josset
  - Emilie Frobert
  - Martine Valette
  - Alexandre Gaymard
  - Les techniciens du CNR

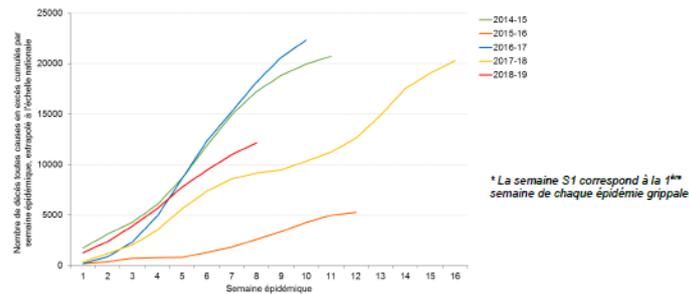


Back-up

# Mortalité associée aux virus influenza en France

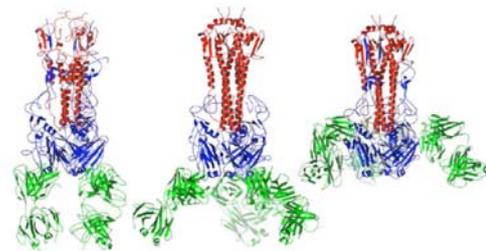
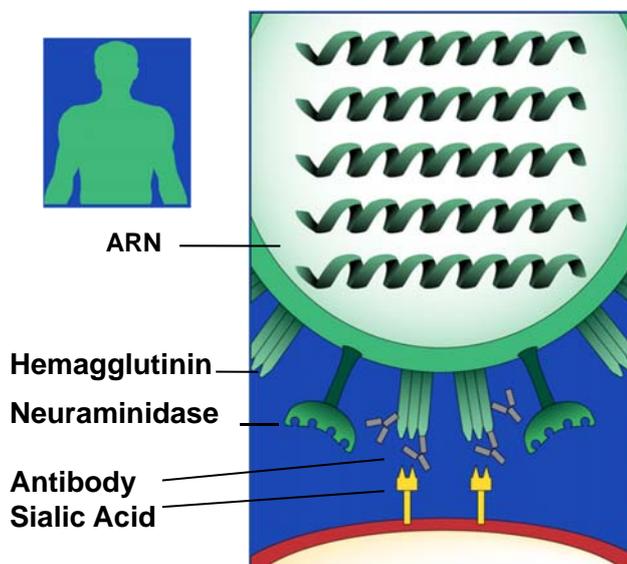


Santé publique France a développé un modèle permettant d'estimer le nombre de décès attribuables à la grippe. Depuis le début de la surveillance de la grippe (semaine 40, du 1<sup>er</sup> au 7 octobre 2018) et jusqu'en semaine 08 (du 18 au 24 février 2019), il est estimé qu'environ 7 200 décès tous âges confondus sont attribuables à la grippe, dont 85% chez les personnes âgées de 75 ans et plus.



Données de Santé Publique France

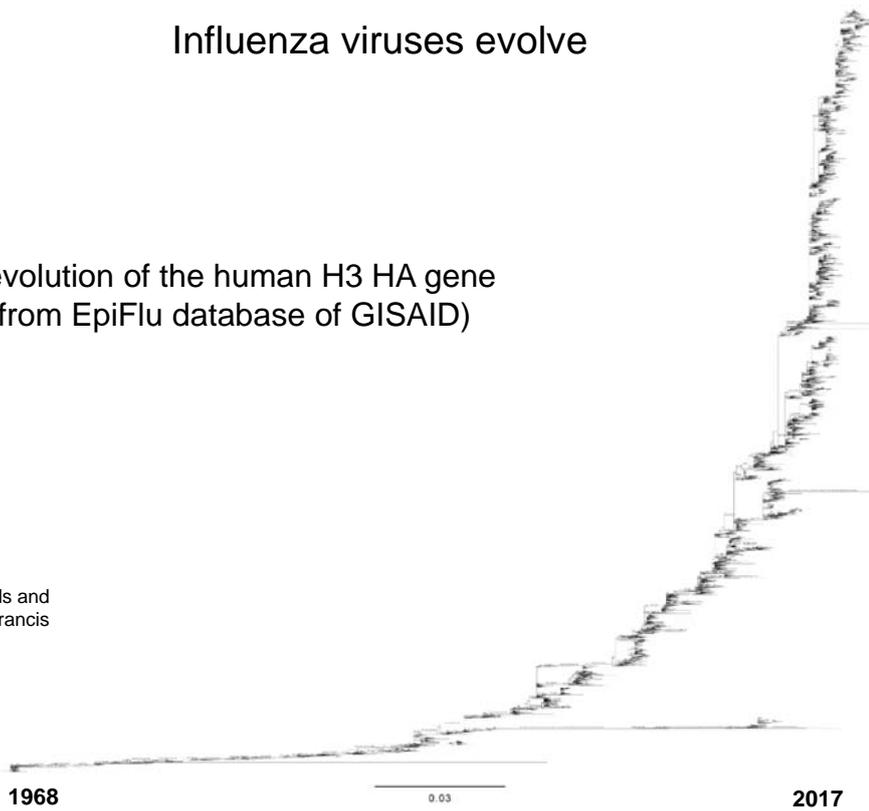
## Anti Ha antibodies are protective



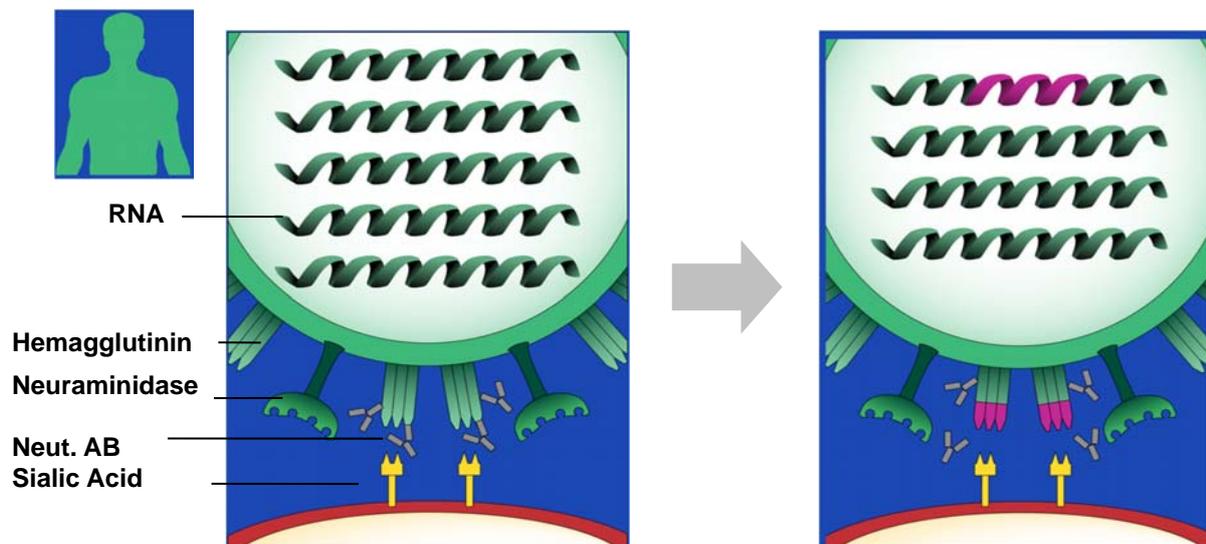
## Influenza viruses evolve

50 years of evolution of the human H3 HA gene  
(Sequences from EpiFlu database of GISAID)

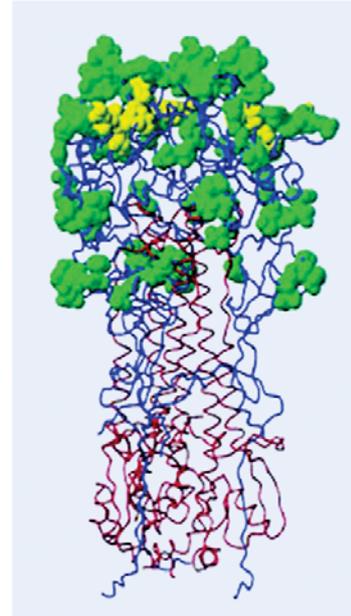
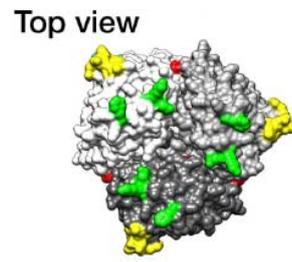
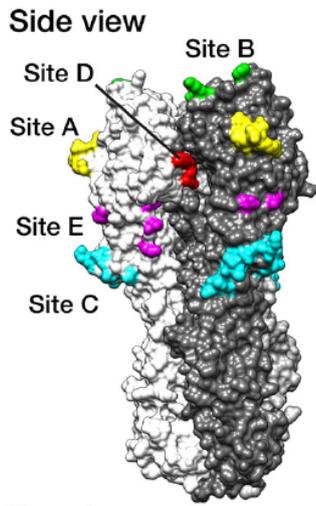
Data from Rod Daniels and  
Saira Hussein, The Francis  
Crick Institute



## Antigenic drift



# Major antigenic sites (A-E) and Ha evolution



Broecker F et al, J Virol 2018