流行性感冒 - 流行病學、病理生理機轉、臨床表現，和實驗室診斷方法 (Epidemiology, Pathophysiology, Clinical Manifestations, and Laboratory Diagnosis of Influenza Pandemic)

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1. 流行性感冒大流行的歷史

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流行性感冒 (Influenza) 大流行的歷史

1918-1919年: 被稱為 “西班牙流感”, 為A型流感病毒 (H1N1) 感染,為已知感冒引起死亡數目最多的一次流行,美國有50多萬人死亡,全世界可能有2千萬至5千萬人死亡,許多人在感染後頭幾天內死亡,其他人則很快死於併發症,死去的人幾乎一半是年輕,健康成人

CDC, January 15, 2004

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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).

4

流行性感冒 (Influenza) 大流行的歷史

1957-1958年:被稱為 “亞洲流感”,為A型流感病毒 (H2N2) 感染,最初在1957年2月下旬于中國發現, 1957年6月傳至美國,在美國大約引起7萬人死亡

1968-1969年: 被稱為 “香港流感”, 為A型流感病毒 (H3N2) 感染,最初在1968年于香港發現,當年晚些時後傳到美國,在美國大約引起3萬4千人死亡; A型 (H3N2) 病毒現在仍在傳播

CDC, January 15, 2004

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表一. 20世紀和21世紀造成世紀大流行的A型流行性感冒病毒感染疫情種類、年份、病毒分型，和估計死亡人數)

Table 1. Influenza pandemics in the twentieth and twenty-first centuries

Pandemic	Years	Influenza A subtype involved	Mortality impact
Spanish flu	1918–1920	H1N1	50–100 million deaths (Taubenberger and Morens 2006)
Asian flu	1957–1958	H2N2	1.1 million deaths (Viboud et al. 2016)
Hong Kong flu	1968–1969	H3N2	1 million deaths (Saunders-Hastings and Krewski 2016)
H1N1pdm09	2009–2010	H1N1	123,000–203,000 deaths (Simonsen et al. 2013)

Ryu S and Cowling B J. Cold Spring Harb Perspect Med. 2021;11:a038356.

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人類感染禽類流行性感冒的歷史

在1997年之前並無微生物學診斷人類感染禽類流行性感冒病毒的病例

1997年: 發生於香港, A型禽流感病毒 (H5N1) 傳染雞與人,為首次發現人類感染禽流感病毒;共有18個人住院,其中6人死亡,主管當局共撲殺150萬隻雞以去除病毒源;調查發現病毒主要由鳥傳染至人,極少發現人與人之間的傳染

CDC, January 15, 2004

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人類感染禽類流行性感冒的歷史

1999年: 發生於香港, 2個孩子被確認感染A型禽流感病毒 (H9N2) , 2個患者均恢復健康;證據顯示家禽為感染源,傳染的主要模式是從鳥到人,但是人之間傳染的可能性無法被排除;

1998-99年間,更多人感染H9N2的數個病例在中國大陸被報告

2003年: 至中國福建省旅行的一香港家庭發生禽流感 (H5N1) , 1人恢復, 1人死亡,另一家庭成員在中國死於一種呼吸道疾病,未作測試

CDC, January 15, 2004

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人類感染禽類流行性感冒的歷史

2003年: 發生於荷蘭,在爆發家禽的禽流感期間,共有89個家禽工作人員與其家庭成員被證實感染A型禽流感病毒 (H7N7) , 症狀大多集中於眼睛感染,部分出現呼吸道感染症狀,有1名患者死亡 (獸醫,曾至被禽流感病毒感染的農場出診) ,證據顯示部分為人與人之間傳佈
2003年: 一個兒童在香港被證實感染禽流感 (H9N2) ,兒童住院治療後恢復健康

CDC, January 15, 2004

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2. 流行性感冒的流行病學

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流行性感冒 (Influenza) 的流行病學

流行性感冒大流行發生為全球性,在新的流感病毒出現,散佈並引起全世界範圍的疾病影響:

- 高發病率
- 高死亡率
- 社會分裂
- 經濟損失

CDC, January 15, 2004

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民國94年2月5日 聯合報 (編輯自美國華盛頓郵報)

禽流感遲早突變 恐奪1億人命

泰越印尼大陸 雞鴨豬人密集相處 東南亞極可能產生大流行的新病毒 殺傷力將超過恐怖攻擊

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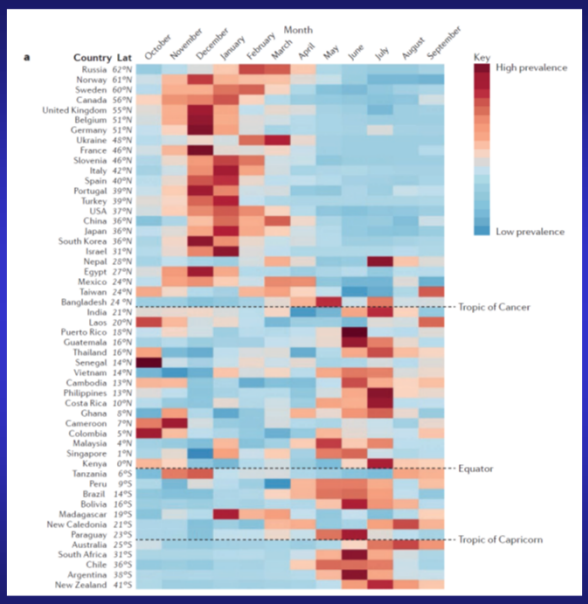

圖四a. 在2000 – 2015 年各種流感病毒 (A/H1A1, A/H3N2, B/Victoria, and B/Yamagata) 在季節 (依照月分) 流行的感染密度

Petrova V N. and Russel C A. Nat Rev Microbiol 2018;16:47-60.

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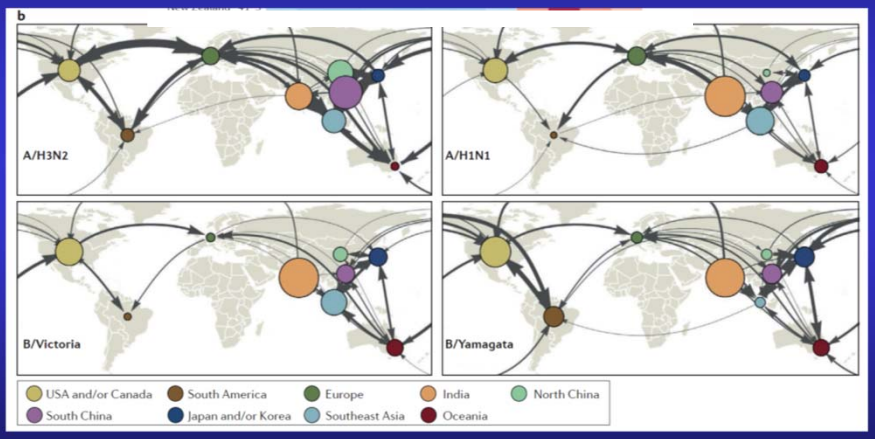
圖四b. 在2000 – 2015 年各種流感病毒 (A/H1A1, A/H3N2, B/Victoria, and B/Yamagata) 在不同區域散佈的能力 (線條厚度 – 每年平均病毒移動事件數目；箭頭 – 病毒移動方向；圓圈範圍 –各原始病毒在原有區域向世界移動的貢獻程度)



Petrova V N. and Russel C A. Nat Rev Microbiol 2018;16:47-60.

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H3N2A型流行性感冒感染病例新聞稿

香港H3N2流感37死 疾管署：病毒變異快

推薦 20

中廣新聞網 – 2015年1月23日 下午12:27

相關內容

香港的H3N2，A型流感，今年(23日)到目前為止，已經造成37人死亡。疾管署表示，目前香港的疫苗有高達60%到70%變異率，疫苗只對三到四成的人有效，再加上目前香港社區流感病毒陽性率高達29.3% ，遠高於目前國內的9%。是這次香港疫情嚴重的主因，目前國內疫苗變異率大約是27%，同期死亡人數只有一人，疫苗對七成以上民眾仍然有效，請民眾安心。

CDC, Taiwan January 23rd, 2015

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圖一. 2009年在香港特別行政區流行的新型 H1N1pdm09 A型流感疫情 – a. 各年齡層感染率；b. 各年齡層的疾病嚴重程度(發生率、住院率、入住加護病房比率，和死亡率)

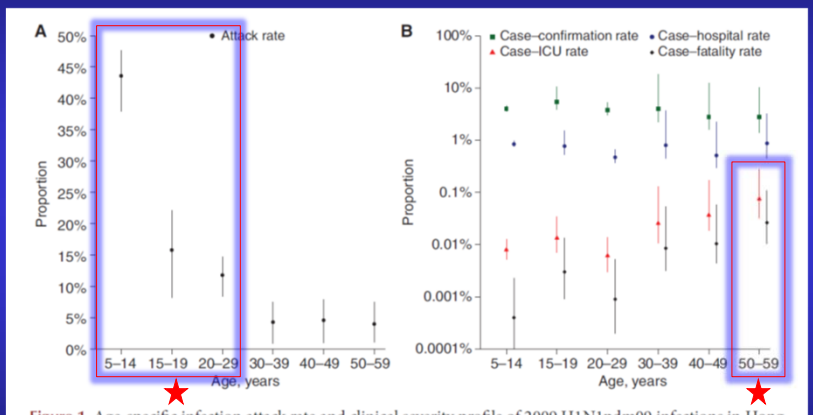

Figure 1. Age-specific infection attack rate and clinical severity profile of 2009 H1N1pdm09 infections in Hong Kong (Wu et al. 2010b). (*A*) Estimates of the risk of infection in each age group based on a large serologic study (Wu et al. 2010b). (*B*) Age-specific estimates of the clinical severity profile of H1N1pdm09 in Hong Kong based on the estimated attack rates and the numbers of severe outcomes recorded in the territory.

Ryu S and Cowling B J. Cold Spring Harb Perspect Med. 2021;11:a038356.

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World Health Organization

Global Alert and Response (GAR)

Avian influenza - situation in Egypt - update 53

Share

16 JUNE 2011 - The Ministry of Health of Egypt has notified WHO of five cases of human infection with avian influenza A (H5N1) virus.

The first case is a 40 years old female from Aswan District, Aswan Governorate. She developed symptoms on 14 May, and was hospitalized. She completed the course of oseltamivir, recovered and was discharged.

The second case is a 21 years old pregnant female from Ashmoun District, Menofia Governorate. She developed symptoms on 21 May, was hospitalized and received oseltamivir. She died on 29 May.

The third case is a 31 years old male from Shobra Elkhima District, Qaliobia Governorate. He developed symptoms on 21 May, was hospitalized and received oseltamivir. He died on 5 June.

The fourth case is a 32 years old male from Elzawya District, Cairo Governorate. He developed symptoms on 23 May was hospitalized and received oseltamivir. He died on 2 June.

The fifth case is a 16 years old male from Ashmoon District, Menofia Governorate. He developed symptoms on 21 May was hospitalized and received oseltamivir. He was in a critical condition but he is recovering.

Investigations into the source of infection indicate that all the cases had exposure to poultry suspected to have avian influenza.

The cases were confirmed by the Egyptian Central Public Health Laboratories, a National Influenza Center of the WHO Global Influenza Surveillance Network.

Of the 149 cases confirmed to date in Egypt, 51 have been fatal .

人類感染H5N1禽流感致死案例－埃及
(截至2011年6月為止,共有149名確認感染病例, 51名死亡,死亡率34.2%)

WHO, June 16th, 2011

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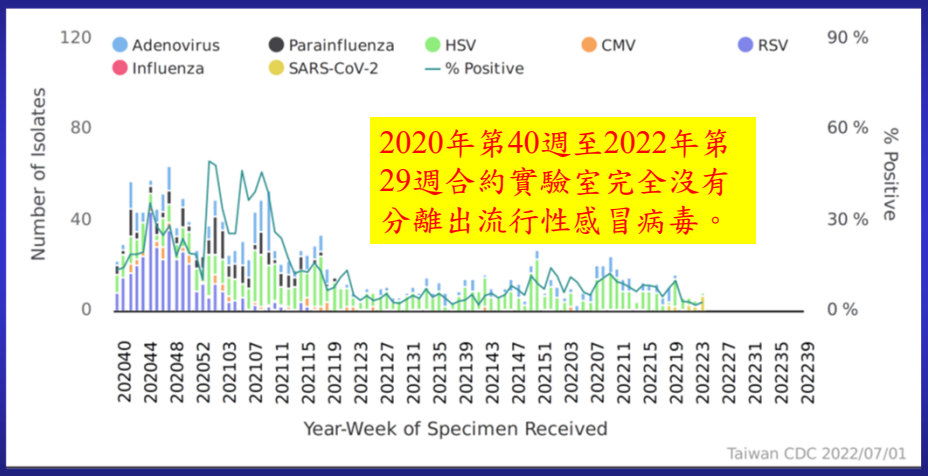
自2020年第40週至2022年第29週衛生福利部疾病管制署合約實驗室的呼吸道病毒監測分離趨勢圖



Taiwan CDC. July 1st, 2022.

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自2020年第40週至2022年第29週執行法定報告傳染病通報至疾病管制署流行性感冒重症個案趨勢圖 (綠色 – 通報個案 黃色 - 檢驗中；紅色 – 確定個案)

Taiwan CDC. July 1st, 2022.

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中部某醫學中心使用多重引子聚合酶反應 (multiplex-PCR, Film Array RP2.0 & RP2.1) 於 COVID-19 疫情前後檢驗兒科/成人呼吸道病毒陽性報告結果

Positive rate and Detected pathogen of pediatric and adult group

	Overall (n=3719)	Pediatric			Adults		
		Total (n=991)	Before (n=642)	After (n=349)	Total (n=2728)	Before (n=327)	After (n=2401)
Detected	19.9% (741)	55.1% (546)	65.0% (417)	37.0% (129)	7.1% (195)	20.5% (67)	5.3% (128)
Not Detected	80.1% (2978)	44.9% (445)	35.9% (225)	63.0% (220)	92.9% (2533)	79.5% (260)	94.7% (2273)

- Overall positive rate is 19.9% (741/3719), with pediatric positive rate (55.1%) higher than adult group (7.1%)
- Top 3 detected pathogen of all group : HRV/EV, Adenovirus, hMPV
- After COVID-19 pandemic:
  - Enhanced Coronavirus HKU1 in adults
  - Decreased Parainfluenza 1 and Coronavirus NL63 in pediatric; *M. pneumoniae* in all age group

	Overall (pathogen=955)	Pediatric		Adults	
		Before COVID-19 (pathogen=571)	After COVID-19 (pathogen=181)	Before COVID-19 (pathogen=73)	After COVID-19 (pathogen=130)
Human Rhinovirus/Enterovirus	389 (40.7%)	220 (38.5%)	82 (45.3%)	29 (39.7%)	58 (44.6%)
Adenovirus	135 (14.1%)	76 (13.3%)	34 (18.8%)	11 (15.1%)	14 (10.8%)
Human Metapneumovirus	113 (11.8%)	66 (11.6%)	27 (14.9%)	3 (4.1%)	17 (13.1%)
RSV	106 (11.1%)	97 (17.0%)	5 (2.8%)	4 (5.5%)	0 (0.0%)
Parainfluenza 3	79 (8.3%)	57 (10.0%)	16 (8.8%)	3 (4.1%)	3 (2.3%)
Parainfluenza 4	40 (4.2%)	21 (3.7%)	11 (6.1%)	2 (2.7%)	6 (4.6%)
Coronavirus HKU1	36 (3.8%)	0 (0.0%)	6 (3.3%)	2 (2.7%)	28 (21.5%)
Coronavirus NL63	18 (1.9%)	16 (2.8%)	0 (0.0%)	1 (1.4%)	1 (0.8%)
Mycoplasma pneumoniae	13 (1.4%)	6 (1.1%)	0 (0.0%)	7 (9.6%)	0 (0.0%)
Parainfluenza 1	11 (1.2%)	10 (1.8%)	0 (0.0%)	1 (1.4%)	0 (0.0%)
Coronavirus 229E	4 (0.4%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	3 (2.3%)
Parainfluenza 2	3 (0.3%)	1 (0.2%)	0 (0.0%)	2 (2.7%)	0 (0.0%)
Influenza A/H1-2009	3 (0.3%)	0 (0.0%)	0 (0.0%)	3 (4.1%)	0 (0.0%)
Coronavirus OC43	2 (0.2%)	0 (0.0%)	0 (0.0%)	2 (2.7%)	0 (0.0%)
Influenza B	2 (0.2%)	0 (0.0%)	0 (0.0%)	2 (2.7%)	0 (0.0%)
Chlamydophila pneumoniae	1 (0.1%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SARS-CoV-2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Mers-CoV	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Influenza A/H1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Influenza A/H3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
				0 (0.0%)	0 (0.0%)
				0 (0.0%)	0 (0.0%)

COVID-19 疫情開始後完全沒有偵測到 influenza (A/H1, A/H1-2009, A/H3, and B)。

Unpublished data from bioMérieux®

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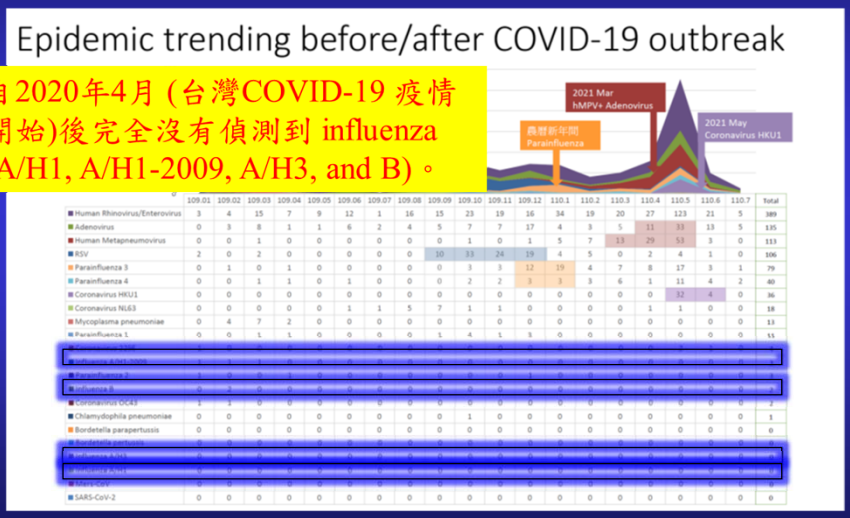
中部某醫學中心使用多重引子聚合酶反應 (multiplex-PCR, Film Array RP2.0 & RP2.1) 於 COVID-19 疫情前後檢驗呼吸道病毒陽性報告結果



Unpublished data from bioMérieux®

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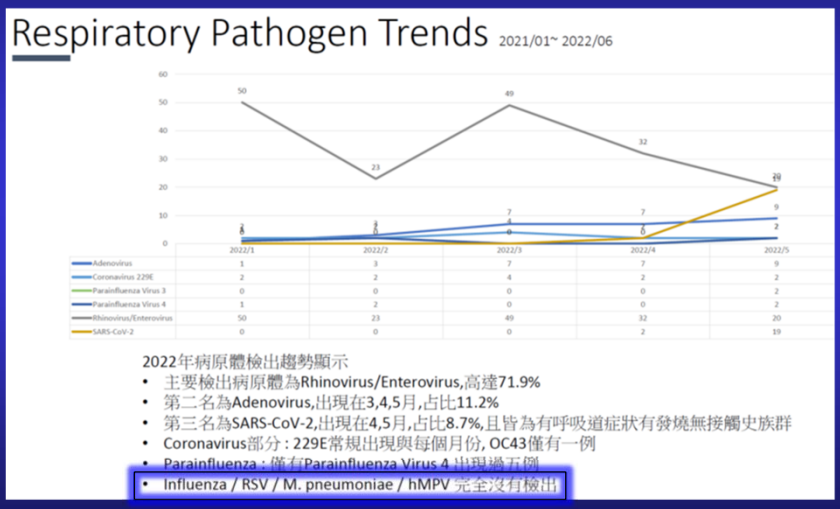
中部某醫學中心使用多重引子聚合酶反應 (multiplex-PCR, Film Array RP2.0 & RP2.1) 於 COVID-19 疫情 (2021年1月) 後檢驗呼吸道病毒陽性報告結果



Unpublished data from bioMérieux®

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圖二. 流行性感冒病毒疫情的非藥物介入措施對於疫情和醫療機構的影響 (“壓平曲線”，包括延後疫情發生時間和減緩嚴重程度、延長疫情時間、維持醫療量能，和為增加醫療量能爭取時間)

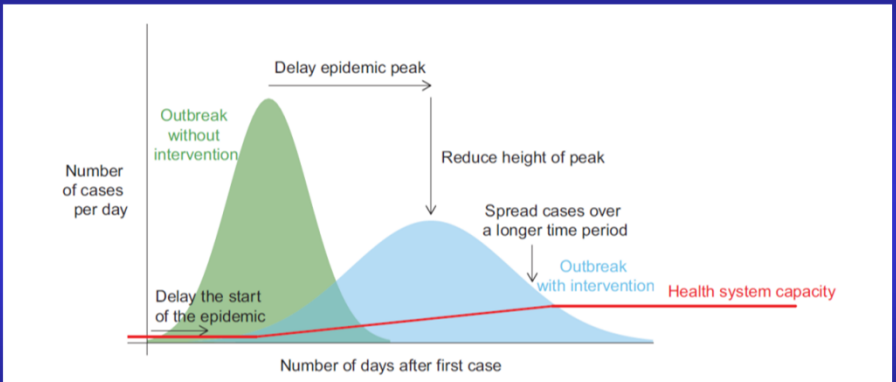

Figure 2. The intended impact of nonpharmaceutical interventions, indicating how “flattening the curve” could allow a greater fraction of patients to be effectively managed by the available health system capacity and could buy time for capacity to be increased.

Ryu S and Cowling B J. Cold Spring Harb Perspect Med. 2021;11:a038356.

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3. 流行性感冒病毒的微生物學與病理生理機轉

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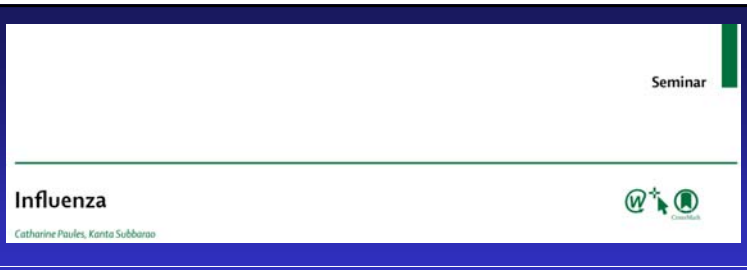

內容摘要：流行性感冒是一種急性呼吸道感染，依病原可分為A、B，和C型三種型別，可在局部地區引起群突發或季節性大規模流行。臨床表現為在接觸後於極短潛伏期 (1-5日) 產生無症狀至嚴重的症狀，這取決於病毒與宿主的特性。當新型病毒自動物宿主因某些原因感染人類族群，A型流感可引起偶發性或全球大流行感染，針對季節流感和全球流感的預防和治療的新策略有其急迫性。本篇論文討論季節流感的臨床表現、傳染途徑、診斷方法、治療模式，和預防方法，並討論動物與人類之間流感傳遞模式，與聚焦於全球大流行的威脅。

Paules C and Subbarao K. Lancet. 2017;390:696-708.

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A型流行性感冒病毒 (Influenza Virus A)

可感染多種動物,包括鳥,豬,馬,海豹,和鯨

依表面蛋白質 (血凝素 hemagglutinin – HA 和神經氨酸 neuraminic acid – NA) 分型,分15種HA亞型 (H1 – H15) (在鳥類可全部發現)

目前已知只有3種HA亞型 (H1, H2, and H3) 和2種NA亞型 (N1 and N2) 在人類廣泛傳佈

禽類流行性感冒病毒通常不會使野鳥生病 (或病情較輕微) ,但可使家禽得重病致死

CDC, January 15, 2004

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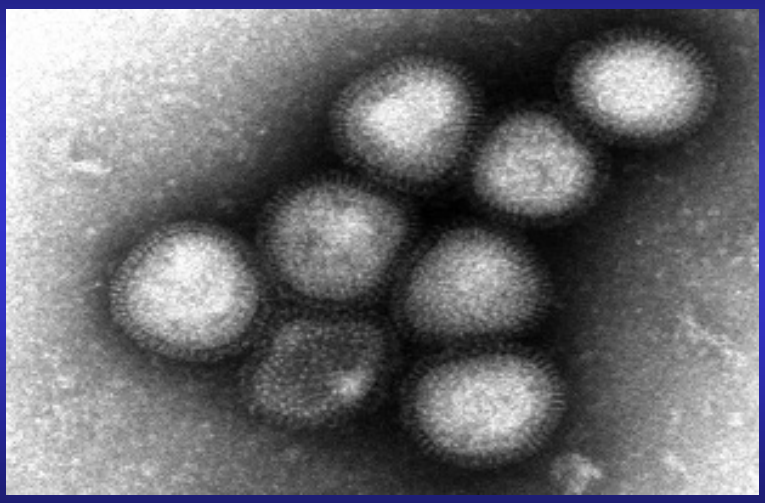
電子顯微鏡下的H7N9流行性感冒病毒



WHO, January 20th, 2014

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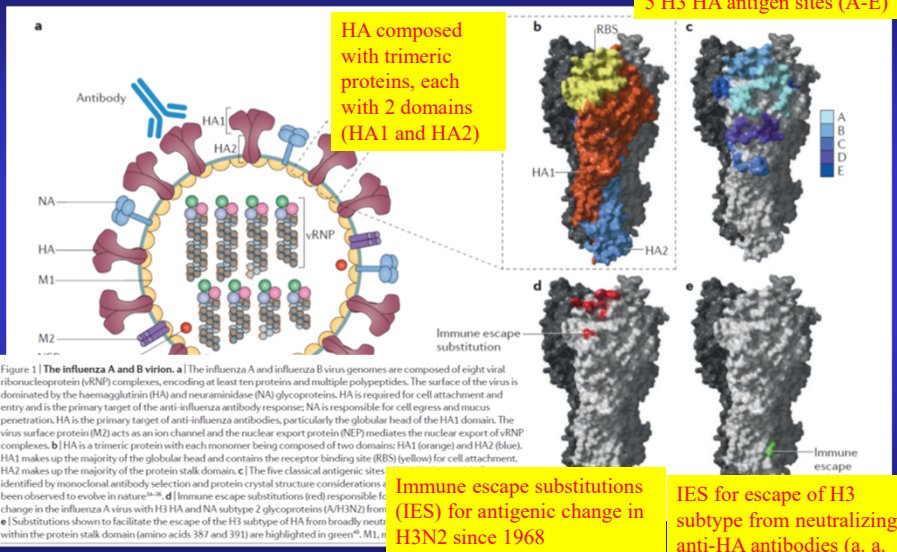
圖一. A型和B型流感病毒結構 (a) (包含8個核糖蛋白－ribonucleoprotein, vRNP) 和相關位置突變位址 (b-e)

5 H3 HA antigen sites (A-E)



HA composed with trimeric proteins, each with 2 domains (HA1 and HA2)

Figure 1 | **The influenza A and B virion. a** | The influenza A and influenza B virus genomes are composed of eight viral ribonucleoprotein (vRNP) complexes, encoding at least ten proteins and multiple polypeptides. The surface of the virus is dominated by the haemagglutinin (HA) and neuraminidase (NA) glycoproteins. HA is required for cell attachment and entry and is the primary target of the anti-influenza antibody response; NA is responsible for cell egress and mucus penetration. HA is the primary target of anti-influenza antibodies, particularly the globular head of the HA1 domain. The virus surface protein (M2) acts as an ion channel and the nuclear export protein (NEP) mediates the nuclear export of vRNP complexes. **b** | HA is a trimeric protein with each monomer being composed of two domains: HA1 (orange) and HA2 (blue). HA1 makes up the majority of the globular head and contains the receptor binding site (RBS) (yellow) for cell attachment. HA2 makes up the majority of the protein stalk domain. **c** | The five classical antigenic sites identified by monoclonal antibody selection and protein crystal structure considerations been observed to evolve in nature[34–38]. **d** | Immune escape substitutions (red) responsible f change in the influenza A virus with H3 HA and NA subtype 2 glycoproteins (A/H3N2) from **e** | Substitutions shown to facilitate the escape of the H3 subtype of HA from broadly neutr within the protein stalk domain (amino acids 387 and 391) are highlighted in green[40]. M1, r

Immune escape substitutions (IES) for antigenic change in H3N2 since 1968

IES for escape of H3 subtype from neutralizing anti-HA antibodies (a. a. 387-391, green color)

Petrova V N. and Russel C A. Nat Rev Microbiol

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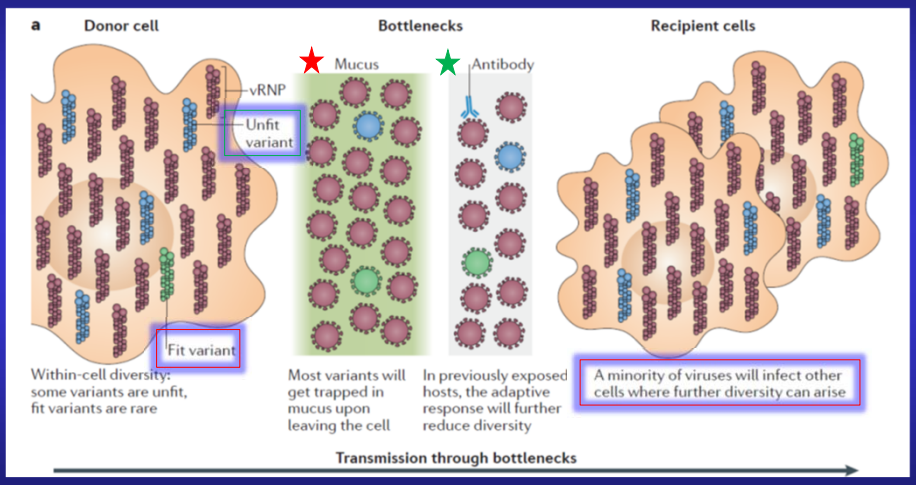
圖二a. 流感病毒變異的瓶頸效應 [降低病毒變異性的機轉] [(自原感染細胞 (donor cells) 至新感染細胞 (recipient cells)]



Petrova V N. and Russel C A. Nat Rev Microbiol 2018;16:47-60.

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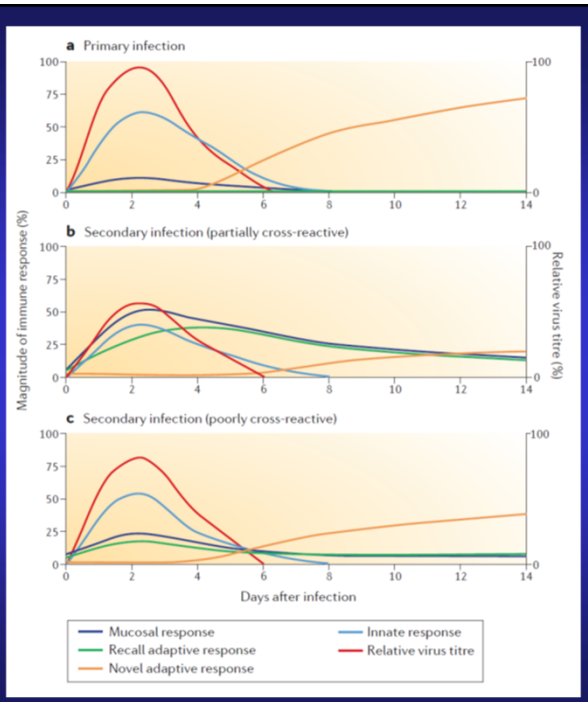

圖三. 在流感病毒感染 (a. 原發性感染；b & c. 續發性感染) 宿主的各項免疫反應變化與時間關係圖 (深藍色 - 黏膜反應；淺藍色 - 本體免疫反應；綠色 - 舊有後天免疫反應；橘色 - 新型後天免疫反應；紅色 - 病毒相對濃度)

Petrova V N. and Russel C A. Nat Rev Microbiol 2018;16:47-60.

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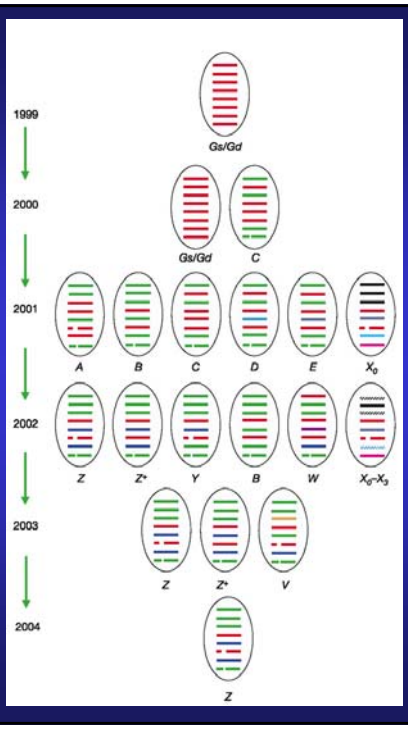
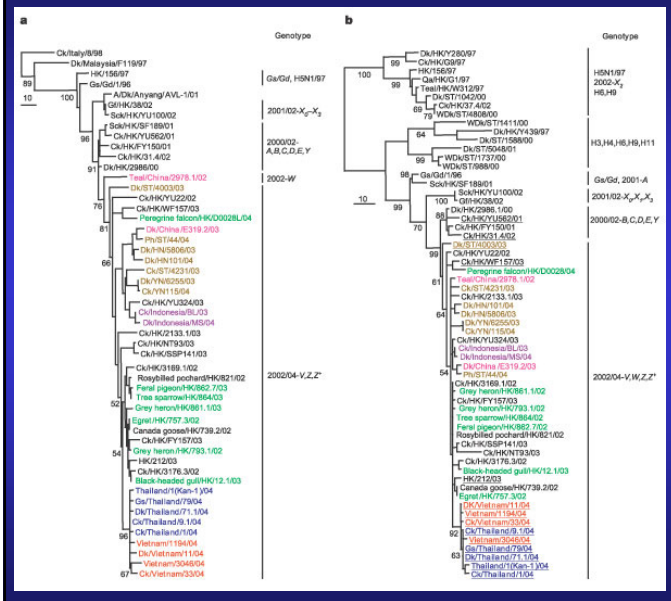


自1999年以來自東亞分離的H5N1禽流感病毒基因重組後基因型的演變 (8種基因片段的變化)

Li KS et al Nature 2004;430:209-213

37



自東南亞分離的A型流行性感冒病毒依血凝素 (hemaglutinin, 左圖) 基因和菌體蛋白 (matrix protein, 右圖) 的基因相似度分型

Li KS et al Nature 2004;430:209-213

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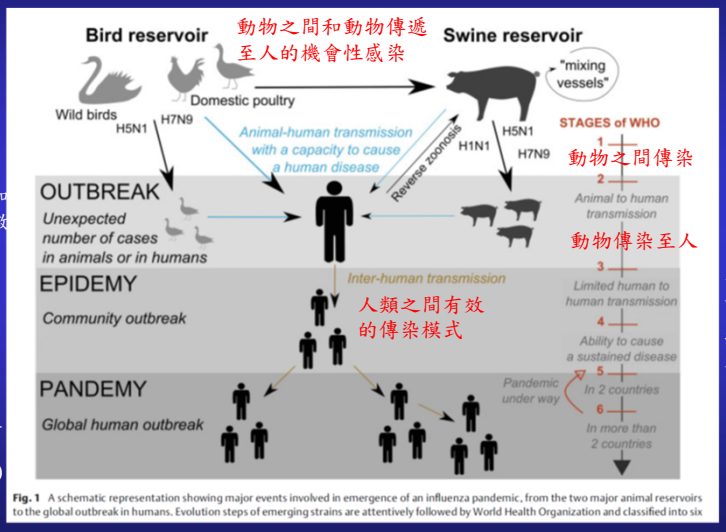
圖一. 流行性感冒病毒造成世紀流行的原始宿主 (鳥和豬) 傳遞至人類和演化造成人類疫情程度 (WHO分級, 1-6級)



群突發 (不預期動物和人類感染數量增加)

流行 (社區群突發)

大流行 (全球性人類大量快速群突發)

有限度的人傳人感染

持續在人類族群傳染

在2個國家內持續人類族群傳染

超過2個國家內持續人類族群傳染

Peteranderl C P. et al. Semin Respir Crit Care Med. 2016;37:487-500.

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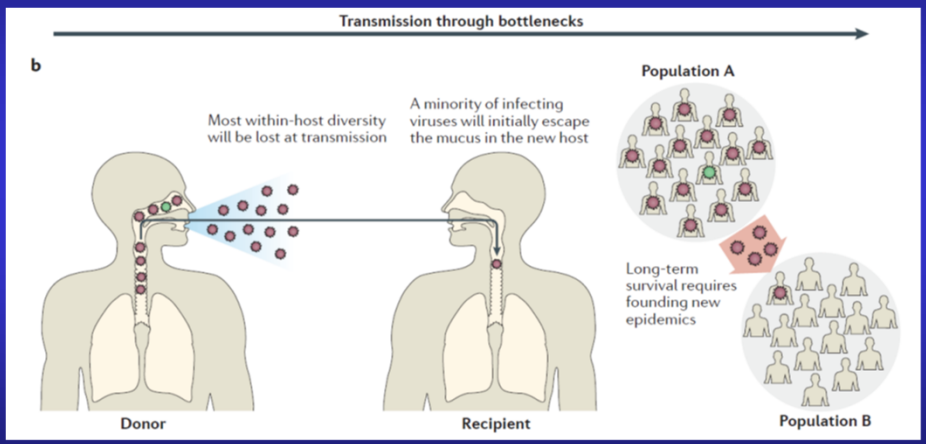
圖二b. 流感病毒自宿主至族群之間散佈的因子 (包括原有宿主分泌因子、接受宿主感染，和大流行散佈等)



Petrova V N. and Russel C A. Nat Rev Microbiol 2018;16:47-60.

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圖二. A型流行性感冒病毒在肺部組織造成人體肺部傷害的病理生理機轉 (巨噬細胞、樹突細胞，和單核細胞等)

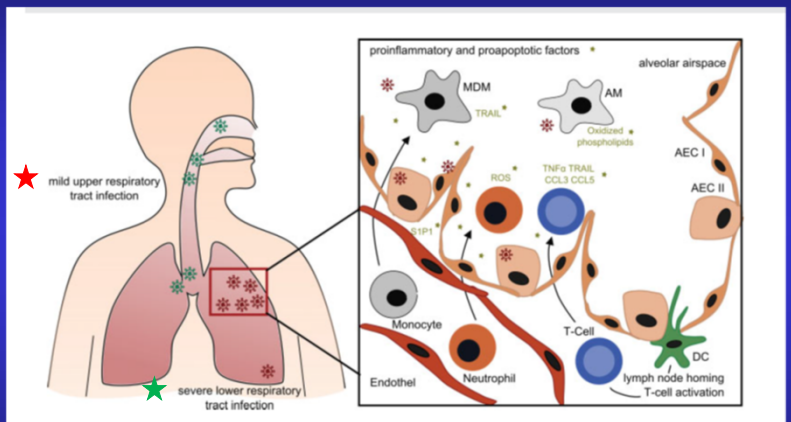

Fig. 2 Key players in influenza A virus (IAV)-induced lung injury. While upper respiratory tract infection results in mild symptomatic IAV infection, severe cases of IAV usually involve spread of the virus to the lower respiratory tract. Here, resident alveolar macrophages (AM) and dendritic cells (DC) sense IAV infection of alveolar epithelial type I (AEC I) and type II (AEC II) cells. Cytokine release and establishment of a proinflammatory milieu in the alveolar lumen lead to recruitment of additional monocyte-derived macrophages (MDM) as well as neutrophils from the blood vessels to the site of infection. DC migration to the lymph nodes further induces generation of antigen-specific T cells into the vessel. An exuberant immune response with massive release of proinflammatory and proapoptotic mediators contributes to IAV-induced lung injury.

Peteranderl C P. et al. Semin Respir Crit Care Med. 2016;37:487-500.

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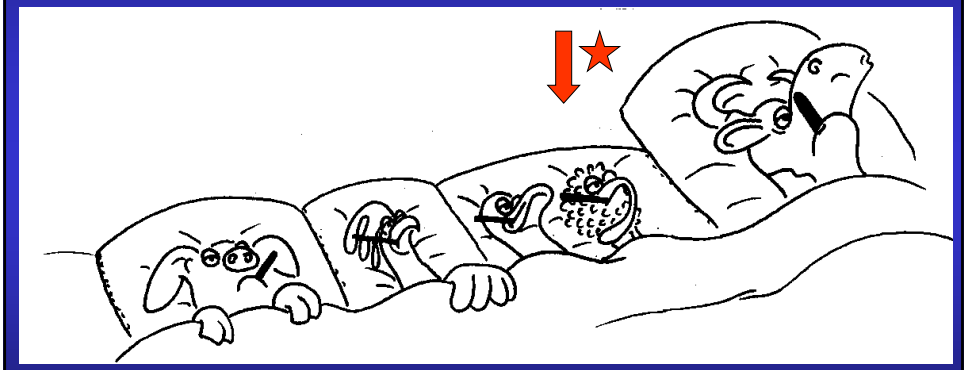
Avian Flu – It Is Enough to Make You Sick



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禽類流行性感冒 – 定義

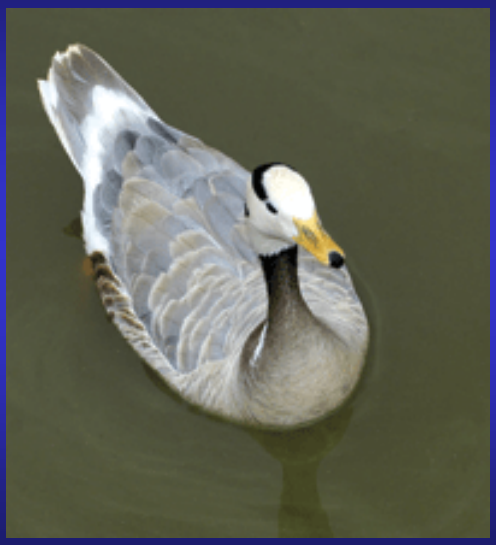
為流行於鳥類 (常見) 與豬 (少見) 中的動物性傳染性疾病

所有鳥類對禽類流行性感冒病毒 (禽流感病毒) 均有感受性

畜養的家禽比野生禽類更易感染禽流感病毒,並造成大規模的疫情

43

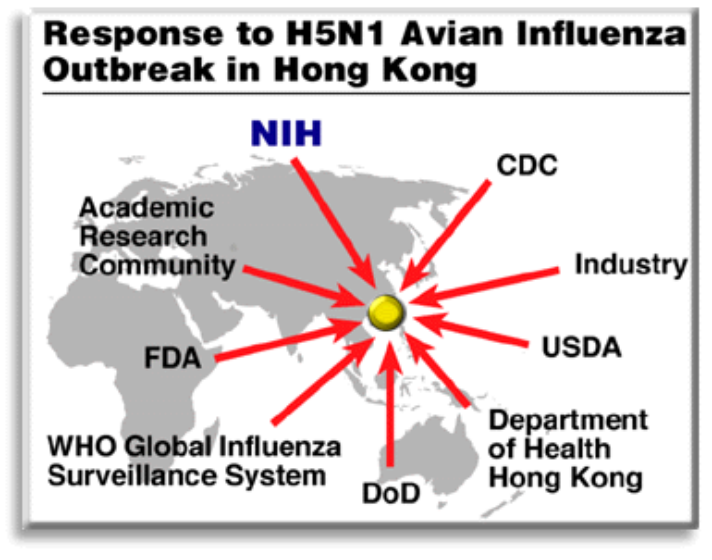
野生候鳥 – 能遠方傳遞高致病性禽流感病毒的宿主



Normile D Science 2005;309(5732):231 (July 8)

44

1997年香港發生人類H5N1禽流感病例後世界各國和組織的反應

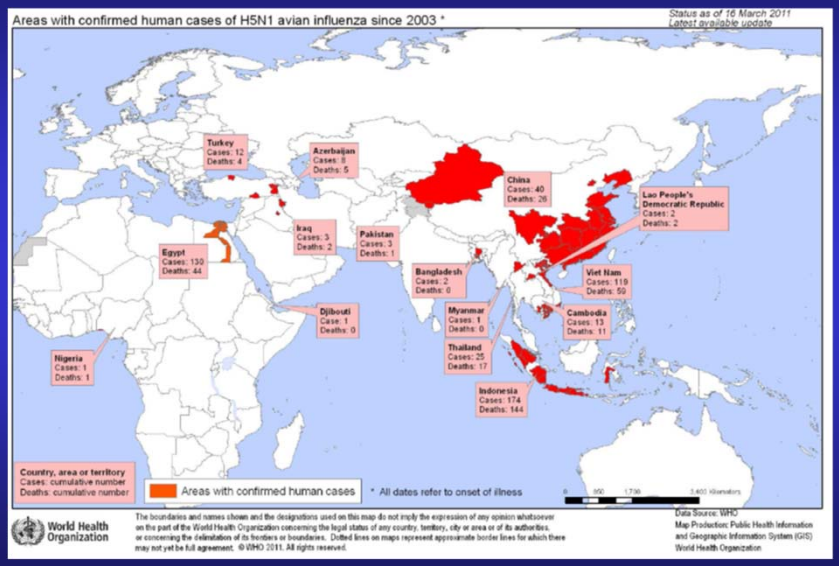


45

市場現宰的雞隻 –
與禽流感必病毒接觸的可能途徑

46

自2003年至2011年3月16日人類感染H5N1禽流感病毒的地區與確診個案和死亡人數



WHO, March 16th, 2011

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H5N1 avian influenza: Timeline of major events

H5N1主要事件時程表

14 July 2008

早期事件
Early Events

發生於動物的事件

發生於人類的事件

Date	Events in Animals	Events in Humans
1996	Highly pathogenic H5N1 virus is isolated from a farmed goose in Guangdong Province, **China**.	
1997	Outbreaks of highly pathogenic H5N1 are reported in poultry at farms and live animal markets in **Hong Kong**.	Human infections with avian influenza H5N1 are reported in **Hong Kong**. Altogether, 18 cases (6 fatal) are reported in the first known instance of human infection with this virus.
Feb 2003		Two human cases of avian influenza H5N1 infection (one fatal) are confirmed in a **Hong Kong** family with a recent travel history to Fujian Province, **China**. A third family member died of severe respiratory disease while in mainland China, but no samples were taken.

WHO, July 14th, 2008

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H5N1 avian influenza: Timeline of major events H5N1主要事件時程表

晚期事件

14 July 2008

	發生於動物的事件	發生於人類的事件
28 May 2008		**Bangladesh** confirms it first human case, in a 16-month-old boy from Komalapur, Dhaka (onset date 27 Jan 2008). The case was identified retrospectively as part of seasonal influenza surveillance activities.
1 Jun 2008	**Japan** reports H5N1 in wild swans in Aomori prefecture.	
3 Jun 2008	**India** reports H5N1 in backyard birds in West Bengal province	
6 Jun 2008	**United Kingdom** reports highly pathogenic avian influenza H7N7 in a commercial flock of chickens in England.	
11 Jun 2008	**Bangladesh** reports H5N1 in commercial poultry in Dhaka	
16 Jun 2008	According to FAO, HPAI remains endemic in **Indonesia** on the islands of Java, Sumatra, Bali, and South Sulawesi and sporadic outbreaks are reported from other areas. [31]	
19 Jun 2008		**Indonesia** confirms its 134th human case in a 16-year old girl from DKI Jakarta (onset date 7 may 2008) and 135th human case, in a 34-year-old woman from Banten (onset date 26 May 2008).

WHO, July 14th, 2008

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病毒檢驗確認感染禽流感病毒 (A/H5N1)的個案數 (依時間與國家別) (自2003年12月至2005年8月)

Table 1. Cumulative Number of Virologically Confirmed Cases of Avian Influenza A (H5N1) in Humans Reported to the WHO since 2003.*

Date of Onset	Vietnam		Thailand		Cambodia		Indonesia		Total 個案數	死亡數
	No. of Cases	No. of Deaths	No. of Cases	No. of Deaths	No. of Cases	No. of Deaths	No. of Cases	No. of Deaths	No. of Cases	No. of Deaths
December 26, 2003, to March 10, 2004	23	16	12	8	0	0	0	0	35	24
July 19, 2004, to October 8, 2004	4	4	5	4	0	0	0	0	9	8
December 16, 2004, to August 5, 2005†	63	20	0	0	4	4	1	1	68	25
Total	90	40	17	12	4	4	1	1	112	57

* Additional details are available at www.who.int/csr/disease/avian_influenza/country/cases_table_2005_08_05/en/print.
† Cases continue to occur. The total number of cases includes fatal ones. This list does not include the 18 patients, 6 of who in Hong Kong in 1997 or the 2 patients, 1 of whom died, identified in Fujian Province, China, in 2003.

死亡率為50.9%

The Writing Committee of the World Health Organization (WHO) Consultation on Human Influenza A/H5

N Engl J Med 2005;353(13):1374-1385

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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

51

H7N9禽流感最新疫情 – (I)

中國衛生暨家庭計畫委員會於2013年3月31日通知世界衛生組織 (WHO), 共有3名經中國疾病管制局實驗室於3月29日確認感染H7N9禽流感病毒的病例,上述病人的檢體確認並未感染A (H1N1)、A(H3N2)、A (H1N1)pdm09、A(H5N1), 和新型冠狀病毒

上述病人來自上海市 (2例) 和安徽省 (1例), 均有呼吸道感染症狀,並進展至嚴重肺炎與呼吸困難,症狀發生於2月19日至3月15日之間,已有兩名病人死亡

上述病人未有流行病學的相關性,流行病學與病毒學的調查仍持續進行, 88名密切接觸者目前並無症狀

WHO, April 1st, 2013

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H7N9禽流感最新疫情 – (XII)

中國衛生主管機關通報另外3名 實驗室確定人類感染

中國大陸H7N9流感病例發生地區有上海市、安徽省、江蘇省及浙江省。大陸已累積24名實驗室確認感染病例 (7死)，其中上海11人 (5死)、安徽2人、江蘇8人、浙江3人 (2死)。

發病日期為3月30日,居住於江蘇省 (嚴重)；64歲男性, 發病日期為4月1日,居住於上海市 (4月7日死亡)

共有24名經實驗室確診為H7N9禽流感感染病例, 其中7名病人死亡, 14名病人病情處於嚴重病情, 3名病人輕症

超過600名接觸者正接受密切觀察,在江蘇省有1名與確定病例有過接觸的接觸者出現呼吸道症狀,目前正在接受持續的調查確認是否感染 (目前無人傳人的證據)

WHO, April 9th, 2013

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Geographical location

Provinces in China with confirmed human cases for influenza A(H7N9) reported to WHO*

依據病例發生地區通報至世界衛生組織確認A型H7N9流感的病例人數與死亡人數

WHO, April 10th 2013

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Cumulative number of confirmed cases for influenza A(H7N9) reported to WHO, by month, 2013

依據月份發生通報至世界衛生組織確認A型H7N9流感的病例人數與死亡人數

Country	February		March		April		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths
China	2	2	23	6	3	1	28	9
Total	2	2	23	6	3	1	28	9

Total number of cases includes number of deaths
WHO reports only laboratory cases
All dates refer to onset of illness

Data in WHO/HQ as of 10 April 2013, 14:22 GMT+1
Source: WHO/GIP

World Health Organization

WHO, April 10th 2013

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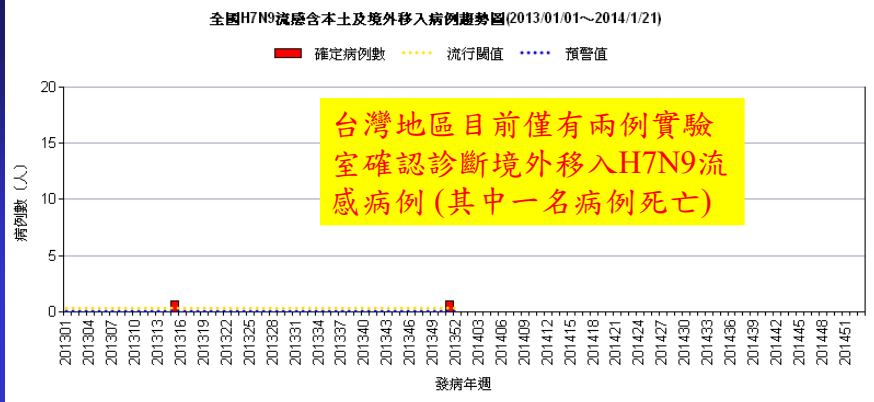


台灣地區目前僅有兩例實驗室確認診斷境外移入H7N9流感病例(其中一名病例死亡)

疾病名稱：H7N9流感

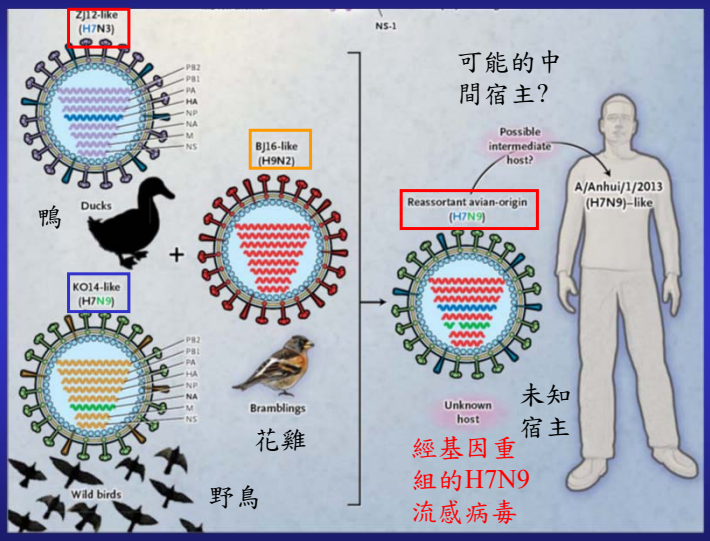
最近一例確定病例發病日	上週累計數	本週累計數	本月累計數	本年累計數	去年確定總數	上週與前三週平均數比較	上週與過去三年同期平均數比較	今年累計確定病例死亡數
2013/12/20	0	0	0	0	2	0.00	0.00	0

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。
註四：因目前全台僅一例個案，為保護病患隱私，故不顯示縣市病例地理分布。

CDC, Taiwan. Jan 22nd, 2014

56

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

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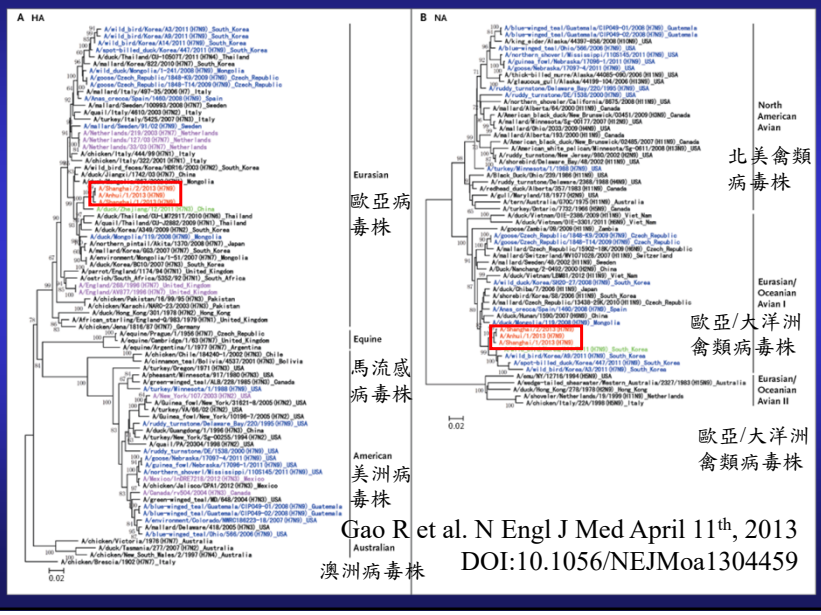
圖一. 新型H7N9流感病毒的基因族譜圖 (基因序列: HA, 左側; NA, 右側)



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

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4. 流行性感冒病毒感染的臨床表現

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流行性感冒症狀：體溫上升(發燒)、咳嗽(多為乾咳)、嚴重咽喉疼痛、關節肌肉酸痛(無關節炎徵象)、頭痛、全身衰弱無力，和部分病人有呼吸困難症狀。

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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

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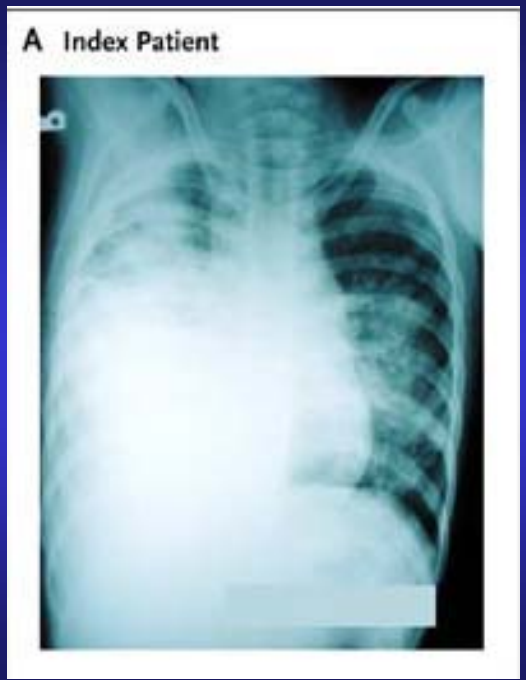

指標病人 (11歲女性病人) 的胸部X光片 (出現症狀第6天) (A/H5N1)

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

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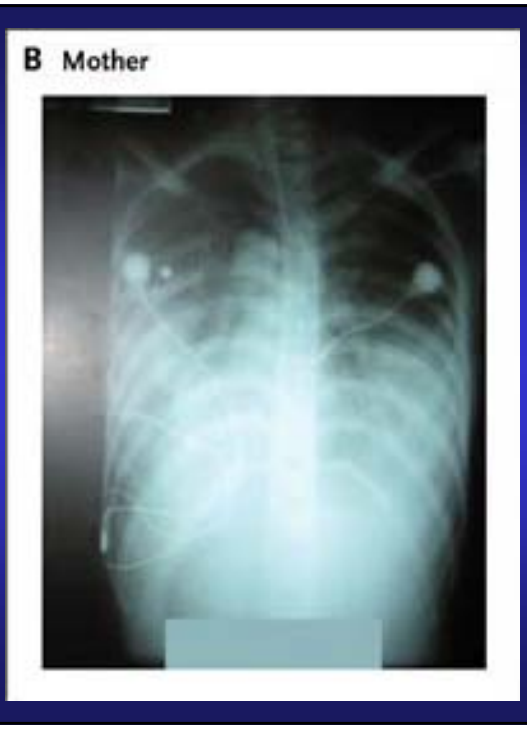

指標病人母親(26歲女性)(A/H5N1)的胸部X光片（出現症狀第9天)

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

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1997年至2005年人類感染高致病性禽類A型流行性感冒(H5N1)病毒的病人的臨床表現

Table 3. Presentation and Outcomes among Patients with Confirmed Avian Influenza A (H5N1).*

Outcome or Measure	Hong Kong, 1997 (N=18)	Thailand, 2004 (N=17)	Vietnam, 2004 (N=10)	Ho Chi Minh City, 2005 (N=10)	Cambodia, 2005 (N=4)
Clinical presentation — no./total no. (%)					
Fever (temperature >38°C) 發燒	17/18 (94)	17/17 (100)	10/10 (100)	10/10 (100)	4/4 (100)
Headache	4/18 (22)	NS	NS	1/10 (10)	4/4 (100)
Myalgia	2/18 (11)	9/17 (53)	0	2/10 (20)	NS
Diarrhea 腹瀉	3/18 (17)	7/17 (41)	7/10 (70)	NS	2/4 (50)
Abdominal pain	3/18 (17)	4/17 (24)	NS	NS	2/4 (50)
Vomiting	6/18 (33)	4/17 (24)	NS	1/10 (10)	0
Cough§ 咳嗽	12/18 (67)	16/17 (94)	10/10 (100)	10/10 (100)	4/4 (100)
Sputum 痰液	NS	13/17 (76)	5/10 (50)	3/10 (30)	NS
Sore throat	4/12 (33)	12/17 (71)	0	0	1/4 (25)
Rhinorrhea	7/12 (58)	9/17 (53)	0	0	NS
Shortness of breath§ 呼吸困難	1/18 (6)	13/17 (76)	10/10 (100)	10/10 (100)	NS
Pulmonary infiltrates 肺部浸潤	11/18 (61)	17/17 (100)	10/10 (100)	10/10 (100)	4/4 (100)
Lymphopenia¶ 淋巴球降低	11/18 (61)	7/12 (58)	NS	8/10 (80)	1/2 (50)
Thrombocytopenia 血小板降低	NS	4/12 (33)	NS	8/10 (80)	1/2 (50)
Increased aminotransferase levels	11/18 (61)	8/12 (67)	5/6 (83)	7/10 (70)	NS

血清肝臟轉胺酶上昇

WHO N Engl J Med 2005;353 (13):1374-1385

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Human Infection with a Novel Avian-Origin Influenza A (H7N9) Virus

Rongbao Gao, M.D., Bin Cao, M.D., Yunwen Hu, M.D., Zijian Feng, M.D., M.P.H., Dayan Wang, M.D., Wanfu Hu, M.D., Jian Chen, M.D., Zhijun Jie, M.D., Haibo Qiu, M.D., Ph.D., Ke Xu, M.D., Xuewei Xu, M.D., Hongzhou Lu, M.D., Ph.D., Wenfei Zhu, M.D., Zhancheng Gao, M.D., Nijuan Xiang, M.D., Yinzhong Shen, M.D., Zebao He, M.D., Yong Gu, M.D., Zhiyong Zhang, M.D., Yi Yang, M.D., Ph.D., Xiang Zhao, M.D., Lei Zhou, M.D., Xiaodan Li, M.D., Shumei Zou, M.D., Ye Zhang, M.D., Xiyan Li, M.D., Lei Yang, M.D., Junfeng Guo, M.D., Jie Dong, M.D., Qun Li, M.D., Libo Dong, M.D., Yun Zhu, M.D., Tian Bai, M.D., Shiwen Wang, M.D., Pei Hao, M.D., Weizhong Yang, M.D., Yanping Zhang, M.D., Jun Han, M.D., Hongjie Yu, M.D., Dexin Li, M.D., George F. Gao, Ph.D., Guizhen Wu, M.D., Yu Wang, M.D., Zhenghong Yuan, Ph.D., and Yuelong Shu, Ph.D.

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表二. 三個感染人類的新型H7N9流感病毒基因分析

Table 2. Molecular Analysis of Three of the 2013 H7N9 Viruses.*

Gene	Sites†	Position	A/Shanghai/1/2013	A/Shanghai/2/2013	A/Anhui/1/2013
	Cleavage site		PEIPKGR↓G	PEIPKGR↓G	PEIPKGR↓G
	RBS positions (H3 numbering), altered receptor specificity				
HA	Q226L	226	Q	L	L
	G228S	228	G	G	G
	Glycosylation motifs		30NGTK, 46NATE, 249NDTV, 421NWTR, 493NNTY (conserved in H7 HA viruses)	30NGTK, 46NATE, 249NDTV, 421NWTR, 493NNTY (conserved in H7 HA viruses)	30NGTK, 46NATE, 249NDTV, 421NWTR, 493NNTY (conserved in H7 HA viruses)
	Stalk		69–73 deletion	69–73 deletion	69–73 deletion
NA	Antiviral resistance R294K (oseltamivir)	294	K	R	R
	Enhanced polymerase activity and increased virulence in mice				
PB2	L89V	89	V	V	V
	E627K	627	K	K	K
	H5 virus transmissible among ferrets				
PB1	H99Y	99	H	H	H
	I368V	368	I	V	V
PB1-F2	Full length		90 aa	90 aa	90 aa
	Increased virulence in mice				
M1	N30D	30	D	D	D
	T215A	215	A	A	A
M2	Antiviral resistance S31N (amantadine)	31	N	N	N
NS1	Increased virulence in mice P42S	42	S	S	S

* Single letters refer to the amino acid (aa) found in the noted gene at a specific site.

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表一. 3名新型H7N9流感病毒感染病人的基本資料、流行病學、病毒學特性、併發症、治療藥物，和臨床預後資料 – (I)

Table 1. Demographic, Epidemiologic, and Virologic Characteristics and Complications, Treatment, and Clinical Outcomes of Three Patients Infected with Avian-Origin Influenza A (H7N9) Virus.*

Characteristic	Patient 1	Patient 2	Patient 3
Age (yr)	87	27	35
Sex	Male	Male	Female
Occupation	Retired	Butcher	Housewife
Underlying conditions	COPD, hypertension	Hepatitis B	Depression, hepatitis B, obesity
Area of origin	Shanghai	Shanghai	Anhui
Exposure to chicken market in past 7 days	No	Yes	Yes
Date of illness onset	February 18, 2013	February 27, 2013	March 13, 2013
Date of admission	February 25, 2013	March 4, 2013	March 19, 2013
Admission to ICU	None	March 6, 2013	March 20, 2013
Date of specimen collection	February 26, 2013	March 5, 2013	March 20, 2013
Date of laboratory confirmation of virus	March 30, 2013	March 30, 2013	March 30, 2013
Viral isolation	A/Shanghai/1/2013 (H7N9)	A/Shanghai/2/2013 (H7N9)	A/Anhui/1/2013 (H7N9)

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表一. 3名新型H7N9流感病毒感染病人的基本資料、流行病學、病毒學特性、併發症、治療藥物，和臨床預後資料 – (II)

Table 1. Demographic, Epidemiologic, and Virologic Characteristics and Complications, Treatment, and Clinical Outcomes of Three Patients Infected with Avian-Origin Influenza A (H7N9) Virus.*

Characteristic	Patient 1	Patient 2	Patient 3
Complications			
Septic shock	No	No	Yes
ARDS	Yes	Yes	Yes
Acute renal damage	No	No	Yes
Encephalopathy	Yes	No	Yes
Rhabdomyolysis	No	Yes	Yes
Secondary infections	No	Yes†	Yes†
Oxygen therapy	Mask‡	Mechanical ventilation	Mechanical ventilation
Extracorporeal membrane oxygenation	No	No	Yes
Continuous renal-replacement therapy	No	No	Yes
Antibiotic therapy	Imipenem, moxifloxacin, and vancomycin	Cefoperazone–sulbactam, levofloxacin, and linezolid	Imipenem and vancomycin
Antiviral agent§	Oseltamivir (started on day 7)	Oseltamivir and amantadine (started on day 7)	Oseltamivir (started on day 8)
Glucocorticoid therapy	Yes	Yes	Yes
Intravenous immune globulin therapy	Yes	Yes	Yes
Length of stay in hospital	6 days	6 days	19 days
Date of death	March 4, 2013	March 10, 2013	April 9, 2013

* ARDS denotes acute respiratory distress syndrome, and CC
† Patients 2 and 3 were infected with carbapenem-resistant A
‡ This patient refused intubation and mechanical ventilation.
§ Oseltamivir was administered in Patient 1 on February 25, 2
tered. Oseltamivir was administered in Patient 2 on March

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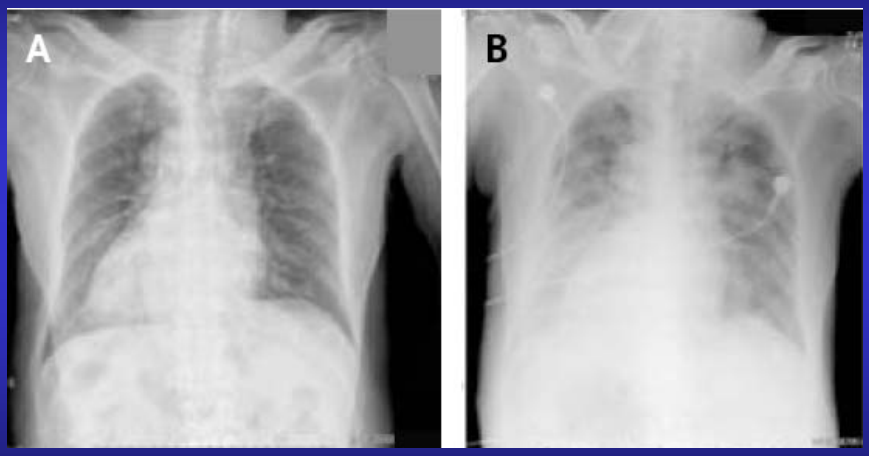
圖三 (A and B). 人類感染新型H7N9流感病毒的胸部X光影像 (Patient 1, 心臟在胸腔右側)



Day 6　　Day 9

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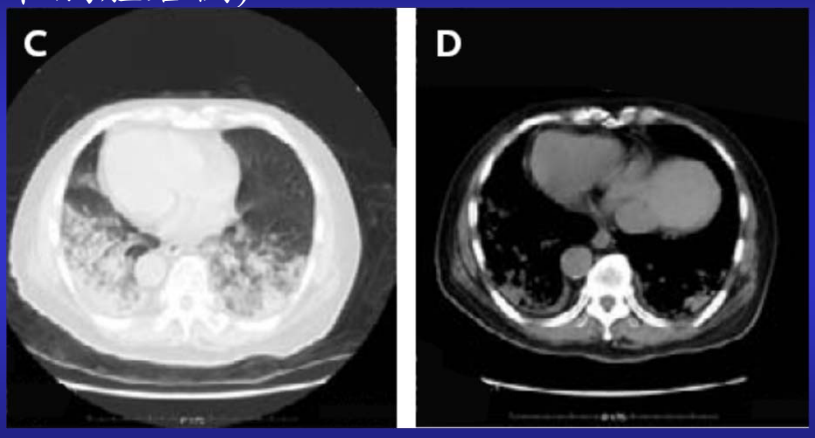
圖三 (C and D). 人類感染新型H7N9流感病毒的電腦胸部X光影像 (Patient 1, 心臟在胸腔右側)



Day 7 (住院第1日)　　Day 7 (住院第1日)

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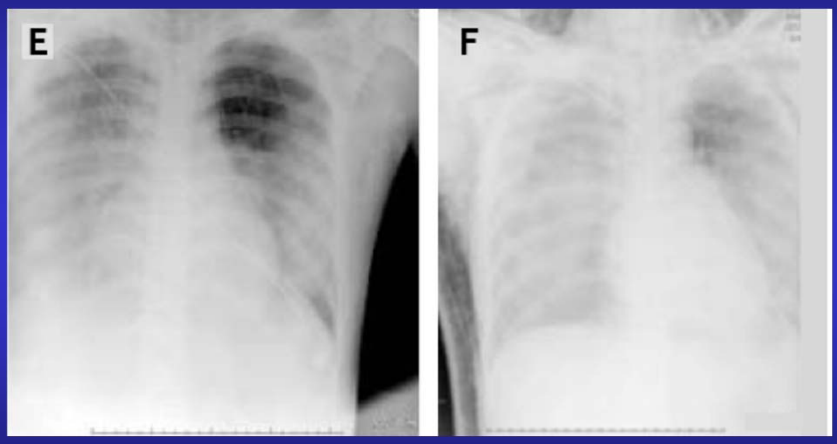
圖三 (E and F). 人類感染新型H7N9流感病毒的胸部X光影像 (Patient 2) (以症狀出現日期計算)



Day 7 Day 13

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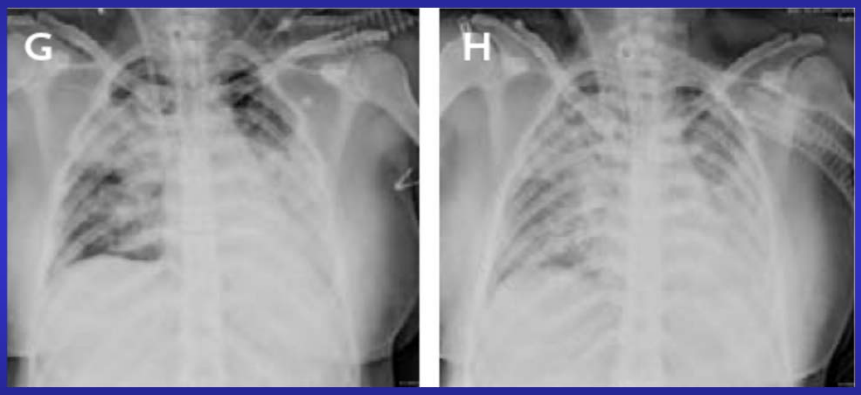
圖三 (G and H). 人類感染新型H7N9流感病毒的胸部X光影像 (Patient 3) (以症狀出現日期計算)



Day 7 Day 13

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ORIGINAL ARTICLE

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

研究方法與目的：自2013年的春天開始，中國大陸開始在人群流行新型H7N9禽類流行性感冒感染，有關此類新型禽流感病毒感染的臨床表現並無文獻報告。
研究方法：自醫療病歷收集自2013年5月開始的111名實驗室檢驗確定診斷新型H7N9禽流感病人的臨床資訊。
研究結果：在111名實驗室檢驗確定H7N9禽類流感病毒感染病人中，有76.6%病人收治加護病房治療，其中27.0%病人死亡。病人年齡中位數為61歲，其中42.3%病人的年齡超過65歲，且61.3%病人具有一種以上的原有疾病。發燒與咳嗽是最常見的症狀，住院時發現有108名病人有肺炎表現。、

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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

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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。

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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

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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)

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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 >25	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)

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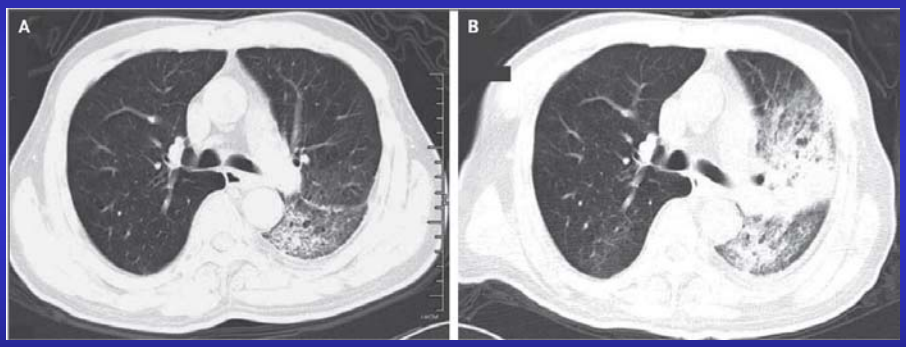
圖一. 一名68歲男性感染H7N9禽流感的連續電腦斷層影像檢查結果 – (I)



症狀出現第7日 (住院第1日)　　症狀出現第9日 (住院第3日)

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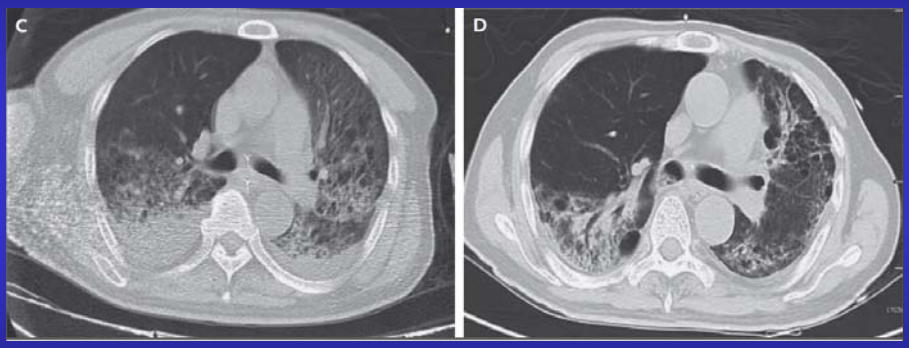
圖一. 一名68歲男性感染H7N9禽流感的連續電腦斷層影像檢查結果 – (II)



症狀出現第16日 (住院第10日)　　症狀出現第42日 (住院第36日) (出院)

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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 – (I)

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)

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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)

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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

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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/mm³	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

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5. 流感病毒感染的實驗室診斷方法

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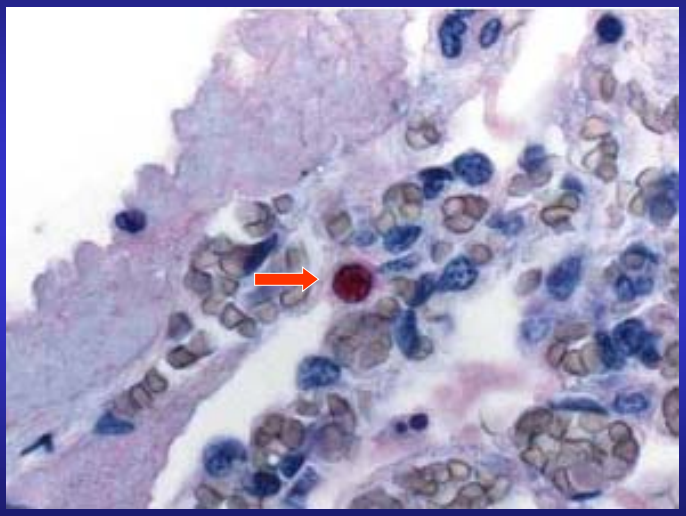
指標病人母親的肺部組織免疫螢光染色 (A/H5N1)



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

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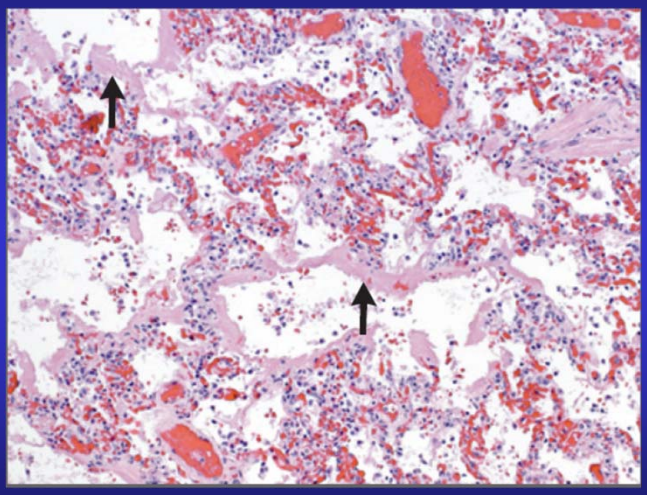
圖一. 一名13歲男性因感染H1N1A型新型流感死亡的肺部切片 – 肺泡傷害合併透明膜 (Hyaline Membrane) (H&E Stain)



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

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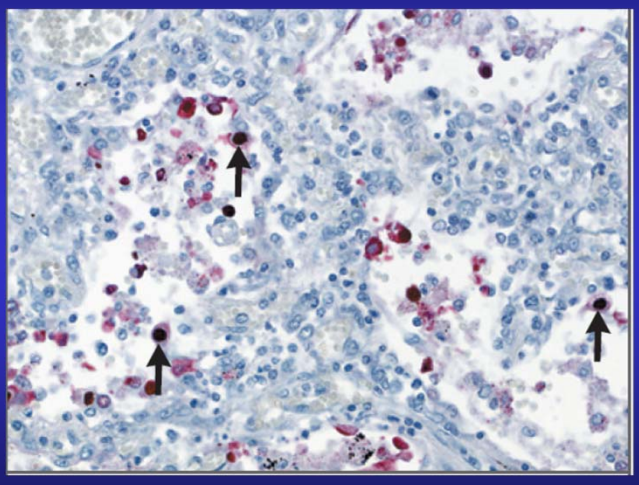
圖二. 一名55歲唐氏症合併B型肝炎女性感染 H1N1A型新型流感的肺部免疫染色病理切片 – 病毒抗原 (紅色) 和肺泡上皮細胞的細胞核 (箭頭)



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

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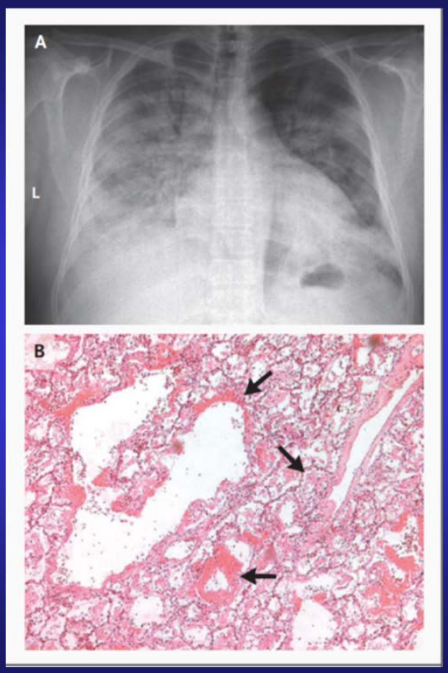

圖三. 墨西哥某病人於2009年經實驗室確定診斷為H1N1A型新型流感合併嚴重肺炎的胸部X光片 (A圖, 兩側肺部肺泡性與間質性浸潤) 和肺部病理切片 (B圖, 肺泡壁壞死, 中性白血球浸潤, 和透明膜 – hyaline membrane 的形成, H&E Stain)

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

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表二. 各種流行性感冒病毒的實驗室診斷方法 (方法種類、診斷標的、採集檢體種類，和診斷所需時間)

流感快篩的敏感度平均約30%，特異度80%以上。

TABLE 2 Diagnostic methods for identification of influenza virus

Tests	Influenza virus type detected	Samples acceptable	Time needed for test
Rapid influenza diagnostic methods 流感病毒快篩	A and B	Throat swab, nasopharyngeal swab, nasal swab,	<30 min
Reverse transcriptase PCR (RT-PCR) assay 反轉錄聚合酶反應	A and B	Throat swab, nasopharyngeal swab, nasal aspirate, sputum	<80 min
Nucleic acid amplification tests 核苷酸複製試驗	A and B	Nasopharyngeal swab	<30 min
Culture 流感病毒培養	A and B	Throat swab, nasal swab or wash, sputum	>3 days

Javanian M et al. J Med Virol. 2021;93:4638-4646.

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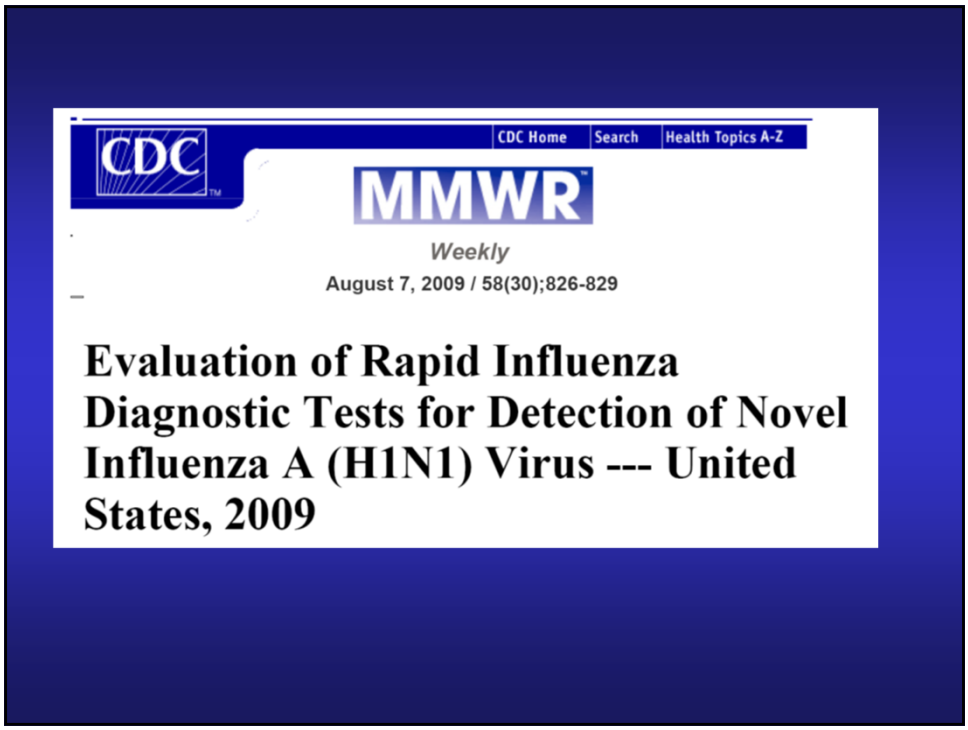

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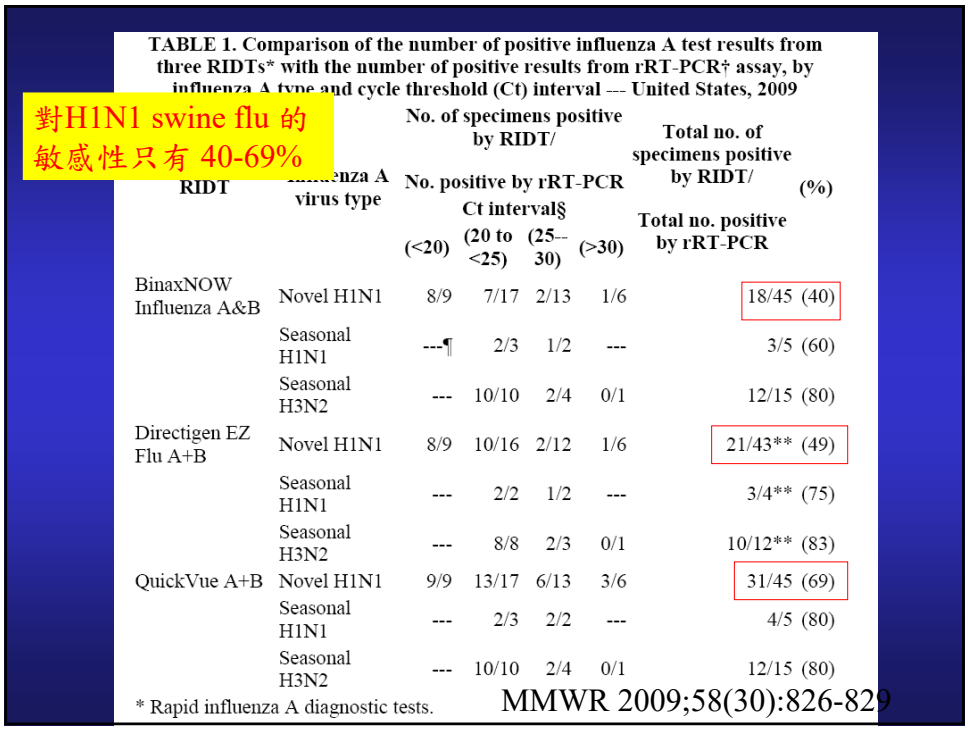

TABLE 1. Comparison of the number of positive influenza A test results from three RIDTs* with the number of positive results from rRT-PCR† assay, by influenza A type and cycle threshold (Ct) interval --- United States, 2009

對H1N1 swine flu 的敏感性只有 40-69%

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

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BinaxNow® Influenza A&B 22 tests/pack

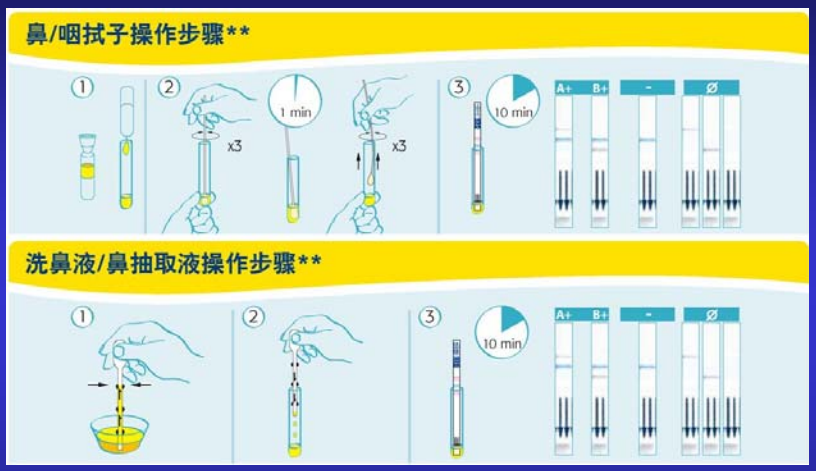
in vitro immunochromatographic assay

93

QuickVue® 25 tests/pack BioMerieux

in vitro immunochromatographic assay

94



Rapid Influenza Diagnostic Test (RIDT) 操作方法

in vitro immunochromatographic assay

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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

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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

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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

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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

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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

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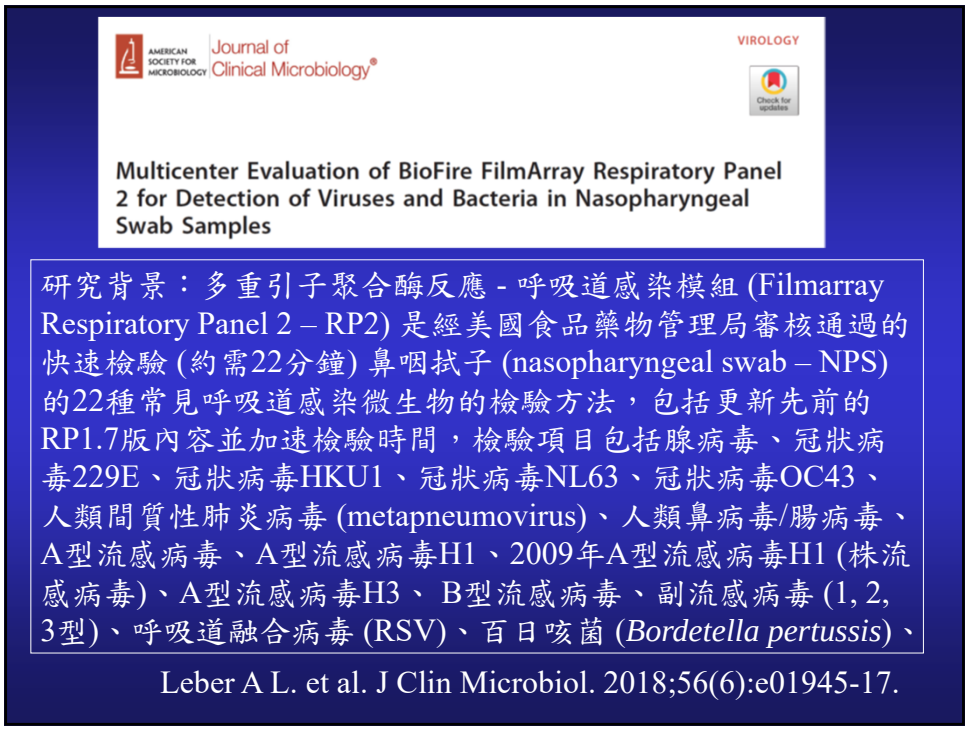
Journal of Clinical Microbiology
VIROLOGY
Multicenter Evaluation of BioFire FilmArray Respiratory Panel 2 for Detection of Viruses and Bacteria in Nasopharyngeal Swab Samples
研究背景：多重引子聚合酶反應 - 呼吸道感染模組 (Filmarray Respiratory Panel 2 – RP2) 是經美國食品藥物管理局審核通過的快速檢驗 (約需22分鐘) 鼻咽拭子 (nasopharyngeal swab – NPS) 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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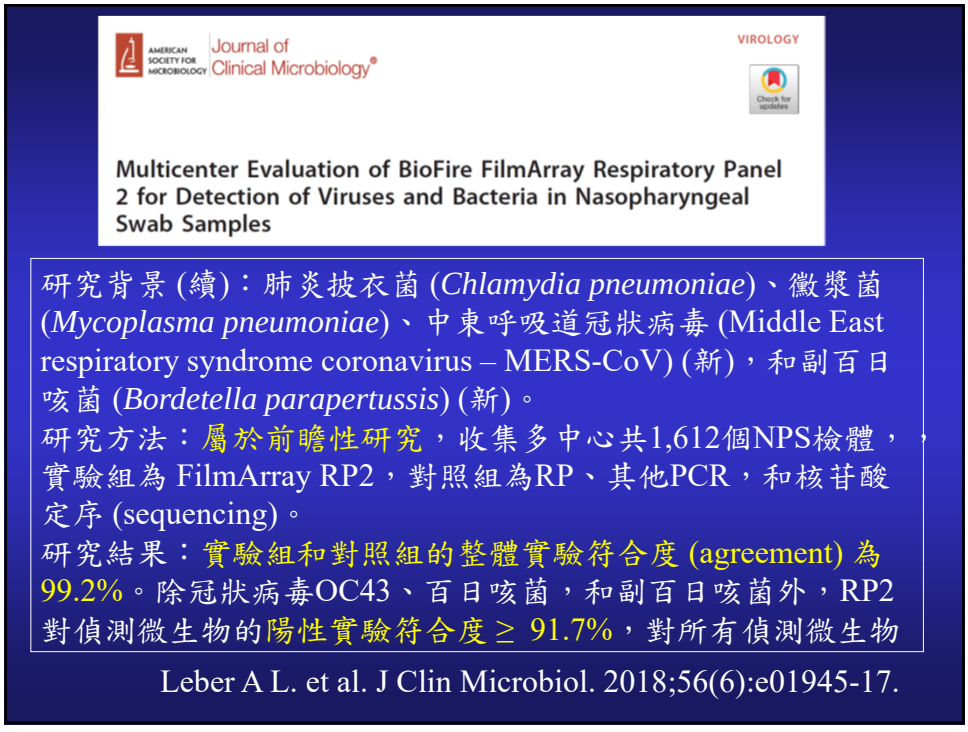
Journal of Clinical Microbiology
VIROLOGY
Multicenter Evaluation of BioFire FilmArray Respiratory Panel 2 for Detection of Viruses and Bacteria in Nasopharyngeal Swab Samples
研究背景 (續)：肺炎披衣菌 (Chlamydia pneumoniae)、黴漿菌 (Mycoplasma pneumoniae)、中東呼吸道冠狀病毒 (Middle East respiratory syndrome coronavirus – MERS-CoV) (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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Journal of Clinical Microbiology

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.

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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/

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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/

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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

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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.

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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.

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Clinical Application of Next Generation Sequencing (NGS) – 次世代定序的臨床應用

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Clinical Microbiology and Infection 24 (2018) 335–341

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journal homepage: www.clinicalmicrobiologyandinfection.com

Review

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

J. Besser, H.A. Carleton, P. Gerner-Smidt*, R.L. Lindsey, E. Trees

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

Besser J. et al. Clin Microbiol Infect. 2018;24:335-341.

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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 (WGS) 實驗步驟圖示

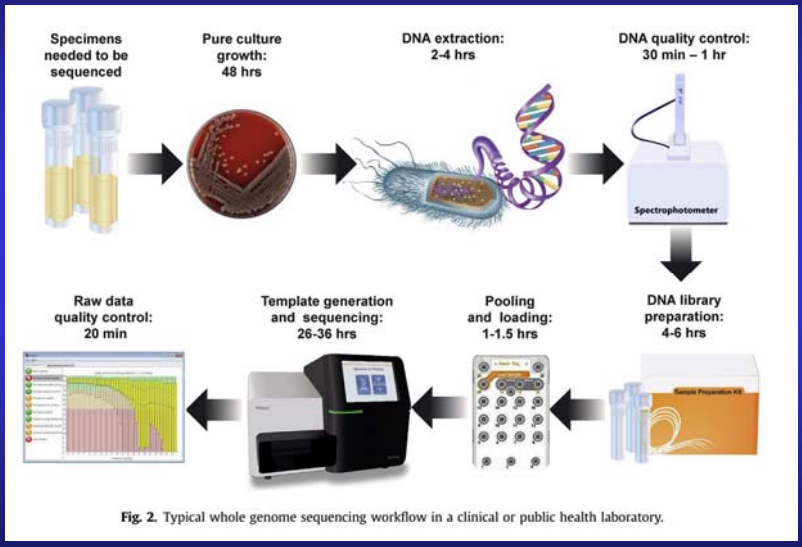

Fig. 2. Typical whole genome sequencing workflow in a clinical or public health laboratory.

Besser J. et al. Clin Microbiol Infect. 2018;24:335-341.

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

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

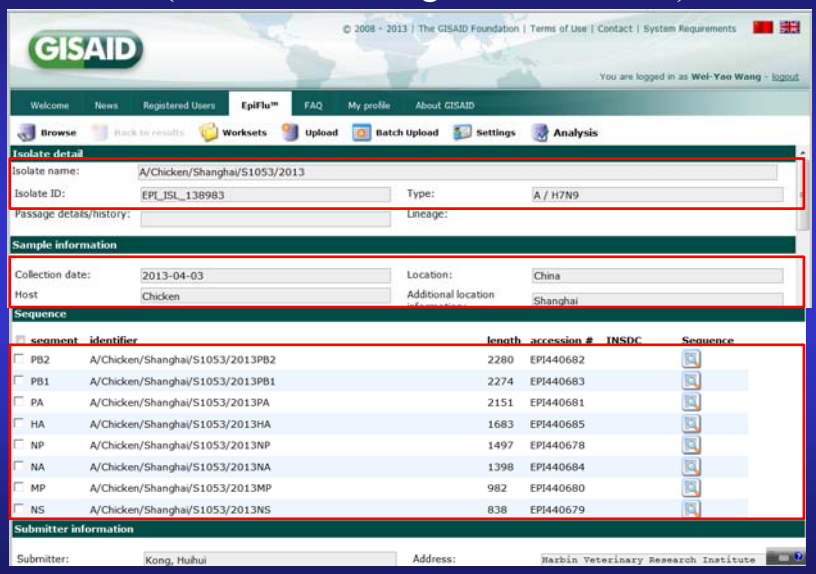
Platform \ Instrument	Throughput range (Gb)[a]	Read length (bp)	Strength	Weakness
Sanger sequencing				
ABI 3500/3730	0.0003	Up to 1 kb	Read accuracy and length	Cost and throughput
Illumina				
MiniSeq	1.7–7.5	1×75 to ×150	Low initial investment	Run and read length
MiSeq	0.3–15	1×36 to 2×300	Read length, 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.

Besser J. et al. Clin Microbiol Infect. 2018;24:335-341.

112

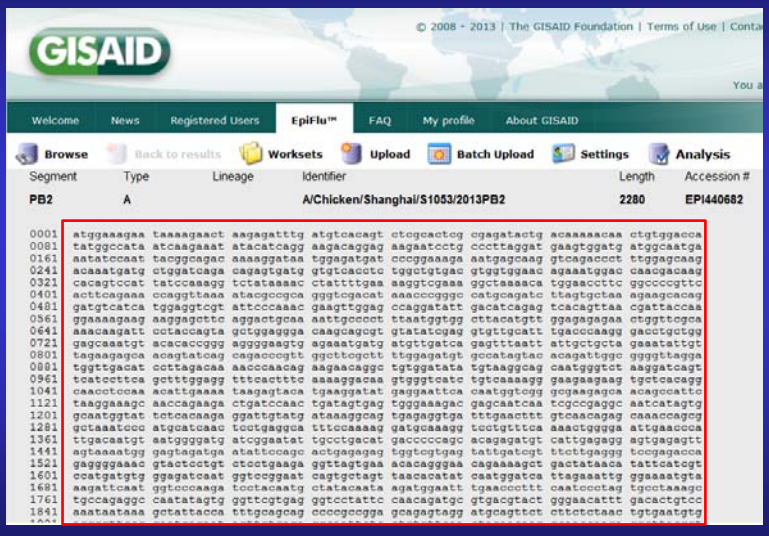
H7N9A型禽流感病毒8段基因序列）(哈爾濱畜牧研究所)
(A/Chicken/Shanghai/S1053/2013)



EpiFlu Database, GISAID, April 8th, 2013

113

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

114

6. 流行性感冒病毒感染 – 結論

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表. 增加流行性感冒的罹病率與死亡率相關因子 - (I)

Panel: Factors associated with increased morbidity and mortality from influenza[1,4,9,12–19]

年齡：

1. 流感在大於65歲的老年族群增加死亡與住院比率的風險。
2. 大規模流感流行在年輕族群 (20-40歲) 增加死亡率的風險。
3. 流感在小於5歲 (特別小於2歲) 兒童族群增加住院率風險。

懷孕：

1. 在懷孕第三期時罹患流感的罹病率 (嚴重程度) 最高。
2. 在1918年和1957年全球流感大流行時懷孕病人族群死亡率最高。
3. 在2009年全球流感大流行和流行間隔期孕婦罹患流感增加住院比率。
4. 孕婦因罹患流感住院時對胎兒預後不佳。

Paules C and Subbarao K. Lancet. 2017;390:696-708.

116

表. 增加流行性感冒的罹病率與死亡率相關因子 - (II)

免疫功能低下族群：
1. 流感在幹細胞移植、實體器官移植，和接受化學治療的病人族群增加死亡風險。
2. 流感在人類免疫不全病毒感染 (HIV) 族群且CD4 細胞數量降低且未接受抗反轉錄病毒藥物 (HAART) 增加死亡風險。
3. 流感在接受免疫功能調節藥物族群 (決定於免疫功能抑制程度) 增加死亡風險。

合併原有疾病：
1. 包括神經肌肉疾病、認知障礙、肺部疾病、心血管疾病、腎臟疾病、肝臟疾病、糖尿病、重度酒精濫用，和肥胖病人族群增加死亡風險。
2. 因其他疾病合併流感亦增加住院率和死亡風險。
4. 孕婦因罹患流感住院時對胎兒預後不佳。

基因的易感受性：
1. 具特定基因 (干擾素誘發經膜蛋白 - IFITM3) 序列增加因流感住院風險。

interferon-stimulated gene

Paules C and Subbarao K. Lancet. 2017;390:696-708.

117

Salzburg, 2017.

感謝您的參與並歡迎討論

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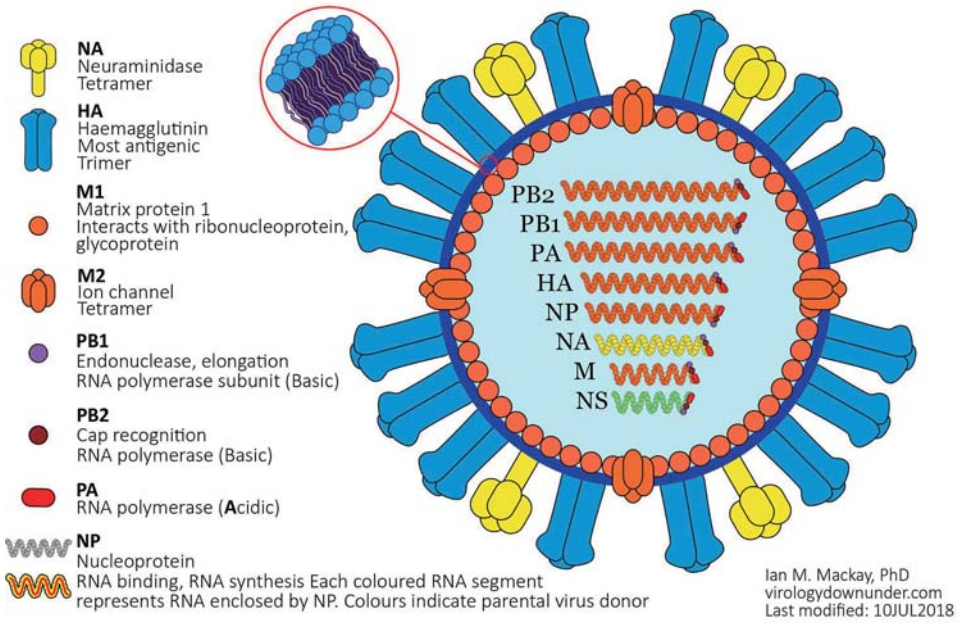
流行性感冒之
抗病毒藥物治療及疫苗預防

中山附醫 兒童感染科 潘蕙嫻

Outline

- **抗病毒藥物介紹**
- **抗病毒藥物的成效及給予時機**
- **流感疫苗的介紹**
- **流感疫苗的政策與展望**

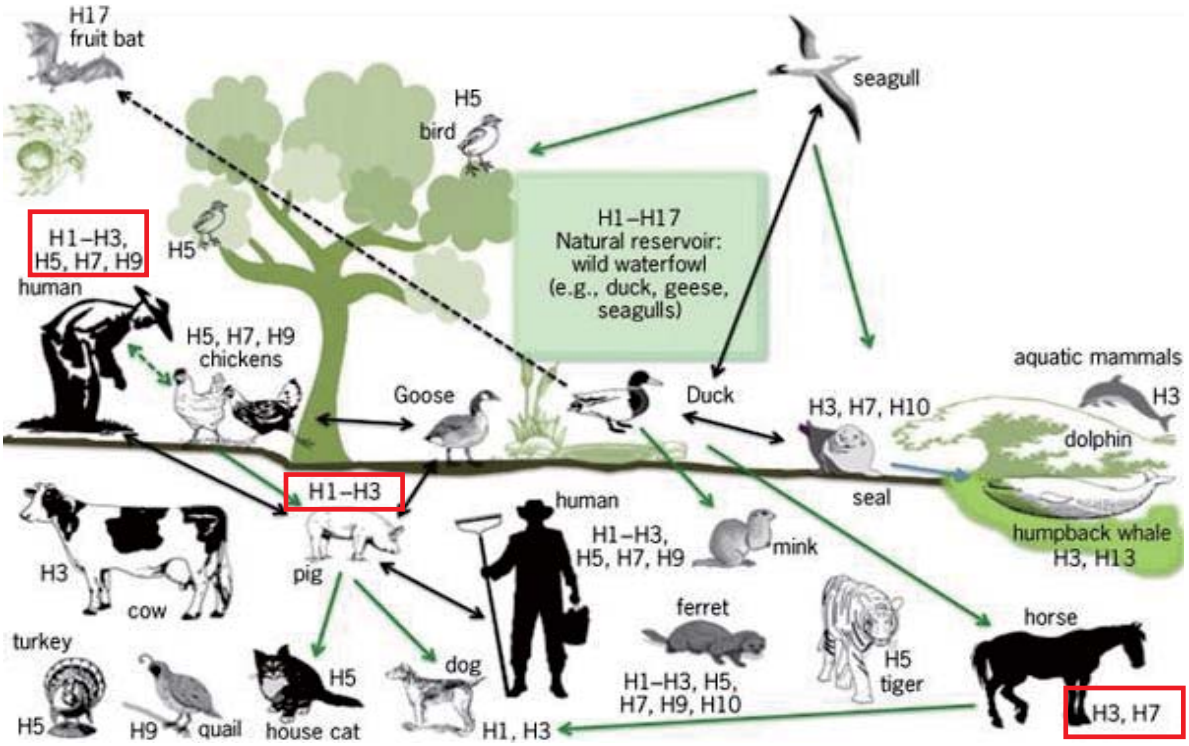
病毒結構



https://figshare.com/articles/Influenza_virus/6817112

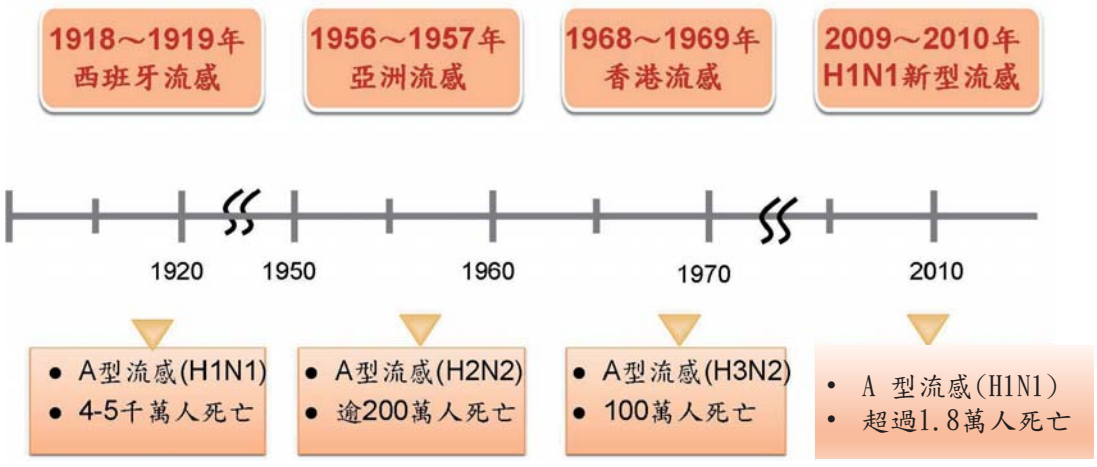
流感病毒的基本構造及分型

- **正黏液病毒科(Orthomyxoviridae)**
- **基因體含8段(A、B型)或7段(C、D型)單股RNA**
- **依NP及M蛋白可分為A型、B型、C型及D型**
  - **A型：人畜共通，會感染人類、哺乳動物與鳥類**
  - B型：只會感染人類
  - C型：感染人類後不造成明顯臨床症狀
  - D型：目前僅主要感染牛隻，對人類是否有致病性仍未知
- **A型流感又可依外套膜上的HA與NA 2種醣蛋白分為各種分型**
- 血球凝集素(Hemagglutinin, HA)，共有18種
- 神經胺酸酶(Neuraminidase, NA)，共有11種



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

二十世紀歷史上流感的大流行
(Influenza pandemics)

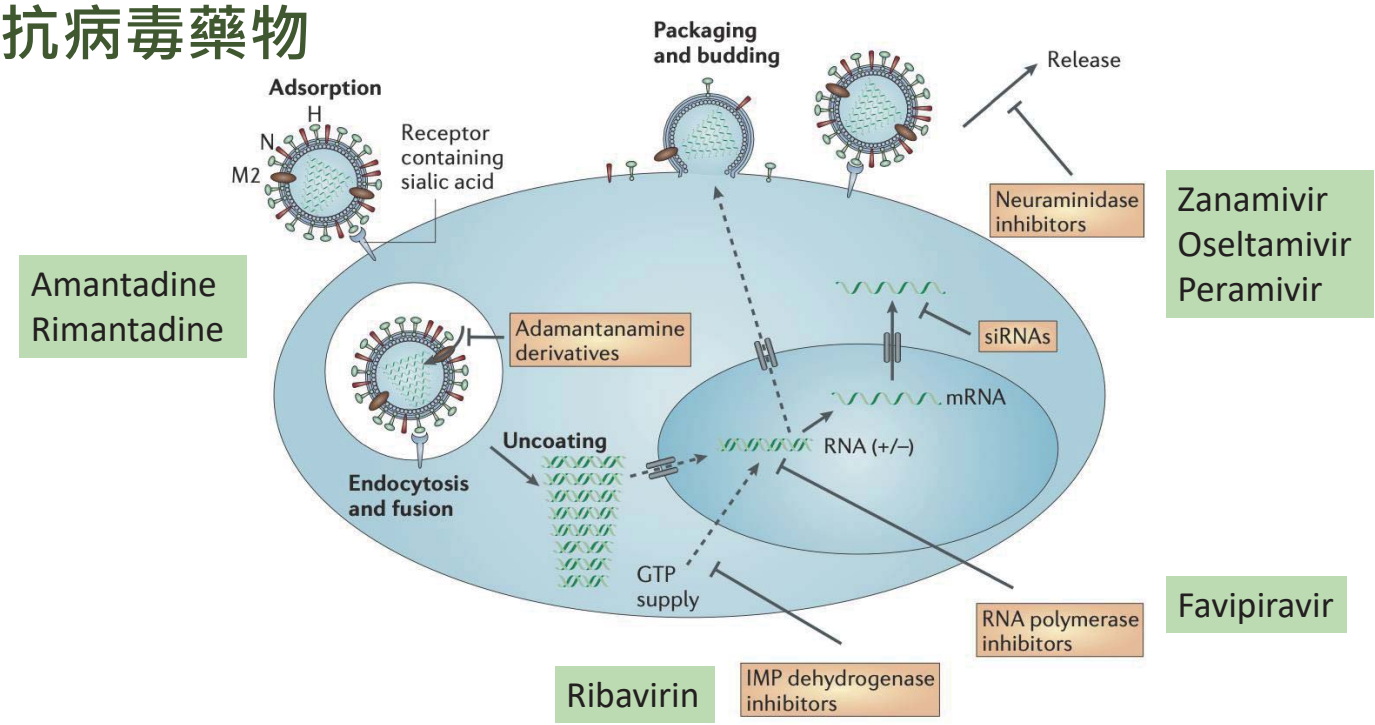


Year	Subtype	Estimate Death (million)	Origin of gene						
			NA	PA	PB1	PB2	NP	M	NS
1918	H1N1	50~100							
1957	H2N2	1~4							
1968	H3N2	1							
2009	H1N1	~0.018							

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

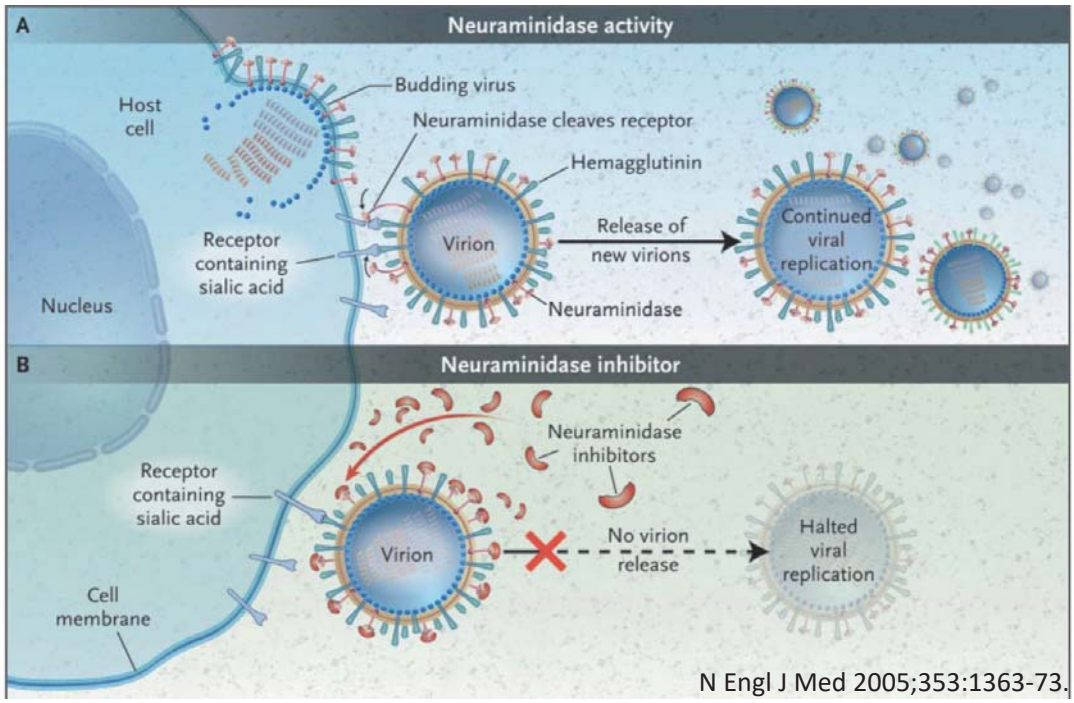
抗病毒藥物介紹

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

Baloxavir(Xofluza®)

□2018年2月在日本核准上市

- 適用於體重10公斤以上孩童及成人
- 上市後迅速成為日本市佔率第一的流感抗病毒藥劑

□2018年10月於美國核准上市

- 適用於12歲以上孩童及成人，發病後48小時內

□2019年取得我國藥證

- 適應症
  - 1. 治療成人及12歲以上兒童之A型及B型流行性感冒病毒急性感染
  - 2. 成人及12歲以上兒童密切接觸流感病人後預防流行性感冒
  - 用法用量：
    - 40-80公斤成人單次20 mg錠2錠 / 80公斤以上成人單次20mg錠4錠
    - 無健保給付

https://www.xofluza.com/hcp/why-xofluza/mechanism-of-action.html

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)

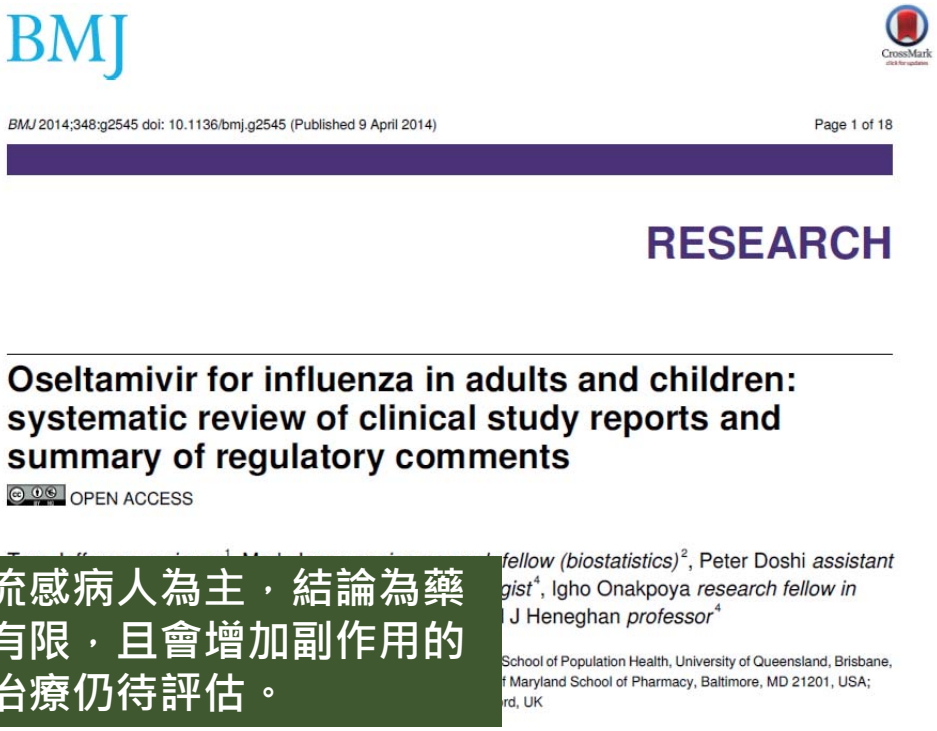
- 類流感等群聚事件經疾病管制署各區管制中心防疫醫師認定需用藥者 註：選填此項者需填寫群聚編號
- 新型A型流感極可能/確定病例之密切接觸者(接觸者名冊經傳染病防治醫療網區正/副指揮官或其授權人員研判需給藥者) 註：選填此項者需填寫所接觸之個案的法傳編號
- 動物流感發生場所撲殺清場工作人員(接觸者名冊經傳染病防治醫療網區正/副指揮官或其授權人員研判需給藥者) 註：選填此項者需填寫禽畜場名稱或編號

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

抗病毒藥物的成效及給予時機



BMJ

BMJ 2014;348:g2545 doi: 10.1136/bmj.g2545 (Published 9 April 2014)

RESEARCH

Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments

OPEN ACCESS

…fellow (biostatistics)[2], Peter Doshi *assistant*
…gist[4], Igho Onakpoya *research fellow in*
… J Heneghan *professor*[4]

…School of Population Health, University of Queensland, Brisbane,
…f Maryland School of Pharmacy, Baltimore, MD 21201, USA;
…rd, UK

這些試驗主要以輕症的流感病人為主，結論為藥物可縮短病程，但效果有限，且會增加副作用的發生。是否用藥預防及治療仍待評估。

Efficacy of oseltamivir treatment started within 5 days of symptom onset to reduce influenza illness duration and virus shedding in an urban setting in Bangladesh: a randomised placebo-controlled trial

Alicia M Fry, Doli Goswami, Kamrun Nahar, Amina Tahia Sharmin, Mustafizur Rahman, Larisa Gubareva, Tasnim Azim, Joseph Bresee, Stephen P Luby, W Abdullah Brooks

Summary

Background Influenza causes substantial morbidity and mortality worldwide. Few data exist for the efficacy of neuraminidase inhibitors, which are the only readily available influenza treatment options, especially in low-income settings. We assessed the efficacy of treatment with the neuraminidase inhibitor oseltamivir to reduce patient illness and viral shedding in people with influenza, in whom treatment was started within 5 days of symptom onset, in an urban setting in Bangladesh.

Methods We undertook a double-blind, randomised, controlled trial between May, 2008, and December, 2010. Patients with a positive rapid influenza test identified by surveillance of households in Kamalapur, Bangladesh were randomly allocated on a 1:1 basis to receive oseltamivir or placebo twice daily for 5 days. Randomisation lists for individuals enrolled less than 48 h and 48 h or longer since illness onset were generated with permuted blocks of variable length between two and eight. Participants and study staff were masked to treatment assignment. Participants provided nasal wash specimens at enrolment and 2, 4, and 7 days after enrolment. Specimens were tested for influenza with reverse-transcription PCR. The primary endpoints were duration of clinical illness and duration of virus shedding in participants enrolled within 48 h since illness onset and the frequency of oseltamivir resistance during treatment. Analyses were intention to treat unless otherwise specified. This trial is registered with ClinicalTrials.gov, number NCT00707941.

Lancet Infect Dis 2014; 14: 109–18

Published Online November 22, 2013 http://dx.doi.org/10.1016/S1473-3099(13)70267-6

This online publication has been corrected. The corrected version first appeared at thelancet.com/infection on January 20,

(A M Fry MD, L Gubareva PhD, J Bresee MD, S P Luby MD); and International Centre for

隨機分配對照試驗發現，雖然在48小時之後才服藥，仍可以縮短一般流感病人之病程，減少病毒傳播

Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials

Joanna Dobson, Richard J Whitley, Stuart Pocock, Arnold S Monto

Summary

Background Despite widespread use, questions remain about the efficacy of oseltamivir in the treatment of influenza. We aimed to do an individual patient data meta-analysis for all clinical trials comparing oseltamivir with placebo for treatment of seasonal influenza in adults regarding symptom alleviation, complications, and safety.

Methods We included all published and unpublished Roche-sponsored randomised placebo-controlled, double-blind trials of 75 mg twice a day oseltamivir in adults. Trials of oseltamivir for treatment of naturally occurring influenza-like illness in adults reporting at least one of the study outcomes were eligible. We also searched Medline, PubMed, Embase, the Cochrane Central Register of Controlled Trials, and the ClinicalTrials.gov trials register for other relevant trials published before Jan 1, 2014 (search last updated on Nov 27, 2014). We analysed intention-to-treat infected, intention-to-treat, and safety populations. The primary outcome was time to alleviation of all symptoms analysed with accelerated failure time methods. We used risk ratios and Mantel-Haenszel methods to work out complications, admittances to hospital, and safety outcomes.

Findings We included data from nine trials including 43[illegible] noted a 21% shorter time to alleviation of all symptoms 95% CI 0·74–0·85; p<0·0001). The median times to alle groups (difference −25·2 h, 95% CI −36·2 to −16·0). Fo effect was attenuated (time ratio 0·85) but remained intention-to-treat infected population, we noted fewer low than 48 h after randomisation (risk ratio [RR] 0·56, 95% risk difference −3·8%, 95% CI −5·0 to −2·2) and also fe 0·17–0·81; p=0·013; 0·6% oseltamivir, 1·7% placebo, ris oseltamivir increased the risk of nausea (RR 1·60, 95% risk difference 3·7%, 95% CI 1·8–6·1) and vomiting (R 3·3% placebo, risk difference 4·7%, 95% CI 2·7–7·3). W or serious adverse events.

Interpretation Our findings show that oseltamivir in a alleviation, reduces risk of lower respiratory tract complications, and admittance to hospital, but increases the occurrence of nausea and vomiting.

Lancet 2015; 385: 1729–37

Published Online January 30, 2015 http://dx.doi.org/10.1016/S0140-6736(14)62449-1

This online publication has been corrected. The corrected version first appeared at thelancet.com on February 2, 2015

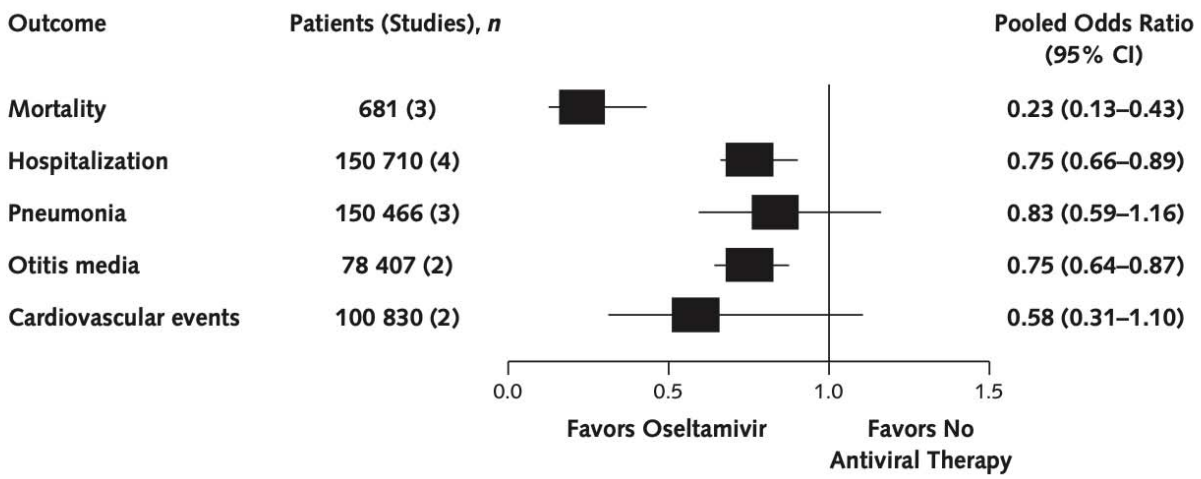
See Comment page 1700

Department of Medical Statistics, London School of

統合分析隨機分配試驗中4,328名病人，發現成年流感病人服用抗病毒藥劑能縮短症狀、降低下呼吸道感染以及住院風險

1. 平均緩解時間：97.5 hrs / 122.7 hrs
2. 下呼吸道感染：4.9% / 8.7%
3. 住院風險：0.6% / 1.7%

Efficacy of Oseltamivir



Evidence summary for Oseltamivir

Outcome	Direct	Indirect	Conclusion
Mortality	8 observational studies (n=4725), aOR 0.38 (95% CI 0.19–0.75), low-quality evidence.	No data	Oseltamivir therapy may reduce mortality in this patient population. Low confidence.
Hospitalization	2 observational studies (n=14 445), aOR 0.65 (95% CI 0.48–0.87), low-quality evidence.	12 RCTs (n=7765), RR 1.07 (95% CI 0.69–1.64), low-quality evidence.	Oseltamivir may reduce hospitalization in this patient population. Low confidence.
ICU admission/mechanical ventilation	4 observational studies (n=4074), aOR 1.07 (95% CI 0.54–2.13), low-quality evidence.	No data	Oseltamivir may have little to no effect on ICU admission/ mechanical ventilation in this patient population. Low confidence.
Complications: pneumonia	2 observational studies (n=14 445), aOR 0.80 (95% CI 0.62–1.04), low-quality evidence.	12 RCTs (n=6494), RR 0.76 (95% CI 0.53–1.09), low-quality evidence.	Oseltamivir therapy may lower the risk of pneumonia in this patient population. Low cont
Complications: cardiac events, including myocardial infarction, stroke, angina, heart failure, sudden cardiac death	1 observational study (n=37 482), aOR 0.41 (95% CI 0.34–0.49), low-quality evidence.	6 RCTs (n=3943), RR 0.49 (95% CI 0.25–0.97), low-quality evidence.	Oseltami lower ris in this pa Low cont
Complications: neuropsychiatric events, including hallucination, psychosis, schizophrenia, paranoia, aggression/hostility and attempted suicide	No data	8 RCTs (n=5616), RR 0.93 (95% CI 0.43–2.03), low-quality evidence and 3 observational studies (n=359 228), aOR 0.86 (95% CI 0.79–0.93), very low-quality evidence.	Oseltami to no eff neuropsy this patie confiden
Complications: serious adverse events (SAEs)	No data	13 RCTs (n=7324), RR 0.91 (95% CI 0.56–1.46), low-quality evidence.	Oseltami no effect Low confidence.
Persistent viral shedding	No data	4 observational studies (n=449), OR 0.51 (95% CI 0.21–1.23), very low-quality evidence.	It is uncertain whether oseltamivir has any effect on persistent viral shedding. Very low confidence.
Emergence of resistance	No data	6 observational studies (n=3549), OR 1.77 (95% CI 0.84–3.74), very low-quality evidence.	It is uncertain whether oseltamivir has any effect on emergence of resistance. Very low confidence.

Oseltamivir 降低

1. 62%死亡風險
2. 35%住院風險
3. 20%產生肺炎併發症的風險

https://apps.who.int/iris/bitstream/handle/10665/352453/9789240040816%20eng.pdf?sequence=1&isAllowed=y

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

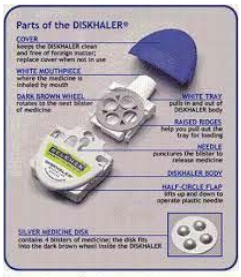


Figure 1: Parts of the DISKHALER

Evidence summary for Zanamivir

Outcome	Direct	Indirect	Conclusion
Mortality	1 observational study (n=87), aOR 0.47 (95% CI 0.02–8.97), very low-quality evidence.	16 RCTs, incomplete data leading to inability to generate a pooled estimate for all-cause mortality.	It is uncertain whether inhaled zanamivir therapy has any effect on the risk of death in this patient population. Very low confidence.
Hospitalization	No data	1 observational study (n=4674), aOR 0.58 (95% CI 0.30–1.13), very low-quality evidence.	It is uncertain whether inhaled zanamivir therapy has any effect on the risk of hospitalization in this patient population. Very low confidence.
ICU admission/mechanical ventilation	No data	1 observational study (n=87), aOR 1.18 (95% CI 0.29–4.83), very low-quality evidence.	It is uncertain whether inhaled zanamivir therapy has any effect on the risk ICU admission/mechanica ventilation in this patient population. Very low confidence.
Complications: pneumonia	No data	13 RCTs (n=6613), RR 0.87 (95% CI 0.57–1.32), low-quality evidence and 1 observational study (n=4674), OR 1.17 (95% CI 0.98–1.39), very low-quality evidence.	Inhaled zanamivir therapy may have little to no effec on the risk of pneumonia this patient population. Low confidence.
Complications: cardiac events, including myocardial infarction, stroke, angina, heart failure, sudden cardiac death	No data	11 RCTs (n=5204), RR 0.98 (95% CI 0.50–1.91), low-quality evidence.	Inhaled zanamivir therapy may have little to no effect on the risk of cardiac events in this patient population. Low confidence.

Zanamivir：uncertain
死亡風險、住院風險、重症插管風險

https://apps.who.int/iris/bitstream/handle/10665/352453/9789240040816%20eng.pdf?sequence=1&isAllowed=y

Peramivir

- 何時考慮使用
  - Severe hospitalized patients (ICU with organ failure)
  - Poor response to the other NAIs
    - Poor GI absorption of oral medication
    - Lower respiratory tract infection, difficult to using inhaled anti-viral agents
  - Avian flu (H7N9 influenza)
- 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 currently approved in the United States.

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 manufacturer to treat patients with life-threatening

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

N Engl J Med 2009; 361:1713-1714

Combination therapy

Oseltamivir, amantadine, and ribavirin vs. Oseltamivir

- Lower nasopharyngeal swab polymerase chain reaction at day 3
- No clinical endpoint improvements, including median duration of symptoms and duration of fever

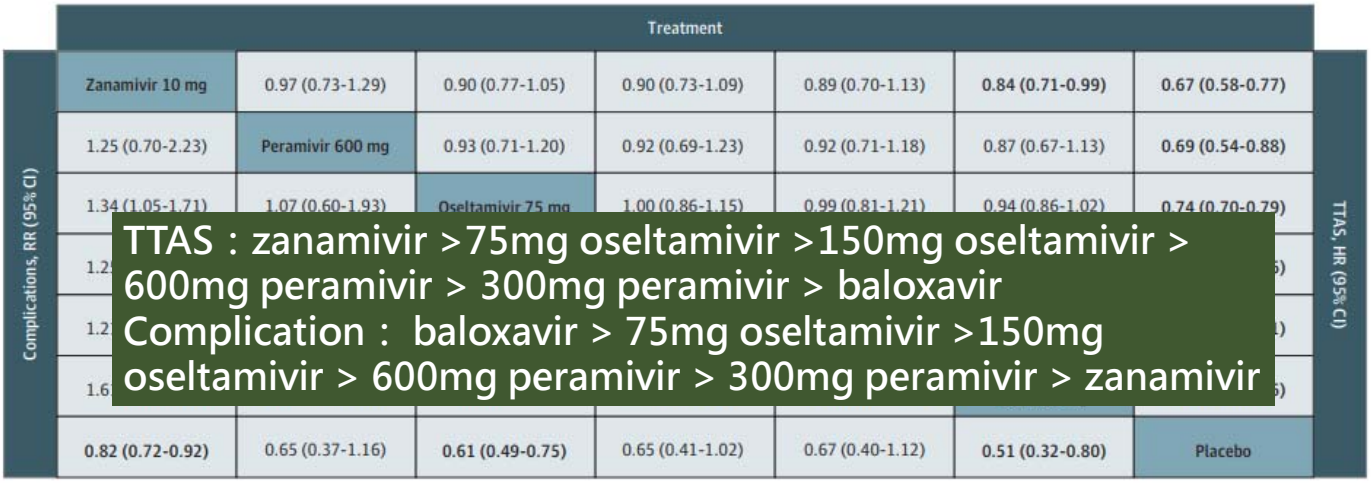
	Total (n=454)	Combination group (n=230)	Monotherapy group (n=224)	p value
Day 0	454	230	224	..
Median viral count, log_{10} copies/mL	6·5 (5·4–7·4)	6·4 (5·6–7·2)	6·7 (5·1–7·7)	..
≥LLOQ	421 (93%)	221 (96%)	200 (89%)	..
≥LOD, < LLOQ	13 (3%)	4 (2%)	9 (4%)	..
<LOD	20 (4%)	5 (2%)	15 (7%)	..
Day 3	437	221	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

Meta-analysis Estimates of Time to Alleviation of Influenza Symptoms (TTAS) and Complications



TTAS：zanamivir >75mg oseltamivir >150mg oseltamivir > 600mg peramivir > 300mg peramivir > baloxavir
Complication： baloxavir > 75mg oseltamivir >150mg oseltamivir > 600mg peramivir > 300mg peramivir > zanamivir

JAMA Network Open. 2021;4(8):e2119151. doi:10.1001/jamanetworkopen.2021.19151

Inhaled Zanamivir vs Oral Oseltamivir to Prevent Influenza-related Hospitalization or Death: A Nationwide Population-based Quasi-experimental Study 台灣健保資料庫

- 2013–2014, 2014–2015, 2015–2016三個流感季的抗病毒用藥資料與健保資料庫回顧統計
- 依年齡與風險因子配對後，比較診斷48小時內使用oseltamivir或zanamivir病患14天內因流感住院或死亡的比率

Table 2. Crude and Propensity Score–Weighted Incidence Rates of Hospitalization or Death Within 2 weeks[a]

	Crude			Propensity Score–Weighted			
Principal Diagnosis for Hospitalization or Death	Number of Events	Total Person- Days	Incidence Rate	Number of Events	Total Person-Days	Incidence Rate	Adjusted Hazard Ratio (95% Confidence Interval)
Influenza, influenza-like illness, or pneumonia[b]							
Zanamivir	10 840	579 476	0.019	14 998	579 461	0.026	1
Oseltamivir	6557	250 909	0.026	6557	250 901	0.026	1.01 (.96–1.06)
Influenza[c]							
Zanamivir	7229	579 949	0.012	10 156	579 943	0.018	1
Oseltamivir	4220	251 588	0.017	4220	251 557	0.017	0.96 (.90–1.02)
Influenza-like illness[d]							
Zanamivir							1
Oseltamivir							1.01 (.96–1.06)

Zanamivir與oseltamivir效果無統計顯著差異

CID 2022:XX (XX XX)

COVID-19 流行期間對流感治療的建議

- COVID-19與流感無法單純以症狀區分
- 即使已確診COVID-19，仍不能排除流感感染的可能性。病患有可能是流感、COVID-19，或共同感染(co infection)
- 需經**檢驗**才能分辨COVID-19與流感感染
- 若COVID-19患者有接受**類固醇**治療又同時有流感病毒感染，可能延長病毒排出時間
- COVID-19疫情期間，對流感檢驗和治療的建議並未改變

輕症門診病患之治療

- 若非屬重症高風險族群或高傳播族群，以支持性療法為主，大多數人可自行痊癒而不需使用抗流感病毒藥物。
- **高風險族群**建議於症狀出現48小時內盡速給予抗病毒藥物治療。
- **高傳播族群**可考慮於症狀出現48小時內給予抗病毒藥物治療。

- 高風險族群建議於症狀出現48 小時內盡速給予抗病毒藥物治療。
- 病程快速進展，出現危險病徵者，建議給予抗病毒藥物治療。
- 無危險徵兆之原本健康**兒童**，若希望縮短病程，可考慮給予治療。

並非所有輕症病患都需要抗病毒藥物治療

住院/重症病患之治療

- 建議**立即給予**抗病毒藥物治療。

- 任何因流感住院病患，不論疫苗接種史或發病時間，建議立即給予抗病毒藥物治療。

- 所有疑似流感住院兒童，均應立即給予抗病毒藥物治療。

住院/重症病患，不需等待確診，不論發病時間，均應立即給予抗病毒藥物治療

預防性投藥

- 發生群聚之**人口密集場所**(醫療院所、護理之家或長照機構等)，針對密切接觸者，可根據個別狀況(暴露時間長短、是否屬高風險族群、是否已接種流感疫苗等因素)，評估投與流感預防性藥物之必要性。
- 為避免藥物濫用與產生抗藥性，一般情形下抗流感藥物不建議用於預防性治療。若為機構或院內群聚感染、感染動物流感或新型流感、流感高危險群兒童，可考慮給予**預防性用藥10天**，使用一半劑量。

並非所有輕症病患都需要抗病毒藥物治療

疫苗

流感疫苗的介紹

流感的預防

- 接種**疫苗**
  - 預防流感最有效的方式
- 暴露後預防藥物
  - 特殊高風險族群、群聚事件
- 感染管制措施
  - 醫療機構、長期照顧機構、人口密集機構
- 個人衛生
  - 咳嗽禮節、手部衛生、戴口罩

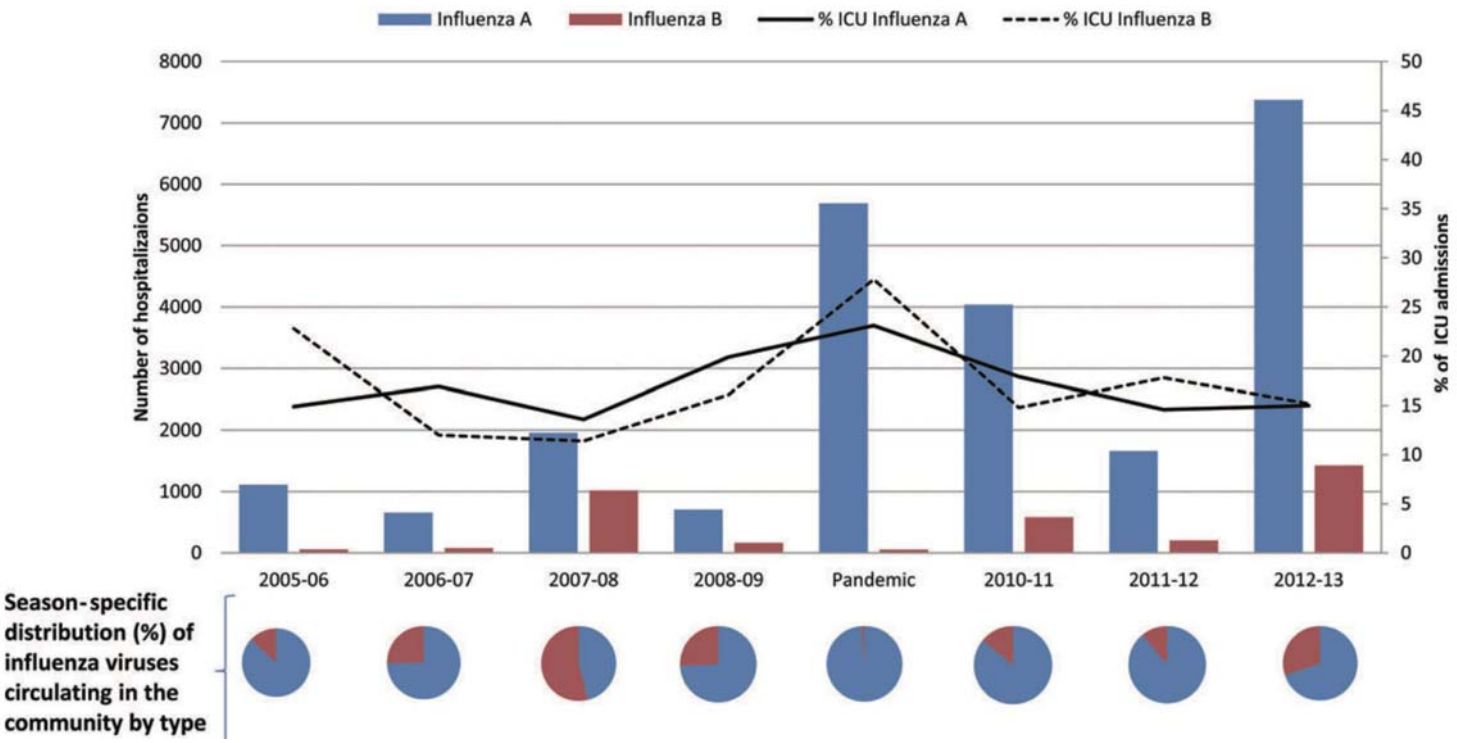
現行流感疫苗種類

分類	說明
疫苗株組成	三價(TIV，2A1B)、四價(QIV，2A2B)
製程	雞胚胎蛋培養、細胞培養、重組疫苗
疫苗病毒活性	不活化疫苗(IIV)、活性減毒疫苗(LAIV)
接種方式	肌肉注射、鼻噴劑、皮內注射
其他	高劑量疫苗(HD)、含佐劑疫苗(A)

Influenza vaccine in 2020-21 in UK

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



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

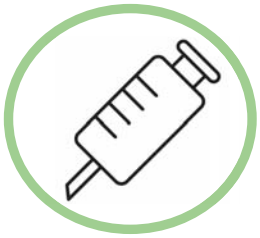
Clinical Infectious Diseases® 2014;59(11):1519–24

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）以下首次接種2 劑，且間隔至少4週
  - 國小學童集中接種，全面施打1劑，若仍自覺需要，至醫療院所自費接種第2劑

Disadvantages of egg-based vaccine

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

Cell - based influenza vaccine

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
6m-2 yrs	Post-marketing study, randomized, observer blind, multicenter study (2017-2019)

Frey S et al. *Clin Infect Dis.* 2010;51:997-1004
Bart S et al. *Hum Vaccin Immunother.* 2016;12(9):2278-2288
Hartvickson R et al. *Int J Infect Dis.* 2015;41:65-72

2022-2023年流感疫苗選株

- 雞胚胎疫苗
  - A/Victoria/2570/2019 (H1N1)pdm09
  - A/Darwin/9/2021 (H3N2)
  - B/Austria/1359417/2021 (B/Victoria)
  - B/Phuket/3073/2013 (B/Yamagata)
- 細胞培養疫苗
  - A/Wisconsin/588/2019 (H1N1)pdm09
  - A/Darwin/6/2021 (H3N2)
  - B/Austria/1359417/2021 (B/Victoria)
  - B/Phuket/3073/2013 (B/Yamagata)

流感疫苗的有效性

Vaccine Efficacy 效力 / Effectiveness 有效性

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)

Effectiveness

1 – adjusted odds ratio [aOR] × 100

- The result is acquired under normal circumstances in the real world

Drugs (2019) 79:1337–1348

FLU vaccine effectiveness varies by type or subtype

在此整合性研究分析中，H3N2：22-42%；B：42-56%；H1N1：56-64%

Pooled VE for all study participants irrespective of age.

Influenza type/subtypes and analyzed subgroups	No. of studies	Pooled VE for all seasons (95% CI)	I-squared statistic (%)	Publication bias (Egger's test p-value)
A(H1N1)pdm09				
Northern hemisphere	39	56 (51–60)	46.4	0.03
Southern hemisphere	11	64 (53–72)	0.0	0.54
Africa	1	44 (−63–81)	NA	NA
Asia	3	67 (37–83)	54.2	NA
Europe	22	51 (44–56)	0.0	0.66
North America	14	60 (53–66)	71.9	<0.01
Oceania	10	65 (54–73)	0.0	0.40
Antigenically similar vaccine	45	57 (53–61)	44.9	<0.01
Antigenically partially similar vaccine	5	42 (−4–68)	0.0	NA
Antigenically dissimilar vaccine	0	–	–	–
			66.9	0.83
			0.0	0.59
		97)	NA	NA
			34.8	NA
			45.6	0.59
			77.4	0.25
Oceania	10	41 (30–50)	0.0	0.17
Antigenically similar vaccine	24	36 (31–41)	18.9	0.67
Antigenically partially similar vaccine	11	22 (14–30)	27.2	0.12
Antigenically dissimilar vaccine	14	1 (−15 to 14)	46.8	0.95
Influenza B				
Northern hemisphere	36	42 (34–49)	71.3	0.59
Southern hemisphere	10	56 (45–64)	2.6	0.70
Africa	1	32 (−217–85)	NA	NA
Asia	4	18 (−49–54)	88.1	NA
Europe	19	40 (29–50)	50.3	0.27
North America	13	51 (46–55)	20.2	0.46
Oceania	9	56 (44–65)	10.4	NA
Antigenically similar vaccine	27	51 (47–55)	25.2	0.66
Antigenically partially similar vaccine	10	39 (20–54)	39.2	0.23
Antigenically dissimilar vaccine	9	20 (−9 to 41)	73.1	N/A

Vaccine 39 (2021) 1225–1240

流感疫苗的保護效果

Pooled VE for all study participants irrespective of age.

Influenza type/subtypes and analyzed subgroups	No. of studies	Pooled VE for all seasons (95% CI)	I-squared statistic (%)	Publication bias (Egger's test p-value)
A(H1N1)pdm09				
Northern hemisphere	39	56 (51–60)	46.4	0.03
Southern hemisphere	11	64 (53–72)	0.0	0.54
Africa	1	44 (-63–81)	NA	NA
Asia	3	67 (37–83)	54.2	NA
Europe	22	51 (44–56)	0.0	0.66
North America	14	60 (53–66)	71.9	
Oceania	10	65 (54–73)	0.0	
Antigenically similar vaccine	45	57 (53–61)	44.9	
Antigenically partially similar vaccine	5	42 (-4–68)	0.0	
Antigenically dissimilar vaccine	0	-	-	
A(H3N2)				
Northern hemisphere	38	22 (15–29)	66.9	
Southern hemisphere	11	42 (31–51)	0.0	
Africa	1	82 (−24 to 97)	NA	
Asia	4	1 (−33–27)	34.8	
Europe	19	16 (3–27)	45.6	
North America	15	29 (20–36)	77.4	
Oceania	10	41 (30–50)	0.0	
Antigenically similar vaccine	24	36 (31–41)	18.9	
Antigenically partially similar vaccine	11	22 (14–30)	27.2	
Antigenically dissimilar vaccine	14	1 (−15 to 14)	46.8	
Influenza B				
Northern hemisphere	36	42 (34–49)	71.3	
Southern hemisphere	10	56 (45–64)	2.6	
Africa	1	32 (−217–85)	NA	
Asia	4	18 (-49–54)	88.1	
Europe	19	40 (29–50)	50.3	0.27
North America	13	51 (46–55)	20.2	0.46
Oceania	9	56 (44–65)	10.4	NA
Antigenically similar vaccine	27	51 (47–55)	25.2	0.66
Antigenically partially similar vaccine	10	39 (20–54)	39.2	0.23
Antigenically dissimilar vaccine	9	20 (−9 to 41)	73.1	N/A
All influenza				
Northern hemisphere	58	37 (32–42)	79.8	0.92
Southern hemisphere	18	54 (48–59)	0.0	0.11
Africa	5	62 (38–77)	39.4	N/A
Asia	7	23 (−8 to 45)	83.4	N/A
Europe	34	34 (25–42)	65.7	0.42
North America	17	45 (39–50)	86.0	0.05
Oceania	13	53 (47–58)	0.0	0.19
Antigenically similar vaccine	46	49 (45–53)	61.5	0.01
Antigenically partially similar vaccine	26	27 (20–34)	43.4	0.53
Antigenically dissimilar vaccine	4	−9 (-28–8)	30.4	N/A

VE = vaccine effectiveness; NA = not applicable.

- 流感疫苗的保護力因**年齡**或**身體狀況**不同而異，平均約可達30-80%
- 疫苗保護效果亦需**視當年疫苗株與實際流行的病毒株型別是否相符**，一般保護力會隨病毒型別差異加大而降低

Vaccine 39 (2021) 1225–1240

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)
					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。在6個月以上至17歲族群中保護力最好(>50%)

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

The Journal of Infectious Diseases

MAJOR ARTICLE

Influenza Vaccine Effectiveness Against Hospitalization in the United States, 2019–2020

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Background. Influenza causes significant morbidity and mortality and stresses hospital resources during periods of increased circulation. We evaluated the effectiveness of the 2019–2020 influenza vaccine against influenza-associated hospitalization in the United States.

Methods. We included adults hospitalized with acute respiratory illness at 14 hospitals and tested for influenza viruses by reserve-transcription polymerase chain reaction. Vaccine effectiveness (VE) was estimated by comparing the odds of current-season influenza vaccination in test-positive influenza cases vs test-negative controls, adjusting for confounders. VE was stratified by age and major circulating influenza types along with A(H1N1)

Results. A total of 3116 participants were included, inclu seven percent (n = 2079) received vaccination. Overall adju 27%–52%). VE against A(H1N1)pdm09 viruses was 40% (95 A(H1N1)pdm09 subgroups (representing 90% of sequenced 34%–75%) whereas no VE was observed against the other group (5A + 156K) (–1% [95% CI, –61% to 37%]).

Conclusions. In a primarily older population, influenza vaccination was associated with a 41% reduction in risk of hospitalized influenza illness.

Keywords. influenza; vaccine effectiveness; hospitalization; elderly; immunocompromised.

2019-2020年美國流感季流感疫苗效果41%，接種流感疫苗可降低4成流感住院風險。

Clinical Infectious Diseases

MAJOR ARTICLE

Influenza Vaccine Effectiveness for Prevention of Severe Influenza-Associated Illness Among Adults in the United States, 2019–2020: A Test-Negative Study

Carlos G. Grijalva,[1,a] Leora R. Feldstein,[2,a] H. Keipp Talbot,[1] Michael Aboodi,[3] Adrienne H. Baughman,[1] Samuel M. Brown,[4] Jonathan D. Casey,[1] Heidi L. Erickson,[5] Matthew C. Exline,[6] D. Clark Files,[7] Kevin W. Gibbs,[7] Adit A. Ginde,[8] Michelle N. Gong,[3] Natasha Halasa,[1] Akram Khan,[9] Christopher J. Lindsell,[1] Samuel K. Nwosu,[1] Ithan D. Peltan,[4] Matthew E. Prekker,[5] Todd W. Rice,[1] Nathan I. Shapiro,[10] Jay S. Steingrub,[11] William B. Stubblefield,[1] Mark W. Tenforde,[2] Manish M. Patel,[2] and Wesley H. Self[1]; for the Influenza and Other Viruses in the Acutely Ill (IVY) Network[b]

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Background. Influenza vaccine effectiveness (VE) against a spectrum of severe disease, including critical illness and death, remains poorly characterized.

Methods. We conducted a test-negative study in an intensive care unit (ICU) network at 10 US hospitals to evaluate VE for preventing influenza-associated severe acute respiratory infection (SARI) during the 2019–2020 season, w drifted A/H1N1 and B-lineage viruses. Cases were adults hospitalized in the ICU and a targete spectrum of severity) with laboratory-confirmed, influenza-associated SARI. Test-negative con hospital, timing of admission, and care location (ICU vs non-ICU). Estimates were adjusted for ag

Results. Among 638 patients, the median (interquartile) age was 57 (44–68) years; 286 (and 42 (6.6%) died during hospitalization. Forty-five percent of cases and 61% of controls overall VE of 32% (95% CI: 2–53%), including 28% (–9% to 52%) against influenza A and was higher in adults 18–49 years old (62%; 95% CI: 27–81%) than those aged 50–64 years ((–3%; 95% CI: –97% to 46%) ($P = .0789$ for interaction). VE was significantly higher against influenza-associated death (86%, 95% CI: 4–96%) than nonfatal influenza illness.

Conclusions. During a season with drifted viruses, vaccination reduced severe influenza-associated illness among adults by 32%. VE was high among young adults.

Keywords. influenza; vaccine effectiveness; critical illness; vaccination; immunization.

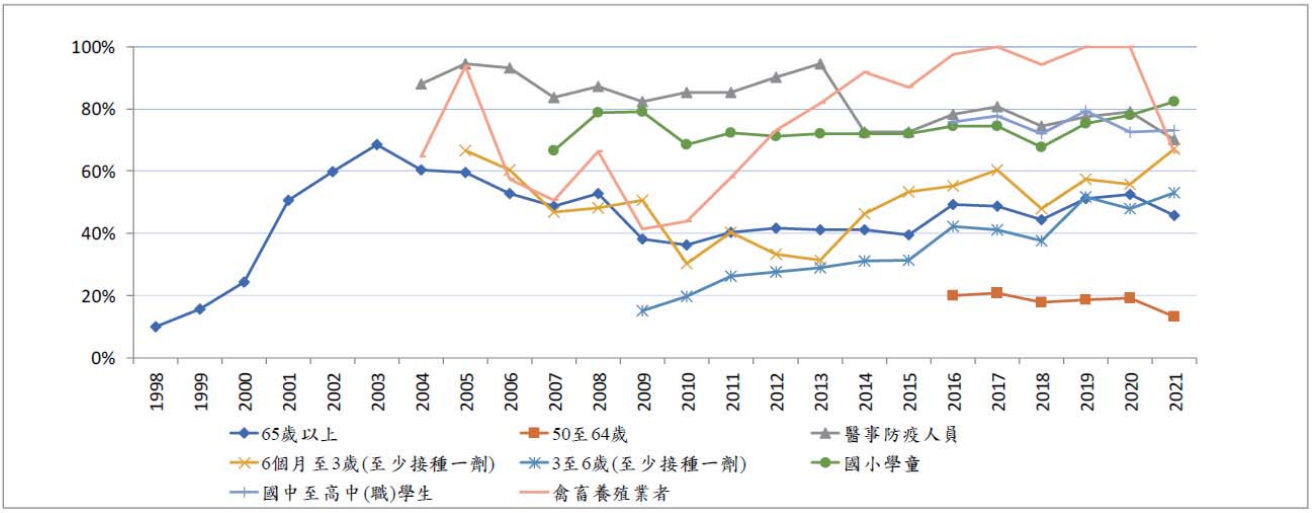
2019-2020年美國流感季流感疫苗效果降低32%流感重症風險。
在18-49歲族群中成效最好。

流感疫苗的政策與展望

公費流感接種對象

- 滿6個月以上至國小入學前幼兒
- 國小、國中、高中、高職、五專一至三年級學生
- 50歲以上成人
- 高風險慢性病、罕見疾病及重大傷病患者
- 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
- 安養、養護、長期照顧等機構住民及其所屬工作人員
- 醫事及衛生等單位之防疫相關人員
- 禽畜養殖等相關行業工作人員、動物園工作人員及動物防疫人員

歷年各類對象流感疫苗接種率



109年度流感疫苗接種計畫成果　　統計日期：110/8/31

接種對象	應接種數	接種數	接種率
65歲以上長者/機構對象*	3,722,162	1,958,073	52.6%
50-64歲成人	5,304,229	1,018,139	19.2%
醫事執登人員	335,121	245,196	73.2%
防疫人員及醫院非執登工作人員	153,882	142,318	92.5%
禽畜養殖業等及動物防疫人員	10,202	10,202	100.0%
國小、國中、高中、高職、五專1至3年級學生	2,443,880	1,840,090	75.3%
3歲以上至入學前幼童--曾接種過	431,360	285,792	66.3%
3歲以上至入學前幼童--未曾接種過(第1劑)	222,842	27,168	12.2%
3歲以上至入學前幼童--未曾接種過(第2劑)		11,162	5.0%
罕見疾病/重大傷病患者		57,423	
19-49歲高風險慢性病人			
孕婦及6個月內嬰兒之父母	-	79,194	-
托育人員及托育機構專業人員	63,122	19,328	30.6%
6個月以上3歲以下幼兒--曾接種過	162,360	162,360	100.0%
6個月以上3歲以下幼兒--未曾接種過(第1劑)	340,333	111,225	32.7%
6個月以上3歲以下幼兒--未曾接種過(第2劑)		81,760	24.0%
擴大對象**	-	101,199	-

近5 年醫事人員流感接種率：66-74%

*為安養等機構之住民及所屬直接照顧工作人員

**自110年1月30日起，除原計畫對象外，擴大至全國出生滿6個月以上尚未接種之民眾

流感疫苗接種禁忌與注意事項

禁忌症

- 已知**對疫苗的成份有過敏**者，不予接種
- 過去注射曾經發生**嚴重不良反應**者，不予接種

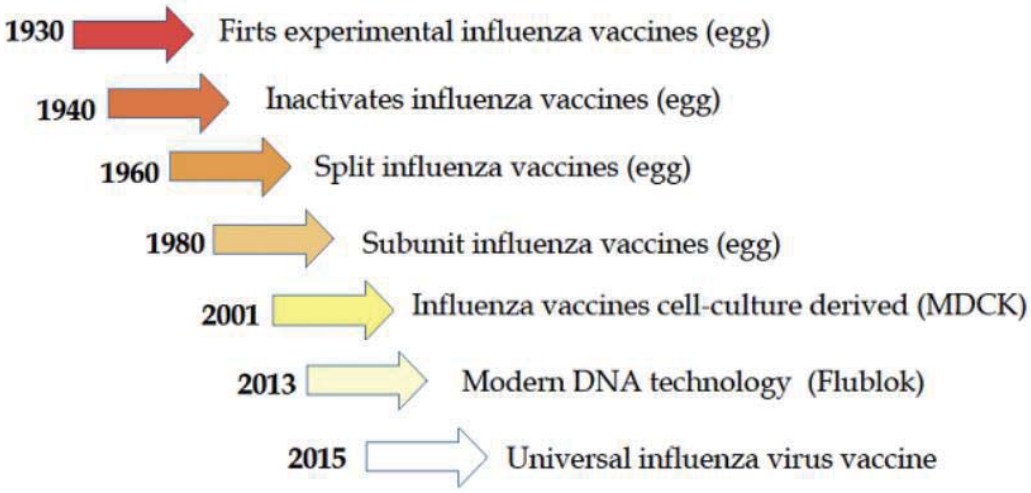
注意事項

- **發燒或正患有急性中重度疾病者**，宜待病情穩定後再接種
- **出生未滿6個月**，因無使用效益及安全性等臨床資料，故不予接種
- 先前接種本疫苗**6週內曾發生Guillain-Barré 症候群(GBS多發性神經炎)**者，宜請醫師評估
- 已知對「**蛋**」之蛋白質有嚴重過敏者，可在門/住診由熟悉處理過敏症狀之醫事人員提供接種，並於接種後觀察30分鐘，無不適症狀再離開
- 其他經醫師評估不適合接種者，不予接種

立即型過敏

- 發生率：**每百萬劑疫苗發生0.65 –1.53次**
- 疫苗種類：所有疫苗，包括麻疹-腮腺炎-德國麻疹、B型肝炎、白喉、破傷風、百日咳、b型嗜血桿菌、小兒麻痺等
- 疫苗提供者需要備有**緊急醫療處置**措施
- **接種流感疫苗**後有極低的可能性發生立即型過敏反應，嚴重可能導致過敏性休克。為了能在事件發生後立即進行醫療處置，接種疫苗後應於接種單位或附近稍做休息，並觀察至少30分鐘以上，待無不適後再離開

Historical path of the development of influenza vaccine



Vaccines 2017, 5, 18

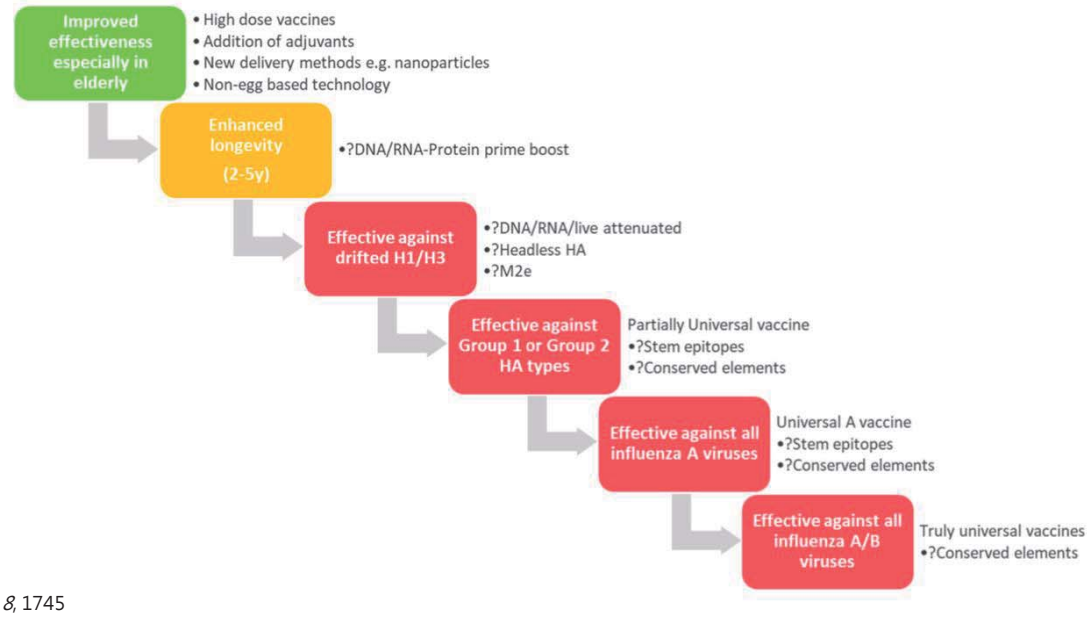
Non-egg-based Influenza Vaccines

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]

Vaccines 2017, *5*, 18

Potential steps and technologies to improve influenza vaccines



Microorganisms 2020, *8*, 1745

總結

- **高風險族群**與**高傳播族群**建議於症狀出現48小時內盡速給予抗病毒藥物治療
- **住院/重症病患**立即給予抗病毒藥物治療
- 發生群聚之**人口密集場所**評估給予預防性用藥10天

- **每年**接種流感疫苗，是預防流感及其併發症最有效的方式
- 接種流感疫苗能夠**降低罹患流感**及**產生後續併發症**的風險
- 接種流感疫苗出現嚴重不良事件的比例極低，建議每年接種流感疫苗


THANK YOU

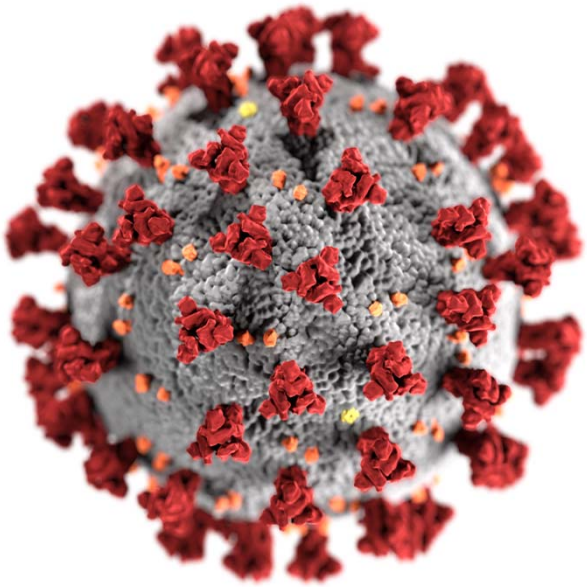
COVID 19流行病學,臨床表現與疫苗預防

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

3

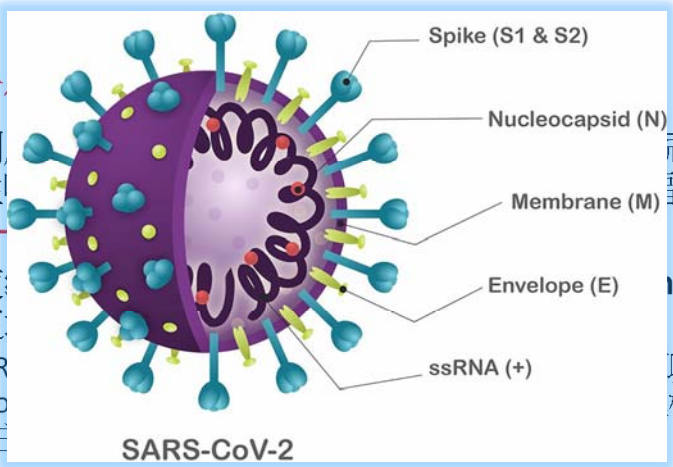
定義

- 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**

4

病毒學

- 冠狀病毒有
- 全基因組測
  與嚴重急性
  相同的**beta-**
- **中東呼吸道**
  乎更加恆定
  - 最接近的R
    要來源; Co
    通過中間



冠狀病毒是
冠狀病毒）

navirus ，似

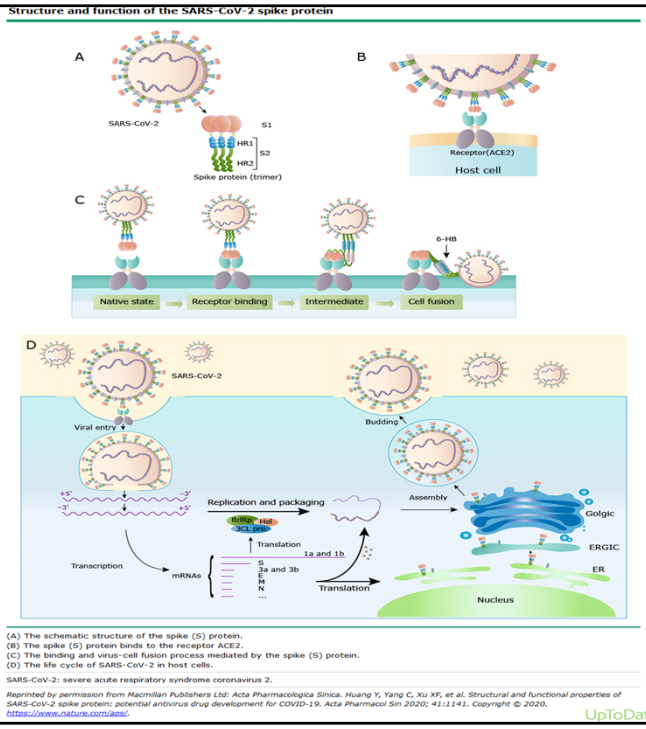
以乎**蝙蝠**是主
機制（例如，

5

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。

6



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[ǂ]	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[ǂ]	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]

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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.

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Variant Classifications

- **Variants being monitored (VBM)**– View current VBM in the United States that continue to be monitored and characterized by federal agencies (非流行病毒株,持續監測)
- **Variant of interest (VOI)**– Currently, no SARS-CoV-2 variants are designated as VOI(具有潛在或輕微影響傳播力與抗體中和能力)
- **Variant of Concern (VOC)**– View current VOC in the United States that are being closely monitored and characterized by federal agencies(大流行具有明顯影響傳播力與抗體中和能力, eg. Omicron)
- **Variant of high consequence (VOHC)**– Currently, no SARS-CoV-2 variants are designated as VOHC (嚴重影響預防與醫療量能)

WHO Label	Pango Lineage	Date of Designation		
Alpha	B.1.1.7 and Q lineages	**VOC**: December 29, 2020		**VBM**: September 21, 2021
Beta	B.1.351 and descendent lineages	**VOC**: December 29, 2020		**VBM**: September 21, 2021
Gamma	P.1and descendent lineages	**VOC**: December 29, 2020		**VBM**: September 21, 2021
Delta	B.1.617.2 and AY lineages	**VOC**: June 15, 2021		**VBM**: April 14, 2022
Epsilon	B.1.427 B.1.429	**VOC**: March 19, 2021	**VOI**: February 26, 2021 **VOI**: June 29, 2021	**VBM**: September 21, 2021
Eta	B.1.525		**VOI**: February 26, 2021	**VBM**: September 21, 2021
Iota	B.1.526		**VOI**: February 26, 2021	**VBM**: September 21, 2021
Kappa	B.1.617.1		**VOI**: May 7, 2021	**VBM**: September 21, 2021
N/A	B.1.617.3		**VOI**: May 7, 2021	**VBM**: September 21, 2021
Zeta	P.2		**VOI**: February 26, 2021	**VBM**: September 21, 2021
Mu	B.1.621, B.1.621.1			**VBM**: September 21, 2021

Current VOC - Omicron

WHO label[1]	Name (Pango lineage*)	Name (Nextstrain*)	First detected	Transmissibility	Associated disease severity	Impact on immunity	Monoclonal antibody therapy activity
Omicron	B.1.1.529	21K	Botswana/South Africa	Sublineages BA.1 and BA.1.1[2-7]			
				• Increased transmissibility compared with Delta	• Decreased disease severity compared with Delta	• Significant reduction in neutralization by sera from individuals with prior infection or from individuals vaccinated with a primary series (infection plus vaccination or primary series plus booster dose appears to restore some neutralizing activity)	• Significant reduction in neutralization by certain monoclonal antibody therapies¶: • Bamlanivimab-etesevimab: **Inactive** (>1013-fold decrease in susceptibility)[8] • Casirivimab-imdevimab: **Inactive** (>1013-fold decrease in susceptibility)[9] • Sotrovimab: No change in susceptibility[10] • Bebtelovimab: No change in susceptibility[11] • Tixagevimab-cilgavimab: **Reduced activity** (12- to 30-fold decrease in susceptibility for BA.1 and 176-fold decrease for BA.1.1)[12]

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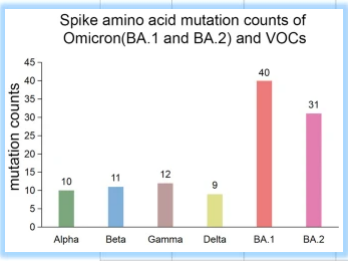
WHO label[1]	Name (Pango lineage*)	Name (Nextstrain*)	First detected	Transmissibility	Associated disease severity	Impact on immunity	Monoclonal antibody therapy activity
				Sublineage BA.2[13]			
				• Increased transmissibility compared with BA.1	• Similar disease severity as BA.1	• Similar reduction in neutralization as BA.1	• Significant reduction in neutralization by certain monoclonal antibody therapies¶: • Sotrovimab: **Unlikely to be active** (15- to 50-fold decrease in susceptibility)[10] • Casirivimab-imdevimab: **Unlikely to be active** (23- to 597-fold decreased susceptibility)[14] • Bebtelovimab: No change in susceptibility[11] • Tixagevimab-cilgavimab: Minimal change in susceptibility (5.4-fold decrease)[12]



18 core mutations of BA.1 (frequency **>99%**) and 27 core mutations of BA.2 (nine more than BA.1) were identified, of which 15 are specific to Omicron

recombination events between two Omicron major subvariants (BA.1 and BA.2) and other variants of concern (VOCs) and variants of interest (VOIs), suggesting that **co-infection** and **subsequent genome recombination** play important roles in the ongoing evolution of SARS-CoV-2.

Junxian Ou, Wendong Lan,.Signal Transduction and Targeted Therapy volume 7, Article number: 138 (2022)

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Omicron variant席捲全球

- Original Omicron (BA.1) (B.1.1.529.1) :
  - high transmissibility and infectivity compared to the Delta variant
  - **hospitalization rates are lower**
  - **less severe progression** (Mohapatra et al., 2022).
- (BA.2) (B.1.1.529.2) :
  - high transmissibility
  - **high severity** (Mohapatra et al., 2022). However, there is presently no evidence on the severity of the BA.2 sub-lineage as per data provided by the FDA (Dhawan & Choudhary, 2022).
- (BA.3) (B.1.1.529.3):
  - spreads slowly and causes fewer cases, may be due to the loss of six mutations that were part of the original BA.1 Omicron variant (Mohapatra et al., 2022).

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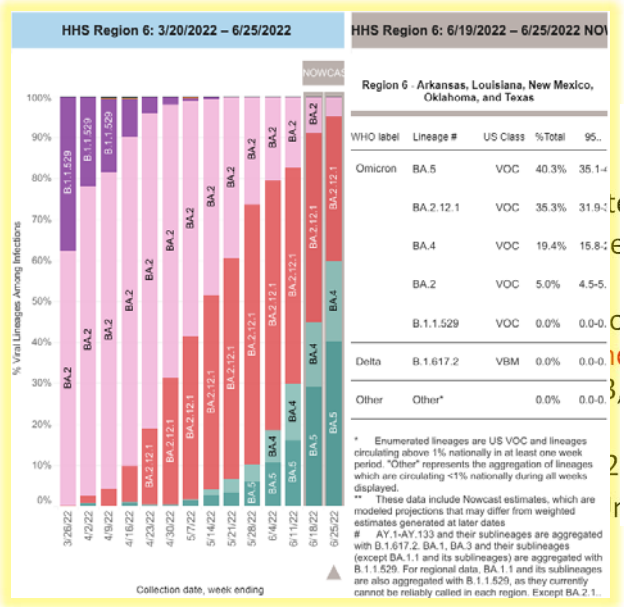
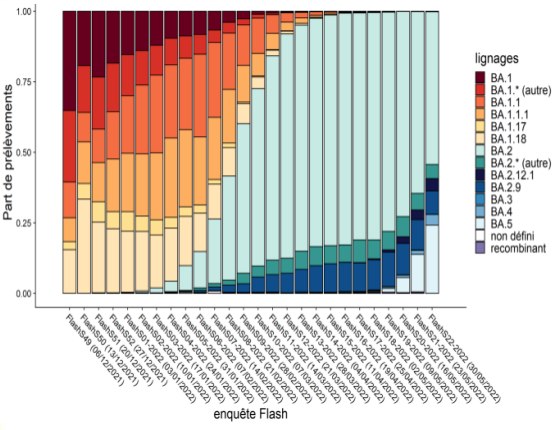


USA CDC



Santé publique France

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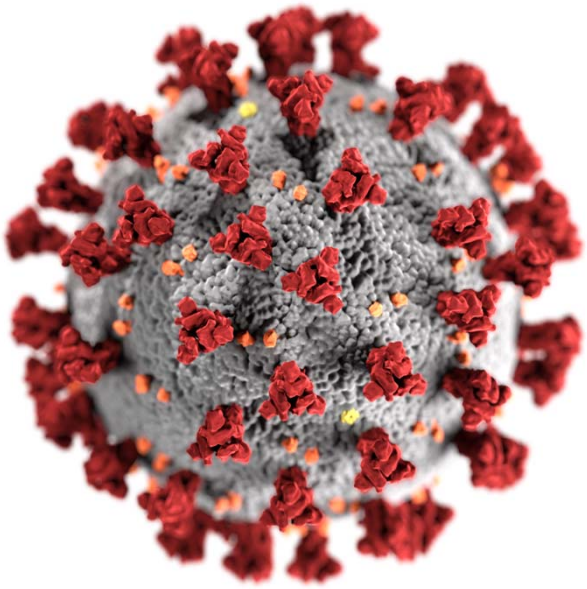
大綱

- 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



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- 全球地理分佈和案例計數，報告了超過**5.48億**的Covid-19確診病例，死亡病例超過634萬。
- 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**。

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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，很可能機會很低。
  - 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%)。

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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，但似乎狗對實驗感染的易感程度是不太敏感的。
  - 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**。

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

A) Temperature*

Time	Virus titre (Log $TCID_{50}$/mL)									
	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1天

The LANCET microbe CORRESPONDENCE| VOLUME 1, ISSUE 1, E10, MAY 01, 2020
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Stability of SARS-CoV-2 at different environmental conditions(2)

B) Surfaces*

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

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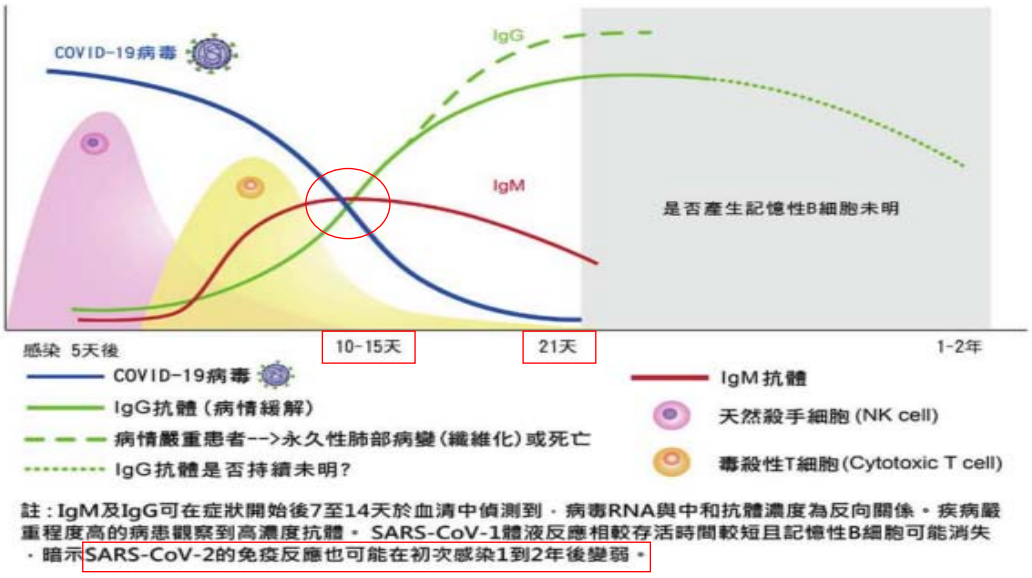
免疫反應

- 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** - 從Covid-19恢復的患者及接受了Covid-19疫苗的個人中鑑定出SARS-COV-2特異性CD4和CD8 T細胞反應，這表明了**潛在性持久的T細胞免疫**反應。



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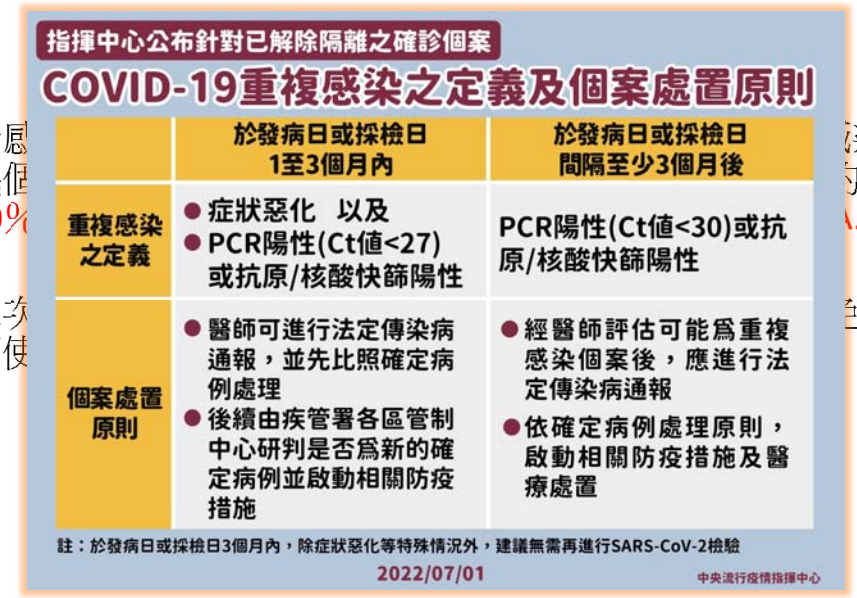
- 重新感 染後的前幾個 的感染風險80% .5的案例。
- 第二次 免疫可能性即使



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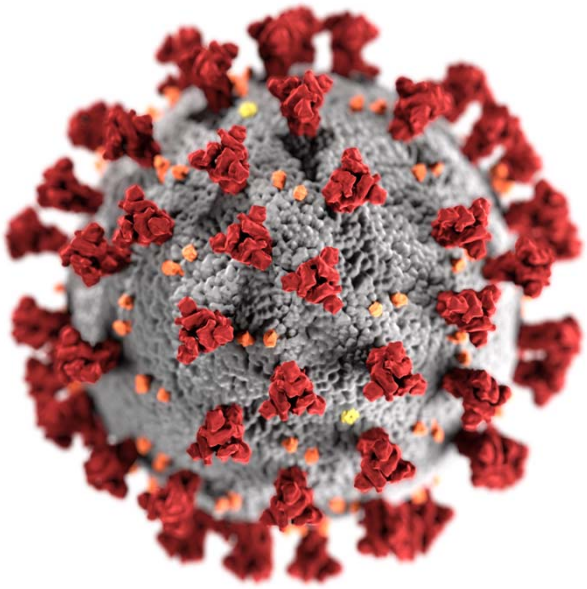
大綱

- 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



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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**）。

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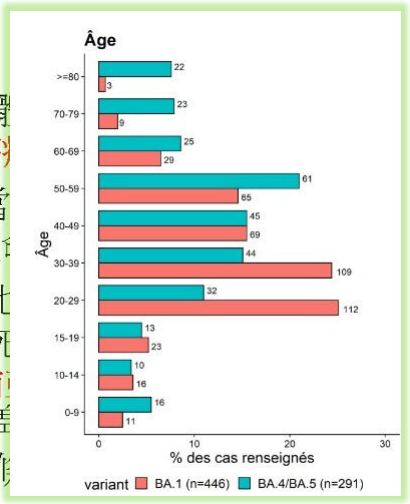
症狀感染的嚴重程度

- 嚴重疾病的危險因素 - 任何年齡的健康個體
  但它主要發生在具有高齡或某些潛在的醫
- 兒童和青少年的症狀感染似乎相對罕見;當
  管小比例（例如，<2%）經驗嚴重甚至致
- 社會經濟背景和性別 - 某些人口統計特徵
  - 男性在全球多個隊列中佔了大量關鍵病例和死
  - 美國和英國的Covid-19，黑人，西班牙裔和南
    比例的增加，這可能與健康社會因素的潛在差
- 合併症 - 與嚴重疾病和死亡率有關的其他



Santé publique France

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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。

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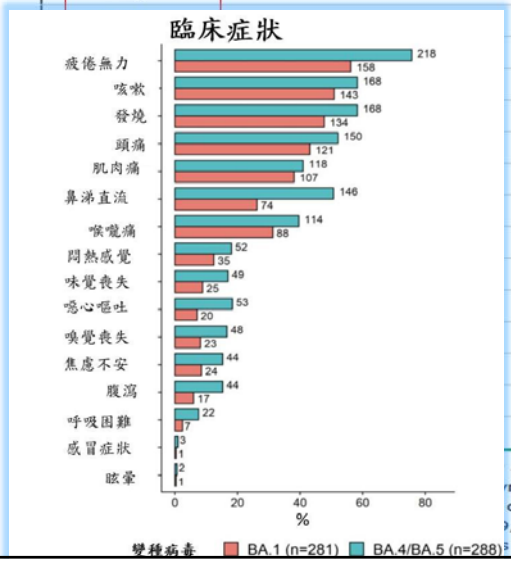
Symptoms associated with coronavirus disease 2019 (COVID-19)[1]

Symptoms that may be seen in patients with COVID-19

- Cough



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%

Santé publique France

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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.

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美國疾病控制及預防中心(CDC)的MIS-A病例定義

年齡≥21歲且住院≥24小時或因疾病而死亡，並符合以下臨床和實驗室標準的患者。病人應無其他更可能解釋病程的疾病診斷(例如細菌性敗血症、慢性疾病惡化)。

臨床標準

住院前、或住院起三天內有主觀發燒或客觀發燒記錄(≥38.0度)達至少24小時，並且住院前、或住院起三天內符合以下臨床標準至少三項。至少一項必須是主要臨床標準。

主要臨床標準

嚴重心臟疾病：
包括心肌炎、心包炎、冠狀動脈擴張/冠狀動脈瘤或新發的左右心室功能障礙(LVEF<50%)、2或3度房室傳導阻滯或室性心動過速。
(註：僅心臟驟停則不符合此標準)

或

皮疹合併非化膿性結膜炎

次要臨床標準

新發的神經系統病徵和症狀包括過去無認知障礙病史患者的腦病變、癲癇、腦膜炎病徵或周圍神經病變(包括格林巴利症候群)

不能歸因於藥物治療(例如鎮靜、透析)的休克或低血壓

腹痛、嘔吐或腹瀉

血小板減少(血小板計數低於150,000/微升)

實驗室標準

同時具有發炎和新冠病毒感染的實驗室證據：

- 以下至少兩項指數升高：CRP, Ferritin, IL-6, ESR, procalcitonin
- SARS-CoV-2 RT-PCR、血清學或抗原檢測陽性

資料來源：美國CDC官網 (https://www.cdc.gov/mis/mis-a/hcp.html)

什麼是MIS-C

孩童多系統炎症徵候群
(Multisystem inflammatory syndrome in children, MIS-C)
感染COVID-19後罕見的高度炎性反應以及多器官系統損傷，國外統計致死率可達1~2%

感染後2-6週觀察期

發生於年齡介於 0-19 歲，年齡層以6-12歲為多

診斷要件：有新冠病毒感染證據、發燒≥3天且實驗室檢查顯示發炎指數上升(ESR、CRP或procalcitonin)，並具至少兩項下列臨床特徵：

- 出疹，或雙側非化膿性結膜炎，或黏膜發炎
- 低血壓或休克
- 心肌功能受損，包括心包膜炎、瓣膜炎或冠狀動脈異常
- 凝血功能異常
- 急性腸胃道症狀，包括腹瀉、嘔吐或腹痛

排除其他可能導致類似臨床表現之感染(包括細菌性敗血症、毒性休克症候群)

2022/06/06 中央流行疫情指揮中心

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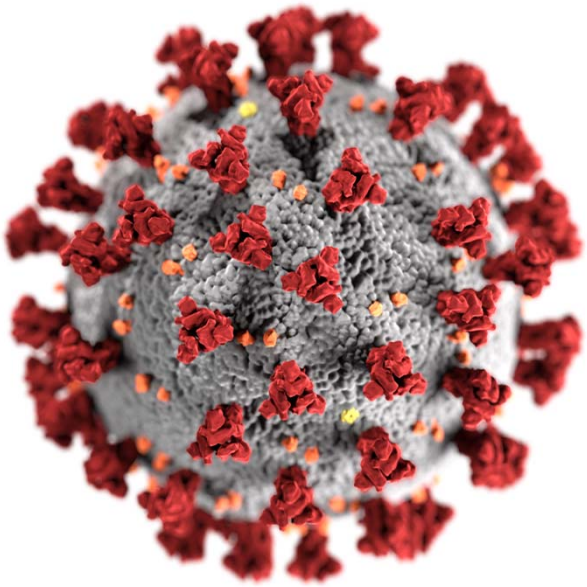
大綱

- 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



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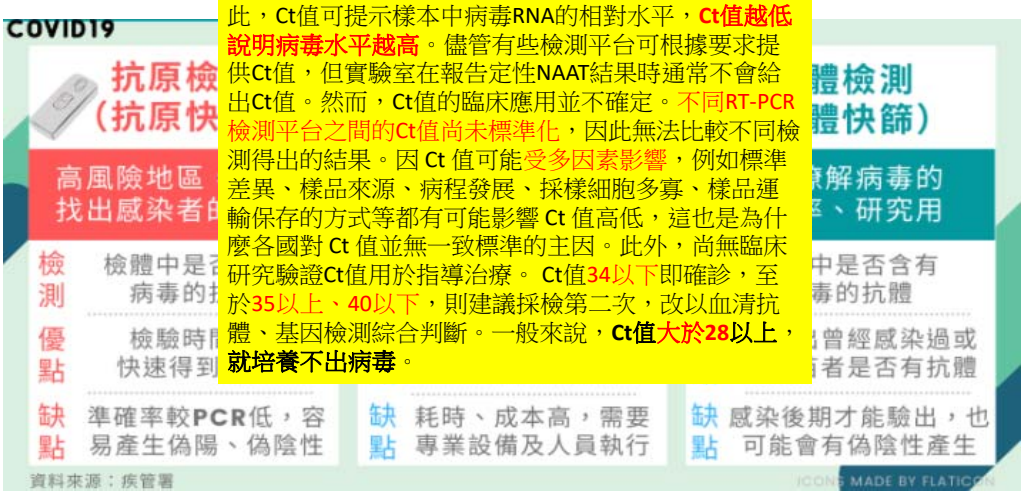

循環閾值 — 循環閾值(cycle threshold, Ct)是指RT-PCR檢測時，將病毒RNA擴增至可檢出水平所需的循環數。因此，Ct值可提示樣本中病毒RNA的相對水平，**Ct值越低說明病毒水平越高**。儘管有些檢測平台可根據要求提供Ct值，但實驗室在報告定性NAAT結果時通常不會給出Ct值。然而，Ct值的臨床應用並不確定。不同RT-PCR檢測平台之間的Ct值尚未標準化，因此無法比較不同檢測得出的結果。因 Ct 值可能受多因素影響，例如標準差異、樣品來源、病程發展、採樣細胞多寡、樣品運輸保存的方式等都有可能影響 Ct 值高低，這也是為什麼各國對 Ct 值並無一致標準的主因。此外，尚無臨床研究驗證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**。

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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

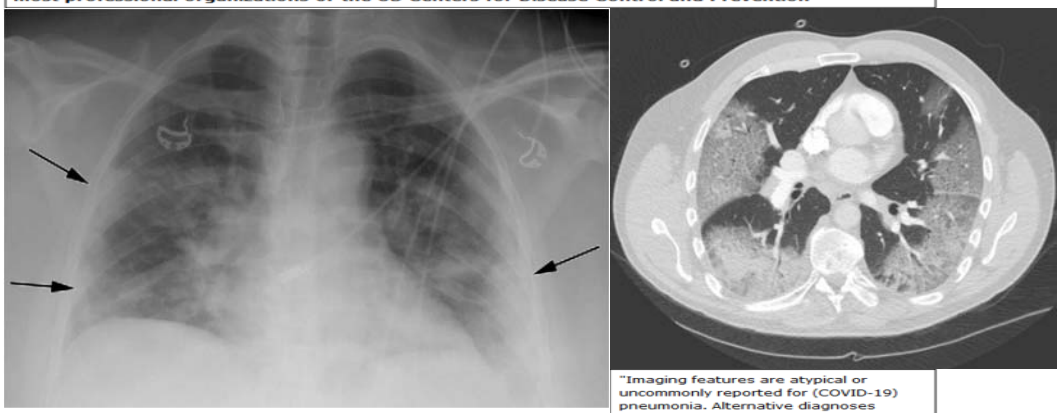

Figure 3: Characteristic chest radiograph in a 41-year-old woman presenting with cough and fever. Chest radiographic findings include bilateral patchy and confluent, bandlike ground-glass and consolidative opacity in a peripheral, mid to lower lung zone distribution (arrows).

"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.

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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.

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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。

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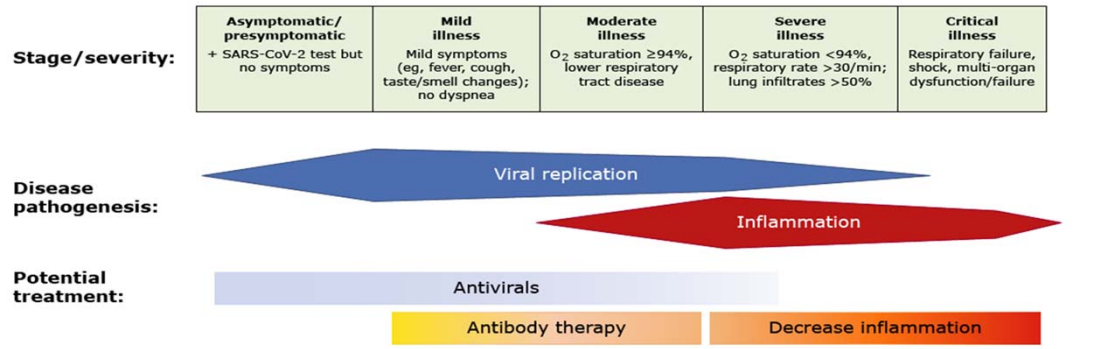
COVID 19 嚴重程度與治療原則

Potential targets of COVID-19 therapies by stage of infection



COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

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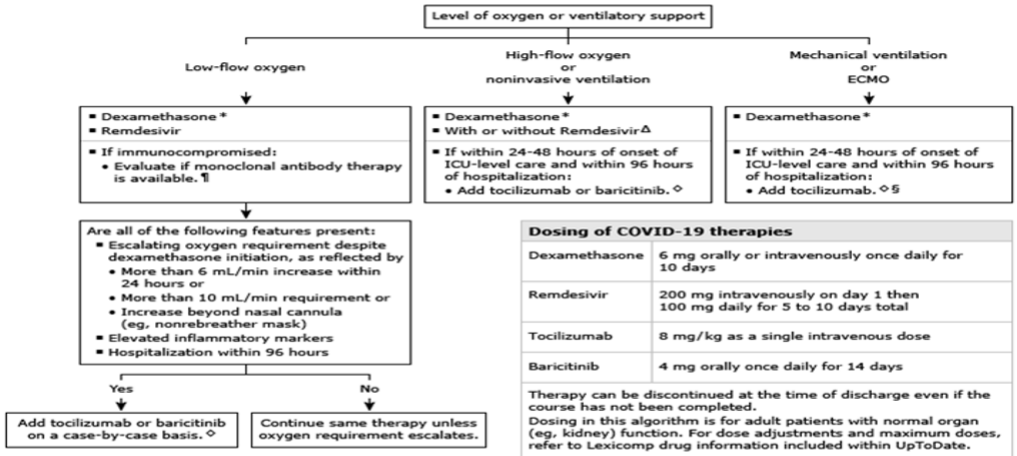
Selection of COVID-19-specific therapy in adults who have severe disease requiring oxygen supplementation



Dosing of COVID-19 therapies

Dexamethasone	6 mg orally or intravenously once daily for 10 days
Remdesivir	200 mg intravenously on day 1 then 100 mg daily for 5 to 10 days total
Tocilizumab	8 mg/kg as a single intravenous dose
Baricitinib	4 mg orally once daily for 14 days

Therapy can be discontinued at the time of discharge even if the course has not been completed.
Dosing in this algorithm is for adult patients with normal organ (eg, kidney) function. For dose adjustments and maximum doses, refer to Lexicomp drug information included within UpToDate.

This algorithm covers our approach to selection of COVID-19-specific therapy only. Refer to other UpToDate content for discussion of other management issues, including management of hypoxia, prevention of thromboembolism, management of other complications, and care of pregnant and postpartum patients. The approach to COVID-19-specific therapy in individuals who have no oxygen requirement or who are seen in the outpatient setting is also covered elsewhere.

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COVID-19
美國NIH與台灣CDC治療指引

	輕度(抗病毒)		中度(抗病毒)		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一考慮使用單株抗體 Bamlanivimab + Etesevimab 或 Casirivimab + Imdevimab		Room air SpO2≧94% Remdesivir 200mg stat 100mg x2 days		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)	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			
	Paxlovid: (150mg 2# &100mg 1#)BID Molnupiravir: 800mg (4#) q12h 5天									

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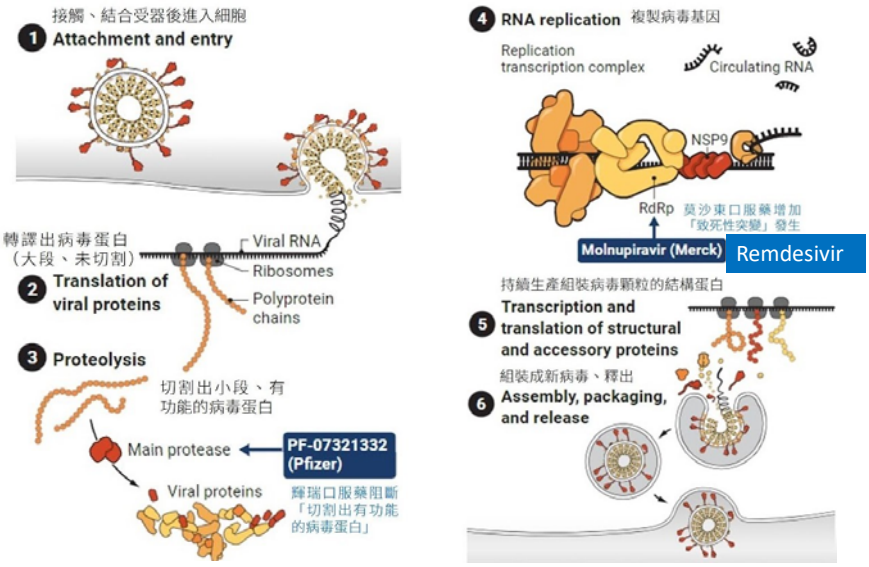

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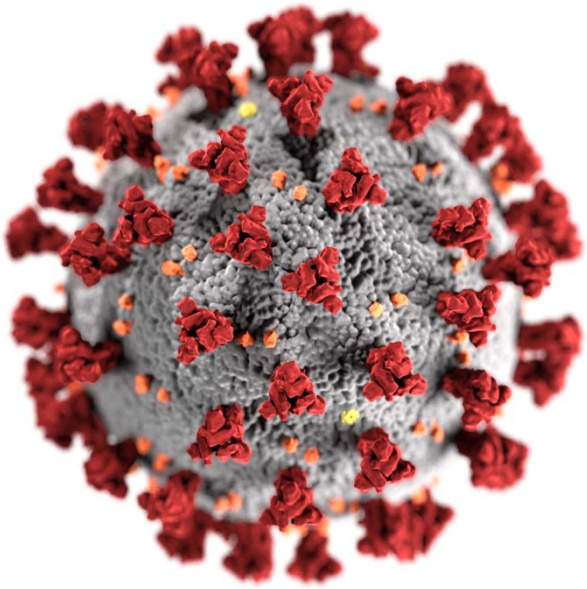
大綱

- 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



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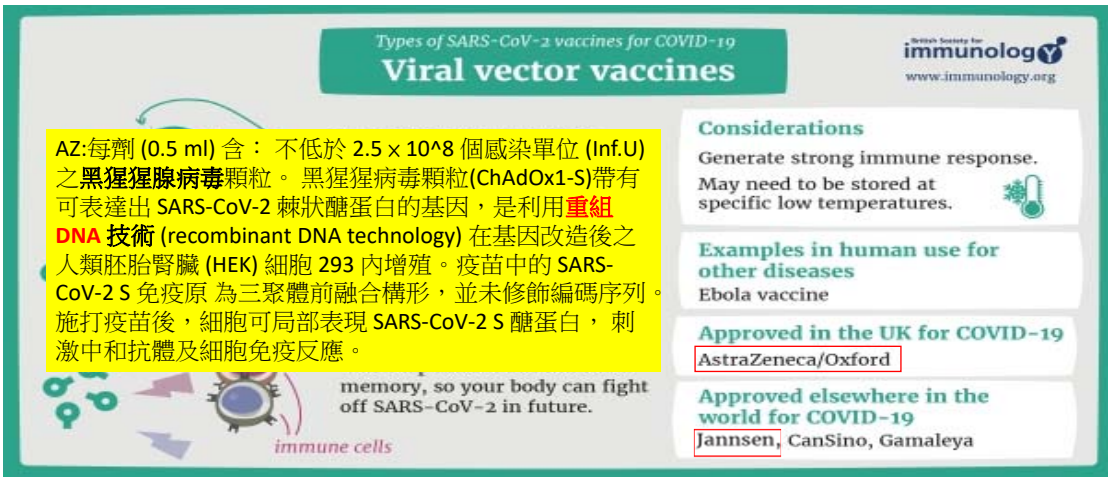
疫苗類型簡介-病毒載體疫苗



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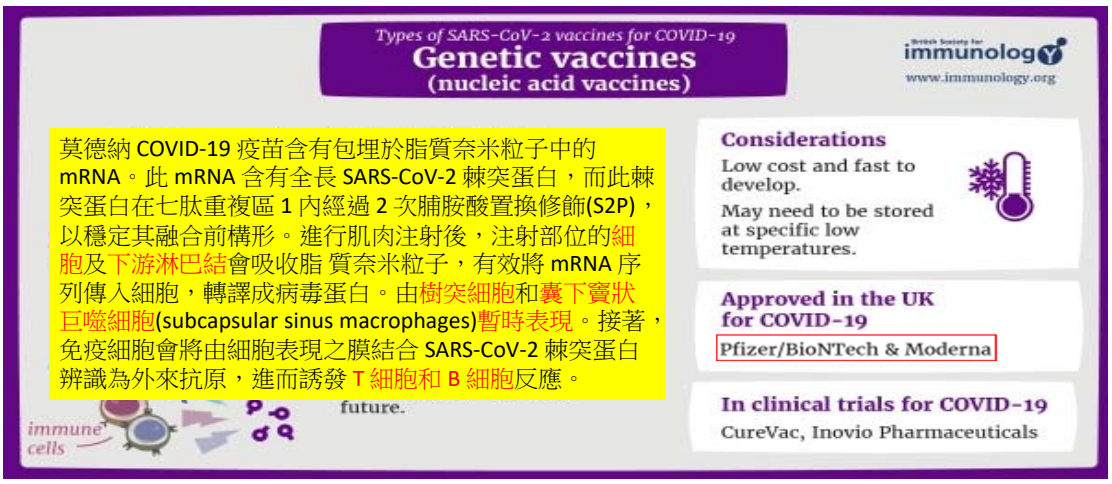
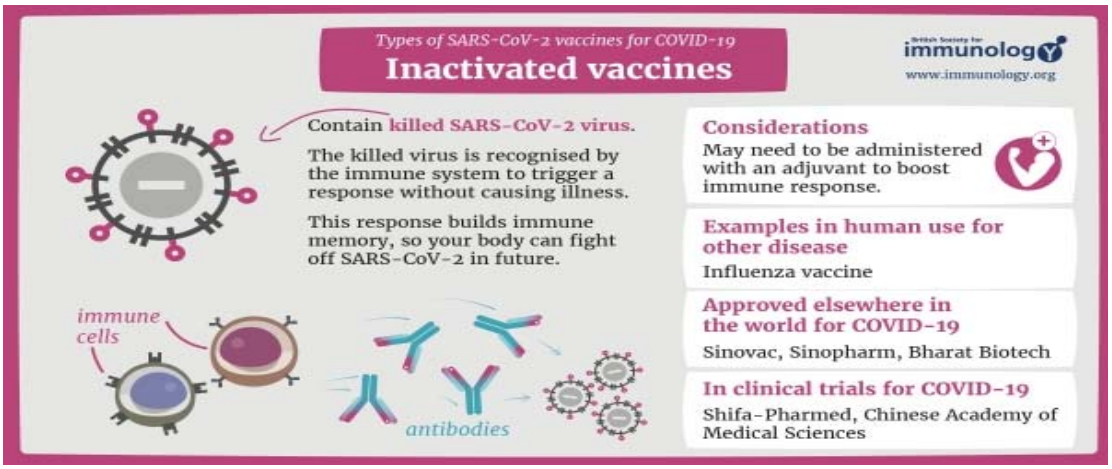
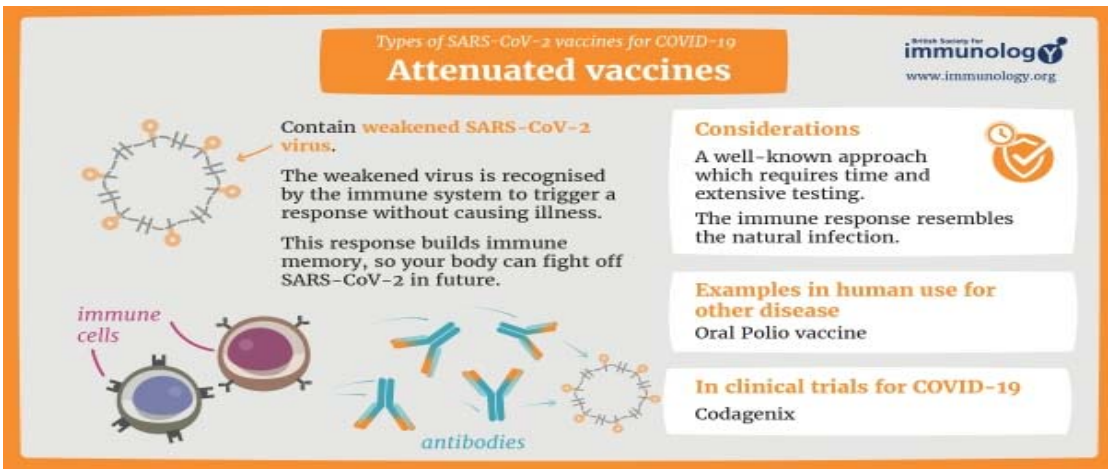
疫苗類型簡介-基因工程疫苗(mRNA疫苗)



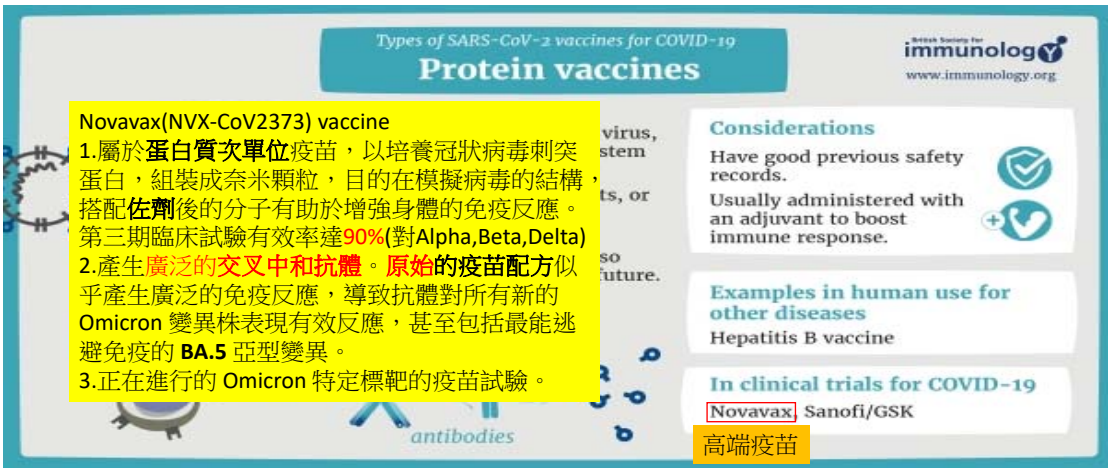
疫苗類型簡介-去活化疫苗



疫苗類型簡介-減毒疫苗



疫苗類型簡介-蛋白質疫苗



Novavax(NVX-CoV2373) vaccine
1.屬於**蛋白質次單位**疫苗，以培養冠狀病毒刺突蛋白，組裝成奈米顆粒，目的在模擬病毒的結構，搭配**佐劑**後的分子有助於增強身體的免疫反應。第三期臨床試驗有效率達90%(對Alpha,Beta,Delta)
2.產生廣泛的**交叉中和抗體**。**原始的疫苗配方**似乎產生廣泛的免疫反應，導致抗體對所有新的 Omicron 變異株表現有效反應，甚至包括最能逃避免疫的 **BA.5** 亞型變異。
3.正在進行的 Omicron 特定標靶的疫苗試驗。

高端疫苗

疫苗基礎2劑比較表

	AZ	Moderna	BNT	高端
類型	腺病毒疫苗	mRNA	mRNA	蛋白次單元
施打間隔	8週以上(8-12週)	4週(4-8週)	4週(3-8週)	4週
兩劑保護力	81%(alpha)	94%(alpha)	95%(alpha)	NA;抗體效價符合標準

接種COVID-19疫苗後一般副作用出現頻率(第三期臨床試驗)

副作用	AZ 疫苗	BNT/輝瑞疫苗	莫德納疫苗
注射部位疼痛	54.2%	84.1%	92.0%
疲倦	53.1%	62.9%	70.0%
頭痛	52.6%	55.1%	64.7%
肌肉痛	44.0%	38.3%	61.5%
畏寒	31.9%	31.9%	45.4%
關節痛	26.4%	23.6%	46.4%
發燒(>38 度)	7.9%	14.2%	15.5%

註：一般副作用發生頻率：(1) 年長者發生頻率低於年輕人；(2) 腺病毒載體疫苗（如 AZ 疫苗）之第一劑高於第二劑；(3) mRNA 疫苗（如 BNT/輝瑞和莫德納疫苗）之第二劑高於第一劑

資料來源：(1) WHO: AZD1222 vaccine against COVID-19 developed by Oxford University and Astra Zeneca: Background paper (10 February 2021); (2) WHO: Background document on the mRNA-1273 vaccine (Moderna) against COVID-19 (3 February 2021); (3) WHO: Background document on the mRNA vaccine BNT162b2 (Pfizer-BioNTech) against COVID-19 (14 January 2021)

2021/2/23 中央流行疫情指揮中心

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疫苗罕見嚴重副作用

廠牌	AZ	Moderna (mRNA)
疾病名稱	**血栓併血小板低下**	**心肌炎或心包膜炎**
發生時間	4-28天	14天內
好發族群	20-40歲,男女皆有,女性略多(0.0001%)	30歲以下,男性居多(0.00126%)
嚴重症狀	嚴重且不斷感到頭痛 視力改變,癲癇 嚴重且超過24小時腹痛 嚴重胸痛,呼吸困難 下肢腫脹,疼痛 皮膚出現自發性出血點,瘀青,紫斑	胸痛, 呼吸急喘 心跳加快,心悸
其他		第2劑後機率更高

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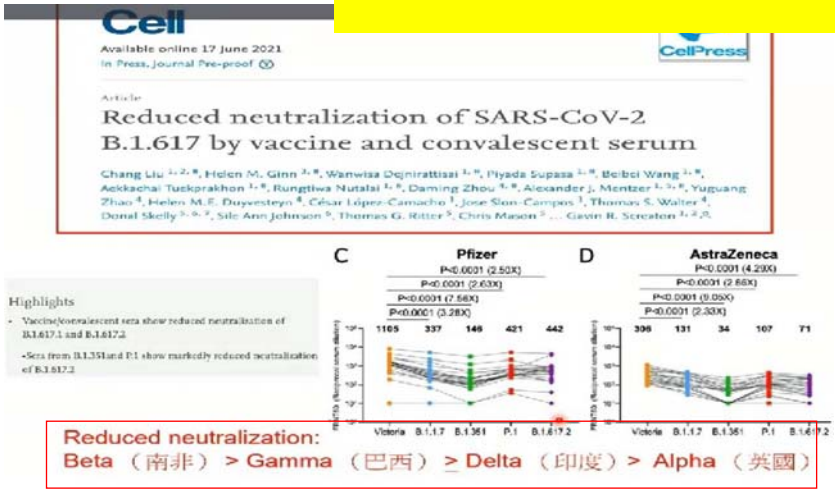
SARS COV-2變異危

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。

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Brief Communication | Open Access | Published: 26 July 2021

Immunogenicity and reactogenicity of heterologous ChAdOx1 nCoV-19/mRNA vaccination In Germany

Tina Schmidt, Verena Klemis, David Schub, Janine Mihm, Franziska Hielscher, Stefanie Marx, Amina Abu-Omar, Laura Ziegler, Candida Guckelmus, Rebecca Urschel, Sophie Schneitler, Sören L. Becker, Barbara C. Gärtner, Urban Sester & Martina Sester

Nature Medicine (2021) | Cite this article n = 213

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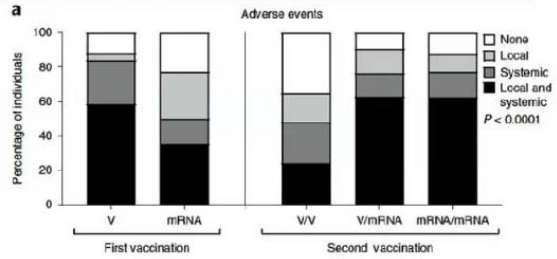

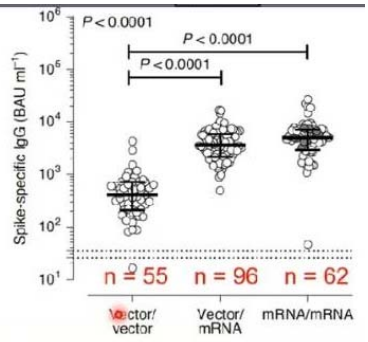

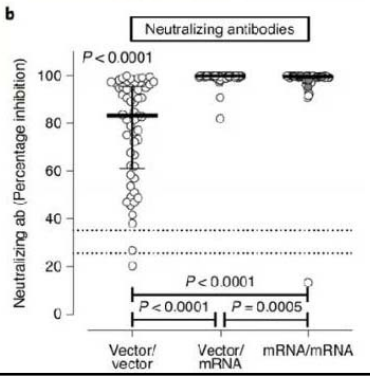

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混打順序影響

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

BNT/BNT ≧ AZ/BNT > BNT/AZ > AZ/AZ

##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

25 Jun,2021 The Lancet

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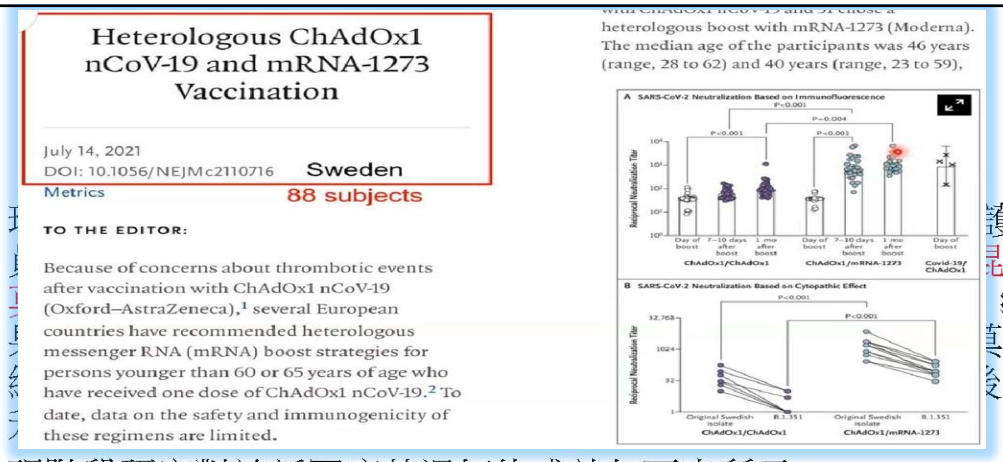

Heterologous ChAdOx1 nCoV-19 and mRNA-1273 Vaccination

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),

- 護人
混打
結
德
僅

- 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	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

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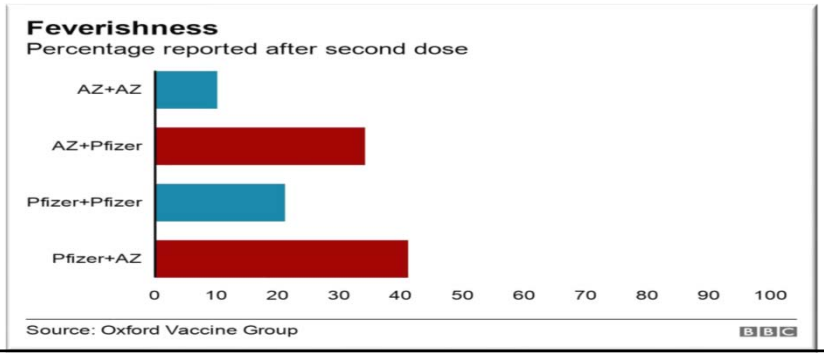
疫苗混打副作用

- 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。



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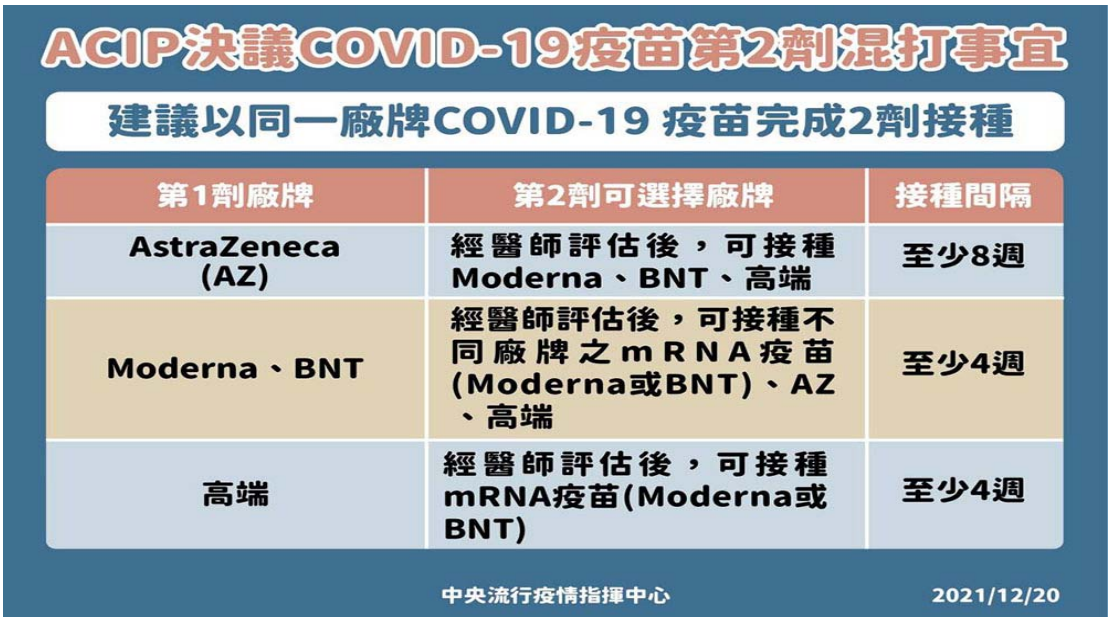
ACIP決議COVID-19疫苗第2劑混打事宜
建議以同一廠牌COVID-19 疫苗完成2劑接種
第1劑廠牌
第2劑可選擇廠牌
接種間隔
AstraZeneca (AZ)
經醫師評估後，可接種Moderna、BNT、高端
至少8週
Moderna、BNT
經醫師評估後，可接種不同廠牌之mRNA疫苗(Moderna或BNT)、AZ、高端
至少4週
高端
經醫師評估後，可接種mRNA疫苗(Moderna或BNT)
至少4週
中央流行疫情指揮中心
2021/12/20

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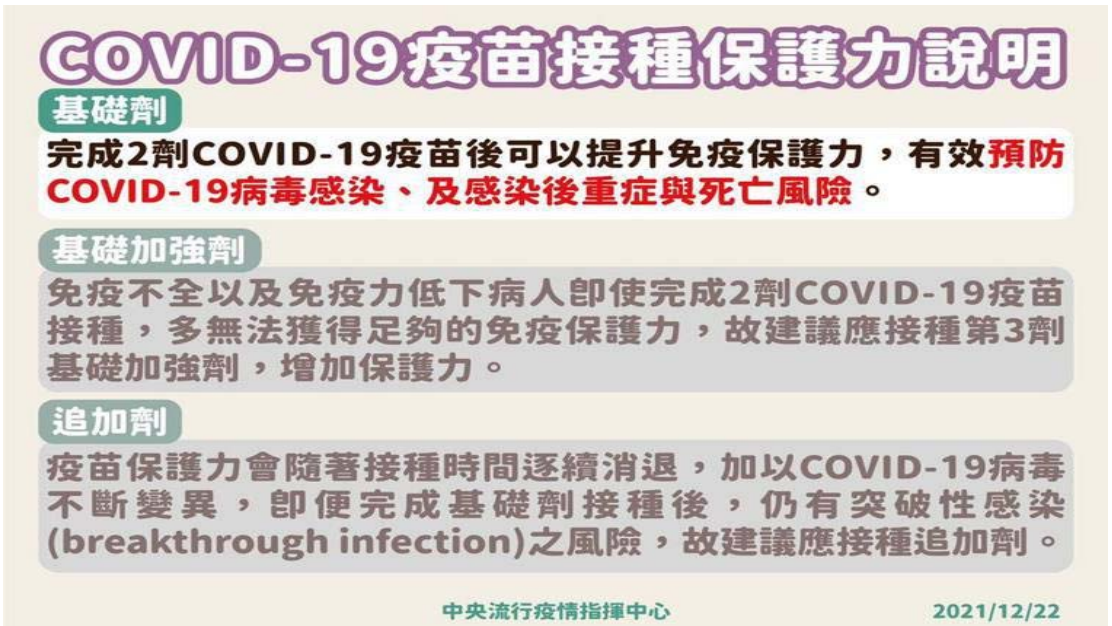
COVID-19疫苗接種保護力說明
基礎劑
完成2劑COVID-19疫苗後可以提升免疫保護力，有效預防COVID-19病毒感染、及感染後重症與死亡風險。
基礎加強劑
免疫不全以及免疫力低下病人即使完成2劑COVID-19疫苗接種，多無法獲得足夠的免疫保護力，故建議應接種第3劑基礎加強劑，增加保護力。
追加劑
疫苗保護力會隨著接種時間逐續消退，加以COVID-19病毒不斷變異，即便完成基礎劑接種後，仍有突破性感染(breakthrough infection)之風險，故建議應接種追加劑。
中央流行疫情指揮中心
2021/12/22

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各國COVID-19疫苗追加劑接種建議

國家	接種建議
歐盟 (EMA/ ECDC)	● 歐盟成員國均建議完成基礎劑接種之民衆，接種追加劑 ● 多數歐盟成員國建議與基礎劑間隔6個月 ● 多數歐盟成員國建議以mRNA疫苗作爲追加劑 ● EMA核准Moderna疫苗追加劑爲半劑量
美國	● 依時程完成兩劑mRNA COVID-19疫苗之18歲以上民衆，應於與基礎劑最後一劑間隔6個月後，接種追加劑；16-17歲青少年，可接種追加劑 ● 接種Janssen疫苗之18歲以上民衆，應於2個月(8週後)，接種追加劑 ● 如使用Moderna疫苗作爲追加劑，劑量爲半劑量
英國	● 建議18歲以上民衆於完成基礎劑接種後3個月，接種追加劑 ● 如使用Moderna疫苗作爲追加劑，劑量爲半劑量
澳洲	● 因應Omicron及Delta變異株，建議18歲以上民衆於完成基礎劑接種後5個月，接種追加劑 ● 如使用Moderna疫苗作爲追加劑，劑量爲半劑量

註：追加劑疫苗種類與劑量：Pfizer-BioNTech全劑量或Moderna半劑量(50μg)

中央流行疫情指揮中心 2021/12/24

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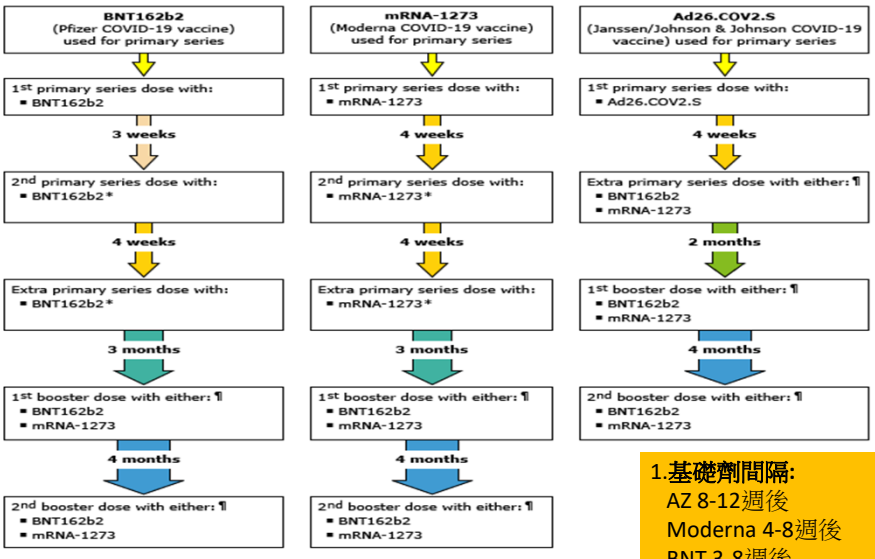

* If possible, the same vaccine formulation is used to complete the primary se
the original vaccine formulation is not available, the other mRNA vaccine (eith
mRNA-1273) can be used.

¶ A different vaccine than that used for the primary series can be used for the
long as that vaccine is approved or authorized for the age group. We suggest
vaccines rather than Ad26.COV2.S. Additionally, Ad26.COV2.S is not authorized for the second
booster dose.

1.**基礎劑間隔:**
AZ 8-12週後
Moderna 4-8週後
BNT 3-8週後
2.**基礎加強劑**:與前劑隔4週(28天)
3.**追加劑(1st and 2nd)**:與前劑隔3-6個月

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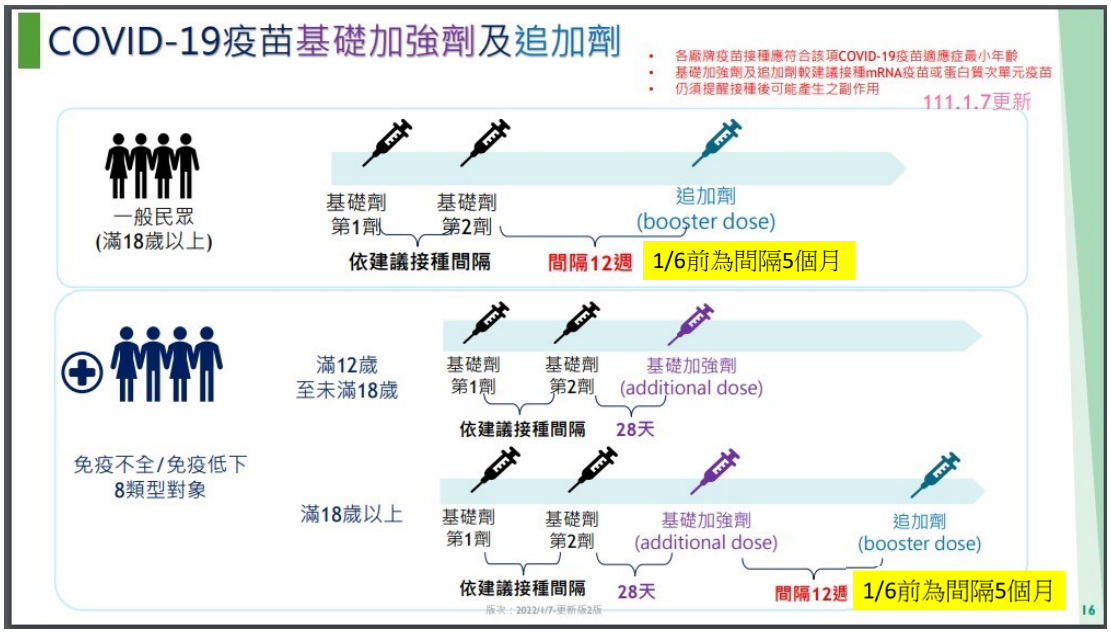

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Name	Company/ developer	Platform	Indicated ages	Primary series	First booster dose and interval*	Second booster dose and interval*¶	Common side effects	Rare adverse effects
BNT162b2[Δ]	Pfizer/BioNTech	mRNA	6 months to 4 years	Three 3 mcg doses at 0, 3, and ≥8 weeks	Booster dose not authorized	Second booster dose not authorized	• Local injection site reactions • Systemic symptoms (fevers, chills, fatigue, myalgias, headache)	• Anaphylaxis (approximately 5 per million doses) • Myocarditis/pericarditis (approximate risk following primary series):[5] • For males 12 to 16 years old: 71 cases/million doses • For males 16 to 17 years old: 106 cases/million doses • For males 18 to 24 years old: 52 cases/million doses • For males 25 to 29 years old: 17 cases/million doses • For females of the same age group: 2 to 11 cases/million doses
			5 to 11 years	Two 10 mcg doses 3 weeks apart◇[§]	One 10 mcg dose 5 months following the primary series[¥]	Second booster dose not authorized		
			12 to 50 years	Two 30 mcg doses 3 weeks apart◇ • Healthy individuals <65 years old can extend the interval to 8 weeks[‡]	One 30 mcg dose 5 months following the primary series[¥]	For individuals with moderately to severely immunocompromising conditions: • One 30 mcg dose 4 months following the first booster dose		
			>50 years	Two 30 mcg doses 3 weeks apart◇ • Healthy individuals <65 years old can extend the interval to 8 weeks[‡]	One 30 mcg dose 5 months following the primary series[¥]	One 30 mcg dose 4 months following the first booster dose		

From Uptodate

1.基礎劑間隔:
AZ 8-12週後
Moderna 4-8週後
BNT 3-8週後
2.基礎加強劑:與前劑隔4週
3.追加劑:與前劑隔3-6個月

BNT劑量:
6mon-4y/o: 3mcg (0,3,8 weeks)(1/10劑)
5-11 y/o:10 mcg (1/3劑量)
12y/o以上:30mcg

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Name	Company/ developer	Platform	Indicated ages	Primary series	First booster dose and interval*	Second booster dose and interval*¶	Common side effects	Rare adverse effects
mRNA-1273Δ	Moderna	mRNA	6 months to 5 years	Two 25 mcg doses 4 weeks apart◇	Booster dose not yet authorized	Second booster dose not authorized	▪ Local injection site reactions ▪ Systemic symptoms (fevers, chills, fatigue, myalgias, headache)	▪ Anaphylaxis (approximately 2.8 per million doses) ▪ Myocarditis/pericarditis (approximate risk following primary series):[5] ▪ For males 18 to 24 years old: 56 cases/million doses ▪ For males 25 to 29 years old: 24 cases/million doses ▪ For females of the same age group: 7 to 8 cases/million doses
			6 to 11 years	Two 50 mcg doses 4 weeks apart◇	Booster dose not yet authorized	Second booster dose not authorized		
			12 to 17 years	Two 100 mcg doses 4 weeks apart◇ ▪ Healthy individuals <65 years old can extend the interval to 8 weeks‡	Booster dose not yet authorized	Second booster dose not authorized		
			18 to 50 years	Two 100 mcg doses 4 weeks apart◇ ▪ Healthy individuals <65 years old can extend the interval to 8 weeks‡	One 50 mcg dose 5 months following primary series¥	For individuals with moderately to severely immunocompromising conditions: ▪ One 50 mcg dose 4 months following the first booster dose		
			>50 years	Two 100 mcg doses 4 weeks apart◇ ▪ Healthy individuals <65 years old can extend the interval to 8 weeks‡	One 50 mcg dose 5 months following primary series¥	One 50 mcg dose 4 months following the first booster dose		

1.基礎劑間隔:
AZ 8-12週後
Moderna 4-8週後
BNT 3-8週後
2.基礎加強劑:與前劑隔4週
3.追加劑:與前劑隔3-6個月

Moderna 劑量:
6mon-5y/o: 25mcg (1/4劑量)
6-11 y/o:50 mcg (1/2劑量)
12y/o以上:100mcg

From Uptodate

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Name	Company/ developer	Platform	Indicated ages	Primary series	First booster dose and interval*	Second booster dose and interval*¶	Common side effects	Rare adverse effects
Ad26.COV2.SΔ	Janssen/Johnson & Johnson	Replication-incompetent adenovirus 26 vector	18 years and older	One 5×10^{10} viral particles dose◇	One 5×10^{10} viral particles dose 2 months following primary series¥	Second Ad26.COV2.S booster dose not authorized; however certain individuals who received Ad26.COV2.S are eligible for a second booster with mRNA vaccine¶	▪ Local injection site reactions ▪ Systemic symptoms (fevers, chills, fatigue, myalgias, headache)	▪ Thrombotic complications associated with thrombocytopenia (approximate risk): ▪ For females 30 to 39 years old: 12.4 cases/million doses ▪ For females 40 to 49 years old: 9.4 cases/million doses ▪ For females in other age ranges and males: 1.3 to 4.7 cases/million doses ▪ Guillain-Barre syndrome (approximately 8 cases/million doses)

From Uptodate

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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。
- Omicron 含高度棘蛋白變異，高傳播性,低致死性,降低中和抗體效果。BA.4和BA.5將成為優勢variant。**Co-infection and recombination為可能機轉**
- 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

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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(for alpha):BNT 95%; Moderna 94%; AZ 81%
  - 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)**
- 增加體內抗體策略:
  - 基礎劑Mixed and matched vaccination
  - 基礎加強劑(for immunocompromised)
  - 追加劑(1st booster and 2nd booster)

1.基礎劑間隔:
AZ 8-12週後
Moderna 4-8週後
BNT 3-8週後
2.基礎加強劑:與前劑隔4週(28天)
3.追加劑(1st and 2nd):與前劑隔3-6個月

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中山醫學大學附設醫院
Chung Shan Medical University Hospital

報告完畢！

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新竹縣政府衛生局
Public Health Bureau of HsinChu County Government

| 公佈日期111.05.20 |

5-17歲 COVID-19疫苗接種

疫苗	Moderna	BNT兒童	BNT青少年
對象	滿6歲以上 (需足歲)	滿5歲至11歲 (需足歲)	滿12歲以上 (需足歲)
劑量	滿6-11歲:0.25ml/劑 滿12歲以上:0.5ml/劑	0.2ml/劑	0.3ml/劑
適用接種劑次	滿6-11歲：基礎劑第1.2劑(需間隔12週) 滿12-17歲：基礎劑第1.2劑(需間隔12週)	基礎劑第1.2劑(需間隔12週)	1.基礎劑第1.2劑(需間隔12週) 2.追加劑 與前劑次需間隔5個月(150天)

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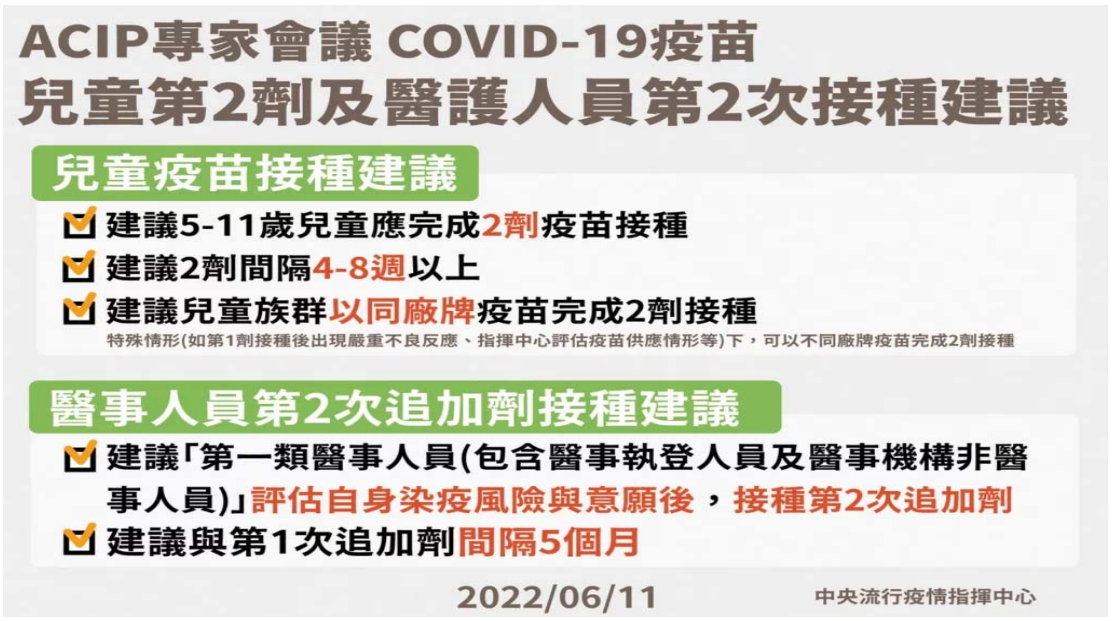
ACIP專家會議 COVID-19疫苗
兒童第2劑及醫護人員第2次接種建議
兒童疫苗接種建議
建議5-11歲兒童應完成2劑疫苗接種
建議2劑間隔4-8週以上
建議兒童族群以同廠牌疫苗完成2劑接種
特殊情形(如第1劑接種後出現嚴重不良反應、指揮中心評估疫苗供應情形等)下，可以不同廠牌疫苗完成2劑接種
醫事人員第2次追加劑接種建議
建議「第一類醫事人員(包含醫事執登人員及醫事機構非醫事人員)」評估自身染疫風險與意願後，接種第2次追加劑
建議與第1次追加劑間隔5個月
2022/06/11
中央流行疫情指揮中心

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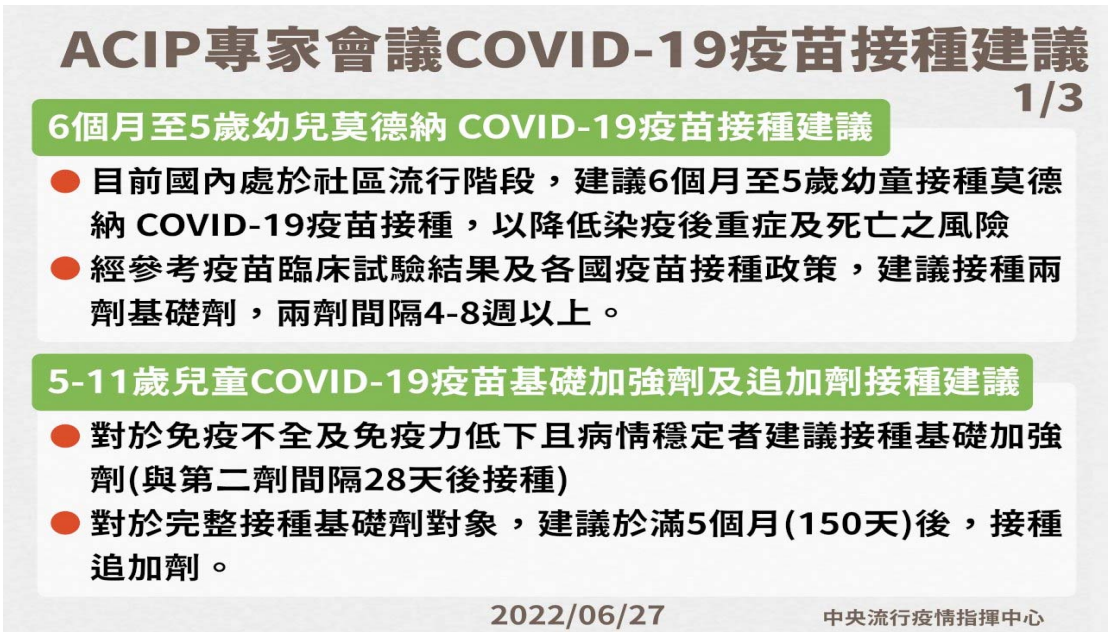
ACIP專家會議COVID-19疫苗接種建議
1/3
6個月至5歲幼兒莫德納 COVID-19疫苗接種建議
目前國內處於社區流行階段，建議6個月至5歲幼童接種莫德納 COVID-19疫苗接種，以降低染疫後重症及死亡之風險
經參考疫苗臨床試驗結果及各國疫苗接種政策，建議接種兩劑基礎劑，兩劑間隔4-8週以上。
5-11歲兒童COVID-19疫苗基礎加強劑及追加劑接種建議
對於免疫不全及免疫力低下且病情穩定者建議接種基礎加強劑(與第二劑間隔28天後接種)
對於完整接種基礎劑對象，建議於滿5個月(150天)後，接種追加劑。
2022/06/27
中央流行疫情指揮中心

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摘錄自ICU醫師陳志金臉書

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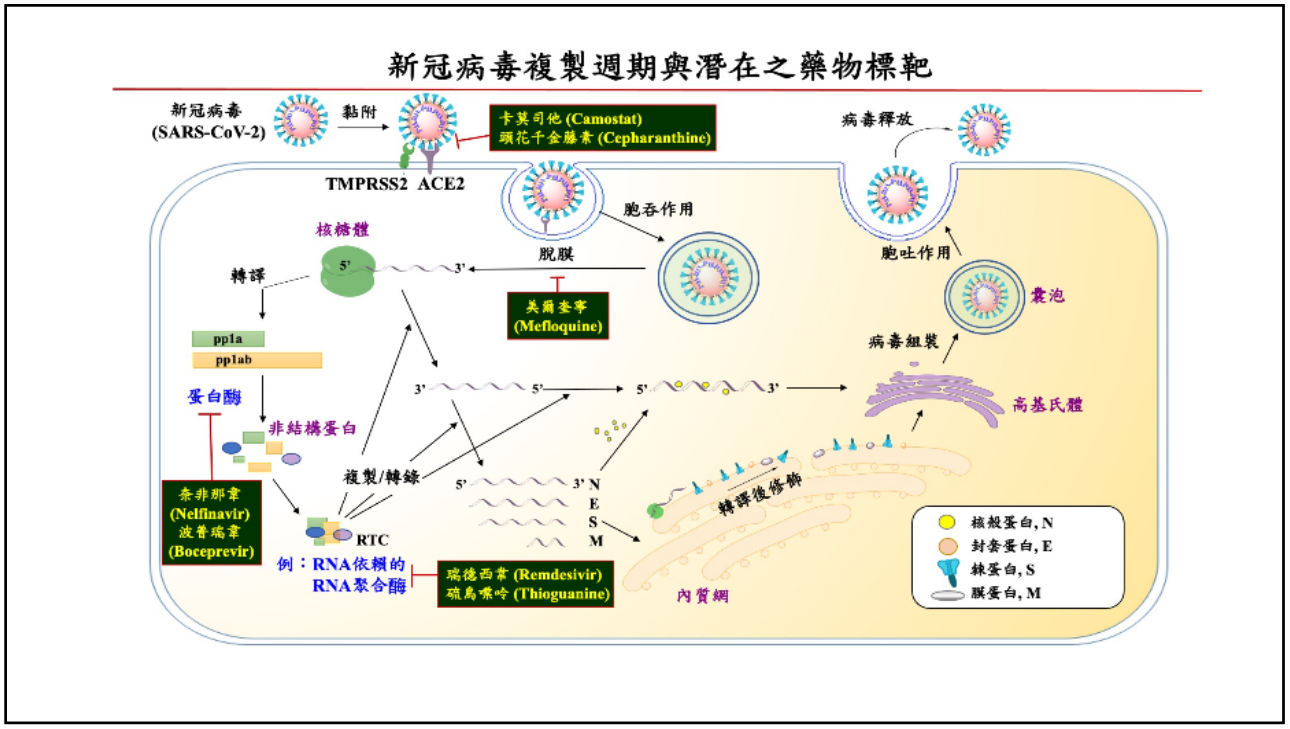

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