流感之臨床處置

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Outline

- Introduction
- Influenza with severe complications
- Diagnosis
- Antiviral therapy

Introduction

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

流感 vs. 感冒

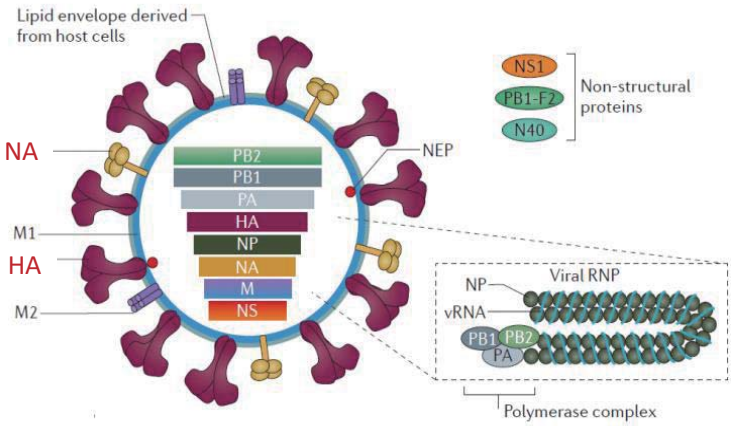
	流感 (Influenza)	感冒 (Common Cold)
致病原	流感病毒	其他許多病毒(鼻病毒、呼吸道融合病 毒、腺病毒等)
影響範圍	全身性	呼吸道局部症狀為主
發病速度	突發性	突發/漸進性
主要臨床症狀	嚴重★★★ 發燒、咳嗽、頭痛、肌肉酸痛、疲 倦、流鼻水、喉嚨痛	症狀較輕微 喉嚨痛、打噴嚏、鼻塞、流鼻水
發燒	高燒3-4天	少發燒，僅體溫些微升高

流感 vs. 感冒

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

圖片來源: 疾病管制署-流感併發重症核心教材

流感病毒
(Influenza virus)

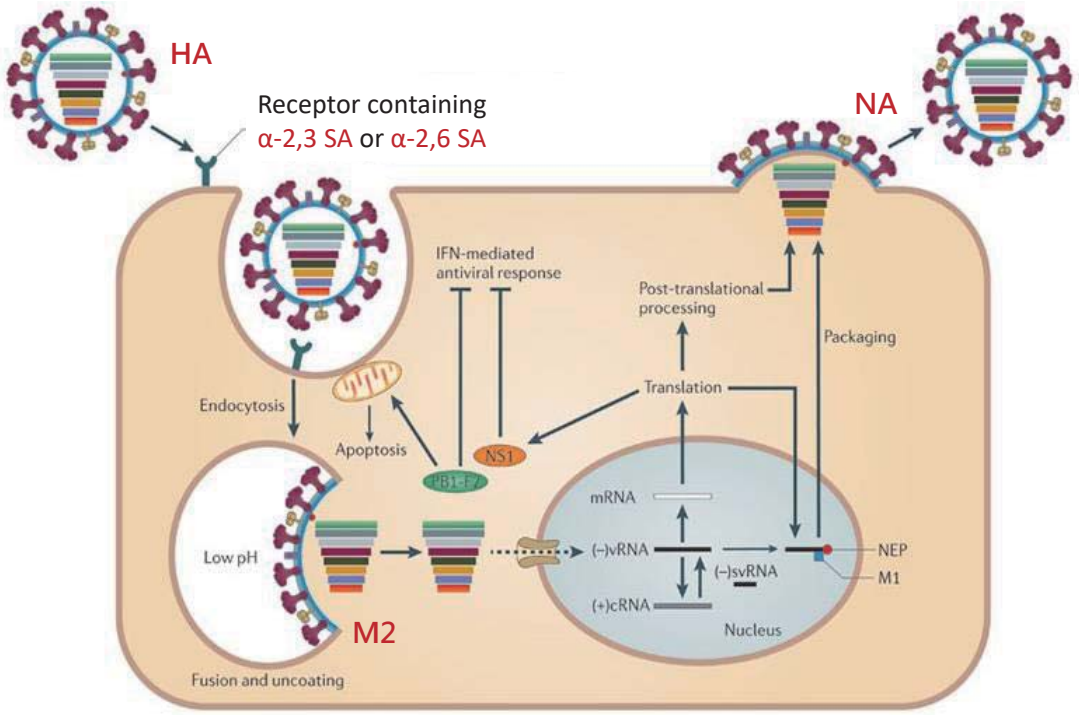


- 正黏液病毒（*orthomyxoviridae*）SS(-), RNA病毒
- 分為**A型**、**B型**、C型及D型
- 外套膜含有2種醣蛋白

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

A型病毒再依據不同的HA及NA區分亞型: 如 H1N1, H3N2

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



SA: sialic acid

Nature Reviews Microbiology

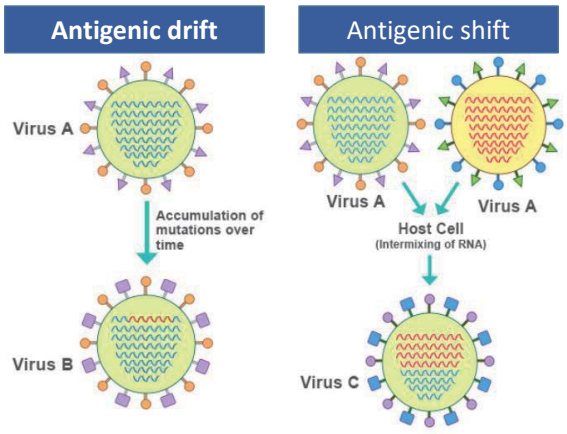
	A 型 流感病毒	B 型 流感病毒	C 型 流感病毒	D 型 流感病毒
基因結構	8條單股負鏈 RNA	8條單股負鏈 RNA	7條單股負鏈 RNA	7條單股負鏈 股 RNA
病毒體結構	11個蛋白質	11個蛋白質	9個蛋白質	9個蛋白質
抗原變異種類	抗原微變 (Antigenic drift) 抗原移型 (Antigenic shift)	抗原微變 (Antigenic drift)	抗原微變 (Antigenic drift)	抗原微變 (Antigenic drift)
抗原變異性	變異性大	抗原性較穩定	抗原性非常穩定	抗原性穩定
自然界宿主	人、豬、馬等哺乳動物、禽鳥類	人	人、豬	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

流感病毒的變異

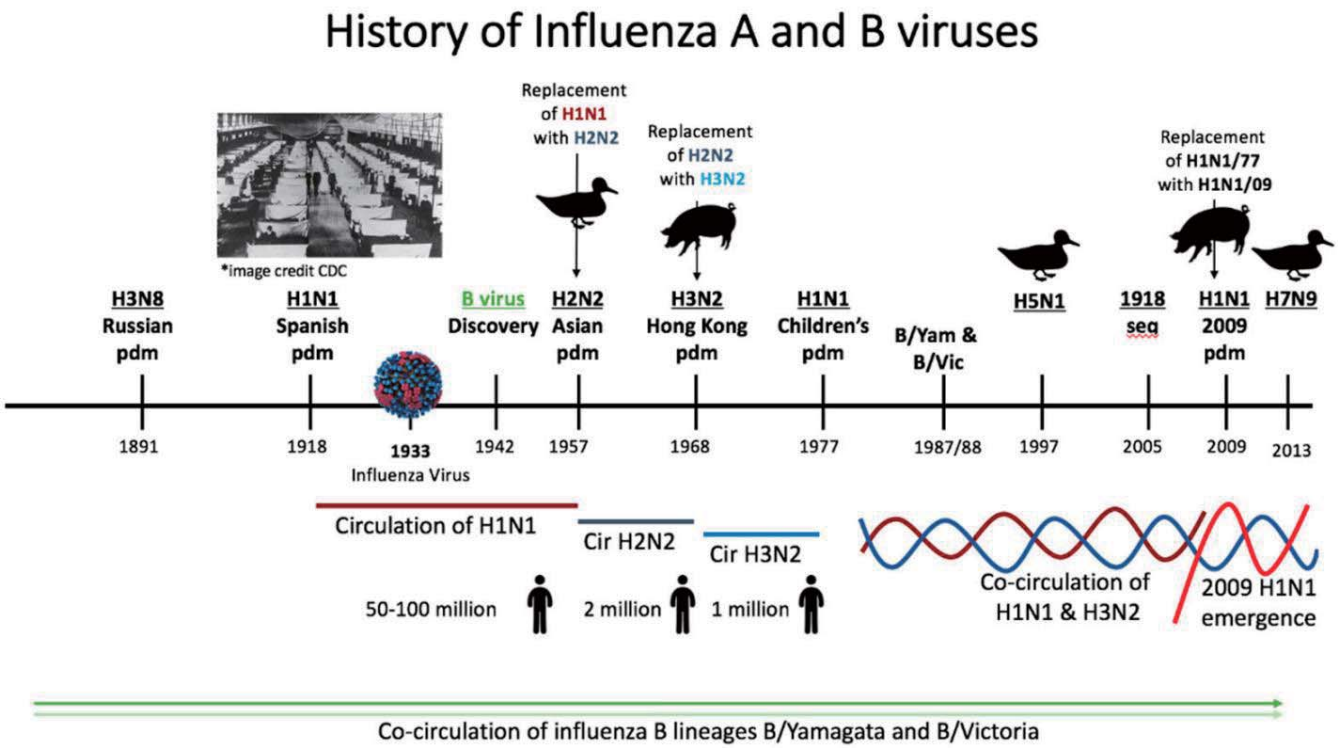
- 流感病毒的抗原變異主要分為下列二種

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

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



- 新型流感病毒株則是由突變和基因重組（Reassortment）產生



Viruses 2019, 11, 122; doi:10.3390

全球流行情形

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

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

台灣流行情形

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

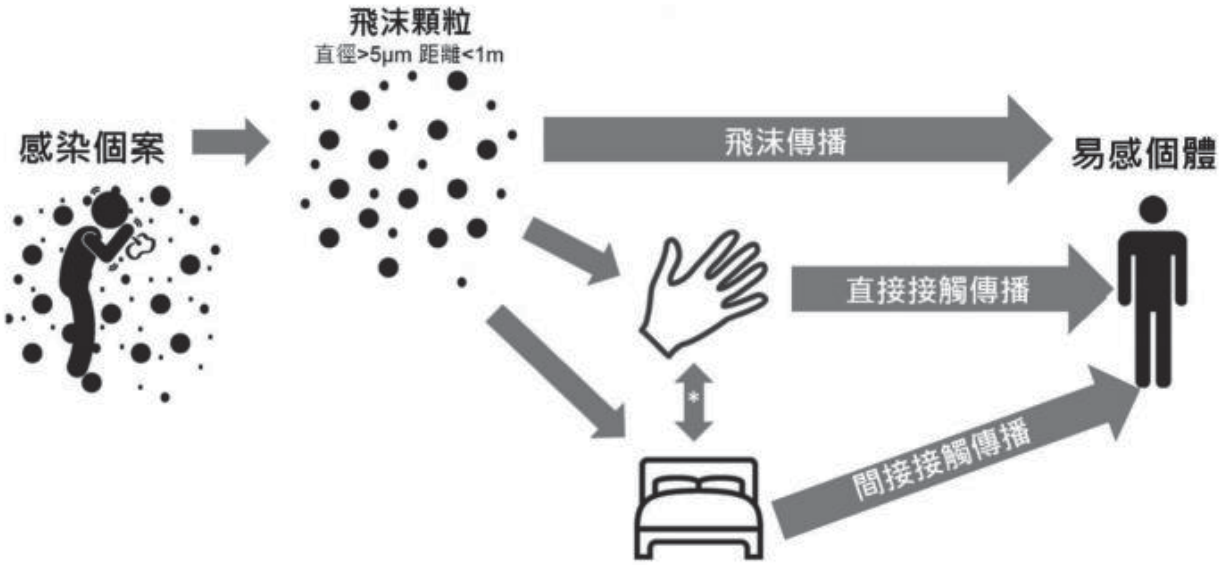
1. 疾病管制署健保IC卡資料庫次級資料2011年至2018年肺炎或流感門診及住院就診人次分析
2. 疾病管制署傳染病通報系統2011年至2018年流感併發重症確定病例統計

流感特徵

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

人人都可能得流感

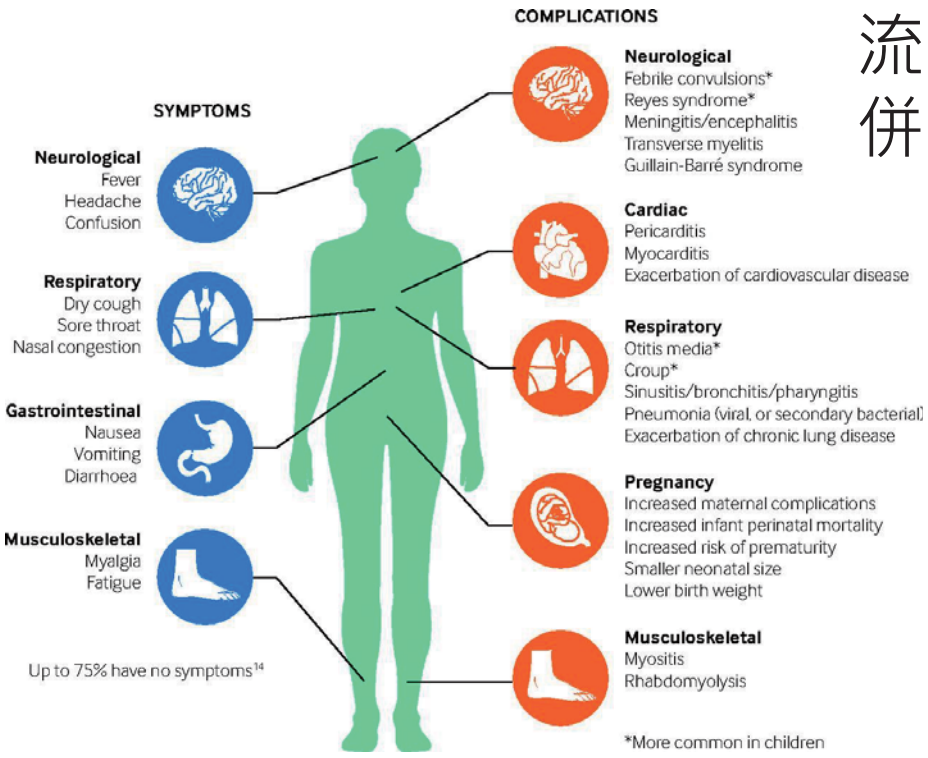
傳播方式



感染過程

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

流感
併發重症



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

流感併發重症（Severe Complicated Influenza）

一、 臨床條件

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

二、 檢驗條件

具有下列任一個條件：

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

（二） 臨床檢體分子生物學核酸檢測陽性。

（三） 臨床檢體抗原檢測陽性。

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

三、 流行病學條件

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

四、 通報定義

符合臨床條件。

類流感症狀

疾管署規定類流感需符合以下三項條件：

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

流感併發症

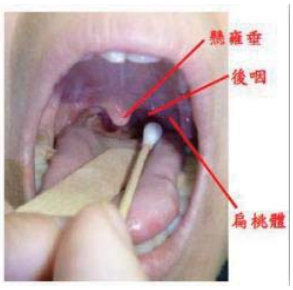
- **1. 肺部併發症(Pulmonary complications)**
  胸部 X 光有新的浸潤或實質化，且需要住院之病人。
- **2. 神經系統併發症(Neurological complications)**：符合下列臨床狀況至少二項，並排除癲癇、熱痙攣等其它病因者：
  (1)急性腦病變：指突發的意識狀態、人格或行為改變、或對人 時地的判斷混淆，持續超過 24 小時者。
  (2)局部或全身性抽筋
  (3)理學檢查呈現局部神經學症候 。
  (4)腦脊髓液中白血球數目大於 5/μL 。
  (5)異常的神經電生理或神經影像學發現。
- **3. 心肌炎(Myocarditis)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

傳染病防治法之規範

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

檢體採檢送驗事項

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



咽喉拭子檢體採集圖解


病毒拭子

Influenza testing

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

流行性感冒的快速診斷檢驗-感控雜誌 2019

Influenza A/B RNA (ID NOW)

流感防治策略

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

多元化監視系統

病毒活動監視

- 病毒性合約實驗室監視通報系統
- 實驗室傳染病自動通報系統(LARS)
- 病毒抗原及抗藥性分析

病例監視

- 傳染病通報系統：流感併發重症
- 症狀通報系統：類流感群聚、國際機場發燒旅客

流行趨勢監視

- 即時疫情監測及預警系統(RODS)、健保資料庫(門診、住院)
- 肺炎及流感死亡監測(P&I)
- 人口密集機構傳染病監視作業登錄系統
- 學校傳染病監視通報資訊系統

流感的預防

維持手部清潔

- 勤洗手，用肥皂和水清洗至少20秒
- 咳嗽或打噴嚏後更應立即洗手
- 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

及早就醫，生病時在家休養

- 出現發燒、咳嗽等類流感症狀，建議及早就醫
- 就醫後儘量在家休息，減少出入公共場所
- 患者應避免搭乘大眾運輸交通工具

注意危險徵兆，掌握黃金治療時期

- 出現呼吸困難、呼吸急促、發紺(缺氧)、血痰或痰液變濃、胸痛、意識改變或低血壓等危險徵兆時，應提高警覺，儘速轉診至大醫院就醫

公費流感抗病毒藥劑使用對象

治療性用藥	
• 符合「流感併發重症」通報病例(需通報於法定傳染病通報系統)	• 符合「新型A型流感」通報定義者(需通報於法定傳染病通報系統)
• 孕婦經評估需及時用藥者	• 肥胖之類流感患者(BMI>=30)
• 未滿5歲及65歲以上之類流感患者	• 確診或疑似罹患流感住院（含急診待床）之病患
• 重大傷病、免疫不全(含使用免疫抑制劑者)或具心肺血管疾病、肝、腎及糖尿病等之類流感患者	• 流行高峰期擴大用藥(有發燒之類流感患者，且家人/同事/同班同學有類流感發病者)
預防性用藥	
• 類流感等群聚事件經疾病管制署各區管制中心認定需用藥者	• 新型A型流感極可能/確定病例之密切接觸者(接觸者名冊經傳染病防治醫療網區正/副指揮官或其授權人員研判需給藥者)
• 動物流感發生場所撲殺清場工作人員(接觸者名冊經傳染病防治醫療網區正/副指揮官或其授權人員研判需給藥者)	

CDC. 109.05.01 適用

抗流感病毒藥物給藥時機

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

感染症醫學會 流感藥物治療建議 2021

抗流感藥物使用

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

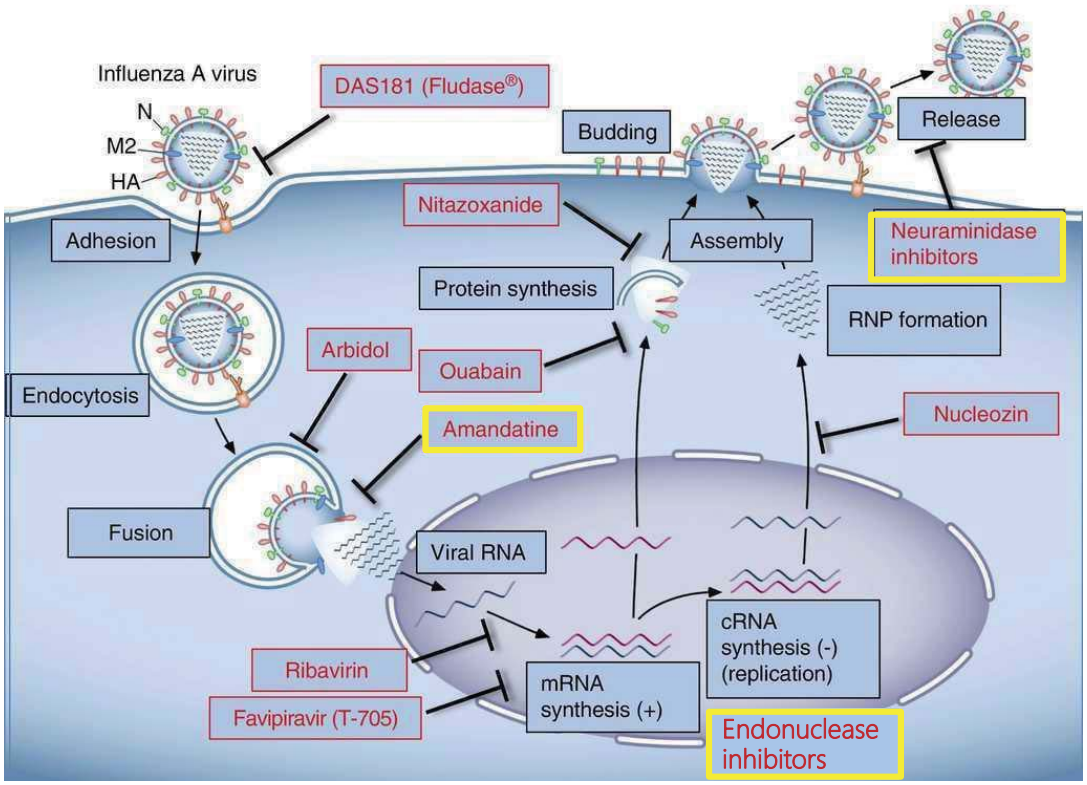
感染症醫學會 流感藥物治療建議 2021

治療方式

- 流感抗病毒藥劑
  - M2 protein抑制劑(M2 protein inhibitor)
    - Amantadine等
    - 抗藥性問題嚴重，已**不建議**用來治療流感

  - **神經胺酸酶抑制劑(Neuraminidase inhibitor)**
    - 口服式之Oseltamivir (Tamiflu® 克流感、Eraflu® 易剋冒)
    - 吸入式之Zanamivir (Relenza® 瑞樂沙)
    - 靜脈注射之Peramivir (Rapiacta® 瑞貝塔)
    - 為目前治療主流

  - **核酸內切酶抑制劑(Endonuclease inhibitor)**
    - 口服式之Baloxavir (Xofluza® , 紓伏效)
- 支持療法 -醫師評估投以症狀緩解藥物



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

發展中抗病毒藥物

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

N Engl J Med 2009; 360:953-956

Oseltamivir (Tamiflu、Eraflu)

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

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

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

CDC 克流感中文仿單 2019.6

注意事項

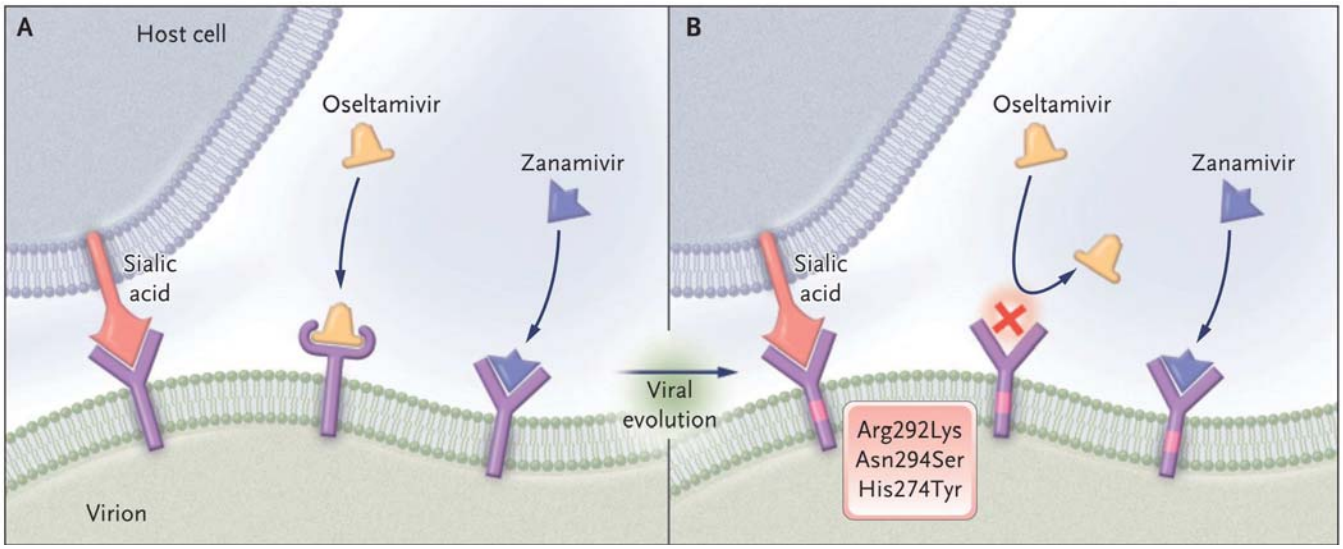
- 已有流感病患在服用 Tamiflu 期間產生**癲癇和類似精神錯亂**的神經精神事件的報告， 大多數為**小孩和青少年**。
- 極少數案例中，此類事件會導致意外傷害。Tamiflu對於這類事件的因果關係還未知，另外也有未服用 Tamiflu之流感病患產生此類事件之報告。
- 三個不同的大型流行病學研究證實，和未接受抗病毒藥物治療的流感患者相比較，接 受 Tamiflu治療之流感患者發生神經精神事件的風險並未較高。
- 須嚴密地監測流感病患(特別是小孩和青少年)之不尋常行為之徵兆。

Drug class	Common neuropsychiatric side effects	Mechanism of neurotoxicity	Clinical relevance	Notes
Neuraminidase inhibitors	Irritability, psychosis, mania, more commonly in children	Unclear; evidence regarding MAO inhibition or monoaminergic modulation inconclusive	Contraindicated in children < 12 years old. Use in individuals with a history of psychiatric disturbances only if benefits clearly outweigh risk.	Relevant only for oseltamivir.

[1, 2]. Oseltamivir phosphate (OP) is an ethyl ester pro-drug requiring ester hydrolysis for conversion to the active form of the neuraminidase inhibitor oseltamivir carboxylate (OC). Oseltamivir inhibits human monoamine oxidase-A (MAO-A), which is related to excitatory behaviors. Regarding acute and chronic psychotic reactions, receptors such as GABA-A, GABA-B, N-methyl D-aspartate (NMDA), and Na+, and Ca2+ channels are thought to be other candidates for investigation. Another study reported that oseltamivir sialylates a serum glycolipid that stimulates D2 dopaminergic receptor. This mechanism is related to abnormal behavior reported in some children taking oseltamivir. Unchanged oseltamivir phosphate is

Cureus. 2020 Aug 3;12(8):e9536

Oseltamivir resistance



N Engl J Med 2009; 360:953-956

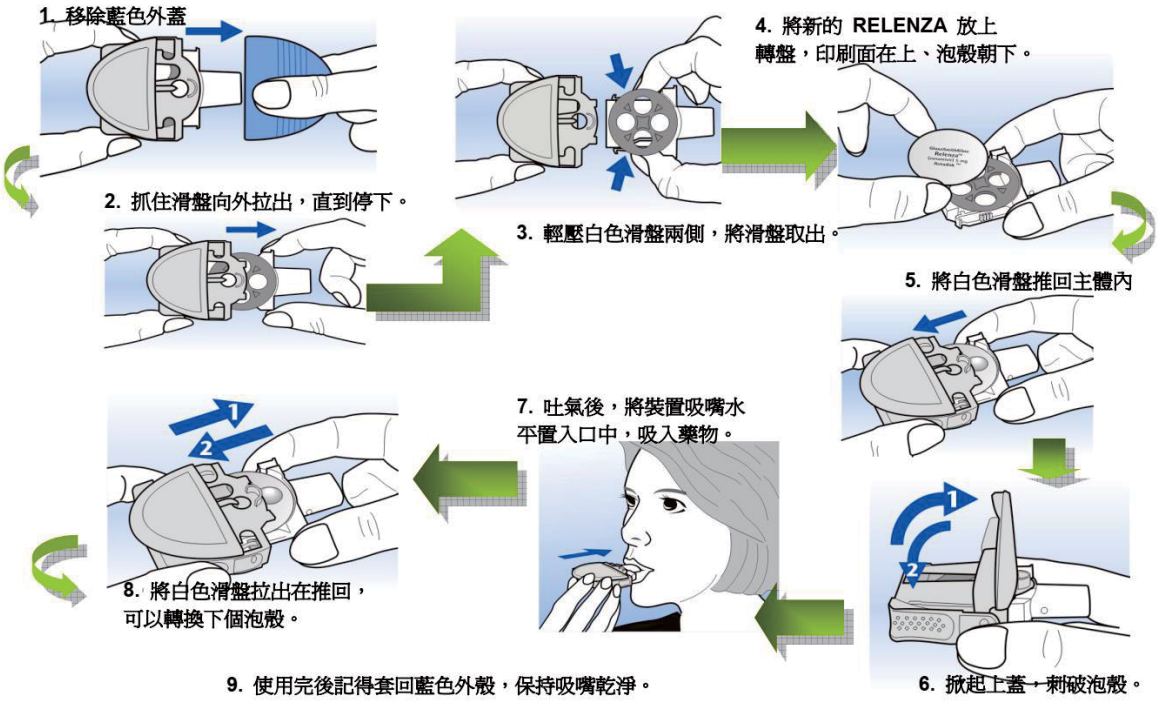
Zanamivir (Relenza) 瑞樂沙

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

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

CDC 瑞樂沙中文仿單 2019.6
抗流感病毒藥物使用建議 2021.3

瑞樂沙 Relenza 旋達碟使用步驟



Peramivir (Rapiacta)瑞貝塔

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

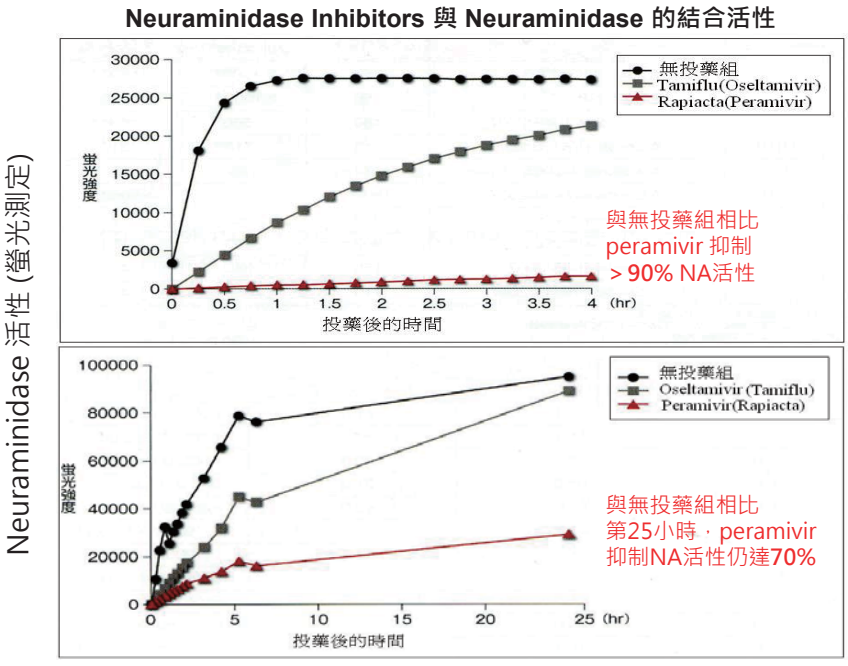
	Japan[1]	US[2]
CCr>50	300 mg once	600 mg once
Severe case	600 mg qd *5-10 days	
Ccr 30-50	100 mg /d	200 mg/d
Ccr 10-30	50 mg /d	100 mg/d
HD	審慎調整劑量	100 mg D1, then 100 mg 2hrs after HD

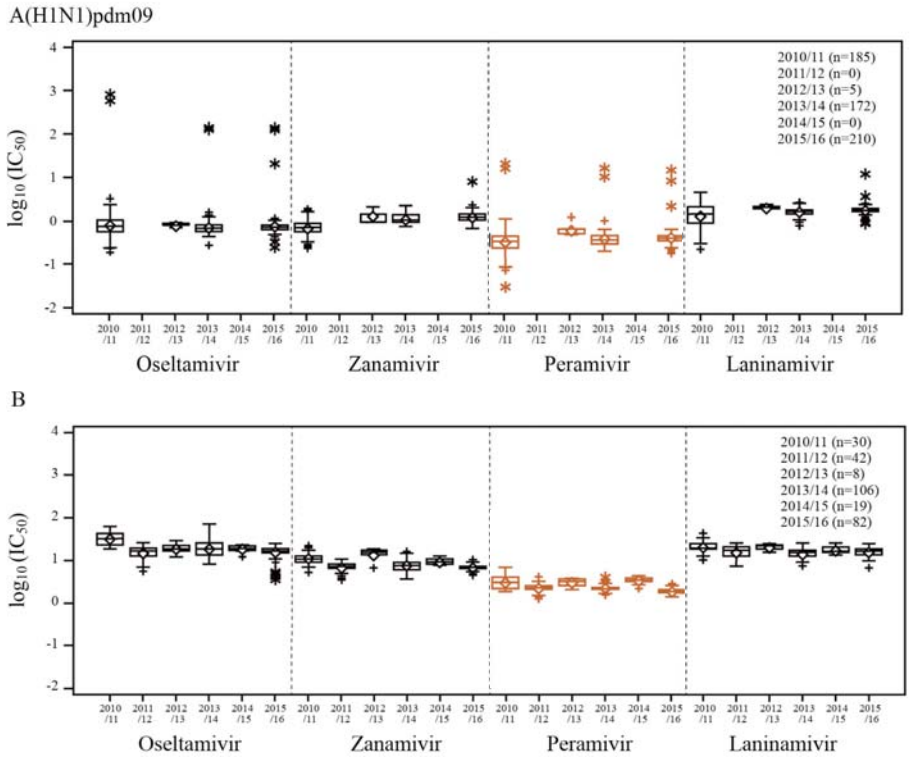
1. 瑞貝塔中文仿單 2. Sanford’ s guide

Rapiacta®特點

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

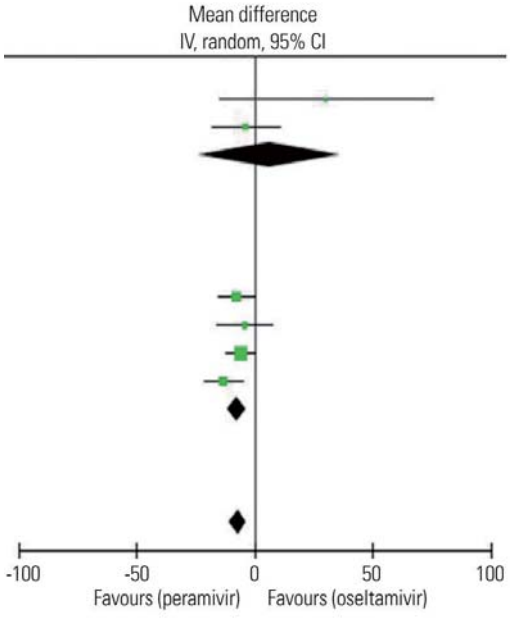
Peramivir 具有高度 Neuraminidase 結合活性 (in vitro)





[illegible] *Infect Chemother* ([illegible]

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



[illegible]

Time **to alleviation of fever**[illegible]

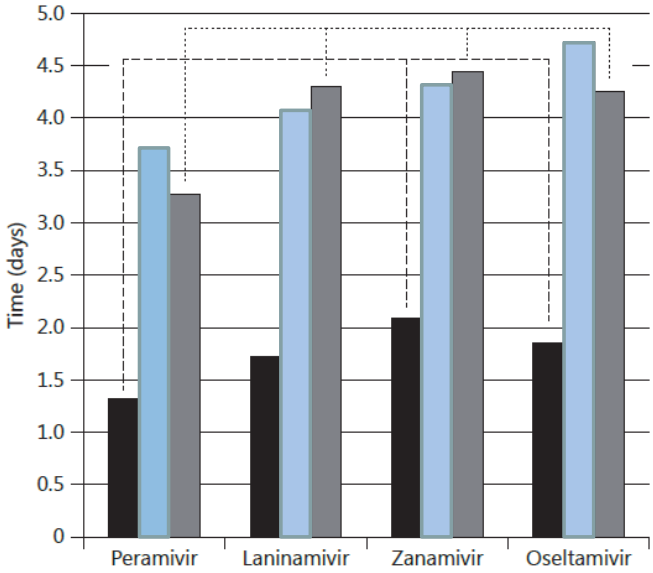
(9[illegible]

[illegible]

[illegible]

Time to **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

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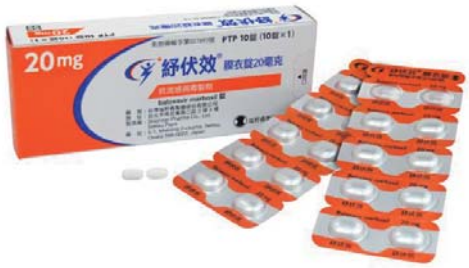
Baloxavir marboxil (Xofluza)紓伏效

- **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:

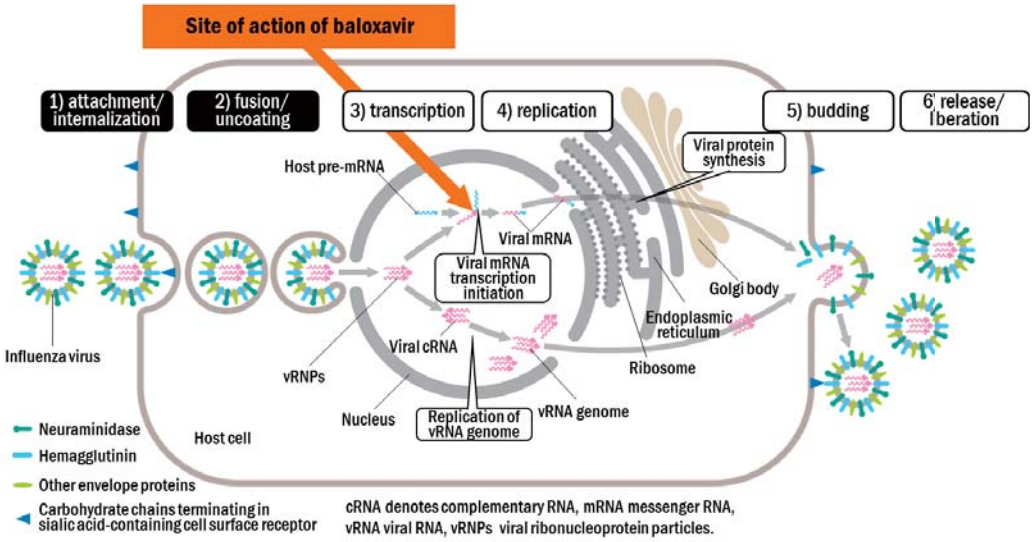
40-80Kg	單次服用 40mg (2 tab)
>80Kg	單次服用 80mg (4 tab)



- 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

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



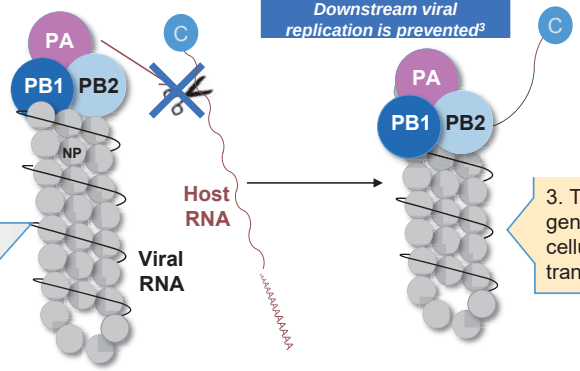
Noshi et al. Antiviral Res. 2018 Dec;160:109-117

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

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

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

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



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

NP: nucleoprotein

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

Baloxavir 特點

一般流感病患[1]	流感高危險群病患[2]	流感預防[3]
• 單次口服即完成療程 • 快速停止排出病毒及降低病毒量 • 快速緩解流感症狀及退燒 • 安全性與安慰劑相當	• 症狀改善所需時間與□□elt□□ i□ir相當 • 顯著較□ □elt□□ i□ir快□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□□□ • 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

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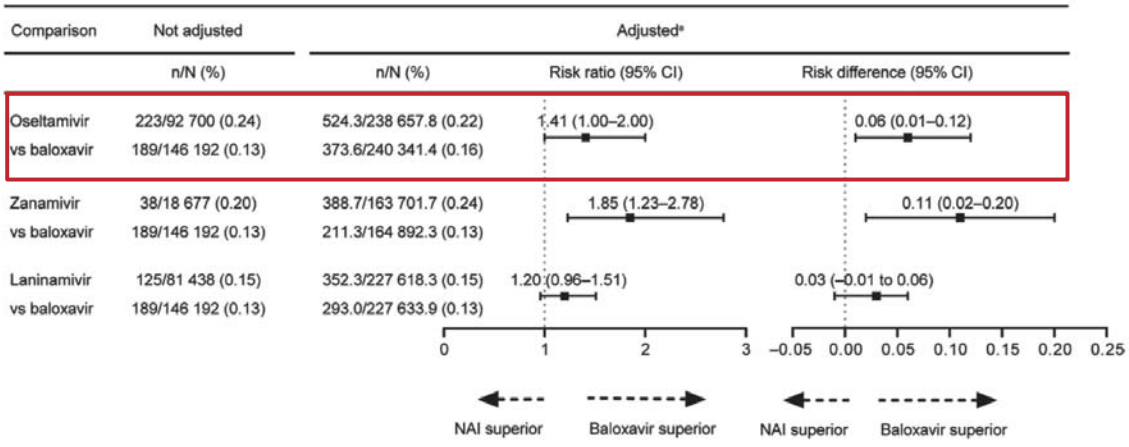
Comparison of Hospitalization Incidence in Influenza Outpatients Treated With Baloxavir Marboxil or Neuraminidase Inhibitors: A Health Insurance Claims Database Study



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

Clin Infect Dis. 2020; ciaa1870

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

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

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

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

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

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

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

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

台灣感染症醫學會-抗流感病毒藥物使用建議

藥物	Oseltamivir Capsule		Oseltamivir Oral Suspension		Zanamivir		Peramivir		Baloxavir Marboxil	
使用方式	吞服□無法吞服者（如需使用鼻胃管者）則打開膠囊泡水或糖漿服用		經調配後服用		經口吸入		單次點滴靜脈注射□□分鐘以上		單次口服	
適用年齡	成人及兒童□含足月新生兒□		成人及兒童□含足月新生兒□		□歲□含□以上		小兒□早產兒及新生兒除外□及成人		成人和青少年□□□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
	□□歲以下依體重調整劑量；□□歲□含□以上或體重4□□□以上者□□□□□□□		4□□□以下兒童依體重調整劑量；4□□□以上兒童或成年人及青少年為□□□□□□□		□□□□□□	不建議使用	成人單次□□□□□□□小兒□□□□□□□□	成人□□□□□□□□□	≧4□至□□□□□單次服用4□□□□；≧□□□□□單次服用□□□□□	現無臨床數據
標準療程	□天	□天	□天	現無臨床數據	□天		單次	可依症狀連續多日反覆投予	單次	
自費價格	124*2*5 = **1240**						**1750**	3500* days	900*2 = **1800**	

感染症醫學會-抗流感病毒藥物使用建議（2021年修訂版）

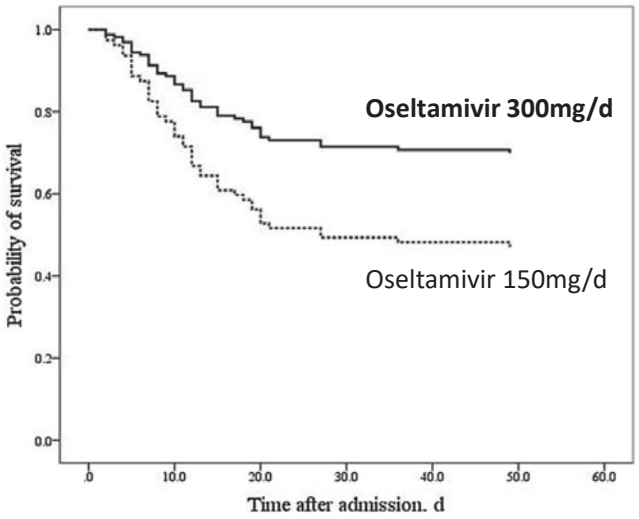
台灣感染症醫學會-抗流感病毒藥物使用建議

預防性抗流感藥物使用對象、劑量與療程

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

感染症醫學會-抗流感病毒藥物使用建議（2021年修訂版）

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

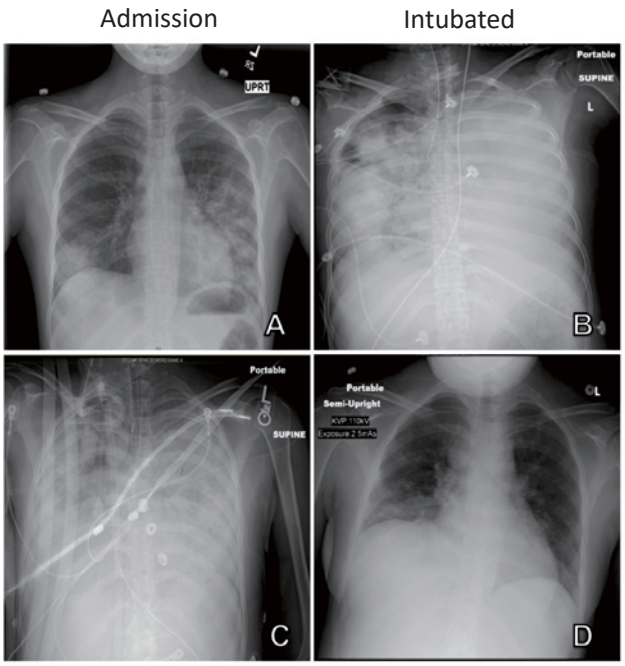
Int J Infect Dis. 2020 Mar;92:208-213.

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.

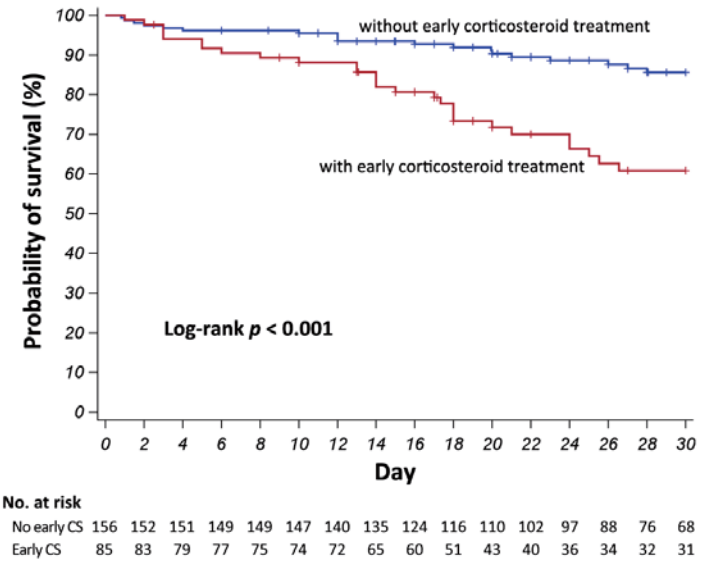
Oseltamivir and baloxavir: Dual treatment for rapidly developing ARDS on a patient with renal disease



- **Oseltamivir** renally adjusted dosage (CrCl 14 mL/min) , then double dose oseltamivir
- **Baloxavir** 40 mg every 72 h for three doses
- **Methylprednisolone** *4 days with a cumulative dose of 1125 mg

IDCases. 2020 May 22;21:e00819.

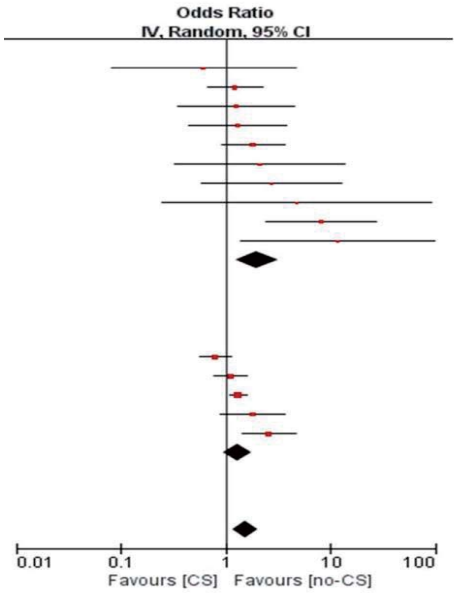
Impact of corticosteroid treatment on clinical outcomes of influenza-associated ARDS: a nationwide multicenter study



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

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

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



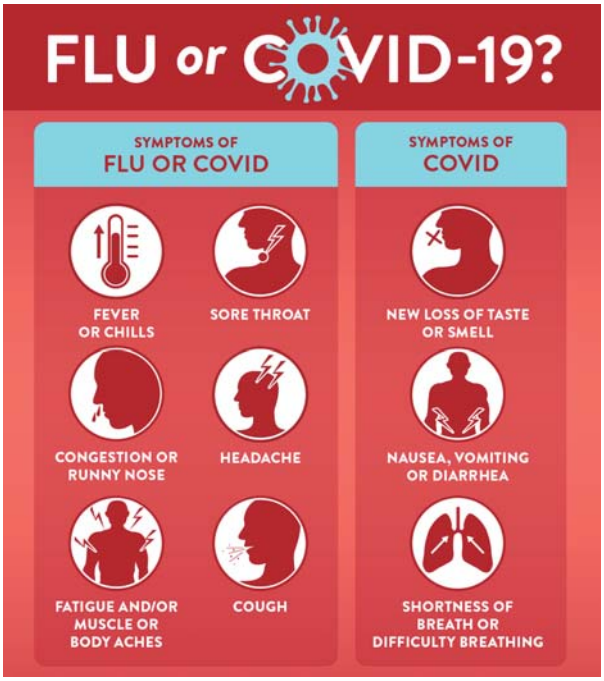
- The meta-analysis results showed that corticosteroid therapy was associated with significantly higher mortality (OR 1.53, 95% CI [1.16, 2.01]) and incidence of nosocomial infection (OR 3.15, 95% CI [1.54, 6.45])
- Current data do not support the routine use of corticosteroids in patients with influenza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

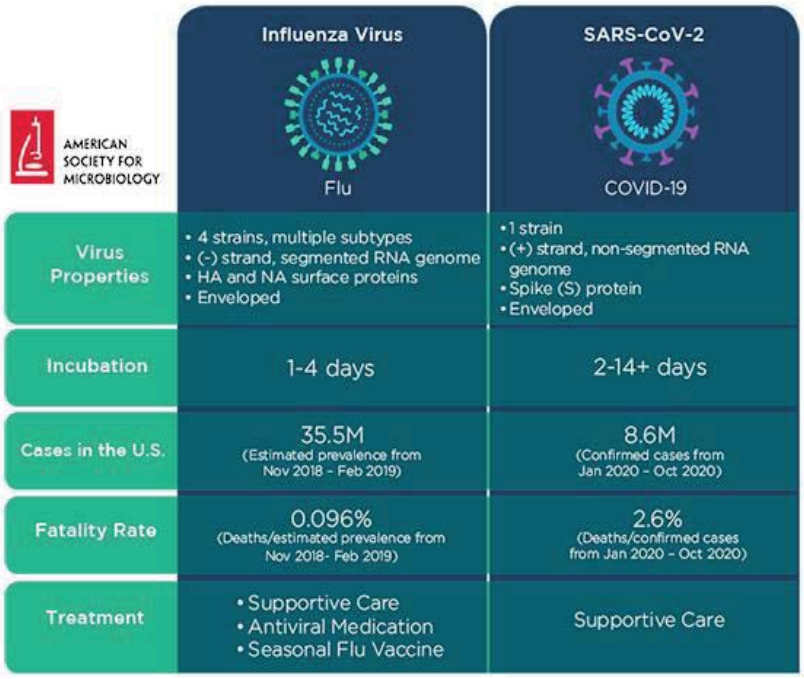
Sci Rep 10, 3044 (2020).

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





ASM. COVID-19 and the Flu. Oct.27.2020

Thank you for your attention

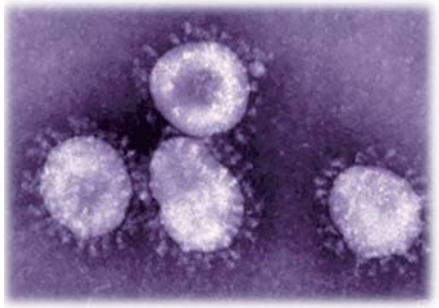
COVID-19疫情下針對流感與呼吸道傳染病共同防治

報告者：感染科 李雋元醫師

Outlines

- The impact of the COVID-19 epidemic on influenza virus
- The impact of the COVID-19 epidemic on other respiratory tract virus
- What might happen after mitigation of nonpharmaceutical interventions for COVID-19 epidemics?
- Non-pharmaceutical interventions for non-COVID-19 human respiratory viruses.
- Should we receive influenza vaccine in the COVID-19 epidemic?

The impact of the COVID-19 epidemic on influenza virus



Double threat of COVID-19 and influenza

Double threat of COVID-19 and influenza

At the time of publication, it looks like the second wave of COVID-19 is well underway in Europe. The weekly tally of new cases has been steadily rising for more than 2 months, but the past few weeks have seen accelerated transmission. Cases have also been trending upwards in the USA. Oct 14, 2020, saw the nation register the highest number of new cases of COVID-19 since Aug 7. In general, countries are much better prepared than they were when severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first exploded onto the scene. But October also marks the beginning of the flu season in the northern hemisphere. If both viruses surge simultaneously, even the best this year, the country has registered 21 156 cases and just 36 deaths. "While influenza testing in Australia and New Zealand is maintained or even increased, very few influenza viruses were detected", stated WHO, in their most recent influenza update. But whether this will translate to an equivalently mild flu season in the northern hemisphere, where the public is becoming increasingly tired of control measures, remains to be seen. The UK, for example, is unlikely to replicate the kind of lockdown it enacted in the early part of the pandemic.

"I think we are probably going to see a great deal more COVID-19 in the USA over the next few months, as sensitive and specific, with a high positive predictive value", Salmon told *The Lancet Respiratory Medicine*. "This is not a situation where we should be making diagnoses based on clinical signs alone." Misdiagnosis could lead to all kinds of problems. Influenza and COVID-19 have different recommended treatments and patients with influenza are not typically told to isolate. "We also need to bear in mind that a diagnosis of COVID-19 or influenza alone would be insufficient to exclude the presence of another co-infecting pathogen", adds Benjamin Singer, assistant professor of medicine (Pulmonary and Critical Care) at Northwestern University (Chicago, Illinois, USA).

Published Online
October 22, 2020
https://doi.org/10.1016/S2213-2600(20)30508-7
See Case Report
Lancet Respir Med 2020; 8: 644-46

1. Declining in numbers of influenza in southern hemisphere last year: true or not?
2. Distinguishing between influenza and COVID-19 by clinical manifestations
3. Is the influenza vaccine protective against SARS-CoV-2?

Travel restrictions

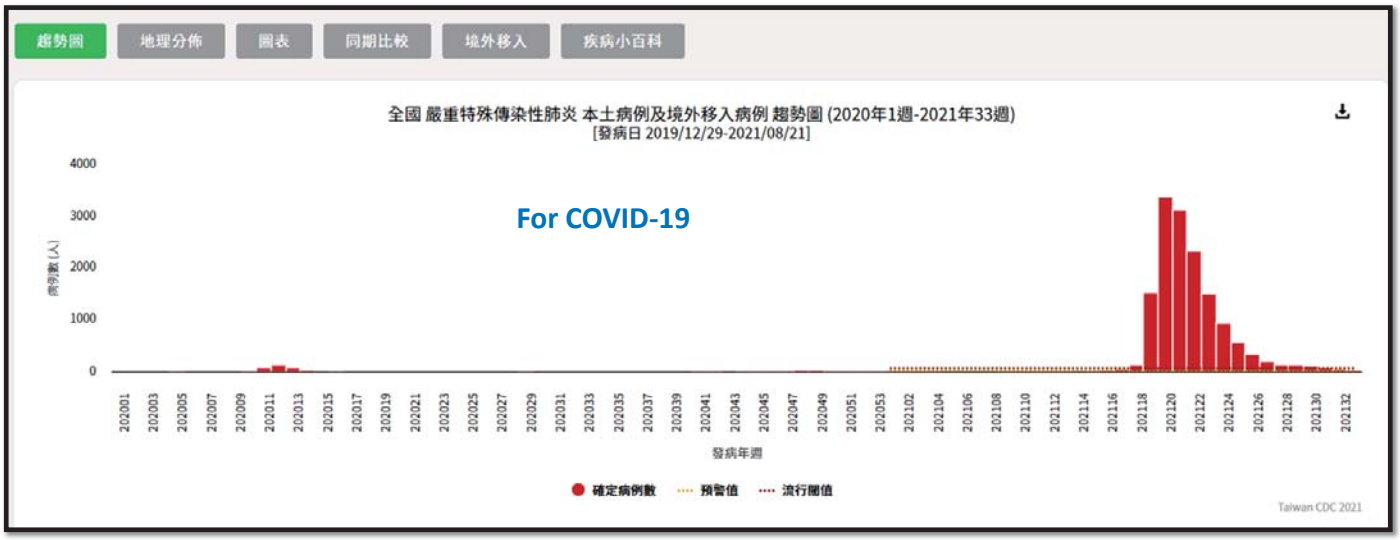
Environmental disinfection

Messaging on handwashing

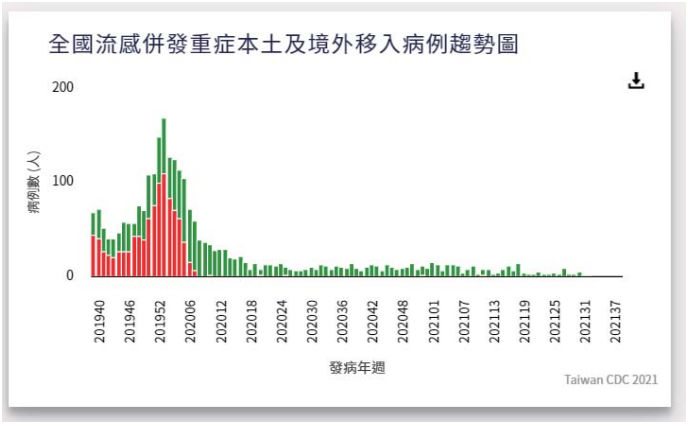
Lockdowns

Physical distancing

Use of face coverings

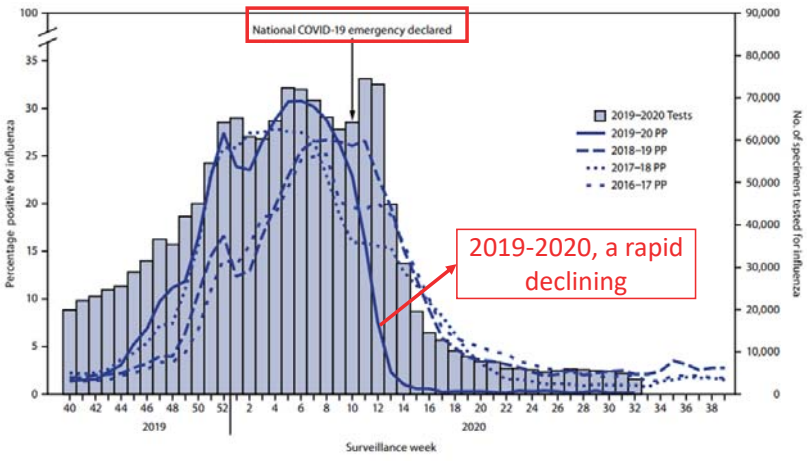


How about the influenza virus?



全國流感併發重症本土病例及境外移入病例統計表-依發病日	
最近一例發病日	2021/03/21
2021年32週 (上週累計數)	0
2021年33週 (本週累計數)	0
2021年08月 (本月累計數)	0
2021年 (今年累計數)	1
2020年(去年總數)	444
上週與前三週平均數比較 (病例數)	0.00
上週與過去三年同期平均數比較 (病例數)	▽23.33
今年累計死亡數	1

Last update: 2021/8/20

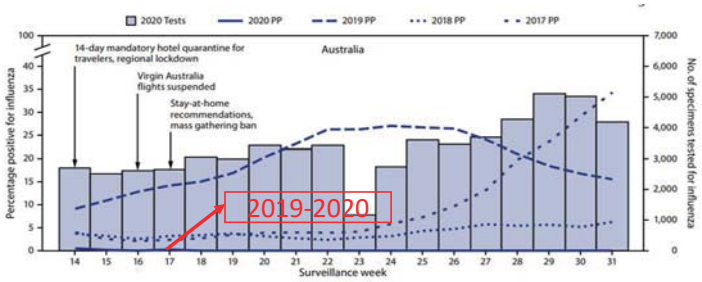


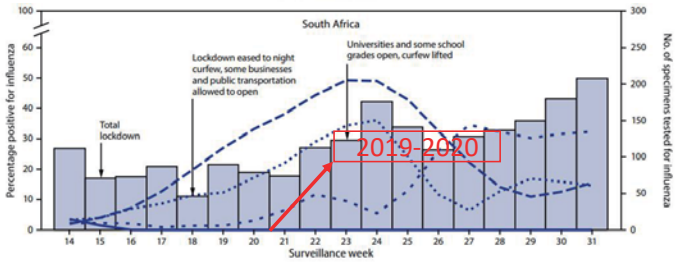
Decreased influenza activity during the COVID-19 pandemic-United States, Australia, Chile, and South Africa, 2020

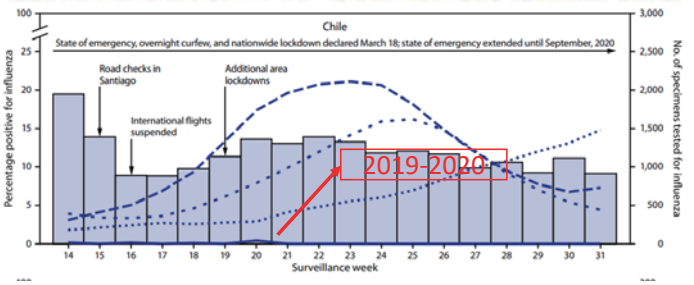
In the United States, influenza virus circulation declined sharply within 2 weeks of the COVID-19 emergency declaration and widespread implementation of community mitigation measures, including school closures, social distancing, and mask wearing, although the exact timing varied by location

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

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



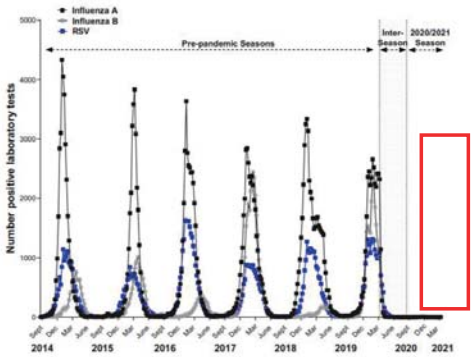




MMWR Morb Mortal Wkly Rep. 2020 Sep 18;69(37):1305-1309

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

A



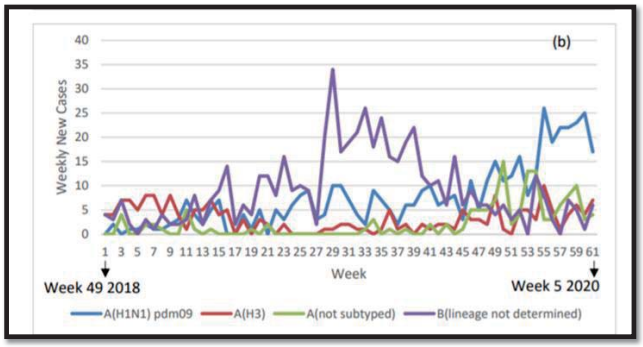
For influenza A and B, the percent positive decreased to 0.0015 and 0.0028 times that of pre-pandemic (2014-2019) levels respectively

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

Correlations between control of COVID-19 transmission and influenza occurrences in Malaysia



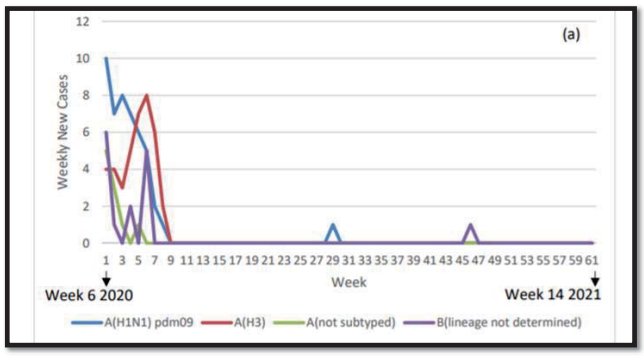


Table 2
Mann–Whitney U-test for Influenza Cases Before and After the Onset of COVID-19.

Pair of Influenza Cases[a]	Mann–Whitney U	Wilcoxon W	Z	Asymptotic Significance (two-tailed)
A1(H1N1) pdm09	371.50	2262.50	−8.05	<0.001
A (H3)	610.00	2501.00	−6.91	<0.001
A (not subtyped)	989.50	2880.50	−5.54	<0.001
B (lineage not determined)	146.50	2037.50	−9.32	<0.001

[a] Week 6 of 2020 to Week 14 of 2021 and Week 49 of 2019 to Week 5 of 2020.

It shows that influenza incidences before and after the onset of COVID-19 were significantly different and that influenza cases have significantly reduced after the onset of COVID-19. The weekly cases of influenza and COVID-19 were significantly and negatively correlated.

Public Health. 2021 Jul 20;198:96-101.

Table 2. Analysis of the annual influenza incidence rates based on laboratory-confirmed test data

Variable	Years of influenza seasons				
	2016–2017	2017–2018	2018–2019	2019–2020	*p* value
Duration of epidemics, wk[a]	14 (influenza A)	19	14 (influenza A)	16	-
Duration of epidemic phases, wk[b]					
Exacerbation phase	4	6	6	13	0.002[c]
Relief phase	10	13	8	3	
Alleviation rates of seasonal epidemics					
Mean positive reduction rate per week, %	−4.85	−4.81	−4.92	−9.20	0.995[d]
Mean reduction in no. of patients per week, %	−13.5	−13.5	−18.3	−34.0	0.452[d]

[a]The period of the epidemic was between when the test positivity of influenza increased by ≥ 5% to the week before it fell to < 5%.
[b]The exacerbation period was from the beginning of the epidemic to the week when the test positivity of influenza was the highest, while the relief period was the period from the peak to the end of the epidemic.
[c]Statistical significance was tested by the linear-by-linear association.
[d]Statistical significance was tested by Kruskal-Wallis test.

- In previous seasons, the exacerbation period was shorter than the relief period when influenza spread rapidly in the community and then slowly recovered.
- Conversely, in the 2019 to 2020 season, the exacerbation period lasted for 13 weeks, with a 3-week relief period, and then, the epidemic quickly ended. When comparing the weekly average number of patient decline, to compare the alleviation rates of the influenza epidemic, yearly, the number of patients declined approximately 1.8 to 2.5 times faster than in the previous year.

Korean J Intern Med. 2021 Aug 18.

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

TABLE 1 | Characteristics of included prevalence studies.

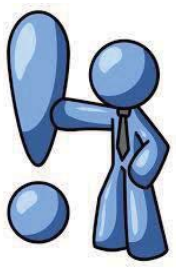
First author	Published time	Country	Patients with COVID-19	Patients with COVID-19–Influenza co-infection (%)	IV-A	IV-B	Co-infected patients	
							Mean age	Male/Female
Castillo et al. (8)	July, 2020	USA	42	1 (2.4)	1	0	21	1/0
Ding et al. (9)	March, 2020	China	115	5 (4.3)	3	2	50.2	2/3
Garazzino et al.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

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

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

Conclusions

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



The impact of the COVID-19 epidemic on other respiratory tract virus

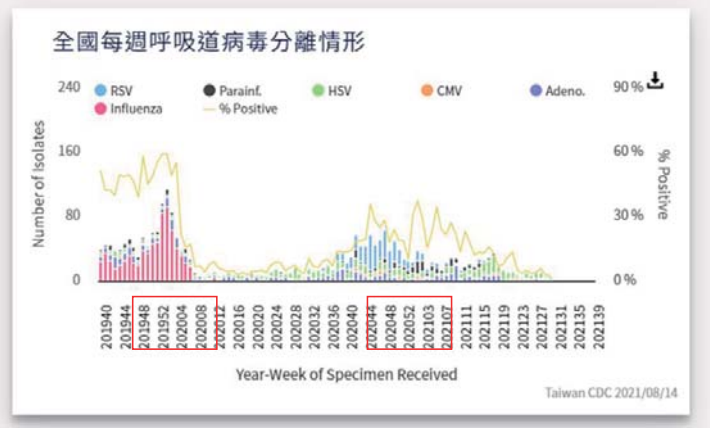


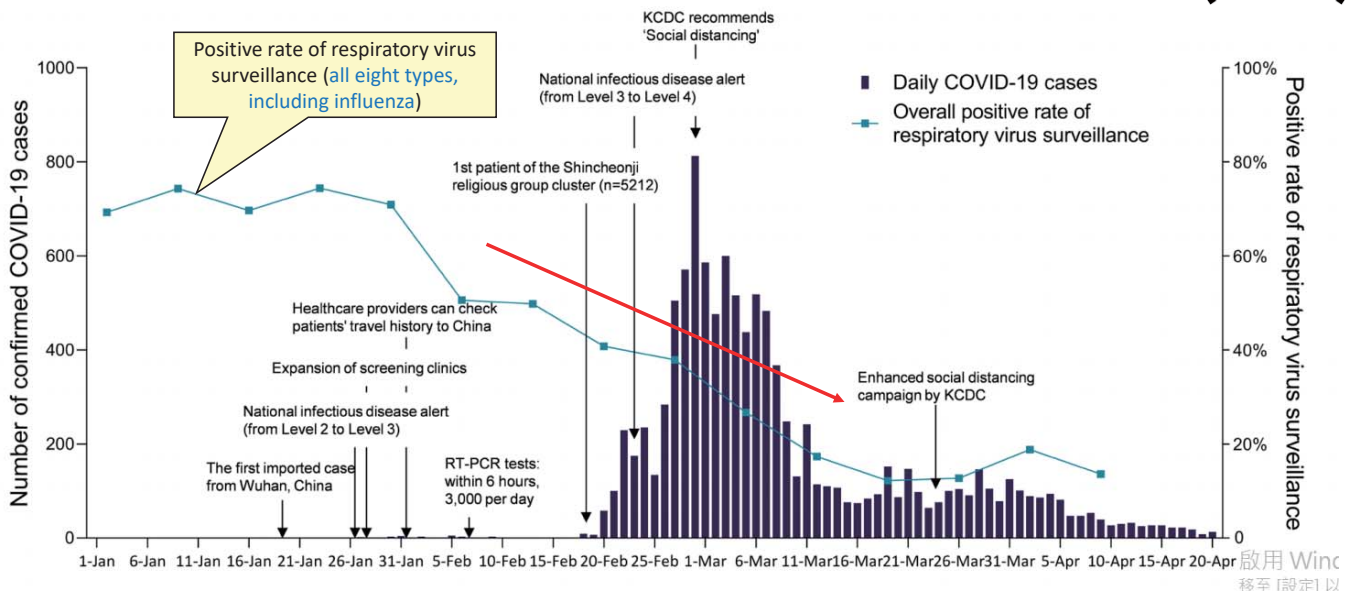
Table 1
Respiratory pathogen testing and detection rates in April–August 2020 compared to April–August 2017–2019

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

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

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

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

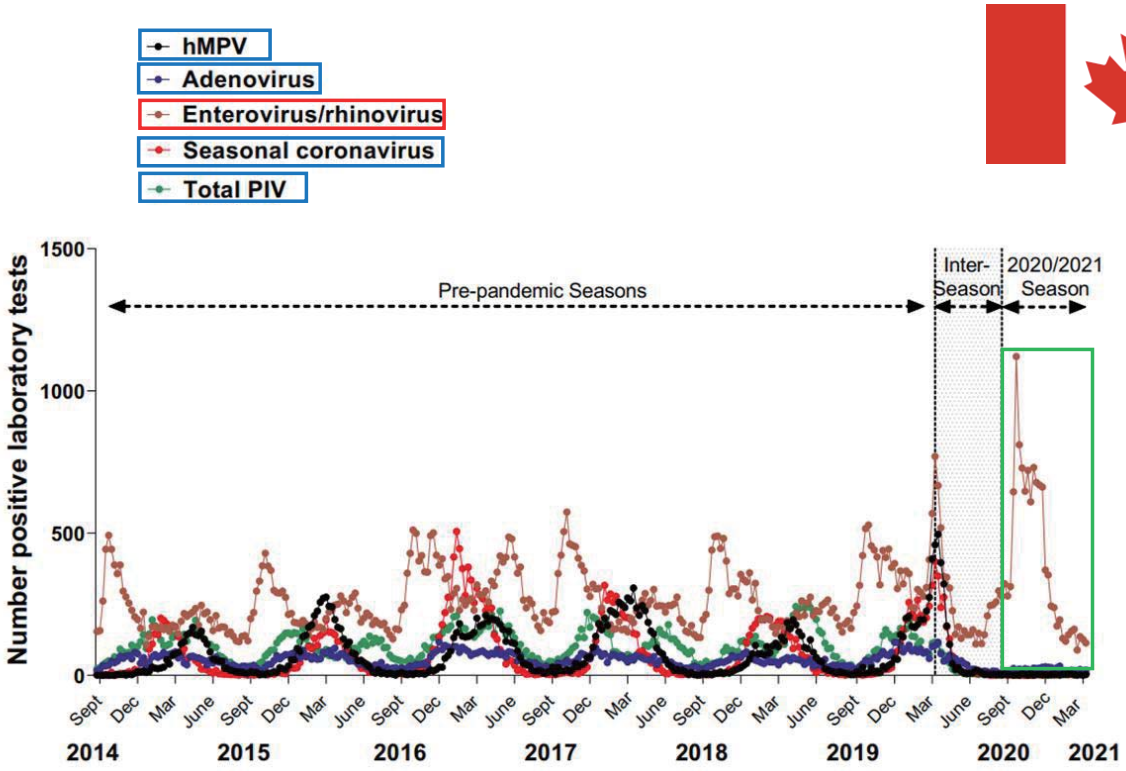


Korean J Intern Med. 2021 Aug 18.

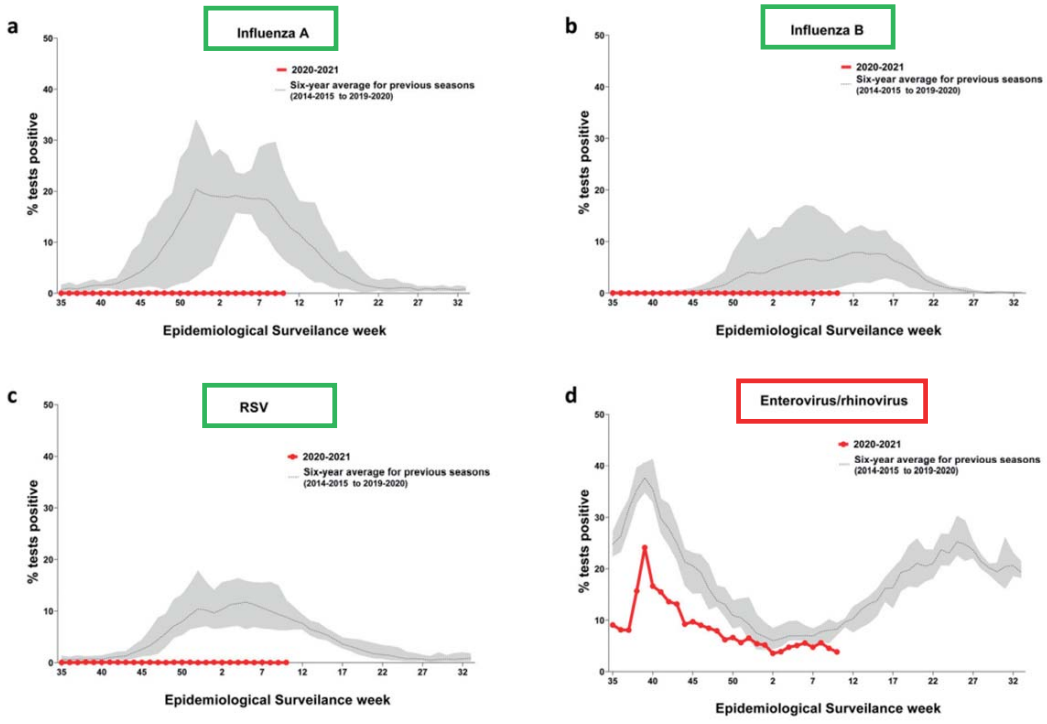
Table 3. Positive rates of respiratory virus infection confirmed during laboratory surveillance, stratified by year and post-influenza epidemic period (8 weeks)

Year or influenza season	Duration, wk	Total	Total positive rate, %	*p* value[b]	Positive rate for individual respiratory virus[a]					
					HCoV, %	HRV, %	HPIV, %	HMPV, %	HAdV, %	IFV, %
2016	53	11,111	59.0	-	5.5	15.0	6.0	4.1	6.3	15.9
2017	52	11,915	56.6	-	4.4	19.4	6.3	5.3	3.7	10.9
2018	52	11,966	63.0	-	5.7	16.3	6.1	4.9	6.8	17.0
2019	52	12,151	60.2	-	2.9	17.2	6.4	5.0	8.0	14.0
2016–17	Post-epidemic, 8[c]	1,702	47.7	0.002	2.2	18.0	14.5	1.3	4.9	1.7
2017–18	Post-epidemic, 8[c]	1,868	69.9	< 0.001	2.1	25.1	10.8	17.3	5.4	2.9
2018–19	Post-epidemic, 8[c]	1,563	67.6	< 0.001	1.2	20.2	18.2	6.9	9.3	1.3
2019–20	Post-epidemic, 8[c]	845	26.5	NA	4.3	6.4	0.2	2.6	6.6	1.3

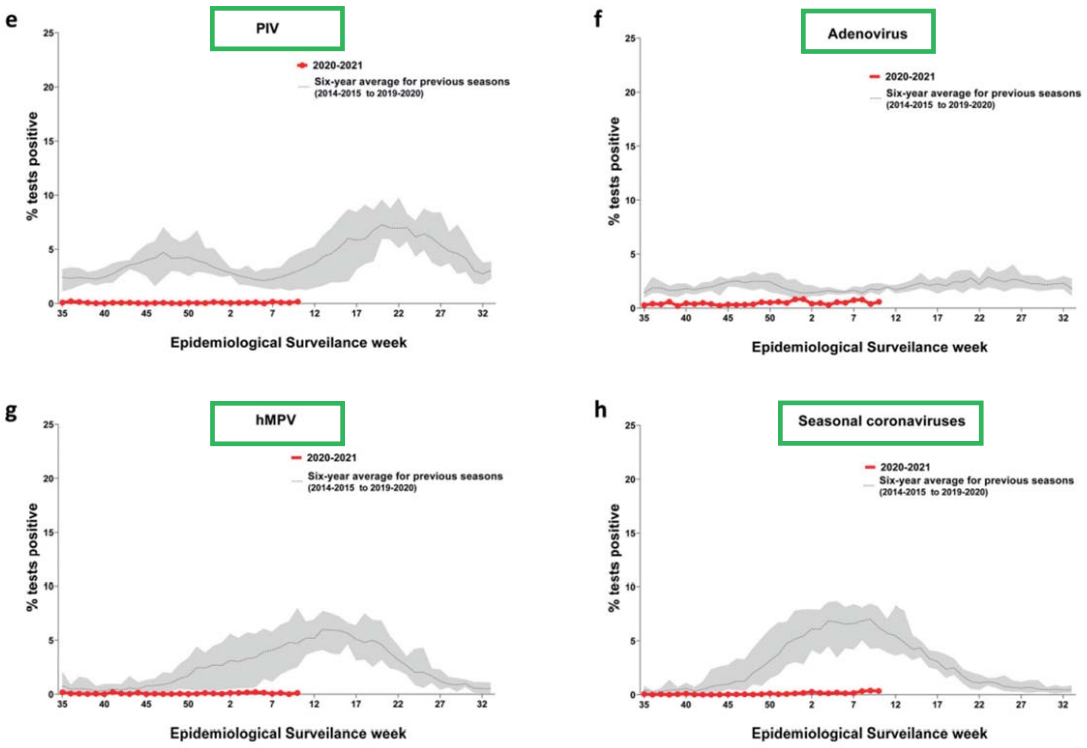
Korean J Intern Med. 2021 Aug 18.



Lancet Reg Health Am. 2021 Jul 17;100015



Lancet Reg Health Am. 2021 Jul 17;100015



Lancet Reg Health Am. 2021 Jul 17;100015

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
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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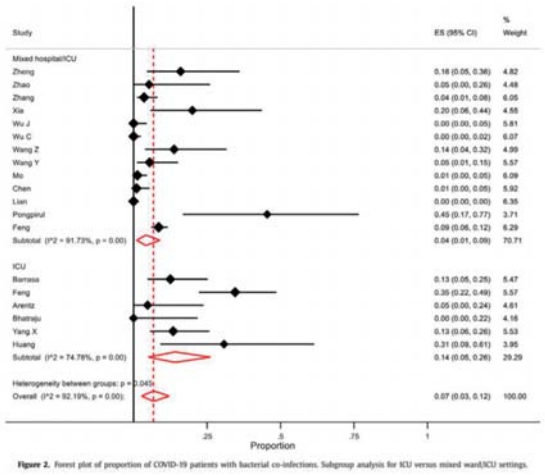
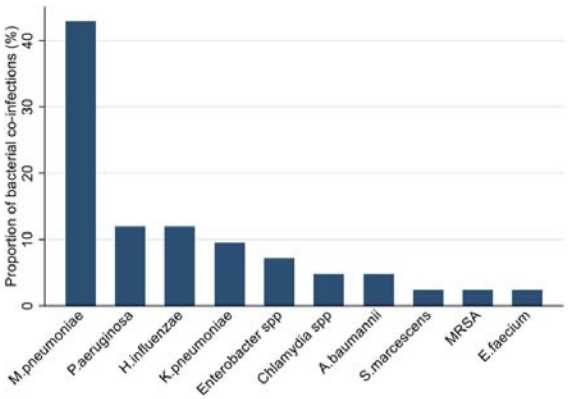
Co-infection of bacteria among COVID-19

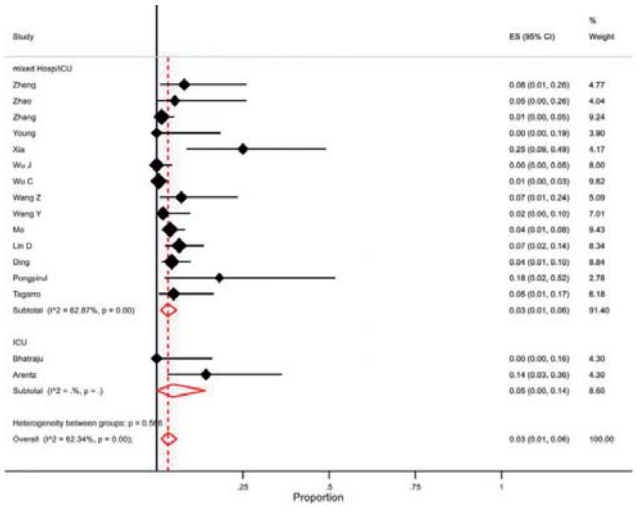


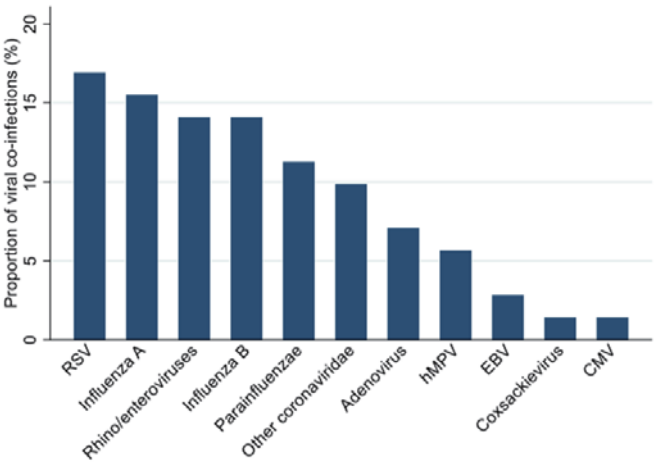


7% of hospitalised COVID-19 patients had a bacterial co-infection (95% CI 3-12%, n=2183, I2=92·2%). A higher proportion of ICU patients had bacterial co-infections than patients in mixed ward/ICU settings (14%, 95% CI 5-26, I2=74·7% versus 4%, 95% CI 1-9, I2= 91·7%). The commonest bacteria were ***Mycoplasma pneumonia***, ***Pseudomonas aerugi***nosa and ***Haemophilus influ***enzae.

J Infect. 2020 Aug;81(2):266-275.

Co-infection of virus among COVID-19



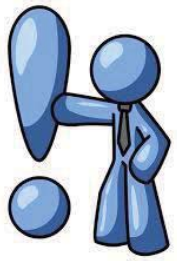


The pooled proportion with a viral co-infection was 3% (95% CI 1-6, n=1014, I2=62·3%), with **Respiratory Syncytial Virus** and **influenza A** the commonest.

J Infect. 2020 Aug;81(2):266-275.

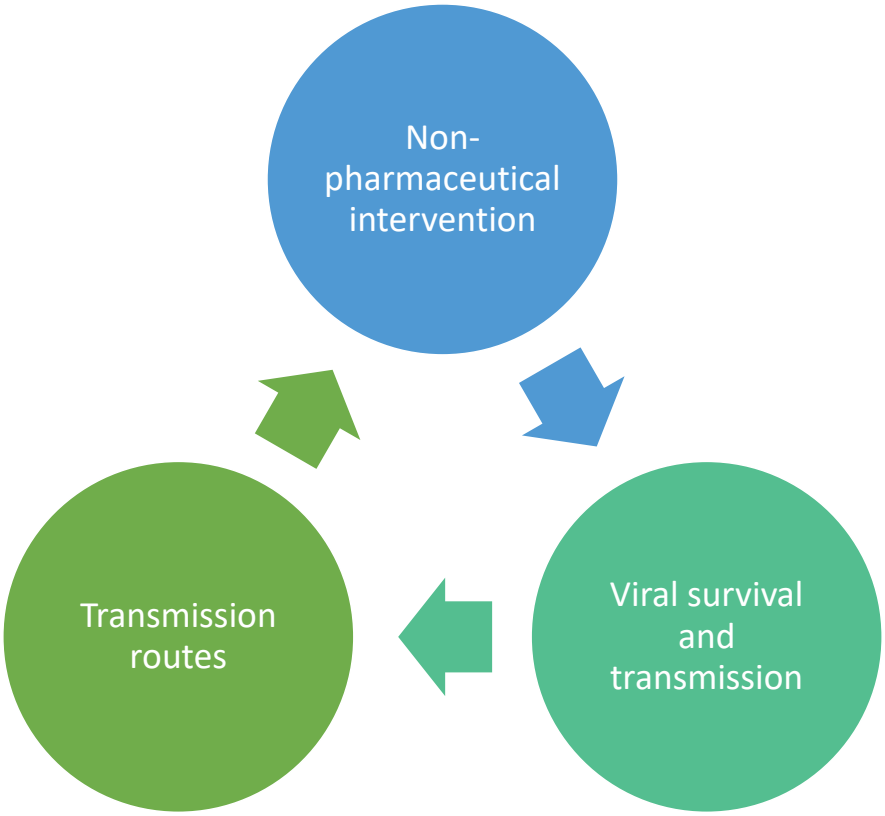
Conclusions

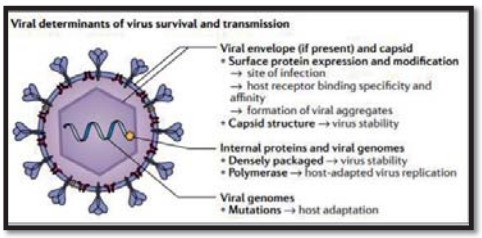
- The beneficial impact of nonpharmaceutical interventions on other respiratory virus remain, except for enterovirus/rhinovirus

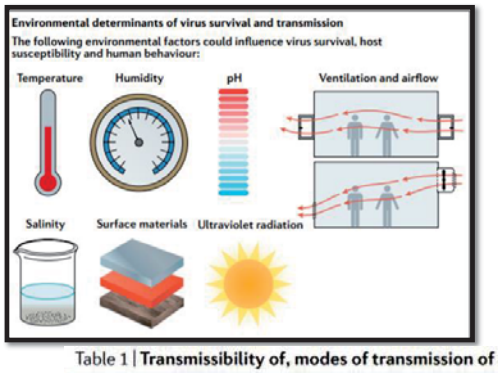


What might happen after mitigation of nonpharmaceutical interventions for COVID-19 epidemics?

- The duration of the effect of the COVID-19 pandemic and associated mitigation measures on respiratory virus circulation is unknown.
- Circulation of other respiratory viruses might continue to change as pandemic mitigation measures are adjusted and as prevalence of and immunity to both SARS-CoV-2, the virus that causes COVID-19, and immunity to these other viruses waxes and wanes.







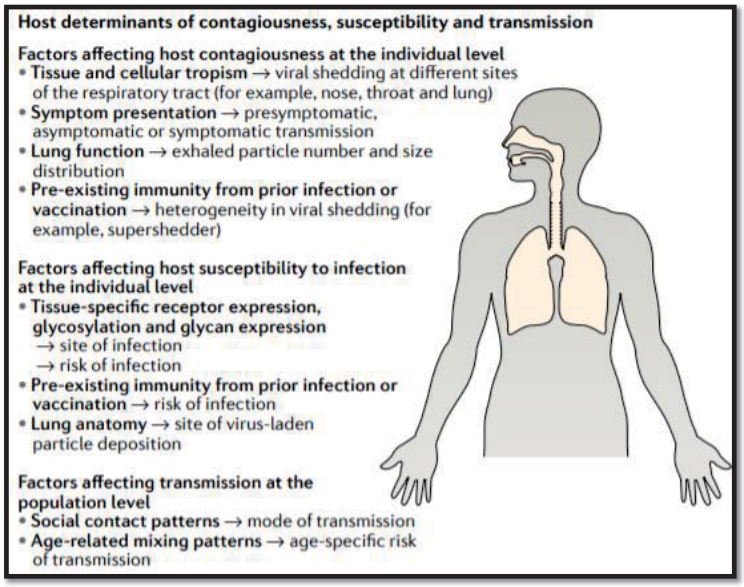
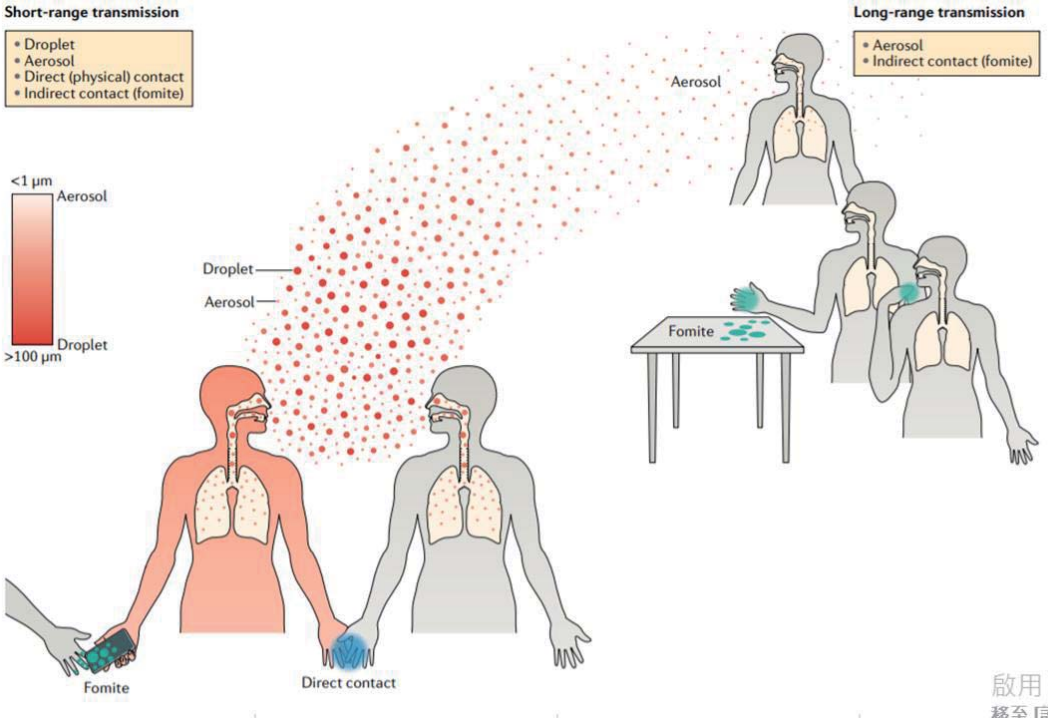


Table 1 | **Transmissibility of, modes of transmission of and transmission-based precautions for common respiratory viruses in humans**

Transmissibility and transmission	HCoV	IV	MeV	PIV	RSV	HMPV	VZV	RhV	HAdV[a]
Transmissibility[b]									
Basic reproduction number (R_0)	0.5–8.0	1.0–21.0	1.4–770	2.3–2.7	0.9–21.9	–	1.2–16.9	1.2–2.7	2.3–5.1
Household SAR (%)	0–38.2	1.4–38.0	52.0–84.6	36.0–67.0	11.6–39.3	–	61.0–78.1	28.0–58.0	–

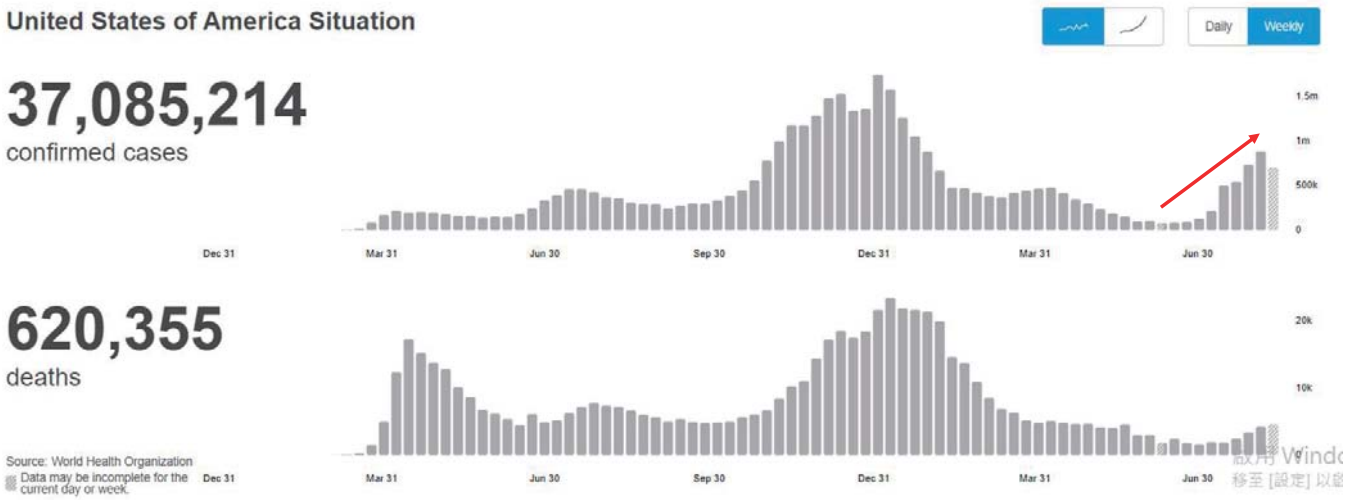
Seasonal influenza virus (R0 = 1.28)/SARS-CoV-2 (R0 = 2–3.5)

Nat Rev Microbiol. 2021 Aug;19(8):528-545.

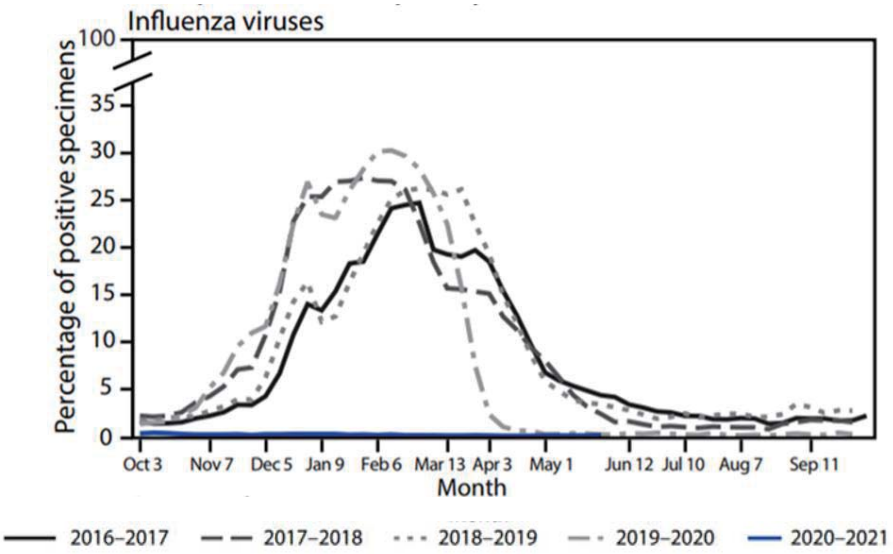


Nat Rev Microbiol. 2021 Aug;19(8):528-545.

In **United States of America**, from **3 January 2020** to **5:22pm CEST, 20 August 2021**, there have been **37,085,214 confirmed cases** of COVID-19 with **620,355 deaths**, reported to WHO. As of **12 August 2021**, a total of **355,480,412 vaccine doses** have been administered.

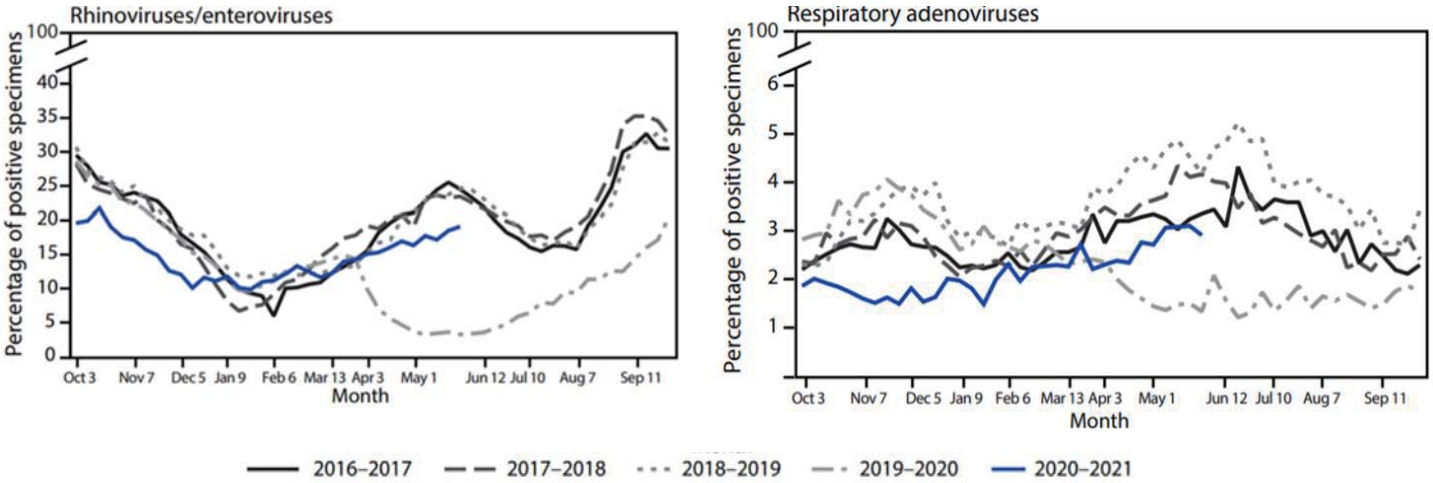


https://covid19.who.int/region/amro/country/us



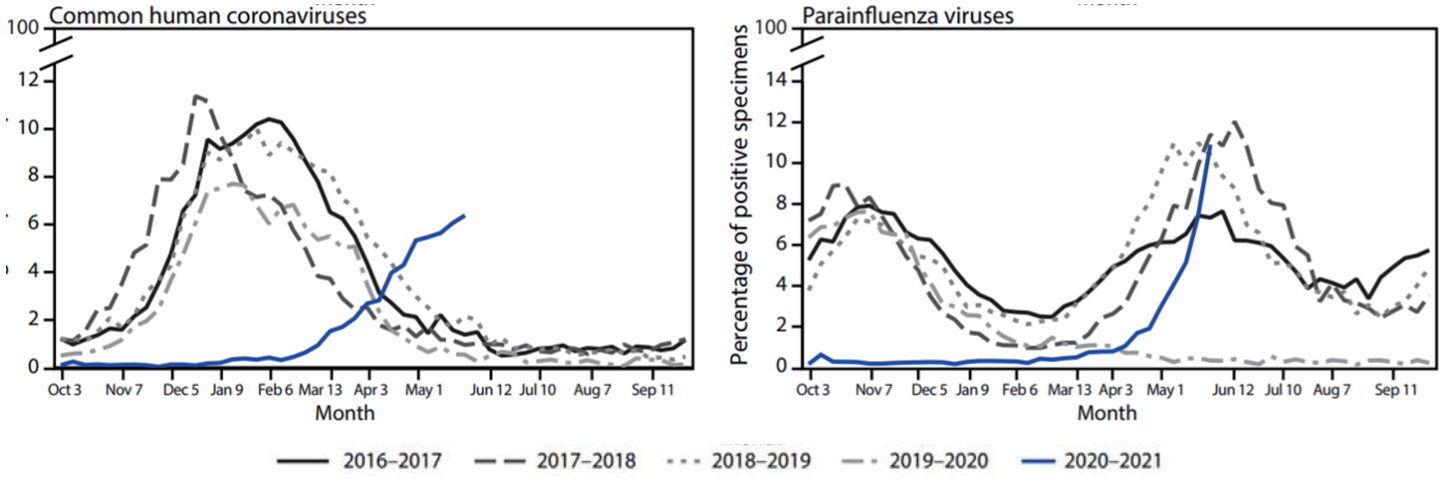
- Reduced circulation of influenza viruses during the past year might affect the severity of the upcoming influenza season given the prolonged absence of ongoing natural exposure to influenza viruses.
- Lower levels of population immunity, especially among younger children, could portend more widespread disease and a potentially more severe epidemic when influenza virus circulation resumes.

MMWR Morb Mortal Wkly Rep. 2021 Jul 23;70(29):1013-1019



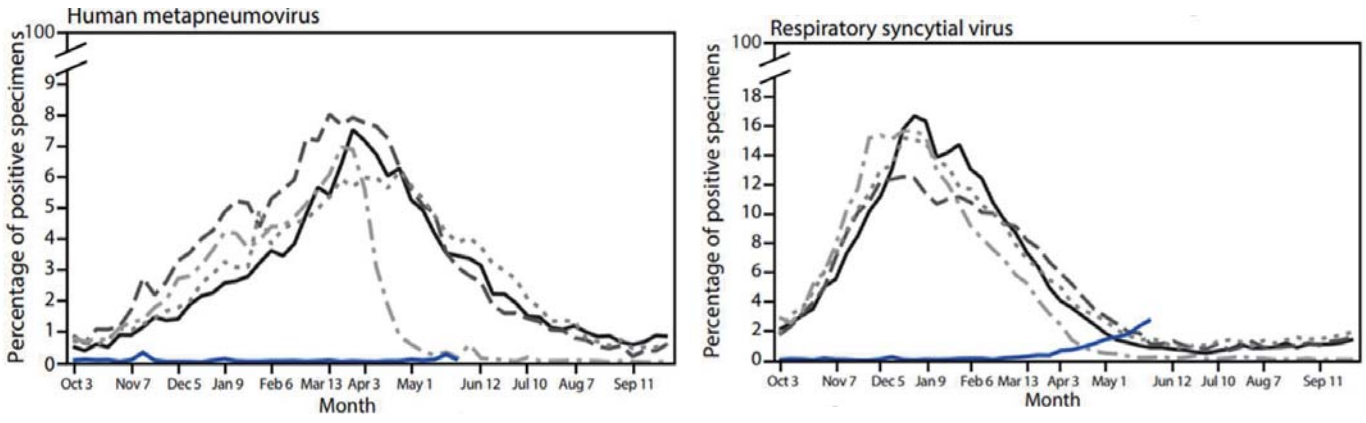
- RAdV and RV/EV activity continued during 2020 and might be returning to prepandemic circulation patterns.
- Factors contributing to this distinct circulation are unclear but might include the relative importance of different transmission mechanisms, such as aerosol, droplet, or contact, the role of asymptomatic transmission, and prolonged survival of these nonenveloped viruses on surfaces, all of which might make these viruses less susceptible to nonpharmaceutical interventions, such as mask-wearing and surface cleaning.

MMWR Morb Mortal Wkly Rep. 2021 Jul 23;70(29):1013-1019



The delay in circulation of PIVs and HCoVs, which circulate at high levels among children, could be related to some schools suspending in-person classes until late winter.

MMWR Morb Mortal Wkly Rep. 2021 Jul 23;70(29):1013-1019



- However, the relative absence of HMPV, which affects a similar age group as RSV (i.e., children aged <2 years) is unexplained.
- The unusual timing of rising RSV detections was also observed in Western Australia.

MMWR Morb Mortal Wkly Rep. 2021 Jul 23;70(29):1013-1019

Conclusions

- The different epidemiologic patterns of respiratory viruses observed during the COVID-19 pandemic in this U.S. surveillance summary raise questions about transmission and prevention, such as the contribution of birth cohort effects, natural immunity, and interventions.

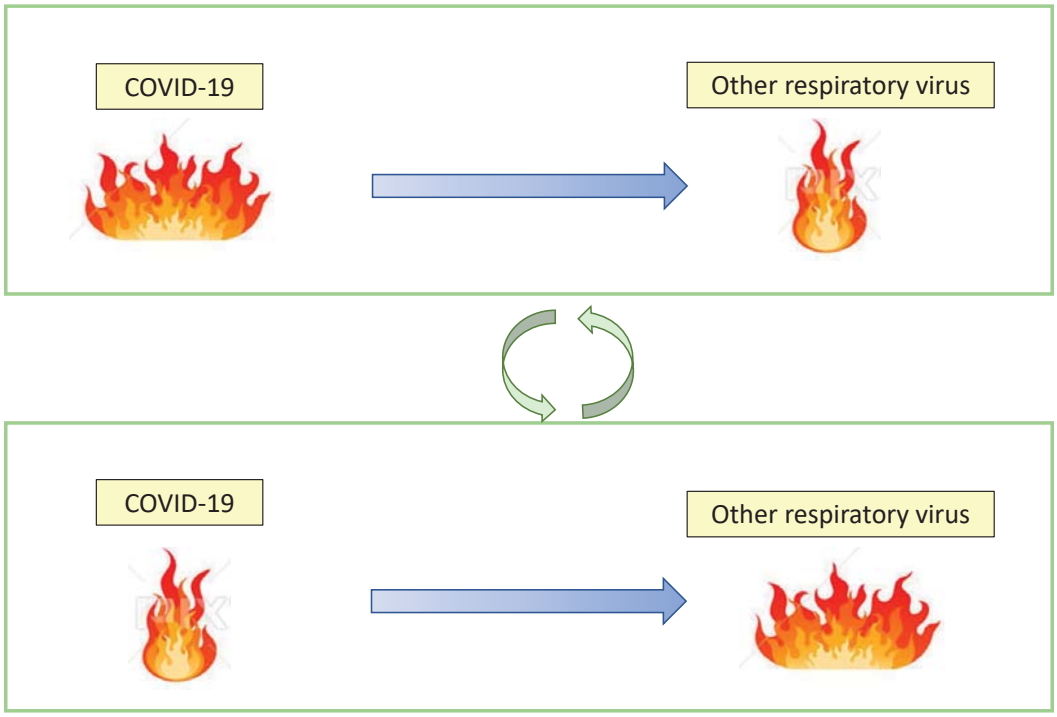
- The respiratory viruses might not exhibit typical seasonal circulation patterns and that a resumption of circulation of certain respiratory viruses is occurring, therefore an increased index of suspicion and testing for multiple respiratory pathogens remain important.

MMWR Morb Mortal Wkly Rep. 2021 Jul 23;70(29):1013-1019

Non-pharmaceutical interventions for non-COVID-19 human respiratory viruses.

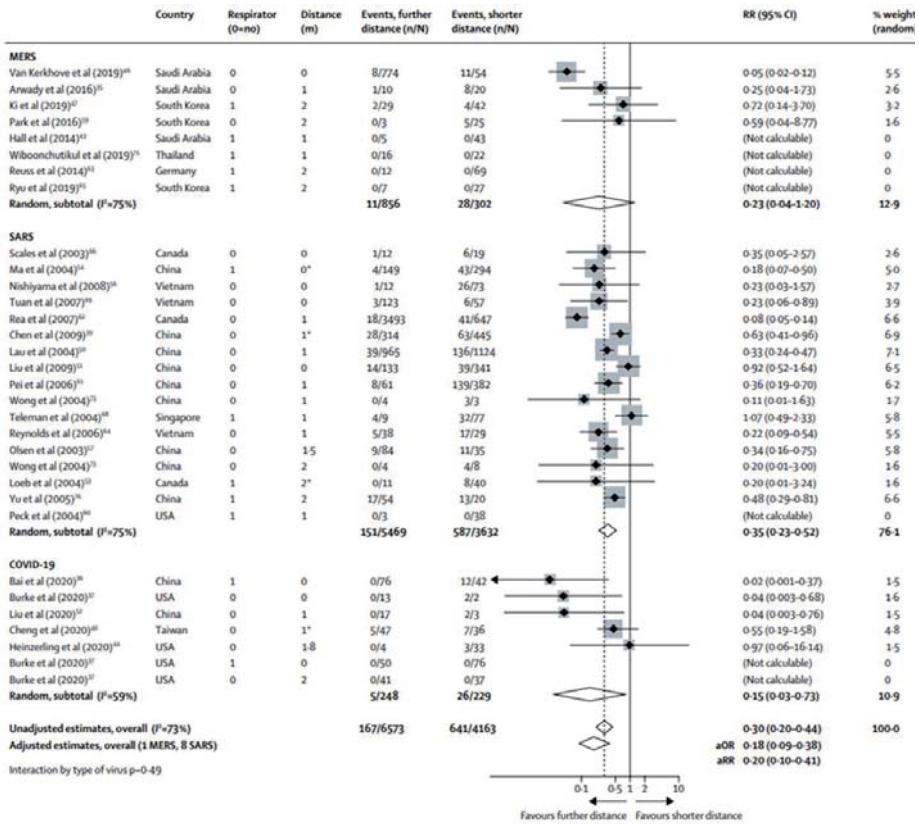
Masking

Social distance



- Keep strict non-pharmaceutical interventions for COVID-19
- Special attention to enterovirus/adenovirus/rhinovirus
- Influenza vaccine.
- COVID-19 vaccine.

- Trade off between the COVID-19 epidemic and economy.
- Partially release the non-pharmaceutical interventions for COVID-19.
- Influenza vaccine.
- COVID-19 vaccine



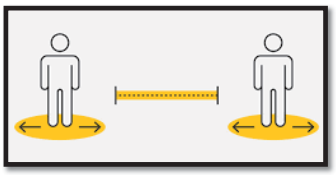
	Country	Respirator (0=no)	Distance (m)	Events, further distance (n/N)	Events, shorter distance (n/N)	RR (95% CI)	% weight (random
MERS							
Van Kerkhove et al (2019)[45]	Saudi Arabia	0	0	8/774	11/54	0·05 (0·02–0·12)	5·5
Arwady et al (2016)[35]	Saudi Arabia	0	1	1/10	8/20	0·25 (0·04–1·73)	2·6
Ki et al (2019)[47]	South Korea	1	2	2/29	4/42	0·72 (0·14–3·70)	3·2
Park et al (2016)[39]	South Korea	0	2	0/3	5/25	0·59 (0·04–8·77)	1·6
Hall et al (2014)[43]	Saudi Arabia	1	1	0/5	0/43	(Not calculable)	0
Wiboonchutikul et al (2019)[74]	Thailand	1	1	0/16	0/22	(Not calculable)	0
Reuss et al (2014)[41]	Germany	1	2	0/12	0/69	(Not calculable)	0
Ryu et al (2019)[46]	South Korea	1	2	0/7	0/27	(Not calculable)	0
Random, subtotal (I^2=75%)				**11/856**	**28/302**	**0·23 (0·04–1·20)**	**12·9**
SARS							
Scales et al (2003)[36]	Canada	0	0	1/12	6/19	0·35 (0·05–2·57)	2·6
Ma et al (2004)[54]	China	1	0*	4/149	43/294	0·18 (0·07–0·50)	5·0
Nishiyama et al (2008)[38]	Vietnam	0	0	1/12	26/73	0·23 (0·03–1·57)	2·7
Tuan et al (2007)[59]	Vietnam	0	0	3/123	6/57	0·23 (0·06–0·89)	3·9
Rea et al (2007)[60]	Canada	0	1	18/3493	41/647	0·08 (0·05–0·14)	6·6
Chen et al (2009)[39]	China	0	1*	28/314	63/445	0·63 (0·41–0·96)	6·9
Lau et al (2004)[58]	China	0	1	39/965	136/1124	0·33 (0·24–0·47)	7·1
Liu et al (2009)[55]	China	0	0	14/133	39/341	0·92 (0·52–1·64)	6·5
Pei et al (2006)[61]	China	0	1	8/61	139/382	0·36 (0·19–0·70)	6·2
Wong et al (2004)[75]	China	0	1	0/4	3/3	0·11 (0·01–1·63)	1·7
Teleman et al (2004)[68]	Singapore	1	1	4/9	32/77	1·07 (0·49–2·33)	5·8
Reynolds et al (2006)[64]	Vietnam	0	1	5/38	17/29	0·22 (0·09–0·54)	5·5
Olsen et al (2003)[57]	China	0	1·5	9/84	11/35	0·34 (0·16–0·75)	5·8
Wong et al (2004)[75]	China	0	2	0/4	4/8	0·20 (0·01–3·00)	1·6
Loeb et al (2004)[53]	Canada	1	2*	0/11	8/40	0·20 (0·01–3·24)	1·6
Yu et al (2005)[76]	China	1	2	17/54	13/20	0·48 (0·29–0·81)	6·6
Peck et al (2004)[66]	USA	1	1	0/3	0/38	(Not calculable)	0
Random, subtotal (I^2=75%)				**151/5469**	**587/3632**	**0·35 (0·23–0·52)**	**76·1**
COVID-19							
Bai et al (2020)[30]	China	1	0	0/76	12/42	0·02 (0·001–0·37)	1·5
Burke et al (2020)[31]	USA	0	0	0/13	2/2	0·04 (0·003–0·68)	1·6
Liu et al (2020)[32]	China	0	1	0/17	2/3	0·04 (0·003–0·76)	1·5
Cheng et al (2020)[40]	Taiwan	0	1*	5/47	7/36	0·55 (0·19–1·58)	4·8
Heinzerling et al (2020)[44]	USA	0	1·8	0/4	3/33	0·97 (0·06–16·14)	1·5
Burke et al (2020)[31]	USA	1	0	0/50	0/76	(Not calculable)	0
Burke et al (2020)[31]	USA	0	2	0/41	0/37	(Not calculable)	0
Random, subtotal (I^2=59%)				**5/248**	**26/229**	**0·15 (0·03–0·73)**	**10·9**
Unadjusted estimates, overall (I^2=73%)				**167/6573**	**641/4163**	**0·30 (0·20–0·44)**	**100·0**
Adjusted estimates, overall (1 MERS, 8 SARS)						aOR 0·18 (0·09–0·38)	
						aRR 0·20 (0·10–0·41)	

Interaction by type of virus p=0·49

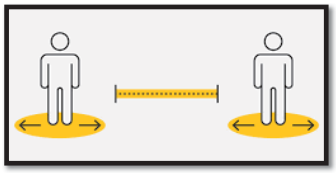
0·1 0·5 1 2 10

Favours further distance Favours shorter distance

Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis



Lancet 2020; 395: 1973–87



	Studies and participants	Relative effect (95% CI)	Anticipated absolute effect (95% CI), eg, chance of viral infection or transmission		Difference (95% CI)	Certainty*	What happens (standardised GRADE terminology)[29]
			Comparison group	Intervention group			
Physical distance ≥1 m vs <1 m	Nine adjusted studies (n=7782); 29 unadjusted studies (n=10 736)	aOR 0·18 (0·09 to 0·38); unadjusted RR 0·30 (95% CI 0·20 to 0·44)	Shorter distance, 12·8%	Further distance, 2·6% (1·3 to 5·3)	−10·2% (−11·5 to −7·5)	Moderate†	A physical distance of more than 1 m probably results in a large reduction in virus infection; for every 1 m further away in distancing, the relative effect might increase 2·02 times
Face mask vs no face mask	Ten adjusted studies (n=2647); 29 unadjusted studies (n=10 170)	aOR 0·15 (0·07 to 0·34); unadjusted RR 0·34 (95% CI 0·26 to 0·45)	No face mask, 17·4%	Face mask, 3·1% (1·5 to 6·7)	−14·3% (−15·9 to −10·7)	Low‡	Medical or surgical face masks might result in a large reduction in virus infection; N95 respirators might be associated with a larger reduction in risk compared with surgical or similar masks§
Eye protection (faceshield, goggles) vs no eye protection	13 unadjusted studies (n=3713)	Unadjusted RR 0·34 (0·22 to 0·52)¶	No eye protection, 16·0%	Eye protection, 5·5% (3·6 to 8·5)	−10·6% (−12·5 to −7·7)	Low‖	Eye protection might result in a large reduction in virus infection

Lancet 2020; 395: 1973–87

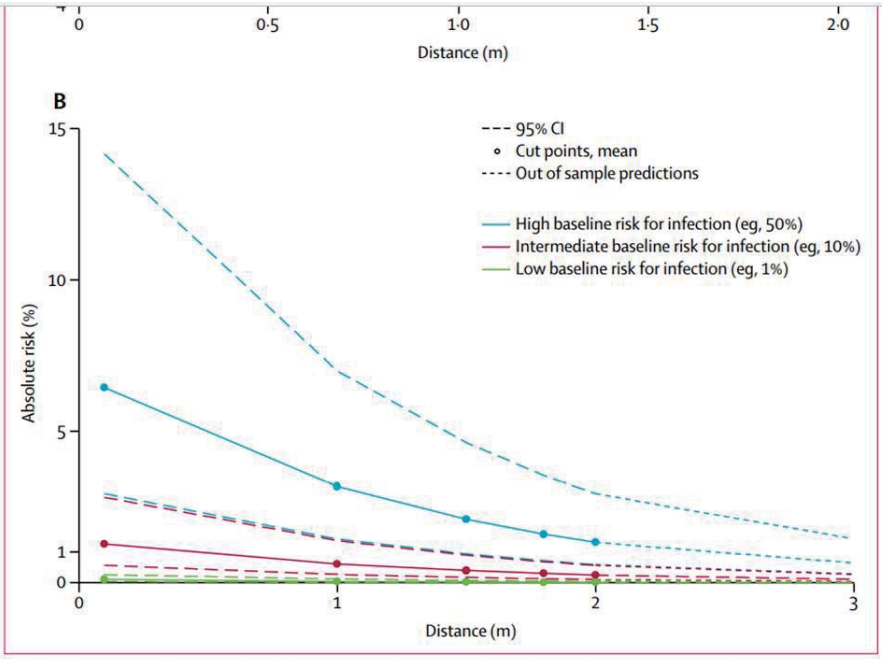
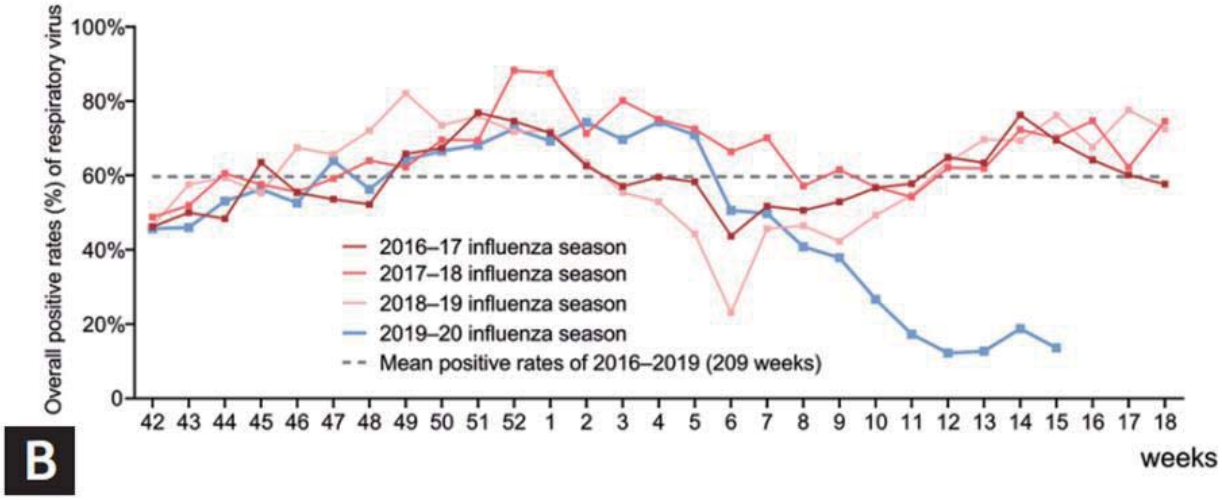
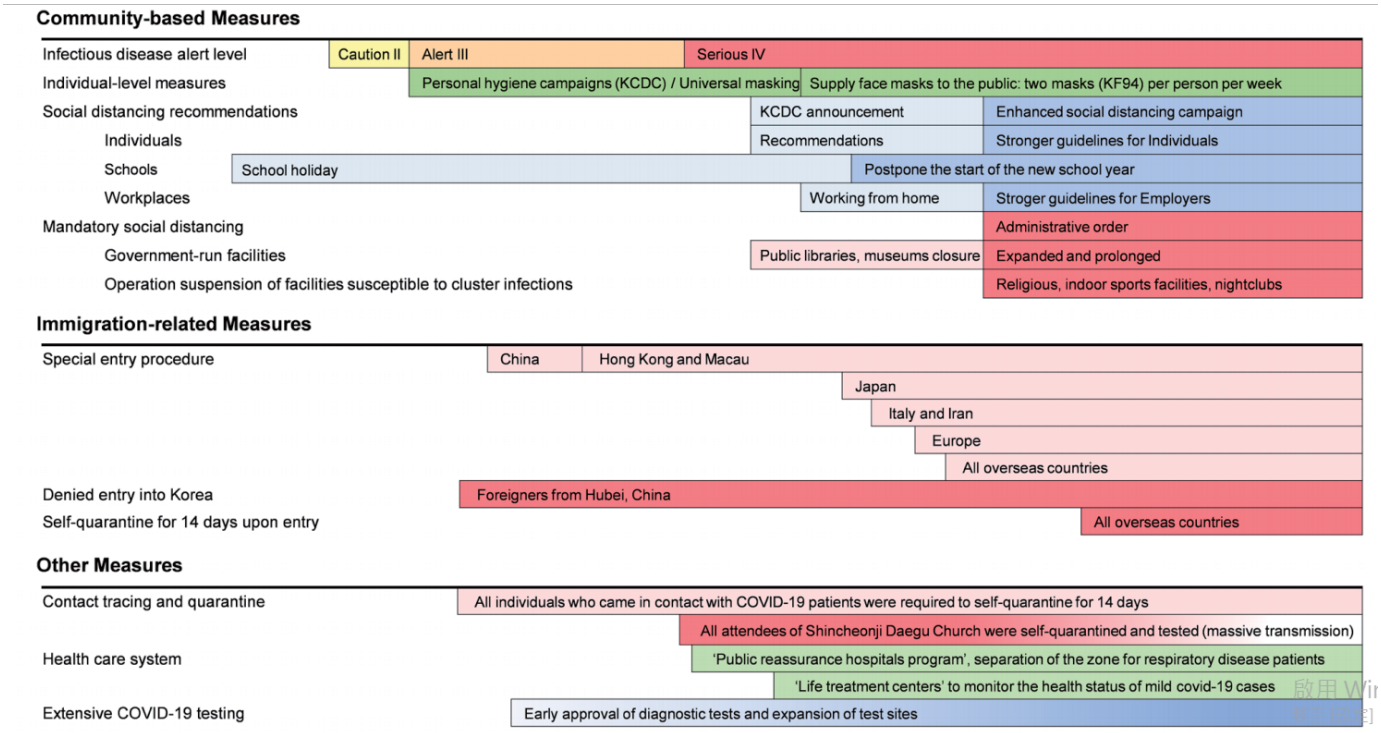


***Figure 3*: Change in relative risk with increasing distance and absolute risk with increasing distance**
Meta-regression of change in relative risk with increasing distance from an infected individual (A). Absolute risk of transmission from an individual infected with SARS-CoV-2, SARS-CoV, or MERS-CoV with varying baseline risk and increasing distance (B). SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. SARS-CoV=severe acute respiratory syndrome coronavirus. MERS-CoV=Middle East respiratory syndrome coronavirus.

Lancet 2020; 395: 1973–87



Korean J Intern Med. 2021 Aug 18.



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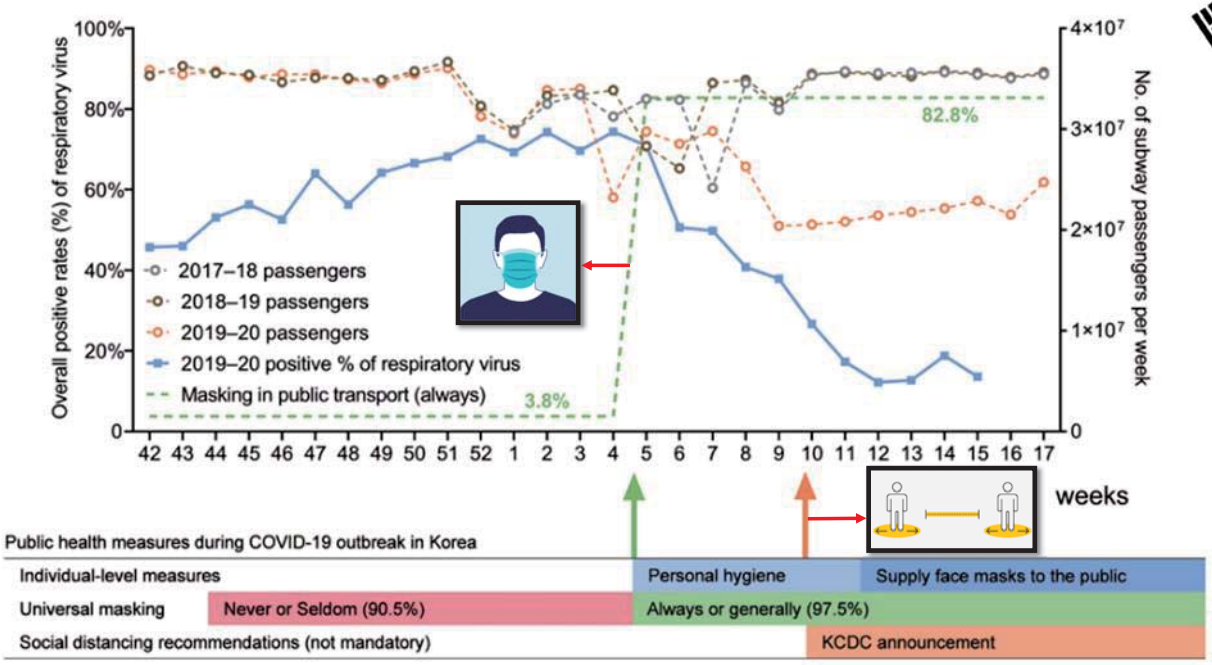

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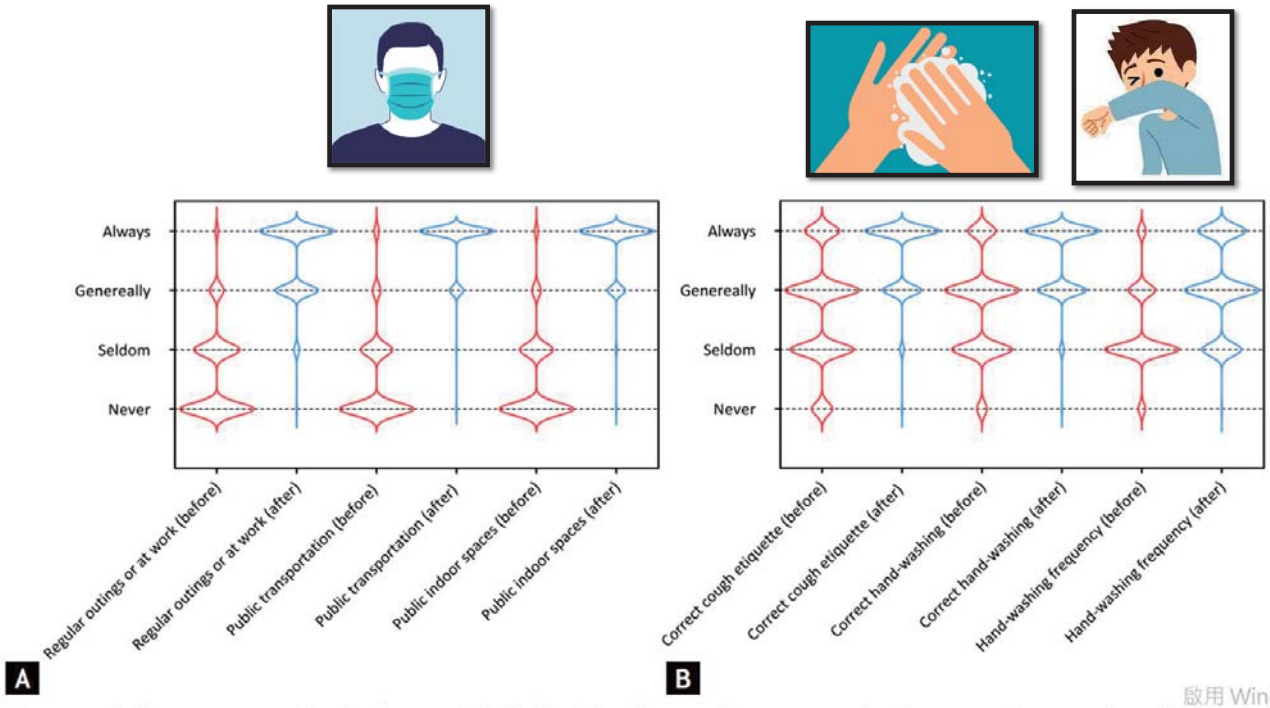


Figure 2. Online survey results for the use of individual-level preventive measures in the pre- and coronavirus disease 2019 (COVID-19) pandemic-periods. (A) Violin plots of universal masks in those at risk of social contact. (B) Violin plots of the ap-

Korean J Intern Med. 2021 Aug 18.

Masking for COVID-19 Is Associated with Decreased Emergency Department Utilization for Non-COVID Viral Illnesses and Respiratory Conditions in Maryland

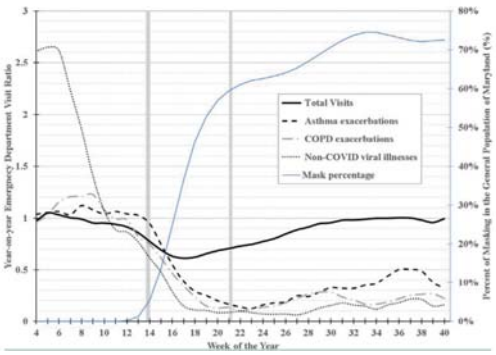


Table Linear Regression Results Showing the Association of Masking Percentage with Year-on-Year Ratios of ED Encounters for NCVI and Exacerbations of Asthma and COPD, Adjusted for Patient Factors and Total Visits, University of Maryland Medical System (Jan-Oct 2019 compared to Jan-Oct 2020).

Outcome	Variable*	Estimate	Standard Error	*P* Value
NCVI	Masking Percentage	−1.702	0.422	.0003
17.0%	Average Age	−3.605	3.711	.34
	Female Sex	0.017	2.184	.99
	Total Visits	1.681	2.542	.51
Asthma Exacerbations	Masking Percentage	−0.881	0.196	<.0001
8.8%	Average Age	−2.011	1.146	.09
	Female Sex	0.342	0.495	.49
	Prevalence of Asthma	−0.112	0.422	.79
	Total Visits	0.317	0.360	.38
COPD Exacerbations	Masking Percentage	−0.939	0.143	<.0001
9.4%	Average Age	−0.389	1.319	.77
	Female Sex	−0.102	0.343	.77
	Prevalence of COPD	0.276	0.076	.001
	Total Visits	0.655	0.313	.04

Masking percentage was not significantly associated with the year-on-year ratio for Total Visits (parameter estimate = 0.00204, P = .98). There were strong associations between masking percentage and year-on-year ratios for specific complaints, after adjusting for patient factors and Total Visits

A 10% percent increase in the prevalence of community masking was associated with a 17.0%, 8.8%, and 9.4% decrease in ED visits for NCVI and exacerbations of asthma exacerbations and chronic obstructive pulmonary disease, respectively (P < .001 for all).

Am J Med. 2021 Jul 7;S0002-9343(21)00410-1

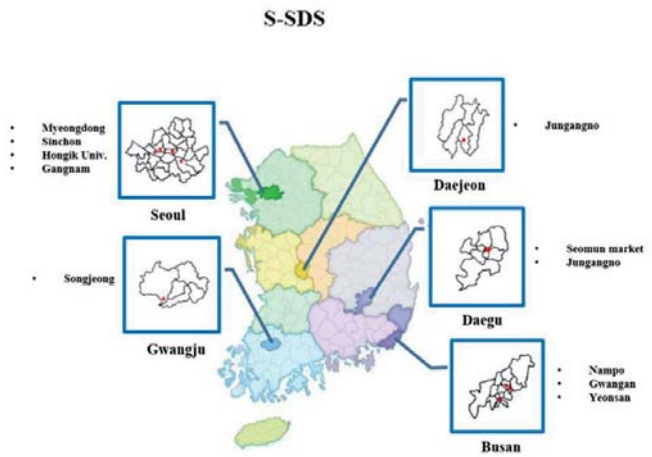


Figure 1. Major subway stations selected to estimate S-SDS. S-SDS was determined based on the number of passengers for 11 major subway stations in five cities of the Republic of Korea. S-SDS, subway use-based social distancing score.

$$\text{Subway use} - \text{based SDS} = \frac{\text{The number of passengers at the subway stations per week}}{\text{The average number of weekly passengers in the last 4 years}}$$

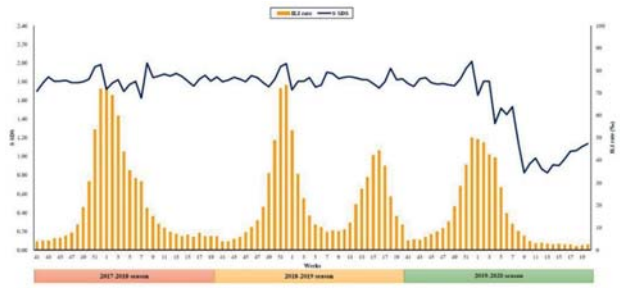


Figure 2. Weekly trend of ILI rates and S-SDS. The weekly trend of ILI rates and S-SDS during three consecutive flu seasons (2017–2018, 2018–2019 and 2019–2020 seasons) is shown. Weekly trend of ILI rate is shown as a bar graph and that of S-SDS is shown as a line graph. ILI, influenza-like illness; S-SDS, subway use-based social distancing score.

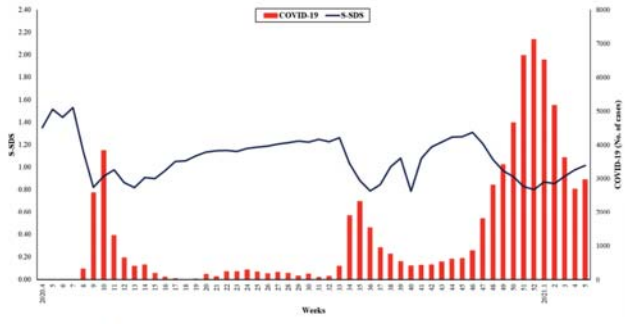


Figure 3. COVID-19 pandemic activity and S-SDS. COVID-19 cases were presented during study periods, between week 5 of 2020 and week 5 of 2021. The weekly trend of COVID-19 activity is shown as a bar graph and that of S-SDS is shown as a line graph. COVID-19, coronavirus disease 2019; S-SDS, subway use-based social distancing score.

J Clin Med. 2021 Jul 29;10(15):3369

Table 1. Dynamic relationship (vector autoregressive model) between subway use-based social distancing score and influenza-like illness/coronavirus disease 2019.

Indicator	Variable	Coefficient	Standard Error	*t*-Statistic	Probability > |*t*|
		S-SDS and ILI rate			
S-SDS	ILI (t-1)	0.00362	0.00251	1.44	0.1519
	ILI (t-2)	0.01137	0.00497	2.29	0.0242
	ILI (t-3)	0.01286	0.00495	2.6	0.0107
	ILI (t-4)	0.00613	0.00244	2.51	0.0137
ILI	S-SDS (t-1)	3.11338	3.85642	0.81	0.4214
	S-SDS (t-2)	5.24173	4.69760	1.12	0.2672
	S-SDS (t-3)	1.08023	4.72556	−0.23	0.8197
	S-SDS (t-4)	6.71900	3.97062	1.69	0.0937
		S-SDS and COVID-19 occurrence			
S-SDS	COVID-19 (t-1)	0	0.00003	−0.17	0.8690
	COVID-19 (t-2)	−0.00002	0.00004	−0.52	0.6081
	COVID-19 (t-3)	0.00001	0.00002	0.32	0.7475
COVID-19	S-SDS (t-1)	−1196.25	909.395	−1.32	0.1952
	S-SDS (t-2)	−2836.55	1125.70	−2.52	0.0154
	S-SDS (t-3)	−344.598	934.842	−0.37	0.7142

S-SDS, subway use-based social distancing score; ILI, influenza-like illness; COVID-19, coronavirus disease; ILI (t-1), ILI reported in a prior week; ILI (t-2), ILI reported in two weeks before; ILI (t-3), ILI reported in three weeks before; ILI (t-4), ILI reported in four weeks before; S-SDS (t-1), S-SDS calculated in a prior week; S-SDS (t-2), S-SDS calculated in two weeks before; S-SDS (t-3), S-SDS calculated in three weeks before; S-SDS (t-4), S-SDS calculated in four weeks before; COVID-19 (t-1), COVID-19 calculated in a prior week; COVID-19 (t-2), COVID-19 calculated in two weeks before; COVID-19 (t-3), COVID-19 calculated in three weeks before.

Interestingly, unlike influenza, S-SDS was not predictive of COVID-19 activity during the study period. The public has been concerned regarding the spread of COVID-19 through public transportation, although this study showed that the COVID-19 pandemic activity was not significantly affected by subway use density.

The impact of social distancing policies on non-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) respiratory pathogens

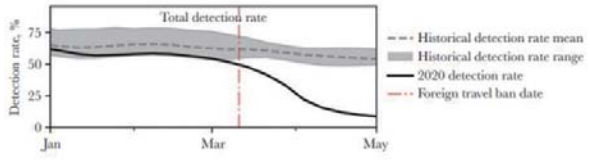


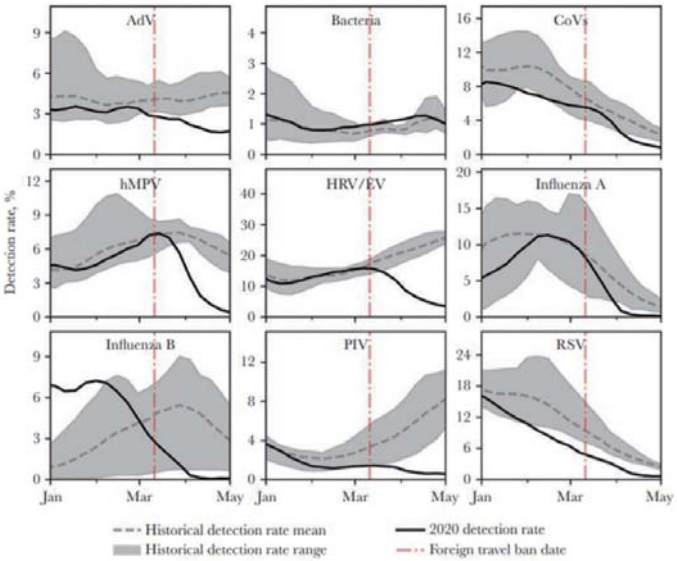
Figure 1. National historical and 2020 total detection rates. The range surrounding the historical rates is from 2015 through 2019.

Linear mixed-effect models were implemented to explore the effects of 5 social distancing policies on non-SARS-CoV-2 respiratory pathogens across 9 states from January 1 through May 1, 2020.

Social distancing policies:

- Federal guidelines
- Foreign travel bans
- Stay at home orders
- Bans on large gatherings
- Public school closures
- Dine-in restaurant closures
- Gym closures

Model results indicate that several social distancing policies were associated with a reduction in total detection rate, by nearly 15%.
Policies were associated with decreases in pathogen circulation of human rhinovirus/enterovirus and human metapneumovirus, as well as influenza A, which typically decrease after winter. Parainfluenza viruses failed to circulate at historical levels during the spring. The total detection rate in April 2020 was 35% less than the historical average. Many of the pathogens driving this difference fell below the historical detection rate ranges within 2 weeks of initial policy



Open Forum Infect Dis. 2021 Mar 17;8(7):ofab133

Conclusions

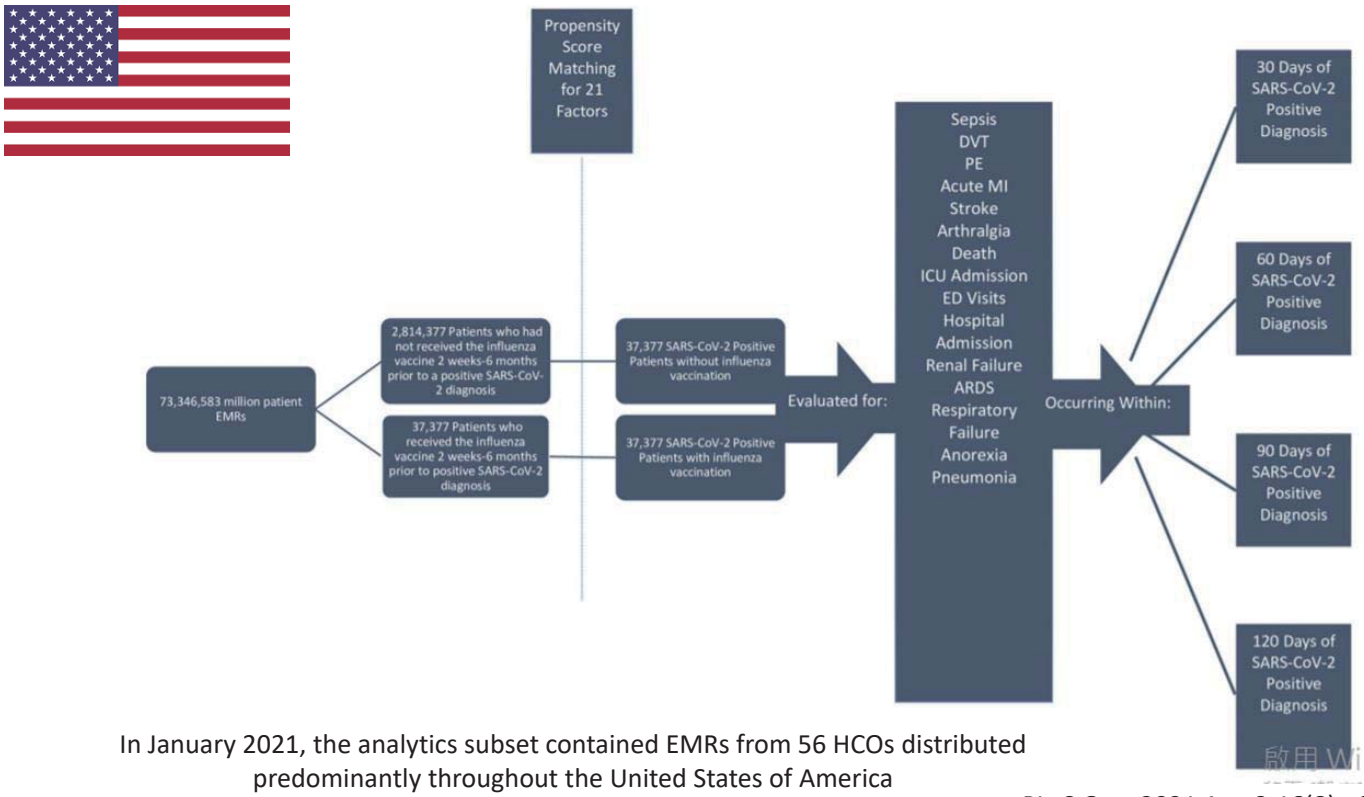
- Non-pharmaceutical interventions for non-COVID-19 human respiratory viruses still work.
- The best combinations after the end of COVID-19 epidemic remain unknown.

Should we receive influenza vaccine in the COVID-19 epidemic?

Protective effect of influenza vaccine on the outcome of COVID-19

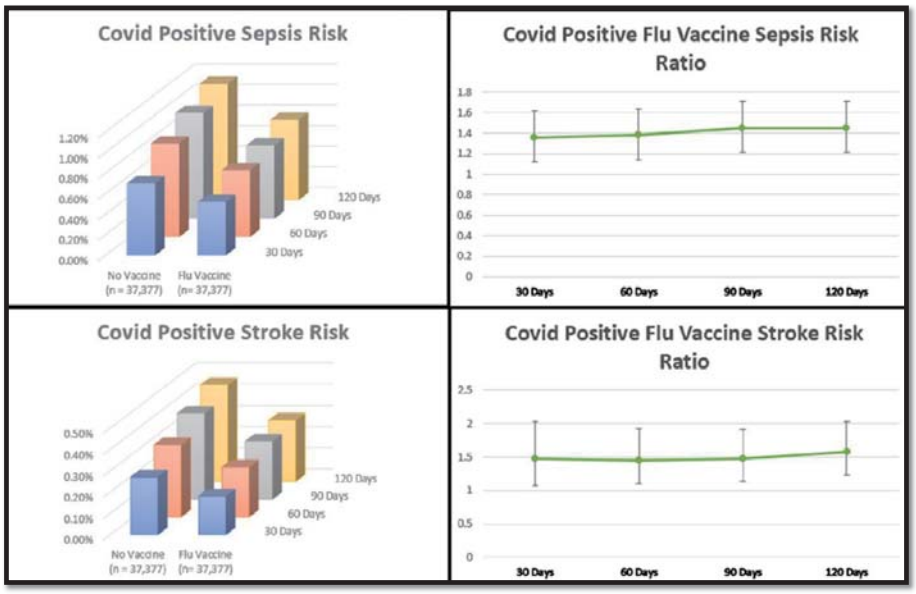
- The first hypothesis centers around the presence of MF59 in the influenza vaccine: an oil-in-water squalene emulsion that has been shown to assist in potentiating an immune response to SARS-CoV variants.
- Alternatively, influenza vaccination's potential protective effect may be explained by its ability to stimulate the activation of natural killer cells, the levels of which have been found to be considerably decreased in moderate and severe SARS-CoV-2 cases.
- Influenza vaccine may lead to decreased risk of cardiovascular events due to potential interaction with immune and inflammatory systems to promote plaque stabilization.

PLoS One. 2021 Aug 3;16(8):e0255541.



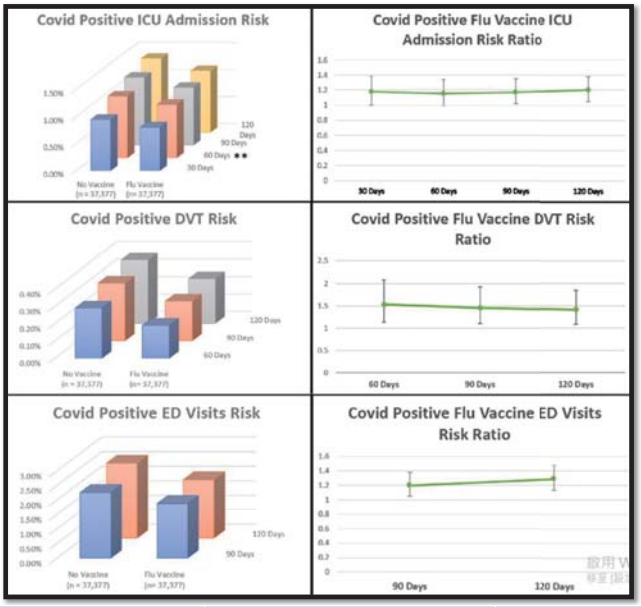
In January 2021, the analytics subset contained EMRs from 56 HCOs distributed predominantly throughout the United States of America

PLoS One. 2021 Aug 3;16(8):e0255541.



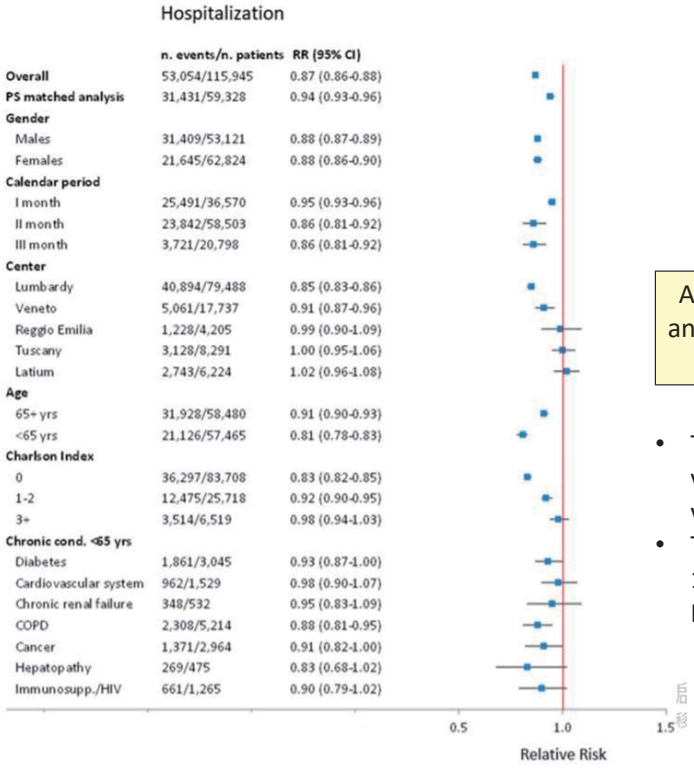
	RR (neg vs. post.)	95% CI	P-value	NNT
Sepsis (30, 60, 90, 120)	1.361–1.450	1.123–1.699	<0.01	286
Stroke (30, 60, 90, 120)	1.451–1.580	1.075–2.034	p<0.02	625

PLoS One. 2021 Aug 3;16(8):e0255541.



	RR (neg vs. post.)	95% CI	P-value	NNT
ICU admissions (30, 90, 120)	1.174–1.200	1.003–1.385	p<0.03	435
DVT (60, 90, 120)	1.41–1.530	1.082–2.076	p<0.02,	1000
ER visit (90, 120)	1.204–1.580	1.050–1.476	P<0.01	176

PLoS One. 2021 Aug 3;16(8):e0255541.



A large multi-database cohort study, in four Italian regions and) and the Reggio Emilia province. N= 115,945 COVID-19 cases, Influenza vaccine (+ vs. -: 34.6% vs.65.4%)

- The adjusted relative risk (RR) of being hospitalized in the vaccinated group when compared with the non-vaccinated group was 0.87 (95% CI: 0.86-0.88).
- This reduction in risk was not confirmed for death (RR = 1.04; 95% CI: 1.01-1.06), or for the combined outcome of ICU admission or death.

Vaccines (Basel). 2021 Jul 1;9(7):716.

Take home messages

- The global trends of declining season influenza and other non-SARS-COV-2 virus because of widespread implementation of measures to mitigate transmission of SARS-CoV-2.
- The resurge of respiratory virus after releasing nonpharmaceutical interventions for COVID-19 epidemics.
- The best combination of nonpharmaceutical interventions for controlling respiratory virus in the epidemic of COVID-19 depends largely on the burden of COVID-19.
- Still need to receive influenza vaccine injection.

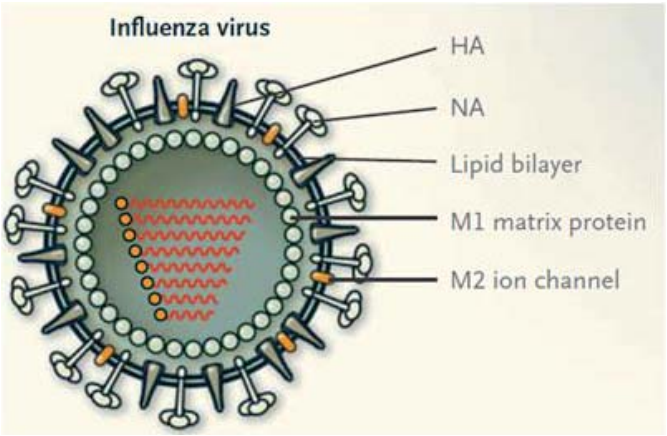
流感疫苗

高雄醫學大學附設中和紀念醫院

小兒感染科 李杰明 醫師

流行性感冒病毒

- ssRNA virus, segmented, Enveloped
- Orthomyxoviridae
- **Hemagglutinin (HA) 紅血球凝集素**
  - 吸附細胞表面唾液酸(sialic acid)接受器，使病毒能進入細胞。
  - 為現今**流感疫苗**的主要標的
- **Neuraminidase (NA) 神經胺酸酶**
  - 切斷病毒表面與宿主細胞唾液酸的glycosidic linkage。
  - 避免病毒顆粒聚集，促進新合成的病毒子代釋出。



N Engl J Med 2010;363:2036-44

流行性感冒病毒

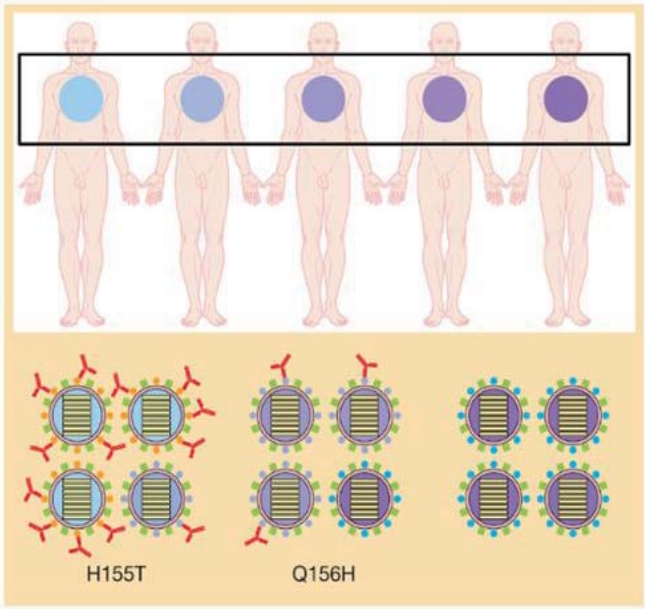


	A型流感病毒	B型流感病毒	C型流感病毒
亞型	H1—H16 N1—N9	無 (維多利亞/山形株)	無
自然宿主	人、豬、馬、禽鳥類、哺乳動物	人	人、豬
抗原變異	抗原移型/微變	抗原微變	抗原微變
流行程度	大流行	地區性流行	偶發性
嚴重度	最嚴重	高危險群嚴重	較輕微/無症狀

Lancet 2017;390:697-708

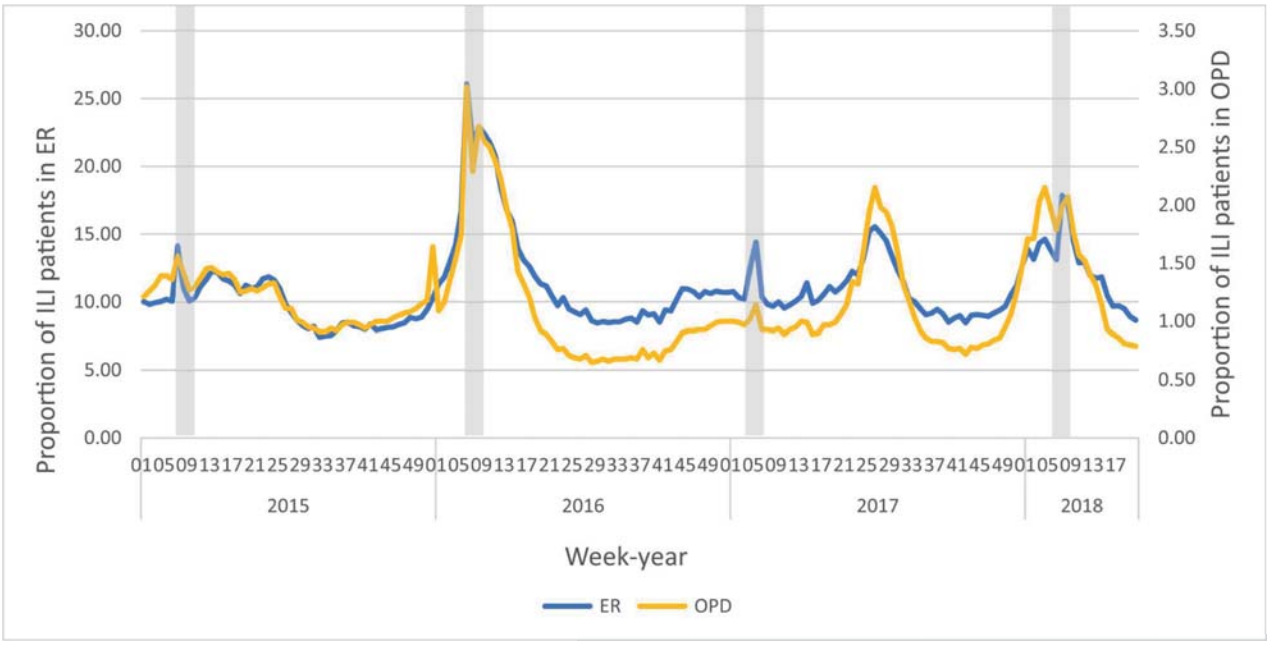
抗原微變 Antigenic Drift

- 流感病毒為一RNA病毒，利用RNA聚合酶進行病毒基因的複製。在複製過程中，容易因為缺乏校正機制而產生一些**點突變**。而流感病毒的HA及NA基因受到這些點突變的影響，可能引起些微抗原性的改變，此現象稱為抗原微變。
- **所有型別的流感病毒**都可能發生
- 與**每年局部的小流行**有關



Vaccine, 6th edition

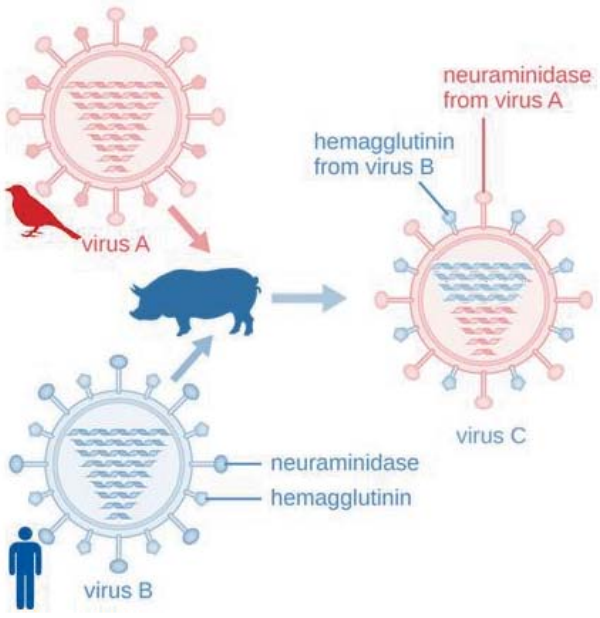
季節性流感 Seasonal Influenza



Journal of the Formosan Medical Association (2019) 118, 657-63

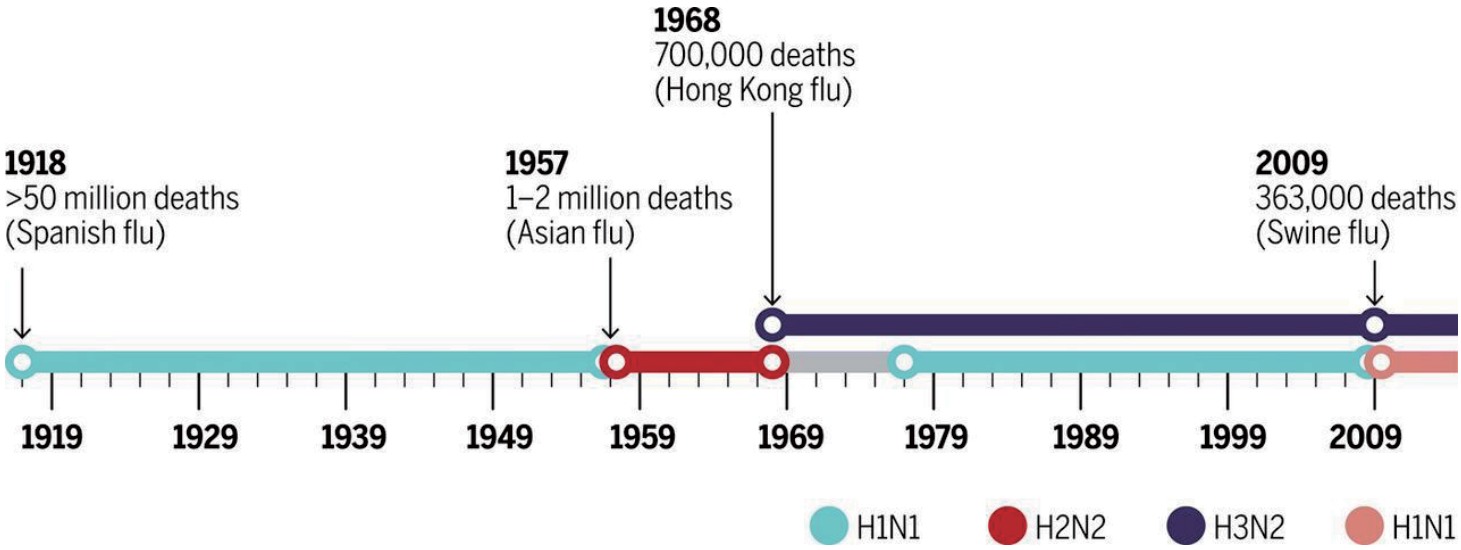
抗原移型 Antigenic Shift

- 當來自不同物種的流感病毒，同時感染一個宿主細胞時，有可能產生互換基因產生不同的排列組合，即**基因體重組**，導致新型流感病毒的誕生及抗原性的巨變。
- 人畜共通的流感病毒可能發生，如: **A型流感病毒**
- 會造成世界性的大流行。



Vaccine, 6th edition

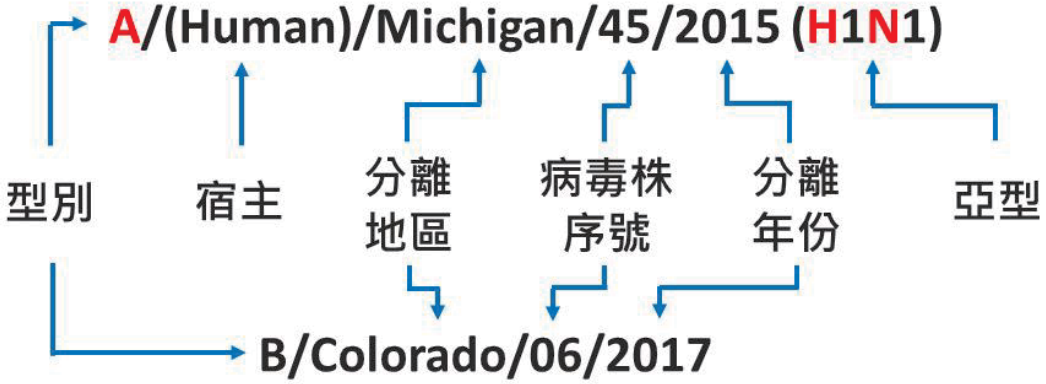
流感大流行 Influenza Pandemic



Science Translational Medicine 24 Jul 2019: Vol. 11, Issue 50

流行性感冒病毒命名

1980 年世界衛生組織

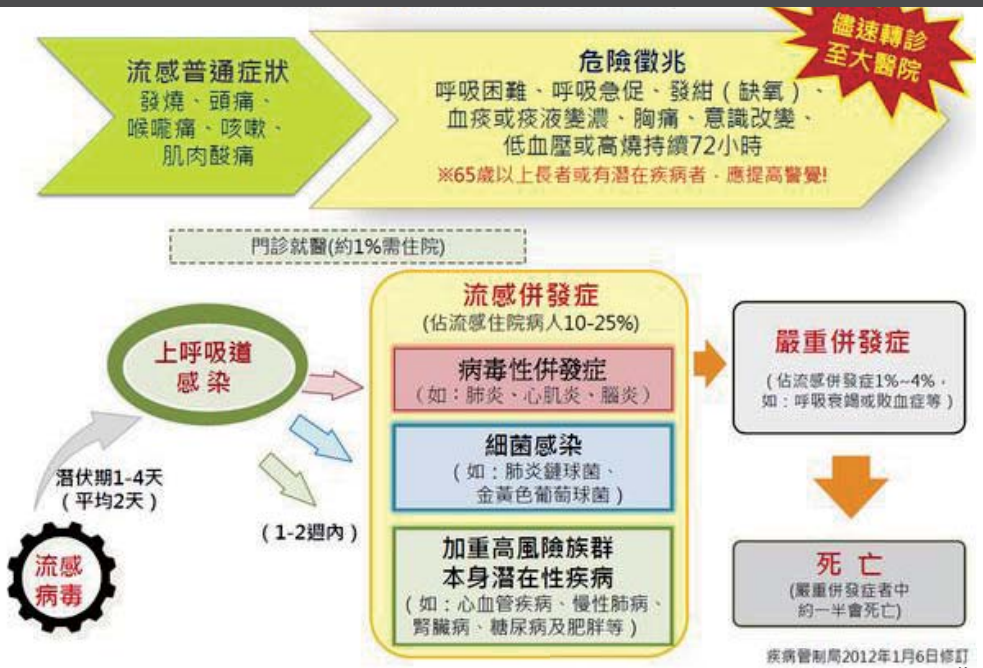


流行性感冒與一般感冒不同

項目	流感(Influenza)	感冒(Cold)
致病源	流感病毒，可分為A、B、C、D四型	大約200多種，包括較常見的:鼻病毒、副流感病毒、呼吸道細胞融合病毒、腺病毒等
臨床症狀	主要為發燒、頭痛、肌肉痛、疲倦、流鼻涕、喉嚨痛及咳嗽等症狀	症狀較輕微，常見包括打噴嚏、流鼻水、鼻塞及喉嚨痛，偶有輕微咳嗽、發燒或全身酸痛的情形
併發症	肺炎，包括病毒性及細菌性肺炎、中耳炎、鼻竇炎、腦炎、腦病變、雷氏症候群及其他嚴重之繼發性感染等	急性中耳炎、急性鼻竇炎、下呼吸道感染
治療方法	依照醫師處方給予抗病毒藥劑治療或支持療法	無特殊抗病毒藥物，以症狀治療為主
預防方法	注重呼吸道衛生及咳嗽禮節，接種流感疫苗	注重呼吸道衛生及咳嗽禮節

衛生福利部疾病管制署

流行性感冒病程樣態



衛生福利部疾病管制署

發生流感併發症的高危險群

小於五歲兒童

懷孕婦女及胎兒

65歲以上老年人

具共病症者:
如免疫不全患者、神經肌肉疾病、認知功能障礙、慢性肺疾病、心血管疾病、糖尿病、慢性腎病、慢性肝病、肥胖

Lancet 2017;390:697-708

發生流感併發症的高危險群

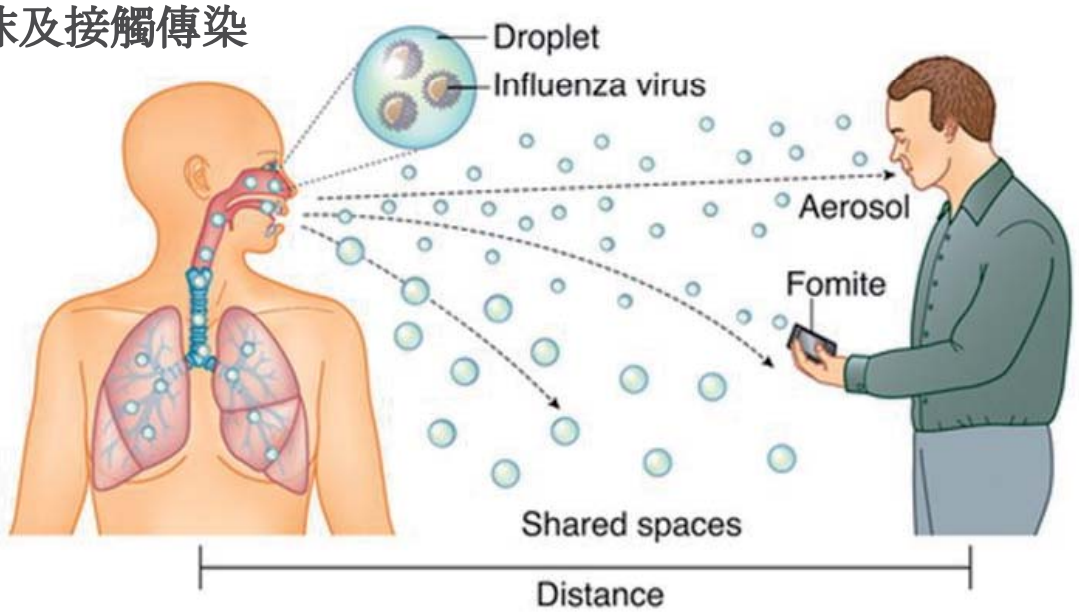
2017/7/1 至 2018/4/16 (依流感季)

年齡別	病例數	死亡數	每十萬人口累積發生率	每十萬人口累積死亡率
小於 3 歲	24	1	3.8	0.2
3-6 歲	19	1	2.3	0.1
7-18 歲	21	0	0.8	0.0
19-24 歲	10	1	0.5	0.1
25-49 歲	118	18	1.3	0.2
50-64 歲	252	45	4.9	0.9
65 歲以上	848	147	26.6	4.6
總計	1,292	213	5.5	0.9

台灣流感速訊 2018年第15週

流行性感冒病毒傳染途徑

- 飛沫及接觸傳染



預防流行性感冒病毒的方式

戴口罩、勤洗手
避免接觸眼鼻口
注意咳嗽禮節

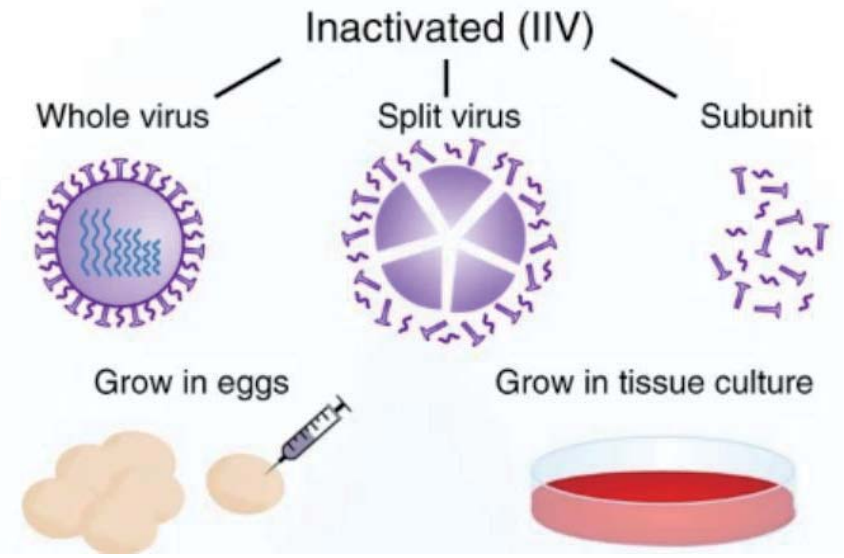
最有效的方式
每年接種流感疫苗

感染管制措施
醫療機構
長照機構
人口密集機構

衛生福利部疾病管制署

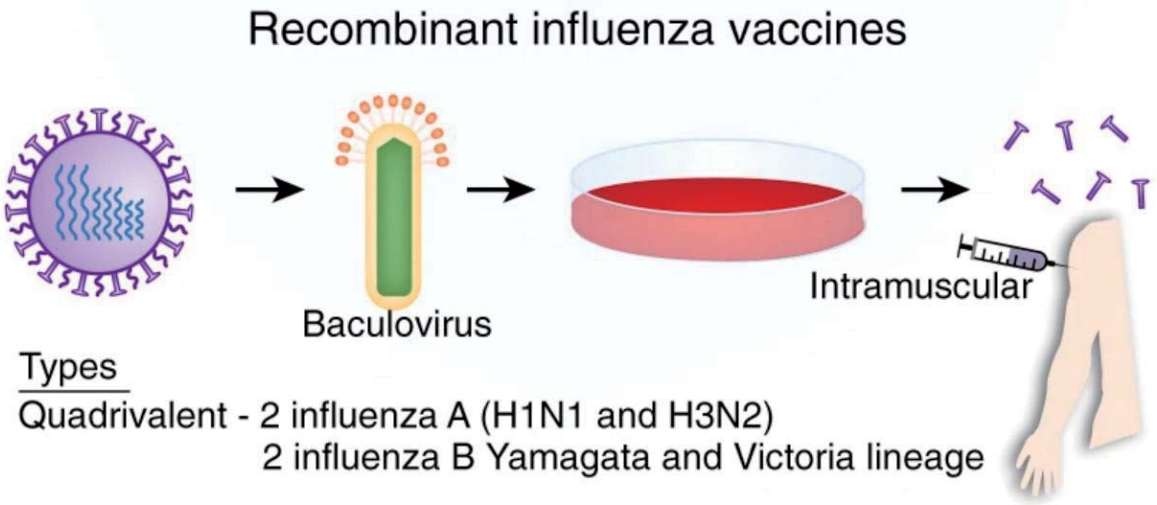
流感疫苗簡介

- 流感疫苗可分為:
  - **<u>不活化疫苗</u>** - 國內僅有不活化疫苗的許可證
    - **雞胚胎培養**
    - **細胞培養**
  - 活性減毒疫苗
    - Nasal spray
  - 基因重組疫苗



Mucosal Immunology volume 13, pages566–573 (2020)

流感疫苗簡介



<u>Flublock</u>, Sanofi 台灣尚未取得藥證, 為美國專案進口, 目前僅可用於18歲以上成人

Mucosal Immunology volume 13, pages566–573 (2020)

流感疫苗簡介

- 每年2月由WHO召集會議宣布北半球四價或三價疫苗建議組成病毒株:
  - **兩種A型**流感病毒(A/**H1N1**及A/**H3N2**)
  - **兩種**或**一種B型**流感病毒(B/**Yamagata** 及/或B/**Victoria**)
- 目前國內公費流感疫苗已**全面採用四價流感疫苗**
  - 接種途徑:**肌肉注射**
  - 接種年紀 : **滿六個月大以上**均建議接種
  - 接種量 : **均為0.5ml**
  - 8歲(含)以下首次接種者接種2劑，且間隔至少4週

衛生福利部疾病管制署

2021-2022流感疫苗抗原成分

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

衛生福利部疾病管制署

國內核准上市之流感疫苗

廠牌	GSK葛蘭素	賽諾菲	國光	Seqirus
	Fluarix Influenza Virus	VAXIGRIP	安定伏裂解型流感疫苗	Influenza Vaccine FLUCELVAX QUADRIVALENT
名稱	伏適流	巴斯德	安定伏裂解型四價	輔流威適
產地	德國	法國	台灣	德國
	雞蛋培養	雞蛋培養	雞蛋培養	細胞培養
				
對象	6個月以上	6個月以上	3歲以上	3歲以上
價數/抗原	4價 (2A2B)	4價 (2A2B)	4價 (2A2B)	4價 (2A2B)
				其中一個A跟其他品牌不同
公費/自費	只有公費	公費＋自費	公費＋自費	公費＋自費

2021-2022公費流感疫苗接種對象

階段順序	實施對象
非公費對象亦建議自費接種	● 醫事及衛生防疫相關人員 ● 65歲以上長者 ● 安養、養護、長期照顧(服務)等機構之受照顧者及其工作人員 ● 滿6個月以上至國小入學前幼兒 ● 孕婦
第一階段	● 具有潛在疾病者，包括(19-64歲)高風險慢性病人、含BMI>=30、罕見疾病患者及重大傷病患者 ● 國小、國中、高中、高職、五專一至三年級學生等 ● 6個月內嬰兒之父母 ● 幼兒園托育人員及托育機構專業人員(含社區公共托育家園) ● 禽畜業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

衛生福利部疾病管制署

流感疫苗的保護力

Immunogenicity 致免力	Efficacy 疫苗效力	Effectiveness 疫苗效果
評估打完疫苗以後: ● 針對病毒的**抗體濃度**是否高於一個標準 ● 是否有**抗體陽轉**(seroconversion) ● **抗體的幾何平均效價**(geometric mean titer)	評估疫苗**直接**的保護力: ● 比較有打流感疫苗者，與沒打流感疫苗者比較起來，發病的機率減少多少。 ● 隨機對照試驗	評估疫苗**直接**及**間接**保護力: ● 包含流行季節期間因為類流感、呼吸道疾病就醫，無法工作或住院 ● 有包含**群體免疫**的效果 ● 觀察性研究

認識流感疫苗 教學手冊 第一版 2011 衛生署疾病管制局

流感疫苗的致免力Immunogenicity

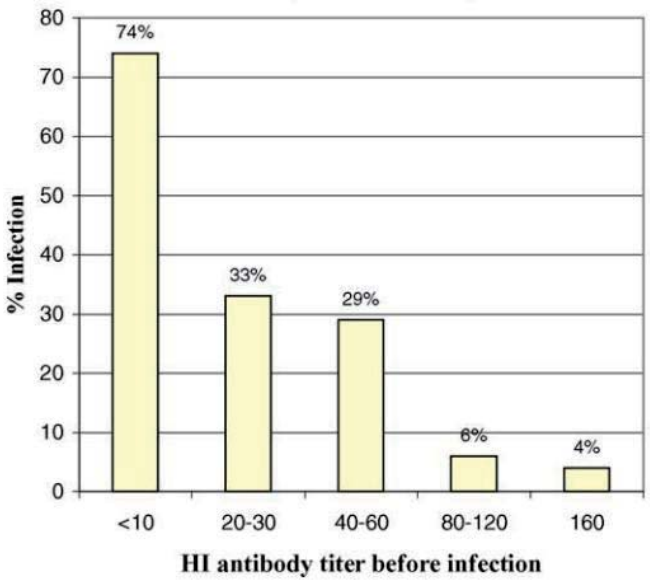
- Europe Committee for Proprietary Medicinal Products (CPMP, Eruope)標準
- Vaccine-induced haemagglutinin inhibition (HI) antibody titres

致免力標準	18-60歲成人	超過60歲成人
血清保護率 第21天HI titre>1:40的比率	>70%	>60%
血清轉換率 第21天HI抗體濃度上升四倍的比率	>40%	>30%
抗體幾何平均效價(GMT)增加倍數 第0天到第21天增加的倍數	>2.5	>2.0

Virus Research 103 (2004) 133–138

流感疫苗的致免力Immunogenicity

- 感染前血球凝集素抑制試驗抗體效價與感染率的關係
- 感染前抗體效價越高，則感染率越低。



Virus Research 103 (2004) 133–138

流感疫苗的保護效力及效果



兒童	
Efficacy	60-90%
中耳炎	30-36%

65歲以下健康成人	
Efficacy	70-90%
類流感症狀	30-36%

65歲以上(社區)		
Efficacy		50-60%
住院	肺炎	33%
	呼吸道疾病	32%
	鬱血性心衰竭	27%
死亡		50%

65歲以上(機構)	
呼吸道疾病	56%
肺炎	53%
住院	48%
死亡	48%

Efficacy: 經實驗室檢驗確認為流感病毒感染

Vaccine 2003 May 1;21(16):1769-75.

流感疫苗的保護效果

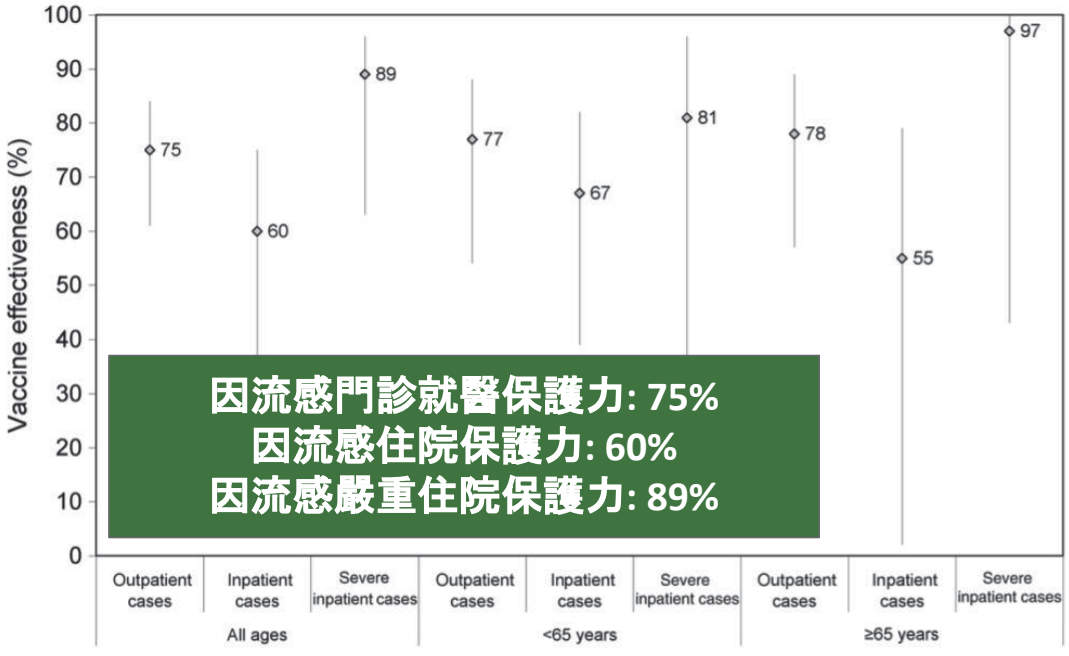
- 美國2018-2019季節性流感疫苗的保護效果: 減少47%因為流感呼吸道症狀的就醫

Influenza type/Age group	Influenza-positive Total	Influenza-positive Vaccinated no. (%)	Influenza-negative Total	Influenza-negative Vaccinated no. (%)	Vaccine effectiveness* Unadjusted % (95% CI)	Vaccine effectiveness* Adjusted % (95% CI)†
Influenza A and B						
Overall	**465**	198 (43)	**2,789**	1,591 (57)	44 (32 to 54)	47 (34 to 57)§
Age group						
6 mos–17 yrs	**173**	58 (34)	**926**	515 (56)	60 (43 to 71)	61 (44 to 73)§
18–49 yrs	**166**	58 (35)	**932**	403 (43)	30 (1 to 50)	37 (9 to 56)§
≥50 yrs	**126**	82 (65)	**931**	673 (72)	29 (-6 to 52)	24 (-15 to 51)
Influenza A(H3N2)						
Overall	**101**	42 (42)	**2,789**	1,591 (57)	46 (20 to 64)	44 (13 to 64)§
Influenza A(H1N1)pdm09						
Overall	**293**	125 (43)	**2,789**	1,591 (57)	44 (29 to 56)	46 (30 to 58)§
Age group						
6 mos–17 yrs	**106**	37 (35)	**926**	515 (56)	57 (35 to 72)	62 (40 to 75)§
18–49 yrs	**113**	38 (34)	**932**	403 (43)	33 (0 to 56)	45 (14 to 64)§
≥50 yrs	**74**	50 (68)	**931**	673 (72)	20 (-33 to 52)	8 (-59 to 46)

- 疫苗保護效果**隨年齡增加而下降**。

MMWR, February 15, 2019, Vol.68, No. 6, US CDC

流感疫苗的保護效果



2010-2011
Spain
Case-control study

Clin Infect Dis 2013 Jul;57(2):167-75

流感疫苗的保護效果

- 01-Jan-2004 to 31-Mar-2015, Systemic review and Meta-analysis.
- Pooled VE to different influenza subtype, 不分年紀

	Vaccine type	Pooled VE (%)	Pooled standard error	VE estimates (n)	p value for heterogeneity	I^2
Type B	Seasonal	54% (46–61)	0·083	36	<0·0001	61·3
H3N2	Seasonal	33% (26–39)	0·050	34	0·005	44·4
H1N1pdm09	Seasonal	61% (57–65)	0·048	29	0·783	0·0
H1N1pdm09	Monovalent	73% (61–81)	0·188	10	0·217	31·4
H1N1 (pre-2009)	Seasonal	67% (29–85)	0·397	5	0·093	57·6

Data in parentheses are 95% CIs. VE=vaccine effectiveness.

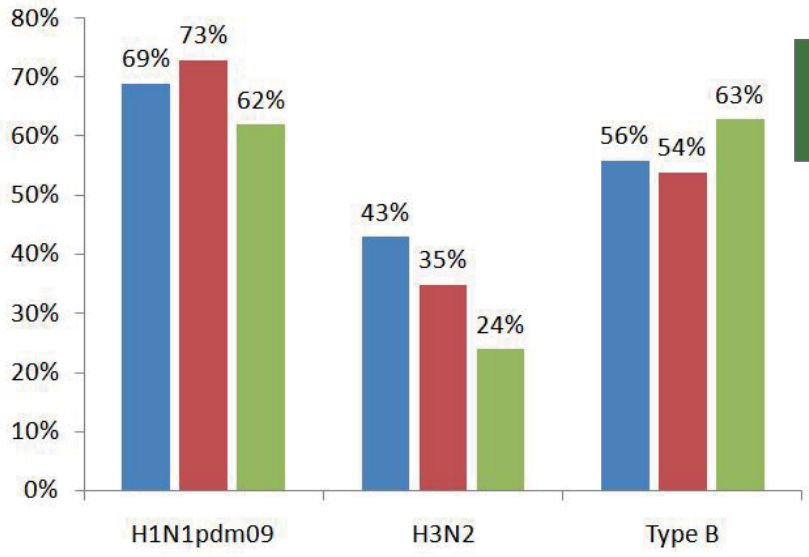
季節性流感疫苗對於H3N2保護力最差

Table 2: Pooled VE by type and subtype in studies without age restriction

Lancet Infec dis, 2016, VOLUME 16, ISSUE 8, P942-951,

流感疫苗的保護效果

- Pooled VE to different influenza subtype, 依不同年齡層區分



- **季節性流感疫苗對於H3N2保護力最差**
- **保護力: 兒童 > 成人 > 老人**

Lancet Infec dis, 2016, VOLUME 16, ISSUE 8, P942-951,

流感病毒對孕婦的影響

Variable	Influenza-Confirmed Hospitalizations, No.	Women-Weeks at Risk, No.	Adjusted Hospitalization Rate per 100 000 Women-Weeks (95% CI)	Adjusted Rate Ratio (95% CI)
Pregnancy trimester				
Nonpregnant	214	12991965	1.7 (1.4–1.9)	1.0
Pregnant	46	759217	5.6 (4.0–7.3)	3.4 (2.5–4.7)
First trimester	7	155651	4.2 (1.1–7.3)	2.5 (1.2–5.4)
Second trimester	19	272456	6.5 (3.5–9.4)	3.9 (2.4–6.3)
Third trimester	19	224448	7.9 (4.3–11.5)	4.8 (3.0–7.7)
Postpartum period	1	106662	0.9 (–.8–2.5)	0.5 (.1–3.7)

- 2012-2015, , Auckland, New Zealand
- 妊娠第1孕期至第3孕期婦女相較於未懷孕女性，**因確診流感而住院**的RR值，分別達到**2.5倍、3.9倍及4.8倍**

The Journal of Infectious Diseases 2019:219, 1893-1903

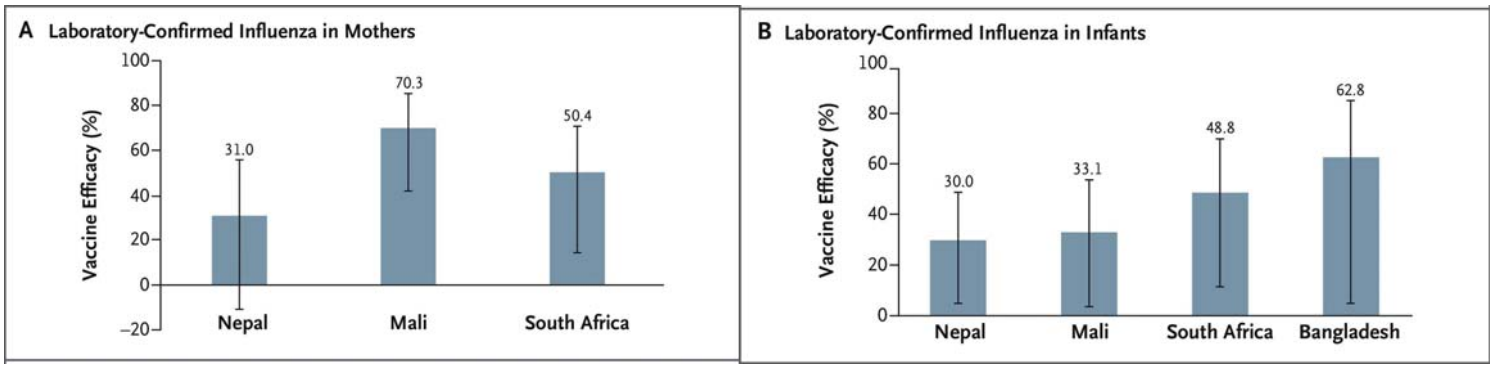
流感病毒對孕婦的影響

	Illness*	No illness*	Crude		Multisite cohort model	
			Effect size (95% CI)	p value	Effect size (95% CI)†	p value
Febrile acute respiratory illness						
Preterm birth‡	1075/9989 (11%)	110/837 (13%)	1·2 (1·0 to 1·5)	0·038	1·4 (1·1 to 1·6)	0·0067
SGA§	2187/9980 (22%)	198/846 (23%)	1·1 (0·9 to 1·3)	0·32	1·1 (0·9 to 1·2)	0·39
Late pregnancy loss¶	170/9980 (2%)	9/846 (1%)	0·6 (0·3 to 1·2)	0·20	1·2 (0·6 to 2·4)	0·59
Birthweights of term singleton infants, g‖	3010 (576)	3006 (605)	−3·3 (−44·3 to 37·6)	0·87	−20·4 (−55·0 to 14·2)	0·25
rtPCR-confirmed influenza**						
Preterm birth‡	1129/10285 (11%)	31/276 (11%)	1·0 (0·7 to 1·5)	0·85	1·4 (0·9 to 2·0)	0·096
SGA§	2320/10263 (23%)	58/298 (19%)	0·8 (0·6 to 1·1)	0·23	1·0 (0·8 to 1·3)	0·97
Late pregnancy loss¶	133/10263 (1%)	5/298 (2%)	1·3 (0·5 to 3·1)	0·60	10·7 (4·3 to 27·0)	<0·0001
Birthweights of term singleton infants, g‖	3010 (576)	3031 (540)	21·8 (−45·2 to 88·7)	0·52	−55·3 (−109·3 to −1·4)	0·045

- 增加**Late pregnancy loss**風險, aHR: 10.7 (95%CI: 4.3 to 27, p<0.0001)
  - 懷孕週數13-21周的流產或是超過22周以上的死產
- **較低的足月單胞胎活產出生體重**, 低55.3gm (95%CI: -109.3 to -1.4, p=0.045)

Lancet Infect Dis 2020, Published Online ctober 29, 2020

流感疫苗對孕婦的保護效力



- Influenza vaccines are efficacious against influenza-like illness and laboratory-confirmed influenza in pregnant women and their infants

N Engl J Med 2017; 376:1256-1267

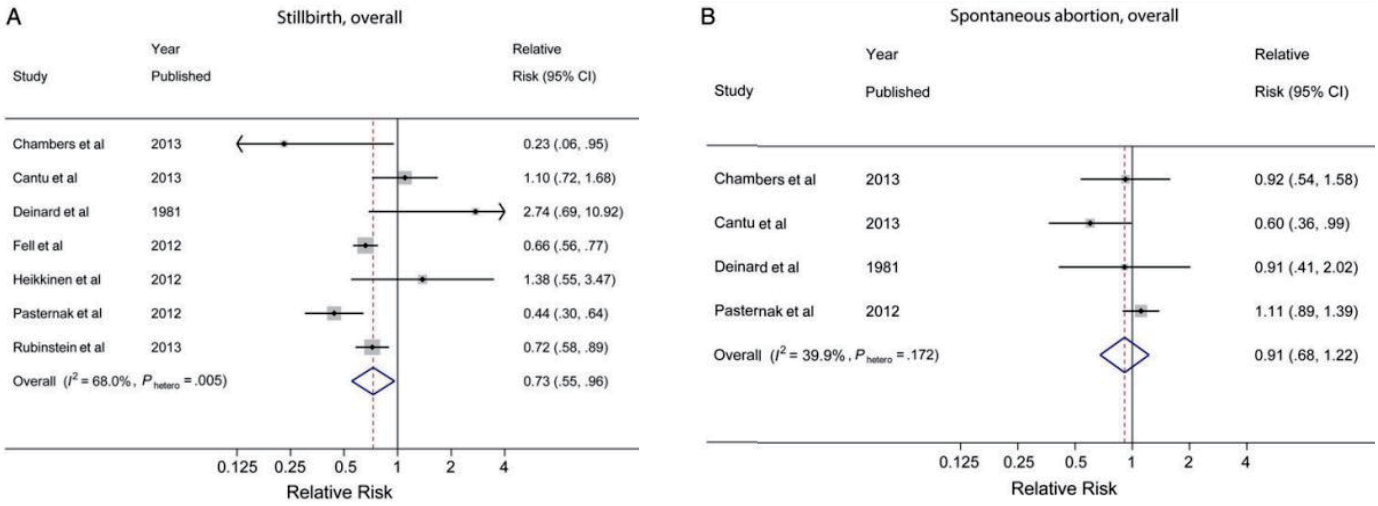
流感疫苗對孕婦的保護效果

First Author	Site	Trial Design	Intervention	Control	Risk of Preterm Birth (95% CI)	Risk of Low Birth Weight (95% CI)	Risk of Small for Gestational Age (95% CI)
Omer, 2011 [27]	Georgia, USA	Retrospective cohort analysis	TIV N = 578	No vaccine N = 3748	OR: 0.28 (.11–.74)	. . .	OR: 0.31 (.13–.75)
Steinhoff, 2012 [28]	Dhaka, Bangladesh	Randomized controlled clinical trial	TIV N = 172	Pneumococcal polysaccharide vaccine N = 168	OR: 0.48 (.08–2.74)	OR: 0.19 (.02–1.64)	OR: 0.43 (.20–.94)
Kallen, 2012 [29]	Sweden	Retrospective population-based cohort analysis	H1N1 vaccine N = 18 612	No vaccine N = 136 914	OR: 0.86 (.77–.96)	OR: 0.86 (.77–.96)	OR: 1.04 (.92–1.17)
Fell, 2012 [30]	Ontario, Canada	Retrospective population-based cohort analysis	H1N1 vaccine N = 23 340	No vaccine N = 32 230	RR: 0.73 (.58–.91)	. . .	RR 0.90 (.85–.96)
Pasternak, 2012 [24]	Denmark	Retrospective population-based cohort study	H1N1 vaccine N = 6989 infants	No vaccine N = 46 443 infants	1st trimester: OR: 1.32 (.76–2.31) 2nd/3rd trimester: OR: 1.00 (.84–1.17)	1st trimester: OR: 0.83 (.41–1.67) 2nd/3rd trimester: OR: 1.14 (.94–1.38)	1st trimester: OR: 0.79 (.46–1.37); 2nd/3rd trimester: OR: 0.97 (.87–1.09)
Richards, 2013 [31]	Georgia, USA	Retrospective cohort analysis	H1N1 vaccine N = 1125	No vaccine N = 1581	OR: 0.63 (.47–.84)	OR: 0.79 (.56–1.10)	OR: 1.26 (.94–1.69)

- The effect of influenza vaccination on birth outcomes, including a potential effect on decreased incidence of **small for gestational age** (SGA), **preterm birth**, and **low birth weight** infants in pregnant women.

Clin Infect Dis 2014 Aug 15;59(4):560-8

流感疫苗對孕婦的保護效果



- Lower likelihood of stillbirth, RR:0.73 (95%CI: 0.55-0.96).
- No significant difference: spontaneous abortion, RR:0.91(95%CI:0.68-1.22)

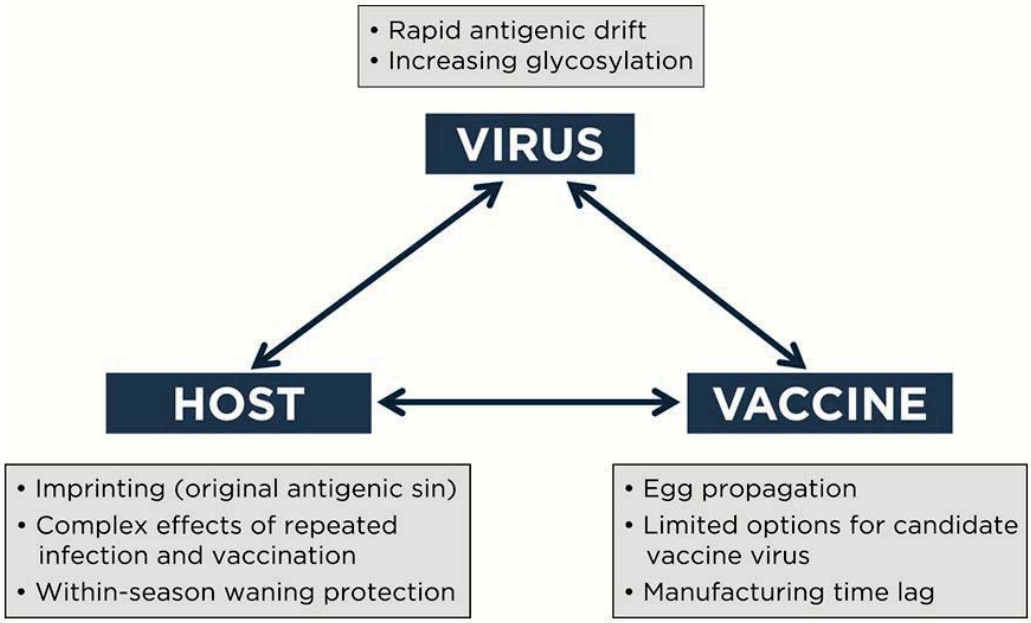
Clin Infect Dis. 2015 Mar 1;60(5):e11-9.

流感疫苗的保護效果

- 影響流感疫苗保護效果的因素:
  - **當年度流行病毒型別與疫苗株相似度**
    - 2014-2015 US, H3N2 mismatch, VE:11%
    - B mismatch, VE:23%
  - **個體免疫生成性不同**
    - 65歲以下的成人，保護效力約在**70-90%**
    - 對老年人的保護力稍差，約可**減少30-70%**流感及肺炎住院率
    - 在幼兒的研究，**可降低70%嬰幼兒**因流感引起的住院比例
    - 孕婦接種流感疫苗能夠降低孕婦、胎兒與新生兒罹患流感及產生後續併發症的風險。

衛生福利部疾病管制署
Clin Infect Dis. 2016 Dec 15;63(12):1564-1573
Vaccine, volume 38, issue 52, 14 December 2020, p. 8387-95

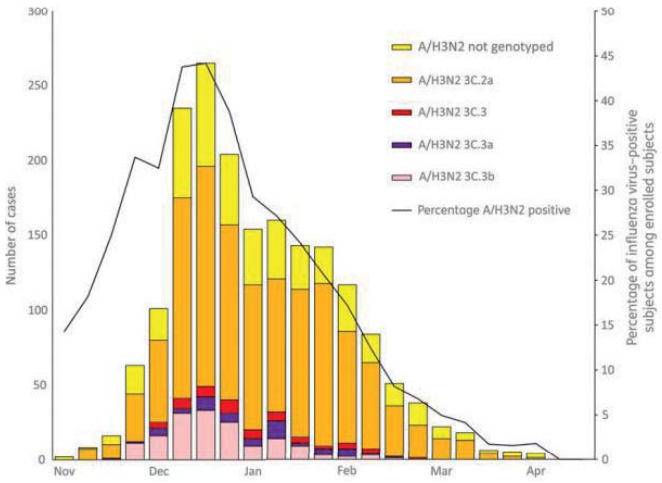
流感疫苗對A/H3N2保護力較差的原因

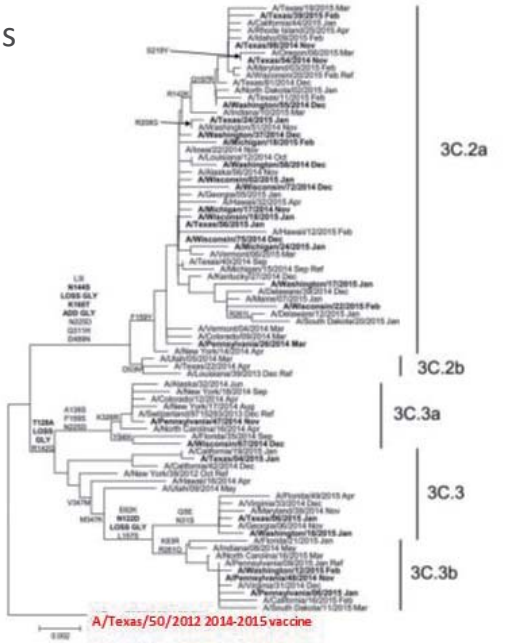


Clinical Infectious Diseases, 2019;69(10):1817–23

抗原微變影響疫苗保護效力

- The long-term rate of A/H3N2 antigenic change was approximately **5–6 times higher relative to B** and about **17 times** higher than **A/H1N1pdm09**





Clinical Infectious Diseases, 2019;69(10):1817–23

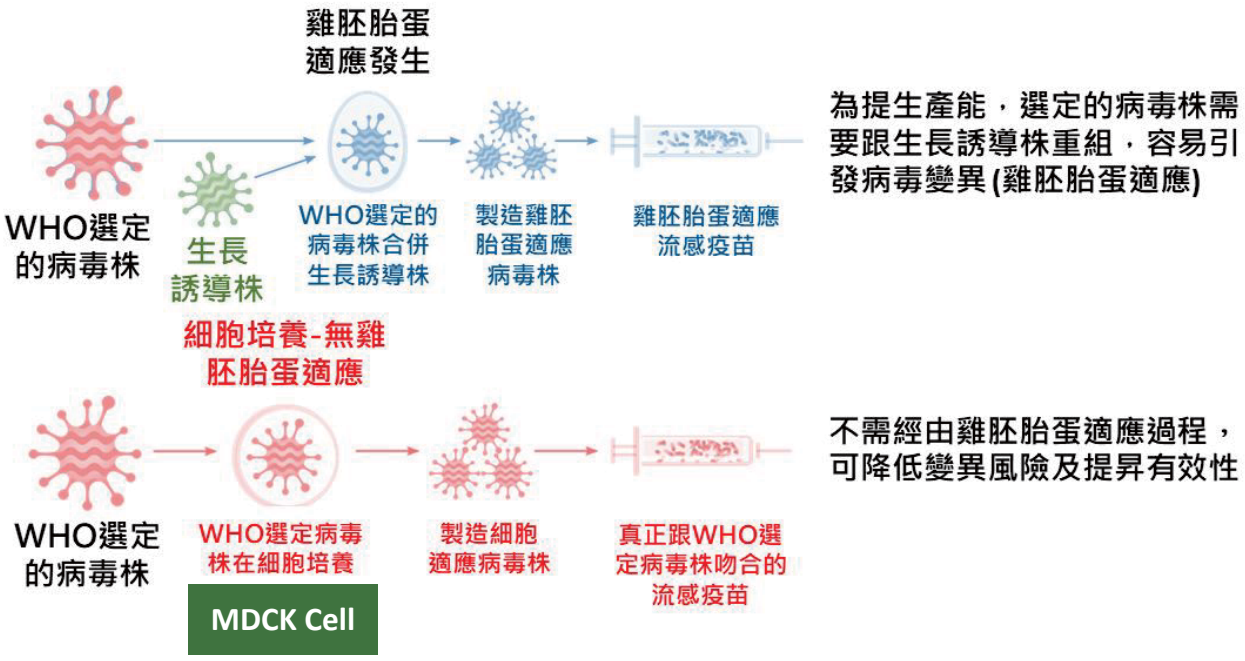
疫苗對於A/H3N2保護效力下降較快

Outcome	Participants, No. (Studies)	Studies, No.	Evidence Certainty[a]	ΔVE (95% CI)	VE (95% CI), by Time After Vaccination	
					15–90 d	91–180 d
Influenza A(H3)	10 736 cases, 27 689 controls	11	Moderate	-33 (-57 to -12)	45 (34 to 54)	13 (-10 to 31)
Influenza B	6424 cases, 17 877 controls	6	Low	-19 (-33 to -6)	62 (52 to 70)	43 (33 to 52)
Influenza A(H1)	5148 cases, 17 044 controls	5	Low	-8 (-27 to 21)	62 (35 to 78)	54 (43 to 63)

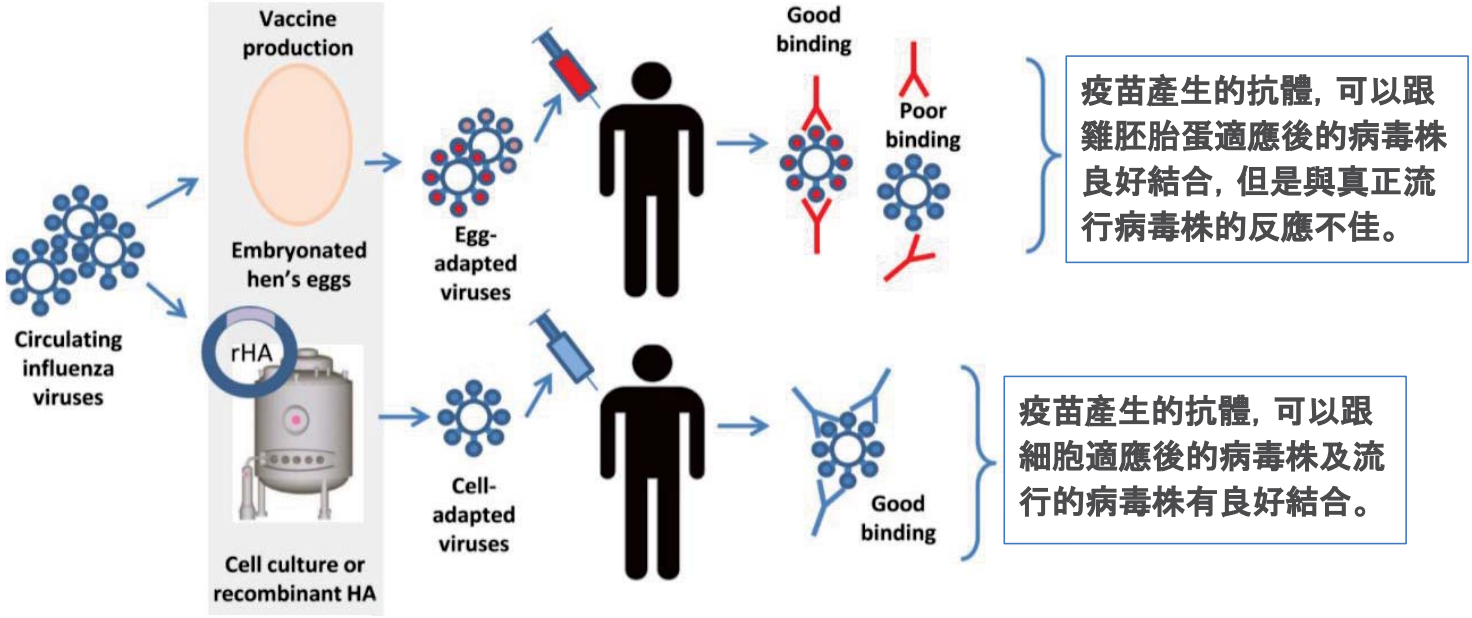
- 流感疫苗注射後180天內，可以觀察到疫苗的保護效力有顯著的下降
- 保護力下降幅度以A/H3N2最明顯，其次是B，最後才是A/H1N1.

The Journal of Infectious Diseases, 2018; 217: 731–41

細胞/雞胚蛋培養流感疫苗

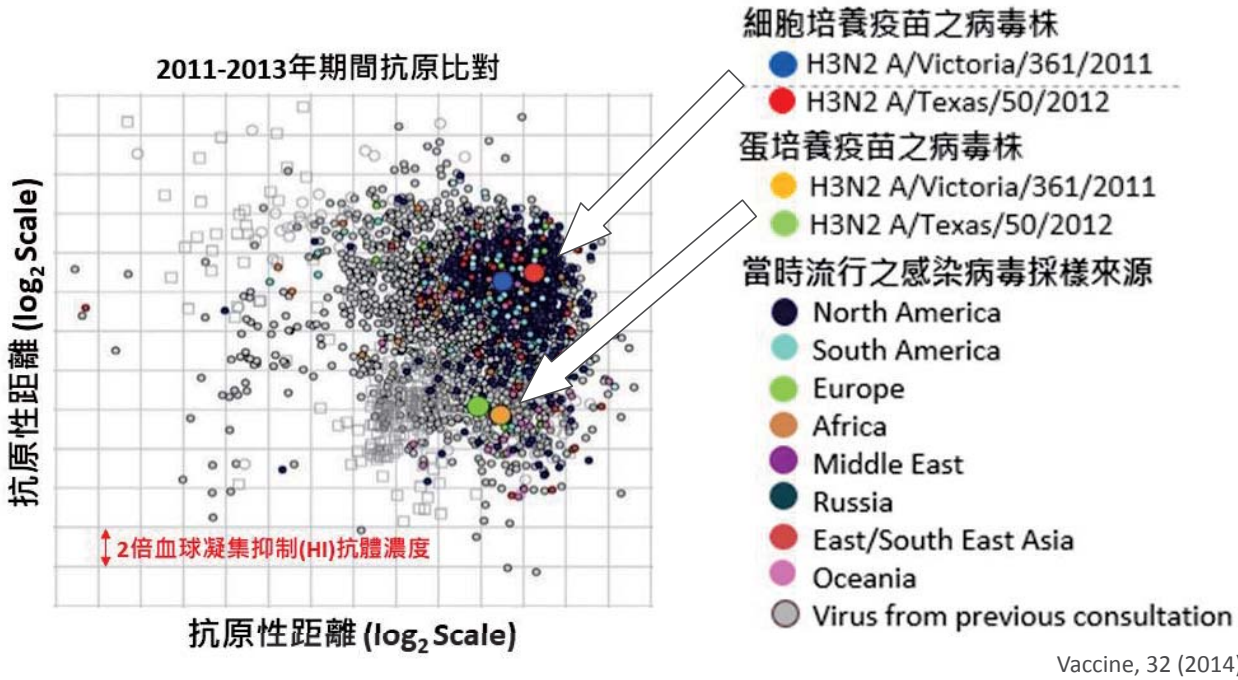


細胞/雞胚蛋培養流感疫苗



Cell Host & Microbe, Volume 25, Issue 6, 12 June 2019, Pages 836-844

細胞培養流感疫苗抗原吻合性較佳



Vaccine, 32 (2014) 4713–25

雞胚胎蛋與細胞培養疫苗製程比較

雞胚胎蛋製程	細胞培養製程
傳統生產技術	現代化生產技術
一旦受新型流感病毒感染，將可能無雞胚胎蛋來生產流感疫苗	僅需細胞株及培養基
必須有後勤組織確保足夠蛋量的取得時間及地點，並於開始生產之前半年便須決定蛋量、與供應商完成採購簽約手續	培養基的品質較易控制及取得
疫苗病毒株必須經過雞胚胎蛋馴化，需較長時間	疫苗病毒株取得較快速
雞胚胎蛋運輸及取得將延宕生產所需時間 由於生產依賴雞胚胎蛋，一旦蛋源成問題就不能保證產量	生產時間較快，疫苗可較早上市 產量穩定、可靠
開放系統 (雞蛋)，品質難以控制；因此整個生產系統可能被一個污染蛋污染	生產全程採密閉式 (生物反應器)，污染的可能性低；同時，如果使用無血清培養基生產，病毒容易純化，疫苗製品純度高且安全
對雞蛋過敏者不適合施打	沒有雞蛋過敏症問題

感染控制雜誌中華民國 102 年 2 月第二十三卷第一期

年長者因流感相關住院較多

TABLE 1 Mean seasonal influenza-related hospitalisation rates in all ages and in adults aged ≥65 y in the United States from 1993 to 2008[16]

Viral strain	All ages	<1 y	1-4 y	5-49 y	50-64 y	≥65 y
A/H1N1	1.9 (0.6-61)	48 (33-233)	3.3 (0-66)	1.0 (0.2-16)	1.0 (0-71)	2.1 (0-268)
A/H3N2	44 (29-98)	90 (70-225)	15 (8-X[a])	8.6 (5.0-22)	46 (28.5-112)	240 (164-486)
B	18 (7.7-77)	13 (3.0-204)	21 (15.6-80)	7.4 (4.6-21)	19 (6.6-88)	68 (23-345)

- Values shown per 100 000 person-years with (95% confidence intervals).
- The vaccination of older adults is a high priority since influenza carries the highest risk of serious disease resulting in hospitalisation in this group

Int J Clin Pract. 2018;72:e13249

年長者因流感相關死亡率較高

Age Group, y	No. of Influenza Deaths			
	A(H1N1)	A(H3N2)	B	Total
	Underlying Respiratory and Circulatory Deaths			
<1	4	15	7	26
1-4	7	42	17	66
5-49	168	484	137	789
50-64	196	2121	306	2623
≥65	1585	26 278	4788	32 651
Total	**1960**	**28 940**	**5255**	**36 155**

死亡率:每10萬人年

Age Group, y	Influenza
	Underlying Respiratory and Circulatory Deaths
<1	0.6
1-4	0.4
5-49	0.5
50-64	7.5
≥65	98.3
Total	13.8

- Estimated annual Age-specific influenza associated Deaths and Mortality for the 1990-1991 through 1998-1999 seasons.

JAMA 2003 Jan 8;289(2):179-86

年長者對流感疫苗產生的抗體反應較差

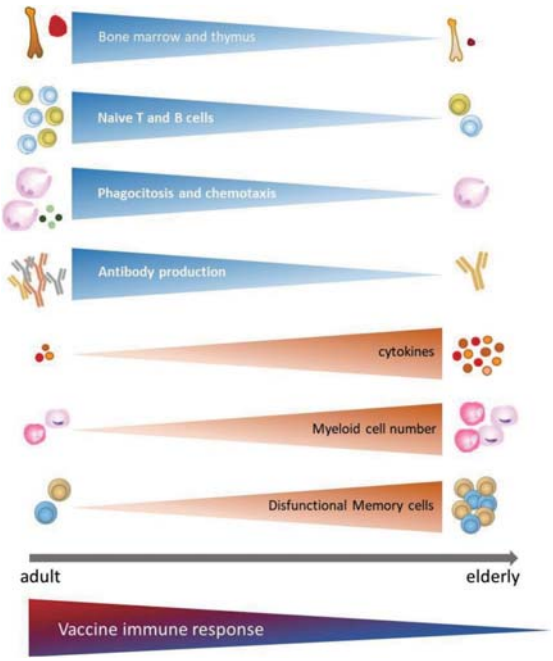
Post-vaccine response (unadjusted) in young vs. elderly across all studies, by influenza sub-type

Vaccine component	Age group	Seroconversion (percentage of subjects with 4-fold Ab increase)			Seroprotection (percentage of subjects with Ab titres > 40)			GMT		
Elderly:58歲以上		No. of subjects	% Positive	Unadjusted OR (95% CI)	No. of subjects	% Positive	Unadjusted OR (95% CI)	No. of subjects	GMT	*P*-value
H1N1	Young	913	60	Ref	1151	83	Ref	814	140	
	Elderly	4492	42	0.48** (0.41–0.55)	4643	69	0.47** (0.40–0.55)	3997	83	0.02*
H3N2	Young	913	62	Ref	1151	84	Ref	814	162	
	Elderly	4492	51	0.63** (0.55–0.73)	4643	74	0.53** (0.45–0.63)	3406	126	0.26
B	Young	913	58	Ref	1151	78	Ref	814	234	
	Elderly	4492	35	0.38** (0.33–0.44)	4643	67	0.58** (0.50–0.67)	3406	100	0.03*

- For all three antigens, **seroconversion** and **seroprotection** rates were significantly higher in the young.
- Post-vaccination GMT levels were also always higher in the younger adults.

Vaccine 24 (2006) 1159–1169

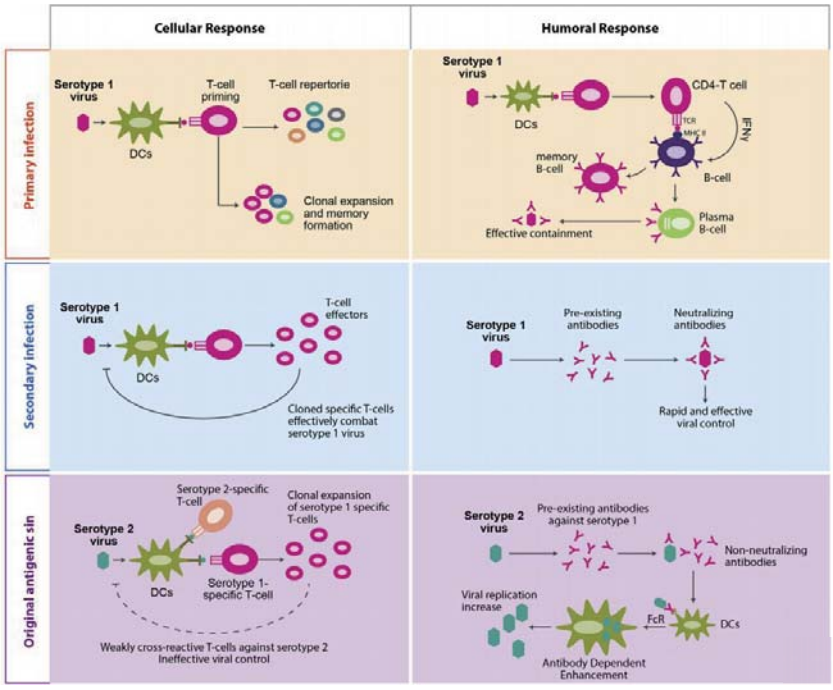
免疫衰老 Immunosenescence

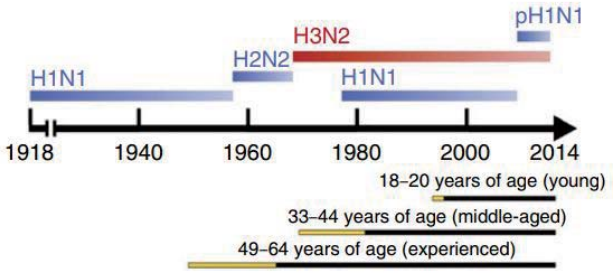


Immunosenescence involves the involution of **primary lymphoid organs** (bone marrow and thymus) with a **reduction of B and T cells progenitors**, **dysfunctional memory cells**, due to chronic antigenic stimulation (including, but not limited to, CMV), **reduction of phagocyte functions** (such as chemotaxis and phagocytosis), with concomitant **increased levels of pro-inflammatory cytokine** production.

Semin Immunol 2018 Dec;40:83-94.

免疫原罪 Original antigenic sin





The responses to influenza vaccines were dependent upon exposure to influenza virus strains during childhood.

Journal of Autoimmunity 83 (2017) 12e21
Nature Immunology volume 18, pages464–473 (2017)

如何增加老年人對流感疫苗的反應

- 增加疫苗中的抗原劑量
- 改變注射途徑
- 增加佐劑
- 重組流感疫苗

Table 1 Influenza vaccine formulations available for older adults

Vaccine	Type	Content	Dose, mL	Route
Inactivated tri- or quadrivalent vaccine	Subunit	15 ug HA per antigen	0.5	IM
Adjuvanted inactivated trivalent influenza vaccine	Subunit	MF59 adjuvant 15 ug HA per antigen	0.5	IM
High-dose inactivated trivalent influenza vaccine	Subunit	60 ug HA per antigen	0.5	IM
Recombinant quadrivalent influenza vaccine	Recombinant	45 ug rHA per antigen	0.5	IM

Drugs & Aging (2019) 36:29–37

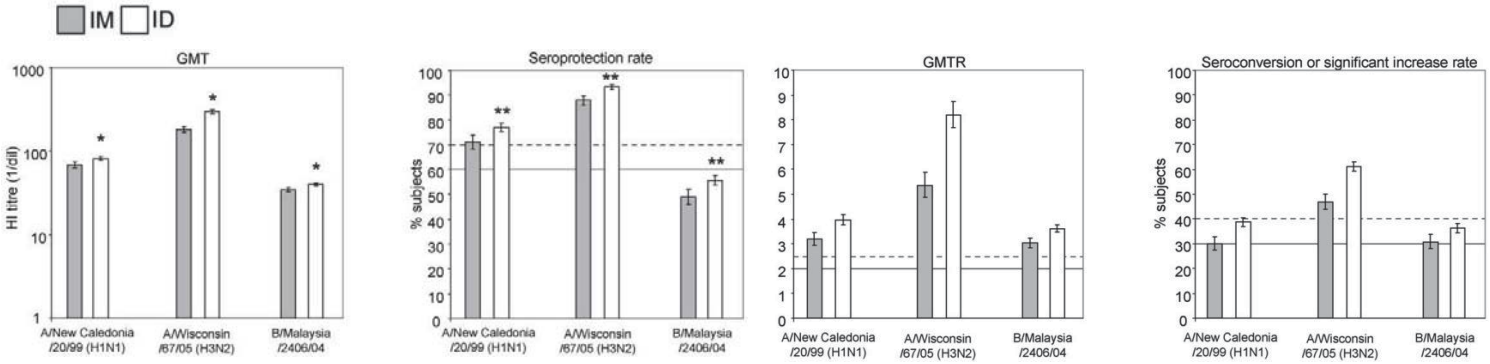
高劑量流感疫苗對老年人的保護效力

Variable	Laboratory-Confirmed Influenza†		
	IIV3-HD (N=15,990)	IIV3-SD (N=15,993)	Relative Efficacy (95% CI)
	no. (%)		%
Protocol-defined influenza-like illness	228 (1.4)	301 (1.9)	24.2 (9.7 to 36.5)‡
Influenza A	190 (1.2)	250 (1.6)	24.0 (7.8 to 37.4)
A/H1N1	8 (<0.1)	9 (0.1)	11.1 (–159.6 to 70.2)
A/H3N2	171 (1.1)	223 (1.4)	23.3 (6.0 to 37.5)
Influenza B	38 (0.2)	51 (0.3)	25.5 (–15.7 to 52.4)

- Double blinded RCT, for patient > 65 y/o
- High dose group: 15990, Standard dose group: 15993
- Relative efficacy estimates were higher in analyses restricted to cases caused by vaccine-similar strains

N Engl J Med 2014;371:635-45.

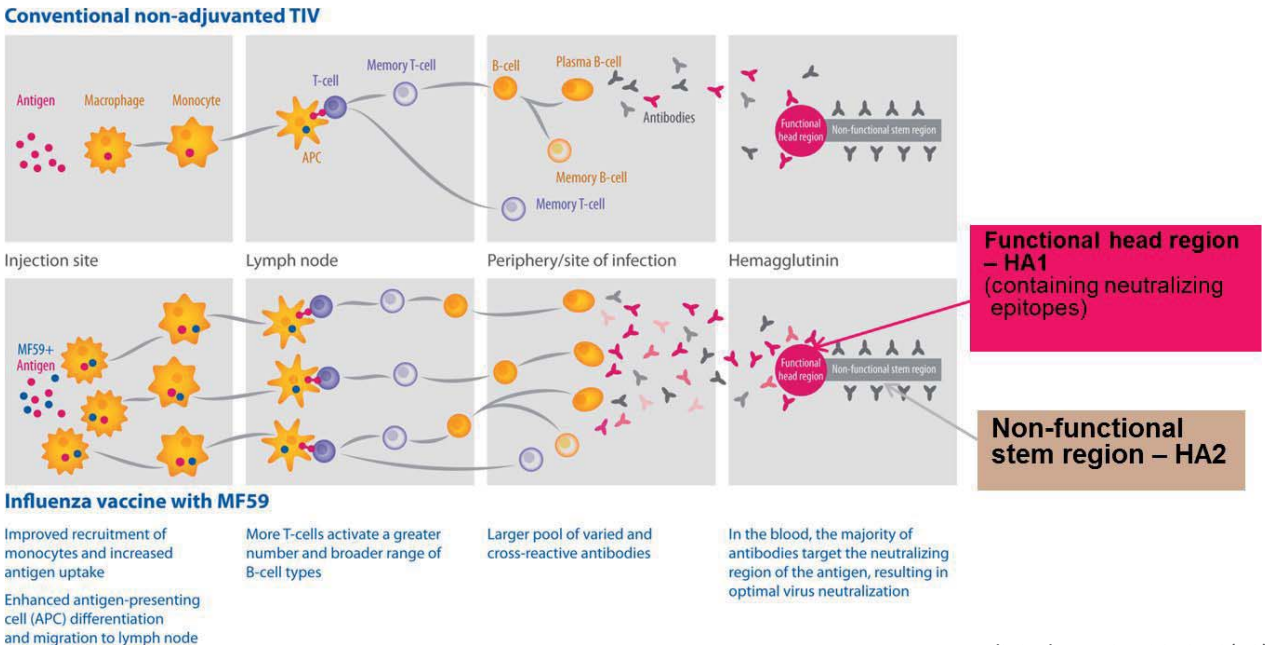
皮內(Iradermal)注射或肌肉注射



- Randomized control trial, Paitents > 60y/o
- 注射後21天，評估Immunogenicity
- ID group:2580, IM group:1070
- More solicited injection site reaction in ID group: 紅、腫、痛、癢

Vaccine 27 (2009) 7304–7312

含佐劑流感疫苗



Int J clinical practice 2018;72(10):e13249

含佐劑流感疫苗

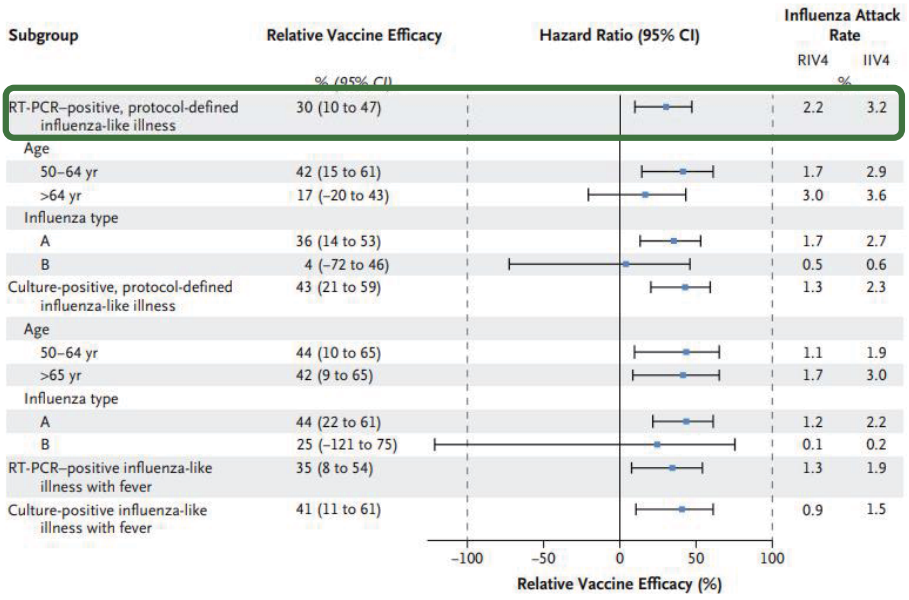
	Entire study population		High-risk group	
	GMT ratio	Difference in seroconversion (%)	GMT ratio	Difference in seroconversion (%)
A/H1N1[a]	1.4 (1.3-1.5)	9.2 (7.1-11.3)	1.4 (1.3-1.5)	11.1 (7.5-14.6)
A/H3N2[a]	1.6 (1.5-1.7)	12.7 (10.5-14.9)	1.6 (1.4-1.7)	13.5 (9.8-17.2)
B Strain[a]	1.2 (1.1-1.2)	5.2 (3.0-7.4)	1.1 (1.0-1.2)	5.0 (1.4-8.5)
A/H3N2[b]	1.5 (1.3-1.6)	11.3 (6.7-15.9)	1.4 (1.1-1.6)	12.3 (4.8-19.9)
A/H3N2[b]	1.7 (1.2-1.5)	11.9 (7.3-16.6)	1.3 (1.1-1.5)	12.6 (5.0-20.2)
B Strain[b]	1.1 (1.0-1.2)	4.0 (−0.4 to 8.4)	1.1 (1.0-1.3)	4.8 (−2.1 to 11.8)

- All values significantly noninferior.
- Statistically significant ratios of GMT and differences in seroconversion were tested on the Full Analysis Set population and multiplicity adjusted P- values were < 0.001 for all strains except theheterologous B strain

Int J clinical practice 2018;72(10):e13249

基因重組疫苗

- RCT, Double-blinded
- RIV (45µg of rHA) : 4303
- SDIIV(15µg of HA) : 4301
- Patients > 50y/o
- 該年度H3N2 mismatched
- RIV4, as compared with IIV4, **improved protection** against laboratory confirmed ILI in adults 50 years of age or older



N Engl J Med 2017;376:2427-36.

流感疫苗的接種禁忌

<u>絕對禁忌症:</u>

- 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

<u>注意事項</u>:

- 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)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**<u>觀察30分鐘</u>**, 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

衛生福利部疾病管制署

流感疫苗的安全性

不良反應 (Adverse effect)	副作用 (Side effect)
	
與疫苗僅時序相關, **沒有因果關係。**	時序相關 並且證實與疫苗**有因果關係。**

流感疫苗常見的不良反應

- 接種後10-50%可能發生注射部位疼痛、紅腫
- 1-2%會出現發燒、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。得到流感之後，Guillain-Barré症候群(GBS)發生率比打疫苗還要高。
- 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。
- 流感疫苗對於HIV患者亦無不良影響

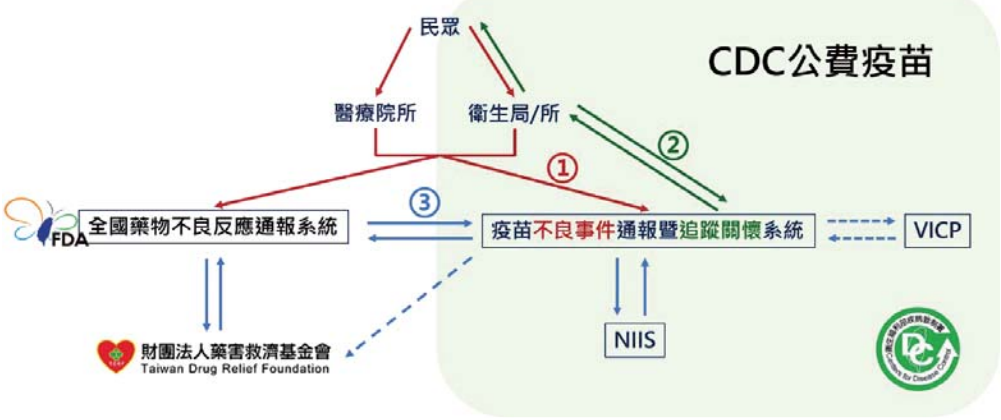
國內的疫苗安全監測

- **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)」***https://vaers.cdc.gov.tw***、**或是**全國藥物不良反應通報中心(ADR)通報，***https://adr.fda.gov.tw/***
  - 或民眾撥打1922專線通報
- **主動監測(必要時進行)**

疫苗接種紀錄 ⟷ **健保或醫院就醫資料**

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

疫苗不良事件通報與追蹤流程



- 民眾透過醫療院所或衛生局/所於「疫苗不良事件通報暨追蹤關懷系統(VAERS)」或全國藥物不良反應通報中心(ADR)進行不良事件通報
- 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
- 疾管署每日與食藥署進行雙向資料交換

衛生福利部疾病管制署

接種後嚴重疫苗不良事件通報與處理

- **接種後嚴重疫苗不良事件**
  - **定義:**包括死亡、危及生命、造成永久性殘疾或傷害、導致病人住院、延長已住院病人住院時間、或胎兒先天畸形者等
  - **通報流程:**若有發現個案，應詳填「流感疫苗接種嚴重疫苗不良事件通報單」**立即**通報衛生局或全國藥物不良反應通報中心(ADR)
  - 填寫說明，可參考全國藥物不良反應通報中心***「上市後疫苗不良事件通報表填寫指引」***
  - **處理流程 :**配合進行個案病情狀況等相關調查，並提供個案必要之醫療協助。

衛生福利部疾病管制署

季節性流感疫苗不良事件通報摘要報告

- Updated during 109-12-31 to 110-01-06
- 自 109 年 10 月 5 日起，季節性流感疫苗接種計畫開始。截至 110 年 1 月 6 日止，全國共施打季節性流感疫苗總數為 **594.9 萬劑**，共接獲疫苗**不良事件通報 505 件**，平均每十萬劑注射通報數約為 8.5 件。
  - 非嚴重不良事件:358
    - 發燒、畏寒、頭暈、嘔吐、皮膚紅疹、接種部位紅腫/疼痛等
  - 嚴重不良事件:147
    - 疑似急性心肌炎、疑似Steven-Johnson Syndrome、疑似GBS、疑似熱痙攣、疑似原發性血小板缺乏紫斑症
- 綜合目前疫苗不良事件通報資料之評估結果，尚未觀察到須採取相關措施之安全疑慮。

衛生福利部疾病管制署

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
  - 疫苗製造或輸入廠商應繳納一定金額，充作預防 接種受害救濟基金，**每一人劑疫苗，徵收新臺幣一點五元**。
- **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

衛生福利部疾病管制署

流感疫苗的受害救濟

- **自102年10月1日至110年4月30日止，公費流感疫苗總接種數為26,932,563劑，共通報1,110件不良事件**
- **期間申請預防接種受害救濟之案件僅336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20件，發生率約為0.07/每十萬人

衛生福利部疾病管制署

預防接種受害救濟給付案前五名疫苗種類

疫苗名稱	審議案例數	給付案例數	
		救濟給付	其他給付
卡介苗疫苗（BCG）	521	473	15
季節流感疫苗（Flu）	519	172	53
新型流感疫苗（H1N1）	553	75	136
白喉、破傷風、百日咳混合疫苗（DTP）	137	69	38
五合一疫苗（5 in 1）	103	45	20

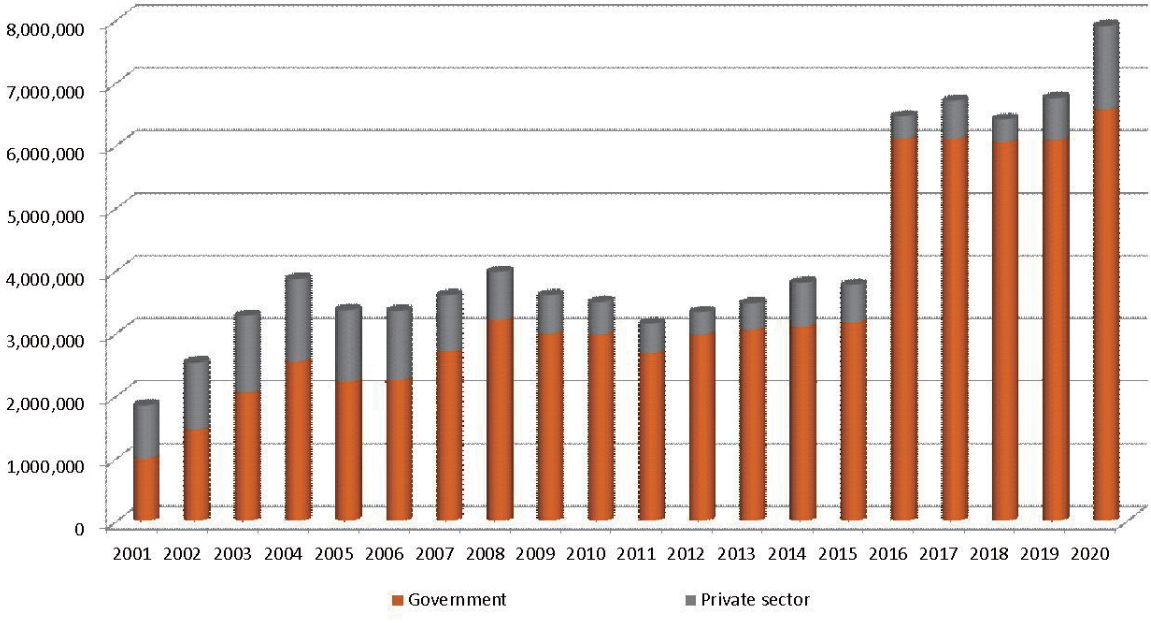
78-110/6/24 衛生福利部疾病管制署

接種異常事件通報

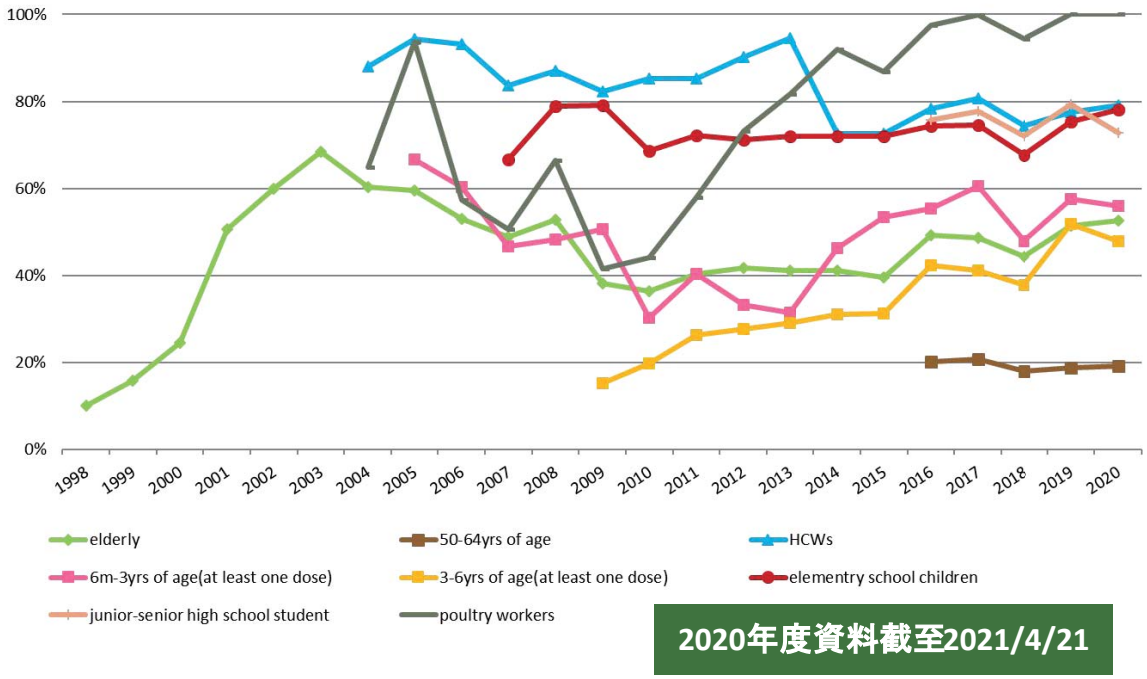
- **接種異常事件**
  - **定義:**接種疫苗時發生疫苗種類/劑量錯誤、重複施打、提前接種等接種異常事件
  - **通報流程:**合約院所於執行接種工作時, 若發生接種異常事件時, **立即**通報衛生局/所
  - **處理流程：**
    - 立即告知受接種個案或家長
    - 追蹤個案狀況並提供必要之醫療協助

衛生福利部疾病管制署

我國流感疫苗使用量



我國歷年各類對象流感疫苗施打率



2020年度資料截至2021/4/21

Take Home Message

- 每年接受流感疫苗接種，是預防流感最有效的方式
  - 保護力會因為該年度流行型別與疫苗株相似度及個體的免疫生成性不同而有差異
  - 若疫苗株與流行株相符，保護力約在70%-90%
  - 老年人保護力稍差，約可**減少30-70%**流感及肺炎住院率
- 流感疫苗安全無虞: 六個月以上兒童、孕婦、免疫低下族群均可施打
- 對雞蛋過敏不是接種流感疫苗的禁忌症
- 流感疫苗的不良反應多為注射部位的紅腫、疼痛，可自行緩解
- 國內有完整的疫苗安全監測系統