



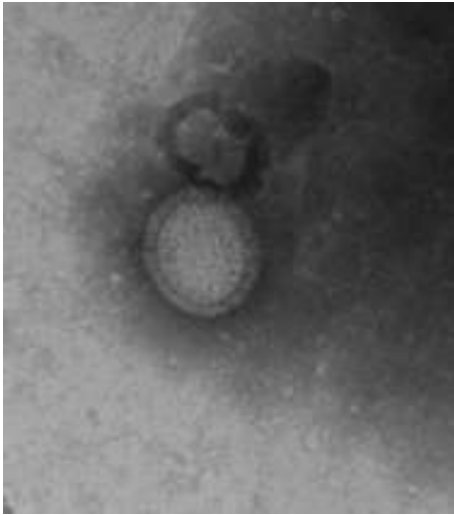
Pathophysiology of pandemic influenza

ID forum

21 February 2011

Kelvin To

Department of Microbiology, HKU



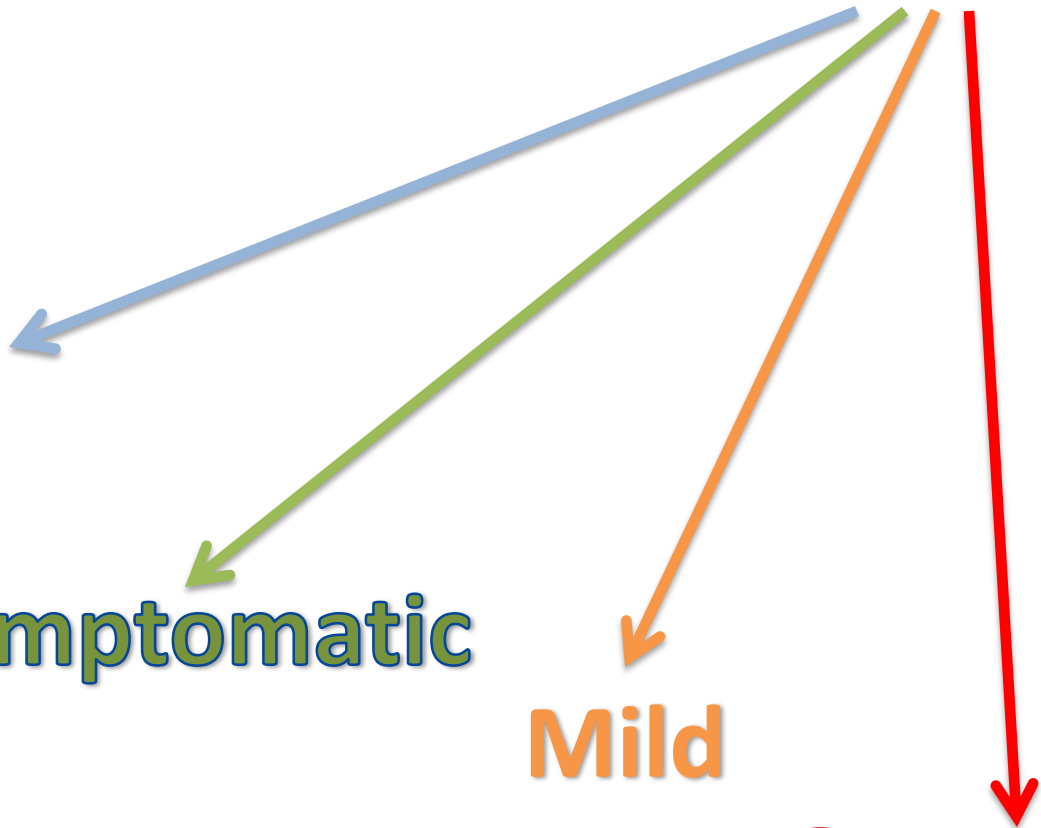
Host

Not infected

Asymptomatic

Mild

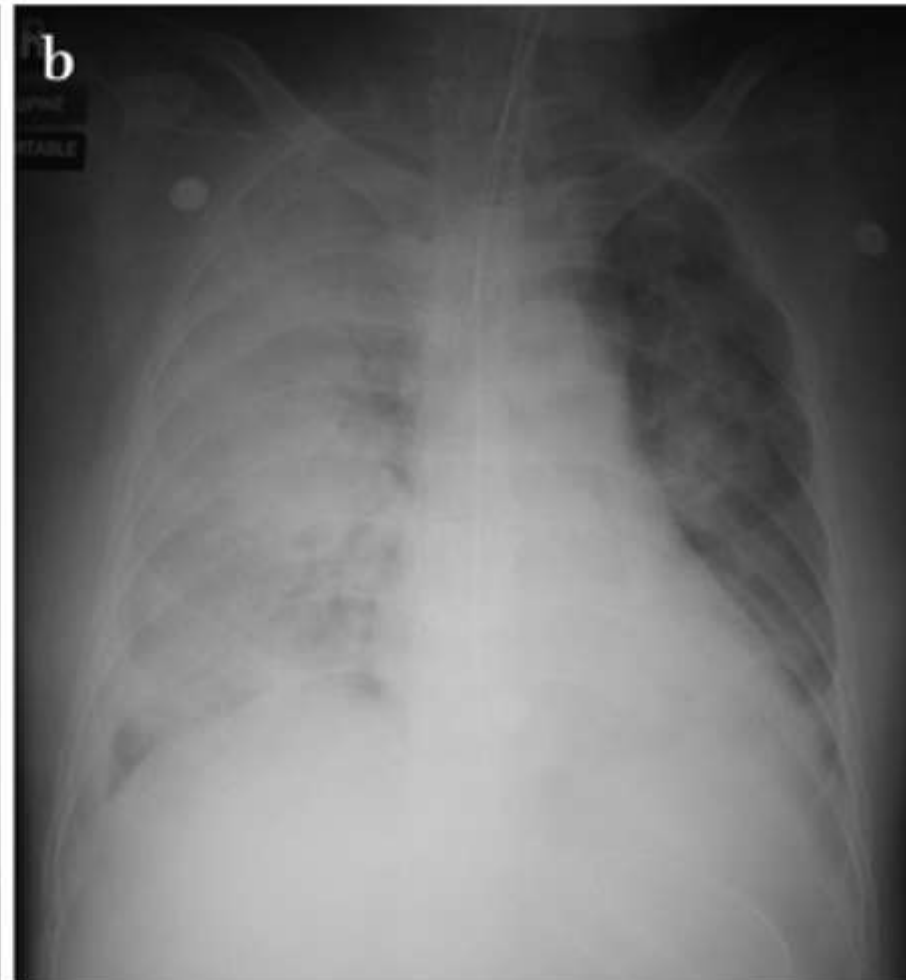
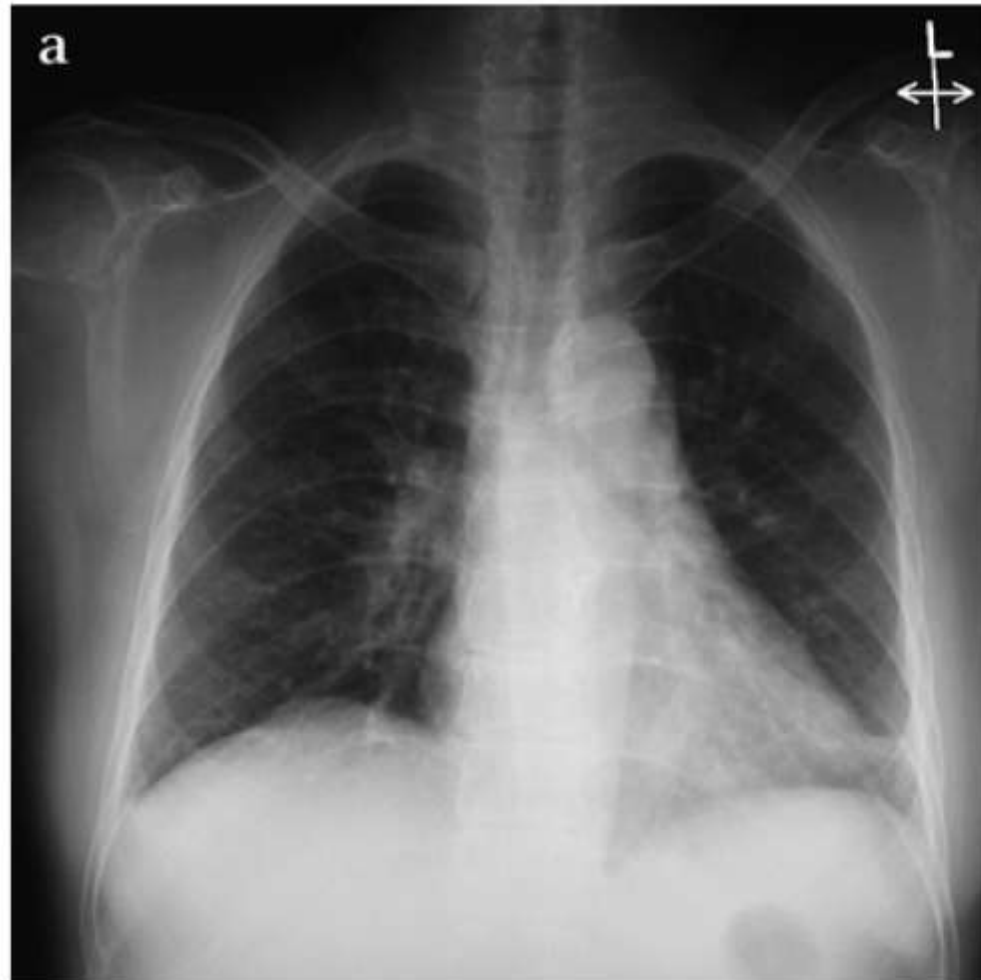
Severe



Rapid progression of pneumonia

On admission

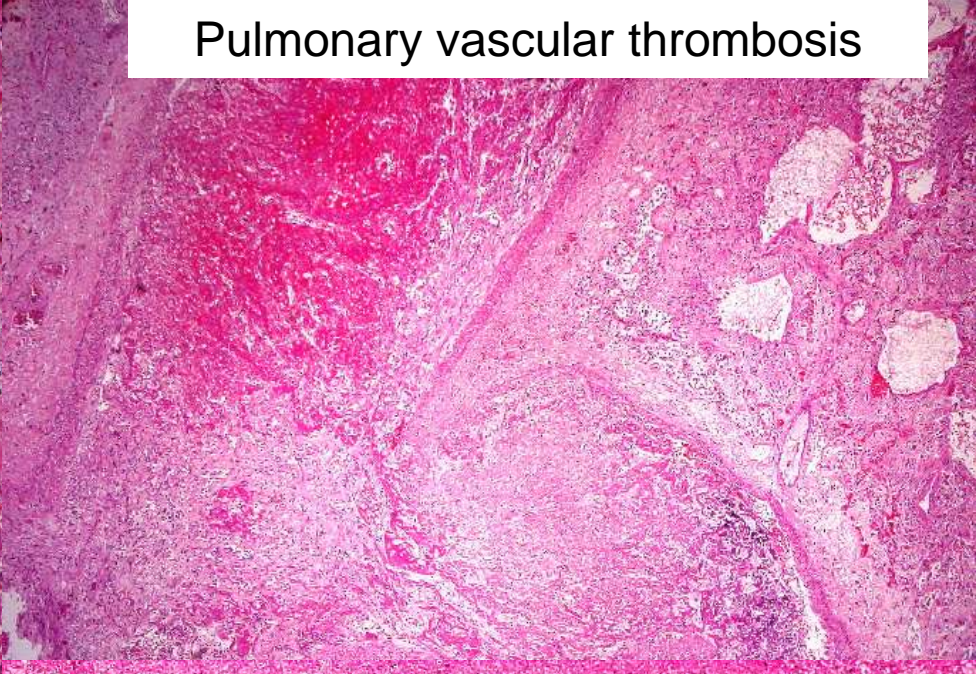
20 hours later



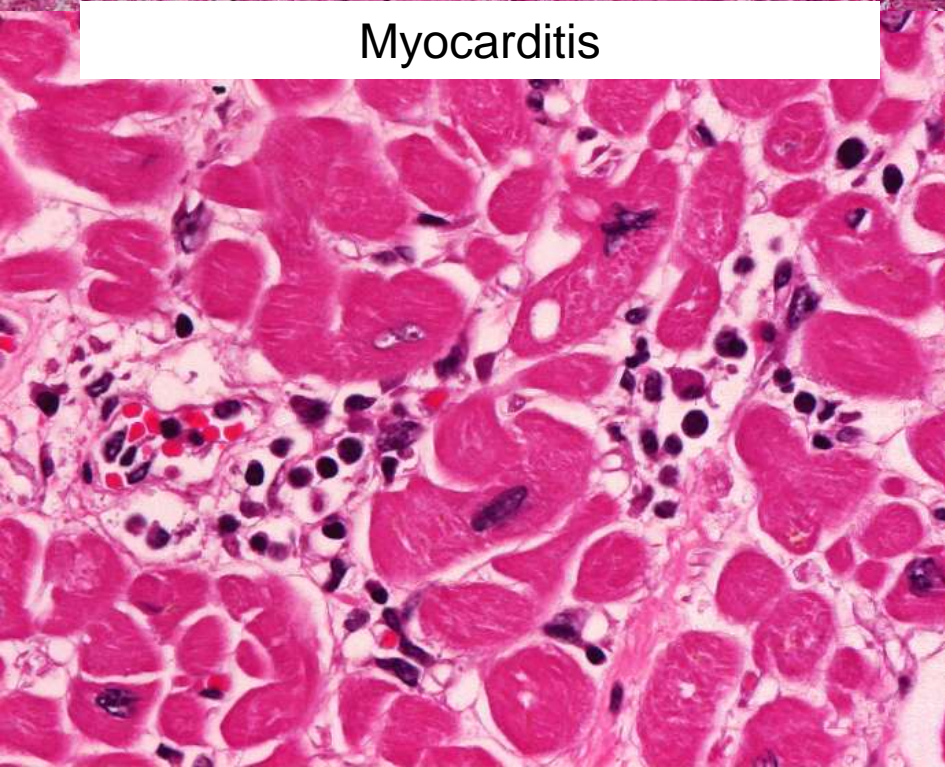
Diffuse alveolar damage



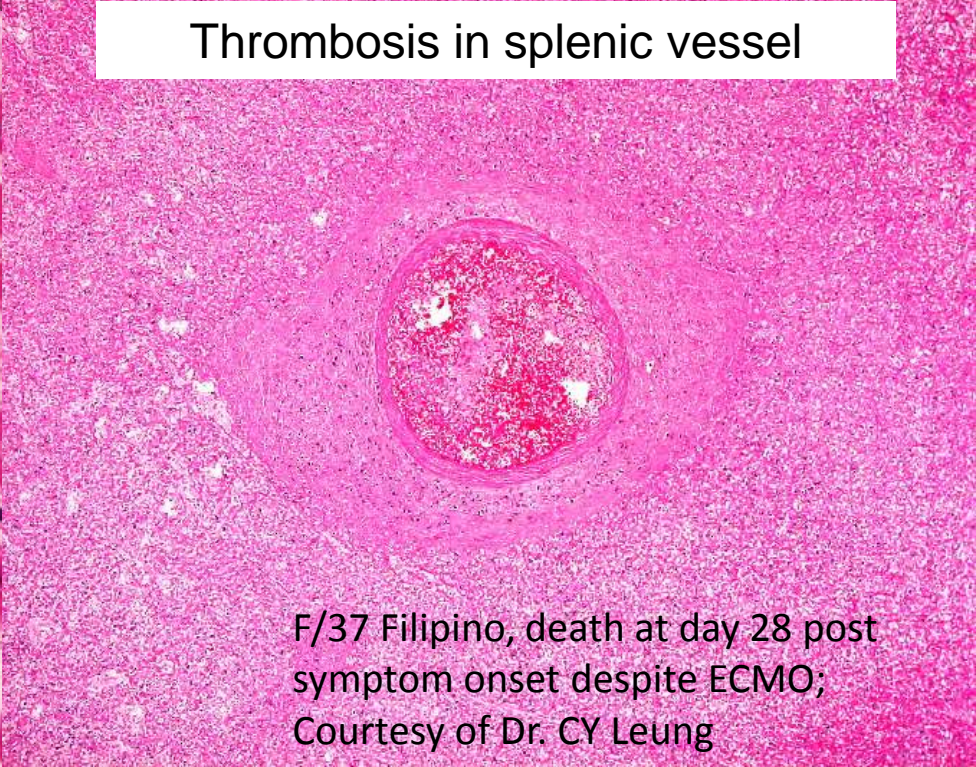
Pulmonary vascular thrombosis



Myocarditis

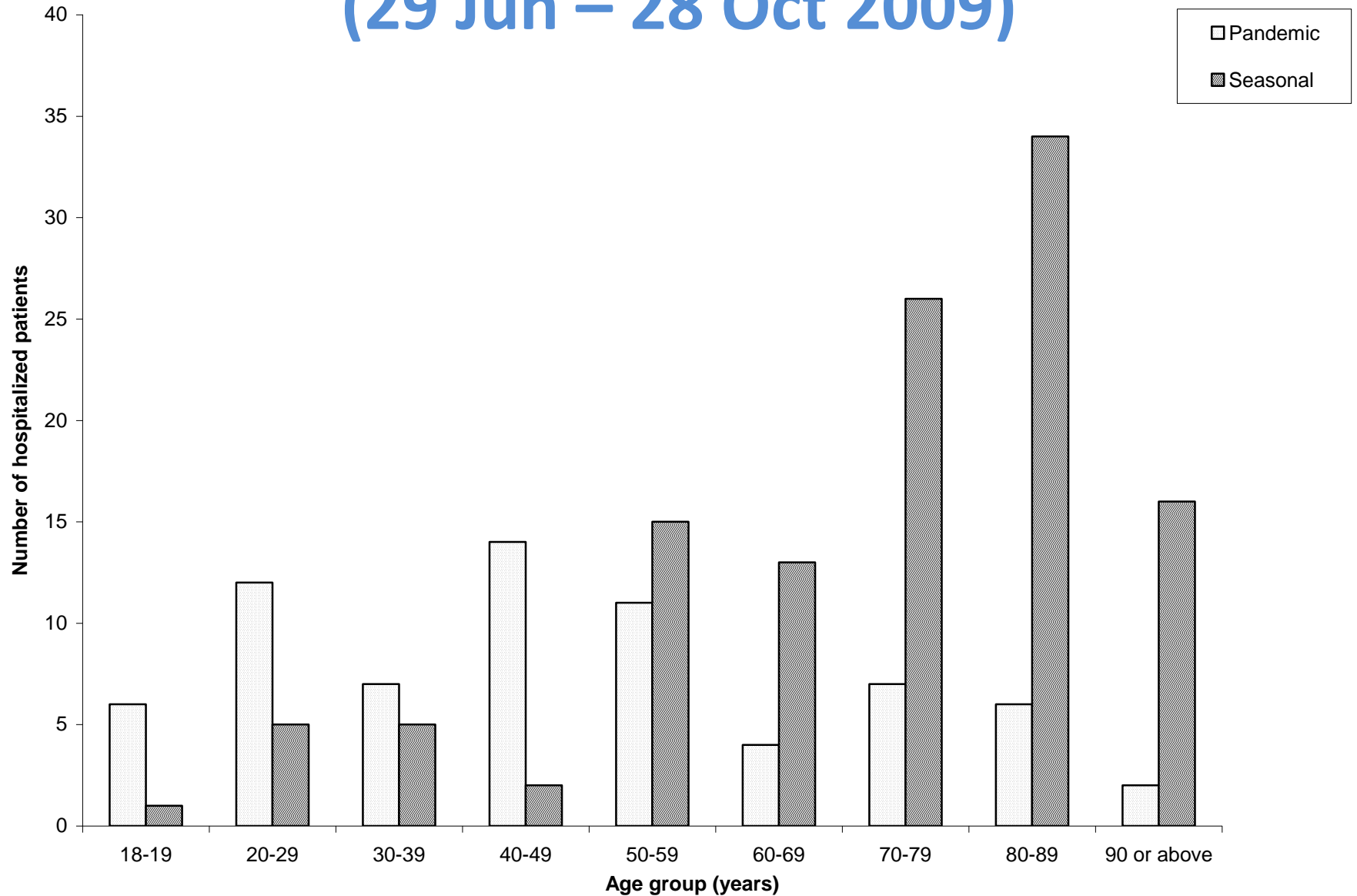


Thrombosis in splenic vessel



F/37 Filipino, death at day 28 post symptom onset despite ECMO;
Courtesy of Dr. CY Leung

Hospitalized patients during the 1st wave (29 Jun – 28 Oct 2009)



Lack of pre-existing immunity

Serum samples collected in 2008

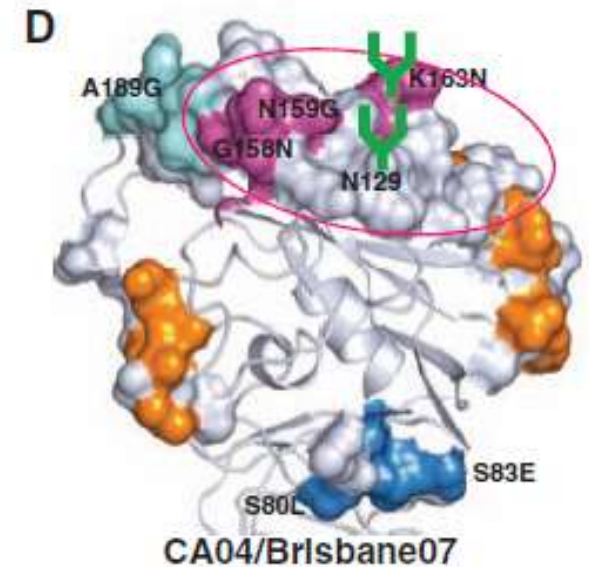
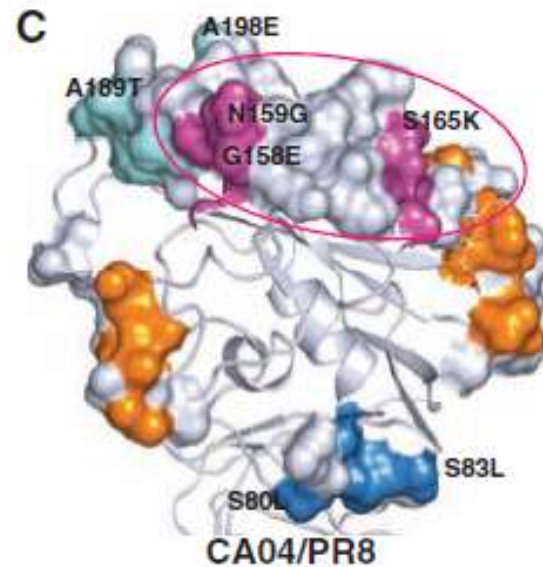
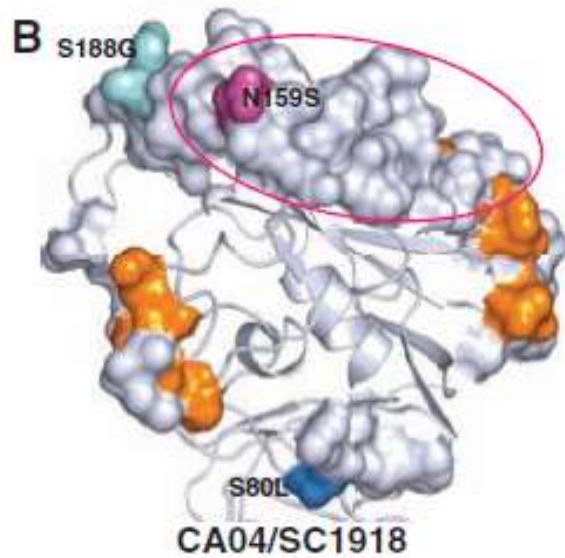
Age group (years)	No. tested	Titer % to seasonal H1			Titer % to pandemic H1		
		<10	10–20	≥40	<10	10–20	≥40
1–4	24	54	21	25	100	0	0
5–9	30	23	10	67	70	30	0
10–19	30	13	27	60	93	7	0
20–29	30	30	40	30	63	33	3
30–39	30	23	40	37	57	43	0
40–49	30	7	60	33	60	37	3
50–65	30	0	33	67	20	63	17
>65	30	3	30	67	13	50	37

Structural similarity to 1918 virus

1918 H1N1

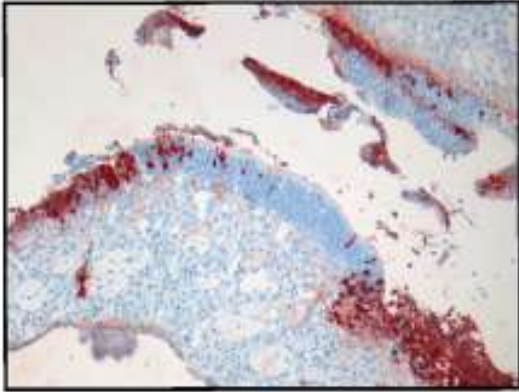
1934
Seasonal
influenza

2007
Seasonal
influenza



A Seasonal A/H1N1

Nasal Turbinates



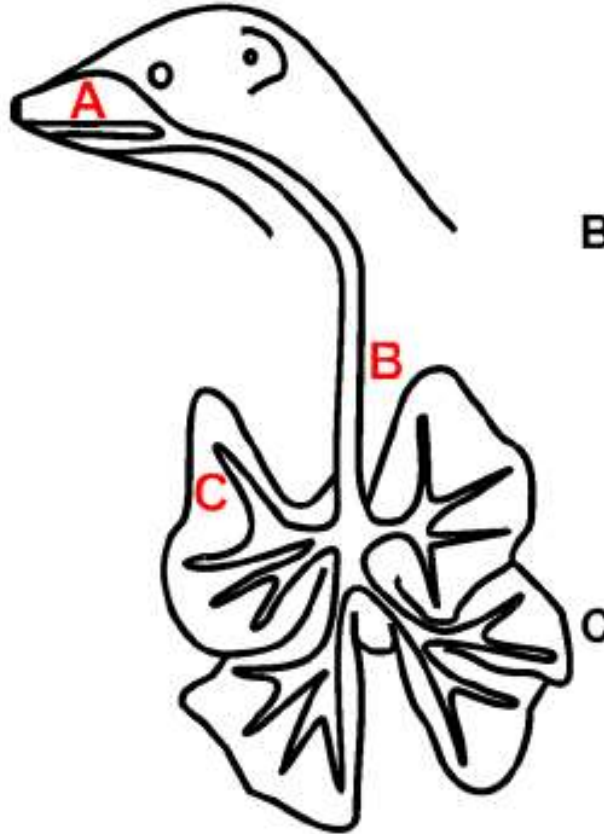
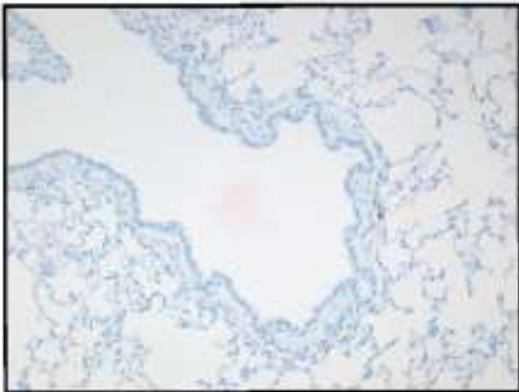
B

Trachea

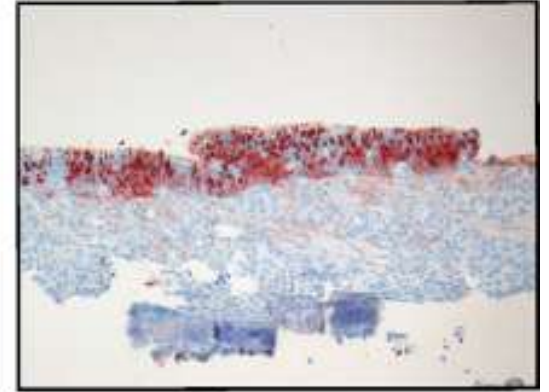


C

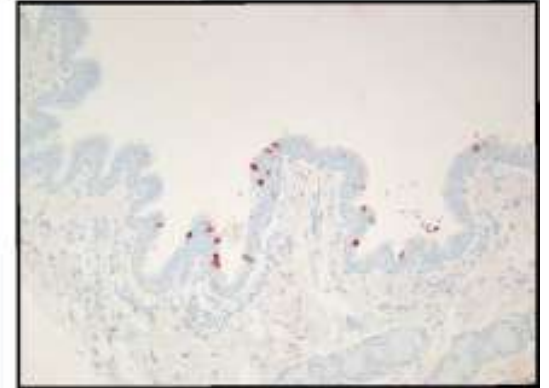
Bronchiole



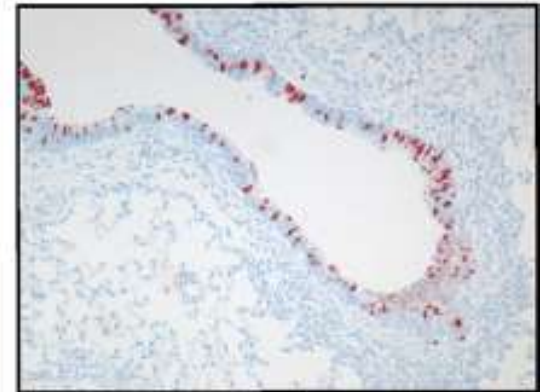
A 2009 A/H1N1



B



C



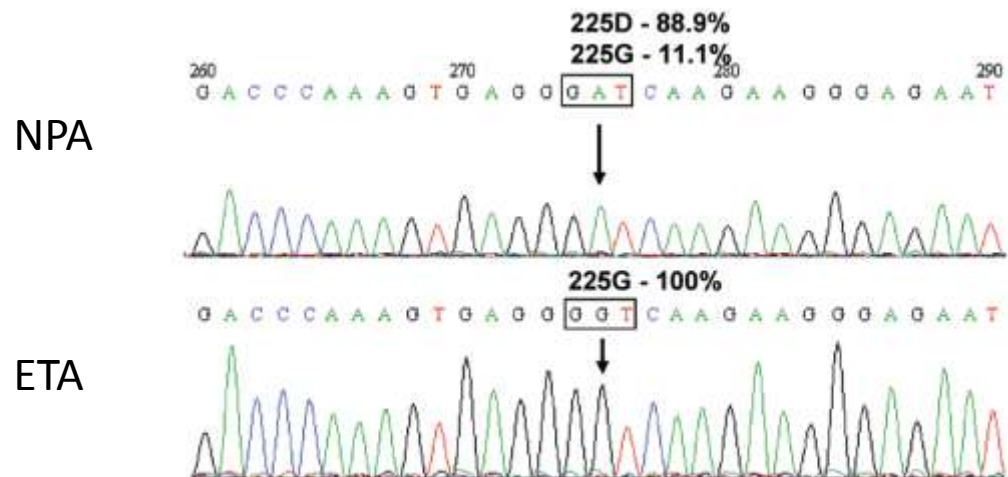
Preliminary review of D222G amino acid substitution in the haemagglutinin of pandemic influenza A (H1N1) 2009 viruses

28 December 2009

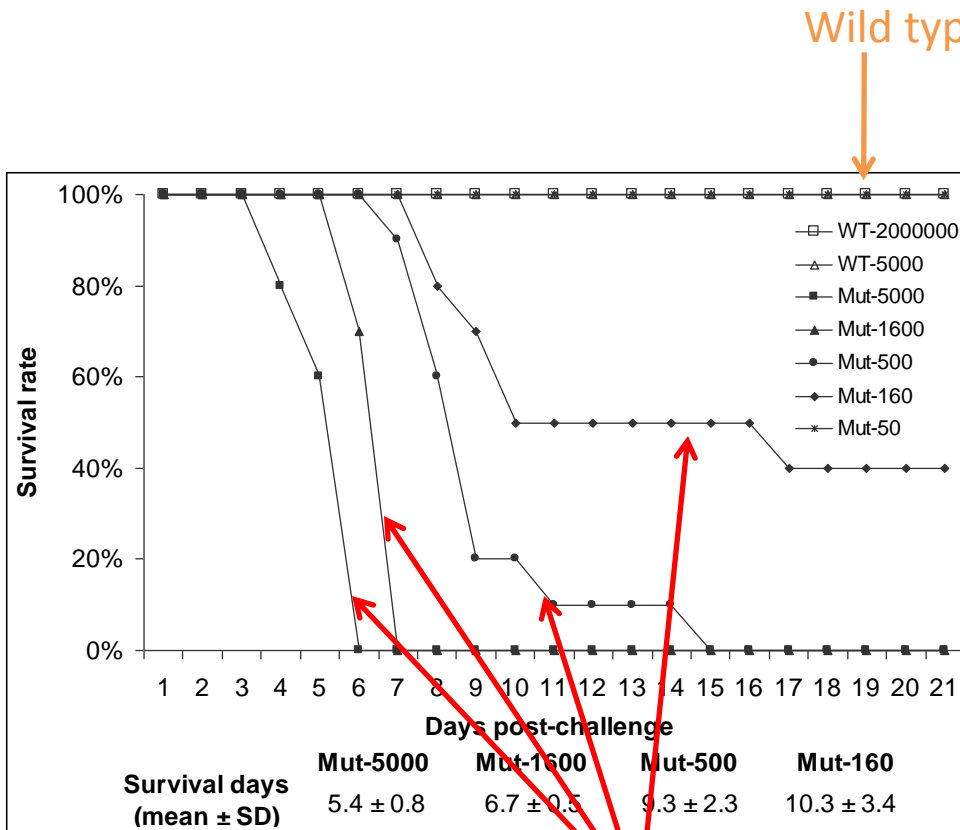
- Prevalence of D222G mutation <1.8% of all cases
- 7.1% of fatal cases had the D222G mutation

D225G/ D222G mutation is associated with severe disease

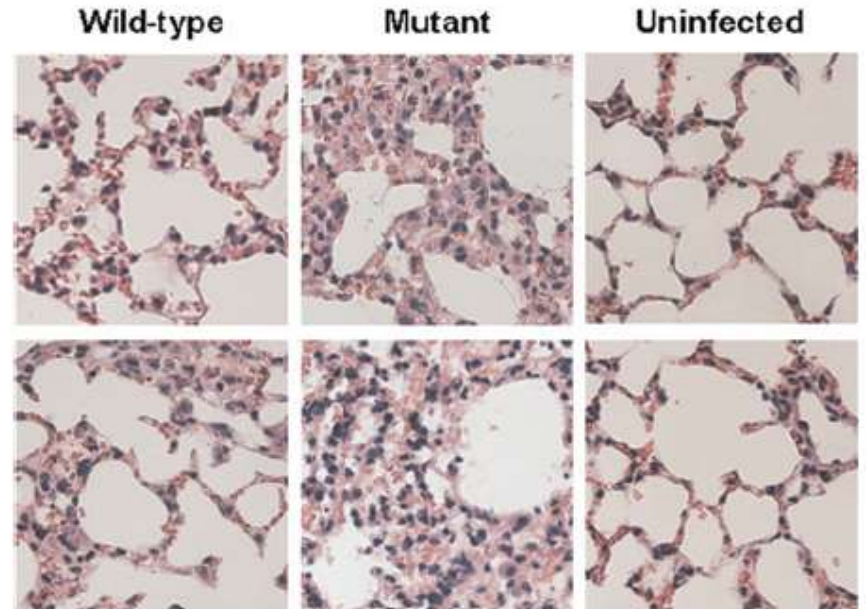
Patient (age in years, sex)	Underlying disease	Mechanical ventilation	ICU admission	ARDS	Outcome	Days of symptoms before specimen collection	Days of oseltamivir before specimen collection ^a	Specimen	
								NPA	ETA
1 (43, F)	Alcohol dependence, depression	+	+	+	Died	12	0	225D, 225G	225G
2 (51, F)	Hypertension, poliomyelitis, osteoarthritis	+	+	+	Survived	6	2	225D	225N
3 (23, F)	Pregnancy	+	+	+	Survived	4	0	225D	225G, 225D
4 (51, M)	Good past health	+	+	-	Survived	7 (ETA) 12 (NPA)	-1 (ETA) 4 (NPA)	225G, 225N	225G, 225N
5 (37, F)	Hypertension	+	+	+	Died	8	-3	225G	NA ^b
6 (30, F)	Good past health	+	+	+	Survived	4	1	225D	225G, 225D
7 (49, F)	Hepatitis B carrier	+	+	+	Survived	2	0	225G	225D
8 (59, F)	Subarachnoid hemorrhage	+	+	+	Died	4	1	225D	225D, 225G
9 (36, F)	Bronchiectasis	+	+	+	Survived	5	2	225E	225D
10 (19, M)	Good past health	-	-	-	Survived	2	1	225E	NA
11 (18, M)	Congenital heart disease ^c	-	-	-	Survived	2	NA	225E	NA
12 (27, F)	Good past health	-	-	-	Survived	4	1	225N	NA



D225G mutants in animal model



Wild type



D225G mutant

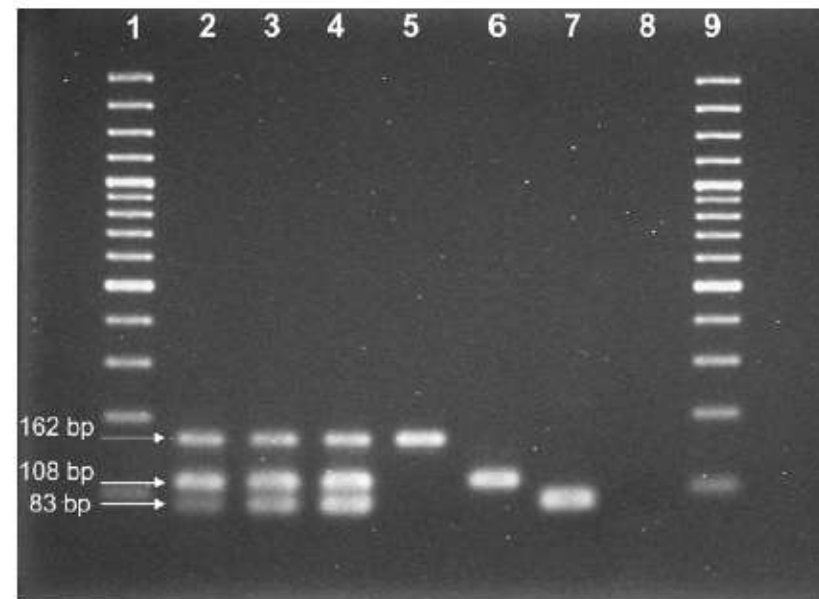
Co-infections in some cases

Bacterial Coinfections in Lung Tissue Specimens from Fatal Cases of 2009
Pandemic Influenza A (H1N1) – United States, May–August 2009

- *S. aureus* (CA-MRSA)
- *S. pneumoniae*
- *S. pyogenes*
- *S. mitis*
- *Haemophilus influenzae*

Fatal co-infection with swine origin influenza
virus A/H1N1 and community-acquired
methicillin-resistant *Staphylococcus aureus*

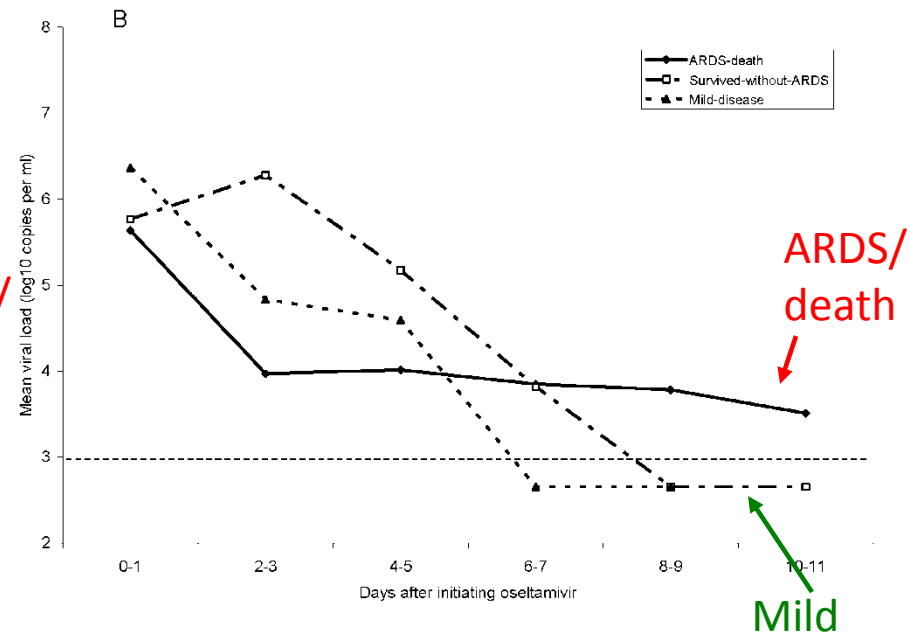
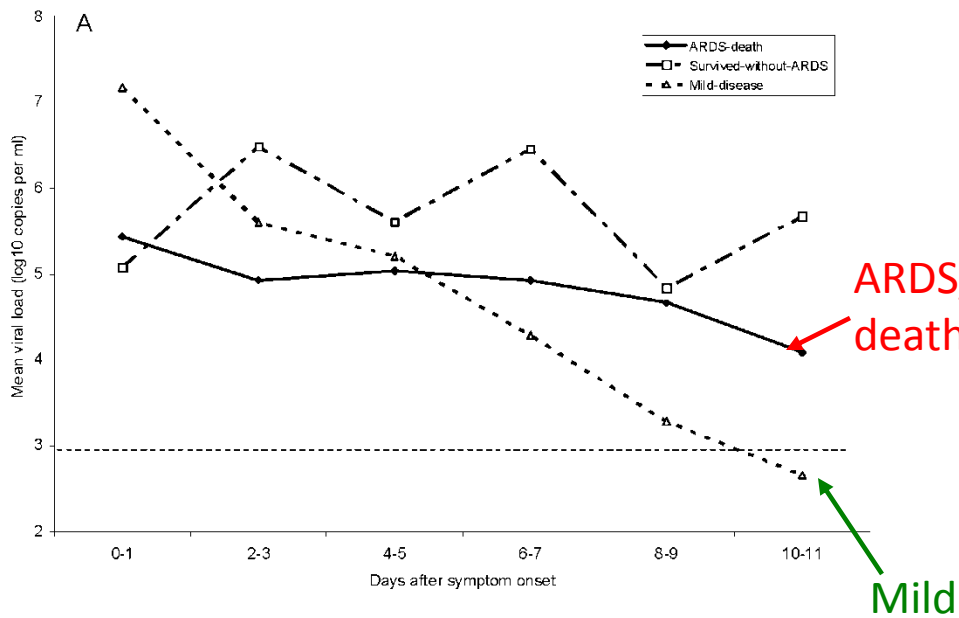
Vincent C.C. Cheng^a, Yuk-Kong Lau^b, Kwok-Lun Lee^b, Kwan-Ho Yiu^c,
Kwok-Hung Chan^a, Pak-Leung Ho^a, Kwok-Yung Yuen^{a,*}



Delayed clearance of virus in respiratory tract

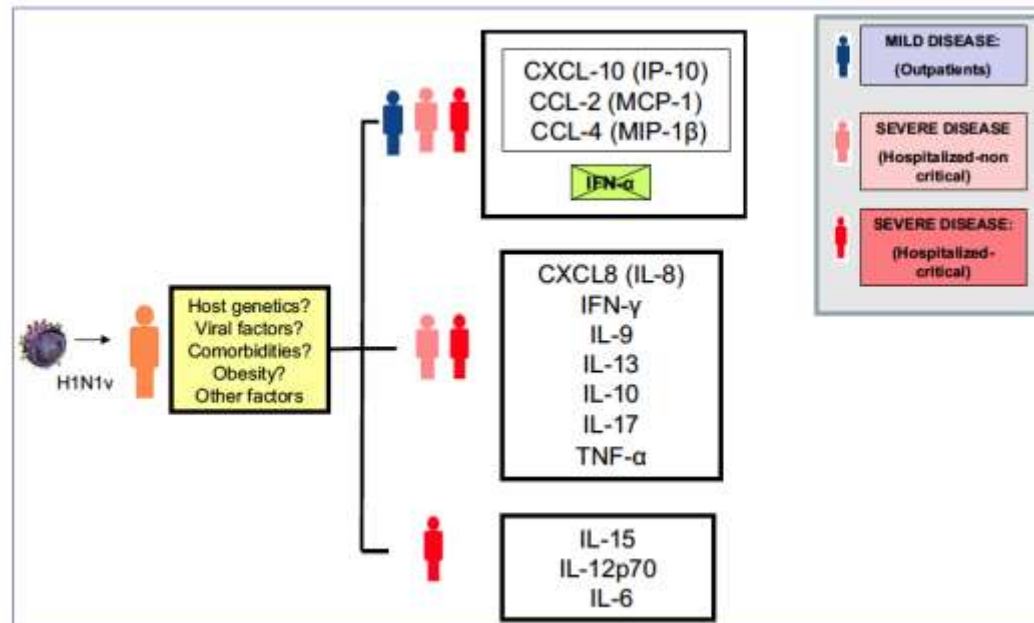
After symptom onset

After oseltamivir



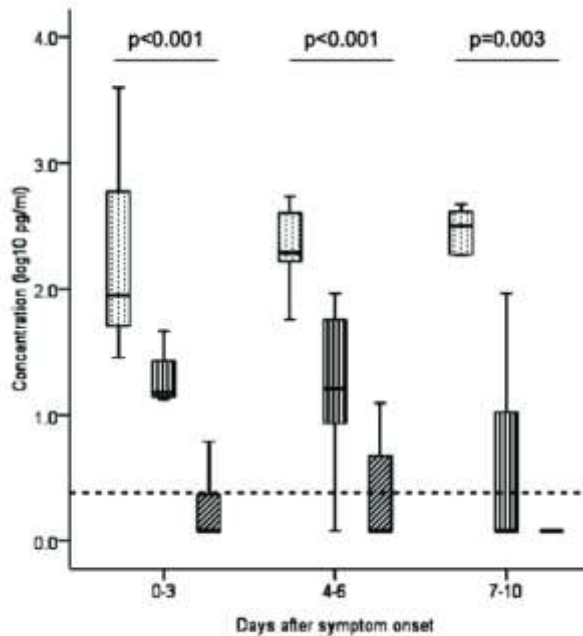
Elevated cytokine/ chemokine

Variable	ARDS-death group (n = 18)	Survived-without-ARDS group (n = 10)	<i>P</i> ^a	Mild-disease group (n = 29)	<i>P</i> ^b
Cytokine or chemokine, log ₁₀ pg/mL ^{c,d}					
G-CSF	2.11 (1.33–3.91)	1.13 (0.19–2.03)	<.001	1.31 (0.74–2.43)	<.001
IFN-α2	1.1 (0.71–2.49)	0.79 (0.71–1.79)	.138	0.71 (0.71–2.07)	.024
IL-1α	2.13 (1.38–2.78)	1.66 (1.17–2.19)	.014	1.59 (0.94–2.46)	<.001
IL-6	2.40 (1.32–4.00)	1.19 (0.81–1.97)	<.001	0.08 (0.08–2.14)	<.001
IL-8	2.25 (1.23–4.02)	1.70 (1.18–3.20)	.084	1.21 (0.78–2.66)	<.001
IL-10	1.80 (1.14–2.70)	1.02 (0.19–2.36)	.002	0.48 (0.19–1.60)	<.001
IL-15	0.92 (0.44–1.70)	0.33 (0.20–2.36)	<.001	0.20 (0.20–0.65)	<.001
IL-17	0.20 (0.20–2.94)	0.20 (0.20–0.87)	.298	0.76 (0.20–2.48)	.074
IP-10	3.83 (3.01–4.01)	3.10 (2.69–4.01)	.065	3.00 (1.80– 3.36)	<.001
MCP-1	3.11 (2.48–3.74)	2.73 (2.41–3.44)	.017	2.58 (1.94–3.00)	<.001
TNF-α	1.19 (0.62–2.12)	0.90 (0.89–1.15)	.002	0.86 (0.80–1.25)	<.001

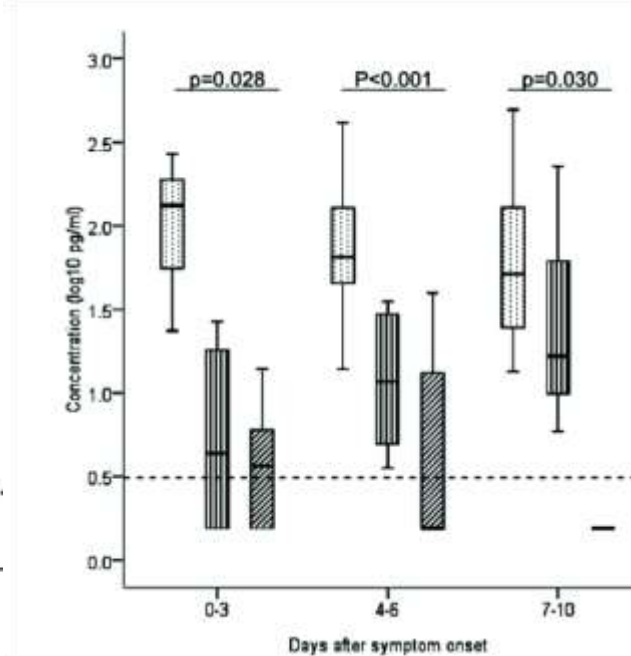


Persistent elevation of IL-6, IL-10, IL-15

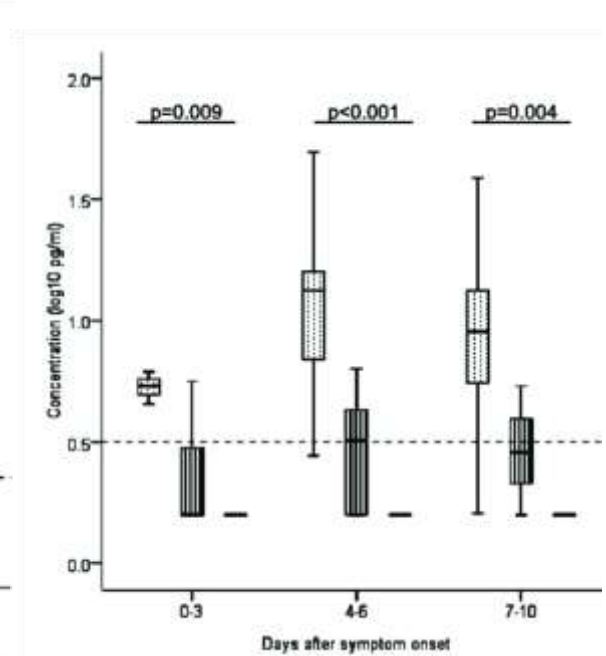
IL-6






IL-10



IL-15



-  ARDS-death
-  Survived-without-ARDS
-  Mild-disease

H1N1 2009 influenza virus infection during pregnancy in the USA

*Denise J Jamieson, Margaret A Honein, Sonja A Rasmussen, Jennifer L Williams, David L Swerdlow, Matthew S Biggerstaff, Stephen Lindstrom, Janice K Louie, Cara M Christ, Susan R Bohm, Vincent P Fonseca, Kathleen A Ritger, Daniel J Kuhles, Paula Eggers, Hollianne Bruce, Heidi A Davidson, Emily Lutterloh, Meghan L Harris, Colleen Burke, Noelle Cocoros, Lyn Finelli, Kitty F MacFarlane, Bo Shu, Sonja J Olsen, and the Novel Influenza A (H1N1) Pregnancy Working Group**

Lancet. 2009 Aug 8;374(9688):451-8.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

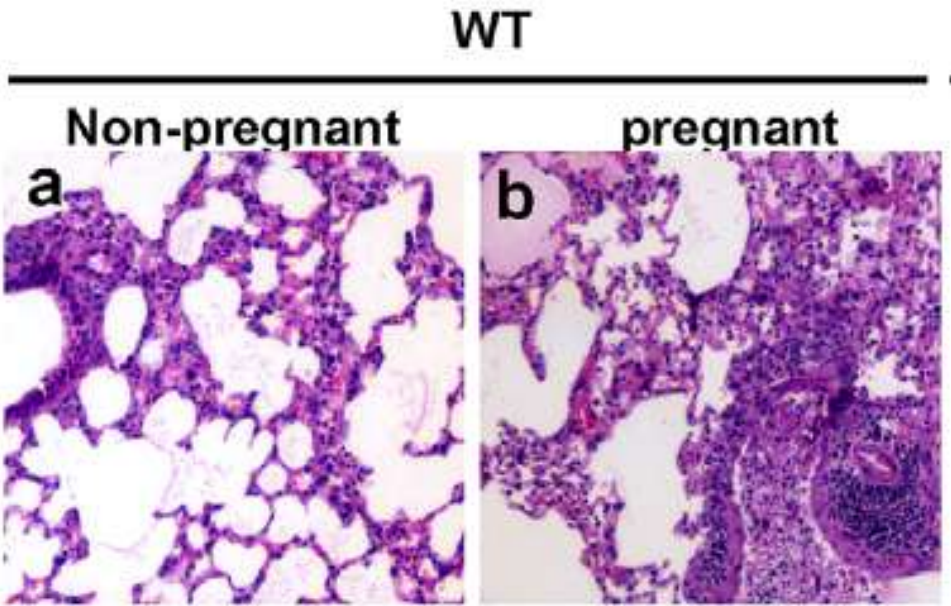
Severe 2009 H1N1 Influenza in Pregnant and Postpartum Women in California

Janice K. Louie, M.D., M.P.H., Meileen Acosta, M.P.H.,
Denise J. Jamieson, M.D., M.P.H., and Margaret A. Honein, Ph.D., M.P.H.,
for the California Pandemic (H1N1) Working Group*

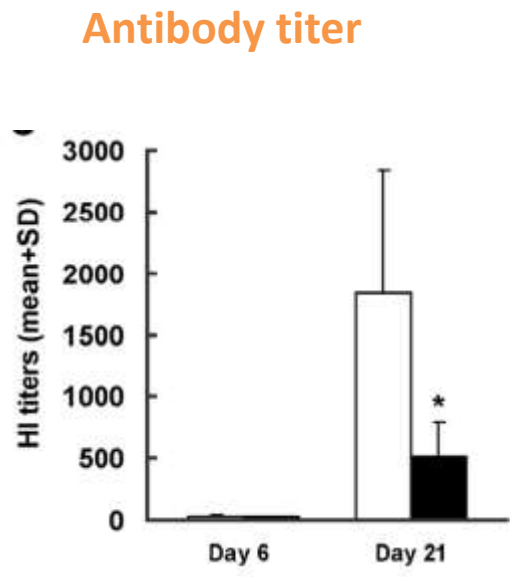
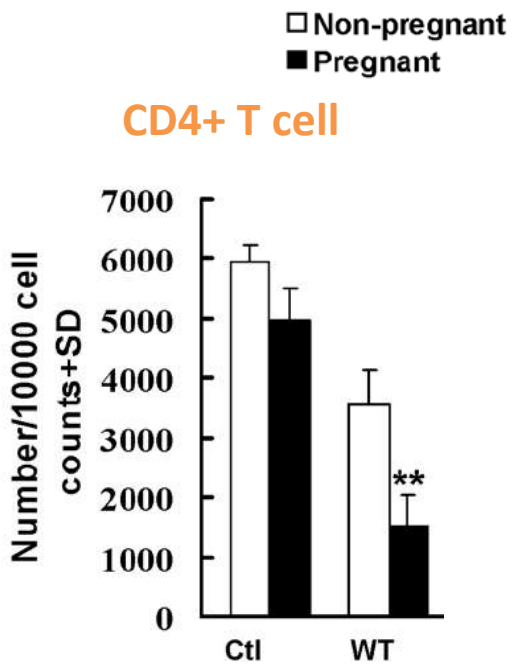
N Engl J Med. 2010 Jan 7;362(1):27-35.

Pregnant mice

- more severe lung damage



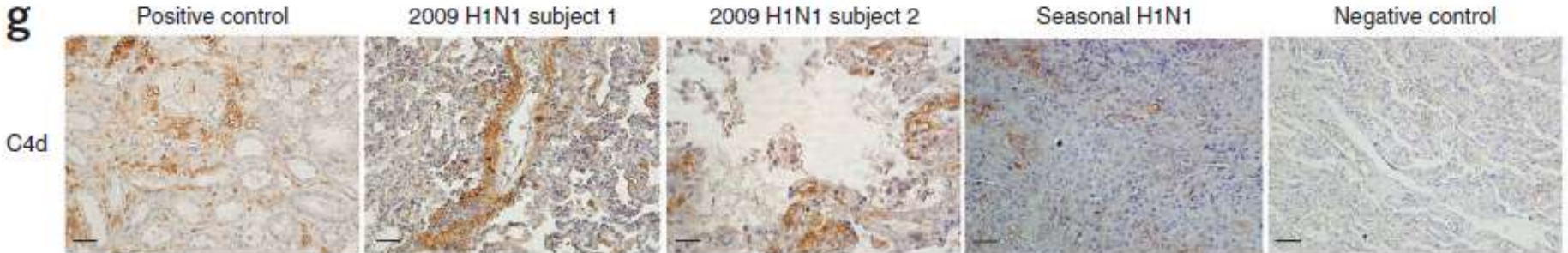
Interstitial bronchitis, epithelial necrosis, alveolitis and alveolar edema



- No virus found in
- Brain
 - Liver
 - Kidney
 - Placenta
 - Fetus

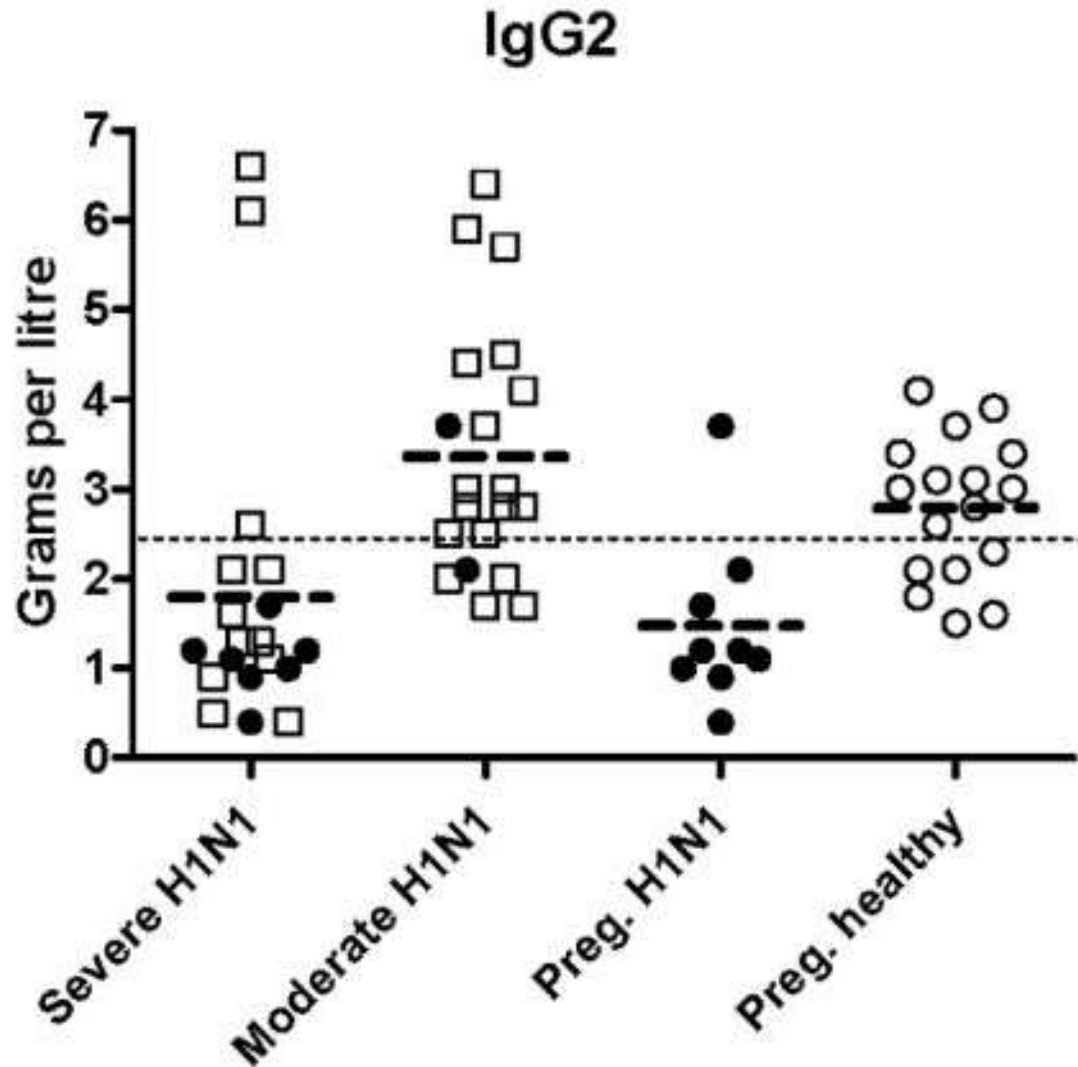
Severe pandemic 2009 H1N1 influenza disease due to pathogenic immune complexes

Ana Clara Monsalvo^{1,9}, Juan P Batalle^{1,9}, M Florencia Lopez^{1,9}, Jens C Krause², Jennifer Klemenc², Johanna Zea Hernandez^{1,2}, Bernardo Maskin³, Jimena Bugna¹, Carlos Rubinstein⁴, Leandro Aguilar⁴, Liliana Dalurzo⁵, Romina Libster¹, Vilma Savy⁶, Elsa Baumeister⁶, Liliana Aguilar³, Graciela Cabral³, Julia Font³, Liliana Solari³, Kevin P Weller², Joyce Johnson⁷, Marcela Echavarria⁸, Kathryn M Edwards², James D Chappell⁷, James E Crowe Jr², John V Williams², Guillermina A Melendi^{1,2} & Fernando P Polack^{1,2}



Deposition of C4d in lung sections

IgG2 deficiency



Severe case has lower IgG2 level

TABLE 4. Initial plasma IgG and cytokine/chemokine levels

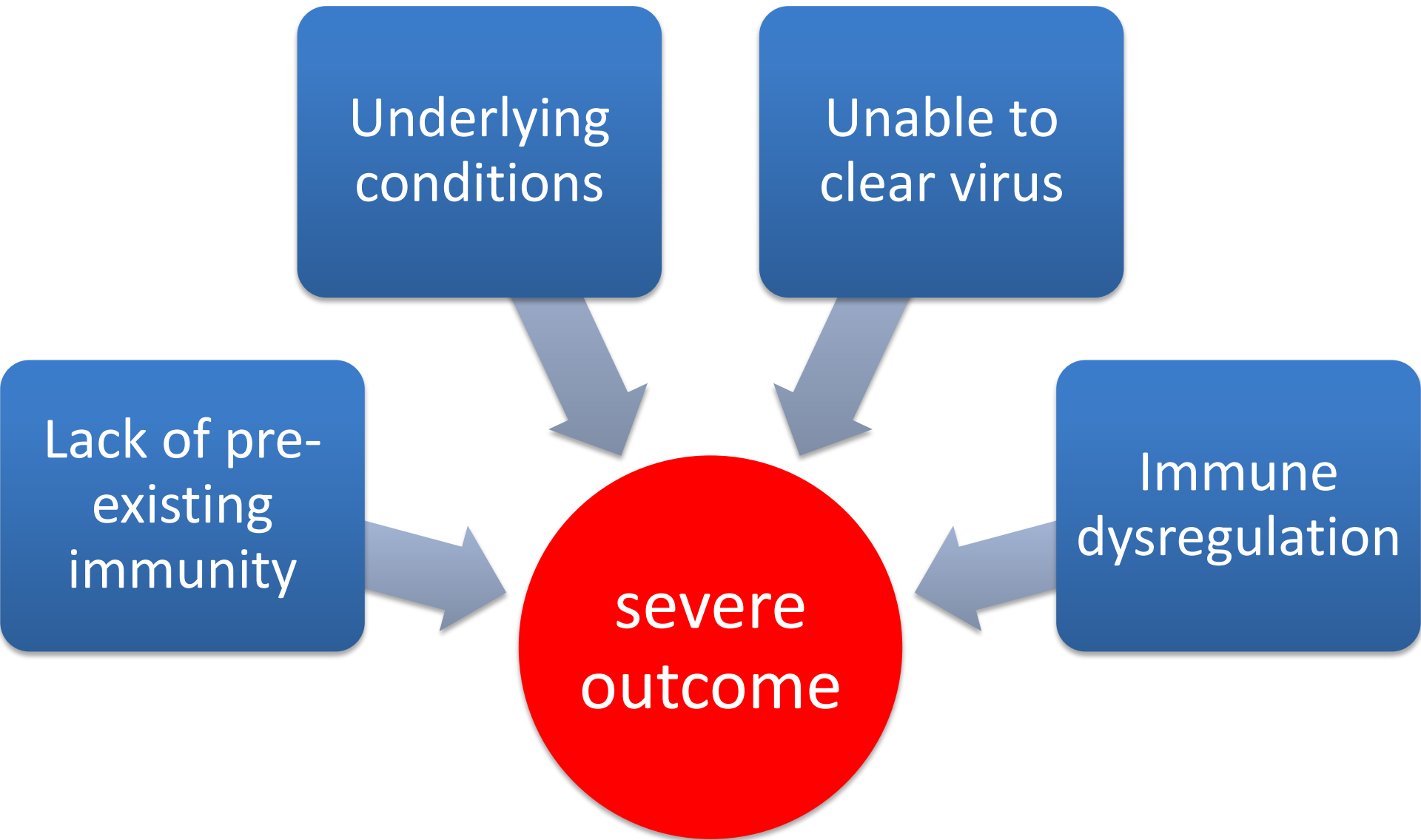
Parameter	Severe cases ^a (<i>n</i> = 38)	Mild cases (<i>n</i> = 36)	<i>P</i> value
IgG level, g/liter			
IgG1, median (range) (normal, 3.65–9.41)	6.55 (1.10–18.00)	6.70 (3.50–12.30)	0.713
IgG2, median (range) (normal, 1.65–5.45)	3.55 (1.10–8.00)	4.75 (2.00–7.95)	0.002
IgG3, median (range) (normal, 0.32–1.16)	0.83 (0.15–4.60)	0.86 (0.32–3.30)	0.689
IgG4, median (range) (normal, 0.06–1.21)	0.54 (0.06–1.85)	0.95 (0.14–3.65)	0.087

TABLE 5. IgHG2 and FcγRIIIa genotypes

Genotype	Severe cases (%) (<i>n</i> = 37)	Mild cases (%) (<i>n</i> = 36)
IgHG2		
n+/n+	18 (48.6)	Not available
n+/n-	14 (37.8)	Not available
n-/n-	5 (13.5)	Not available
FcγRIIIa		
H131H	23 (62.2)	16 (44.4)
H131R	9 (24.3)	17 (47.2)
R131R	5 (13.5)	3 (8.3)

Lower IgG2 level independently associated with:

- Overall cytokine/chemokine level
- Serum globulin level



Underlying conditions

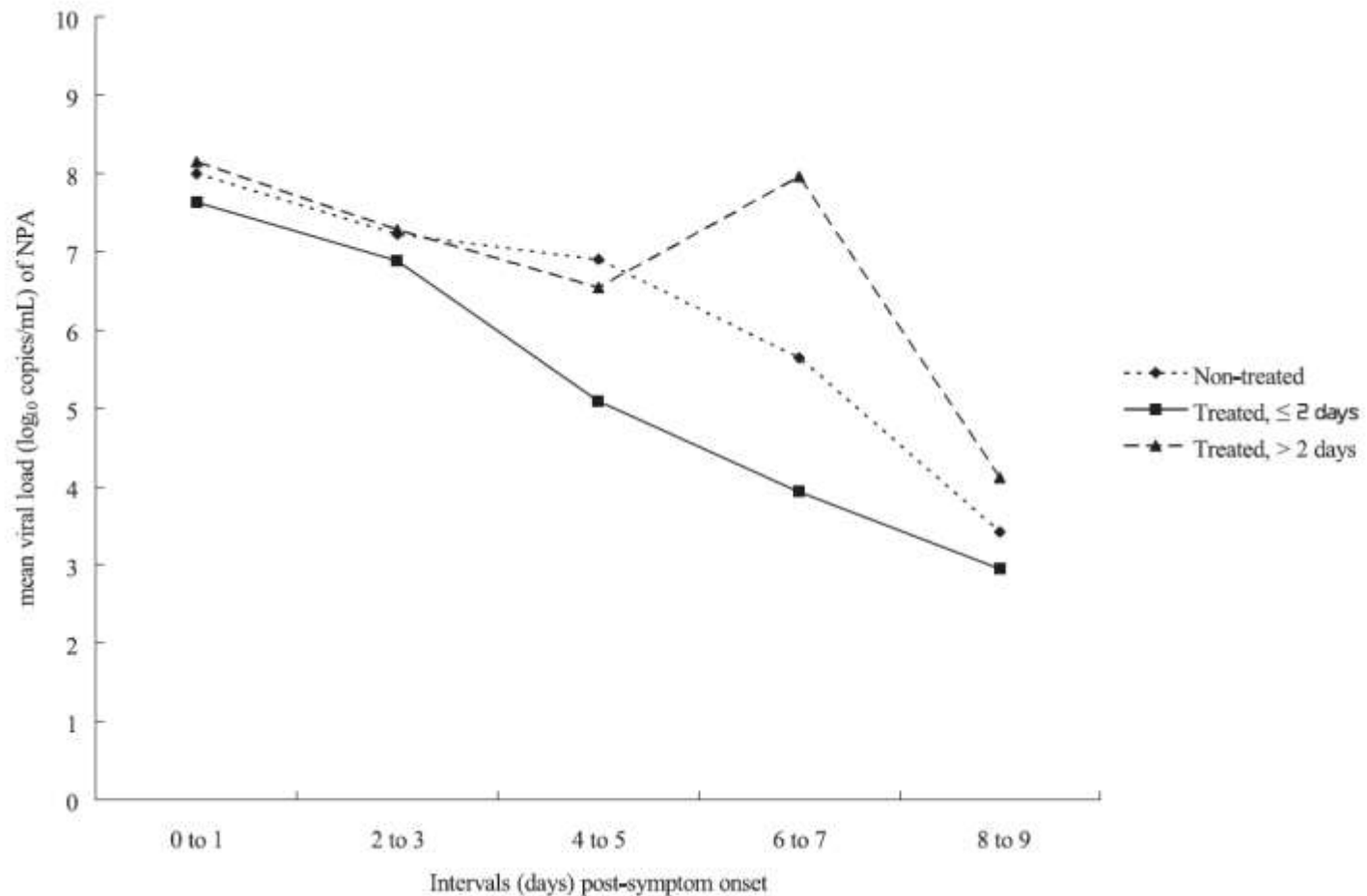
Unable to clear virus

Lack of pre-existing immunity

Immune dysregulation

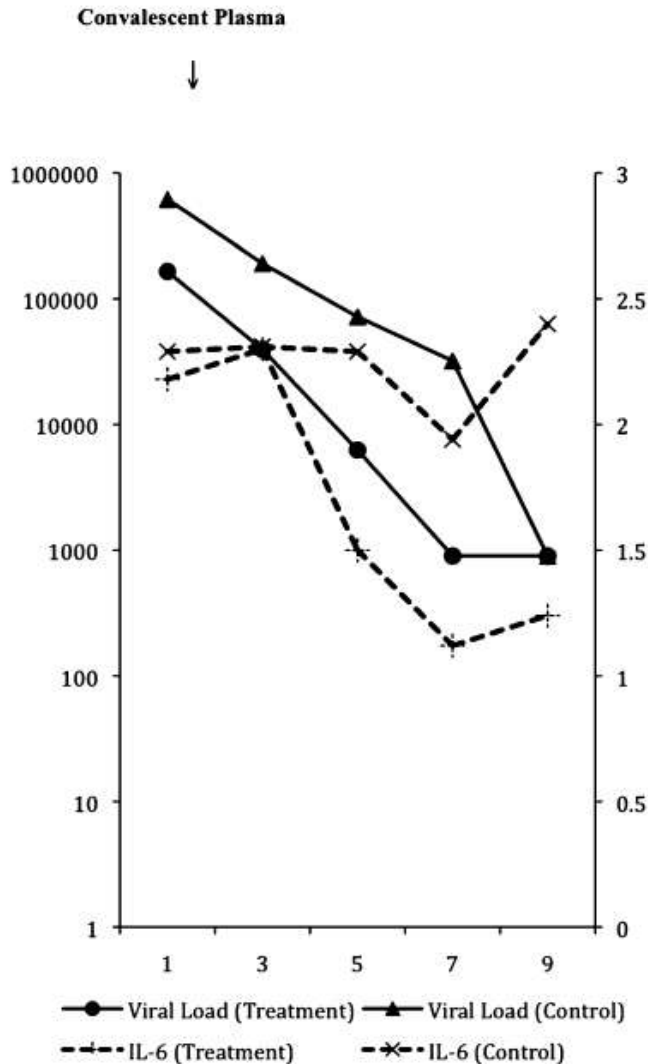
severe outcome

Oseltamivir has limited antiviral activity, especially after 5 days



Convalescent plasma treatment

Viral Load (\log_{10} copies/mL) IL6 Level (\log_{10} pg/mL)



Mortality:

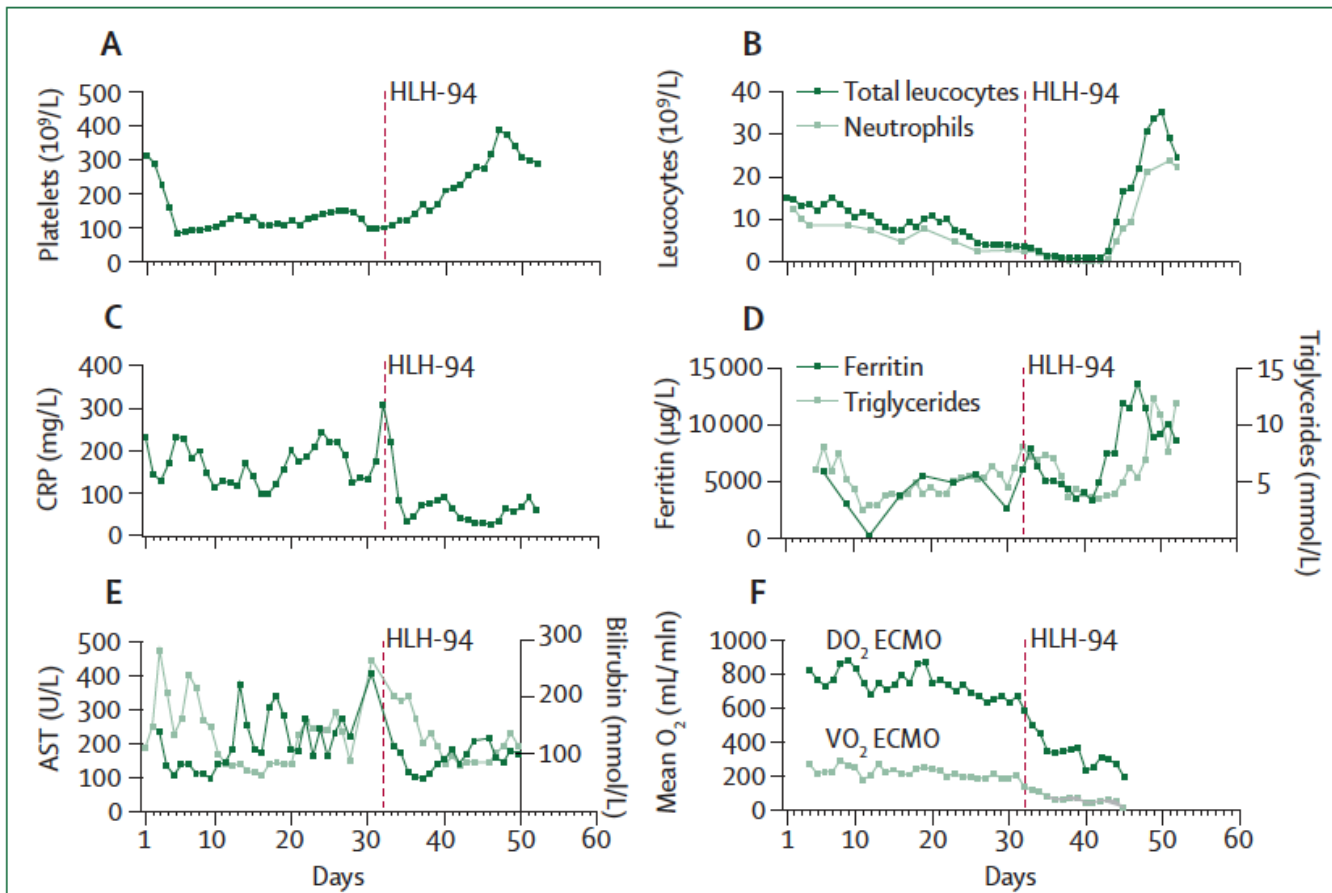
Treatment group:
20%

Control group:
54.8%

Cytotoxic therapy for severe swine flu A/H1N1

Jan-Inge Henter, Kajsa Palmkvist-Kaijser, Bernhard Holzgraefe, Yenan T Bryceson, Kenneth Palmér

Etoposide, betamethasone



Not all immunotherapy works

Accepted Manuscript

Title: Effect of immunomodulatory therapies in patients with pandemic influenza a (h1n1) 2009 complicated by pneumonia

Authors: Diego Viasus, José Ramón Paño-Pardo, Elisa Cordero, Antoni Campins, Francisco López-Medrano, Aroa Villoslada, Maria C. Fariñas, Asunción Moreno, Jesús Rodríguez-Baño, José Antonio Oteo, Joaquín Martínez-Montauti, Julián Torre-Cisneros, Ferrán Segura, Jordi Carratalà



- Anti-inflammatory therapy (corticosteroid, macrolides, statins) did not prevent development of severe disease

Acknowledgement

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- Jasper Chan
- Iris Li
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- Chi-Wai Leung
- Yat-Wah Kwan
- Tak-Keung Ng
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- Cindy W. S. Tse
- Bone S. F. Tang
- Wing-Kin To
- Sandy K. Y. Chau