



H7N9流感診斷、治療與醫院感染管制

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課程大綱

1. 流感病毒簡介

2. H7N9 流感病例

3. 流行性感冒的治療



1. 流感病毒簡介

Time Line of Detection of H7N9

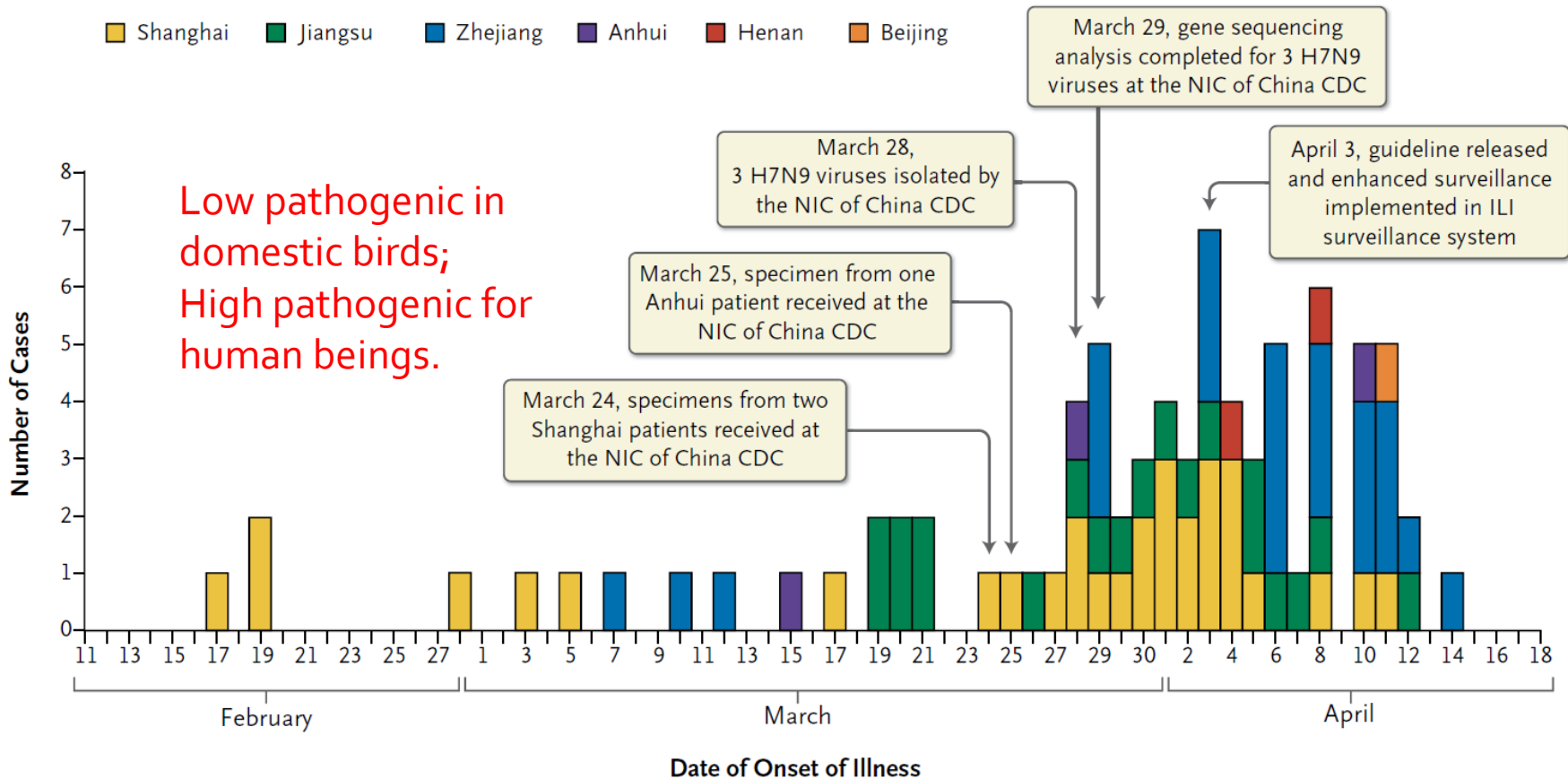
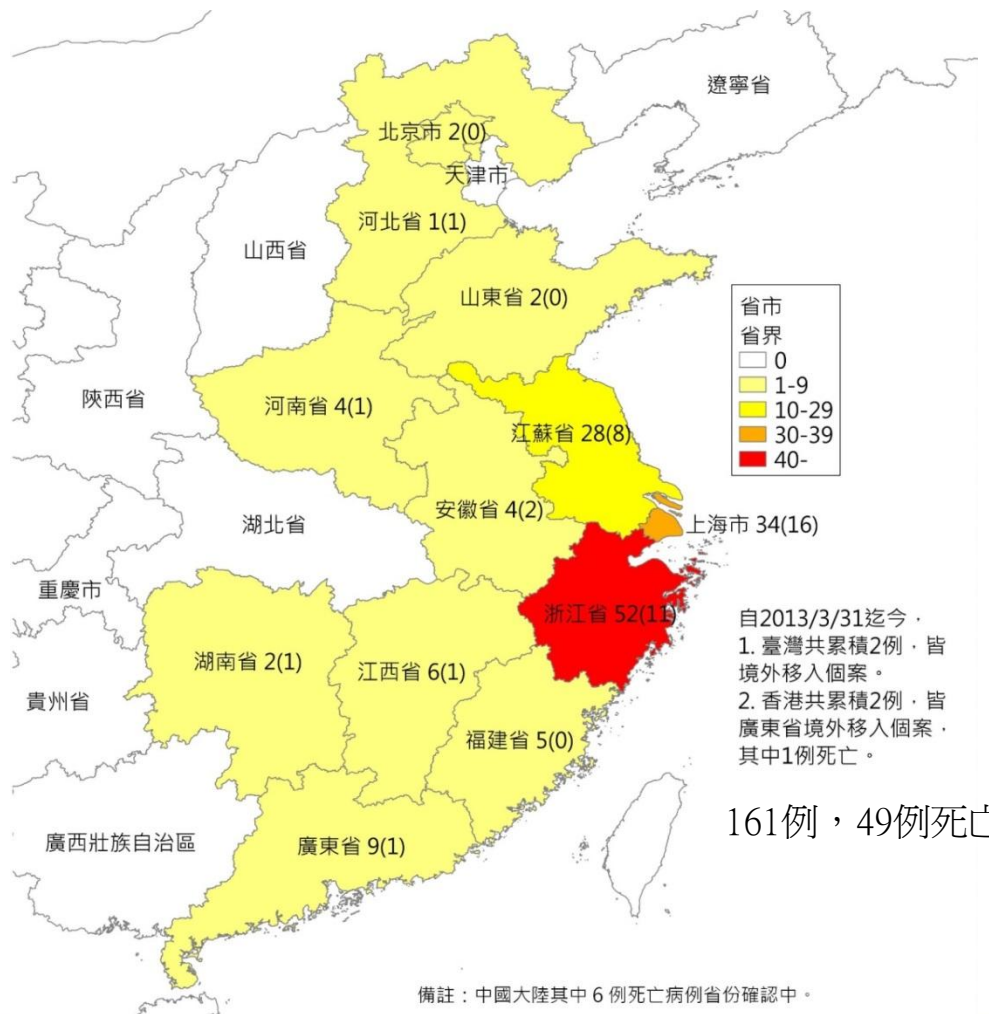


Figure 1. Date of Onset of Illness in First 82 Patients with Confirmed H7N9 Virus Infection, According to Province in China. CDC denotes Chinese Center for Disease Control and Prevention, ILI influenza-like illness, and NIC National Influenza Center.

人類感染H7N9病毒之現況

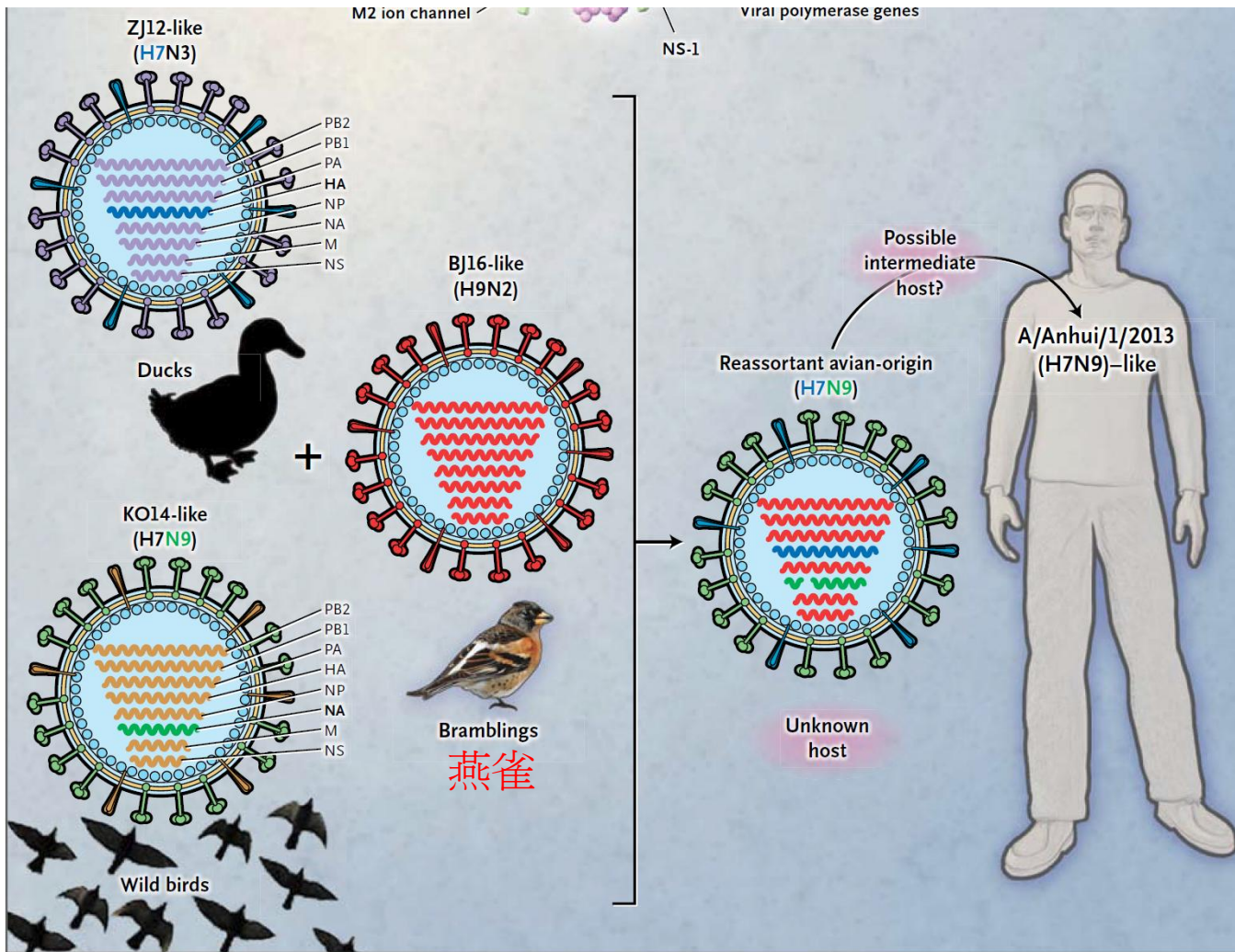


備註：中國大陸其中6例死亡病例省份確認中。

流感病毒的特性(1/5)

- 可區分為A、B、C三型
 - 只有A型流感會造成全世界的大流行
 - 以水鳥類為天然宿主
 - 抗原特質由hemagglutinin(H抗原)及neuraminidase(N抗原)決定
 - H：有16種；N：有9種
 - Antigen drift: mutation
 - Antigen shift: re-assortment(不同流感病毒間)
 - 禽流感：
 - 只能在禽鳥間有效傳遞的流感病毒，感染人類的的能力十分有限(H5N1，H7N9)

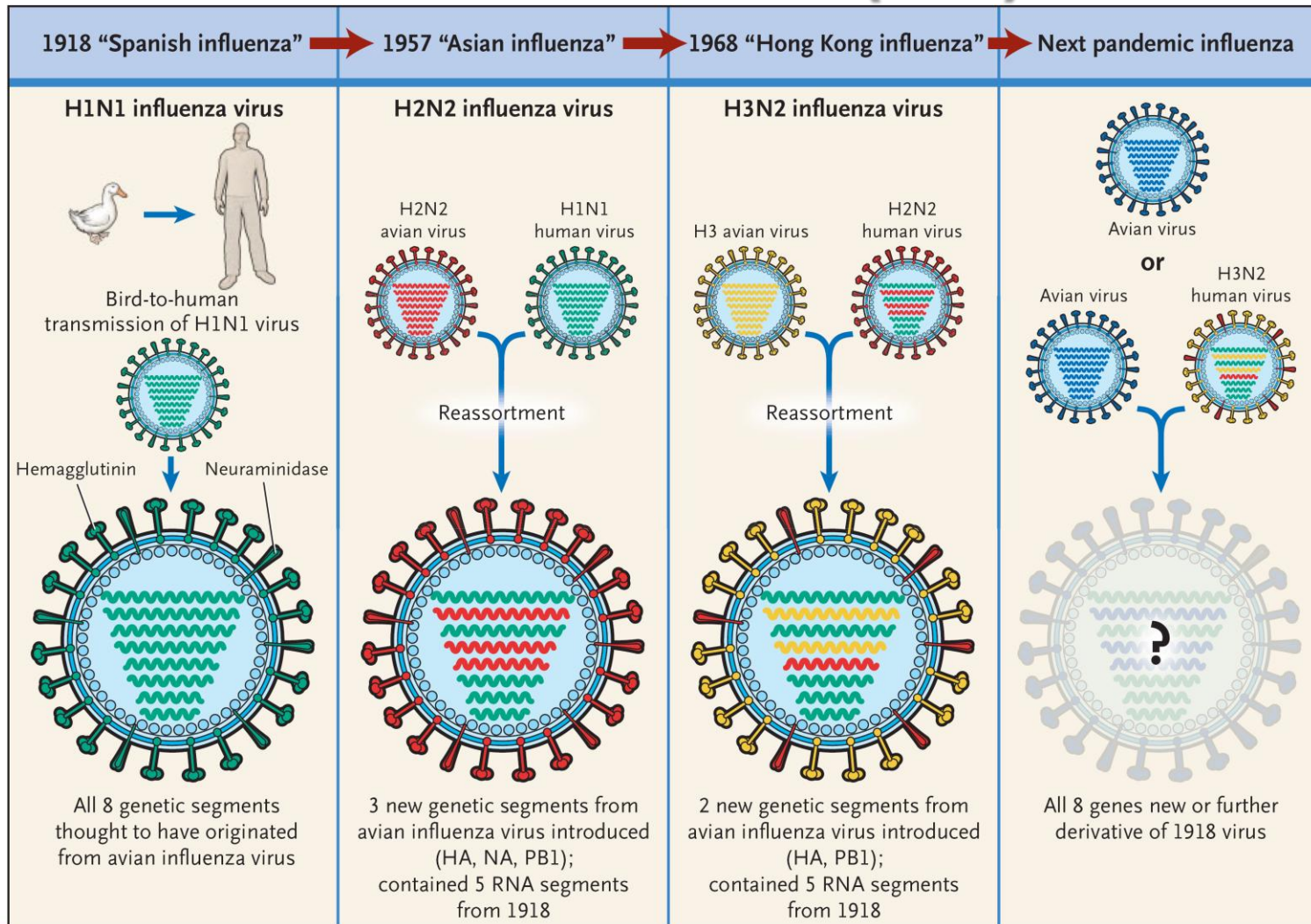
流感病毒的特性(2/5)



流感病毒的特性(3/5)

- 人流感：可在人與人之間有效傳遞的流感
 - 季節流感：既存的、在人類世界中流傳已久的
 - 新型流感：新發生、抗原特性不同於季節流感的流感
 - 由季節流感病毒和禽流感病毒發生re-assortment所造成。(H2N2、H3N2等)
 - 也可因為禽流感病毒不斷累積突變，導致轉變為可以有效感染人類的病毒。(1918 H1N1)
 - 也可因為多種禽流感、豬流感病毒，發生re-assortment而成。(2009 H1N1)

流感病毒的特性(4/5)



流感病毒的特性(5/5)

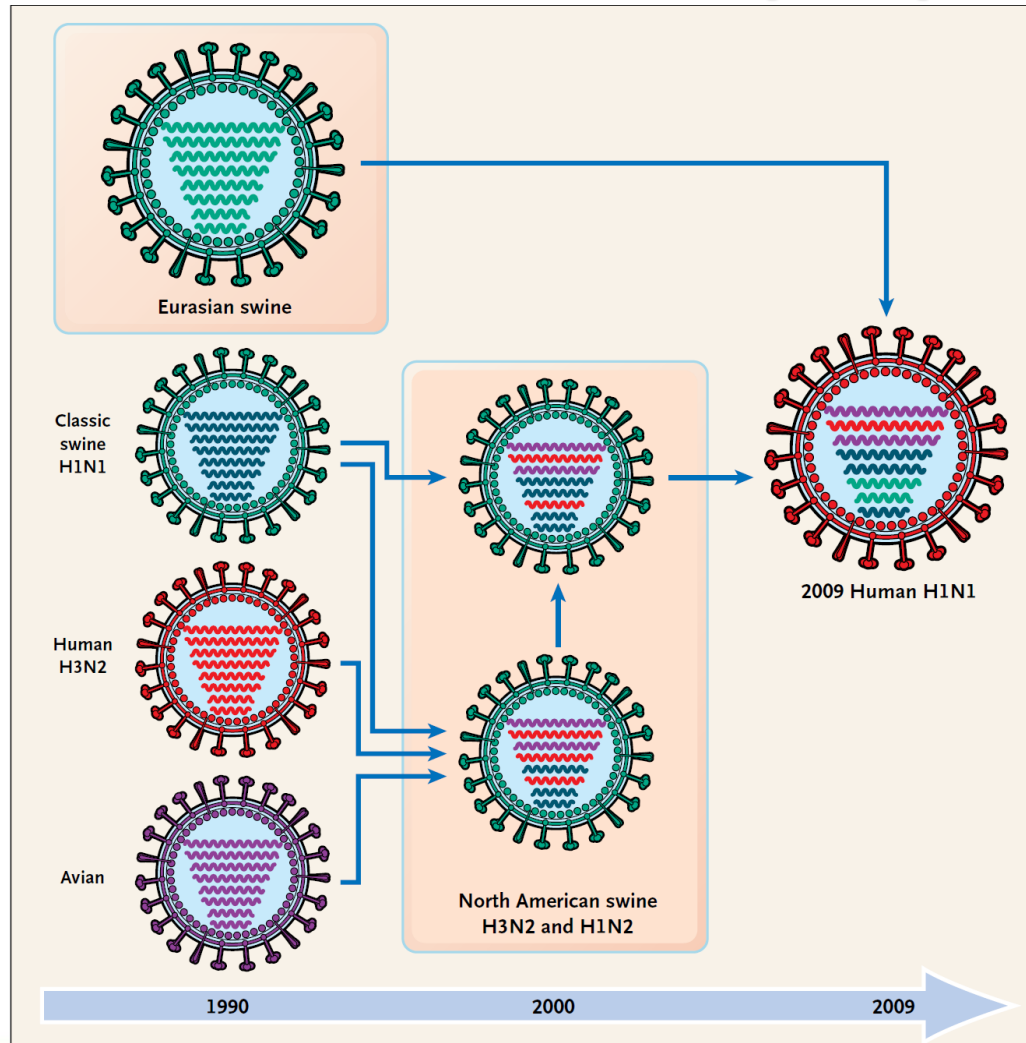


Figure 1. History of Reassortment Events in the Evolution of the 2009 Influenza A (H1N1) Virus.

流感與一般感冒(Cold)的症狀比較

症狀	流感	一般感冒
發作期 (Onset)	突然	漸進
發燒 (Fever)	常見，且溫度高 (超過 38.3°C)；維持3至4天	少見
咳嗽 (Cough)	有時會很嚴重	乾咳
頭痛 (Headache)	明顯	少見
肌肉痛 (Myalgia)	常見，通常嚴重	輕微
疲勞 (Fatigue) 虛弱 (Weak)	維持2至3週	輕微
極度疲乏	明顯	少見
胸部不適感	常見	輕至中度
鼻塞 (Stuffy nose)	偶爾	常見
打噴嚏 (Sneezing)	偶爾	經常
喉嚨痛 (Sore throat)	偶爾	常見

Clinical Manifestation of H7N9 Infection

- Initial presentation
 - Fever, cough, headache, myalgia, chills, malaise
 - No upper airway symptoms
- Progression
 - 5-7 (3-4) days later, persistent high fever
 - Dyspnea, hemoptysis, pneumonia, ARDS, septic shock, multi-organ (?) failure
 - Decrease of viral load: 15-20 days after onset
- Laboratory findings
 - Leukopenia/lymphopenia; CK, GPT, Cre, LDH, CRP 上升
 - Leukocytosis, marked elevation of cytokines while ARDS



Symptoms of H7N9 Infection: No Upper Airway Symptoms

Temperature (°C)	39.5	39.5	39.4
Sore throat	-	-	-
Rhinorrhoea	-	-	-
Conjunctivitis	-	-	-
Cough	+	+	+
Sputum	+	+	+
Haemoptysis	+	+	-
Dyspnoea	+	+	+
Nausea or vomiting	-	-	-
Diarrhoea	+	-	-
Abdominal pain	+	-	-
Myalgia	-	-	-
Fatigue	+	+	-
Skin rash	-	-	-





流行性感冒的診斷

- 臨床症狀與病史：Cluster
- Rapid antigen test
- Virus isolation
- RT-PCR
- Specific antibody reaction
- Microarray

類流感的定義

- All of the following
 - Sudden onset of fever ($>38^{\circ}\text{C}$)
 - Absence of other known cause
 - At least one of the following two respiratory symptoms
 - Dry cough
 - Sore throat



資料來源：WHO. Clinical Management of Pandemic (H1N1) 2009 Virus Infection. WHO Document 2009;Sep. 17.



流行性感冒的實驗室檢查發現

- Leukopenia
- Lymphopenia
- Thrombocytopenia
- Abnormal liver function
- Abnormal renal function
- Hyperglycemia



2.H7N9流感病例

H7N9流感病例定義及通報(1/2)

- 臨床條件(all of the following)
同時符合以下兩項條件
 - 急性呼吸道感染，臨床症狀至少包括發燒($\geq 38^{\circ}\text{C}$)及咳嗽。
 - 臨床、放射線診斷或病理學上顯示肺部實質疾病。
- 檢驗條件(any of the following)
 - 臨床檢體培養分離及鑑定出H7N9流感病毒。
 - 分子生物學H7N9核酸檢測陽性。
 - 血清學抗體檢測呈現為H7N9最近感染。

H7N9流感病例定義及通報(2/2)

- 發病前14日內，具有下列任一條件
 - 曾經與出現症狀的確定病例有密切接觸，包括在無適當防護下提供照護、相處、或有呼吸道分泌物、體液之直接接觸。
 - 曾至有出現H7N9流感疫情流行地區之旅遊史或居住史。
 - 曾有禽鳥接觸史或至禽鳥類相關場所。
 - 在實驗室或其它環境，無適當防護下處理動物或人類之檢體，而該檢體可能含有H7N9流感病毒。

臨床條件第1項加上流行病學條件第1項若同時出現，亦符合通報定義！

H7N9疾病分類

- 極可能病例
 - 雖未經實驗室檢驗證實，但符合臨床條件，且於14日內，曾經與出現症狀的確定病例有密切接觸者。
- 確定病例
 - 符合檢驗條件者。

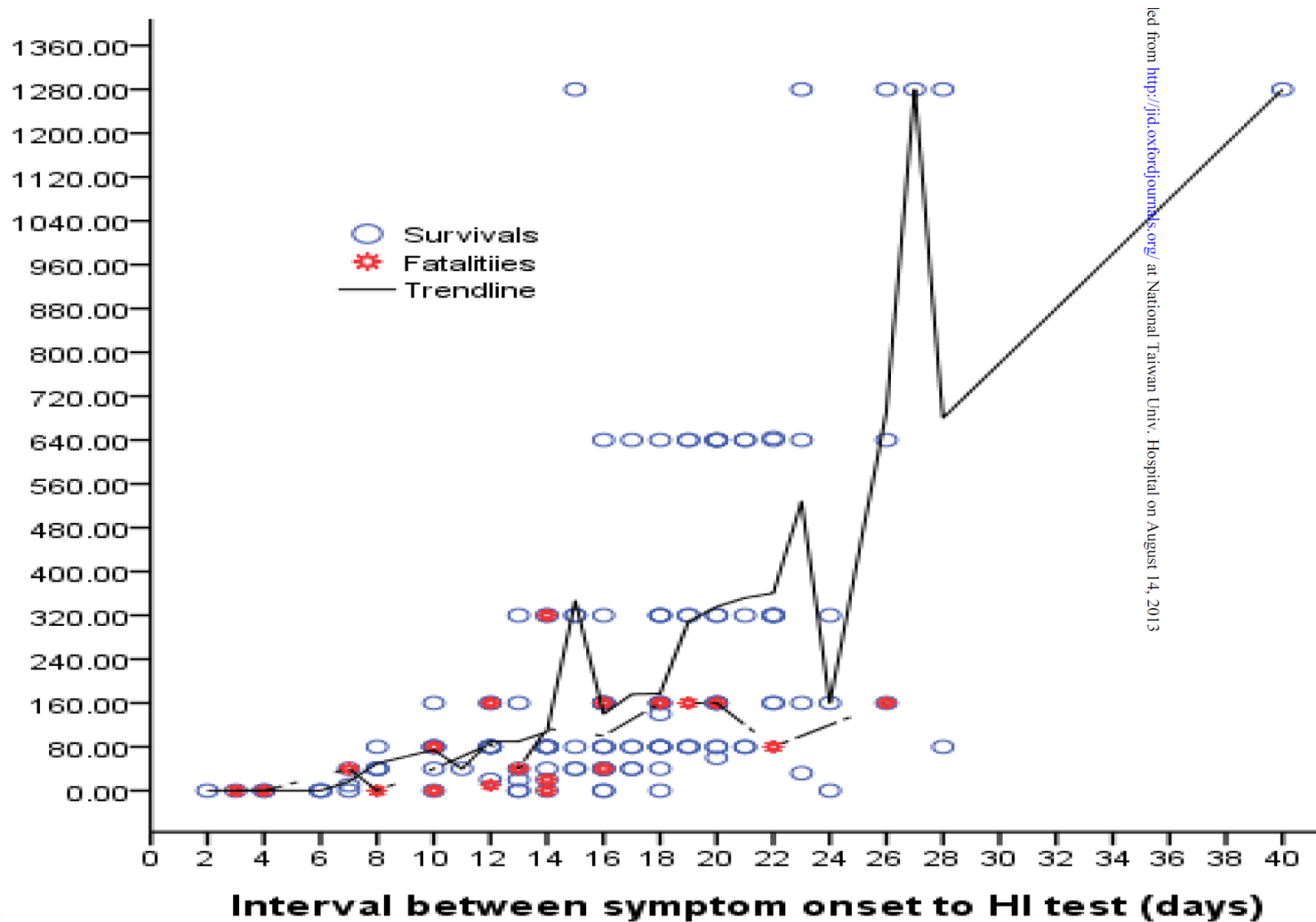


WHO: RT-PCR Standards: 2013/4/8

ID	Sequence	Note
H7		
CNIC-H7F	5'-AGAAATGAAATGGCTCCTGTCAA-3'	Primer
CNIC-H7R	5'-GGTTTTTTCTTGTATTTTATATGACTTAG-3'	Primer
CNIC-H7P	5'FAM-AGATAATGCTGCATTCCCGCAGATG-BHQ1-3'	Probe
N9		
CNIC-N9	5' TGGCAATGACACACACTAGTCAGT 3'	Primer
CNIC-N9R	5' ATTACCTGGATAAGGGTCGTTACT 3'	Primer
CNIC-N9P	5'FAM- AGACAATCCCCGACCGAATGACCC -BHQ1-3'	Probe
FluA		
InfA Forward	5' GACCRATCCTGTACCTCTGA C 3'	Primer
InfA Reverse	5' AGGGCATTYTGGACAAAKCGTCTA3'	Primer
InfA Probe1	5' FAM-TGC AGT CCT CGC TCA CTG GGC ACG-BHQ1-3'	Probe
RnaseP		
RnaseP Forward	5' AGATTTGGACCTGCGAGCG 3'	Primer
RnaseP Reverse	5' GAGCGGCTGTCTCCACAA GT3'	Primer
RnaseP Probe1	5'FAM-TTCTGACCTGAA GGCTCTGCGCG-BHQ1-3'	Probe



H7N9病毒感染後之特異性抗體反應



Basic Data

- Age : 53 year-old
- Gender : male
- Admission date : 2013/4/20
- Chief complaint :
 - Dyspnea for one day
- Past history
 - HBV carrier
 - Hypertension without medical control
 - Gastric ulcer with *Helicobacter pylori* infection



TOCC History

- T : 3/28 -4/9 at 蘇州
- O : Officer of one company
- C : Denied any contact history
- C : Denied any cluster history



Brief History(1/4)

4/9

– Coming back to Taiwan

4/12

– Feel a little malaise, fatigue and heat sensation at night

– No cough, no dyspnea, no muscle soreness no diarrhea, no abdominal discomfort

4/16

– Symptoms progressed → visited LMD and body temperature was 40°C at that time

– Transfer to Hospital A



Brief History(2/4)

4/16

- At ER, Influenza rapid test : negative
- H7N9 (CDC) : negative reported later
- CXR initially grossly normal
- Prescribed Tamiflu 75mg BID

4/17

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4/18

- Admitted to ward
- Still fever but no severe cough or dyspnea
- Follow up CXR on 4/18 : RLL interstitial pneumonia
- Used IV Moxifloxacin

4/19

- Arrange Chest CT : right lower lung consolidation, left lingular segment focal alveolar infiltration



Brief History(3/4)

4/19

- However, fever with chills noted again
- Progressive dyspnea developed at night
- Followed up CXR : progressive bilateral lower
- Lung consolidation

4/20

- Transfer to NTUH ER
- Intubation due to impending respiratory distress
- Admitted to 6E1
- Used Tamiflu 150 mg BID and Levofloxacin
- Sent sample to CDC
- Sent influenza-A RT-PCR to our Lab



Brief History(4/4)

4/21

- Lung protective strategy was used for ARDS
- Desaturation was still noted under FiO_2 100%
- iNO was added → desaturation persisted
- Add Ceftazidime for combination therapy

4/22

- ECMO was indicated → VV-ECMO
- Transferred to 4B1
- RT-PCR confirm H7N9 infection

4/23

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4/26

- Keep aggressive treatment

Lab at Hospital A

- 2013/4/17

WBC	Hb	PLT	Seg	Lym	Cre	BUN	AST
7950	14.6	111K	44%	48.7%	1.2	20.7	52

- 2013/4/19

WBC	Hb	PLT	Cre	BUN
4650	13.5	87K	1.2	19.4

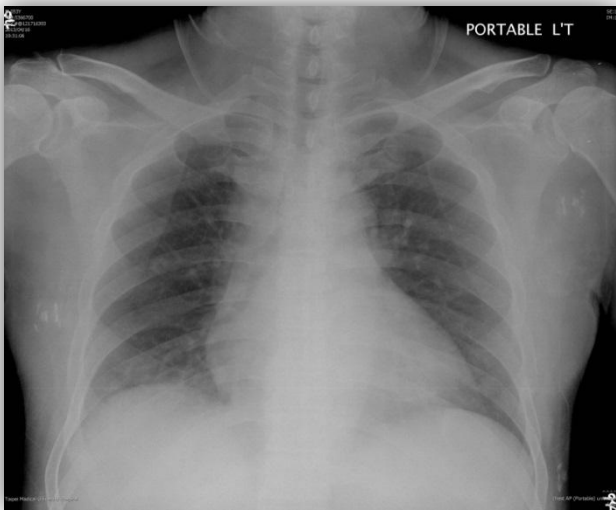
Mycoplasma Ab	Urine <i>Legionella</i> Ag	Urine pneumococcus Ag	Anti-HIV
Negative	Negative	Negative	Negative
4/16	Blood culture (1) : Negative		

Lab at NTUH

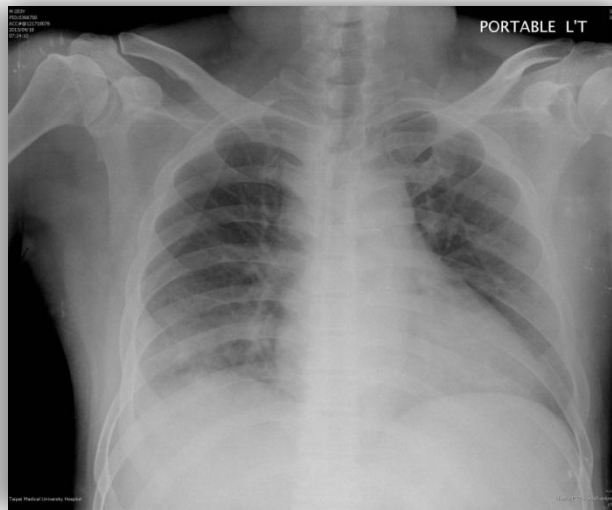
	WBC	Hb	PLT	Seg	Lym	Cre	BUN	ALT	CRP
4/20	4440	15.1	96K	60.6%	38.3%	1.1	-	36	
4/21	9620	14.8	131K	-	-	1.4	26.3		11.02
4/22	6520	12.1	118K	52%	10%(atypical lymphocyte)	-	-	-	10.18
4.23	6710	12.1	68K	49.4%	47.1%	2.7	39.5	32	

4/22	Procalcitonin							56.59	
4/22	Sputum , Influenza virus type A RNA PCR (qualitative test)						Positive		
4/22	Sputum AFS for three sets						Negative		
4/22	Sputum Chlamydiae Ag						Negative		
4/22	CMV IgG			Negative		CMV IgM		Negative	
4/21	Sputum culture						Mix flora		

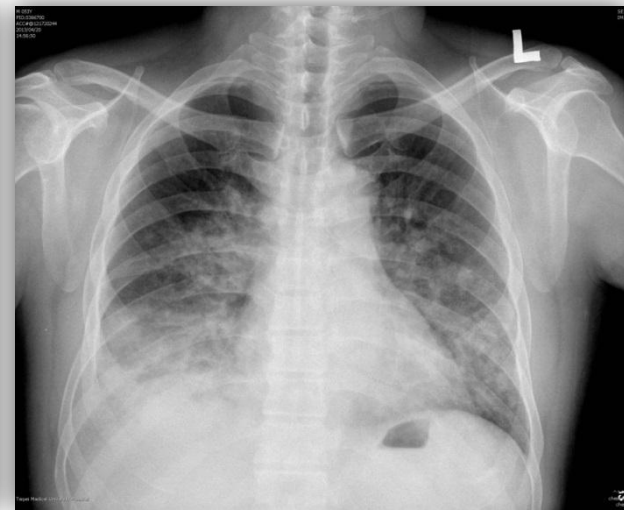
Serial CXR at Hospital A



4/16

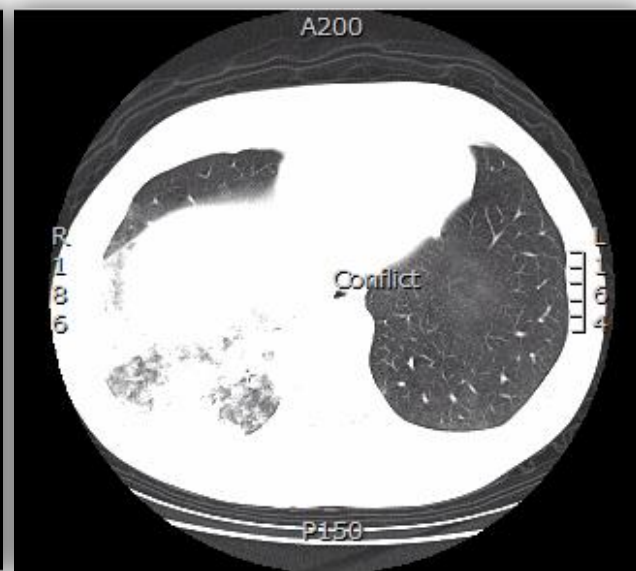
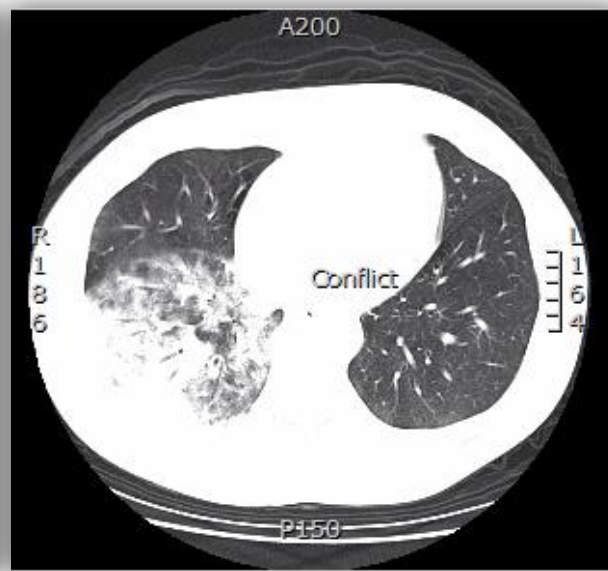
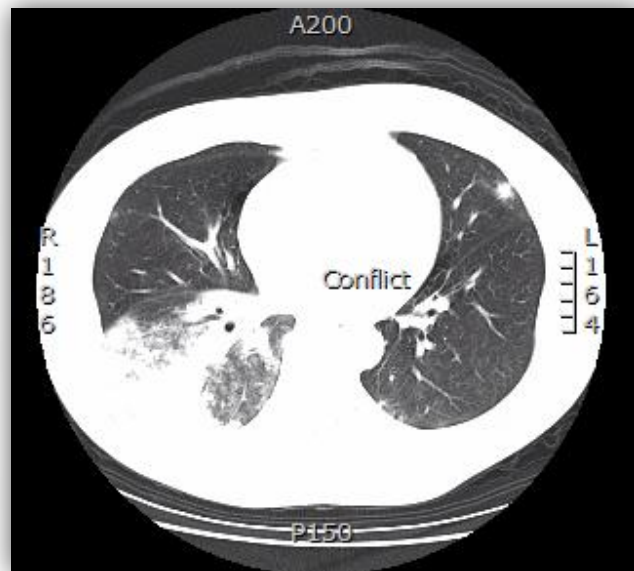


4/18

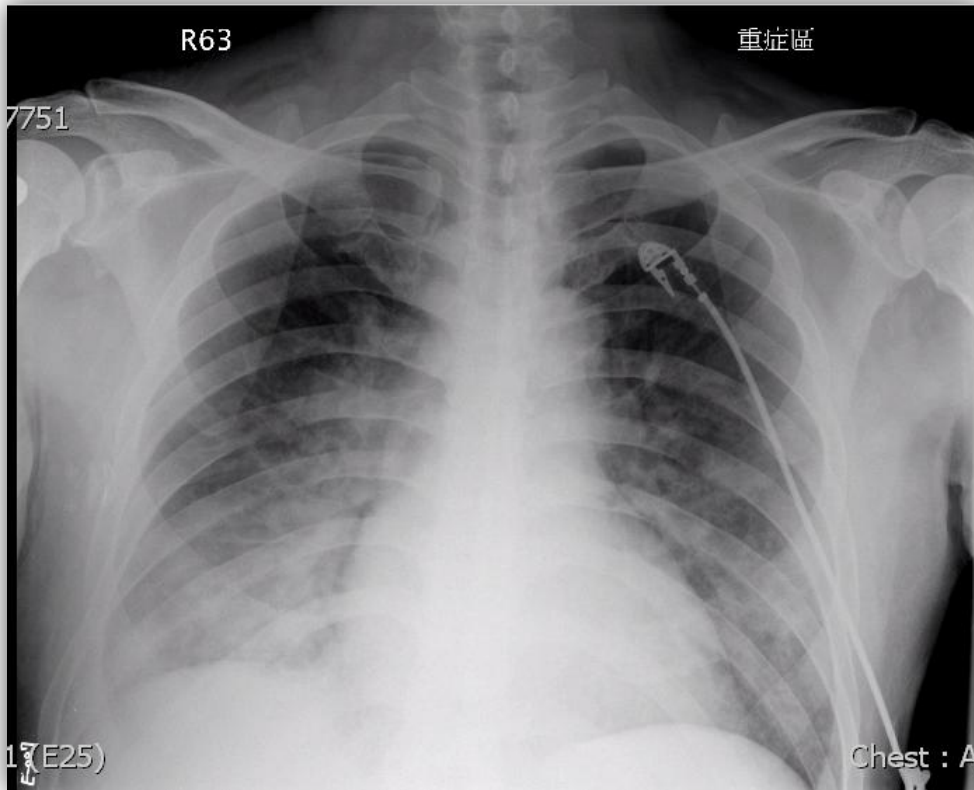


4/20凌晨
Before transfer to NTUH

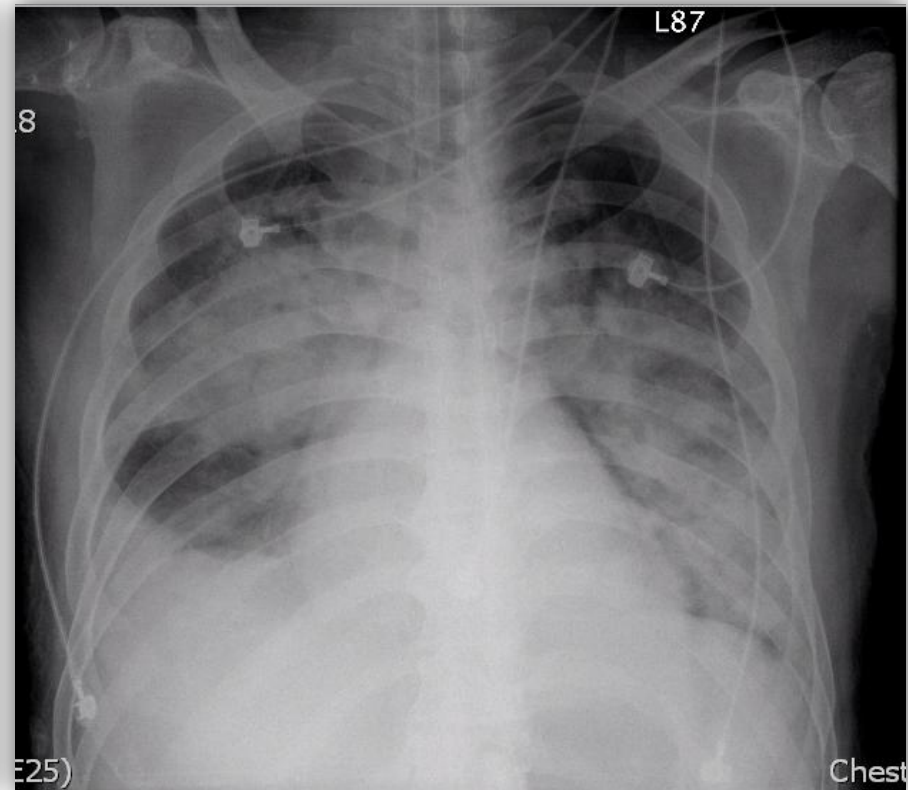
Chest CT on 4/19 at Hospital A



Serial CXR at NTUH (1/2)

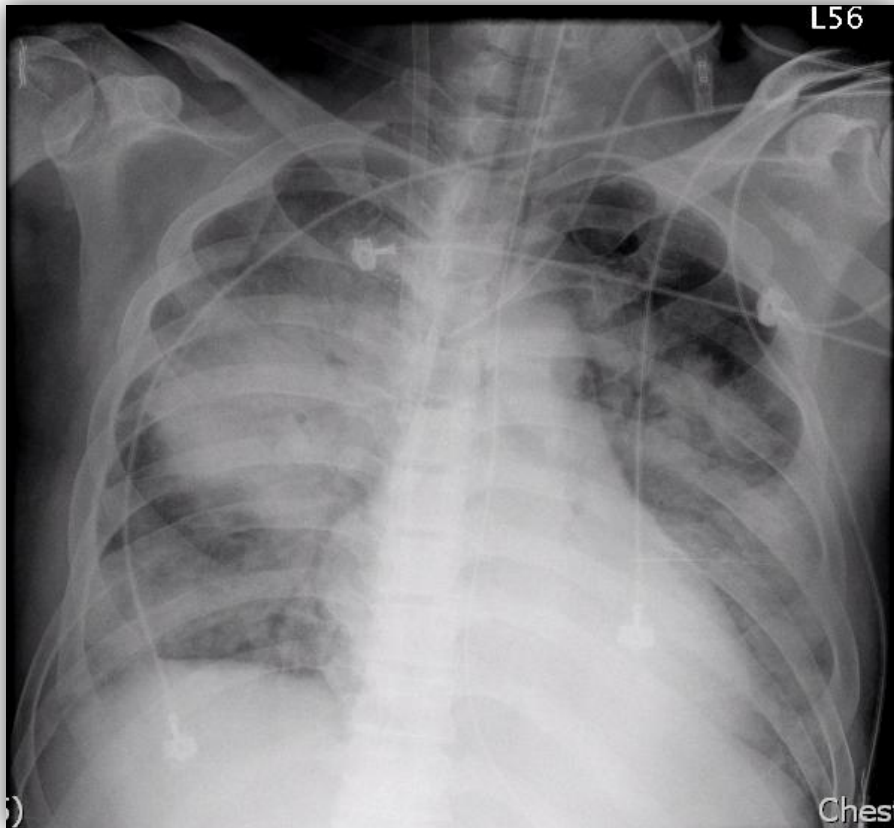


4/20

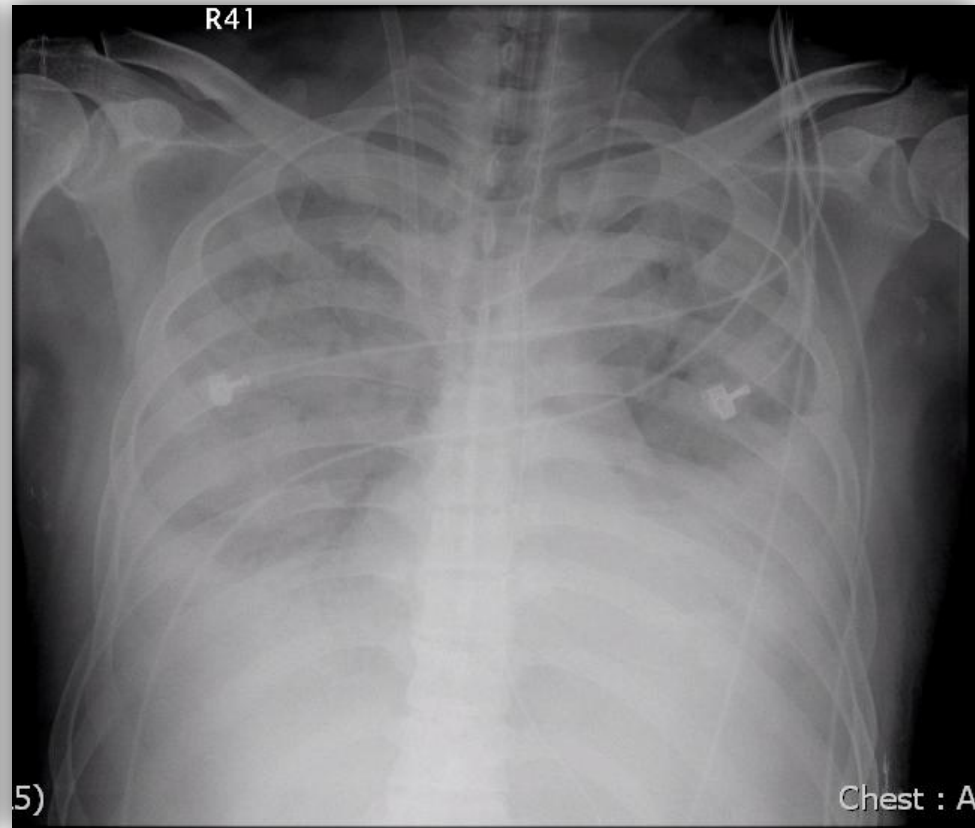


4/21

Serial CXR at NTUH (2/2)



4/22



4/23



3. 流行性感冒的治療

流行性感冒的治療

	Oseltamivir	Zanamivir	M2 inhibitors
Pandemic A(H1N1) 2009	Susceptible ^a	Susceptible	Resistant
Seasonal A (H1N1)	Mostly resistant	Susceptible	Mostly susceptible
Seasonal A (H3N2)	Susceptible	Susceptible	Resistant
Influenza B	Susceptible	Susceptible	Resistant
Avian influenza (H5N1)	Susceptible	Susceptible	Variable resistant

a A small number of isolated cases of resistance to oseltamivir have been reported

資料來源：

WHO Guidelines for Pharmacological Management of Pandemic (H1N1) 2009 Influenza and other Influenza Viruses. Available from http://www.who.int/csr/resources/publications/swineflu/h1n1_guidelines_pharmaceutical_mngt.pdf

Anti-Viral Agents (1/3)

Agent	Age Groups (yrs)					
	Duration	1-4	5-9	10-12	13-64	≥ 65
Amantadine^a						
	5 days	5 mg/kg/day up to 150 mg in 2 divided doses	5 mg/kg/day up to 150 mg in 2 divided doses	100 mg twice daily	100 mg twice daily	≤ 100 mg/day
Rimantadine^b						
	5 days	Not licensed for use	Not licensed for use	Not licensed for use	100 mg twice daily	100 mg/day
Oseltamivir						
	5 days	Weight-adjusted doses ^c : - 30 mg twice daily for ≤ 15 kg - 45 mg twice daily for >15 to 23 kg - 60 mg twice daily for >23 to 40 kg - 75 mg twice daily for >40 kg			75 mg twice daily ^c	75 mg twice daily ^c
Zanamivir						
	5 days	Not licensed for use	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily

Anti-Viral Agents (2/3)

藥劑總類	克流感膠囊		克流感粉劑		瑞樂沙		Rapiacta
服用方式	吞服；無法吞服者且無法取得液劑時則打開膠囊泡水或糖漿服用		調成液劑服用		經口吸入		單次點滴靜脈注射 15 分鐘以上
適用年齡	1 歲(含)以上		1 歲(含)以上		5 歲(含)以上		小兒(早產兒及新生兒除外，其投予之安全性尚未確立)及成人
劑量	治療	預防	治療	預防	治療	預防	治療
	13 歲以下依體重調整劑量； 13 歲(含)以上或體重 40kg 以上者 75mg 每日 2 次	13 歲以下依體重調整劑量； 13 歲(含)以上或體重 40kg 以上者 75mg 每日 1 次	13 歲以下依體重調整劑量； 13 歲(含)以上或體重 40kg 以上者 75mg 每日 2 次	13 歲以下依體重調整劑量； 13 歲(含)以上或體重 40kg 以上者 75mg 每日 1 次	10mg 每日 2 次	10mg 每日 1 次	成人每日投予 300mg、重症者 600mg、小兒 10mg/kg

Anti-Viral Agents (3/3)

藥劑總類	克流感膠囊		克流感粉劑		瑞樂沙		Rapiacta
服用方式	吞服；無法吞服者且無法取得液劑時則打開膠囊泡水或糖漿服用		調成液劑服用		經口吸入		單次點滴靜脈注射 15 分鐘以上
適用年齡	1 歲(含)以上		1 歲(含)以上		5 歲(含)以上		小兒(早產兒及新生兒除外，其投予之安全性尚未確立)及成人
療程	5 天	10 天	5 天	10 天	5 天	10 天	可依症狀連續多日反覆投予；反覆投予時，請以發燒等之臨床症狀來判斷繼續給藥之必要性，故請勿貿然持續使用。另，連續投與 3 天以上之經驗有限。

Anti-Viral Agents for H7N9

- Resistant to M2 channel inhibitors
 - Amantadine, rimantadine
- Usually susceptible to neuraminidase inhibitor
 - Oseltamivir (Tamiflu), zanamivir (Relenza), peramivir (Rapiacta)
 - Mutation of R292K
 - Decreased susceptibility to oseltamivir and zanamivir
 - Clinical impact: need to clarify
 - Taiwan data:
 - Resistant to oseltamivir / zanamivir, not to peramivir

Consideration of Peramivir

- Poor GI absorption of oral medication
 - Problem of oseltamivir
- Lower respiratory tract infection / on VCR, difficult to using inhaled anti-viral agents
 - Problem of zanamivir
- Peramivir
 - 國內未領有藥證，但曾獲WHO緊急授權使用。
 - 與請病患或代理人填具同意書，經轄區指揮官同意後使用。

流行性感冒的併發症

- Pneumonia
 - Viral pneumonia
 - Bacterial pneumonia (super infection)
 - *S. pneumoniae*, *S. aureus*
- Encephalitis
- Other rare complication
 - Vital organ involvement
 - Viral invasion or immune-mediated?

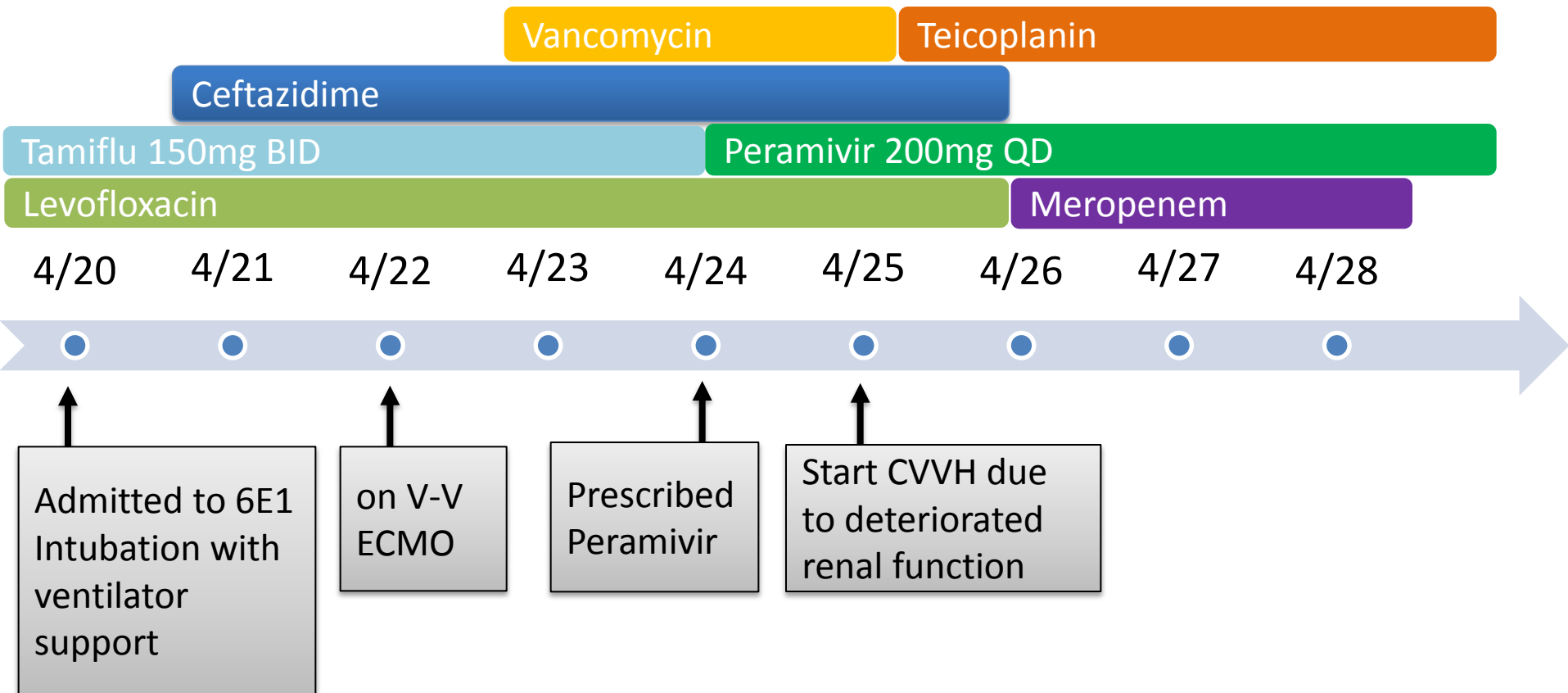
Complication of H7N9 Infection

- Usual complication
 - Pneumonia, ARDS
 - Rhabdomyolysis
 - Acute renal failure
 - Encephalopathy
 - Superimposed bacterial infection / sepsis
- Mortality rate
 - $45/135 = 33.3\%$

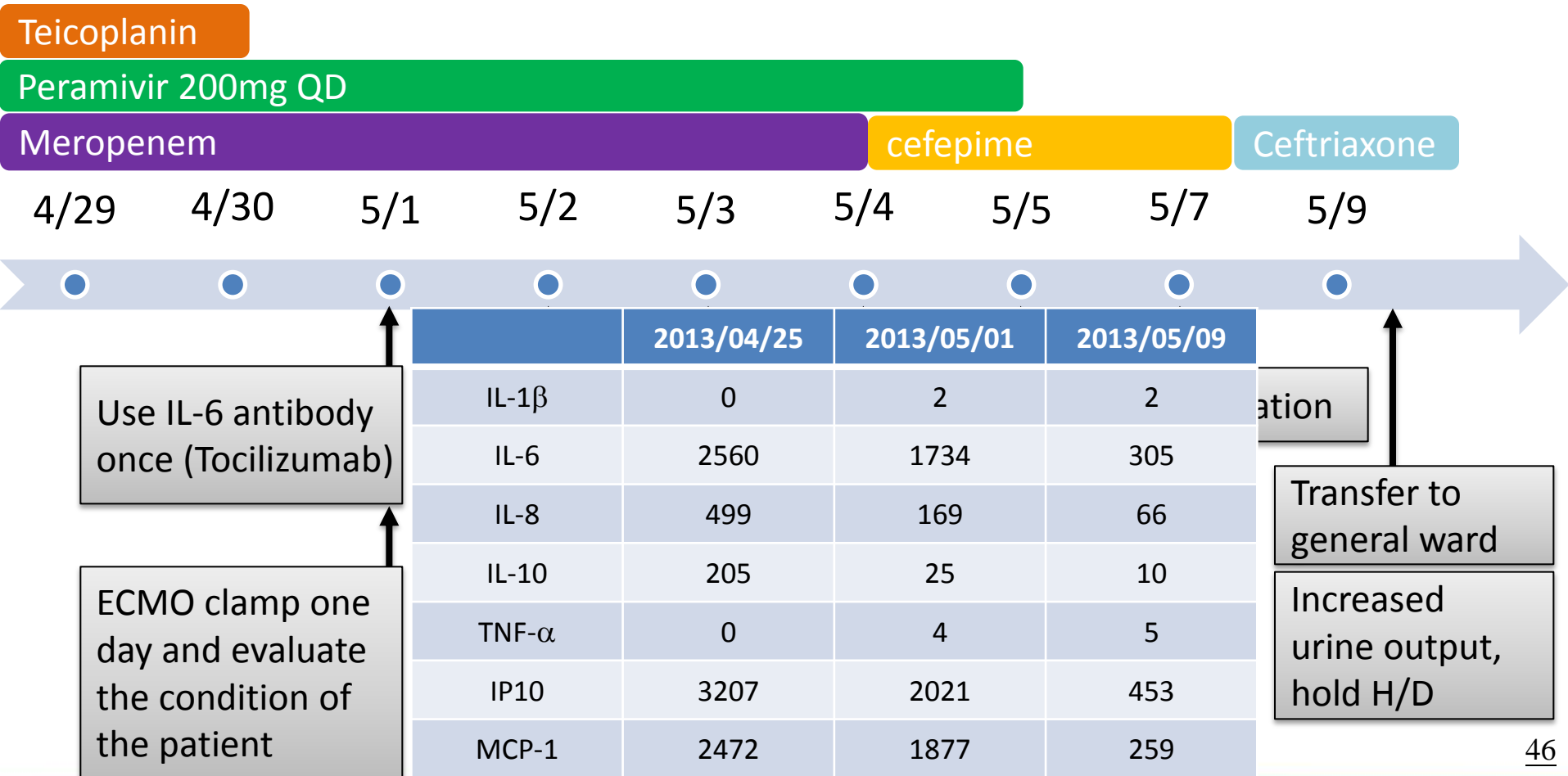
呼吸輔助治療

- Indication
 - $\text{PaO}_2/\text{FiO}_2 < 100$; 或使用 non-rebreathing mask 後 ,
 $\text{PaO}_2 < 80 \text{ mmHg}$
- Lung-protective strategies
 - Low airway pressure
- 吐氣管路末端加掛高效能過濾功能之人工鼻
- 使用 in-line suction
- 拋棄式管路
- 盡量減少 inhalation therapy

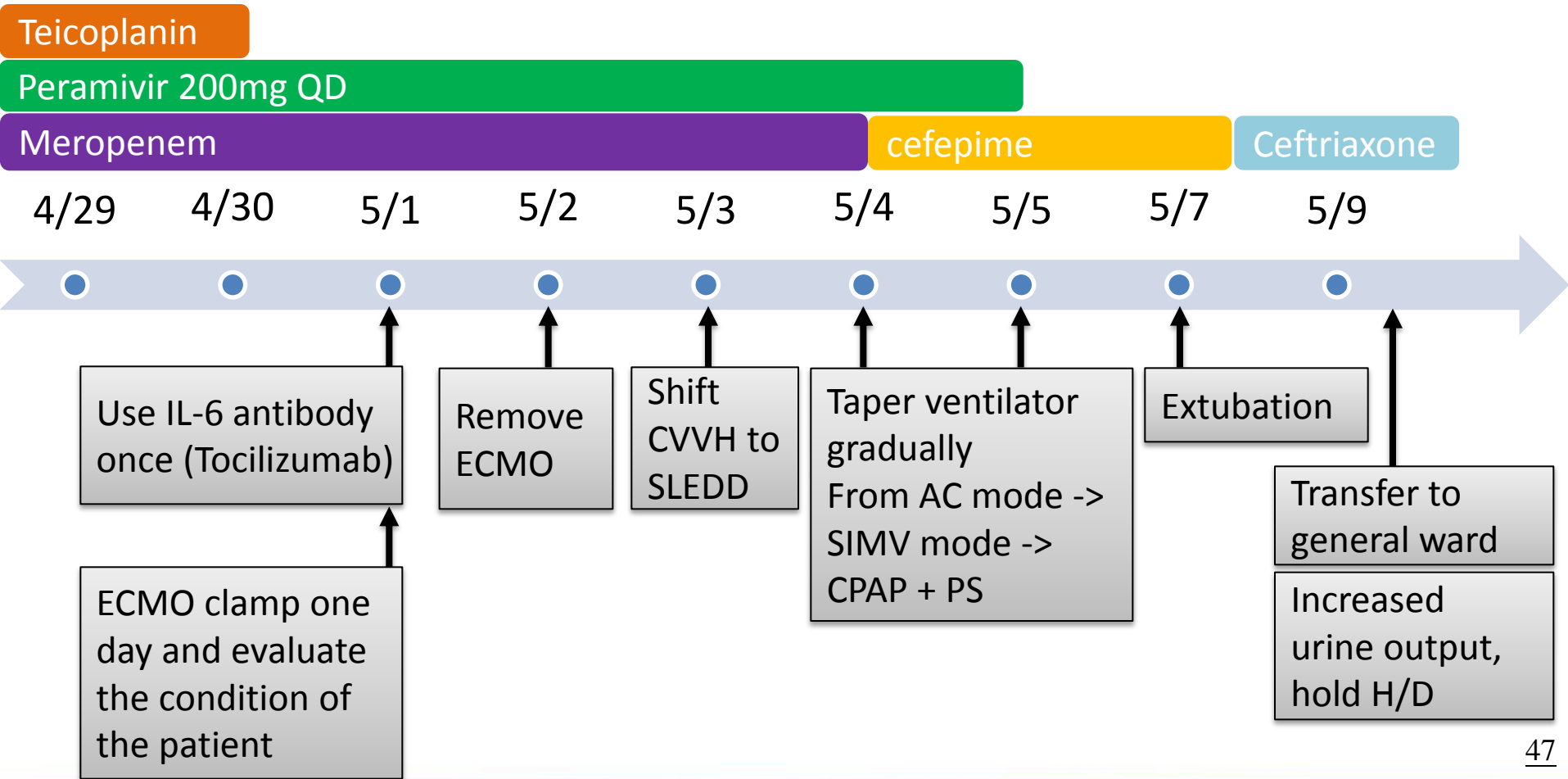
住院病程(1/4)



住院病程(2/4)



住院病程(3/4)



住院病程(4/4)

Ceftriaxone

5/10

5/15

5/17

5/20

5/23

5/24

Hb : 8.9 -> 7.5
Stool OB 2+
Suspected GI loss
Consider PES and discuss with patient

Follow up Chest CT to evaluate the lung condition after recovery

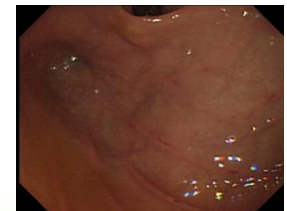
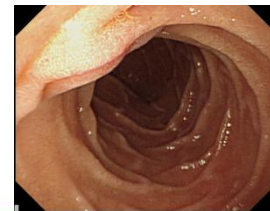
Arrange PES and recheck stool OB (-)

PES : Gastric erosion, fundus and upper body no ulcer

Prepare discharge

Partially resolved RLL patchy consolidation. Increased interstitial change and ground-glass opacity at bilateral lungs. Smaller mediastinal and axillary LNs. Less pleural effusion.

Pulmonary function test

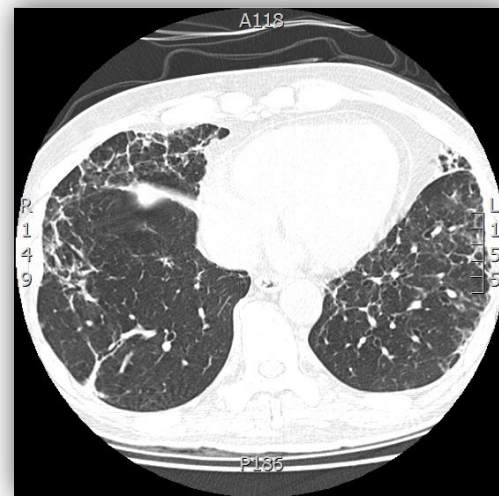
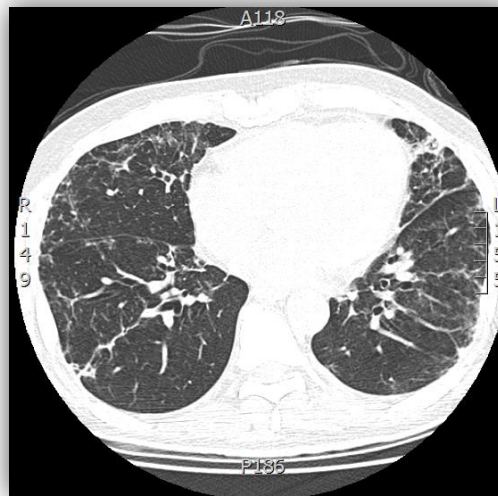
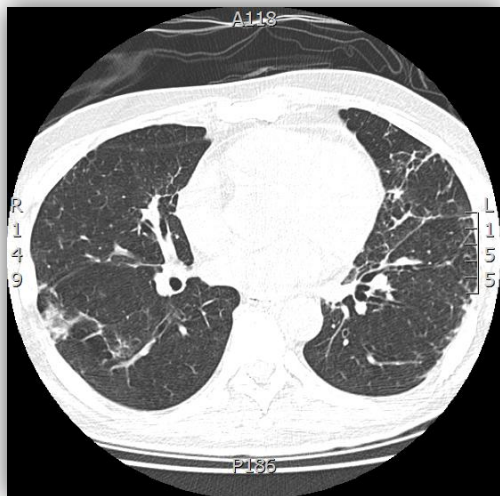
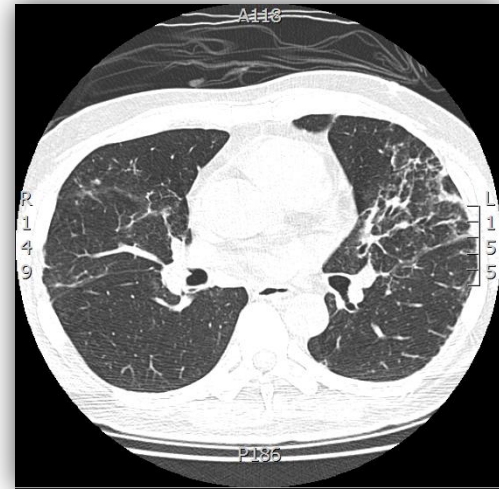
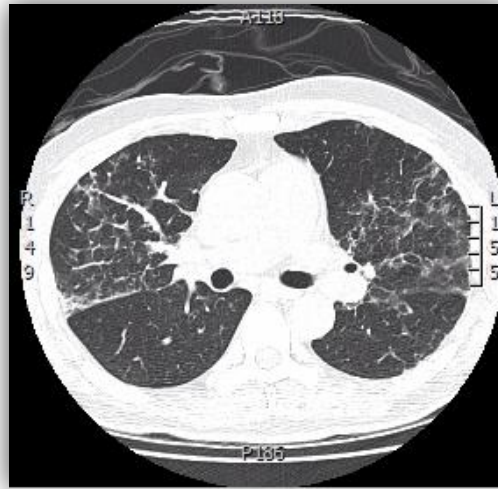
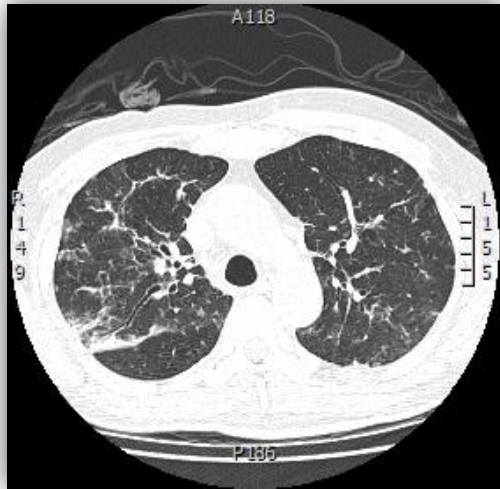


Pulmonary Function Test

1 Flow-Volume-Test(BTPS,Sitting-Position)			
	Observed	Predicted	% Predicted
FVC(L)	3.52	3.96	88.82
FEV1.0(L)	3.05	3.3	92.34
% FEV1.0 (%)	86.65	80.93	
2 Lung-Volume Test(L,BTPS,Sitting Position)			
	Observed	Predicted	% Predicted
VC	3.67	3.96	92.61
IC	2.03		
ERV	1.64	1.6	102.62
FRC	2.94	3.57	82.38
RV	1.3	1.71	75.87
TLC	4.97	5.67	87.65
RV/TLC(%)	26.16	30.2	
3 Ventilation			
MVV(L/min)	139.3	110.25	126.35
	TV: 1.01L	RR: 13/min	MV: 13.27L/min
4 Diffusion Capacity (ml/min/mmHg, STPD)			
	Observed	Predicted	% Predicted
DLCO	10.58	27.26	38.82
VA	4.83	5.94	81.33
DLCO/VA	2.19	4.67	46.89
HB	9		
DLCOcorr	13.29	27.26	48.76

Report : Normal standard spirometry, Severe impairment of diffusion capacity

Chest CT on 5/17



Serial CXR after Admission(1/3)

4/29



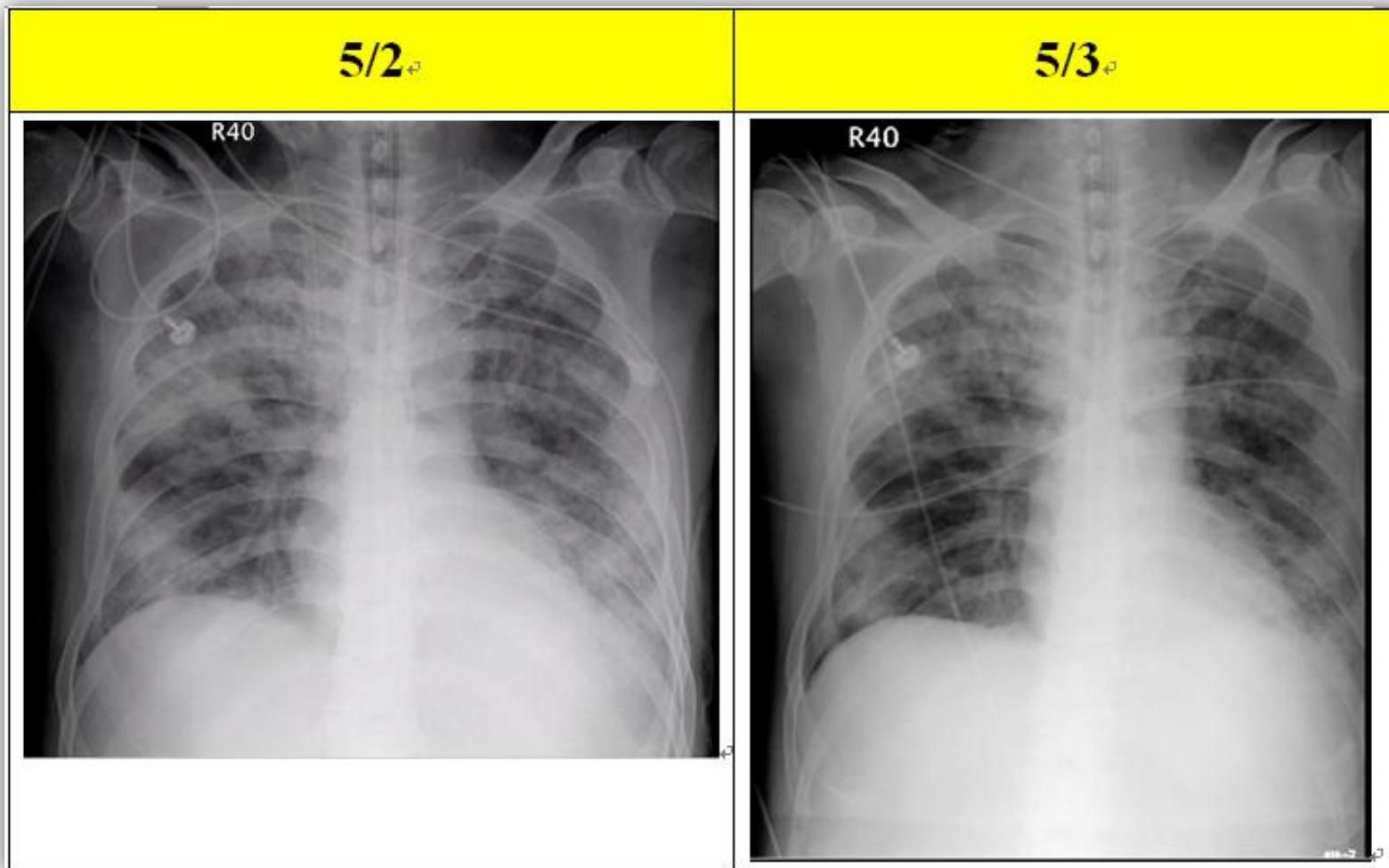
4/30



5/1



Serial CXR after Admission(2/3)



Serial CXR after Admission(3/3)

5/12[Ⓜ]



5/18[Ⓜ]



Immunosuppressive Agents

- Steroid
 - For refractory septic shock only
 - Low dose (1 mg/kg. day prednisolone), tapering it when inotropic agents able to be tapered
- Anti-IL-6 receptor antibody
 - Role of IL-6
 - Involved in several important immune responses and a stimulator for B and T cells maturation
 - Why tocilizumab
 - Proven for RA, effective for other auto-immune diseases
 - Neoplastic B cell of our patients

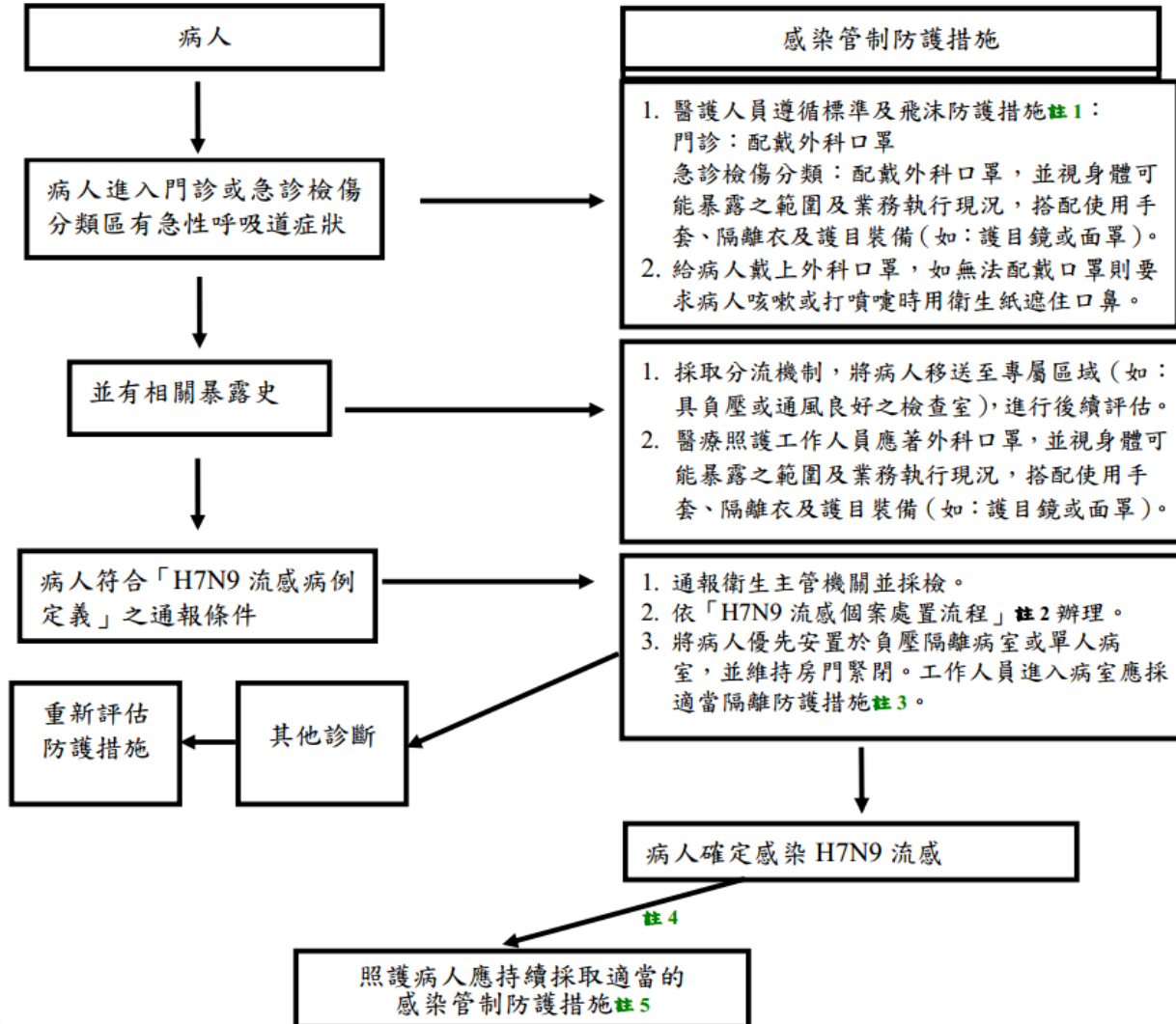
Potential Role of ECMO

- Not a routine therapeutic module
- Probable role
 - Septic shock results in massive fluid replacement, which in turn leads to marked lung edema refractory respiratory failure un-response to VCR
 - Support oxygenation, facilitate fluid replacement
 - Removing while recovery of septic shock, lung edema, and response to VCR support only

Transmission of H7N9

- Seasonal flu: droplet transmission (within 1 m)
- H7N9:
 - Limited person-to-person transmission
 - Incubation period: 2 -10 (maybe up to 14) days
- 感染管制措施的原則：under investigation, suspected, probable, confirmed
 - 基本要求：飛沫、接觸傳染與標準防護措施
 - 單人病室
 - 較好的要求：空氣、接觸傳染與標準防護措施
 - 負壓隔離病室

H7N9 流感感染管制措施



因應H7N9流感之醫療照護工作人員防護裝備建議

處置項目	場所	呼吸防護		手套	隔離衣	護目裝備
		外科口罩	N95 (含) 以上			
理學檢查及收集病史資料	門診或急診檢傷區	√		√	√	√
執行住院疑似病人之常規醫療照護	收治病室 (以負壓隔離室為優先)	√		√	√	√
執行可能引發飛沫微粒之醫療行為	收治病室或專屬區域 (如負壓或通風良好的檢查室)		√	√	√	√
環境清消		√		√	√	√
協助病人或接觸者就醫、病人轉送	病室、救護車		√	√	√	√
屍體處理、解剖	病室、太平間、解剖室		√	√	√	√

照護H7N9流感極可能病例與確定病例之醫療工作人員的健康監測與管理(1/2)

- 曾經照護H7N9流感極可能病例與確定病例的工作人員，於最後一次照護病人後14日內皆應進行自主健康管理，並由院方列冊追蹤管理；若出現任何急性呼吸道症狀或癥候，應主動通報單位主管。
- 曾經在無適當防護下照護H7N9流感極可能病例與確定病例的工作人員，於最後一次照護病人後14日內，若出現任何急性呼吸道症狀或癥候，除應主動通報單位主管外，在有症狀期間不應該繼續工作，並須確實遵循呼吸道衛生及咳嗽禮儀，及立即接受所需之醫療協助。

照護H7N9流感極可能病例與確定病例之醫療工作人員的健康監測與管理(2/2)

- 曾經在無適當防護下照護H7N9流感極可能病例與確定病例但無症狀的工作人員，自主健康管理期間儘量於家中作息與活動。惟若考量單位人力需求，這些人員可以在服用預防性用藥，且於醫療照護單位工作期間全程配戴口罩的情況下，繼續工作。
- 所謂適當防護並非僅限於配戴口罩，還包括如手套、隔離衣、護目鏡或面罩等，並應注意正確使用相關防護裝備及落實手部衛生。



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