呼吸道感染症的檢驗方法與判讀－以流行性感冒和新型冠狀病毒為例

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課程大綱

社區性肺炎感染的診斷與治療準則文獻整理的常見致病微生物與診斷方法

流行性感冒 (含新型流感) 的實驗室檢驗方法的敏感度與特異度比較

新興呼吸道傳染病的歷史與診斷標準

診斷新興呼吸道傳染病實驗方法的展望

社區性感染肺炎對流行病學和醫療的重要性

KEY CLINICAL POINTS

1. 社區性感染肺炎仍是全世界和美國主要死因之一。
2. 雖然嘗試於大部分病人找尋致病微生物，但原有心肺疾病和肺炎的不典型臨床表現在老年病人常會導致遲延診斷肺炎。
3. 大部分因社區性感染肺炎住院病人可以使用治療呼吸道感染的氟奎酮或合併使用頭孢子素和巨酯類抗生素。
4. 依據是否出現與醫療機構有關肺炎、特定因素(如肺部結構性疾病)，和特定症候群(社區感染的具抗藥性金黃色葡萄球菌毒素休克症候群 – CA-MRSA toxic shock syndrome) 的多重危險因子選擇適當抗生素治療。
5. 現今與醫療機構有關肺炎治療準則造成過度使用廣效性抗生素，與肺炎有關的多重危險因子的出現與否可以聚焦適當診斷肺炎方法和抗生素治療。
6. 肺炎病人若出現至少三個嚴重肺炎的次要危險因子(BUN上升、意識不清，和呼吸速率增快等) 需要在急診室接受廣泛性診斷和界措施，並考慮入住加護病房接受嚴密生命徵象監測與治療。

Wunderink R. G. and Waterer G. W. N Engl J Med. 2014;370:543-551.

1917-1918年西班牙流感 (Spanish Flu) 在美國軍營內大規模的感染

1917-1918年流感死亡人數全球預估為3至5千萬人，多數為年青族群，當時僅有支持性治療。

The National Museum of Health and Medicine, Armed Forces Institute of Pathology, Washington, D.C. Sharp P.A. Science 2005;310(5145):17 (October 7).

圖三. 2019-nCoV 在穿透性電子顯微性下的型態 (A圖 – 負向染色；B圖 – 人類呼吸道上皮細胞超薄切片影像)

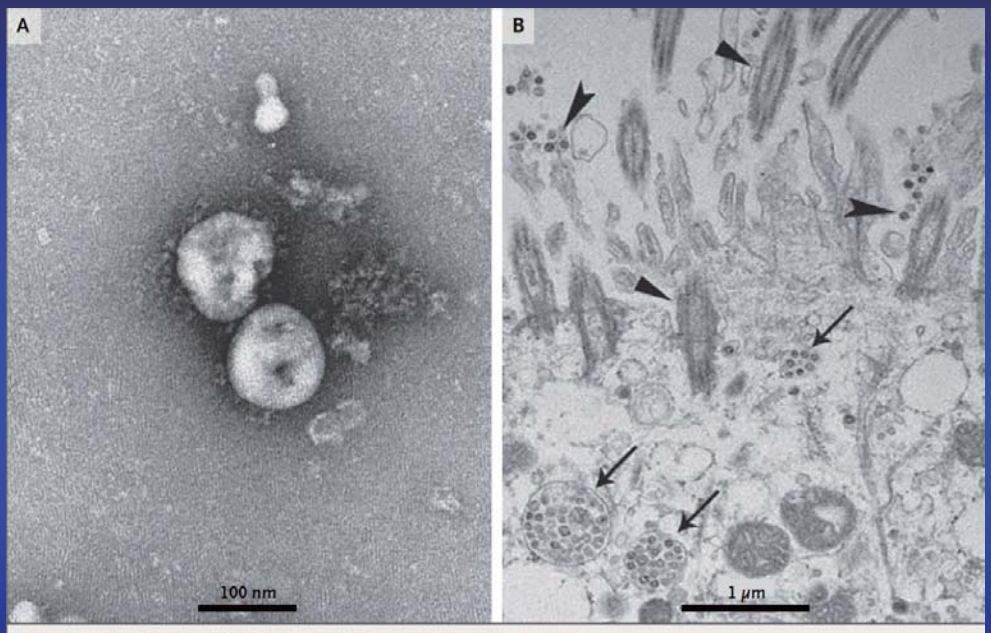
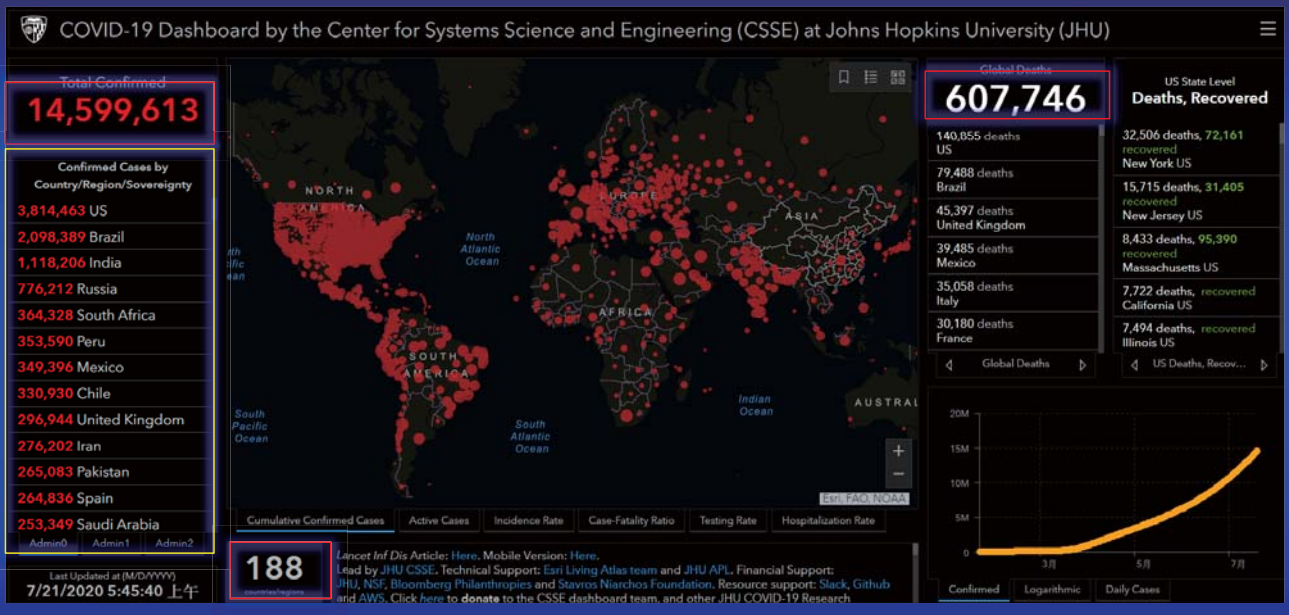


Figure 3. Visualization of 2019-nCoV with Transmission Electron Microscopy.
Negative-stained 2019-nCoV particles are shown in Panel A, and 2019-nCoV particles in the human airway epithelial cell ultrathin sections are shown in Panel B.

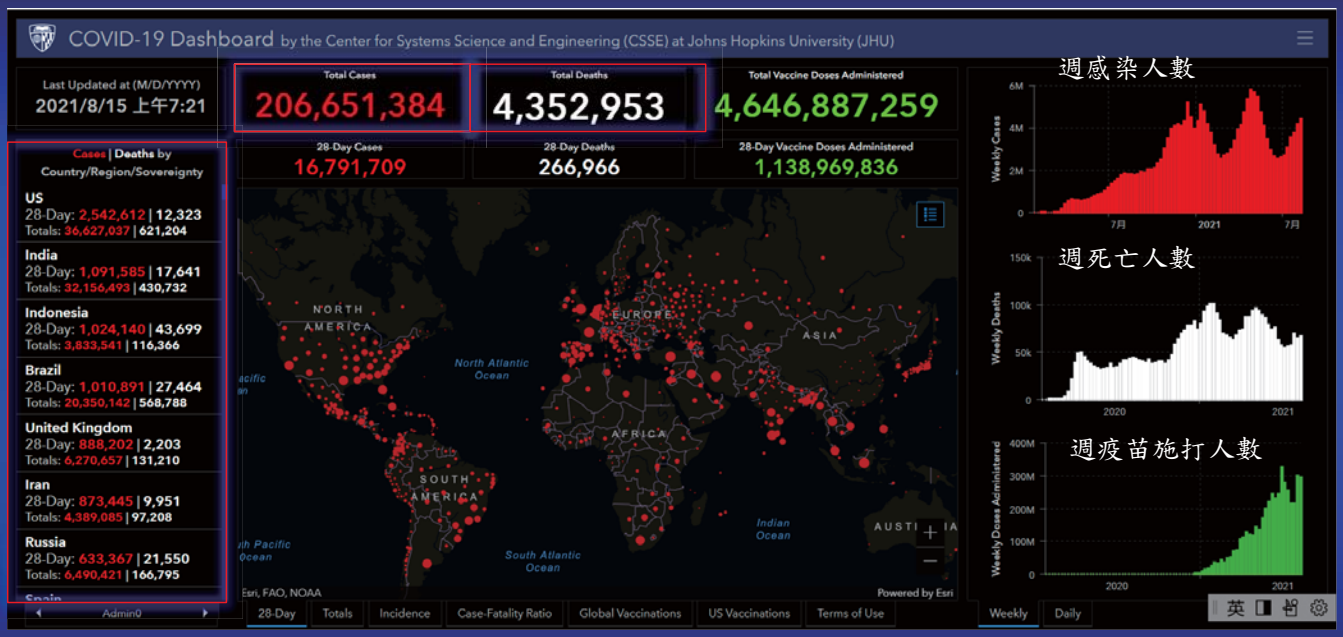
Zhu N. et al. N Engl J Med. Jan 24th, 2020.
DOI: 10.1056/NEJMoa2001017.

美國約翰霍普金斯大學建立 COVID-19 世界即時疫情網站 (即時更新實驗室確定感染地區分布、感染人數、死亡人數，和痊癒人數)



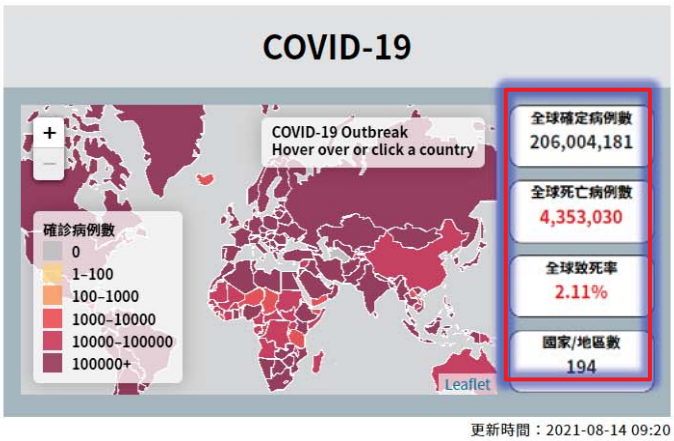
AM 05:45 Jul 21st, 2020. https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6

美國約翰霍普金斯大學建立 COVID-19 即時疫情網站 (即時更新實驗室確定感染地區分布、感染人數、死亡人數，和疫苗施打人數)

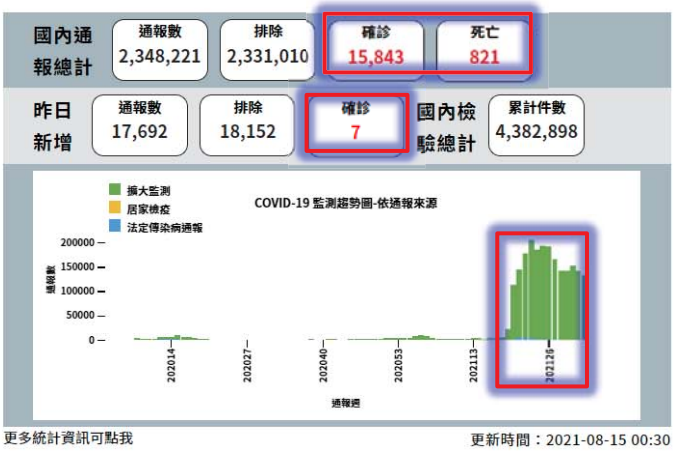


AM 07:21 Aug 15th, 2021. https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6

圖. 截至2021年08月14日PM 3:30 臺灣疾病管制署統計全世界各地 (206,004,181人) 和台灣 (15,843人) 經實驗室確定診斷 COVID-19 感染病例的通報人數與地區分布



更新時間：2021-08-14 09:20



更多統計資訊可點我

更新時間：2021-08-15 00:30

CDC, Taiwan. August 14th, 2021.

採檢結果出爐！高雄15學生上呼吸道群聚案 是鼻病毒感染

2020-06-14 16:45 聯合報 / 記者邱宜君／台北即時報導

TTV & UDN. Jun 14th, 2020.

病人主訴各種呼吸道感染症狀 (咳嗽、發燒、濃稠黃色痰液、呼吸困難，和胸痛 等)。

↓

病人至醫療院所求診，醫療人員詢問病史 (原有疾病、症狀，和TOCC等) 並執行理學檢查。

↓

醫療人員依據現有流行病疫情、臨床經驗、現有醫療設備，和病人意願等執行必要的影像學與實驗室檢查。

↓

醫療人員依據本職學能和臨床經驗，和各項影像學與實驗室檢查結果， 判讀可能致病微生物，並給予適當經驗性或標靶性抗生素治療。

病情未改善或惡化，考慮更改診斷與追蹤。

病情改善並出院接受後續門診追蹤。

呼吸道感染致病微生物診斷方法

臨床表現與徵候 (特定族群與特定時間和地點等)

直接染色 (格蘭氏染色、耐酸性染色，和螢光染色等)

電子顯微鏡檢查 (electronic microscopic examination)

病理組織切片與特殊染色 (tissue pathology and special stains)

微生物培養 (microbiologic cultures)

特定抗體偵測 (如 COVID-19 和黴漿菌抗體等)

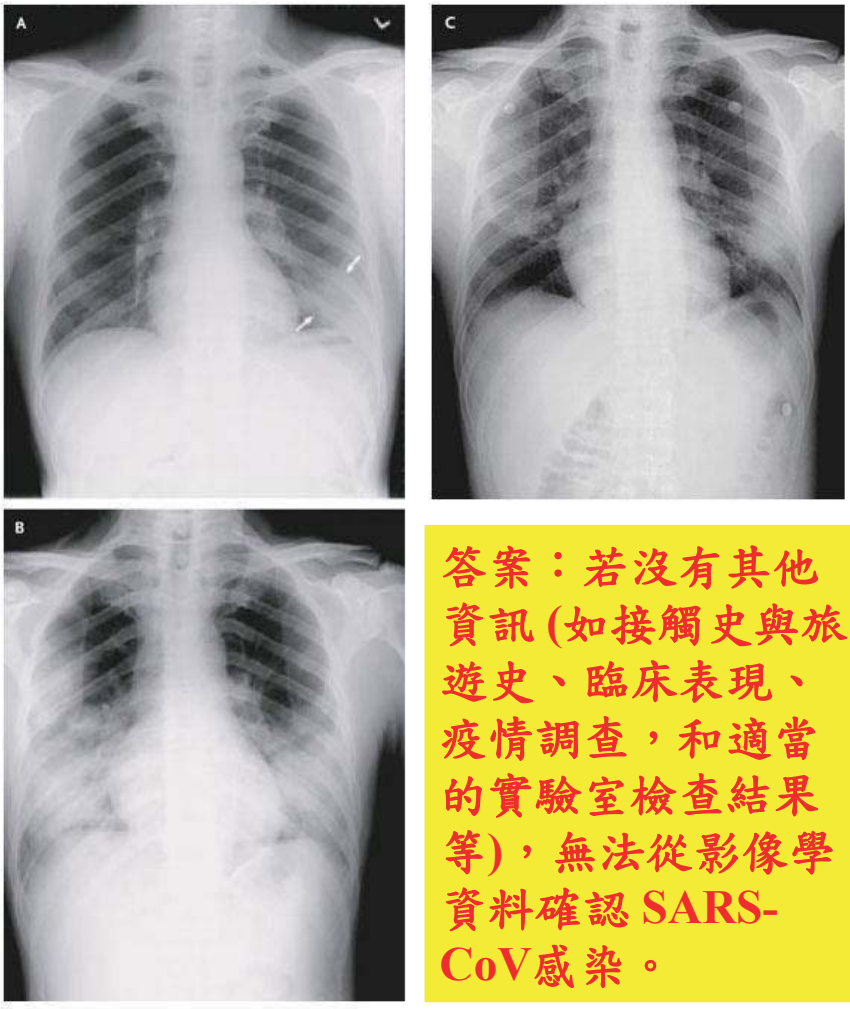
分子生物學檢驗 (DNA & RNA)

蛋白質譜學檢查 (如 MALDI-TOF 等)

全基因體定序 (whole genome sequencing – WGS)

46歲女性社區感染肺炎接受治療前後胸部X光片)

可以從胸部X光片預測可能致病微生物並採取適當治療與感染控制措施?



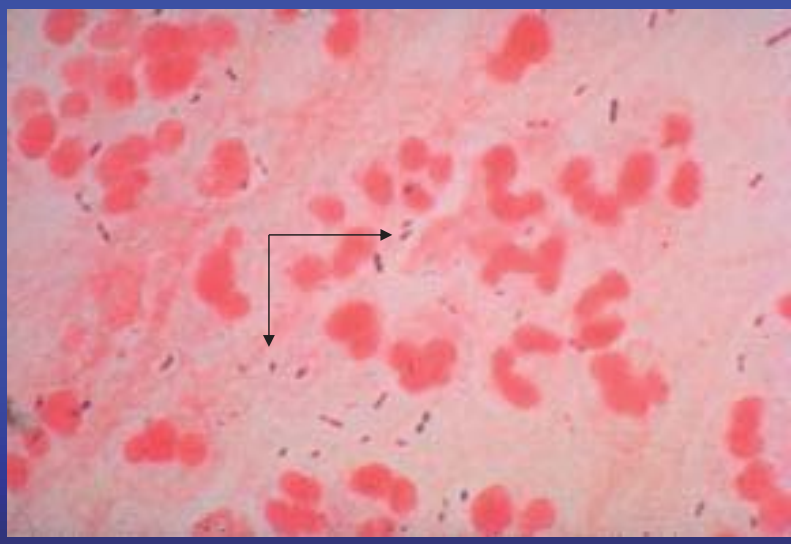
答案：若沒有其他資訊 (如接觸史與旅遊史、臨床表現、疫情調查，和適當的實驗室檢查結果等)，無法從影像學資料確認 SARS-CoV感染。

Lee N et al.
N Engl J Med.
2003;348:1986-1995.

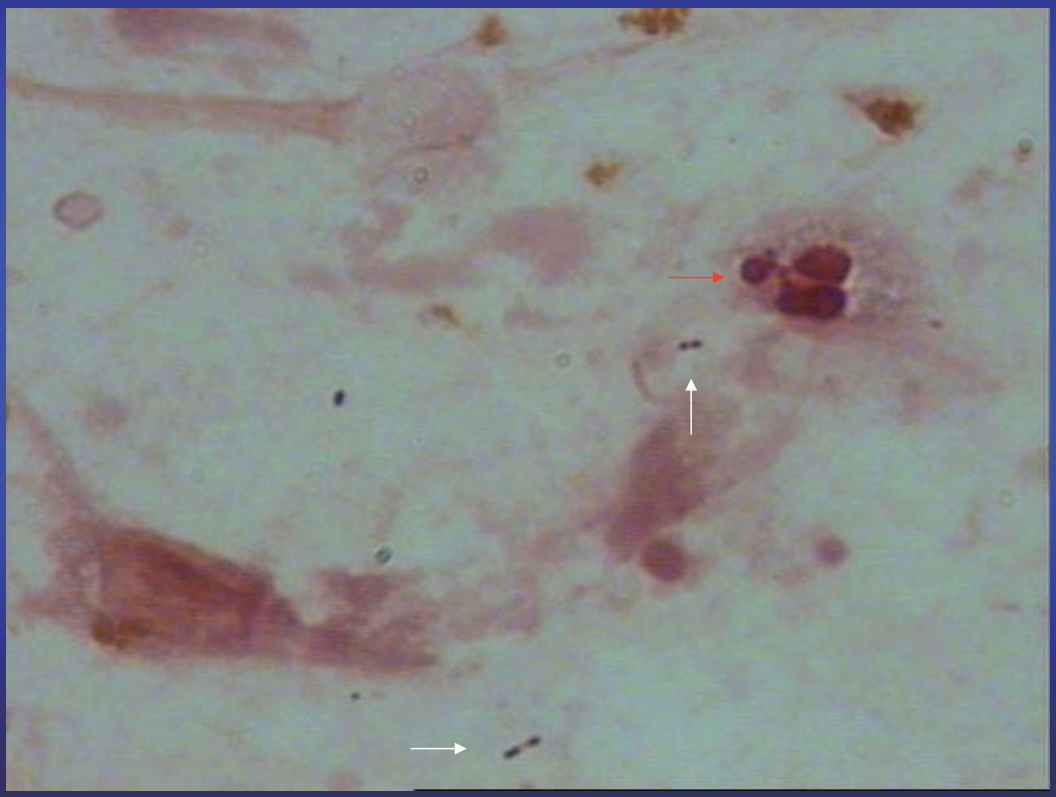
肺炎雙球菌 (*Streptococcus pneumoniae*) – 菌落外觀 (左圖) 與格蘭氏染色 (右圖)

在5%羊血培養皿呈現α型 (不完全) 溶血

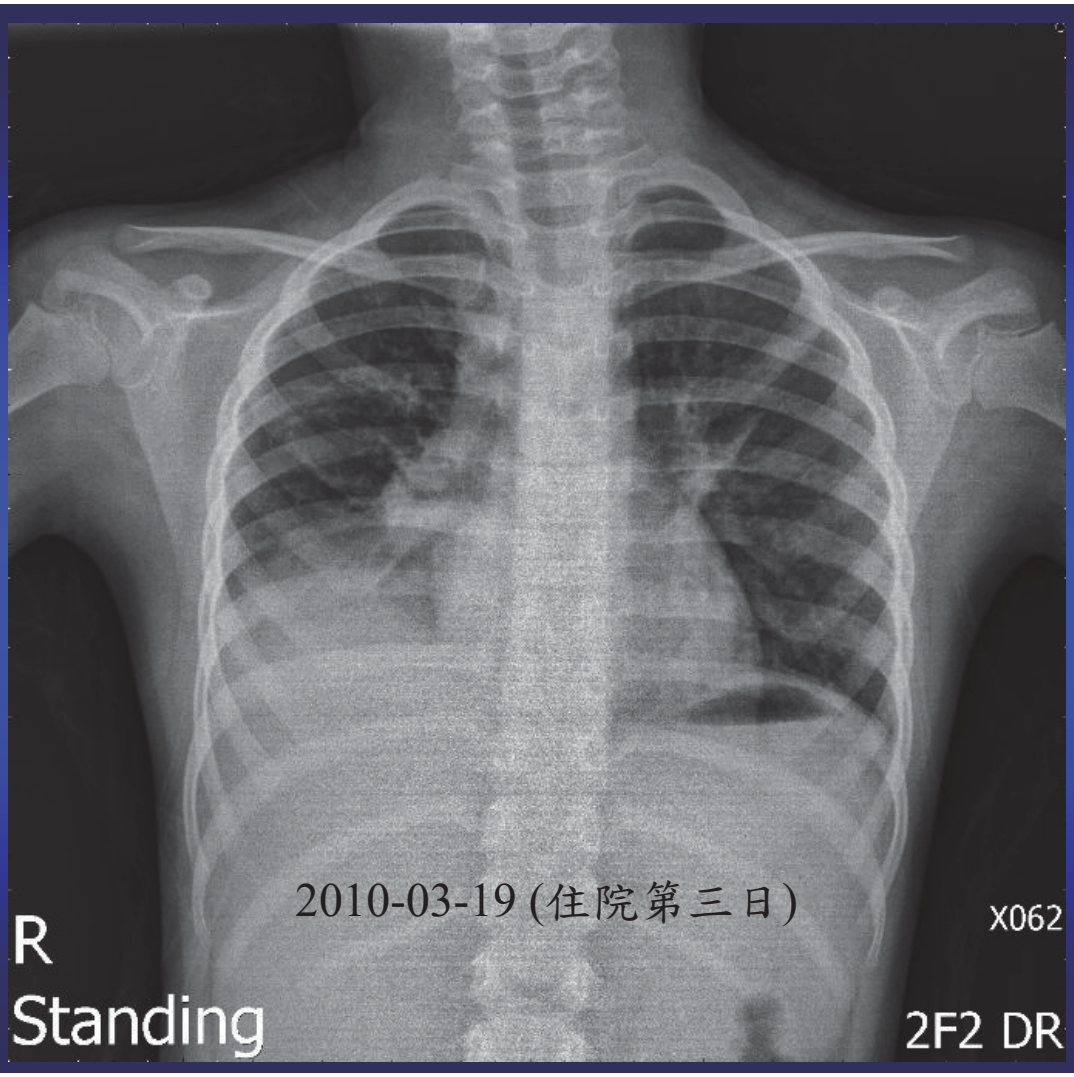
1,000倍光學顯微鏡下為格蘭氏陽性 (紫色) 具莢膜雙球菌



痰液的格蘭氏染色 (Gram Stain x 1,000) – 中性白血球 (紅色箭頭) 與格蘭氏陽性雙球菌合併莢膜 (白色箭頭)




5歲小妹妹因間歇性咳嗽和
高燒 (超過 39 ^{0}C) 與畏寒等
症狀來到急診室求診。
2010-03-17 (住院當日)


2010-03-19 (住院第三日)
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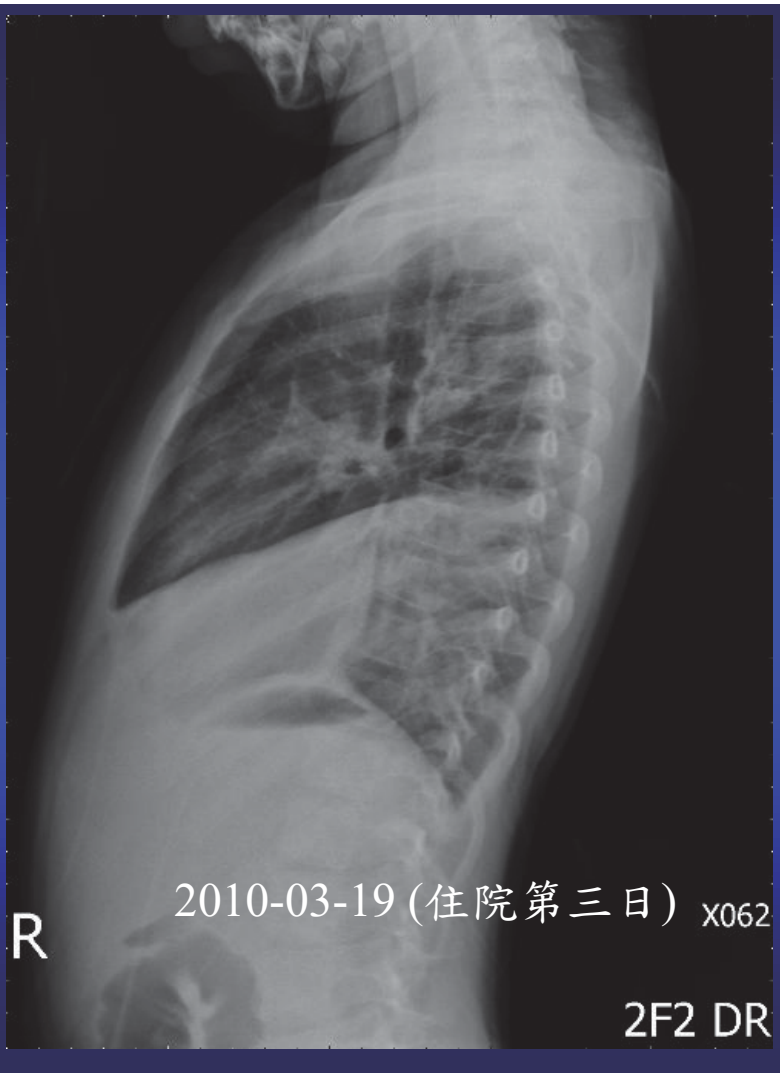
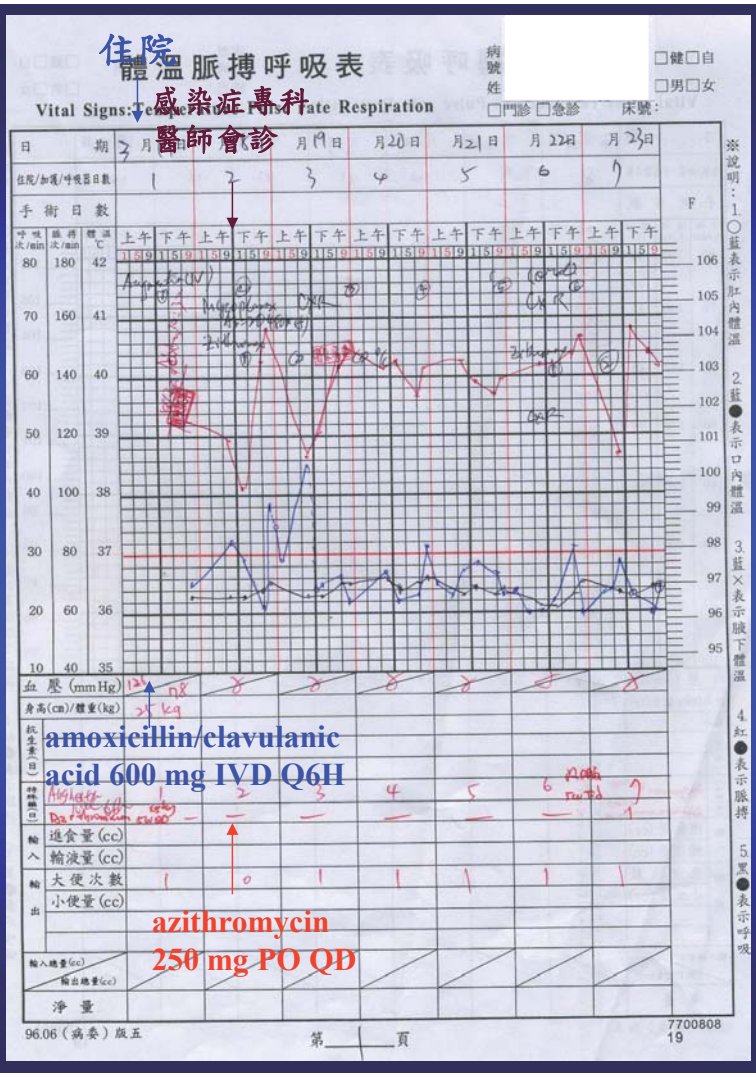


實驗室檢查 – (I)

Date/Items	WBC	Hb	Hct	MCV	Platelet	N/L/M (%)
99-03-17	9,380	13.1	39.7	77.5	216,000	71.7/18.2/7.0

Date/Items	BUN	Cr	Na	K	CRP
99-03-17	9.9	0.5	137	5.1*	3.06

*: hemolysis 2+



住院期間的生命徵象紀錄 (TPR Chart) – (I)

微生物學檢查

Blood culture (99-03-17, one set) : no growth

Urine pneumococcal antigen: Negative

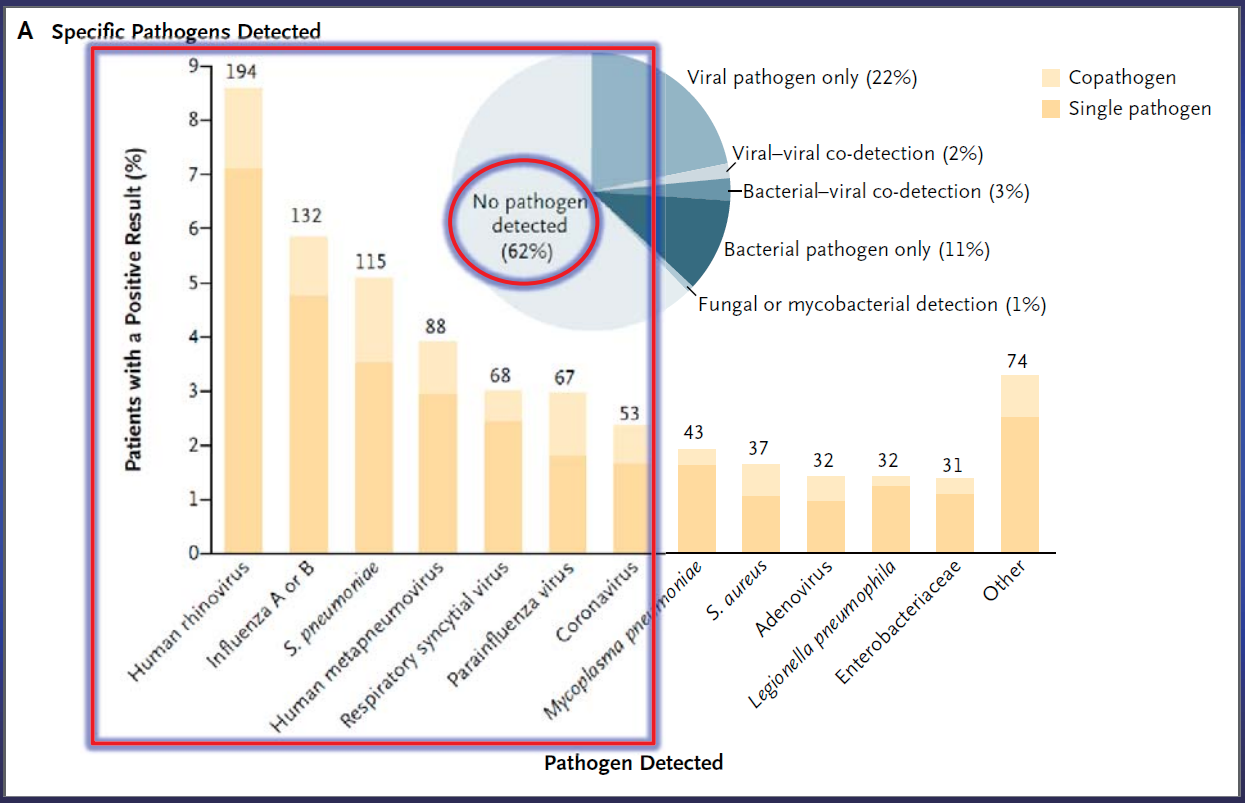
Serum mycoplasma antibody: (+) (1:20480)

確定診斷 (Definite Diagnosis)

1. 肺炎黴漿菌 (*Mycoplasma pneumoniae*) 引起的非典型社區感染性肺炎 (右下葉)
2. 僧帽瓣脫垂合併逆流 (mitral valve prolapse with mitral regurgitation) 和右側房室瓣逆流 (tricuspid regurgitation)

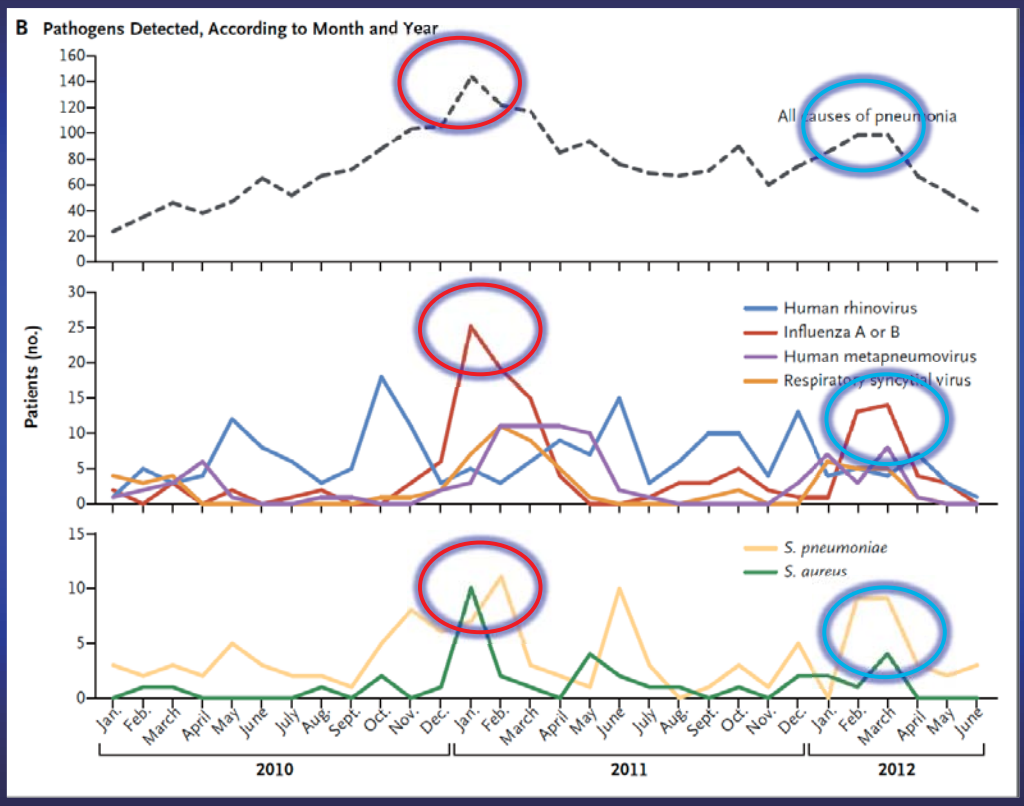
1. 社區性肺炎感染的診斷與治療準則文獻整理的常見致病微生物與診斷方法

圖二A. 於 2010-2012因社區感染性肺炎住院的2,259名成人病人，於835名病人中分離出996個各種致病原比率



Jain S. et al. N Engl J Med. 2015;373:415-427.

圖二B. 於 2010-2012因社區感染性肺炎住院的2,259名成人病人，診斷人數與致病微生物分離數和診斷年月相關趨勢



Jain S. et al. N Engl J Med. 2015;373:415-427.

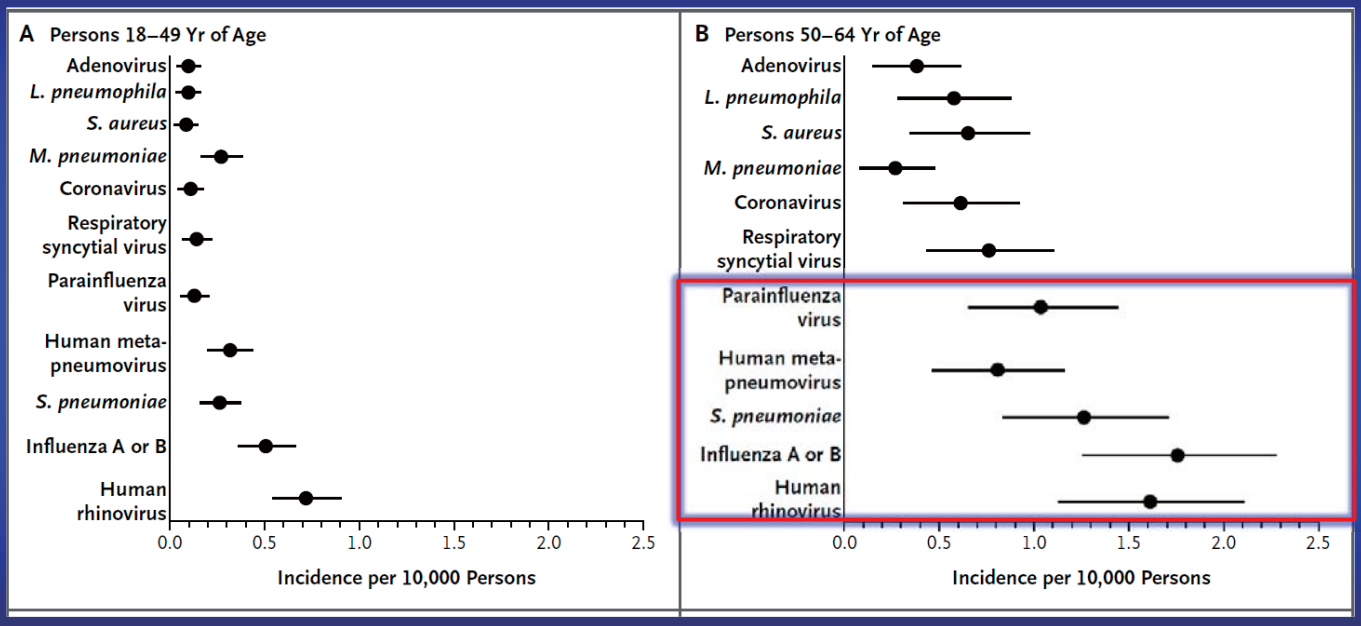
表二. 成人社區性感染肺炎的主要致病微生物種類與分離比率

Table 2. Estimated Annual Incidence Rates of Hospitalization for Community-Acquired Pneumonia, According to Year of Study, Study Site, Age Group, and Pathogen Detected.*

Pathogen detected‡	
Human rhinovirus	2.0 (1.7–2.3)
Influenza A or B virus	1.5 (1.3–1.8)
Streptococcus pneumoniae	1.2 (1.0–1.4)
Human metapneumovirus	0.9 (0.7–1.2)
Parainfluenza virus	0.8 (0.6–1.0)
Respiratory syncytial virus	0.7 (0.5–0.9)
Coronavirus	0.6 (0.4–0.7)
Mycoplasma pneumoniae	0.5 (0.4–0.7)
Staphylococcus aureus	0.4 (0.3–0.6)
Legionella pneumophila	0.4 (0.2–0.5)
Adenovirus	0.4 (0.2–0.5)

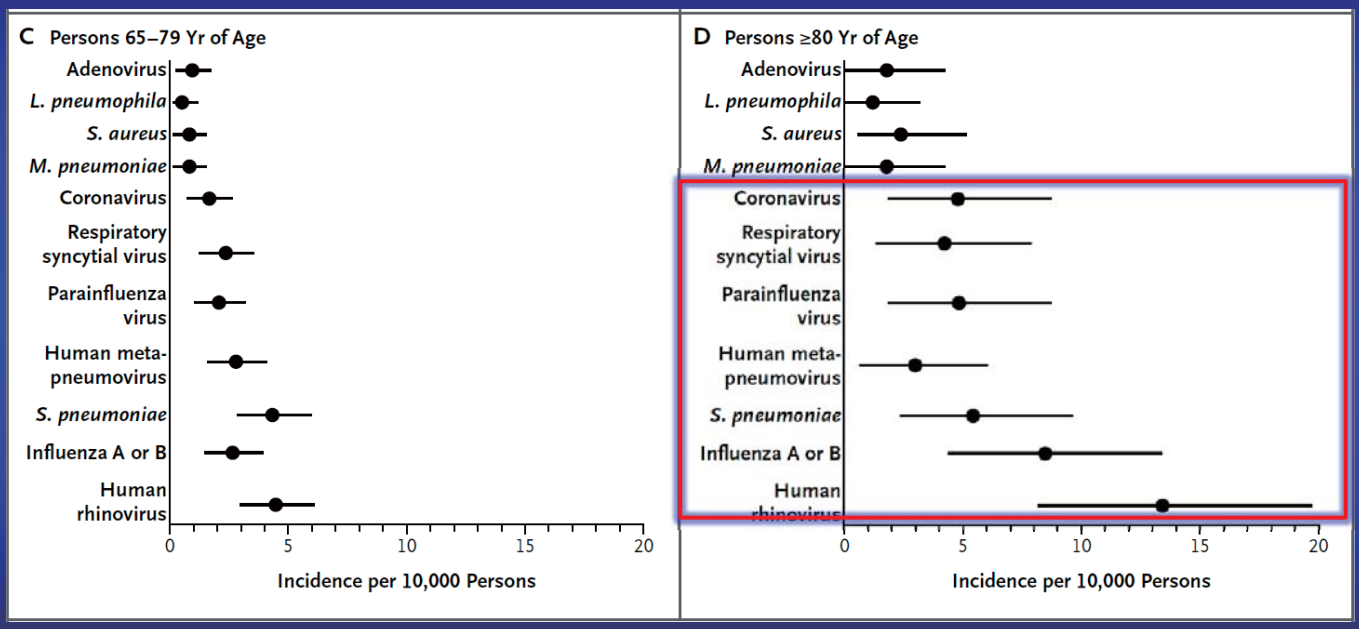
Jain S. et al. N Engl J Med. 2015;373:415-427.

圖二A&B. 因社區性感染肺炎住院治療的成人病人所分離各種致病微生物發生率與病人年齡相關性 (I)



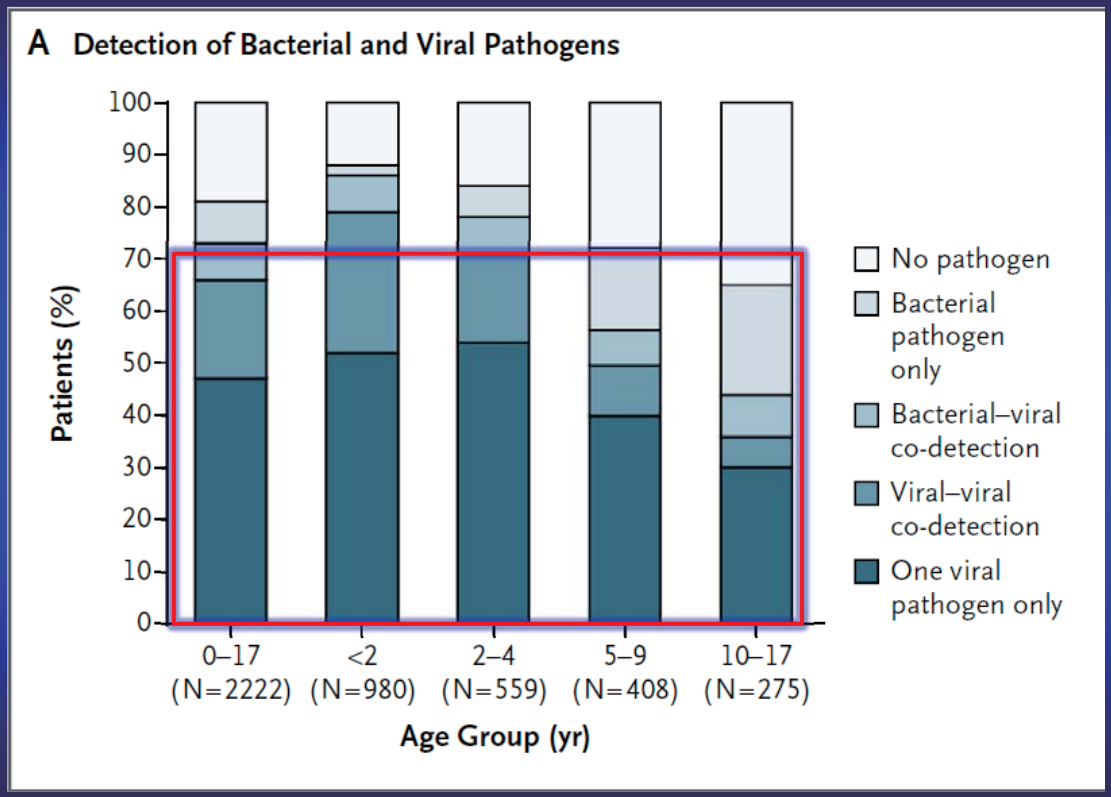
Jain S. et al. N Engl J Med. 2015;373:415-427.

圖二 C&D.因社區性感染肺炎住院治療的成人病人所分離各種致病微生物發生率與病人年齡相關性 (II)



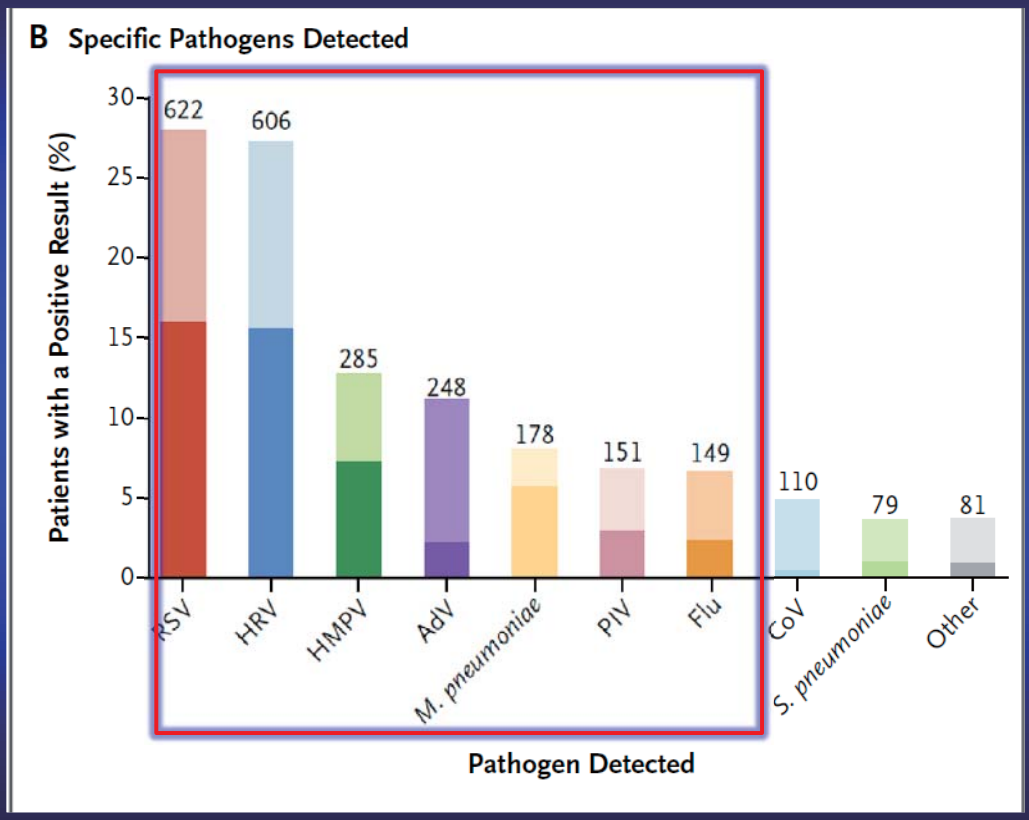
Jain S. et al. N Engl J Med. 2015;373:415-427.

圖二A. 於 2010-2012因社區感染性肺炎住院的2,222名兒科病人，於1,802名病人中分離出2,533個各種致病原依年齡層分離比率



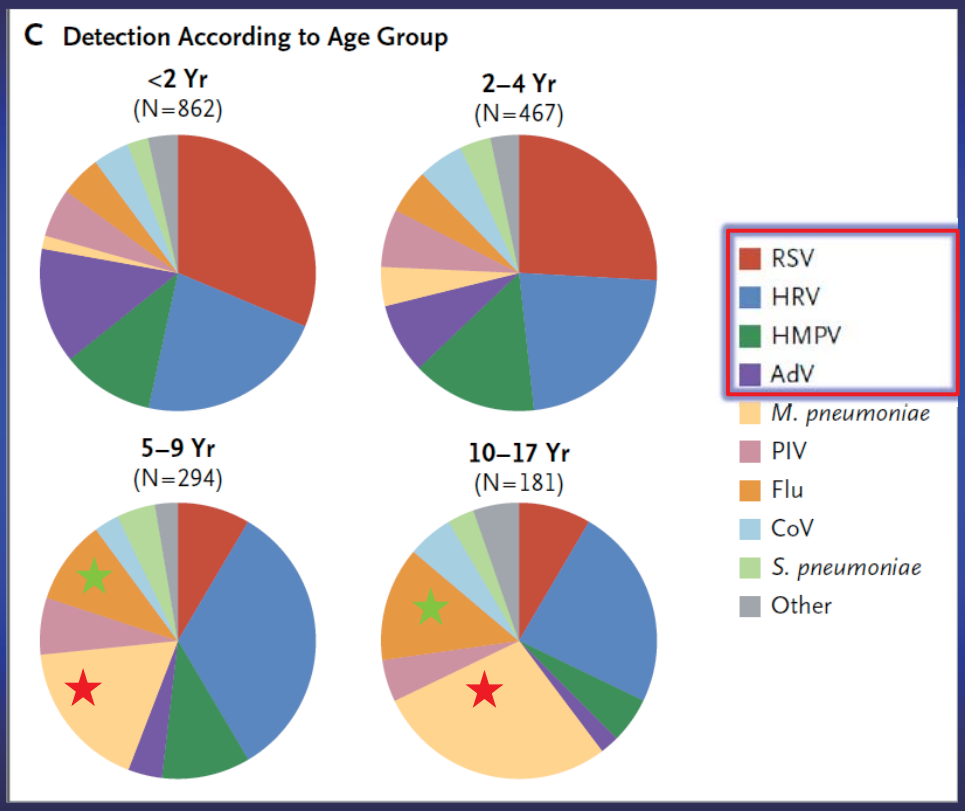
Jain S. et al. N Engl J Med. 2015;372:835-845.

圖二B. 於 2010-2012因社區感染性肺炎住院兒科病人所分離2,533個各種致病原種類與比率 (下層：單一分離，上層：多種分離)



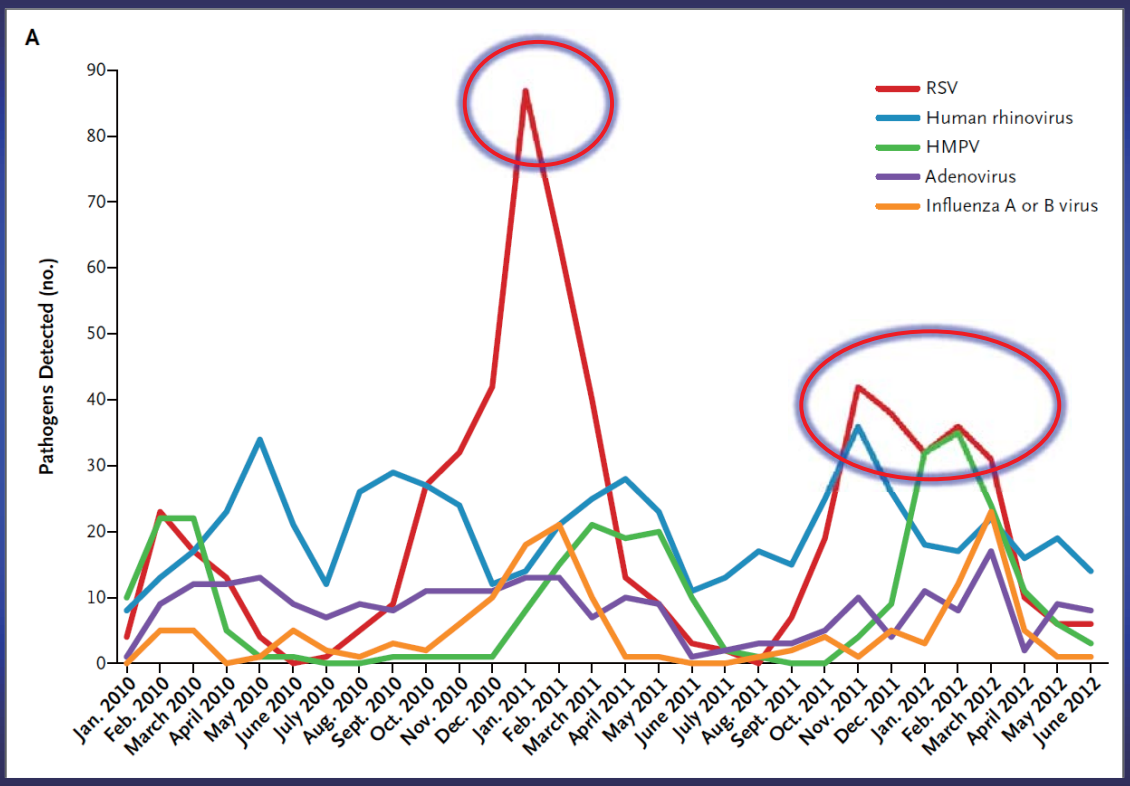
Jain S. et al. N Engl J Med. 2015;372:835-845.

圖二C. 於 2010-2012因社區感染性肺炎住院的2,222名兒科病人，於1,802名病人中分離出2,533個各種致病原依年齡層分離比率



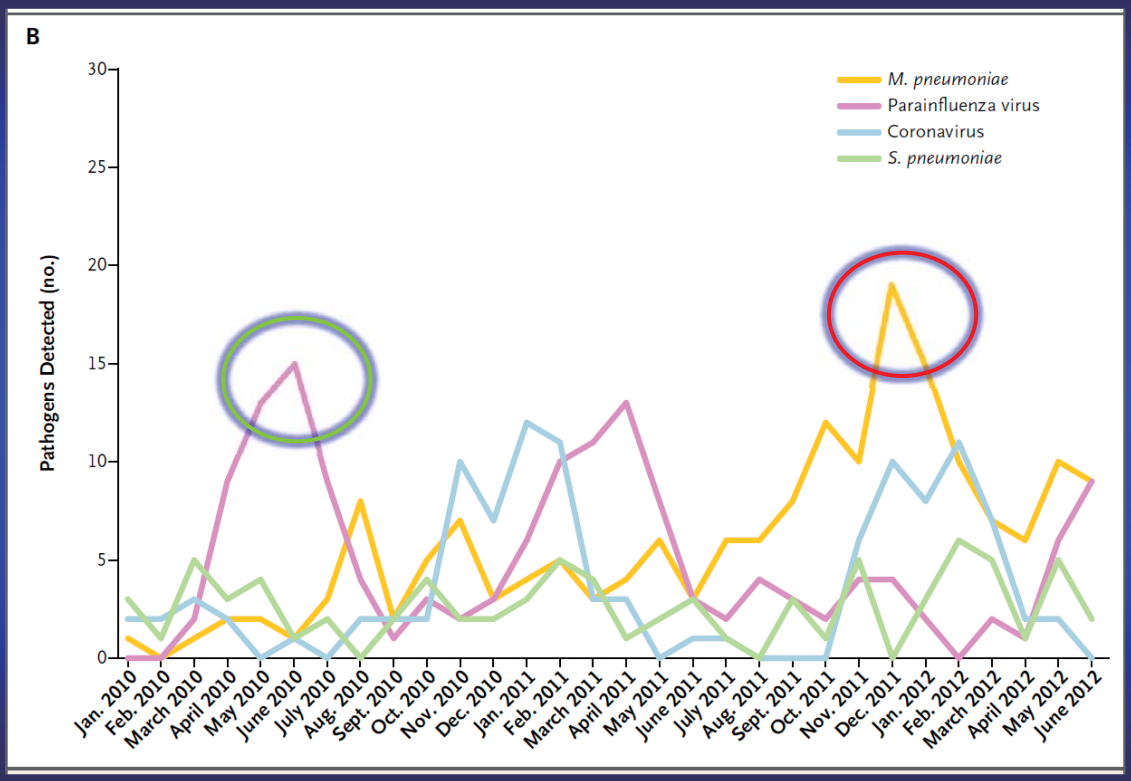
Jain S. et al. N Engl J Med. 2015;372:835-845.

圖三.因社區感染性肺炎住院的兒科病人分離致病微生物數量與分離年月的相關性 (A)



Jain S. et al. N Engl J Med. 2015;372:835-845.

圖三.因社區感染性肺炎住院的兒科病人分離致病微生物數量與分離年月的相關性 (B)



Jain S. et al. N Engl J Med. 2015;372:835-845.

表二. 兒科病人社區性感染肺炎的致病微生物種類與分離比率

Table 2. Estimated Annual Incidence Rates of Hospitalization for Community-Acquired Pneumonia, According to Year of Study, Study Site, Age Group, and Pathogen Detected.*

Pathogen detected‡	
Respiratory syncytial virus	4.6 (4.3–5.1)
Human rhinovirus	4.1 (3.7–4.4)
Human metapneumovirus	1.9 (1.6–2.1)
Adenovirus	1.6 (1.4–1.8)
Mycoplasma pneumoniae	1.4 (1.2–1.6)
Influenza A or B virus	1.1 (0.9–1.3)
Parainfluenza virus	0.9 (0.8–1.1)
Coronavirus	0.8 (0.7–1.0)
Streptococcus pneumoniae	0.5 (0.4–0.6)

Jain S. et al. N Engl J Med. 2015;372:835-845.

表五. 各種特殊表現的社區感染性肺炎所需診斷項目

Table 5. Clinical indications for more extensive diagnostic testing.

Indication 適應症	血液培養 Blood culture	痰液培養 Sputum culture	退伍軍人菌尿液抗原 *Legionella* UAT	肺炎雙球菌尿液抗原 Pneumococcal UAT	其他 Other
Intensive care unit admission	X	X	X	X	X[a]
Failure of outpatient antibiotic therapy		X	X	X	
Cavitary infiltrates	X	X			X[b]
Leukopenia	X			X	
Active alcohol abuse	X	X	X	X	
Chronic severe liver disease	X			X	
Severe obstructive/structural lung disease		X			
Asplenia (anatomic or functional)	X			X	
Recent travel (within past 2 weeks)			X		X[c]
Positive *Legionella* UAT result		X[d]	NA		
Positive pneumococcal UAT result	X	X		NA	
Pleural effusion	X	X	X	X	X[e]

NOTE. NA, not applicable; UAT, urinary antigen test.

[a] Endotracheal aspirate if intubated, possibly bronchoscopy or nonbronchoscopic bronchoalveolar lavage.
[b] Fungal and tuberculosis cultures.
[c] See table 8 for details.
[d] Special media for *Legionella*.
[e] Thoracentesis and pleural fluid cultures.

Mandell LA et al. Clin Infect Dis 2007;44:S27-72

Table 6. Most common etiologies of community-acquired pneumonia.

Patient type	Etiology
Outpatient 門診病人	*Streptococcus pneumoniae* *Mycoplasma pneumoniae* *Haemophilus influenzae* *Chlamydophila pneumoniae* Respiratory viruses[a]
Inpatient (non-ICU) 住院但非加護病房病人	*S. pneumoniae* *M. pneumoniae* *C. pneumoniae* *H. influenzae* *Legionella* species Aspiration Respiratory viruses[a]
Inpatient (ICU) 加護病房病人	*S. pneumoniae* *Staphylococcus aureus* *Legionella* species Gram-negative bacilli *H. influenzae*

NOTE. Based on collective data from recent studies [171]. ICU, intensive care unit.

[a] Influenza A and B, adenovirus, respiratory syncytial virus, and parainfluenza.

表六. 美國依據病人屬性 (病情嚴重程度) 的社區感染性肺炎的常見致病微生物

Mandell LA et al. Clin Infect Dis 2007;44:S27-72

表八. 自流行病學與危險因子預測社區感染性肺炎致病菌 (II)

Table 8. Epidemiologic conditions and/or risk factors related to specific pathogens in community-acquired pneumonia.

Condition	Commonly encountered pathogen(s)
HIV infection (early)	*S. pneumoniae, H. influenzae, M. tuberculosis*
HIV infection (late)	The pathogens listed for early infection plus *Pneumocystis jirovecii, Cryptococcus, Histoplasma, Aspergillus,* atypical mycobacteria (especially *Mycobacterium kansasii*), *P. aeruginosa, H. influenzae*
Hotel or cruise ship stay in previous 2 weeks	*Legionella* species
Travel to or residence in southwestern United States	*Coccidioides* species, *Hantavirus*
Travel to or residence in Southeast and East Asia	*Burkholderia pseudomallei,* avian influenza, SARS
Influenza active in community	Influenza, *S. pneumoniae, Staphylococcus aureus, H. influenzae*
Cough >2 weeks with whoop or posttussive vomiting	*Bordetella pertussis*
Structural lung disease (e.g., bronchiectasis)	*Pseudomonas aeruginosa, Burkholderia cepacia, S. aureus*
Injection drug use	*S. aureus,* anaerobes, *M. tuberculosis, S. pneumoniae*
Endobronchial obstruction	Anaerobes, *S. pneumoniae, H. influenzae, S. aureus*
In context of bioterrorism	*Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), *Francisella tularensis* (tularemia)

Mandell LA et al. Clin Infect Dis 2007;44:S27-72

注意事項一. 特定社區感染肺炎致病微生物的臨床表現

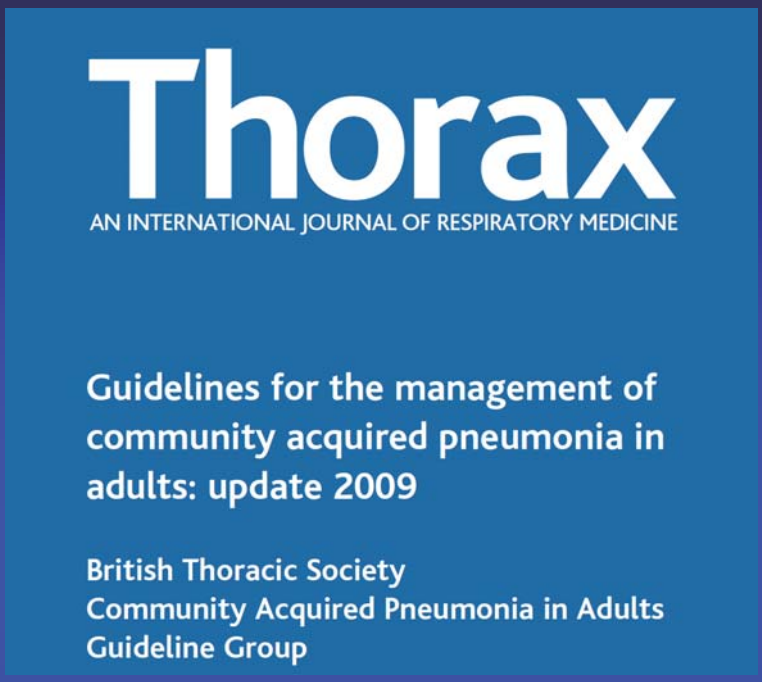
Box 1 Some clinical features reported to be more common with specific pathogens (references are given in the text)

- *Streptococcus pneumoniae*: increasing age, comorbidity,

肺炎雙球菌：成年或老年人、多具潛在疾病、急性發作、高燒、和肋膜性胸痛。
肺炎雙球菌核病菌血症：女性病人、酒癮、糖尿病、慢性肺部阻塞性疾病，和乾咳。
退伍軍人肺炎桿菌：青年人、抽菸、無潛在疾病、腹瀉、神經學症狀、症狀較為嚴重且有影響多重器官(如肝腎功能異常等)。
肺炎黴漿菌：青年人和兒科病人、先前接受過抗生素治療、較少影響多重器官。
肺炎披衣菌：住院前肺炎症狀持續時間較久，和頭痛。
Q熱桿菌：男性病人、乾咳，和高燒等。

- *Coxiella burnetii*: males, dry cough, high fever.

Wedzicha JA et al. Thorax 2009;64 (Suppl III) iii1-iii55



英國胸腔醫學會聯合英國皇家醫師學會、臨床醫師學會、急診醫學會、老人醫學會、感染症醫學會、抗微生物製劑治療學會、呼吸道照護學會、國民健康局，和急重症醫學會，於2009年聯合制定成人社區感染性肺炎的治療準則

Wedzicha JA et al. Thorax 2009;64 (Suppl III) iii1-iii55

表四. 對社區感染肺炎病人執行微生物學檢查的適應症 (II)

肺炎嚴重程度分類　　建議接受治療地點　　建議微生物學檢查項目

Table 4 Recommendations for the microbiological investigation of community acquired pneumonia (CAP)

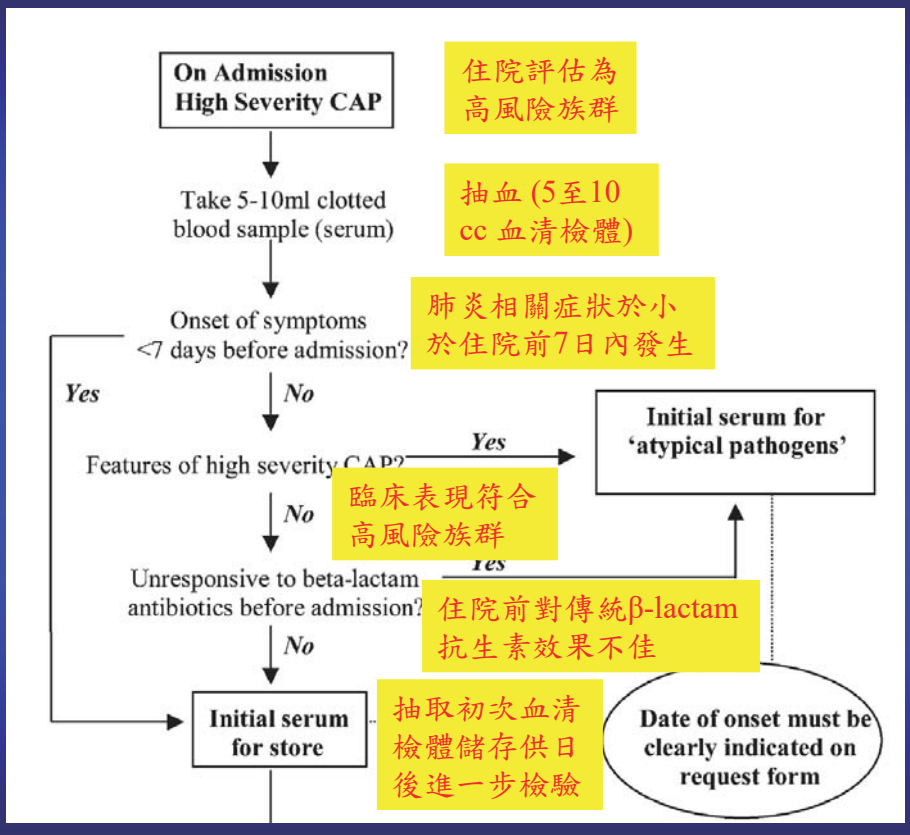
Pneumonia severity (based on clinical judgement supported by severity scoring tool)	Treatment site	Preferred microbiological tests
High severity (eg, CURB65 = 3–5, 15–40% mortality) 高風險族群	Hospital	Blood cultures (minimum 20 ml) Sputum or other respiratory sample‡ for routine culture and sensitivity tests (±Gram stain†) Pleural fluid, if present, for microscopy, culture and pneumococcal antigen detection. Pneumococcal urine antigen test Investigations for legionella pneumonia: (a) Urine for legionella antigen (b) Sputum or other respiratory sample‡ for legionella culture and direct immunofluorescence (if available) Investigations for atypical and viral pathogens:** (a) If available, sputum or other respiratory sample for PCR or direct immunofluorescence (or other antigen detection test) for *Mycoplasma pneumoniae Chlamydia* spp, influenza A and B, parainfluenza 1–3, adenovirus, respiratory syncytial virus, *Pneumocystis jirovecii* (if at risk) (b) Consider initial and follow-up viral and "atypical pathogen" serology§

須執行血液、痰液或其他呼吸道分泌物培養、肺炎雙球菌尿液抗原、退伍軍人菌檢查 (尿液抗原、血清抗體，和痰液直接免疫螢光染色)、**其他非典型致病菌與病毒學檢查 (A型與B型流感病毒、副流感病毒**、披衣菌、黴漿菌、腺病毒、呼吸道融合病毒，和肺囊胞蟲肺炎等) (PCR或直接螢光染色等)

*If PCR for respiratory viruses and atypical pathogens is readily available or obtainable locally, then this would be preferred to serological investigations.
†The routine use of sputum Gram stain is discussed in the text.
‡Consider obtaining lower respiratory tract samples by more invasive techniques such as bronchoscopy (usually after intubation) or percutanous fine needle aspiration for those who are skilled in this technique.
§The use of paired serology tests for patients with high severity CAP is discussed in the text. If performed, the date of onset of illness should be clearly indicated on the laboratory request form.
¶Patients with clinical or epidemiological risk factors (travel, occupation, comorbid disease). Investigations should be considered for all patients with CAP during legionella outbreaks.
**For patients unresponsive to β-lactam antibiotics or those with a strong suspicion of an "atypical" pathogen on clinical, radiographic or epidemiological grounds.

Wedzicha JA et al. Thorax 2009;64 (Suppl III) iii1-iii55

圖六. 針對嚴重程度社區感染肺炎的血清學診斷流程 (I)



住院評估為高風險族群

抽血 (5至10 cc 血清檢體)

肺炎相關症狀於小於住院前7日內發生

臨床表現符合高風險族群

執行初次非典型肺炎致病菌血清抗體檢查

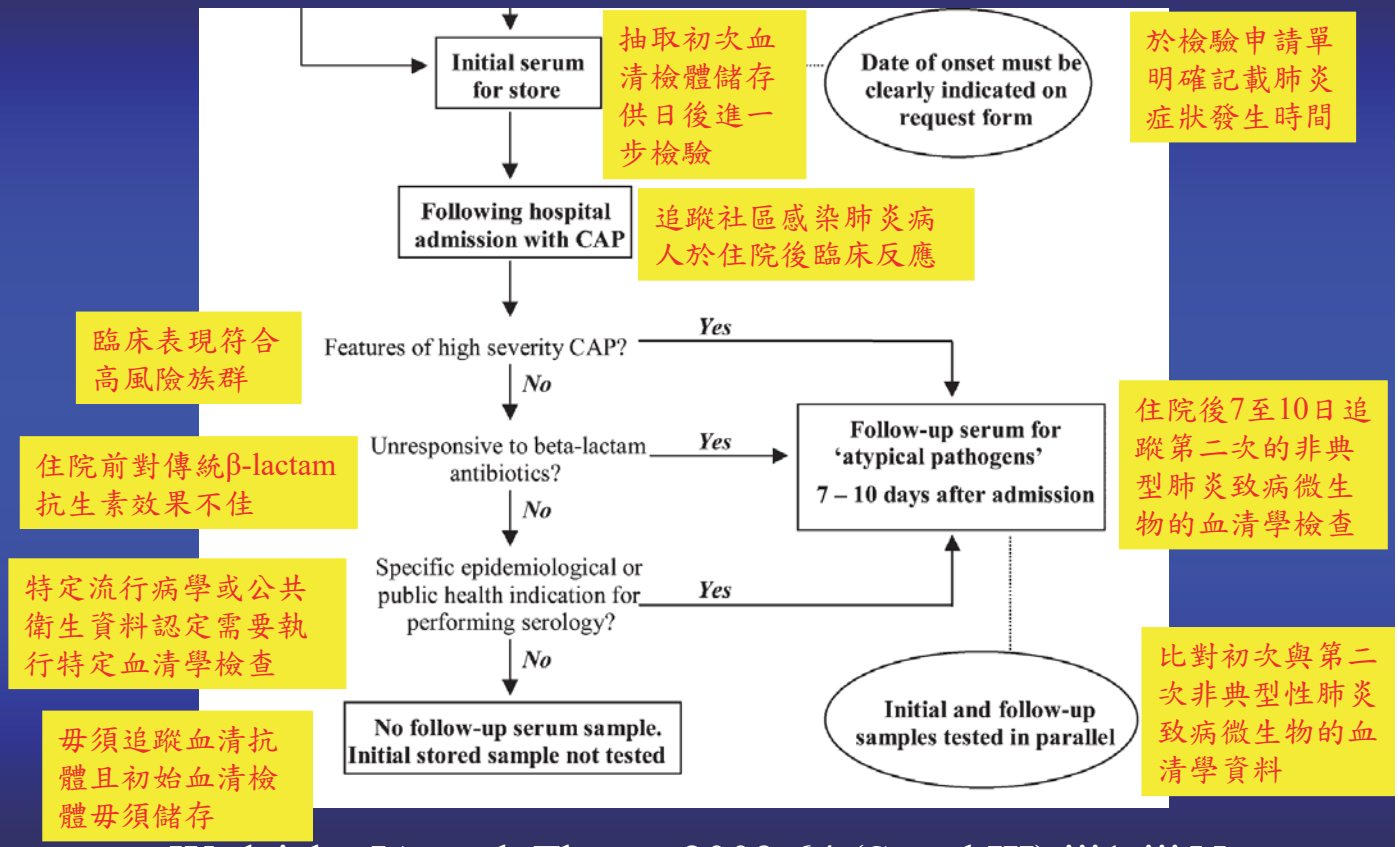
住院前對傳統β-lactam抗生素效果不佳

抽取初次血清檢體儲存供日後進一步檢驗

於檢驗申請單明確記載肺炎症狀發生時間

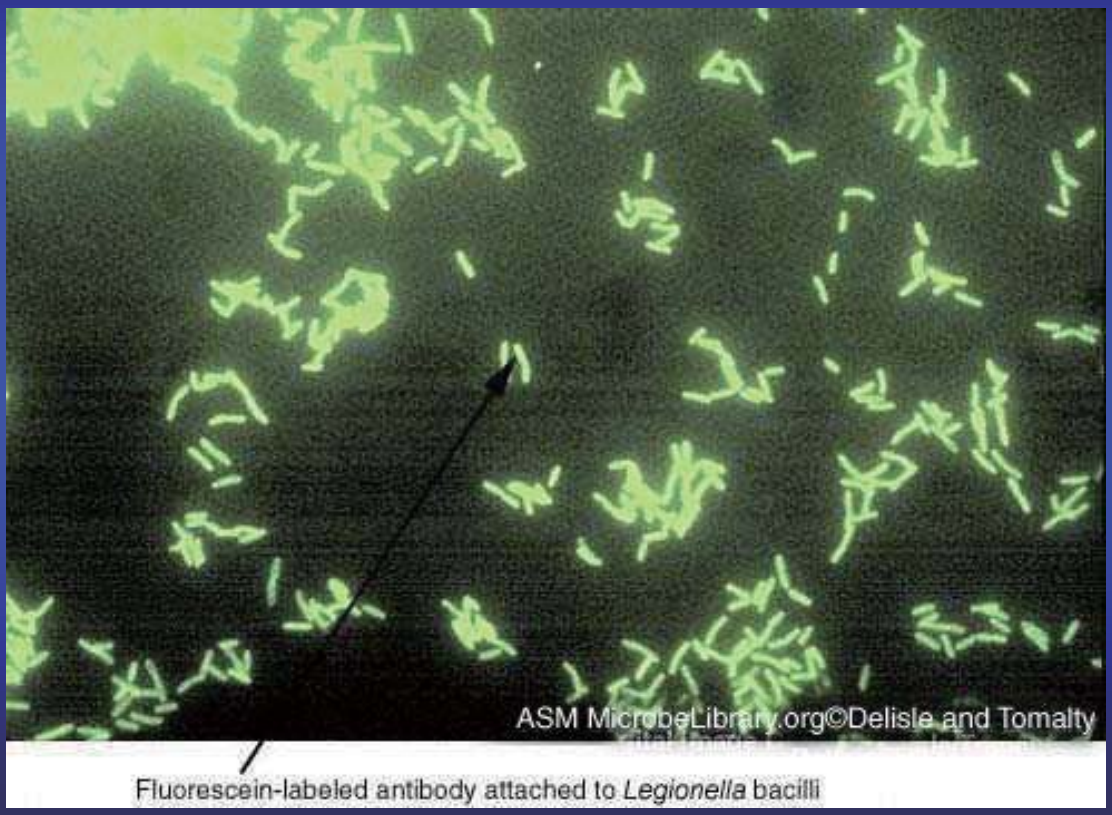
Wedzicha JA et al. Thorax 2009;64 (Suppl III) iii1-iii55

圖六. 針對嚴重程度社區感染肺炎的血清學診斷流程 (II)

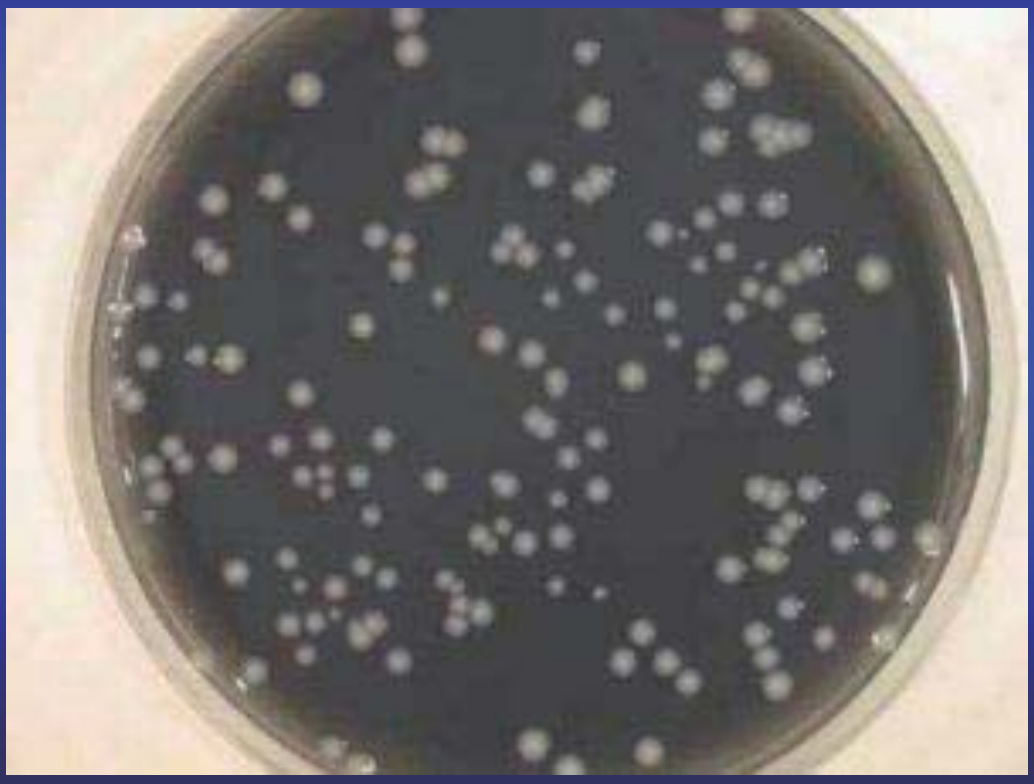


Wedzicha JA et al. Thorax 2009;64 (Suppl III) iii1-iii55

螢光顯微鏡下使用直接螢光抗體 (Direct Fluorescent Antibody – DFA) 對檢體中 *L. pneumophila* 的染色

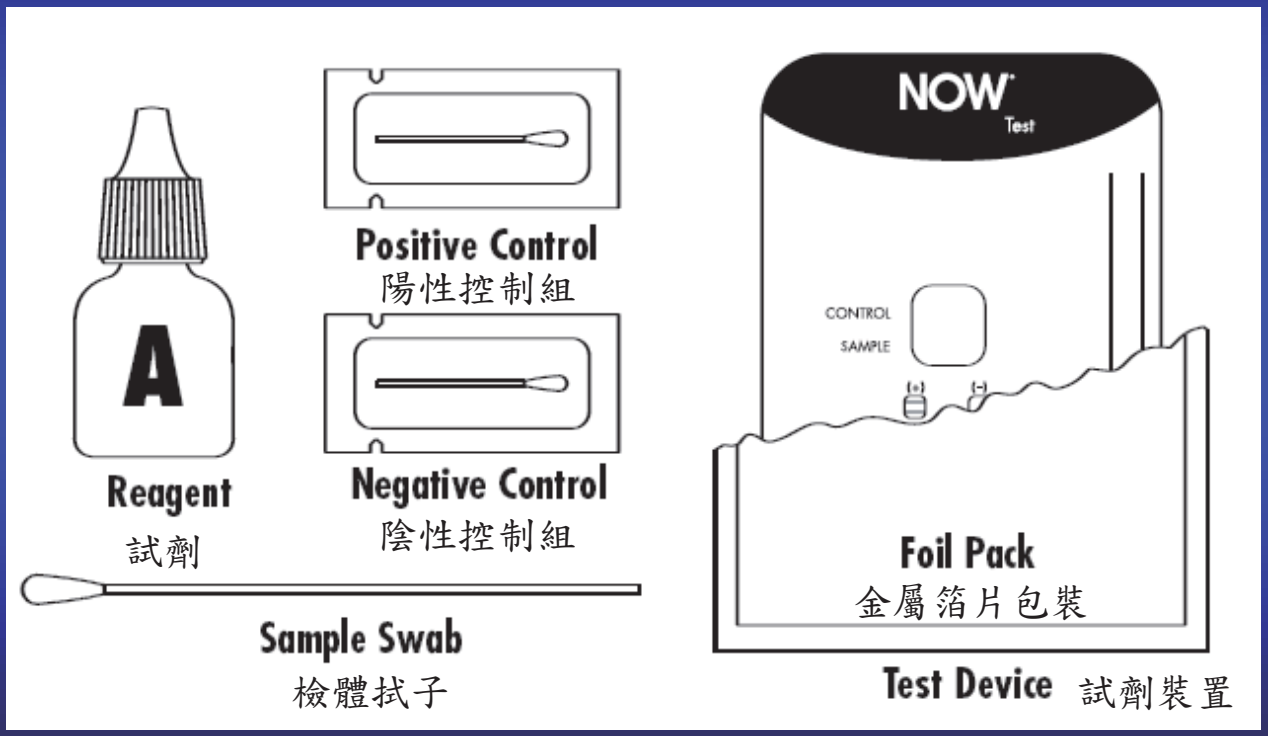


Buffered-Charcoal Yeast-Extract (BCYE) Agar 和所培養退伍軍人症桿菌 (*Legionella pneumophila*) 菌株

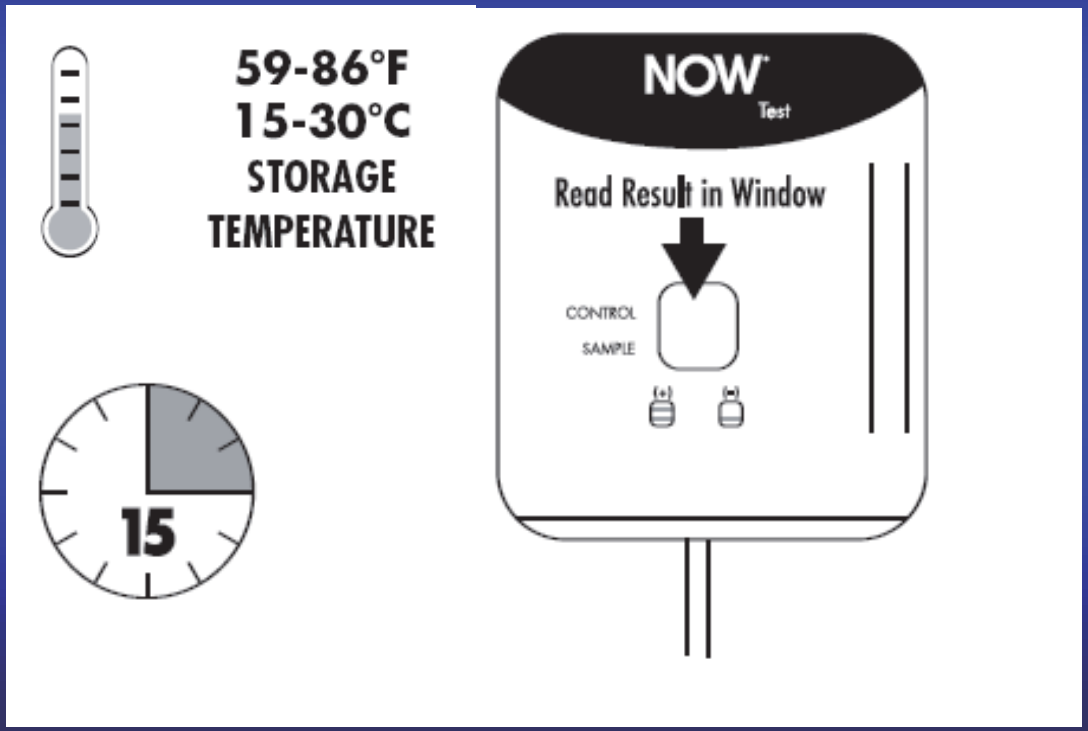


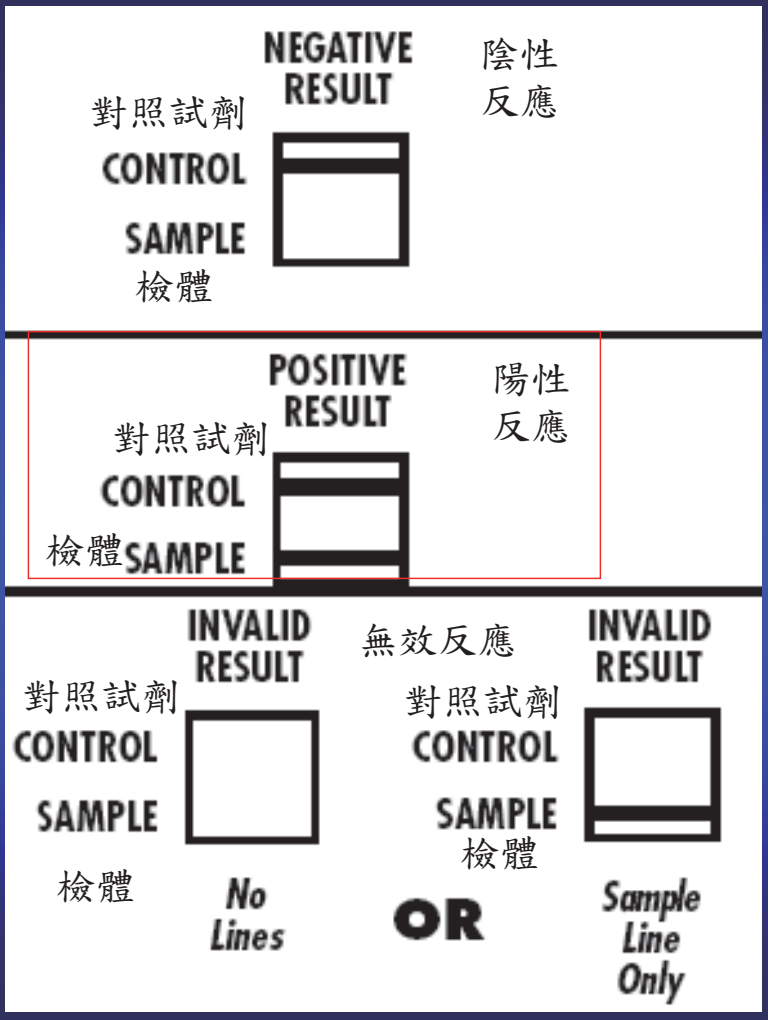
使用 BinaxNow® 試劑偵測尿液中 *L. pneumophila* Serogroup 1 抗原

使用 BinaxNow® 試劑偵測尿液中 *L. pneumophila* Serogroup 1 抗原 – 檢驗工具



使用 BinaxNow® 試劑偵測尿液中 *L. pneumophila* Serogroup 1 抗原 – 保存溫度 (15-30 ^{0}C) 和偵測時間 (15分鐘)





使用 BinaxNow® 試劑偵測尿液中 *L. pneumophila* Serogroup 1 抗原的原理

退伍軍人症的實驗室診斷方法,敏感度,與特異度分析

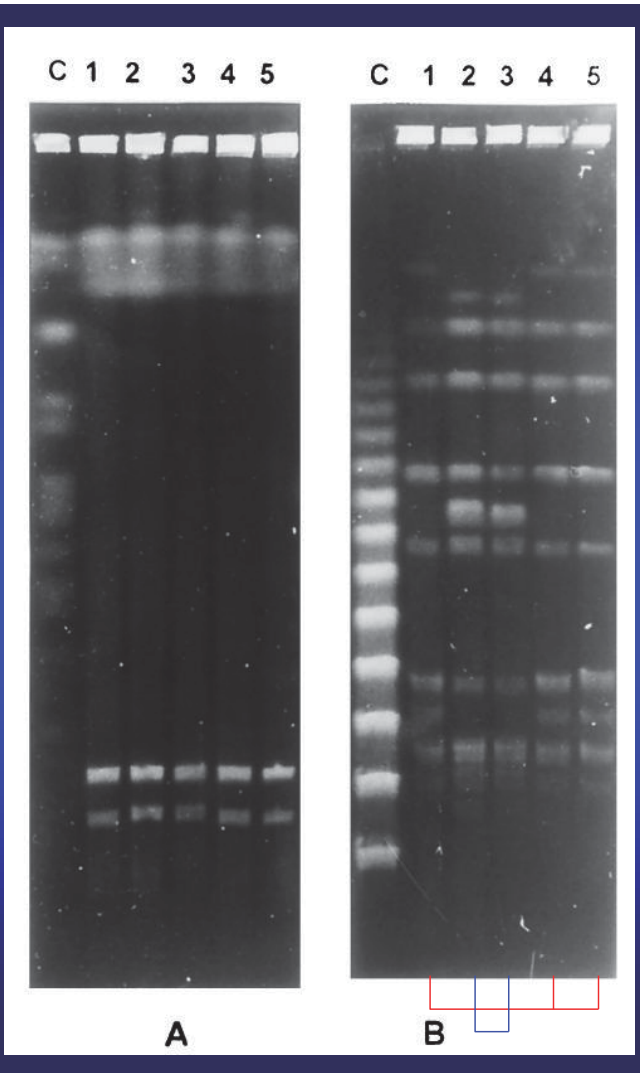
TABLE 1. USEFULNESS OF SPECIALIZED LABORATORY TESTS FOR THE DIAGNOSIS OF LEGIONNAIRES' DISEASE.

只偵測 *L. pneumophila* serogroup 1

兩次血清抗體有4倍以上的上昇或單一抗體 ≥ 1:256 即判定為陽性

TEST	SENSITIVITY 敏感度	SPECIFICITY 特異度
	percent	
Sputum culture 痰液培養	80	100
Direct fluorescent-antibody stain of sputum 痰液螢光抗體染色	33–70	96–99
Urinary antigen assay† 尿液抗原分析	70	100
Serologic tests for antibody‡ 血清抗體分析	40–60	96–99

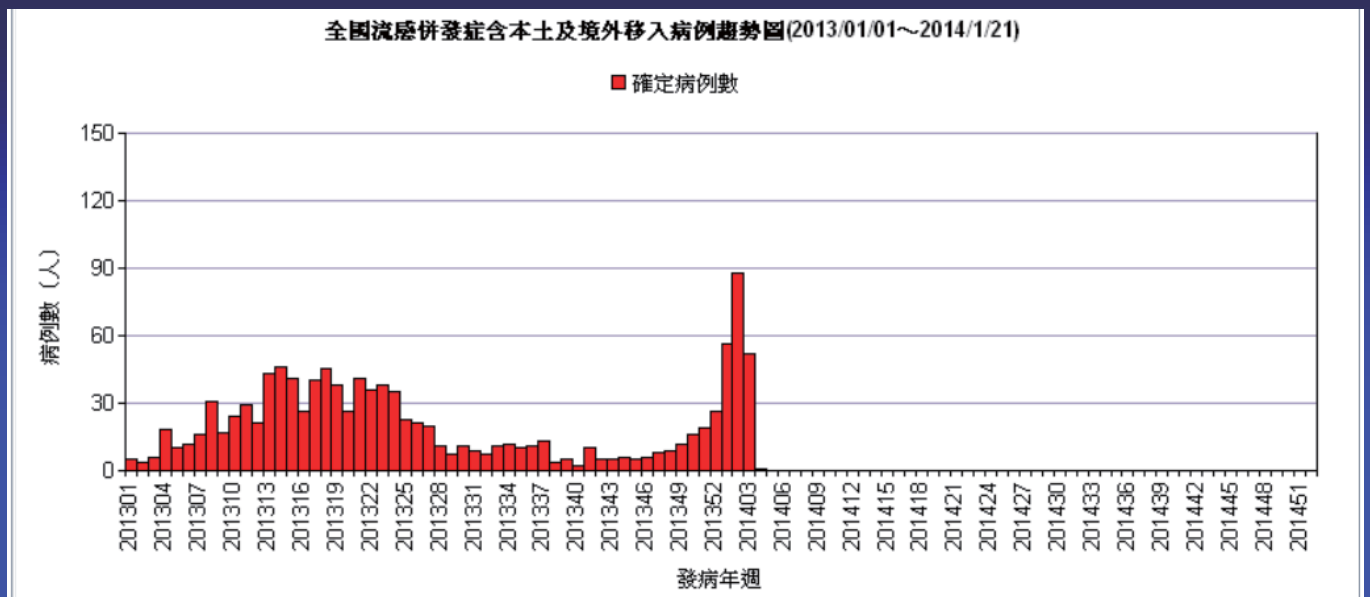
Stout JE and Yu VL. N Engl J Med 1997;337(10):682-687



西班牙兒童醫院中腎臟移植病房的5例兒科病人發生院內退伍軍人症感染的脈衝電場膠質電泳法 (Pulse-Field Gel Electrophoresis – PFGE) 使用限制酶 *Not*I (A圖) 和*SfiI* (B圖) 切割臨床菌株圖

Campins M et al.
Pediat Infect Dis J
2000;19:228-34

2. 流行性感冒 (含新型流感) 的實驗室檢驗方法的敏感度與特異度比較



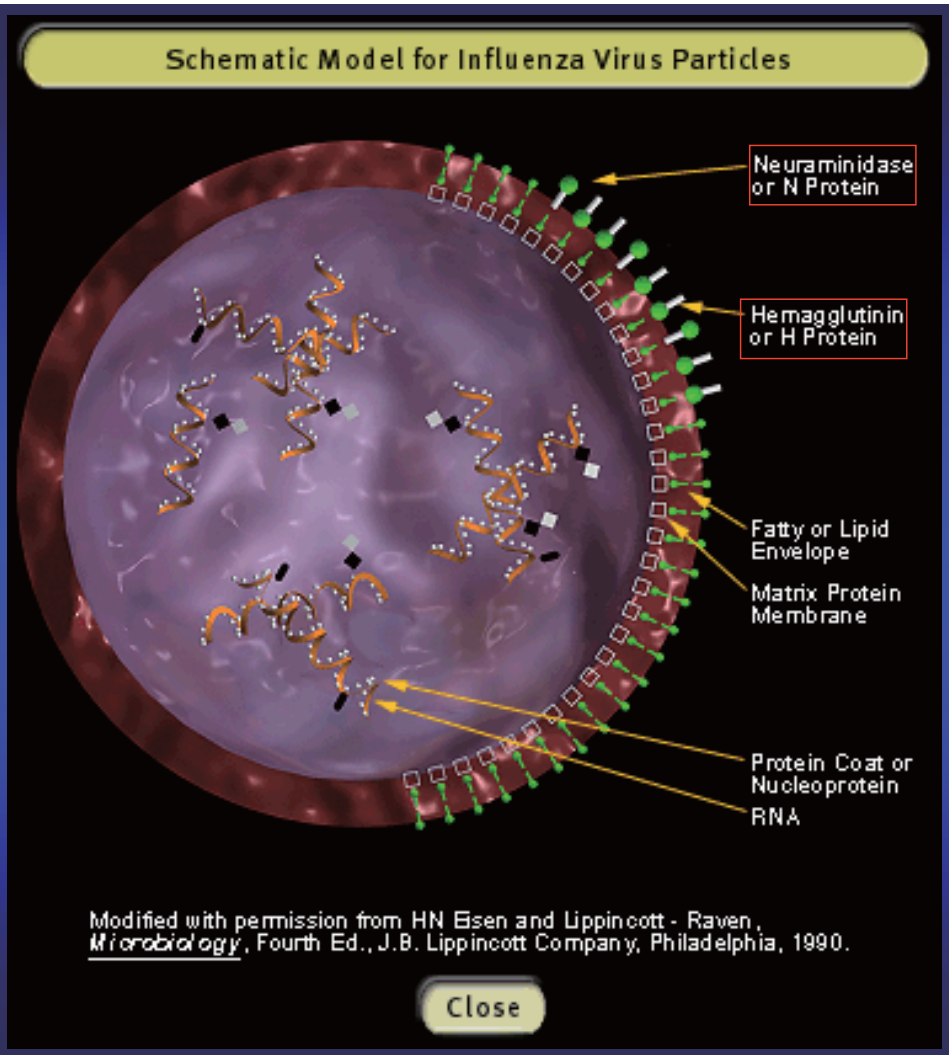
疾病名稱：流感併發症

最近一例確定病例發病日	上週累計數	本週累計數	本月累計數	本年累計數	去年確定總數	上週與前三週平均數比較	上週與過去三年同期平均數比較	今年累計確定病例死亡數
2014/1/19	52	1	185	185	964	▽4.67	▽56.33	4

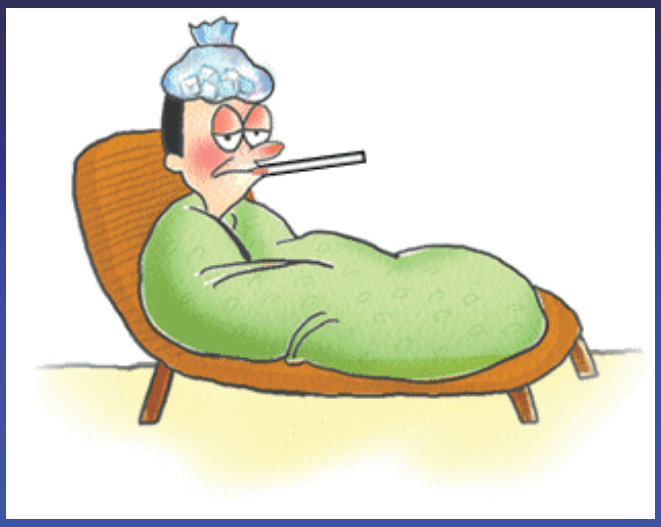
註一：資料更新時間為2014/1/22 6:43 AM，本週為【2014/04】週，本月為【2014/1】月。
註二：本查詢結果為系統自動產生，數據隨時可能因未來修正而變動。
註三：本年累計數，係以發病年統計。

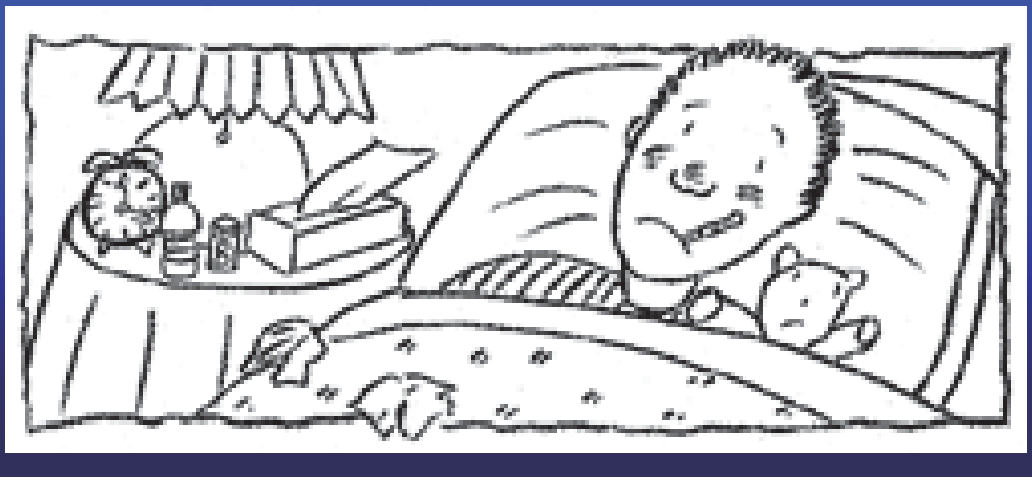
CDC, Taiwan. Jan 22nd, 2014

流行性感冒病毒結構圖

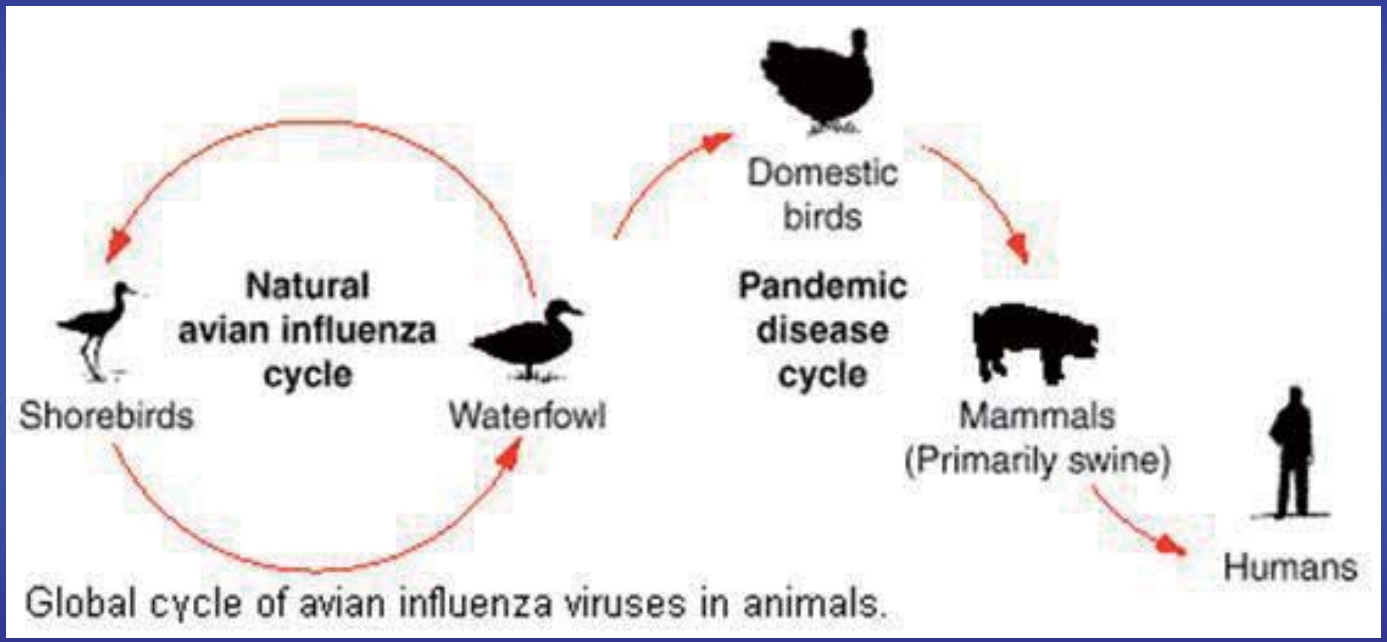


流行性感冒症狀:
高燒、咽喉疼痛、頭痛、肌肉關節酸痛、鼻塞和流鼻水(少見)、嘔吐(少見)，腹瀉(少見)、





禽流感病毒 (Avian Influenza Virus) 存在動物傳播途徑



世界衛生組織 (World Health Organization – WHO) 公佈最新國際疫情 Influenza H7N9

WHO (www.who.int). April 3rd, 2013

H7N9禽流感自2013年4月3日起公告為第五類法定報告傳染病 (需於24小時內通報並給予適當隔離)

CDC, Taiwan, April 3rd , 2013

H7N9A型流行性感冒 - 臨床條件定義

具有下列任一條件：

1. 急性呼吸道感染，臨床症狀至少包括發燒（≧38℃）及咳嗽；
2. 臨床、放射線診斷或病理學上顯示肺部實質疾病。

CDC, Taiwan, April 3rd, 2013

H7N9A型流行性感冒 - 檢驗條件定義

具有下列任一條件：

1. 臨床檢體培養分離及鑑定出H7N9流感病毒；
2. 分子生物學H7N9核酸檢測陽性；
3. 血清學抗體檢測呈現為最近感染。

CDC, Taiwan, April 3rd, 2013

H7N9A型流行性感冒 - 流行病學條件定義

發病前7日內，具有下列任一個條件：

1. 曾經與出現症狀的確定病例有密切接觸，包括照護、相處、或有呼吸道分泌物、體液之直接接觸；
2. 曾至有出現H7N9流感人類病例地區之旅遊史或居住史；
3. 在實驗室或其他環境，處理動物或人類之檢體，而該檢體可能含有H7N9流感病毒。

CDC, Taiwan, April 3rd, 2013

H7N9A型流行性感冒 - 通報條件

具有下列任一條件：

1. 符合臨床條件及流行病學條件。
2. 符合檢驗條件 (確定病例)。

CDC, Taiwan, April 3rd, 2013

H7N9A型流行性感冒 - 檢體採檢注意事項

採檢項目	檢體種類	採檢目的	採檢時間	採檢量及規定	送驗方式	注意事項
H7N9流感	咽喉擦拭液	病原體檢測	發病3天內	以無菌病毒拭子之棉棒擦拭咽喉，插入病毒保存輸送管。	低溫	見2.8.5備註說明及咽喉採檢步驟請參考第3.7節及圖3.7。
	血清	抗體檢測（檢體保留）	急性期（發病1-5天）；恢復期(發病14-20天之間)	以無菌試管收集至少3 mL血清。		1. H7N9流感第2次血清採檢時機，由本局昆陽辦公室通知。 2. 血清檢體見2.8.3及2.8.4備註說明及血清採檢步驟請參考第3.3節。

CDC, Taiwan, April 3rd, 2013

World Health Organization

Real-time RT-PCR Protocol for the Detection of A(H7N9) Influenza Virus

使用分子生物學 (即時聚合酶連鎖反應 – real time PCR) 對咽喉拭子檢體檢驗H7N9流感病毒的血凝素 (hemaglutinin – HA) 和神經激胺酶 (neuramidase – NA) 的支配基因 (H7和N9)。

The WHO Collaborating Center for Reference and Research on Influenza at the Chinese National Influenza Center, Beijing, China, has made available attached real-time RT-PCR protocol for influenza A(H7N9).

WHO, April 8th 2013

使用即時聚合酶連鎖反應 (Real-Time PCR) 偵測H7N9流感病毒的實驗設備與材料

2.1 Real-time fluorescence quantitative PCR analysis system

2.2 Bench top centrifuge for 1.5mL Eppendorf tubes

2.3 10, 200, 1000μL pipettors and plugged tips

2.4 Vortex

2.5 QIAGEN RNeasy Mini Kit

2.6 AgPath one-step RT-PCR kit

2.7 The specific primers and probes for the H7and N9 genes are summarized in the table below. In addition, the use of a primer and probe targeted M gene and house-keeping gene such a RNP is recommended for typing all influenza A virus and internal control in the tests.

WHO, April 8th 2013

使用即時聚合酶連鎖反應 (Real-Time PCR) 偵測H7N9流感病毒所需的探針核苷酸序列

Table of PCR primers and probes

ID	Sequence	Note
H7		
CNIC-H7F	5'-AGAAATGAAATGGCTCCTGTCAA-3'	Primer
CNIC-H7R	5'-GGTTTTTTCTTGTATTTTTATATGACTTAG-3'	Primer
CNIC-H7P	5'FAM-AGATAATGCTGCATTCCCGCAGATG-BHQ1-3'	Probe
N9		
CNIC-N9	5′ TGGCAATGACACACACTAGTCAGT 3′	Primer
CNIC-N9R	5′ ATTACCTGGATAAGGGTCGTTACACT 3′	Primer
CNIC-N9P	5′FAM- AGACAATCCCCGACCGAATGACCC -BHQ1-3′	Probe
FluA		
InfA Forward	5′ GACCRATCCTGTCACCTCTGA 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

Note: FluA and RNase primer/probe sets were from published WHO protocol provided by CDC, Atlanta.

WHO, April 8th 2013

使用即時聚合酶連鎖反應 (Real-Time PCR) 偵測H7N9流感病毒所需的各項實驗材料與劑量

Components	volume（μL）
2× RT-PCR Master Mix	12.5
primer-forward（40μM）	0.5
primer-reverse（40μM）	0.5
Probe （20 μM）	0.5
QuantiTect RT Mix	1
Template RNA	5.0
RNase Free H_2O	5
Total	25

WHO, April 8th 2013

偵測H7N9流感病毒使用即時聚合酶連鎖反應 (Real-Time PCR) 的反應條件與判讀結果標準

The results are determined if the quality controls work.

(1) The specimen is negative if the value of Ct is undetectable,

(2) The specimen is positive if Ct value is ≤38.0.

(3) It is suggested that specimens with a Ct higher than 38 are repeated. The specimen can be considered positive if the repeat results are the same as before i.e. Ct is higher than 38. If the repeat Ct is undetectable, the specimen is considered negative.

WHO, April 8th 2013

ORIGINAL ARTICLE

Clinical Findings in 111 Cases of Influenza A (H7N9) Virus Infection

Gao H-N et al. N Engl J Med 2013;368:2277-2285

表一. 中國大陸確認感染H7N9流感病毒的111名病人的基本資料與流行病學資料 – (I)

Table 1. Demographic and Epidemiologic Characteristics of 111 Patients Infected with H7N9 Virus in China.

Characteristic	Value
Age	
Median (range) — yr	61 (3–88)
Subgroup — no. (%)	
0–4 yr	1 (0.9)
5–14 yr	1 (0.9)
15–49 yr	28 (25.2)
50–64 yr	34 (30.6)
≥65 yr	47 (42.3)
Female sex — no. (%)	35 (31.5)

大部分感染H7N9流感的病人為成年男性病人

Gao H-N et al. N Engl J Med 2013;368:2277-2285

表一. 中國大陸確認感染H7N9流感病毒的111名病人的基本資料與流行病學資料 – (II)

Coexisting condition — no. (%)	
Any	68 (61.3)
Hypertension	51 (45.9)
Diabetes	18 (16.2)
Coronary heart disease	11 (9.9)
Immunosuppression*	10 (9.0)
Chronic obstructive pulm	
Cancer†	
Cerebrovascular disease	
Hepatitis B infection‡	
Chronic renal disease	
Pregnancy	
Current smoker — no. (%)	27 (24.3)
Exposure to live poultry	
In previous 14 days — no. (%)	62 (55.9)
Median incubation time since exposure (interquartile range) — days	5 (2–8)
Hospitalization — no. (%)	109 (98.2)

多數感染H7N9流感的病人具有原有疾病、有1/4病人抽煙、超過半數病人於發病前14天內有禽鳥接觸史，幾乎所有病人接受住院診斷治療。

Gao H-N et al. N Engl J Med 2013;368:2277-2285

表二. 中國大陸確認感染H7N9流感病毒的111名病人的臨床表現和實驗室檢查結果 – (I)

Table 2. Clinical Characteristics and Selected Laboratory Abnormalities of 111 Patients Infected with H7N9 Virus *

Characteristic 臨床表現	Value 數值
Fever	
Any — no. (%)	111 (100.0)
Maximal temperature — °C	39.2±0.8
Subgroup — no. (%)	
37.3–38.0°C	11 (9.9)
38.1–39.0°C	43 (38.7)
>39.0°C	57 (51.4)
Fatigue — no. (%)	40 (36.0)
Conjunctivitis — no. (%)	0
Cough — no. (%)	100 (90.1)
Sputum production — no. (%)	62 (55.9)
Hemoptysis — no. (%)	27 (24.3)
Shortness of breath — no. (%)	62 (55.9)
Diarrhea or vomiting — no. (%)	15 (13.5)

多數感染H7N9流感病人多有高燒和咳嗽有痰等症狀

Gao H-N et al. N Engl J Med 2013;368:2277-2285

表二. 中國大陸確認感染H7N9流感病毒的111名病人的臨床表現和實驗室檢查結果 – (II)

多數的感染H7N9流感病人血液的白血球小於4,000 cells/mm3 、淋巴球數目低下、 血小板數目低下，和發炎指數上升等異常實驗室檢查結果

實驗室檢查項目	數值
White cells	
Median — per mm³	4450
Interquartile range — p	2900–6230
Subgroup — no. (%)	
>10,000 per mm³	5 (4.5)
<4000 per mm³	51 (45.9)
Lymphocytes — per mm³	
Median	460
Interquartile range	320–700
Lymphocytopenia — no. (%)	98 (88.3)
Hemoglobulin — g/dl	12.9±3.1
Platelets — per mm³	
Median	115,500
Interquartile range	82,000–149,500
Thrombocytopenia — no. (%)	81 (73.0)
C-reactive protein >10 mg/liter — no. (%)	85 (76.6)
Procalcitonin >0.5 ng/ml — no. (%)	28 (37.3)

Gao H-N et al. N Engl J Med 2013;368:2277-2285

表二. 中國大陸確認感染H7N9流感病毒的111名病人的臨床表現和實驗室檢查結果 – (III)

多數的感染H7N9流感病人血液的肝功能、乳酸去氫酶、肌酐激酶，和肌肉球蛋白數值上升，血氧濃度與氧氣分壓比值下降，和D-dimer數值上升；胸部影像學檢查發現多為兩側肺部病灶、堅實化病變，和毛玻璃病變

實驗室檢查項目	數值
Aspartate aminotransferas	73 (65.8)
Creatinine >133 μmol/liter	10 (9.0)
Lactate dehydrogenase >2	91 (82.0)
Creatine kinase >200 U/lit	49 (44.1)
Myoglobulin >80 μg/ml —	16 (55.2)
PaO_2:FIO_2	
Median	144.0
Interquartile range	107.1–226.9
Potassium — mmol/liter	3.8±0.5
Sodium — mmol/liter	136.8±6.0
D-dimer >0.5 mg/liter — no. (%)	47 (90.4)
Chest radiologic findings — no. (%)	
Involvement of both lungs	60 (54.1)
Ground-glass opacity	62 (55.9)
Consolidation	99 (89.2)

Gao H-N et al. N Engl J Med 2013;368:2277-2285

表三. 中國大陸確認感染H7N9流感病毒的111名病人的併發症、治療模式

感染H7N9流感病人多出現肺炎、急性呼吸窘迫症候群，和休克等併發症；有四分之一的病人的檢體培養出細菌，絕大多數的病人接受抗流感藥物

Table 3. Complications, Treatment, and Clinical Outcomes in 111 Patients Infected with H7N9 Virus.*

Variable 併發症種類	Value 人數 (%)
	no. of patients (%)
Complications	
Pneumonia	108 (97.3)
Acute respiratory distress syndrome	79 (71.2)
Shock	29 (26.1)
Acute kidney injury	18 (16.2)
Rhabdomyolysis	11 (9.9)
Treatment 治療模式種類	
Bacteria isolation from culture	29 (26.1)
Administration of oseltamivir or peramivir	108 (97.3)

Gao H-N et al. N Engl J Med 2013;368:2277-2285

表三. 中國大陸確認感染H7N9流感病毒的111名病人的併發症、治療模式，和預後 – (II)

感染H7N9流感病人多數於症狀出現3天後才開始接受抗流感藥物，超過8成的病人使用呼吸器，約四分之一病人需要接受血液透析治療，合併使用抗生素的病人超過7成

治療模式種類	
Timing from onset of illn of antiviral therap	
0–2 days	
3–5 days	32 (28.8)
≥6 days	65 (58.6)
Oxygen therapy	111 (100)
Mechanical ventilation	
Noninvasive	31 (27.9)
Invasive	65 (58.6)
Admission to an intensive care unit	85 (76.6)
Extracorporeal membrane oxygenation	20 (18.0)
Continuous renal-replacement therapy	29 (26.1)
Artificial-liver-support-system therapy*	17 (15.3)
Antibiotics	79 (71.2)

Gao H-N et al. N Engl J Med 2013;368:2277-2285

表三. 中國大陸確認感染H7N9流感病毒的111名病人的併發症、治療模式，和預後 – (III)

治療模式種類	人數 (%)
Antifungal drugs	1 (0.9)
Glucocorticoids	69 (62.2)
Intravenous immune globulin	59 (53.2)
Clinical outcome 臨床預後	
Death	30 (27.0)
Cause of death	
Refractory hypoxemia	22 (73.3)
Shock	1 (3.3)
Acute heart failure	2 (6.7)
Secondary bacterial or fungal infection	3 (10)
Arrhythmia	2 (6.7)
Discharge from hospital†	49 (44.1)

感染H7N9流感病人死亡率為27%，且死因多為頑固性低血氧症

Gao H-N et al. N Engl J Med 2013;368:2277-2285

表四. 中國大陸確認感染H7N9流感病毒的97名病人與急性呼吸窘迫症候群相關的危險因子 (多變數分析)

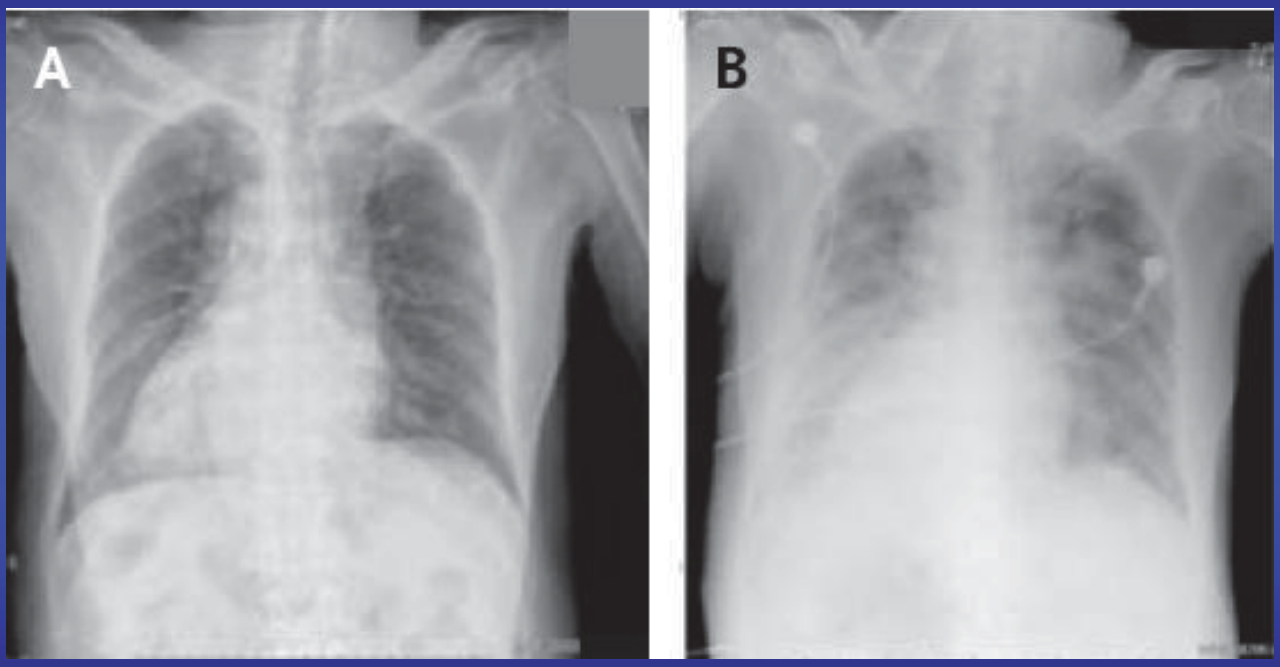
Table 4. Multivariate Analysis of Risk Factors for the 79 Patients with the Acute Respiratory Distress Syndrome.

Risk Factor	Odds Ratio (95% CI)*	P Value
Age ≥65 yr	1.01 (0.99–1.03)	0.30
Coexisting medical condition	3.42 (1.21–9.70)	0.02
Lymphocyte count <1000 cells/mm^3	2.73 (0.60–12.52)	0.20
Aspartate aminotransferase level >40 U/liter	1.37 (0.42–4.43)	0.60
Creatine kinase level >200 U/liter	1.80 (0.59–5.48)	0.30
Time from symptom onset to initiation of antiviral therapy >3 days	2.42 (0.49–11.99)	0.28

感染H7N9流感病人合併急性呼吸窘迫症候群與病人具有原發性疾病有密切相關

Gao H-N et al. N Engl J Med 2013;368:2277-2285

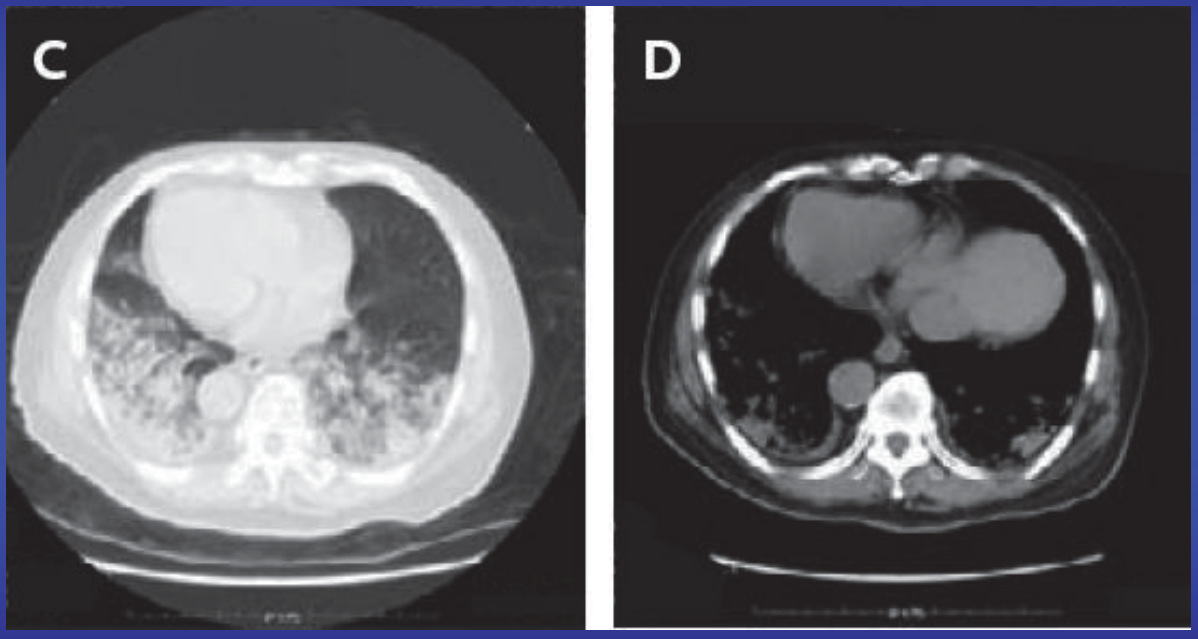
圖三 (A and B). 人類感染新型H7N9流感病毒的胸部X光影像 (Patient 1, 心臟在胸腔右側)



Day 6　　Day 9

Gao R et al. N Engl J Med April 11th, 2013
DOI:10.1056/NEJMoa1304459

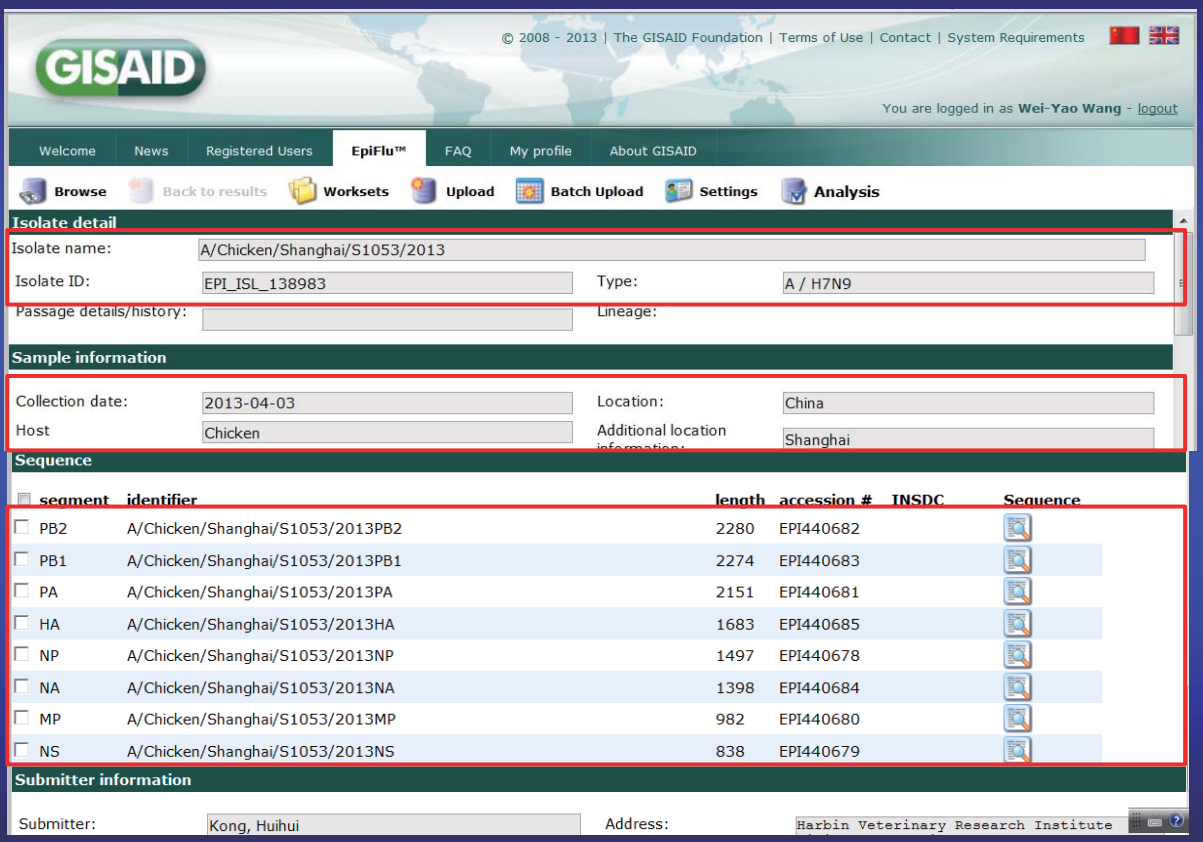
圖三 (C and D). 人類感染新型H7N9流感病毒的電腦胸部X光影像 (Patient 1, 心臟在胸腔右側)



Day 7 (住院第1日)　　Day 7 (住院第1日)

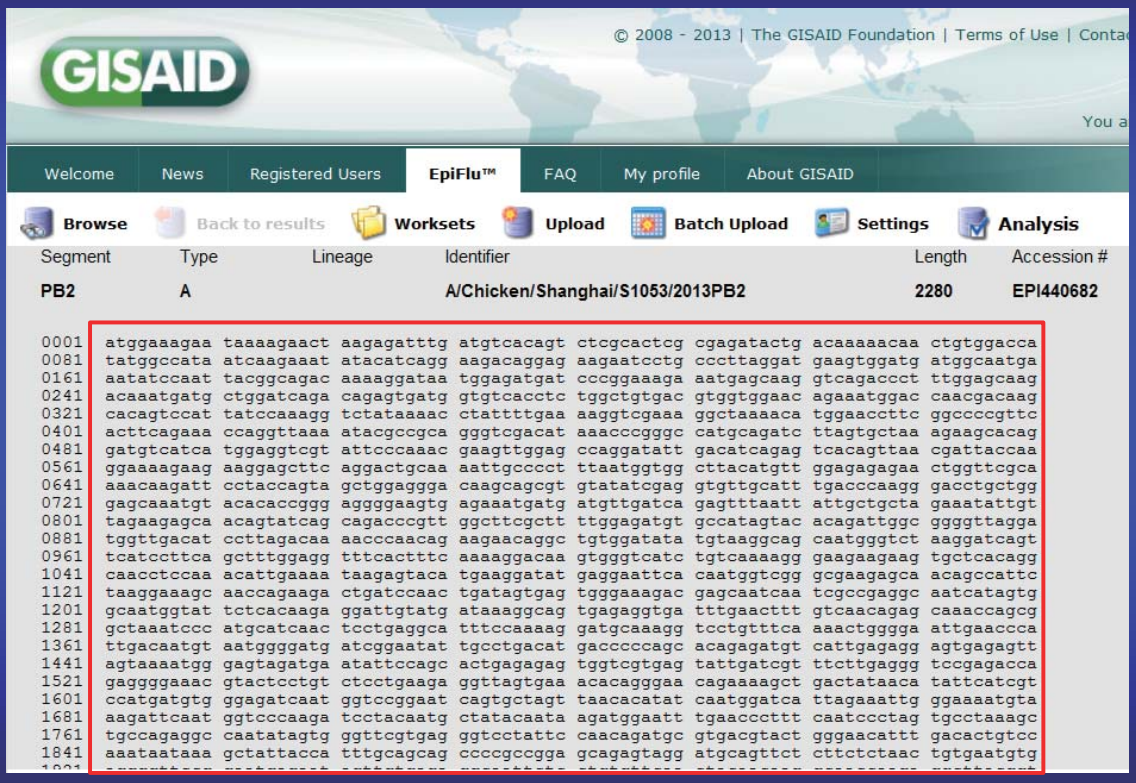
Gao R et al. N Engl J Med April 11th, 2013
DOI:10.1056/NEJMoa1304459

H7N9A型禽流感病毒8段基因序列）(哈爾濱畜牧研究所)
(A/Chicken/Shanghai/S1053/2013)



EpiFlu Database, GISAID, April 8th, 2013

H7N9A型禽流感病毒PB2基因序列）(哈爾濱畜牧研究所)
(A/Chicken/Shanghai/S1053/2013PB2)

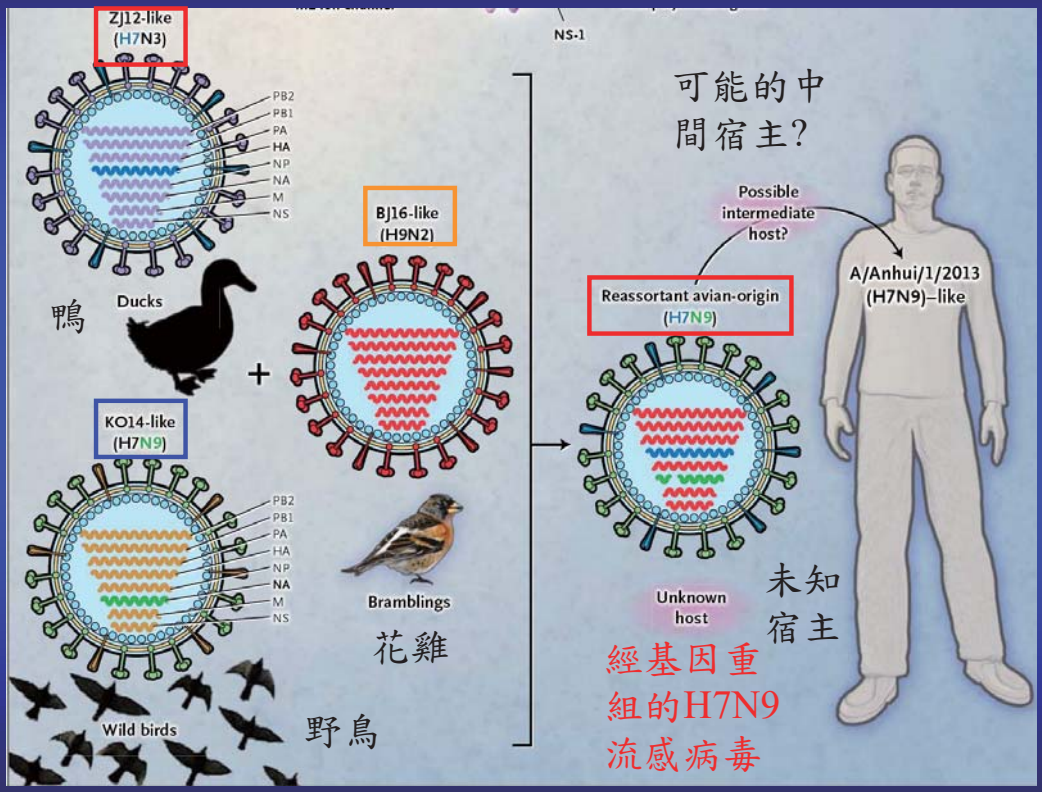


EpiFlu Database, GISAID, April 8th, 2013

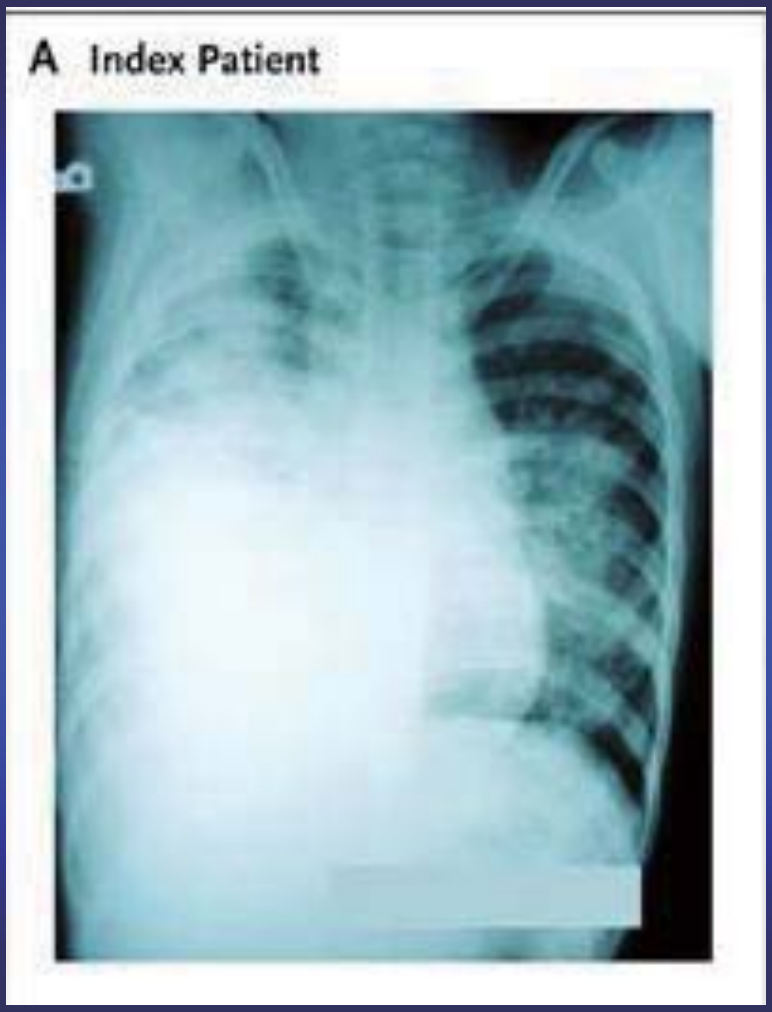
圖一. 新型H7N9流感病毒的基因族譜圖 (基因序列: HA, 左側; NA, 右側)

Gao R et al. N Engl J Med April 11th, 2013
DOI:10.1056/NEJMoa1304459

圖二. 新型H7N9流感基因重組病毒推斷的宿主與基因片段來源



Gao R et al. N Engl J Med April 11th, 2013 DOI:10.1056/NEJMoa1304459

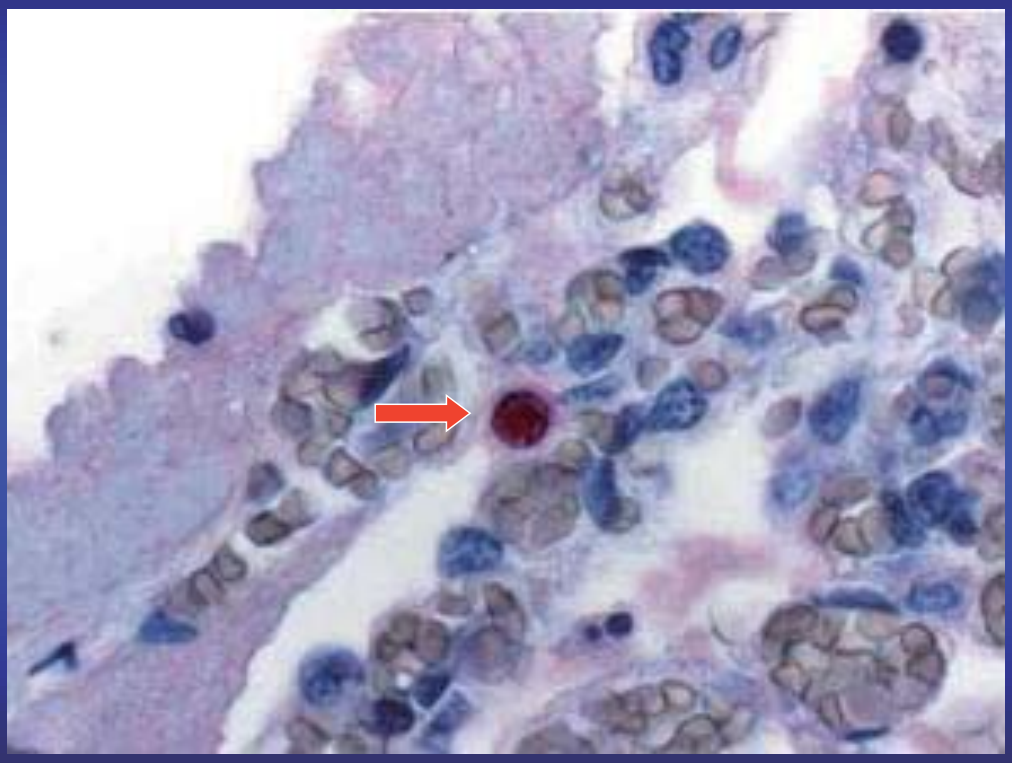


H5N1流感指標病人(11歲女性病人)的胸部X光片(出現症狀第6天)

Kumnuan U et al

N Engl J Med
2005;352(4):333-340

H5N1流感指標病人母親的肺部組織免疫螢光染色



Kumnuan U et al N Engl J Med 2005;352(4):333-340

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MMWR

Weekly

August 7, 2009 / 58(30);826-829

Evaluation of Rapid Influenza Diagnostic Tests for Detection of Novel Influenza A (H1N1) Virus --- United States, 2009

對H1N1 swine flu 的敏感性只有 40-69%

TABLE 1. Comparison of the number of positive influenza A test results from three RIDTs* with the number of positive results from rRT-PCR† assay, by influenza A type and cycle threshold (Ct) interval --- United States, 2009

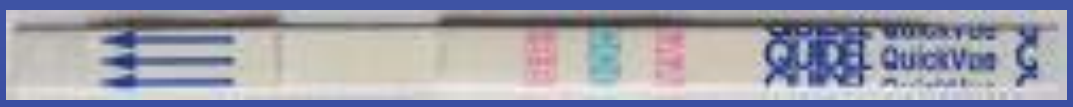
RIDT	Influenza A virus type	No. of specimens positive by RIDT/ No. positive by rRT-PCR Ct interval§ (<20)	(20 to <25)	(25–30)	(>30)	Total no. of specimens positive by RIDT/ Total no. positive by rRT-PCR (%)
BinaxNOW Influenza A&B	Novel H1N1	8/9	7/17	2/13	1/6	18/45 (40)
	Seasonal H1N1	---¶	2/3	1/2	---	3/5 (60)
	Seasonal H3N2	---	10/10	2/4	0/1	12/15 (80)
Directigen EZ Flu A+B	Novel H1N1	8/9	10/16	2/12	1/6	21/43** (49)
	Seasonal H1N1	---	2/2	1/2	---	3/4** (75)
	Seasonal H3N2	---	8/8	2/3	0/1	10/12** (83)
QuickVue A+B	Novel H1N1	9/9	13/17	6/13	3/6	31/45 (69)
	Seasonal H1N1	---	2/3	2/2	---	4/5 (80)
	Seasonal H3N2	---	10/10	2/4	0/1	12/15 (80)

* Rapid influenza A diagnostic tests.

MMWR 2009;58(30):826-829

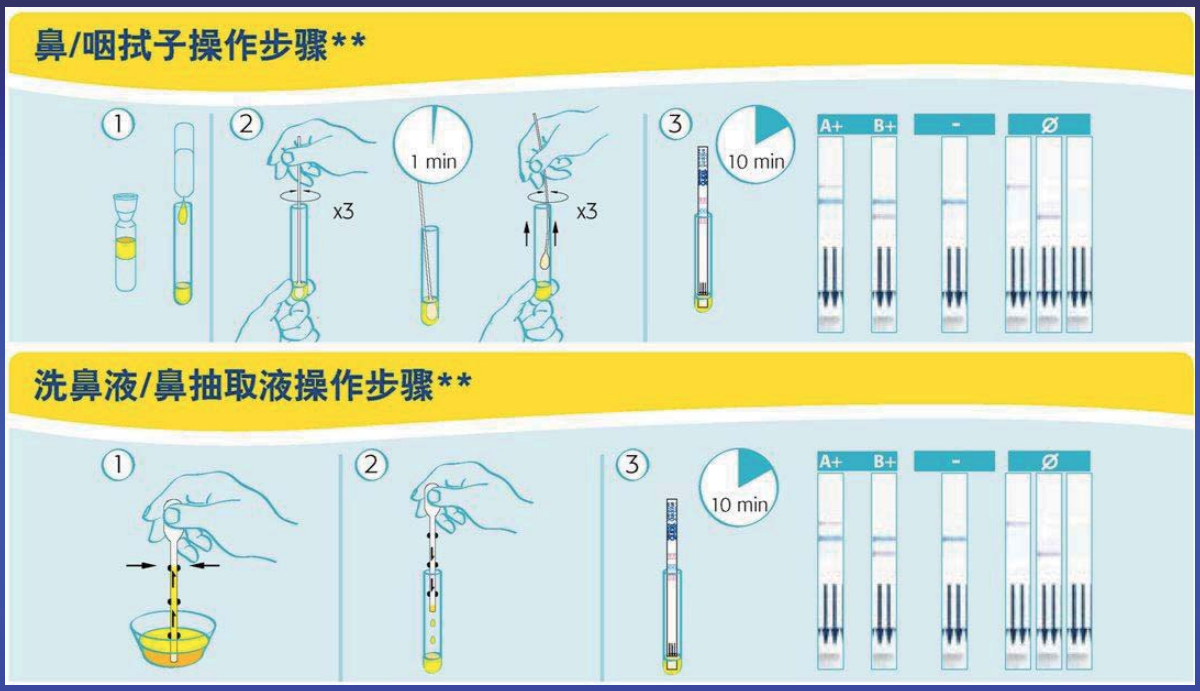
BinaxNow® Influenza A&B 22 tests/pack

in vitro immunochromatographic assay



QuickVue® 25 tests/pack BioMerieux

in vitro immunochromatographic assay



Rapid Influenza Diagnostic Test (RIDT) 操作方法

in vitro immunochromatographic assay

臨床條件（Clinical criteria）

具有急性發燒呼吸道疾病（Acute febrile respiratory illness）（發燒超過攝氏 38℃），且其臨床症狀包括從輕微的類流感（influenza-like illness）到較為嚴重的肺炎（pneumonia）等。

檢驗條件（Laboratory criteria）

經中央主管機關，檢出 H1N1 新型流感病毒陽性，其檢驗方法*包括下列任何一項：

1.real-time RT-PCR。

2.病毒培養。

3.H1N1 新型流感病毒中和抗體 4 倍上升。

檢驗方法必須依照目前最新之檢驗指引進行檢驗。

流行病學條件（Epidemiology criteria）

具有下列任一個條件：

一、曾經與確定病例或極可能病例具有密切接觸（close contact），即照護、同住、或與確定病例有呼吸道分泌物、體液之直接接觸。

二、具有確定病例或極可能病例所在地區之旅遊史。

中華民國衛生署疾病管制局針對H1N1新型流感的病例定義中各項診斷標準

CDC. Taiwan
April 30th, 2009

中華民國衛生署疾病管制局針對H1N1新型流感的病例診斷分類

調查病例（Person under investigation）：

符合臨床條件及流行病學條件。

極可能病例（Probable case）：

符合臨床條件，且經檢驗為流感病毒 A 型陽性，惟其亞型無法以季節性流感之檢測方法分型

或

符合臨床條件及流行病學條件，或不明原因之急性呼吸道症狀死亡之個案，與極可能或確定病例具有流行病學之關聯。

確定病例（Confirmed case）：

符合臨床條件及檢驗條件。

CDC. Taiwan April 30th, 2009

世界衛生組織對於豬 H1N1 A型流感 [Swine Influenza A (H1N1)] 的病例定義 (需通報WHO)

- ✓ 急性發燒呼吸道病變 (acute febrile respiratory illness): 體溫超過華氏100度 (攝氏37.7度) 且有合併呼吸道症狀自輕微類流感症狀至嚴重程度 (如肺炎)
- ✓ 確定病例 (confirmed case): 病人符合急性發燒呼吸道病變症狀且實驗室確定診斷為 swine influenza A (H1N1) 感染 (如病毒培養、real time RT-PCR, 或4倍特異 swine influenza A (H1N1) 中和抗體的上昇)
- ✓ 可能病例 (probable case): 病人符合急性發燒呼吸道病變症狀,且A型流感檢驗陽性,但使用傳統檢驗流感病毒無法分型

April 29th, 2009. WHO
http://www.who.int/csr/disease/swineflu/WHO_case_definition_swine_flu_2009_04_29.pdf

美國疾病管制局對於豬來源的A型H1N1流感 [Swine origin Influenza A (H1N1) – S-OIV] 的病例定義

- ✓ 急性發燒呼吸道病變 (acute febrile respiratory illness): 體溫超過華氏100度 (攝氏37.7度) 且最近有合併一種或以上的呼吸道感染症狀如流鼻水或鼻塞,咽喉疼痛,和咳嗽
- ✓ 確定病例 (confirmed case): 病人符合急性發燒呼吸道病變症狀且實驗室確定診斷為S-OIV感染 (如病毒培養或 real time RT-PCR) 的病例

April 30th, 2009. CDC, U.S.A.
http://www.cdc.gov/h1n1flu/casedef_swineflu.htm

美國疾病管制局對於豬來源的A型H1N1流感 [Swine Origin Influenza A (H1N1) – S-OIV] 的病例定義

- ✓ 可能病例 (probable case): 病人符合急性發燒呼吸道病變症狀,且A型流感檢驗陽性,但使用傳統檢驗流感病毒的反轉錄聚合酶反應 (RT-PCR) 檢驗H1和H3均為陰性
- ✓ 疑似病例 (suspected case): 病人符合急性發燒呼吸道病變症狀,且符合下列三種條件之一:

  症狀發生內7日與確定 S-OIV 感染病人親密接觸

  症狀發生內7日曾至美國或至有一例和以上確定 S-OIV 感染病例的國家旅遊

  居住在有一例和以上確定 S-OIV 感染病例的國家

April 30th, 2009. CDC, U.S.A.
http://www.cdc.gov/h1n1flu/casedef_swineflu.htm

台灣 H1N1 新型流感之因應暨最初 61 例確定病例之分析

謝明君[1]、鄒宗珮[1]、陳婉青[1]、郭旭崧[2]

表一、各國 H1N1 新型流感確定病例臨床症狀之比較

臨床症狀	美國, n=642	加拿大, n=173	日本, n=217	台灣, n=61
年齡(中位數, 範圍)，年	20(0.25-81)	22(1-61)	16(1-69)	22(3-57)
發　　燒	94%	87%	95%	82%
咳　　嗽	92%	87%	59%	82%
喉 嚨 痛	66%	48%	39%	39%
流 鼻 水	—	27%	33%	38%
腹　　瀉	25%	23%	6%	5%
嘔　　吐	25%	15%	2%	3%
頭　　痛	—	38%	13%	23%
倦　　怠	—	35%	31%	31%
肌肉酸痛	—	35%	19%	30%
關節酸痛	—	13%		5%

疫情報導 2009 (Aug 6);25(8):501-509

台灣 H1N1 新型流感之因應暨最初 61 例確定病例之分析

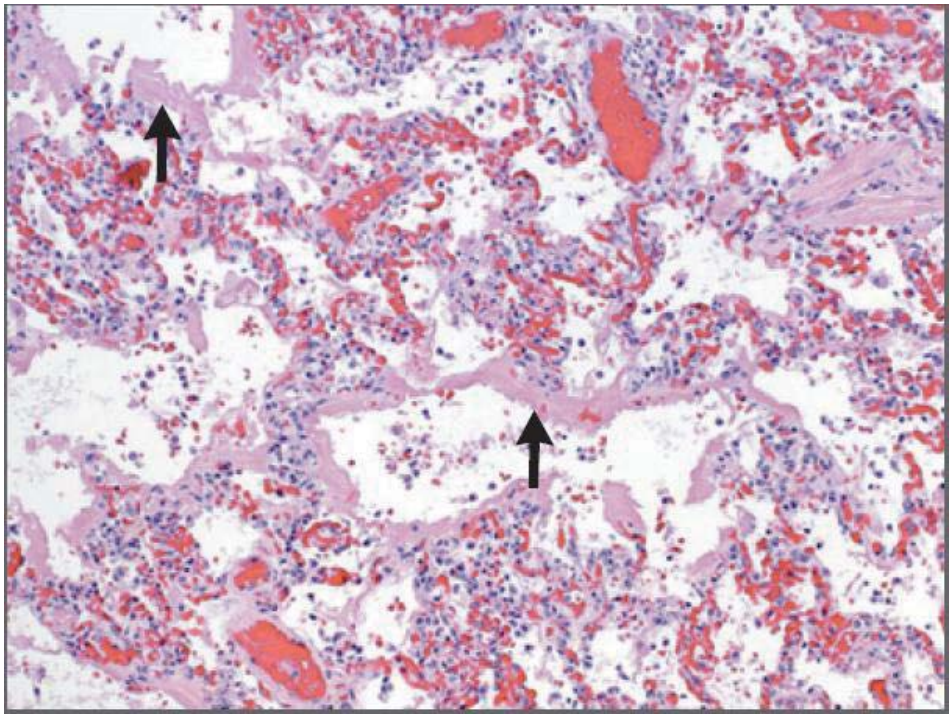
謝明君[1]、鄒宗珮[1]、陳婉青[1]、郭旭崧[2]

表二、前 40 例新型流感確定病例 RT-PCR 追蹤結果

累積病例數 (%)	發病至 RT-PCR 陰轉 (n=40)	治療至 RT-PCR 陰轉 (n=40)	退燒至 RT-PCR 陰轉 (n= 15)
第一天			3(20.0%)
第二天		3(7.5%)	10(66.7%)
第三天	1(2.5%)	15(37.5%)	11(73.3%)
第五天	16(40.0%)	29(72.5%)	12(80.0%)
第七天	29(72.5%)	36(90.0%)	14(93.3%)

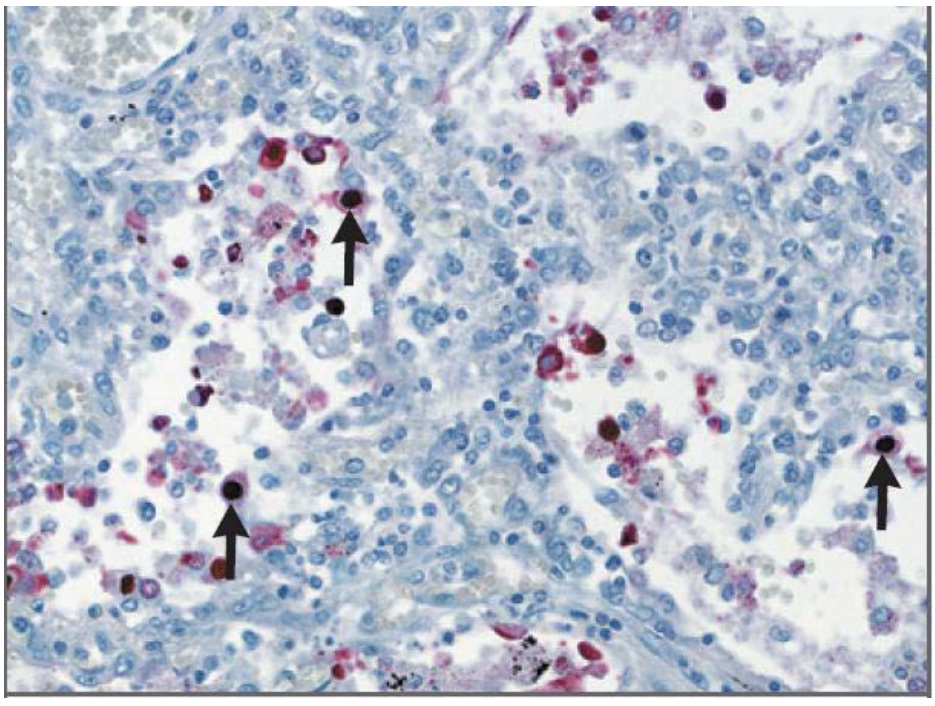
疫情報導 2009 (Aug 6);25(8):501-509

圖一. 一名13歲男性因感染H1N1A型新型流感死亡的肺部切片 – 肺泡傷害合併透明膜 (Hyaline Membrane) (H&E Stain)

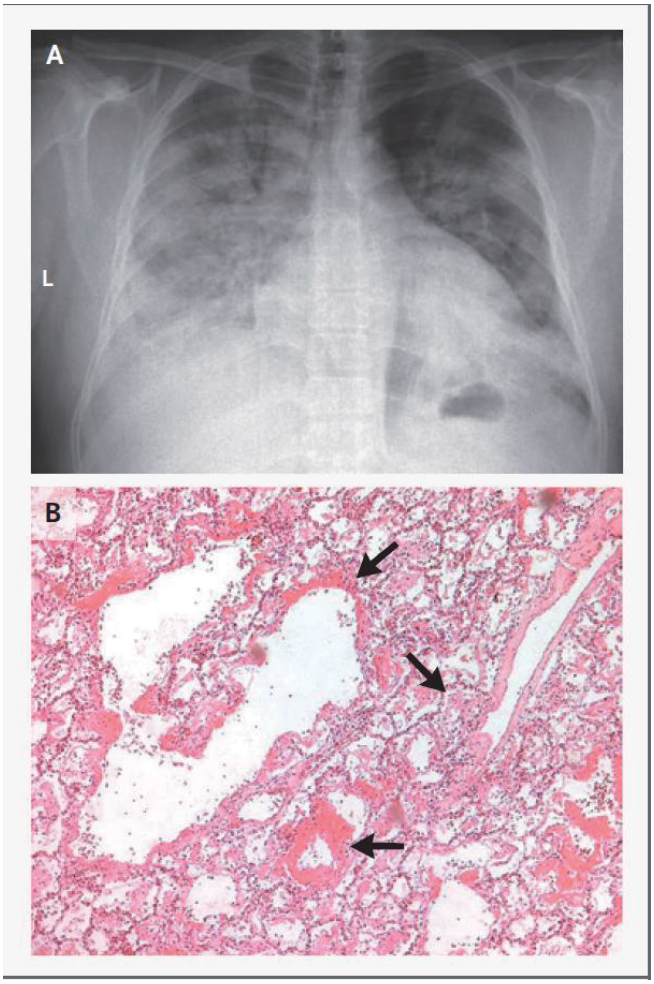


WHO Consultation Committee. N Engl J Med 2010;362(18):1708-1719

圖二. 一名55歲唐氏症合併B型肝炎女性感染H1N1A型新型流感的肺部免疫染色病理切片 – 病毒抗原 (紅色) 和肺泡上皮細胞的細胞核 (箭頭)



WHO Consultation Committee. N Engl J Med 2010;362(18):1708-1719

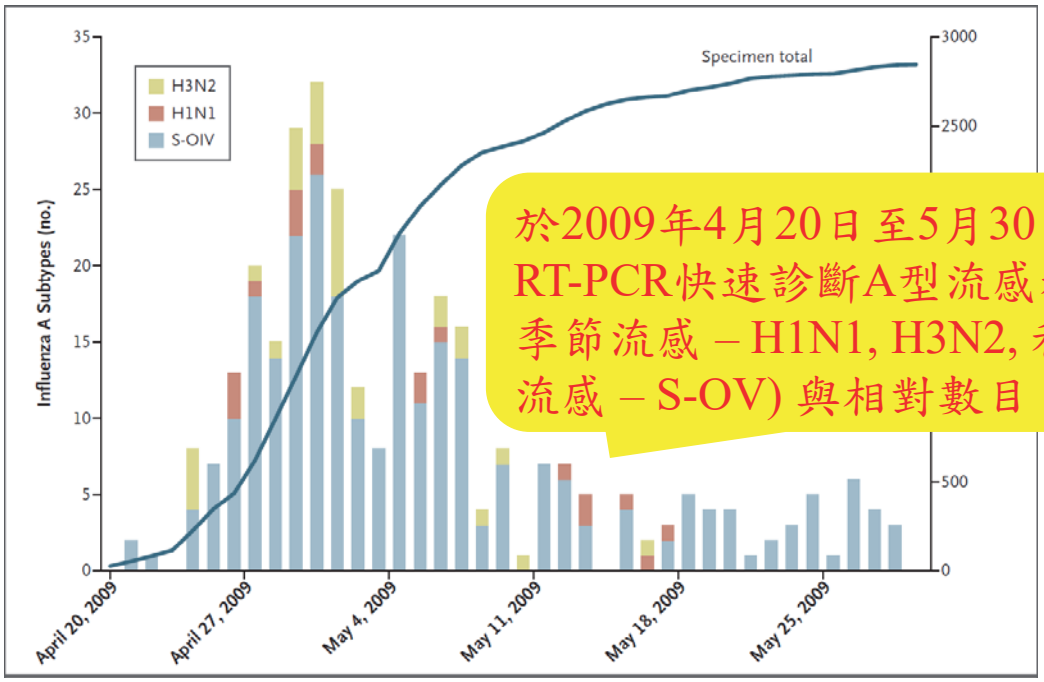


圖三. 墨西哥某病人於2009年經實驗室確定診斷為H1N1A型新型流感合併嚴重肺炎的胸部X光片 (A圖, 兩側肺部肺泡性與間質性浸潤) 和肺部病理切片 (B圖, 肺泡壁壞死, 中性白血球浸潤, 和透明膜 – hyaline membrane 的形成, H&E Stain)

Perez-Padilla R et al.
N Engl J Med
2009;361(7):680-689

The NEW ENGLAND JOURNAL of MEDICINE

Rapid-Test Sensitivity for Novel Swine-Origin Influenza A (H1N1) Virus in Humans

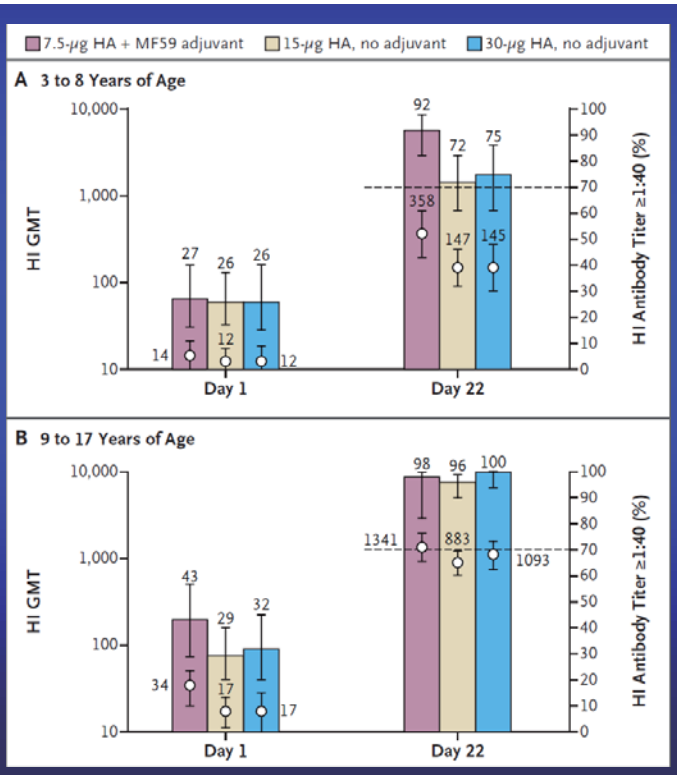


於2009年4月20日至5月30日以RT-PCR快速診斷A型流感種類 (季節流感 – H1N1, H3N2, 和新型流感 – S-OV) 與相對數目

Faix DJ et al. N Engl J Med 2009;361(7):728-729

Responses to 2009 H1N1 Vaccine in Children 3 to 17 Years of Age

TO THE EDITOR: The current 2009 pandemic influenza A (H1N1) virus is associated with substantial morbidity in children, with 45% of hospitalizations occurring in patients under 18 years of age.[1] One possible reason for this trend is a lack of preexisting immunity against the 2009



圖一. 不同年齡層 (3-8歲 – A圖和9-17歲 – B圖) 針對不同種類 (HA劑量與佐劑) 的H1N1A型新型流感疫苗的抗體產生濃度比較

不同種類的H1N1A型新型流感疫苗均可產生有效的保護性抗體濃度

Arguedas A et al.
N Engl J Med
2010;362(4):370-372

大眾對於H1N1A型流感疫苗的情緒反應

The Emotional Epidemiology of H1N1 Influenza Vaccination

Danielle Ofri, M.D., Ph.D.

民眾陷入恐慌

Last spring, when 2009 H1N1 influenza first came to our attention, my patients were in a panic. Our clinic was flooded with calls and walk-in patients, all with the same question: "When will there be a vaccine?"

It was all so new then, and we didn't have an answer. That lack of answer seemed to fuel anxiety to a fever pitch. A substantial cohort of my patients continued calling, almost on a weekly basis, to ask about the vaccine.

These, of course, were the same patients who routinely refused the seasonal flu vaccine. Each year when they demanded the H1N1 vaccine last spring, I reminded them of their reluctance over the seasonal flu shot. "Oh, that's different," they said.

Six months have passed. Flu season is now here. After repeated delays, H1N1 vaccine finally arrived in our clinic earlier this month to the uniform relief of the medical staff. But my formerly desperate patients were now leery. "It's not tested," they said. "Everyone knows there are problems with the vaccine." "I'm not putting that in my body."

I was unprepared for this reod. It seems to reflect a sort of psychological contagion of myth and suspicion.

Just as there are patterns of infection, there seem to be patterns of emotional reaction ("emotional epidemiology") associated with new illnesses. When 2009 H1N1 influenza was first detected, it fit a classic pattern that Priscilla Wald recently outlined in her book *Contagious*[1]: It was novel and mysterious; it emerged from a teeming third-world city, and it was now making its insidious — and seemingly unstoppable — way toward the "civilized" world.

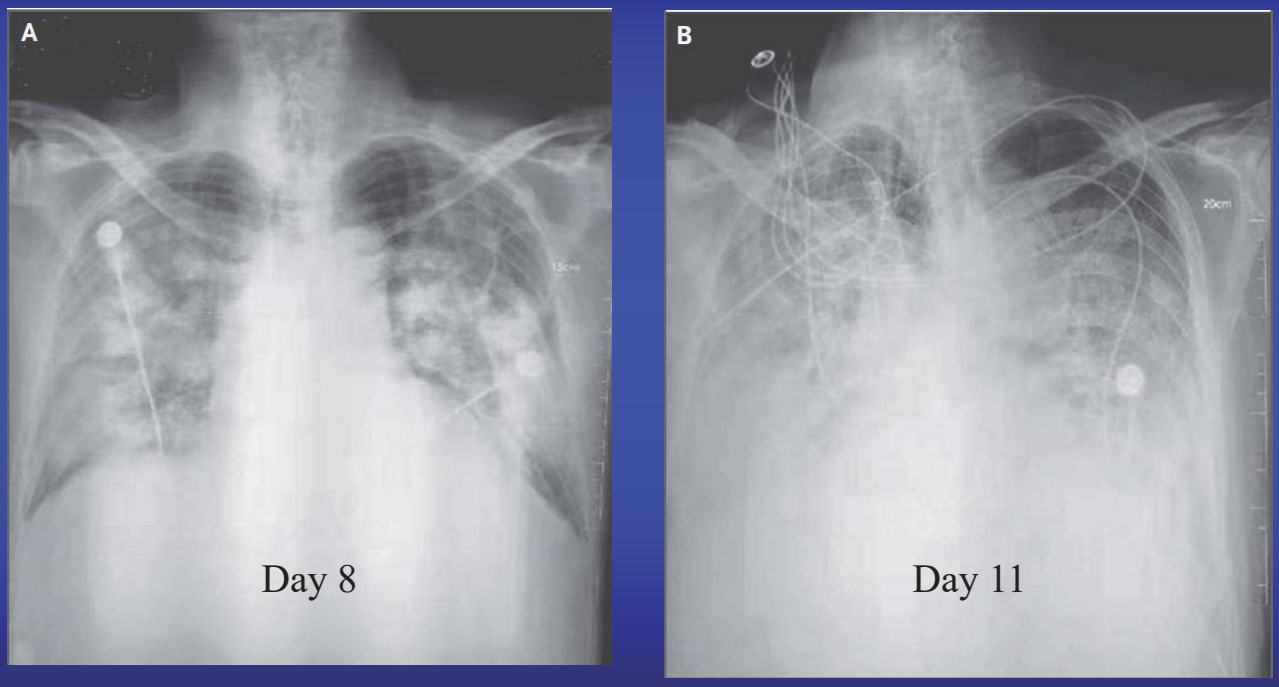
新型神秘的疾病來自第三世界的城市，未能察覺且無法停止地散播到文明世界

Ofri D. N Engl J Med 2009;361(27):2594-2595

3. 新興呼吸道傳染病的歷史與診斷標準

(以新型冠狀病毒感染 – COVID-19為例)

圖一. 武漢一名61歲男性在2019年12月20日出現發燒和咳嗽症狀被診斷為 2019-nCoV 重症病例的影像學檢查 (A圖&B圖 – 症狀出現第8日和第11日) (經常造訪華南海鮮市場)



Zhu N. et al. N Engl J Med. Jan 24th, 2020.
DOI: 10.1056/NEJMoa2001017.

圖二. 深圳市一家6人至武漢市旅遊確認 2019-nCoV 家庭內群聚感染事件其中4人胸部電腦斷層影像 (多處毛玻璃狀病灶)

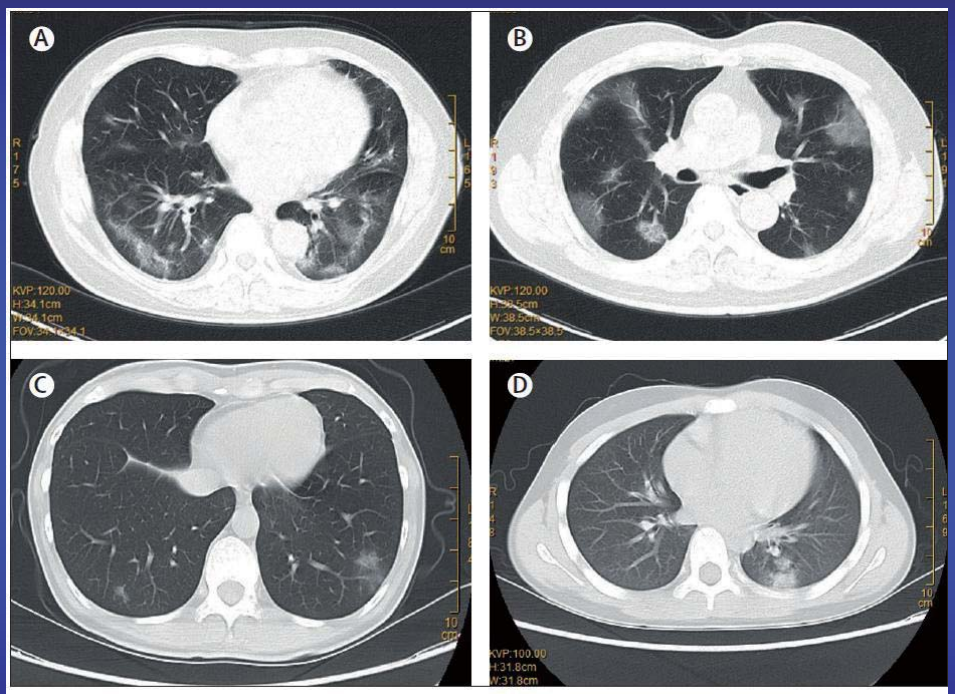


Figure 2: Representative images of the thoracic CT scans showing multifocal ground-glass changes in the lungs of patient 1 (A), patient 2 (B), patient 3 (C), and patient 5 (D)

Chan J F-W. et al. Lancet. Jan 24th, 2020.
https://doi.org/10.1016/ S0140-6736(20)30154-9

圖二. 2019-nCoV 在人類呼吸道上皮細胞培養的光學顯微鏡變化 (A圖 – 對照組；B圖 - 細胞病理效應)

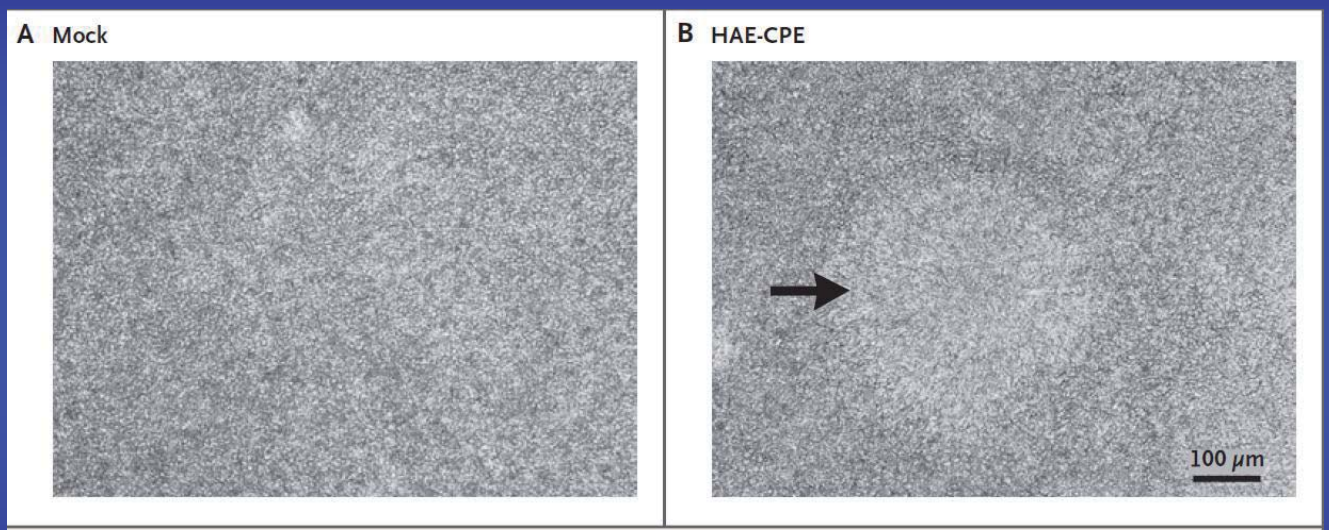


Figure 2. Cytopathic Effects in Human Airway Epithelial Cell Cultures after Inoculation with 2019-nCoV.

Zhu N. et al. N Engl J Med. Jan 24th, 2020.
DOI: 10.1056/NEJMoa2001017.

圖三. 2019-nCoV 在穿透性電子顯微性下的型態 (A圖 – 負向染色；B圖 – 人類呼吸道上皮細胞超薄切片影像)

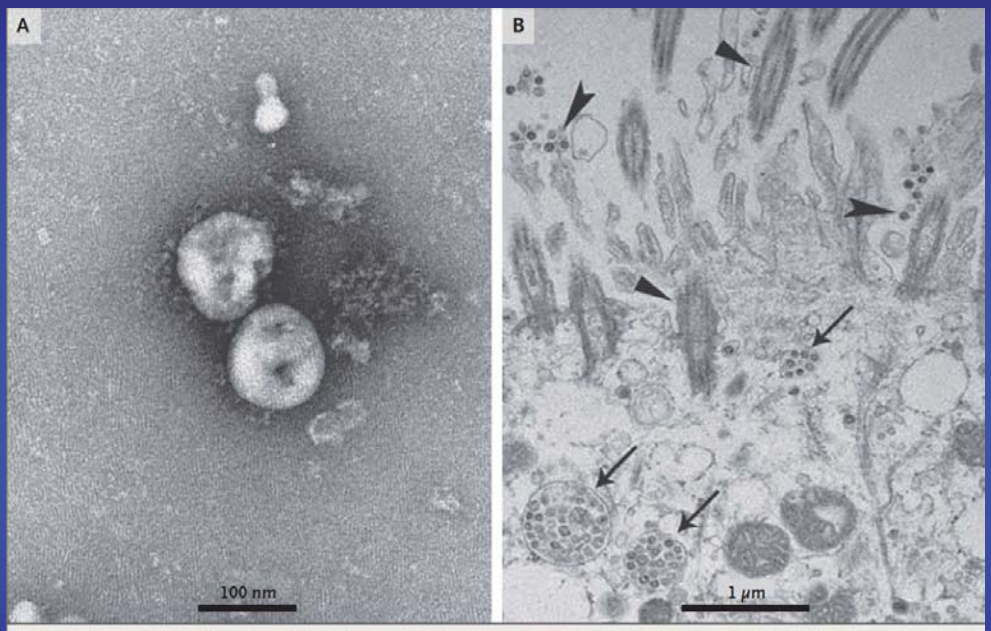


Figure 3. Visualization of 2019-nCoV with Transmission Electron Microscopy.
Negative-stained 2019-nCoV particles are shown in Panel A, and 2019-nCoV particles in the human airway epithelial cell ultrathin sections are shown in Panel B.

Zhu N. et al. N Engl J Med. Jan 24th, 2020.
DOI: 10.1056/NEJMoa2001017.

香港大學公共衛生學院偵測 2019-nCoV 的反轉錄聚合酶反應 (RT-PCR) 的分子生物檢驗方法

HKU Med
LKS Faculty of Medicine
School of Public Health
香港大學公共衛生學院

Detection of 2019 novel coronavirus (2019-nCoV) in suspected human cases by RT-PCR

https://www.who.int/docs/default-source/coronaviruse/peiris-protocol-16-1-20.pdf?sfvrsn=af1aac73_4

香港大學公共衛生學院偵測 2019-nCoV 的反轉錄聚合酶反應 (RT-PCR) 的分子生物檢驗方法 – 實驗材料

Materials required

- QIAamp Viral RNA Mini Kit (QIAGEN, Cat#52906) or equivalent
- TaqMan Fast Virus Master mix (TheromFisher, Cat# 4444432)
- Ethanol (96–100%)
- MicroAmp Fast Optical 96-well reaction plate (TheromFisher, Cat# 4346907)
- MicroAmp optical adhesive film (TheromFisher, Cat# 4311971)
- Microcentrifuge (adjustable, up to 13 000 rpm)
- Adjustable pipettes (10, 20, 100, 200 µl)
- Sterile, RNase-free pipette tips with aerosol barrier
- Vortex
- Microcentrifuge tubes (0.5ml and 1.5 ml)
- Thermocycler (TheromFisher, ViiA™ 7 Real-Time PCR)
- Positive control (Available from HKU, e-mail: llmpoon@hkucc.hku.hk)
- Primer sets

https://www.who.int/docs/default-source/coronaviruse/peiris-protocol-16-1-20.pdf?sfvrsn=af1aac73_4

香港大學公共衛生學院偵測 2019-nCoV 反轉錄聚合酶反應 (RT-PCR) 分子生物檢驗方法 – 引子與探針序列

Primer and probe sequences

Assay 1 (Target: ORF1b-nsp14)

Forward primer (HKU-ORF1b-nsp14F): 5'-TGGGGYTTTACRGGTAACCT-3'

Reverse primer (HKU- ORF1b-nsp14R): 5'-AACRCGCTTAACAAAGCACTC-3'

Probe (HKU-ORF1b-nsp141P): 5'-FAM-TAGTTGTGATGCWATCATGACTAG-TAMRA-3'

Assay 2 (Target: N)

Forward primer (HKU-NF): 5'-TAATCAGACAAGGAACTGATTA-3'

Reverse primer (HKU-NR): 5'-CGAAGGTGTGACTTCCATG-3'

Probe (HKU-NP): 5'-FAM-GCAAATTGTGCAATTTGCGG-TAMRA-3'

https://www.who.int/docs/default-source/coronaviruse/peiris-protocol-16-1-20.pdf?sfvrsn=af1aac73_4

香港大學公共衛生學院偵測 2019-nCoV 反轉錄聚合酶反應 (RT-PCR) 的分子生物檢驗方法 – 實驗步驟 (I)

Procedures

1. Extract viral RNA from clinical specimens by using QIAamp viral RNA mini kit according to manufacturer's instructions.

2. Prepare master mixture for one-step monoplex RT-PCR as below:

Reagent	Vol for a single rxn (µl)
H_2O (RNase free)	8.5
4x Reaction mix*	5
Forward primer (10 µM)	1
Reverse primer (10 µM)	1
Probe (10 µM)	0.5
RNA sample	4
Final rxn volume	20

*Reaction mix from TaqMan Fast Virus Master mix

https://www.who.int/docs/default-source/coronaviruse/peiris-protocol-16-1-20.pdf?sfvrsn=af1aac73_4

香港大學公共衛生學院偵測 2019-nCoV 反轉錄聚合酶反應 (RT-PCR) 的分子生物檢驗方法 – 實驗步驟 (II)

3. Set the follow RT-PCR conditions*:

Temperature (°C)	Time (minute:second)	No. of cycle
50 95	5:00 0:20	1
95 60	0:05 0:30	40

*Both monoplex assays can be conducted under the same conditions.

https://www.who.int/docs/default-source/coronaviruse/peiris-protocol-16-1-20.pdf?sfvrsn=af1aac73_4

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VIROLOGY

Multicenter Evaluation of BioFire FilmArray Respiratory Panel 2 for Detection of Viruses and Bacteria in Nasopharyngeal Swab Samples

研究背景：多重引子聚合酶反應 - 呼吸道感染模組 (Filmarray Respiratory Panel 2 – RP2) 是經美國食品藥物管理局審核通過的快速檢驗 (約需22分鐘) 鼻咽拭子 (nasopharyngeal swab – NPS) 的22種常見呼吸道感染微生物的檢驗方法，包括更新先前的RP1.7版內容並加速檢驗時間，檢驗項目包括腺病毒、冠狀病毒229E、冠狀病毒HKU1、冠狀病毒NL63、冠狀病毒OC43、人類間質性肺炎病毒 (metapneumovirus)、人類鼻病毒/腸病毒、A型流感病毒、A型流感病毒H1、2009年A型流感病毒H1 (株流感病毒)、A型流感病毒H3、 B型流感病毒、副流感病毒 (1, 2, 3型)、呼吸道融合病毒 (RSV)、百日咳菌 (*Bordetella pertussis*)、

Leber A L. et al. J Clin Microbiol. 2018;56(6):e01945-17.

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VIROLOGY

Multicenter Evaluation of BioFire FilmArray Respiratory Panel 2 for Detection of Viruses and Bacteria in Nasopharyngeal Swab Samples

研究背景 (續)：肺炎披衣菌 (*Chlamydia pneumoniae*)、黴漿菌 (*Mycoplasma pneumoniae*)、中東呼吸道冠狀病毒 (Middle East respiratory syndrome coronavirus – MERS-CoV) (新)，和副百日咳菌 (*Bordetella parapertussis*) (新)。

研究方法：屬於前瞻性研究，收集多中心共1,612個NPS檢體，實驗組為 FilmArray RP2，對照組為RP、其他PCR，和核苷酸定序 (sequencing)。

研究結果：實驗組和對照組的整體實驗符合度 (agreement) 為99.2%。除冠狀病毒OC43、百日咳菌，和副百日咳菌外，RP2對偵測微生物的陽性實驗符合度 ≥ 91.7%，對所有偵測微生物

Leber A L. et al. J Clin Microbiol. 2018;56(6):e01945-17.

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VIROLOGY

Multicenter Evaluation of BioFire FilmArray Respiratory Panel 2 for Detection of Viruses and Bacteria in Nasopharyngeal Swab Samples

研究結果 (續)：的陰性實驗符合度均 ≥ 93.8%。RP2可以偵測所有腺病毒的基因型，並且試驗的敏感度較對照組提昇。
結論： FilmArray RP2 較先前版本 FilmArray RP 對於常見呼吸道感染微生物的偵測有較高的敏感度和特異度，並且檢驗時間縮短，這對於不同情境 (如門診和住院與加護病房肺炎病人)的呼吸道感染症提供快速和可信賴的檢驗結果。

Leber A L. et al. J Clin Microbiol. 2018;56(6):e01945-17.

圖. 診斷呼吸道感染使用 FilmArray RP2 的操作畫面

https://www.biofiredx.com/products/the-filmarray-panels/filmarrayrp/

圖. 診斷呼吸道感染使用 FilmArray RP2 與傳統實驗室檢驗方法相比的優點

減少在加護病房治療時間

減少抗生素使用時間

減少醫療費用 (陽性與陰性RP2結果均適用)

Improve Economic Outcomes

The BioFire RP Panel has been shown to reduce overall healthcare costs. Significant savings were demonstrated in an adult ICU population in both patients that tested positive for a respiratory pathogen as well as those that tested negative.[4]

https://www.biofiredx.com/products/the-filmarray-panels/filmarrayrp/

表一. 使用 FilmArray RP2 診斷呼吸道感染的標的 (病毒與細菌) 種類和舊版 (FilmArray RP) 的相異

TABLE 1 Analytes detected by the FilmArray RP2

Analyte	Change relative to RP[a]
Viruses	
Adenovirus	Updated primers[b], additional assays
Coronavirus 229E	Updated primers
Coronavirus HKU1	Not modified
Coronavirus NL63	Not modified
Coronavirus OC43	Updated primers
Human metapneumovirus	Updated primers
Human rhinovirus/enterovirus	Updated primers
Influenza A virus	Updated primers
H1	Updated primers
H1-2009	Not modified
H3	Updated primers
Influenza B virus	Not modified
Middle East respiratory syndrome coronavirus (MERS-CoV)	New
Parainfluenza virus 1	Updated primers
Parainfluenza virus 2	Updated primers
Parainfluenza virus 3	Updated primers
Parainfluenza virus 4	Updated primers
Respiratory syncytial virus	Updated primers
Bacteria	
Bordetella parapertussis (IS*1001*)	New
Bordetella pertussis (*ptxP*)	Not modified
Chlamydia pneumoniae	Not modified
Mycoplasma pneumoniae	Updated primers

[a]General pouch chemistry improvements led to increased sensitivity overall.
[b]Assay modified for broader inclusivity.

Leber A L. et al. J Clin Microbiol. 2018;56(6):e01945-17.

表二. 收集多中心共1,612個鼻咽拭子 (NPS) 執行 FilmArray RP2 的檢驗結果和陽性率與年齡分布相關性

TABLE 2 Positivity rate for FilmArray RP2 for all samples and by age groups

Sample type/result	No. of samples	% of total
All samples		
Negative samples	592	36.7
Positive samples	1,020	63.3
Single detections	775	48.1
Codetections	245	15.2
Positive samples by age group		
≤5 yrs (n = 885)	698	78.9
6–21 yrs (n = 331)	196	59.2
22–49 yrs (n = 128)	53	41.4
50+ yrs (n = 268)	73	27.2

Leber A L. et al. J Clin Microbiol. 2018;56(6):e01945-17.

表三. 使用 FilmArray RP2 診斷呼吸道感染的標的 (病毒與細菌) 種類和整體與各年齡層的陽性率

TABLE 3 Prevalence of FilmArray RP2-detected analytes stratified by age group

	Prevalence of analyte in indicated subject group									
	Overall (n = 1,612)		≤5 yrs (n = 885)		6–21 yrs (n = 331)		22–49 yrs (n = 128)		≥50 yrs (n = 268)	
Analyte	No.	%	No.	%	No.	%	No.	%	No.	%
Viruses										
Adenovirus	118	7.3	96	10.8	18	5.4	2	1.6	2	0.7
Coronavirus 229E	16	1.0	3	0.3	7	2.1	1	0.8	5	1.9
Coronavirus HKU1	55	3.4	37	4.2	9	2.7	2	1.6	7	2.6
Coronavirus NL63	50	3.1	41	4.6	6	1.8	2	1.6	1	0.4
Coronavirus OC43	38	2.4	28	3.2	7	2.1	0	0	3	1.1
Human metapneumovirus	81	5.0	60	6.8	12	3.6	3	2.3	6	2.2
Human rhinovirus/enterovirus	502	31.1	379	42.8	88	26.6	16	12.5	19	7.1
Influenza virus A	78	4.8	29	3.3	20	6.0	13	10.2	16	6.0
H1	0	0	0	0	0	0	0	0	0	0
H1-2009	74	4.6	26	2.9	19	5.7	13	10.2	16	6.0
H3	4	0.2	3	0.3	1	0.3	0	0	0	0
Influenza B	16	1.0	7	0.8	7	2.1	1	0.8	1	0.4
Middle East respiratory syndrome coronavirus (MERS-CoV)	0	0	0	0	0	0	0	0	0	0
Parainfluenza virus 1	10	0.6	9	1.0	0	0	1	0.8	0	0
Parainfluenza virus 2	54	3.3	39	4.4	10	3.0	1	0.8	4	1.5
Parainfluenza virus 3	53	3.3	44	5.0	6	1.8	2	1.6	1	0.4
Parainfluenza virus 4	16	1.0	13	1.5	1	0.3	0	0	2	0.7
Respiratory syncytial virus	199	12.3	168	19.0	10	3.0	8	6.3	13	4.9
Bacteria										
Bordetella parapertussis (IS*1001*)	6	0.4	4	0.5	2	0.6	0	0	0	0
Bordetella pertussis (*ptxP*)	3	0.2	0	0	3	0.9	0	0	0	0
Chlamydia pneumoniae	6	0.4	1	0.1	4	1.2	1	0.8	0	0
Mycoplasma pneumoniae	28	1.7	10	1.1	14	4.2	3	2.3	1	0.4

Leber A L. et al. J Clin Microbiol. 2018;56(6):e01945-17.

表四. 使用 FilmArray RP2 和對照組相比的陽性結果符合度 (positive percent agreement – PPA) 與陰性結果符合度 (negative percent agreement – NPA)

TABLE 4 Performance summary and characteristics of FilmArray RP2 versus those of the comparator assays[a]

Analyte	PPA[b] TP/(TP + FN)	%	95% CI	NPA TN/(TN + FP)	%	95% CI
Viruses						
Adenovirus	70/74	94.6	86.9–97.9	1,490/1,538	96.9	95.9–97.6
Coronavirus 229E	11/12	91.7	64.6–98.5	1,595/1,600	99.7	99.3–99.9
Coronavirus HKU1	43/43	100	91.8–100	1,557/1,569	99.2	98.7–99.6
Coronavirus NL63	40/40	100	91.2–100	1,562/1,572	99.4	98.8–99.7
Coronavirus OC43	33/41	80.5	66.0–89.8	1,566/1,571	99.7	99.3–99.9
Human metapneumovirus	73/75	97.3	90.8–99.3	1,529/1,537	99.5	99.0–99.7
Human rhinovirus/enterovirus	425/436	97.5	95.5–98.6	1,099/1,176	93.5	91.9–94.7
Influenza virus A	78/78	100	95.3–100	1,531/1,531	100	99.7–100
H1	0/0			1,609/1,609	100	99.8–100
H1-2009	74/74	100	95.1–100	1,535/1,535	100	99.8–100
H3	4/4	100	51.0–100	1,605/1,605	100	99.8–100
Influenza virus B	14/14	100	78.5–100	1,596/1,598	99.9	99.5–100
Middle East respiratory syndrome coronavirus (MERS-CoV)	0/0			1,612/1,612	100	99.8–100
Parainfluenza virus 1	9/9	100	70.1–100	1,602/1,603	99.9	99.6–100
Parainfluenza virus 2	46/47	97.9	88.9–99.6	1,557/1,565	99.5	99.0–99.7
Parainfluenza virus 3	43/45	95.6	85.2–98.8	1,557/1,567	99.4	98.8–99.7
Parainfluenza virus 4	9/9	100	70.1–100	1,596/1,603	99.6	99.1–99.8
Respiratory syncytial virus	175/176	99.4	96.9–99.9	1,412/1,436	98.3	97.5–98.9
Bacteria						
Bordetella parapertussis (IS*1001*)	6/7	85.7	48.7–97.4	1,605/1,605	100	99.8–100
Bordetella pertussis (*ptxP*)	2/3	66.7	20.8–93.9	1,608/1,609	99.9	99.6–100
Chlamydia pneumoniae	5/5	100	56.6–100	1,606/1,607	99.9	99.6–100
Mycoplasma pneumoniae	23/24	95.8	79.8–99.3	1,583/1,588	99.7	99.3–99.9

[a]These data are presented based on a comparator assay only and do not reflect any discordant analysis.
[b]The terms PPA (positive percent agreement) and NPA (negative percent agreement) are used instead of sensitivity and specificity to indicate that a non-gold standard comparator (e.g., PCR) was used for the analysis.

Leber A L. et al. J Clin Microbiol. 2018;56(6):e01945-17.

表五. 使用 FilmArray RP2 診斷呼吸道感染的品質監測結果 (true positive, false positive, true negative, and true positive)

TABLE 5 Results of discrepant investigation for FilmArray RP2

Analyte	FN[a] Original result (total)	Discrepant investigation outcome[b] RP2 confirmed (TN)	RP2 unconfirmed (FN)	FP Original result (total)	Discrepant investigation outcome RP2 confirmed (TP)	RP2 unconfirmed (FP)
Viruses						
Adenovirus	4	1	3	48	40	8
Coronavirus 229E	1	1	0	5	0	5
Coronavirus HKU1	0			12	3	9
Coronavirus NL63	0			10	3	7
Coronavirus OC43	8	2	6[c]	5	2	3
Human metapneumovirus	2	2	0	8	6	2
Human rhinovirus/enterovirus	11	6	5	77	33	44
Influenza virus A	0			0		
H1	0			0		
H1-2009	0			0		
H3	0			0		
Influenza virus B	0			2	2	0
Middle East respiratory syndrome coronavirus (MERS-CoV)	0			0		
Parainfluenza virus 1	0			1	0	1
Parainfluenza virus 2	1	1	0	8	5	3
Parainfluenza virus 3	2	0	2	10	4	6
Parainfluenza virus 4	0			7	1	6
Respiratory syncytial virus	1	1	0	24	8	16
Bacteria						
Bordetella parapertussis (IS*1001*)	1	0	1	0		
Bordetella pertussis (*ptxP*)	1	0	1	1	1	0
Chlamydia pneumoniae	0			1	1	0
Mycoplasma pneumoniae	1	0	1	5	5	0
Total	33	14	19	224	114	110

[a]Result disposition based on initial testing versus comparator.
[b]RP2 confirmed, the results of discrepant analysis supported the original FilmArray RP2 result as true negative (TN) or true positive (TP). RP2 unconfirmed, the results of discrepant analysis did not support the original FilmArray RP2 result, and the result was considered false negative (FN) or false positive (FP).
[c]Six FN specimens were all TP for coronavirus HKU1 due to a known cross-reactivity in the comparator method (9).

Leber A L. et al. J Clin Microbiol. 2018;56(6):e01945-17.

表六. 使用 FilmArray RP2 診斷腺病毒感染的基因型的品質監測結果 (與先前版本 RP 比較)

TABLE 6 Summary of species determinations for all adenovirus-positive samples

Adenovirus species	Original RP2 result characterization compared to that of RP[a]		
	No. of TP	No. of FN	No. of FP[b]
A	0	0	2
B	20	0	7
C	47	3	17[c]
D	0	0	1
E	0	0	0
F	0	0	11[c]
Unable to determine species	3	1	11
Total	70	4	48

[a]TP, true positives = positive with RP and RP2; FN, false negatives = RP positive, RP2 negative; FP, false positives = RP negative, RP2 positive.
[b]For specimens yielding a species identification (n = 40), adenovirus was considered confirmed (3 FN missed by RP2, and 37 FP missed by RP).
[c]One specimen indicated a coinfection with adenovirus species C and F.

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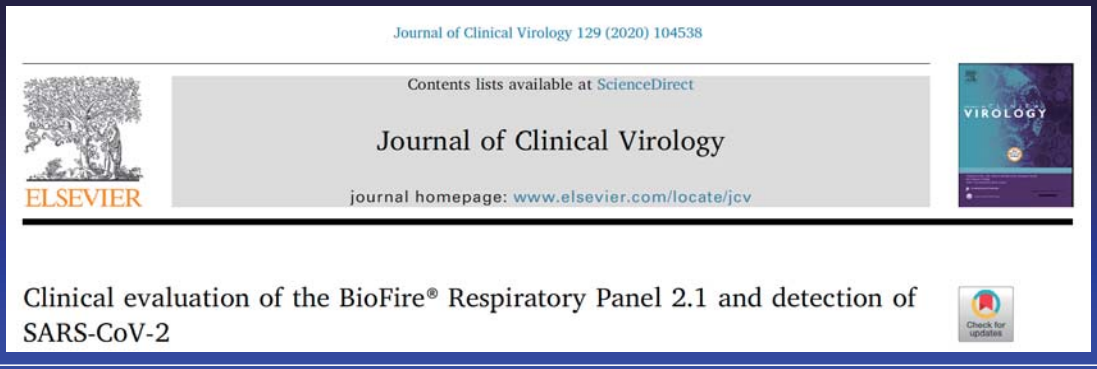
Journal of Clinical Virology 129 (2020) 104538

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Clinical evaluation of the BioFire® Respiratory Panel 2.1 and detection of SARS-CoV-2

摘要：多重引子聚合酶反應 - 呼吸道感染模組 (Filmarray Respiratory Panel 2 – RP2) 是經美國食品藥物管理局審核通過的快速檢驗 (約需22分鐘) 鼻咽拭子的22種常見呼吸道感染微生物的檢驗方法，RP2.1版本為RP2 加入緊急授權法令 (EUA) 授權FDA核准加入 SARS CoV-2 的 RT-PCR 檢驗方法。本次研究探討使用RP2.1和其他經過EUA核准的 SARS CoV-2 RT-PCR 檢驗方法比較，發現RP2.1與上述檢驗方法的相關的陽性實驗符合度高達98% (48/49)，陰性實驗符合度100% (49/49)。本次研究的鼻咽拭子 SARS CoV-2陽性的 RT-PCR 的試驗循環閾值 (Ct) 有30%為大於30，代表檢體低病毒量檢測對於臨床有重大意義。

Creager H M. et al. J Clin Virol. 2020;129:104538.

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Clinical evaluation of the BioFire® Respiratory Panel 2.1 and detection of SARS-CoV-2

摘要 (續)：因此使用高病毒量樣本，以10倍方式逐次稀釋樣本的病毒量 (每個濃度均執行3次後平均)，並與其他6種經 FDA EUA核准 RT-PCR 檢驗方法比較其效度，發現 BioFire® 2.1 panel 和其他4種檢驗方法 (Roche cobas, Cepheid Xpert Xpress, BioFire® Defense COVID19, and NECoV19) 的檢驗結果一致，均可以在高病毒樣本檢體稀釋 7次 (濃度為原本的10^{-7}倍) 仍能偵測 SARS CoV-2 的存在。本次研究證實 BioFire® 2.1 panel 可以有效診斷 SARS CoV-2 的急性感染病人，並可於疾病演變過程中的低病毒量亦可有效偵測 SARS CoV-2 存在。

Creager H M. et al. J Clin Virol. 2020;129:104538.

圖一. 使用經 FDA EUA核准的5種 RT-PCR 檢驗方法檢驗 SARS CoV-2 陽性的臨床檢體的 RT-PCR 試驗循環閾值 (Ct) 的分布 (水平線代表各種檢驗方法的Ct中位數)

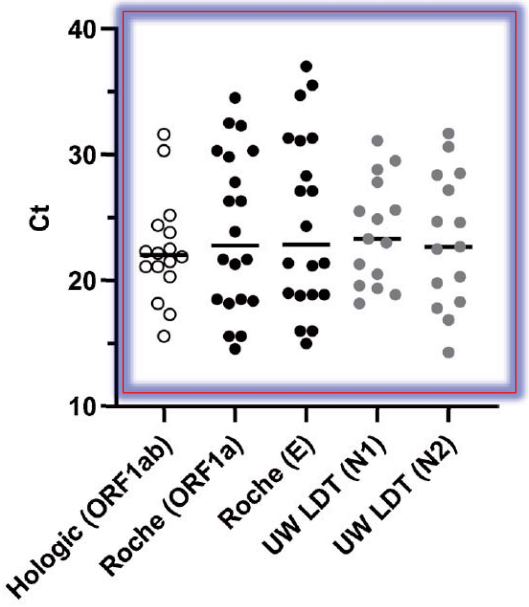

Fig. 1. Ct distribution of specimens tested in clinical study.
Ct values are shown for each assay used for characterizing clinical specimens, as indicated on the X axis. Horizontal bars represent Ct median values for each assay.

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表一. 使用 BioFire® 2.1 panel 和其他3種經 FDA EUA核准 RT-PCR 檢驗方法檢驗 SARS CoV-2 陽性和陰性臨床檢體實驗陽性和陰性符合度

Table 1
BioFire RP2.1 SARS-CoV-2 target clinical performance.

Comparator Assay	PPA	NPA[a]
Roche cobas	19/19	–
Hologic Fusion	14/15	–
Univ Wash LDT	15/15	–
Total	48/49 (98.0 %)	49/49 (100 %)

[a] NPA compared against presumptive SARS-CoV-2 negative specimens collected prior to December 2019.

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表二. 使用高病毒量樣本，以10倍方式逐次稀釋樣本的病毒量(每個濃度均執行3次後平均)，比較 BioFire® 2.1 panel 與其他6種經 FDA EUA核准的 RT-PCR 檢驗方法的效度

Table 2
Results of dilution series testing.

Dilution	NECoV19[a] (E^b)	Roche cobas[a] (E^b)	Cepheid Xpert Xpress[a] ($N2^b$)	Hologic Aptima[a]	BioFire RP 2.1[a]	BioFire Defense COVID-19 Test[a]	Abott ID NOW[a]
1×10^{-5}	6/6 (27.3 ± 0.5)	2/2 (29.9, 30.8)	NA	NA	NA	NA	3/3
1×10^{-6}	7/7 (30.7 ± 0.6)	3/3 (33.2, 33.3, 33.5)	3/3 (35.6, 35.8, 36.5)	6/6	3/3	3/3	1/3
1×10^{-7}	7/7 (34.0 ± 0.4)	3/3 (34.8, 35.3, 36.0)	3/3 (38.2, 39.5, 39.6)	2/6	3/3	3/3	0/3
5×10^{-8}	7/9 (36.3 ± 2.8)	3/3 (35.3, 36.7, 37.6)	3/3 (39.5, 40.6, 44.2)	2/6	1/3	2/3	NA
2.5×10^{-8}	6/9 (35.1 ± 2.6)	2/3 (36.3, 37.6)	3/3 (39.3, 40.8, 41.6)	0/6	1/3	2/3	NA
1.25×10^{-8}	3/8 (32.5, 32.9, 36.4)	2/3 (37.5, 39.6)	2/3 (40.5, 40.7)	0/6	1/3	0/3	NA
1×10^{-8}	3/7 (38.1, 37.1, 36.5)	0/3	1/3 (42.1)	1/12	0/3	1/3	0/3

[a] Number of replicates which tested posi
[b] Ct values for this target (individual val
high Ct values is shown).

使用 BioFire® 2.1 panel 可以於樣本稀釋7次 (濃度為原本的10^{-7}倍) 仍能偵測 SARS CoV-2 的存在。

Creager H M. et al. J Clin Virol. 2020;129:104538.

FilmArray RP2.1 已於2020年05月04日取得美國食品暨藥物管理局 (Food and Drug Administration – FDA) 的緊急使用許可用於診斷 SARS-CoV-2 感染

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bioMérieux: BIOFIRE® Respiratory Panel 2.1 (RP2.1) with SARS-CoV-2 Obtains FDA Emergency Use Authorization

May 04, 2020 01:00 AM Eastern Daylight Time

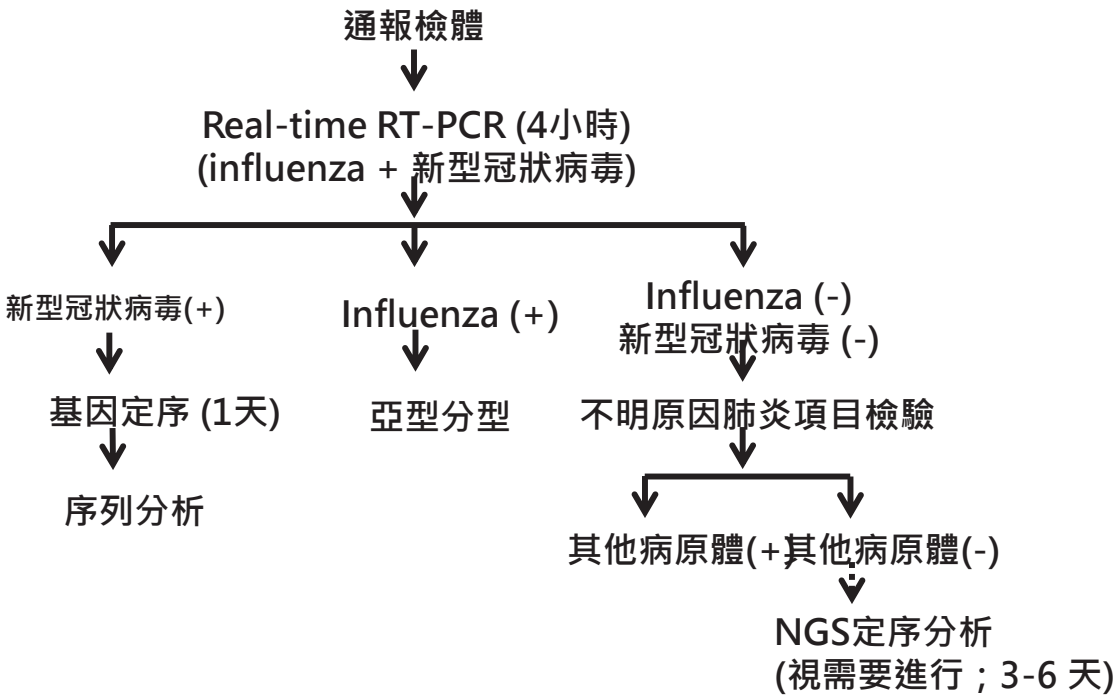
MARCY L'ÉTOILE, France--(BUSINESS WIRE)--Regulatory News:

bioMérieux (Paris:BIM), a world leader in the field of *in vitro* diagnostics, today announced that BioFire Diagnostics, its subsidiary specialized in syndromic infectious disease testing, has received Emergency Use Authorization by the U.S. Food and Drug Administration for the BIOFIRE® RP2.1 panel, which includes 22 pathogens that cause respiratory infections, including SARS-CoV-2 (the cause of COVID-19 disease).

The inclusion of SARS-CoV-2 in the BIOFIRE® RP2.1 panel allows healthcare providers to quickly identify patients with common respiratory pathogens, as well as those with COVID-19, using one simple test. The BIOFIRE® RP2.1 panel takes approximately 45 minutes and tests nasopharyngeal swab samples in transport media. It runs on the fully automated FILMARRAY® 2.0 and FILMARRAY® TORCH systems and is extremely easy to use.

https://www.businesswire.com/news/home/20200503005054/en/bioM%C3%A9rieux-BIOFIRE%C2%AE-Respiratory-Panel-2.1-RP2.1-SARS-CoV-2

疾病管制署國家級實驗室疫情因應檢驗流程



CDC, Taiwan. Jan 17th, 2020.

□. 診斷新興呼吸道傳染病實驗方法的展望

C□ini□a□□ □□i□ati□n □□□ □t □□n□ati□n □□□□n□in□ □□ □□□– 次世代定序的臨床應用

中山醫學大學醫學系

中臺科技大學醫學檢驗生物技術系暨研究所

臺中科技大學中護健康學院護理系

中山醫學大學附設醫院內科部感染科　王唯堯醫師

圖一. 圖示臨床微生物實驗室鑑定和分型的實驗方法

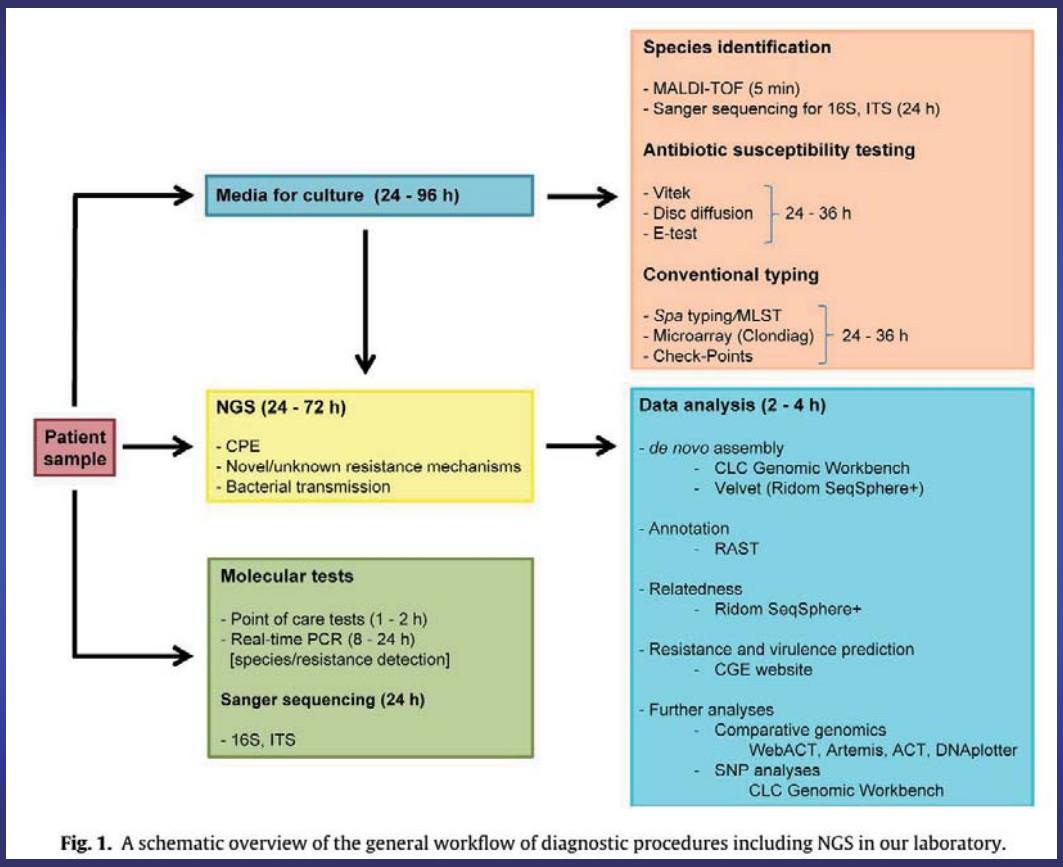


Fig. 1. A schematic overview of the general workflow of diagnostic procedures including NGS in our laboratory.

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表一. 上市的次世代定序 □n□□t □□n□ati□n □□□□n□in□–□□□□平台的基本資料 □包含公司名稱、使用設備、定序資料輸出量 □□□次□、序列片段讀取長度 □□□□、讀取產物股數，和執行時間□

Table 1
Properties of current NGS platforms.

Company	Equipment	Output/run (Gb)	Maximum read length (bp)	Reads (x10^6)	Running time
Illumina	MiniSeq	0.6–7.5	2 × 150	25	4–24 h
Illumina	Miseq	0.3–15	2 × 300	25	5–55 h
Illumina	NextSeq	20–120	2 × 150	130/400	12–30 h
Illumina	HiSeq 3000	125–700	2 × 150	2500	<1–3.5 days
ThermoFisher	Ion PGM™	0.03–2	200–400	0.4–5.5	2–7 h
ThermoFisher	Ion 5S™	0.6–15	200–400	3–80	2.5–4 h
ThermoFisher	Ion 5S™ XL	0.6–15	200–400	3–80	<24 h
Oxford Nanopore	MinION	21–42	230,000–300,000	2.2–4.4	1 min–48 h
Pacific Biosciences[a]	Sequel	0.75–1.25	>20,000	370,000	30 min–6 h
Pacific Biosciences[a]	RSII	0.5–1	>20,000	55,000	30 min–4 h

[a] The Pacific Biosciences data are per smart cell; both the Sequel and the RSII can run 1–16 smart cells in one run.

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圖二. 執行次世代定序資料的各階段分析所需的套裝軟體

Table 2
Software packages frequently used for NGS data analyses in our laboratory.

Application	Software	Link	Note
Annotation	Prokka	www.vicbioinformatics.com	
	RAST	http://rast.nmpdr.org	
Assembly	BioNumerics	www.applied-maths.com	Commercial software
	CLC Genomic Workbench	www.clcbio.com	Commercial software
	SeqSphere	www.ridom.de	Commercial software
	SPAdes	http://bioinf.spbau.ru/spades	Unix-based
	Velvet	www.ebi.ac.uk/~zerbino/velvet	Unix-based
Data quality check	BaseSpace	https://basespace.illumina.com	Commercial software
	BioNumerics	www.applied-maths.com	Commercial software
	CLC Genomic Workbench	www.clcbio.com	Commercial software
	FastQC	www.bioinformatics.babraham.ac.uk	
Identification	K-merFinder	www.genomicepidemiology.org	
	NCBI BLAST	www.ncbi.nlm.nih.gov/blast	
Metagenomics	MEGAN	http://ab.inf.uni-tuebingen.de/software/malt	
Phylogeny	FastTree	www.microbesonline.org/fasttree	
	RAxML	http://sco.h-its.org/exelixis/software.html	
	SeqSphere	www.ridom.de	Commercial software
	SNPTree	www.genomicepidemiology.org	
Resistance	ARDB	https://ardb.cbcb.umd.edu	
	CARD	https://card.mcmaster.ca	
	ResFinder	www.genomicepidemiology.org	
SNP calling	BioNumerics	www.applied-maths.com	Commercial software
	CLC Genomic Workbench	www.clcbio.com	Commercial software
	Samtools	www.htslib.org	
	SeqSphere	www.ridom.de	Commercial software
Typing (wgMLST)	BIGSdb	http://bigsdb.readthedocs.io	
	BioNumerics	www.applied-maths.com	Commercial software
	CLC Genomic Workbench	www.clcbio.com	Commercial software
	EnteroBase	https://enterobase.warwick.ac.uk	
	SeqSpere	www.ridom.de	Commercial software
Virulence	VFDB	www.mgc.ac.cn/VFs	
	VirulenceFinder	www.genomicepidemiology.org	
Visualisation & comparative study	ACT	www.sanger.ac.uk/science/tools	
	Artemis	www.sanger.ac.uk/science/tools	
	BRIG	https://sourceforge.net/projects/brig/	
	ClustalW	www.genome.jp/tools/clustalw	
	DNA plotter	www.sanger.ac.uk/science/tools	
	WebACT	www.webact.org	

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圖二. 在大學附設醫院、復健中心，和其他醫院的 CT□□□ □ 1□□□□□□□in□□T1□*Klebsiella pneumoniae* 感染群突發疫情的傳播模式 □流行病學調查和□□□資料分析□

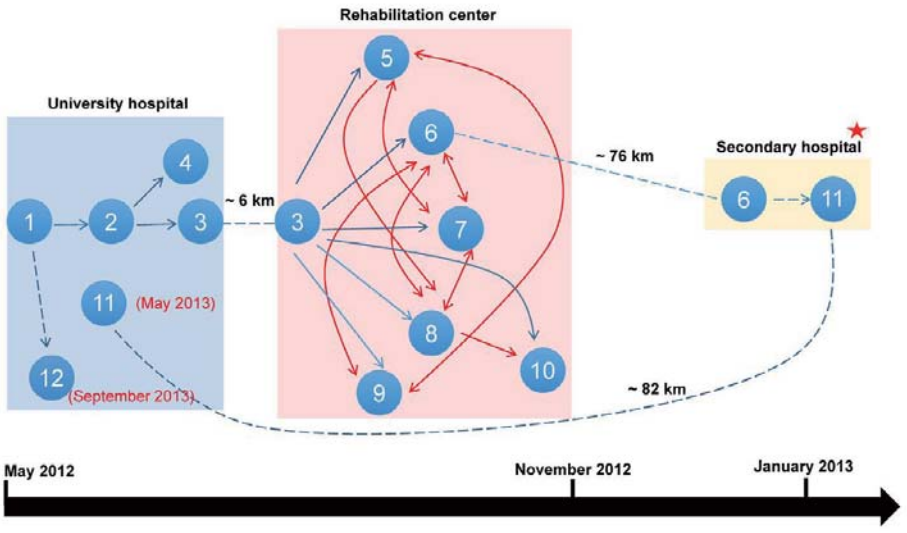

Fig. 2. The transmission route was reconstructed by epidemiological and genomic data. Each node represents a patient, and an arrow indicates a possible transmission event from one patient to another. The blue arrow with solid line represents a direct transmission event supported by both epidemiological data and genetic data, the blue arrow with dash line represents an indirect transmission (e.g. via environment) supported by epidemiological data, and the red arrow indicates the equally parsimonious transmission link which cannot be resolved by neither epidemiological data nor genetic data. The inter-institutional transfer of the patient is shown by dash lines, on which the distance between institutions is indicated. The red star represents an outbreak at a secondary hospital, but the isolates were unavailable for further research (Zhou et al., 2016). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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圖三. 利用次世代定序 □□□□□對糞便檢體宏基因組學 □□□ta□□n□□i□□□鑑定菌株種類和估算數量佔率□□顏色代表特定的菌種家族□

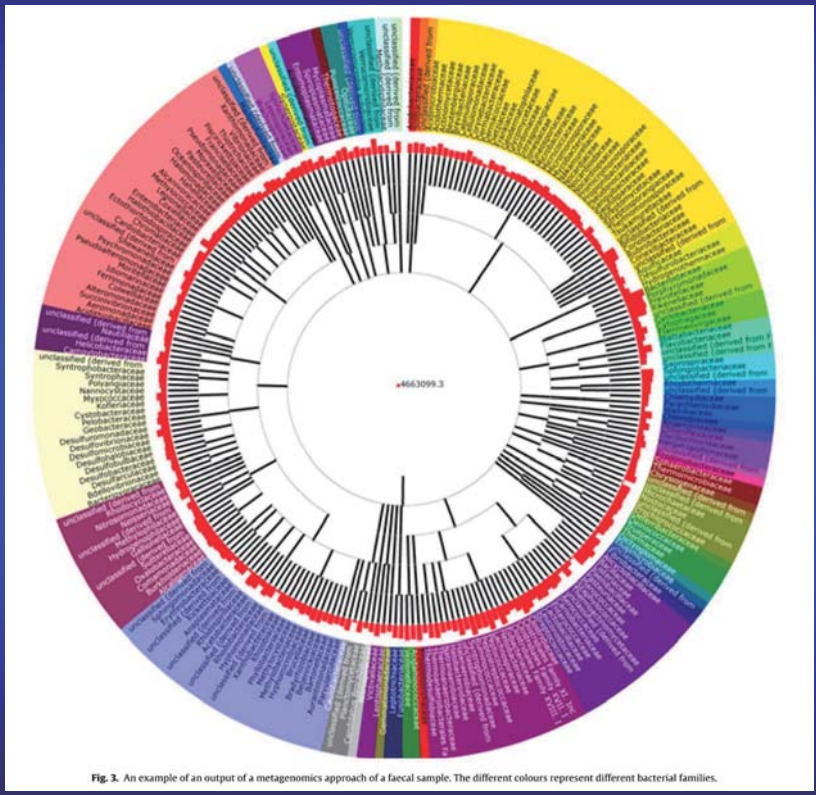

Fig. 3. An example of an output of a metagenomics approach of a faecal sample. The different colours represent different bacterial families.

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Clinical Microbiology and Infection 24 (2018) 335–341

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Review

Next-generation sequencing technologies and their application to the study and control of bacterial infections

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Enteric Diseases Laboratory Branch, Center for Disease Control & Prevention, Atlanta, GA, USA

□□□□□J. □t a□C□in □ i□□□i□□n□□t. 201□2□□□□□□□1.

圖一. 比較脈衝電泳法 □□□□□□ i□□□ □□□□□□□t□□□h□□□□i□□□□□ □□□白色柱狀□和全基因定序 □wh□□□□n□□ □□□□□□n□in□– □ □□□□黑色柱狀□偵測美國李斯特菌感染群突發疫情數與罹患人數

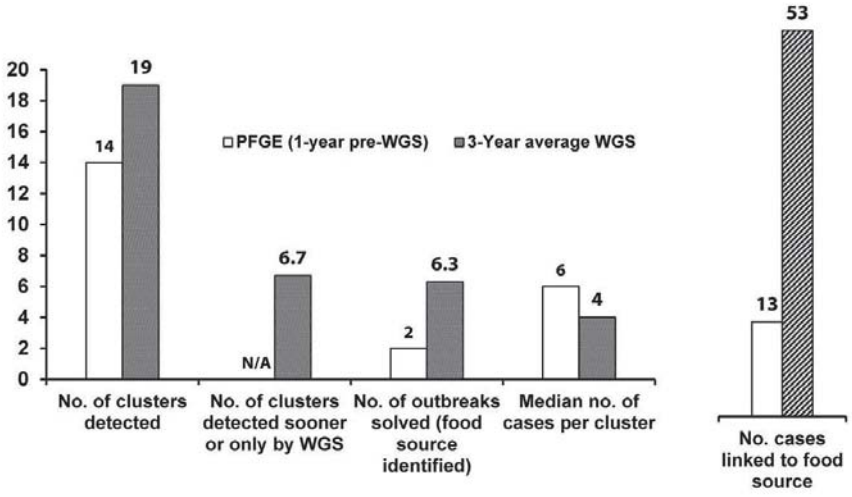


Fig. 1. Metrics illustrating the benefits of using whole genome sequencing compared with pulsed field gel electrophoresis for real-time outbreak laboratory surveillance for listeriosis in the United States.

□□□□□J. □t a□C□in □ i□□□i□□n□□t. 201□2□□□□□□□□1.

圖二. 在臨床實驗式或公共衛生機關實驗室典型全基因定序 □□ □□□實驗步驟圖示

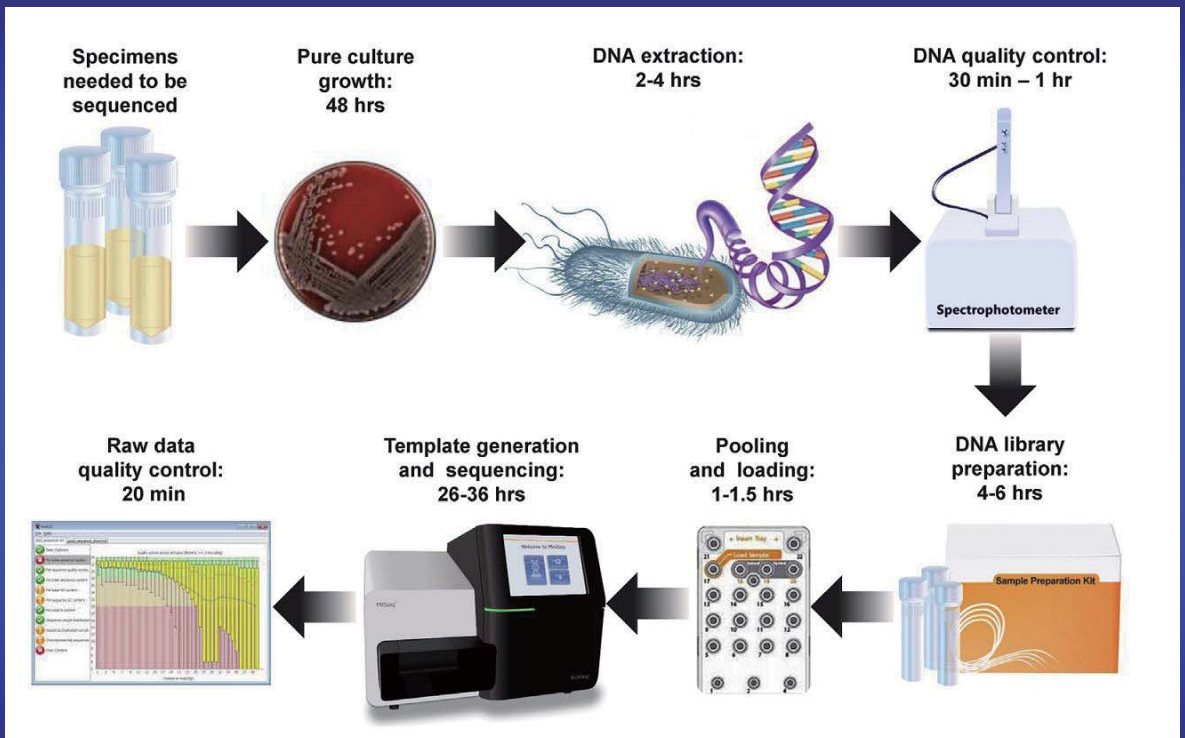


Fig. 2. Typical whole genome sequencing workflow in a clinical or public health laboratory.

□□□□□J. □t a□C□in □ i□□□i□□n□□t. 201□2□□□□□□□□1.

表二. 常見的基因定序實驗平台的種類、定序資料輸出量 □□次□、序列片段讀取長度 □□□，和優點與缺點等

Table 2
Characteristics, strengths and weaknesses of commonly used sequencing platforms

Platform \ Instrument	Throughput range (Gb)[a]	Read length (bp)	Strength	Weakness
Sanger sequencing				
ABI 3500/3730	0.0003	Up to 1 kb	Read accuracy and length	Cost and throughput
Illumina				
MiniSeq	1.7–7.5	1×75 to ×150	Low initial investment	Run and read length
MiSeq	0.3–15	1×36 to 2×300	Read length, scalability	Run length
NextSeq	10–120	1×75 to 2×150	Throughput	Run and read length
HiSeq (2500)	10–1000	×50 to ×250	Read accuracy, throughput,	High initial investment, run
NovaSeq 5000/6000	2000–6000	2×50 to ×150	Read accuracy, throughput	High initial investment, run
IonTorrent				
PGM	0.08–2	Up to 400	Read length, speed	Throughput, homopolymers[c]
S5	0.6–15	Up to 400	Read length, speed,	Homopolymers[c]
Proton	10–15	Up to 200	Speed, throughput	Homopolymers[c]
Pacific BioSciences				
PacBio RSII	0.5–1[b]	Up to 60 kb	Read length, speed (Average 10 kb, N50 20 kb)	High error rate and initial
Sequel	5–10[b]	Up to 60 kb	Read length, speed (Average 10 kb, N50 20 kb)	High error rate
Oxford Nanopore				
MInION	0.1–1	Up to 100 kb	Read length, portability	High error rate, run length,

[a] The throughput ranges are determined by available kits and run modes on a per run basis. As an example of a 15-GB throughput, thirty-five 5-MB genomes can be sequenced to a minimum coverage of 40× on the Illumina MiSeq using the v3 600 cycle chemistry.
[b] Per one single-molecule real-time cell.
[c] Results in increased error rate (increased proportion of reads containing errors among all reads) which in turn results in false-positive variant calling.

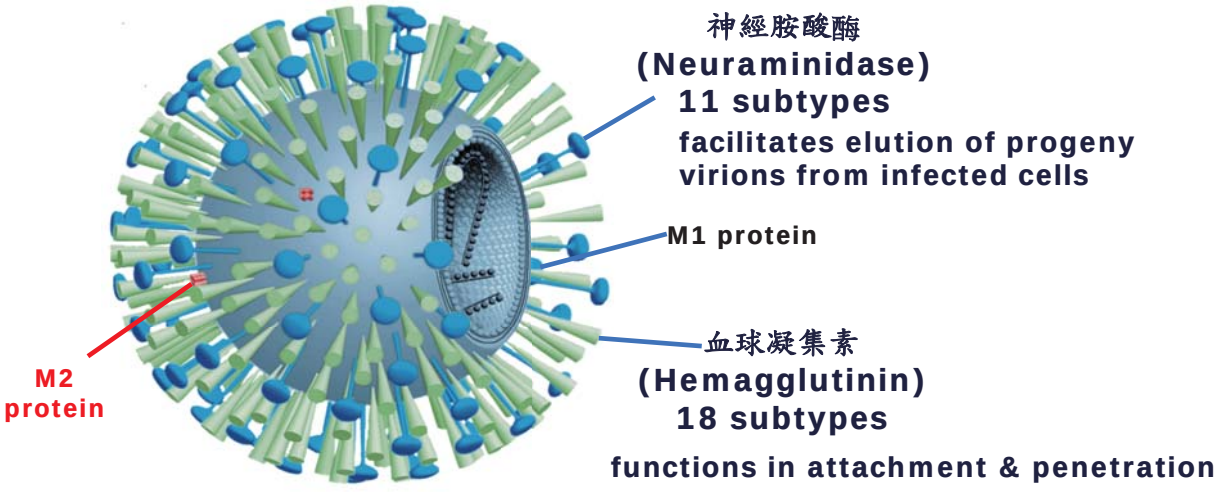
□□□□□J. □t a□.C□in □i□□□i□□n□□t. 201□2□□□□□□□□1.

感謝您的參與並歡迎討論

流行性感冒之
抗病毒藥物治療及疫苗預防

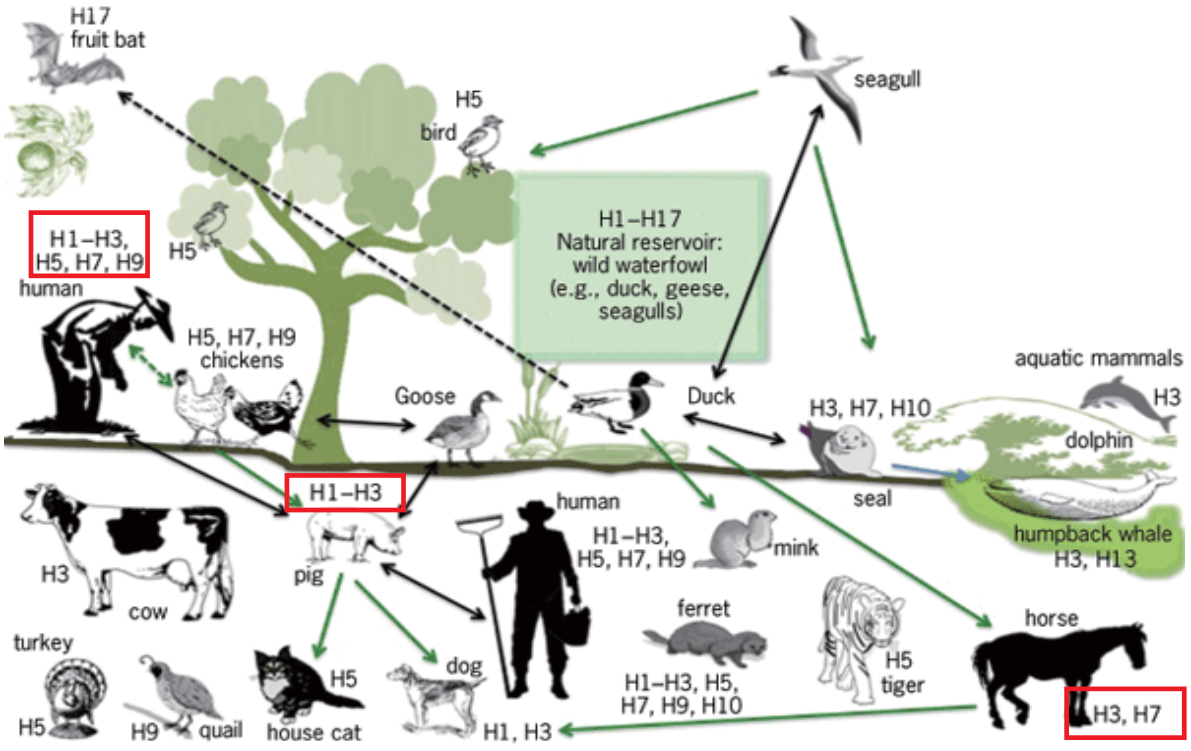
中山附醫 兒童感染科 潘蕙嫻

病毒結構



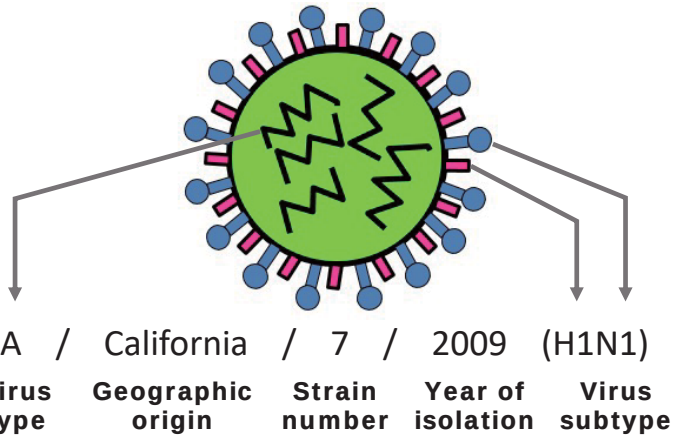
流感種類

	A型流感病毒	B型流感病毒	C型流感病毒
疾病嚴重程度	++++	++	+
帶原動物宿主	+	-	+
人類間的傳佈	大流行	地區性流行	偶發個案
抗原變異	Shift飄變/drift飄移	Drift 飄移	Drift 飄移
RNA片段數	8	8	7
病毒蛋白數	11	11	9

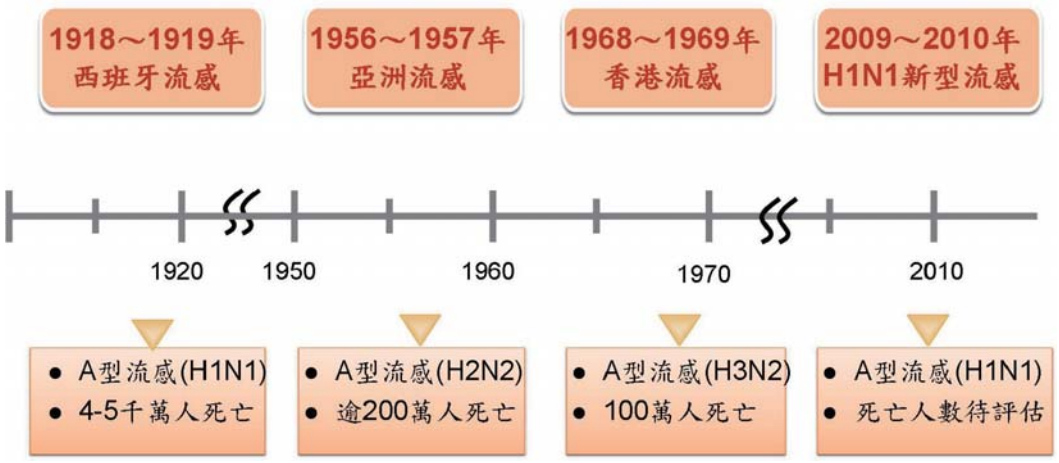


http://www.accessscience.com/search.aspx?rootID=802694

流感命名

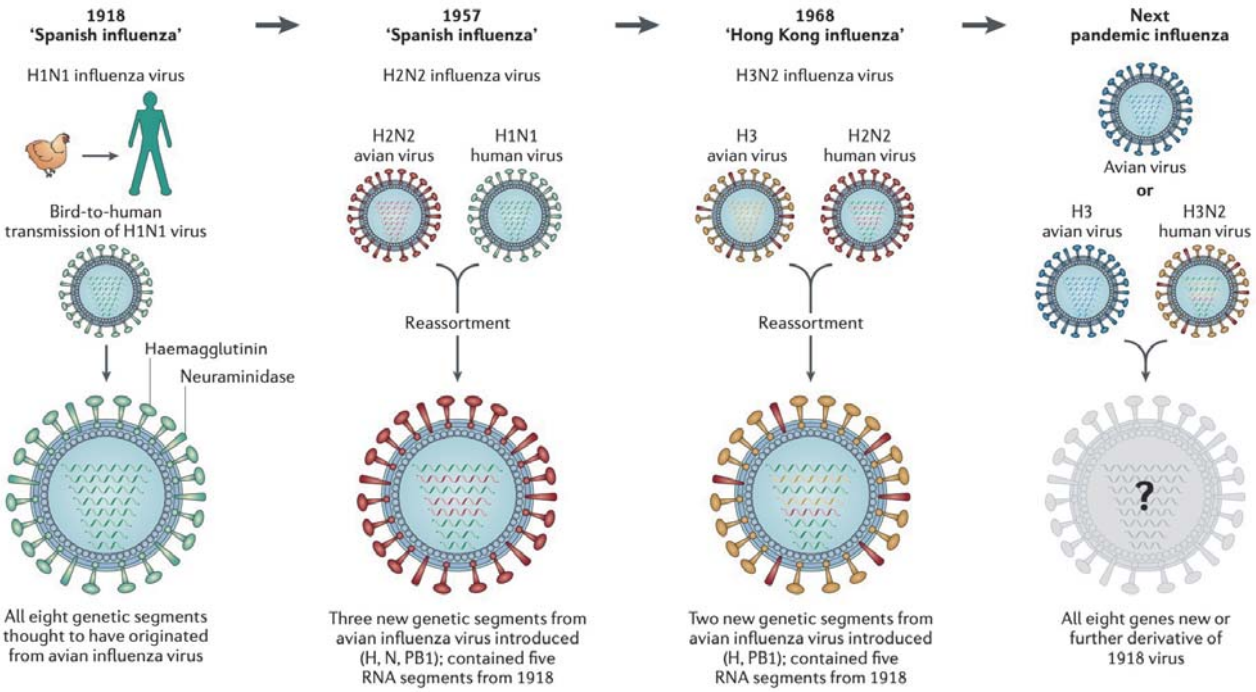


二十世紀歷史上流感的大流行 (Influenza pandemics)



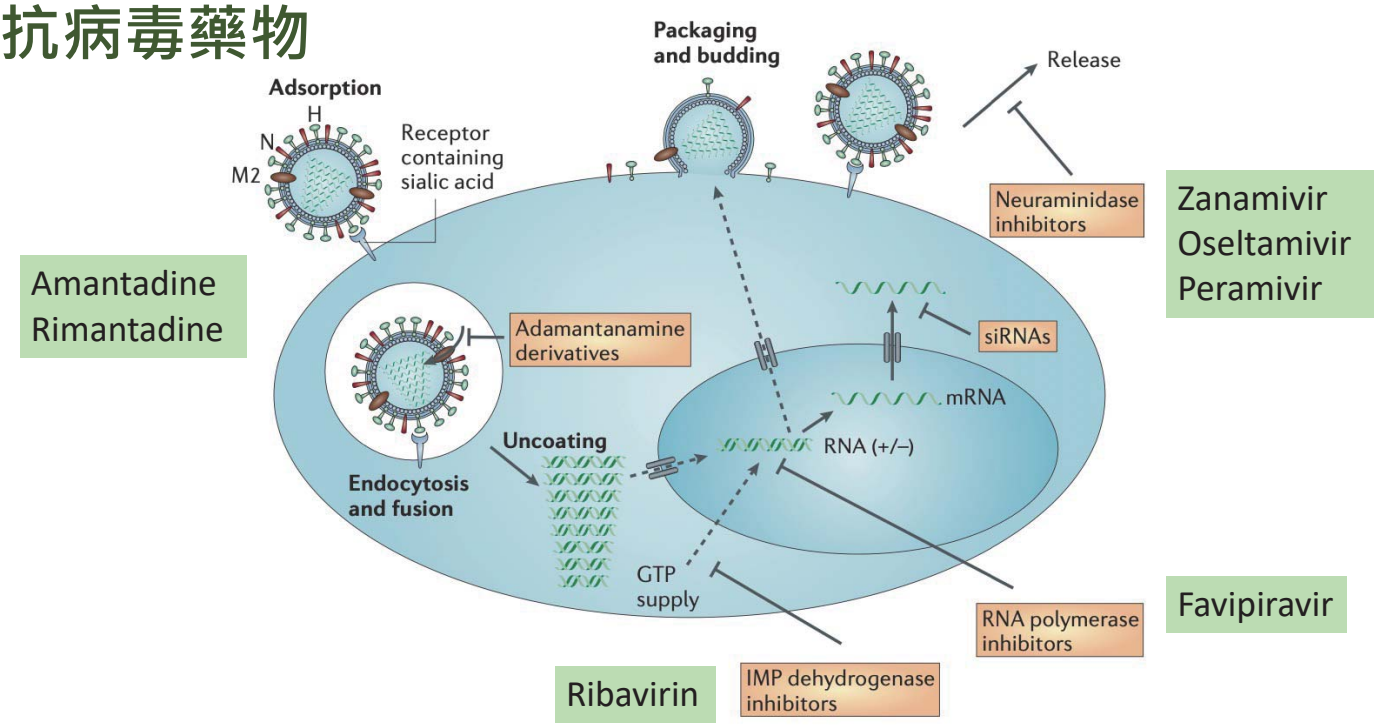
Year	Subtype	Estimate Death (million)	Origin of gene						
			NA	PA	PB1	PB2	NP	M	NS
1918	H1N1	50~100							
1957	H2N2	1~4							
1968	H3N2	1							
2009	H1N1	~0.018							

Reid et al 2004, SOIA Novel et al 2009, Taubenberger et al 2005, Zimmer and Burke, 2009



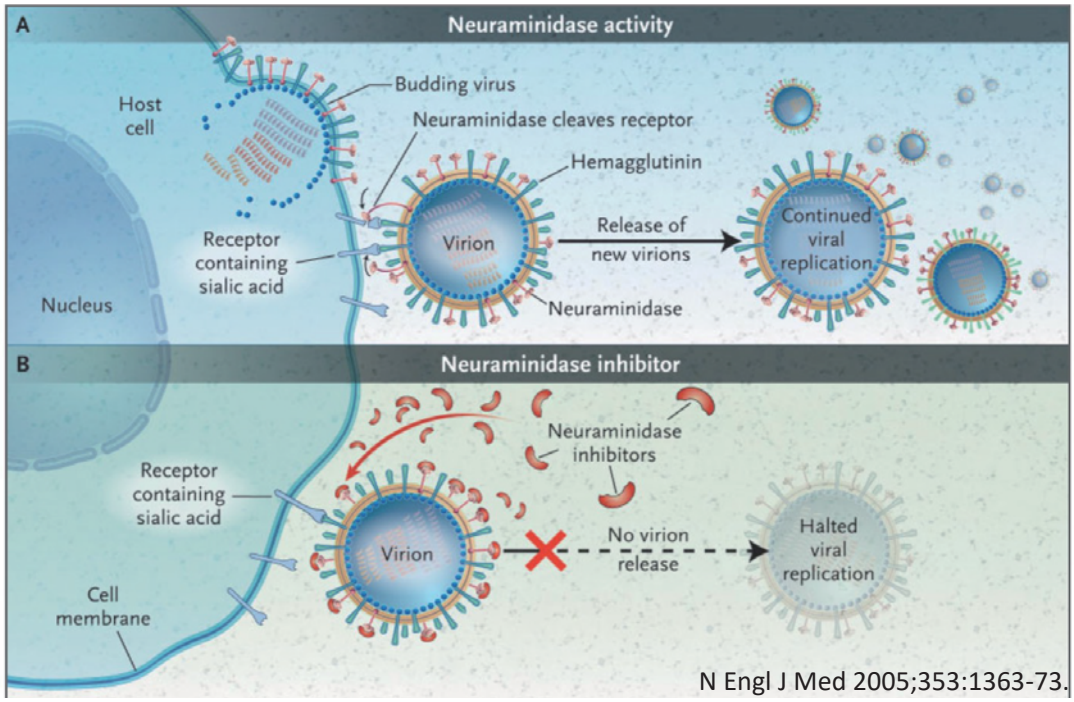
De Clercq E. Nat Rev Drug Discov. 2006.

抗病毒藥物



De Clercq E. Nat Rev Drug Discov. 2006.

Mechanism of Neuraminidase Inhibitor



N Engl J Med 2005;353:1363-73.

抗病毒藥物

- **M2 protein inhibitor**
  - Amantadine/Rimantadine
  - 抗藥性問題嚴重，目前不適用
- **Neuraminidase inhibitor**
  - Oseltamivir (oral) / zanamivir (INH) / peramivir (IV)
  - 流感抗病毒藥物主流
  - 抑制病毒表面之神精氨酸酶，阻止複製完成之病毒自宿主細胞內釋出
  - 預防疾病、減輕症狀、縮短病程

- **RNA polymerase inhibitor**
  - Favipiravir (Avigan)
  - 干擾RNA病毒的複製過程，抑制感染細胞內的病毒基因複製以防止繁殖
  - 用於治療新型流感（限於其他抗流感病毒藥物無效）
  - 日本藥政許可
- **Polymerase Acidic Endonuclease inhibitor**
  - Baloxavir marboxi (Xofluza)
  - 作用於流感病毒複製過程所必需的Cap-snatching mechanism，可抑制流感病毒的複製增生，亦可阻斷流感病毒的傳播
  - 108年藥證許可

流感抗病毒藥劑種類

學名	Oseltamivir	Zanamivir	Peramivir	Favipiravir	Baloxavir marboxil
商品名	克流感/易剋冒	Relenza	Rapiacta	Avigan	Xofluza
包裝	75毫克膠囊	碟型吸入器x1 4孔間隔之泡囊x5	點滴用注射袋300mg	淡黃色膜衣錠，每錠200mg	20毫克膜衣錠
使用方式	口服	吸入	注射	口服	口服
對象	>=1個月	>=5歲	>=1個月	成人	>=12歲且體重>=40kg
劑量	75mg BID，5 days 2-3mg/kg BID	2孔 BID，5 days	成人：300mg（max 600mg） 兒童：10mg/kg	1600mg BID，1 day 600mg BID，4day	40-80公斤：口服單次40mg；大於80公斤：口服單次80mg
腎功能調整劑量	是	否	是	是	否

公費流感抗病毒藥劑儲備目的

- 因應全球新型流感大流行之整備需求，疾管署依世界衛生組織及國內專家建議，採購及儲備流感抗病毒藥劑
- 訂定公費藥劑使用對象，提供醫療使用於感染流感後容易併發重症的高危險群
- 於高峰期釋出效期最短的藥物，避免造成屆期銷毀之浪費情形

公費流感抗病毒藥劑使用對象

- 「流感併發重症」通報病例(需通報於法定傳染病通報系統)
- 「新型A型流感」通報病例(屬第五類法定傳染病需通報於法定傳染病通報系統) 註：選填此項者需填寫法傳編號
- 孕婦經評估需及時用藥者(領有國民健康署核發孕婦健康手冊之婦女)
- 未滿5歲及65歲以上之類流感患者
- 確診或疑似罹患流感住院(含急診待床)之病患 註：罹患流感因病況嚴重而需住院治療的病患，並不包括門診病人，依此條件使用公費藥劑者須備有「住院紀錄」
- 具重大傷病、免疫不全(含使用免疫抑制劑者)或流感高風險慢性疾病之類流感患者
- 肥胖之類流感患者(BMI>=30)

- 類流感等群聚事件經疾病管制署各區管制中心防疫醫師認定需用藥者 註：選填此項者需填寫群聚編號
- 新型A型流感極可能/確定病例之密切接觸者(接觸者名冊經傳染病防治醫療網區正/副指揮官或其授權人員研判需給藥者) 註：選填此項者需填寫所接觸之個案的法傳編號
- 動物流感發生場所撲殺清場工作人員(接觸者名冊經傳染病防治醫療網區正/副指揮官或其授權人員研判需給藥者) 註：選填此項者需填寫禽畜場名稱或編號

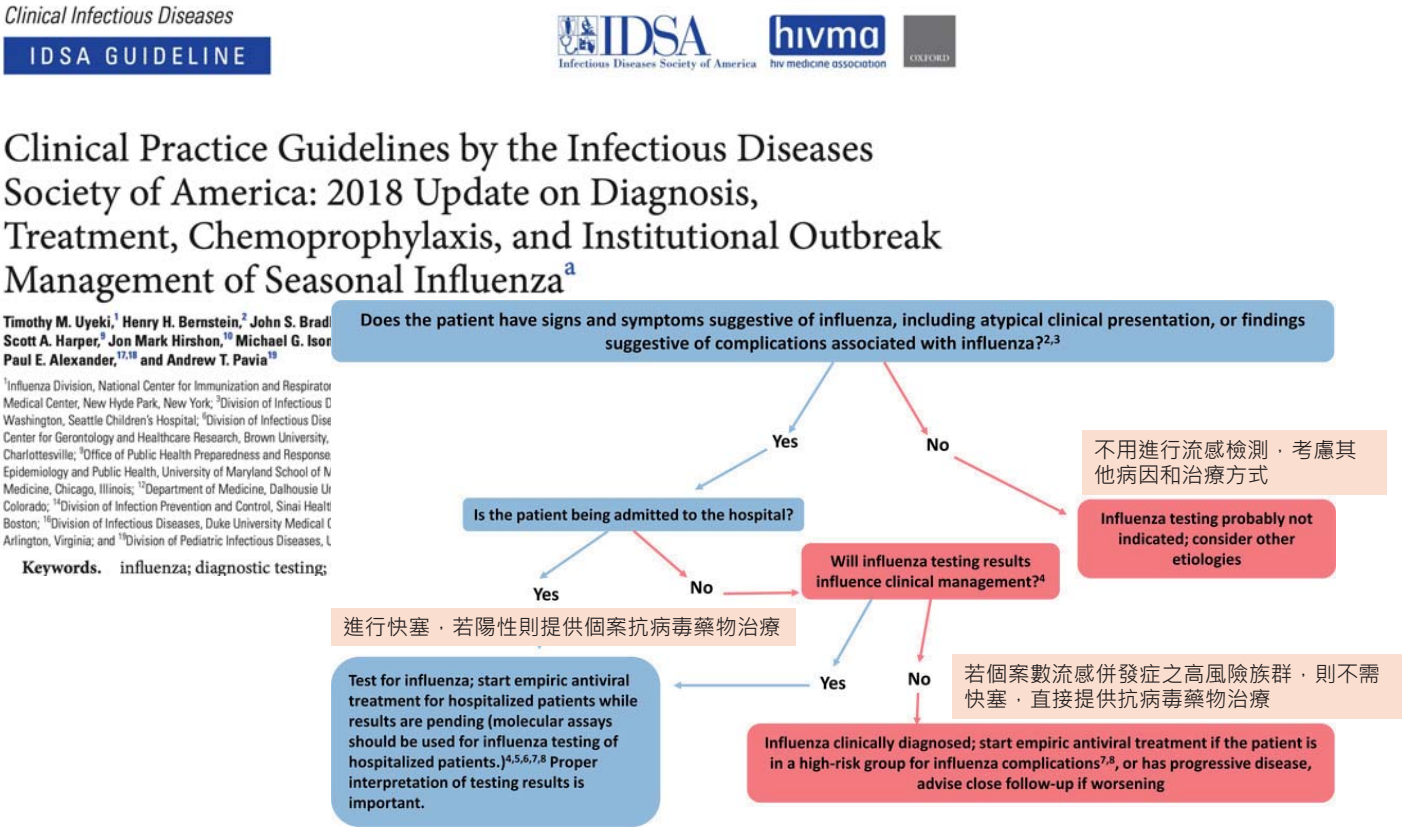
12月~3月

- 因應流感季高峰期防治需求之擴大用藥對象

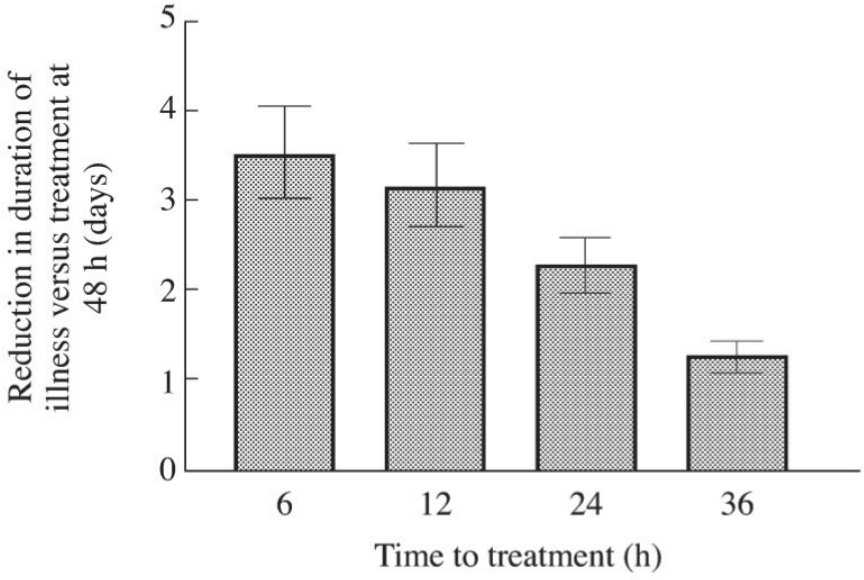
公費流感抗病毒藥劑擴大使用對象

- 擴大使用期間：流感流行季
  - 每年12 月1日至隔年3月31日
  - 將視每年疫情狀況調整
- 擴大使用對象
  - 有發燒之類流感症狀，且家人/同事/同班同學有類流感發病者

- 經醫師評估符合公費流感病毒藥劑使用對象，無需進行快篩，即可依醫師專業判斷開立公費藥劑
- 公費藥劑使用對象須為本國籍，倘非本國籍人士，除通報流感併發重症及新型A型流感等法定傳染病患者外，應有居留證（18歲（含）以下孩童其父母需一方為本國籍或持有居留證

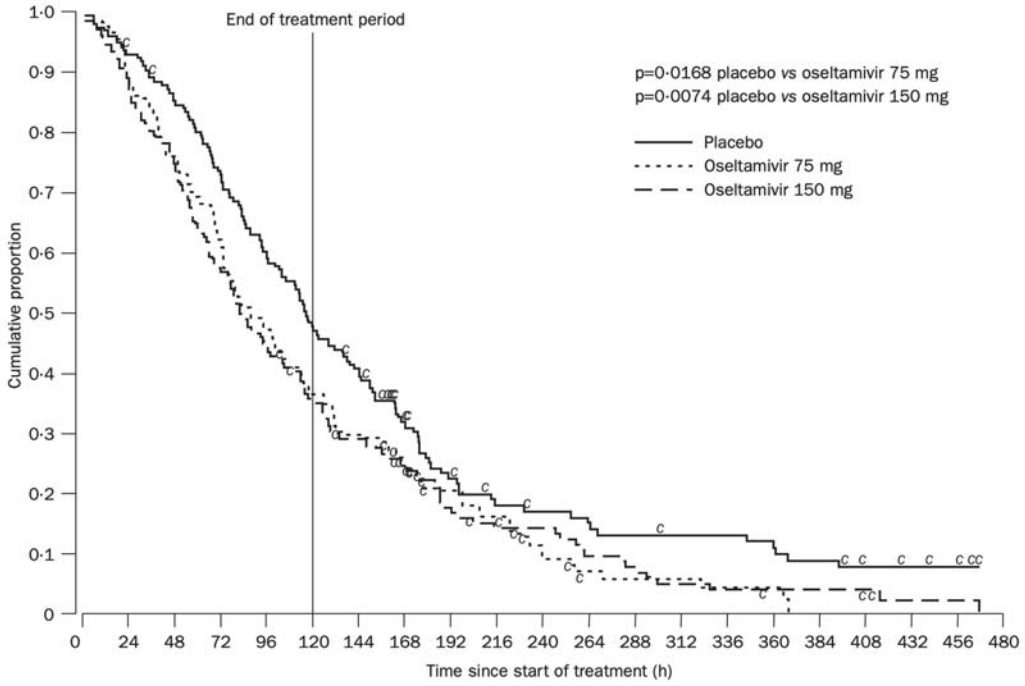


Efficacy of Oseltamivir



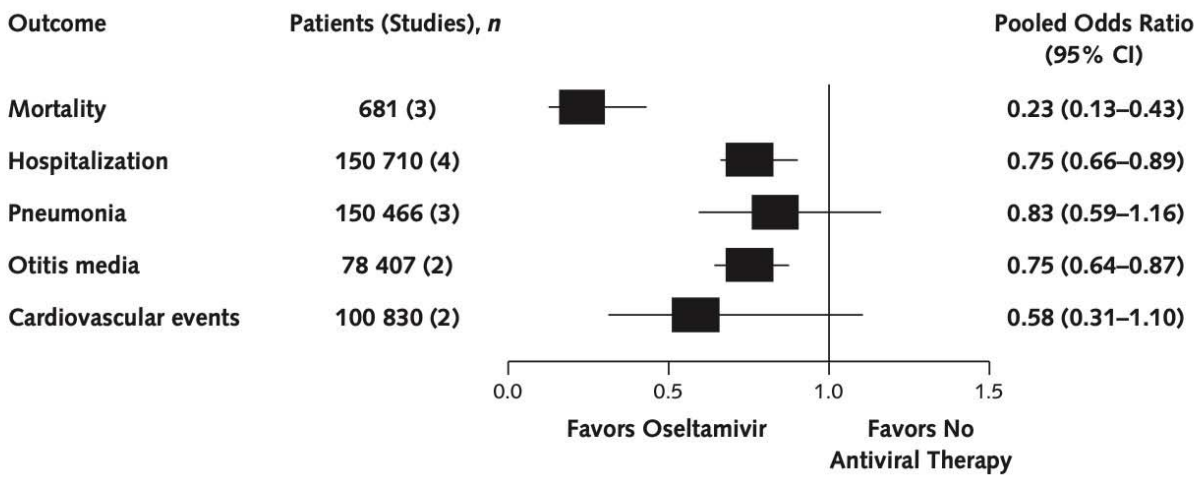
Journal of Antimicrobial Chemotherapy (2003) **51**, 123–129

Efficacy of Oseltamivir



Lancet 2000; **355:** 1845–50

Efficacy of Oseltamivir



Zanamivir

- Zanamivir(10mg BID for 5 days) inhaled early in the course in previously healthy adults and children 5-12 years old shortens the times to illness resolution and return to usual activities by **1-3 days**.
- In individuals with influenza B illness, zanamivir reduces the medial duration of fever by 32% from **53 hours to 36 hours**, compared to oseltamivir

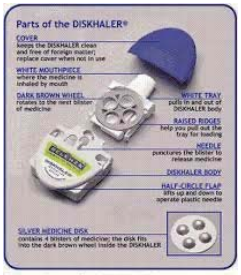


Figure 1. Parts of the DISKHALER

Peramivir

- 何時考慮使用
  - [illegible]
  - [illegible] A[illegible]
    - Poor GI absorption of oral medication
    - Lower respiratory tract infection, difficult to using inhaled anti-viral agents
  - A[illegible]
- 通過衛福部藥證，自費使用
- 公費限新型流感，經轄區指揮官同意使用

Favipiravir

- RNA polymerase inhibitor
- 無藥證，限新型流感通報病例使用，經轄區指揮官同意使用
- 具致畸胎性，孕婦及有懷孕可能的婦人禁止使用

Baloxavir marboxil

- 抑制CAP依存性內切酶來終止病毒mRNA的轉錄
- 跟Oseltamivir比較，緩解流感**症狀**和**退燒**的程度，無顯著差異
- 抗病毒能力， Baloxavir在**抑制病毒數量**或者**效率**上都比對照組和Oseltamivir來的顯著
- 病毒本身有I38T/M/F取代變異的特性將會使得Baloxavir對於該病毒的抑制效果較不佳

Use of Ribavirin to Treat Influenza

TO THE EDITOR: Ribavirin, an antiviral drug with in vitro activity against both DNA and RNA viruses, is approved in the United States for the treatment of hepatitis C and respiratory syncytial virus.[1] Hepatitis C is treated with approved oral formulations in combination with interferon products; respiratory syncytial virus is treated with an aerosol formulation. Intravenous ribavirin is not curren

tion of therapy and the onset of symptoms (or viral inoculation in challenge studies), and the reporting of clinical outcomes, microbiologic data, and adverse events. Reported adverse events were consistent with the labeling of approved aerosol and oral formulations.[4,5]

Since the late 1980s, clinicians have requested access to intravenous ribavirin from the manu- eatening

Clinical data regarding its efficacy have been inconclusive; thus, it is not recommended for the treatment of influenza infection

N Engl J Med 361;17

Combination therapy

Oseltamivir, amantadine, and ribavirin vs. Oseltamivir

1. Lower nasopharyngeal swab polymerase chain reaction at day 3

2. No clinical endpoint improvements, including median duration of symptoms and duration of fever

	Total (n=454)	Combination group (n=230)	Monotherapy group (n=224)	p value
Day 0	454	230	224	..
Median viral count, log_{10} copies/mL	6·5 (5·4–7·4)	6·4 (5·6–7·2)	6·7 (5·1–7·7)	..
≥LLOQ	421 (93%)	221 (96%)	200 (89%)	..
≥LOD, < LLOQ	13 (3%)	4 (2%)	9 (4%)	..
<LOD	20 (4%)	5 (2%)	15 (7%)	..
Day 3	437	221	216	..
Median viral count, log_{10} copies/mL	3·4 (3·2–4·6)	3·4 (3·2–4·2)	3·9 (3·2–5·0)	0·004
≥LLOQ	152 (35%)	65 (29%)	87 (40%)	0·009
≥LOD, <LLOQ	47 (11%)	22 (10%)	25 (12%)	..
<LOD	238 (54%)	134 (61%)	104 (48%)	..
Day 7	431	216	215	..
Median viral count, log_{10} copies/mL	<3·2 (<3·2–3·4)	<3·2 (<3·2–3·4)	<3·2 (<3·2–3·4)	0·38
≥LLOQ	43 (10%)	19 (9%)	24 (11%)	0·24
≥LOD, <LLOQ	11 (3%)	4 (2%)	7 (3%)	..
<LOD	377 (87%)	193 (89%)	184 (86%)	..

Data are median (IQR) or n (%).Primary endpoint was the percentage of participants with virus detectable by PCR (ie, ≥LLOQ and ≥LOD, <LLOQ). LLOQ=lower limit of quantification of PCR assay. LOD=limit of detection of PCR assay.

Table 2: **Influenza virus over time in the efficacy population**

Lancet Infect Dis. 2017;17(12):1255

Vaccine

流感的預防

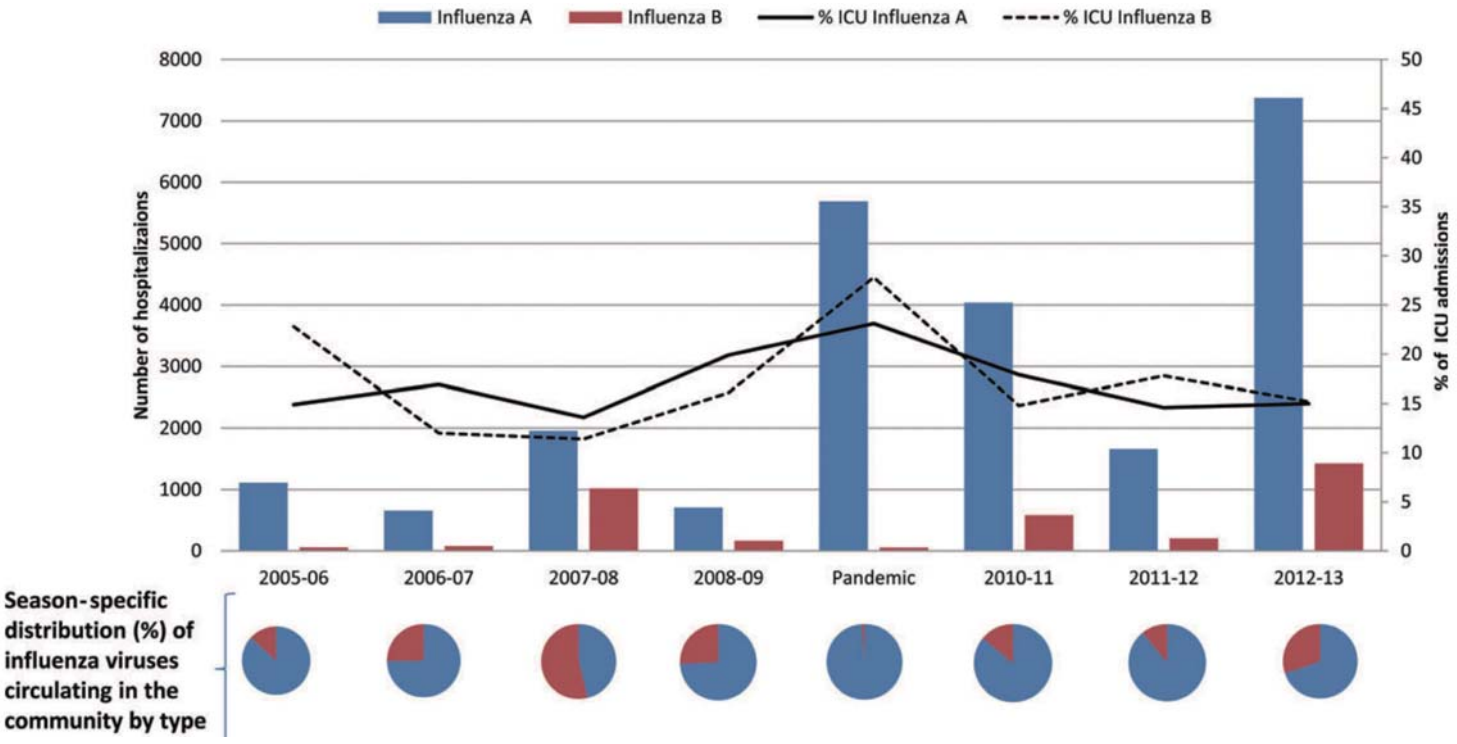
- 接種**疫苗**
  - □ □ 流感□ 有□ □ 方□
- 暴露後預防藥物
  - □ □ □ □ □ □ □ □ □ □ 事□
- 感染管制措施
  - 醫□ □ □ □ □ 期□ □ □ □ □ 人□ □ □ □ □
- 個人衛生
  - □ □ □ □ □ □ □ □ □ □ □ □ □

2021-2022年流感疫苗

- 不活化疫苗
- 四價疫苗
- 6個月以上均接種0.5mL
- 接種劑量與間隔
  - 8歲（含）以下□ □ □ □ 2 劑，且間隔至□ □□
  - 國□ 學童□ □ □ □ ，□ □ □ □ 1劑，□ □ □ □ 需□ ，至醫□ □ □ □ 費□ □ □ 2劑

2021-2022流感疫苗抗原成分

- 雞胚胎蛋培養疫苗
  - an A/Victoria/2570/2019 (H1N1) pdm09-like virus;
  - an A/Cambodia/e0826360/2020 (H3N2)-like virus;
  - a B/Washington/02/2019- like virus (B/Victoria lineage);
  - a B/Phuket/3073/2013-like virus (B/Yamagata lineage)
- 細胞培養疫苗
  - an A/Wisconsin/588/2019 (H1N1) pdm09-like virus;
  - an A/Cambodia/e0826360/2020 (H3N2)-like virus;
  - a B/Washington/02/2019- like virus (B/Victoria lineage);
  - a B/Phuket/3073/2013-like virus (B/Yamagata lineage).



Clin Infect Dis 2014 July 15

Match and Mismatch Between the Vaccine and Circulating Strains of Influenza B Viruses

Season	Vaccine B Lineage	Circulating B Lineages	Lineage-Level Vaccine Match, %	Lineage-Level Vaccine Mismatch, %
1999–2000	Yamagata	Yamagata (100%)	100	0
2000–2001	Yamagata	Yamagata (100%)	100	0
2001–2002	Yamagata	Yamagata (100%)	100	0
2002–2003	Victoria	Victoria (90%), Yamagata (10%)	90	10
2003–2004	Victoria	Yamagata (60%), Victoria (40%)	40	60
2004–2005	Yamagata	Yamagata (100%)	100	0
2005–2006	Yamagata	Victoria (95%), Yamagata (5%)	5	95
2006–2007	Victoria	Yamagata (100%)	0	100
2007–2008	Victoria	Yamagata (100%)	0	100
2008–2009	Yamagata	Victoria (100%)	0	100
2010–2011	Victoria	Victoria (90%), Yamagata (10%)	90	10
2011–2012	Victoria	Victoria (100%)	100	0

Clinical Infectious Diseases® 2014;59(11):1519–24

公費流感接種對象（暫定）

- **第一階段**
  - 醫事人員
  - 國小、國中、高中、高職、五專1至3年級學生等
  - 65歲以上長者
  - 滿6個月以上至國小入學前幼兒
  - 衛生防疫人員
  - 安養、養護、長照機構
  - 禽畜業及動物防疫人員
  - 孕婦及6個月內嬰兒之父母
  - 幼兒園托育人員及托育機構專業人員(含社區公共托育家園)
  - 具有潛在疾病者，包括高風險慢性病人、BMI大於等於30者、罕見疾病患者及重大傷病患者
- **第二階段**
  - 50-64歲成人

108年度流感疫苗接種計畫成果　　統計日期：109/9/30

接種對象	應接種數	接種數	接種率
65歲以上長者/機構對象*	3,537,314	1,813,931	51.3%
50-64歲成人	5,289,099	990,641	18.7%
醫事執登人員	329,622	230,269	69.9%
防疫人員及醫院非執登工作人員	147,985	139,744	94.4%
禽畜養殖業等及動物防疫人員	8,386	8,386	100.0%
國小、國中、高中、高職、五專1至3年級學生	2,372,287	1,834,474	77.3%
3歲以上至入學前幼童--曾接種過	402,028	290,870	72.4%
3歲以上至入學前幼童--未曾接種過(第1劑)	238,153	39,948	16.8%
3歲以上至入學前幼童--未曾接種過(第2劑)		18,572	7.8%
罕見疾病/重大傷病患者			
19-49歲高風險慢性病人			
孕婦及6個月內嬰兒之父母	-	89,559	-
托育人員及托育機構專業人員	50,450	12,950	25.7%
6個月以上3歲以下幼兒--曾接種過	142,554	136,434	95.7%
6個月以上3歲以下幼兒--未曾接種過(第1劑)	365,480	155,579	42.6%
6個月以上3歲以下幼兒--未曾接種過(第2劑)		112,357	30.7%

*為安養等機構之住民及所屬直接照顧工作人員

近5 年醫事人員流感接種率：66-74%

Vaccine Efficacy

(1 - relative risk) x 100

- Relative risk was the ratio of the percentages of vaccine recipients with influenza to placebo recipients with influenza(P vaccine/P placebo)

Drugs (2019) 79:1337–1348

FLU vaccine effectiveness varies by type or subtype

在此整合性研究分析中，
H3N2：33%；B：54%；
H1N1：67%

	Pooled VE (%)	Pooled standard error	VE estimates (n)*	p value for heterogeneity	I^2
H3N2 by season					
2010–11	46% (30 to 58)	0·131	5	0·368	26·1
2011–12	32% (23 to 40)	0·063	9	0·626	0·0
2012–13	40% (32 to 46)	0·059	6	0·644	0·0
2013–14	10% (−25 to 35)	0·164	3	0·913	0·0
2014–15	7% (−32 to 34)	0·179	3	0·051	74·3
H3N2 by antigenic similarity					
Variant	23% (2 to 40)	0·126	6	0·081	55·6
Similar	33% (22 to 43)	0·080	12	0·014	56·1
H1N1pdm09 by season					
2010–11	60% (54 to 65)	0·071	12	0·894	0·0
2011–12	68% (50 to 80)	0·239	3	0·541	7·2
2012–13	55% (41 to 66)	0·142	6	0·930	0·0
2013–14	62% (52 to 70)	0·117	6	0·260	35·2
Type B by season†					
2005–06	52% (25 to 70)	0·231	3	0·648	0·0
2007–08	50% (29 to 64)	0·172	5	0·235	41·2
2010–11	55% (48 to 62)	0·080	11	0·554	0·0
2011–12	49% (0 to 74)	0·343	7	<0·0001	89·7
2012–13	55% (46 to 62)	0·087	7	0·566	0·0

Data in parentheses are 95% CIs. VE=vaccine effectiveness. *Seasons with fewer than three VE estimates for a given subtype were not included. †2009–10 is not shown because only one estimate for type B during that season existed.

Ann Intern Med. 2012;156:512-524.

2019–20 Seasonal Influenza Vaccine Effectiveness — United States,

TABLE 2. Number and percentage of outpatients with acute respiratory illness and cough (N = 4,112) receiving 2019–20 seasonal influenza vaccine, by influenza real-time reverse transcription–polymerase chain reaction (RT-PCR) test result status, age group, and vaccine effectiveness* against all influenza A and B, B/Victoria and A(H1N1)pdm09 — U.S. Influenza Vaccine Effectiveness Network, October 23, 2019–January 25, 2020

	Influenza-positive		Influenza-negative		Vaccine effectiveness	
Influenza type/Age group	Total	Vaccinated no. (%)	Total	Vaccinated no. (%)	Unadjusted % (95% CI)	Adjusted† % (95% CI)
Influenza A and B						
Overall	**1,060**	**390 (37)**	**3,052**	**1,682 (55)**	**53 (45 to 59)**	**45 (36 to 53)**
Age group						
6 mos–17 yrs	**462**	142 (31)	**934**	492 (53)	60 (50 to 69)	55 (42 to 65)
18–49 yrs	**413**	143 (35)	**1,084**	452 (42)	26 (6 to 42)	25 (3 to 41)
≥50 yrs	**185**	105 (57)	**1,034**	738 (71)	47 (27 to 62)	43 (19 to 60)
					60 (52 to 66)	**50 (39 to 59)**
					62 (51 to 71)	56 (42 to 67)
					54 (42 to 64)	32 (11 to 48)
Influenza A(H1N1)pdm09						
Overall	**326**	**138 (42)**	**3,052**	**1,682 (55)**	**40 (25 to 53)**	**37 (19 to 52)**
Age group						
6 mos–17 yrs	**98**	35 (36)	**934**	492 (53)	50 (23 to 68)	51 (22 to 69)
18–49 yrs	**125**	48 (38)	**1,084**	452 (42)	13 (-27 to 40)	5 (–45 to 37)
≥50 yrs	**103**	55 (53)	**1,034**	738 (71)	54 (31 to 69)	50 (20 to 68)

* Vaccine effectiveness was estimated as 100% x (1 – odds ratio [ratio of odds of being vaccinated among outpatients with CDC's real-time RT-PCR influenza-positive test results to the odds of being vaccinated among outpatients with influenza-negative test results]); odds ratios were estimated using logistic regression.
† Adjusted for study site, age group, sex, race/ethnicity, self-rated general health, number of days from illness onset to enrollment, and month of illness using logistic regression.

2019-2020年美國流感季流感疫苗效果45%，接種流感疫苗可降低快5成流感就醫風險

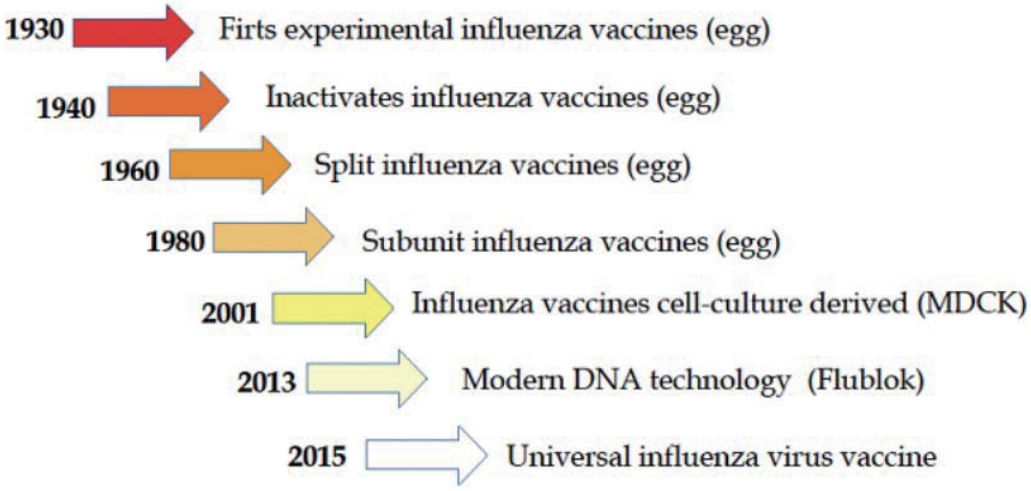
MMWR / February 21, 2020 / Vol. 69 / No. 7

流感大事紀

1918	**Spanish Flu caused by H1N1**
1933	Isolation of influenza virus[36]
1935-1941	Early vaccination studies identified the importance of dose and matching strains[36]
1942-45	Trials with concentrated and inactivated vaccines[36]
1945	First commercial influenza vaccine available in the US[36]
1947	Global surveillance initiated by WHO
1957	**"Asian flu" caused by H2N2**
1960s	Attempts to generate attenuated viruses
1968	**Pandemic caused by H3N2**
1976-1977	Subunit influenza vaccine was developed and found to be less reactogenic than inactivated whole virus vaccines[47-49]
1976-1977	Swine flu (H1N1) outbreak in Fort Dix, US, prompting a short-lived mass vaccination campaign
1977-1978	**"Russian flu" outbreak (H1N1)**
1980s	Russians developed cold-adapted attenuated vaccine strains[64,65]
1997	**Outbreak of highly pathogenic H5N1 in Hong Kong**
1990s	Reverse-genetics system developed, leading to attenuated H5 vaccine strains[78,79]
2003	FluMist, intranasal LAIV licensed by FDA for adults*
2003-2004	**Outbreak of highly pathogenic H5N1 in Asia**
2007	H5 vaccine from Sanofi-Pastuer approved by FDA*
2007	Optaflu, MDCK-cell derived vaccine approved for use in Europe^
2009	**Swine Flu pandemic (swine origin H1N1)**
2009	FluZone High Dose licensed and recommeded by ACIP for elderly#
2009	Adjuvanted vaccines against 2009 swine flu strain approved under exceptional circumstance for use in Europe^
2010	ACIP recommends National Influenza vaccination for all ages 6 months and older#
2011	FluZone Intradermal licensed by FDA*
2012	Vepacel, Vero-cell derived influenza vaccine by GSK, licensed in Europe^, Flucelvax, MDCK-cell derived vaccine, Fluarix (quadrivalent TIV) and FluMist Quadrivalent, approved by FDA*
2013	FluBlok (baculovirus-derived) approved by FDA*

Clin Microbiol Rev. 2013 Jul;26(3):476-92.

Historical path of the development of influenza vaccine



Vaccines 2017, 5, 18

[illegible]

Age Group	Recommended Vaccine	Live vaccine?	Types of flu strains protected	Reason for recommendation
Children aged 6 months to 2 years	Egg-grown quadrivalent vaccine (QIVe)	**No**	**Four**	LAIV is not suitable for children under two
Children aged 2 – 17 years	Live attenuated influenza vaccine (LAIV)	**Yes**	**Four**	Nasal vaccine helps to reduce spread of flu virus in children
Adults aged 18 – 64 years	Quadrivalent influenza vaccine: Egg-grown (QIVe) Cell-based (QIVc)	**No**	**Four**	Quadrivalent vaccines protect against four types of flu strain
Adults aged 65 or over	Adjuvanted trivalent influenza vaccine (aTIV)	**No**	**Three**	"Adjuvant" is added to the vaccine to make it more effective in older people

https://vk.ovg.ox.ac.uk/vk/inactivated-flu-vaccine

□□□□□□□□ □ 流感□ □

- 全面四價
- 增加細胞型流感疫苗

持有許可證廠商/品名	劑型	適用年齡
賽諾菲股份有限公司 / Vaxigrip Tetra巴斯德四價流感疫苗	0.5mL	提供6個月以上使用
國光生物科技股份有限公司 / AdimFlu-S(QIS)“安定伏”裂解型四價流感疫苗	0.5mL	提供3歲以上使用
台灣東洋藥品工業股份有限公司 /FLUCELVAX QUAD輔流威適流感疫苗	0.5mL	提供3歲以上使用

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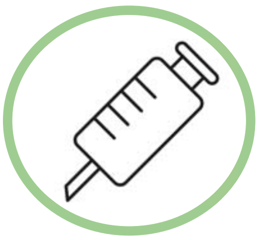
Supply of eggs
Egg allergies



Haemagglutinin proteins mutation
H3N2

1. ESMO Open. 2019;4(1):e000481
2. Vaccines. 2018;6(19):E19
3. NPJ Vaccines.2018;3:44

[illegible]

18-49yrs	TIVc/TIVe Phase 3, randomized, placebo-controlled, multicenter study (2007-2008) in the US, Finland, and Poland
18-64 yrs/ >65yrs	TIVc/QIVc Phase 3, randomized, double blind, multicenter study (2013-2014) in the United States
4-17 yrs	TIVc/QIVc Phase 3, randomized, double blind, multicenter study (2013-2014) in the United States
2/3-17 yrs	Phase 3, randomized, observer blind, multicenter study (2017-2019) in EUR, South America, AST, ASIA

[illegible]

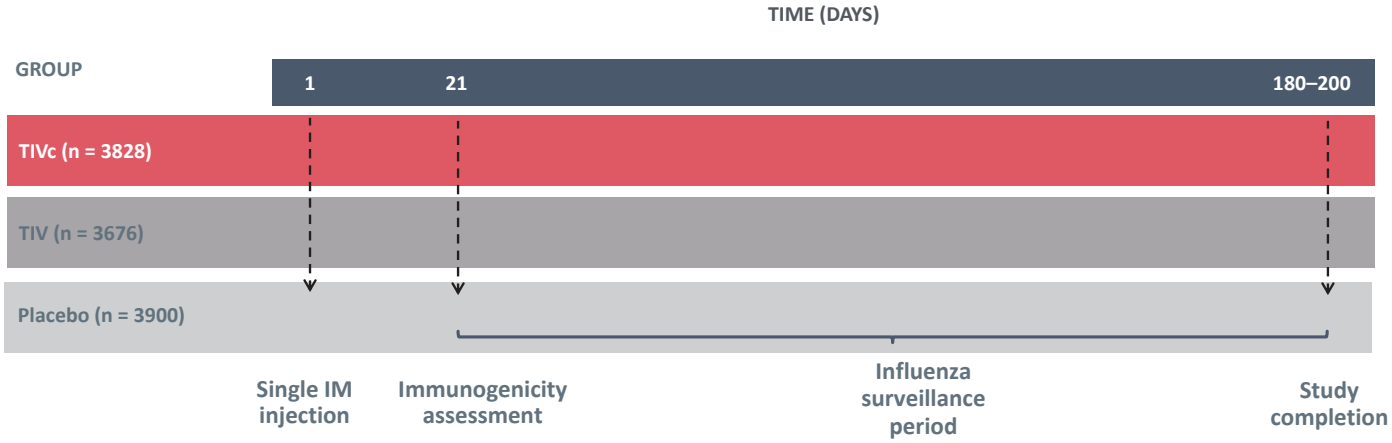
CBER (USA Center for Biologics Evaluation and Research) /CHMP immunogenicity criteria

- Lower limit of the 2-sided 95% CIs for the percentage of subjects achieving an **HI antibody titer 1:40** should be 70% and 60% for subjects aged 18 to <65 y and 65 y
- Lower limit of the 2-sided 95% CIs for the percentage of subjects achieving **seroconversion** should be 40% and 30% for subjects aged 18 to <65 y and 65 y
- **Seroconversion rate**
  - HI titer <1:10 → HI titer ≥1:40
  - HI titer ≥1:10 → at least a 4-fold increase

Drugs (2019) 79:1337–1348

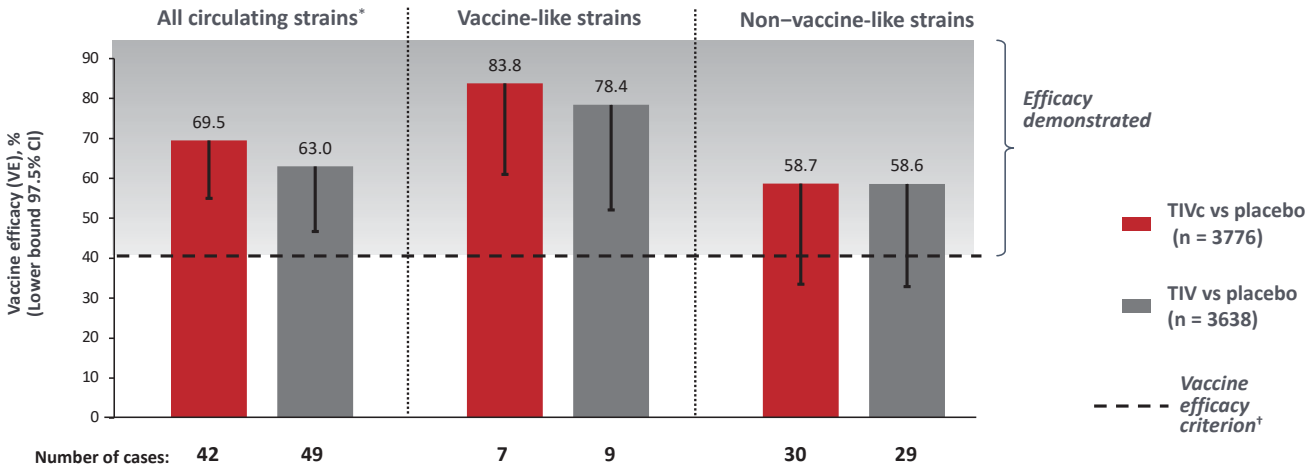
Efficacy study of TIVc and TIV vs placebo

Phase 3, randomized, placebo-controlled, multicenter study (2007-2008) in the United States, Finland, Poland



Frey □ e□al. *Clin □□ec□□i□* 2010;□1:997-1004.

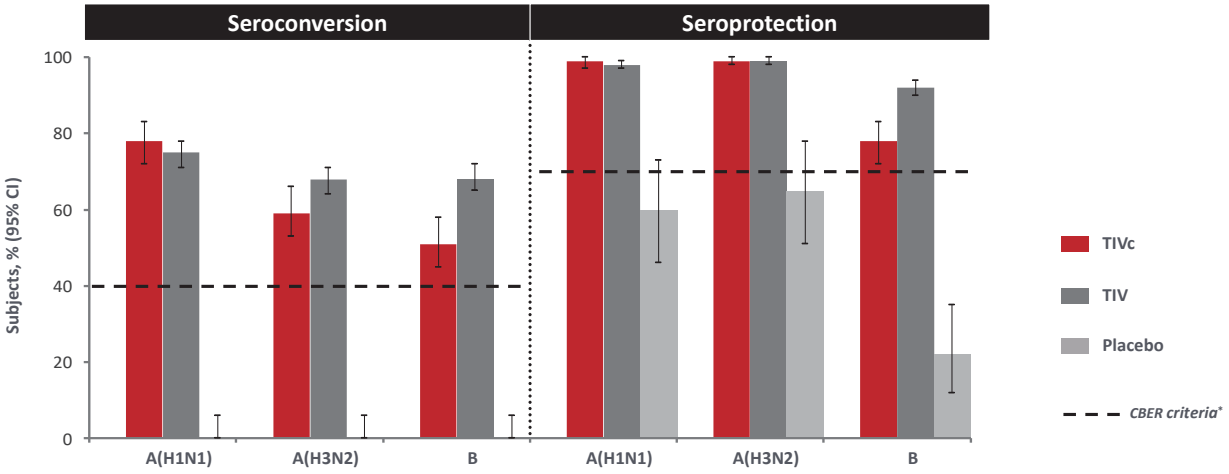
Efficacy of TIVc and TIV against circulating strains vs placebo in adults aged 18-49 years



Efficacy : (1 - P vaccine/P placebo) x 100

Frey □ e□al. *Clin □□ec□□i□* 2010;□1:997-1004.

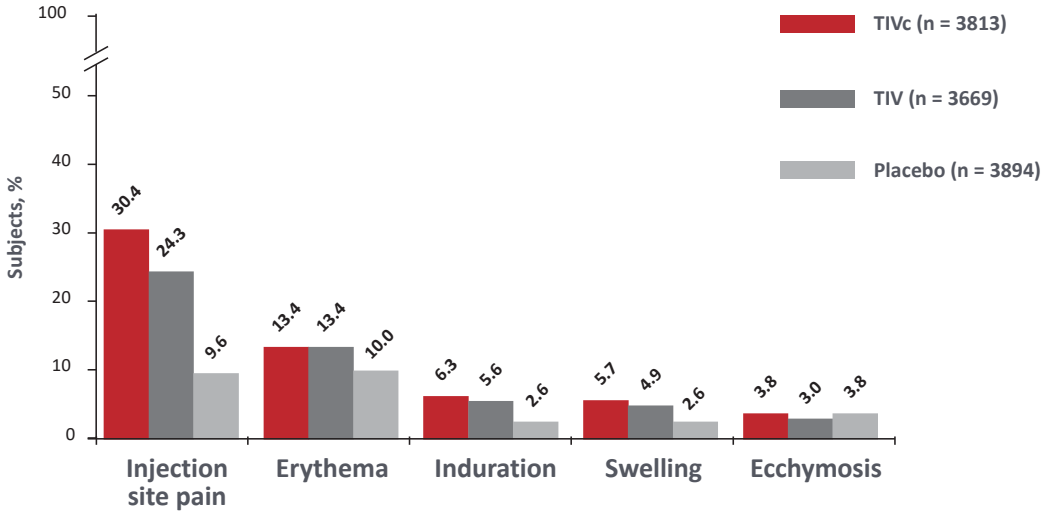
Seroconversion and seroprotection with TIVc and TIV vs placebo in adults aged 18-49 years



1) **Seroconversion** should be 40% 2) **HI antibody titer 1:40** should be 70%

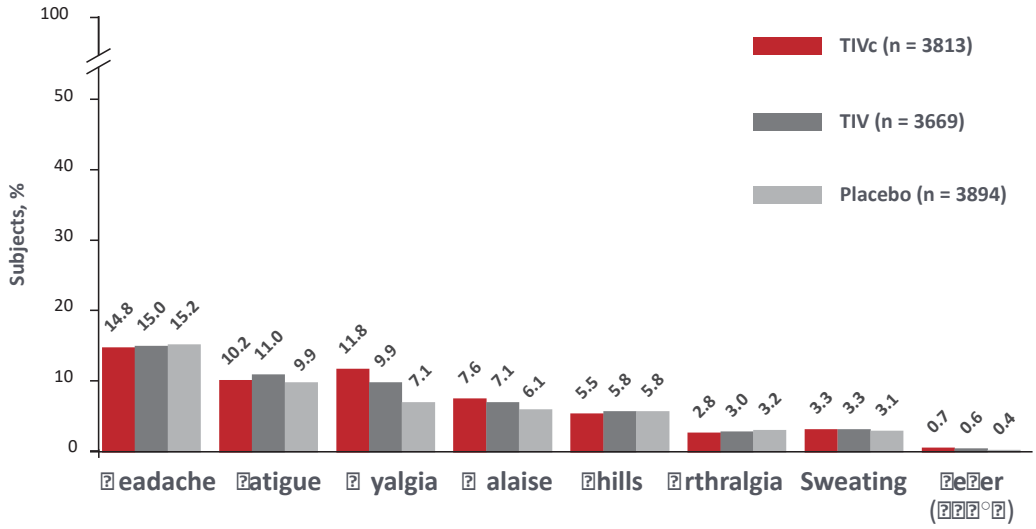
Frey □ e□al. *Clin □h□ec□□i□* 2010;□1:997-1004.

Solicited local reactions within 7 days post-vaccination in adults aged 18-49 years



1. Frey S et al. *Clin Infect Dis.* 2010;51:997-1004.
2. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/results/NCT00630331?view=results. Accessed May 11, 2019.

Solicited systemic reactions within 7 days post-vaccination in adults aged 18-49 years



1. Frey S et al. *Clin Infect Dis.* 2010;51:997-1004.
2. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/results/NCT00630331?view=results. Accessed May 11, 2019.

COMPARATIVE TRIAL OF QIVC IN HEALTHY ADULTS

Phase 3, randomized, double blind, multicenter study (2013-2014) in the United States

Primary objective(s)	Primary: To evaluate noninferiority of QIVc vs comparator TIVc Secondary: • To demonstrate superiority of QIVc against the unmatched B strain in TIVc • To evaluate immunogenicity of QIVc and TIVc according to CBER and CHMP criteria • To demonstrate safety and tolerability of each vaccine
Study population	Healthy adults (aged 18-64 years) and older adults (aged ≥65 years): N = 2680
Exposure(s)	**QIVc**
Comparator(s)	TIV1c (containing B/Yamagata lineage) or TIV2c (containing B/Victoria lineage)

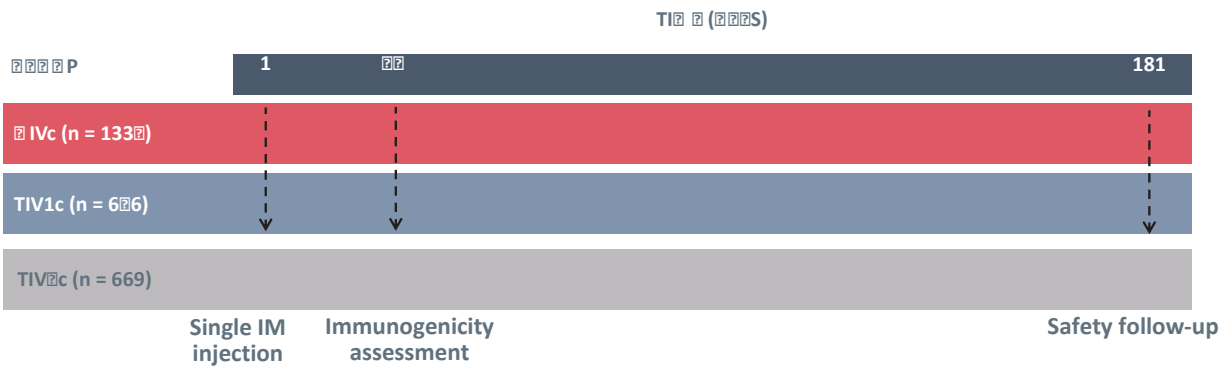
Non-Inferiority

- Upper limit (UL) of the 2-sided 95% confidence intervals (CI) of the vaccine group ratio of **GMTs** (TIV1c or TIV2c divided by QIVc) was <1.5
- UL of the 2-sided 95% CI for the difference in **SCR** (TIV1c or TIV2c minus QIVc) was <10%

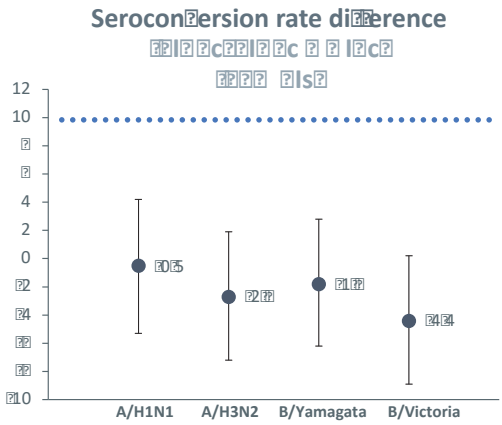
Drugs (2019) 79:1337–1348

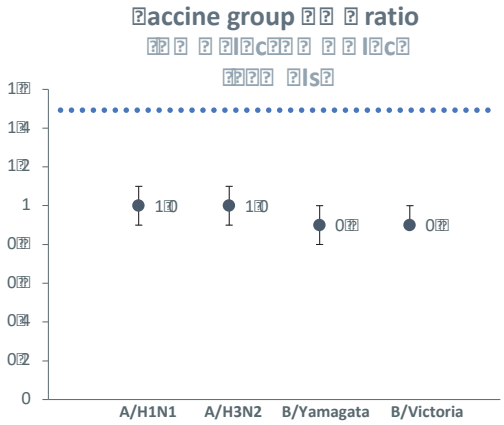
Comparative trial of QIVc in healthy adults

Phase 3, randomized, double blind, multicenter study (2013-2014) in the United States



Immunogenicity of QIVc is non-inferior to TIVc on seroconversion rates and GMTs in adults

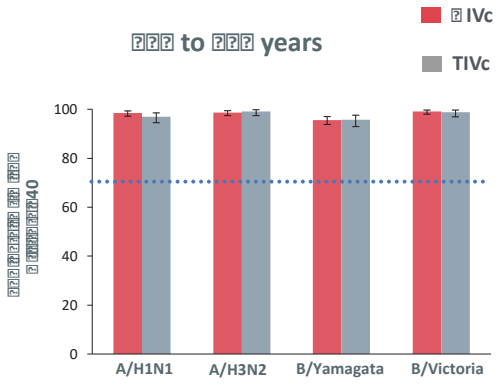


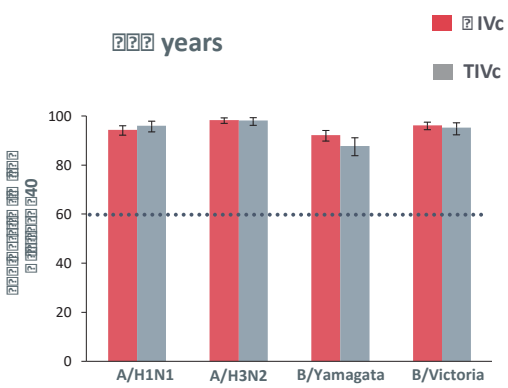


TIV1c or TIV2c minus QIVc <10%
TIV1c or TIV2c divided by QIVc <1.5

Hum Vaccin Immunother 2016;12:2220–2232

QIVc induced immune response (seroprotection) comparable to TIVc in adults

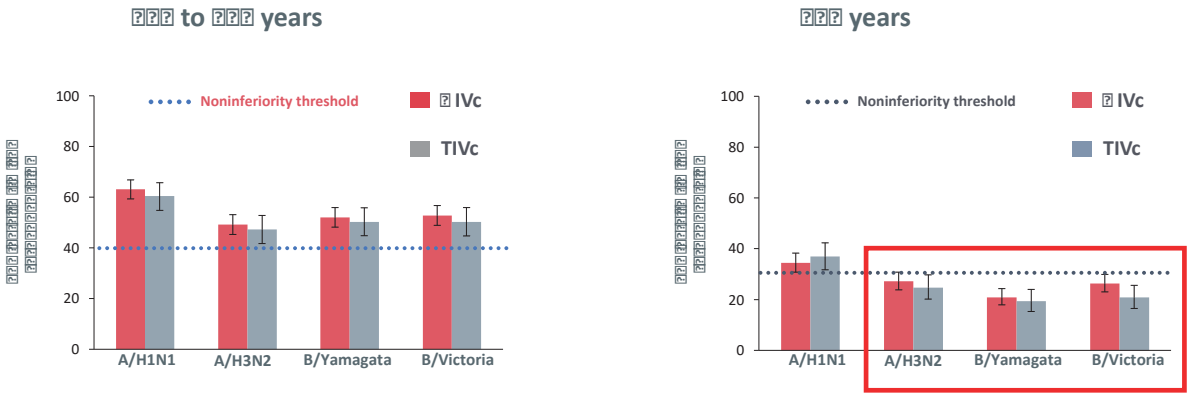




HI antibody titer 1:40 should be 70% and 60% for subjects aged 18 to <65 y and 65 y

Hum Vacc and Immuno. 2016;12:2220–2232

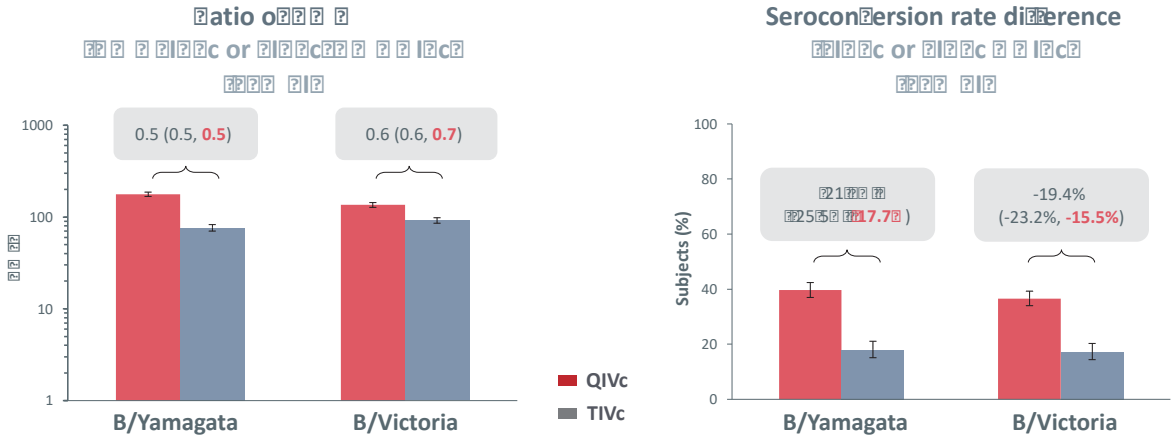
QIVc induced immune response (seroconversion) comparable to TIVc in adults



Seroconversion should be 40% and 30% for subjects aged 18 to <65 y and 65 y

Hum Vacc and Immuno. 201 22 22

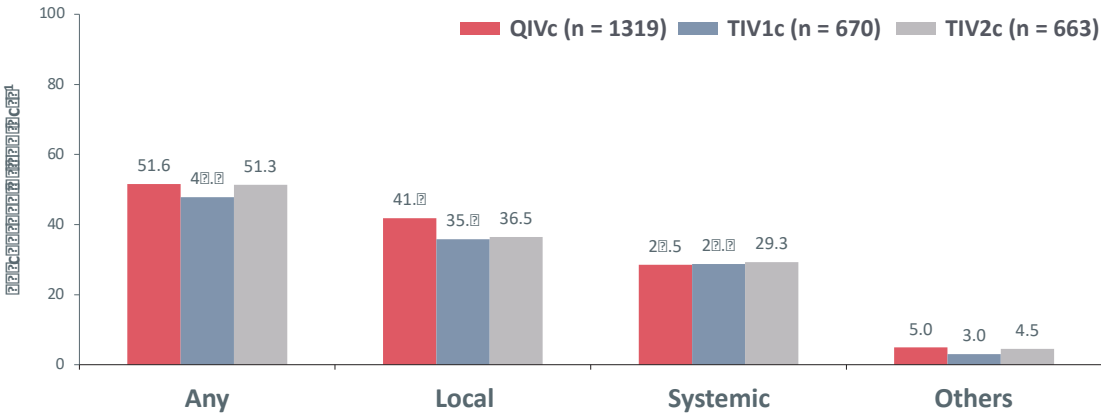
Superiority of QIVc relative to TIVc against unmatched B strains in adults



1) TIV1c or TIV2c divided by QIVc <1 2) TIV1c or TIV2c minus QIVc <0

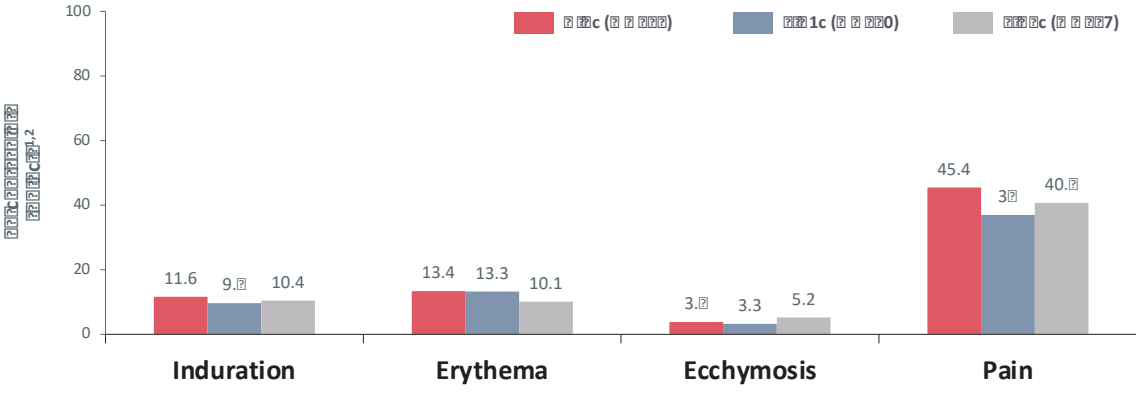
Hum Vaccin Immunother 201 12 22 22

Tolerability profiles of QIVc and TIVc were similar in adults



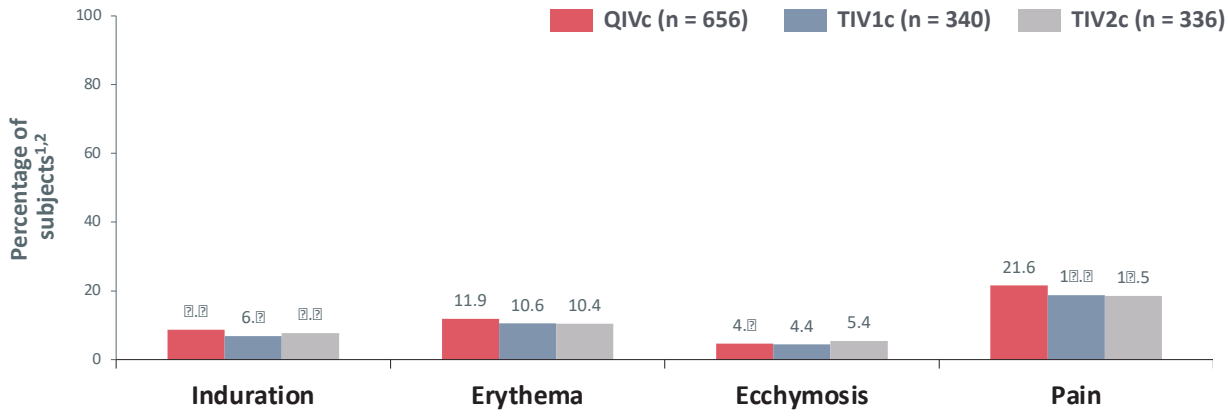
1. ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/results/NCT01992094?term=NCT01992094&rank=1&sect=X301256#evnt. Accessed March 30, 2019. 2. Bart S et al. *Hum Vaccin Immunother*. 2016;12(9):2278-2288.

Local adverse events within 7 days postvaccination with QIVc and TIVc in adults aged ≥18 to <65 years



Flucelvax Quadrivalent [package insert]. Summit, NJ. Seqirus, Inc. July 2018.

Local adverse events within 7 days postvaccination with QIVc and TIVc in adults aged ≥ 65 years



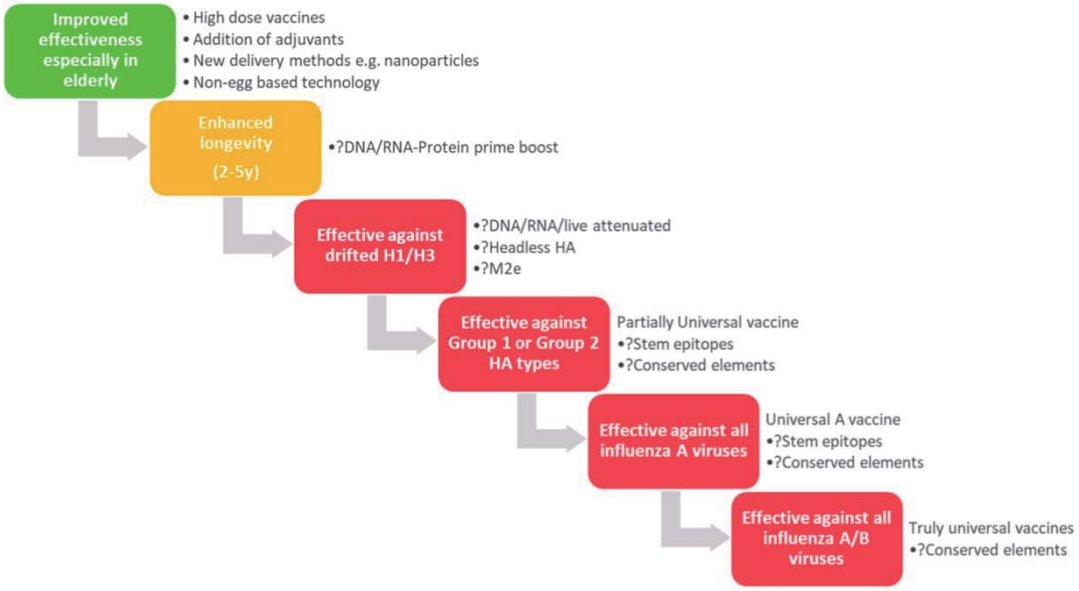
Flucelvax Quadrivalent [package insert]. Summit, NJ. Seqirus, Inc. July 2018.

Non-egg-based Influenza Vaccines

Company	Phase	Administration	Reference
Recombinant			
BiondVax	Phase III	Oral	[19]
Imutex	Phase II	SC	[20]
Recombinant—VLP			
Novavax	Phase III	IM	[21]
Osivax	Phase II	IM	[22]
Medicago	Phase III/discontinued	IM	[23]
Medigen	Phase II	IM	[24]
Recombinant—H5 protein fragment			
Generex	Phase I	Oral	[25]
Live attenuated			
Codagenix	Phase I	Nasal	[26]
FluGen	Phase II	Nasal	[27]
Vivaldi	Phase II	Nasal	[28]
Polymun	Phase I	Nasal	[29]
Vector—adenovirus			
Vaccitech	Phase II	IM	[30]
Vaxart	Phase II	Oral	[31]
Altimmune	Phase II	Nasal	[32]
Vector—alphavirus			
AlphaVax	Phase II	IM	[33]

Company	Phase	Administration	Reference
Adjuvant—novel			
BlueWillow	Phase I	Nasal	[34]
Nitto Denko	Phase I	Sublingual	[35]
Mercia	Phase II	IM	[36]
Adjuvant—toxin			
Mucosis	Phase I	Nasal	[37]
Eurocine	Phase I/II	Nasal	[38]
Advagene	Phase II	Nasal	[39]
mRNA			
Moderna Therapeutics	Phase I	IM	[40]
DNA vaccine			
Inovio	Phase I	IM	[41]
Virosomes			
Mymetics	Phase II	Nasal	[42]
Dendritic cells			
CEL-SCI	Phase I	IM	[43]

Potential steps and technologies to improve influenza vaccines



Microorganisms **2020**, *8*, 1745

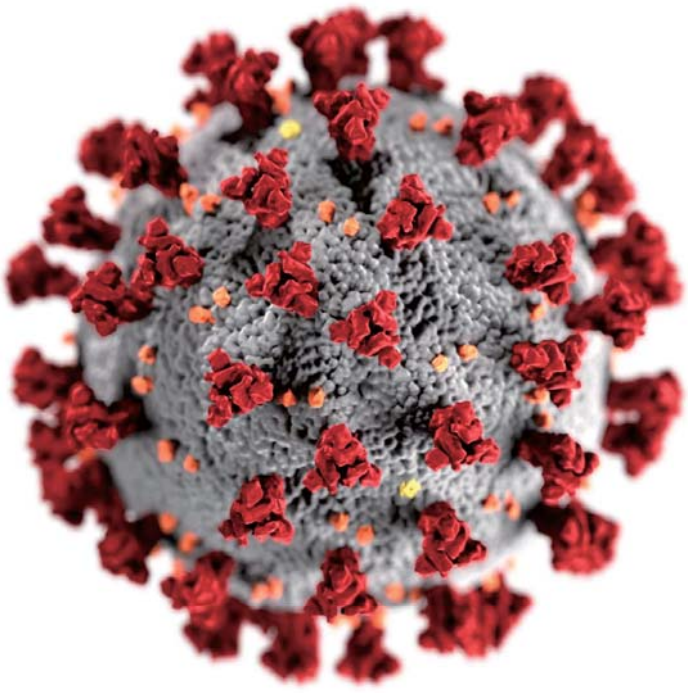
COVID 19流行病學,臨床表現與疫苗預防

中山學大學附設醫院 感染科
李鑒峯醫師

部分圖片資料擷取自網路,僅供教學使用

大綱

- SARS COV-2 介紹
- 流行病學
- 致病機轉與臨床表現
- 診斷與治療
- 疫苗預防



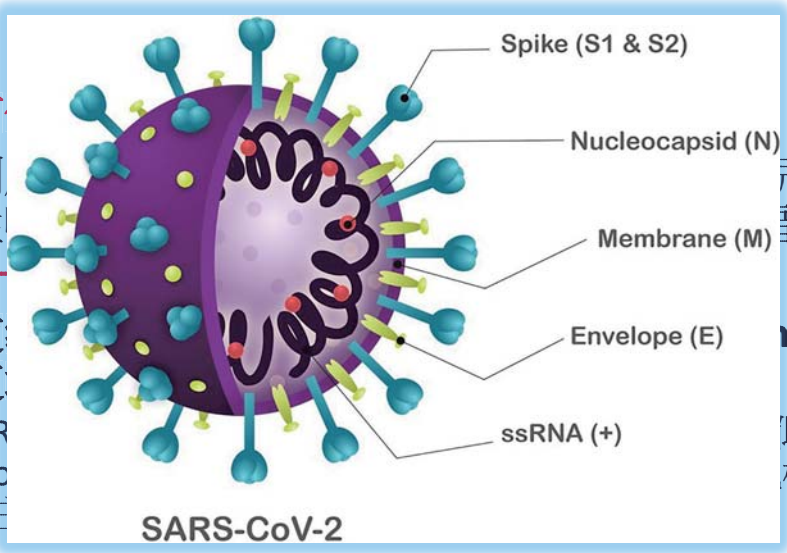
SARS COV-2 介紹

定義

- 冠狀病毒是重要的人類和動物病原體。截至2019年底，新的冠狀病毒被鑑定為武漢湖北省武漢肺炎患者群體的原因。它迅速傳播，導致中國的流行病，其次是全球大流行。
  - 二月2020年，世界衛生組織指定其疾病名為**COVID-19**，它代表冠狀病毒病2019
  - 造成COVID-19的病毒被指定名為**SARS-CoV-2**

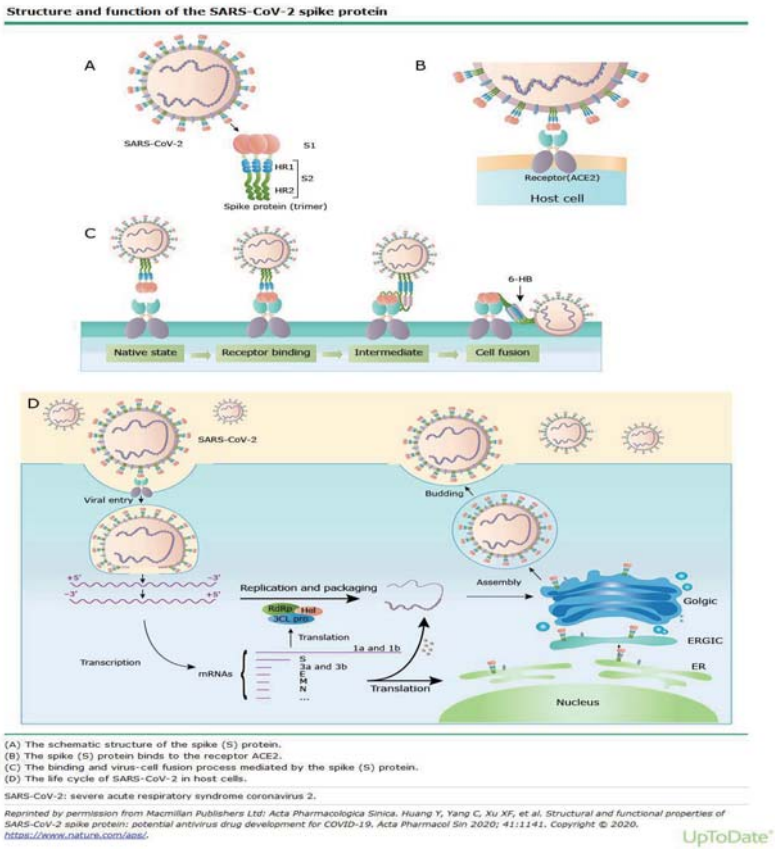
病毒學

- 冠狀病毒有
- 全基因組測 冠狀病毒是與嚴重急性 冠狀病毒）相同的**beta-**
- **中東呼吸道 navirus ，似乎更加恆定**
  - 最接近的R 以乎**蝙蝠**是主要來源; Co 機制（例如，通過中間



棘蛋白與變異

- SARS-COV-2進入細胞的宿主受體與SARS-COV相同，即血管緊張素轉換酶2（**ACE2**）。
- SARS-COV-2通過其**棘蛋白(spike protein)**的受體結合結構域與ACE2結合（下圖）。細胞蛋白酶TMPRSS2對於SARS-COV-2細胞入口也很重要。
- 與其他病毒一樣，SARS-COV-2隨著時間的推移而發展， SARS-COV-2基因組中大多數**突變**對病毒功能沒有影響。
- 某些變體由於快速大量的出現和傳播或臨床意義的證據而聞名。這些被認為是關注的變異。世界衛生組織（WHO）根據希臘字母的命名法指定了特定Pango基因譜系突變體的名稱。



變異機制

- 在大流行早期，針對SARS-COV-2的棘蛋白的**氨基酸的變化**鑑定了D614G（甘氨酸對天冬氨酸）的相互取代，其隨時間變成全球顯性多態性。
  - 在動物和體外研究中，攜帶**G614多態性**的病毒在呼吸道中表現出較高水平的感染病毒，與**ACE-2的結合增強**，與D614多態性相比增加了**複製和傳播性**。
  - G614變體似乎沒有與較高的住院風險相關聯或阻止抗棘抗體的結合。
- 現在最常見存在於循環的SARS-COV-2譜系中，包括下面列出的關注的變異體。在美國，在CDC網站上詳細說明了循環病毒的比例。
  - 針對傳播性,致病嚴重性與抗體的規避性三方面作比較

SARS-CoV-2 Variants of Concern

WHO label[1]	Name (Pango lineage*)	Name (Nextstrain*)	Spike protein substitutions (receptor-binding domain substitutions in bold)	First detected	Known attributes
Alpha	B.1.1.7¶	20I/501Y.V1	Δ69/70 Δ144Y **(E484K◇)** **(S494P◇)** **N501Y** A570D D614G P681H	United Kingdom	▪ ~50% increased transmission[2] ▪ Potential increased severity based on hospitalizations and case fatality rates[3] ▪ Minimal impact on neutralization by monoclonal antibody therapies§ • Bamlanivimab-etesevimab: No change in susceptibility[4] • Casirivimab-imdevimab: No change in susceptibility[5] • Sotrovimab: No change in susceptibility[6] ▪ Minimal impact on neutralization by convalescent and post-vaccination sera[7-13]
Beta	B.1.351	20H/501.V2	**K417N** **E484K** **N501Y** D614G	South Africa	▪ ~50% increased transmission[14] ▪ Significant impact on neutralization by some monoclonal antibody therapies§ • Bamlanivimab-etesevimab: Unlikely to be active (>45-fold decrease in susceptibility)[4] • Casirivimab-imdevimab: No change in susceptibility[5] • Sotrovimab: No change in susceptibility[6] ▪ Moderate reduction in neutralization by convalescent and post-vaccination sera
Gamma	P.1	20J/501Y.V3	**K417N/T** **E484K** **N501Y** D614G	Japan/Brazil	▪ Significant impact on neutralization by some monoclonal antibody therapies§ • Bamlanivimab-etesevimab: Unlikely to be active (>511-fold decrease in susceptibility)[4] • Casirivimab-imdevimab: No change in susceptibility[5] • Sotrovimab: No change in susceptibility[6] ▪ Reduced neutralization by convalescent and post-vaccination sera[15]
Delta	B.1.617.2¥	20A	T19R (G142D◇) Δ156 Δ157 R158G **L452R** **T478K** D614G P681R D950N	India	▪ Increased transmissibility compared with B.1.1.7 (Alpha)[16] ▪ Potential increased severity based on associated hospitalization rate[16,17] ▪ Potential minimal reduction in neutralization by monoclonal antibody therapies§ ▪ Potential modest/moderate reduction in vaccine effectiveness against symptomatic COVID-19 without significant impact on vaccine effectiveness against severe disease[17-20]
Epsilon	B.1.427 and B.1.429‡	20C/S:452R	**L452R** D614G S13I (B.1.429 only) W152C (B.1.429 only)	US-California	▪ ~20% increased transmissibility[21] ▪ Significant impact on neutralization by some monoclonal antibody therapies§ • Bamlanivimab-etesevimab: Unlikely to be active (7.4-fold decrease in susceptibility)[4] • Casirivimab-imdevimab: No change in susceptibility[5] • Sotrovimab: No change in susceptibility[6] ▪ Moderate reduction in neutralization by convalescent and post-vaccination sera[21]

Variant	Phenotypic Change	Amino Acid Position in Prototype Virus and Proposed Effect of Changing It*						
		Δ69–70 Increase transmission	K417 Decrease neutralization	L452 Decrease neutralization	E484 Decrease neutralization	N501 Increase transmission	D614 Increase transmission	P681 Increase transmission
B.1.1.7 (or alpha)	Increase transmission	69–70 deleted			K (later change)	Y	G	H
B.1.351 (or beta)	Increase transmission and virulence		N		K	Y	G	
B.1.1.28.1 (or gamma or P.1)	Increase transmission and virulence, decrease neutralization		N/T		K	Y	G	
B.1.617.2 (or delta)	Increase transmission, decrease neutralization			R			R	R
B.1.617.1 (or kappa)	Increase transmission, decrease virulence			R	Q		G	R

N Engl J Med 2021; 385:179-186. SARS-CoV-2 Variants and Vaccines
Philip R. Krause, M.D., Thomas R. Fleming, Ph.D., Ira M. Longini, Ph.D., Richard Peto, F.R.S., Sylvie Briand, M.D., David L. Heymann, M.D., Valerie Beral, F.R.C.P., Matthew D. Snape, M.D., Helen Rees, M.R.C.G.P., Alba-Maria Ropero, B.Sc., Ran D. Balicer, M.D., Jakob P. Cramer, M.D., et al.

流行病學

- 全球地理分佈和案例計數，報告了超過**2.02億**的Covid-19確診病例。
- 傳播 - 人對人的傳播是SARS-COV-2傳輸的主要模式。
  - 主要通過近距離**飛沫接觸**（即，大約六英尺或兩米）通過呼吸粒子發生。
  - 通過**空氣傳播**的路線傳播更長的距離（通過吸入留在空中懸浮的微粒），但這種傳輸模式對大流行產生的程度是不確定的。
  - 受污染的表面， **間接接觸**而感染。
- SARS-COV-2的潛在傳播風險在症狀出現之前就開始，並且在疾病過程中最早期是最高的，估計傳染病在症狀發作**前兩天和後一天**達到最高，七天內下降。;此後傳輸的風險減少。疾病**7至10天后**的傳播不太可能，特別是對於免疫健全的輕症患者。即使檢測出病毒RNA檢測也不一定表明感染性病毒的存在。
- **潛伏期**
  依據世界衛生組織公告，感染新型冠狀病毒SARS-CoV-2至發病之潛伏期為**1至14天**（多數為5至6天）。
- **可傳染期**
  依據世界衛生組織資訊，確診病人發病**前2天**即可能具傳染力。另，確診病人發病後呼吸道病毒持續排出（viral shedding）期間仍無法正確得知，唯依國內經驗與國際文獻得知，確診病人**上呼吸道**檢體可持續檢測SARS-CoV-2核酸陽性平均達**兩週以上**，且**下呼吸道檢體檢出病毒的時間可能更久**。

傳播風險

- 與具有Covid-19的個體接觸後的傳播風險隨著接觸的**近距離**和**持續時間**而增加，並且在**室內環境中長時間接觸**似乎最高。
  - 在一般家庭生活的接觸(Among household contacts)
  - 在**未使用**個人防護設備的醫療環境（包括醫院和長期護理設施）中
  - 在其他聚集的環境中，個人居住或在近區工作的人（例如，巡航船，無家可歸者避難所，拘留設施，高校宿舍和食品加工設施）。
  - 傳播的風險與更多間接接觸（例如，在街道上接觸有感染的人，處理以前由感染的人用過的物品）並不明確，很可能很低。
  - 無症狀或症狀前傳播 - 從感染的個體傳播SARS-COV-2，但沒有症狀（包括後來發展症狀的人(症狀前傳播)）:從無症狀的人傳播的風險似乎少於來自有症狀的人。但這些人無法被隔離，增加了接觸機會。CDC建模研究估計，59%的傳播率可能歸因於沒有症狀的個體(症狀前傳播35%;無症狀傳播24%)。

傳播風險

- **動物接觸風險** - SARS-COV-2感染被認為最初從動物宿主傳播給人類，但通過動物接觸的持續風險是不確定的。沒有證據表明動物（包括馴養動物）是人類感染的主要來源。
  - 感染的風險可能因物種而異。在一項研究中，在鼻病毒接種後的動物中評估感染，SARS-COV-2在雪貂和貓中有效地複製;在狗中也檢測到病毒複製，但它們似乎對實驗感染的易感程度是不太敏感的(**無症狀**感染)。
  - 貂似乎高度易受SARS-COV-2的影響。
  - 美國CDC建議寵物遠離家庭以外的其他動物;或者具有確認或疑似Covid-19的人盡量避免與家庭寵物緊密接觸。

已知宿主
冠狀病毒科的動物宿主包括蝙蝠（最大宗）、豬、牛、火雞、貓、狗、雪貂等。並有零星的**跨物種傳播**報告。引起COVID-19之新型冠狀病毒SARS-CoV-2是否有動物宿主，**仍待研究與證實**。

Stability of SARS-CoV-2 at different environmental conditions(1)

A) Temperature*

Virus titre (Log $TCID_{50}$/mL)

Time	4°C		22°C		37°C		56°C		70°C	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
1 min	N.D.	N.D.	6.51	0.27	N.D.	N.D.	6.65	0.1	5.34	0.17
5 mins	N.D.	N.D.	6.7	0.15	N.D.	N.D.	4.62	0.44	U	-
10 mins	N.D.	N.D.	6.63	0.07	N.D.	N.D.	3.84	0.32	U	-
30 mins	6.51	0.27	6.52	0.28	6.57	0.17	U	-	U	-
1 hr	6.57	0.32	6.33	0.21	6.76	0.05	U	-	U	-
3 hrs	6.66	0.16	6.68	0.46	6.36	0.19	U	-	U	-
6 hrs	6.67	0.04	6.54	0.32	5.99	0.26	U	-	U	-
12 hrs	6.58	0.21	6.23	0.05	5.28	0.23	U	-	U	-
1 day	6.72	0.13	6.26	0.05	3.23	0.05	U	-	U	-
2 days	6.42	0.37	5.83	0.28	U	-	U	-	U	-
4 days	6.32	0.27	4.99	0.18	U	-	U	-	U	-
7 days	6.65	0.05	3.48	0.24	U	-	U	-	U	-
14 days	6.04	0.18	U	-	U	-	U	-	U	-

溫度越低存活越久,37度仍可存活

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Stability of SARS-CoV-2 at different environmental conditions(2)

B) Surfaces*

Virus titre (Log $TCID_{50}$/ml)

Time	Paper		Tissue paper		Wood		Cloth		Glass	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
0 min	4.76	0.10	5.48	0.10	5.66	0.39	4.84	0.17	5.83	0.04
30 mins	2.18	0.05	2.19	0.17	3.84	0.39	2.84	0.24	5.81	0.27
3 hrs	U	-	U	-	3.41	0.26	2.21#	-	5.14	0.05
6 hrs	U	-	U	-	2.47	0.23	2.25	0.08	5.06	0.31
1 day	U	-	U	-	2.07#	-	2.07#	-	3.48	0.37
2 days	U	-	U	-	U	-	U	-	2.44	0.19
4 days	U	-	U	-	U	-	U	-	U	-
7 days	U	-	U	-	U	-	U	-	U	-

Time	Banknote		Stainless steel		Plastic		Mask, inner layer		Mask, outer layer	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
0 min	6.05	0.34	5.80	0.02	5.81	0.03	5.88	0.69	5.78	0.10
30 mins	5.83	0.29	5.23	0.05	5.83	0.04	5.84	0.18	5.75	0.08
3 hrs	4.77	0.07	5.09	0.04	5.33	0.22	5.24	0.08	5.11	0.29
6 hrs	4.04	0.29	5.24	0.08	4.68	0.10	5.01	0.50	4.97	0.51
1 day	3.29	0.60	4.85	0.20	3.89	0.33	4.21	0.08	4.73	0.05
2 days	2.47	0.23	4.44	0.20	2.76	0.10	3.16	0.07	4.20	0.07
4 days	U	-	3.26	0.10	2.27	0.09	2.47	0.28	3.71	0.50
7 days	U	-	U	-	U	-	U	-	2.79	0.46

常見器物表面至少存在2~7天(口罩外表面最長)

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Stability of SARS-CoV-2 at different environmental conditions(3)

C) Disinfectants*

Disinfectant (Working concentration)	Virus titre (Log $TCID_{50}$/mL) 5 mins	15 mins	30 mins
Household bleach (1:49)	U	U	U
Household bleach (1:99)	U	U	U
Hand soap solution (1:49)	3.6#	U	U
Ethanol (70%)	U	U	U
Povidone-iodine (7.5%)	U	U	U
Chloroxylenol (0.05%)	U	U	U
Chlorhexidine (0.05%)	U	U	U
Benzalkonium chloride (0.1%)	U	U	U

D) pH*

pH (60 mins)	Virus titre (Log $TCID_{50}$/mL) Mean	±SD
3	5.55	0.25
4	5.67	0.36
5	5.73	0.04
6	5.75	0.08
7	5.58	0.22
8	5.70	0.14
9	5.54	0.44
10	5.51	0.11

漂白水, 70%酒精, 優碘, chlorhexidine 有效

洗手!洗手!洗手!

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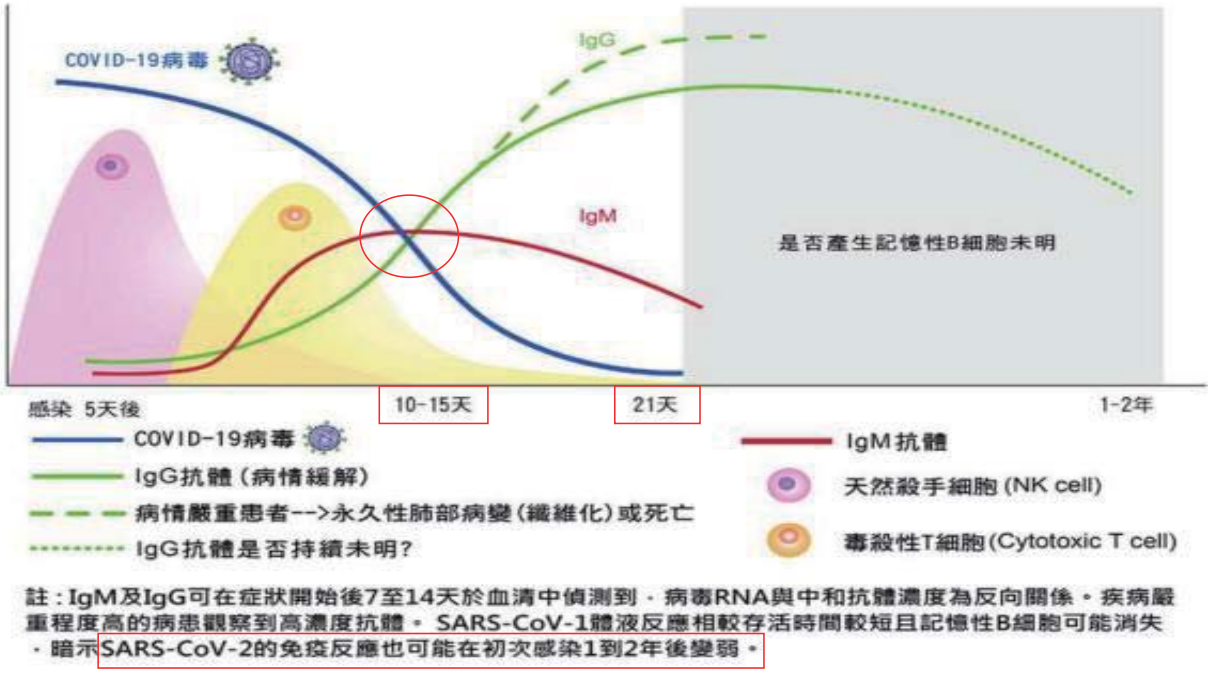
免疫反應

- SARS-COV-2特異性抗體和細胞介導的反應。證據表明，這些反應中的一些是保護性的，並且可以在感染後至少每年進行檢測到。
  - **體液免疫** - 患有SARS-COV-2的感染後，大多數患者為病毒棘蛋白的受體結合結構域發展可檢測的血清抗體和相關的中和活性。然而，抗體反應的幅度可能與疾病的嚴重程度相關，並且患有輕度感染的患者可能無法帶有可檢測的中和抗體。通常在感染後幾個月下降，儘管研究報告了最多12個月的可檢測的中和活性。
  - **細胞介導的免疫** - 鑑定了從Covid-19恢復的患者及接受了Covid-19疫苗的個人中的SARS-COV-2特異性CD4和CD8 T細胞反應，這表明了**潛力持久的T細胞免疫**反應。



- 重新感染的風險 - 重新感染的短期風險（例如，在初始感染後的前幾個月內）很低。現有感染降低了隨後的六到七個月的感染風險80％至85％。
- 第二次感染是無症狀的或更溫和的，提高了初始感染的免疫可能性即使它不會阻止它也可能會衰減再感染的嚴重程度。

臨床表現

無症狀的感染

- **無症狀的感染**已經充分了解。一篇審查估計，33%的SARS-COV-2感染從未發展症狀。
- 無症狀感染的患者可能具有客觀的臨床異常。
  - 胸部電腦斷層掃描（CT）的無症狀感染患者的研究中，50%有典型的磨碎玻璃不透明度或斑塊陰影，另外20%具有非典型成像異常。
  - 一些在診斷時無症狀的個體繼續發展症狀（即，它們實際上是**症狀前時期**）。

症狀感染的嚴重程度

- 嚴重疾病的危險因素 - 任何年齡的健康個體都會發生嚴重疾病，但它主要發生在具有**高齡**或某些潛在的**醫療合併症**的成年人中。
- 兒童和青少年的症狀感染似乎相對罕見;當發生時，通常溫和，儘管小比例（例如，<2%）經驗嚴重甚至致命疾病。
- 社會經濟背景和性別 - 某些人口統計特徵也與更嚴重的疾病有關。
  - 男性在全球多個隊列中佔了大量關鍵病例和死亡。
  - 美國和英國的Covid-19，黑人，西班牙裔和南亞人的感染和死亡人數不成比例的增加，這可能與健康社會因素的潛在差異有關。
- 合併症 - 與嚴重疾病和死亡率有關的其他條件包括:

Comorbidities the CDC classifies as risk factors for severe COVID-19*[1,2]

1. Established and probable risk factors (comorbidities that have been associated with severe COVID-19 in at least 1 meta-analysis or systematic review [starred conditions], or in observational studies)
   - Cancer*
   - Cerebrovascular disease*
   - Children with certain underlying conditions¶
   - Chronic kidney disease*
   - COPD* and other lung disease (including interstitial lung disease, pulmonary fibrosis, pulmonary hypertension)
   - Diabetes mellitus, type 1* and type 2*
   - Down syndrome
   - Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies)*
   - HIV
   - Neurologic conditions, including dementia
   - Obesity* (BMI ≥30 kg/m^2) and overweight (BMI 25 to 29 kg/m^2)
   - Pregnancy*
   - Smoking* (current and former)
   - Sickle cell disease
   - Solid organ or blood stem cell transplantation
   - Substance use disorders
   - Use of corticosteroids or other immunosuppressive medications
2. Possible risk factors (supported by mostly case series, case reports, or, if other study design, the sample size is small)
   - Cystic fibrosis
   - Thalassemia
3. Possible risk factors but evidence is mixed (comorbidities have been associated with severe COVID-19 in at least 1 meta-analysis or systematic review, but other studies had reached different conclusions)
   - Asthma
   - Hypertension
   - Immune deficiencies
   - Liver disease

死亡個案多具有潛在病史，如糖尿病、慢性肝病、腎功能不全、心血管疾病等。報告指出，約有14%出現嚴重症狀需住院與氧氣治療，5%需加護病房治療。

Symptoms associated with coronavirus disease 2019 (COVID-19)[1]

Symptoms that may be seen in patients with COVID-19
▪ Cough
▪ Fever
▪ Myalgias
▪ Headache
▪ Dyspnea (new or worsening over baseline)
▪ Sore throat
▪ Diarrhea
▪ Nausea/vomiting
▪ Anosmia or other smell abnormalities
▪ Ageusia or other taste abnormalities
▪ Rhinorrhea and/or nasal congestion
▪ Chills/rigors
▪ Fatigue
▪ Confusion
▪ Chest pain or pressure

Most patients with confirmed COVID-19 have fever an
acute respiratory illness. However, various other symp
associated with COVID-19; this list is not inclusive of
These symptoms are also not specific for COVID-19, a
of a single symptom in the diagnosis of COVID-19 is ur

目前已知罹患COVID-19確診個案之臨床表現包含發燒、乾咳、倦怠，約三分之一會有呼吸急促。其他症狀包括肌肉痛、頭痛、喉嚨痛、腹瀉等，另有部分個案出現嗅覺或味覺喪失（或異常）等。

WHO公布新冠肺炎十大症狀	
發燒	87.9%
乾咳	67.7%
倦怠	38.1%
有痰	33.4%
呼吸急促	18.6%
肌肉或關節痛	14.8%
喉嚨痛	13.9%
頭痛	13.6%
發冷	11.4%
噁心想吐	5.0%

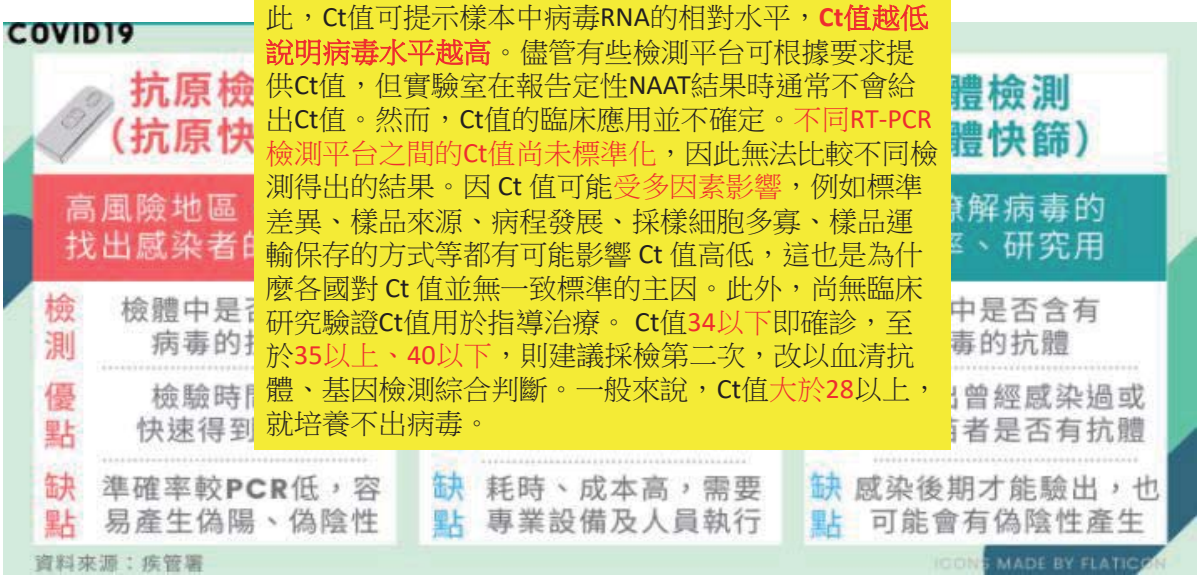
Type, proportion, and duration of persistent COVID-19 symptoms*

Persistent symptom ¶	Proportion of patients affected by symptom	Approximate time to symptom resolution Δ
Common physical symptoms		
Fatigue	15 to 87%[1,2,6,9,14]	3 months or longer
Dyspnea	10 to 71%[1,2,6-9,14]	2 to 3 months or longer
Chest discomfort	12 to 44%[1,2]	2 to 3 months
Cough	17 to 34%[1,2,9,12]	2 to 3 months or longer
Anosmia	10 to 13%[1,3-5,9,11]	1 month, rarely longer
Less common physical symptoms		
Joint pain, headache, sicca syndrome, rhinitis, dysgeusia, poor appetite, dizziness, vertigo, myalgias, insomnia, alopecia, sweating, and diarrhea	<10%[1,2,8,9,11]	Unknown (likely weeks to months)
Psychologic and neurocognitive		
Post-traumatic stress disorder	7 to 24%[6,10, 14]	6 weeks to 3 months or longer
Impaired memory	18 to 21%[6,15]	weeks to months
Poor concentration	16%[6]	Weeks to months
Anxiety/depression	22 to 23%[2,7,8,10, 12,13, 14]	Weeks to months
Reduction in quality of life	>50%[8]	Unknown (likely weeks to months)

COVID-19: coronavirus disease 2019.
* These data are derived from an earlier period in the pandemic; information on patient recovery and persistent symptoms is evolving, and these figures may change as longer-term data emerge.
¶ More than a third of patients with COVID-19 experience **more than one** persistent symptom.
Δ Time course for recovery varies depending on premorbid risk factors and illness severity and may be shorter or longer than that listed. Hospitalized patients, and in particular critically ill patients, are more likely to have a more protracted course than those with mild disease.

診斷與治療

循環閾值 — 循環閾值(cycle threshold, Ct)是指RT-PCR檢測時，將病毒RNA擴增至可檢出水平所需的循環數。因此，Ct值可提示樣本中病毒RNA的相對水平，**Ct值越低說明病毒水平越高**。儘管有些檢測平台可根據要求提供Ct值，但實驗室在報告定性NAAT結果時通常不會給出Ct值。然而，Ct值的臨床應用並不確定。不同RT-PCR檢測平台之間的Ct值尚未標準化，因此無法比較不同檢測得出的結果。因 Ct 值可能受多因素影響，例如標準差異、樣品來源、病程發展、採樣細胞多寡、樣品運輸保存的方式等都有可能影響 Ct 值高低，這也是為什麼各國對 Ct 值並無一致標準的主因。此外，尚無臨床研究驗證Ct值用於指導治療。 Ct值34以下即確診，至於35以上、40以下，則建議採檢第二次，改以血清抗體、基因檢測綜合判斷。一般來說，Ct值大於28以上，就培養不出病毒。



Proposed reporting language for CT findings related to COVID-19

Routine screening CT for diagnosis or exclusion of COVID-19 is currently not recommended by most professional organizations or the US Centers for Disease Control and Prevention	

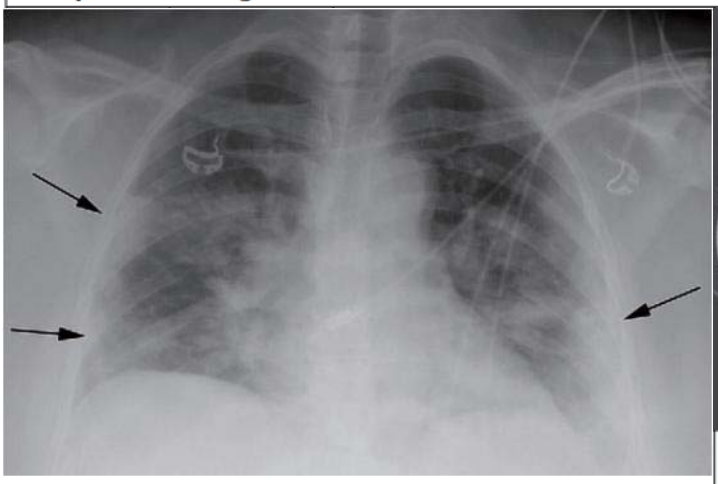
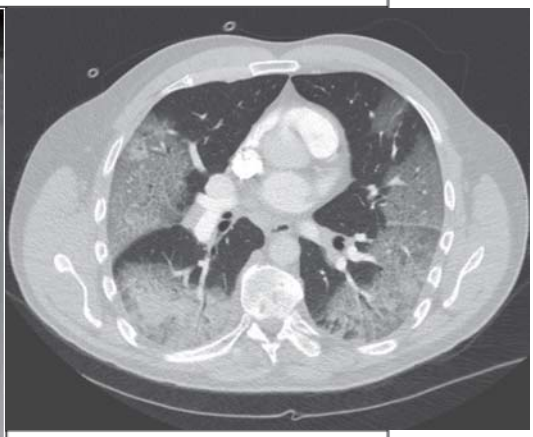

	

Figure 3: Characteristic chest radiograph in a 41-year-old woman presenting with cough and fever. Chest radiographic findings include bilateral patchy and confluent, bandlike ground-glass and consolidative opacity in a peripheral, mid to lower lung zone distribution (arrows).	"Imaging features are atypical or uncommonly reported for (COVID-19) pneumonia. Alternative diagnoses should be considered."
	"No CT findings present to indicate pneumonia. (NOTE: CT may be negative in the early stages of COVID-19.)"

NOTES:
1. Inclusion in a report of items noted in parenthesis in the Suggested reporting language column may depend upon clinical suspicion, local prevalence, patient status as a PUI, and local procedures regarding reporting.
2. CT is not a substitute for RT-PCR, consider testing according to local recommendations and procedures for and availability of RT-PCR.

Laboratory features associated with severe COVID-19 [1-6]

Abnormality	Possible threshold
Elevations in:	
▪ D-dimer	>1000 ng/mL (normal range: <500 ng/mL)
▪ CRP	>100 mg/L (normal range: <8.0 mg/L)
▪ LDH	>245 units/L (normal range: 110 to 210 units/L)
▪ Troponin	>2× the upper limit of normal (normal range for troponin T high sensitivity: females 0 to 9 ng/L; males 0 to 14 ng/L)
▪ Ferritin	>500 mcg/L (normal range: females 10 to 200 mcg/L; males 30 to 300 mcg/L)
▪ CPK	>2× the upper limit of normal (normal range: 40 to 150 units/L)
Decrease in:	
▪ Absolute lymphocyte count	<800/microL (normal range for age ≥21 years: 1800 to 7700/microL)

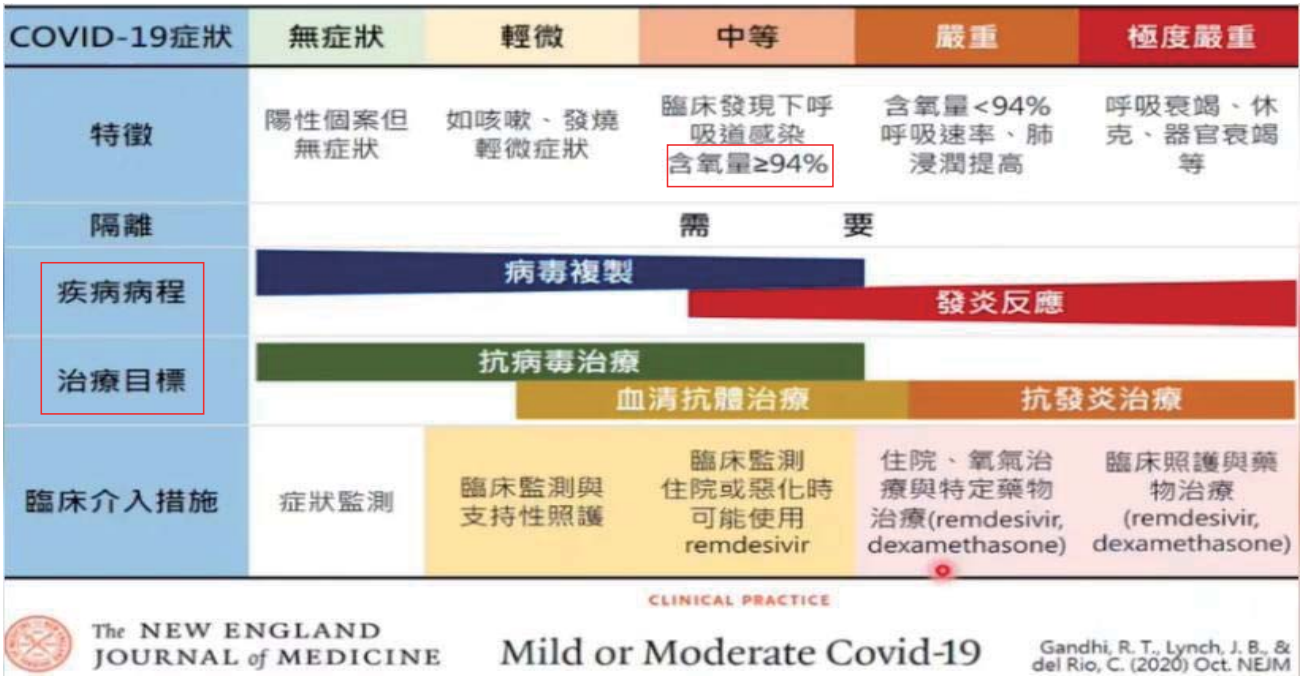
Although these laboratory features are associated with severe disease in patients with COVID-19, they have not been clearly demonstrated to have prognostic value. We use the thresholds listed above to identify patients who may be at risk for severe disease; they are extrapolated from published cohort data and individualized to the reference values used at our laboratory. However, the specific thresholds are not well established and may not be applicable if laboratories use other reference values.

表二、SARS-CoV-2 確診個案常規檢驗及檢查追蹤頻率建議

	入院時	住院期間可考慮檢驗或於需要時加驗	附註
CBC/DC	V	V	
PT/aPTT	V		
D-dimer	V	V	
BUN	V	V	
Creatinine	V	V	
Na	V	V	
K	V	V	
AST	V	V	
ALT	V	V	
ALP	V	V	
Total bilirubin	V	V	
Albumin	V	V	
LDH	V	V	
Creatine kinase	V	V	
Myoglobin	V		如醫院有此檢驗
Glucose	V		
CRP	V	V	
ESR	V		
IL-6	V		如醫院有此檢驗
Serum ferritin	V		
Procalcitonin	V		如醫院有此檢驗
HIV test*	V		
Urine routine	V		
CXR	V	V	

*HIV 感染為 COVID-19 重症風險因子。建議臨床醫師對確診個案評估 HIV 檢驗之必要性。檢驗 HIV 須經當事人同意，不限形式。

COVID 19 嚴重程度與治療原則



COVID-19
美國NIH與台灣CDC治療指引

	輕度(單株抗體)	中度	嚴重 (抗病毒+抗發炎)	極度嚴重 (抗發炎)	
嚴重度	第一級	第二級	第三級	第四級	第五級 / 第六級
狀態	不需住院 / 不需供氧	住院 / 不需供氧	住院 / 需供氧	住院 / NPV/HF	住院 / MV；住院 / ECMO
美國 NIH 建議	症狀治療、支持性療法。 疾病惡化高風險群[註]考慮使用單株抗體 Bamlanivimab + Etesevimab 或 Casirivimab + Imdevimab	Room air SpO2≧94% Remdesivir (? 因為證據不足)	Remdesivir (氧氣需求量不大) 或 Dexamethasone (無法取得 Remdesivir時) 或 Remdesivir + dexamethasone (尤其是需氧量持續增加)	Remdesivir + Dexamethasone + Tocilizumab (尤其是需氧量快速增加、發炎指數過高)	Dexamethasone + Tocilizumab (尤其是快速惡化，如住院後24小時內入住 ICU)
				Baricitinib 無法使用 Dexamathasone，則與 Remdesivir 併用 不建議與 Dexamethasone 併用、不建議與 Tocilizumab 併用	

疫苗簡介

Characteristics of select COVID-19 vaccines[1]

Name	Company/developer	Platform	Doses and intended interval	Efficacy against symptomatic COVID-19*	Rate of severe COVID-19	Storage requirements	Common side effects	Rare adverse effects
BNT162b2¶	Pfizer/BioNTech	mRNA	2 doses 3 weeks apart	95%	1 in vaccine group (n≈18,000) 9 in placebo group (n≈18,000)	Ultracold freezer (−80 to −60°C) then freezer (−25 to −15°C) for up to 2 weeks cumulative time then refrigerated (2 to 8°C) for up to 1 month	▪ Local injection site reactions ▪ Systemic symptoms (fevers, chills, fatigue, myalgias, headache)	▪ Anaphylaxis (approximately 5 per million) ▪ Myocarditis/pericarditis (approximately 16 per million among 16-39 year olds)
mRNA-1273¶	Moderna	mRNA	2 doses 4 weeks apart	94%	0 in vaccine group (n≈14,000) 30 in placebo group (n≈14,000)	Freezer (−25 to −15°C) then refrigerated (2 to 8°C) for up to 30 days	▪ Local injection site reactions ▪ Systemic symptoms (fevers, chills, fatigue, myalgias, headache)	▪ Anaphylaxis (approximately 2.8 per million) ▪ Myocarditis/pericarditis (approximately 16 per million among 16-39 year olds)
ChAdOx1 nCoV-19/AZD1222	AstraZeneca/University of Oxford/Serum Institute of India	Replication-incompetent chimpanzee adenovirus vector	2 doses ▪ 4 to 12 weeks apart (manufacturer recommendation) ▪ 8 to 12 weeks apart (WHO recommendation)	70%	0 in vaccine group (n≈6000) 2 in placebo group (n≈6000)	Refrigerated (2 to 8°C)	▪ Local injection site reactions ▪ Systemic symptoms (fevers, chills, fatigue, myalgias, headache)	▪ Very rare thrombotic complications associated with thrombocytopenia: ▪ Cerebral venous sinus thrombosis (169 of ≈ 34 million) ▪ Splanchnic vein thrombosis (54 of ≈ 34 million) ▪ Guillain-Barre syndrome (227 cases/51 million)

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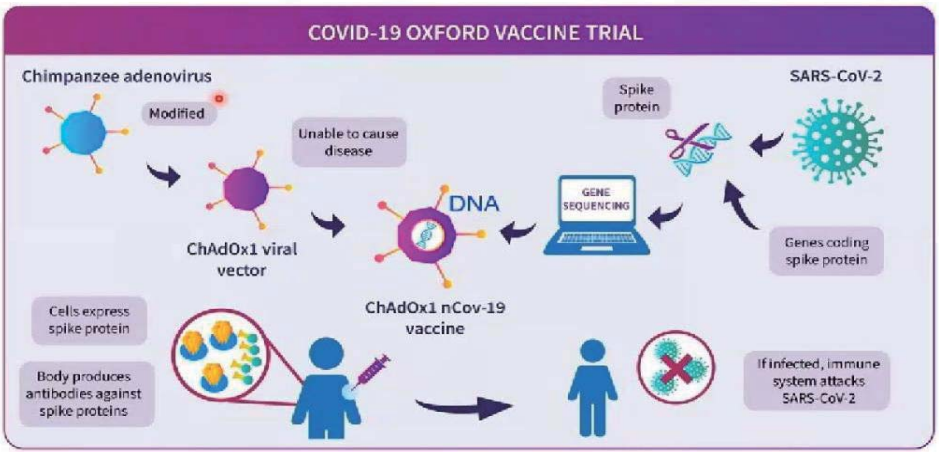
每劑 (0.5 ml) 含： 不低於 2.5 x 108 個感染單位 (Inf.U)之**黑猩猩腺病毒**顆粒。黑猩猩病毒顆粒(ChAdOx1-S)帶有可表達出 SARS-CoV-2 棘狀醣蛋白的基因，是利用**重組 DNA 技術** (recombinant DNA technology) 在基因改造後之人類胚胎腎臟 (HEK) 細胞 293 內增殖。疫苗中的 SARS-CoV-2 S 免疫原 為三聚體前融合構形，並未修飾編碼序列。施打疫苗後，細胞可局部表現 SARS-CoV-2 S 醣蛋白， 刺激中和抗體及細胞免疫反應。

- **疫苗概述**
  - 含有SARS-CoV-2
  - 已通過WHO、歐
- **冷儲條件**:2 ~8°C
  存和使用，唯不
- **接種劑量及間隔**
  - 目前依據疫苗仿
  - **接種劑次為2劑**，
    依我國衛生福利
    上。
  - 接種途徑為肌肉

Adenovirus-vectored vaccine
(AZ牛津疫苗; Janssen (嬌生J&J), CanSino解放軍疫苗)



AstraZeneca COVID-19疫苗

- **安全性及保護效果**
  - 本疫苗不含可複製之SARS-CoV-2病毒顆粒，不會因為接種本疫苗而罹患COVID-19。
  - 完成2劑接種可預防63%有症狀感染之風險，另依臨床試驗資料分析，當接種間隔12週且完成2劑接種，保護力約81% (60% ~ 91%)。基此我國衛生福利部傳染病防治諮詢會預防接種組（ACIP）建議兩劑間隔至少8 週，而間隔10-12 週，疫苗接種效果更佳。
- 在評估的294名患者中有170個確定和50例可能的VITT案件。所有患者均已接受一劑AZ疫苗，疫苗接種後5至48天（中位數，14天）出現症狀。年齡範圍為18至79歲（中位數，48歲），沒有性別差異，沒有可識別的醫療風險因素。總體死亡率為22%。腦靜脈竇血栓形成的患者中，死亡的機率增加了2.7倍（95%的信賴區間，1.4～5.2）;在基線血小板計數減少50%為1.7倍（95%CI，1.3～2.3）;每在基礎D-dimer水平中增加10,000個纖維蛋白原當量單位增加1.2倍（95%CI，1.0至1.3）;對於基線纖維蛋白原水平降低50%會增加1.7倍（95%CI，1.1至2.5）。多變量分析確定了血小板計數和顱內出血的存在，與死亡獨立相關;血小板計數低於30,000/立方毫米和顱內出血的患者中觀測到的死亡率為73%。

  August 11, 2021 DOI: 10.1056/NEJMoa2109908. Clinical Features of Vaccine-Induced Immune Thrombocytopenia and Thrombosis
  List of authors.Sue Pavord, F.R.C.Path., Marie Scully, M.D., etc.

AstraZeneca COVID-19疫苗

接種注意事項

- 發燒或正患有急性中重度疾病者，宜待病情穩定後再接種。
- **AstraZeneca COVID-19疫苗與注射後非常罕見的血栓併血小板症候群可能有**
  險後再接種。
- **過去曾發生血栓合併血小板低下症候群，或肝素引起之血小板低下症者，**
- **本疫苗不得與其他廠牌交替使用**。若不慎使用了兩劑不同COVID-19疫苗產
- **本疫苗不得與其他疫苗同時接種**。COVID-19 疫苗**與其他疫苗的接種間隔，**
  則各該疫苗亦無需再補種。
- 免疫功能低下者，包括接受免疫抑制劑治療的人，對疫苗的免疫反應可能
  抑制治療者的數據)
- 目前缺乏孕婦接種COVID-19 疫苗之臨床試驗及安全性資料，而臨床觀察性
  較一般人容易併發重症。孕婦若為COVID-19 之高職業暴露風險者或其慢性
  種疫苗之效益與風險後，評估是否接種。
- 若哺乳中的婦女為建議接種之風險對象(如醫事人員)，應完成接種。目前
  性、疫苗對母乳或受哺嬰兒之影響尚未完全得到評估，但一般認為**並不會造成相關風險**。接種COVID-19疫苗後，
  仍**可持續哺乳**。

AstraZeneca COVID-19疫苗

接種後注意事項

- 為即時處理接種後發生率極低的立即型嚴重過敏反應，接種後應於接種單位或附近稍作休息**留觀15分鐘**，離開後請**自我密切觀察15分鐘**，但針對先前曾因接種疫苗或任何注射治療後發生急性過敏反應之民眾，接種後仍請於接種處或附近**留觀至少30分鐘**。
- **使用抗血小板或抗凝血藥物或凝血功能異常者施打後於注射部位加壓至少2分鐘**，並觀察是否仍有出血或血腫情形。

AstraZeneca COVID-19疫苗

接種後可能發生之反應及因應措施

- 本疫苗接種後可能發生的**反應大多為接種部位疼痛**、紅腫，通常於數天內消失，可適度冰敷，請勿揉；抓接種部位。
- **接種疫苗後可能有發燒反應(≧38℃)，通常約48小時可緩解**。其他可能反應包含疲倦、頭痛、肌肉痠痛、體溫升高、畏寒、關節痛及噁心，這些**症狀隨年齡層增加而減少**，通常輕微並於數天內消失。
- **如有接種部位紅腫及硬塊發生膿瘍、持續發燒或嚴重過敏反應(如呼吸困難、氣喘、眩暈、心跳加速、全身紅疹)等不適症狀**，應儘速就醫並告知醫師曾接種疫苗，以做為診斷之參考，同時請醫師通報當地衛生局或疾病管制署。

- 依據疫苗第三期臨床試驗結果，接種後可能發生之反應及頻率參考資料

常見副作用	頻率
注射部位疼痛	54.2%
疲倦	53.1%
頭痛	52.6%
肌肉痛	44.0%
畏寒	31.9%
關節痛	26.4%
發燒(>38度)	7.9%

- 其他可能之反應及頻率

發生率	症狀
常見(1/10~1/100)	接種部位硬塊、嘔吐
不常見(1/100~1/1,000)	淋巴結腫大、食慾下降、頭暈、腹痛

AstraZeneca COVID-19疫苗

- **接種疫苗後28天內，若出現以下任一症狀，請立即就醫並說明疫苗接種史：**

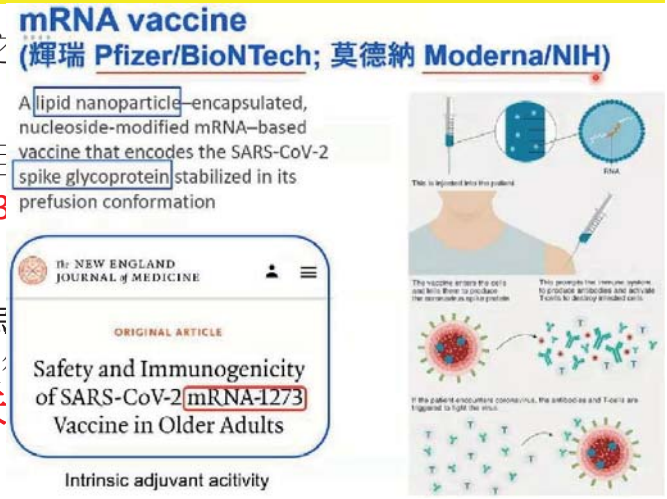
***嚴重持續性頭痛、視力改變或癲癇**
***嚴重且持續腹痛超過24小時以上**
***嚴重胸痛或呼吸困難**
***下肢腫脹或疼痛**
***皮膚出現自發性出血點、瘀青、紫斑等**

- 完成疫苗接種後，雖可降低罹患COVID-19的機率，但仍有可能感染SARS-CoV-2，民眾仍需注重保健與各種防疫措施，以維護身體健康。

Moderna

莫德納 COVID-19 疫苗含有包埋於脂質奈米粒子中的 mRNA。此 mRNA 含有全長 SARS-CoV-2 棘突蛋白，而此棘突蛋白在七肽重複區 1 內經過 2 次脯胺酸置換修飾(S2P)，以穩定其融合前構形。進行肌肉注射後，注射部位的細胞及下游淋巴結會吸收脂 質奈米粒子，有效將 mRNA 序列傳入細胞，轉譯成病毒蛋白。由樹突細胞和囊下竇狀巨噬細胞(subcapsular sinus macrophages)暫時表現。接著，免疫細胞會將由細胞表現之膜結合 SARS-CoV-2 棘突蛋白辨識為外來抗原，進而誘發 T 細胞和 B 細胞反應。

- **疫苗概述**
  - 是SARS-CoV-2病毒棘蛋白(S protein)之
- **冷儲條件**
  - -25~-15°C冷凍保存，不得低於-40°C
  - 若轉置到2~8°C冷藏設備保存必須於3
- **接種劑量及間隔**
  - 目前依據疫苗仿單之**適用接種年齡為**
  - **接種劑次為2劑**，目前依國際指引及
    種組(ACIP)**建議接種間隔為至少28 天**
  - 接種途徑為肌肉注射。



Moderna

- **安全性及保護效果**
  - 本疫苗不含可複製之SARS-CoV-2病毒顆粒，不會因為接種本疫苗而罹患COVID-19。
  - 接種2劑可預防94%有症狀之感染。
- **接種禁忌**
  對於疫苗成分有嚴重過敏反應史，或對於先前接種之疫苗劑次發生嚴重過敏反應者不予接種。
- **接種注意事項(與A-Z 相同)**
- **接種後注意事項(與A-Z 相同)**
- **接種後可能發生之反應及因應措施(與A-Z 相同)**

Moderna

- 依據疫苗第三期臨床試驗結果，接種後可能發生之反應及頻率參考資料

常見副作用	頻率
注射部位疼痛	92.0%
疲倦	70.0%
頭痛	64.7%
肌肉痛	61.5%
關節痛	46.4%
畏寒	45.4%
發燒(>38度)	15.5%

- 其他可能之反應及頻率

頻率	疫苗接種後不良反應
常見(≥1/100 to <1/10)	接種部位紅斑、蕁麻疹、泛紅
不常見(≥1/1,000 to <1/100)	接種部位搔癢
罕見(<1/1000)	顏面神經麻痺；臉部腫脹

Pfizer-BioNTech

- **疫苗概述**
  - 含有SARS-CoV-2病毒棘蛋白(S protein)之mRNA疫苗
- **冷儲條件**
  - -60至-80°C超低溫冷凍保存。
  - 若轉置到2~8°C冷藏設備保存必須於**5天內**使用完畢(我國CDC)。
- **接種劑量、間隔及途徑**
  - 目前依據疫苗仿單之適用接種**年齡為12歲以上**，接種劑量為0.3 mL。
  - **接種劑次為2劑**，依疫苗仿單建議接種間隔為21天以上；目前依衛生福利部傳染病防治諮詢會預防接種組(ACIP)**建議接種間隔為至少28 天**。
  - 接種途徑為肌肉注射。

Pfizer-BioNTech

- **安全性及保護效果**
  - 本疫苗不含可複製之SARS-CoV-2病毒顆粒，不會因為接種本疫苗而罹患COVID-19。
  - 依據目前臨床試驗結果資料顯本疫苗接種完成2劑接種7天後之保護力約95%(90.3% ~ 97.6%)，疫苗的保護效果需視接種對象的年齡或身體狀況而異。
- **接種禁忌**
  對於疫苗成分有嚴重過敏反應史，或對於先前接種之疫苗劑次發生嚴重過敏反應者不予接種。
- **接種注意事項(與A-Z 相同)**
- **接種後注意事項(與A-Z 相同)**
- **接種後可能發生之反應及因應措施(與A-Z 相同)**

Pfizer-BioNTech

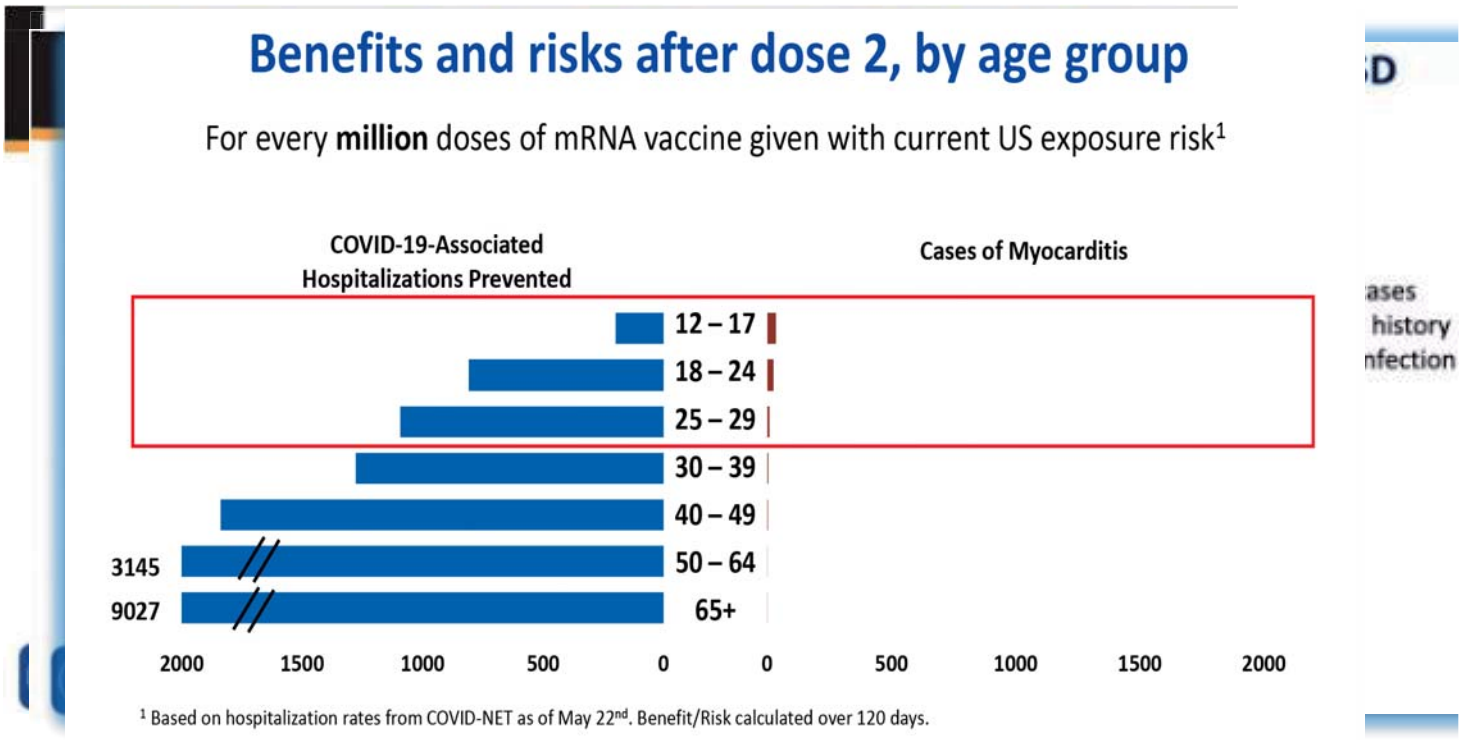
- 依據疫苗第三期臨床試驗結果，接種後可能發生之反應及頻率參考資料

常見副作用	頻率
注射部位疼痛	84.1%
疲倦	62.9%
頭痛	55.1%
肌肉痛	38.3%
畏寒	31.9%
關節痛	23.6%
發燒(>38度)	14.2%

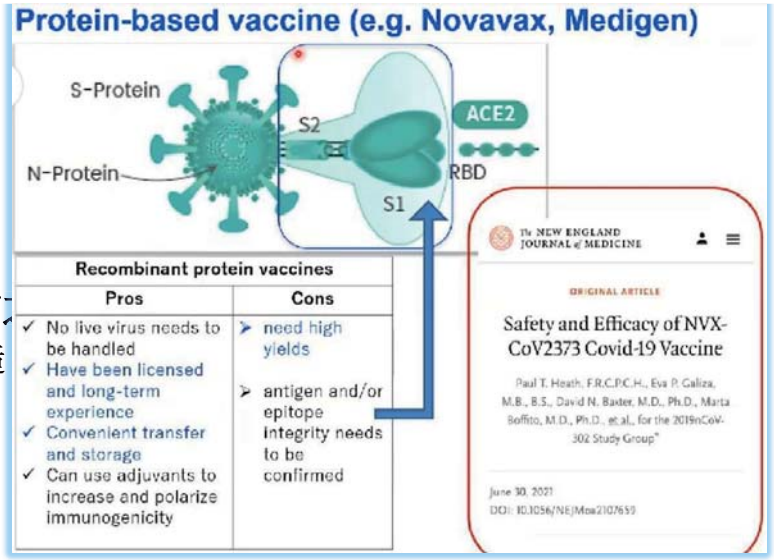
- 其他可能之反應及頻率

發生率	症狀
常見(1/10~1/100)	接種部位腫脹、泛紅、噁心
不常見(1/100~1/1,000)	淋巴結腫大、不適
罕見(1/1,000~1/10,000)	任一側臉部麻痺

- 未預期之嚴重不良反應非常罕見，通常發生在疫苗接種後數分鐘至1小時內，包括呼吸困難、臉部及咽喉腫脹、心跳加速、全身紅疹、暈眩及身體虛弱等症狀。

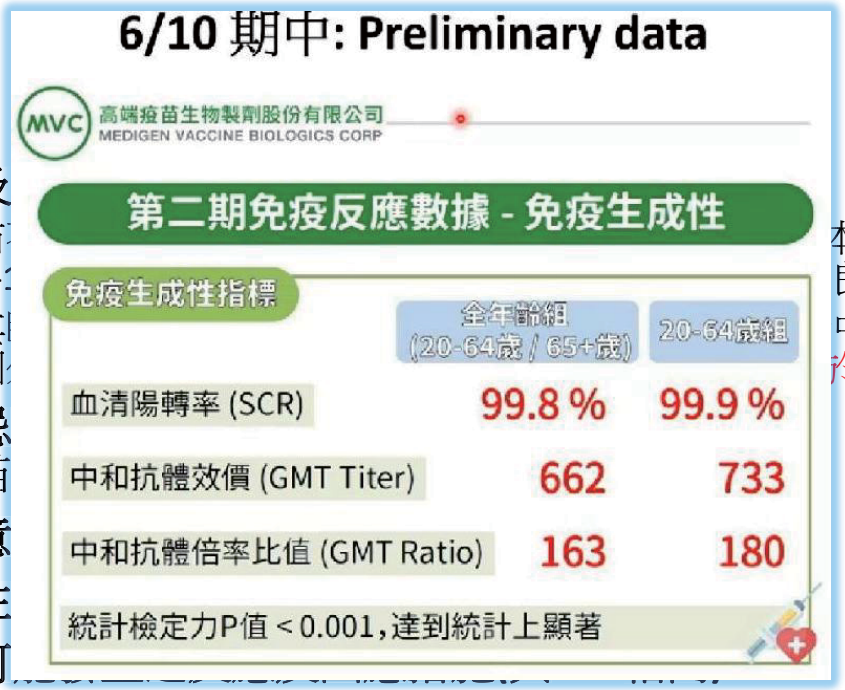


高端新冠肺炎疫苗



- 疫苗概述
  - 含**SARS-CoV-2重組棘蛋白的疫苗**
  - 本疫苗已通過我國核准專案製造
- 冷儲條件
  2 ~8°C 冷藏儲存。
- 接種劑量及間隔
  - 目前依據疫苗仿單之適用接種**年齡為20歲以上**，接種劑量為0.5 mL。
  - **接種劑次為2劑，間隔28天**。
  - 接種途徑為肌肉注射。

高端



- 安全性及
  - 本疫苗
    COVID-
  - 另依其
    經與國
- 接種禁忌
  對於疫苗
- 接種注意
- 接種後注
- 接種後可

本疫苗而罹患
良好。
中和抗體數據，
於保護力標準。

高端

- **依據疫苗床試驗結果，接種後可能發生之反應及頻率參考資料**

常見副作用	頻率
注射部位疼痛/壓痛	71.2%
疲痛/全身無力	36%
肌肉痛	27.6%
頭痛	22.2%
腹瀉	15.1%
注射部位腫脹/硬結	10.5%
噁心/嘔吐	7.7%
注射部位泛紅	4.9%
發燒	0.7%

- **其他可能之反應及頻率**

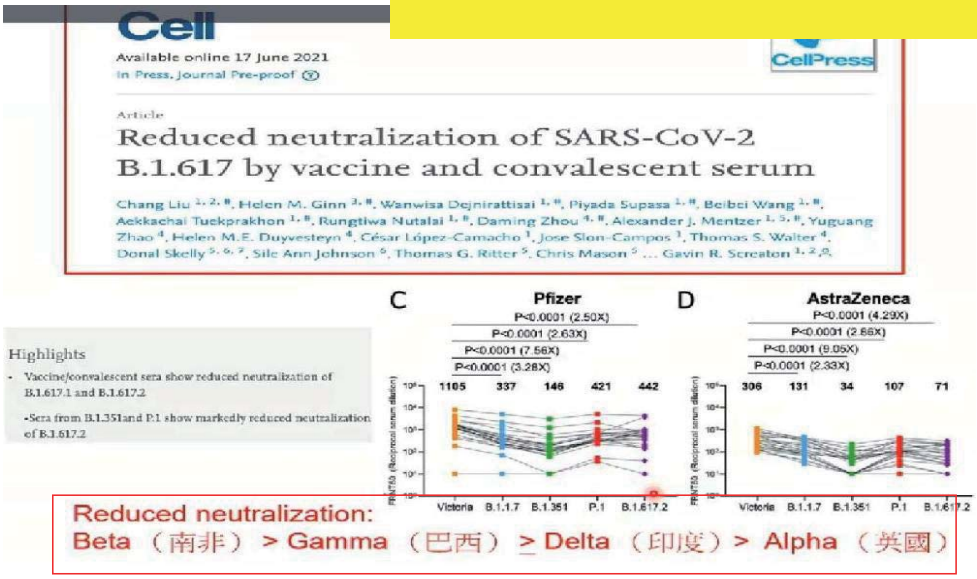
頻率	疫苗接種後不良反應
不常見(≥1/1,000 to <1/100)	接種部位搔癢、寒顫、皮疹、鼻咽炎、口咽疼痛、心悸
罕見(<1/1000)	顏面神經麻痺*、眼壓過高

*在安全性追蹤期間，高端新冠肺炎疫苗組有一位受試者通報出現急性周邊性顏面神經麻痺。受試者是在接種第2劑後13天發生此不良反應

SARS COV-2變異危

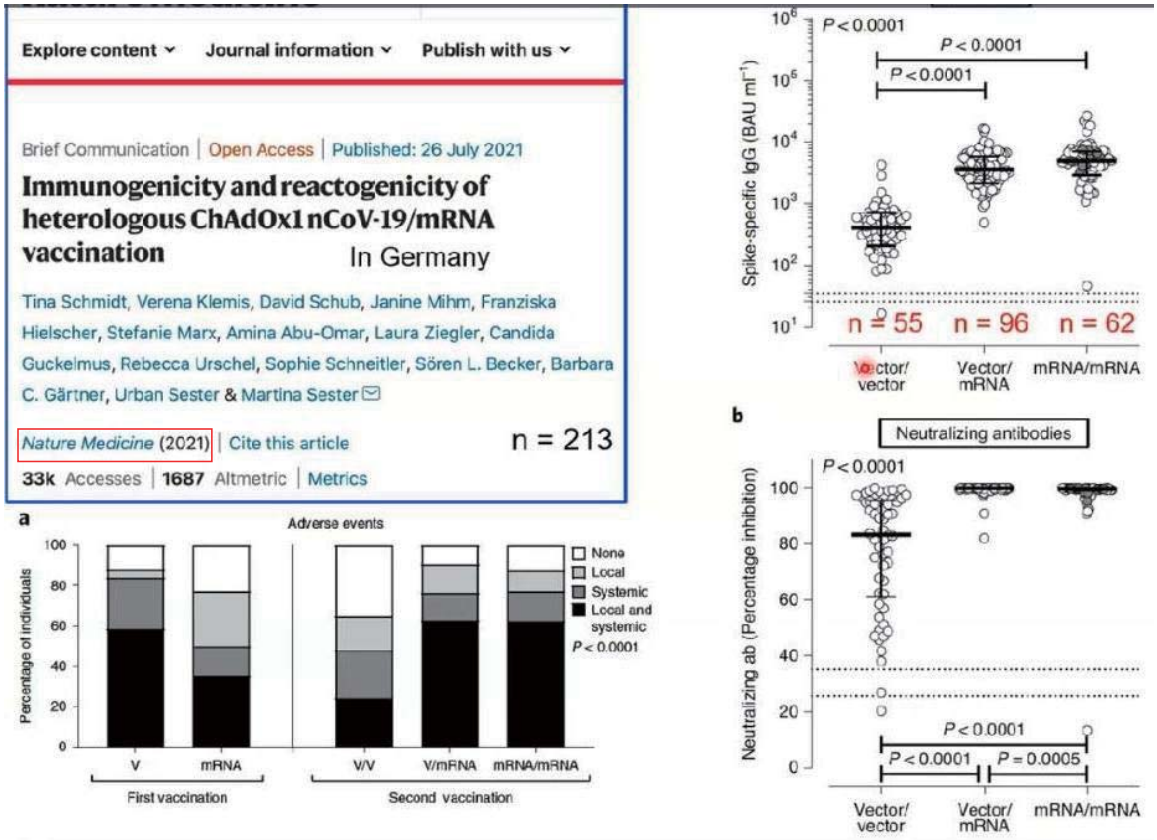
兩劑 BNT162b2 疫苗 對alpha變種94%有效，對delta變種88%有效。
ChAdOx1 nCoV-19疫苗的相應百分比較低，分別為74%和67%。

July 21, 2021
DOI: 10.1056/NEJMoa2108891,Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) VariantJ. Lopez Bernal and Others



疫苗混打效果比較

- 疫苗混打以AZ（腺病毒疫苗）、輝瑞以及莫德納（兩者皆為mRNA疫苗）為主。
- AZ疫苗除了血栓問題外，另一個問題在於第二劑之後的效果非常有限，因為以大猩猩腺病毒為載體，人體免疫系統也會隨著時間對腺病毒產生抗體，因此AZ若要接種第三甚至第四劑時效果只會不斷變差。
- 國外實驗發現不同原料的疫苗由於刺激誘發抗體的機轉不同，或許能發揮類似互補的作用，讓疫苗效果更好，且研究指出混打疫苗在對抗變種病毒上效力更高。



混打順序影響

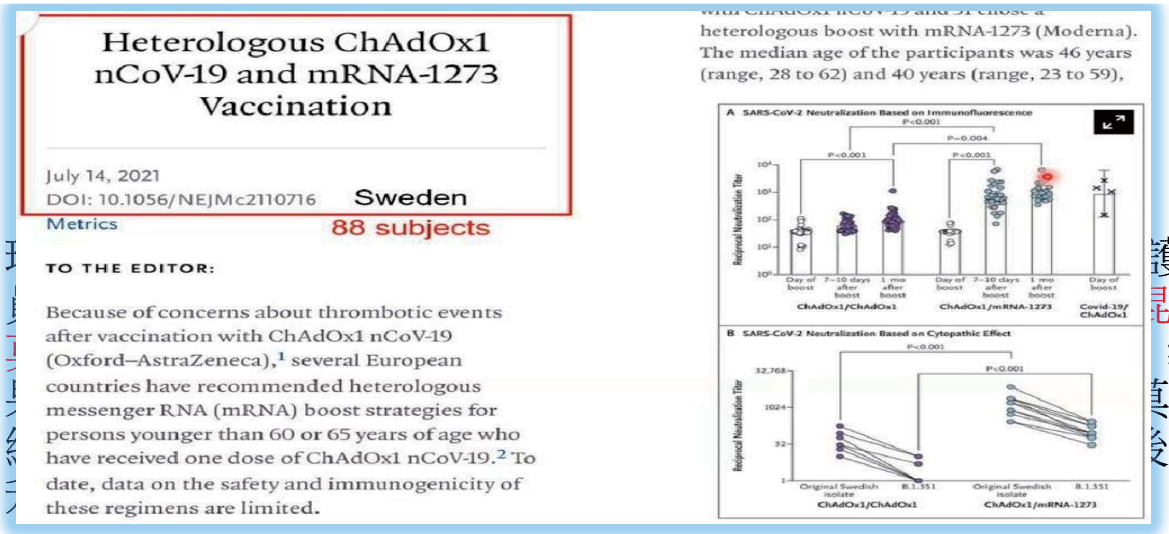
626 **Table 3 Immune responses between heterologous and homologous prime/boost schedules in the 28-day boost study arms***

	Prime with ChAd			Prime with BNT		
	ChAd/ChAd-28 N=105	ChAd/BNT-28 N=108	p value¶	BNT/BNT-28 N=110	BNT/ChAd-28 N=109	p value¶
SARS-CoV-2 anti-spike IgG, ELU/ml						
D7§	25 (25-25) [n=21]	25 (25-25) [n=19]	NA	25 (25-25) [n=23]	25 (25-25) [n=23]	0.95
Above the LLOQ	0/21, 0% (0%, 16%)	0/19, 0% (0%, 18%)	>0.99	2/23, 9% (1%, 28%)	2/23, 9% (1%, 28%)	>0.99
D14§	87 (54-141) [n=21]	198 (96-408) [n=19]	0.073	967 (718-1304) [n=23]	735 (495-1092) [n=23]	0.3
Above the LLOQ	14/21, 67% (43%, 85%)	16/19, 84% (60%, 97%)	0.28	23/23, 100% (85%, 100%)	23/23, 100% (85%, 100%)	>0.99
D28	501 (394-638) [n=105]	613 (485-776) [n=108]	0.23	1487 (1233-1795) [n=110]	1715 (1447-2033) [n=109]	0.29
Above the LLOQ	100/105, 95% (89%, 98%)	104/108, 96% (91%, 99%)	0.75	110/110, 100% (97%, 100%)	109/109, 100% (97%, 100%)	>0.99
D35§	1151 (825-1605) [n=22]	15365 (11764-20068) [n=20]	<0.0001	17011 (12446-23248) [n=22]	6798 (5060-9133) [n=24]	0.00015
Above the LLOQ	22/22, 100% (85%, 100%)	20/20, 100% (83%, 100%)	>0.99	22/22, 100% (85%, 100%)	24/24, 100% (86%, 100%)	>0.99

#LLOQ: lower limit of quantification
##Sera were analysed at Nexelis, (Laval, Canada) to determine SARS-CoV-2 anti-spike IgG concentrations by ELISA (reported as ELISA Laboratory Unit (ELU)/ml) and the 50% Neutralising Antibody Titre (NT50) for SARS-CoV-2 pseudotype virus neutralisation assay (PNA), using a vesicular stomatitis virus backbone adapted to bear the 2019-nCOV SARS-CoV-2 spike protein

BNT/BNT ≧ AZ/BNT > BNT/AZ > AZ/AZ

25 Jun,2021 The Lancet


Heterologous ChAdOx1 nCoV-19 and mRNA-1273 Vaccination

July 14, 2021
DOI: 10.1056/NEJMc2110716 Sweden
Metrics 88 subjects

TO THE EDITOR:

Because of concerns about thrombotic events after vaccination with ChAdOx1 nCoV-19 (Oxford–AstraZeneca),[1] several European countries have recommended heterologous messenger RNA (mRNA) boost strategies for persons younger than 60 or 65 years of age who have received one dose of ChAdOx1 nCoV-19.[2] To date, data on the safety and immunogenicity of these regimens are limited.

heterologous boost with mRNA-1273 (Moderna). The median age of the participants was 46 years (range, 28 to 62) and 40 years (range, 23 to 59),

A SARS-CoV-2 Neutralization Based on Immunofluorescence

B SARS-CoV-2 Neutralization Based on Cytopathic Effect

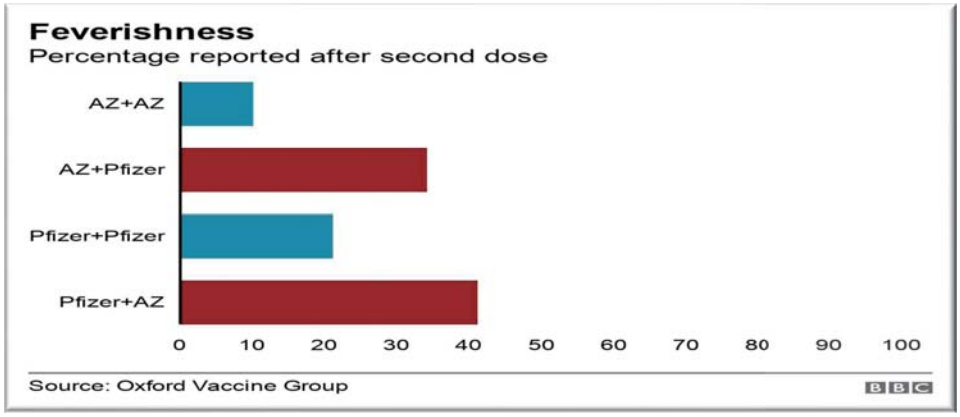
- 現階段研究對於新冠疫苗混打的成效如下表所示：

混打方式	免疫表現
AZ＋BNT（目前主流）	效果佳
AZ＋莫德納（已陸續進行試驗）	效果不亞於AZ＋BNT
BNT＋AZ	效果較差,但優於2劑AZ
莫德納＋AZ	類似BNT+AZ

國際研究指出，疫苗施打的順序必須以腺病毒疫苗為先，mRNA疫苗為後才有效果，原理在於混打的疫苗不能比第一劑差，至少保護力要對等

疫苗混打副作用

- 研究發現，打AZ第一劑發燒的人達40%，接種AZ第二劑發燒的狀況變少，但在混打莫德納的受試者中，發燒、疲勞、頭痛等副作用則高出3成，而AZ混打輝瑞BNT的受試者雖然頻繁出現輕中度不良反應，但症狀非常短暫，應不至於造成太大人體危害。



Take home message

- 冠狀病毒有包膜的正股RNA病毒,由棘蛋白與細胞ACE2受器結合進入細胞。
- SARS COV-2變異株早期為D614G（甘氨酸對天冬氨酸）的相互取代(G614高複製和傳播性,低致死性。)，其隨時間變成全球顯性多態性。變異株中出現K417,L452,E484突變會減少對中和抗體的感受性;其他位置突變以增加傳播性為主。
- SARS-COV-2傳輸的主要模式:飛沫,亦可由空氣與接觸污染的環境傳染 潛伏期2週,最高傳染期為症狀發作前兩天和後一天,7至10天後傳染性減低
- 抗體反應的幅度可能與疾病的嚴重程度相關,感染後幾個月下降

Take home message

- 嚴重疾病的危險因素 - 任何年齡的健康個體都會發生嚴重疾病，但它主要發生在具有**高齡**或某些潛在的**醫療合併症**的成年人中。
- 2劑疫苗效果:BNT 95%; Moderna 94%; AZ 70%
- 變異株降低中和抗體效果能力: **Beta(南非)>Gamma(巴西)≧Delta(印度)>Alpha(英國)**
- 混打效果:

混打方式	免疫表現
AZ＋BNT（目前主流）	效果佳
AZ＋莫德納（已陸續進行試驗）	效果不亞於AZ＋BNT
BNT＋AZ	效果較差,但優於2劑AZ
莫德納＋AZ	類似BNT+AZ