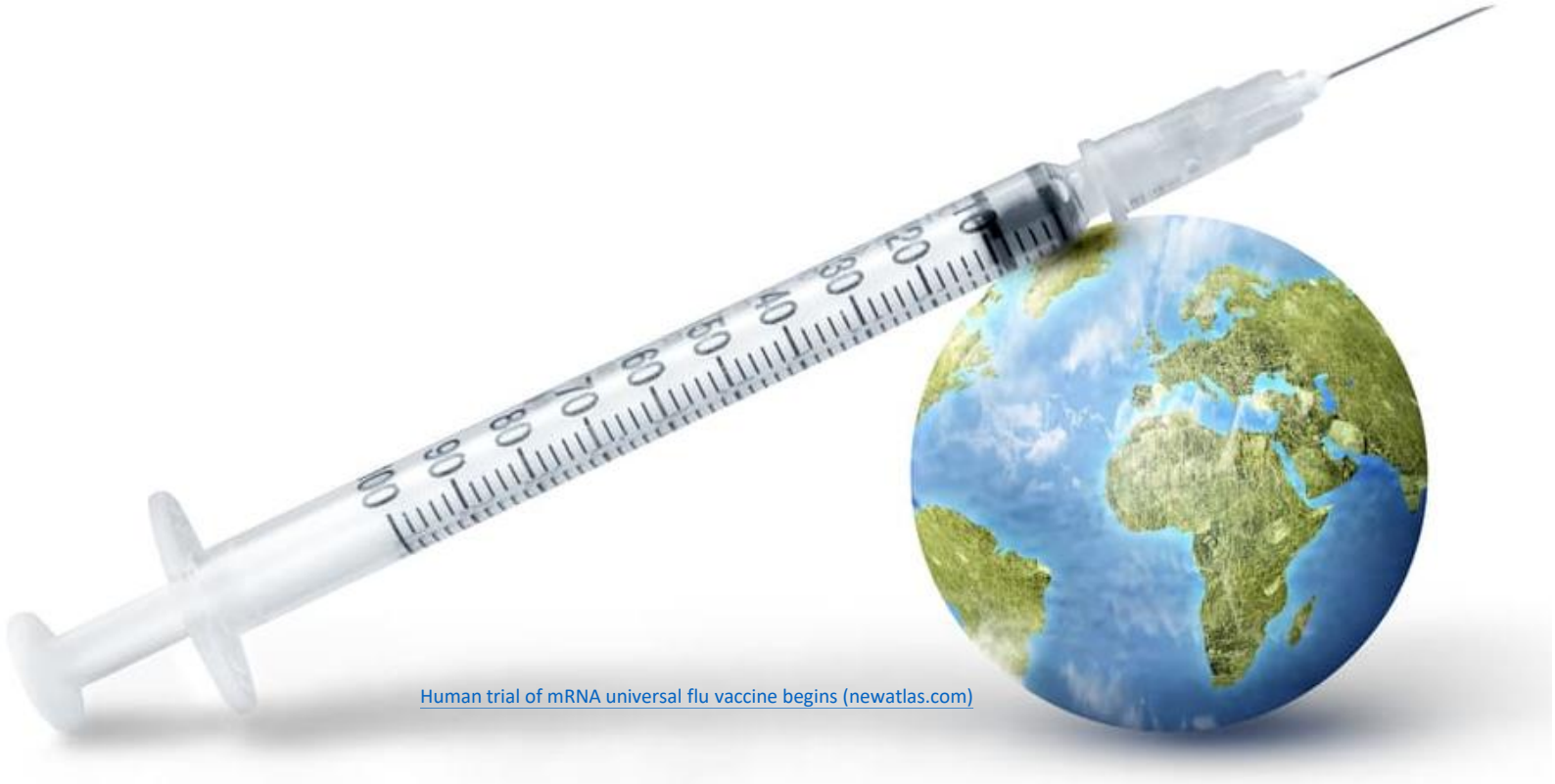
流感防治與疫苗接種政策



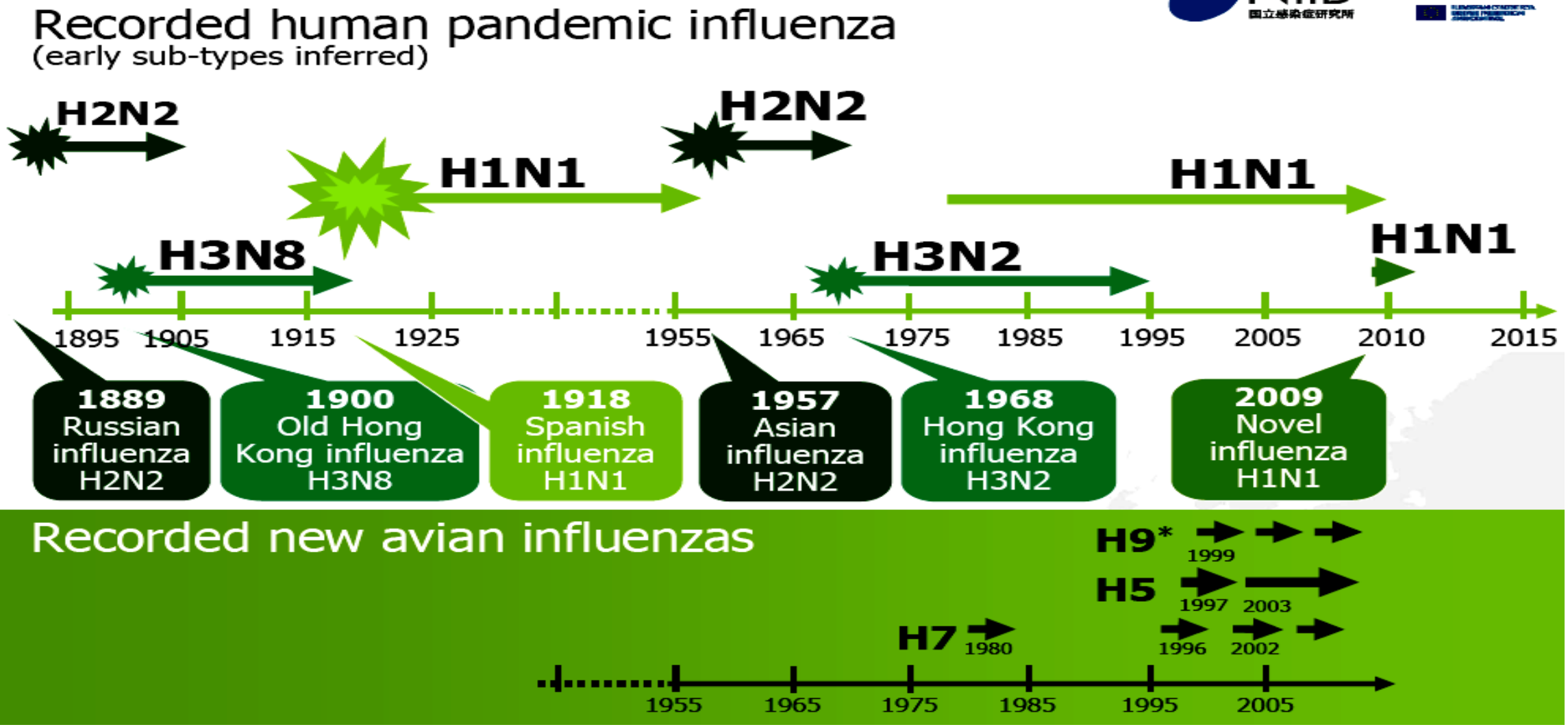
臺中榮民總醫院 兒童感染科 潘蕙嫻

大綱

- 流感簡介
- 我國流感防治政策
- 流感的診斷、治療與預防

流感簡介

歷史上流行性感冒大流行與演變



史上流感大流行 (Influenza Pandemics)

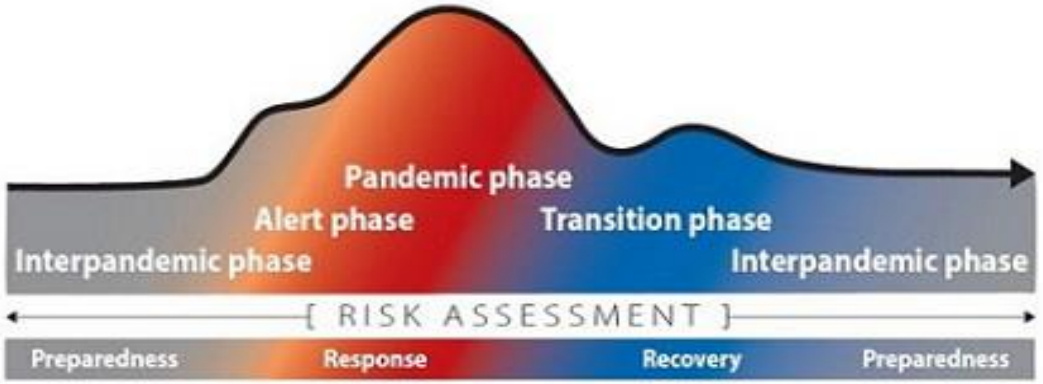
Year	Subtype	Estimate Death	Origin of gene						
			NA	PA	PB1	PB2	NP	M	NS
1918	H1N1	4-5千萬							
1957	H2N2	逾2百萬							
1968	H3N2	1百萬							
2009	H1N1	逾1.8萬							

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

流感大流行的要件及威脅性

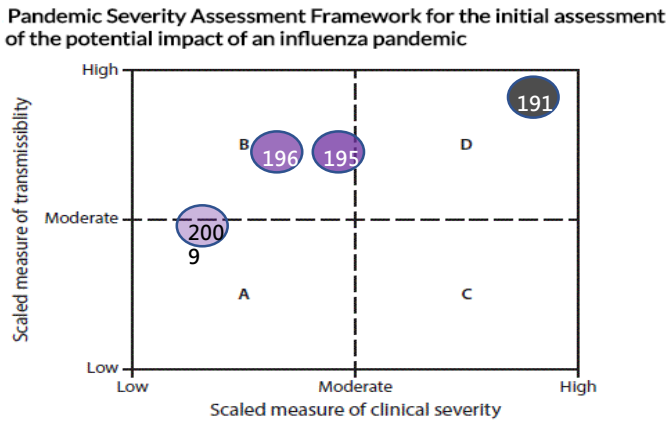
- **大流行之要件**
  - 病毒可有效人傳人
  - 人類對此病毒幾乎無免疫力
- **大流行之威脅性**
  - 依病毒傳染性及臨床嚴重程度評估

WHO Pandemic phases



Severity of pandemic **PSAF**

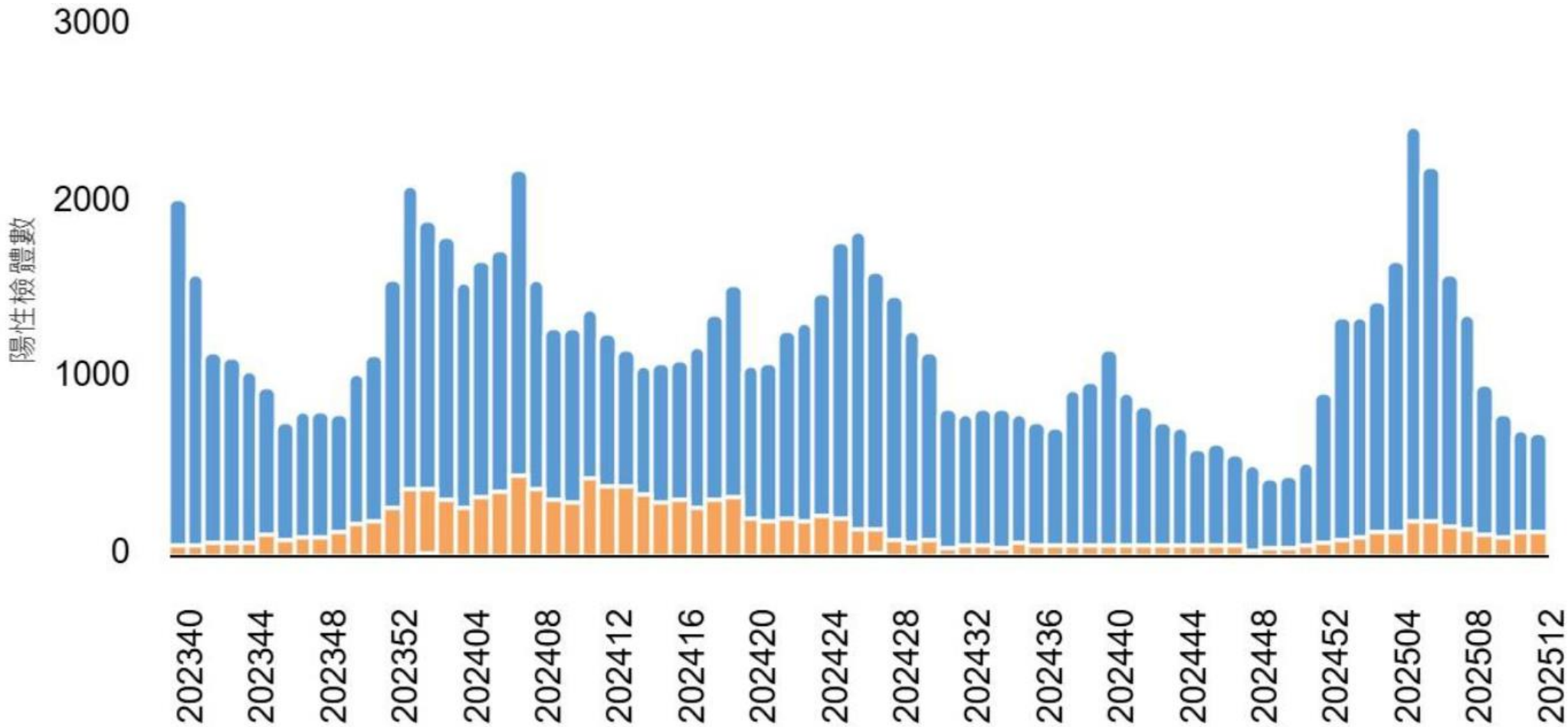
1918 西班牙流感	Very high severity (very severe to extreme pandemic)	D
1957 亞洲流感	High severity (severe pandemic)	B
1968 香港流感	Moderate to high severity (moderate to severe pandemic)	B
2009 H1N1流感	Low to moderate severity (mild to moderate pandemic)	A



台灣的流感監測系統

- **病例監測**
  - 法定傳染病監視通報系統：流感併發重症、新型A型流感
  - 症狀監視通報系統：類流感聚集、國際機場入境發燒旅客
- **流行趨勢監測**
  - 即時疫情監測及預警系統(RODS)
  - 肺炎及流感死亡監視
  - 人口密集機構傳染病監視通報系統
  - 學校傳染病監視通報系統
  - 定點醫師監測系統
- **病毒活動監測**
  - 病毒性合約實驗室監視通報系統
  - 病毒抗原及抗藥性分析

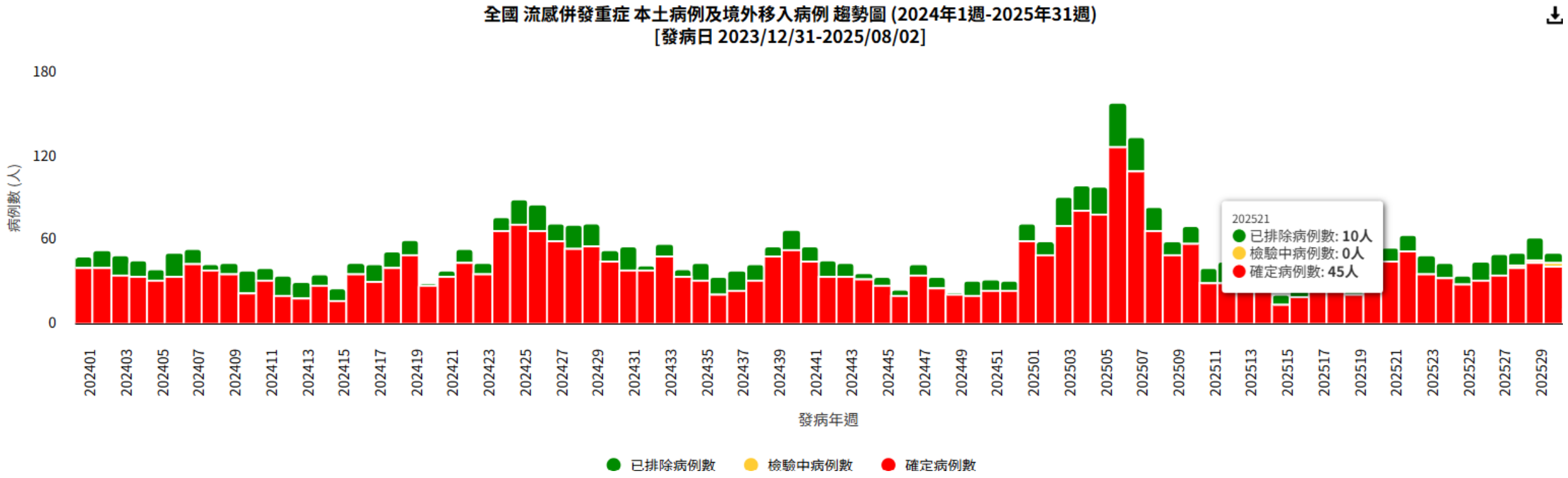
臺灣流感陽性個案



台灣流感速迅 2025年第 12週 (2025/3/16 – 2025/3/22)

臺灣流感重症個案

2024，共計1908 例重症病例
2025至今，共計1394 例重症病例



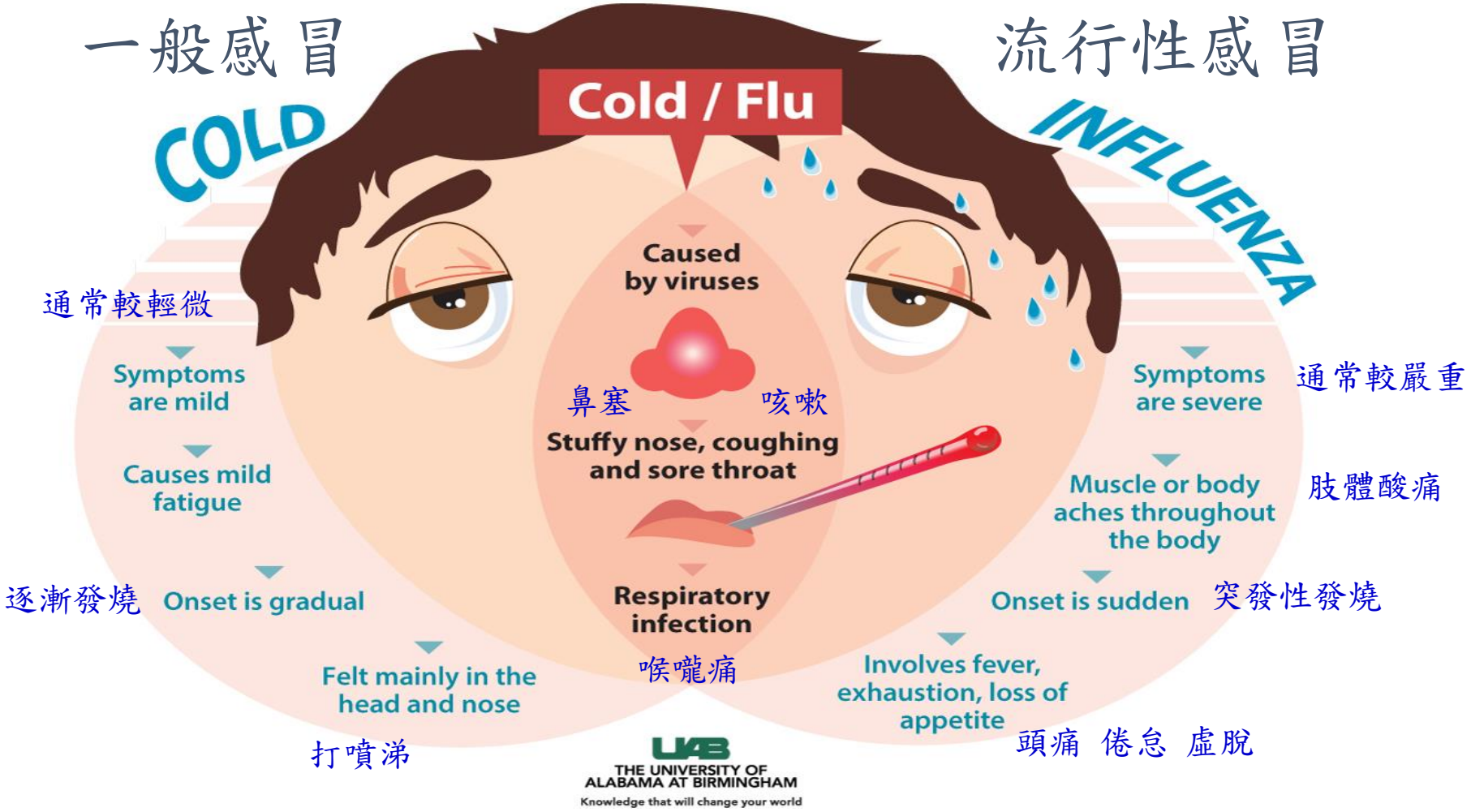
傳染病統計資料查詢系統

類流感的臨床疾病定義 Influenza-like illness, ILI

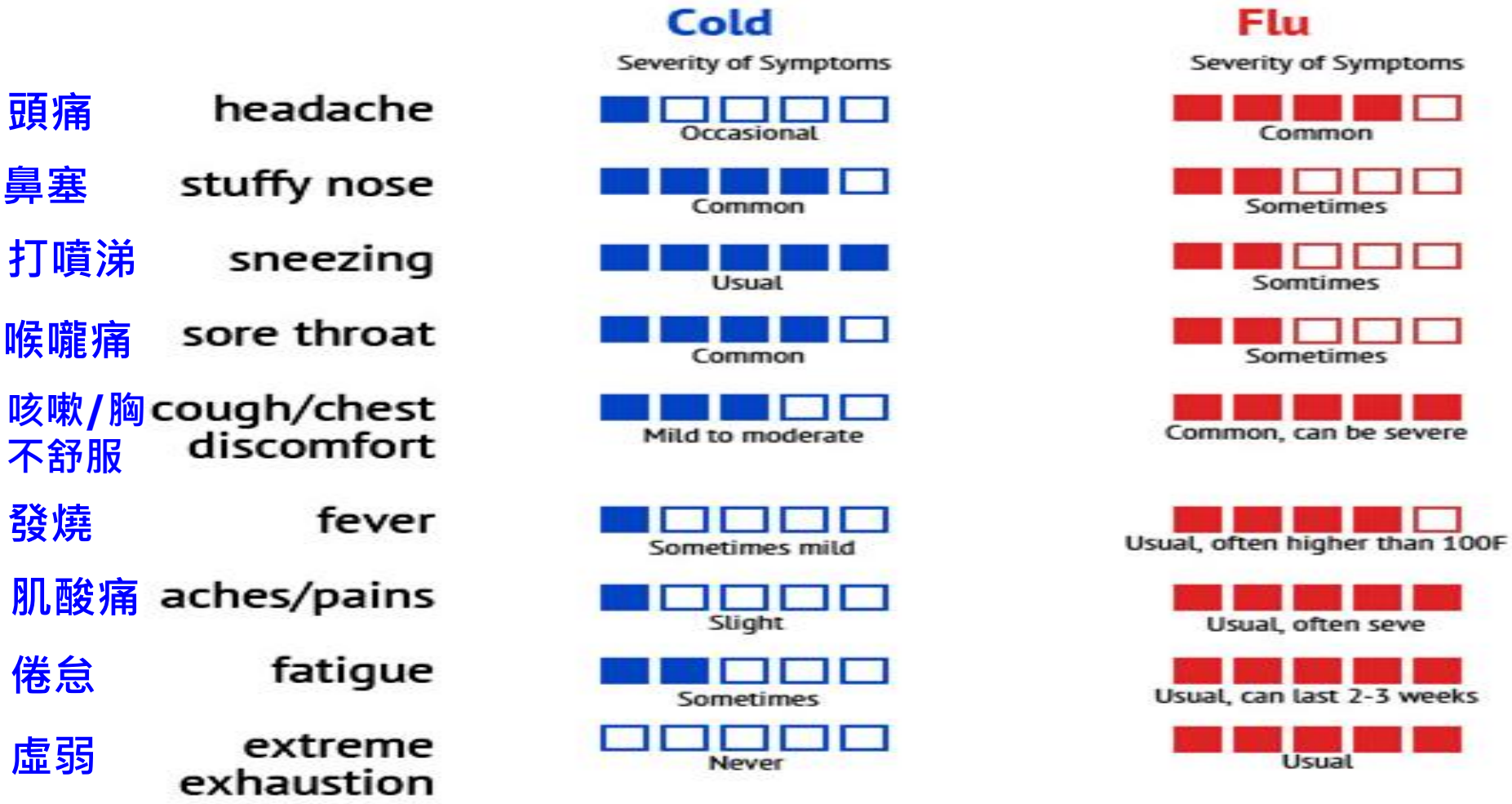
- 即疑似流感病例，臨床上同時出現
- ①突然發病、有發燒(耳溫≧38℃)及呼吸道症狀；
- **②且有肌肉酸痛或頭痛或極度倦怠感；**
- ③需排除單純性流鼻水、扁桃腺炎及支氣管炎；
- 但未經實驗室證實者謂之。

+ 群聚現象: 全家感冒一起看病,好朋友或同學都感冒了

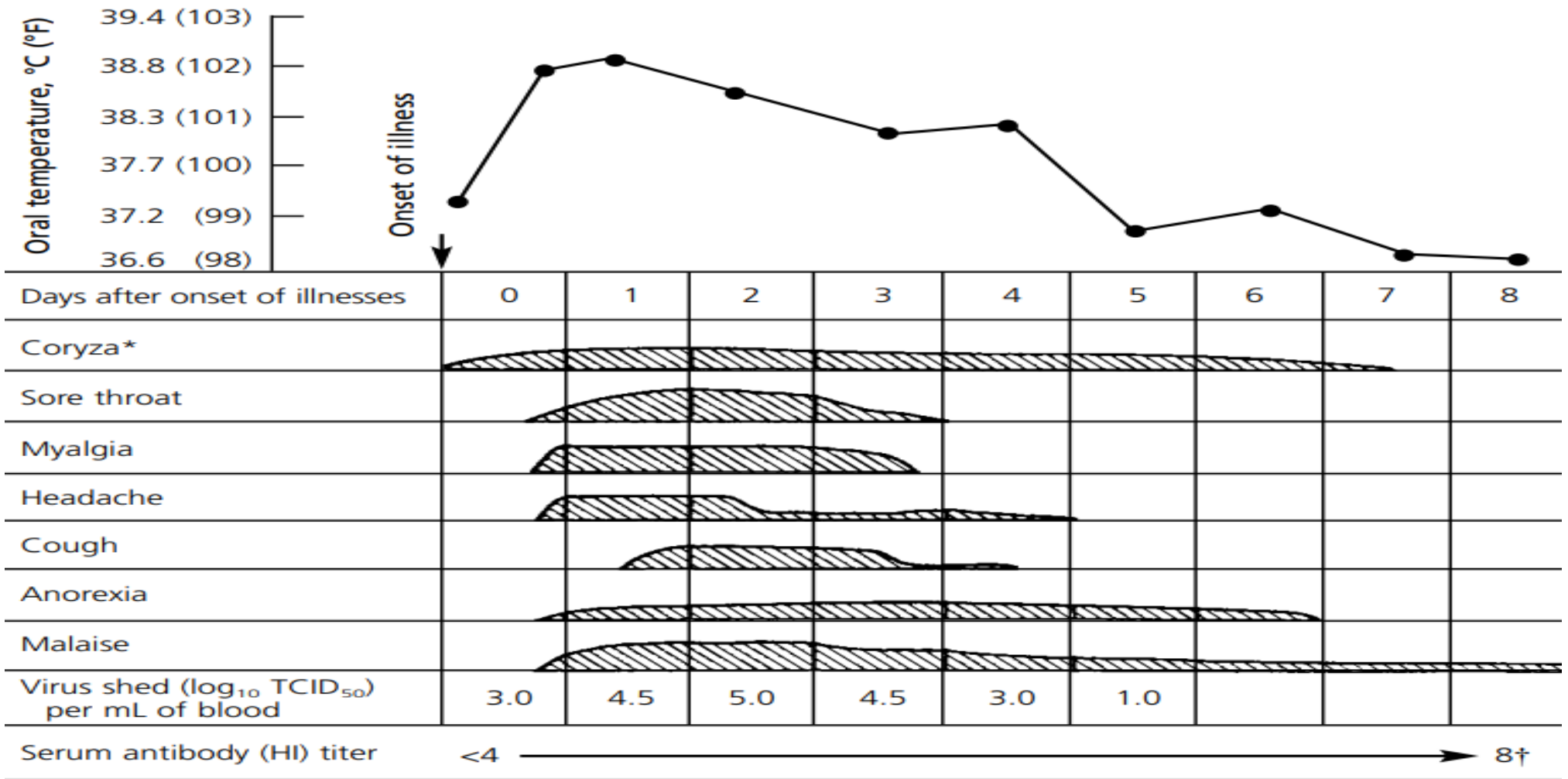
感冒與流感症狀的比較


一般感冒
流行性感冒
COLD
INFLUENZA
Cold / Flu
Caused by viruses
通常較輕微
Symptoms are mild
Causes mild fatigue
逐漸發燒
Onset is gradual
Felt mainly in the head and nose
打噴涕
鼻塞
咳嗽
Stuffy nose, coughing and sore throat
Respiratory infection
喉嚨痛
Symptoms are severe
通常較嚴重
Muscle or body aches throughout the body
肢體酸痛
Onset is sudden
突發性發燒
Involves fever, exhaustion, loss of appetite
頭痛 倦怠 虛脫
THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Knowledge that will change your world

感冒與流感症狀的比較


Cold
Severity of Symptoms
Flu
Severity of Symptoms
頭痛 headache
Occasional
Common
鼻塞 stuffy nose
Common
Sometimes
打噴涕 sneezing
Usual
Somtimes
喉嚨痛 sore throat
Common
Sometimes
咳嗽/胸不舒服 cough/chest discomfort
Mild to moderate
Common, can be severe
發燒 fever
Sometimes mild
Usual, often higher than 100F
肌酸痛 aches/pains
Slight
Usual, often seve
倦怠 fatigue
Sometimes
Usual, can last 2-3 weeks
虛弱 extreme exhaustion
Never
Usual

人類感染流感的病程症狀和病毒量



流鼻水
喉嚨痛
肌酸痛
頭痛
咳嗽
食慾差
倦怠

*—*Coryza is an acute inflammatory condition of the nasal mucous membranes with a profuse discharge from the nose.*

†—*Serum antibody titer was 64 at day 21.*

Am Fam Physician. 2003;67(1):111-118

名詞釋疑

- **季節性流感 (Seasonal influenza)**
  - 在人類每年發生季節性流行的流感
  - 有效人傳人，有疫苗可供預防
- **禽流感 (Avian influenza)**
  - 主要在禽類間流行的流感，分為高病原性與低病原性
  - 偶然感染人類，主要為禽傳人，H5N1可能具備有限性人傳人的能力
  - 人類病例多出現於禽類疫情發生處，且多有禽鳥接觸史
- **豬流感(Swine influenza)**
  - 主要在豬隻間流行的流感
  - 通常很少經由人與人傳播，但2009年H1N1新型流感經過基因重組後，造成大流行
- **大流行流感(Pandemic influenza)**
  - 如演化出新型流感病毒，人類無免疫力，且可人傳人，導致全球發生大流行，此疾病稱為「大流行流感」
- **新型A型流感(Novel Influenza A Virus Infections)**
  - 指除了每年週期性於人類之間流行的季節性流感（A/H1N1及A/H3N2）外，偶發出現感染人類的其他A型流感病毒亞型

流感病程

- **季節性流感病毒造成人與人間的傳染**
  - 潛伏期1-4天
- **傳染途徑**
  - 主要透過飛沫傳染與接觸傳染
- **大多數病人症狀輕微，但部分高危險族群可能出現嚴重併發症，常以細菌性及病毒性肺炎表現**
  - 懷孕、心肺血管疾病、肝、腎疾病及糖尿病患者
  - 長者(≧65歲)及幼兒(<5歲)

流感的併發症


流感普通症狀
發燒、頭痛、
喉嚨痛、咳嗽、
肌肉酸痛
危險徵兆
呼吸困難、呼吸急促、發紺(缺氧)、
血痰或痰液變濃、胸痛、意識改變、
低血壓或高燒持續72小時
65歲以上長者或有潛在疾病者，應提高警覺
儘速轉診
至大醫院
門診就醫(約1%需住院)
流感病毒
潛伏期1-4天
(平均2天)
上呼吸道
感染
(1-2週內)
流感併發症
(佔流感住院病人10-25%)
病毒性併發症
(如：肺炎、心肌炎、腦炎)
細菌感染
(如：肺炎鏈球菌、
金黃色葡萄球菌)
加重高風險族群
本身潛在性疾病
(如：心血管疾病、慢性肺病、
腎臟病、糖尿病及肥胖等)
嚴重
併發症
(佔流感併發症
1%~4%，如：
呼吸衰竭或敗
血症等)
死亡
(嚴重併發症
者中約一半
會死亡)

流感與新冠肺炎病毒特性比較

Selected comparisons between influenza virus and SARS-CoV-2

Parameter	Influenza virus	SARS-CoV-2
Receptor usage 受體	Sialic acid	ACE2
Viral surface protein processing 病毒蛋白	Haemagglutinin processing by trypsin-like proteases	Spike protein processing by host proteases, including TMPRSS2, cathepsin L and furin, neuropilin 1
Cellular tropism	Respiratory epithelial cells: types I and II alveolar epithelial cells; ciliated cells	Respiratory epithelial cells: type II alveolar epithelial cells, ciliated cells and secretory cells; sustentacular and horizontal basal cells of the olfactory epithelium Intestinal epithelial cells; endothelial cells; renal parenchymal cells
Tissues affected and pathology 影響器官組織	Upper respiratory tract; lower respiratory tract (severe cases)	Upper respiratory tract; lower respiratory tract; intestinal tract; cardiovascular or endothelial system; kidneys; nervous system
Viral recognition in airway epithelial cells	TLR3; RIG-I; ZBP1	TLR3; RIG-I; MDA5
Site of viral replication	Nuclear	Cytoplasmic
Viral evasion of initial host response	NS1; PB2; PB1-F2	NSP1; ORF6; NSP13; others? (extrapolated from other coronaviruses)
Extrapulmonary complications 常見器官併發症	Limited; cardiac: myocarditis (rare); neurological: encephalitis (rare)	Extensive; olfactory: anosmia; endothelial: thrombosis; neurological: stroke, encephalitis, neuropsychiatric; gastrointestinal: nausea, vomiting, diarrhoea
Viral evolution 病毒演化 and antigenicity	Antigenic shift; antigenic drift	Antigenic drift?
Prior immunity 免疫力	Previous infection; vaccination; subtype specificity	No specific SARS-CoV-2 immunity prior to late 2019–2020; protective immunity from other human coronaviruses unclear; vaccination started December 2020

Flerlage T. Nature Reviews Microbiology 2021;19:425–441

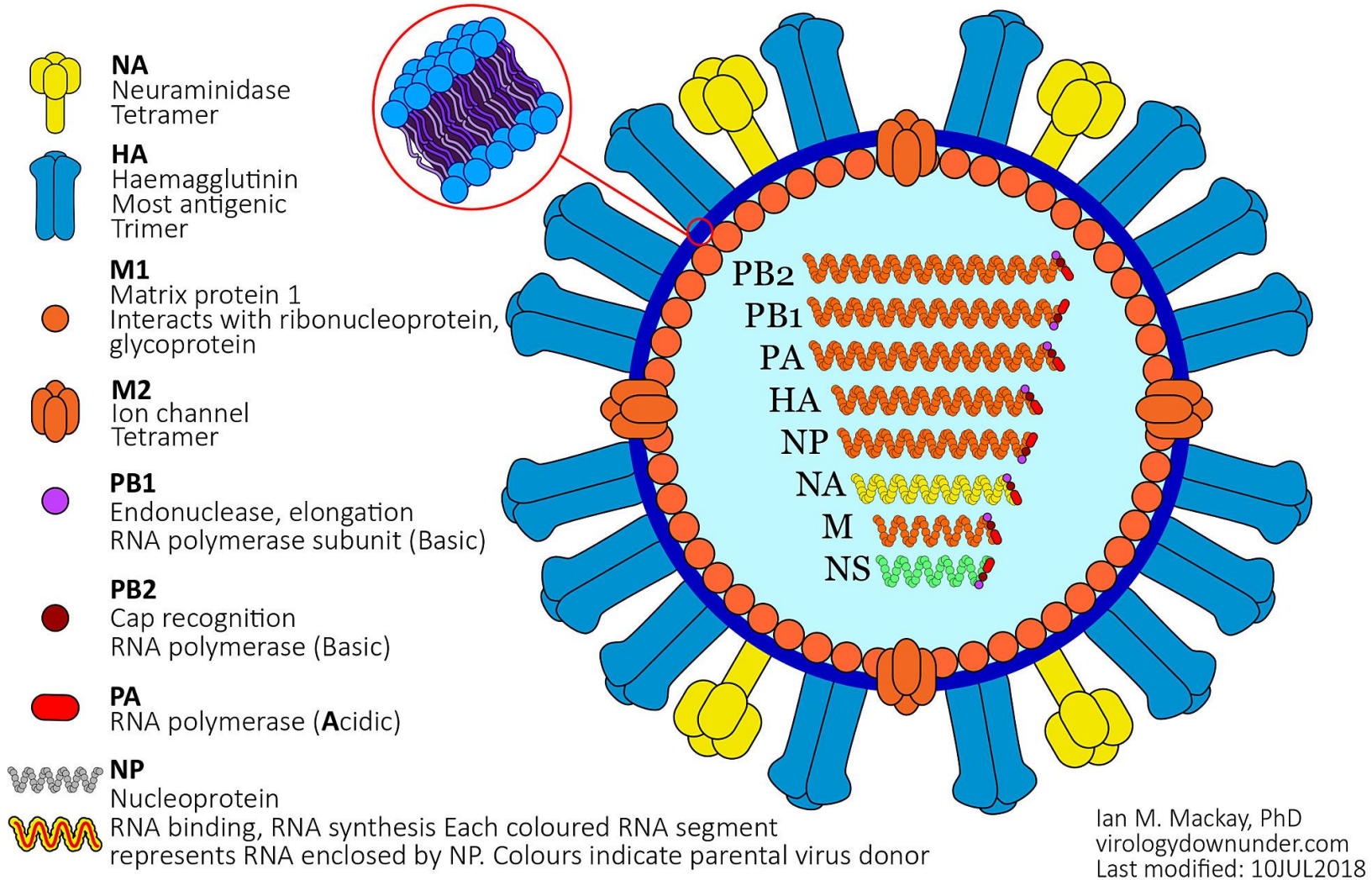
新冠病毒與流感病毒在感染呼吸道的差異

Distinct airway epithelial immune responses after infection with SARS-CoV-2 compared to H1N1

- **Children** are less likely than adults to suffer severe symptoms when infected with severe SARS-CoV-2, while influenza A H1N1 **severity** is comparable across ages except for the **very young or elderly**. **Airway epithelial cells** play a vital role in the early defence against viruses via their barrier and immune functions. We **investigated viral replication and immune responses** in SARS-CoV-2-infected bronchial epithelial cells from healthy paediatric (n = 6; 2.5~5.6 years old) and adult (n = 4; 47~63 years old) subjects and compared cellular responses following infection with SARS-CoV-2 or Influenza A H1N1.
- While infection with **either virus triggered robust** transcriptional **interferon responses**, including induction of type I (IFNB1) and type III (IFNL1) interferons, markedly **lower levels of interferons & inflammatory proteins (IL-6, IL-8) were released following SARS-CoV-2** compared to H1N1 infection. **Only H1N1 infection caused disruption of the epithelial layer**. Interestingly, H1N1 infection resulted in sustained upregulation of SARS-CoV-2 entry factors FURIN and NRP1. We did not find any differences in the epithelial response to SARS-CoV-2 infection between paediatric and adult cells. Overall, **SARS-CoV-2 had diminished potential to replicate**, affect morphology and evoke immune responses in bronchial epithelial cells compared to H1N1.

Stölting H. Mucosal Immunology 2022;15:952–963

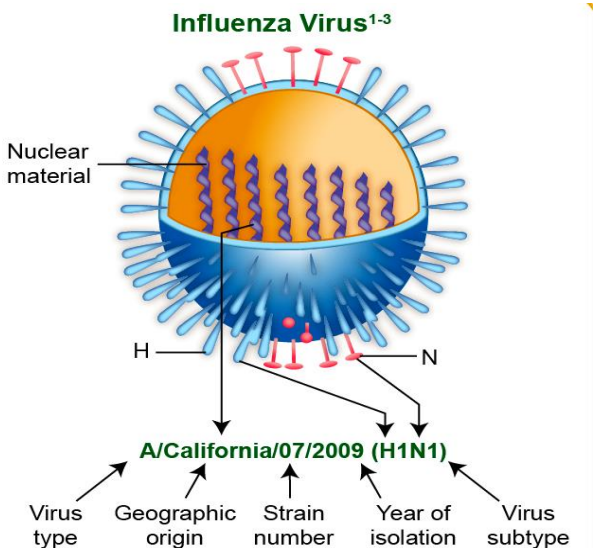
病毒結構



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

流行性感冒病毒

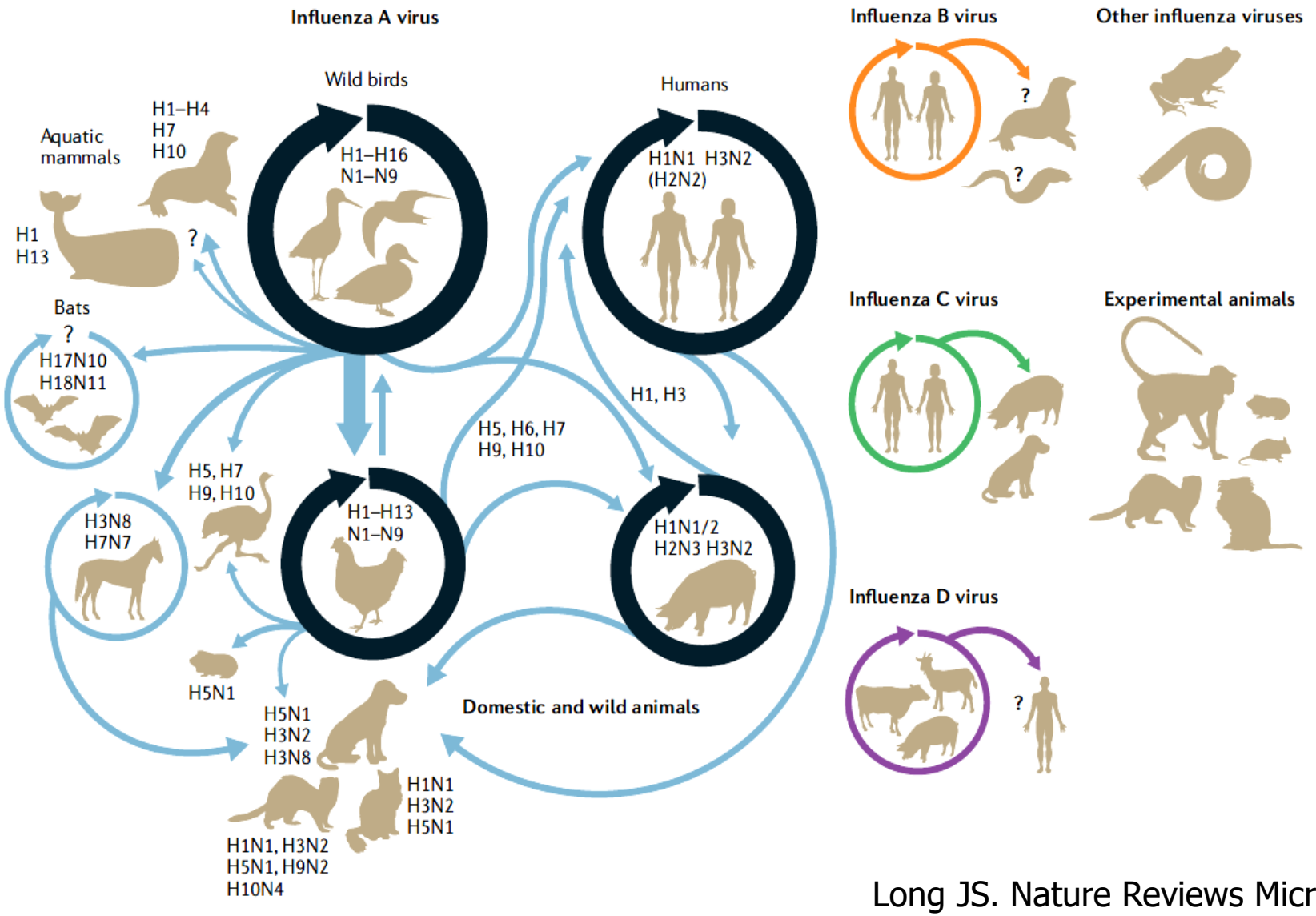
- ✓A、B、C 、D型
- ✓A型流感病毒以兩種表面抗原蛋白來區分 (H1N1, H3N2, H2N2?)
- ✓B型流感為單一血清型，但分為兩個分枝 (抗原性)：
  1. Victoria lineage (維多利亞株)
  2. Yamagata lineage (山形株)



	Type A	Type B	Type C	Type D
全球大流行 (pandemic influenza)	✓			
局部性流行 (epidemic influenza)	✓	✓		
症狀較輕微的上呼吸道感染			✓	
可感染人類、豬與鳥類	✓			✓
在各年齡層造成中度到嚴重的疾病	✓	✓	大部人都感染過 (主要於學齡前)	2016.9

流感病毒的生態學

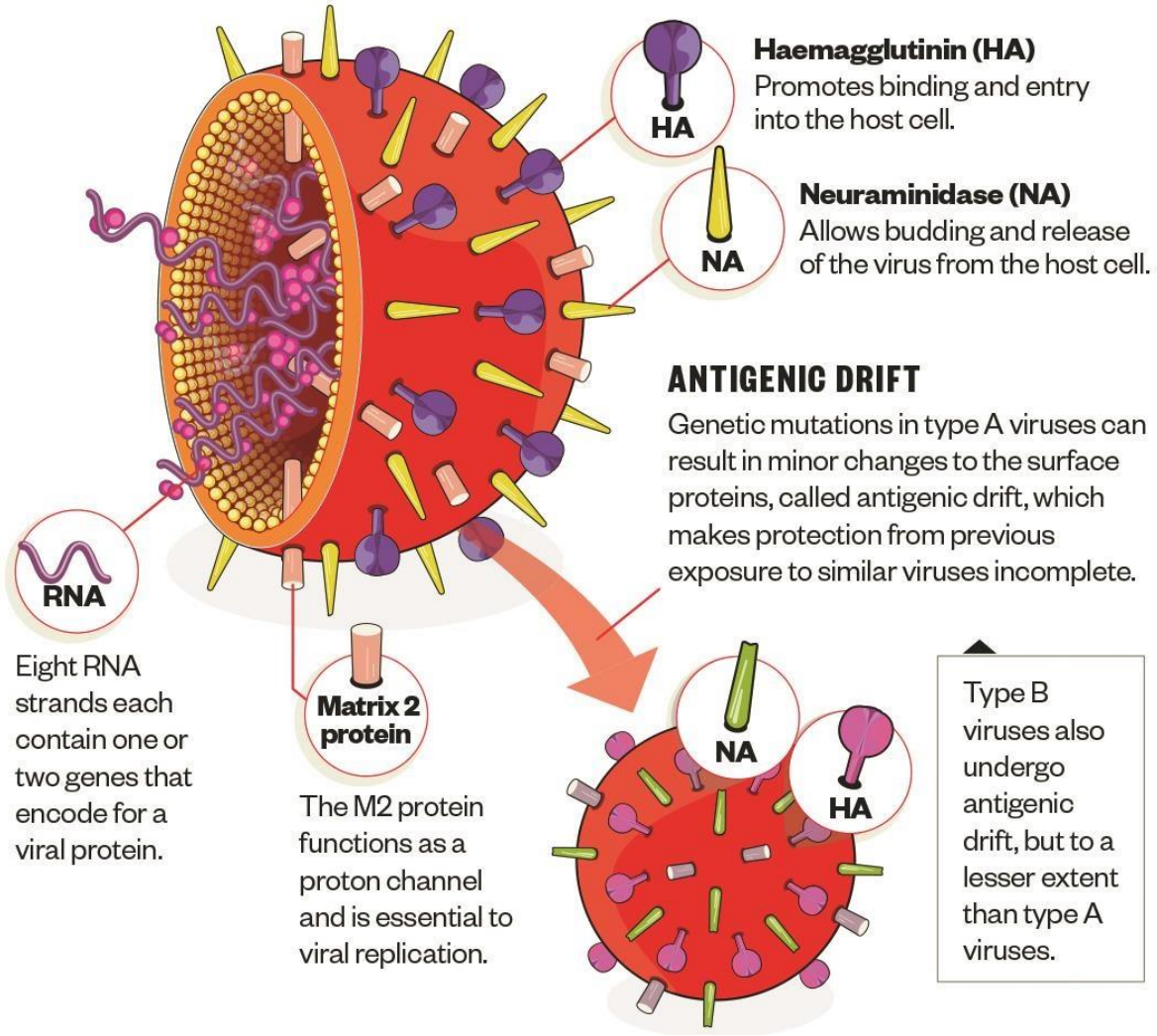
Ecology of influenza viruses

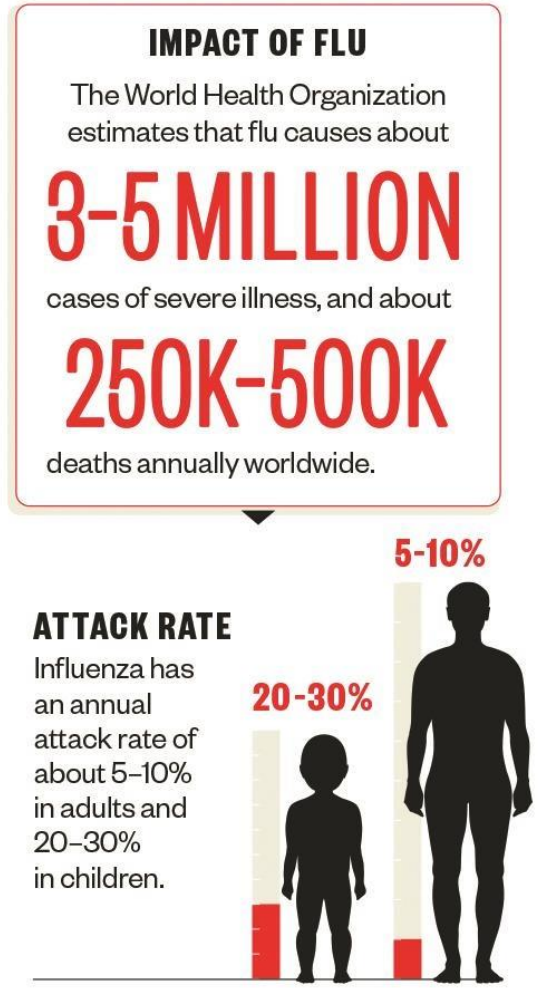


Long JS. Nature Reviews Microbiol 2019;17:67~81

流感病毒對世界的衝擊與挑戰

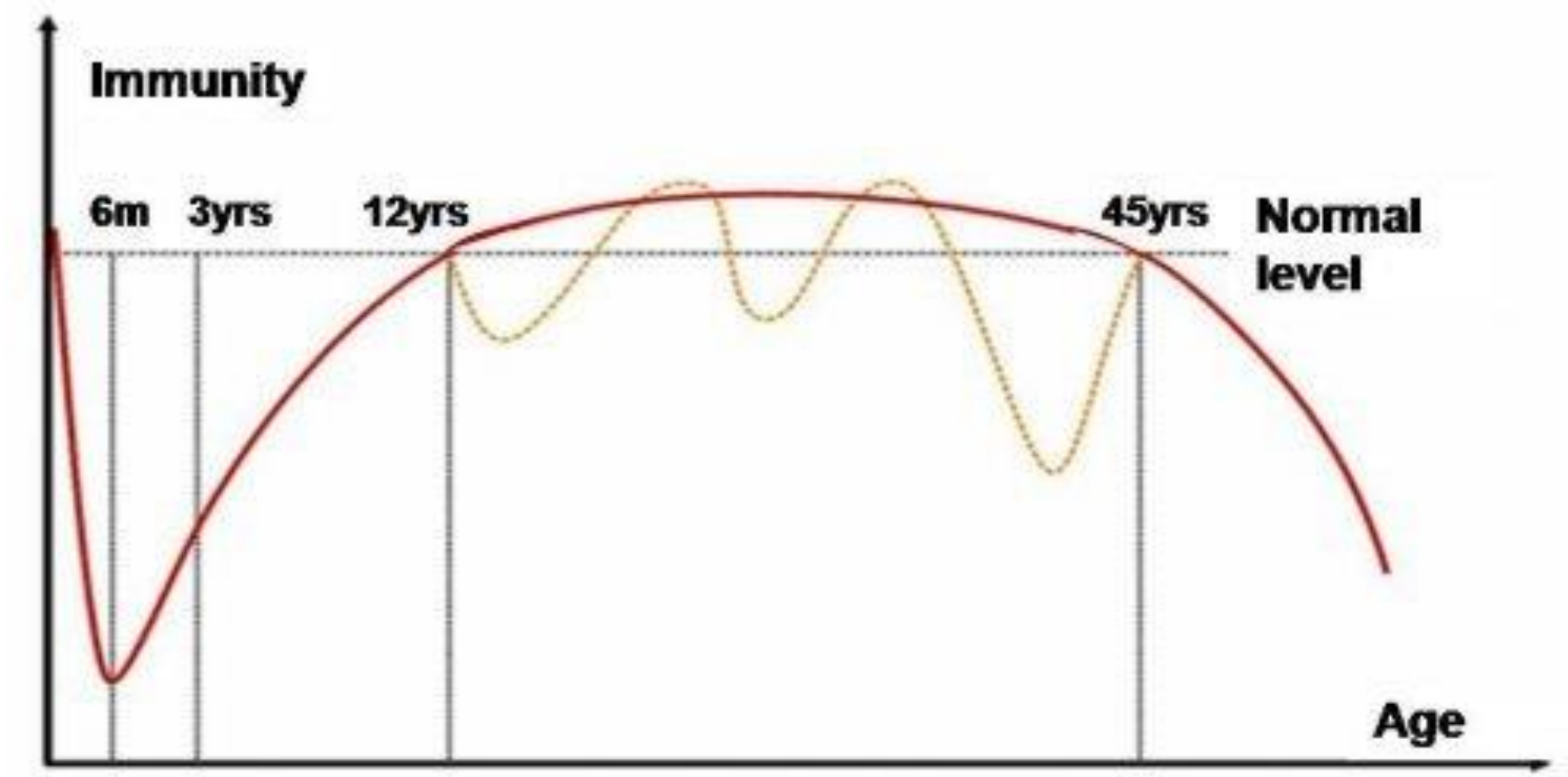
Impact and challenges of the flu virus



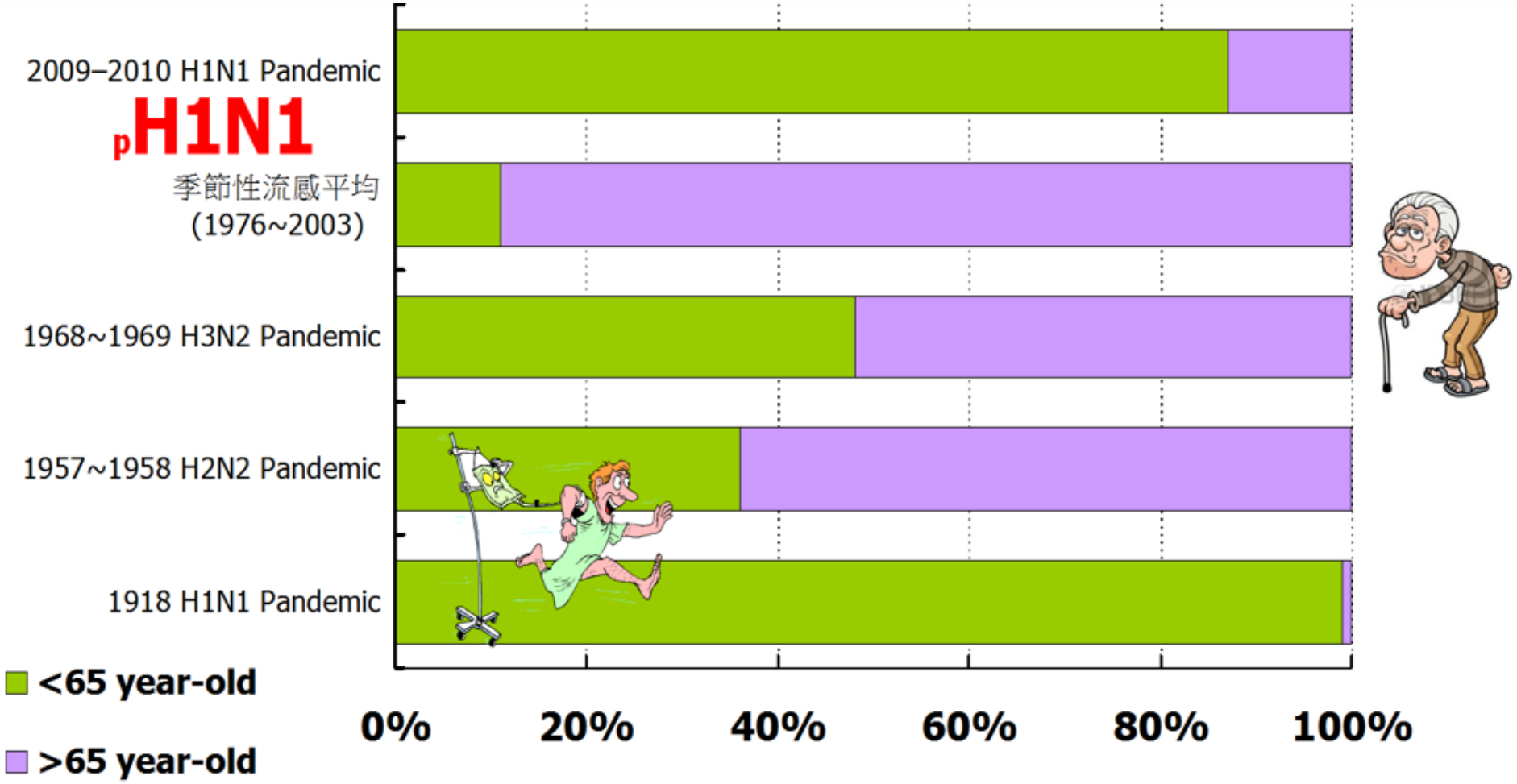


The Pharmaceutical Journal 29 OCT 2015

人體抵抗力(免疫力)發展



季節性流感與大流行流感時期老年人死亡所佔比例



2011 Jan 1:52 Suppl 1:S44-9

我國流感防治政策

因應流感大流行之準備

準備計畫

1. 行政院核定之最高指導綱領
2. 爭取經費支應各項準備

策略計畫

1. 依準備計畫所定策略
2. 防治措施之原理原則
3. 各機關制定因應實務之依據

工作指引

1. 依策略計畫所訂作業指引
2. 實務執行防疫工作指導方針

流感防治策略

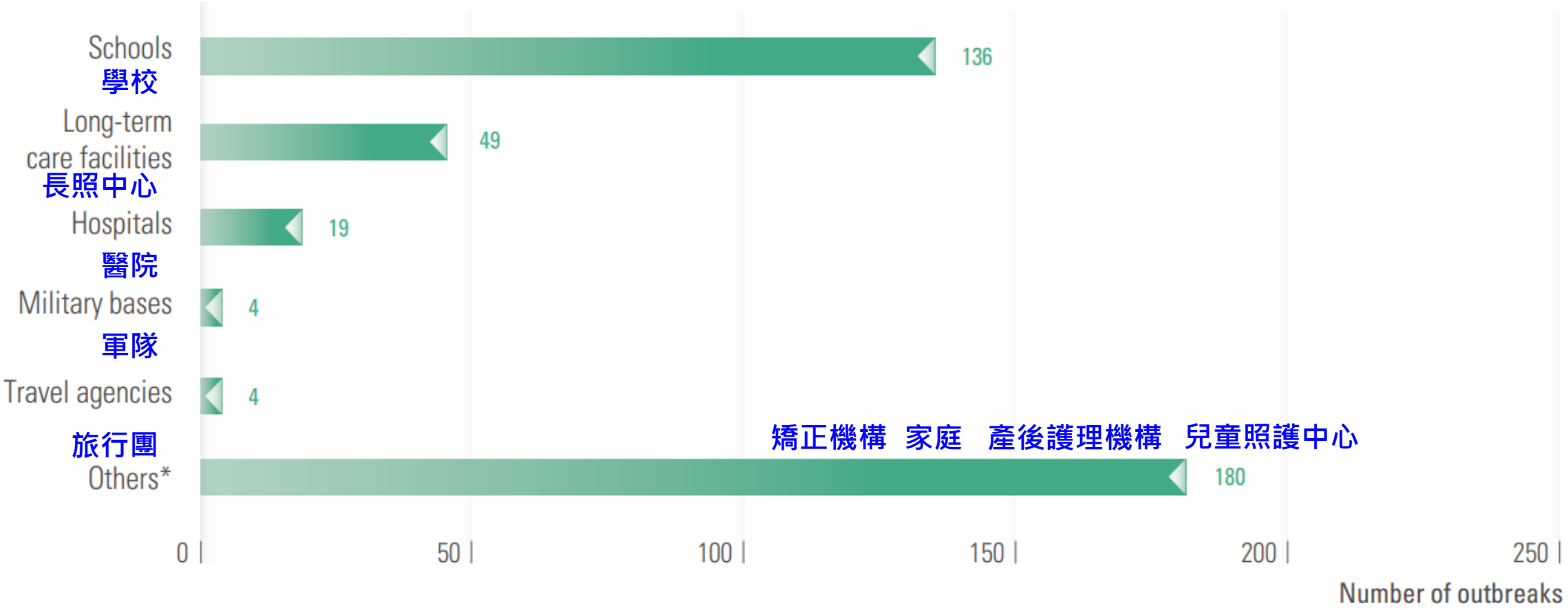
	季節性流感	流感大流行
疫情監視	重症病例監視 流行趨勢監視 病毒活動監視	重症病例監視 流行趨勢監視 病毒活動監視
民眾溝通	個人衛生 人口密集機構	個人衛生 機關團體防疫
疫苗接種	高危險群、高傳播族群	全民
抗病毒藥劑使用	縮短症狀持續時間 降低重症與死亡率	圍堵 預防性投藥 重症治療
公共衛生介入	自主健康管理	隔離、檢疫、停課

主要工作項目

- **疫苗之儲備規劃**
  - 規劃以預購協議建立大流行疫苗之儲備模式
  - 季節性流感疫苗接種規劃
  - 採購所需之流感疫苗並進行使用規劃
- **永續防疫物資儲備規劃**
  - 儲備及管理流感抗病毒藥劑及個人防護裝備等防疫物資
- **醫療體系之維持與量能提升**
  - 維持「傳染病防治醫療網」，強化傳染病診斷及治療量能
- **整體防疫量能之強化**
  - 持續風險溝通，提升社區動員量能，加強國際交流

台灣機構群聚症候群感染事件統計

Number of Outbreaks by Setting— Taiwan, 2022



*Other settings including household, workplace, restaurants, correctional facilities and unknown.

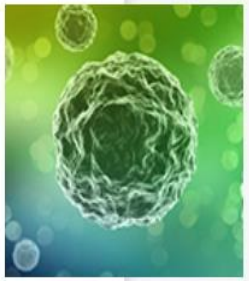
Note: COVID-19 outbreaks were not included in the analysis.

Taiwan CDC Annual Report 2022

臺灣疾病管制署流感疾病資訊

疾病資訊

疾病介紹



最新消息及疫情訊息

- 新聞稿
- 致醫界通函
- 流感防治一網通-公費…
- 統計資料查詢

更多...

重要指引及教材

- 季節性流感防治工作…
- 傳染病病例定義暨防…
- 「流感併發重症」核…
- 學校/幼兒園/補習班/…

更多...

流感疫苗

- 年度流感疫苗接種計畫
- 流感疫苗接種工作手冊
- 合約醫療院所專區
- 校園集中接種

更多...

流感抗病毒藥劑

- 儲備目的及使用原則
- 公費流感疫苗暨抗病…
- 公費流感抗病毒藥劑…
- 公費流感抗病毒藥劑…

更多...

Q & A

- 季節性流感防治
- 季節性流感疫苗
- 流感抗病毒藥劑

更多...

https://www.cdc.gov.tw/Disease/SubIndex/x7jzGIMMuIeuLM5izvwg_g

衛生福利部疾病管制署~公費疫苗項目與接種時程

年度流感疫苗接種計畫

- 114年度公費對象及疫苗介紹
- 114年度流感疫苗接種計畫
- 工作手冊 (114年7月更新)
- 教育訓練
- 各縣市流感疫苗合約醫療院所
- 歷年接種數 (2023)
- 接種嚴重不良事件統計

防疫物資儲備

- **流感抗病毒藥劑**
  - 克流感、易剋冒、瑞樂沙、瑞貝塔、Avigan
- **個人防護裝備**
  - 外科口罩、N95口罩、隔離衣、防護衣

公費流感抗病毒藥劑儲備目的

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

各國流感抗病毒藥劑儲備及使用情形

	美國	紐西蘭	英國	日本	台灣
政府儲備藥劑使用時機	大流行用 (2022年季節性流感疫情嚴峻時，聯邦政府釋出儲備之Tamiflu予州政府使用)	大流行用	大流行用	大流行用	大流行用 (流感疫情高峰期放寬公費藥劑使用條件，釋出效期最短之藥劑做為季節性流感治療使用，提供民眾一般醫療需求)
季流期間非儲備藥物之使用方式	保險給付為主 (國家保險如Medicare、Medicaid，以及私人保險)	自費 (提供部分民眾，如免疫功能較弱具併發症高風險之住院者免費藥劑；其餘自費)	健保給付 (英格蘭地區之二級醫療機構可開藥予疑似季流患者；家庭醫師僅能在DHSC宣布社區流行時始可依相關規定開藥)	健保給付	自費
季流用藥指引建議使用對象	長者、兒童、孕婦、肥胖、具潛在疾病者、機構住民等高風險群	與美國相似	與美國相似	政府未公布治療指南，而是依仿單(定期更新)；醫師可開立處方予門診病患， 不限是否具高風險情形	與美國相似
儲備依據及全人口儲備比例	1. 國家戰略儲備系統(Strategic National Stockpile, SNS) 2. 全國儲備目標為8,100萬人份(約25%)(5,000萬人份聯邦政府、3,100萬人份州政府)(2008)	1. 流感大流行計畫行動框架(New Zealand Influenza Pandemic Plan: A framework for action, NZIPAP)(2017) 2. 全國儲備約60萬人份(約12%)(2021)	1. 流感防治戰略(UK Influenza Preparedness Strategy) 2. 全國儲備3,000-3,300萬人份(約50%)(2009、2023)	1. 流感大流行防治指南(新型インフルエンザ等対策ガイドライン)、医療及び公衆衛生分科会第１回資料(2022) 2. 全國儲備目標為4,500萬人(約36%)份(3,500萬人份政府、1,000萬人份市場流通)，並滾動式調整各類藥劑儲備比例並評估儲備新藥(2022)	1. 新興傳染病暨流感大流行應變整備及邊境檢疫計畫 2. 全國儲備目標為維持全人口數10-15%比例；多元儲備原則

傳染病防治醫療網

域別	應變醫院名稱
北	衛福部桃園醫院-新屋分院

域別	應變醫院名稱
中	衛福部臺中醫院

域別	應變醫院名稱
南	衛福部臺南醫院

域別	應變醫院名稱
臺北	臺北市立聯合醫院和平婦幼院區

域別	應變醫院名稱
東	衛福部花蓮醫院

域別	應變醫院名稱
高屏	高雄市立民生醫院

傳染病指定隔離醫院及應變醫院公告與名單
https://www.cdc.gov.tw/Category/MPage/Hdl9E5pIZIe6ma8HcfAHDw

全國6個網區約140家隔離醫院，其中6家為網區應變醫院。傳染病防治醫療網以收治新型流感個案為主

民眾衛教

- **手部衛生**
  - 勤洗手，用肥皂和水清洗至少20秒，特別是咳嗽或打噴嚏後
  - 不要用手直接碰觸眼睛、鼻子和嘴巴
- **注意呼吸道衛生及咳嗽禮節**
  - 有呼吸道症狀時戴口罩，當口罩沾到口鼻分泌物立即更換
  - 打噴嚏時，應用面紙或手帕遮住口鼻，或用衣袖代替
  - 有呼吸道症狀，與他人交談時，儘可能保持1公尺以上
- **生病時在家休養**
  - 在家中休息至症狀緩解後24小時以上
  - 患者應避免搭乘航機、船舶等交通工具
- **擴大社交距離**
  - 流感流行季期間，減少出入公共場所或人多擁擠地方

流感的診斷、治療與預防

流感的診斷

- 臨床醫師應以患者之**臨床症狀**及**流行病學**依據逕行診斷，搭配年齡、潛在疾病、發病時間、疾病嚴重程度等給予適當處置。
- 即使病患已接種當季流感疫苗，不能因此排除流感診斷的可能。

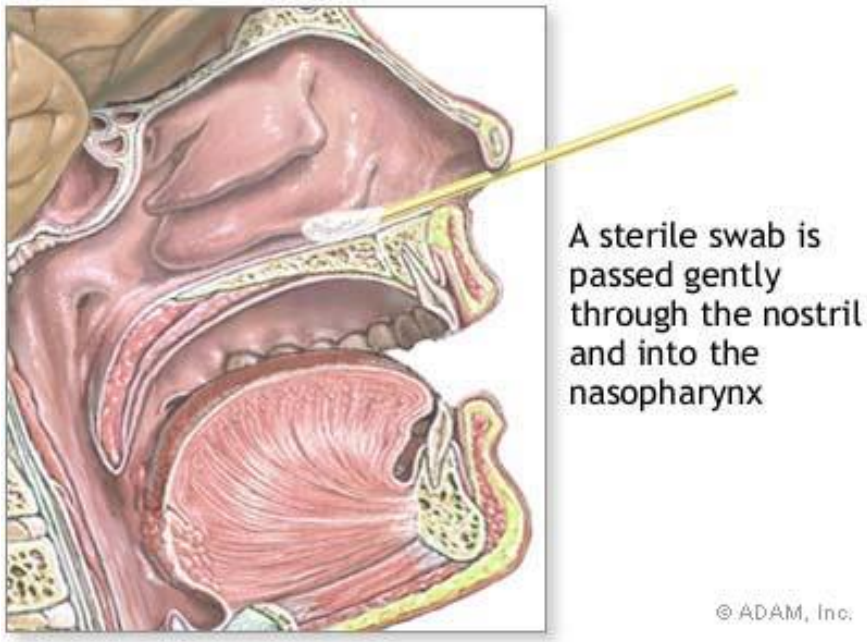
- 是否進行實驗室診斷，需視檢驗結果是否影響臨床處置而定。若臨床與流行病學表現已足夠診斷，便應開始給予治療。

- 快速篩檢鼻咽部流感抗原檢驗的**特異性很高，但敏感性有限**，不建議用快速篩檢結果作為是否給予藥物的唯一依據。

季節性流感防治工作手冊建議：由於採檢時機、技術與檢驗工具敏感性之限制，於流感流行期間，即使快篩結果為陰性，仍不能排除流感，**故不建議單以流感快篩結果，作為診斷及是否用藥之唯一依據**

診斷方式

- **臨床診斷**
  - 症狀
  - 接觸史
  - 群聚史
- **實驗診斷**
  - 快篩(Rapid Influenza Diagnostic Tests)
  - PCR檢驗
  - 病毒培養、免疫螢光染色等



流感快篩(快速抗原檢測)

- 酵素免疫分析法
- 偵測流感病毒的核蛋白（NP）
- 快速檢測A型或B型流感病毒感染
- 敏感性約50-70%，特異性約90-95%
- 國內外感染症學會均建議，不應以快篩結果作為診斷流感的唯一依據
- 發生併發症的高風險族群，建議依照臨床症狀診斷並即時治療

流感的檢測方法

TABLE 2 Influenza virus testing methods

Method	Types detected	Acceptable specimens	Test time	CLIA waived
Viral cell culture (conventional)	A and B[a]	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	3-10 d	No
Rapid cell culture (shell vials; cell mixtures)	A and B[a]	As above	1-3 d	No
Immunofluorescence, direct (DFA) or indirect (IFA) antibody staining	A and B[a]	NP swab or wash, bronchial wash, nasal or endotracheal aspirate	1-4 h	No
RT-PCR[b] (singleplex and multiplex; real-time and other RNA-based) and other molecular assays	A and B[a]	NP swab, throat swab, NP or bronchial wash, nasal or endotracheal aspirate, sputum	Varied (generally 1-6 h)	No[c]
Rapid influenza diagnostic tests[d]	A and B	NP swab (throat swab), nasal wash, nasal aspirate	<30 min	Yes/No

Abbreviations: CLIA, Clinical Laboratory Improved Amendments; DFA, direct immunofluorescence assay; IFA, indirect immunofluorescence assay; NP, nasopharyngeal; RT-PCR, reverse transcriptase polymerase chain reaction.

[a]May be adapted for identification of specific subtypes.

[b]Including FDA-approved test systems, reference laboratory testing using analyte-specific reagents or laboratory-developed reagents.

[c]Random-access, single-cartridge tests may be moderately complex.

[d]Immunochromatographic lateral flow and membrane-based immunoassays.

From Centers for Disease Control and Prevention[32] and Leland DS, et al.[33]

Chaves SS. August 01, 2013

流感的檢測方法的優缺點

Advantages & disadvantages of influenza diagnostic tests

Diagnostic assay	Description	Advantages	Disadvantages
Virus culture	Virus detected by the appearance of cytopathic effect, HA assay or direct fluorescence antibody staining	• High specificity (>95%)[237] • Enables characterization of novel viruses • Enables surveillance of antiviral sensitivity and antigenic drift	• Slow (>3 days) • Requires specialized skills and equipment • Lower sensitivity than RT-PCR
RT-PCR	Primers to conserved genes can be used in combination with those for HA	• High specificity (>99%)[238] • High sensitivity (>99%)[238] • Can be multiplexed[238] • Can be automated in relatively high throughput • Moderately fast (hours) • Can be used to simultaneously type and subtype viruses[239]	• Expensive • More prone to false positive results (by nucleic acid contamination) than virus culture[238]
Rapid antigen test	Immunoassay detection of the presence of viral antigen in the sample	• Fast (15 min) • Low cost • Point of care • Can detect both influenza A and influenza B	• Low sensitivity (70–50%)[240,241] • Prone to false negative results[241] (96% negative predictive value) • Cannot provide subtype information
Rapid molecular assay	Based on isothermal nucleic acid amplification; requires simple heat source and fluorescence detection	• Fast (15 min) • High specificity (>99%)[240] • Good sensitivity (66–100%)[240] • Point of care	Expensive

HA, haemagglutinin; RT-PCR, reverse transcription PCR.

Krammer F. Nature Reviews Disease Primers 2018;4:3

輕症門診病患之治療

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

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

並非所有輕症病患都需要抗病毒藥物治療

住院/重症病患之治療

- 建議**立即給予**抗病毒藥物治療。
- 任何因流感住院病患，不論疫苗接種史或發病時間，建議立即給予抗病毒藥物治療。
- 所有疑似流感住院兒童，均應立即給予抗病毒藥物治療。

住院/重症病患，不需等待確診，不論發病時間，均應立即給予抗病毒藥物治療

預防性投藥

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

並非所有輕症病患都需要抗病毒藥物治療

抗流感病毒藥物的治療與預防性劑量

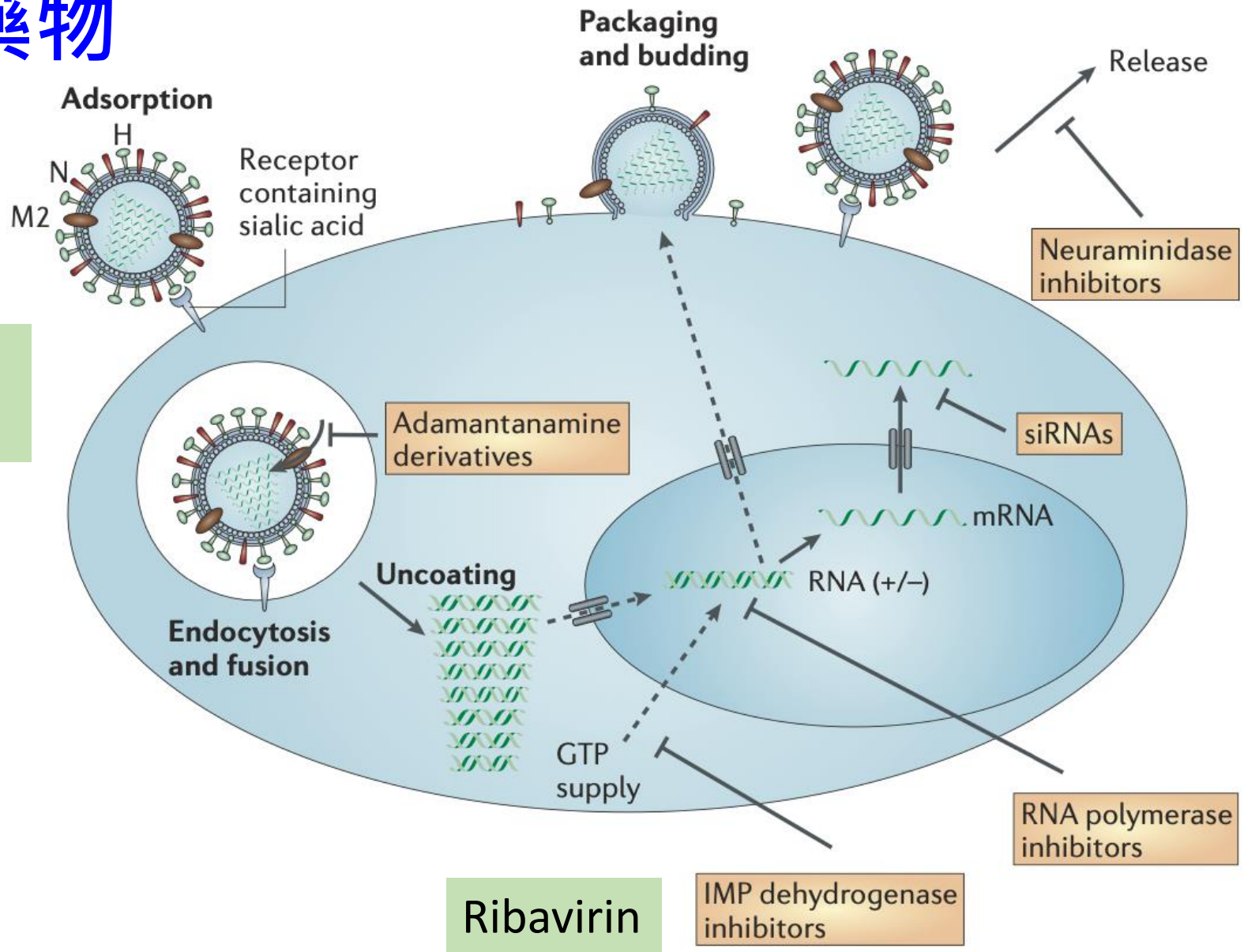
Recommended dosing of oseltamivir & zanamivir for the treatment / Prophylaxis of influenza

Treatment	0–1 months	1–3 months	3–12 months	1–13 years <15 kg	1–13 years 15–23 kg	1–13 years 23–40 kg	1–13 years >40 kg	Adults (13 years and over)
Oseltamivir orally (treatment course = 5 days)	2 mg/kg/dose twice daily	2.5 mg/kg/dose twice daily	3 mg/kg/dose twice daily	30 mg twice daily	45 mg twice daily	60 mg twice daily	75 mg twice daily	75 mg twice daily
Zanamivir inhaled (treatment course = 5 days)	Not licensed for children <5 years			Children >5 years 10 mg twice daily				10 mg twice daily

Treatment	0–1 months	1–3 months	3–12 months	1–13 years <15 kg	1–13 years 15–23 kg	1–13 years 23–40 kg	1–13 years >40 kg	Adults (13 years and over)
Oseltamivir orally (prophylaxis course = 10 days)	2 mg/kg/dose once daily	2.5 mg/kg/dose once daily	3 mg/kg/dose once daily	30 mg once daily	45 mg once daily	60 mg once daily	75 mg once daily	75 mg once daily
Zanamivir inhaled (prophylaxis course = 10 days)	Not license for children <5 years			Children >5 years 10 mg once daily				10 mg once daily

British J Hospital Medicine 2013;74(10):C157~

抗病毒藥物



Amantadine
Rimantadine

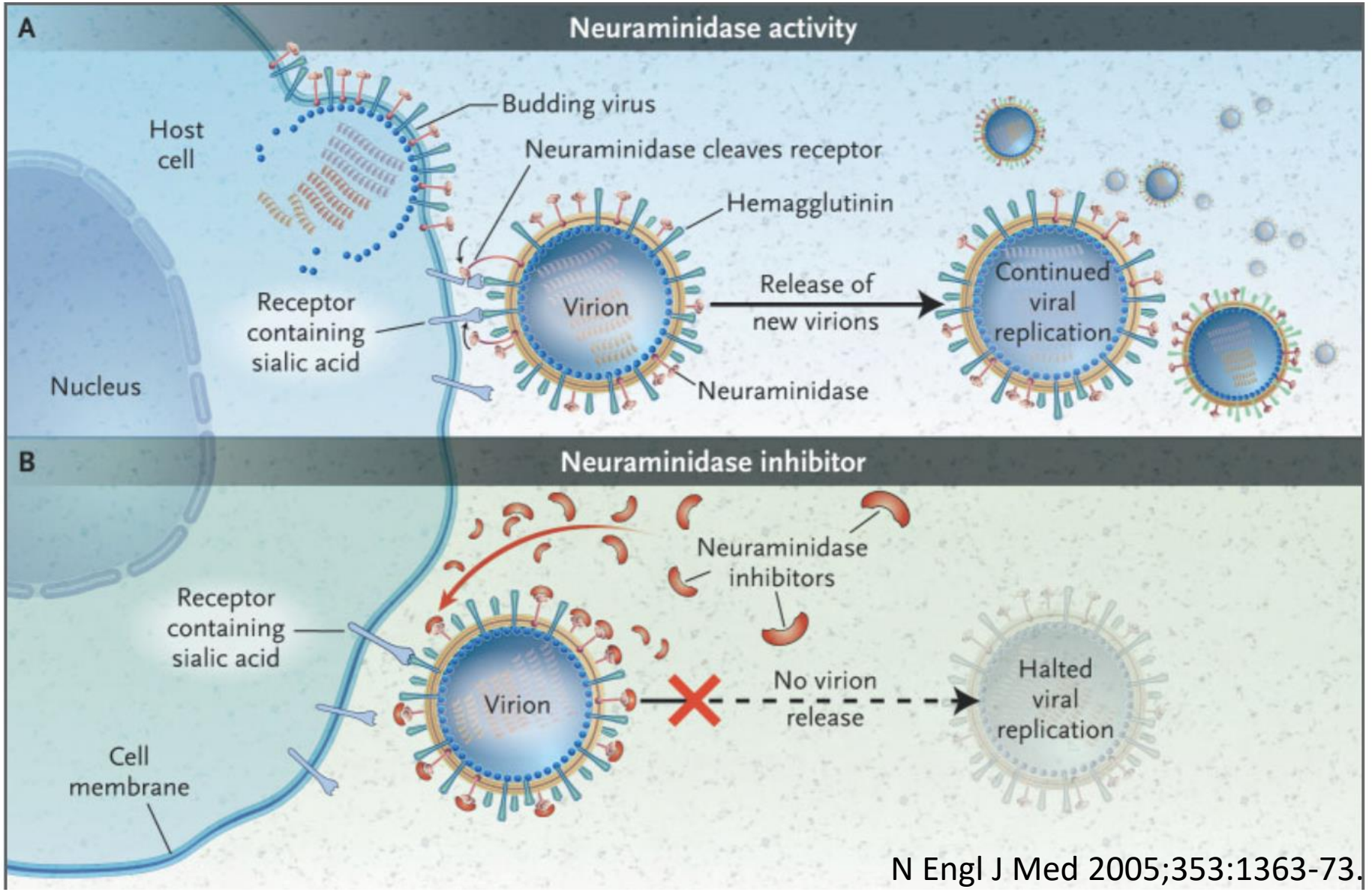
Zanamivir
Oseltamivir
Peramivir

Favipiravir

Ribavirin

De Clercq E. Nat Rev Drug Discov. 2006.

Mechanism of Neuraminidase Inhibitor



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

流感抗病毒藥物種類

- M2 protein inhibitor
  - Amantadine / Rimantadine
  - 因抗藥性問題嚴重，目前已**不適宜**用來治療流感病患
- Neuraminidase inhibitor
  - **Oseltamivir / Zanamivir / Peramivir**
  - **為目前流感抗病毒藥物的主流**
  - 藉由抑制病毒表面之神經胺酸酶，阻止複製完成之病毒自宿主細胞內釋出
  - 可預防疾病、減輕症狀、縮短病程

公費

- RNA polymerase inhibitor
  - **Favipiravir（Avigan）**
  - 干擾 RNA 病毒的複製過程，抑制感染細胞內的病毒基因複製以防止繁殖
  - **用於治療新型流感病毒感染（限於其他抗流感病毒藥物無效或效力不足的情況）**
  - 已取得日本藥證許可
- Polymerase Acidic Endonuclease inhibitor
  - Baloxavir marboxil（ Xofluza® ）
  - 作用於流感病毒複製過程所必需的Cap-snatching mechanism(搶帽機制)，可抑制流感病毒的複製增生，亦可阻斷流感病毒的傳播
  - **已於108年間取得我國藥證許可**

流感抗病毒藥劑種類

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

公費流感抗病毒藥劑使用對象-治療性用藥條件

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

公費流感抗病毒藥劑使用對象-預防性用藥條件

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

公費流感抗病毒藥劑擴大使用對象

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

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

Antiviral resistance of circulating influenza viruses

Influenza virus (strain)	Resistance (% of isolates tested)		
	Adamantanes	Oseltamivir	Zanamivir
Pre-2009 pandemic			
Influenza A (seasonal H1N1)	0.6	98.8[a]	0
Influenza A (H3N2)	100	0	0
Influenza B	N/A	0	0
2015–2016 season			
Influenza A (2009 H1N1)	100	0.8	0
Influenza A (H3N2)	100	0	0
Influenza B	N/A	0	0

Data are from the US Centers for Disease Control and Prevention surveillance for the 2008–2009 and 2015–2016 seasons in the United States. N/A, not applicable. [a]Most seasonal influenza A H1N1 viruses were sensitive to oseltamivir until late 2007.

抗病毒藥物的成效及給予時機

BMJ

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

RESEARCH

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

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

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

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

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

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

Summary

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

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

Lancet Infect Dis 2014; 14: 109–18

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

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

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

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

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

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

Summary

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

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

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

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

Lancet 2015; 385: 1729–37

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

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

See Comment page 1700

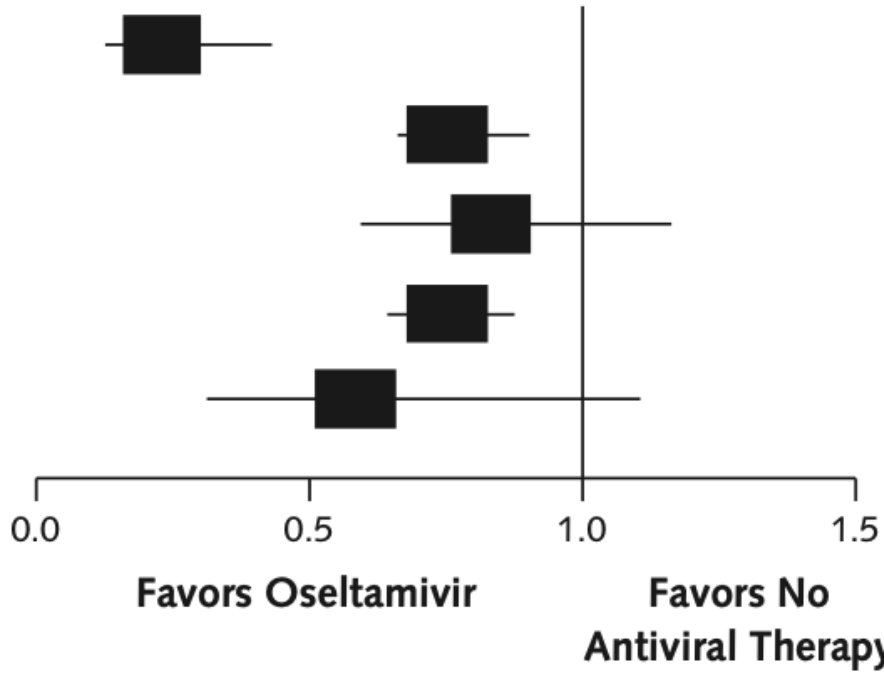
Department of Medical Statistics, London School of

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

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

Efficacy of Oseltamivir

Outcome	Patients (Studies), *n*	Pooled Odds Ratio (95% CI)
Mortality	681 (3)	0.23 (0.13–0.43)
Hospitalization	150 710 (4)	0.75 (0.66–0.89)
Pneumonia	150 466 (3)	0.83 (0.59–1.16)
Otitis media	78 407 (2)	0.75 (0.64–0.87)
Cardiovascular events	100 830 (2)	0.58 (0.31–1.10)



Evidence summary for Oseltamivir

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

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

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

Zanamivir

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

Figure 1. Parts of the DISKHALER

Evidence summary for Zanamivir

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

Zanamivir：uncertain
死亡風險、住院風險、重症插管風險

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

Peramivir

- 何時考慮使用
  - Severe hospitalized patients (ICU with organ failure)
  - Poor response to the other NAIs
    - Poor GI absorption of oral medication
    - Lower respiratory tract infection, difficult to using inhaled anti-viral agents
  - **Avian flu** (H7N9 influenza)
- 通過衛福部藥證，自費使用
- 公費限**新型流感**，經轄區指揮官同意使用

Favipiravir

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

Baloxavir marboxil

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

Use of Ribavirin to Treat Influenza

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

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

Since the late 1980s, clinicians have requested access to intravenous ribavirin from the manufacturer to treat patients with life-threatening

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

N Engl J Med 2009; 361:1713-1714

Combination Therapy

Oseltamivir, amantadine, and ribavirin vs. Oseltamivir

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

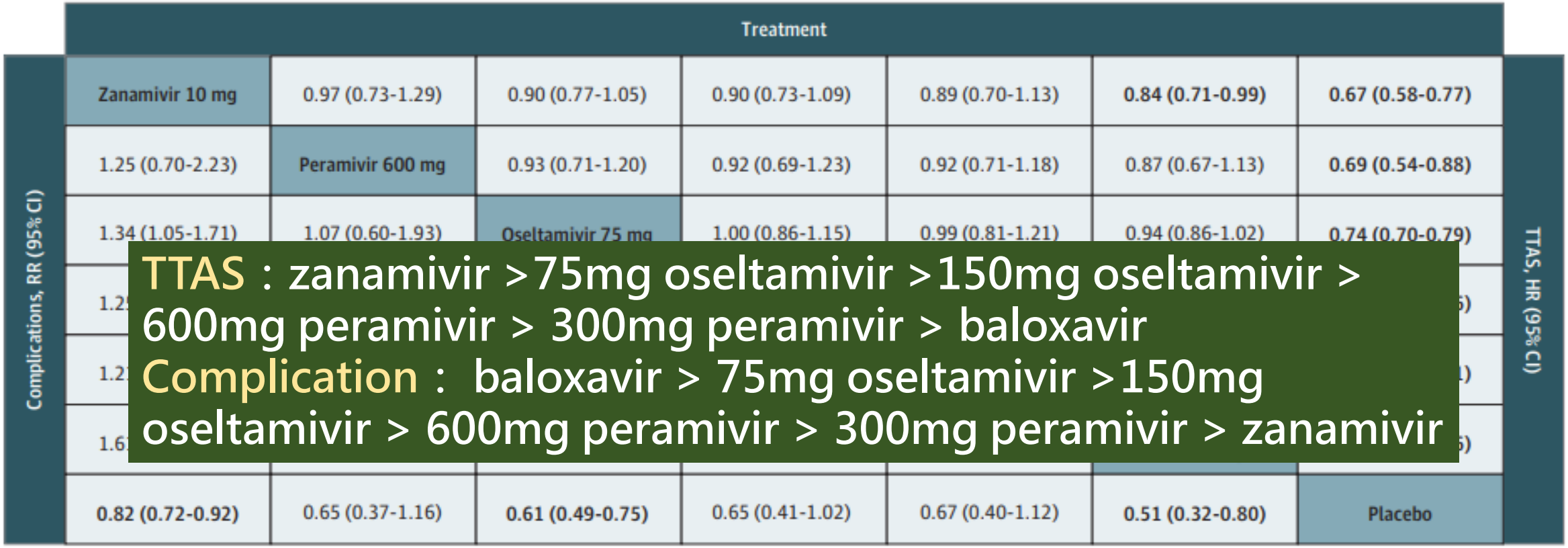
	Total (n=454)	Combination group (n=230)	Monotherapy group (n=224)	p value
Day 0	454	230	224	..
Median viral count, log_{10} copies/mL	6·5 (5·4–7·4)	6·4 (5·6–7·2)	6·7 (5·1–7·7)	..
≥LLOQ	421 (93%)	221 (96%)	200 (89%)	..
≥LOD, < LLOQ	13 (3%)	4 (2%)	9 (4%)	..
<LOD	20 (4%)	5 (2%)	15 (7%)	..
Day 3	437	221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

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

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

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

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



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

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

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

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

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

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

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

抗流感病毒藥物使用建議

台灣感染症醫學會

制定：2018 年 11 月 26 日

第一次修訂：2019 年 11 月 13 日

第二次修訂：2021 年 3 月 30 日

Clinical Infectious Diseases

IDSA GUIDELINE

Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza[a]

Timothy M. Uyeki,[1] Henry H. Bernstein,[2] John S. Bradley,[3,4] Janet A. Englund,[5] Thomas M. File Jr,[6] Alicia M. Fry,[1] Stefan Gravenstein,[7] Frederick G. Hayden,[8] Scott A. Harper,[9] Jon Mark Hirshon,[10] Michael G. Ison,[11] B. Lynn Johnston,[12] Shandra L. Knight,[13] Allison McGeer,[14] Laura E. Riley,[15] Cameron R. Wolfe,[16] Paul E. Alexander,[17,18] and Andrew T. Pavia[19]

兒童流感治療建議

Recommendations for the Use of Anti-influenza Agents in Children

台灣兒童感染症醫學會

國家衛生研究院兒童醫學及健康研究中心

Pediatric Infectious Diseases Society of Taiwan

Child Health Research Center, National Health Research Institutes

流感的預防

流感的預防

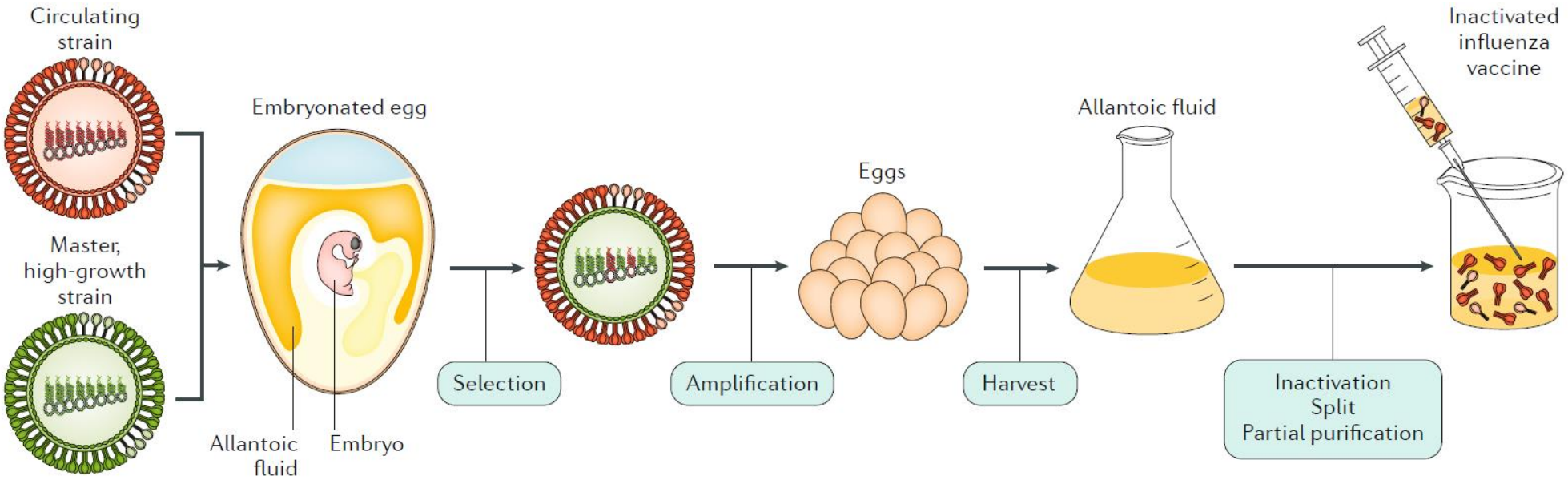
- 接種**疫苗**
  - 預防流感最有效的方式
- 暴露後預防藥物
  - 特殊高風險族群、群聚事件
- 感染管制措施
  - 醫療機構、長期照顧機構、人口密集機構
- 個人衛生
  - 咳嗽禮節、手部衛生、戴口罩

現行流感疫苗種類

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

傳統雞胚流感疫苗(不活化)的製作流程

Inactivated influenza A virus vaccine manufacture

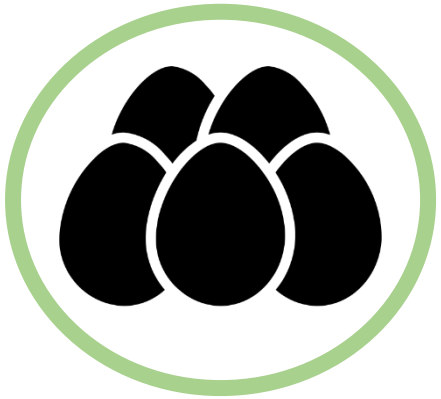


high- growth influenza A/Puerto Rico/8/1934 (PR8) virus strain

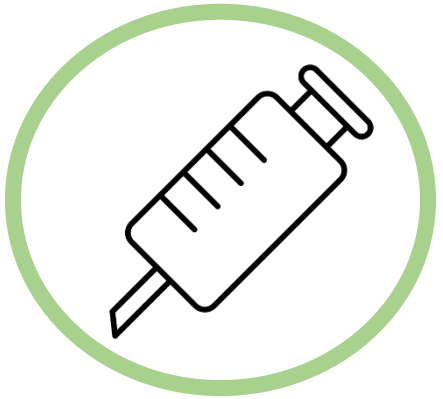
5 WHO Collaborating Centres for Reference & Research on Influenza, which are located in
1.the United States
2.the United Kingdom
3.Australia
4.Japan
5.China

Krammer F. Nature Reviews Disease Primers 2018;4:3

細胞培養疫苗的優點



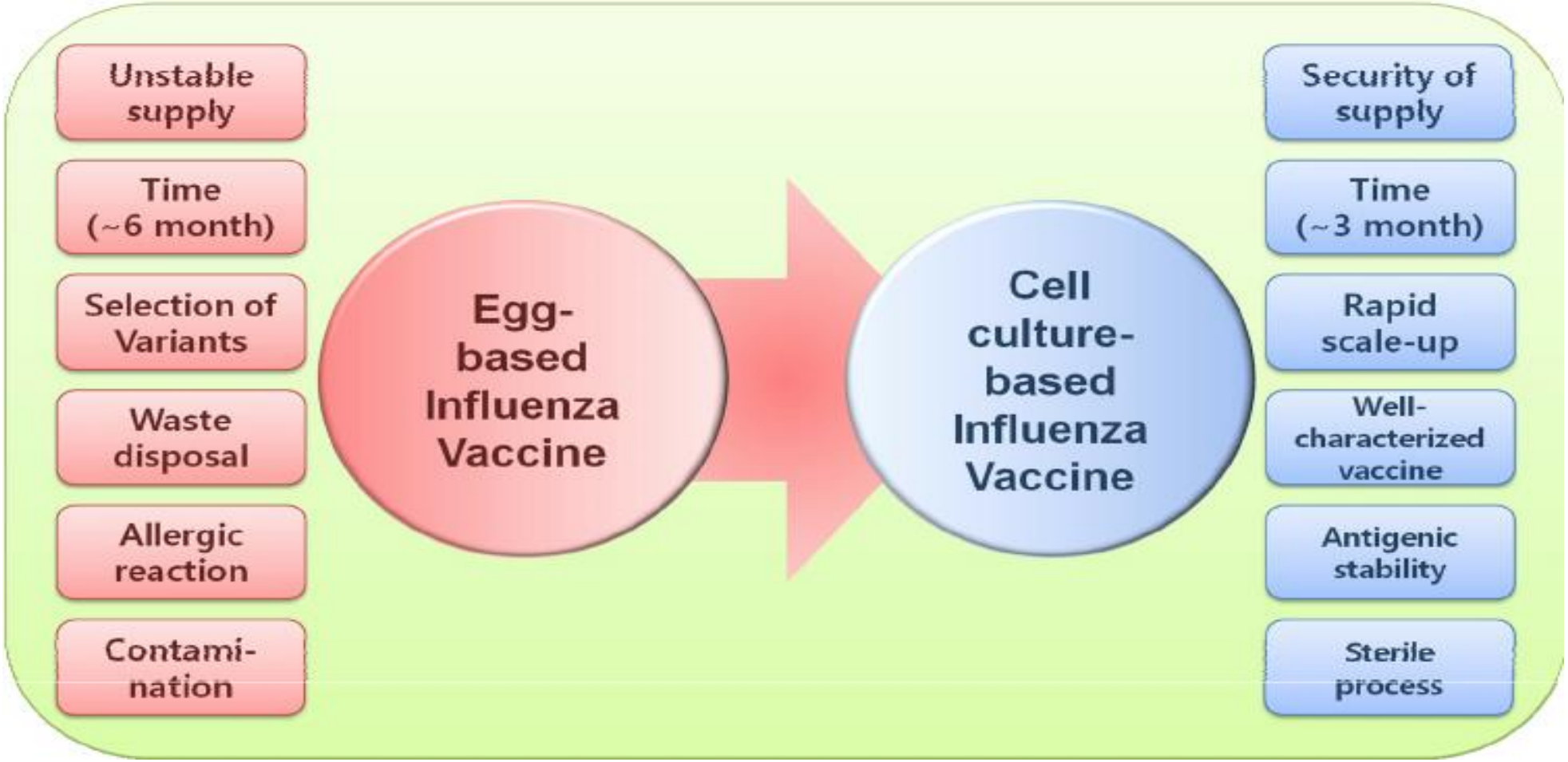
Supply of eggs
Egg allergies



Haemagglutinin proteins mutation
H3N2

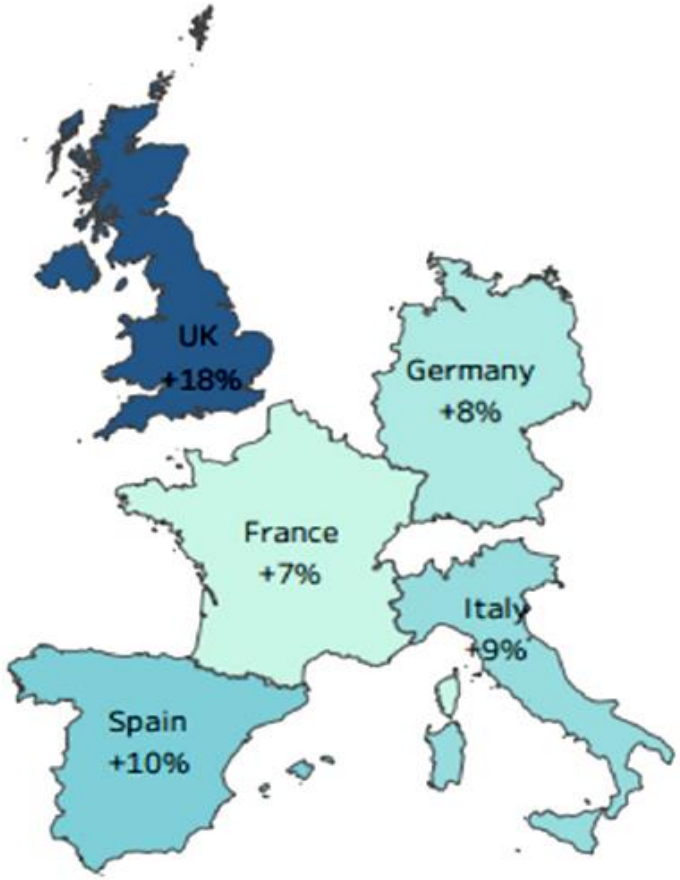
1. ESMO Open. 2019;4(1):e000481
2. Vaccines. 2018;6(19):E19
3. NPJ Vaccines.2018;3:44

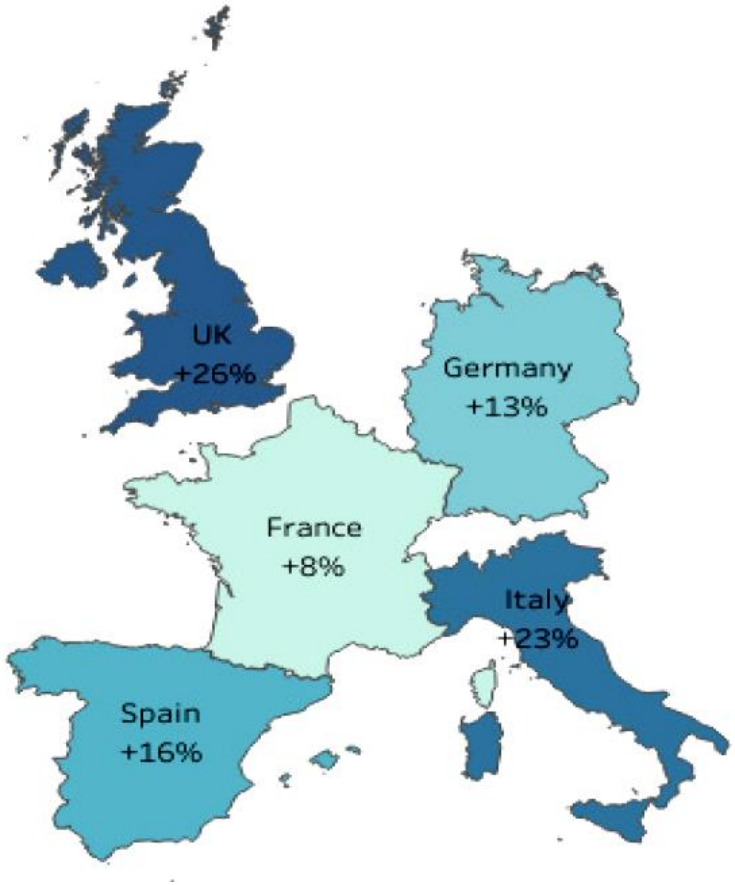
細胞培養比雞蛋培養流感疫苗的優點



J Bacteriology and Virology March 2013;43(1):9 DOI: 10.4167/jbv.2013.43.1.9

Mean estimates of the increase in IVE in the absence of egg adaptations



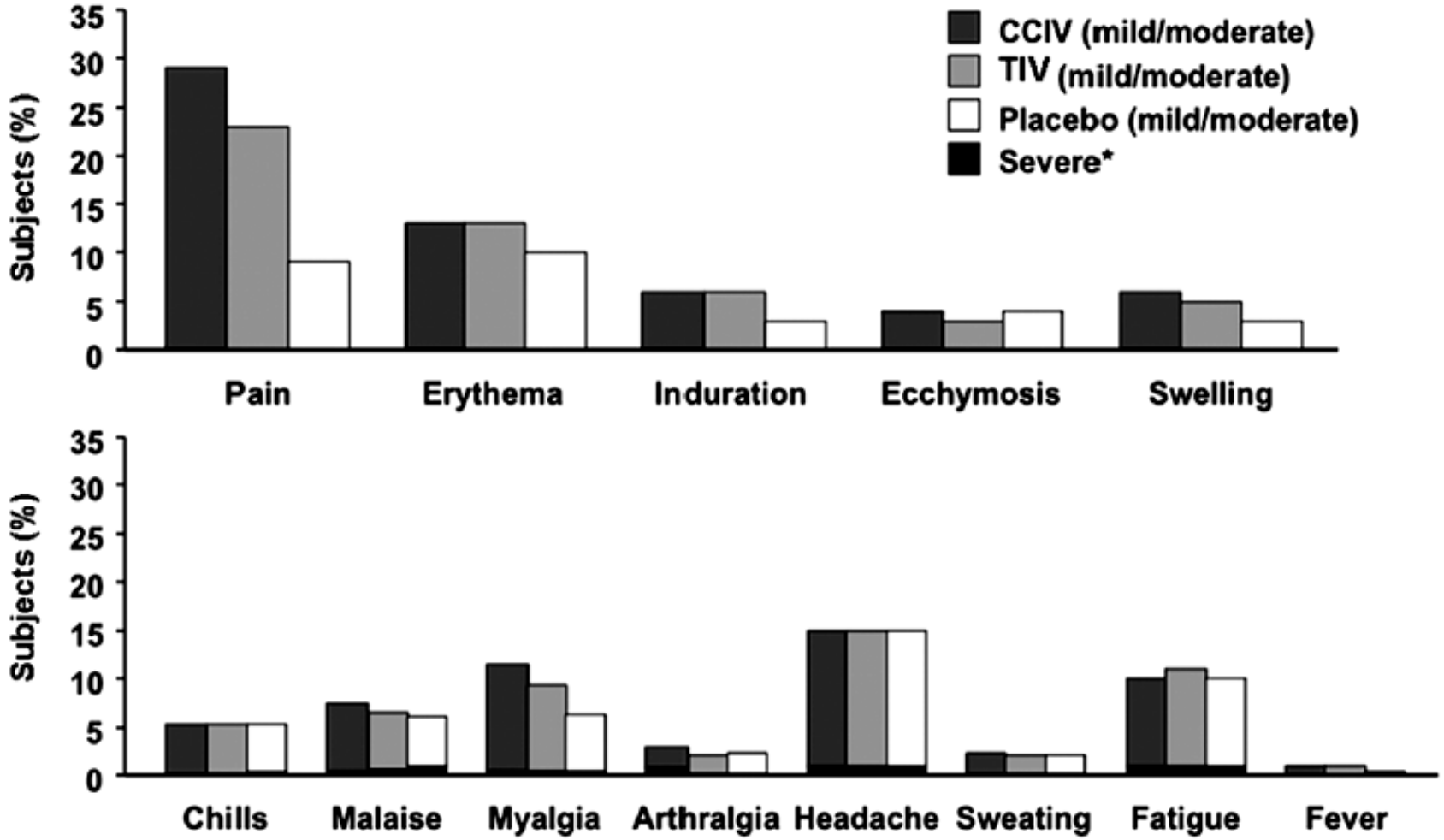


For **all strains** per country (TIV & QIV only) for **A (H3N2)** per country (TIV & QIV only)

Lejarazu-Leonardo RO. Vaccines 2021;9:1255. https://doi.org/10.3390/vaccines9111255

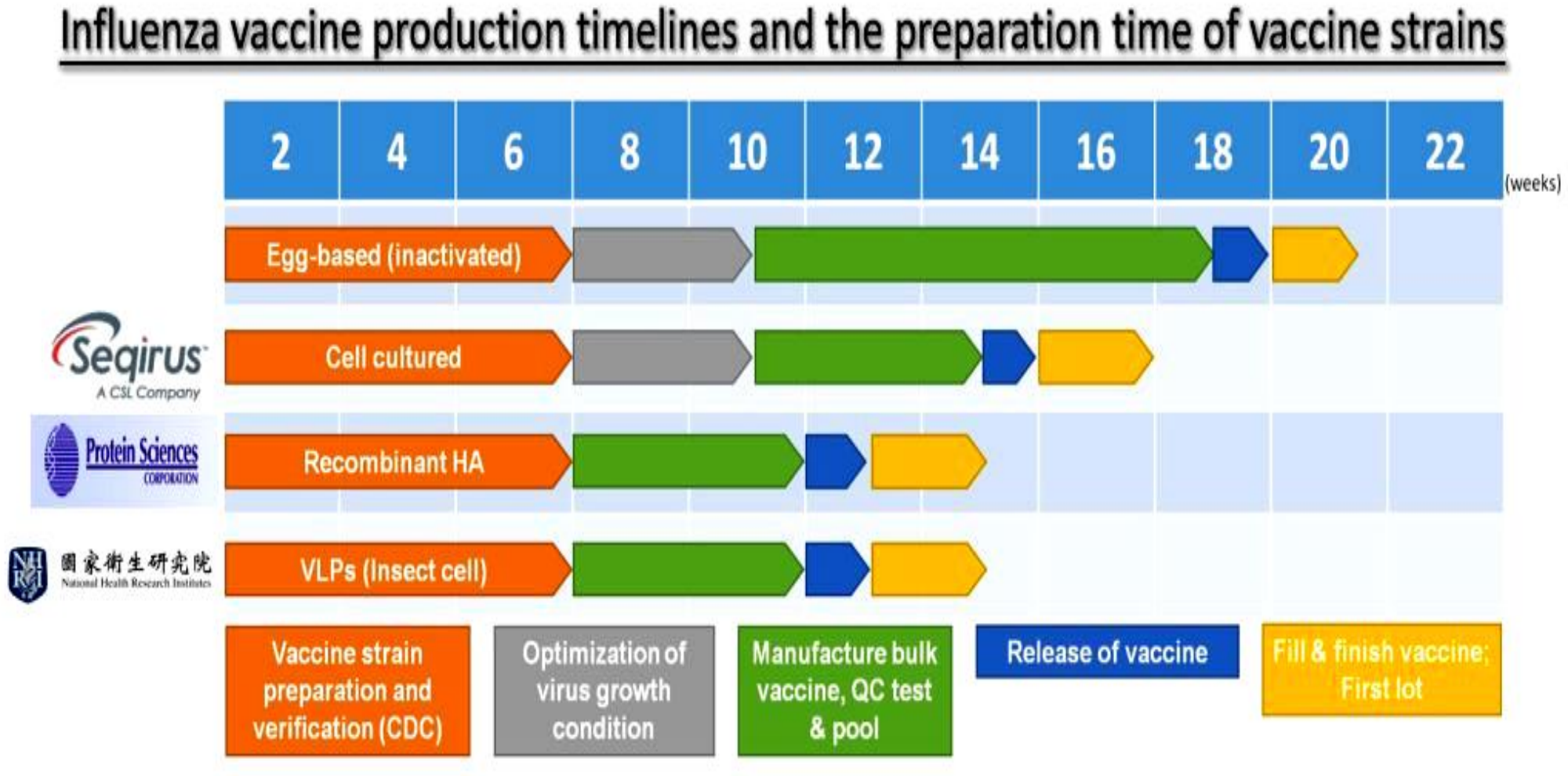
細胞型流感疫苗與雞胚型流感疫苗接種反應比較(7天)

Solicited local and systemic reactions in the 7 days after vaccination



Frey S. Clin Infect Dis 2010;51:997~1004.

流感疫苗製作的差異與時程



https://www.futuretech.org.tw/futuretech/index.php?action=product_detail&prod_no=P0008700002331&web_lang=en-us

英國不同年齡流感疫苗施打建議

Age Group	Recommended vaccine	Live vaccine	If the preferred vaccine is not available
6m-2yrs	QIVc	No	QIVe
2yrs-17yrs	LAIV	Yes	QIVc
18-64 yrs	QIVc QIVr	No	QIVe
>65yrs	aQIV QIVr	No	QIVc

Flu vaccine (inactivated) | Vaccine Knowledge Project (ox.ac.uk)

美國流感疫苗種類與特性比較

Comparative characteristics of selected seasonal influenza vaccines

	Egg-based inactivated virus vaccine 雞蛋培養流感疫苗	Cell-based inactivated virus vaccine 細胞培養流感疫苗	Recombinant HA vaccine 基因重組流感疫苗
Immunogen production 抗原製造方法	Influenza virions produced in eggs or cell cultures are purified, lysed with detergent to release hemagglutinin (HA) and neuraminidase (NA) oligomers, which form "rosettes"		Insect cells are lysed with detergent to release HA oligomers, which form "rosettes". Does not contain NA
Required seeds 疫苗病毒株	Candidate vaccine virus (CVV) "seed" must be produced – typically several weeks; possibly very few suitable CVV's become available	Candidate vaccine virus (CVV) "seed" must be produced – typically several weeks; generally several suitable CVV's become available	Recombinant vaccine virus "seed" must be produced – typically several weeks; do not need CVV, just HA sequence
Mutation risk 抗原突變風險	Propagation of CVV in eggs selects mutations that decrease antigenic relatedness to native virus and may impact vaccine effectiveness	Production of CVV in mammalian cells minimizes risk of mutation and potential impact on vaccine effectiveness	Product made from stable (cell isolate) gene sequence, negligible mutation risk, but glycosylation may vary depending on host cells
Immunogen yields 抗原產量	Variable depending on virus strain – often improved by further passaging or reassorting CVV (with increased risk of further mutations)	Variable depending on virus strain – may be improved by further passaging or reassorting CVV	Consistent productivity independent of virus strain, additional optimization of process possible
Vaccine manufacture cost 價格	Low – eggs are a relatively inexpensive production platform	Greater than egg-based – improvement may be possible with process optimization and larger production scale	
Current US-licensed manufacturers	GSK Sanofi Pasteur Seqirus	Seqirus	Protein Sciences Corp. (now Sanofi Pasteur)
Current share of US market 美國市佔率	85–90%	10–15%	1–2%

[a]Based on influenza vaccines licensed for use in the United States

https://www.mercurynews.com/2013/02/08/scientists-seek-a-better-longer-lasting-and-more-effective-flu-vaccine/

流感疫苗

- 不活化疫苗
- 四價疫苗
- 6個月以上均接種0.5mL
- 接種劑量與間隔
  - 8歲（含）以下首次接種2 劑，且間隔至少4週
  - 國小學童集中接種，全面施打1劑，若仍自覺需要，至醫療院所自費接種第2劑

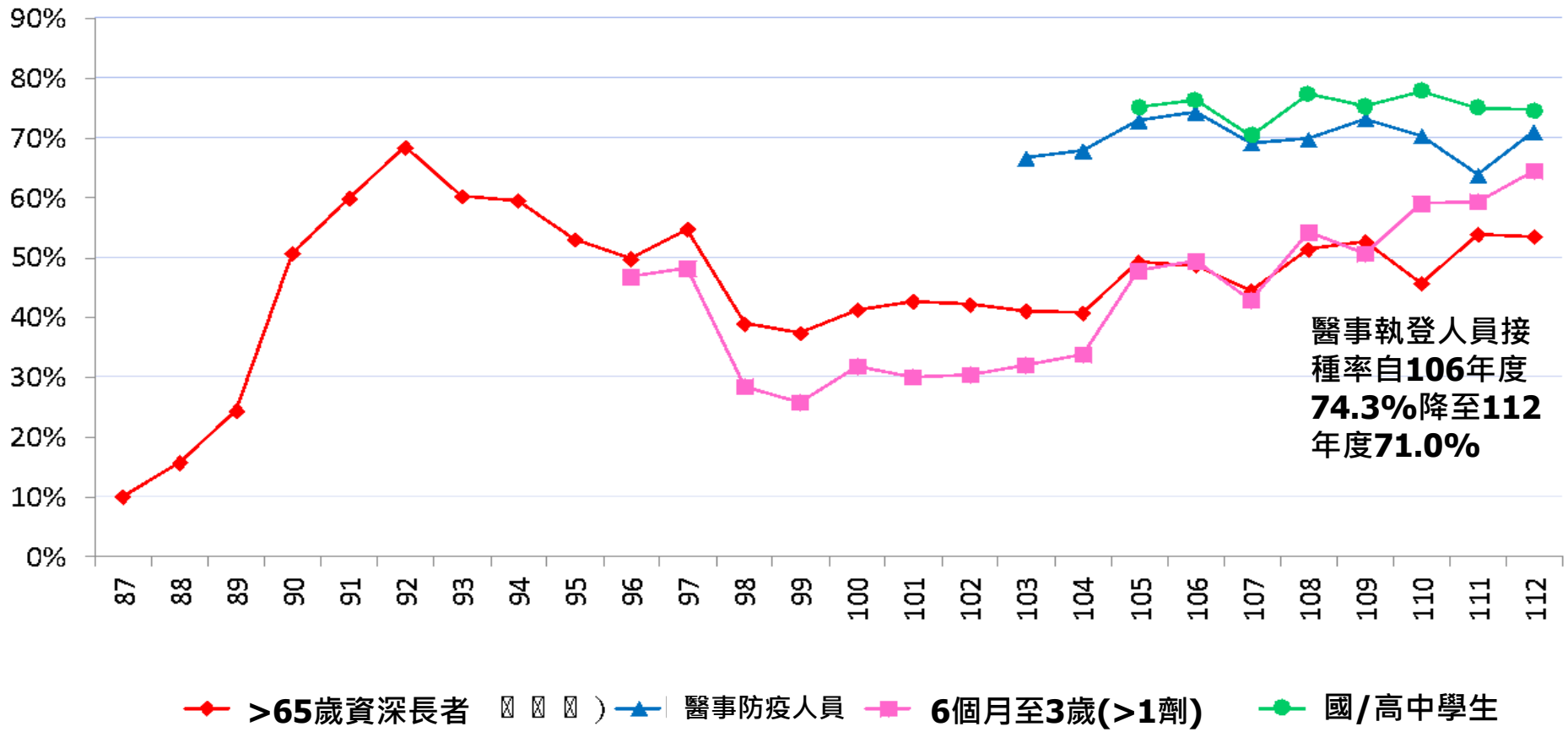
114年度現行公費流感疫苗接種對象與順序

階段順序	公費接種對象
第一階段	◻ 醫事及衛生防疫(含法醫師)相關人員。 ◻ 65歲以上者。 ◻ 55歲以上原住民。 ◻ 安養、長期照顧(服務)等機構之受照顧者及其所屬工作人員。 ◻ 滿6個月以上至國小入學前幼兒。 ◻ 孕婦。 ◻ 具有潛在疾病者，包括(19-64歲)高風險慢性病人、BMI≧30者、罕見疾病患者及重大傷病患者。 ◻ 6個月內嬰兒之父母。 ◻ 幼兒園托育人員、托育機構專業人員及居家托育人員(保母)。 ◻ 國小、國中、高中、高職、五專一至三年級學生。 ◻ 禽畜相關及動物防疫相關人員。
第二階段	50至64歲無高風險慢性病成人。

114年度台灣現行流感疫苗

廠牌	賽諾菲	國光	臺灣東洋	GSK葛蘭素	台灣東洋	高端	阿斯特捷利康
名稱	巴斯德 Vaxigrip	安定伏 AdimFlu-S	輔流威適 FLUCELVAC	伏適流 Fluarix	Fluad	高端流感 疫苗	能伏鼻 FluMist
製造產地	法國	台灣	德國	德國	英國	韓國	美國
培養方式	雞蛋胚胎	雞蛋胚胎	MDCK細胞培養	雞蛋胚胎	雞蛋胚胎	雞蛋胚胎	雞蛋胚胎
價數	3價	3價	3價	3價	3價	3價	3價
施打對象	6個月以上	>3歲	6個月以上	6個月以上	>65歲成人	>3歲	2-18歲
公費/自費	公費/自費	公費/自費	公費/自費	公費/自費	自費	公費/自費	自費

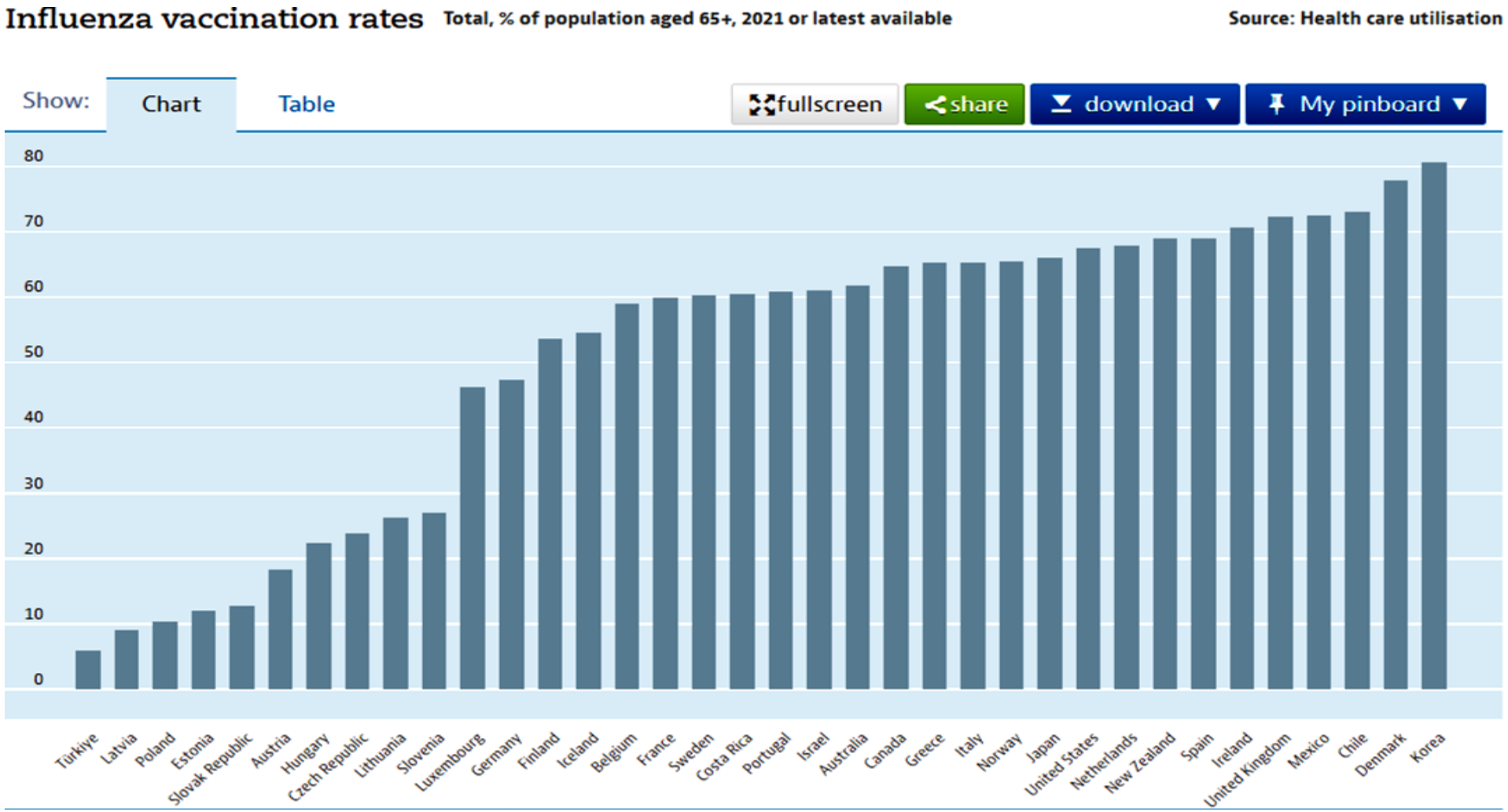
歷年各類對象流感疫苗接種率



註1：流感季定義：每年10月1日至隔年9月30日期間。
註2：112年度資料截至113/6/17。
註3：103年起改以執業登記人數為分母統計接種率。

資深長者流感疫苗涵蓋率 (OECD)

Flu vaccination rates OECD countries



https://data.oecd.org/healthcare/influenza-vaccination-rates.htm

感染流感與不同製程流感疫苗的免疫反應

Antibody responses induced by natural influenza virus infection and vaccination

	自然感染	鼻噴減毒疫苗		裂解/次單元疫苗	HA基因重組疫苗
Antibody response type	Natural influenza virus infection	LAIV	Whole inactivated virus vaccine 全細胞不活化疫苗	Split virus or subunit vaccine	Recombinant HA-based vaccine
Serum antibody response 血清抗體反應	Strong	Moderate induction in children	Strong	Strong ✔	Strong ✔
Mucosal antibody response 黏膜抗體反應	Strong	Moderate induction in children ✔	Weak or none	Weak or none	Weak or none
HA-specific response	Strong	Moderate	Strong	Strong ✔	Strong ✔
NA-specific response	Strong	Weak	Moderate	Weak	None
Antibodies to M2	Detectable	Unclear	Unclear; probably none	Unclear; probably none	None
Antibodies to internal proteins	Detectable	Unclear	Detectable	Detectable	None
Longevity 抗體保護持久性	Very long-lived or lifelong	Moderate ✔	Most likely short	Short	Short
Breadth 保護廣泛性	Moderate	Some breadth ✔	Narrow	Narrow	Some breadth

HA, haemagglutinin; LAIV, live-attenuated influenza virus vaccine; M2, influenza A virus ion channel; NA, neuraminidase.

Krammer F. Nature Reviews Immunology 2019;19:383–97.

哪一種流感疫苗保護力比較好?

- 不同劑型流感疫苗保護力或有不同，可能受流型株與病毒株抗原吻合度、抗原含量、佐劑使用與否與接種者本身免疫力影響
- 已核准使用的流感疫苗，均有實證支持其對預防罹病、重症與死亡的效果與安全性
- 分眾接種策略或可讓不同族群都獲得最佳的保護力，但最重要的還是提升接種率

疫苗種類	和雞蛋培養疫苗較之相對保護力(18 歲以上成人)	
	實驗室確診流感感染	實驗室確診流感住院
含佐劑疫苗(MF 59)	無差異(-30~88)	59.2(14.6~80.5)
高劑量疫苗	24(11~36)	27(-1~48)
細胞培養疫苗	無差異(-5.8~21.4)	無差異(-75.9~52.3)
重組疫苗	30 (10~47)	無資料

https://www.ecdc.europa.eu/en/publications-data/systematic-review-update-efficacy-effectiveness-and-safety-newer-and-enhanced

2025-2026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/Croatia/10136RV/2023 (H3N2)-like virus
- B/Austria/1359417/2021 (B/Victoria lineage)-like virus

➢ 細胞培養或重組疫苗

- A/Wisconsin/67/2022 (H1N1)pdm09-like virus
- A/District of Columbia/27/2023 (H3N2)-like virus
- B/Austria/1359417/2021 (B/Victoria 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

WHO近期對B/Yamagata病毒株抗原成分自流感疫苗移除建議之因應

- **自2020 年3 月以來， WHO 未檢測到有自然發生的B/Yamagata 株， 評估B/Yamagata 病毒已不再於人群中傳播，所造成之公衛威脅大幅下降。**
- 製造和使用含有B/Yamagata病毒株的活性與非活性流感疫苗，理論上有風險導致該病毒株重新在人群流行，而將B/Yamagata病毒株移除，可去除此風險。
- 因此，WHO流感疫苗病毒株組成諮詢委員會認為，在流感疫苗中不再需要包含B/Yamagata病毒株的抗原，建議儘速自疫苗組成中移除。
- 各國主管機關應評估是否使用TIV/QIV及其相對效益。
- **藥政單位監管挑戰：**
  - ✓在不同地區，恢復到三價配方的藥政單位監管過程存在差異
  - ✓在美國，所有四價疫苗的製造商最初都獲得了生產三價疫苗的許可
  - ✓儘管目前有些三價疫苗仍然獲得許可，但目前處於「停產」狀態
- **製造挑戰：**國際上大多數流感疫苗製程已變更為QIV適用，但各製造廠變更幅度與內容可能不同
- **B/Yamagata 病毒再度出現的風險：**
  - ✓目前的監測系統足以監控B/Yamagata病毒株是否再次出現
  - ✓保留QIV許可證將有助於提供適當的疫苗應變

為什麼要每年打?

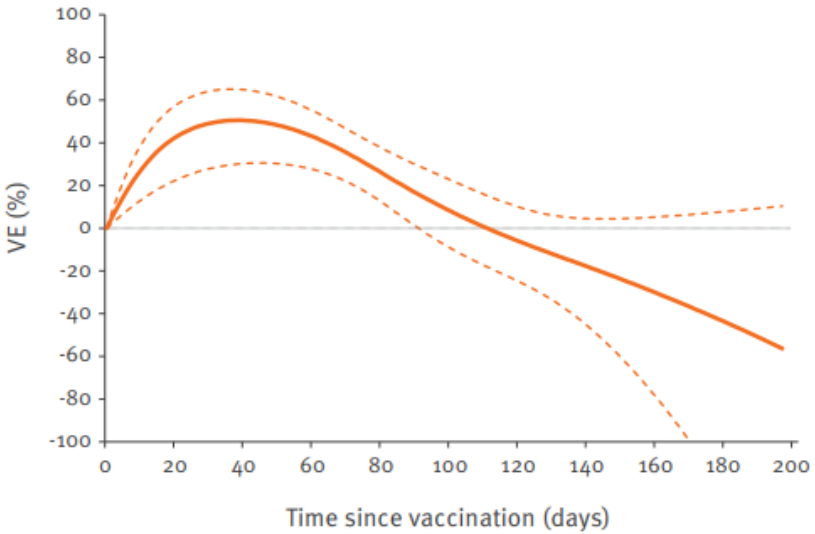
接種後疫苗保護力每月約下降7.5-10%，且65歲以上長者下降較快

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

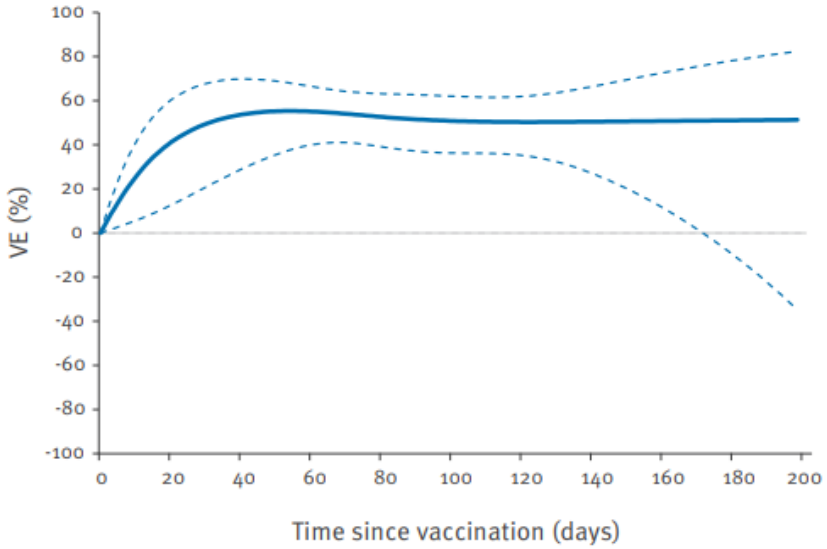
Influenza Type/Subtype	Influenza Seasons Included	No. of Cases/Controls	Estimated VE Decline per Month, Absolute % (95% CI)	*P* Value[a]
Influenza A(H3N2)[b]				
Aged ≥18 y	2016–2017, 2017–2018	754/2262	7.5 (.3–16.3)	.05
Aged ≥65 y	2016–2017, 2017–2018	395/1185	10.8 (2.6–23.8)	.02
Influenza A(H1N1)pdm09[c]				
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

Clinical Infectious Diseases 2021;73(4):726–9

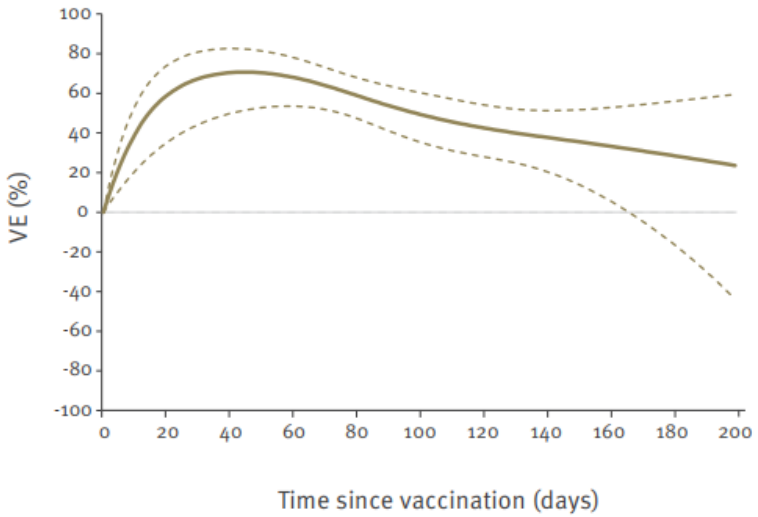
疫苗保護力可以持續多久?



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.

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

流感疫苗的有效性

Vaccine Efficacy 效力 / Effectiveness 有效性

Efficacy

(1 - relative risk) x 100

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

Effectiveness

1 – adjusted odds ratio [aOR] × 100

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

Drugs (2019) 79:1337–1348

Vaccine Effectiveness: How Well Do the Flu Vaccines Work?

Questions & Answers

疫苗株與當季流行病毒株吻合時，流感疫苗降低疾病的風險只有40-60%

Español | Other Languages

How effective is the flu vaccine?

CDC conducts studies each year to determine how well the influenza (flu) vaccine protects against flu illness. While vaccine effectiveness (VE) can vary, recent studies show that flu vaccination reduces the risk of flu illness by between 40% and 60% among the overall population during seasons when most circulating flu viruses are well-matched to the flu vaccine. In general, current flu vaccines tend to work better against influenza B and influenza A(H1N1) viruses and offer lower protection against influenza A(H3N2) viruses. See "Does flu vaccine effectiveness vary by type or subtype?" and "Why is flu vaccine typically less effective against influenza A H3N2 viruses?" for more information.

FLU vaccine effectiveness varies by type or subtype

Pooled VE for all study participants irrespective of age.

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

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

Vaccine 39 (2021) 1225–1240

流感疫苗的保護效果

Pooled VE for all study participants irrespective of age.

Influenza type/subtypes and analyzed subgroups	No. of studies	Pooled VE for all seasons (95% CI)	I-squared statistic (%)	Publication bias (Egger's test p-value)
A(H1N1)pdm09				
Northern hemisphere	39	56 (51–60)	46.4	0.03
Southern hemisphere	11	64 (53–72)	0.0	0.54
Africa	1	44 (-63–81)	NA	NA
Asia	3	67 (37–83)	54.2	NA
Europe	22	51 (44–56)	0.0	0.66
North America	14	60 (53–66)	71.9	
Oceania	10	65 (54–73)	0.0	
Antigenically similar vaccine	45	57 (53–61)	44.9	
Antigenically partially similar vaccine	5	42 (-4–68)	0.0	
Antigenically dissimilar vaccine	0	–	–	
A(H3N2)				
Northern hemisphere	38	22 (15–29)	66.9	
Southern hemisphere	11	42 (31–51)	0.0	
Africa	1	82 (−24 to 97)	NA	
Asia	4	1 (−33–27)	34.8	
Europe	19	16 (3–27)	45.6	
North America	15	29 (20–36)	77.4	
Oceania	10	41 (30–50)	0.0	
Antigenically similar vaccine	24	36 (31–41)	18.9	
Antigenically partially similar vaccine	11	22 (14–30)	27.2	
Antigenically dissimilar vaccine	14	1 (−15 to 14)	46.8	
Influenza B				
Northern hemisphere	36	42 (34–49)	71.3	
Southern hemisphere	10	56 (45–64)	2.6	0.70
Africa	1	32 (−217–85)	NA	NA
Asia	4	18 (-49–54)	88.1	NA
Europe	19	40 (29–50)	50.3	0.27
North America	13	51 (46–55)	20.2	0.46
Oceania	9	56 (44–65)	10.4	NA
Antigenically similar vaccine	27	51 (47–55)	25.2	0.66
Antigenically partially similar vaccine	10	39 (20–54)	39.2	0.23
Antigenically dissimilar vaccine	9	20 (−9 to 41)	73.1	N/A
All influenza				
Northern hemisphere	58	37 (32–42)	79.8	0.92
Southern hemisphere	18	54 (48–59)	0.0	0.11
Africa	5	62 (38–77)	39.4	N/A
Asia	7	23 (−8 to 45)	83.4	N/A
Europe	34	34 (25–42)	65.7	0.42
North America	17	45 (39–50)	86.0	0.05
Oceania	13	53 (47–58)	0.0	0.19
Antigenically similar vaccine	46	49 (45–53)	61.5	0.01
Antigenically partially similar vaccine	26	27 (20–34)	43.4	0.53
Antigenically dissimilar vaccine	4	−9 (-28–8)	30.4	N/A

VE = vaccine effectiveness; NA = not applicable.

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

Vaccine 39 (2021) 1225–1240

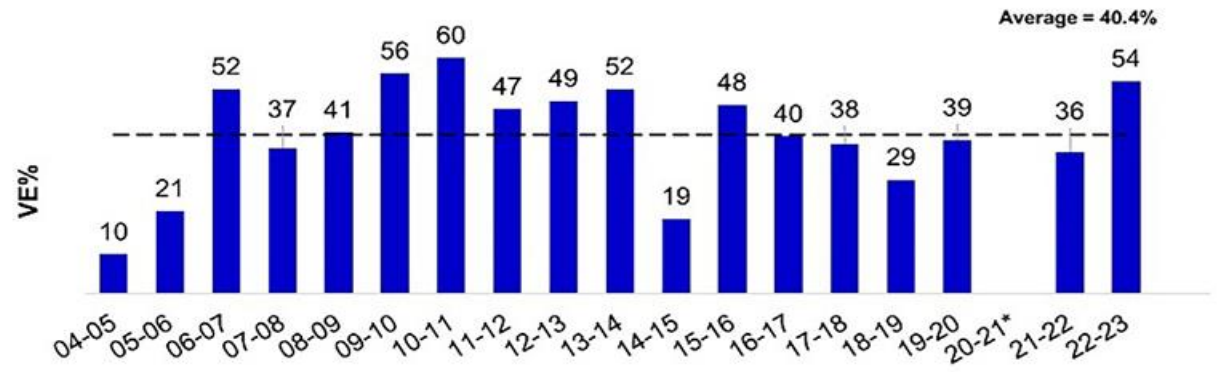
Match and Mismatch Between the Vaccine and Circulating Strains of Influenza B Viruses

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

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

美國季節流感疫苗的有效性

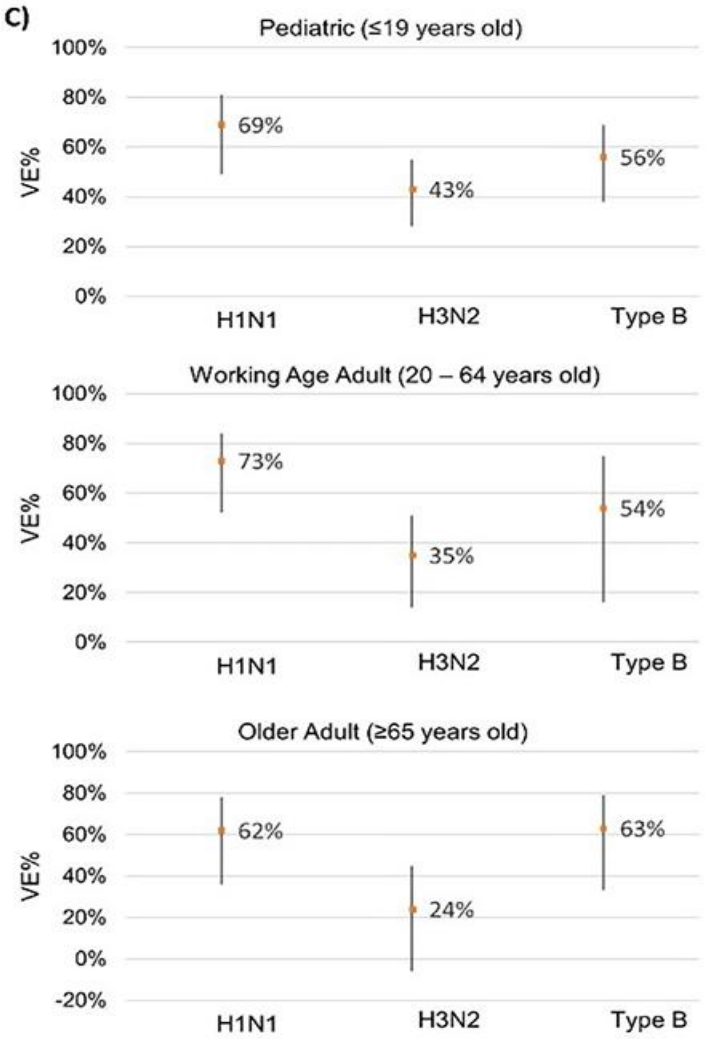
A)



B)

	'11 - '12	'12 - '13	'13 - '14	'14 - '15	'15 - '16	'16 - '17	'17 - '18	'18 - '19	'19 - '20
6 mo – 8 yr	45%	57%	45%	25%	51%	57%	68%	48%	39%
9 -17 yr	58%	39%	53%	25%	59%	36%	32%	7%	43%
18-49 yr	44%	39%	54%	7%	52%	19%	33%	25%	45%
50-64 yr	54%	65%	59%	20%	26%	40%	30%	14%	44%
≥65 yr	43%	26%	50%	32%	42%	20%	17%	12%	34%
VE% Across all ages	47%	49%	52%	19%	48%	40%	38%	29%	45%

C)



Drug Discovery Today 2024;29(9):1~17

2019–20 Seasonal Influenza Vaccine Effectiveness — United States,

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

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

* Vaccine effectiveness was estimated as 100% x (1 – odds ratio [ratio of odds of being vaccinated among outpatients with CDC's real-time RT-PCR influenza-positive test results to the odds of being vaccinated among outpatients with influenza-negative test results]); odds ratios were estimated using logistic regression.

† Adjusted for study site, age group, sex, race/ethnicity, self-rated general health, number of days from illness onset to enrollment, and month of illness using logistic regression.

2019-2020年美國流感季流感疫苗效果45%，接種流感疫苗可降低快5成流感就醫風險。
在6個月以上至17歲族群中保護力最好(>50%)。

The Journal of Infectious Diseases

MAJOR ARTICLE

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

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

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

Results. A total of 3116 participants were included, inclu seven percent (n = 2079) received vaccination. Overall adju 27%–52%). VE against A(H1N1)pdm09 viruses was 40% (95 A(H1N1)pdm09 subgroups (representing 90% of sequenced H1N1 viruses), VE against one group (5A + 187A,189E) was 59% (95% CI, 34%–75%) whereas no VE was observed against the other group (5A + 156K) (–1% [95% CI, –61% to 37%]).

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

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

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

Clinical Infectious Diseases

MAJOR ARTICLE

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

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

Methods. We conducted a test-negative study in an intensive care unit (ICU) netw
influenza-associated severe acute respiratory infection (SARI) during the 2019–202
drifted A/H1N1 and B-lineage viruses. Cases were adults hospitalized in the ICU an
spectrum of severity) with laboratory-confirmed, influenza-associated SARI. Test-n
hospital, timing of admission, and care location (ICU vs non-ICU). Estimates were adjusted for age, comorbidities, and other confounders.

Results. Among 638 patients, the median (interquartile) age was 57 (44–68) years; 286 (44.8%) patients were treated in the ICU and 42 (6.6%) died during hospitalization. Forty-five percent of cases and 61% of controls were vaccinated, which resulted in an overall VE of 32% (95% CI: 2–53%), including 28% (−9% to 52%) against influenza A and 52% (13–74%) against influenza B. VE was higher in adults 18–49 years old (62%; 95% CI: 27–81%) than those aged 50–64 years (20%; −48% to 57%) and ≥65 years old (−3%; 95% CI: −97% to 46%) (P = .0789 for interaction). VE was significantly higher against influenza-associated death (80%; 95% CI: 4–96%) than nonfatal influenza illness.

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

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

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

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
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Interim Estimates of 2022–23 Seasonal Influenza Vaccine Effectiveness — Wisconsin, October 2022–February 2023

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TABLE 2. Estimated 2022–23 influenza vaccine effectiveness* — Wisconsin, October 2022–February 2023

	Test-negative case-control study, persons aged 6 mos–64 yrs					Community cohort study, persons aged 1–17 yrs				
	Positive influenza test result		Negative influenza and SARS-CoV-2 test results			Vaccinated		Not vaccinated		
Influenza type	Total	No. of persons vaccinated (%)	Total	No. of persons vaccinated (%)	Adjusted VE,* % (95% CI)	No. of person-days	No. of positive influenza test results	No. of person-days	No. of positive influenza test results	Adjusted VE,† % (95% CI)
A	116	26 (22)	429	160 (37)	54 (23–73)	7,292	6	15,678	28	71 (31–90)
A(H3N2)	86	16 (19)	429	160 (37)	60 (25–79)	NE	NE	NE	NE	NE

MMWR Morb Mortal Wkly Rep February 24, 2023 / 72(8);201–205

- ✓ 2021-2022年流感季美國威斯康辛州Marshfield門診醫療體系的兩項研究發現，於6個月至64歲族群，整體對急性上呼吸道疾病(A型流感)之VE為54%；於未滿18歲之兒童與青少年族群，對有症狀A型流感感染之VE為71%。顯示流感疫苗可降低未滿65歲者感染後重症風險及兒童與青少年感染流感(有症狀)風險。

  惟該研究期間尚處COVID-19流行期間，流感病毒活性、民眾就醫頻率與整體醫療利用等因素，都可能影響VE評估，需謹慎解讀研究結果。

- ✓ 美國CDC建議，只要流感病毒持續傳播，仍應對6個月以上民眾進行每年一次的流感疫苗接種

RAPID COMMUNICATION

Vaccine effectiveness estimates from an early-season influenza A(H3N2) epidemic, including unique genetic diversity with reassortment, Canada, 2022/23

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2022-2023年流感季加拿大研究顯示，流感疫苗針對1歲以上兒童與成人族群實驗室確診A(H3N2)保護力約為54%

The Canadian Sentinel Practitioner Surveillance Network estimated vaccine effectiveness (VE) during the unusually early 2022/23 influenza A(H3N2) epidemic. Like vaccine, circulating viruses were clade 3C.2a1b.2a.2, but with genetic diversity affecting haemagglutinin positions 135 and 156, and reassortment such that H156 viruses acquired neuraminidase from clade 3C.2a1b.1a. Vaccine provided substantial protection with A(H3N2) VE of 54% (95% CI: 38 to 66) overall. VE was similar against H156 and vaccine-like S156 viruses, but with potential variation based on diversity at position 135.

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

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

各類對象流感風險(WHO)

Working Group's Assessment of Influenza Risk and Influenza Vaccine Characteristics in

	疫苗可行性	流感嚴重度	流感疫苗有效度	疫苗間接效益
Risk Group 危險群	Feasibility of Delivery	Disease Severity	Vaccine Effectiveness	Indirect Benefits
Pregnant women 孕婦	++	+++	+++	++
Healthcare workers醫療人員	++	+	+++	+
Children, 2-5 years 幼童	+	++	++	- ++
Children, < 2 years 幼兒	++	+++	+	- ++
Elderly 長者	+	+++	+	-
Underlying Health Conditions 潛在疾病	+	+++	+	-

http://www.who.int/influenza/vaccines/SAGE_information/en/#

流感疫苗接種對象優先順序緣起

計畫實施對象*

~**高風險族群：**50歲以上成人、機構對象、6個月以上之學齡前幼兒、重大傷病及罕病患者、孕婦、高風險慢性病人(含BMI≥30)、6個月嬰兒之父母(原產後6個月內之婦女併入該類對象)、幼兒園托育人員及托育機構專業人員

~**高傳播族群：**醫事防疫相關人員、禽畜養殖業者、國小學童、國中生、高中/職及五專1-3年級學生

面臨問題：

~機構對象定義是否包含老人日間照護中心之受照顧者及工作人員

~近年來各類團體/民眾反映爭取納入公費接種計畫對象

~境外臺校學生，依現行修正操作型行定義並非「學生族群」之接種對象，是否納入公費接種計畫對象

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**

流感疫苗安全嗎？

Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

Recommendations and Reports / Vol. 65 / No. 5

August 26, 2016

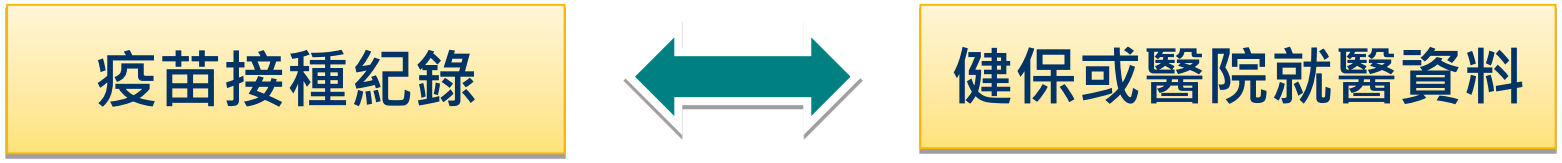
Prevention and Control of Seasor
Recommendations of the Advisory
Practices — United States, 201

A large postlicensure population-based study asse
safety in 251,600 children aged <18 years (includi
vaccinations in children aged 6–23 months) enroll
of five health care organizations within the Vacci
Datalink (VSD; http://www.cdc.gov/vaccinesafety/
vsd.html) during 1993–1999. This study indicated n
in clinically important medically attended events d
2 weeks after IIV administration compared with contr
2–4 weeks before and after vaccination (*277*). In a ret
cohort study using VSD data from 45,356 child
6–23 months during 1991–2003, IIV3 was not assoc
statistically significant increases in any clinically i
medically attended events other than gastritis/d
during the 2 weeks after vaccination compared wit
time periods before and after vaccination. Most v
children with a diagnosis of gastritis/duodenitis had s
vomiting or diarrhea. Several diagnoses, including ac
respiratory illness, otitis media and asthma, were sig
less common during the 2 weeks after influenza va
Although there was a temporal relationship with va
the vaccine did not necessarily cause or prevent these
(*278*). A subsequent VSD study of 66,283 child
24–59 months noted diagnoses of fever, gastrointes

- 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

國內的疫苗安全監測

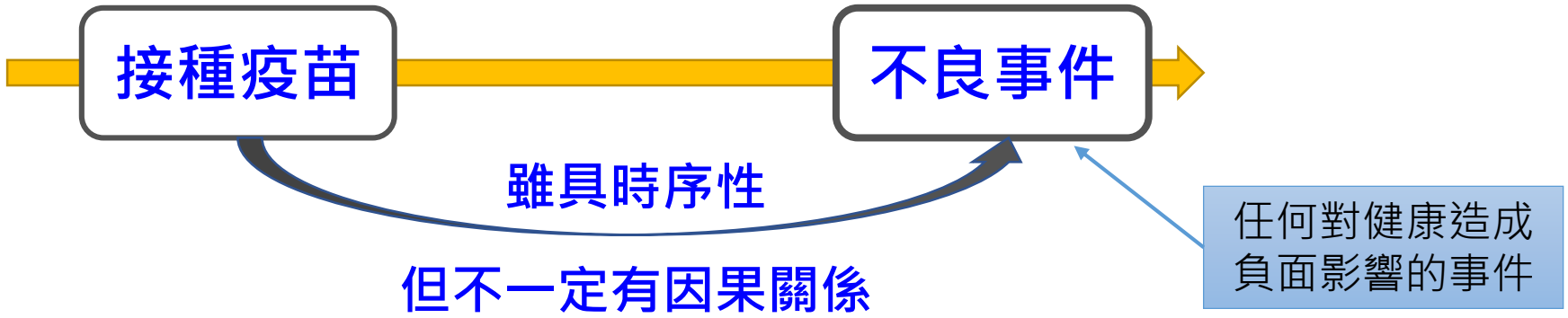
- **被動監測（常規進行）**
  - ✓由醫師或公共衛生人員於「疫苗不良事件通報暨追蹤關懷系統(VAERS)」通報
- **主動監測（必要時進行）**



- **個案審議**
  - ✓預防接種受害救濟審議委員會(VICP) 或司法相驗

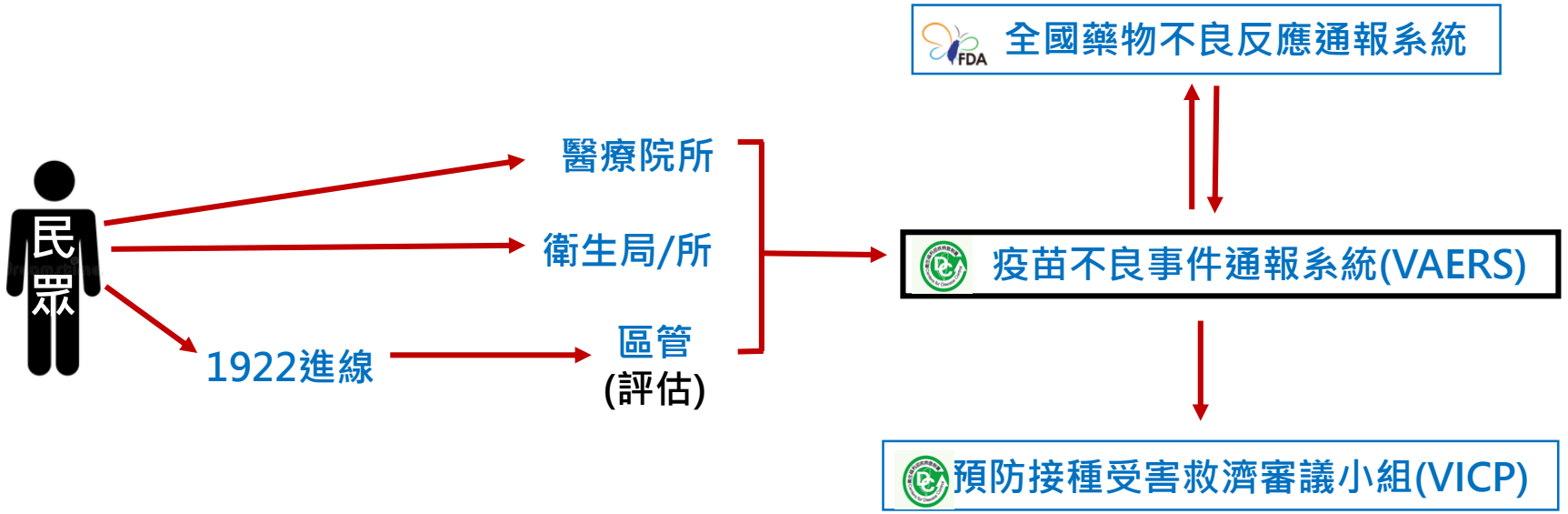
預防接種不良事件/反應

- **不良事件**：依照世界衛生組織的定義，預防接種不良事件(adverse events following immunization, AEFI) 是指在預防接種後所發生任何對健康造成負面影響的事件，該事件與預防接種之間**雖有時序上的關聯性**(temporal association)，**但不一定有因果關係(causal association)**。
- **不良反應**：接種疫苗後所發生之有害**且與接種疫苗具有合理因果關係**之反應
- 兩者都發生在接種疫苗之後，且對健康造成負面影響；但**不良反應跟接種疫苗有因果關係，而不良事件則不一定有因果關係**。



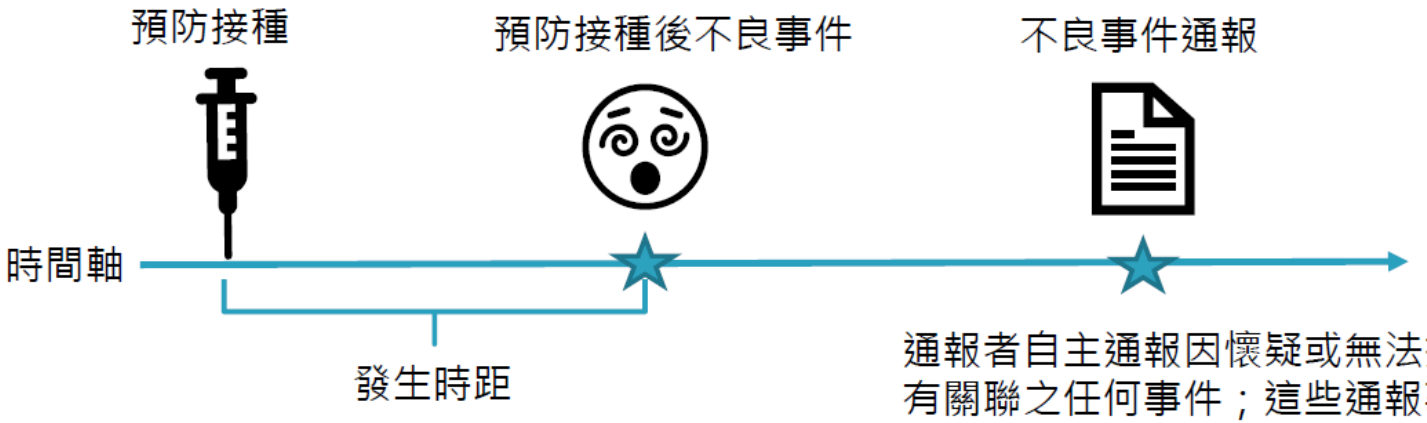
疫苗不良事件通報及因應

- 監測接種計畫期間因接種疫苗引起嚴重不良反應個案，藉由相關調查，早期偵測疫苗危害，並及時因應



- 民眾透過醫療院所、衛生局/所或進線1922於「疫苗不良事件通報系統(VAERS)」通報不良事件
- 系統會依通報院所所在地之縣市自動派案，並由衛生局/所就個案進行後續追蹤關懷作業

接種後不良事件通報



通報者自主通報因懷疑或無法排除與疫苗施打有關聯之任何事件；這些通報事件時序上發生於疫苗接種之後，但不表示為接種疫苗所致。

非嚴重

嚴重

嚴重藥物不良反應通報辦法第4條

一、死亡。

二、危及生命。

三、造成永久性殘疾。

四、胎嬰兒先天性畸形。

五、導致病人住院或延長病人住院時間。

六、其他可能導致永久性傷害需做處置者。

不良事件嚴重性

- 盡可能**以客觀事實來判定**， 盡量避免以通報者對嚴重程度(Severity)的感知來判定 。
- 應以不良事件**發生當下**之情形來判定，若後續病人情況好轉或康復，可於『 不良事件後續結果 』欄位勾選不良事件最新之後續結果，**不可於追蹤通報中將不良事件嚴重性往下調整。**

如：病人接種疫苗後因嚴重過敏反應住院(初始通報為導致病人住院或延長病人住院時間)，後續病人經醫療處置後出院，**不可將嚴重性下調為非嚴重** 。

- 若後續病人情況惡化，且經判定可能與原通報不良事件為**同一個臨床病程進展**，**則可將嚴重性上調**。

  如：病人接種疫苗後通報頭痛(非嚴重)，但隔天追蹤時發現病人在半夜腦出血住院，依醫學常理可合理懷疑這是同一個臨床病程進展，追蹤通報中應將嚴重性上調至” 導致病人住院” 。

  但若追蹤發現病人在2個月後因細菌性肺炎入院後敗血性休克死亡，則不應將嚴重性上調至"死亡"。

112年度流感疫苗不良事件通報案件統計

- **112年度流感疫苗接種計畫(自112年10月1日截至113年5月1日止)公費流感疫苗總接種數為656.2萬劑，共通報113件疫苗不良事件**
- **平均每十萬劑注射通報數約為 1.72件**
- 綜合目前季節性流感疫苗**不良事件通報資料之評估結果，尚未觀察到**須立即採取相關措施之安全疑慮。

預防接種受害救濟審議委員會（VICP）

民國75年

- 出現口服小兒麻痺疫苗後造成小兒麻痺症個案

民國77年6月

- 參考歐美等先進國家制度，成立預防接種受害救濟基金

民國78年

- 預防接種諮詢小組召開第一次會議審議

民國81年至今

- 設置獨立審議小組進行審議

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……

通報 vs. 救濟

不良事件通報

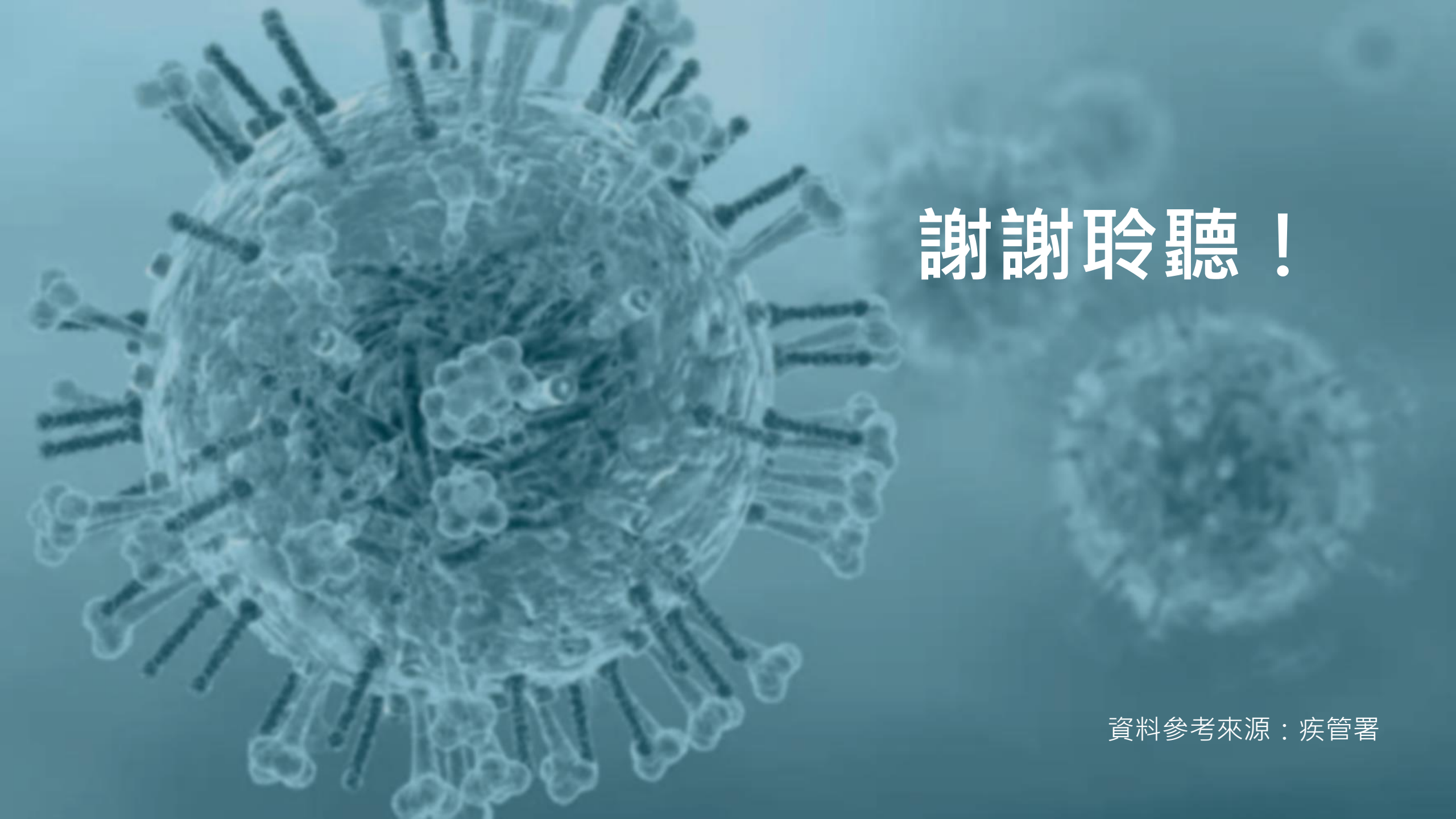
- 疫苗產品安全性監視
- 偵測疫苗安全訊號

https://www.taiwan-pharma.org.tw/weekly/2239/2239-4-2.htm

總結

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

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



謝謝聆聽！

資料參考來源：疾管署