Emerging infectious disease threats and the ID physicians in Asia

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ORIGINAL ARTICLE

A Major Outbreak of Severe Acute Respiratory Syndrome in Hong Kong

Nelson Lee, M.D., David Hui, M.D., Alan Wu, M.D., Paul Chan, M.D., Peter Cameron, M.D., Gavin M. Joynt, M.D., Anil Ahuja, M.D., Man Yee Yung, B.Sc., C.B. Leung, M.D., K.F. To, M.D., S.F. Lui, M.D., C.C. Szeto, M.D., Sydney Chung, M.D., and Joseph J.Y. Sung, M.D.

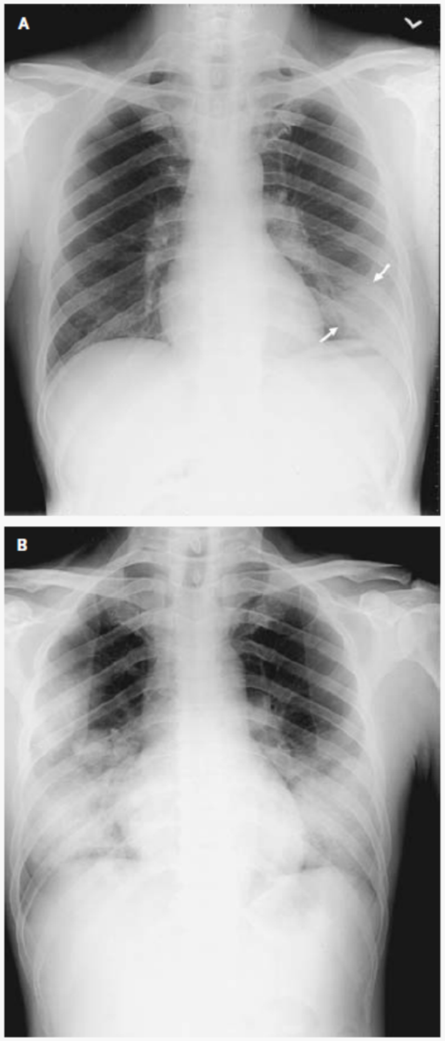


Figure 2. **Frontal Chest Radiographs in a 46-Year-Old Man.**
Panel A shows an obvious area of air-space shadowing (arrows) on the left side. A follow-up chest radiograph showed progression of the disease, with multiple, bilateral areas of involvement (Panel B). A subsequent chest radiograph shows improvement of bilateral lung opacities after therapy (Panel C).

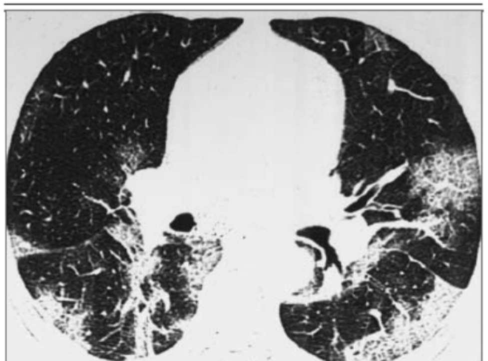
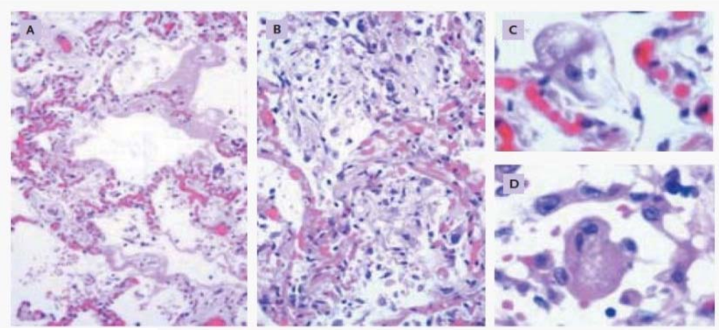


Figure 3. **A High-Resolution CT Scan Showing the Characteristic Ground-Glass Abnormality in a Subpleural Location.**
There is no cavitation. A conventional CT scan did not show pleural effusion or lymphadenopathy.

>138 HCWs, inpatients and students infected

Table 2. **Univariate Analyses of Clinical and Laboratory Variables Associated with the Combined Outcome of ICU Care or Death.***

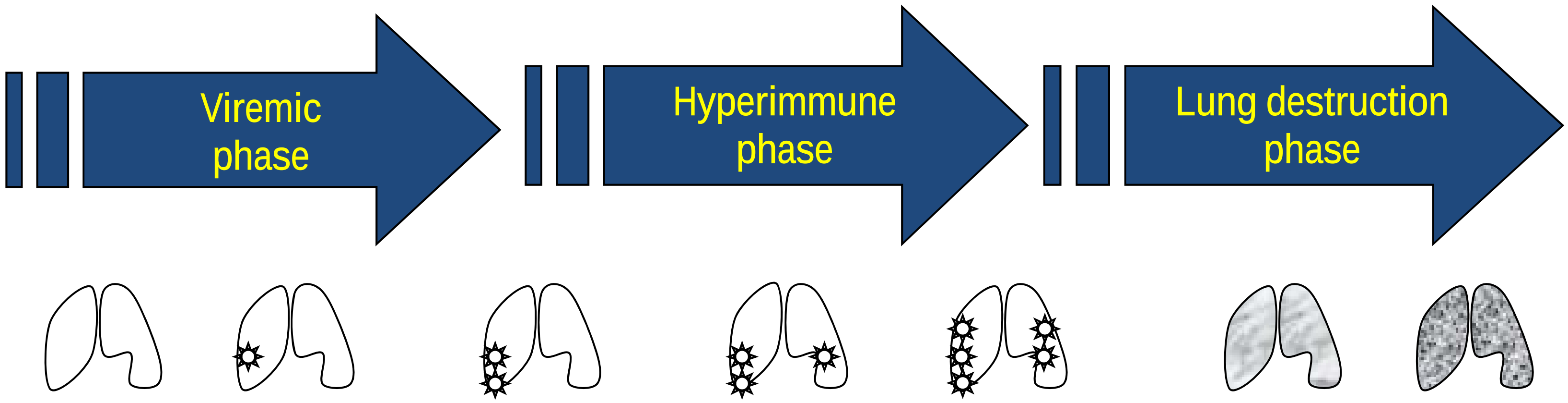
Variable	No ICU Care	ICU Care or Death	P Value
Age (yr)	36.1±14.6	50.2±18.4	0.007
Male sex (%)	41.9	66.7	0.01
Peak D-dimer (ng/ml)	951.0±1197.9	1686.9±2132.3	0.31
Platelets (×10⁻⁹/liter)	156.8±61.2	131.7±64.9	0.06
Neutrophils (×10⁻⁹/liter)	3.7±1.9	4.6±2.1	0.02
Lymphocytes (×10⁻⁹/liter)	0.9±0.7	0.8±0.5	0.49
Activated partial-thromboplastin time (sec)	41.0±7.5	43.6±11.7	0.23
Sodium (mmol/liter)	136.1±2.7	134.0±4.6	0.02
Urea (mmol/liter)	3.8±1.1	7.3±9.6	0.05
Creatinine (μmol/liter)†	86.1±19.4	135.5±218.0	0.21
Alanine aminotransferase (IU/liter)	46.5±81.4	99.4±262.0	0.27
Creatine kinase (U/liter)			
On presentation	268.5±434.8	609.3±973.2	0.06
Peak	352.7±544.0	697.4±971.1	0.04
Lactate dehydrogenase (U/liter)			
On presentation	287.7±143.3	558.0±258.0	<0.001
Peak	310.0±153.8	629.7±283.5	<0.001



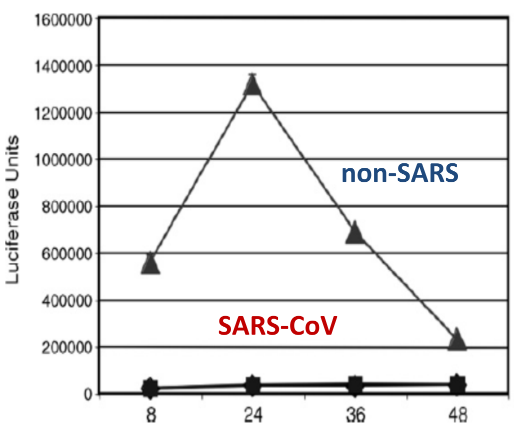
Citation >1900; WHO & CDC/US clinical guidelines

Lee N et al. *NEJM* 2003

SARS: a Tri-phasic Disease

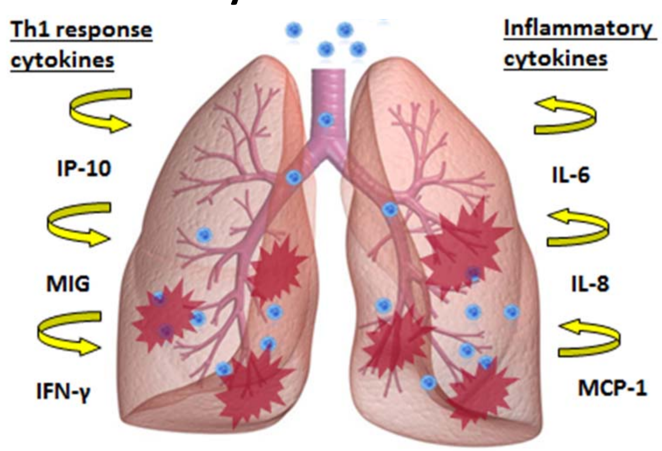


Immune Evasion



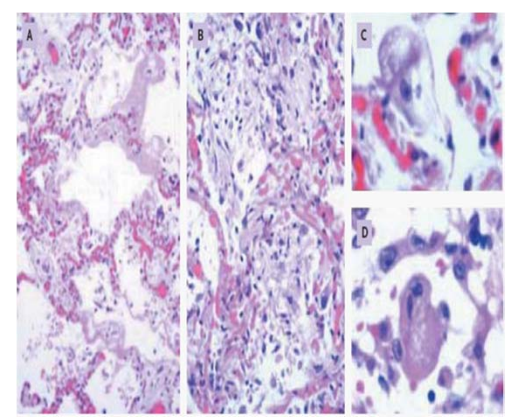
(ineffective Type I IFN responses)

Cytokine storm



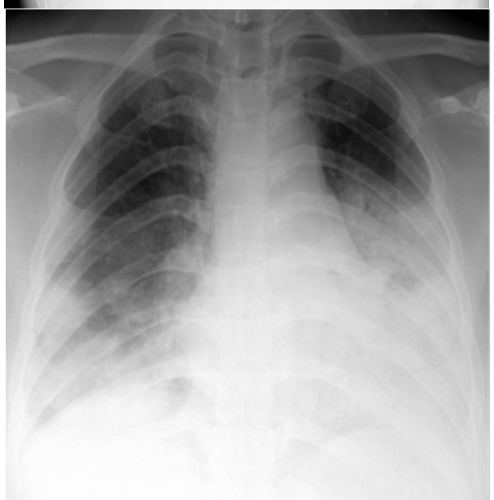
(lymphopenia: CD4↓↓ CD8 ↓↓)

DAD & ARDS

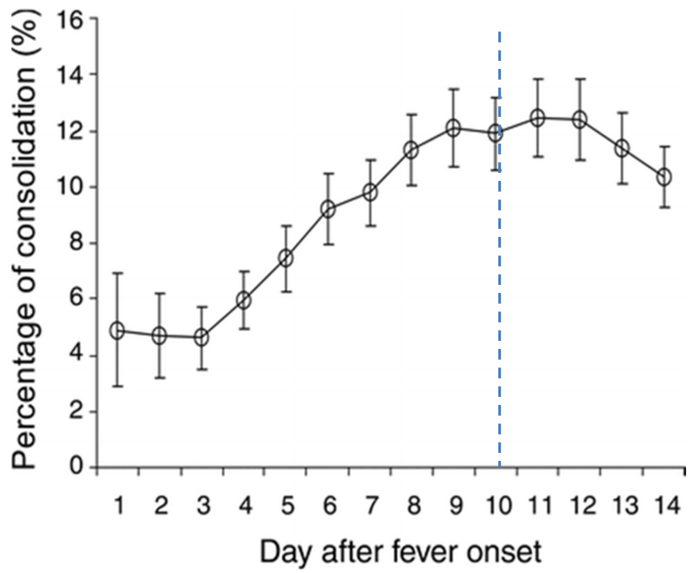


(lung and GI tract viral replic.)

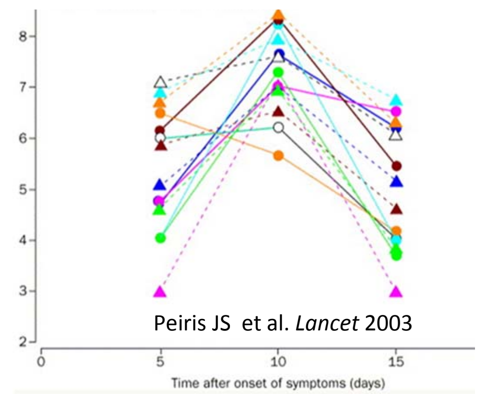
Wong CK, *Clin Exp Immu* 2004; Tang NL, *Clin Chem* 2005; Wong RS, *BMJ* 2003; Tse GM, *J Clin Patho* 2004; Leung WK, *Gastroenterology* 2003; Peiris JSM, *Nature Med* 2004; Cameron MJ, *J Virol* 2007



Radiographic progression, SARS



Pneumonia extent & viral load peak at D10



Peiris JS et al. *Lancet* 2003

Nosocomial transmission

Clinical Outcomes and Radiographic Correlations for 138 Patients with SARS

Radiographic Feature	Patients Who Required ICU Care and/or Died	Surviving Patients Who Did Not Require ICU Care
Extent of consolidation*		
Day 0	3.30 (1.70–8.78)	1.70 (0–3.30)
Day 7	15.00 (6.48–28.73)	5.00 (2.50–7.50)
Number of lung zones involved		
Day 0		
≤1 (n = 89)	14 (15.7)	75 (84.3)
>1 (n = 49)	24 (49)	25 (51)
Day 7		
≤1 (n = 56)	3 (5.4)	53 (94.6)
>1 (n = 82)	35 (42.7)	47 (57.3)
Consolidation at day 0		
Unilateral (n = 67)	13 (19.4)	54 (80.6)
Bilateral (n = 41)	22 (53.7)	19 (46.3)
Chest radiograph		
Type 1 (n = 97)	17 (17.5)	80 (82.5)
Non–type 1 (n = 41)	21 (51.2)	20 (48.8)

Hui DS et al. *Radiology* 2004; Wong KT et al. *Radiology* 2003, 2003

Severe acute respiratory syndrome: report of treatment and outcome after a major outbreak

J J Y Sung, A Wu, G M Joynt, K Y Yuen, N Lee, P K S Chan, C S Cockram, A T Ahuja, L M Yu, V W Wong, D S C Hui

[PWH managed >320 SARS cases]

Thorax 2004;**59**:414–420. doi: 10.1136/thx.2003.014076

Table 1 Clinical response to treatment

	Broad spectrum antimicrobial* (n = 138)	Ribavirin + corticosteroid† (n = 138)	IV methylprednisolone‡ (n = 107)
Sustained response	0 (0)	16 (11.6%)	50 (46.7%)
Partial response	0 (0)	9 (6.5%)	45 (42.1%)
No response	138 (100%)	113 (81.9%)	12 (11.2%)

Early-Phase Clinical Outcomes: 37 patients (26.8%) required admission to the intensive care unit and 21 (15.2%) required invasive mechanical ventilation. There were 15 deaths (mortality rate 10.9%), most with significant co-morbidities, whereas 122 (88.4%) had been discharged

Sung JY et al. *Thorax* 2004; Lee N, et al. *J Clin Virol* 2004; Lee N, Hui DS. *Lancet* 2012

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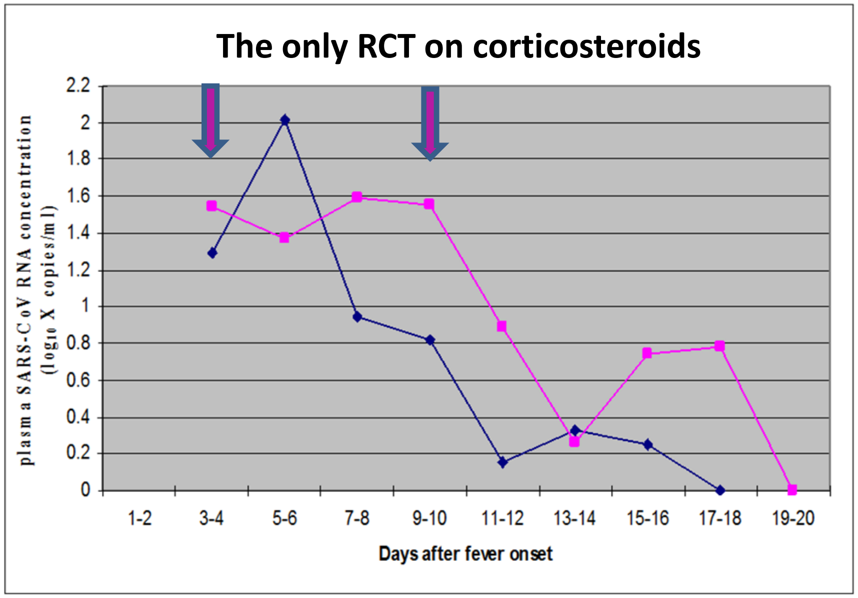


Early corticosteroid treatment may increase viral replication:

→ implications on management of avian influenza (H5N1, H7N9) and MERS-CoV

[WHO guidelines]

Sung JY et al. *Thorax* 2004; Lee N, et al. *J Clin Virol* 2004; Lee N, Hui DS. *Lancet* 2012

The controversies of corticosteroids therapy

PROS	CONS
Clinical & Radiological responses [Sung JJ, Thorax 2004; Chen RC, Chest 2006; Ho JC, AJRCCM 2003]	**Metabolic complications**: hyper-glycaemia, hypertension, hypokalemia [Stockman LJ, PLoS Med 2006]
Suppression of cytokine [Wong CK, Clin Exp Immun 2004; Jones BM, Clin Exp Immun 2004]	**Increased bacterial superinfections** [Ho JC, AJRCCM 2003; Poutanen SM, ICHE 2005; Yap F, Clin Inf Dis 2004]
	Avascular osteonecrosis (AVN) (0.6% if CS use < 3 g) [Griffith JF, Radiol 2005; Hong H, Clin Radiol 2004]
	Reduced viral clearance [Lee N. JCV 2004; WHO 2004]
	Others (e.g. acute psychosis) [Stockman LJ, PLoS Med 2006]

WHO guidelines: low-dose HC for 'septic shock', adrenal insufficiency; clinical trial setting?

-- lower doses? e.g. Pred. 150-250 mg/d

-- later time? e.g. when viral load drops

Chen RC, Chest 2006; Lee N, JCV 2004; Sung JY, Thorax 2004

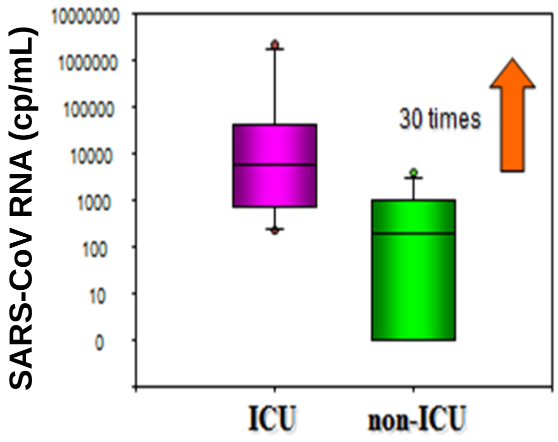
Quantitative Analysis and Prognostic Implication of SARS Coronavirus RNA in the Plasma and Serum of Patients with Severe Acute Respiratory Syndrome

Enders K.O. Ng,[1] David S. Hui,[3] K.C. Allen Chan,[1] Emily C.W. Hung,[2] Rossa W.K. Chiu,[1] Nelson Lee,[3] Alan Wu,[3] Stephen S.C. Chim,[1] Yu K. Tong,[1] Joseph J.Y. Sung,[3] John S. Tam,[4] and Y.M. Dennis Lo[1*]

Clin Chem 2003

Detects viraemia within 3.6 days (WHO endorsed)

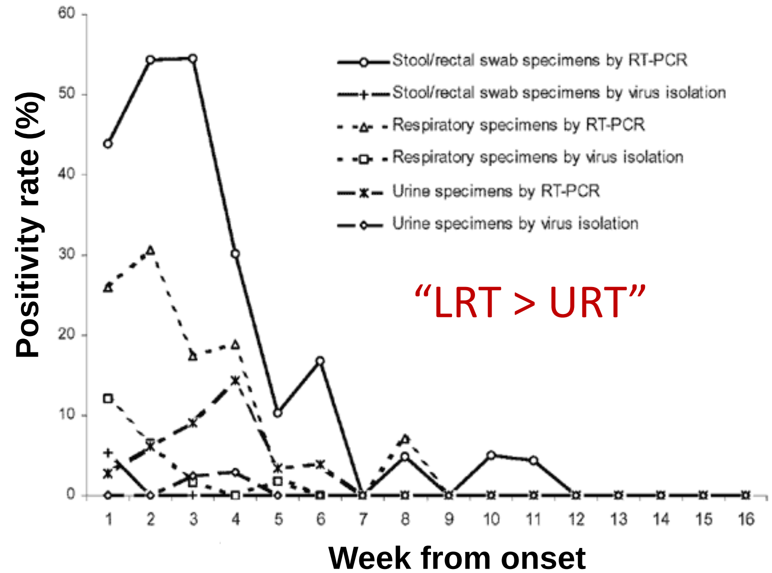
prognostication



Laboratory Diagnosis of SARS

Chan PK, *Emerg Inf Dis* 2004; Ip M, *Clin Infect Dis* 2004

Combination of Upper/Lower respiratory, stool, and blood samples to optimize diagnosis

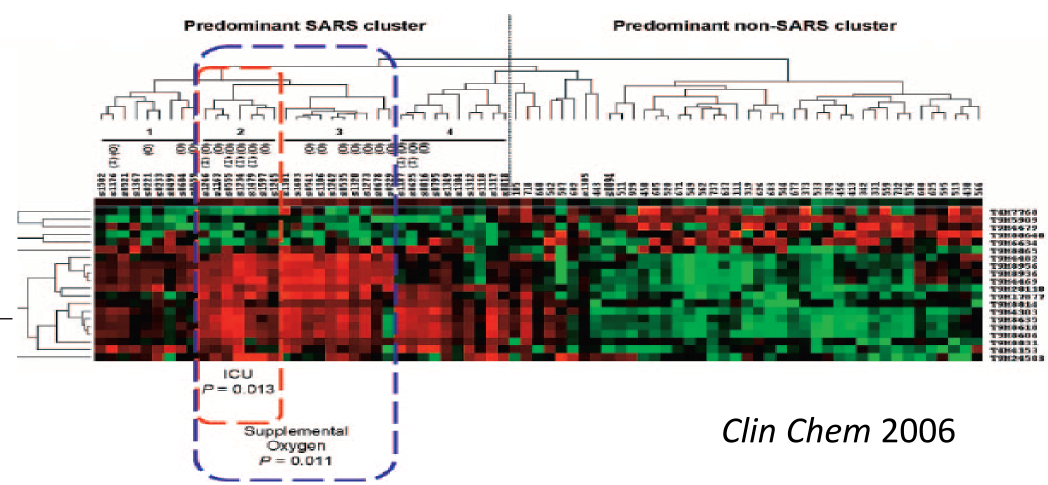


"LRT > URT"

Serum Proteomic Fingerprints of Adult Patients with Severe Acute Respiratory Syndrome

Ronald T.K. Pang,[1,2] Terence C.W. Poon,[1,2*] K.C. Allen Chan,[1,3] Nelson L.S. Lee,[2] Rossa W.K. Chiu,[1,3] Yu-Kwan Tong,[1,3] Ronald M.Y. Wong,[2] Stephen S.C. Chim,[3] Sai M. Ngai,[4] Joseph J.Y. Sung,[1,2] and Y.M. Dennis Lo[1,3]

Pathogenesis (e.g. complement activation), diagnosis, prognostication



Clin Chem 2006

Disease transmission

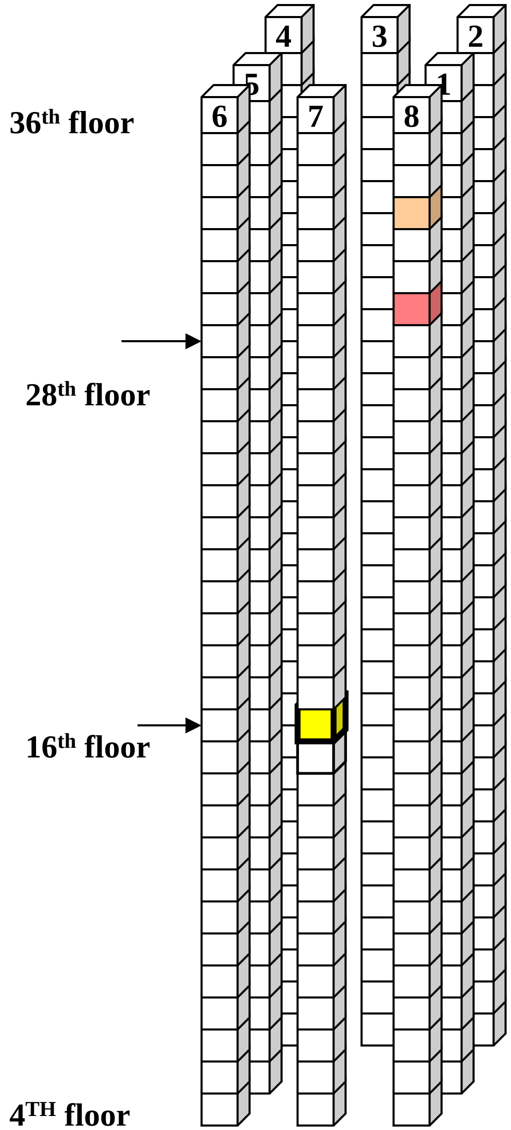
Hotel 'Metropole'

Estate 'Amoy Garden'

Amoy Gardens SARS Outbreak
Block E

Cumulative Cases per Apartment By Day of Disease Onset

21st Mar, 2003



Apartment Number

(Same on each floor)

0 cases

1 case

2 cases

3 cases

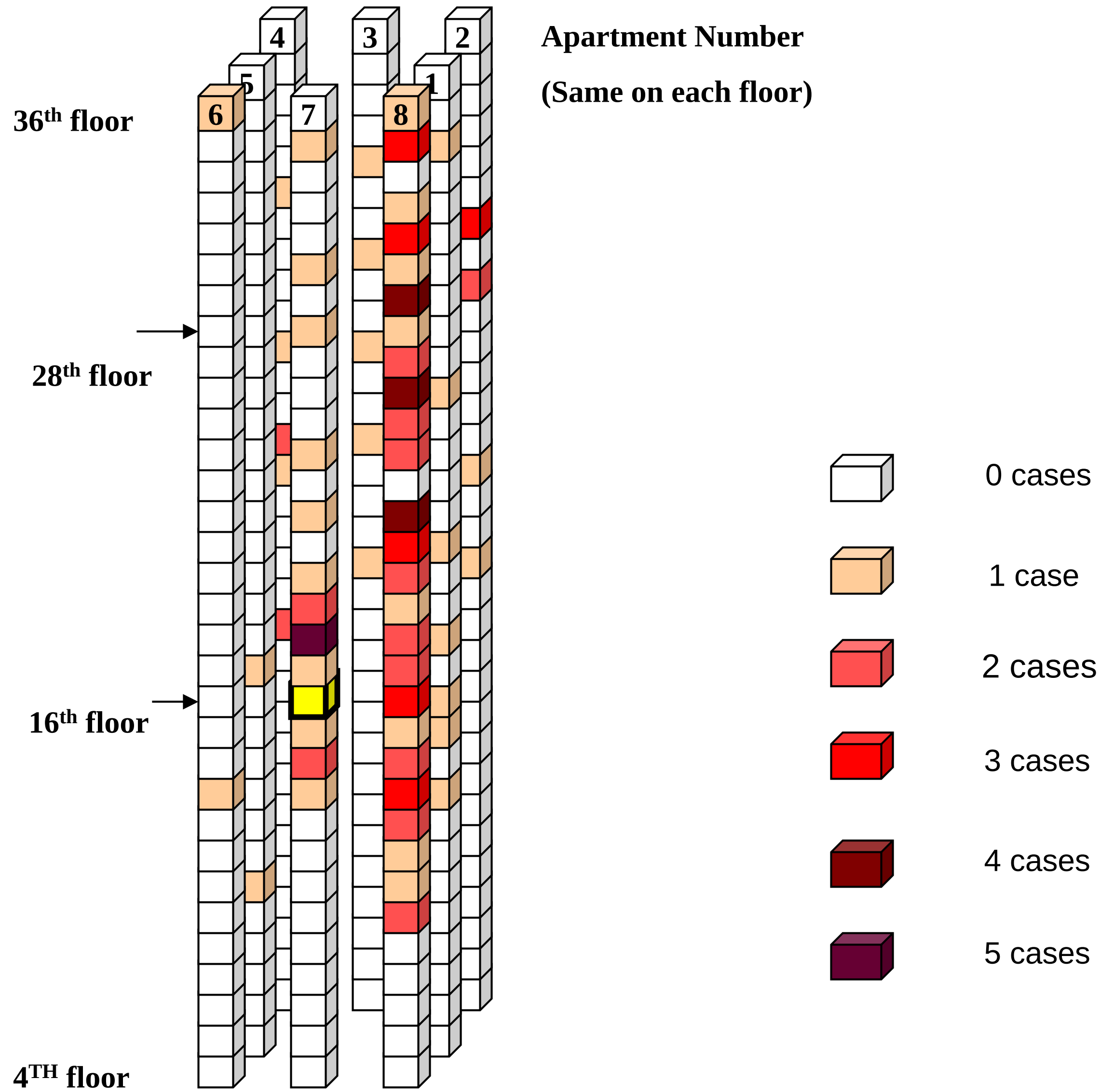
4 cases

Index case/apartment

Amoy Gardens SARS Outbreak
Block E

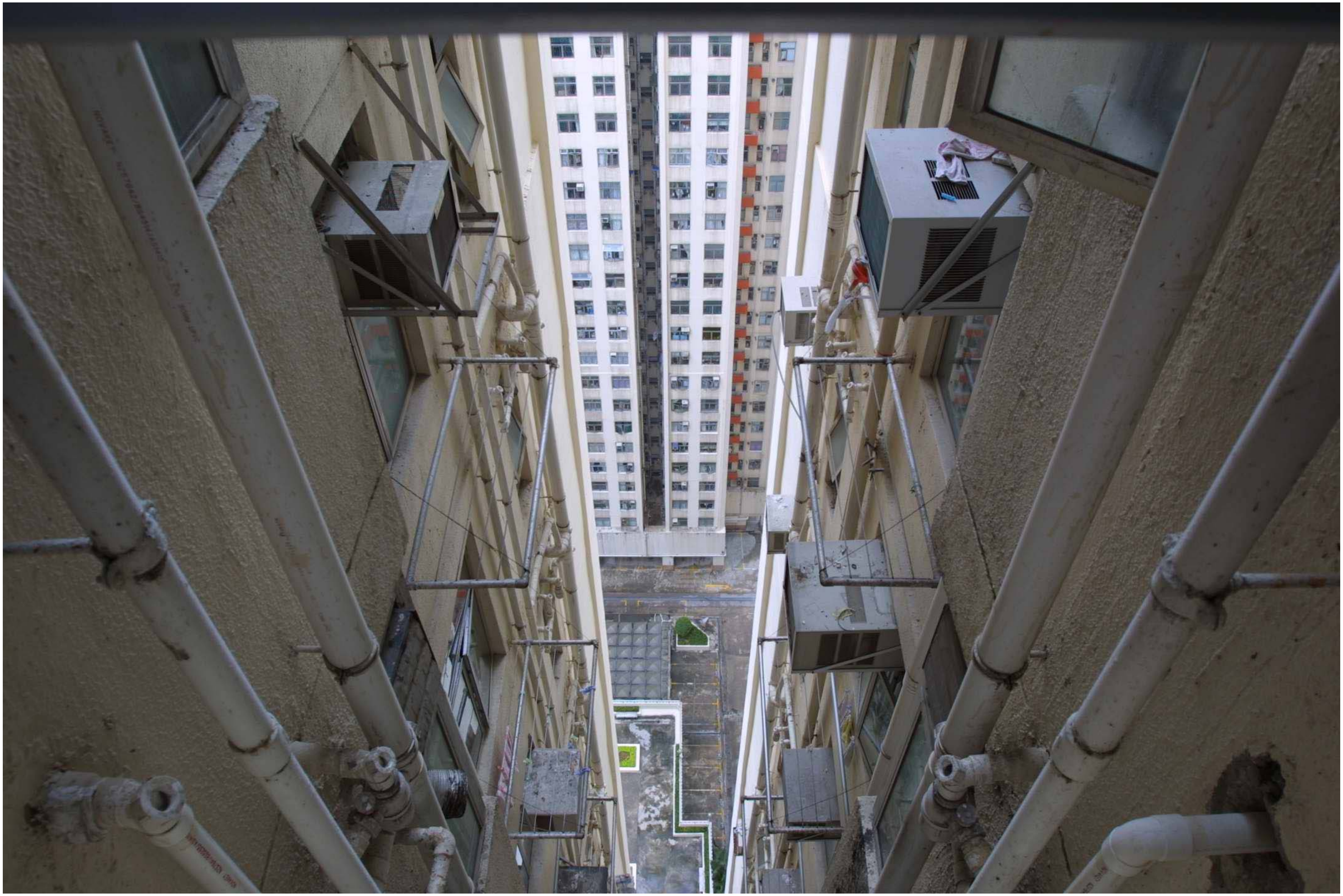
Cumulative Cases per Apartment By Day of Disease Onset

28th Mar, 2003



Index case/apartment

Re-entrant of infectious aerosols



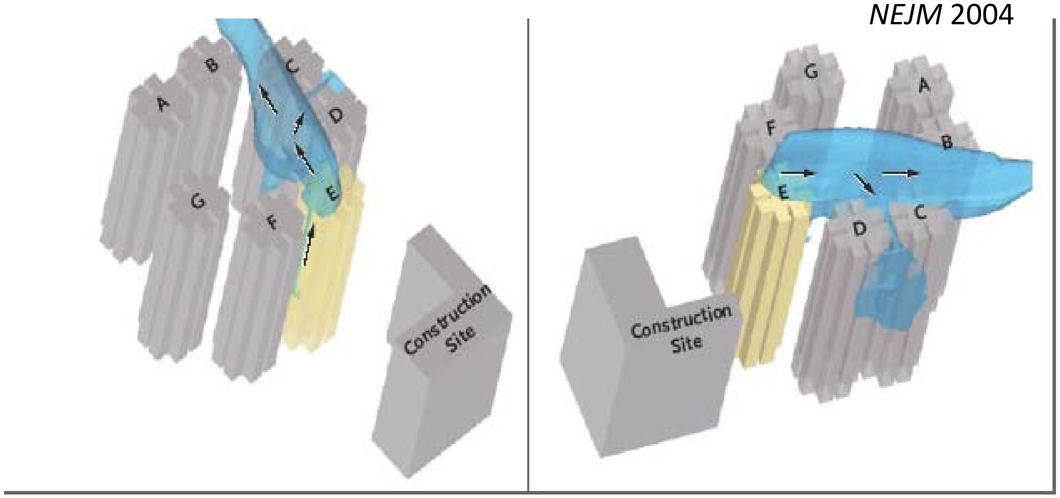
'Super-spreading events'

ORIGINAL ARTICLE

Evidence of Airborne Transmission of the Severe Acute Respiratory Syndrome Virus

Ignatius T.S. Yu, M.B., B.S., M.P.H., Yuguo Li, Ph.D., Tze Wai Wong, M.B., B.S., Wilson Tam, M.Phil., Andy T. Chan, Ph.D., Joseph H.W. Lee, Ph.D., Dennis Y.C. Leung, Ph.D., and Tommy Ho, B.Sc.

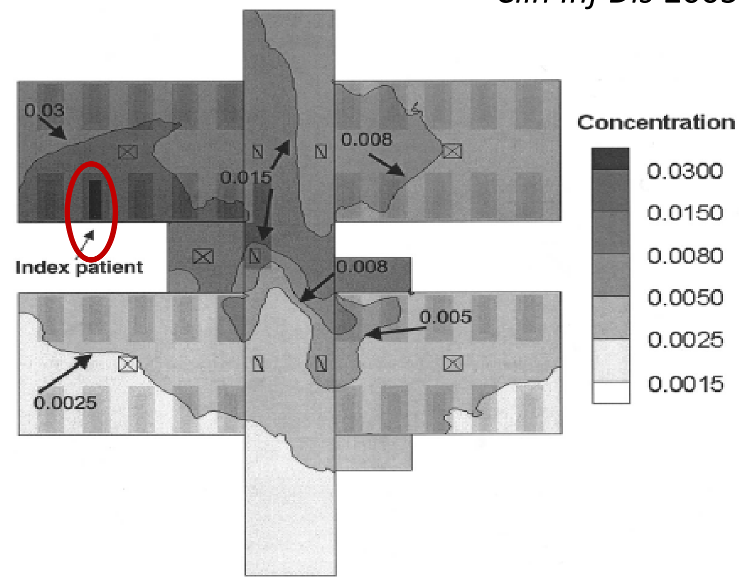
NEJM 2004



Temporal-Spatial Analysis of Severe Acute Respiratory Syndrome among Hospital Inpatients

Ignatius T. S. Yu,[1] Tze Wai Wong,[1] Yuk Lan Chiu,[1] Nelson Lee,[2] and Yuguo Li[3]

Clin Inf Dis 2005



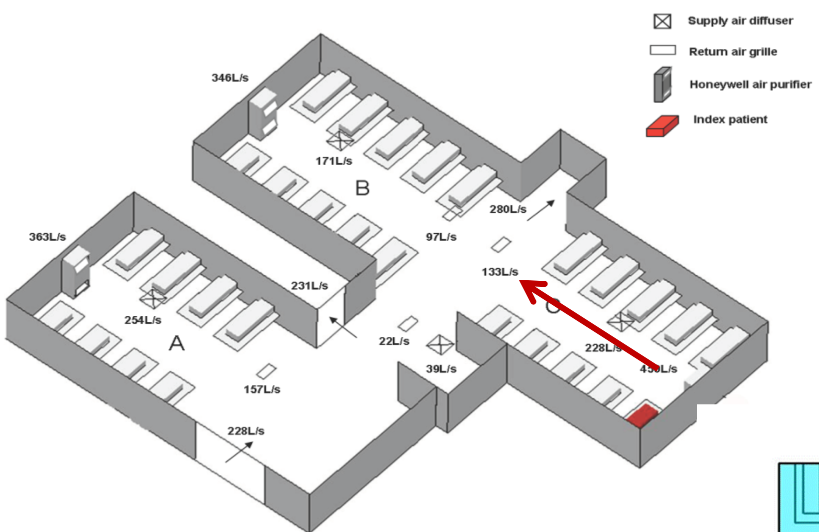
‘Super-spreading events’

Airborne transmission of influenza

Possible Role of Aerosol Transmission in a Hospital Outbreak of Influenza

Clin Infect Dis 2010

Bonnie C. K. Wong,[1] Nelson Lee,[1] Yuguo Li,[4] Paul K. S. Chan,[2] Hong Qiu,[3] Zhiwen Luo,[4] Raymond W. M. Lai,[2] Karry L. K. Ngai,[2] David S. C. Hui,[1] K. W. Choi,[1] and Ignatius T. S. Yu[3]



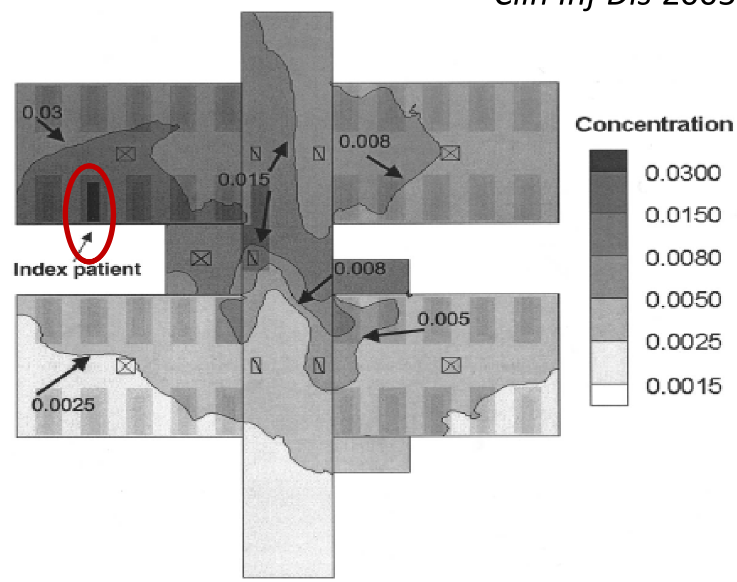
Computational fluid dynamics modeling

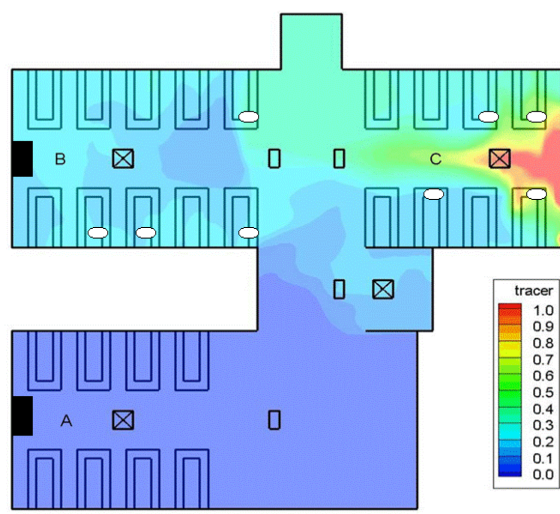
“International Young Investigator Award”
Infectious Diseases Society of America (IDSA) conference, 2010

Temporal-Spatial Analysis of Severe Acute Respiratory Syndrome among Hospital Inpatients

Ignatius T. S. Yu,[1] Tze Wai Wong,[1] Yuk Lan Chiu,[1] Nelson Lee,[2] and Yuguo Li[3]

Clin Inf Dis 2005





9 infected patients

distributed along airborne virus gradient

Emerging Infectious Diseases

MERS-CoV: the new SARS?

SARS-CoV

- Origin: bats virus
- Intermediate host: civet cat?
- >30 countries affected
- total no. of cases 8096
- R_0 2.2-3.7
  - nosocomial outbreaks √
  - super-spreading events
- pneumonia, ARDS
- no. of deaths 774 (9.6%)
  - range 6-16%
- ICU admission 15-25%

MERS-CoV

- Origin: bat virus
- Intermediate host: camels?
- >10 middle-east countries
- total no. of cases >700
- R_0 ?
  - nosocomial outbreaks √
  - super-spreading events?
- pneumonia, ARDS, renal failure
- no. of deaths >200 (~30-50%)
- 'majority have comorbid illnesses and critically ill'

WHO 2004, 2013
Lee N. *Crit Care Clinics* 2013

Infectious Disease Units, Hong Kong

2004-2014: we managed & studied >4000 influenza cases

[Lee N et al, *Antiv Ther* 2007; *Clin Infect Dis* 2010; *Thorax* 2010; *J Infect Dis* 2011, etc.]

We reported:

- clinical manifestations
- complications, outcomes
- antiviral effectiveness
- pathogenesis, virokinetics

in adults hospitalized for severe influenza

- annual seasonal flu
- 2009/2010 H1N1 pandemic
- 2013/2014 H7N9 epidemic

[IDSA 2010; CDC 2011-13; WHO/*NEJM* 2010; *UpToDate* 2011-13]

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[IDSA 2010; CDC 2011-13; WHO/*NEJM* 2010; *UpToDate* 2011-13]

Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

Recommendations and Reports / Vol. 60 / No. 1 January 21, 2011

Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

26. Lee N, Chan PK, Choi KW, et al. Factors associated with early hospital discharge of adult influenza patients. Antivir Ther 2007;12:501–8.
27. Lee N, Cockram CS, Chan PKS, et al. Antiviral treatment for patients hospitalized with severe influenza infection may affect clinical outcomes. Clin Infect Dis 2008;46:1323–4.

35. Wong BC, Lee N, Li Y, et al. Possible role of aerosol transmission in a hospital outbreak of influenza. Clin Infect Dis 2010;51:1176–83.

43. Lee N, Chan PK, Hui DS, et al. Viral loads and duration of viral shedding in adult patients hospitalized with influenza. J Infect Dis 2009;200:492–500.

150. Lee N, Choi KW, Chan PK, et al. Outcomes of adults hospitalised with severe influenza. Thorax 2010;65:510–5.

CDC Centers for Disease Control and Prevention

CDC 24/7: Saving Lives. Protecting People.™

Interim Guidance on the Use of Antiviral Agents for Treatment of Human Infections with Avian Influenza A (H7N9)

Viral Loads and Duration of Viral Shedding in Adult Patients Hospitalized with Influenza

The Journal of Infectious Diseases

The Journal of Infectious Diseases 2009; 200:492–500

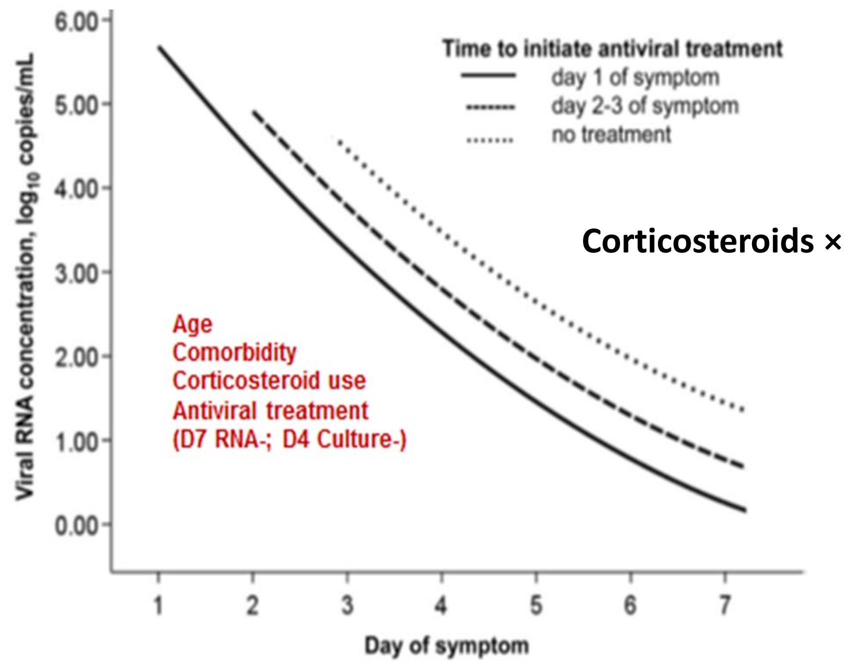
Nelson Lee,[1,3] Paul K. S. Chan,[2,3] David S. C. Hui,[1,3] Timothy H. Rainer,[4] Eric Wong,[5] Kin-Wing Choi,[1] Grace C. Y. Lui,[1] Bonnie C. K. Wong,[1] Rita Y. K. Wong,[1] Wai-Yip Lam,[2] Ida M. T. Chu,[2] Raymond W. M. Lai,[2] Clive S. Cockram,[1] and Joseph J. Y. Sung[1,3]

- **Hospitalized patients > outpatients**
  [~1.5 $\log_{10}$copies/mL; P<0.01]
- **Correlation with symptom scores and complications**:
  [Spearman's ρ, +0.22; P=0.01]
- **Slow clearance in compromised host**
  [β +0.77, P=0.032]
- **Poorer response in influenza B**
  [30% vs 67%; P=0.01]

N=147

Variable affecting viral concentration	β (95% CI)	SE	*P*
Day from symptom onset (continuous)	−0.457 (−0.668 to −0.246)	0.107	<.001
Comorbidity, major (yes vs no)	+0.765 (+0.065 to +1.465)	0.354	.032
Antiviral initiated (yes vs no)	−0.899 (−1.592 to −0.206)	0.351	.011

Antiviral treatment improves viral clearance



Variable	Patients with viral RNA detected at symptom day 7, %	*P*	Patients with virus isolated on symptom day ≥4, %	*P*
Oseltamivir initiation time				
Day 1–2	14.3	.004	2.3	<.001
Day 3–4	35.3		18.2	
Not received	57.1		38.5	

Antiviral treatment improves patient survival
Evidence of effectiveness with later treatment >48 h

Outcomes of adults hospitalised with severe influenza

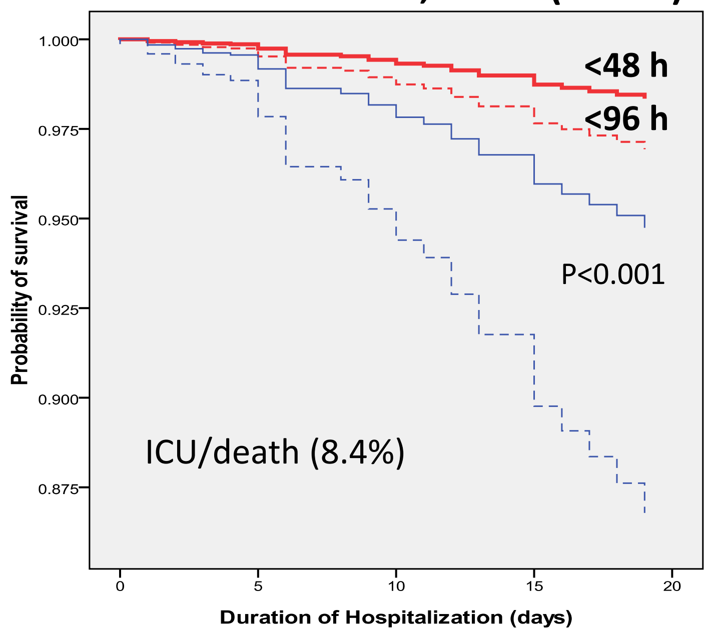
N Lee,[1] K W Choi,[1] P K S Chan,[2] D S C Hui,[1] G C Y Lui,[1] B C K Wong,[1] R Y K Wong,[1] W Y Sin,[1] W M Hui,[1] K L K Ngai,[2] C S Cockram,[1] R W M Lai,[2] J J Y Sung[1]

Thorax 2010;**65**:510–515.

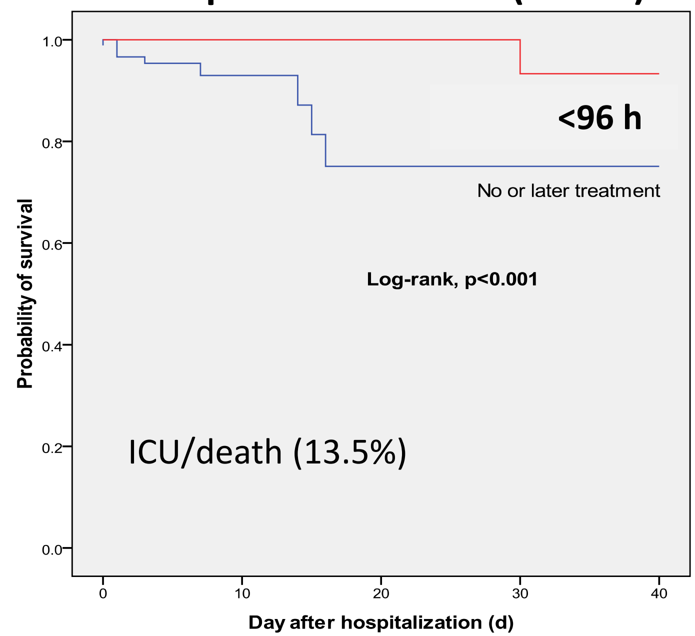
Complications and Outcomes of Pandemic 2009 Influenza A (H1N1) Virus Infection in Hospitalized Adults: How Do They Differ From Those in Seasonal Influenza?

The Journal of Infectious Diseases 2011;203:1739–47

Seasonal Influenza, H3N2 (n=754)



H1N1pdm09 influenza (n=382)



Antiviral within 4 days: ~73% ↓ in mortality risk (~20% ↑ in risk per day delay); shorten O_2 therapy and hospital LOS (-30%); bacterial superinfection x2 mortality risk

MAJOR ARTICLE

A Prospective Intervention Study on Higher-Dose Oseltamivir Treatment in Adults Hospitalized With Influenza A and B Infections

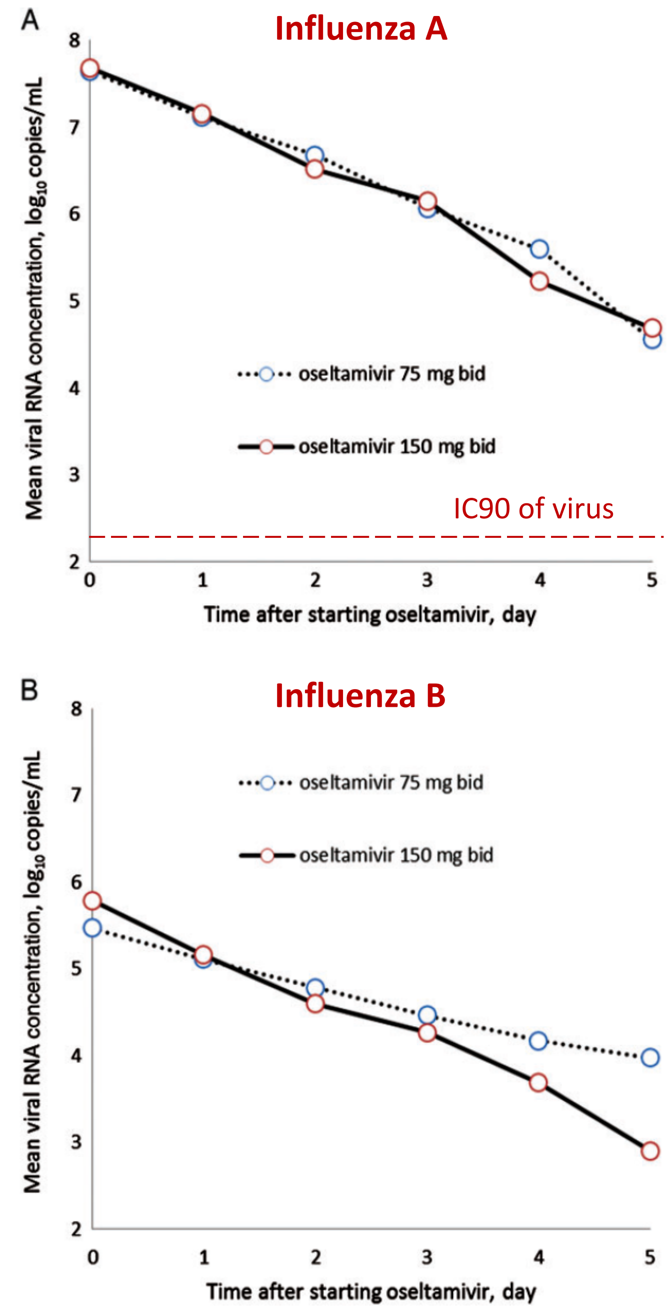
N. Lee,[1,2] D. S. C. Hui,[1,2] Z. Zuo,[3] K. L. K. Ngai,[4] G. C. Y. Lui,[1] S. K. Wo,[3] W. W. S. Tam,[5] M. C. W. Chan,[4] B. C. K. Wong,[1] R. Y. K. Wong,[1] K. W. Choi,[1] W. W. Y. Sin,[1] E. L. Y. Lee,[1] B. Tomlinson,[1] F. G. Hayden,[6] and P. K. S. Chan[2,4]

Clinical Infectious Diseases 2013;57(11):1511–9

(n=155)

No advantage of double-dose (150mg bid) oseltamivir over conventional dosage (75mg bid) in influenza A (H3N2, pH1N1)

Improves viral clearance in influenza B



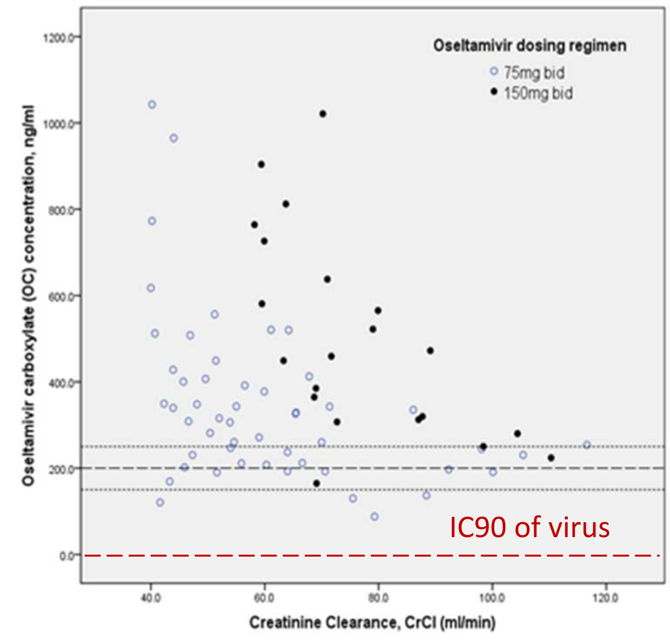
MAJOR ARTICLE

A Prospective Intervention Study on Higher-Dose Oseltamivir Treatment in Adults Hospitalized With Influenza A and B Infections

N. Lee,[1,2] D. S. C. Hui,[1,2] Z. Zuo,[3] K. L. K. Ngai,[4] G. C. Y. Lui,[1] S. K. Wo,[3] W. W. S. Tam,[5] M. C. W. Chan,[4] B. C. K. Wong,[1] R. Y. K. Wong,[1] K. W. Choi,[1] W. W. Y. Sin,[1] E. L. Y. Lee,[1] B. Tomlinson,[1] F. G. Hayden,[6] and P. K. S. Chan[2,4]

Clinical Infectious Diseases 2013;57(11):1511–9

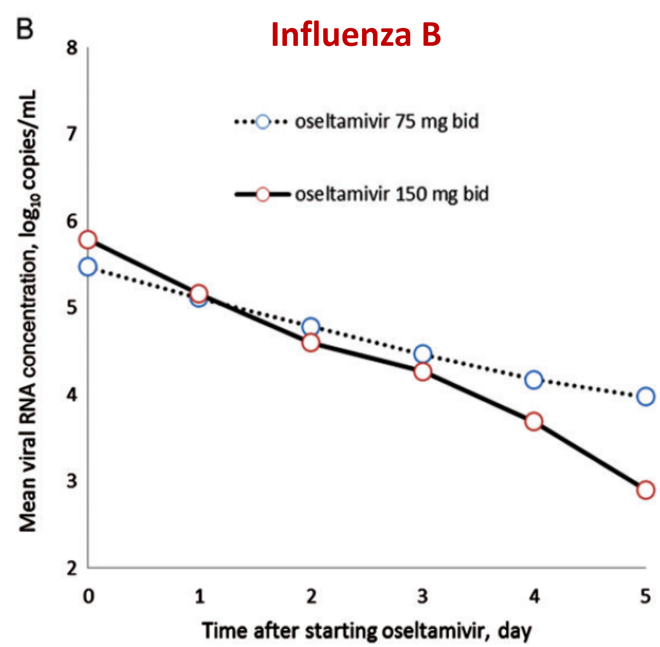
(n=155)

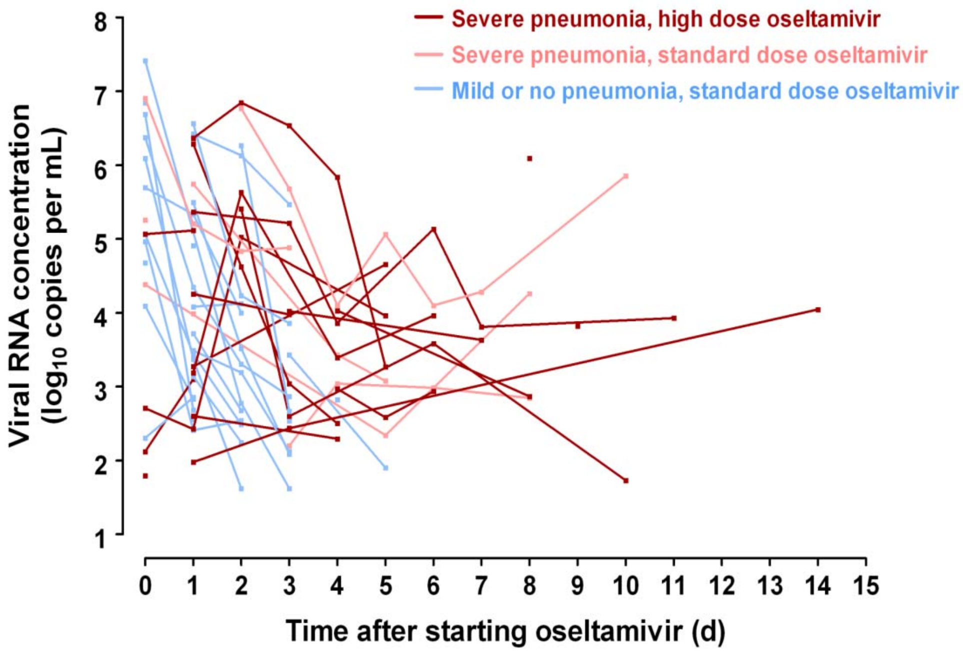


No advantage of double-dose (150mg bid) oseltamivir over conventional dosage (75mg bid) in influenza A (H3N2, pH1N1)

Improves viral clearance in influenza B

~40% PCR+ at treatment end; therapy >5 days may be necessary in severe cases

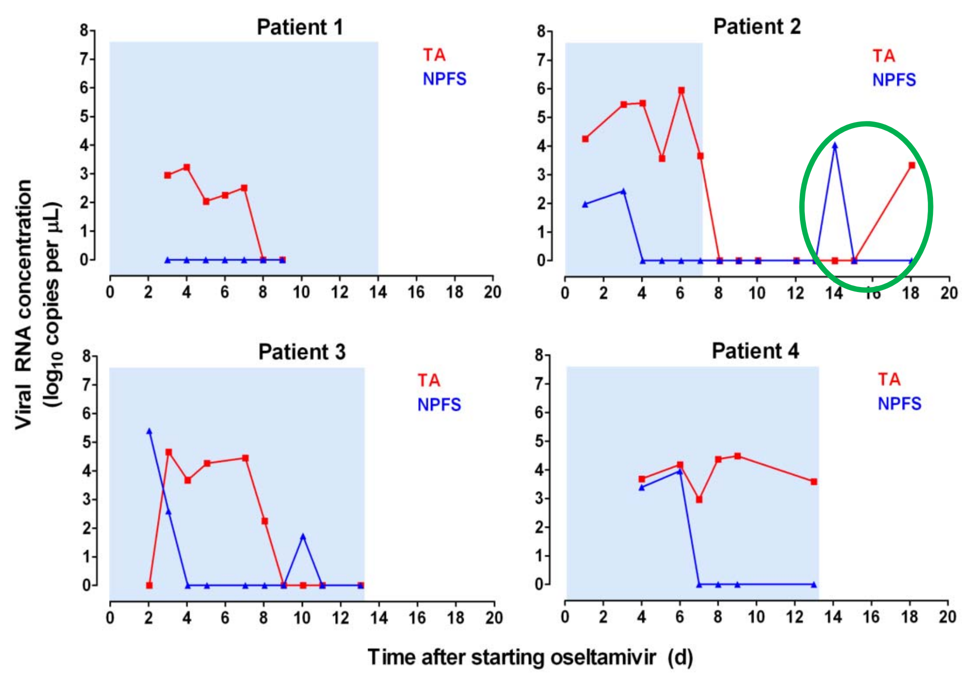




pH1N1 influenza pneumonia

Viral replication continues beyond 5 days of treatment

Lee N et al. *Antiv Ther* 2011



Longer duration in the lower respiratory tract and lung

- Antiviral treatment >10 days
- False-ve URT sample

Cited by WHO. *NEJM* 2010

MAJOR ARTICLE

Determinants of Antiviral Effectiveness in Influenza Virus A Subtype H5N1

Paul K. S. Chan,[1] Nelson Lee,[1] Mukhtiar Zaman,[3] Wiku Adisasmito,[4] Richard Coker,[5] Wanna Hanshaoworakul,[7] Viktor Gasimov,[8] Ahmet Faik Oner,[9] Nazim Dogan,[10] Owen Tsang,[2] Bounlay Phommasack,[11] Sok Touch,[12] Ebun Bamgboye,[13] Anna Swenson,[14] Stephen Toovey,[6] and Nancy A. Dreyer[14]

J Infect Dis 2012

Effectiveness of Antiviral Treatment in Human Influenza A(H5N1) Infections: Analysis of a Global Patient Registry

Wiku Adisasmito,[1] Paul K. S Chan,[2] Nelson Lee,[2] Ahmet Faik Oner,[3] Viktor Gasimov,[5] Faik Aghayev,[6] Mukhtiar Zaman,[7] Ebun Bamgboye,[8] Nazim Dogan,[4] Richard Coker,[10] Kathryn Starzyk,[9] Nancy A. Dreyer,[9] and Stephen Toovey[11]

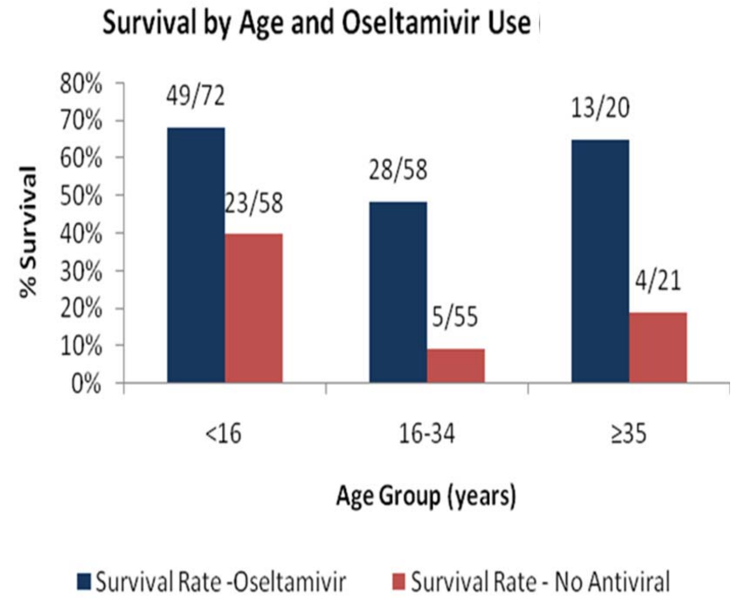
J Infect Dis 2010

H5N1 Avian Influenza in Children

Ahmet Faik Oner,[1] Nazim Dogan,[2] Viktor Gasimov,[3] Wiku Adisasmito,[4] Richard Coker,[5] Paul K. S. Chan,[7] Nelson Lee,[7] Owen Tsang,[8] Wanna Hanshaoworakul,[9] Mukhtiar Zaman,[10] Ebun Bamgboye,[11] Anna Swenson,[12] Stephen Toovey,[6] and Nancy A. Dreyer[12]

Clin Infect Dis 2012

(N >400)



H5N1 disease

(1) Limited human-to-human transmission
(2) children 0-5 yrs have lowest death risk
(3) antiviral effectiveness shown within 6-8 days from onset;
(4) unless complicated by ARDS ('cytokine storm')

Dexamethasone in community-acquired pneumonia

*Nelson Lee, David S C Hui

The Lancet 2011

Evidence suggests that use of corticosteroids in influenza virus pneumonia:

1. cannot control excessive inflammation, but
2. compromises the immune response, leading to longer viral shedding, secondary bacterial and fungal infections, and
3. increased mortality

Clinical reports	Findings
Lee N et al.[4] (n=147)	Seasonal influenza; slowed viral clearance
Boudreault AA et al. (n=143)	Seasonal influenza; slowed viral clearance
Giannella M et al. (n=64)	2009 A/H1N1 ; slowed viral clearance
Brun-Buisson C et al.[3] (n=208)	2009 A/H1N1; increased mortality, increased secondary infections, longer duration of ventilation*
Kim SH et al. (n=245)	2009 A/H1N1; increased mortality, increased secondary infections, longer duration of ventilation and ICU care
Xi X et al. (n=155)	2009 A/H1N1; increased mortality, increased secondary infections
Han Ke et al. (n=83)	2009 A/H1N1; increased risk of progression to critical illness and death
Viasus D et al. (n=197)	2009 A/H1N1; no benefit in preventing progression, longer time to clinical stability, increased secondary infections
Martin-Loeches I et al. (n=220)	2009 A/H1N1; no benefit in preventing progression, increased secondary infections
Liem NT et al. (n=67)	H5N1; increased mortality
Hien ND et al. (n=29)	H5N1; no benefit in preventing progression**

www.thelancet.com Vol 378 September 10, 2011

"Alternative immunomodulatory agent is needed"

Hui DS & Lee N. Antiv Res 2013; IORV 2013

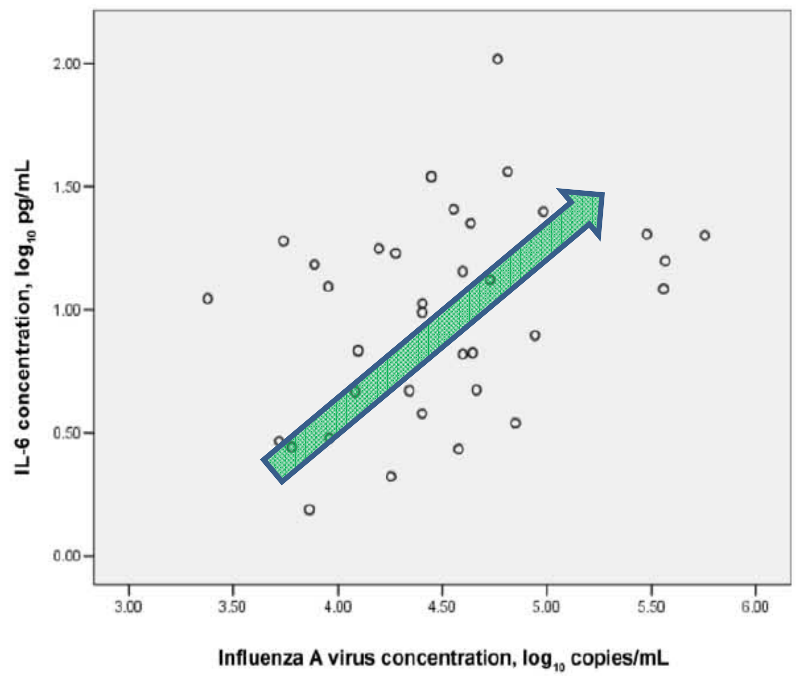
Hypercytokinemia and Hyperactivation of Phospho-p38 Mitogen-Activated Protein Kinase in Severe Human Influenza A Virus Infection

N. Lee,[1,a] C. K. Wong,[2,a] P. K. S. Chan,[3,4] S. W. M. Lun,[2] G. Lui,[1] B. Wong,[1] D. S. C. Hui,[1,4] C. W. K. Lam,[2] C. S. Cockram,[1,4] K. W. Choi,[1] A. C. M. Yeung,[3] J. W. Tang,[3] and J. J. Y. Sung[1,4]

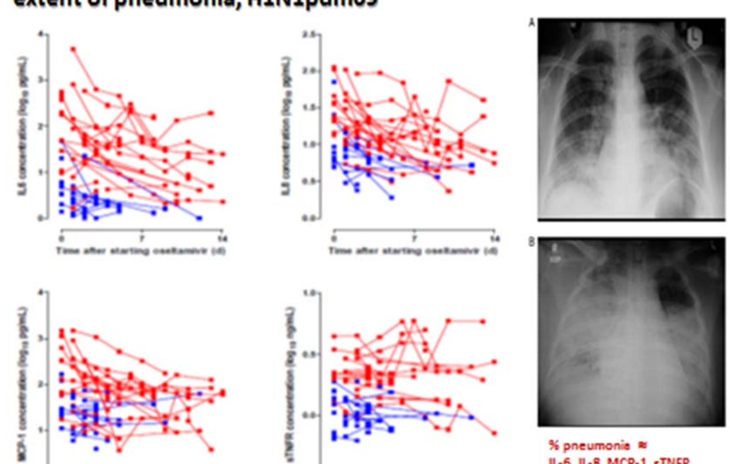
Cytokine or chemokine	Concentration, median pg/mL (IQR)		
	Acute-phase samples	Convalescent-phase samples	Reference range,[a] pg/mL
IL-6	10.6[b] (4.2–18.4)	2.9 (1.6–7.0)	<3.1
IL-8	5.4[b] (2.5–8.7)	2.1 (0.2–3.5)	<5.0
IP-10	7043.0[c] (4025.1–12381.1)	1423.6 (931.8–1634.8)	202–1480
MIG	992.1[c] (499.1–1992.3)	431.7 (198.4–792.9)	48–482
IFN-γ	16.0 (13.5–18.6)	15.7 (10.1–16.7)	<15.6
IL-12	1.8 (1.8–1.9)	1.8 (1.7–1.9)	<7.8
TNF-α	1.7 (1.6–1.8)	1.7 (1.6–1.8)	<10.0
IL-10	4.5 (2.5–6.5)	2.2 (1.9–2.8)	<7.8
IL-1β	1.4 (1.4–1.9)	1.4 (1.4–1.7)	<3.9
RANTES	1851.8 (667.4–4774.3)	4742.8[d] (2767.5–5169.7)	4382–18783
MCP-1	76.5 (49.5–97.0)	56.6 (41.2–84.8)	10–57

Clinical Infectious Diseases 2007; 45:723–31

Uncontrolled viral load and cytokine storm



Sustained proinflammatory cytokine responses correlate with extent of pneumonia, H1N1pdm09



Hui DS, Lee N. Chest 2010
Lee N, Antiviral Therapy 2011

Hypercytokinemia and Hyperactivation of Phospho-p38 Mitogen-Activated Protein Kinase in Severe Human Influenza A Virus Infection

N. Lee,[1,a] C. K. Wong,[2,a] P. K. S. Chan,[3,4] S. W. M. Lun,[2] G. Lui,[1] B. Wong,[1] D. S. C. Hui,[1,4] C. W. K. Lam,[2] C. S. Cockram,[1,4] K. W. Choi,[1] A. C. M. Yeung,[3] J. W. Tang,[3] and J. J. Y. Sung[1,4]

(1) relationship between uncontrolled viral replication and 'cytokine storm' (e.g. IL-6, IL-8, MCP-1, TNF-α)

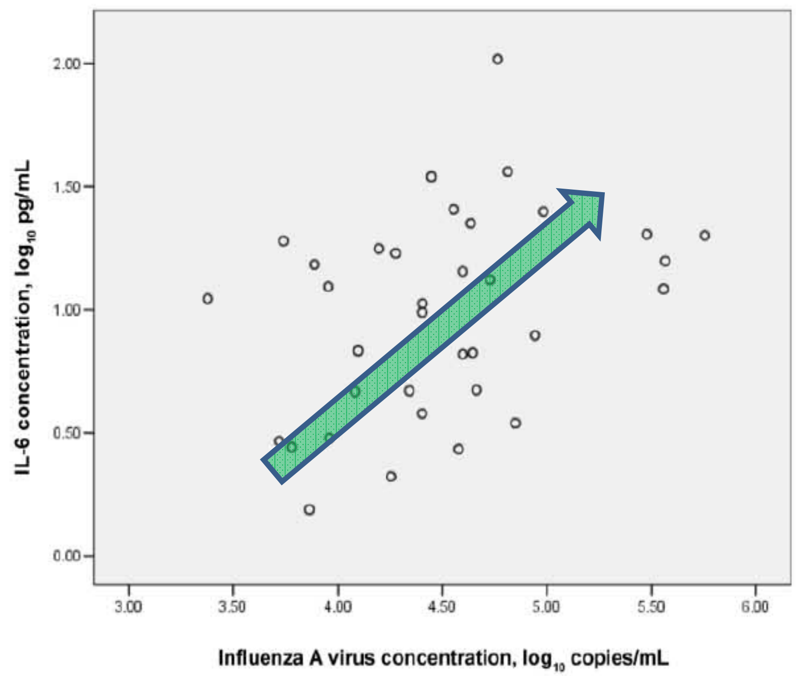
(2) their clinical significance and correlations with disease severity

(3) suppressed adaptive immunity (e.g. Th1, Th17) in severe influenza

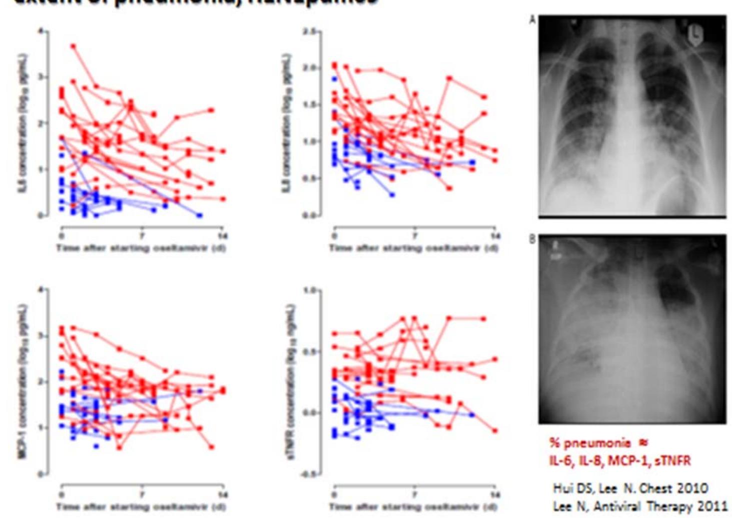
(4) role of innate immunity (e.g. TLR)

Lee N and CK Wong et al. *Clin Infect Dis* 2007; *Antiv Ther* 2011; *PLoS One* 2012; *IORV* 2013

Uncontrolled viral load and cytokine storm



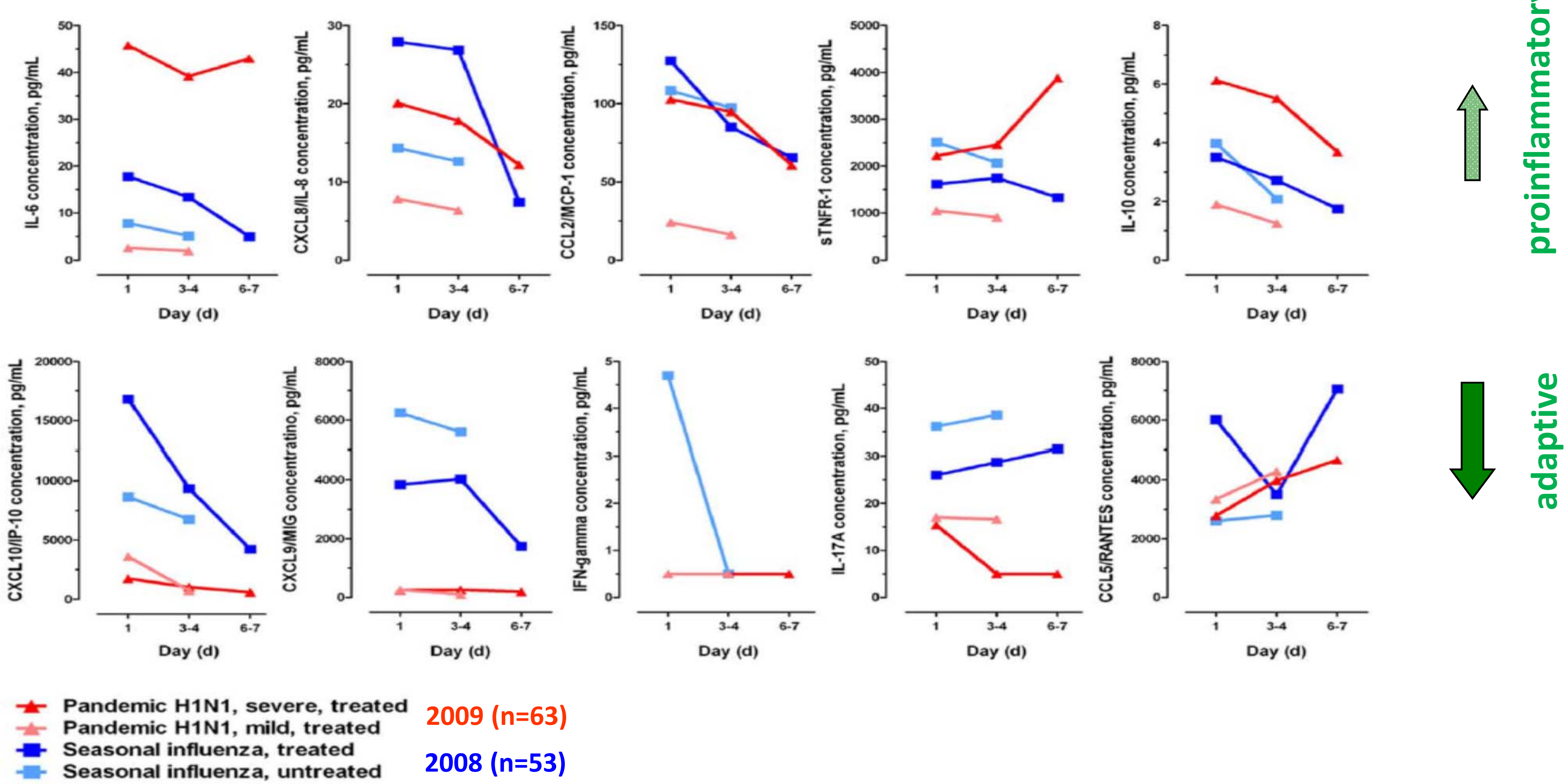
Sustained proinflammatory cytokine responses correlate with extent of pneumonia, H1N1pdm09



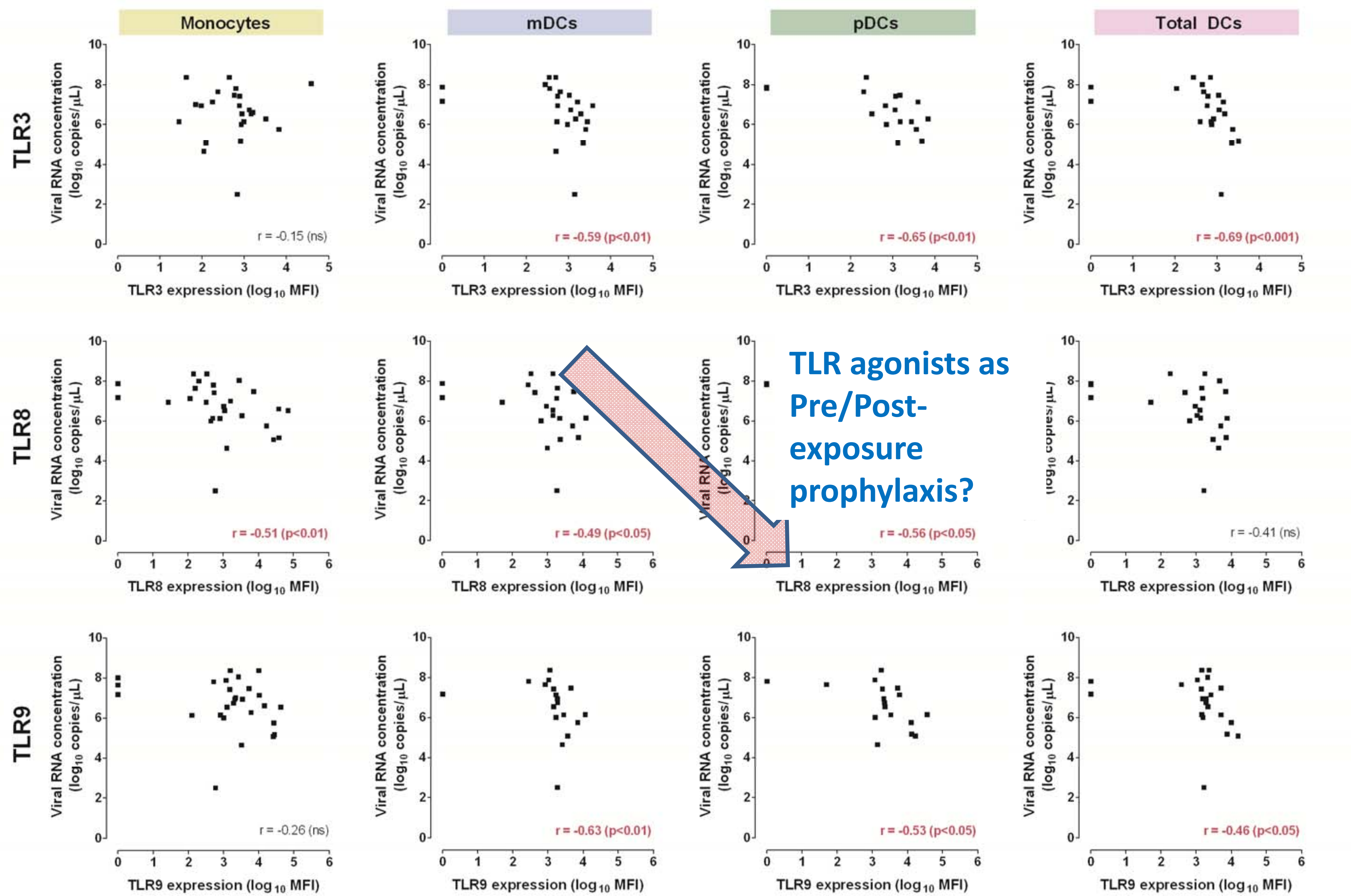
OPEN ACCESS Freely available online
PLoS one

Cytokine Response Patterns in Severe Pandemic 2009 H1N1 and Seasonal Influenza among Hospitalized Adults

Nelson Lee[1,2*], Chun Kwok Wong[3], Paul K. S. Chan[2,4], Martin C. W. Chan[1], Rity Y. K. Wong[1], Samantha W. M. Lun[3], Karry L. K. Ngai[4], Grace C. Y. Lui[1], Bonnie C. K. Wong[1], Sharon K. W. Lee[1,3], Kin Wing Choi[1], David S. C. Hui[1,2]



Negative correlations between expressions of TLRs and influenza viral load in the respiratory tract [Lee N, et al. IORV 2013]



On-going works

- **Newer antiviral treatment** (e.g. IV peramivir, IV zanamivir, laninamivir, favipiravir, DAS 181, combination therapy; monoclonal antibodies)
  - Lee N and Ison MG. *Clin Infect Dis* 2012; *Antiv Ther* 2012

- **Immunomodulatory therapy**
  - Hui DS, Chan PK, Lee N. *Antiv Res* 2013; *IORV* 2013

- **Rapid diagnosis, primary and secondary antiviral resistance**
  - Chan MC, Lee N, Chan PK et al. *J Clin Microb* 2014;. *J Clin Virol* 2013; *IORV* 2012; *J Clin Virol* 2011

- **Vaccine prevention**
  - Chan PK, Chor JS, Lee N et al. *Clin Infect Dis* 2013; *Vaccine* 2011; *BMJ* 2009

- **Other respiratory viruses causing influenza-like illness and pneumonia in adults (e.g. RSV)**
  - Lee N et al. *Clin Infect Dis* 2013; *Crit Care Clin* 2013; *ARJ* 2014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Thank you