流感流行病學update

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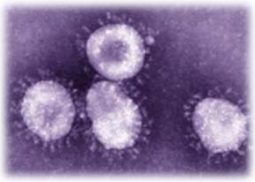
2023/06/17

大綱

- Topic 1:
  - 在之前COVID-19疫情下，流感的疫情如何呢?
- Topic 2:
  - 在之前COVID-19疫情下，其它「呼吸道」與「非呼吸道」病毒的疫情如何呢?
- Topic 3:
  - 放寬non-pharmaceutical interventions管制後，呼吸道感染的疫情可能會如何呢?
  - 台灣目前的流感疫情情況如何呢?
- Topic 4:
  - 為什麼我們要來認識流感的威脅呢?
- Topic 5:
  - 流感的症狀、併發症與其它病原菌的共同感染

Topic 1

- 在之前COVID-19疫情下，流感的疫情如何呢?



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Travel restrictions

Environmental disinfection

Messaging on handwashing

Lockdowns

Physical distancing

Use of face coverings

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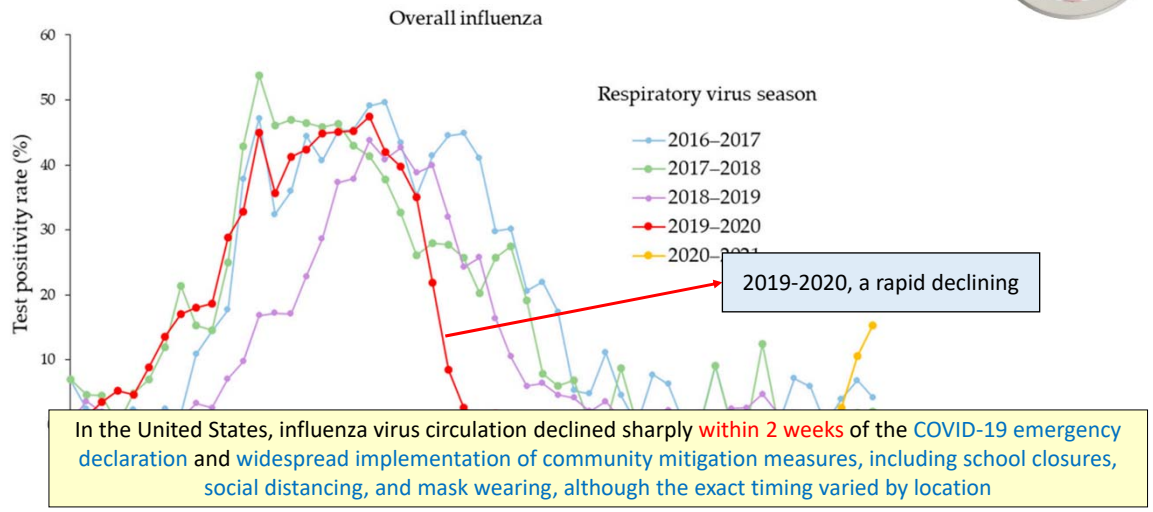
All data were obtained from the US Department of Defense Global Respiratory Pathogen Surveillance Program over five consecutive respiratory seasons from 2016-2017 through to 2020-2021.



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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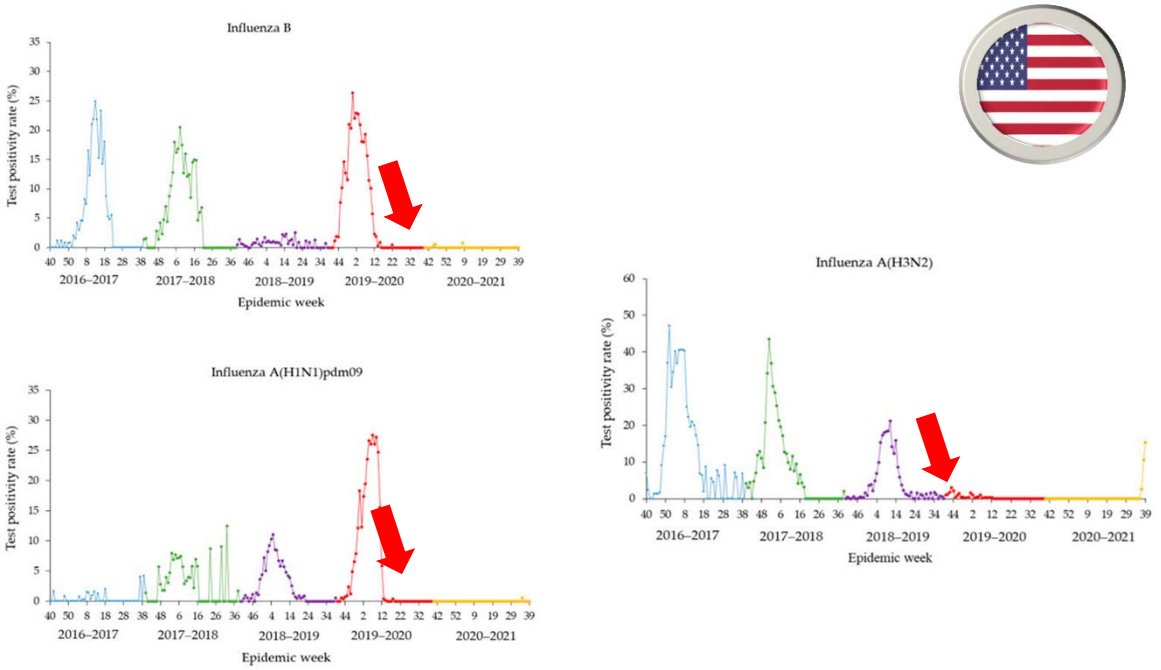

Int J Environ Res Public Health. 2022 May 13;19(10):5942

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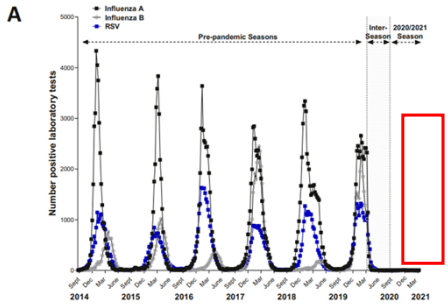
The impact of the COVID-19 pandemic on influenza, respiratory syncytial virus, and other seasonal respiratory virus circulation in Canada: A population-based study



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*
Influenza A	6982 (1311 - 17681)	10•40 (0•11 - 33•97)	12856 (4996 - 20971)	0•012 (0 - 0•04)	0•0015 (0•0009–0•0024)	<0•001
Influenza B	6892 (1311 - 17681)	2•60 (0 - 17•02)	12856 (4996 - 20971)	0•006 (0 - 0•04)	0•0028 (0•0012–0•0065)	<0•001

Lancet Reg Health Am. 2021 Jul 17;100015

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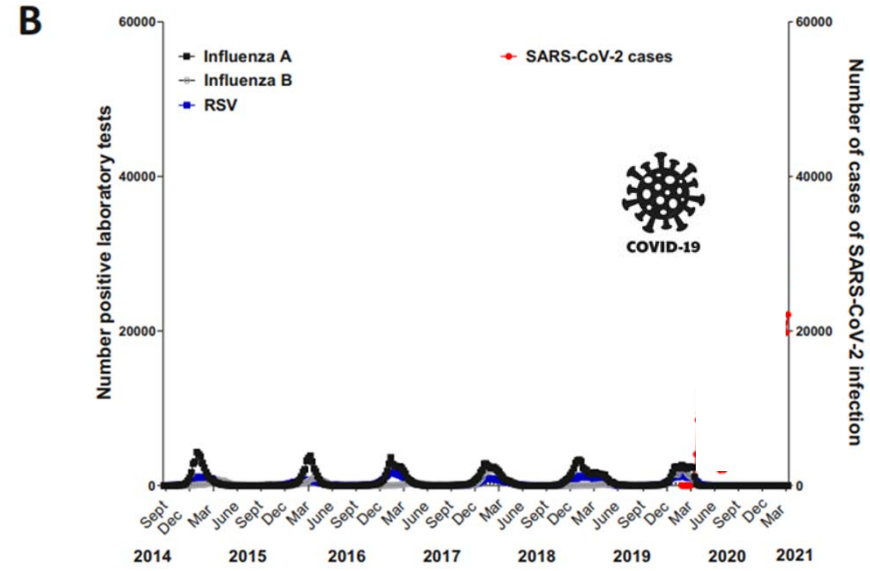

Lancet Reg Health Am. 2021 Jul 17;100015

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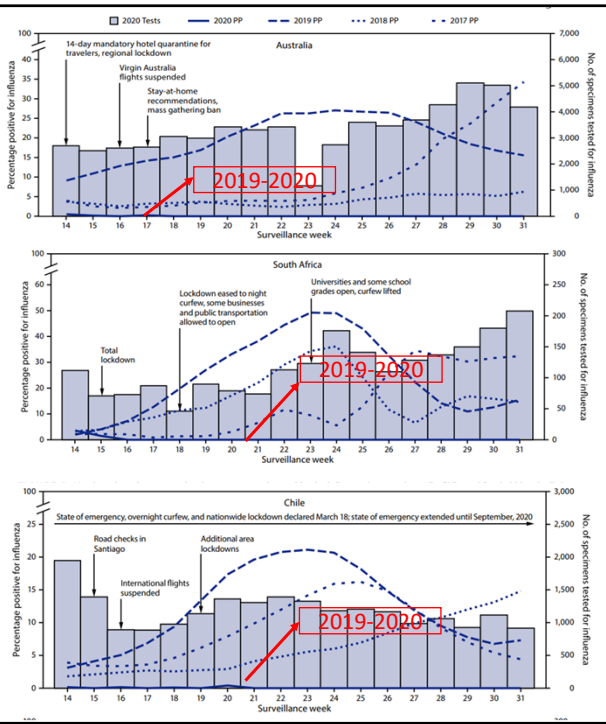
Influenza data reported to the World Health Organization's (WHO's) FluNet platform from three Southern Hemisphere countries that serve as robust sentinel sites for influenza from Oceania (Australia), South America (Chile), and Southern Africa (South Africa) showed very low influenza activity during June–August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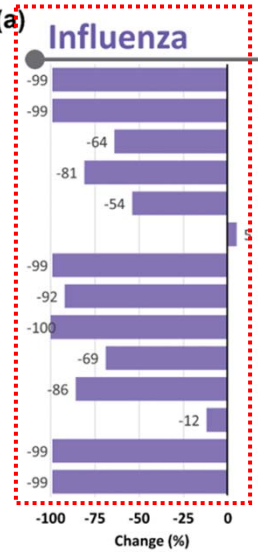

Drop in: (parameter)	During: (index period)	vs. (reference period)	Country/ Region	Ref.
notifications	2020 (Apr–Sep)	2015–2019 (Apr–Sep)	Australia	[15]
cases in children <16 YOA	2020 (Apr–Aug)	2012 – 2019 (Apr–Aug)	Australia	[16]
crude average annual incidence (/100,000)	2020	2014–2019	China	[11]
notifications	2020 (Jan–Dec)	2014–2019 (Jan–Dec)	China	[17]
notifications	2020 (Mar–Aug)	Jan 2016–Feb 2020	Germany	[18]
positive samples in a pediatric clinic	2020	2017–2019	Germany	[12]
positive samples in a pediatric clinic	2021	2017–2019	Germany	[12]
mean number of hospitalized patients/week	Feb 2020–Jan 2021	Jan 2016–Jan 2020	South Korea	[19]
positive samples from hospitalized patients	Apr 2020 – Mar 2021	Apr 2016–May 2019	Poland	[20]
positive samples from ILI patients	2020 (Jan–Oct)	2013–2019 (Jan–Oct)	South Africa	[30]
positive samples of hospitalized SRI patients	2020 (Jan–Oct)	2013–2019 (Jan–Oct)	South Africa	[30]
cases	Oct 2019–May 2020	2016–2019 (Oct–May)	Taiwan	[21]
cases in children <18 YOA	Mar–Apr 2020	Mar–Apr 2019	US	[22]
incidence of hospitalizations (/100,000)	2020–2021 (Oct–May)	2016–2020 (Oct–May)	US	[23]

Expert Rev Vaccines. 2022 Nov;21(11):1541-1553.

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How about the co-infection of COVID-19 and influenza?

A systematic literature search was performed on September 28, 2019 for original research articles published in Medline, Web of Science, and Embase databases from December 2019 to September 2020 using relevant keywords.

TABLE 1 | Characteristics of included prevalence studies.

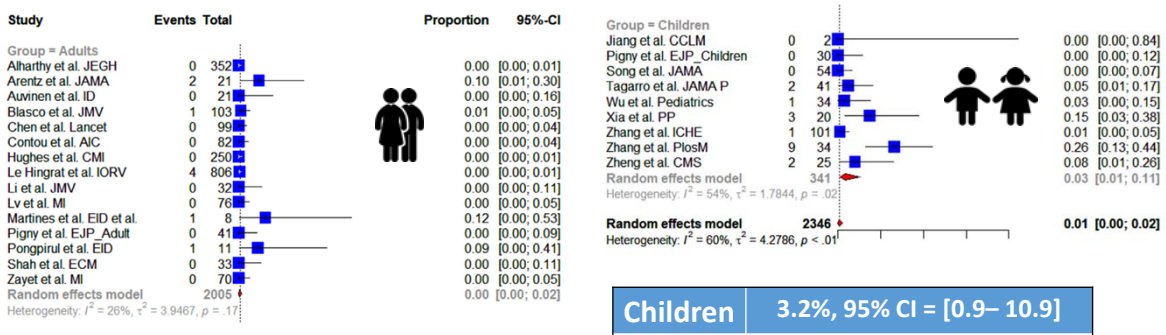
First author	Published time	Country	Patients with COVID-19	Patients with COVID-19–Influenza co-infection (%)	IV-A	IV-B	Co-infected patients	
							Mean age	Male/Female
Castillo et al. (8)	July, 2020	USA	42	1 (2.4)	1	0	21	1/0
Ding et al. (9)	March, 2020	China	115	5 (4.3)	3	2	50.2	2/3
Garazzino et al. (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
							15–44	Nr

Region	Overall	Asia	America
Percentage	0.8	4.5	0.4

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.



Children	3.2%, 95% CI = [0.9– 10.9]
Adult	0.3%, 95% CI = [0.1 – 1.2]

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

結論

- 因為對抗COVID-19的疫情的措施，使得季節性流感的全球(不管在北半球還是南半球)趨勢有下降。
- 在早期COVID-19疫情初期時，COVID-19和流感的共同感染比例是低的。

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Topic 2

- 在之前COVID-19疫情下，其它「**呼吸道病毒**」的疫情如何呢?
- 在之前COVID-19疫情下，其它「**非呼吸道病毒**」的疫情如何呢?

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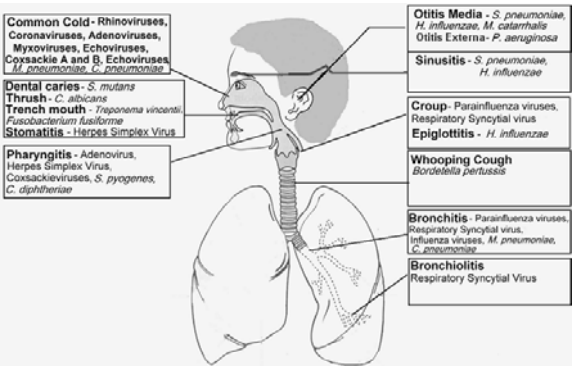
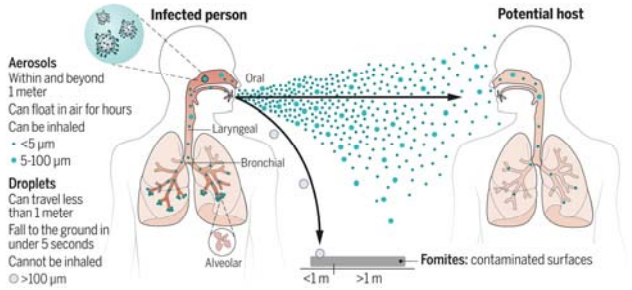
呼吸道感染還有哪些病原菌呢?





https://www.atsu.edu/faculty/chamberlain/website/lectures/lecture/introurt.htm

Science. 2021 Aug 27;373(6558):eabd9149.

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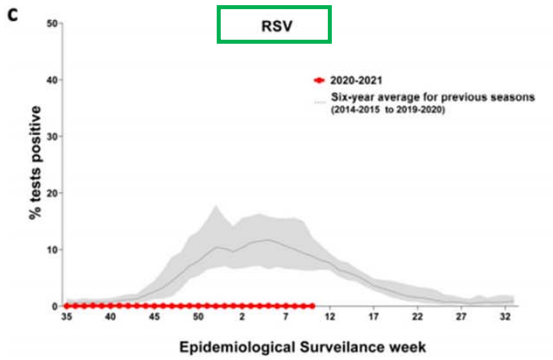

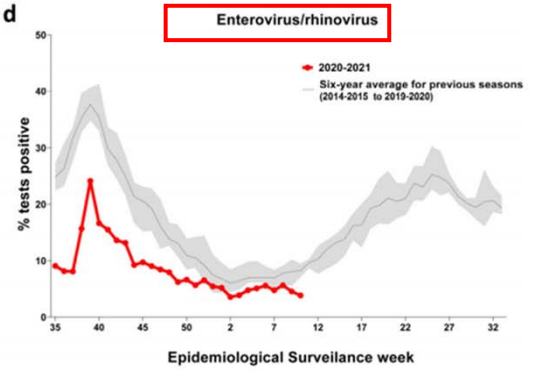

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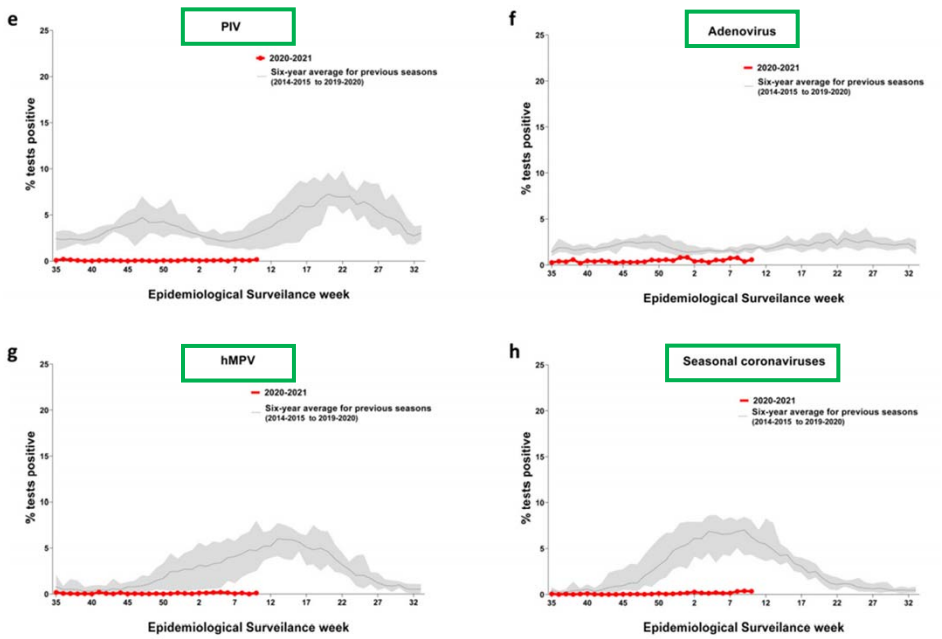

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RSV	6207 (1327 - 16348)	5·96 (0·22 - 17·80)	8890 (4952 -18413)	0·047 (0 - 0·10)	0·0169 (0·0122–0·0235)	<0·001
PIV	3242 (1155 - 7187)	3·09 (1·15 – 7.00)	4586 (2034 - 8486)	0·067 (0 - 0·20)	0·0190 (0·0144–0·0250)	<0·001
Adenovirus	3412 (1164 - 7207)	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

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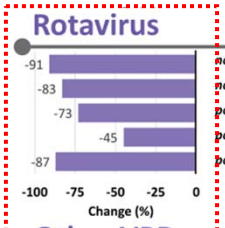

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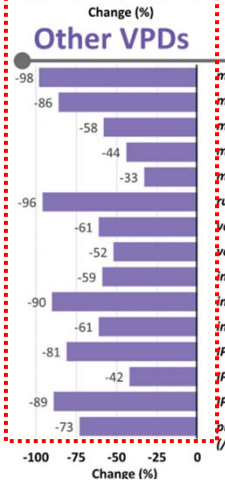

Drop in: (parameter)	During: (index period)	vs. (reference period)	Country/ Region	Ref.
measles crude average annual incidence (/100,000)	2020	2014–2019	China	[11]
measles notifications	2020 (Mar–Aug)	Jan 2016–Feb 2020	Germany	[18]
mumps crude average annual incidence (/100,000)	2020	2014–2019	China	[11]
mumps notifications	2020 (Jan–Dec)	2014–2019 (Jan–Dec)	China	[17]
mumps notifications	2020 (Mar–Aug)	Jan 2016–Feb 2020	Germany	[18]
rubella crude average annual incidence (/100,000)	2020	2014–2019	China	[11]
varicella-zoster notifications	2020 (Apr–Sep)	2015–2019 (Apr–Sep)	Australia	[15]
varicella notifications	2020 (Mar–Aug)	Jan 2016–Feb 2020	Germany	[18]
invasive meningococcal disease notifications	2020 (Mar–Aug)	Jan 2016–Feb 2020	Germany	[18]
invasive meningococcal disease cases	Nov 2020–Apr 2021	Nov 2019–Apr 2020	England	[27]
invasive Hemophilus influenzae notifications	2020 (Mar–Aug)	Jan 2016–Feb 2020	Germany	[18]
IPD incidence: bacterial pneumonia (<5 YOA)	2020–2021	2016–2019	Israel	[28]
IPD incidence: excluding pneumonia (<5 YOA)	2020–2021	2016–2019	Israel	[28]
IPD hospitalization incidence (/100,000)	Mar 2020–Mar 2021	Jan 2015–Dec 2019	Hong Kong	[29]
pneumococcal pneumonia hospitalization incidence (/100,000)	Mar 2020–Mar 2021	Jan 2015–Dec 2019	Hong Kong	[29]

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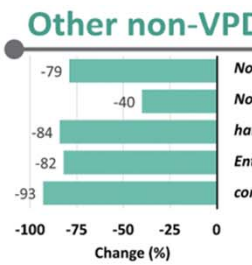

Drop in: (parameter)	During: (index period)	vs. (reference period)	Country/ Region	Ref.
Norovirus notifications	2020 (Mar–Aug)	Jan 2016–Feb 2020	Germany	[18]
Norovirus positive samples from hospitalized patients	Apr 2020 – Mar 2021	Apr 2016–May 2019	Poland	[20]
hand, foot and mouth disease notifications	2020 (Jan–Dec)	2014–2019 (Jan–Dec)	China	[17]
Enterovirus cases	Oct 2019–May 2020	2016–2019 (Oct–May)	Taiwan	[21]
common cold cases in children <18 YOA	Mar–Apr 2020	Mar–Apr 2019	US	[22]

針對其它流感以外的「呼吸道」以及「非呼吸道」感染症的負擔也看到有下降的表現。
研究也指出，NPIs雖然對一些非套膜(non-enveloped)的病毒(rhinovirus, adenoviruses, and norovirus)也有保護的效果，但保護效果較不顯著，使得這些病毒在封城的時仍維持一定程度地傳播

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關於CDC
傳染病與防疫專題
預防接種
國際旅遊與健康
進階搜尋
通報
檢驗
宣導
統計專區
申請
網址：https://www.cdc.gov.tw
1
2
3
統計專區
傳染病統計資料查詢系統
疾病管制署資料開放平臺
流感速訊
2022-2023流感流行季
顯示 10 筆結果
顯示筆數
項次
週別
連結
29
第16週(2023/4/16-2023/4/22)
流感速訊_2023年第16週.pdf
28
第15週(2023/4/9-2023/4/15)
流感速訊_2023年第15週.pdf
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第14週(2023/4/2-2023/4/8)
流感速訊_2023年第14週.pdf
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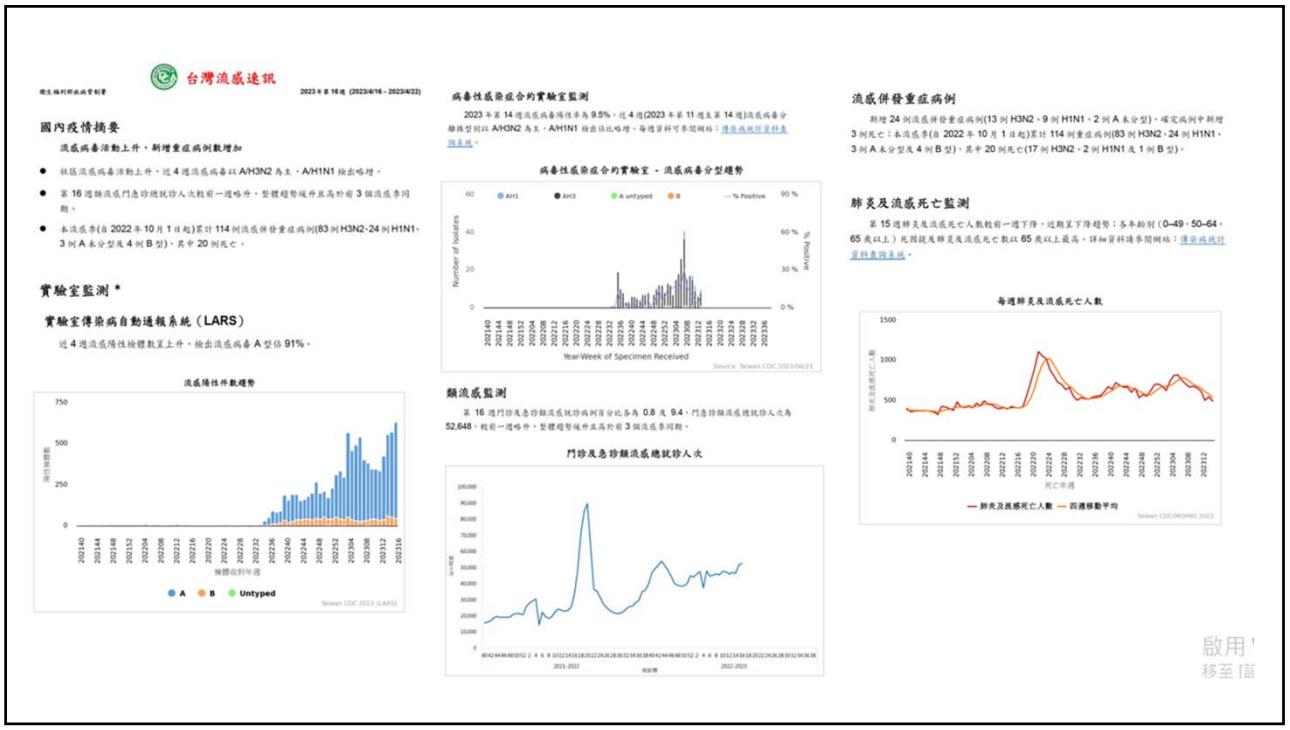
台灣流感速訊
國內疫情摘要
實驗室監測 *
實驗室傳染病自動通報系統（LARS）
病毒性感染症合約實驗室監測
類流感監測
流感併發重症病例
肺炎及流感死亡監測
每週肺炎及流感死亡人數
啟用
移至

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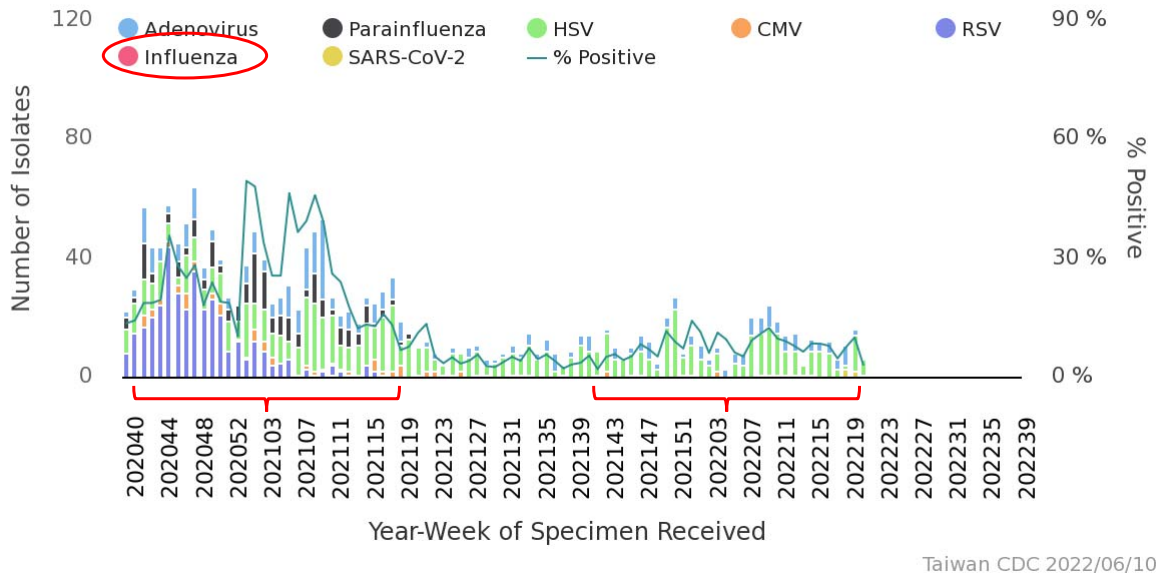

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結論

- 因為對抗COVID-19的疫情的措施，使得其它呼吸道以及非呼吸道病原菌的疾病負擔有下降的趨勢。
- NPIs雖然對一些非套膜(non-enveloped)的病毒(rhinovirus, adenoviruses, and norovirus)也有保護的效果，但保護效果較不顯著，使得這些病毒在封城的時仍維持一定程度地傳播

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Topic 3

- 放寬non-pharmaceutical interventions管制後，呼吸道感染的疫情可能會如何呢?
- 放寬管制後，台灣目前的流感疫情情況如何呢

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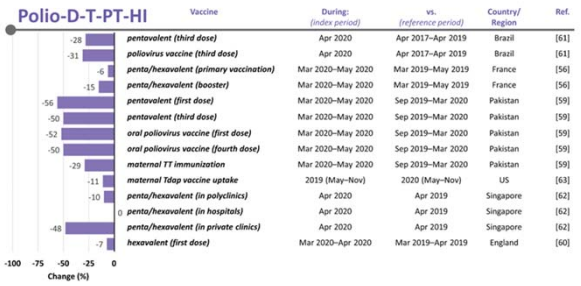

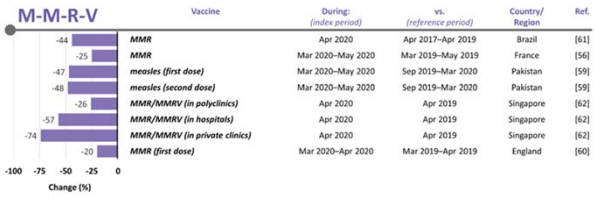

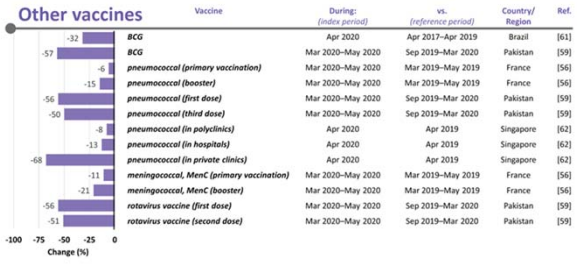

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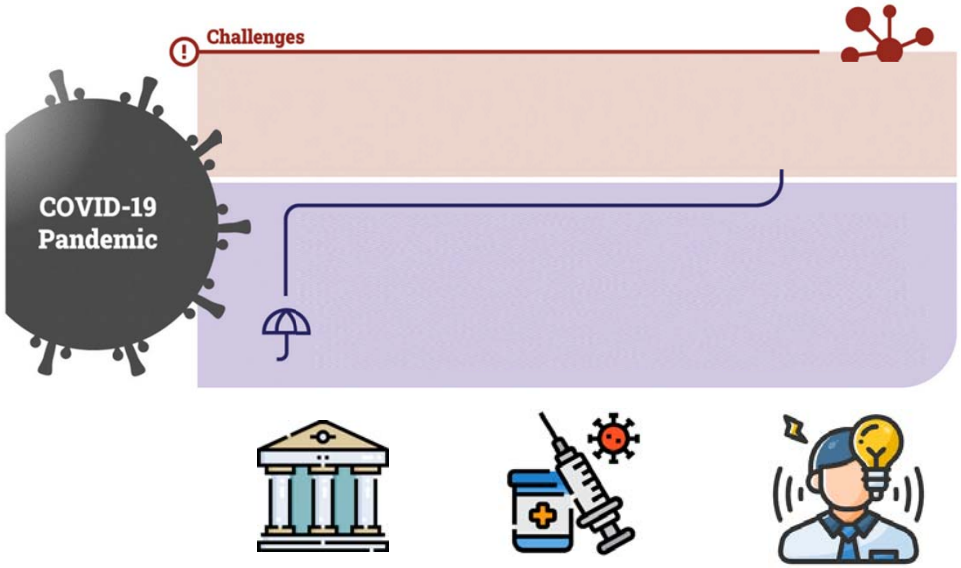

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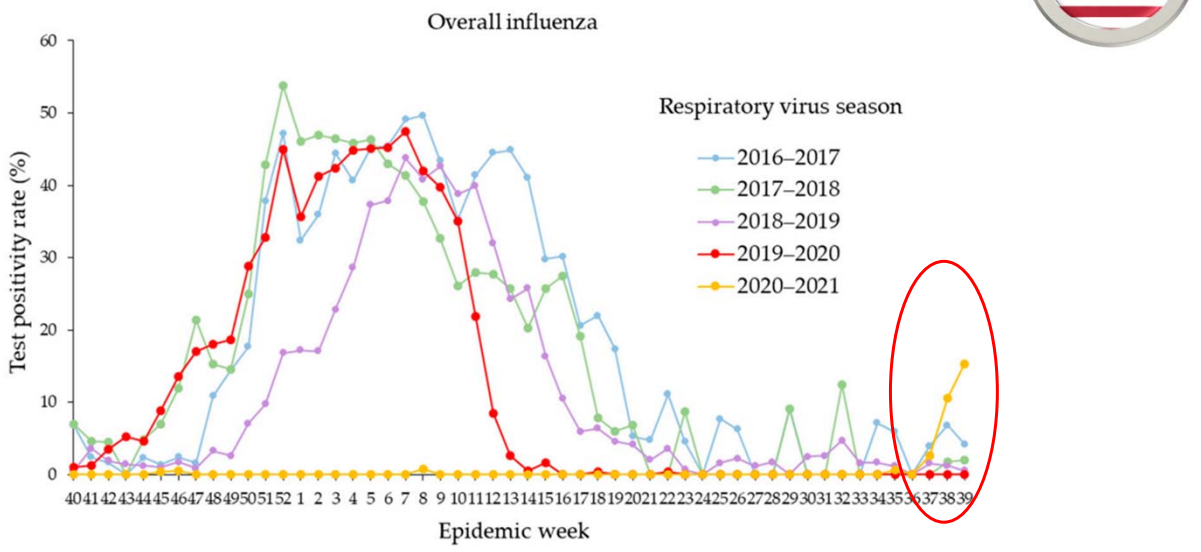

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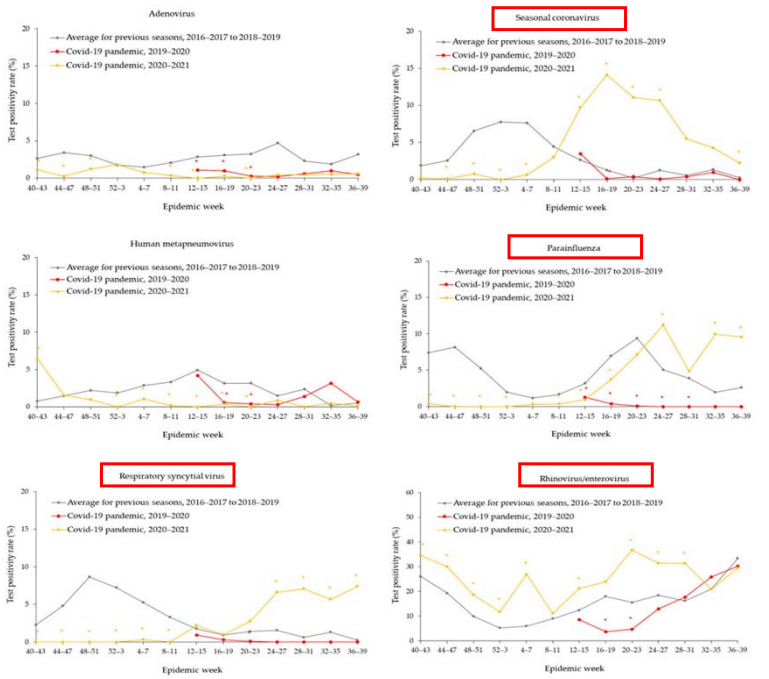

許多呼吸道病毒(seasonal coronavirus, parainfluenza, RSV, rinhovirus/enterovirus)隨著隔離政策的鬆綁，疫情有復燃的跡象。

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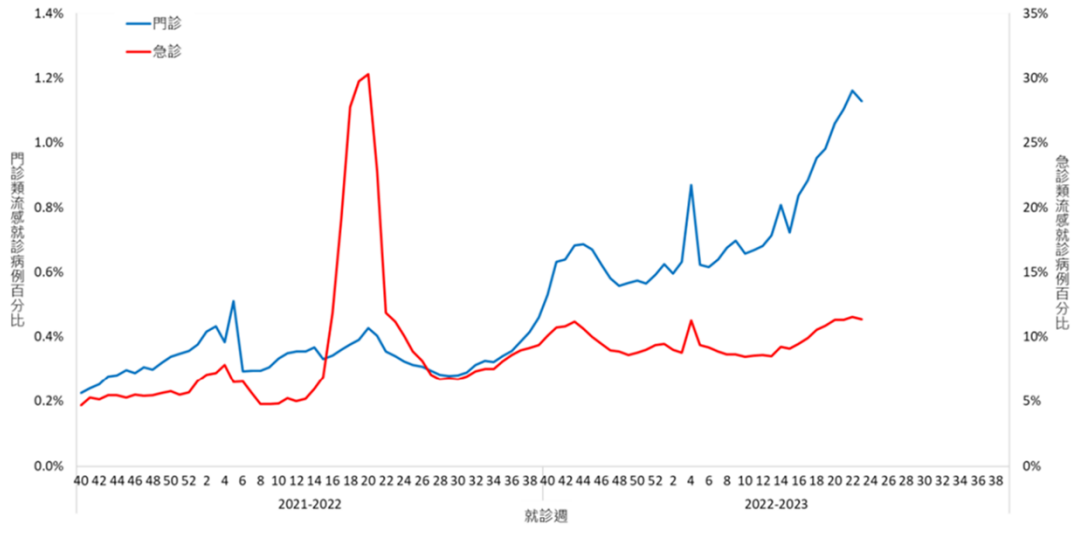
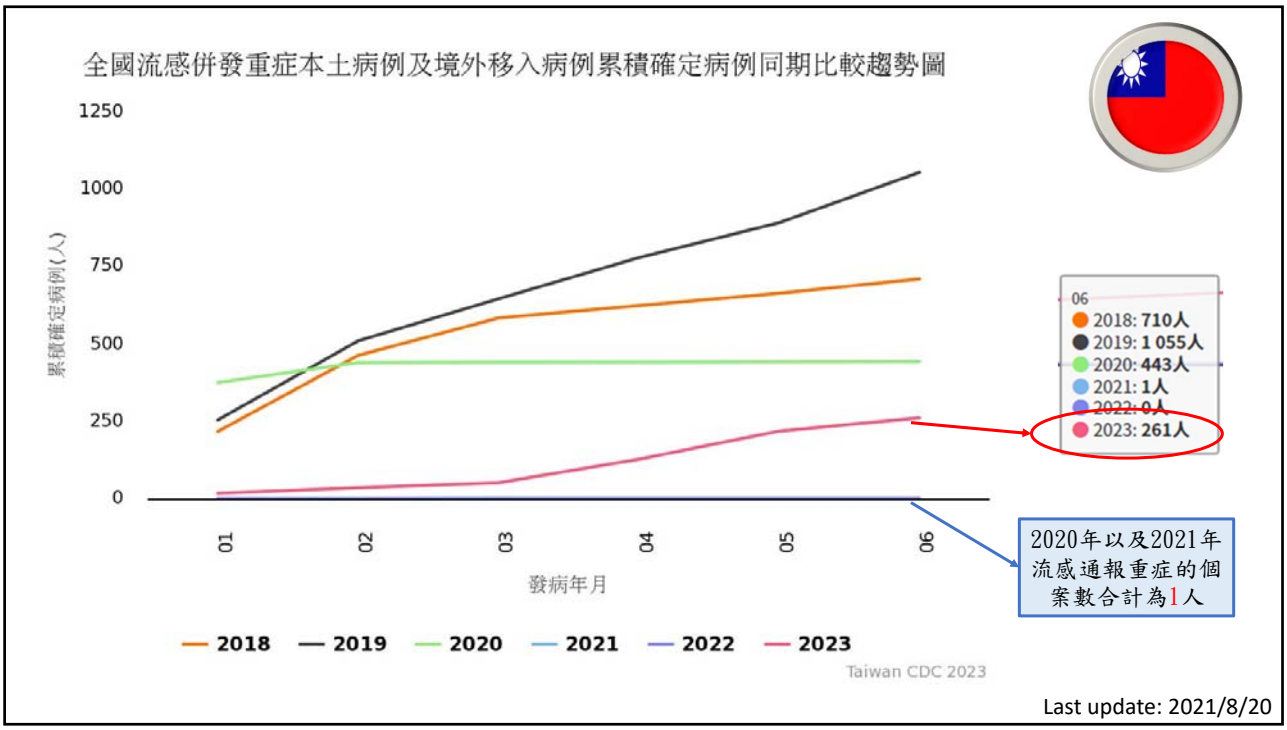
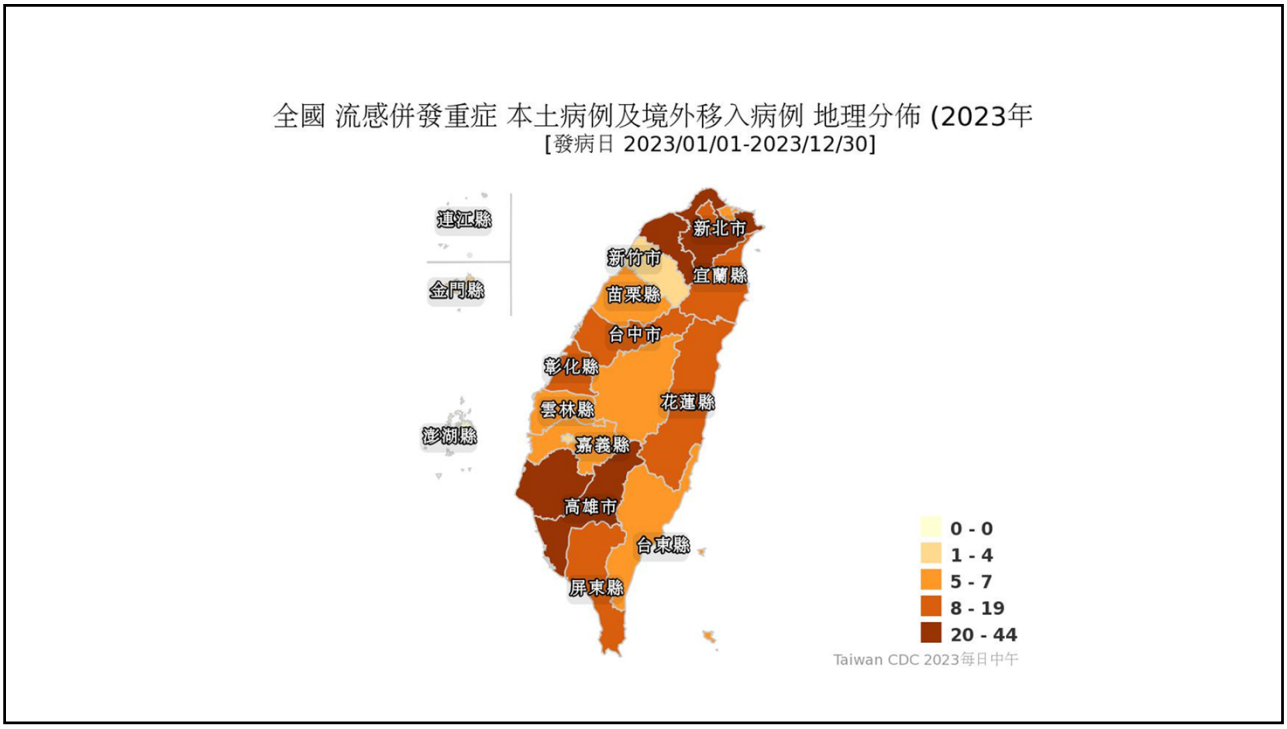
門診及急診類流感就診病例百分比



30


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
累積確定病例(人)
1250
1000
750
500
250
0
01
02
03
04
05
06
發病年月
2018
2019
2020
2021
2022
2023
Taiwan CDC 2023
06
2018: 710人
2019: 1 055人
2020: 443人
2021: 1人
2022: 0人
2023: 261人
2020年以及2021年流感通報重症的個案數合計為1人
Last update: 2021/8/20

31


全國 流感併發重症 本土病例及境外移入病例 地理分佈 (2023年
[發病日 2023/01/01-2023/12/30]
連江縣
金門縣
澎湖縣
新北市
新竹市
宜蘭縣
苗栗縣
台中市
彰化縣
雲林縣
花蓮縣
嘉義縣
高雄市
台東縣
屏東縣
0 - 0
1 - 4
5 - 7
8 - 19
20 - 44
Taiwan CDC 2023每日中午

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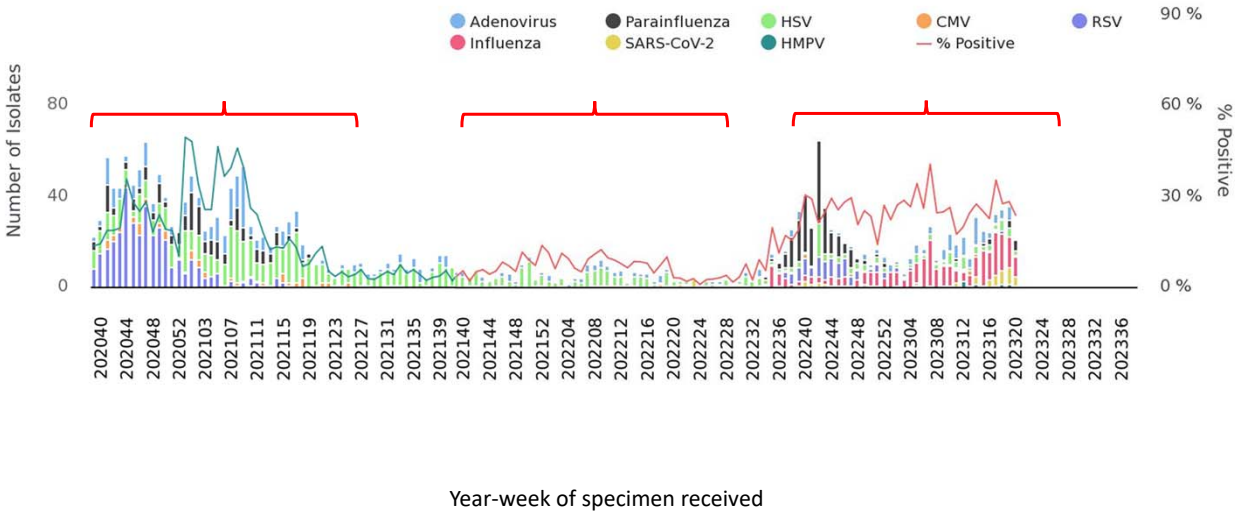

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Topic 4

為什麼我們要來認識流感的威脅呢?

跨物種間的感染

流感病毒抗原多變性

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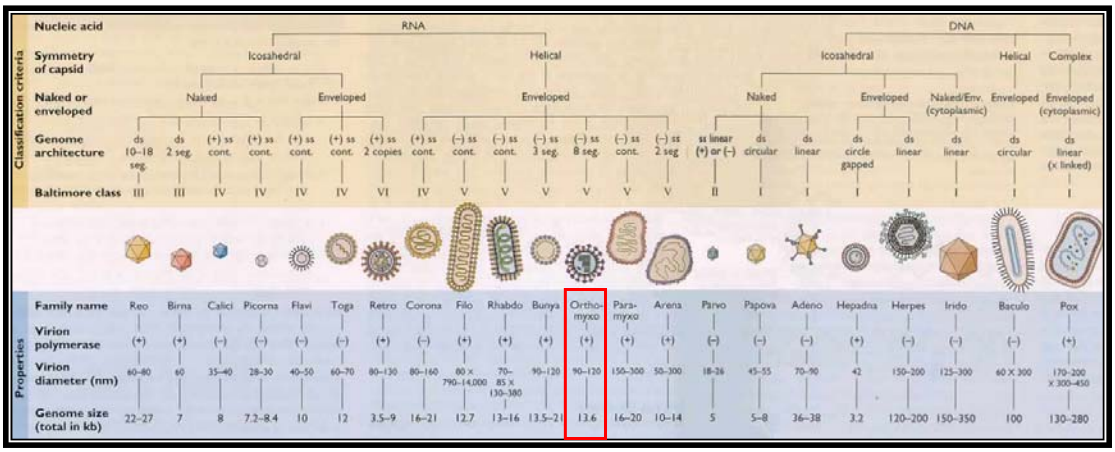
病毒分類



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

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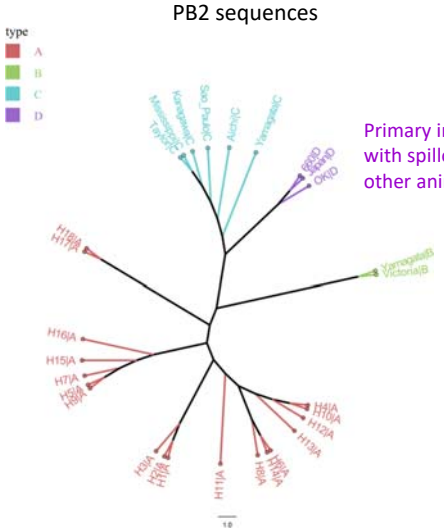
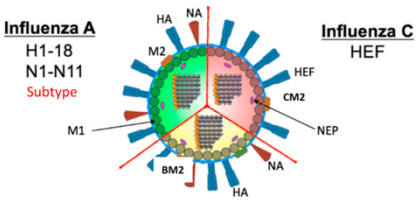
Phylogenetic tree of Influenza viruses based on PB2 sequences

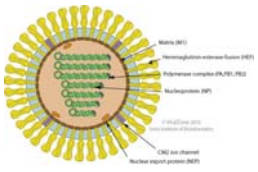


Influenza Virus Types



抗原血球凝集素（H 抗原）
神經胺酸酉每（N 抗原）

Influenza C



- **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.

- 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	引可能發生”Antigenic	

- 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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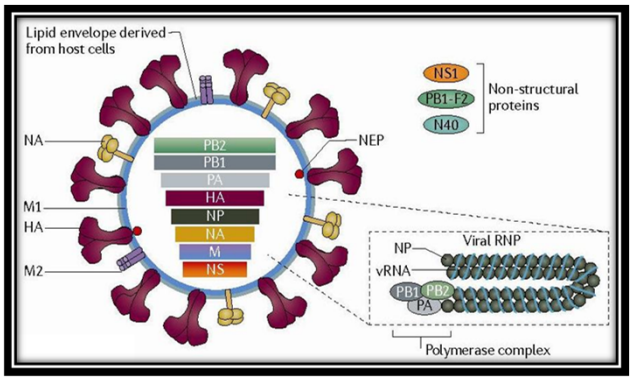

- PB1, PB2, PA節段編碼的是RNA聚合酶（RNA polymerase）
- HA節段負責編碼血球凝集素
- NP節段負責編碼核蛋白（nucleoprotein）
- NA節段編碼的是神經胺酸酶
- M節段編碼基質蛋白
- NS節段編碼的是具有剪接RNA（RNA splicing）功能的非結構蛋白（nonstructural protein）

- 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
- B型分兩個linage:
  - B/Victoria/2/87以及B/Yamagata/16/88

在這18個H以及11個N的亞型，H1-H16以及N1-N9是主要是地方性禽類上的傳播，尤其是水鳥。

而H17N10 以及H18N11 virus被發現在新世界的蝙蝠上，其使用的受器以及臨床表現上與常見的A型流感不同。

Lancet. 2022 Aug 27;400(10353):693-706

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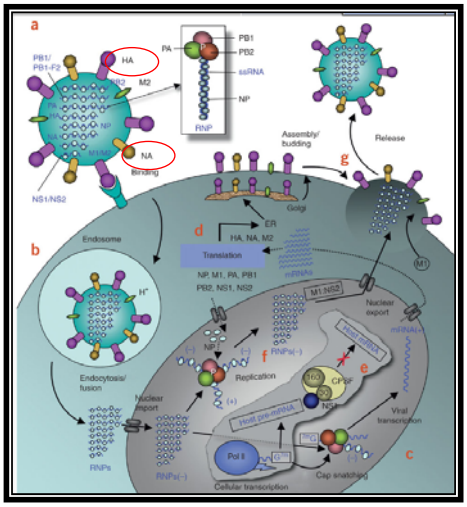
A型流感的生命週期

- **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。

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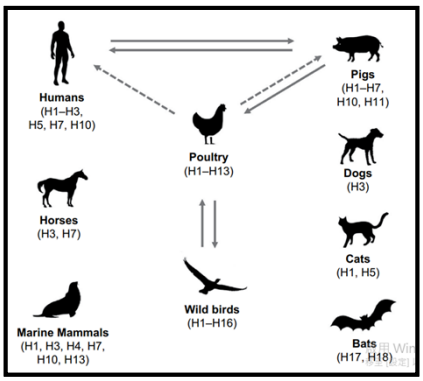
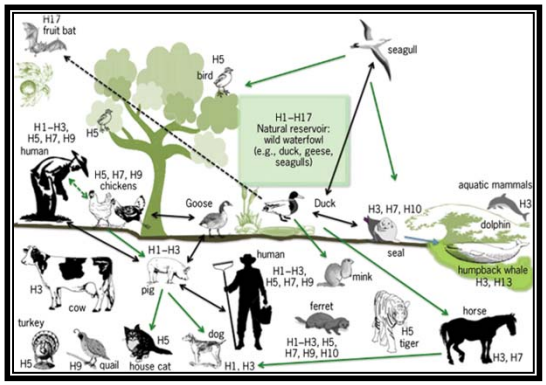
各種A型流感亞型的宿主





- 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

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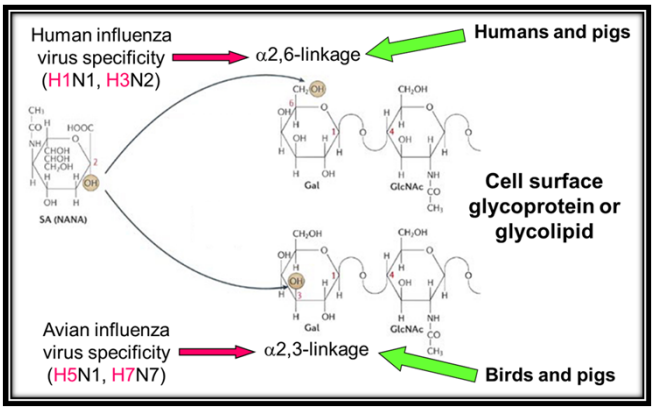
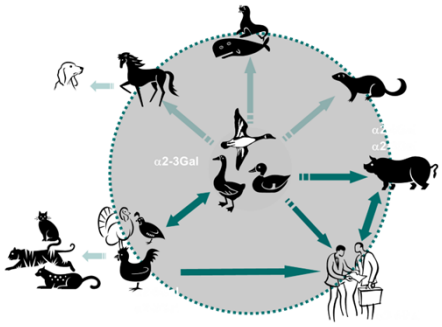
Sialic acid的鍵結決定了流感病毒HA受器的連結





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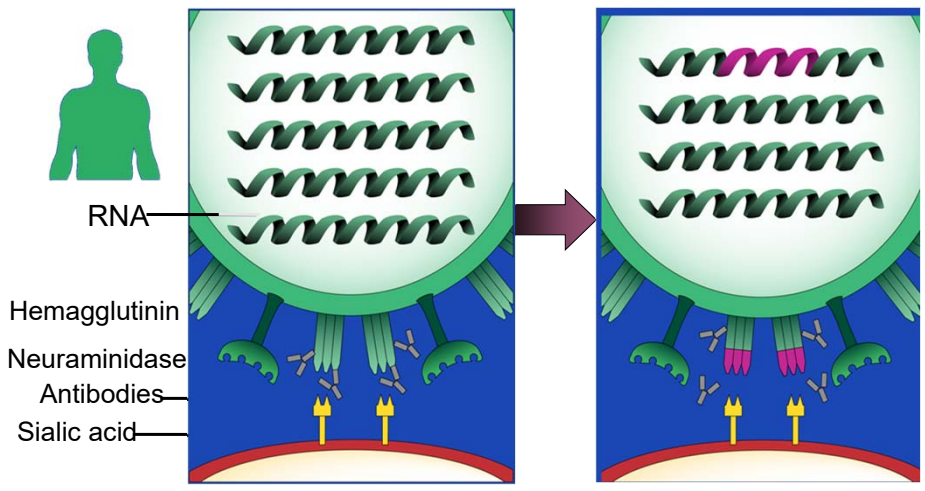
- **抗原的漂變（Antigenic Drift）：**
  - 是在病毒的HA/NA上緩慢、相對上持續的過程，又稱為抗原的連續性變異。
  - 病毒基因複製所累積的點突變（point mutation）所導致，進而產生新的strain。
  - 在A型以及B型流感皆有可能。
  - 因為這新的strain導致之前的抗體無法提供”完全”的保護力，所以流感疫苗必須時時更新。

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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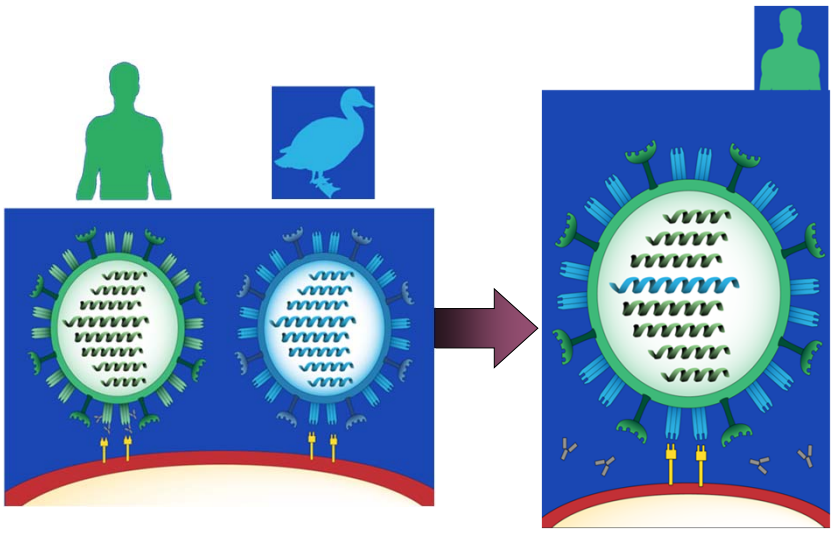
抗原性轉變(Antigenic Shift)



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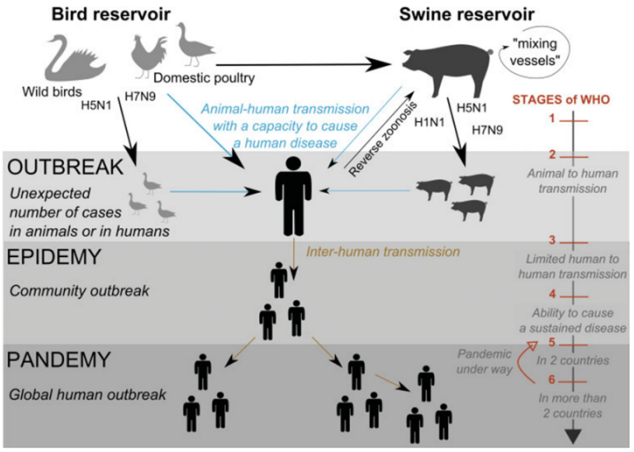
A schematic representation showing major events involved in emergence of an influenza pandemic, from the two major animal reservoirs to the global outbreak in humans



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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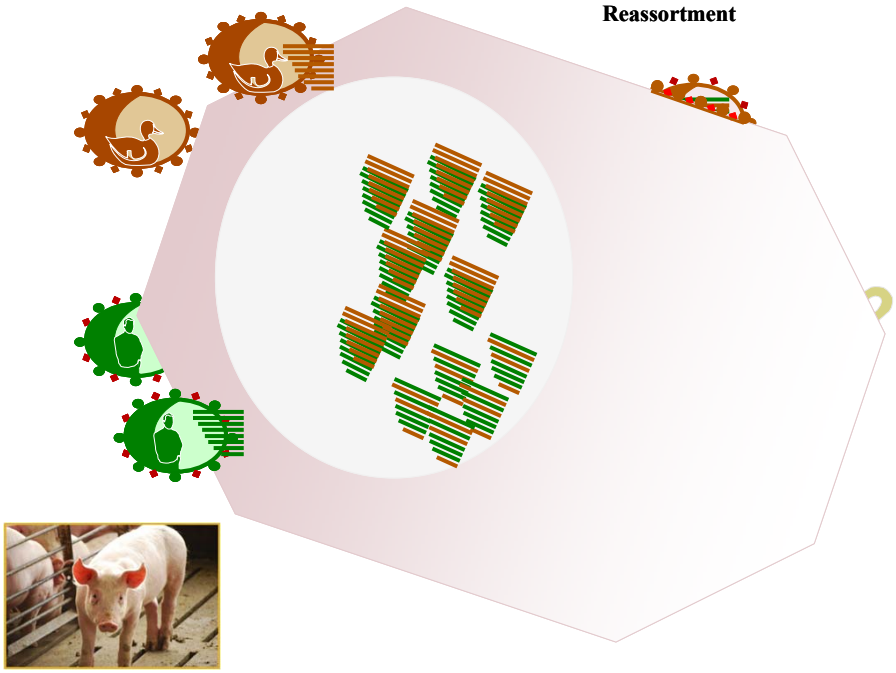

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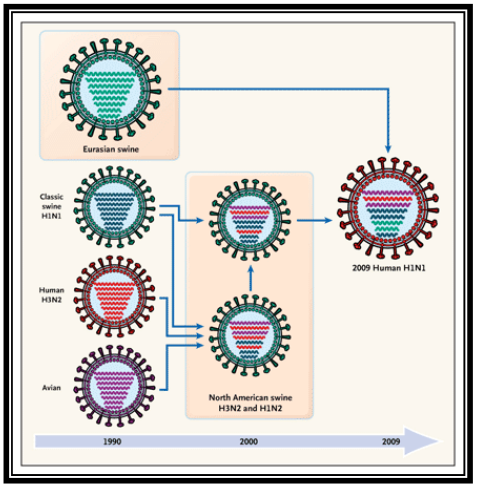
Origin of 2009 pandemic H1N1 influenza strain "quadruple reassortant"



- 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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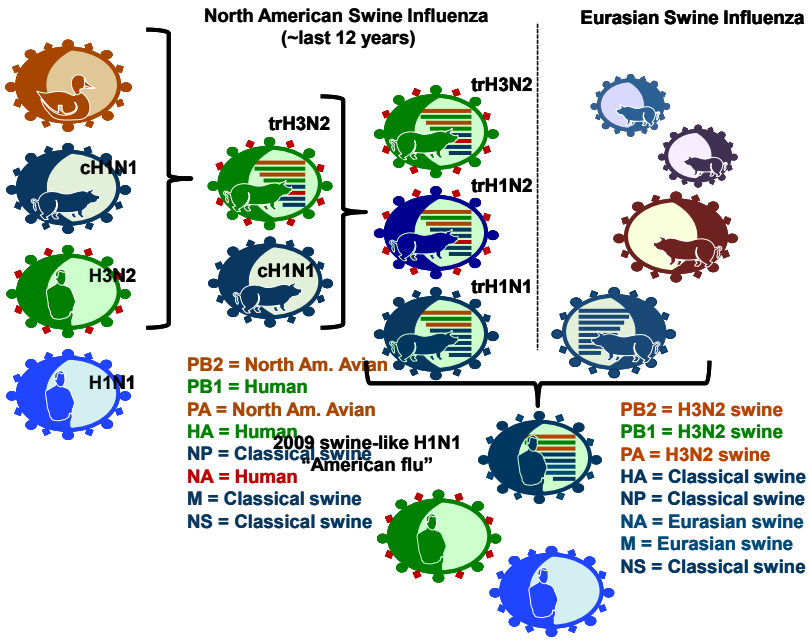

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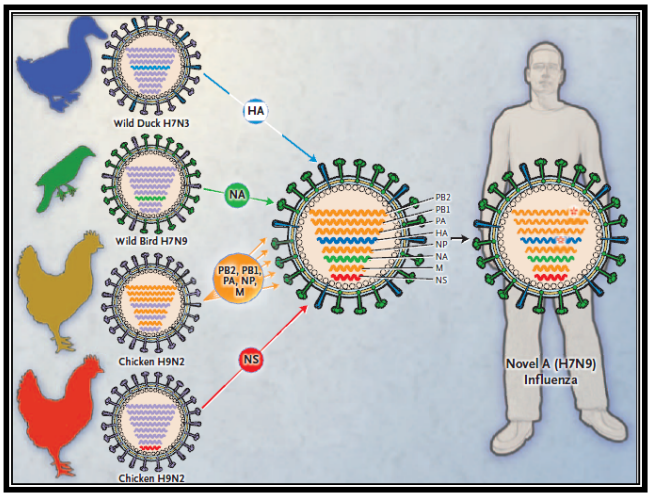
Origin of the novel avian influenza A H7N9 virus



N Engl J Med 2013; 368:2345-2348

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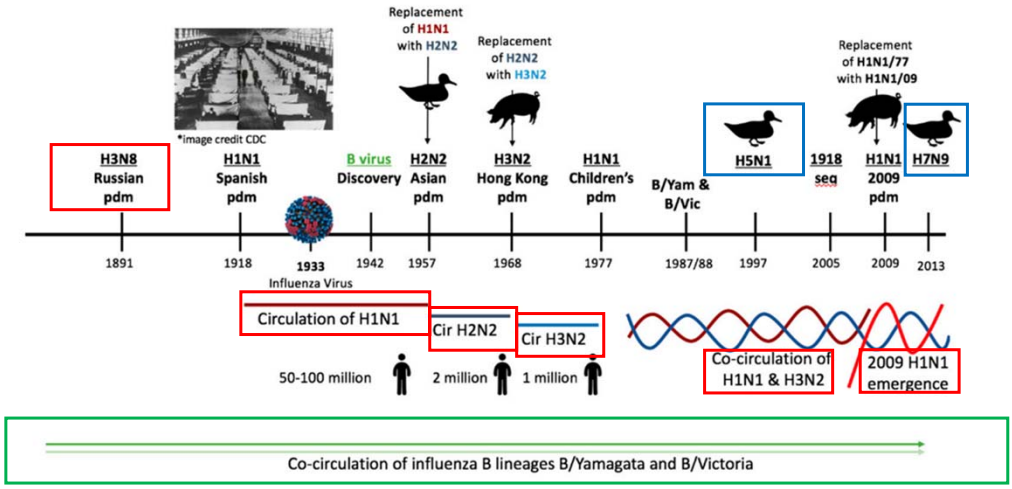
Timeline of the history of influenza virus circulation in humans since 1890s



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

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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。

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“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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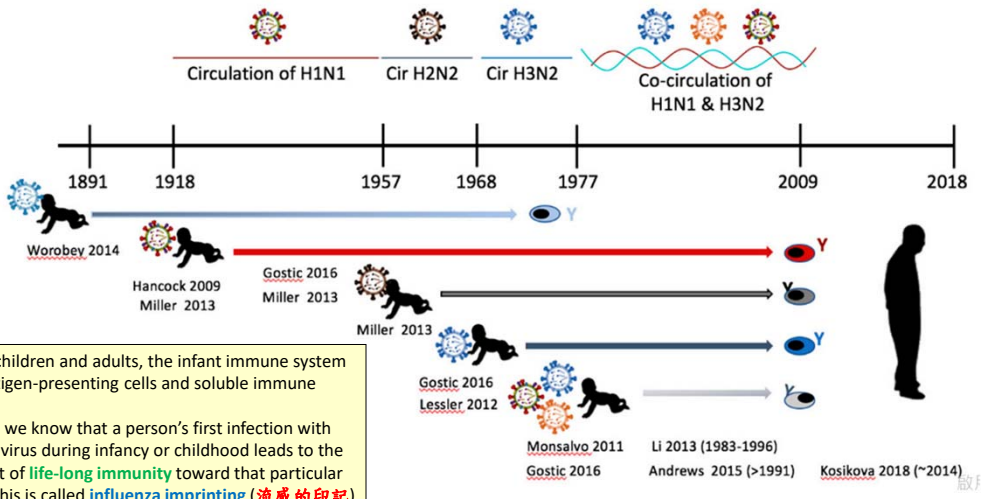
Influenza immune imprinting and the history of circulating influenza viruses



- 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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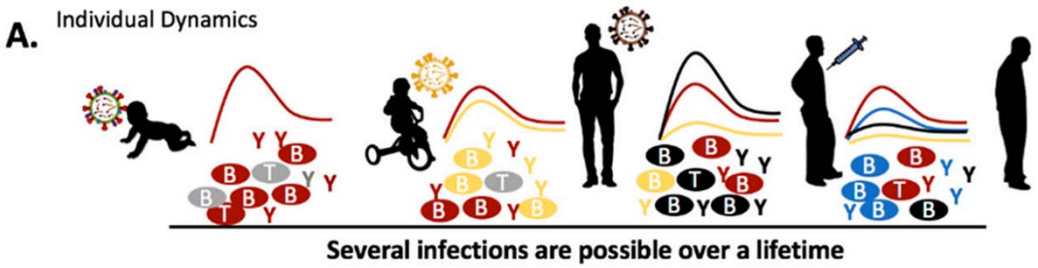
Influenza immune background development following recurrent infections and vaccinations



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

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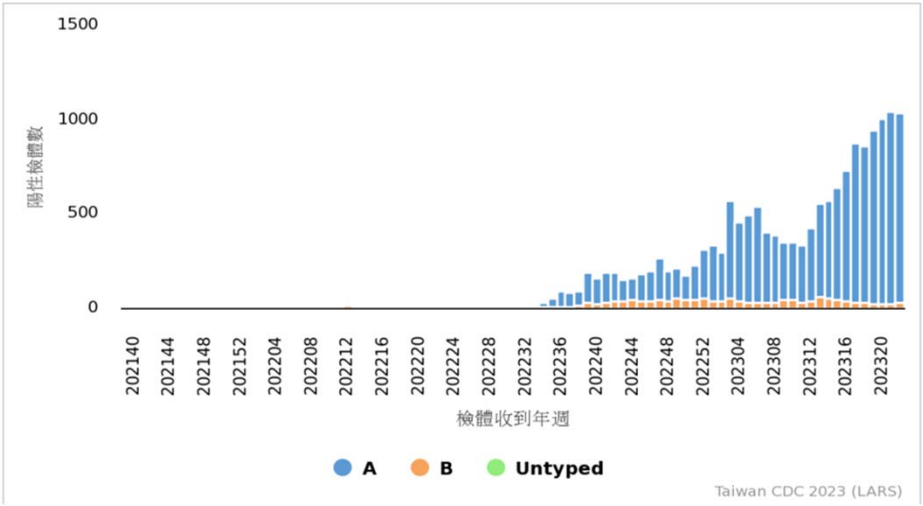
實驗室傳染病自動通報系統（LARS）

近 4 週流感陽性檢體數呈上升，檢出流感病毒 A 型佔 97%。

流感陽性件數趨勢



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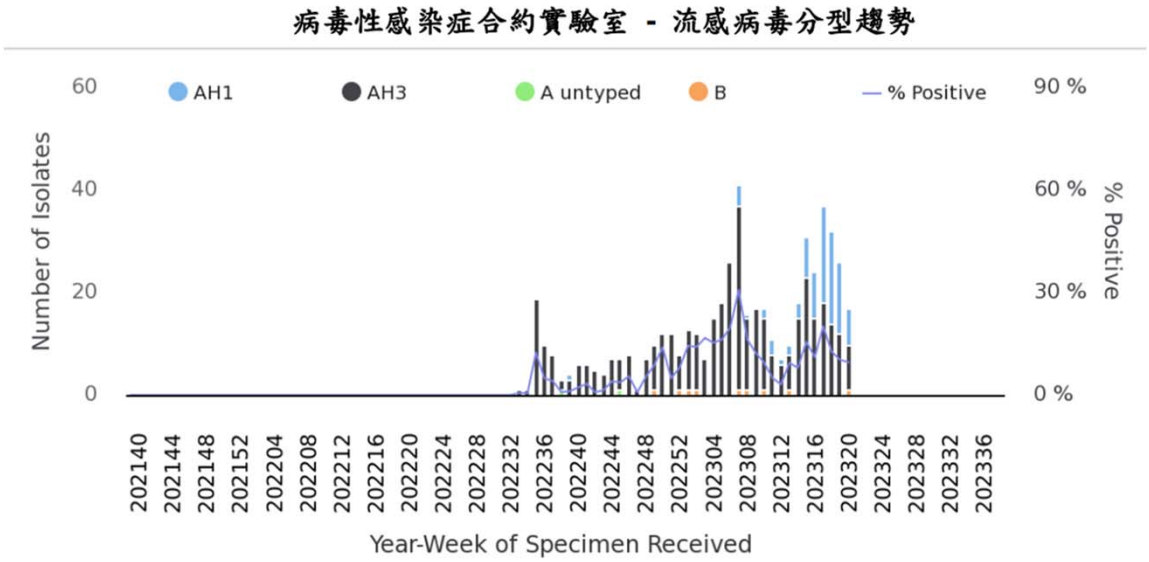

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Topic 5

流感的症狀、併發症與其它病原菌的共同感染

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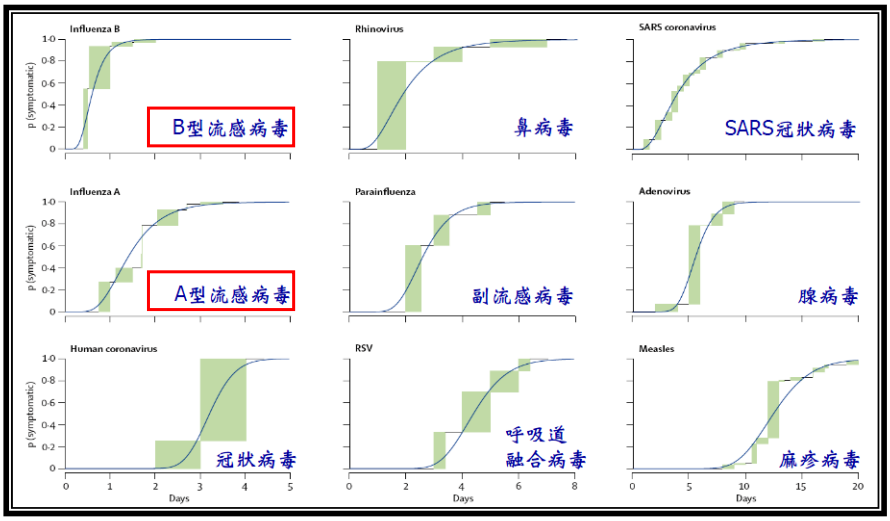
病毒感染的潜伏期

	Median incubation period
Influenza A	1.4
Influenza B	0.6



Lancet Infect Dis 2009;9:291-300

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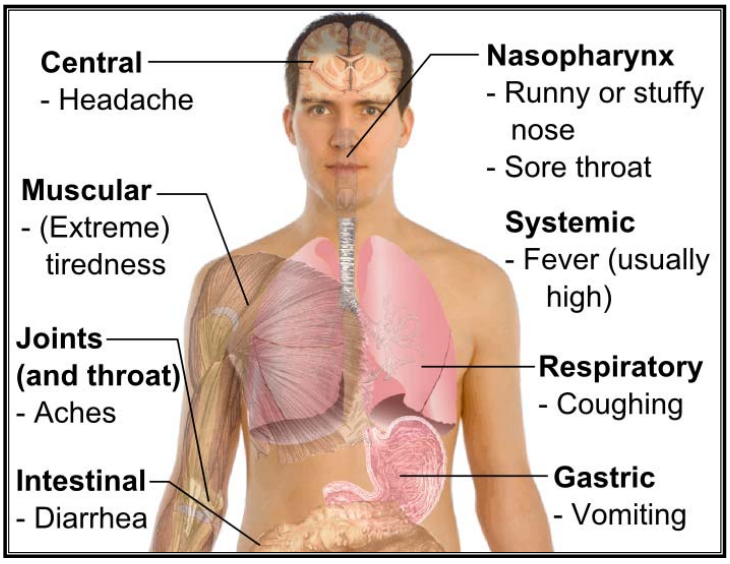
流感的症狀



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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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流感的併發症

	Complications	Considerations
Upper-respiratory complications	Otitis media, parotitis, sinusitis, and laryngotracheobronchitis	Otitis media, parotitis, and laryngotracheobronchitis are more common in children than adults
Lower-respiratory complications	Bronchiolitis, bronchitis, reactive airway disease, pneumonia, respiratory failure, and acute respiratory distress syndrome	Bronchiolitis is more common in young children than in adults
Cardiac complications	Myocardial infarction, myocarditis, pericarditis, and heart failure	Influenza might precipitate myocardial infarction or heart failure in people with coronary artery disease; cardiac complications can result in critical illness with fatal outcomes
Gastrointestinal complications	Hepatitis, pancreatitis, and severe acute abdomen-like pain	Hepatic failure is rare
Musculoskeletal complications	Myositis, rhabdomyolysis, and compartment syndrome	Severe myositis (soleus and gastrocnemius) can occur in school-age children; myoglobinuria can cause acute kidney injury
Renal complications	Acute kidney injury and kidney failure	Can occur with severe pneumonia

Lancet. 2022 Aug 27;400(10353):693-706

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	Complications	Considerations
Neurological complications	Encephalopathy, encephalitis, meningoencephalitis, febrile seizures, cerebrovascular accident, transverse myelitis, acute demyelinating encephalomyelitis, Reye syndrome with salicylate exposure, and Guillain-Barré syndrome	Encephalopathy and encephalitis are more common in young children, can be acute or postinfectious with full neurological recovery, sequelae, or fatal outcomes; Reye syndrome is rare in children without salicylate exposure, and Guillain Barre syndrome is uncommon
Co-infections	Pneumonia, ventilator-associated pneumonia, tracheitis, and meningitis	Invasive bacterial, viral, and fungal coinfections can cause critical illness and fatal outcomes
Other complications	Exacerbation of chronic disease, dehydration, sepsis, toxic shock syndrome, sepsis-like syndrome or sudden death in young infants, premature labour, and fetal loss in pregnant people	People of all ages with chronic disease can experience worsening of underlying conditions (eg, chronic obstructive pulmonary disease exacerbation in adults, acute chest syndrome with sickle cell disease, worsening of asthma, and heart failure)

Adapted from Uyeki and colleagues.[26]

Table 2: **Complications associated with influenza**

Lancet. 2022 Aug 27;400(10353):693-706

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The frequency of influenza and bacterial coinfection

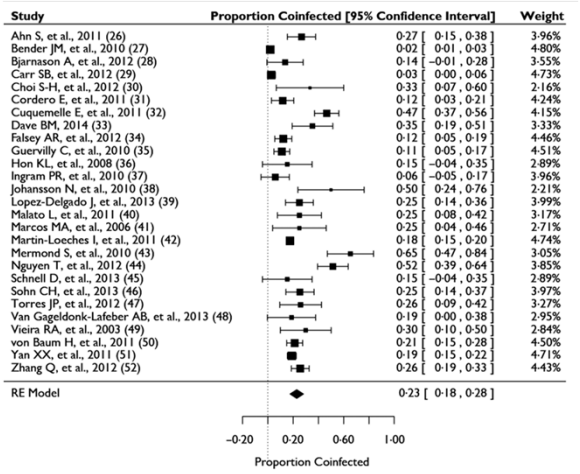

Figure 3. Frequency of bacterial coinfection in hospitalized patients with laboratory confirmed influenza.

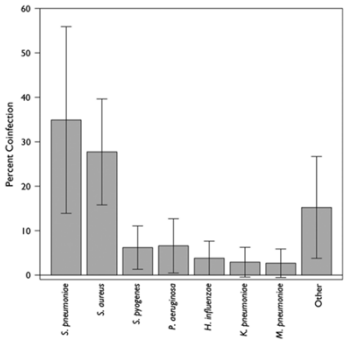

Figure 4. Percent of laboratory confirmed influenza infections that were coinfected by each bacterial species.

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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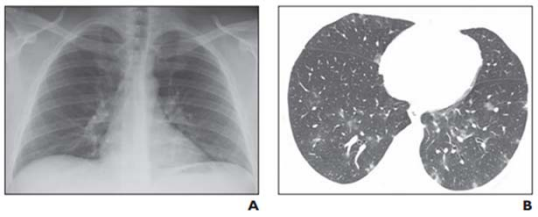
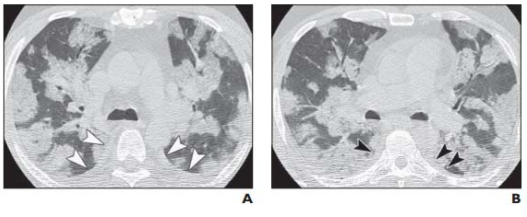
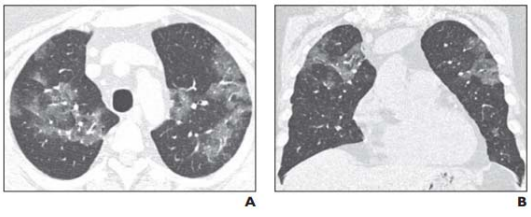


32-year-old man with H1N1 pneumonia. A, Chest radiograph shows normal lungs. B, CT image obtained on same day as A shows mild ground-glass opacity in both lungs that predominates in lower lobes.



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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哪些族群是得到併發症的高風險族群呢？

高風險族群	
老年人（大於60歲），尤其是在機構內	
長期接受阿斯匹靈的孩童和青少年（六個月至18歲）	
懷孕婦女	
病人具有以下特徵	
	慢性肺部疾病
	慢性心臟病
	慢性代謝性疾病（糖尿病）
	疾病或治療所引起的免疫缺陷（HIV
	慢性腎臟病

Palache AM. Influenza subunit vaccine - ten years experience. *Eur J Clin Res* 1992; 3: 117–38.

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Take home message

- 儘管新冠感染疫情的管制措施使得許多的呼吸道以及非呼吸道感染的疾病負擔有顯著下降，但隨著管制解禁以及可能疫苗施打率的下降，導致這些疾病有捲土重來，甚至以更嚴峻的形勢再次出現。
- 台灣目前正處於流感疫情上升的階段，通報重症的個案數也較前年顯著上升，97%為A型流感。
- 在門診以及住院的個案若有呼吸道症狀，除了新冠病毒外，也要想到流感病毒。

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Clinical management of Influenza

2023.06.17

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流感臨床處置

2023.06.17

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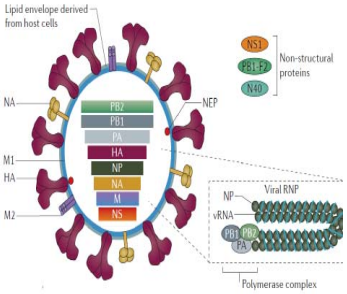
大綱

- 流感與併發症
- 流感藥物介紹
- 合併療法與類固醇在流感嚴重肺部併發症之角色

流感與併發症

流感病毒的介紹

- 流感病毒（Influenza virus）
  - 屬正黏液病毒科（orthomyxoviridae）
  - 分為A型、B型、C型及D型
    - 依NP及M蛋白分型
  - 外套膜含有2種醣蛋白
    - 紅血球凝集素（hemagglutinin：HA）
    - 神經胺酸酶（neuraminidase：NA）
  - A型病毒再依據不同的HA及NA區分亞型



圖片來源：Nature Reviews Microbiology 9, 590-603 (August 2011)

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流感分型

	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

資料來源:衛生福利部疾病管制署-季節性流感防治工作手冊(2022年12月)

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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歲以上老年人
- 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及B/Victoria兩個lineage
- 台灣地區流行期約自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

資料來源:衛生福利部疾病管制署 7

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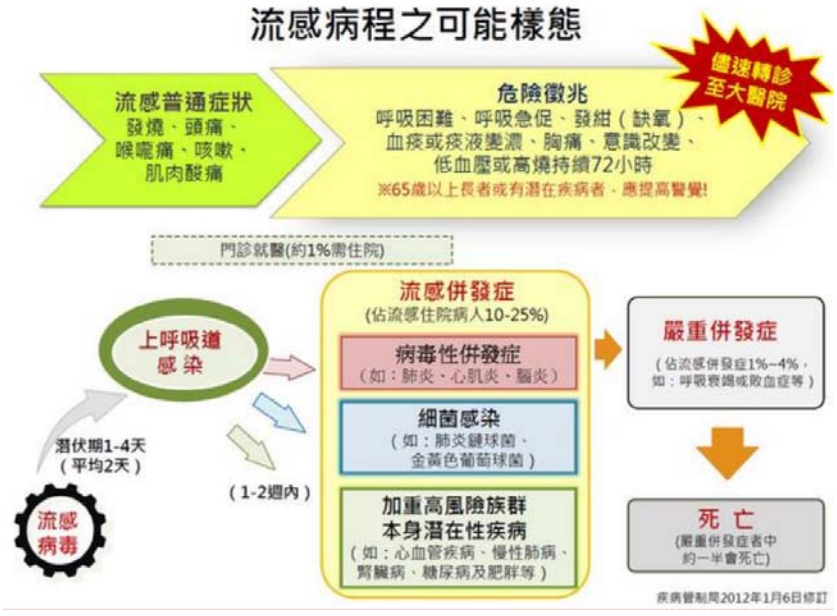

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臨床症狀

- 發燒、咳嗽、喉嚨痛、肌肉酸痛、頭痛與疲勞。
- 部分病例伴有腹瀉、嘔吐症狀。
- 多數人通常約可在1週內康復。

流感併發重症

- **流感併發重症(此為第四類法定傳染病需1週內通報)**
  - 有些人感染流感病毒後可能引起**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**等嚴重併發症，而需住院治療，甚至導致死亡，稱之為流感併發重症
- 可能併發重症之**高危險群**
  - 老年人、嬰幼兒、孕婦
  - 患有氣喘、糖尿病、心血管、肺臟、肝臟、腎臟等慢性疾病
  - 免疫功能不全者
  - 肥胖(身體質量指數BMI≧30)

流感併發重症

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。

五、 疾病分類

（一）可能病例：

符合臨床條件。

（二）極可能病例：

符合臨床條件及流行病學條件。

（三）確定病例：

符合臨床條件及檢驗條件。

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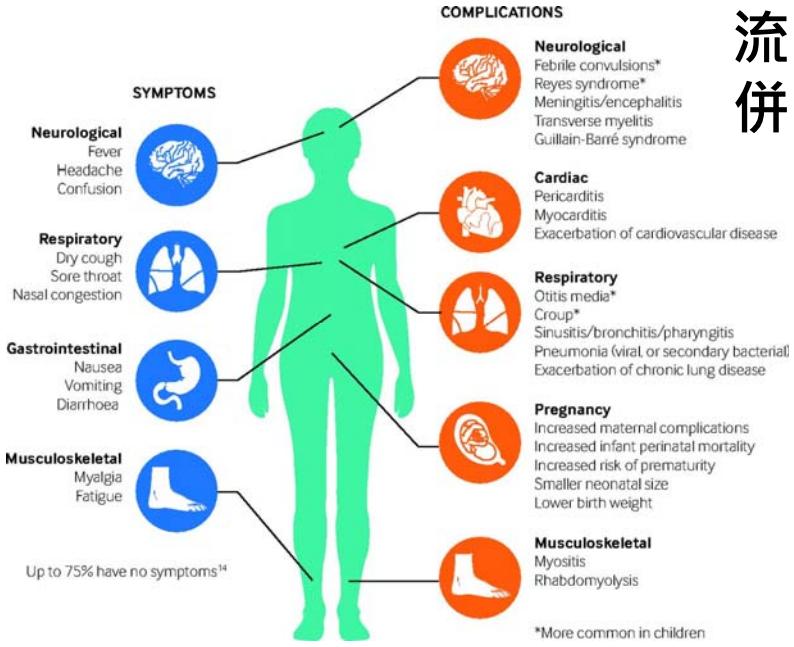
流感併發症



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

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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

- **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。

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流感藥物介紹

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公費流感藥物對象

一、「流感併發重症」通報病例(屬第四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
二、「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
三、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)
四、未滿 5 歲及 65 歲以上之類流感患者
五、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」
六、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 註： 1.重大傷病：IC 卡註記為重大傷病或持有重大傷病證明紙卡者。 2.流感高風險慢性疾病之 ICD CODE 為 B20 , Z21 , D80-84 , D86 , D89 , E08-13 , E66 , E85 , G09 , G20 , G30-32 , G35-37 , G40 , G45-46 , G65 , G70 , G72 , I00-02 , I05-09 , I11-13 , I20-22 , I24-25 , I27-28 , I34-37 , I42-43 , I44-45 , I47-49 , I50-51 , I60-62 , I63 , I67-69 , I70 , I71, I72 , I73-74 , I77 , I79 , J40-45 , J47 , J60-70 , J82 , J84 , J96 , J98 , J99 , K70-72 , K73-76 , B18-19 , M05-06 , M30-31 , M32-34 , M35 , M94.1 , N00-01 , N03 , N05 , N04 , N18-19 , N26-27 , Q89.01 , Z90.81。
七、肥胖之類流感患者(BMI≧30)
八、有類流感症狀，且家人/同事/同班同學有類流感發病者 適用期間：111 年 12 月 1 日至 112 年 3 月 31 日

下列 9 至 11 項為預防性用藥條件，需通報衛生局進行疫情調查，並經本署各區管制中心防疫醫師或傳染病防治醫療網區正/副指揮官或其授權人員同意後始可用藥。

九、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
十、「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
十一、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

無須快篩陽性

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2022 U.S. CDC Summary of Influenza Antiviral Treatment Recommendations

Early antiviral treatment can

- Shorten the duration of fever and illness symptoms, and may reduce the risk of complications from influenza (e.g., otitis media)
- Reduce death for hospitalized patients
- Shorten the duration of hospitalization in hospitalized children

Antiviral treatment is recommended <u>as early as possible</u> for patients with confirmed or suspected influenza who:

- is hospitalized
- has severe, complicated, or progressive illness
- is at higher risk for influenza complications

Clinical benefit is greatest when antiviral treatment is administered early, especially within **<u>48 hours</u>** of influenza illness onset

Antiviral treatment also can be considered for

- any previously healthy, symptomatic outpatient not at high risk with confirmed or suspected influenza on the basis of clinical judgment

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

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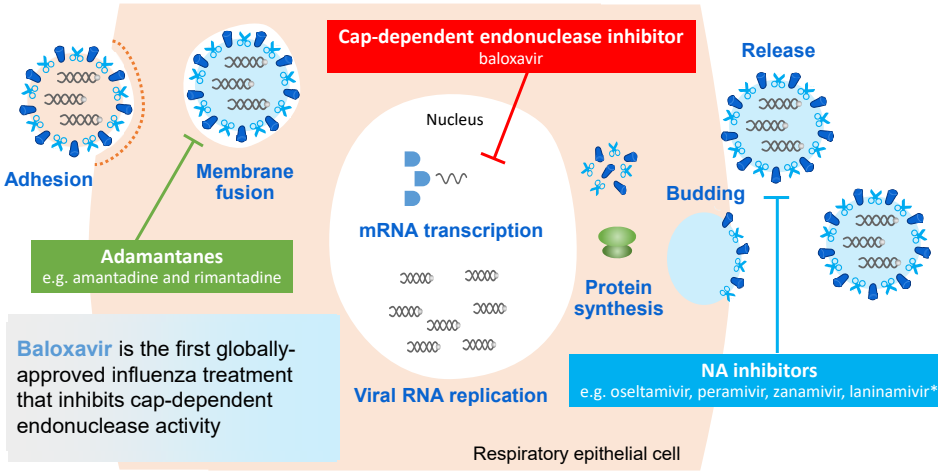
流感抗病毒藥物

	M2 蛋白抑制劑 (M2 protein inhibitor)		神經胺酸酶抑制劑 (Neuraminidase inhibitor)			核酸內切酶抑制劑 (Endonuclease inhibitor)
藥物學名	Amantadine	Rimantadine	Oseltamivir	Zanamivir	Peramivir	Baloxavir
商品名	Amantadin Amandin Amanta Amandine	Flumadine	Tamiflu, Eraflu	Relenza	Rapiacta	Xofluza
	Zneil 等					
對抗流感型別	A	A	A及B	A及B	A及B	A及B
預防	可	可	可	可	非適應症	可
治療	不建議	不建議	可	可	可	可
病程縮短	約1天	約1天	約1-1.5天	約1-1.5天	約1天	約1天
常見副作用	噁心、頭暈、失眠(5-10%)	噁心、頭暈、失眠(1-3%)	噁心(10%)、嘔吐(8%)、頭痛(2%)	噁心、腹瀉、鼻竇炎(3%)	腹瀉(5-10%)、噁心、嘔吐(5%)	腹瀉(3%)、氣管炎(2%)
抗藥性	廣泛	廣泛	曾有報告	曾有報告	曾有報告	曾有報告
國內許可證	有	無	有	有	有	有

- **M2 protein抑制劑**
  - 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**
  - 目前治療主流
  - Oseltamivir(Tamiflu®克流感、Eraflu®易剋冒)
  - 吸入式之Zanamivir(RelenzaTM瑞樂沙)
  - 靜脈注射之Peramivir(Rapiacta®瑞貝塔)
- **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

各流感藥物作用機轉



von Itzstein M. Nat Rev Drug Discov. 2007 Dec;6(12):967-74
Noshi T., et al. Antiviral Res. 2018 Dec;160:109-117 18

台灣感染症醫學會 The Infectious Diseases Society of Taiwan

台灣感染症醫學會-抗流感病毒藥物使用建議

抗流感藥物使用對象、劑量與療程

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 懷孕哺乳: 利>弊投與		單次點滴靜脈注射15分鐘以上 懷孕哺乳: 利>弊投與		單次口服 懷孕哺乳不建議	
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	

台灣感染症醫學會 The Infectious Diseases Society of Taiwan

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

公費流感抗病毒藥劑種類

RNA polymerase inhibitor

藥物學名	Oseltamivir	Zanamivir	Peramivir	Favipiravir
商品名	克流感/易剋冒	Relenza 瑞樂沙	Rapiacta	Avigan
包裝	75 毫克膠囊 10 入之盒裝	盒裝有碟型吸入器 1 枚，及含 4 孔規則間隔之泡囊 5 入	點滴用注射袋 300mg	淡黃色膜衣錠，每錠200mg
使用方式	口服	吸入	注射	口服
使用對象	成人及兒童（含足月新生兒）	五歲以上	成人及一個月大以上兒童	成人
用法用量	每日2次，每次75mg，共5日	每日2次，每次吸 2 孔，共5日	每日 300mg	每日2次，第1日每次服用 1600mg。第2日起每次服用600mg，共5日
小兒是否需調整劑量	是	否	是	本藥劑具致畸胎性，禁使用於兒童，且無小兒投藥經驗
腎功能不佳是否調整劑量	是	否	是	是
備註	可能出現輕微噁心及嘔吐，未成年病患需注意神經精神症狀	用於慢性呼吸系統病患時需特別注意支氣管痙攣及呼吸困難等症狀	提供新型A型流感通報病例使用，且需由醫院申請並經醫療網指揮官同意	無我國藥物許可證，提供新型A型流感通報病例使用（限於其他抗流感病毒藥物無效或效力不足的情況），且需由醫院向區管中心申請並經醫療網指揮官同意。本藥劑具致畸胎性，孕婦及有懷孕可能的婦人禁止使用

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Oseltamivir (Tamiflu®)

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Oseltamivir in seasonal influenza: cumulative experience in low- and high-risk patients

Regina Dutkowski*

Clinical Development – Virology, Hoffmann-La Roche Inc., 340 Kingsland Street, Nutley, NJ 07110-1199, USA

J Antimicrob Chemother 2010; **65** Suppl 2: ii11–24
doi:10.1093/jac/dkq012

Journal of Antimicrobial Chemotherapy

Oseltamivir significantly reduces the frequency of secondary illnesses and exacerbation of underlying conditions; survival is also significantly improved in seriously ill patients who are hospitalized with severe influenza

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 remai
We aimed to do an individual patient data meta-analy
treatment of seasonal influenza in adults regarding s

Methods We included all published and unpublished
trials of 75 mg twice a day oseltamivir in adults. Trials
illness in adults reporting at least one of the study
Embase, the Cochrane Central Register of Controlled
trials published before Jan 1, 2014 (search last upda
intention-to-treat, and safety populations. The primar

Findings We included data from nine trials including 4328 patients. In the intention-to-treat infected population, we noted a 21% shorter time to alleviation of all symptoms for oseltamivir versus placebo recipients (time ratio 0·79, 95% CI 0·74–0·85; p<0·0001). The median times to alleviation were 97·5 h for oseltamivir and 122·7 h for placebo groups (difference –25·2 h, 95% CI –36·2 to –16·0). For the intention-to-treat population, the estimated treatment effect was attenuated (time ratio 0·85) but remained highly significant (median difference –17·8 h). In the intention-to-treat infected population, we noted fewer lower respiratory tract complications requiring antibiotics more than 48 h after randomisation (risk ratio [RR] 0·56, 95% CI 0·42–0·75; p=0·0001; 4·9% oseltamivir *vs* 8·7% placebo, risk difference –3·8%, 95% CI –5·0 to –2·2) and also fewer admittances to hospital for any cause (RR 0·37, 95% CI 0·17–0·81; p=0·013; 0·6% oseltamivir, 1·7% placebo, risk difference –1·1%, 95% CI –1·4 to –0·3). Regarding safety, oseltamivir increased the risk of nausea (RR 1·60, 95% CI 1·29–1·99; p<0·0001; 9·9% oseltamivir *vs* 6·2% placebo, risk difference 3·7%, 95% CI 1·8–6·1) and vomiting (RR 2·43, 95% CI 1·83–3·23; p<0·0001; 8·0% oseltamivir *vs* 3·3% placebo, risk difference 4·7%, 95% CI 2·7–7·3). We recorded no effect on neurological or psychiatric disorders or serious adverse events.

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

Lancet. 2015 May 2;385(9979):1729-1737.

Guidelines for the clinical management of severe illness from influenza virus infections

March 2022, WHO

3.1 Oseltamivir (oral)

RECOMMENDATION 1

In persons with suspected or confirmed influenza virus infection with or at risk of severe illness (i.e. including seasonal influenza, pandemic influenza and zoonotic influenza), **we suggest administering oseltamivir as soon as possible (vs not administering oseltamivir)** (conditional recommendation, low-quality evidence).

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 confidence.

根據現有證據，有重症風險因子之疑似或確診流感病患，建議及早給予oseltamivir治療

觀察性研究顯示可降低62%死亡風險

觀察性研究顯示可降低36%住院風險
但隨機對照研究結果則無顯著差異

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

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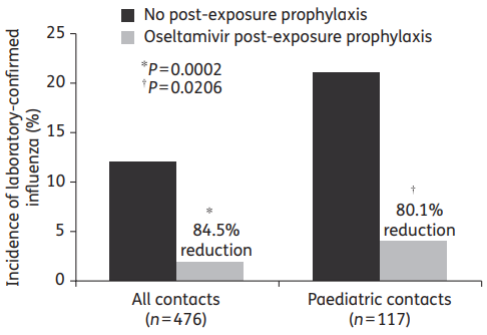
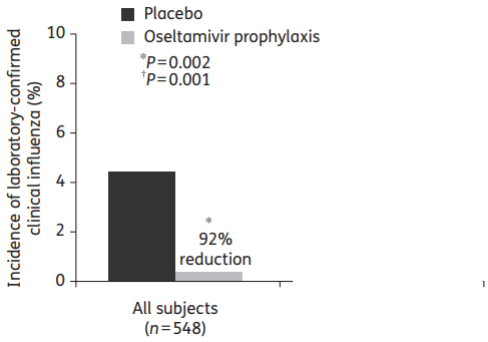
Prophylaxis with Oseltamivir in seasonal influenza



Household contacts



Elderly nursing home residents

Dutkowski R. Oseltamivir in seasonal influenza: cumulative experience in low- and high-risk patients. J Antimicrob Chemother. 2010 Apr;65 Suppl 2(Suppl 2):ii11-ii24.

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Oseltamivir phosphate (Tamiflu®)

成人及青少年(≥ 13 歲)

CCr	>60	30-60	10-30	≤ 10	HD	CAPD
Treatment dose	75mg BID	30mg BID	30mg QD	X	30mg stat, then 30mg after every HD	30mg stat, single dose
Prophylaxis dose	75mg QD	30mg QD	30mg QOD	X	30mg stat, then 30mg after alternate HD	30mg stat, then QWK

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Oseltamivir phosphate (Tamiflu®)

1 歲或以上兒童

體重	*建議劑量，為期 5 天*	*藥局調製口服懸浮液的容量 (6 mg/mL)*	HD
≤ 15 公斤	30 毫克，每天 2 次	5.0 毫升，每天 2 次	7.5mg every HD
> 15 - 23 公斤	45 毫克，每天 2 次	7.5 毫升，每天 2 次	10mg every HD
> 23 - 40 公斤	60 毫克，每天 2 次	10.0 毫升，每天 2 次	15mg every HD
> 40 公斤	75 毫克，每天 2 次	12.5 毫升，每天 2 次	30mg every HD

Sanford guide 2023
克流感仿單2016

Oseltamivir phosphate (Tamiflu®)

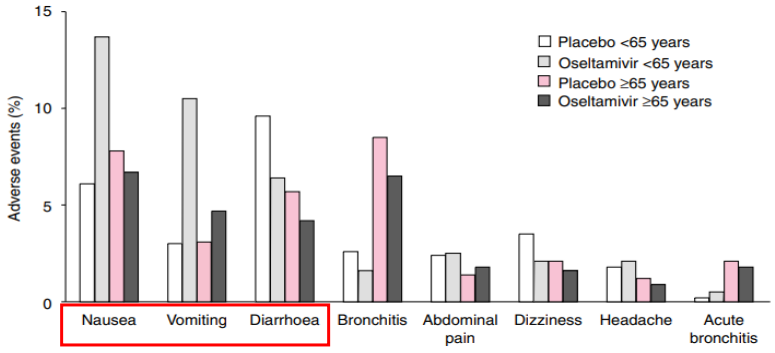
未滿1歲兒童 (3mg/kg)

體重	*建議劑量，為期 5 天*	*藥局調製口服懸浮液的容量 (6 mg/mL)*
3 公斤	9 毫克，每天 2 次	1.5 毫升，每天 2 次
4 公斤	12 毫克，每天 2 次	2.0 毫升，每天 2 次
5 公斤	15 毫克，每天 2 次	2.5 毫升，每天 2 次
6 公斤	18 毫克，每天 2 次	3.0 毫升，每天 2 次
7 公斤	21 毫克，每天 2 次	3.5 毫升，每天 2 次
8 公斤	24 毫克，每天 2 次	4.0 毫升，每天 2 次
9 公斤	27 毫克，每天 2 次	4.5 毫升，每天 2 次
10 公斤	30 毫克，每天 2 次	5.0 毫升，每天 2 次

此建議劑量不適用於胎齡未滿 36 週的嬰兒

Safety

- North America, Europe and the Southern Hemisphere
- N=11675
- Including healthy adults, elderly/ high-risk subjects, and children aged 1–12 years
- Oseltamivir 5 days course



Dutkowski R, Thakrar B, Froehlich E, Suter P, Oo C, Ward P. Safety and pharmacology of oseltamivir in clinical use. Drug Saf. 2003;26(11):787-801.

Safety

系統器官類別 藥物不良反應	治療研究		預防性治療		發生頻率類別 [a]
	Oseltamivir (75 毫克每天兩次) N=2647	安慰劑 N=1977	Oseltamivir (75 毫克每天一次) N=1945	安慰劑 N=1588	
胃腸道疾患					
噁心	10%	6%	8%	4%	極常見
嘔吐	8%	3%	2%	1%	常見
神經學與神經系統疾患					
頭痛	2%	1%	17%	16%	極常見
全身性疾患					
疼痛	<1%	<1%	4%	3%	常見

克流感仿單2016 31

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Zanamivir (Relenza®)

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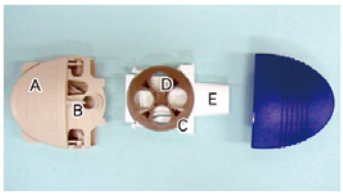
Zanamivir

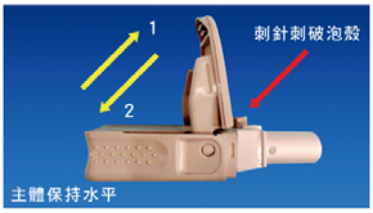
裝置說明

A. **上蓋**：掀開可將刺針刺破含藥泡殼。
B. **刺針**：刺破含藥泡殼準備上藥。
C. **指握部分（按壓）**：將滑盤從主體取出。
D. **轉盤**：置入含藥泡殼（一片四個泡殼）。
E. **吸嘴**：兩側各有一個氣孔。



奇美醫院藥劑部衛教資訊網站
https://www.chimei.org.tw/main/cmh_department/59012/info/5500/A5500265.html

Zanamivir



作用

治療及預防成人及兒童（>5歲）之A型及B型流行性感冒。

用法

1. 請遵照醫師處方之用法及劑量服用。
2. 治療流行性感冒：每日二次，每次二個劑量（10毫克），連續五天。
3. 預防流行性感冒：每日一次，每次二個劑量（10毫克），連續十天。

吸入藥物

1. 輕吐氣（勿對藥物吸嘴處吐氣）。
2. 吸嘴置入齒間(勿啃咬吸嘴)，緊閉雙唇包住吸嘴（請勿阻塞吸嘴側邊的氣孔）。
3. 快速深吸一口氣，憋氣數秒可將吸嘴由口中移開，但仍維持屏息狀態，以舒適範圍內盡可能延長憋氣時間，正常呼吸。
4. 完成吸入完整劑量後，請以紙巾擦拭吸嘴，並將藍色外蓋裝回原位。

奇美醫院藥劑部衛教資訊網站
https://www.chimei.org.tw/main/cmh_department/59012/info/5500/A5500265.html

JAMA Network Open

Original Investigation | Infectious Diseases

Comparison of Antiviral Agents for Seasonal Influenza Outcomes in Healthy Adults and Children

A Systematic Review and Network Meta-analysis

Jen-Wei Liu, MS; Shen-Hua Lin, BS; Lin-Chien Wang, MS; Hsiao-Yean Chiu, PhD; Jen-Ai Lee, PhD

Abstract

IMPORTANCE Antiviral treatment of influenza is recommended for patients with influenza-like illness during periods of community cocirculation of influenza viruses and SARS-CoV-2; however, questions remain about which treatment is associated with the best outcomes and fewest adverse events.

OBJECTIVE To compare the efficacy and safety of neuraminidase inhibitors and the endonuclease inhibitor for the treatment of seasonal influenza among healthy adults and children.

DATA SOURCES Medline, Embase, and the Cochrane Register of Clinical Trials were searched from inception to January 2020 (the last search was updated in October 2020).

STUDY SELECTION Included studies were randomized clinical trials conducted among patients of all ages with influenza treated with neuraminidase inhibitors (ie, oseltamivir, peramivir, zanamivir, or laninamivir) or an endonuclease inhibitor (ie, baloxavir) compared with other active agents or placebo.

DATA EXTRACTION AND SYNTHESIS Two investigators identified studies and independently abstracted data. Frequentist network meta-analyses were performed; relative ranking of agents was conducted using P-score probabilities. Quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations criteria. Data were analyzed in October 2020.

MAIN OUTCOMES AND MEASURES The time to alleviation of influenza symptoms (TTAS), complications of influenza, and adverse events (total adverse events, nause

RESULTS A total of 26 trials were identified that investigated antiviral drugs a these trials included 11 897 participants, among whom 6294 (52.9%) were me age was 32.5 (16.9) years. Of all treatments comparing with placebo in efficac quality evidence indicated that zanamivir was associated with the shortest TT 95% CI, 0.58-0.77), while baloxavir was associated with the lowest risk of infl complications (risk ratio [RR], 0.51; 95% CI, 0.32-0.80) based on moderate-qu safety outcomes, baloxavir was associated with the lowest risk of total adverse 95% CI, 0.74-0.96) compared with placebo based on moderate-quality evider strong evidence of associations with risk of nausea or vomiting among all com mg oseltamivir, which was associated with greater occurrence of nausea (RR, 1. and vomiting (RR, 1.88; 95% CI, 1.47-2.41).

Abstract (continued)

CONCLUSIONS AND RELEVANCE In this systematic review and network me antiviral agents assessed were associated with shortening TTAS; zanamivir w shortest TTAS, and baloxavir was associated with reduced rate of influenza-r

JAMA Netw Open. 2021;4(8):e2119151

Key Points

Question What antiviral agents for treating seasonal influenza are associated with the most safety and best outcomes among healthy adults and children?

Findings This network meta-analysis of 26 randomized clinical trials, including 11 897 patients, found that antiviral agents were associated with

considered.

依系統性文獻回顧及網絡統合分析結果，發現抗病毒藥物皆可縮短病程，其中zanamivir效果最好。
另針對容易併發重症的高風險族群，可考慮使用baloxavir。

Inhaled Zanamivir vs Oral Oseltamivir to Prevent Influenza-related Hospitalization or Death: A Nationwide Population-based Quasi-experimental Study 台灣本土研究

- 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]

Principal Diagnosis for Hospitalization or Death 主診斷	Crude			Propensity Score–Weighted			Adjusted Hazard Ratio (95% Confidence Interval)
	Number of Events	Total Person-Days	Incidence Rate	Number of Events	Total Person-Days	Incidence Rate	
流感，類流感或肺炎 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)
流感 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)
類流感 Influenza-like illness[d]							
Zanamivir	10 083	579 564	0.017	13 878	579 539	0.024	1
Oseltamivir	6072	251 053	0.024	6070	250 995	0.024	1.01 (.96–1.06)

Zanamivir與oseltamivir效果無統計顯著差異

不適用吸入型 Zanamivir 的情況

- 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)。

季節性流感之診斷與治療 內科學誌2020：31：11-17 37

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Peramivir (Rapiacta®)

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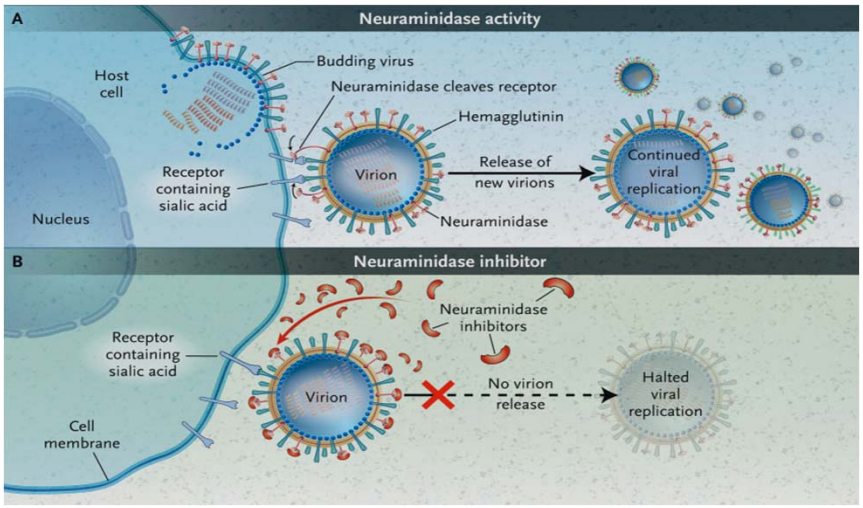
Mechanism of Neuraminidase Inhibitor



Panel A shows the action of neuraminidase in the continued replication of virions in influenza infection. The replication is blocked by neuraminidase inhibitors (Panel B), which prevent virions from being released from the surface of infected cells.

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

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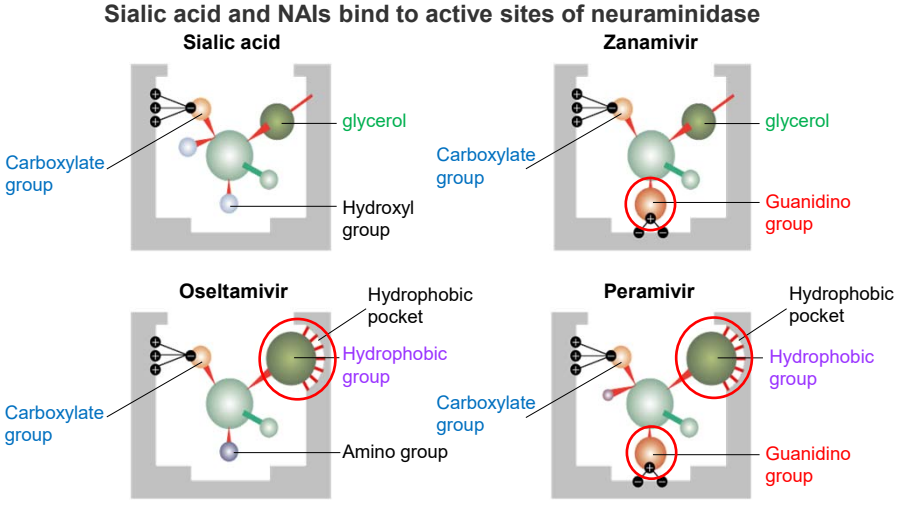
Peramivir binds to Most active sites of Neuraminidase



Gray area: active site of neuraminidase

The orientation of the guanidino group of peramivir is different from that of zanamivir.

Laver WG, et al. Sci Am 1999 Jan; 280(1):78-87.; Babu YS, et al. J Med Chem 2000 Sep; 43(19):3482-6.

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Susceptibility to NAIs (in vitro)

Virus Susceptibility to NAIs in Peramivir-Treated Subjects (ITTI Population)

	IC_{50}, Median (Range), nmol/L		
Virus Subtype	Peramivir	Oseltamivir	Zanamivir
Influenza A/ H3N2			
Baseline	0.17 (0.12–0.29) (n = 62)	0.29 (0.01–0.79) (n = 61)	0.34 (0.20–0.52) (n = 63)
Last positive culture	0.17 (0.12–0.55) (n = 61)	0.28 (0.01–0.79) (n = 59)	0.35 (0.20–1.07) (n = 63)
Fold change from baseline	1.0 (0.65–2.62) (n = 24)	0.94 (0.33–3.43) (n = 23)	1.06 (0.48–3.57) (n = 25)
Influenza A/ 2009 H1N1			
Baseline	0.18 (0.02–43.92) (n = 50)	0.86 (0.13–499.70) (n = 50)	0.48 (0.09–1.65) (n = 50)
Last positive culture	0.18 (0.00–38.56) (n = 50)	0.88 (0.17–416.70) (n = 50)	0.37 (0.08–1.93) (n = 50)
Fold change from baseline	1.0 (0.00–104.22) (n = 40)	0.95 (0.16–323.17) (n = 40)	0.94 (0.25–2.97) (n = 40)
Influenza B			
Baseline	1.09 (0.01–3.33) (n = 33)	19.93 (2.36–41.41) (n = 32)	2.10 (0.81–4.48) (n = 33)
Last positive culture	1.16 (0.24–4.61) (n = 33)	19.36 (5.18–51.77) (n = 32)	2.38 (0.81–5.97) (n = 33)
Fold change from baseline	1.26 (0.61–40.00) (n = 21)	0.98 (0.22–8.11) (n = 21)	1.10 (0.70–2.75) (n = 21)

IC_{50}, median inhibitory concentration; ITTI, intent-to-treat infected; NAIs, neuraminidase inhibitors

Clin Infect Dis. 2014 Dec 15;59(12):e172-85 41

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Clinical Study

Chemotherapy 2013;59:373–378
DOI: 10.1159/000362436

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Published online: May 10, 2014

Clinical Effects of Oseltamivir, Zanamivir, Laninamivir and Peramivir on Seasonal Influenza Infection in Outpatients in Japan during the Winter of 2012–2013

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Masahiro Ichikawa[c] Shogo Miyagawa[f] Jun Matsumoto[g]

[a]Kamijyo Clinic, Izumiotsu, [b]Ikezoe Clinic, Kishiwada, [c]Ichikawa Pediatric Clinic, Kaizuka, and [d]Asai Pediatric Clinic, [e]Mori-Yano Clinic, [f]Miyagawa Clinic, and [g]Matsumoto Clinic, Osaka, Japan

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試驗概要

試驗目的: 評估各抗病毒藥物治療門診流感病患之效果

試驗組別：**Peramivir 成人: 300mg; 兒童: 10mg/kg IV Infusion over 15-30min once**

Oseltamivir 兒童 > 37.5 kg及成人: 150mg BID PO 5 days;

兒童 < 37.5kg: 4mg/kg/day PO 5 days

Zanamivir > 5歲兒童及成人: 20mg BID INH 5 days

Laninamivir > 10歲兒童及成人40mg or 20mg INH once

共191例 (Open Label) (6m - 95y)

Influenza Onset < 48hr

尚未接受任何治療

無其他疾病

peramivir 53例 | laninamivir 44例 | oseltamivir 51(47*)例 | zanamivir 39例

*No records were available for 4 patients.

療效指標：

1. Time to alleviate fever (from > 37.5℃ to < 37℃)
2. Time to alleviate symptoms (cough, rhinorrhea, arthralgia, general malaise)
3. Time to eliminate the influenza virus

試驗國家: Japan (November 2012 to March 2013)

Takemoto Y, et al. Chemotherapy 2013;59:373–378 43

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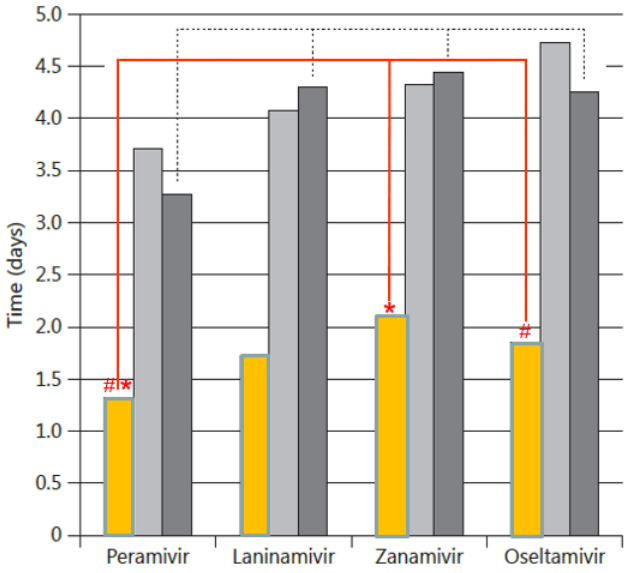
Time to alleviate fever



Peramivir tended to reduce fever duration

Peramivir: 1.32 ± 0.79 days
Laninamivir: 1.72 ± 1.03 days
Zanamivir: 2.10 ± 1.12 days
Oseltamivir: 1.86 ± 1.02 days

*p=0.002
#p=0.0059

Fever duration
Elimination of influenza
Symptoms

Takemoto Y, et al. Chemotherapy 2013;59:373–378 44

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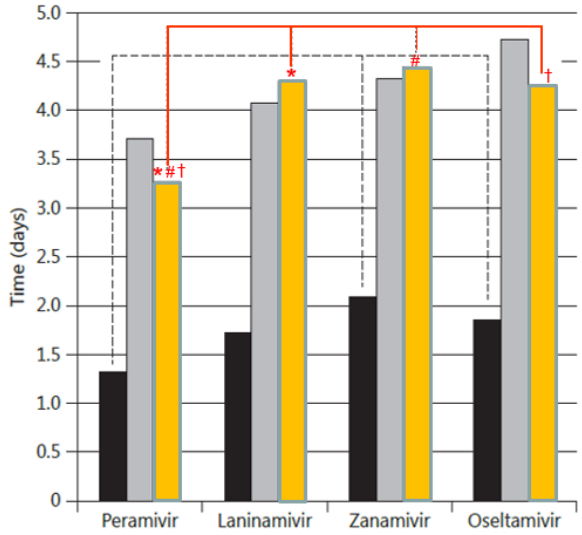
Recover from symptoms



Peramivir rapidly alleviated clinical symptoms

Peramivir: 3.28 ± 1.35 days
Laninamivir: 4.31 ± 0.92 days
Zanamivir: 4.46 ± 0.84 days
Oseltamivir: 4.27 ± 1.08 days

*p=0.002
#p＜0.001
†p=0.002

Fever duration
Elimination of influenza
Symptoms

Takemoto Y, et al. Chemotherapy 2013;59:373–378 45

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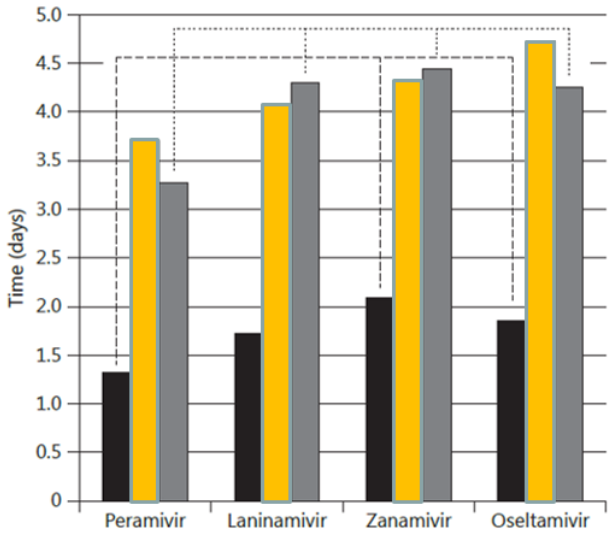
Eliminate the Influenza Virus



Peramivir tended to eliminate the virus sooner

Peramivir: 3.71 ± 1.38 days
Laninamivir: 4.09 ± 1.23 days
Zanamivir: 4.33 ± 1.38 days
Oseltamivir: 4.75 ± 1.47 days

Fever duration
Elimination of influenza
Symptoms

Takemoto Y, et al. Chemotherapy 2013;59:373–378 46

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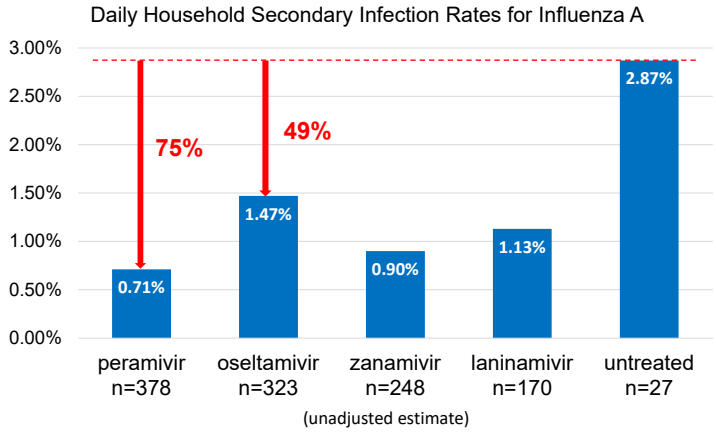
Daily Household Secondary Infection Rate

- Compared with no treatment, all NAIs reduced the daily SIR of influenza A, with the extent of daily SIR reduction ranging from 49% with oseltamivir to 75% with peramivir.



Hirotsu N., et al. Influenza Other Respir Viruses. 2018 Jul 10. doi: 10.1111/irv.12590. 47

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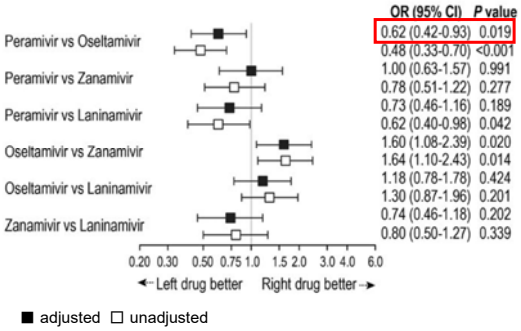
相較於未使用抗病毒藥物治療者，Rapiacta較Oseltamivir降低38%每天傳染給家人的機會

Daily Household Secondary Infection Rate

Type A

Daily secondary infection rate	Peramivir n = 378	Oseltamivir n = 323	Zanamivir n = 248	Laninamivir n = 170	Untreated n = 27
Unadjusted estimate	0.71%	1.47%	0.90%	1.13%	2.87%
95% CI	0.53-0.96	1.18-1.83	0.66-1.24	0.81-1.58	2.32-3.54



Adjusting for the following covariates of patients with infectious ability in a household using the logit link function: age, time from onset to start of treatment, and influenza vaccine in the same season

Hirotsu N., et al. Influenza Other Respir Viruses. 2018 Jul 10. doi: 10.1111/irv.12590. 48

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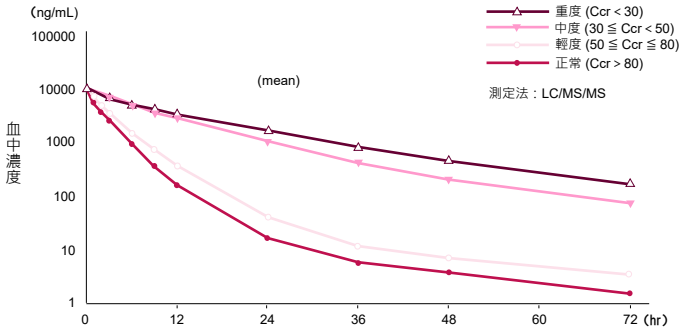
Rapiacta®適應症及用法用量

適應症: 治療成人及一個月大以上兒童之A型及B型流感病毒急性感染

＜本藥限由醫師使用＞

- 宜於症狀發生後48小時內使用本藥。
- 成人建議劑量為300 mg，每次最多不得超過600 mg，15分鐘以上
- 單次點滴靜脈注射。
- 兒童建議劑量為10 mg/kg，每次最多不得超過600 mg，15分鐘以上單次點滴靜脈注射。
- 連續投與之經驗有限。
- 腎功能不全病人：請依腎功能情況調整投與劑量 血液透析病人請於透析後投與

Rapiacta®腎功能不全患者之血中濃度及建議劑量



腎功能不全患者之建議劑量

Ccr (mL/min)	1 次投與量
	一般情形
Ccr≥50	300 mg
30 ≦ Ccr < 50	100 mg
10* ≦ Ccr < 30	50 mg

Ccr: Creatinine clearance (肌酐酸清除率)
*Creatinine clearance <10 mL/min及接受血液透析的病患，請審慎調整投與量。Peramivir會因血液透析而快速自血中清除。

Peramivir dosage recommendations for impaired renal function

Creatinine Clearance (CrCl) or Estimated Clearance (CL_{CRRT} + Residual Renal CL)					
Recommended Dose	**Mild Renal Impairment 50 ≦ Ccr mL/min**	**Moderate Renal Impairment 30 ≦ Ccr ＜50 mL/min**	**Severe Renal Impairment 10 ≦ Ccr ＜30 mL/min**	**CrCl < 10 mL/min, not on dialysis or renal replacement therapy[2]**	**ESRD on Intermittent Hemodialysis (HD)[2]**
Adult[1,3] Usual	300 mg QD	100 mg QD	50 mg QD	100 mg on Day 1, followed by 15 mg QD thereafter[2]	100 mg on Day 1, then 100 mg 2 hrs after each HD session on dialysis days only[2]
Adult Patients at risk of increased severity*[3]	600 mg QD	200 mg QD	100 mg QD		

CrCl, creatinine clearance

*Patients with comorbidities, including chronic respiratory diseases (e.g. COPD, bronchial asthma, interstitial pneumonia and lung cancer), chronic cardiovascular diseases (e.g. congestive heart failure and ventricular dysfunction), chronic kidney diseases (e.g. undergoing hemodialysis and after renal transplantation) or immunosuppressive state (e.g. taking immunosuppressive agents, human immunodeficiency virus infection and congenital immunodeficiency), who were determined to have a risk of increased severity of influenza by the attending clinician.

1. Rapiacta 仿單; 2. Emergency Use Authorization of Peramivir IV Fact Sheet for Health Care Providers (2009)
https://www.fda.gov/downloads/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm187811.pdf
3. Clin Respir J. 2015 Apr;9(2):228-32

Rapiacta®不良反應

- **主要不良反應：**
  - 腹瀉(5.8%)、嗜中性白血球減少(2.8%)、蛋白尿(2.5%)

- **其他不良反應：**

不良反應類別	**發生頻率 ≧ 1%**
消化道	噁心、嘔吐
肝臟	AST(GOT)、ALT(GPT)上升
腎臟	蛋白尿、尿中β_2微球蛋白 (β_2-microglobulin)上升、NAG上升
血液	淋巴球增加
其他	血中葡萄糖增加

第 II 期臨床試驗

Highlight of Adverse Events

Incidence of all adverse events for peramivir was **comparable to that for placebo**. Adverse events were generally mild to moderate.

	Peramivir		Placebo
	300 mg QD N=99	600 mg QD N=99	N=100
No. (%) of patients with ≥ 1 event	87 (87.9)	90 (90.9)	91 (91.0)
Adverse events (≥ 6% in either group) 〔n (%) of patients〕			
Monocyte % increased	20 (20.2)	18 (18.2)	31 (31.0)
Blood glucose increased	18 (18.2)	17 (17.2)	18 (18.0)
Diarrhea	14 (14.1)	15 (15.2)	17 (17.0)
Lymphocyte % increased	14 (14.1)	14 (14.1)	5 (5.0)
Proteinuria present	9 (9.1)	11 (11.1)	18 (18.0)
β2 Microglobulin in urine increased	14 (14.1)	8 (8.1)	11 (11.0)
Blood bilirubin increased	7 (7.1)	8 (8.1)	7 (7.0)
Alanine aminotransferase increased	4 (4.0)	7 (7.1)	8 (8.0)
Aspartate aminotransferase increased	1 (1.0)	7 (7.1)	6 (6.0)
Nausea	3 (3.0)	6 (6.1)	1 (1.0)
β-N-Acetyl-D-glucosaminidase	9 (9.1)	5 (5.1)	5 (5.0)

Kohno S, et al. Antimicrob Agents Chemother. 2010;54(11):4568-74 53

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第 III 期臨床試驗

Rapiacta®不良事件(AE)與藥物不良反應(ADR)

	Number of Patients (%)		
	Peramivir 300 mg (N=364)	Peramivir 600 mg (N=364)	Oseltamivir 75 mg (N=365)
≥ 1 AEs	**170 (46.7)**	**174 (47.8)**	**178 (48.8)**
Neutrophil count decreased	39 (10.7)	38 (10.4)	34 (9.3)
Diarrhea	24 (6.6)	30 (8.2)	27 (7.4)
Protein present in urine	17 (4.7)	16 (4.4)	22 (6.0)
Blood glucose increased	11 (3.0)	14 (3.8)	12 (3.3)
Urine positive for WBCs	14 (3.8)	8 (2.2)	16 (4.4)
Nausea	8 (2.2)	8 (2.2)	20 (5.5)
Vomiting	2 (0.5)	6 (1.6)	15 (4.1)
≥ 1 ADRs	**51 (14.0)***	**66 (18.1)**	**73 (20.0)**
Diarrhea	14 (3.8)	20 (5.5)	19 (5.2)
Neutrophil count decreased	9 (2.5)	14 (3.8)	13 (3.6)
Nausea	2 (0.5)	7 (1.9)	16 (4.4)

AEs, adverse events; ADRs, adverse drug reactions; WBCs, white blood cells (*p=0.0382)
Data are shown only for AEs or ADRs that occurred at a frequency of 3% in any of the three groups

Kohno S, et al. *Antimicrob Agents Chemother*. 2011 Nov;55(11):5267-76 54

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Post-marketing evaluation - 門診病人(包含兒童) ADRs

- The most frequently reported ADRs were diarrhea, vomiting, and nausea (1.87%, 0.68% and 0.85%).
- No ADR was reported as serious.
- Of 78 ADRs, 47.4% (37 events) developed on the day of administration, 29.5% (23 events) on the following day, and 14.1% (11 events) at 2 days after administration.
- Apart from the one event whose outcome was unknown, all ADRs resolved or improved without after effects.
- Resolution was swift in most cases and noted on the day of onset (12 events, 15.4%) or 1 day (33 events, 42.3%), 2 days (15 events, 19.2%), 3 days (2 events, 2.6%), or 4-7 days after onset (13 events, 16.7%), i.e., mostly within 7 days after onset (75 events, 96.2%).

Incidence rates of adverse drug reactions (ADRs).

Number of patients evaluated for safety	1174
Number of patients with ADRs	51
Number of ADRs	78
Incidence of ADRs	4.34%
Type of ADRs	Incidence of ADRs [number (%)]
Metabolism and nutrition disorders	3 (0.26)
Decreased appetite	3 (0.26)
Psychiatric disorders	6 (0.51)
Abnormal dreams	1 (0.09)
Insomnia	5 (0.43)
Nervous system disorder	9 (0.77)
Dizziness	5 (0.43)
Headache	4 (0.34)
Respiratory, thoracic, and mediastinal disorders	1 (0.09)
Nasal congestion	1 (0.09)
Gastrointestinal disorders	37 (3.15)
Abdominal discomfort	4 (0.34)
Abdominal pain	4 (0.34)
Diarrhea	22 (1.87)
Nausea	8 (0.68)
Vomiting	10 (0.85)
Skin and subcutaneous tissue disorders	4 (0.34)
Pruritus	2 (0.17)
Rash	2 (0.17)
Urticaria	2 (0.17)
General disorders and administration site conditions	4 (0.34)
Asthenia	1 (0.09)
Fatigue	1 (0.09)
Pyrexia	2 (0.17)
Investigations	1 (0.09)
Lymphocyte count increased	1 (0.09)

Takuji Komeda, et al. J Infect Chemother 20 (2014) 689-695 55

55

Baloxavir (Xofluza®)

56

56

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 57

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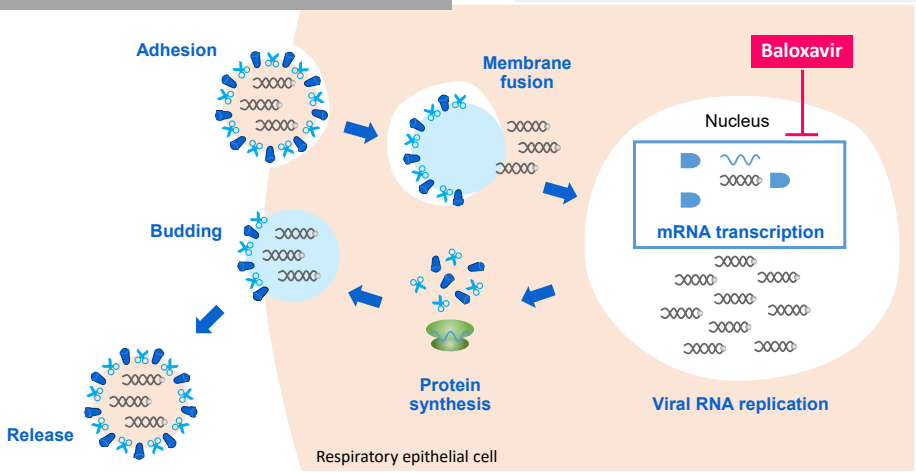
Baloxavir inhibits the viral cycle at a very early stage by blocking viral replication

Baloxavir blocks viral mRNA transcription by inhibiting cap-dependent endonuclease activity

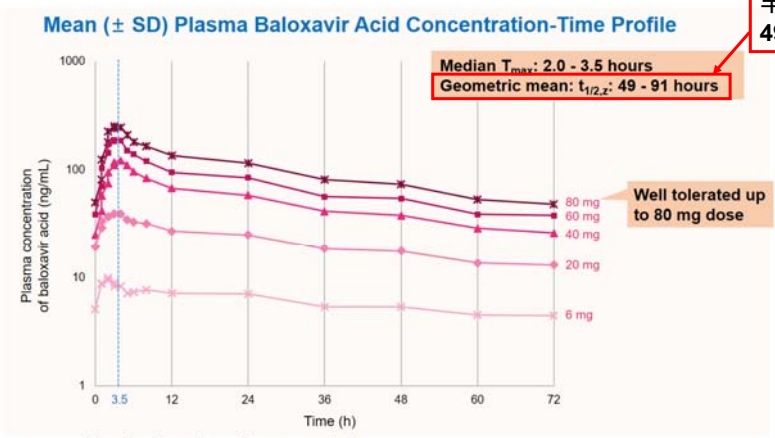
Baloxavir is the first in this new antiviral class that inhibits the viral cycle at a very early stage



Noshi T., et al. Antiviral Res. 2018 Dec;160:109-117. 58

58

Baloxavir藥物動力學特性支持單次口服使用



XOFLUZA (baloxavir marboxil)

Koshimichi H., et al. Clin Drug Investig. 2018 Dec;38(12):1189-1196.

18

59

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Xofluza針對門診流感病患的效果及安全性 (CAPSTONE-1 Study)

Phase III, randomised, double-blind study of baloxavir vs placebo or oseltamivir in otherwise healthy adults and adolescents with influenza

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 6, 2018 VOL. 379 NO. 10

Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents

Frederick G. Hayden, M.D., Norio Sugaya, M.D., Nobuo Hirotsu, M.D., Ph.D., Nelson Lee, M.D., Menno D. de Jong, M.D., Ph.D., Aeron C. Hurt, Ph.D., Tadashi Ishida, M.D., Ph.D., Hisakuni Sekino, M.D., Ph.D., Kota Yamada, M.D., Simon Portsmouth, M.D., Keiko Kawaguchi, M.Sc., Takao Shishido, Ph.D., Masatsugu Arai, M.Sc., Kenji Tsuchiya, M.Sc., Takeki Uehara, Ph.D., and Akira Watanabe, M.D., Ph.D., for the Baloxavir Marboxil Investigators Group*

Hayden et al. N Engl J Med. 2018 Sep 6;379(10):913-923

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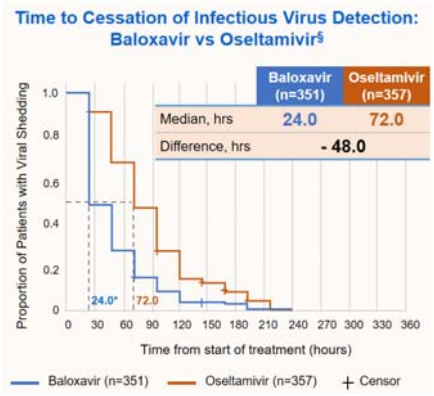
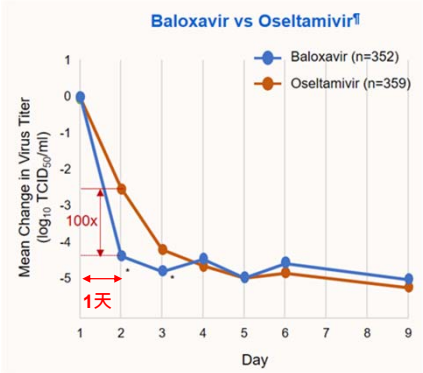
Baloxavir停止排出病毒及降低病毒量較Oseltamivir快

Baloxavir較Oseltamivir快3倍時間停止排出病毒



Baloxavir使用24小時即能較Oseltamivir多降低100倍的病毒量



	Baloxavir	Oseltamivir
Median Reductions from Baseline 1 day after trial regimen ($log_{10}TCID_{50}$/ml)	- 4.8	- 2.8

Hayden et al. N Engl J Med. 2018 Sep 6;379(10):913-923

61

Baloxavir提早緩解流感症狀及退燒

Baloxavir較Placebo快一天緩解症狀

	Baloxavir (n=455)	Placebo (n=230)
Median (95% CI), hours	**53.7** (49.5, 58.5)	**80.2** (72.6, 87.1)
Difference (95% CI), hours	**−26.5** (−35.8, −17.8)	
P-value*	<0.001	

Baloxavir較Placebo快一天退燒

	Baloxavir	Placebo	*p* value
Median Time to Resolution of Fever*	**24.5 hrs**	**42.0 hrs**	P < 0.001

Hayden et al. N Engl J Med. 2018 Sep 6;379(10):913-923

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Xofluza針對家內傳播預防

- Multicenter, double-blind, randomized, placebo-controlled trial
- 2018–2019 season in Japan
- 374 in the baloxavir group and 375 in the placebo group

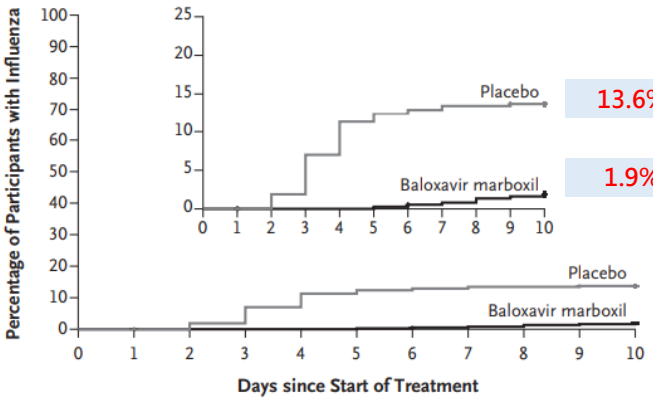
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 23, 2020 VOL. 383 NO. 4

Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts

Hideyuki Ikematsu, M.D., Frederick G. Hayden, M.D., Keiko Kawaguchi, M.S., Masahiro Kinoshita, M.Pharm., Menno D. de Jong, M.D., Nelson Lee, M.D., Satoru Takashima, M.S., Takeshi Noshi, M.S., Kenji Tsuchiya, M.S., and Takeki Uehara, Ph.D.

Xofluza可減少家內傳播發生



13.6%

1.9%

Adjusted risk ratio, 0.14
95% confidence interval
(0.06 to 0.30; P<0.001)

Ikematsu H, Hayden FG, Kawaguchi K, Kinoshita M, de Jong MD, Lee N, Takashima S, Noshi T, Tsuchiya K, Uehara T. Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts. N Engl J Med. 2020 Jul 23;383(4):309-320

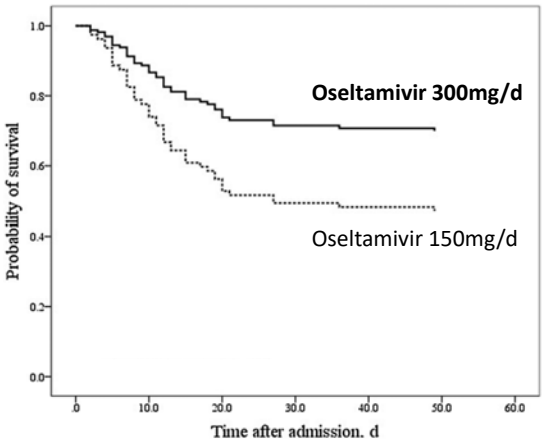
Baloxavir 特點

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.

Combination therapy in severe Influenza

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 67

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. 68

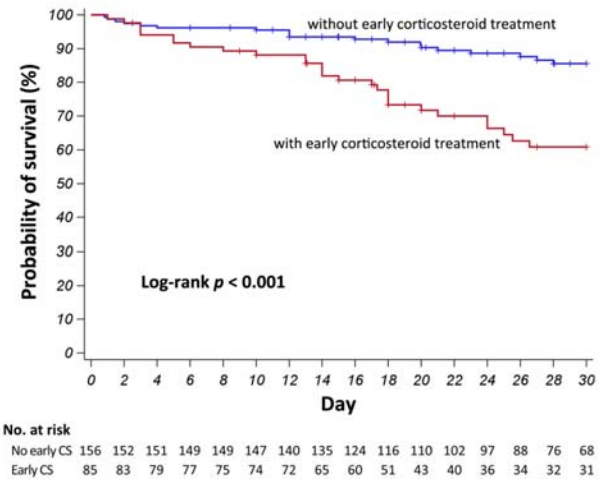
Combining baloxavir marboxil with standard-of-care neuraminidase inhibitor in patients hospitalised with severe influenza (FLAGSTONE): a randomised, parallel-group, double-blind, placebo-controlled, superiority trial

Deepali Kumar, Michael G Ison, Jean-Paul Mira, Tobias Welte, Jick Hwan Ha, David S Hui, Nanshan Zhong, Takefumi Saito, Laurie Katugampola, Neil Collinson, Sarah Williams, Steffen Wildum, Andrew Ackrill, Barry Clinch, Nelson Lee

Lancet Infect dis.
2022 May;22(5):718-730. doi: 10.1016/S1473-3099(21)00469-2. Epub 2022 Jan 24.

- Double blind RCT, 124 centres across 25 countries, Jan 8, 2019 ~March 16, 2020
- Patients aged 12 years or older, hospitalization
- National Early Warning Score 2 ≥ 4
- Baloxivir + NAIs (208) VS. Placebo + NAIs (114)
- Aim: Median time to clinical improvement
- **Combining baloxavir with NAIs did not result in superior clinical outcomes compared with NAIs alone.**

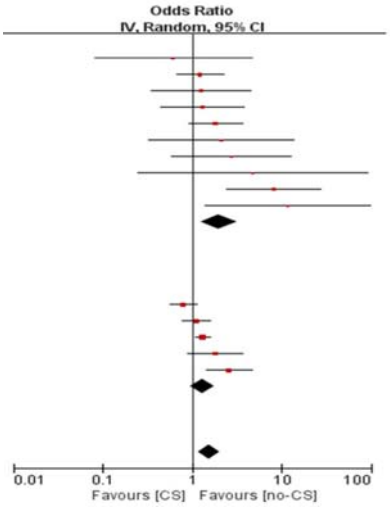
Impact of corticosteroid treatment on clinical outcomes of influenza-associated ARDS: a nationwide multicenter study



- Taiwan, 241 patients, October 2015 - March 2016, 8 centers
- 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.

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).

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COVID-19 and Influenza

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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

COVID-19 and Influenza co-infection

	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**

- UK, Feb 6, 2020 to Dec 8, 2021
- SARS-CoV-2, 6965 patients
- Co-infection with influenza, 227 patients (3.2%)
- More in-hospital mortality, and invasive mechanical ventilation in co-infection with influenza

Swets MC, Russell CD, Harrison EM, et al. SARS-CoV-2 co-infection with influenza viruses, respiratory syncytial virus, or adenoviruses. Lancet. 2022 Apr 16;399(10334):1463-1464.

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Summary

- Early antiviral agent can shorten the course of influenza and reduce complication
- Baloxavir can accelerate influenza viral shedding, and alleviate fever and symptoms faster than Oseltamivir
- The benefit of antiviral agent combination therapy is controversial in Influenza A-associated severe pneumonia
- The routine use of steroid in influenza-associated acute respiratory distress syndrome and severe pneumonia is not recommended
- The co-infection of influenza and COVID-19 virus lead to more in-hospital mortality and invasive mechanical ventilation

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新冠疫情後的流感疫苗接種

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

我國現行公費流感疫苗接種對象

一. 滿6個月以上至國小入學前幼兒

二. 國小、國中、高中、高職、五專一至三年級學生

三. 50歲以上成人

四. 高風險慢性病、罕見疾病及重大傷病患者

五. 孕婦及6個月內嬰兒之父母

六. 幼兒園托育人員及托育機構專業人員

七. 安養、養護、長期照顧(服務)等機構之受照顧者及其所屬工作人員

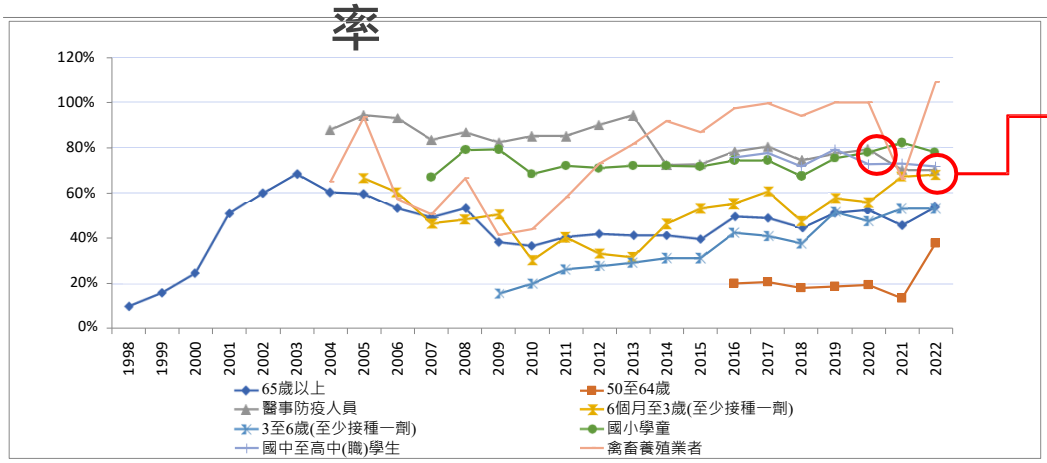
八. 醫事及衛生等單位之防疫相關人員

九. 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

2

2

歷年各類對象流感疫苗接種率



醫事防疫人員接種率自 2020年79.2%降至2022年70.1%

2014年起改以執業登記人數為分母統計接種率

2022年度資料截至2023/5/7

3

流感的預防

- **接種流感疫苗**
  - 目前預防流感的最有效方式
- **暴露後預防藥物　　Post-exposure prophylaxis**
  - 群聚事件中之高危險族群
- **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、有症狀時戴口罩

4

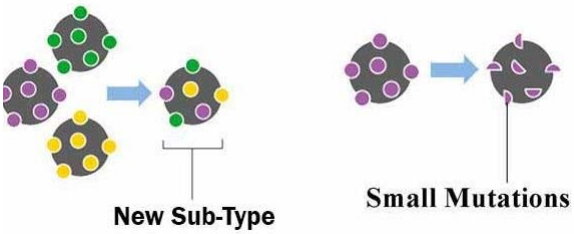
流感疫苗介紹

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
其他	高劑量疫苗(HD)、含佐劑疫苗(A)

為什麼每年都要接種流感疫苗?

- 流感病毒極易產生變異，幾乎**每年流行的病毒株都會稍有不同**，原施打疫苗對不同抗原型之病毒保護效果減低
- 即使病毒未發生變異，疫苗**接種4-6個月後保護效果即可能下降**，保護力一般不超過1年
- 建議每年均須接種1次，是**全球一致性**的作法



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接種後疫苗保護力每月約下降7.5-10%，且65歲以上長者下降較快

Clinical Infectious Diseases

BRIEF REPORT

Waning Vaccine Effectiveness Against Influenza-Associated Hospitalizations Among Adults, 2015–2016 to 2018–2019, United States Hospitalized Adult Influenza Vaccine Effectiveness Network

Table 1. Estimated Decline in Influenza Vaccine Effectiveness per Month Postvaccination Among Adults Enrolled in the United States Hospitalized Influenza Vaccination Network (HAIVEN), 2015–2016 Through 2018–2019

Influenza Type/Subtype	Influenza Seasons Included	No. of Cases/Controls	Estimated VE Decline per Month, Absolute % (95% CI)	*P* Value[a]
Influenza A(H3N2)[b]				
Aged ≥18 y	2016–2017, 2017–2018	754/2262	7.5 (.3–16.3)	.05
Aged ≥65 y	2016–2017, 2017–2018	395/1185	10.8 (2.6–23.8)	.02
Influenza A(H1N1)pdm09[c]				
Aged ≥18 y	2015–2016, 2018–2019	373/1119	8.5 (3.0–17.0)	.003
Aged ≥65 y	2015–2016, 2018–2019	132/396	9.6 (−3.3 to 32.7)	.14
Influenza B/Yamagata[b]				
Aged ≥18 y	2016–2017, 2017–2018	265/795	8.0 (1.4–21.9)	.02
Aged ≥65 y	2016–2017, 2017–2018	134/402	10.8 (1.4–33.9)	.03

https://academic.oup.com/cid/article/73/4/726/6104243?login=true

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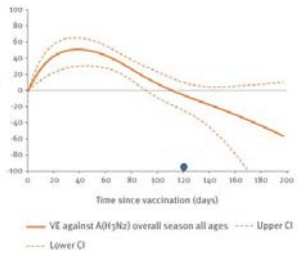
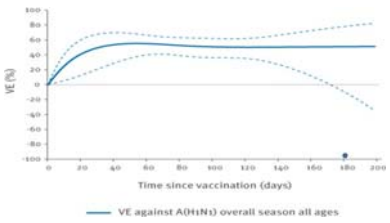
疫苗保護力可以持續多久?

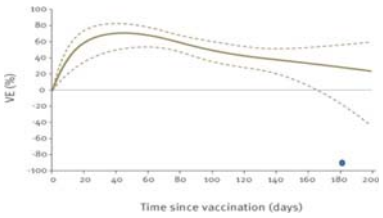
***完整接種後至少2週才有足夠保護力**



A/H3N2
至少約120天



A/H1N1
至少約180天



B
至少約180天

Euro Surveill. 2016;21(16):pii=30201

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9

流感疫苗的保護效果

- ★ 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
- ★ 根據國際研究顯示，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
- ★ 在免疫系統尚未成熟的6至12個月年齡層，接種流感疫苗對確診流感的保護力也有8成
- ★ 孕婦接種流感疫苗除可降低罹患 流感與住院風險外，亦可降低新生兒確診流感風險

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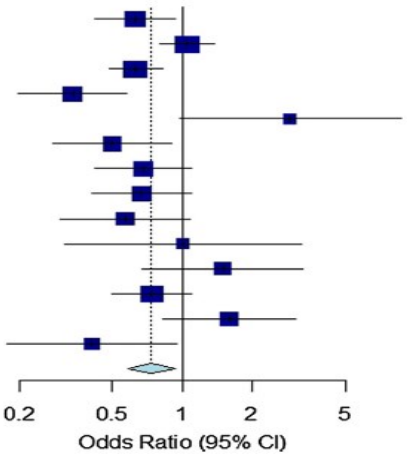
Flu vaccination with **26% reduction** in odds of **ICU admission** among adults

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) 3678–369

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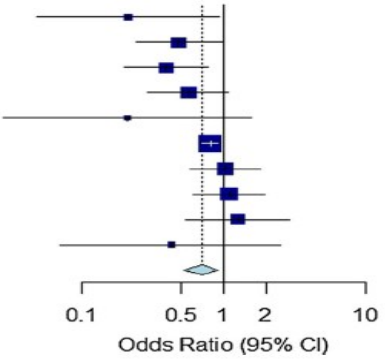
Vaccinated patients had **31% reduced risk of death** compared with unvaccinated patients

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) 3678–369

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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

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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, Bershewa, 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

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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

「雞蛋過敏」已不再列為流感疫苗接種的禁忌症

★ 依國際文獻資料顯示，對「蛋」的蛋白質有嚴重過敏者，接種流感疫苗後**出現嚴重過敏反應之機率極低**

★ 我國傳染病防治諮詢會預防接種組專家建議參依美、英等國作法，將「已知對『蛋』之蛋白質有嚴重過敏者」自**接種禁忌症移除**，惟應於**注意事項**(precaution)加列對蛋嚴重過敏者接種疫苗之相關說明內容

★ 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

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

醫事人員流感疫苗接種情形

國家	2022-23年度	2021-22年度	2020-21年度	2019-20年度	資料來源
美國	-	79.9%	75.9%	80.7%	US CDC(MMWR)-Influenza(Flu) Coverage by Population、Influenza and COVID-19 Vaccination Coverage Among Health Care Personnel — United States, 2021–22
英國	49.9% (cumulative data from 1 September 2022 to 28 February 2023)	60.5%	76.8%	74.3%	UKHSA-Seasonal influenza vaccine uptake in frontline healthcare workers (HCWs) in England (Final data for 1 September 2021 to 28 February 2022)
臺灣	70.1%	70.2%	79.2%	77.5%	衛生福利部疾病管制署(截至2023年5月7日)

醫護人員接種流感疫苗之重要性

- ★醫療照護人員接種流感疫苗，可避免在執行照護工作時受到病人的傳染，或因自身感染流感而將病毒傳染給病人。
- ★對於醫療機構來說，機構內醫療照護人員的流感疫苗接種，可避免工作場所因流感爆發而影響其健康照護工作的執行，節省醫療成本支出。醫療照護人員每年接種流感疫苗，是保障病人安全的重要措施。
- ★面對民眾之疫苗猶豫，醫護人員扮演風險溝通要角及可靠的訊息來源，自身的知識及態度影響自身接種率、向病人說明的意圖及病人接種率。
- ★提升醫事人員接種流感疫苗，對其病患有決定性的正向影響力，亦有助於提升民眾接種意願。

國際流感疫苗接種政策

各國流感疫苗公費接種對象

(截至2022-2023流感季)

澳洲	英國	加拿大	日本	韓國
1. 6個月以上的原住民和托雷斯海峽島民 2. 孕婦 3. 6個月以上至5歲以下的兒童 4. 65歲以上 5. 所有6個月以上以上且有高風險慢性疾病者 (have a higher risk of getting serious disease including心臟疾病. 慢性肺病.神經.腎臟. 免疫疾病者等)	1. 6-11歲(國小)學齡兒童 2. 2-3歲兒童 3. 65歲以上 4. 6個月至65歲之有臨床疾病風險者(in clinic risk groups) 5. 孕婦 6. 長照機構住民 7. 老年人或殘疾人的主要照顧者 8. 免疫力低下者的密切接觸者 9. 雇主未提供健康保險之療養院. 護理之家. 家庭護理等機構之工作人員	1. 除魁北克省外，其他地區均全民公費 2. 魁北克省提供75歲以上長者、孕婦BMI≥40…等對象公費疫苗	1. 65歲以上 2. 60-65歲心/腎或呼吸器官功能缺損者 (相當於一級傷殘) 3. 因人類免疫缺陷病毒致免疫功能受損者(相當於一級傷殘)	1. 6個月-12歲兒童 2. 65歲以上長者 3. 13-64歲有高風險慢性病者 4. 孕婦

註：藍字為台灣已列入之公費流感疫苗接種對象

112年度流感疫苗接種政策

我國現行公費流感疫苗接種對象

一. 滿6個月以上至國小入學前幼兒

二. 國小、國中、高中、高職、五專一至三年級學生

三. 50歲以上成人

四. 高風險慢性病、罕見疾病及重大傷病患者

五. 孕婦及6個月內嬰兒之父母

六. 幼兒園托育人員及托育機構專業人員

七. 安養、養護、長期照顧(服務)等機構之受照顧者及其所屬工作人員

八. 醫事及衛生等單位之防疫相關人員

九. 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

2023-2024年WHO流感疫苗建議病毒株

➢ 雞胚胎蛋培養疫苗

- A/Victoria/4897/2022 (H1N1)pdm09-like virus
- A/Darwin/9/2021(H3N2)-like virus
- B/Austria/1359417/2021 (B/Victoria lineage)-like virus
- B/Phuket/3073/2013 (B/Yamagata lineage)-like virus

➢ 細胞培養或重組疫苗

- A/Wisconsin/67/2022 (H1N1)pdm09-like virus
- A/Darwin/6/2021(H3N2)-like virus
- B/Austria/1359417/2021 (B/Victoria lineage)-like virus
- B/Phuket/3073/2013 (B/Yamagata lineage)-like virus

紅字表雞胚胎蛋培養疫苗與細胞培養/重組疫苗採不同病毒株

淺藍色底表該病毒株與2021-2022疫苗株不同

2023-2024年流感季流感疫苗

- **疫苗特性：不活化疫苗**
- **接種途徑：肌肉注射**
- **接種劑量與間隔：**
  - 四價疫苗
    - 均接種0.5mL

※ 未滿9歲兒童，首次接種者應接種2劑，且間隔至少4週。針對學生於 學校集中接種，全面提供1劑公費疫苗，若仍自覺需要，可於學校接種第 1劑至少隔4週後，至醫療院所自費接種第2劑。

2023-24 年流感季流感疫苗(成分、劑型、使用方法)

	雞蛋培養疫苗(eIIV)	細胞培養疫苗(ccIIV)
商品名	眾多	Flucelvax
廠商	眾多	Seqirus/ 東洋
劑量	0.5 mL 單次注射	0.5 mL 單次注射
劑型	0.5 mL 預充填針筒 5 mL 多劑型 (US only)	0.5 mL 預充填針筒 5 mL 多劑型 (US only)
接種方式	肌肉注射	肌肉注射
培養細胞株	雞胚蛋	MDCK
WHO建議細胞株	Egg-based strain	Cell-based strain
HA含量	每型別病毒15 ug HA	每型別病毒15 ug HA
NA含量	不一定，但含量通常很低	不一定，但含量通常很低

112年度流感疫苗
供貨廠商/適用年齡及供貨數量一覽表

許可證持有廠商	疫苗品名	適用年齡[1]	劑型	供貨數量[2]	疫苗製程
賽諾菲股份有限公司	Vaxigrip Tetra 菲流達 四價流感 疫苗	6個月以上	0.5mL	192萬1,400劑	雞胚胎蛋培養(egg-based)
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	3歲以上	0.5mL	349萬3,450劑	
高端疫苗生物製劑股份有限公司	MVC FLU Quadrivalent pre-filled syringe injection 高端四價流感疫苗	3歲以上	0.5mL	70萬7,420劑	
台灣東洋藥品工業股份有限公司	Flucelvax Quad 輔流威適流感疫苗	6個月以上	0.5mL	86萬4,630劑	細胞培養 (cell-based)

註1: 以食藥署核准之仿單說明為準

註2: 包含中央及地方代購疫苗量；包含開口式量能40萬劑

提醒

國光公司及高端公司疫苗不可接種於3歲以下幼兒

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接種流感疫苗的好處

- 避免流感及相關疾病
- 降低流感相關住院的風險
- 預防慢性病相關事件(如重症、住院等)
- 保護懷孕婦女與胎兒及產後婦女
- 降低幼童因流感重症死亡機率
- 接種流感疫苗後仍感染流感者，降低流感重症風險
- 群體免疫

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流感疫苗安全嗎？

流感疫苗安全嗎

–政府採購流感疫苗皆符合我國衛生福利部食品藥物管理署查 驗登記規定，且經其**核准使用/ 進口，安全無虞**

–持續監測疫苗不良事件

疫苗的副作用

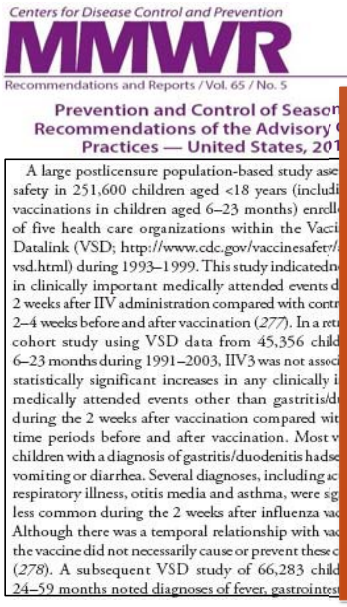
–疫苗與其他任何藥品一樣可能造成副作用，一般發生在1-2 天內自然恢復

流感疫苗常見的副作用

◦接種後10-50%可能發生注射部位 疼痛、紅腫

◦1-2%出現發燒、虛弱等全身性反 應

◦嚴重的反應如全身性過敏反應或Guillain-Barré症候群(GBS)發生 率在**百萬分之1以下**


Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Recommendations and Reports / Vol. 65 / No. 5
August 26, 2016
Prevention and Control of Seasonal Influenza with Vaccines
Recommendations of the Advisory Committee on Immunization Practices — United States, 2016

A large postlicensure population-based study assessed safety in 251,600 children aged <18 years (including vaccinations in children aged 6–23 months) enrolled in the Vaccine Datalink (VSD; http://www.cdc.gov/vaccinesafety/ vsd.html) during 1993–1999. This study indicated no increase in clinically important medically attended events during 2 weeks after IIV administration compared with control 2–4 weeks before and after vaccination (277). In a retrospective cohort study using VSD data from 45,356 children aged 6–23 months during 1991–2003, IIV3 was not associated with statistically significant increases in any clinically important medically attended events other than gastritis/duodenitis during the 2 weeks after vaccination compared with control time periods before and after vaccination. Most vaccinated children with a diagnosis of gastritis/duodenitis had nausea, vomiting or diarrhea. Several diagnoses, including acute respiratory illness, otitis media and asthma, were significantly less common during the 2 weeks after influenza vaccination. Although there was a temporal relationship with vaccination, the vaccine did not necessarily cause or prevent these conditions (278). A subsequent VSD study of 66,283 children aged 24–59 months noted diagnoses of fever, gastrointestinal

流感疫苗安全嗎？

- ✓ 在美國的疫苗安全監測資料中，兒童、青少年雖有通報接種後出現腸胃道症狀、上呼吸道疾病、氣喘、中耳炎等症狀，但不一定與接種流感疫苗有因果關係
- ✓ 成年人接種後雖較常出現肌肉痠痛、發燒及頭痛等症狀，但通常可於兩天內緩解
- ✓ 懷孕接種流感疫苗，在過去研究中，不但沒有增加造成胎兒損害、先天畸形、流產、死胎及早產等風險，甚至有降低死胎風險
- ✓ 目前沒有任何研究顯示接種流感疫苗對免疫低下(HIV感染)者有 臨床上重要的影響
- ✓ 雖然接種流感疫苗發生GBS的風險約百萬分之一，但研究顯示感染流感後發生GBS的風險高於接種流感疫苗
- ✓ 在回溯性世代追蹤、病例對照、安慰劑對照、上市後主動監測等研究並沒有觀察到流感疫苗對任何族群有安全疑慮

預防接種受害救濟審議委員會（VICP）案件統計

如疑似因預防接種而受害，民眾得依「預防接種受害救濟基金徵收及審議辦法」及其規定向衛生局申請預防接種受害救濟

- **自102年10月1日至112年5月1日止，公費流感疫苗總接種數為39,364,715劑，共通報1,274件不良事件**
- **期間申請預防接種受害救濟之案件僅393件**
  - ✓其中經預防接種受害救濟審議小組(VICP)審定結果與流感疫苗相關之案件僅31件，發生率約為0.07/每十萬人

VICP審議結果：流感疫苗

與疫苗相關

- 急性過敏反應、類蜂窩性組織炎……

無法排除與疫苗相關

- 血小板低下性紫斑、皮膚癢疹、神經性聽力損失、GBS、全身性過敏、氣喘、免疫性血小板低下症……

近年疑似流感疫苗接種致死，申請VICP案例，審議結果均與疫苗無關

- 腦血管疾病、敗血性休克、腸壞死……

流感疫苗不良事件影響民眾接種意願

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疫苗猶豫(Vaccine hesitancy)

- 定義：即使可接種疫苗，但因某些原因延遲或拒絕接種
- WHO於2019年列為世界十大健康威脅之一
- 全球性的議題，但不同國家之狀況或有不同
- 和時間、地域、疫苗種類、接種計畫均有相關
- 存在已久，但近年較為人所關注
- 較常在新疫苗，或大規模接種(mass campaigns)發生

Report of the SAGE working group on vaccine hesitancy (WHO, 2014)

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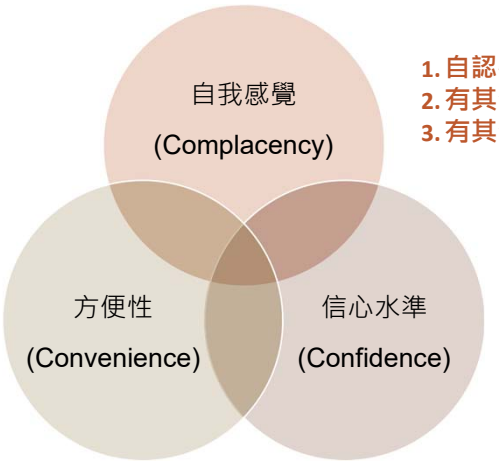
造成疫苗猶豫的因素



1. 自認罹病風險不高
2. 有其他方法可預防疾病
3. 有其他更重要的事要做

疫苗價格、接種可近性、對衛教知識的理解程度

對政府、公衛系統、決策者與疫苗的整體信任程度

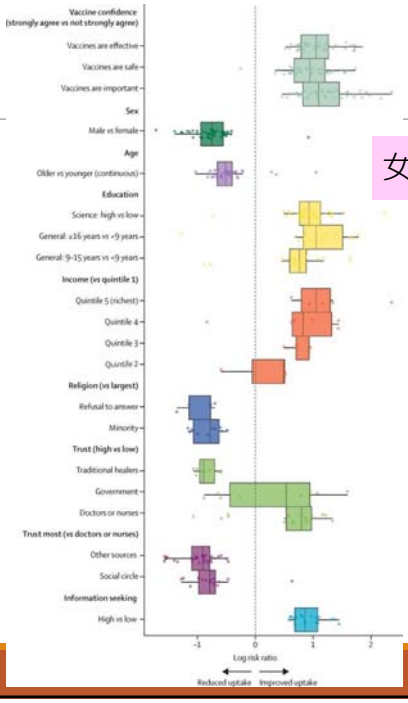
https://pharmaceutical-journal.com/article/ld/how-to-address-vaccine-hesitancy

影響接種疫苗意願之因素

對疫苗是否有信心

有效性

安全性 必要性



女性與年輕人意願較高

教育程度影響有限

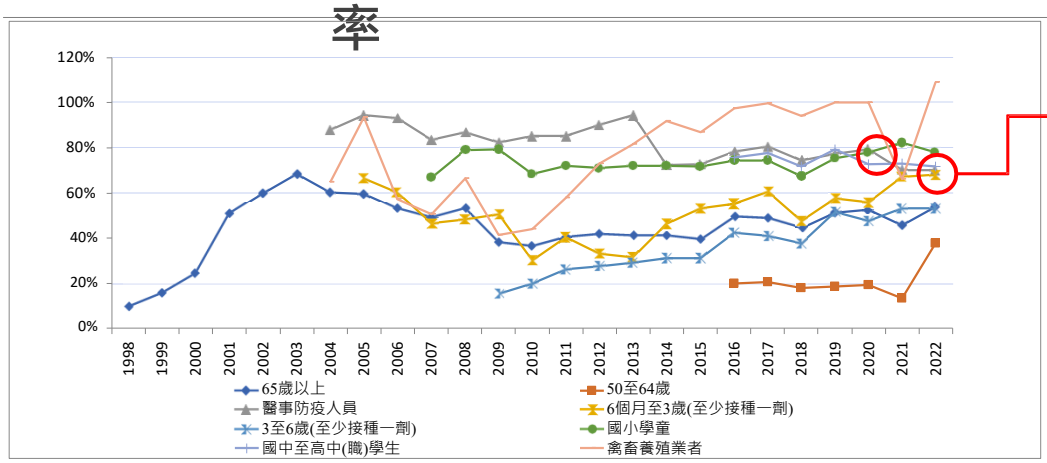
對政府信任程度兩極

醫護鼓勵接種最有效

社群負面影響較大

Ref: Global Public Health 2018；Lancet 2020; 396: 898–908

歷年各類對象流感疫苗接種率



醫事防疫人員接種率自 2020年79.2%降至2022年70.1%

2014年起改以執業登記人數為分母統計接種率

2022年度資料截至2023/5/7

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流感疫苗可否和其他疫苗或COVID-19疫苗同時接種？

- 目前實證顯示流感疫苗和COVID-19疫苗同時接種並不影響疫苗 之有效性或安全性。
- 為提升接種效率及提高接種涵蓋率，經111年2月25日衛生福利 部傳染病防治諮詢會流感防治組及預防接種組聯席會議建議，流 感疫苗與COVID-19疫苗，**可以同時接種**，民眾**可依其需求選擇 同時或間隔一段時間接種**。同時接種流感疫苗與COVID-19疫苗 之接種部位，考量臨床接種實務之可行性與參考WHO指引，**建 議接種於不同肢體**。

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CDC網站：流感疫苗資訊

https://www.cdc.gov.tw/Category/List/AKPdJaFAQVIhcWC3k0iYkw

感謝聆聽 歡迎討論

疾管署全球資訊網 www.cdc.gov.tw
免付費疫情通報與諮詢專線 1922