流感的流行病學

李雋元

高醫附院 感染科

1

大綱

- 在COVID-19疫情下，流感的疫情如何呢?
- 在COVID-19疫情下，其它呼吸道病毒的疫情如何呢?
- 放寬non-pharmaceutical interventions管制後，呼吸道感染的疫情可能會如何呢?
- 為什麼我們要來認識流感的威脅呢?
- 流感的症狀、併發症與其它病原菌的共同感染
- 抗藥性流感病毒株

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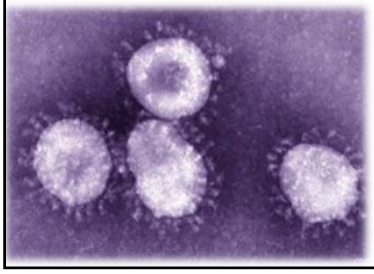

Travel restrictions

Environmental disinfection

Messaging on handwashing

Lockdowns

Physical distancing

Use of face coverings

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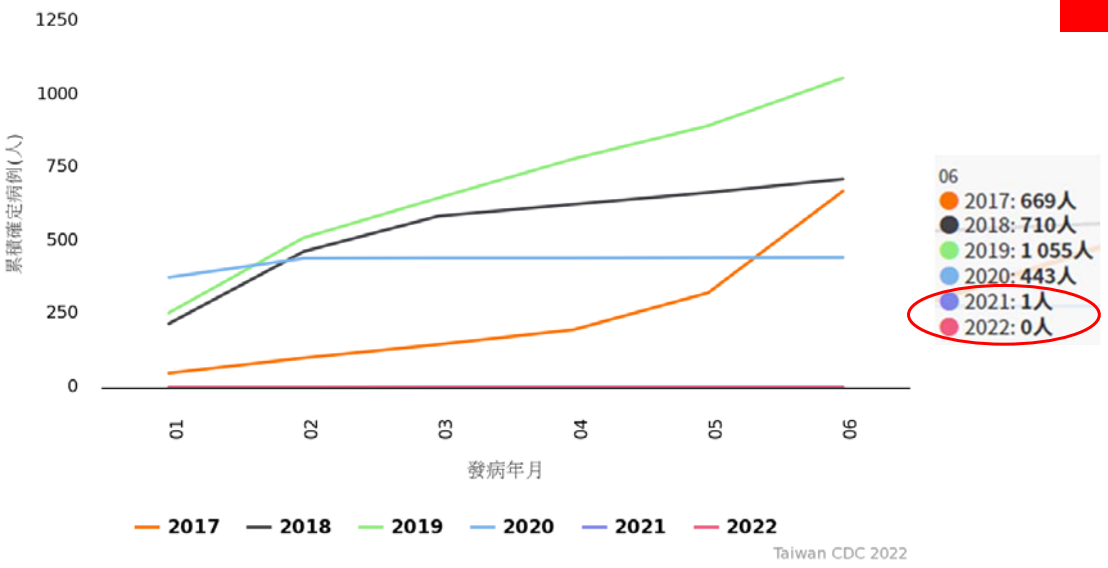
全國流感併發重症本土病例及境外移入病例累積確定病例同期比較趨勢圖



Last update: 2021/8/20

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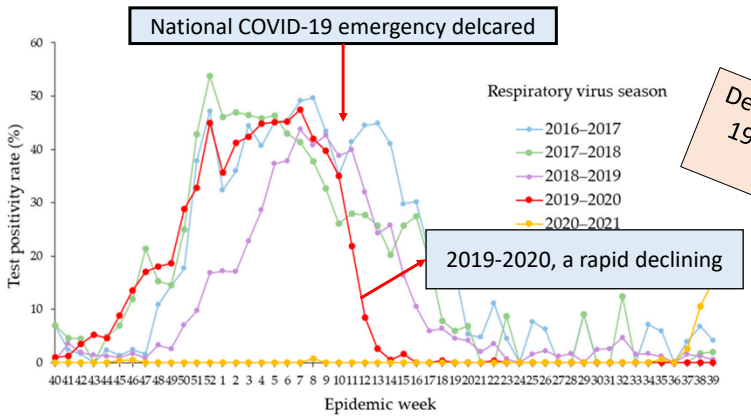

Decreased influenza activity during the COVID-19 pandemic-United States, Australia, Chile, and South Africa, 2020

In the United States, influenza virus circulation declined sharply within 2 weeks of the COVID-19 emergency declaration and widespread implementation of community mitigation measures, including school closures, social distancing, and mask wearing, although the exact timing varied by location

Int J Environ Res Public Health. 2022 May 13;19(10):5942

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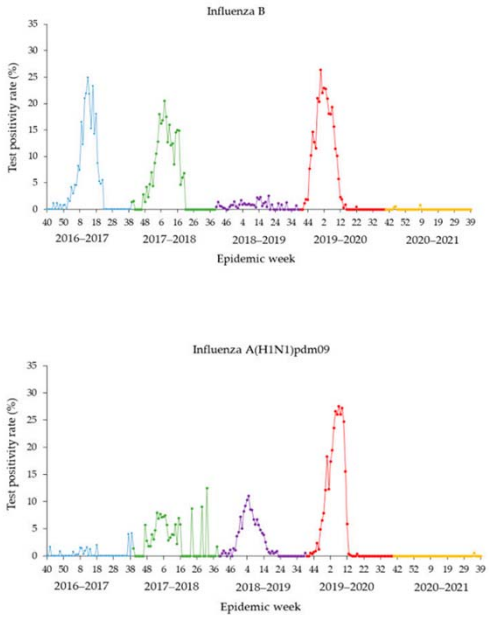

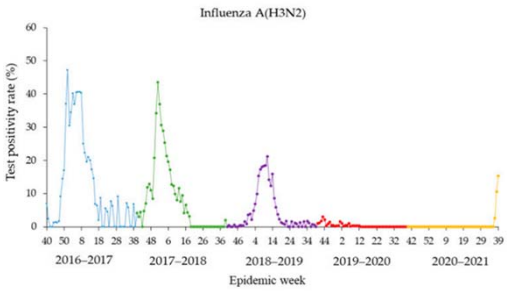

Int J Environ Res Public Health. 2022 May 13;19(10):5942

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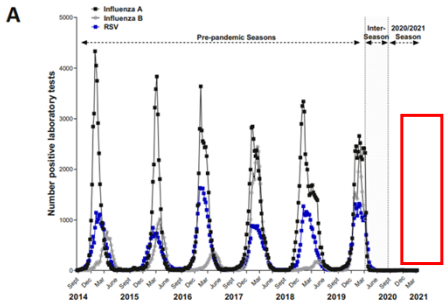
The impact of the COVID-19 pandemic on influenza, respiratory syncytial virus, and other seasonal respiratory virus circulation in Canada: A population-based study



For influenza A and B, the percent positive decreased to 0.0015 and 0.0028 times that of pre-pandemic (2014-2019) levels respectively

Table 1
Average weekly testing numbers and percentage positive tests for non-SARS-CoV-2 respiratory viruses at sentinel laboratories in Canada for the 2020/2021 season and 2014-2019 pre-pandemic seasons.

	Pre-pandemic		2020/2021 season			
Virus	Average weekly no. of laboratory tests (min-max)	Average weekly % positive tests(min-max)	Average weekly no. of laboratory tests(min-max)	Average weekly % positive tests (min-max)	Rate ratio of % positivity for 2020/2021 season versus pre-pandemic period (95% CI)*	p-value*
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Lancet Reg Health Am. 2021 Jul 17;100015

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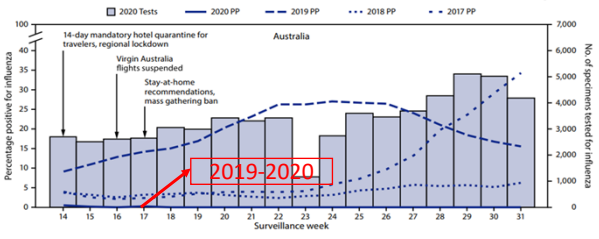
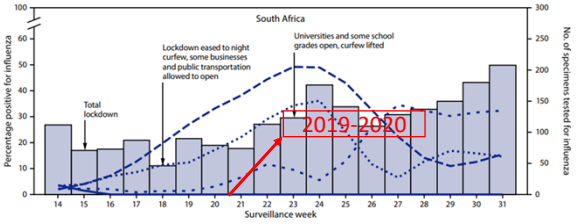
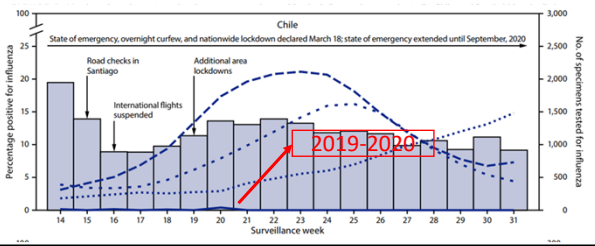
Influenza data reported to the World Health Organization's (WHO's) FluNet platform from three Southern Hemisphere countries that serve as robust sentinel sites for influenza from Oceania (Australia), South America (Chile), and Southern Africa (South Africa) showed very low influenza activity during June–August 2020, the months that constitute the typical Southern Hemisphere influenza season







MMWR Morb Mortal Wkly Rep. 2020 Sep 18;69(37):1305-1309

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COVID-19 and Influenza Co-infection: A Systematic Review and Meta-Analysis

TABLE 1 | Characteristics of included prevalence studies.

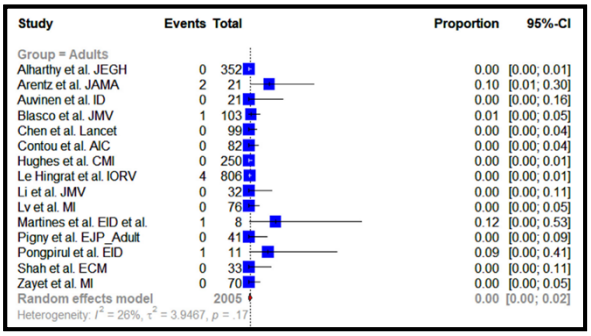
First author	Published time	Country	Patients with COVID-19	Patients with COVID-19–Influenza co-infection (%)	IV-A	IV-B	Co-infected patients	
							Mean age	Male/Female
Castillo et al. (8)	July, 2020	USA	42	1 (2.4)	1	0	21	1/0
Ding et al. (9)	March, 2020	China	115	5 (4.3)	3	2	50.2	2/3
Garazzino et al. (10)	May, 2020	Italy	168	1 (0.6)	1	nr	nr	Nr
Hashemi1 et al. (11)	July, 2020	Iran	105	23 (21.9)	23	0	nr	14/9
Hu et al. (12)	March, 2020	China	70	32 (45.7)	32	0	62.8	13/19
Kim et al. (13)	April, 2020	USA	116	1 (0.9)	1	0	74	Nr
Leuzinger et al. (14)	July, 2020	Switzerland	930	2 (0.2)	2	0	>16	Nr
de Suoza Luca et al. (15)	May, 2020	Brazil	115	1 (0.9)	0	1	36	Nr
Ma et al. (16)	Jun, 2020	China	250	3 (1.2)	2	1	nr	Nr
Takahashi et al. (17)	Sep, 2020	USA	902	3 (0.3)	nr	Nr	nr	Nr
Zhu et al. (18)	May, 2020	China	257	7 (2.7)	2	5	15–44	Nr

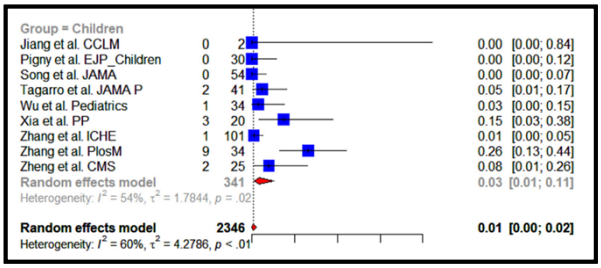
The prevalence of influenza infection was **0.8%** in patients with confirmed COVID-19. The frequency of influenza virus co-infection among patients with COVID-19 was **4.5%** in Asia and **0.4%** in the America.

Front Med (Lausanne). 2021 Jun 25;8:681469.

Rates of co-infection with SARS-CoV-2 and influenza virus in COVID-19 children and adult patients

18,021 patients infected with SARS-CoV-2 who were tested for influenza viruses.
Of them, 143 patients were co-infected.





The proportion of co-infection in children was 3.2%, 95% CI = [0.9– 10.9] and that among adult patients was 0.3%, 95% CI = [0.1 – 1.2]

J Clin Virol Plus. 2021 Sep;1(3):100036.

Conclusions

- The global trends of season influenza decline because of widespread implementation of measures to mitigate transmission of SARS-CoV-2.
- Therefore, the co-infection of influenza and COVID-19 remain low.

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Hospitalized patients in Hadassah Medical Center (1100 inpatient beds tertiary medical centre in Jerusalem), April-August 2020.

Table 1
Respiratory pathogen testing and detection rates in April–August 2020 compared to April–August 2017–2019

	April-August 2017-19			April-August 2020			Reduction %	P-value
	Tests yearly mean ± SD	Positive yearly mean ± SD	Detection rate %	Total number of tests	Number of positives	Detection rate %		
Adenovirus	1108.7 ± 171	72.3 ± 35.5	6.52	173	1	0.60	91	<0.001
HMPV	1108.0 ± 171	47.0 ± 17.1	4.24	173	0	0.00	100	<0.001
Influenza A H3N2	1108.3 ± 171	6.3 ± 5.5	0.57	173	0	0.00	100	0.81
Influenza A H1N1	1106.7 ± 171	8.7 ± 8.1	0.78	173	0	0.00	100	0.53
Influenza B	1108.3 ± 171	9.7 ± 11.5	0.87	173	0	0.00	100	0.39
Parainfluenza 1	1108.0 ± 171	15.7 ± 18.0	1.41	173	1	0.61	55.6	0.60
Parainfluenza 2	1108.0 ± 171	1.0 ± 1.7	0.09	173	0	0.00	100	0.73
Parainfluenza 3	1108.0 ± 171	45.3 ± 15.3	4.09	173	1	0.61	85	0.007
RSV	1108.3 ± 171	5.3 ± 4.0	0.48	173	0	0.00	100	0.88
Mycoplasma pneumoniae	499.3 ± 144.8	28.7 ± 11.9	5.74	223	0	0.00	100	0.001
Bordetella pertussis	62.7 ± 18.4	9.7 ± 5.0	15.43	24	2	8.33	46	0.535

Test numbers are presented in *yearly means* ± SD for 2017–2019 and *absolute number* for 2020; p was calculated for comparing number for positive/totals in 2020 versus the total numbers in 2017–2019. There was a reduction in vancomycin-resistant enterococcus (VRE) testing from an average of 5836.3 ± 1132.1 (mean ± standard deviation) in 2017–2019 to 2976 tests in April–August 2020, a reduction of 49%.
HMPV, human metapneumovirus; RSV, respiratory syncytial virus; SD, standard deviation.

Clin Microbiol Infect. 2020 Dec 31;27(5):811-812.

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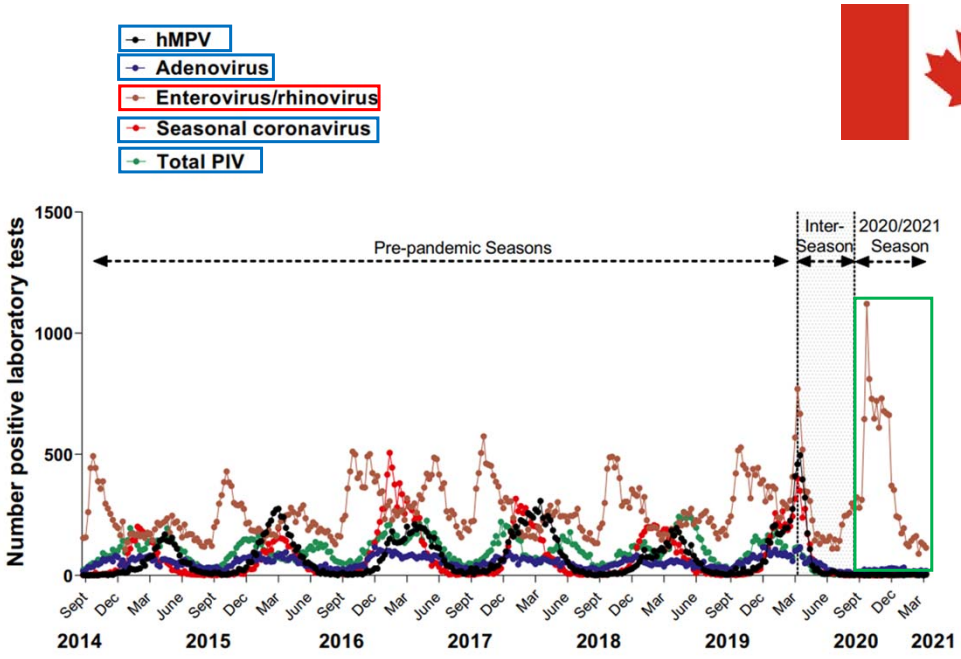

Lancet Reg Health Am. 2021 Jul 17;100015

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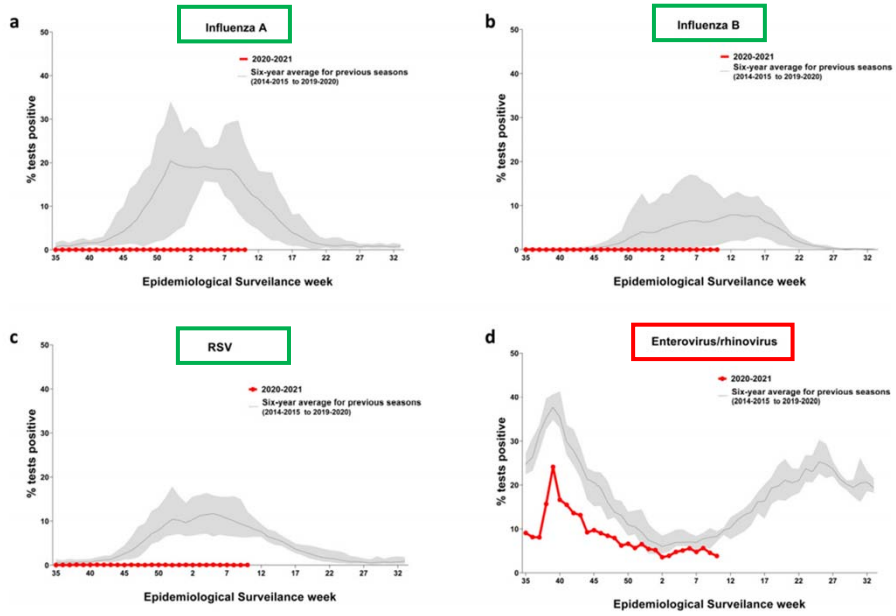

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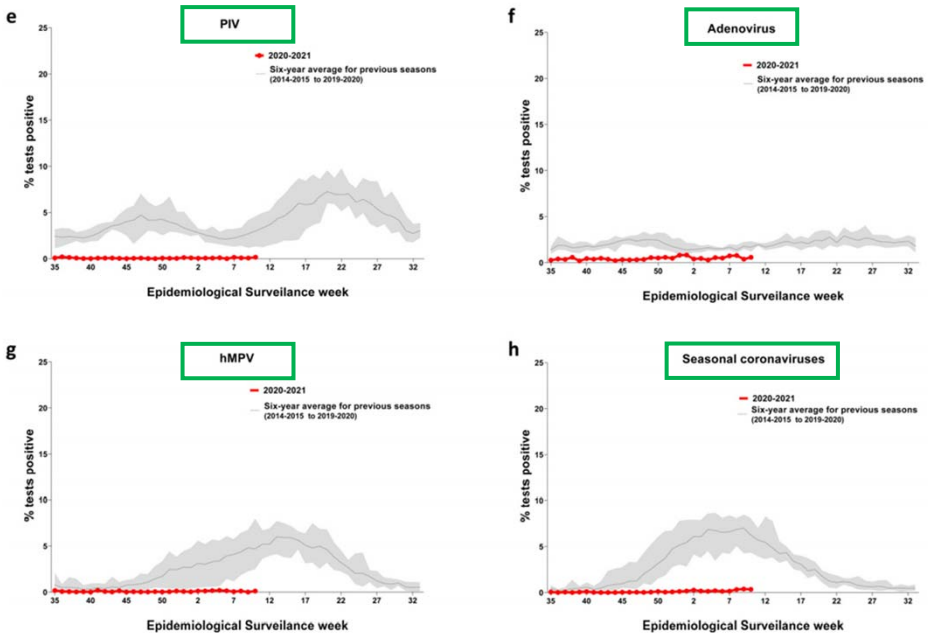

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RSV	6207 (1327 - 16348)	5•96 (0•22 - 17•80)	8890 (4952 -18413)	0•047 (0 - 0•10)	0•0169 (0•0122–0•0235)	<0•001
PIV	3242 (1155 - 7187)	3•09 (1•15 – 7.00)	4586 (2034 - 8486)	0•067 (0 - 0•20)	0•0190 (0•0144–0•0250)	<0•001
Adenovirus	3412 (1164 - 7207)	1•85 (0•85 – 3.34)	4551 (2039 – 7986)	0•460 (0•19 - 0•82)	0•2336 (0•2002–0•2725)	<0•001
hMPV	3263 (971 - 6890)	1•85 (0 – 6.74)	4578 (2077 - 8485)	0•074 (0 - 0•19)	0•0379 (0•0243–0•0592)	<0•001
Entero/ rhinovirus	2254 (595 - 5980)	17•05 (4•31 - 41•29)	4459 (1868 - 8334)	8•463 (3•56 - 24•12)	0•5331 (0•4795–0.5927)	<0•001
Coronaviruses**	2495 (815 - 6413)	3•16 (0 - 8•57)	3789 (2032 - 6743)	0•105 (0 - 0•38)	0•0275 (0•0186–0•0406)	<0•001

We report an effective absence of the annual seasonal epidemic of most seasonal respiratory viruses in 2020/2021. This dramatic decrease is likely related to implementation of multi-layered public health measures during the pandemic. The impact of such measures may have relevance for public health practice in mitigating seasonal respiratory virus epidemics and for informing responses to future respiratory virus pandemics

Lancet Reg Health Am. 2021 Jul 17;100015

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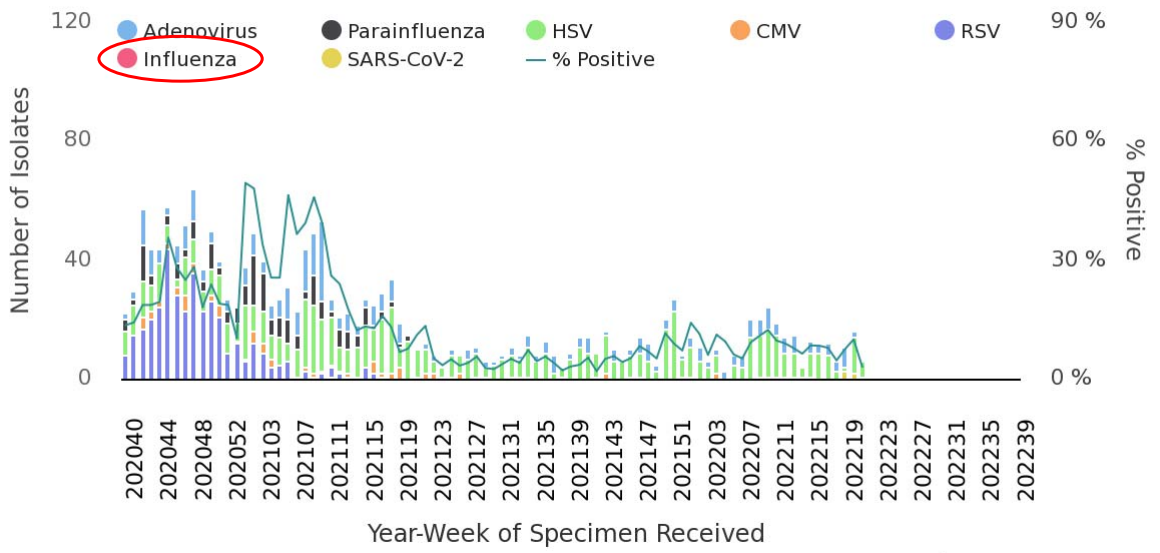

Taiwan CDC 2022/06/10

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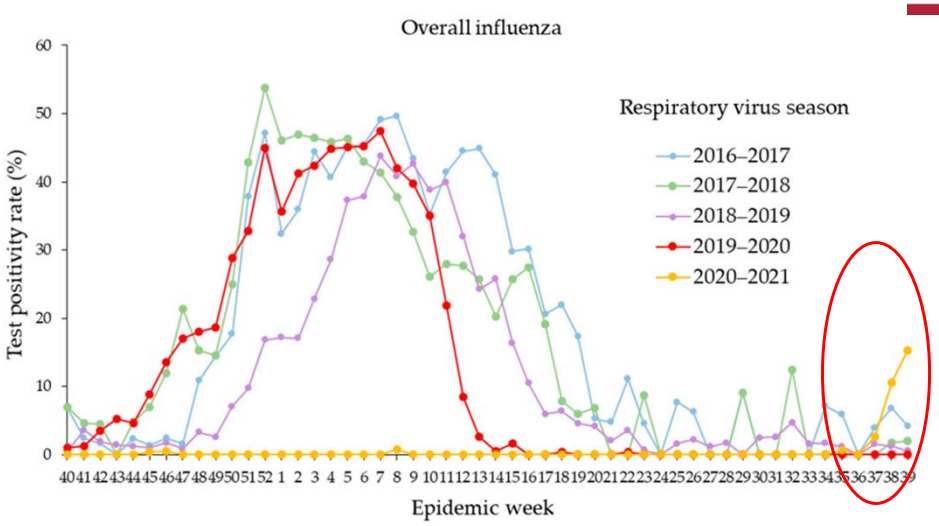

Int J Environ Res Public Health. 2022 May 13;19(10):5942

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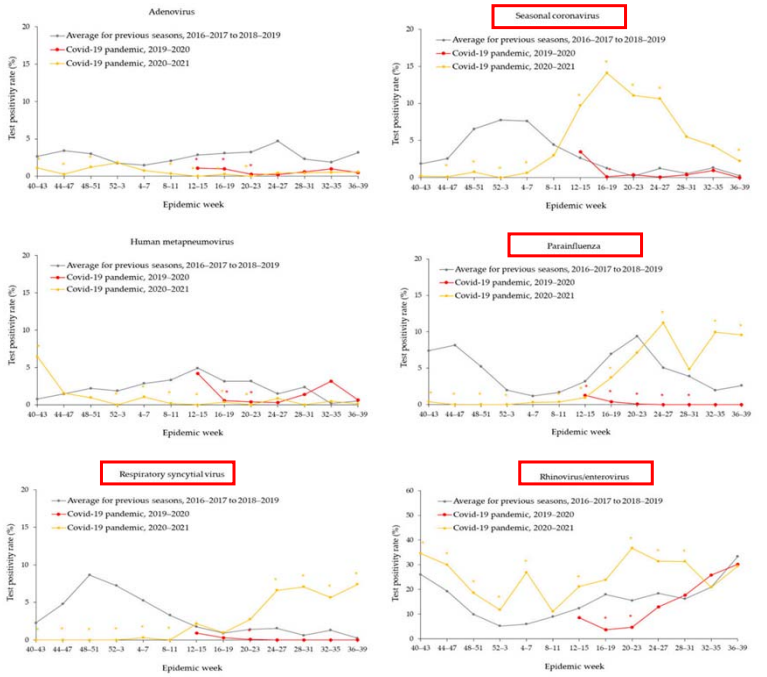

許多呼吸道病毒(seasonal coronavirus, parainfluenza, RSV, rinhovirus/enterovirus)隨著隔離政策的鬆綁，疫情有復燃的跡象。

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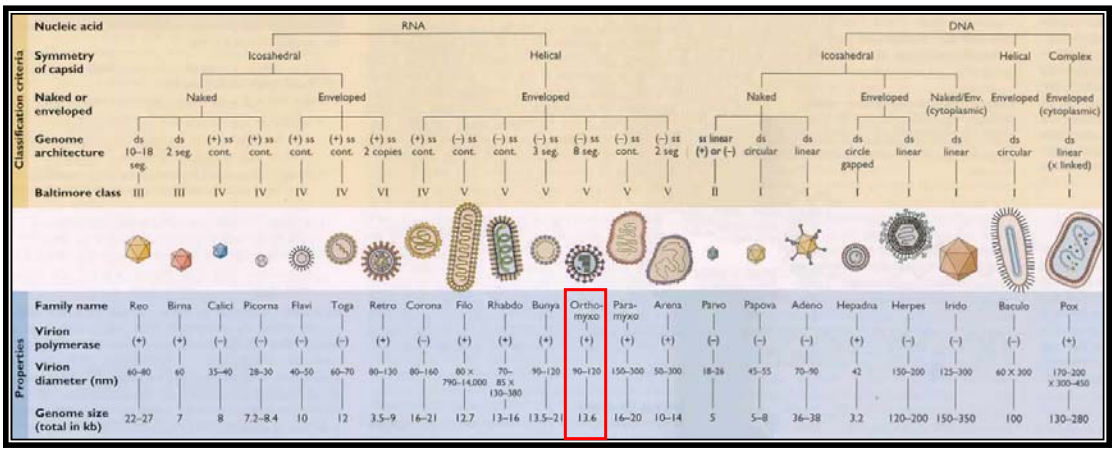
病毒分類



流感病毒為RNA病毒，屬正黏液病毒科（*Orthomyxoviridae* family）

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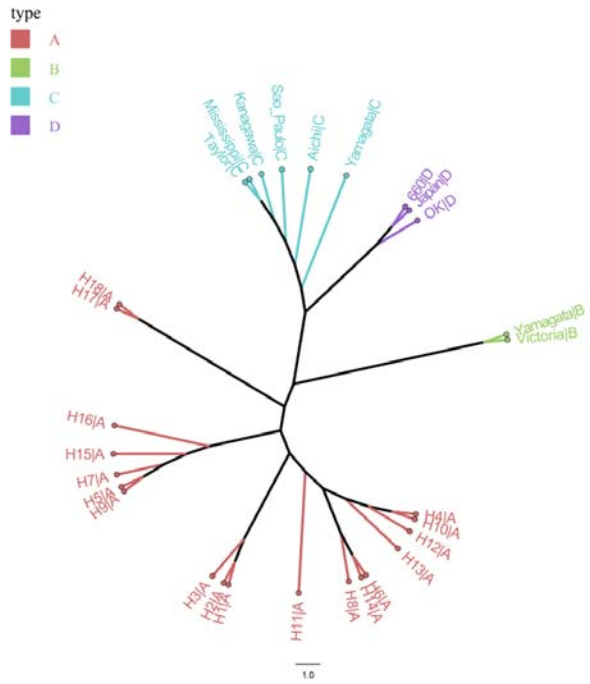

Phylogenetic tree of Infuenza viruses based on PB2 sequences

- **流感病毒可以分為：** type A、type B、 type C、 type D:
  - 只有type A、 type B、type C會感染人類。
  - Type C流感很罕見，只會造成輕微的上呼吸道感染。

Virol J. 2021 Nov 22;18(1):230.

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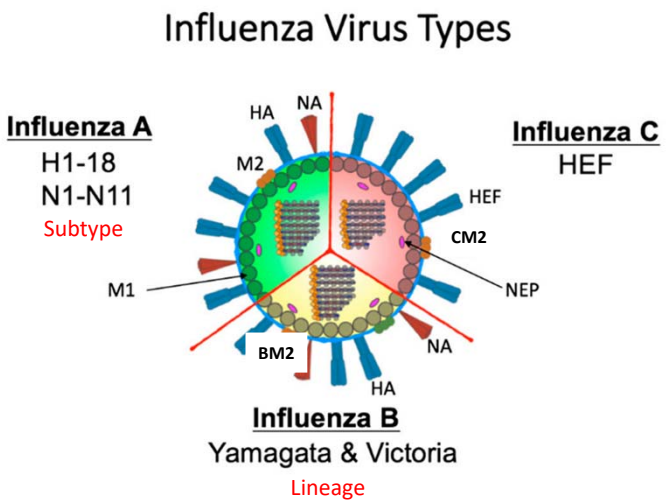
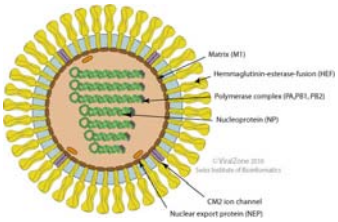
A、B 、C型流行性感冒病毒的結構





- The surface of influenza C virus is defined by a single spike protein referred to as hemagglutinin-esterase-fusion glycoprotein (HEF).
- This protein has host receptor binding abilities, membrane fusion capabilities, and enzymatic activity for egress.

Viruses. 2019 Jan 30;11(2):122.

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	A型流感病毒	B型流感病毒	C型流感病毒
基因結構	有八個基因片段	有八個基因片段	有七個基因片段
病毒體結構	11個蛋白質	11個蛋白質	9個蛋白質
抗原變異種類	Antigenic drift, antigenic shift	Antigenic drift	Antigenic drift
抗原變異性	變異性大,可能會發生抗原性大變異,會產生一個新的病毒株	抗原變異性較穩定	抗原性非常穩定
自然界宿主	人,豬,馬,禽鳥類,哺乳動物	人,海豹	人,豬
引起疾病嚴重度	高危險群感染後容易引發嚴重併發症,且所引起之症狀最嚴重	引起症狀較A型輕微,通常會於老年人及幼童等高危險群發生嚴重併發症	症狀較輕微,甚至無症狀
發生流行程度	易發生變異,如出現一種新的病毒亞型,將會引起	引可能發生”Antigenic drift”,故恐會引起地	無季節性

- A 型流感病毒除了感染人類，還可能出現**跨物種**間的傳播，如豬、馬、雞、鴨等，而 B 型則至今**只**曾出現在人類（其餘只有在雪貂和海豹有表現出對B型流感的敏感性）。
- 只有A型與B型可以引起大規模的季節性流行。

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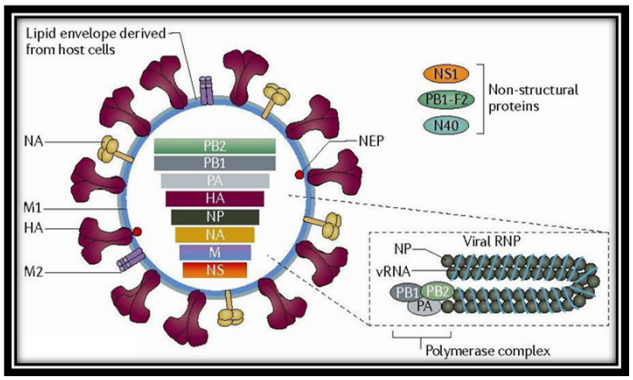

- PB1, PB2, PA節段編碼的是RNA聚合酶（RNA polymerase）
- HA節段負責編碼血球凝集素
- NP節段負責編碼核蛋白（nucleoprotein）
- NA節段編碼的是神經胺酸酶
- M節段編碼基質蛋白
- NS節段編碼的是具有剪接RNA（RNA splicing）功能的非結構蛋白（nonstructural protein）

- A型可依表面抗原血球凝集素（H 抗原）及神經胺酸酉每（N 抗原）的不同，還可分為許多亞型：
  - 其中H 抗原亞型共有18 種，為H1-H18。
  - N 抗原亞型共11 種，為N1-N11。

B 型及C 型流感病毒則不區分亞型

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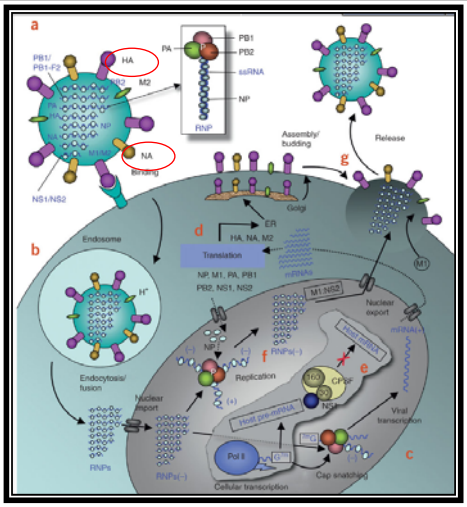
A型流感的生命週期

- **Hemagglutinin (HA)：**
  - Receptor binding (sialic acid)
  - Membrane fusion
  - Neutralizing antibody target
- **Neuraminidase (NA)：**
  - Remove sialic acid residues
  - Virion release
- **Ion channel (M2)：**
  - H^+-dependent uncoating
  - Influenza A only



Nature Structural & Molecular Biology 17,530–538(2010

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A型流感病毒有甚麼獨特之處?

跨物種間的感染

流感病毒抗原多變性

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水鳥是A型流感病毒的天然宿主

短頸野鴨

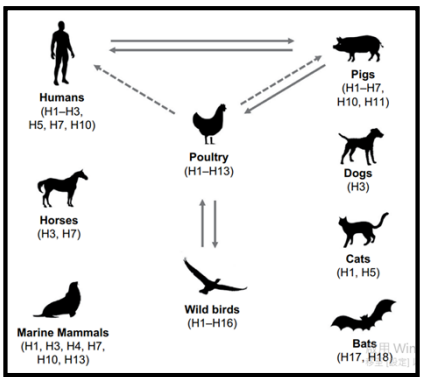
綠頭鴨

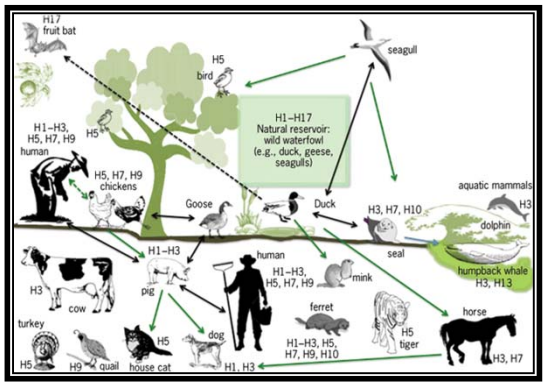
銀鷗

- 水鳥（aquatic waterfowl）是A型流感病毒的天然宿主，在牠們身上可以分離出大部分的亞型，通常感染的水鳥並不會有症狀。
- 病毒在水鳥的腸道內繁殖，藉由季節性的遷徙，將流感病毒帶到世界各地，經由糞口傳播的途徑傳染給當地的家禽，或更進一步傳染給當地其它的動物。

32

各種A型流感亞型的宿主



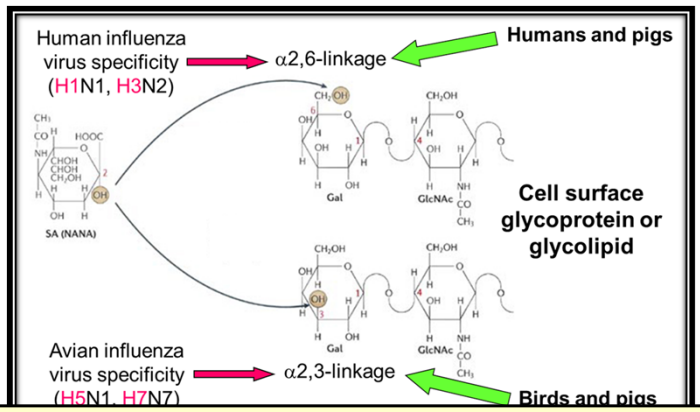


- A型流感的自然宿主多為野生水禽，經過長時間的候鳥遷徙、攜帶病毒感染不同宿主，並持續在物種間演化，目前多種A型流感病毒亞型已能感染不同物種。
- 其中最常見的亞型包括H1-H3，主要感染哺乳類動物，以及H5、H7、H9，主要感染家禽。

Infect Drug Resist. 2017 Apr 20;10:121-134. http://www.accessscience.com/search.aspx?rootID=802694

33

Sialic acid的鍵結決定了流感病毒HA受器的連結



流感病毒藉由血球凝集素HA和宿主細胞的表面接受器唾液酸（sialic acid）結合，進而與細胞膜融合，感染宿主細胞。

--鳥類的呼吸道細胞的唾液酸是以α2,3方式與半乳糖結合（SAα2,3Gal），只能和禽流感病毒結合。

--而人類呼吸道細胞的唾液酸是以α2,6方式和半乳糖結合（SAα2,6Gal），只能和人類流感病毒結合。

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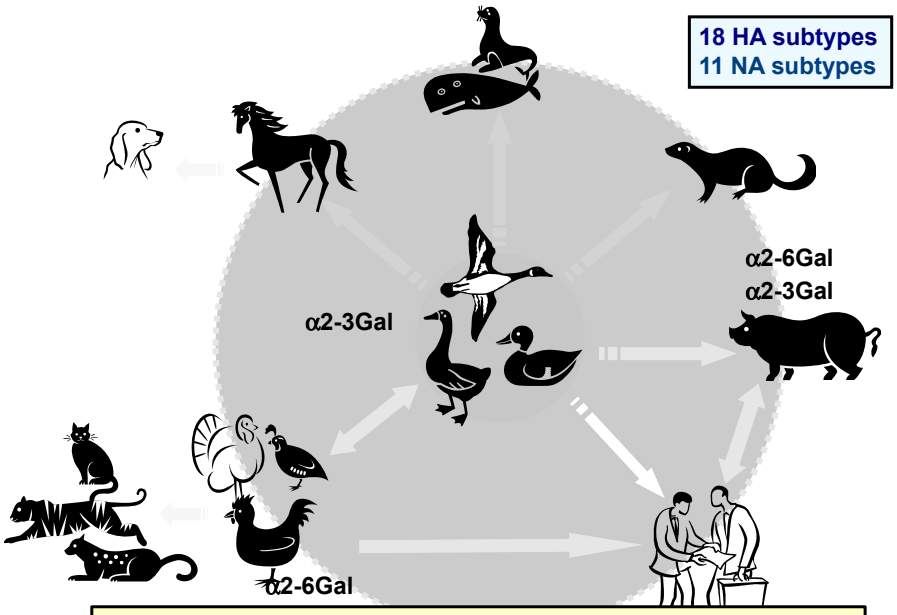

這種病毒與接受器的結合是有專一性的，也是流感病毒感染為何會有物種障礙的原因之一。

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流感病毒抗原多變性

- 流感病毒的一個很重要的特徵是具有抗原改變的能力。

抗原的漂變 (Antigenic Drift)
抗原性轉變 (Antigenic Shift)

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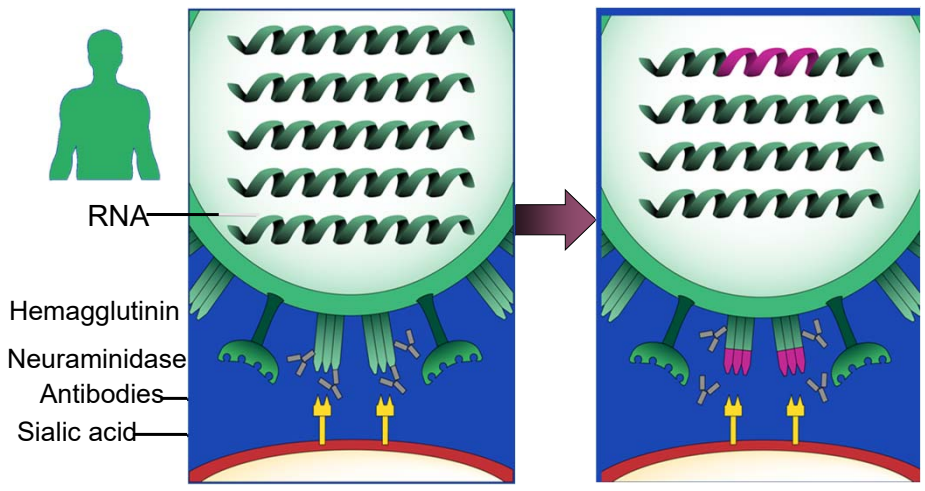
- **抗原的漂變（Antigenic Drift）：**
  - 是在病毒的HA/NA上緩慢、相對上持續的過程，又稱為抗原的連續性變異。
  - 病毒基因複製所累積的點突變（point mutation）所導致，進而產生新的strain。
  - 在A型以及B型流感皆有可能。
  - 因為這新的strain導致之前的抗體無法提供完全的保護力，所以流感疫苗必須時時更新。

抗原的漂變(Antigenic Drift)



血球凝集素 (Hemagglutinin) 神經胺酸酶 (Neuraminidase) 抗體 (Antibody)

- **抗原性轉變 （Antigenic Shift）：**
  - 是一較劇烈、突然的過程，又稱為抗原的不連續性變異。
  - 只有A型流感會。
  - 當某一A型流感病毒株帶有在人類已許久沒有流通的HA/NA蛋白時在人類間出現時，便可能造成pandemic。
  - 可能的機轉為：
    - 涉及基因段的互換，例如當不同來源的病毒株同時感染同一宿主時，病毒於複製過程就可能產生基因段互換及重新排列組合（reassortment）。
    - 從動物身上(豬、鳥等)的病毒株直接感染人，而沒有經過基因重組。
    - 某一病毒株從某一動物身上(鳥)經由中間宿主(豬)傳到人身上。

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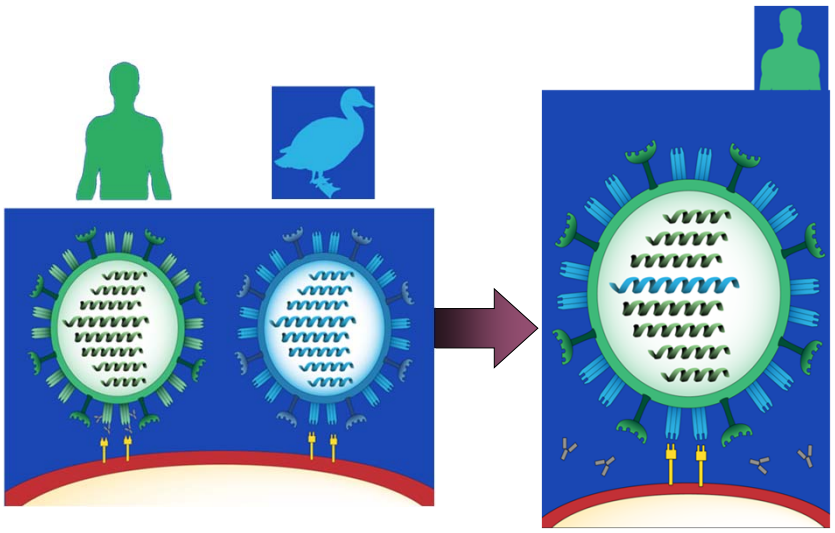
抗原性轉變(Antigenic Shift)



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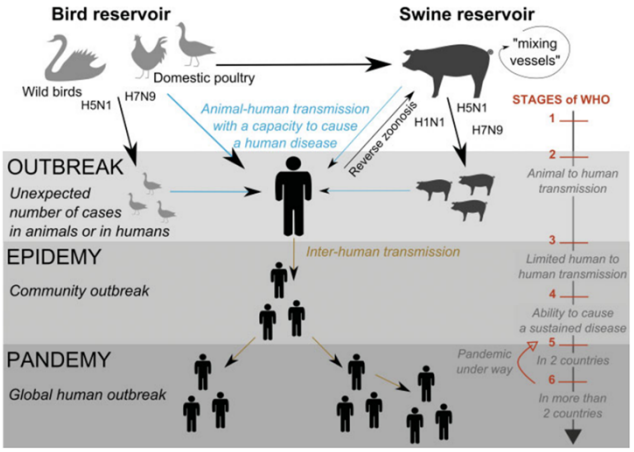
A schematic representation showing major events involved in emergence of an influenza pandemic, from the two major animal reservoirs to the global outbreak in humans



因為豬的呼吸道同時表現出鳥禽與人類的流感受器，所以豬就像是一個 “mixing vessels”，可以讓不同物種間的A型流感產生重組。

Semin Respir Crit Care Med. 2016 Aug;37(4):487-500.

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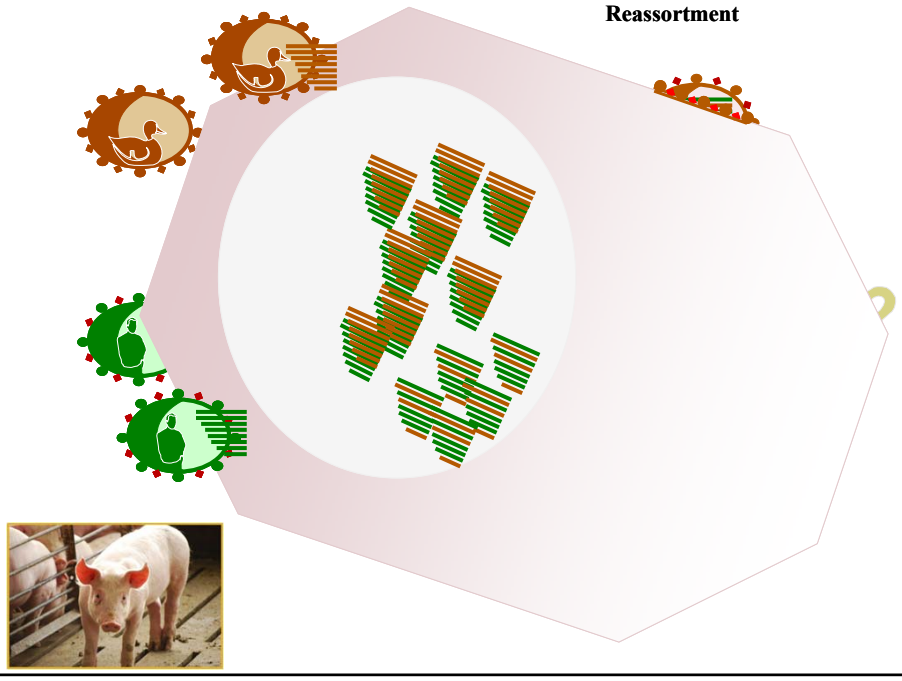
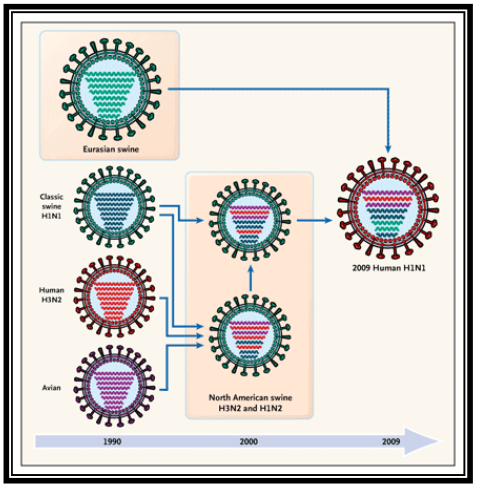


42

Origin of 2009 pandemic H1N1 influenza strain "quadruple reassortant"



- 2009的新型流感病毒其祖先可能在1998年之前已存在北美豬群，但僅有少量流傳，且已是人，禽及豬流感病毒基因型三重組株（triple reassortant）
- 與後來傳入北美豬群的歐亞形似禽型（Avian-like）豬流感病毒發生基因重排組，形成現有可傳播至人類身上且在人際之間大流行的病毒基因組態（gene constellation）

Trifonov et al., NEJM 361:115, 2009

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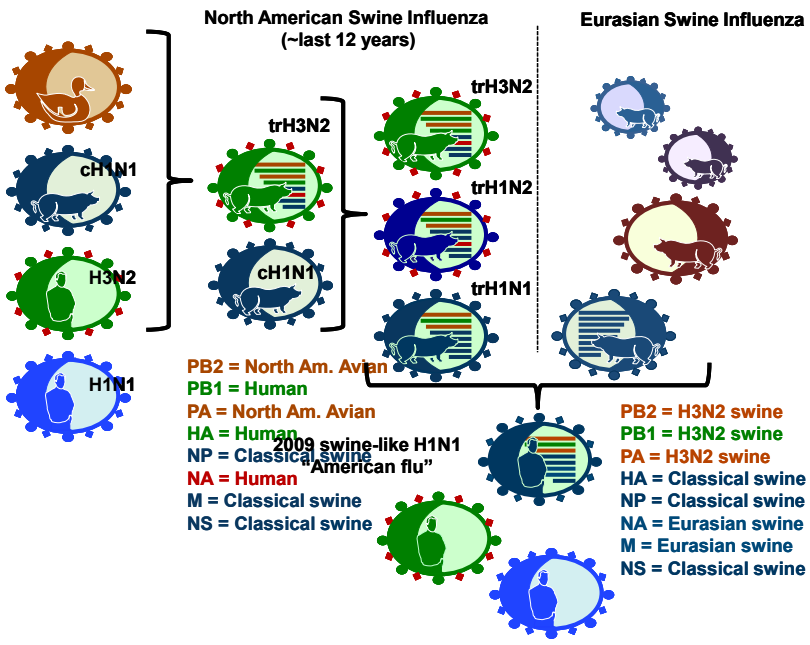

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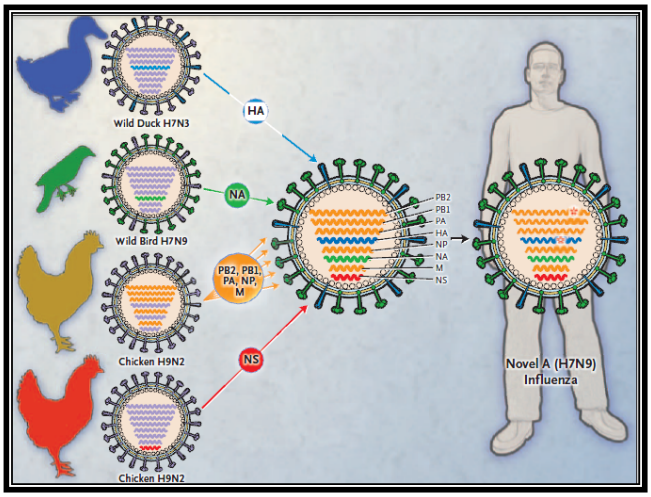
Origin of the novel avian influenza A H7N9 virus



N Engl J Med 2013; 368:2345-2348

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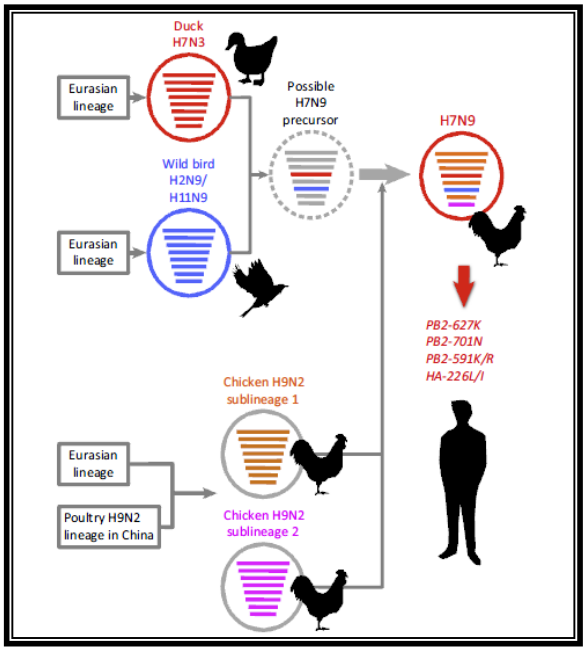

Trends in Microbiology xx (2014) 1–9 1

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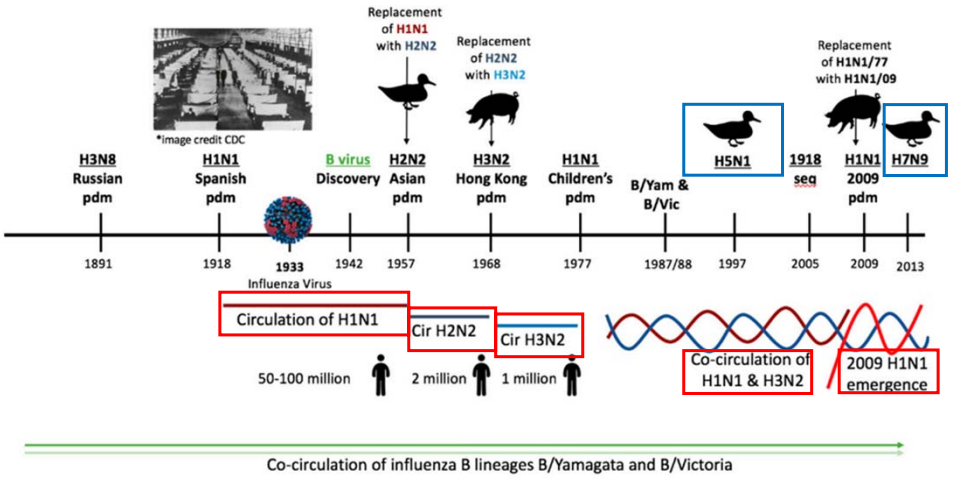
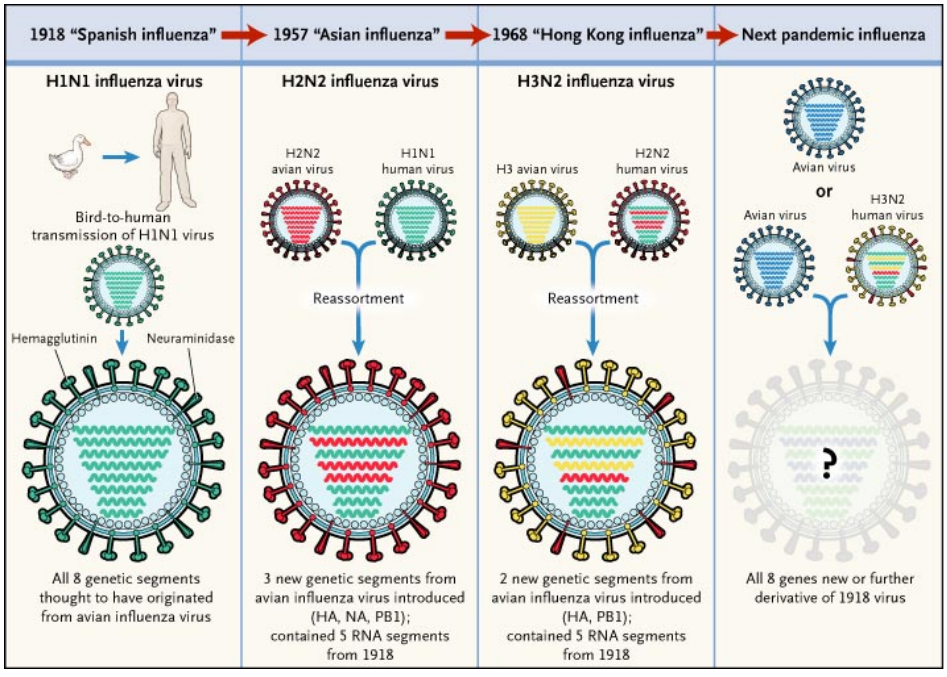
Timeline of the history of influenza virus circulation in humans since 1890s



Viruses. 2019 Jan 30;11(2):122.

47



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“西班牙流感 ”A(H1N1):*1918 -19*

全球2千萬人死亡,美國60萬人死亡。

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“亞洲流感 ” A(H2N2): *1956- 57*

全球1百萬人死亡,
美國7萬人死亡。

51

“香港流感 ” A(H3N2):*1968 -69*

全球1百萬人死亡,美國3萬4千人死亡。

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其它曾感染過人類的新型A型流感亞型

- 不同亞型流感病毒對人類的感染力及所造成疾病嚴重度不相同，目前曾造成人類嚴重疾病的亞型包括於1997年首次出現的H5N1流感，及2013年發現的H7N9流感，其致死率分別約為60%及30%。
- 另有些流感病毒亞型感染人類後僅引發輕微症狀或無症狀，例如H7N3流感及H9N2流感等。

病毒亞型	西元年	個案數(死亡數)	發生國家	臨床症狀
H3N2v	2011~	340 (1)	United States	類似季節性流感
H5N1	1997 2003 2003~	18 (6) 2 (1) 641 (380)	起始於Hong Kong，近5年集中於 Bangladesh, Cambodia, China, Egypt Indonesia, Vietnam等6國	類流感、嚴重肺炎
H5N6	2013	1 (1)	China	類流感、嚴重肺炎
H6N1	2013	1 (0)	Taiwan	類流感、輕微肺炎
H7N2	2002 2003 2007	1 1 4	United States (Virginia) New York United Kingdom	結膜炎、類流感
H7N3	2004 2006	2 1	Canada (British Columbia) United Kingdom	結膜炎、類流感
H7N7	1996 2003	1 89 (1)	United Kingdom Netherlands	多為結膜炎、類流感， 一名獸醫出現嚴重肺炎 後死亡
H7N9	2013~	450 (158)	China, Hong Kong, Taiwan, Malaysia	類流感、嚴重肺炎
H9N2	1999 2003 2007 2008	2 1 1 1	Hong Kong Hong Kong Hong Kong China	類流感
H10N7	2004 2010	2 2	Egypt Australia	結膜炎、類流感
H10N8	2013	3 (2)	China	類流感、嚴重肺炎

Reference: http://www.cidrap.umn.edu/infectious-disease-topics/avian-influenza-bird-flu#overview&1-5

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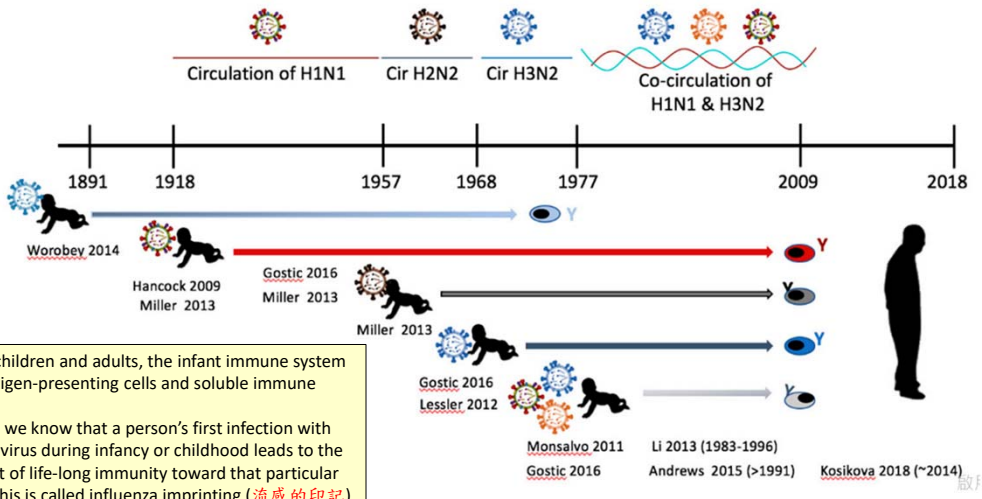
Influenza immune imprinting and the history of circulating influenza viruses



- Unlike older children and adults, the infant immune system has fewer antigen-presenting cells and soluble immune factors.
- Paradoxically, we know that a person's first infection with the influenza virus during infancy or childhood leads to the establishment of life-long immunity toward that particular virus strain. This is called influenza imprinting (流感的印記)

Viruses. 2019 Jan 30;11(2):122.

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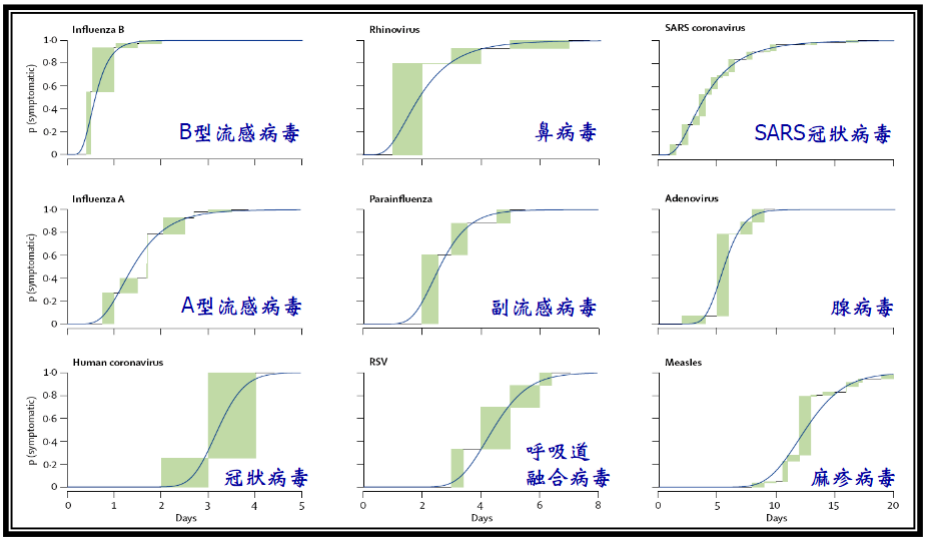
大綱

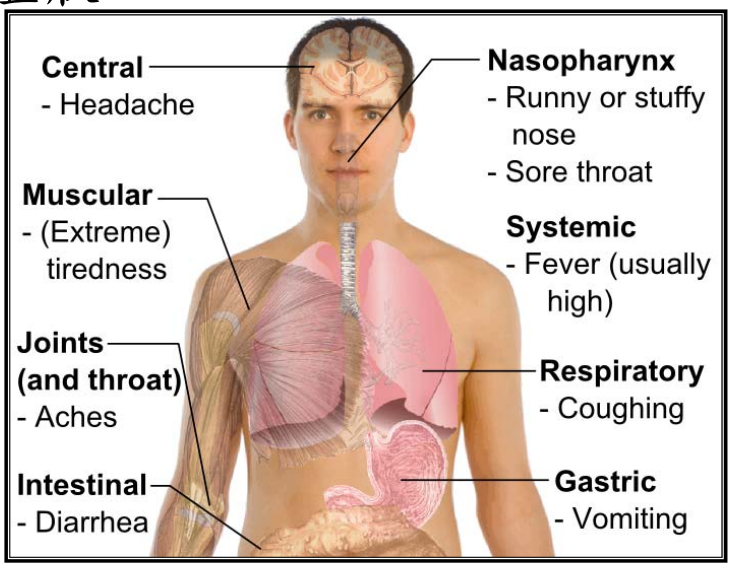
- 在COVID-19疫情下，流感的疫情如何呢?
- 在COVID-19疫情下，其它呼吸道病毒的疫情如何呢?
- 放寬non-pharmaceutical interventions管制後，呼吸道感染的疫情可能會如何呢?
- 為什麼我們要來認識流感的威脅呢?
- 流感的症狀、併發症與其它病原菌的共同感染
- 抗藥性流感病毒株

病毒感染的潛伏期



Lancet Infect Dis 2009;9:291-300

流感的症狀



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流感，一般感冒，及H5N1流感比較表			
項目	**流感**	**一般感冒**	**H5N1流感**
至病原	流感病毒，可分為A(H1N1及H3N2)，B，C三型	大約有200多種病毒可引起，常見的由鼻病毒，副流感病毒，呼吸道融合性病毒，腺病毒等	流感病毒(H5N1)
臨床症狀			
發燒	有，高燒，約可持續3天	少發燒，僅體溫些微升高	有，高燒
喉嚨痛	明顯的喉嚨痛	較不嚴重	常見
頭痛	通常伴隨著嚴重頭痛	偶而輕微頭痛	常見
全身痠痛及疲倦	全身肌肉酸痛，關節痛，會有明顯且持續的倦怠感與全身無力	較輕微或少見	常見
肌肉痛	少部分幼童會有小腿肌肉酸痛		肌肉痛
打噴嚏與流鼻水	症狀出現之初1~2天內會出現打噴嚏，流鼻水	通常會有打噴嚏與鼻塞	常見
咳嗽	出現在症狀開始後1~2天之內		常見
腹瀉	少見	無或少	常見
其它	寒顫		肺炎，呼吸困難，呼吸衰竭，多重器官衰竭及死亡
潛伏期	約1~4天	約1天	2~8天

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流感，一般感冒，及H5N1流感比較表			
項目	**流感**	**一般感冒**	**H5N1流感**
高危險族群	所有年齡族群	所有年齡族群	農牧業，屠宰業，醫療照護業，相關研究實驗室
傳染途徑	飛沫傳染；接觸傳染	飛沫傳染；接觸傳染	1. 禽傳人：接觸H5N1流感病患肢動物或其排遺，至吸入或接觸掩鼻黏膜 2. 有限人傳人：與病例密切接觸
病程	1~2週	短期間可復原	自發病死亡介於1~30天（中位數9天）
治療	依照醫師處方給予抗病毒藥物治療及支持性療法	感冒多半可自癒，支持性療法	48小時內給予抗病毒藥物
預後	佳	佳	部份轉為病毒性肺炎，嚴重時會死亡，致死率高
併發症	肺炎，心肌炎，腦病變，腦炎，雷氏症候群等	較少出現合併症	肺炎，腦炎，血球吞噬症候群
預防方法	有疫苗	無疫苗	無疫苗

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Complications of Influenza

Cardiovascular[26]
- Cerebrovascular accidents
- Ischemic heart disease
- Myocarditis

Hematologic[26]
- Hemolytic uremic syndrome
- Hemophagocytic syndrome
- Thrombotic thrombocytopenic purpura

Musculoskeletal[19,26]
- Myositis
- Rhabdomyolysis

Neurologic[26]
- Acute disseminated encephalomyelitis
- Encephalitis
- Guillain-Barré syndrome
- Postinfluenza encephalopathy (neurologic symptoms occurring after resolution but within 3 weeks of primary infection)
- Reye syndrome
- Transverse myelitis

Ocular[26]
- Conjunctivitis (most common)
- Optic neuritis
- Retinopathy
- Uveal effusion syndrome

Pulmonary[8,25,27]
- Acute respiratory distress syndrome
- Diffuse alveolar hemorrhage
- Hypoxic respiratory failure
- Primary viral pneumonia
- Secondary bacterial pneumonia

Renal[26]
- Acute kidney injury (e.g., acute tubulointerstitial nephritis, glomerulonephritis, minimal change disease)
- Multiorgan failure

Am Fam Physician. 2019;100(12):751-758

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The frequency of influenza and bacterial coinfection

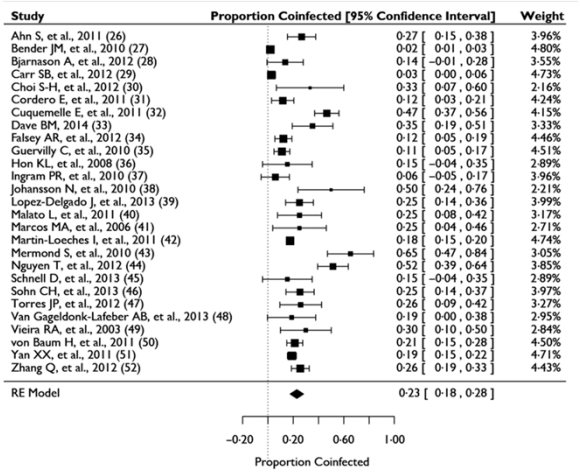

Figure 3. Frequency of bacterial coinfection in hospitalized patients with laboratory confirmed influenza.

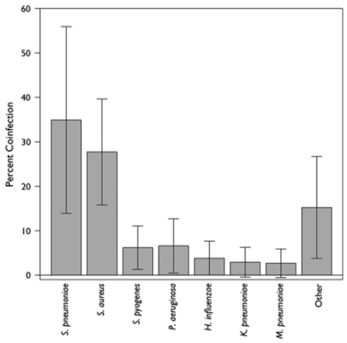

Figure 4. Percent of laboratory confirmed influenza infections that were coinfected by each bacterial species.

Streptococcus pneumoniae and *Staphylococccus* aureus were the most common pathogens accounting for 35% (95% CI, 14%–56%) and 28% (95% CI, 16%–40%) of identified coinfecting bacteria, respectively

Influenza Other Respir Viruses. 2016 Sep;10(5):394-403.

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TABLE 165-4 Comparative Features of Pulmonary Complications of Influenza

	Primary Viral Pneumonia	*Secondary Bacterial Pneumonia*	*Mixed Viral and Bacterial Pneumonia*	*Localized Viral Pneumonia*
Setting	Cardiovascular disease; pregnancy; young adult	Age, >65 y; pulmonary disease	Any associated with A or B	?Normal
Clinical history	Relentless progression from classic 3-day influenza	Improvement, then worsening after 3-day influenza	Features of both primary and secondary pneumonia	Continuation of classic 3-day syndrome
Physical examination	Bilateral findings, no consolidation	Consolidation	Consolidation	Area of rales
Sputum bacteriology	Normal flora	*Pneumococcus, Staphylococcus, H. influenzae*	*Pneumococcus, Staphylococcus, H. influenzae*	Normal flora
Chest radiography	Bilateral findings	Consolidation	Consolidation	Segmental infiltrate
White blood cell count	Leukocytosis with shift to left	Leukocytosis with shift to left	Leukocytosis with shift to left	Usually normal
Isolation of influenza virus	Yes	No	Yes	Yes
Response to antibiotics	No	Yes	Often	No
Mortality	High	Low	Variable	Very low

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病毒性肺炎常見的電腦斷層表現

- The imaging findings seen in patients with H1N1 infection include:
  - Consolidations
  - Ground-glass opacities
  - Interlobular septal thickening
  - Small nodules
  - Findings suggestive of small airways disease

American Journal of Roentgenology. 2011;196: W723-W728

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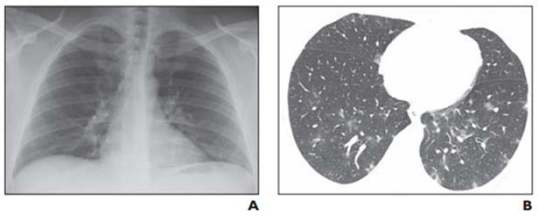
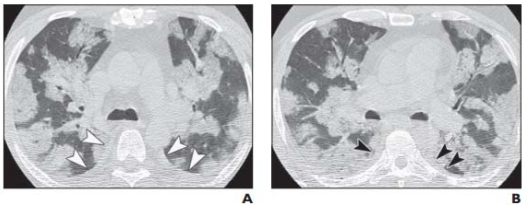
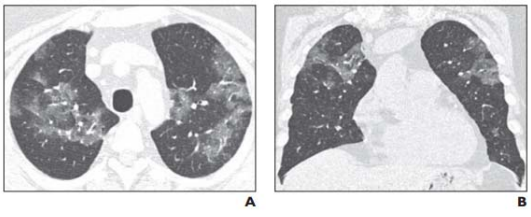


32-year-old man with H1N1 pneumonia. A, Chest radiograph shows normal lungs. B, CT image obtained on same day as A shows mild ground-glass opacity in both lungs that predominates in lower lobes.



44-year-old man with H1N1 pneumonia. A and B, CT images at carina level (A) and main bronchi level (B) show bilateral round consolidations with peribronchovascular distribution. Also seen is small bilateral pleural effusion (arrowheads).



35-year-old woman with H1N1 pneumonia. A–C, Axial CT image (A), coronal reformatted image (B), and sagittal reformatted image (

American Journal of Roentgenology. 2011;196: W723-W728

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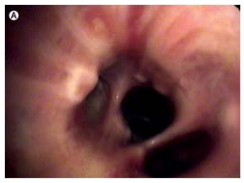
The frequency of influenza and IPA coinfection

References		Location	Influenza Season
Schauwvlieghe, et al. (2018) [5]	Belgium and The Netherlands	2009–2016	Findings
Wauters, et al. (2012) [10]	Belgium	2009–2011	19% of influenza-infected patients were diagnosed with IPA, IPA was associated with 51% mortality
van de Veerdonk, et al. (2017) [6]	The Netherlands	2015–2016	23% of influenza-infected patients were diagnosed with IPA
Huang, et al. (2020) [11]	China	2017–2019	16% of influenza-infected patients were diagnosed with IPA
Ku, et al. (2017) [9]	Taiwan	2015–2016	31% of influenza-infected patients were diagnosed with IPA, IPA was associated with 58% mortality
Coste, et al. (2021) [13]	France	2009–2018	17% of influenza-infected patients were diagnosed with IPA, IPA was associated with 66% mortality
Schwartz, et al. (2020) [14]	Canada	2014–2019	5.3% of influenza-infected patients were diagnosed with IPA
Martin-Loeches, et al. (2017) [15]	Spain	2009–2015	7.2% of influenza-infected patients were diagnosed with IPA
Sharma, et al. (2020) [16]	United States	2005–2014	7.2% of influenza-infected patients were diagnosed with IPA
Wu, et al. (2017) [12]	Taiwan	2016–2019	0.17% of influenza-infected patients were diagnosed with IPA



J Fungi (Basel). 2022 Apr 22;8(5):428.

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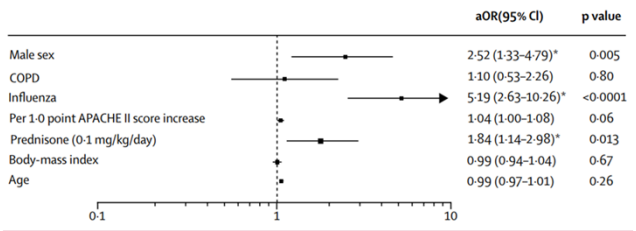
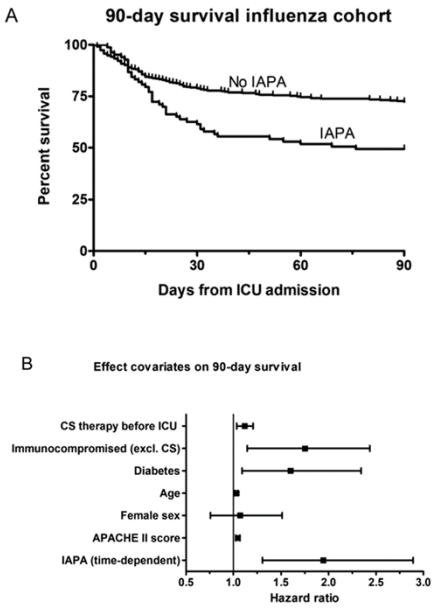
Forest plots of risk factors for the development of invasive pulmonary aspergillosis



Lancet Respir Med. 2018 Oct;6(10):782-792



Clin Infect Dis. 2020 Oct 23;71(7):1764-1767.

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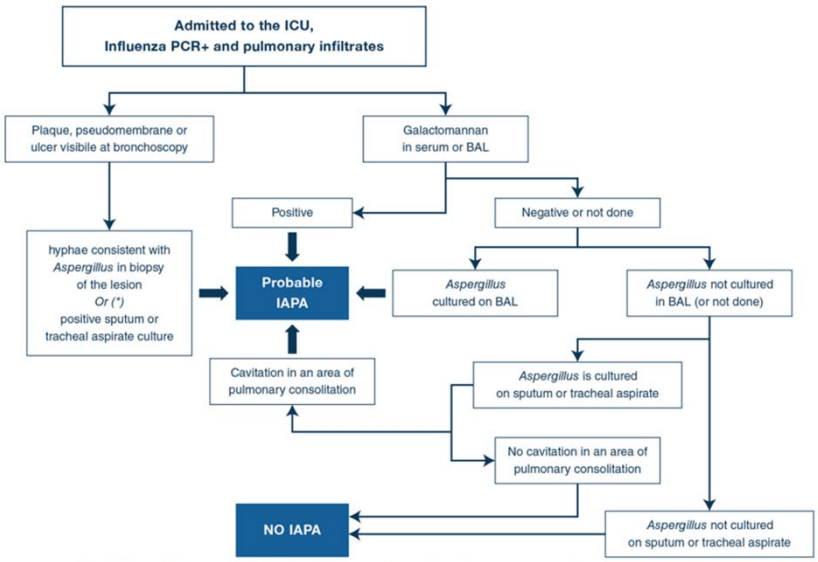
Table 1 Proposed case definition for IAPA in ICU patients

Entry criteria: influenza-like illness + positive influenza PCR or antigen + temporally relationship		
	***Aspergillus* tracheobronchitis**	**IAPA in patients without documented *Aspergillus* tracheobronchitis**
Proven	Biopsy or brush specimen of airway plaque, pseudomembrane or ulcer showing hyphal elements and *Aspergillus* growth on culture or positive *Aspergillus* PCR in tissue	Lung biopsy showing invasive fungal elements and *Aspergillus* growth on culture or positive *Aspergillus* PCR in tissue
Probable	Airway plaque, pseudomembrane or ulcer and at least one of the following: Serum GM index > 0.5 *or* BAL GM index ≥ 1.0 *or* Positive BAL culture *or* Positive tracheal aspirate culture *or* Positive sputum culture *or* Hyphae consistent with *Aspergillus*	**A**: Pulmonary infiltrate and at least one of the following: Serum GM index > 0.5 *or* BAL GM index ≥ 1.0 *or* Positive BAL culture ***OR*** **B**: Cavitating infiltrate (not attributed to another cause) and at least one of the following: Positive sputum culture *or* Positive tracheal aspirate culture

Intensive Care Med. 2020 Aug;46(8):1524-1535.



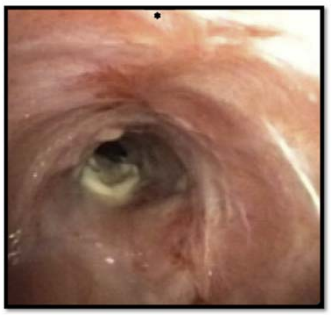


Fig. 4. Tracheobronchitis with obstruction in bronchoscopy. *Ventral wall.

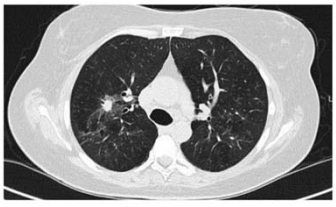


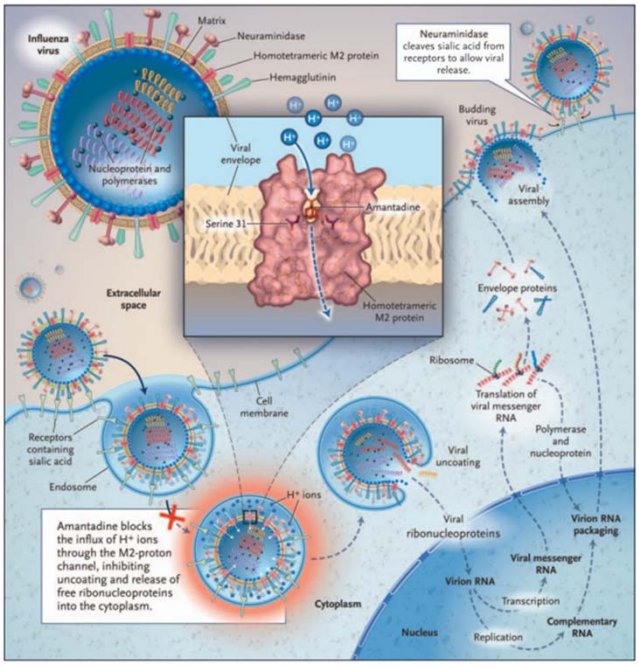
Fig. 5. Chest computed tomography.

Fig. 1 Flowchart of probable IAPA classification. (*)If hyphae consistent with *Aspergillus* are documented in a biopsy of an airway lesion AND *Aspergillus* is grown from sputum or a tracheal aspirate, the case fulfills the definition of proven IAPA

Intensive Care Med. 2020 Aug;46(8):1524-1535.

大綱

- 在COVID-19疫情下，流感的疫情如何呢?
- 在COVID-19疫情下，其它呼吸道病毒的疫情如何呢?
- 放寬non-pharmaceutical interventions管制後，呼吸道感染的疫情可能會如何呢?
- 為什麼我們要來認識流感的威脅呢?
- 流感的症狀、併發症與其它病原菌的共同感染
- 抗藥性流感病毒株



- Amantadine與Rimantadine均可作用於貫穿於病毒外膜上由M2 protein組成的離子通道（ion channel）。
- 當病毒進入細胞內時，氫離子會進入病毒的M2 protein離子通道，並引發病毒複製之後續機序。
- 一旦Amantadine與Rimantadine進入M2 protein 離子通道，則將阻斷氫離子進入病毒的M2 protein離子通道，抑制病毒於細胞內複製。

N Engl J Med. 2006 Feb 23;354(8):785-8.

M2 protein inhibitor

藥名	金剛烷（Amantadine）	甲基金剛烷（Rimantadine）
作用機轉（Mechanism）	干擾A型流感病毒複製 對B型流感病毒無效	干擾A型流感病毒複製 對B型流感病毒無效
效力（Efficacy）	48小時內投藥可降低病情嚴重度及縮短病程	48小時內投藥可降低病情嚴重度及縮短病程
適應症（Indications）	兒童及成人	成人

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- **M2 protein inhibitor 的限制：**
  - 只對A型流感有效，因B型流感病毒沒有M2 protein 。
  - 副作用發生頻率高，包括中樞神經副作用(CNS side effect，焦慮，無法集中)及腸胃道副作用等。
  - 在現行流行的A型流感廣泛出現抗藥性。

現在已沒再用來治療流感了!!

1, CDC MMWR April 20, 2001
2, Antimicrob Agents Chemother 1991; 35:1741~7
3, Arch Intern Med 1995; 155:533~7

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Table 1. Frequency of recovering drug-resistant influenza A (H3N2) virus during rimantadine treatment

Reference	Year of study	Patient group	Patients treated (*n*)	Patients shedding resistant virus	
				(*n*)	(%)
HALL et al. (1987)	1983	Children	37	10	27
HAYDEN et al. (1989)	1988	Children	21	6	29
HAYDEN et al. (1989)	1988	Adults	7	2	29
HAYDEN et al. (1991)	1988	Adults	6	3	50
BETTS (personal communication)	1986	Elderly	26	3	11

對amantadine產生抗藥的病毒株:

- 在治療過程中很快就會出現，甚至在治療後的2-3天就會出現。
- 這樣的突變在基因上是穩定的，在實驗室中經過好幾代的傳播，依然可以保持其表現型。
- 儘管沒有選擇性壓力的存在，high-level抗藥性依然持續在circulating influenza A中存在
- 在被感染的家庭或是養護機構的研究可以發現這個突變菌株是可以傳播的，且造成典型的流感症狀。

Curr Top Microbiol Immunol. 1992;176:119-30

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Incidence of M2-Inhibitor Resistance among Human Influenza A (H3N2) Viruses in the United States.*

Period	No. of Isolates Tested	No. That Showed Resistance (%)
1992–1995	991	8 (0.8)
1996–1997	508	2 (0.4)
1998–1999	510	11 (2.2)
2000–2001	283	4 (1.4)
2002	290	4 (1.4)
2003	174	3 (1.7)
2004	466	9 (1.9)
October 2004–March 2005	636	92 (14.5)
October–December 2005	209	193 (92.3)

N Engl J Med. 2006 Feb 23;354(8):785-8.

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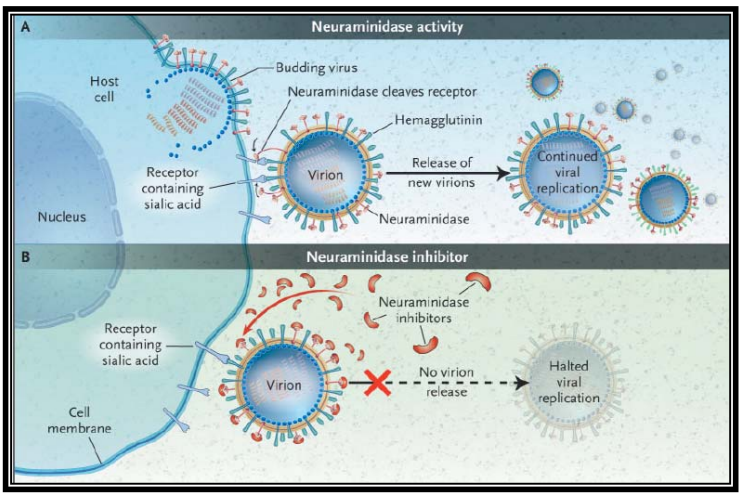
神經胺酸酶抑制劑

- 和M2抑制劑比起來，副作用少相當多。
- 和M2抑制劑比起來較不易造成抗藥性菌株。
- 對所有的病毒株都有效，這在大流型疫情時非常重要。

因為流感病毒株的複製在疾病開始後的24至72小時內達到最高點，因此作用在病毒複製期的身經安酶抑制劑必須在疾病開始盡量越早給藥越好

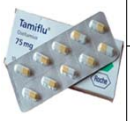
The New England Journal of Medicine 2005, 353:1363-1373

神經氨酶抑制劑的作用機轉



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

Antiviral Medications Recommended for Treatment and Chemoprophylaxis of Influenza – U.S. CDC

Antiviral Agent		Use	Recommended For	Not Recommended for Use in	Adverse Events
Oral Oseltamivir		Treatment	Any age[1]	N/A	**Adverse events:** nausea, vomiting. Post marketing reports of serious skin reactions and sporadic, transient neuropsychiatric events (self-injury or delirium; mainly reported among Japanese adolescents and adults).
		Chemo-prophylaxis	3 months and older[1]	N/A	
Inhaled Zanamivir		Treatment	7 yrs and older	people with underlying respiratory disease (e.g., asthma, COPD)[2]	**Allergic reactions:** oropharyngeal or facial edema. **Adverse events:** diarrhea, nausea, sinusitis, nasal signs and symptoms, bronchitis, cough, headache, dizziness, and ear, nose and throat infections.
		Chemo-prophylaxis	5 yrs and older	people with underlying respiratory disease (e.g., asthma, COPD)[2]	
Intravenous Peramivir		Treatment	**2 yrs and older**	N/A	**Adverse events:** diarrhea. Post marketing reports of serious skin reactions and sporadic, transient neuropsychiatric events (self-injury or delirium; mainly reported among Japanese adolescents and adults).
		Chemo-prophylaxis	N/A	N/A	

N/A = not applicable, COPD = chronic obstructive pulmonary disease

US CDC, http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

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四種神經胺酶抑制劑與涎酸(sialic acid)的結構比較

	Structural features			
Structure	Carboxylate group	Glycerol group	Guanidine group	Pentyl (hydrophobic) side group
Sialic Acid	✓	✓		
Zanamivir	✓	✓	✓	
Oseltamivir	✓			✓
Peramivir	✓		✓	✓

因為結構不完全相同，彼此間不見得會有交互抗藥性

Current Opinion in Virology 2014, 8:22–29

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Table 1 Centers for Disease Control and Prevention (CDC; USA data) and Public Health England (PHE; England data) influenza resistance data

Influenza season	CDC	PHE
2013–2014	Influenza A H1N1: 98.8% oseltamivir susceptible to oseltamivir and 100% zanamivir susceptible No specific date for influenza A H3N2 or B identified 'High-level' adamantane resistance	1.9% neuraminidase resistance
2014–2015	Influenza A H1N1: 98.4% oseltamivir susceptible to oseltamivir and 100% zanamivir susceptible Influenza A H3N2 and B: 100% susceptible to oseltamivir and zanamivir	0.5% neuraminidase resistance
2015–2016	Influenza A H1N1: 99.2% oseltamivir and peramivir susceptible and 100% zanamivir susceptible No specific date for influenza A H3N2 or B identified 'High-level' adamantane resistance	0.8% neuraminidase resistance
2016–2017	Influenza A (all subtypes) and B: 100% susceptible to oseltamivir, peramivir and zanamivir 'High-level' adamantane resistance	0.2% neuraminidase resistance
2017–2018	Influenza A H1N1: 99% oseltamivir and peramivir susceptible, 100% zanamivir susceptible Influenza A H3N2 and B: 100% susceptible to oseltamivir, peramivir and zanamivir 'High-level' adamantane resistance	–

Eur J Clin Microbiol Infect Dis. 2020 Jul;39(7):1201-1208.

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Influenza Subtype	NA Mutation*	Virus Source/NAI Used for Selection	Phenotype in NA Inhibition Assays†			
			Oseltamivir	Zanamivir	Peramivir	A-315675
H1N1	H274Y	Clinic/oseltamivir	R	S	R	S
	Q136K	Clinic/none	S	R	?	?
pH1N1	N294S	Reverse genetics	R	S	I/R	S
	H274Y	Clinic/oseltamivir	R	S	R	S
	H274Y/I222V	Clinic/oseltamivir	R	S	?	?
		Reverse genetics	R	S	R	S
	H274Y/I222R	Clinic/oseltamivir	R	I/R	R	?
	E119G	Reverse genetics	S	R	R	R
	E119V	Reverse genetics	R	R	R	R
H5N1	N294S	Clinic/oseltamivir	R	S	?	?
	H274Y	Clinic/oseltamivir	R	S	?	?
	D198G	In vitro/zanamivir	I	R	?	?
	E119G	In vitro/zanamivir	I	R	?	?
H3N2	N294S	Clinic/oseltamivir	R	?	?	?
	R292K	Clinic/oseltamivir	R	?	?	?
		In vitro/zanamivir	R	R	?	?
	Deletion 245–248	Clinic/oseltamivir	R	I	S	R
	D151A/D	Clinic/none	S	R	?	?
	Q136K	Clinic/none	S	R	?	?
	I222V/E119V	Clinic/oseltamivir	R	S	S	S
	E119V	Clinic/oseltamivir	R	S	S	S
	E119I	Clinic/oseltamivir	R	I/R	R	I/R
B	R371K	Clinic/none	R	R	?	?
	I222T	Clinic/none	I	I	?	?
	D198N	Clinic/oseltamivir	R	R	S	S
	R152K	Clinic/zanamivir	R	R	R	R

Semin Respir Crit Care Med. 2011 Aug;32(4):409-22.

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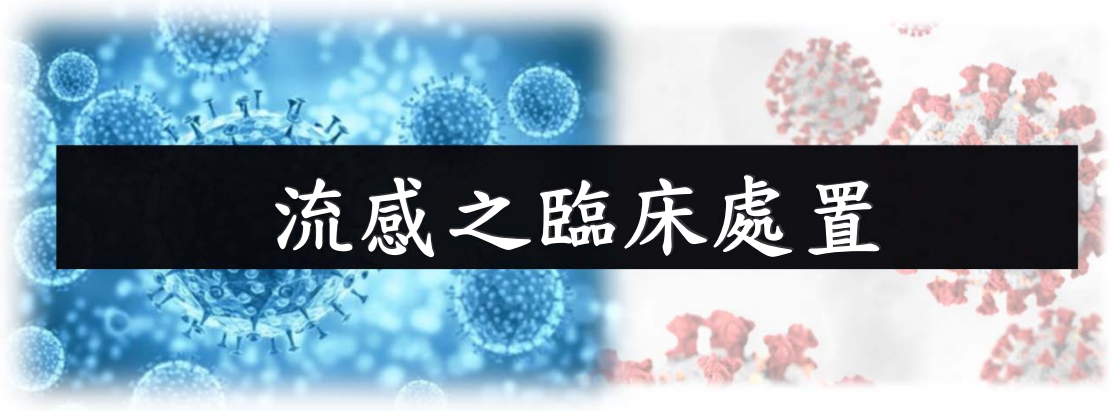

流感之臨床處置

2022. 6. 11
高雄醫學大學附設中和紀念醫院
感染科 蔡毓德
stareel.w@hotmail.com

Outline

- Introduction
- Influenza with severe complications
- Diagnosis
- Antiviral therapy
- Co-infection of Influenza and COVID-19

Introduction

- 流感是一種**急性病毒性呼吸道**疾病
- 致病原為**流感病毒**
- 每年發生**季節性**流行
- 流行期間內，爆發快，散播範圍廣泛
- 以北半球而言，好發於秋、冬兩季，約在每年11月至隔年3月期間流行
- 可能出現嚴重併發症，常以細菌性及病毒性肺炎表現，多見於**65歲以上長者、嬰幼童及慢性疾病患者**
- 可依流行程度引起全球大流行、季節性流行、散發病例

流感 vs. 感冒

	流感 (Influenza)	感冒 (Common Cold)
致病原	流感病毒	其他許多病毒(鼻病毒、呼吸道融合病 毒、腺病毒等)
影響範圍	全身性	呼吸道局部症狀為主
發病速度	突發性	突發/漸進性
主要臨床症狀	嚴重★★★ 發燒、咳嗽、頭痛、肌肉酸痛、疲 倦、流鼻水、喉嚨痛	症狀較輕微 喉嚨痛、打噴嚏、鼻塞、流鼻水
發燒	高燒3-4天	少發燒，僅體溫些微升高

流感 vs. 感冒

	流感 (Influenza)	感冒 (Common cold)
病程	1-2週	約2-5天
傳染途徑	飛沫傳染；接觸傳染	飛沫傳染；接觸傳染
傳染性	高傳染性★★★	傳染性不一
併發症	肺炎、腦炎、心肌炎及其他嚴重之 繼發性感染或神經系統疾病等	少見(中耳炎或肺炎)
治療方法	抗病毒藥劑及支持性療法	支持性療法
預防方法	勤洗手、注重呼吸道衛生及咳嗽禮 節	勤洗手、注重呼吸道衛生及咳嗽禮節
疫苗	季節性流感疫苗	無

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圖片來源: 疾病管制署-流感併發重症核心教材

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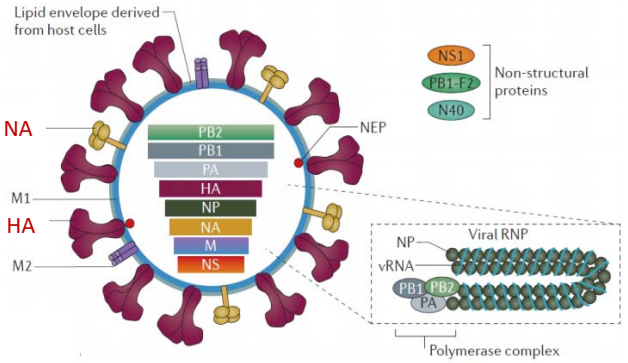
流感病毒
(Influenza virus)



- 正黏液病毒（*orthomyxoviridae*) SS(-), RNA病毒
- 分為**A型**、**B型**、C型及D型
- 外套膜含有2種醣蛋白

- **血球凝集素** (hemagglutinin: HA), 18種(附著細胞膜所需，引發中和抗體)
- **神經胺酸酶** (neuraminidase: NA), 11種(切斷連結，釋放病毒所需)

A型病毒再依據不同的HA及NA區分亞型: 如 H1N1, H3N2

Nature Reviews Microbiology 9, 590-603 (August 2011)

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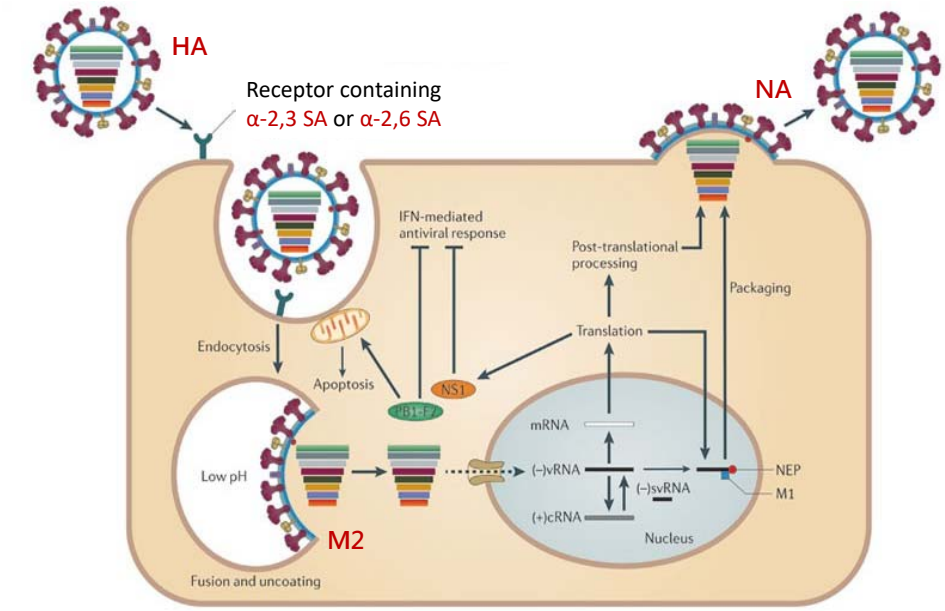

SA: sialic acid

Nature Reviews Microbiology

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	A 型 流感病毒	B 型 流感病毒	C 型 流感病毒	D 型 流感病毒
基因結構	8條單股負鏈RNA	8條單股負鏈RNA	7條單股負鏈RNA	7條單股負鏈股 RNA
病毒體結構	11個蛋白質	11個蛋白質	9個蛋白質	9個蛋白質
抗原變異種類	抗原微變(Antigenic drift) 抗原移型(Antigenic shift)	抗原微變(Antigenic drift)	抗原微變(Antigenic drift)	抗原微變(Antigenic drift)
抗原變異性	變異性大	抗原性較穩定	抗原性非常穩定	抗原性穩定
自然界宿主	人、豬、馬等哺乳動物、禽鳥類	人	人、豬	豬及牛
引起疾病嚴重度	高危險族群感染後容易引發嚴重併發症，且所引起之症狀最為嚴重	引起症狀較 A 型輕微，於高危險族群感染後容易引發嚴重併發症	症狀較輕微，甚至無症狀	無人類感染病例
發生流行程度	可引起季節性流行。如發生抗原移型而出現新的病毒亞型，將可能引起全球大流行	可引起季節性流行。可能因發生抗原微變而引起地區性的流行	無季節性	無季節性

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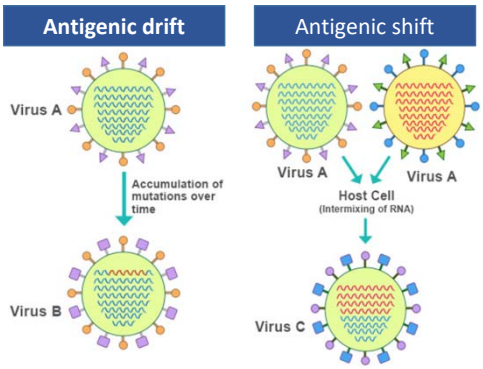
流感病毒的變異

- 流感病毒的抗原變異主要分為下列二種

1. 抗原微變(Antigenic drift)：
   - 連續變異
   - 與地區性流行(epidemic)有關
   - HA(H1-18)或NA(N1-11)基因突變

2. 抗原移型(Antigenic shift)：
   - 不連續變異
   - 不同病毒株引發的基因重組, 不常發生
   - 與全球大流行(pandemic)有關



- 新型流感病毒株則是由突變和基因重組（Reassortment）產生

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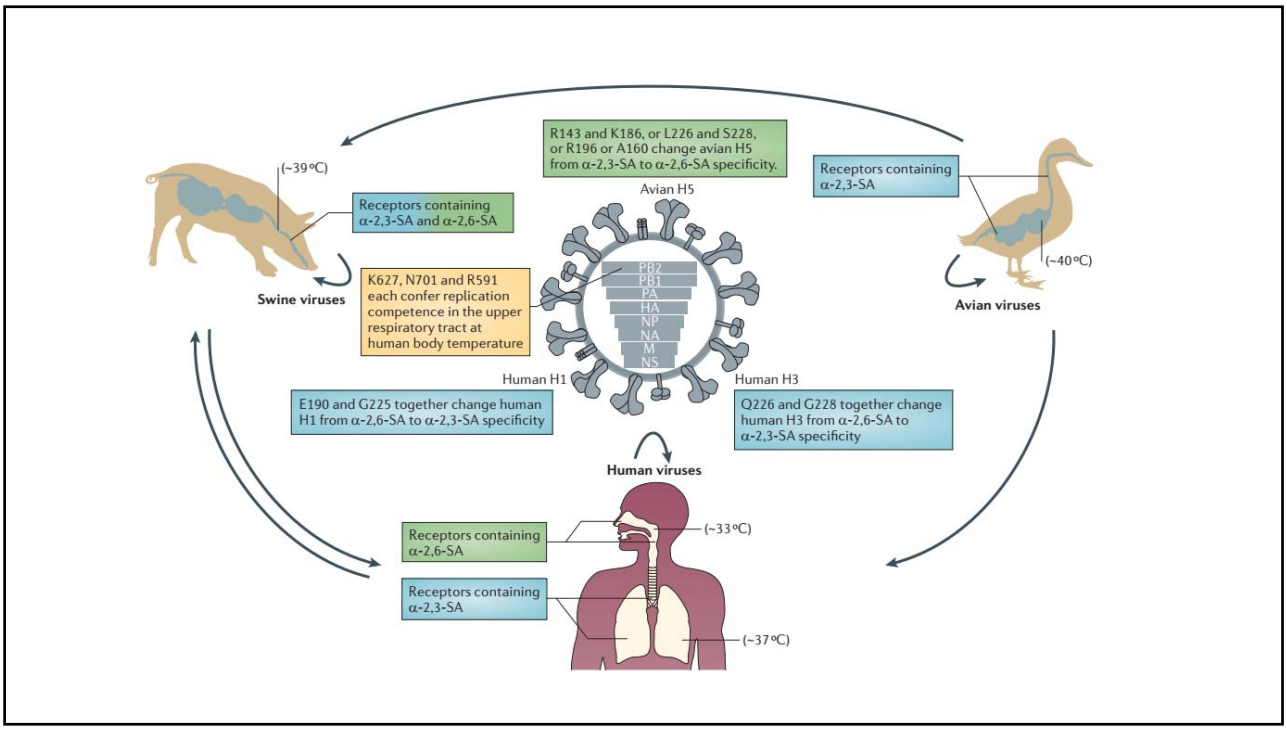

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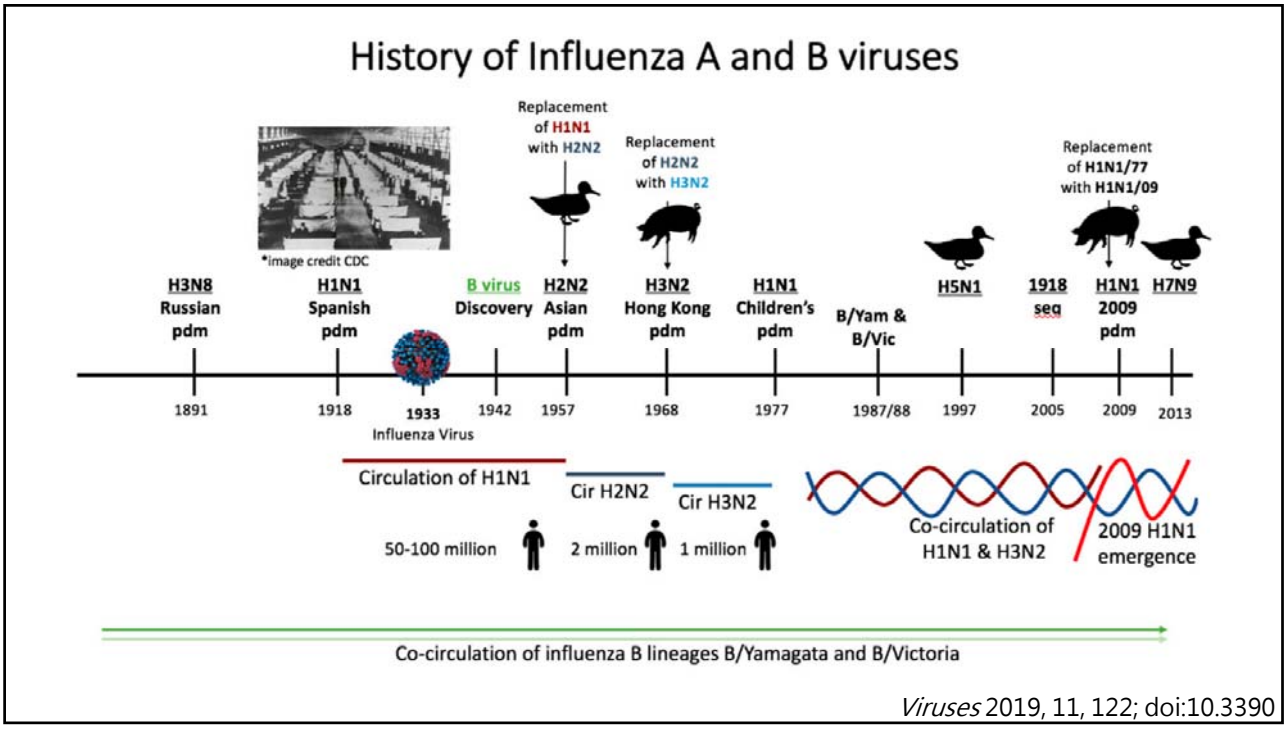

Viruses 2019, 11, 122; doi:10.3390

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全球流行情形

- 每年併發重症人數約300~500萬
- 每年死亡人數約29~65萬人，多數死亡者為65歲以上長者
- 流感年侵襲率在成人約5~10%，小孩約20~30%
- 主要流行病毒型別為A、B兩型，其中A型又以H1N1及H3N2兩亞型為主，B型依抗原性分為B/Yamagata(山形株)及B/Victoria(維多利亞株)兩個種系 (lineage)

1.WHO. The world health report 2007 : a safer future : global public health security in the 21st century. WHO; 2007: 45-48.
2.WHO. Influenza (Seasonal). Available at:http://www.who.int/mediacentre/factsheets/fs211/en/

台灣流行情形

- 流行約自11月開始，於12月至隔年3月達到流行高峰
- 主要流行病毒型別與全球相同，可能為A/H3N2、A/H1N1、B/Yamagata、B/Victoria任一或共同流行
- 以2011年至2018年台灣健保資料庫之次級資料及疾病管制署傳染病通報系統估算
  – 每年約有 14%的人因肺炎或流感而就醫
  – 門診就醫之流感病患中，約有0.6%需住院治療，其中約8%的病患需住加護病房治療；流感併發重症個案中，流感相關死亡率約為2成

1. 疾病管制署健保IC卡資料庫次級資料2011年至2018年肺炎或流感門診及住院就診人次分析
2. 疾病管制署傳染病通報系統2011年至2018年流感併發重症確定病例統計

流感特徵

傳播方式	可傳染期	併發症 高危險族群
• 飛沫傳染 • 接觸傳染	• 發病前即有傳染力，持續至症狀出現後約3~7天 • 免疫不全者可長達數週	• 老年人、嬰幼兒、孕婦 • 具慢性疾病患者 • 免疫功能不全者 • 肥胖(BMI≧30)

人人都可能得流感

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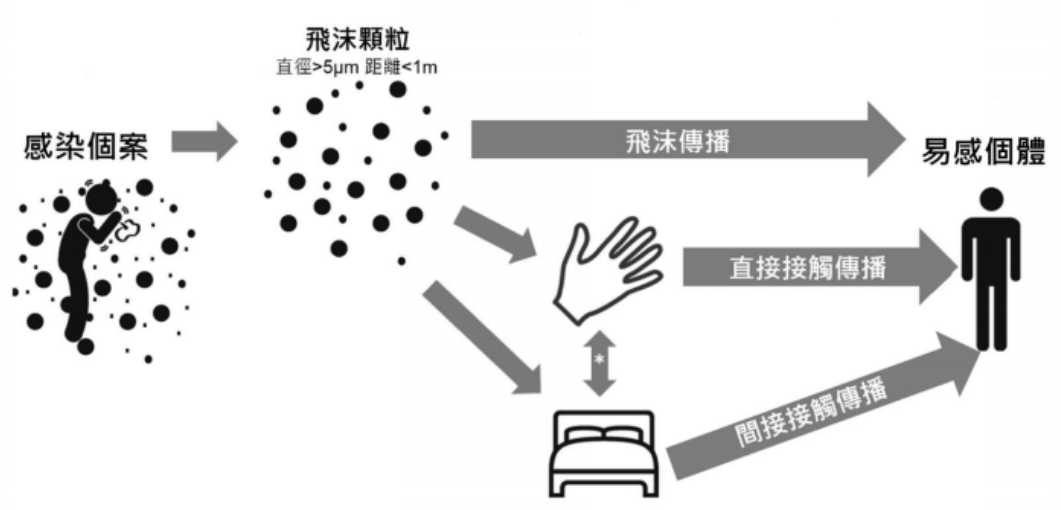
傳播方式



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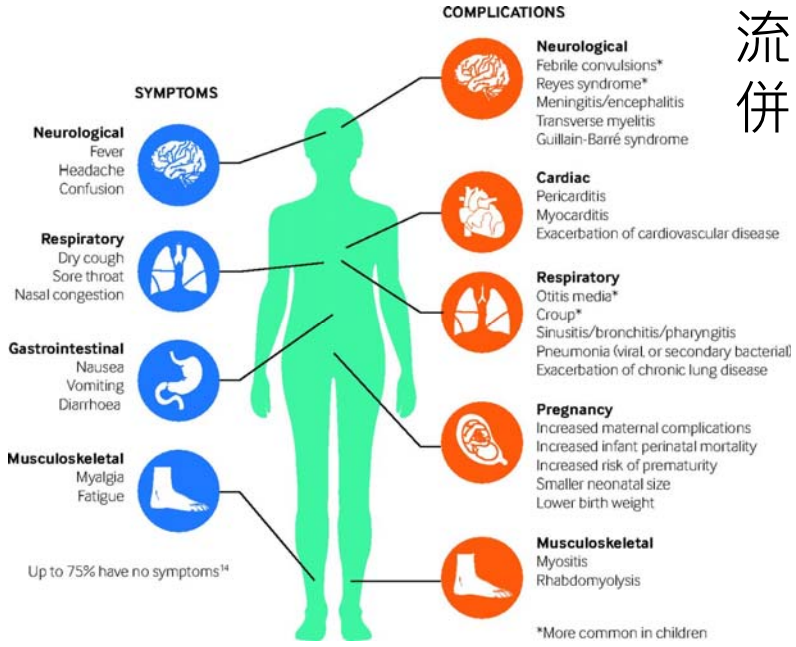
感染過程

- 潛伏期
  - 通常約1~4天
  - 出現併發症的時間約在發病後的1~2週
- 可傳染期
  - 發病前1~2天即具傳染力
  - 大約持續至症狀出現後3~5天
  - 兒童及免疫不全者其排放病毒之時間則較長，可長達數週或數月
- 感受性及免疫力
  - 對於首次接觸的流感病毒，各年齡層均具有相同的感受性
  - 感染後可針對此次感染的病毒抗原產生免疫力
  - 感染免疫力維持的期間及效力則視病毒抗原變異的狀況及感染的次數而定

流感併發重症



Sam Ghebrehewet et al. BMJ 2016;355:bmj.i6258

流感併發重症（Severe Complicated Influenza）

一、 臨床條件

出現類流感症狀後兩週內因併發症(如肺部併發症、神經系統併發症、侵襲性細菌感染、心肌炎或心包膜炎等)而需加護病房治療或死亡者。

二、 檢驗條件

具有下列任一個條件：

（一）呼吸道臨床檢體（咽喉擦拭液等）分離並鑑定出流感病毒（Influenza virus）。

（二）臨床檢體分子生物學核酸檢測陽性。

（三）臨床檢體抗原檢測陽性。

（四）臨床檢體血清學抗體檢測陽性：急性期與恢復期流感病毒血清抗體效價≧4 倍上升。

三、 流行病學條件

曾經與經實驗室證實之確定病例具有密切接觸（close contact），即照護、同住、或與其呼吸道分泌物、體液之直接接觸。

四、 通報定義

符合臨床條件。

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類流感症狀

疾管署規定類流感需符合以下三項條件：

- 突然發病，有發燒（耳溫≧38℃）及呼吸道症狀（例如：發燒、咳嗽、流鼻水、喉嚨痛等。）。
- 具有肌肉酸痛、頭痛、極度倦怠感其中一種症狀。
- 需排除單純性流鼻水、扁桃腺炎與支氣管炎。

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流感併發症

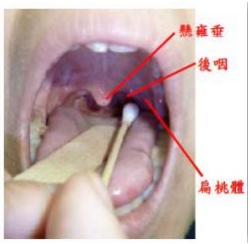
- **1. 肺部併發症(Pulmonary complications)**
  胸部 X 光有新的浸潤或實質化，且需要住院之病人。
- **2. 神經系統併發症(Neurological complications)**：符合下列臨床狀況至少二項，並排除癲癇、熱痙攣等其它病因者：
  (1)急性腦病變：指突發的意識狀態、人格或行為改變、或對人 時地的判斷混淆，持續超過 24 小時者。
  (2)局部或全身性抽筋
  (3)理學檢查呈現局部神經學症候 。
  (4)腦脊髓液中白血球數目大於 5/μL 。
  (5)異常的神經電生理或神經影像學發現。
- **3. 心肌炎(Myocarditis)或心包膜炎(Pericarditis)**
  過往無心臟疾病病史之急性心衰竭個案，符合下列任一項臨床表現，且經心臟科醫師臨床診 斷，或病理組織切片診斷為心肌炎或心包膜炎者：
  (1)心肌酵素(CK-MB or Troponin-I/T)異常升高。
  (2)發病時的心電圖需有新的傳導異常，或心電圖變化需符合心肌炎或心包膜炎的診斷。
  (3)心臟超音波顯示有左心室收縮異常或心包膜積液 。
- **4. 侵襲性細菌感染(Invasive bacterial infection)**
  符合下列臨床狀況至少一項者：
  (1)於正常情況下之無菌處檢體，如：血液、腦脊髓液、肋膜液、 心包膜液、或關節液等，培養分離出細菌，或抗原快速檢驗為陽性者。
  (2)敗血症或毒性休克症候群 (sepsis or toxic shock syndrome)。
- **5. 其他 (Others)** 非符合上述 1～4 項臨床症狀，但個案需於加護病房治療或死亡者。

傳染病防治法之規範

- **流感輕症**非屬法定傳染病，不需逐例通報
- **流感併發重症**
  – **第四類傳染病；應於一週內通報**
  – 主要目的為監測重症個案之發生趨勢與其感染之流感病毒型別，以掌握流感疾病嚴重度，及流行病毒株與疫苗株吻合情形
  – 亦可早期發現病毒變異

檢體採檢送驗事項

傳染病名稱	採檢項目	採檢目的	採檢時間	採檢量及規定	送驗方式	應保存種類(應保存時間)	注意事項
流感併發重症	咽喉擦拭液	病原體檢測	發病3天內	以病毒拭子之棉棒擦拭咽喉，插入病毒保存輸送管。	2-8°C (B類感染性物質包裝)	病毒株(30日)	見本署傳染病檢體採檢手冊 2.8.5 備註說明；咽喉採檢步驟請參考第 3.7 節及圖 3.7。



咽喉拭子檢體採集圖解


病毒拭子

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Influenza testing

Method	Types Detected	Time to result	Comments
Rapid Influenza Diagnostic tests (Antigen detection) 快速抗原檢測	A and B	15-30 min	• Low-moderate sensitivity, high specificity • 操作簡單快速 • 流感流行期間， 快篩陰性不能排除流感
Rapid molecular assay (Influenza viral RNA or nucleic acid detection) 快速分子/核酸檢測	A and B	<30 min	• High sensitivity and specificity • 相比傳統RT-PCR(1-8 hours)快速
Direct or Indirect Immunofluorescence 免疫螢光檢驗	A and B	1-4 hours	• Moderate high sensitivity, high specificity
Serology test 血清學檢驗抗體	A and B		• 需急性期及恢復期兩次抗體指數比較，在臨床使用上無法即時提供結果
Viral culture 病毒培養	A and B	1-3 days 7-10 days	• High sensitivity and specificity • 不具時效性

流行性感冒的快速診斷檢驗-感控雜誌 2019

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Influenza A/B RNA (ID NOW)

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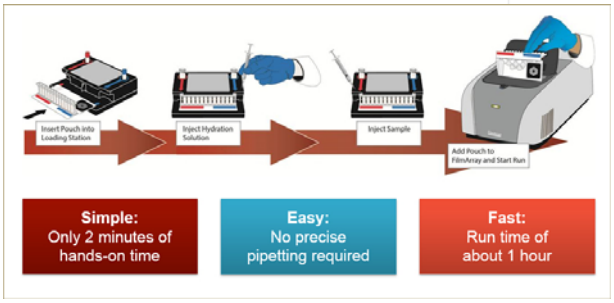
Multiplex assays

Virus Detection Method	Platform/Instrument	Influenza Viruses Detected	Influenza A Virus Subtypes Differentiated	Other Respiratory Viruses Differentiated	Approved Specimens[3]	Test Time[4]
Nucleic Acid Detection	FILMARRAY® 2.0 and FILMARRAY® TORCH systems	Influenza A, Influenza B	A(H1), A(H1)pdm09, A(H3)	SARS-CoV-2, Adenovirus, Coronavirus 229E, Coronavirus HKU1, Coronavirus NL63, Coronavirus OC43, Human Metapneumovirus, Human Rhinovirus/Enterovirus, Parainfluenza Virus 1, Parainfluenza Virus 2, Parainfluenza Virus 3, Parainfluenza Virus 4, Respiratory Syncytial *Virus*	NPS	1 hour



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流感防治策略

疫情監視	• 病毒活動監視 • 重症病例監視 • 流行趨勢監視
衛教宣導	• 個人衛生 • 生病在家休息不上課、不上班
疫苗接種	• 高危險族群 • 高傳播族群
抗病毒藥劑	• 流感併發重症通報病例 • 可能併發重症之類流感患者 • 新型A型流感通報病例
公共衛生介入	• 自主健康管理 • 人口密集機構/醫院/學校/軍營感染管制措施 • 集會活動之流感群聚防治指引

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公費流感抗病毒藥劑使用對象

治療性用藥	
• 符合「流感併發重症」通報病例(需通報於法定傳染病通報系統)	• 符合「新型A型流感」通報定義者(需通報於法定傳染病通報系統)
• 孕婦經評估需及時用藥者	• 肥胖之類流感患者(BMI>=30)
• 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
• 重大傷病、免疫不全(含使用免疫抑制劑者)或具心肺血管疾病、肝、腎及糖尿病等之類流感患者	• 流行高峰期擴大用藥(有發燒之類流感患者，且家人/同事/同班同學有類流感發病者)
預防性用藥	
• 類流感等群聚事件經疾病管制署各區管制中心認定需用藥者	• 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)
• 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)	

CDC. 109.05.01 適用

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抗流感病毒藥物給藥時機

- 當決定給予抗病毒藥劑治療，就應儘快給予，**不需**等到檢驗確診才給藥。
- 症狀開始後 48 小時內開始治療，療效最佳。
- 然而 有些研究顯示病情較嚴重或需住院病人若症狀超過48小時才投予抗 流感藥物，仍有縮短住院天數或減低死亡率的助益

感染症醫學會 流感藥物治療建議 2021

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抗流感藥物使用

- **肥胖**、**孕婦**及**ECMO**病人 Oseltamivir ，劑量與一般成人相同。
- 流感**重症**病人病毒量高，帶病毒時間長，可依個別病情，評估是否需**增加藥物劑量或延長治療療程**。
- 病況於藥物5天後仍未見緩解，**可重新採檢** (下呼道檢體為佳) ，檢測呼吸道是否仍有病毒，並延長治療療程，再視病況決定是否需繼續使用藥物。
- **嚴重免疫不全病人**(尤其血液幹細胞移植後病人)，流感病毒排出時間較長，**較有機會產生抗藥性**，須持續追蹤患者情況是否得到緩解。若病況未改善，應考慮延長用藥及重新採檢送驗，抗藥性及換藥需要。

感染症醫學會 流感藥物治療建議 2021

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治療方式

- 流感抗病毒藥劑
  - M2 protein抑制劑(M2 protein inhibitor)
    - Amantadine等
    - 抗藥性問題嚴重，已**不建議**用來治療流感
  - **神經胺酸酶抑制劑(Neuraminidase inhibitor)**
    - 口服式之Oseltamivir (Tamiflu® 克流感、Eraflu® 易剋冒)
    - 吸入式之Zanamivir (Relenza® 瑞樂沙)
    - 靜脈注射之Peramivir (Rapiacta® 瑞貝塔)
    - 為目前治療主流
  - **核酸內切酶抑制劑(Endonuclease inhibitor)**
    - 口服式之Baloxavir (Xofluza® , 紓伏效)
- 支持療法 -醫師評估投以症狀緩解藥物

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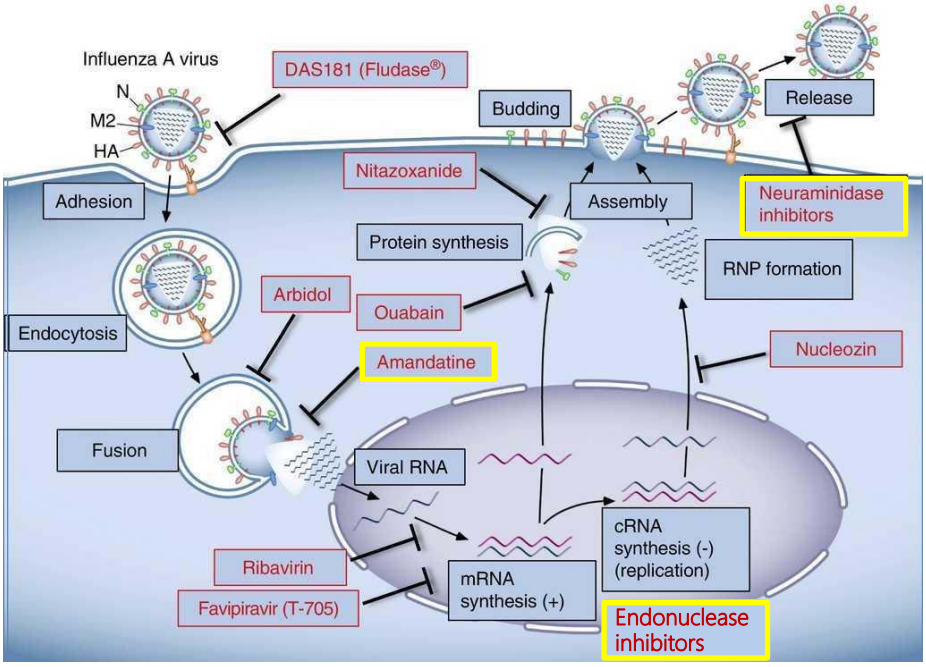

Arch Bronconeumol. 2017 Jan; 53(1): 19–26.

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發展中抗病毒藥物

藥物	特色	上市
Zanamivir (IV)	可給予重症病人或不適合 使用吸入藥物病人	N
Peramivir (IV)	靜脈或肌肉注射	Y
Long-acting inhaled NI	增加zanamivir的效果, 單 一劑量治療	N
Fludase (DAS181)	siladise fusion construct切 除呼吸道上皮細胞的silic acid receptor	N
Cynovirin-N	Hemagglutinin inhibitor	N
siRNAs	short interfering RNAs	N
Falvipiravir (T-705)	抑制病毒RNA polymerase	Y
Baloxavir marboxil	抑制病毒endonuclease	Y

N Engl J Med 2009; 360:953-956

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Oseltamivir (Tamiflu、Eraflu)

- 口服，經肝臟代謝成具活性的 oseltamivir carboxylate
- 血漿中半衰期 6-10 小時
- 99%由腎臟排出，腎衰竭病人必須調整劑量
- 常見副作用為噁心、嘔吐
- 適用成人和兒童（包含足月新生兒）
- 孕婦及哺乳中婦女首選藥物

Adult/child	>40kg	75mg bid	* 5d
Child 1-12yr	23kg-40kg	60mg bid	* 5d
	15kg-23kg	45mg bid	* 5d
	<15kg	30mg bid	* 5d
Child < 1yr	3mg/kg		* 5d

CCr>60	75mg bid
Ccr 30-60	30mg bid
Ccr 10-30	30mg qd
Ccr <10	no data
HD	30mg TIW after HD

CDC 克流感中文仿單 2019.6

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注意事項

- 已有流感病患在服用 Tamiflu 期間產生**癲癇和類似精神錯亂**的神經精神事件的報告， 大多數為**小孩和青少年**。
- 極少數案例中，此類事件會導致意外傷害。Tamiflu對於這類事件的因果關係還未知，另外也有未服用 Tamiflu之流感病患產生此類事件之報告。
- 三個不同的大型流行病學研究證實，和未接受抗病毒藥物治療的流感患者相比較，接 受 Tamiflu治療之流感患者發生神經精神事件的風險並未較高。
- 須嚴密地監測流感病患(特別是小孩和青少年)之不尋常行為之徵兆。

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Zanamivir (Relenza) 瑞樂沙

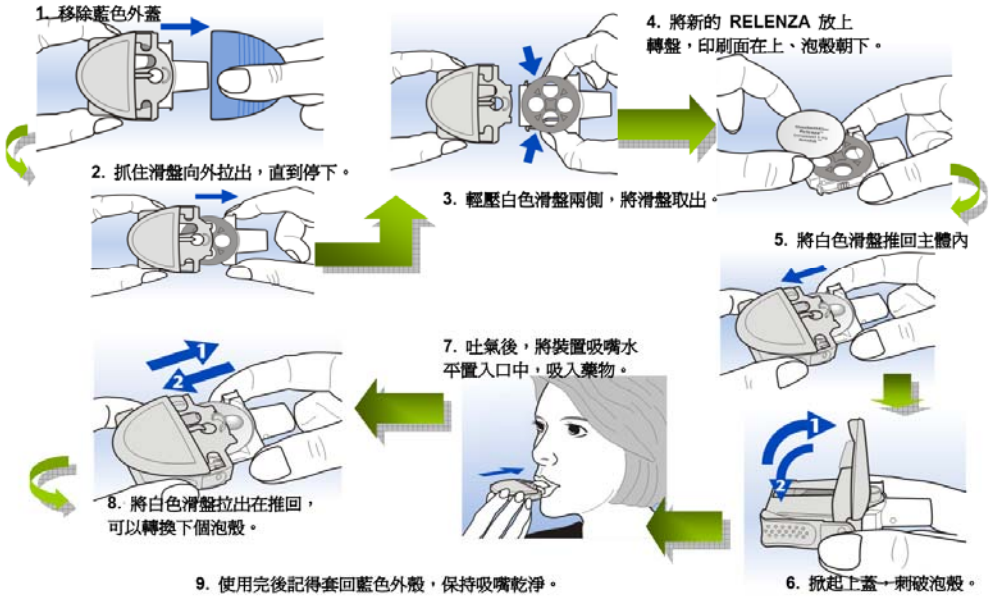
- 乾粉吸入劑型，投與途徑為經口吸入呼吸道
- 約78%沉積於口咽部，約15%到達支氣管及肺
- 口服吸收生體可用率僅2%，無需考慮對全身性影響。
- 肝腎功能異常**不需**調整劑量
- 適用成人及兒童(> 5 歲)
- 使用: 每次兩劑，10mg bid * 5 days

不建議使用吸入型 zanamivir 治療病人
流感肺炎需住院治療者
免疫不全病人流感快篩檢驗陽性
預期無法配合正確使用吸入型者
預期吸入粉末型藥物後可能會出現支氣管痙攣者(如 COPD 及氣喘病人)

CDC 瑞樂沙中文仿單 2019.6
抗流感病毒藥物使用建議 2021.3

36

瑞樂沙 Relenza 旋達碟使用步驟



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Peramivir (Rapiacta)瑞貝塔

- **靜脈**注射: 300mg/60ml , 單次滴注 >15分鐘
- 無法口服/吸入者可考慮使用此藥
- 可作為懷疑或確定受 **oseltamivir 抗藥性**流感病毒株感染之病人治療之替代藥物
- **腎功能**不良病患使用需調整劑量
- 副作用: 腹瀉、白血球下降
- 適用成人及一個月大以上兒童
- 使用: 成人單次300mg、小兒 10mg/kg; 每次最多不得超過 600mg

	Japan[1]	US[2]
CCr>50	300 mg once	600 mg once
Severe case	600 mg qd *5-10 days	
Ccr 30-50	100 mg /d	200 mg/d
Ccr 10-30	50 mg /d	100 mg/d
HD	審慎調整劑量	100 mg D1, then 100 mg 2hrs after HD

1. 瑞貝塔中文仿單 2. Sanford’ s guide

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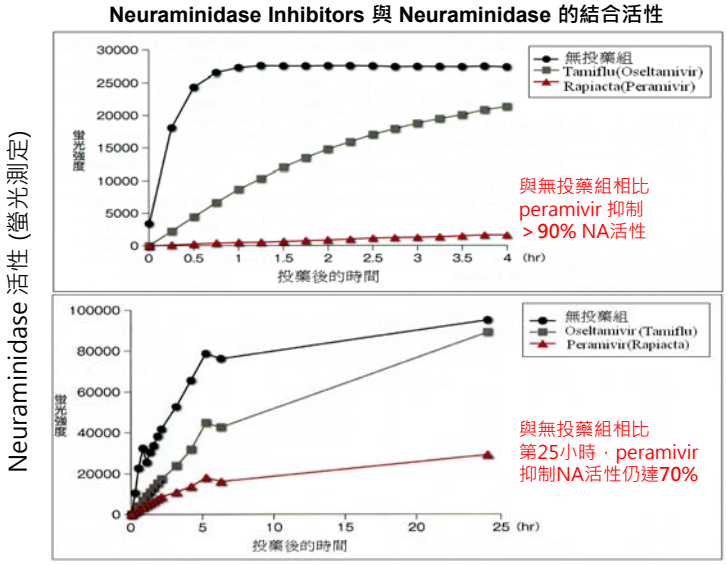
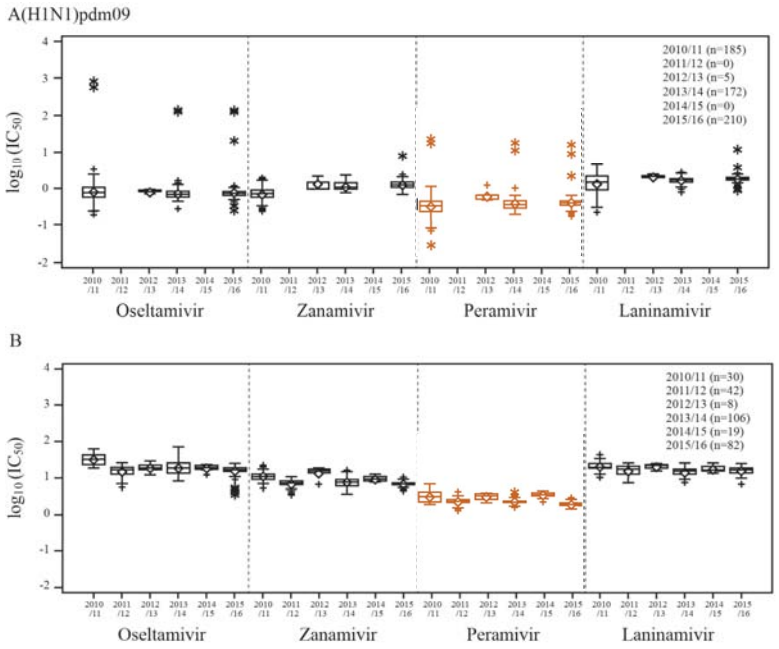
Rapiacta®特點

- 與神經胺酸酶(NA)高度結合，IC_{50}較低
- 點滴靜脈注射一劑相當於傳統口服五天效果
- 更快退燒、緩解症狀及降低病毒量

Peramivir 具有高度 Neuraminidase 結合活性 (in vitro)



Rapiacta 医薬品インタビューフォーム

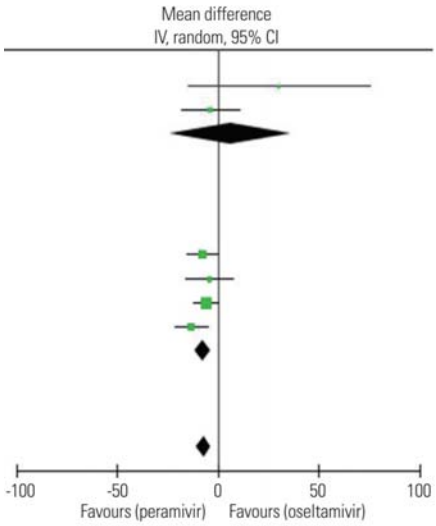


IC50: inhibitory concentration

Ikematsu et al. *J Infect Chemother* (2017)

41

Comparison of Efficacy of Intravenous Peramivir and Oral Oseltamivir for the Treatment of Influenza : Systematic Review and Meta-Analysis



Peramivir vs. oseltamivir

Time **to alleviation of fever**: - 7.17 hours (95% CI -11.00 to -3.34)

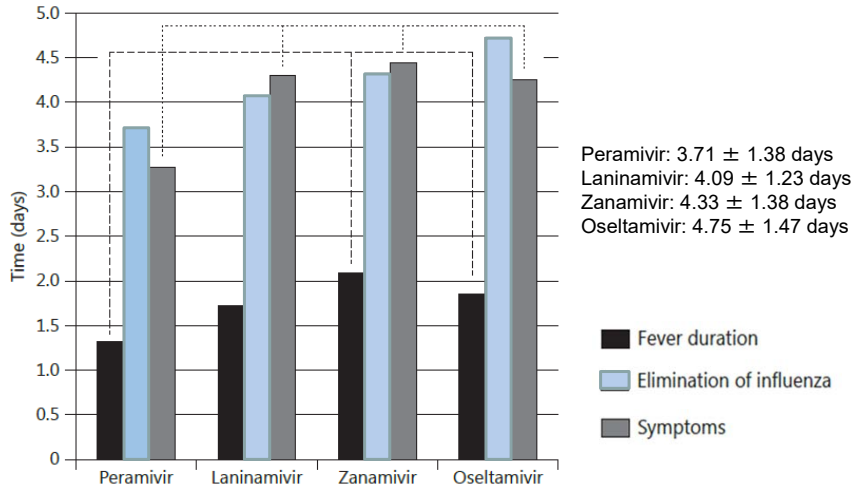
Mortality, length of hospital stay, change in virus titer 48 hours after admission, and the incidence of adverse events not significantly different

Yonsei Med J 2017 Jul;58(4):778-785

42

Time to **eliminate the influenza virus**

Peramivir tended to eliminate the virus sooner.



Takemoto Y, et al. Chemotherapy 2013;59:373–378

43

Baloxavir marboxil (Xofluza)紓伏效

- **口服**劑型 (20mg/tab)，僅需服用**單次**劑量
- 於2018年在日本及美國先後取得許可證上市的 Baloxavir ，藉由抑制流感病毒的 **Cap 依賴型核酸內切酶(Cap dependent endonuclease)**破壞病毒在人體複製機制
- 適用成人及12歲以上兒童
- 副作用: 腹瀉，噁心
- 肝腎功能: CCr>30, Child A-B無需調整劑量
- 使用:

40-80Kg	單次服用 40mg (2 tab)
>80Kg	單次服用 80mg (4 tab)

- 服藥時，可與或不與食物併服，但應避免和乳製品、高鈣飲品、含多 價陽離子緩瀉劑、抗酸劑或口服補充劑(例如：鈣、鐵、鎂、硒或鋅) 併服。

紓伏效中文仿單

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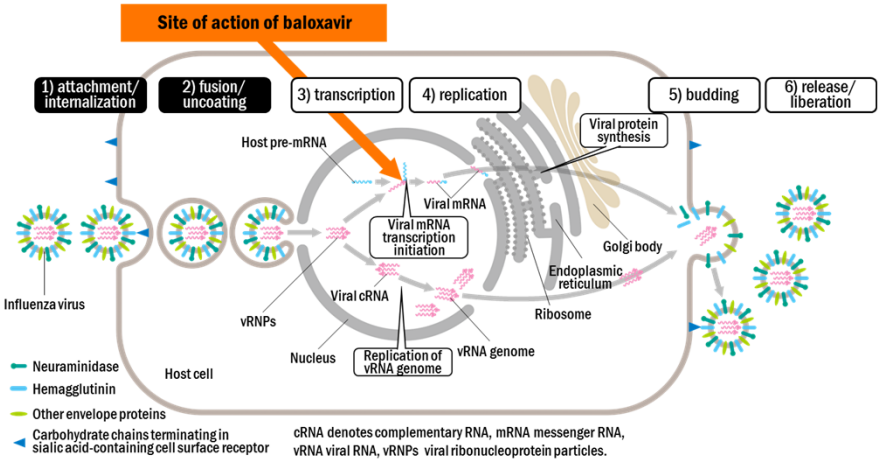
Baloxavir: a cap-dependent endonuclease inhibitor that prevents viral replication



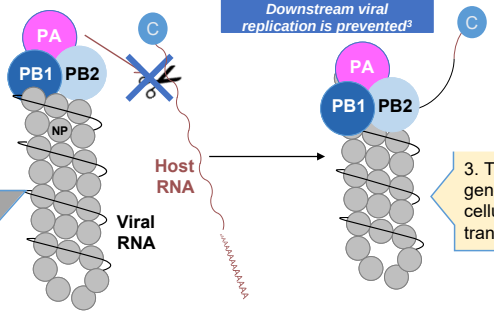
Noshi et al. Antiviral Res. 2018 Dec;160:109-117

Baloxavir is a novel influenza molecule that inhibits viral cap-dependent endonuclease activity

2. The PA subunit of the RNA polymerase complex possesses **cap-dependent endonuclease** activity – an influenza-specific enzyme that processes host pre-mRNAs to serve as primers for viral mRNA transcription by **'cap-snatching'**[2]

Baloxavir stops 'cap-snatching' by inhibiting endonuclease activity of the PA subunit. Downstream viral replication is prevented[3]

1. The influenza viral **RNA polymerase complex** consists of:
- viral RNA segments
- multiple NP molecules
- a single, trimeric polymerase complex comprising PA, PB1 and PB2 subunits[1,2]



3. Transcription of the viral genome starts with the cellular 'cap' as a primer to transcribe viral mRNA

NP: nucleoprotein

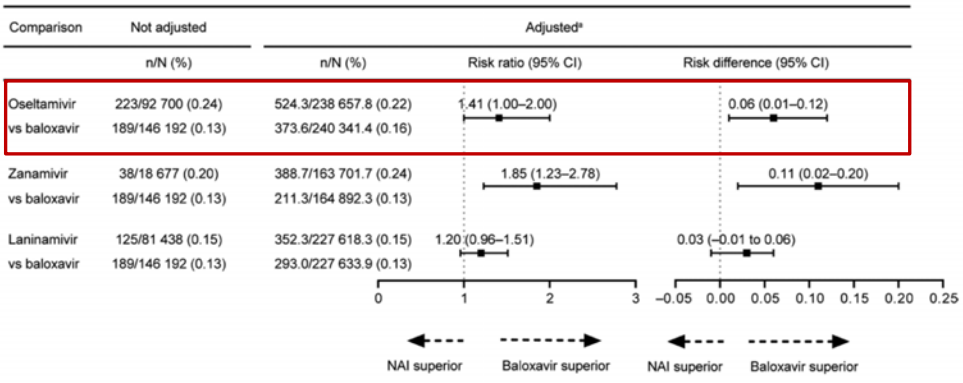
1. Eisfeld et al. Nat Rev Microbiol 2015
2. Reich S., et al. Nature. 2014 Dec 18;516(7531):361-6
3. Noshi T., et al. Antiviral Res. 2018 Dec;160:109-117

Baloxavir 特點

一般流感病患[1]	流感高危險群病患[2]	流感預防[3]
• 單次口服即完成療程 • 快速停止排出病毒及降低病毒量 • 快速緩解流感症狀及退燒 • 安全性與安慰劑相當	• 症狀改善所需時間與Oseltamivir相當 • 顯著較Oseltamivir快2天停止排出病毒 • 顯著較安慰劑降低流感併發症發生率 • 安全性與安慰劑相當	• 可預防暴露後罹患流感風險達86% • 對兒童、成人、是否具高危險因子、是否接種過疫苗，預防流感之效果皆相當 • 安全性與安慰劑相當

1. Hayden et al. N Engl J Med. 2018 Sep 6;379(10):913-923
2. Ison MG et al. Lancet Infect Dis. 2020 Oct;20(10):1204-1214.
3. Ikematsu H, et al. N Engl J Med. 2020 doi: 10.1056/NEJMoa1915341.

Comparison of Hospitalization Incidence in Influenza Outpatients Treated With Baloxavir Marboxil or Neuraminidase Inhibitors: A Health Insurance Claims Database Study



The incidence of hospitalization was greater in the oseltamivir group than in the baloxavir group. RR 1.41 [1.00-2.00]

Clin Infect Dis. 2020; ciaa1870

Clinical outcomes of baloxavir versus oseltamivir in patients hospitalized with influenza A

	Baloxavir ($n = 359$)	Oseltamivir ($n = 431$)	P
Hypoxia resolution, n (%)	$n = 273$ 224 (82.051)	$n = 348$ 263 (75.575)	0.052[a]
Hours from antiviral to hypoxia resolution, median (IQR)	$n = 273$ 51.717 (25.3–89.317)	$n = 348$ 71.95 (37.463–123)	<**0.001**[b]
Fever resolution, n (%)	$n = 265$ 262 (98.868)	$n = 314$ 306 (97.452)	0.241[c]
Hours from antiviral to fever resolution, median (IQR)	$n = 265$ 25.067 (8.5–40.183)	$n = 314$ 25.275 (11.204–41.492)	0.501[b]
LOS (days), median (IQR)	4 (3–6)	5 (3–6)	0.45[b]
ICU LOS (days), median (IQR)	$n = 50$ 2 (1–4)	$n = 52$ 3 (2–5)	0.44[b]
30 day all-cause mortality, n (%)	12 (3.343)	26 (6.032)	0.079[c]

- **Patients who received baloxavir had a significantly faster time to hypoxia resolution**

J Antimicrob Chemother. 2020 Oct 1;75(10):3015-3022.

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Subgroup of patients who received therapy within 48 h of symptom onset

	baloxavir ($n = 190$)	oseltamivir ($n = 232$)	P
Hypoxia resolution, n (%)	$n = 138$ 117 (84.783)	$n = 183$ 141 (77.049)	0.084[a]
Hours from antiviral to hypoxia resolution, median (IQR)	$n = 138$ 47.025 (22.146–86.433)	$n = 183$ 71.9 (33.925–124.733)	<**0.001**[b]
Fever resolution, n (%)	$n = 155$ 154 (99.355)	$n = 188$ 184 (97.872)	0.383[c]
Hours from antiviral to fever resolution, median (IQR)	$n = 155$ 25.183 (8.85–40.117)	$n = 188$ 24.075 (10.158–39.175)	0.934[b]
LOS (days), median (IQR)	4 (3–6)	5 (3–6)	0.47[b]
ICU LOS (days), median (IQR)	$n = 24$ 3 (1–4.25)	$n = 28$ 3 (2–4.25)	0.948[b]
30 day all-cause mortality, n (%)	3 (1.579)	14 (6.034)	**0.024**[c]

- **Baloxavir was associated with a significantly reduced 30 day all-cause mortality rate and time from antiviral to hypoxia resolution compared with oseltamivir**

J Antimicrob Chemother. 2020 Oct 1;75(10):3015-3022.

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台灣感染症醫學會-抗流感病毒藥物使用建議

藥物	Oseltamivir Capsule		Oseltamivir Oral Suspension		Zanamivir		Peramivir		Baloxavir Marboxil	
使用方式	吞服/無法吞服者（如需使用鼻胃管者）則打開膠囊泡水或糖漿服用		經調配後服用		經口吸入		單次點滴靜脈注射 15 分鐘以上		單次口服	
適用年齡	成人及兒童 (含足月新生兒)		成人及兒童 (含足月新生兒)		5 歲(含)以上		小兒(早產兒及新生兒除外)及成人		成人和青少年 (12 歲以上)	
標準治療劑量	輕症	重症	輕症	重症	輕症	重症	輕症	重症	輕症	重症
	13 歲以下依體重調整劑量；13 歲(含)以上或體重40kg 以上者75mg BID		40kg 以下兒童依體重調整劑量；40kg 以上兒童或成年人及青少年為 75mg BID		10mg BID	不建議使用	成人單次 300mg 小兒 10mg/kg	成人 600mg QD	≧ 40 至 <80kg 單次服用 40mg；≧80kg 單次服用 80mg	現無臨床數據
標準療程	5天	5天	5天	現無臨床數據	5天		單次	可依症狀連續多日反覆投予	單次	
自費價格	124*2*5 = **1240**						**1750**	3500* days	900*2 = **1800**	

感染症醫學會-抗流感病毒藥物使用建議（2021年修訂版）

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台灣感染症醫學會-抗流感病毒藥物使用建議

預防性抗流感藥物使用對象、劑量與療程

藥物	Oseltamivir Capsule	Zanamivir	Baloxavir Marboxil
使用方式	吞服；無法吞服者（如需使用鼻胃管者）則打開膠囊泡水或糖漿服用	經口吸入	口服
適用年齡	成人及兒童 (含足月新生兒)	5 歲(含)以上	成人和青少年 (12 歲以上)
建議療程	• 非群突發狀況下,建議使用七天 • 群突發狀況下建議使用 14 天或直至最後一位病患發生症狀起七天後	• 非群突發狀況下,建議使用七天 • 群突發狀況下建議使用 14 天或直至最後一位病患發生症狀起七天後	單次口服
建議劑量	13 歲以下依體重調整劑量；13 歲(含)以上或體重 40kg 以上者75mg QD	10mg QD	≧40 至 <80kg 單次服用 40mg；≧80kg 單次服用 80mg

感染症醫學會-抗流感病毒藥物使用建議（2021年修訂版）

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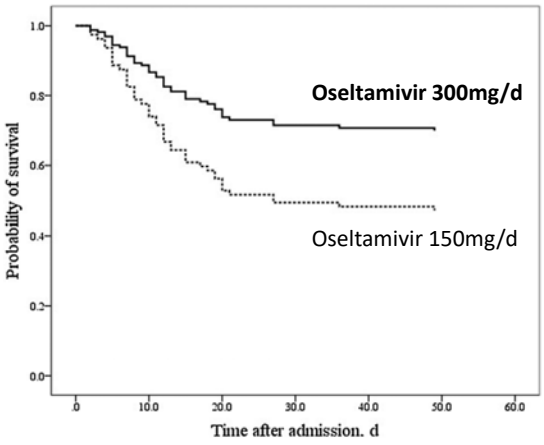
Influenza A-associated severe pneumonia in hospitalized patients: Risk factors and NAI treatments



Variables	Oseltamivir (n=122)	Peramivir (n=40)	Oseltamivir + Peramivir (n=29)	P values
Demographics				
Age	64 (48.8-77)	67 (46.3-72.8)	66 (57-73)	.839
Male (%)	81 (66.4)	32 (80.0)	18 (62.1)	.196
Comorbidity (%)	84 (68.9)	26 (65.0)	18 (62.1)	.748
Oseltamivir administered ≤48h (%)	6 (4.9)	1 (2.5)	0 (0)	.243
SOFA score	7 (6-8)	7 (6-8.5)	7 (7-8.5)	.574
Outcomes				
60-day mortality, n (%)	49 (40.2)	15 (37.5)	9 (31.0)	.658

Int J Infect Dis. 2020 Mar;92:208-213.

53

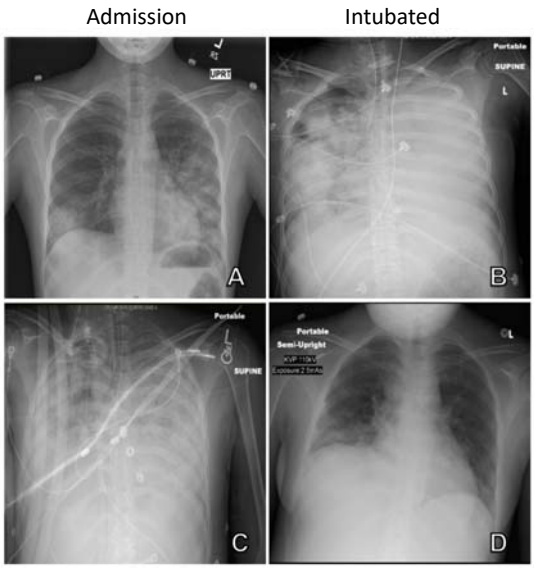
Combination treatment with the cap-dependent endonuclease inhibitor baloxavir marboxil and a neuraminidase inhibitor in a mouse model of influenza A virus infection

Combination treatment with **baloxavir acid** and **oseltamivir acid** in vitro and **baloxavir marboxil** and **oseltamivir phosphate** in mice produced **synergistic responses** against influenza virus infections, suggesting that treating humans with the combination may be beneficial.

J Antimicrob Chemother. 2019 Mar 1;74(3):654-662.

54

Oseltamivir and baloxavir: Dual treatment for rapidly developing ARDS on a patient with renal disease

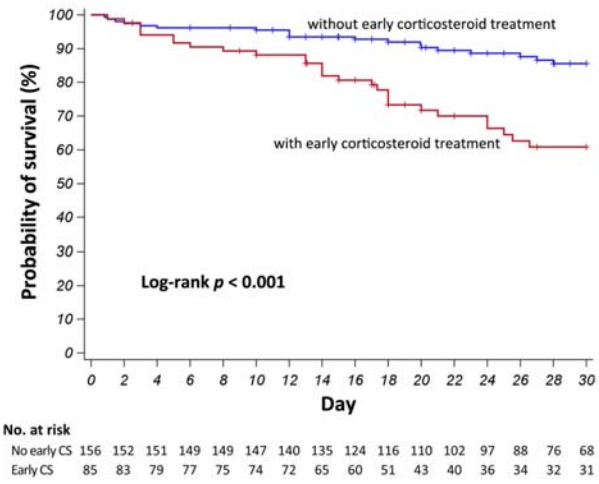


- **Oseltamivir** renally adjusted dosage (CrCl 14 mL/min) , then double dose oseltamivir
- **Baloxavir** 40 mg every 72 h for three doses

IDCases. 2020 May 22;21:e00819.

55

Impact of corticosteroid treatment on clinical outcomes of influenza-associated ARDS: a nationwide multicenter study

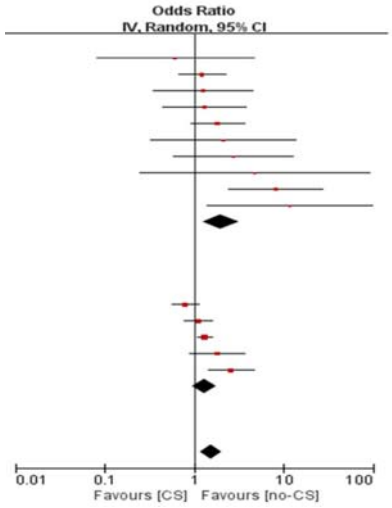


- Early corticosteroid treatment was associated with a significantly **increased hospital mortality** in adult patients with influenza-associated ARDS.

MJ Tsai. et al. Ann Intensive Care. 2020 Feb 27;10(1):26.

56

Use of corticosteroids in influenza-associated acute respiratory distress syndrome and severe pneumonia: a systemic review and meta-analysis



- The meta-analysis results showed that corticosteroid therapy was associated with significantly higher mortality (OR 1.53, 95% CI [1.16, 2.01]) and incidence of nosocomial infection (OR 3.15, 95% CI [1.54, 6.45])
- Current data do not support the routine use of corticosteroids in patients with influenza severe pneumonia or ARDS.

Sci Rep **10,** 3044 (2020).

57

Co-infections with Influenza

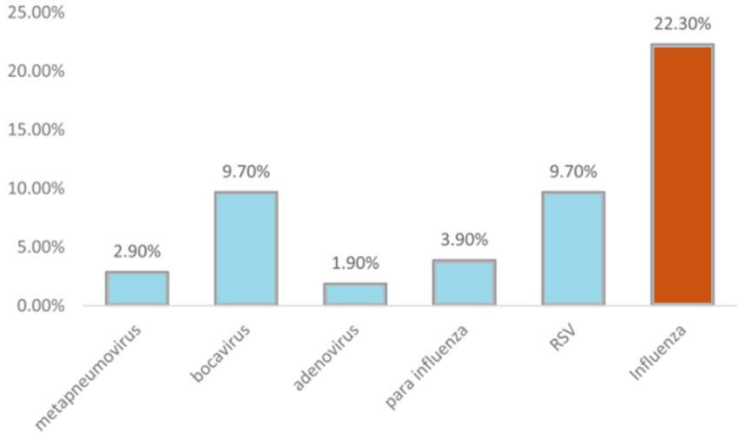
- Bacterial pneumonia- *S. pneumoniae , Staphylococcus aureus*
- Invasive **Aspergillosis**
- SARS-CoV-2
  - Influenza and COVID-19 have **overlapping** signs and symptoms
  - Co-infection should be considered, particularly in hospitalized patients with severe respiratory disease
  -**Testing** can help distinguish; positive SARS-CoV-2 test result does not preclude influenza virus infection

CDC, NCIRD, May 6, 2021

Clin Infect Dis. 2020 Jan 2;70(2):349-350

58

Coinfection with other respiratory viruses in SARS-CoV-2 positive dead patients



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Co-infected COVID-19 and Influenza

11 prevalence studies, 3070 patients

patients with COVID-19 and Influenza		Prevalence% (95% CI)	Number of studies	Number of patients	I-squared
Overall		0.8 (0.4–1.3)	11	79	76.6%
Continent	America	0.4 (0.0–0.7)	4	6	43.4%
	Asia	4.5 (0.1–7.9)	5	70	84.4%
Country	China	3.1 (0.2–6)	4	47	81.7%
	USA	0.7 (0.0–1.4)	3	5	52.6%
Gender	Male	5.3 (1.3–9.4)	4	30	80.1%
	Female	9.1 (0.6–17.2)	3	31	83.5%
Virus type	Influenza virus A	8 (5.6–10.4)	9	67	62.6%
	Influenza virus B	5.5 (2.8–8.3)	4	9	52.9%
Age	<50 years	1.7 (0.4–3)	3	9	51.2%
	More than 50 years	4.6 (1.4–10.6)	3	38	87.6%

M Dadashi. 2021; 8: 681469.

60

6965 adults infected with COVID-19, UK

	Unweighted		Weighted	
	OR (95% CI)	p value	OR (95% CI)	p value
Invasive mechanical ventilation				
Adenovirus	1·22 (0·72–1·99)	0·44	0·64 (0·18–1·68)	0·42
Influenza virus	1·68 (1·14–2·45)	0·0073	4·14 (2·00–8·49)	0·0001
Respiratory syncytial virus	1·05 (0·68–1·59)	0·82	0·78 (0·15–2·70)	0·73
In-hospital mortality				
Adenovirus	1·60 (1·03–2·44)	0·033	1·53 (0·67–3·33)	0·29
Influenza virus	1·49 (1·04–2·12)	0·027	2·35 (1·07–5·12)	0·031
Respiratory syncytial virus	1·20 (0·84–1·72)	0·31	0·60 (0·69–2·10)	0·47

Model is adjusted for the following confounders: age, sex, number of comorbidities, treatment with corticosteroids, days since the start of the pandemic, co-infection, and 4C Mortality Score. OR=odds ratio.

Table: **Multivariable model of the effect of co-infection compared with SARS-CoV-2 monoinfection**

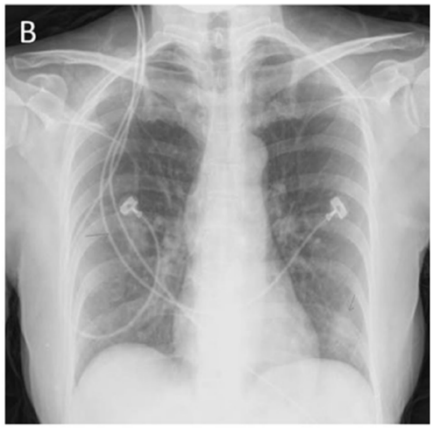
Lancet. 2022 Apr 16;399(10334):1463-1464.

Treatment and clinical outcome in co-infected cases

	Case 1	Case 2	Case 3	Case 4	Case 5
					ARDS
Oseltamivir	Yes	No	Yes	Yes	Yes
Antibiotic therapy	No	No	No	Yes	Yes
Remdesivir	Yes	Yes	Yes	Yes	Yes
Dexamethasone	Yes	Yes	Yes	No	Yes
Length of hospital stay- days	4	6	12	3	20
Outcome	Alive	Alive	Alive	Alive	Expired

R Ali. Cureus 13(8): e17597

Co-infection of influenza B virus and SARS-CoV-2 in Taiwan



48 y/o female, contact with COVID-19 patient
- RIDT: Influenza B (+)
- RT-PCR for SARS-CoV-2 (+)

Oseltamivir -> Baloxavir marboxil
Hydroxychloroquine

BR Huang.J Microbiol Immunol Infect. 2021

63

Considerations in co-infected cases

- Corticosteroids
  - cautious use in Influenza due to the negative effects on the morbidity and mortality
  - recommended in COVID-19 : dexamethasone 6mg daily
- Drug-Drug interactions
  - new oral antiviral agents for COVID-19: Paxlovid, Molnupiravir

64

Paxlovid (nirmatrelvir/ritonavir) DDI

Oseltamivir (Tamiflu)	Nirmatrelvir/ritonavir (5 days) [Please read the interaction details as management of these interactions may be complex.]	Oseltamivir Oseltamivir	No Interaction Expected Nirmatrelvir/ritonavir (5 days) [Please read the interaction details as management of these interactions may be complex.]
Peramivir (Rapiacta)	Peramivir 於體外試驗對主要人體肝酵素 Cytochrome P450 (CYP) 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 及 3A4 並未出現抑制作用，對 CYP1A2, 2A6, 2C9, 2D6 及 3A4 亦無誘導作用。		
Baloxavir marboxil (xofluza)	依據體外試驗結果，baloxavir marboxil為CYP2B6、CYP2C8、CYP3A的濃度依賴性弱抑制劑，baloxavir marboxil活性物則為CYP2B6、CYP3A濃度依賴性的弱抑制劑。		

Liverpool COVID-19 Drug Interactions
Rapiacta, Xofluza 仿單

65

Take home messages

- Risk factors for influenza complications
- Multiplex assays to detect Influenza and SARS-CoV-2
- Neuraminidase inhibitors
  - oral Oseltamivir (Tamilfu,Eraflu)
  - inhaled Zanamivir (Relenza)
  - intravenous Peramivir (Rapiacta)
- Endonuclease inhibitor
  - oral Baloxavir (Xofluza), single dose
- Co-infected COVID-19 and Influenza
  - increased hospitalization and mortality
  - corticosteroid remains controversial
  - possible drug-drug interaction

66

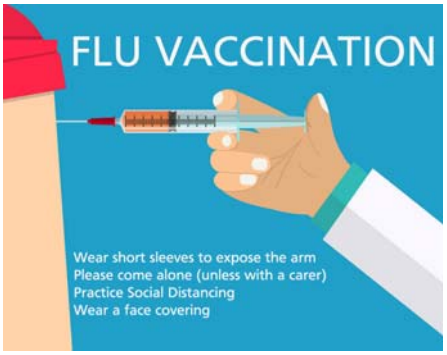
Thank you for your attention

流感疫苗

高雄醫學大學附設中和紀念醫院
衛生福利部屏東醫院
感染科 郭政諭醫師

1

A yearly flu vaccine as the first and most important step in protecting against flu viruses



2

Why should people get vaccinated against flu?

- Influenza is **a potentially serious disease** that can lead to hospitalization and sometimes even death.

3

Why do I need a flu vaccine every year?

1. A person's immune protection from vaccination **declines over time.**
2. Because **flu viruses are constantly changing**, the composition of flu vaccines is reviewed annually
   - vaccines are updated to protect against the viruses that research indicates will be most common during the upcoming flu season.

4

Flu vaccination can keep you from getting sick with flu

- Flu vaccination **prevents** millions of illnesses and flu-related doctor's visits each year.
  - during 2019-2020 flu vaccination prevented
    - 7.5 million influenza illnesses,
    - 3.7 million influenza-associated medical visits,
    - 105,000 influenza-associated hospitalizations,
    - 6,300 influenza-associated deaths.
- During seasons when flu vaccine viruses are similar to circulating flu viruses,
  - flu vaccine has been shown to **reduce the risk** of having to go to the doctor with flu by **40% to 60%.**

5

Flu Vaccine Reduces Risk of Severe Illness

The study was conducted over four flu seasons from 2012 to 2015 and found that flu vaccination prevented severe disease

- Flu vaccination among adults reduced the risk of being admitted to the hospital with flu
  - placed in a general ward bed by 37 percent.
- Flu vaccination was even more effective in preventing the most severe forms of flu
  - reduced the risk of being admitted to an ICU with flu by 82 percent.

6

Flu vaccines prevented influenza-associated ICU admissions
Have higher effectiveness in ICU than GW hospital settings

- Influenza vaccine effectiveness for GW patients was 41% (95% CI = 29–51%)
- Influenza vaccine effectiveness for ICU patients was **86%** (95% CI = 54–96%)

- In the propensity adjusted models, for all estimated seasons, influenza virus (sub)types, with or without chronic medical conditions, and by age group (<65 vs. 65 years)
  - influenza vaccine effectiveness point estimates for ICU patients were > 70% (range = 73–95%) and consistently higher than influenza vaccine effectiveness point estimates among GW patients (range = 14–66%)

Vaccine, 18 September 2018, Pages 5916-5925

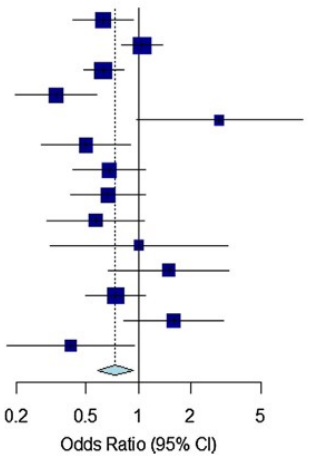
7

Flu vaccination with **26% reduction** in odds of **ICU admission** among adults

Source	Age (yr)	Season	OR (95% CI)
Arriola (2017)	18-49	2013-14: H1	0.63 (0.42, 0.93)
Arriola (2017)	50-64	2013-14: H1	1.05 (0.80, 1.37)
Arriola (2017)	65+	2013-14: H1	0.63 (0.48, 0.81)
Casado (2018)	65+	2013-15: H1/H3	0.34 (0.20, 0.58)
Joshi (2015)	18+	2013-14: H1/H3	2.89 (0.97, 8.60)
Loubet (2016)	18+	2012-15: H1/H3/B	0.50 (0.28, 0.90)
Martinez (2019)	18+	2010-16: H1	0.68 (0.42, 1.10)
Martinez (2019)	18+	2010-16: H3	0.67 (0.41, 1.10)
Martinez (2019)	18+	2010-16: B	0.57 (0.30, 1.08)
Segaloff (2018)	18+	2014-15: H1/H3	1.00 (0.30, 3.10)
Taylor (2016)	16+	2006-09: A/B	1.49 (0.68, 3.33)
Taylor (2016)	16+	2009-10: H1	0.74 (0.50, 1.09)
Taylor (2016)	16+	2010-12: A/B	1.59 (0.82, 3.03)
Thompson (2018)	18+	2012-15: H1/H3/B	0.41 (0.18, 0.96)
Total			

Heterogeneity: $\chi^2_{13} = 35.82$ ($P < .001$), $I^2 = 64\%$

Overall OR= 0.74 (0.58, 0.93)



Vaccine 39 (2021) 3678–3695

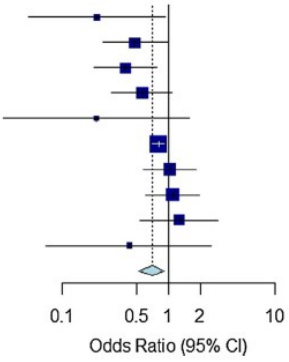
8

Vaccinated patients had **31% reduced risk of death** compared with unvaccinated patients

Source	Age (yr)	Season	OR (95% CI)
Arriola (2017)	18-49	2013-14: H1	0.21 (0.05, 0.97)
Arriola (2017)	50-64	2013-14: H1	0.48 (0.24, 0.97)
Arriola (2017)	65+	2013-14: H1	0.39 (0.17, 0.66)
Casado (2016)	65+	2013-14: H1/H3	0.56 (0.29, 1.06)
Gutierrez-Pizarraya (2012)	14+	2010-11: H1	0.21 (0.03, 1.70)
Gutierrez-Pizarraya (2012)	14+	2010-11: B	0.80 (0.70, 0.90)
Martinez (2019)	18+	2010-16: H1	1.02 (0.58, 1.79)
Martinez (2019)	18+	2010-16: H3	1.09 (0.61, 1.96)
Martinez (2019)	18+	2010-16: B	1.25 (0.54, 2.90)
Suzuki (2018)	65+	2012-14: H1/H3/B	0.42 (0.07, 2.48)
Total			

Heterogeneity: $\chi^2_9 = 15.45$ ($P = .08$), $I^2 = 42\%$

Overall OR= 0.69 (0.52, 0.92)



Vaccine 39 (2021) 3678–3695

9

Effectiveness of Influenza Vaccine Against Life-threatening RT-PCR-confirmed Influenza Illness in US Children, 2010–2012

Jill M. Ferdinands,[1,2] Lauren E. W. Olsho,[3] Anna A. Agan,[4] Niranjan Bhat,[5] Ryan M. Sullivan,[4] Mark Hall,[6] Peter M. Mourani,[7] Mark Thompson,[1] and Adrienne G. Randolph[4] on behalf of the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network

[1]Influenza Division, US Centers for Disease Control and Prevention, and [2]Battelle Memorial Institute, Atlanta, Georgia; [3]Abt Associates, Inc., Cambridge, and [4]Department of Anesthesia, Perioperative and Pain Medicine (Critical Care), Boston Children's Hospital, Massachusetts; [5]Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; [6]Division of Critical Care Medicine, Nationwide Children's Hospital, Columbus, Ohio and [7]Section of Critical Care Medicine, Department of Pediatrics, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora

(See the editorial commentary by Peters and Poehling on pages 671–3.)

Flu vaccination reduced **children's risk** of flu-related pediatric intensive care unit (**PICU**) admission by **74 percent** during flu seasons from 2010-2012.

The Journal of Infectious Diseases 2014;210:674–83

10

Clinical Infectious Diseases
MAJOR ARTICLE

Influenza Vaccine Effectiveness in Preventing Influenza-associated Hospitalizations During Pregnancy: A Multi-country Retrospective Test Negative Design Study, 2010–2016

Mark G. Thompson,[1] Jeffrey C. Kwong,[2,3,4,5,6] Annette K. Regan,[7,8] Mark A. Katz,[9,10,11] Steven J. Drews,[12,13] Eduardo Azziz-Baumgartner,[1] Nicola P. Klein,[14] Hannah Chung,[2] Paul V. Effler,[15] Becca S. Feldman,[9] Kimberley Simmonds,[16,17] Brandy E. Wyant,[18] Fatimah S. Dawood,[1] Michael L. Jackson,[19] Deshayne B. Fell,[2,20,21] Avram Levy,[22] Noam Barda,[9] Lawrence W. Svenson,[17,23,24,25] Rebecca V. Fink,[18] Sarah W. Ball,[18] and Allison Naleway[26]; for the PREVENT Workgroup*

[1]Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia; [2]Institute for Clinical Evaluative Sciences, [3]Public Health Ontario, [4]Department of Family and Community Medicine and [5]Dalla Lana School of Public Health, University of Toronto, and [6]University Health Network, Toronto, Ontario, Canada; [7]School of Public Health, Curtin University, Perth, and [8]Westfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute, Subiaco, Western Australia, Australia; [9]Chief Physician's Office, Clalit Health Services, Clalit Research Institute, Tel Aviv, and [10]School of Public Health, Medical School for International Health, Ben Gurion University, Bersheva, Israel; [11]University of Michigan School of Public Health, Ann Arbor; [12]University of Alberta, and [13]ProvLab Alberta, Edmonton, Canada; [14]Kaiser Permanente Vaccine Study Center, Kaiser Permanente Northern California, Oakland; [15]Communicable Disease Control Directorate, Department of Health Western Australia, Perth, Australia; [16]Cumming School of Medicine, University of Calgary, and [17]Alberta Health, Edmonton, Canada; [18]Abt Associates, Cambridge, Massachusetts; [19]Kaiser Permanente Washington Health Research Institute, Seattle, Washington; [20]School of Epidemiology and Public Health, University of Ottawa, and [21]Children's Hospital of Eastern Ontario Research Institute, Ottawa, Canada; [22]Department of Microbiology, QEII Medical Centre, PathWest Laboratory Medicine, Nedlands, Western Australia, Australia; [23]Division of Preventive Medicine and [24]School of Public Health, University of Alberta, Edmonton, and [25]Department of Community Health Sciences, University of Calgary, Alberta, Canada; and [26]Center for Health Research, Kaiser Permanente Northwest, Portland, Oregon

(See the Editorial Commentary by Munoz on pages 1454-5.)

Getting a flu shot reduced **a pregnant person's risk** of being **hospitalized** with flu by an average of **40 percent** from 2010-2016

Clinical Infectious DiseasesR 2018;68(9):1444–53

Who Should Vaccinate?

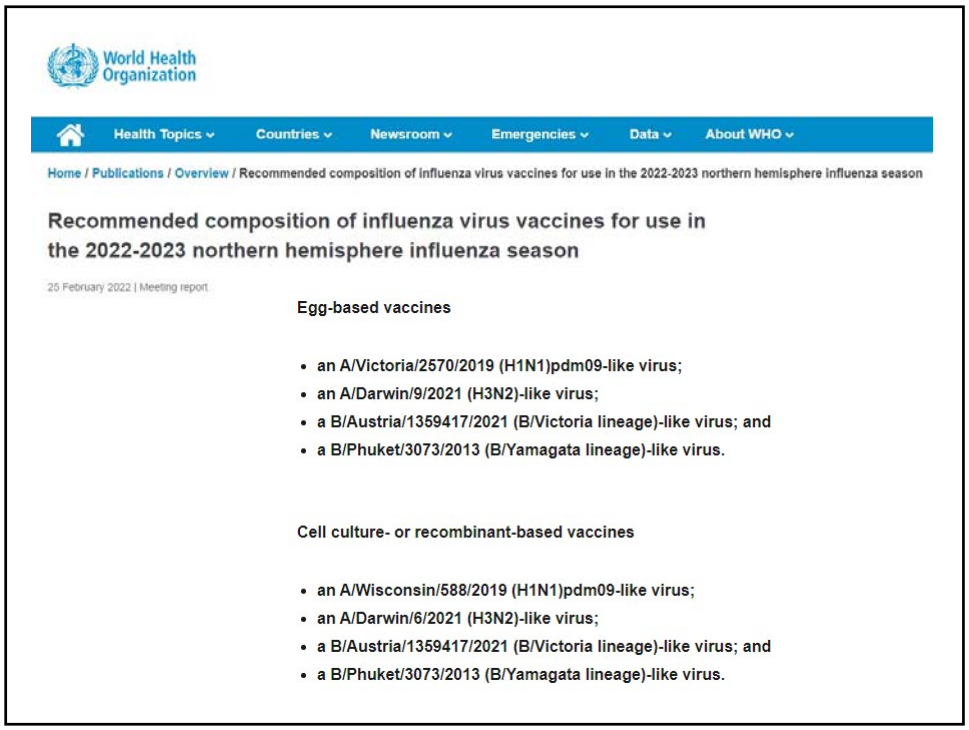
- Everyone **6 months of age and older** should get an influenza vaccine every season with rare exception.

110 年度流感疫苗接種計畫各類實施對象

- 滿 6 個月以上至國小入學前幼兒
- 國小、國中、高中、高職、五專 1 至 3 年級學生
- 50 歲以上成人
- 具有潛在疾病，符合下列條件之一者
  - 高風險慢性病人，符合下列條件之一者： （一）具有糖尿病、慢性肝病（含肝硬化）、心血管疾病（不含單純高 血壓）、慢性肺病、腎臟疾病及免疫低下（HIV 感染者）等疾病 之門、住診紀錄之患者（疾病代碼供參如附件 1）。 （二）無法取得上開疾病之門、住診紀錄，但經醫師評估符合者。 （三）BMI≧30 者。
  - 罕見疾病患者。
  - 重大傷病患者（健保卡內具註記或領有重大傷病證明紙卡者）。
- 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(服務)等機構之受照顧者及所屬工作人員
- 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

How Influenza Vaccines Are Made

- Egg-Based Flu Vaccines
- Cell-Based Flu Vaccines
- Recombinant Flu Vaccines



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Home / Publications / Overview / Recommended composition of influenza virus vaccines for use in the 2022-2023 northern hemisphere influenza season

Recommended composition of influenza virus vaccines for use in the 2022-2023 northern hemisphere influenza season

25 February 2022 | Meeting report

Egg-based vaccines

- an A/Victoria/2570/2019 (H1N1)pdm09-like virus;
- an A/Darwin/9/2021 (H3N2)-like virus;
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus; and
- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

Cell culture- or recombinant-based vaccines

- an A/Wisconsin/588/2019 (H1N1)pdm09-like virus;
- an A/Darwin/6/2021 (H3N2)-like virus;
- a B/Austria/1359417/2021 (B/Victoria lineage)-like virus; and
- a B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

15

Different Types of Flu Vaccines

- Live Attenuated Influenza Vaccine [LAIV] (The Nasal Spray Flu Vaccine)
- Quadrivalent Influenza Vaccine
- Fluzone High-Dose Seasonal Influenza Vaccine
- Adjuvanted Flu Vaccine
- Cell-Based Flu Vaccines
- Recombinant Influenza Vaccine
- Flu Vaccination by Jet Injector

16

Live Attenuated Influenza Vaccine (The Nasal Spray Flu Vaccine)

- The nasal spray flu vaccine is approved for use in healthy **non-pregnant** people, **2 through 49 years old**.

17

Who should **not** get the nasal spray flu vaccine

- Children younger than 2 years old
- Adults 50 years and older
- People with a history of severe allergic reaction to any ingredient of the vaccine or to a previous dose of any flu vaccine
- Children 2 through 17 years old who are receiving aspirin- or salicylate-containing medications.
- Children 2 through 4 years old who have asthma or who have had a history of wheezing in the past 12 months
- People with weakened immune systems (immunosuppression) from any cause
- People who care for severely immunocompromised persons who require a protected environment
- People without a spleen, or with a non-functioning spleen
- Pregnant people
- People with an active leak between the CSF and the mouth, nose, ear, or other place within the skull
- People with cochlear implants
- People who have taken flu antiviral drugs within a certain amount of time. (48 hours for oseltamivir and zanamivir, 5 days for peramivir, and 17 days for baloxavir.)

18

Quadrivalent Influenza Vaccine

- Adding a B virus from the second lineage was done to give broader protection against circulating flu viruses.

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

19

Fluzone High-Dose Seasonal Influenza Vaccine

- A four-component (quadrivalent) flu vaccine approved for **people 65 years and older**.
- Fluzone High-Dose Quadrivalent contains **four times** the antigen than Fluzone Quadrivalent and other standard-dose inactivated flu vaccines.
  - The higher dose of antigen in the vaccine is intended to give people 65 years and older **a better immune response** to vaccination, and therefore, better protection against flu.

20

Fluzone High-Dose Seasonal Influenza Vaccine

- **A stronger immune response** (i.e., higher antibody levels) occured after vaccination with Fluzone High-Dose.
- The high-dose vaccine was **24% more effective** in preventing flu in adults 65 years and older relative to a standard-dose vaccine.
- People 65 years and older who got Fluzone High-dose had a **lower risk of hospital admission** compared with people in that age group who got the standard-dose Fluzone, especially those living in long-term care facilities.
- Some side effects were reported more frequently after vaccination with trivalent Fluzone **High-Dose** than after standard-dose inactivated flu vaccines.

N Engl J Med 2014; 371:635-645
Lancet Respir Med. 2017 Sep;5(9):738-746

21

Adjuvanted Flu Vaccine

- An adjuvant is an ingredient of a vaccine that helps promote **a better immune response**.
- Adjuvants also can reduce the amount of virus needed for production of a vaccine,
  - can allow for greater supplies of vaccine to be manufactured.

22

Cell-Based Flu Vaccines

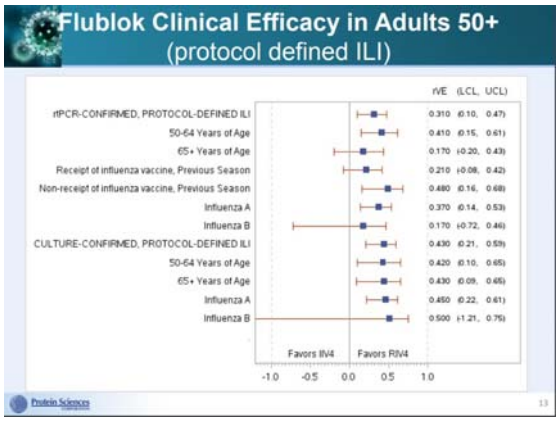
- The cell-based vaccine manufacturing process uses animal cells (Madin-Darby Canine Kidney, or **MDCK cells**) as a host for the growing flu viruses instead of fertilized chicken eggs.
- Growing flu viruses in eggs can introduce changes (called egg-adapted changes) that can cause differences between the viruses in the vaccine and the ones that are circulating.

持有許可證廠商 / 品名	劑型	適用年齡
台灣東洋藥品工業股份有限公司 / FLUCELVAX QUAD輔流威適流感疫苗	0.5mL	提供3歲以上使用

23

Recombinant Influenza Vaccine

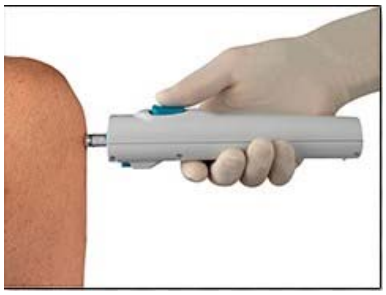
- Recombinant influenza (flu) vaccines are produced using **recombinant technology**.



24

Flu Vaccination by Jet Injector

- **A jet injector** is a medical device used for vaccination
  - uses a high-pressure, narrow stream of fluid to penetrate the skin instead of a needle.



25

Are any of the available flu vaccines recommended over others?

- inactivated influenza vaccine (IIV4), recombinant influenza vaccine (RIV4), or live attenuated nasal spray influenza vaccine (LAIV4) with **no preference expressed for any one vaccine over another**.

26

流感疫苗安全嗎? 會有什麼副作用 ?

- 疫苗與其他任何藥品一樣有可能造成副作用，包括接種後可能會有**注射部位疼痛、紅腫**，少數的人則會有全身性的輕微反應，如：**發燒、頭痛、肌肉酸痛、噁心、皮膚搔癢、蕁麻疹或紅疹**等，一般會在發生後1-2天內自然恢復。
- 嚴重的副作用，如**立即型過敏反應**，甚至**過敏性休克**等不適情況（臨床表現包括呼吸困難、聲音沙啞、氣喘、眼睛或嘴唇腫脹、頭昏、心跳加速等），發生機率非常低，若不幸發生，通常於**接種後幾分鐘至幾小時內**即出現症狀。
- 其他曾被零星報告過之不良事件包括神經系統症狀（如：臂神經叢炎、顏面神經麻痺、熱痙攣、腦脊髓炎、以對稱性神經麻痺為表現的Guillain-Barré症候群等）和血液系統症狀（如：暫時性血小板低下，臨床表現包括皮膚出現紫斑或出血點、出血時不易止血等）。

27

哪些人不適合接種流感疫苗?

- **已知對疫苗的成分有過敏者**，不予接種
- **過去注射曾經發生嚴重不良反應者**，不予接種

28

對雞蛋/蛋的蛋白質過敏者是否可接種流感疫苗？

- 雞蛋過敏大多發生於接觸後30分鐘內，常見症狀是皮膚出疹與搔癢
- 依現有針對雞胚胎蛋培養製造法之不活化流感疫苗研究顯示，對於曾因吃蛋發生嚴重過敏症狀者，仍可在門/住診由熟悉處理過敏症狀醫事人員提供接種，並於接種後觀察30分鐘，無不適症狀再離開。

29

接種流感疫苗有哪些注意事項？

- 發燒或正患有急性中重疾病者，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)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。

30

流感疫苗接種後注意事項 ？

- 接種疫苗後有相當小的機率會發生立即型過敏反應，並導致過敏性休克。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。
- 使用抗血小板或抗凝血藥物或凝血功能異常者，施打後於**注射部位加壓至少2分鐘**，並觀察是否仍有出血或血腫情形。
- 接種後應注意有無持續發燒（超過48小時）、呼吸困難、心跳加速、意識或行為改變等異常狀況，如有不適，應儘速就醫，告知醫師相關症狀、症狀發生時間、疫苗接種時間，以做為診斷參考，並通報當地衛生局。

31

流感疫苗可否與其他疫苗或COVID-19疫苗同時接種?

- 流感疫苗是不活化疫苗，可以和其他疫苗同時接種於不同部位，或間隔任何時間接種。
- 經110年8月28日衛生福利部傳染病防治諮詢會預防接種組建議，為避免一旦發生不良事件時無法釐清歸因，接種流感疫苗應與COVID-19疫苗間隔至少7天。

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Conclusion

- The best way to reduce your risk from seasonal flu and its potentially serious complications is to get vaccinated every year.

謝謝聆聽

接種流感疫苗的保護效果如何?

- 根據國外文獻，流感疫苗之保護力因年齡或身體狀況不同而異，**平均約可達30-80%**。
- 對18歲以上成人因確診流感而住院的保護力約有41%，入住加護病房的流感重症保護力則可達82%。
- 6個月至未滿18歲兒童青少年族群接種流感疫苗之保護力與成人相仿。
- 此外，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。