流感流行病學與疫苗

2022.8.20

成大醫院感染科 李明吉

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聯合新聞網 | 51.7k 人追蹤 ☆ 追蹤

後疫時代防流感 秋季記得打疫苗

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陳書農 / 彰化秀傳紀念醫院小兒心臟科主治醫師

2022年8月18日 週四 上午6:38

最近兒童呼吸道感染問題多，除了新冠肺炎是首要考量，流感也開始跑出來了！在急診看到發燒的孩子，兩個鼻孔都要插著棒子，一邊做新冠快篩、另一邊做流感快篩。這讓人擔心其他病毒會重新來襲，勤洗手與戴口罩不能鬆懈外，秋後記得要接種流感疫苗。

今年六月一份法國研究發現，在新冠肺炎流行期間，兒童侵襲性肺炎鏈球菌感染（菌血症或是細菌性腦炎）、流感與支氣管炎（常是起因於呼吸道融合病毒感染）發生率大幅下降。法國學者推測，民眾普遍實施「非藥物介入措施」的成果。

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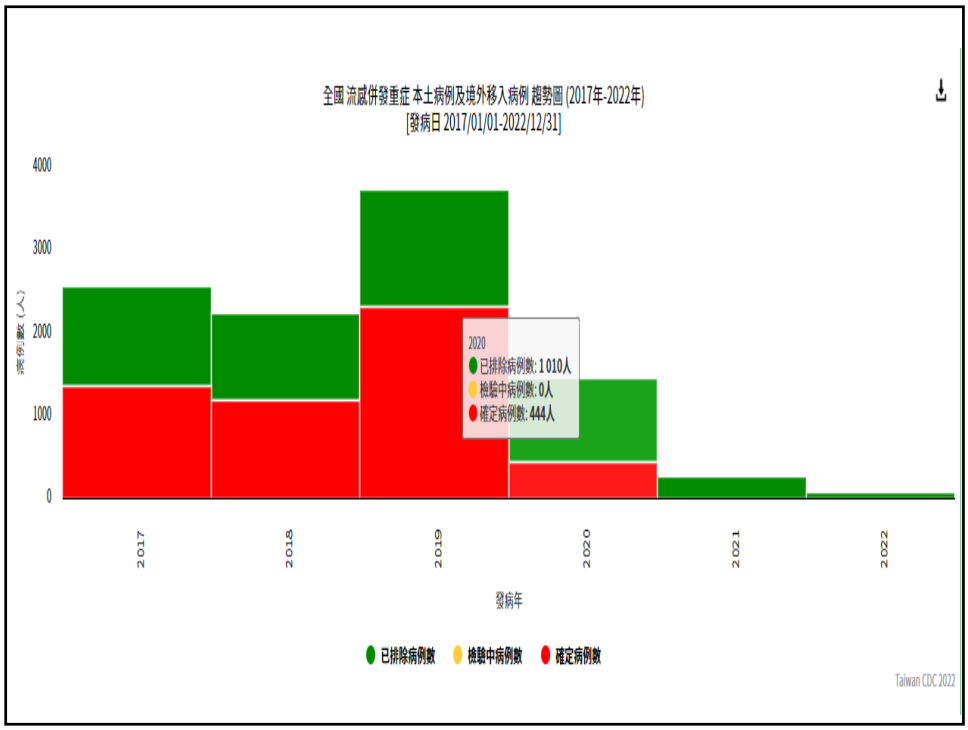
全國 流感併發重症 本土病例及境外移入病例 趨勢圖 (2017年-2022年)
[發病日 2017/01/01-2022/12/31]
4000
3000
2000
1000
0
病例數（人）
2020
已排除病例數: 1010人
檢驗中病例數: 0人
確定病例數: 444人
2017
2018
2019
2020
2021
2022
發病年
已排除病例數
檢驗中病例數
確定病例數
Taiwan CDC 2022

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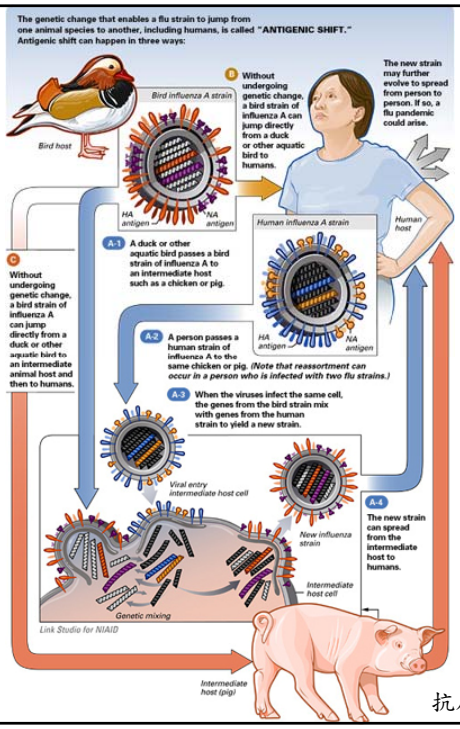
衛生福利部疾病管制署
Taiwan Centers for Disease Control
流感大流行的歷史
百年間主要之全球性大流行：
1918
1957
1968
1977
2009
20XX
H1N1 (Spanish flu)
H2N2 (Asian flu)
H3N2 (Hong Kong flu)
H1N1 (Russian flu)
H1N1
H7N9?
H5N1?
H7N9?
HA
NA
Direct adaptation: mutation (bird)
Reassortment (bird–human)
Reassortment (bird–human)
Re-emergence of H1N1 strain
Reassortment (bird–pig–human)
Direct adaptation or reassortment?
TRENDS in Microbiology
4~5千萬人死亡
逾200萬人死亡
100萬人死亡
70萬人死亡
超過1.8萬人死亡

4



A型流感病毒可在不同物種間重組

抗原移型(Antigenic shift)

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流行情形

- 近年各國主要流行之季節性流感病毒型別以A(H3N2)、A(H1N1)，以及B型流感為主。
- 美國疾病管制中心統計資料顯示，每年流感活動多自10月開始，持續至隔年5月。
- 我國每年流感病例約自11月開始逐漸增加，於12月至隔年3月份達到流行高峰。
- 自2019年底COVID-19爆發大流行後，南北半球國家均發現流感活動度顯著下降。

疾病管制署 季節性流感防治工作手冊
2021 11月修訂

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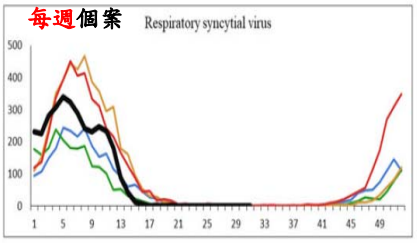
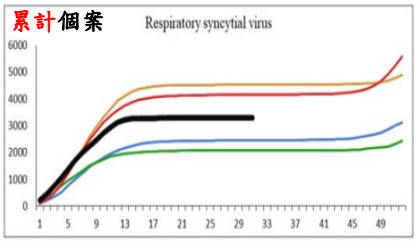
COVID-19 preventive measures coincided with a marked decline in other infectious diseases in Denmark, spring 2020

每週個案 Respiratory syncytial virus



累計個案 Respiratory syncytial virus

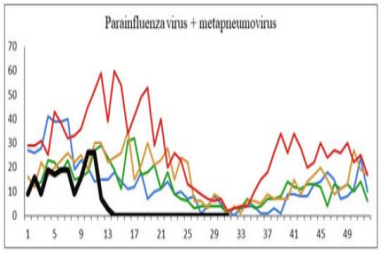


黑色：2020 其他色：2016~2019

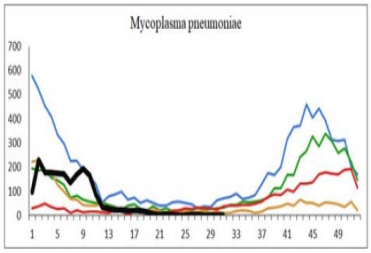
7

每週個案

Parainfluenza virus + metapneumovirus

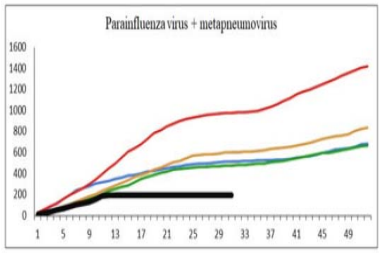


Mycoplasma pneumoniae

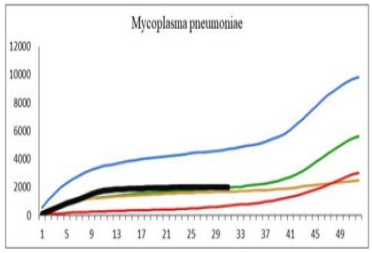


累計個案

Parainfluenza virus + metapneumovirus



Mycoplasma pneumoniae



Epidemiol Infect 2022 Jul 28;150:e138

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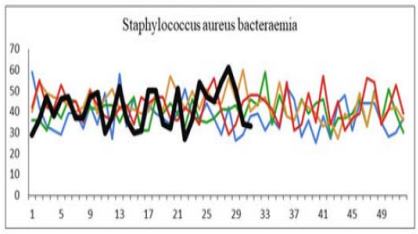
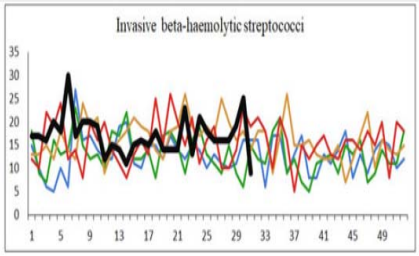
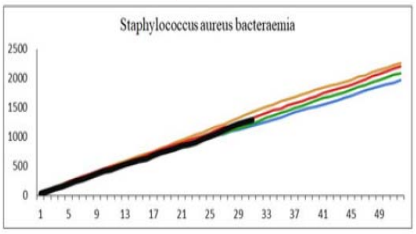
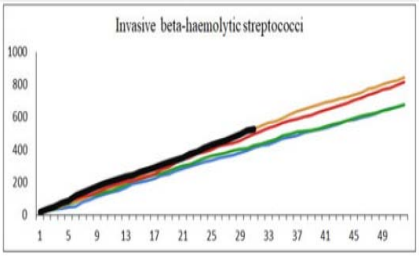
每週個案





累計個案





Epidemiol Infect 2022 Jul 28;150:e138

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衛生福利部疾病管制署
Taiwan Centers for Disease Control

台灣的流感監測系統

病例監測
- 法定傳染病監視通報系統：流感併發重症、新型A型流感
- 症狀監視通報系統：類流感聚集、國際機場入境發燒旅客

流行趨勢監測
- 即時疫情監測及預警系統(RODS)
- 肺炎及流感死亡監視
- 人口密集機構傳染病監視通報系統
- 學校傳染病監視通報系統
- 定點醫師監測系統

病毒活動監測
- 病毒性合約實驗室監視通報系統
- 病毒抗原及抗藥性分析

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關於CDC 傳染病與防疫專題 預防接種 國際旅遊與健康
COVID-19
通報
檢驗
宣導
統計專區
申請
研究
出版品
網址：https://www.cdc.gov.tw
1
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關於CDC 傳染病與防疫專題 預防接種
首頁 > 應用專區 > 統計專區
應用專區
«統計專區
傳染病統計資料查詢系統
疾病管制署資料開放平臺
流感速訊
統計專區
傳染病統計資料查詢系統
疾病管制署資料開放平臺
流感速訊
腸病毒疫情週報
項次
週別
連結
24
2022年第11週
2022年第11週(2022_03_13-2022_03_19).pdf (下期速訊將視流感疫情適時出刊)
23
2022年第10週
2022年第10週(2022_03_06-2022_03_12).pdf
22
2022年第9週
2022年第9週(2022_02_27-2022_03_05).pdf

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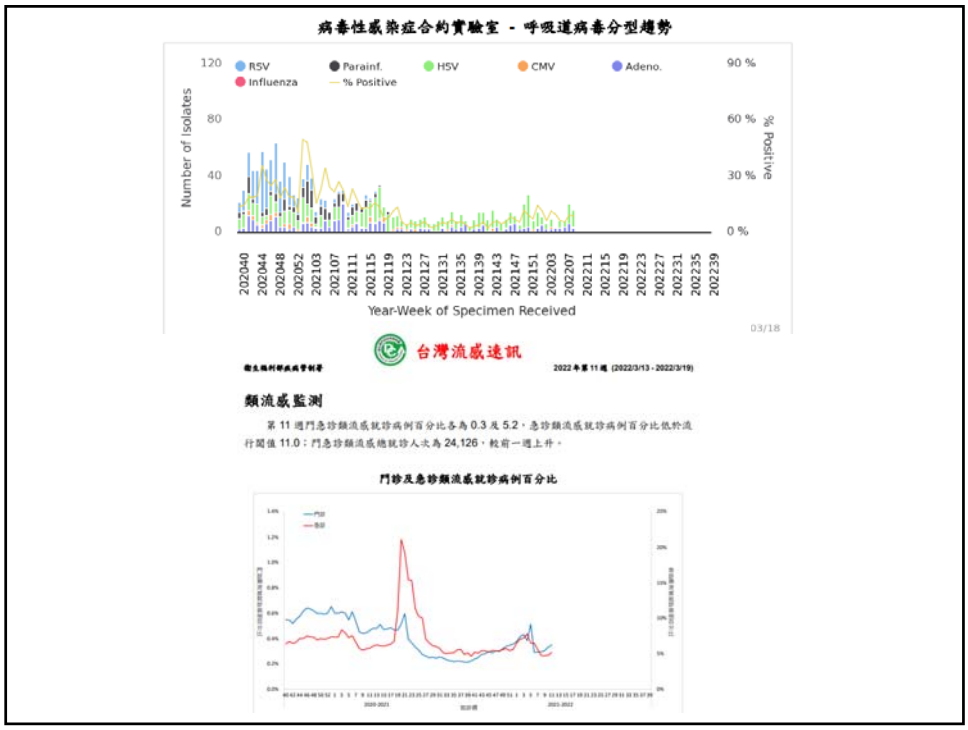
病毒性感染症合約實驗室 - 呼吸道病毒分型趨勢
RSV
Parainf.
HSV
CMV
Adeno.
Influenza
% Positive
Number of Isolates
% Positive
Year-Week of Specimen Received
台灣流感速訊
2022 年第 11 週 (2022/3/13 - 2022/3/19)
類流感監測
第 11 週門急診類流感就診病例百分比各為 0.3 及 5.2，急診類流感就診病例百分比低於流行閾值 11.0；門急診類流感總就診人次為 24,126，較前一週上升。
門診及急診類流感就診病例百分比

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流感的預防

- 接種流感疫苗
  - 目前預防流感的最有效方式
- 暴露後預防藥物 Post-exposure prophylaxis
  - 特殊高風險族群、群聚事件
- 感染管制措施
  - 醫療機構、長期照顧機構、人口密集機構
- 個人衛生
  - 咳嗽禮節、手部衛生、有症狀時戴口罩

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衛生福利部疾病管制署
Taiwan Centers for Disease Control

我國現行公費流感疫苗接種對象

一. 滿6個月以上至國小入學前幼兒
二. 國小、國中、高中、高職、五專一至三年級學生
三. 50歲以上成人
四. 高風險慢性病、罕見疾病及重大傷病患者
五. 孕婦及6個月內嬰兒之父母
六. 幼兒園托育人員及托育機構專業人員
七. 安養、養護、長期照顧等機構住民及其所屬工作人員
八. 醫事及衛生等單位之防疫相關人員
九. 禽畜養殖等相關行業工作人員、動物園工作人員及動物防疫人員

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流感高危險族群 與 高傳播族群

- 高危險族群係因自身免疫力關係，比非高危險族群有較多機會感染流感及出現嚴重併發症，包括有65歲以上長者、嬰幼兒、孕婦、免疫功能不全者，以及罹患氣喘、糖尿病、心血管、肺臟、肝臟、腎臟等疾病或BMI≧30者等。

- 高傳播族群係指因工作因素可能傳染給高危險族群或是處於容易造成傳播之場所者，包括醫療院所之醫護工作人員、慢性照護機構之工作人員，以及學校之學生等。

疾病管制署 季節性流感防治工作手冊
2021 11月修訂

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衛生福利部疾病管制署
Taiwan Centers for Disease Control

歷年流感疫苗採購量

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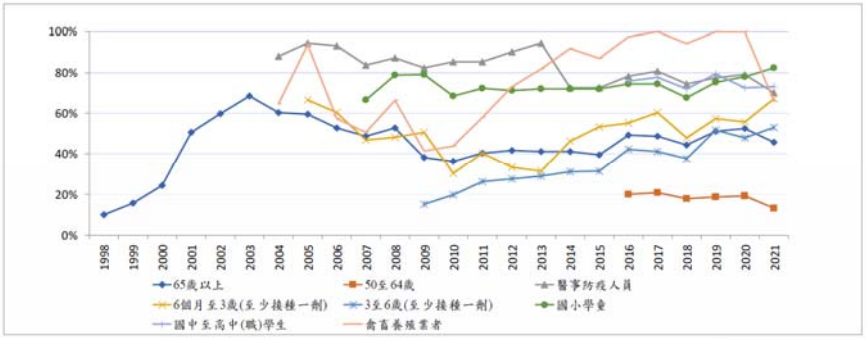
衛生福利部疾病管制署
Taiwan Centers for Disease Control

歷年各類對象流感疫苗接種率



2021年度資料截至2022/6/5

2014年起改以執業登記人數為分母統計接種率

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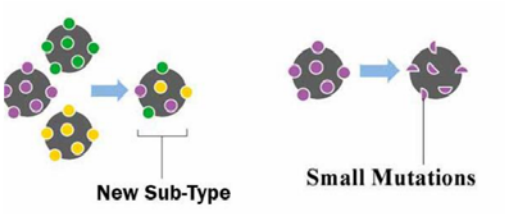
衛生福利部疾病管制署
Taiwan Centers for Disease Control

為什麼每年都要接種流感疫苗?

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



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CDC Centers for Disease Control and Prevention

衛生福利部疾病管制署
Taiwan Centers for Disease Control

Vaccine Effectiveness: How Well Do the Flu Vaccines Work?

Questions & Answers

Getting a flu vaccine is more important than ever during 2020-2021 to protect yourself and the people around you from flu, and to help reduce the strain on healthcare systems responding to the COVID-19 pandemic.

How effective is the flu vaccine?

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

當疫苗株與當季流行病毒株吻合，
疫苗能使族群中感染的風險降低40-60%

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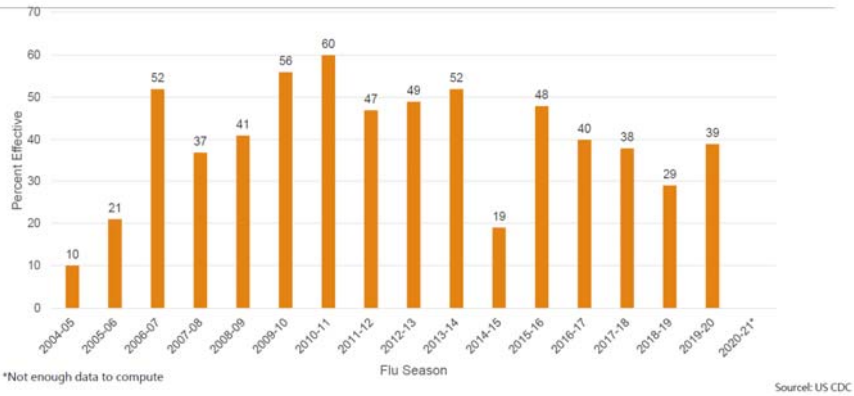
衛生福利部疾病管制署
Taiwan Centers for Disease Control

Effectiveness of Seasonal Flu Vaccines from the 2005 – 2020 Flu Seasons in the US



*Not enough data to compute

Source: US CDC

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衛生福利部疾病管制署
Taiwan Centers for Disease Control

流感疫苗的保護效果

- 流感疫苗的保護力因**年齡**或**身體狀況**不同而異，平均約可達**30-80%**
- 疫苗保護效果亦需**視當年疫苗株與實際流行的病毒株型別是否相符**，一般保護力會隨病毒型別差異加大而降低
- 根據國際研究顯示，對18歲以上成人因確診流感而住院的保護力約有41%，入住加護病房的流感重症保護力則可達82%
- 6個月至未滿18歲兒童青少年族群接種流感疫苗之保護力與成人相仿
- 在免疫系統尚未成熟的6至12個月年齡層，接種流感疫苗對確診流感的保護力也有8成
- 孕婦接種流感疫苗除可降低罹患 流感與住院風險外，亦可降低新生兒確診流感風險

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2022-2023年流感季流感疫苗

- 疫苗特性：不活化疫苗
- 接種途徑：肌肉注射
- 接種劑量與間隔：
  - 四價疫苗
    - 6個月以上均接種0.5mL

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

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衛生福利部疾病管制署
Taiwan Centers for Disease Control

2022-23 年流感季流感疫苗(成分、劑型、使用方法)

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

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衛生福利部疾病管制署
Taiwan Centers for Disease Control

111年度流感疫苗
供貨廠商/適用年齡及供貨數量一覽表

許可證持有廠商	疫苗品名	適用年齡	劑型	供貨數量	疫苗製程
賽諾菲股份有限公司	Vaxigrip Tetra 菲流達四價流感疫苗	6個月以上	0.5mL	190萬劑	雞胚胎蛋培養 (egg-based)
國光生物科技股份有限公司	AdimFlu-S（QIS） 安定伏裂解型 四價流感疫苗	3歲以上	0.5mL	327萬5,190劑	
台灣東洋藥品工業股份有限公司	Flucelvax Quad 輔流威適流感疫苗	3歲以上	0.5mL	113萬	細胞培養 (cell-based)

註1: 以食藥署核准之仿單說明為準

註2: 包含中央及地方代購疫苗量

提醒 國光及台灣東洋公司疫苗不可使用於3歲以下幼兒

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東洋代理流感疫苗 獲准施打至六個月以上至3歲嬰幼兒

本文共941字

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2022/06/30 19:16:38

經濟日報 記者謝柏宏／即時報導 讚 15

台灣東洋（4105）今（30）日舉行法說會，總經理侯靜蘭表示，近年推展四價流感疫苗產品，今年將提供113萬劑公費疫苗及20多萬劑的自費疫苗，整體營收將較去年高度成長。

此外，東洋代理的四價流感疫苗，也在上周獲得食藥署核批，取得六個月以上至3歲嬰幼兒童的新適應症，這表示台灣東洋細胞流感疫苗，經醫師評估後，只要是六個月以上民眾都能施打；另外，考量老年人的防疫需求，東洋也規劃於明年上市含佐劑的新型流感疫苗。

https://money.udn.com/money/story/5618/6427590

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「雞蛋過敏」已不再列為流感疫苗接種的禁忌症

- 依國際文獻資料顯示，對「蛋」的蛋白質有嚴重過敏者，接種流感疫苗後**出現嚴重過敏反應之機率極低**
- 我國傳染病防治諮詢會預防接種組專家建議參依美、英等國作法，將「已知對『蛋』之蛋白質有嚴重過敏者」自**接種禁忌症移除**，惟應於**注意事項**(precaution)加列對蛋嚴重過敏者接種疫苗之相關說明內容
- 已知對「**蛋**」之蛋白質有嚴重過敏者，**可在門/住診由熟悉處理過敏症狀之醫事人員提供接種**，並於接種後觀察30分鐘，無不適症狀再離開

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流感疫苗接種禁忌與注意事項

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

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

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立即型過敏

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

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流感疫苗常見的副作用

- 接種後10-50%可能發生注射部位疼痛、紅腫
- 1-2%出現發燒、虛弱等全身性反應
- 嚴重的反應如全身性過敏反應或Guillain-Barré症候群(GBS)發生率在**百萬分之1以下**

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Q&A-7

流感疫苗可否和其他疫苗或COVID-19疫苗同時接種？

目前實證顯示流感疫苗和COVID-19疫苗同時接種並不影響疫苗之有效性或安全性。

為提升接種效率及提高接種涵蓋率，經111年2月25日衛生福利部傳染病防治諮詢會流感防治組及預防接種組聯席會議建議，流感疫苗與COVID-19疫苗，**可以同時接種**，民眾**可依其需求選擇同時或間隔一段時間接種**。同時接種流感疫苗與COVID-19疫苗之接種部位，考量臨床接種實務之可行性與參考WHO指引，**建議接種於不同肢體**。

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預防接種不良事件/反應

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

衛生福利部疾病管制署
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預防接種受害救濟審議委員會（VICP）

民國75年
- 出現口服小兒麻痺疫苗後造成小兒麻痺症個案

民國77年6月
- 參考歐美等先進國家制度，成立預防接種受害救濟基金

民國78年
- 預防接種諮詢小組召開第一次會議審議

民國81年至今
- 設置獨立審議小組進行審議

VICP審議結果：流感疫苗

與疫苗相關

- 急性過敏反應、類蜂窩性組織炎.....

無法排除與疫苗相關

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

近年疑似流感疫苗接種致死，申請VICP案例，審議結果均與疫苗無關

- 腦血管疾病、敗血性休克、腸壞死.....

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疫苗猶豫(Vaccine hesitancy)

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

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

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流感疫苗安全無虞

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

- 自102年10月1日至111年4月30日止，公費流感疫苗總接種數為32,975,009劑，共通報1,208件不良事件
- 期間申請預防接種受害救濟之案件僅370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0.05/每十萬人

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預防重複接種

- 再次與民眾確認是否接種該年度流感疫苗
- 確實核對幼兒預防紀錄接種表
- 確實登載於幼兒預防紀錄接種表
- 落實三讀五對(確認當日接種疫苗為流感疫苗)
- 利用資訊系統查核接種紀錄
  - 健保卡預防保健紀錄
  - NIIS查詢
  - 醫療院所預防接種紀錄查詢子系統

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醫療院所預防接種紀錄查詢子系統

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CDC網站：流感疫苗資訊

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小結

定期接種流感疫苗，是預防流感及其併發症最有效的方式

接種流感疫苗能夠降低罹患流感及產生後續併發症的風險

接種流感疫苗出現嚴重不良事件的比例極低，建議每年接種流感疫苗

流感臨床診斷與檢驗

成大醫院 感染科
羅景霳

1

流感季節時，
哪個診斷工具CP最高

2

哪個診斷工具CP最高

- 快篩
- **PCR**
- 血清抗體
- 我有一個大膽的想法

哪個診斷工具CP最高

- 快篩
- **PCR**
- 血清抗體
- 我有一個大膽的想法

Clinical Diagnosis

病史詢問

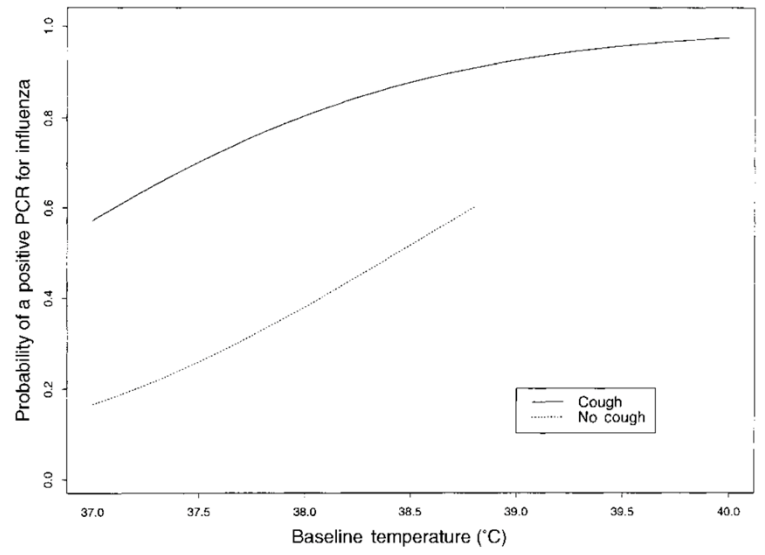
5

病史詢問

80~90%準確率

6

病史詢問與流感診斷



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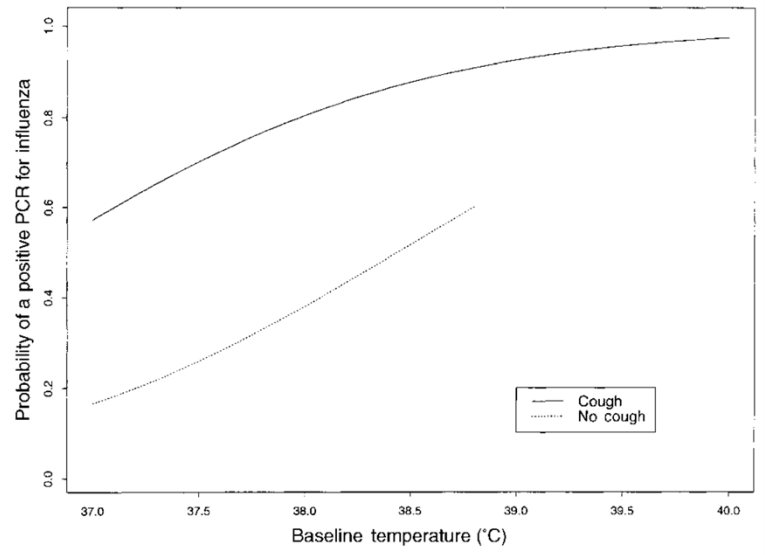
病史詢問與流感診斷

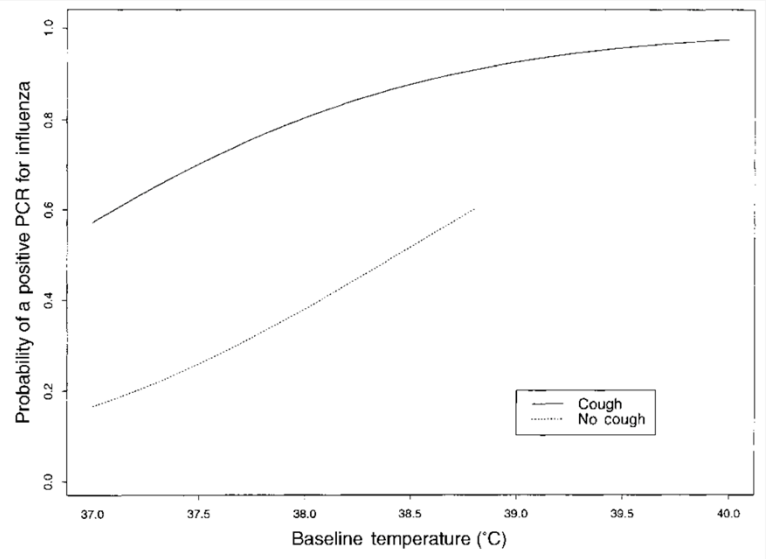
核酸陽性預測值



8

病史詢問與流感診斷

核酸陽性預測值



發燒
咳嗽

9

流感臨床診斷與檢驗

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流感臨床診斷與檢驗

- 臨床表現

11

流感臨床診斷與檢驗

- 臨床表現
- 診斷工具

12

流感臨床診斷與檢驗

- 臨床表現
- 診斷工具
- 鑑別診斷

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流感臨床診斷與檢驗

- 臨床表現
- 診斷工具
- 鑑別診斷

14

流感臨床表現

- **Uncomplicated**
- **Complication**

15

Uncomplicated influenza

Onset

Incubation | Disease period

16

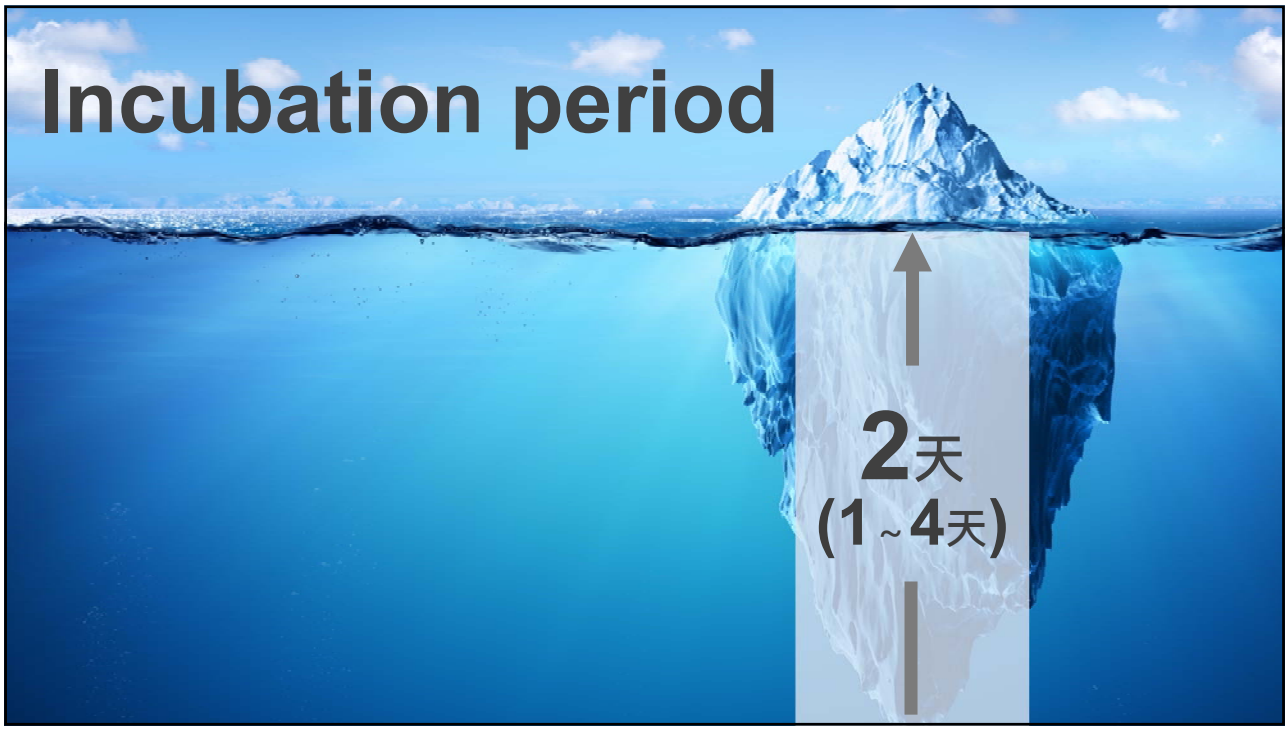
Uncomplicated influenza

Onset

Incubation | Disease period

17

18



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Uncomplicated influenza

Onset

Incubation | Disease period

20

講到流感症狀

你會想到什麼?

21

Symptom — Uncomplicated influenza

- Systemic symptom
- Respiratory symptom

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Symptom

- **Systemic symptom**
- Respiratory symptom

Systemic symptom

- Fever/Chillness
- Myalgia/Headache
- Malaise/Anorexia

Systemic symptom

Uncomplicated influenza

- Fever
  - Abrupt onset

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Systemic symptom

Uncomplicated influenza

- Fever
  - Abrupt onset
  - 知道明確時間

26

Systemic symptom

- Fever
  - 37.8 ~ 40.0°C

Systemic symptom

- Fever
  - 37.8 ~ 41.1°C

Systemic symptom

- Fever
  - Highest on D1

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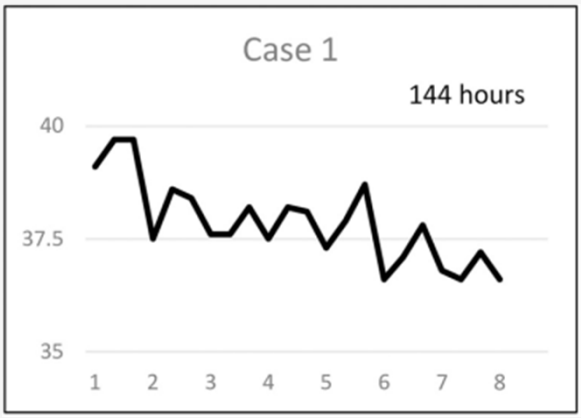
Systemic symptom

- Fever
  - Highest on D1
  - 0.3~0.6^{o}C lower afterward

30

Fever curve of influenza



PLoS ONE 14(11): e0224683

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Systemic symptom

Uncomplicated influenza

- Fever duration
  - 3 days

32

Systemic symptom

Uncomplicated influenza

- Fever duration
  - 3 days (4~8 days)

33

Systemic symptom

Uncomplicated influenza

- Myalgia/Headache

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Systemic symptom

- Myalgia/Headache
  - Most troublesome

Systemic symptom

- Myalgia/Headache
  - Most troublesome
  - Relate to height of fever

Systemic symptom

Uncomplicated influenza

- Myalgia
  - Extremities
  - Long muscle of back

Systemic symptom

Uncomplicated influenza

- Myalgia
  - Extremities
  - Long muscle of back
  - Eye muscle

Systemic symptom

- Myalgia
  - Extremities
  - Long muscle of back
  - Eye muscle
    - pain while gazing laterally

Symptom

- Systemic symptom
- Respiratory symptom

Respiratory symptom

Uncomplicated influenza

- Dry cough
- Severe pharyngeal pain
- Nasal obstruction and discomfort

41

Respiratory symptom

Uncomplicated influenza

- **Dry cough**
- Severe pharyngeal pain
- Nasal obstruction and discomfort

42

Respiratory symptom

Uncomplicated influenza

- After systemic symptom diminish
  - Recurrent cough
  - Hoarseness
  - Dry or sore throat

Respiratory symptom

Uncomplicated influenza

- After systemic symptom diminish
  - Recurrent cough
  - Hoarseness
  - Dry or sore throat

不是變嚴重

Typical Symptom

Uncomplicated influenza

- Systemic symptom
- Respiratory symptom

45

Atypical Symptom

Uncomplicated influenza

46

Atypical Symptom

Uncomplicated influenza

- Age > 65 years old
- Immunocompromised

47

Atypical Symptom

Uncomplicated influenza

- No fever
- Milder systemic symptom

48

Atypical Symptom

Uncomplicated influenza

- No fever
- Milder systemic symptom
- Generalized symptom

Atypical Symptom

Uncomplicated influenza

- No fever
- Milder systemic symptom
- Generalized symptom
  - Anorexia/Malaise/Weakness
  - Dizziness

Atypical Symptom

- Older adults

51

Atypical Symptom

- Older adults
  - Altered mental status

52

Uncomplicated influenza

Onset

Incubation	Disease period
2天	3天 +數天

53

沒有在天天過年

54

流感臨床表現

Uncomplicated

Complication

55

Risk of complication

56

Risk of complication

- Children < 5 years old
  - Esp. < 2 years old
- Adult ≥ 65 years old
- Pregnant women / 2 weeks postpartum
- Residents of nursing homes and long-term care facilities
- People with medical condition

Risk of complication — Medical condition

Risk of complication — Medical condition

- Neurological and neurodevelopmental conditions
- Asthma
- Chronic lung disease
- Heart disease
- Endocrine disorders
- Kidney disorder
- Liver disorders
- Blood disorder
- Metabolic disorder
- Weakened immune system
- BMI ≥ 40
- Children<19 y/o under long-term ASA

59

Complication of influenza

- Respiratory
- Extrapulmonary

60

Complication of influenza

- Respiratory
- Extrapulmonary

61

Pneumonia

62

Symptom of pneumonia

- Cough with dyspnea
- Tachypnea
- Hypoxia
- Fever

Types of pneumonia

- Primary influenza viral pneumonia
- Secondary bacterial pneumonia
- Mixed viral and bacterial pneumonia

Types of pneumonia

- Primary influenza viral pneumonia
  - Persistent fever and symptom after 3-5 days of symptom

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Types of pneumonia

- Secondary bacterial pneumonia
  - Improvement of influenza symptom
  - Relapse of fever and cough with purulent sputum

66

Types of pneumonia

- Mixed viral and bacterial pneumonia
  - Gradual progression
  - or Transient improvement followed by worsening

Complication of influenza

- Respiratory
- Extrapulmonary

Extrapulmonary complication

- Cardiac
- Central nervous system
- Myositis and rhabdomyolysis
- Multisystem organ failure
- Concomitant infection

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Extrapulmonary complication

- Cardiac
  - Myocardial infarction
  - Myocarditis/Pericarditis

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Extrapulmonary complication

- Central nervous system
  - Guillain-Barre syndrome

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Extrapulmonary complication

- Central nervous system
  - Guillain-Barre syndrome
    - Incidence after influenza
      - 90 days: 7.35 (95% CI: 4.36-12.38)
      - 30 days: 16.64 (95% CI: 9.37-29.54)

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臨床表現

- 在流感流行期，臨床診斷的正確率高
- Uncomplicated influenza中，全身症狀，如發燒和肌肉痠痛等，是流感的特色
- Influenza complication中，肺炎是最常見的併發症，如果病程超出預期，要特別注意

73

流感臨床診斷與檢驗

臨床表現

診斷工具

鑑別診斷

74

診斷工具的目的

- Symptom may be typical
- Physical examination few finding
- Laboratory test nonspecific
- Image generally normal

診斷工具

- Whom to test
- What to test
- How to test

診斷工具

- Whom to test
- What to test
- How to test

77

Whom to test 原則

78

什麼狀況下

你會想要做流感檢驗

79

Whom to test?

原則

- 病患免疫不好
- 病人年齡超過65歲
- 決定是否治療
- 想要決定病人的下一步處置

80

Whom to test

原則

- If result will influence management
- Public health activity

81

Whom to test

原則

- If result will influence management
  - Antiviral or antimicrobial agents
  - Further diagnostic evaluation
  - Prophylaxis for high risk contacts
  - Infection control intervention

82

Whom to test

原則

- Public health activity
  - Interventions for outbreak management

83

Whom to test

不同背景

- Influenza is circulating
- Influenza is not circulation

84

Influenza not circulating

Whom

85

Influenza not circulating

Whom

- 九月～隔年四月

86

Influenza not circulating

Whom

- 九月～隔年四月
- 十一月～隔年三月

87

Influenza is circulating

Whom

- Present influenza-like illness
  - Immunocompromised
  - high risk of complication
- Acute respiratory symptoms
  - Exacerbation of chronic medical condition
  - Influenza complication
- Hospitalized patients
  - Acute respiratory symptoms
  - Exacerbations of chronic medical condition

88

流行期間

有風險/症狀惡化可檢驗

89

Whom to test 不同背景

- Influenza is circulating
- Influenza is not circulation

90

Influenza not circulating

Whom

- Relevant epidemiologic exposure

91

Influenza not circulating

Whom

- Relevant epidemiologic exposure
  - Exposure to person with influenza
  - Outbreak of respiratory illness of uncertain cause
  - Recent travel in an area with influenza activity

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非流行期間

要有曝觸才要驗

93

診斷工具

- Whom to test
- What to test
- How to test

94

What to test

- Molecular assay
- Antigen detection assay
- Others

Molecular assay

- High sensitivity
- High specificity

Molecular assay

What to test

- Conventional RT-PCR
- Multiplex RT-PCR
- Rapid molecular tests

97

Molecular assay

What to test

- Conventional RT-PCR
- Multiplex RT-PCR
- Rapid molecular tests

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Conventional RT-PCR

Molecule

- Distinguish influenza A and B
- Influenza A subtype

Conventional RT-PCR

Molecule

- Distinguish influenza A and B
- Influenza A subtype

- Turnaround time: 1-8 hours

Multiplex RT-PCR

Molecule

- Several pathogens detection

101

Multiplex RT-PCR

Molecule

- Several pathogens detection
- For
  - Immunocompromised
  - Requiring hospitalization
  - During period of influenza and COVID-19

102

Filmarray respiratory panel

- Adenovirus
- Human Rhinovirus/ Enterovirus
- Influenza virus
- Respiratory syncytial virus
- Parainfluenza
- Human metapneuovirus
- Coronavirus
  - Severe acute respiratory syndrome coronavirus 2
- Chlamydia pneumoniae
- Bordetella pertussis
- Bordetella parapertussis
- Mycoplasma pneumoniae

103

Rapid molecular tests

Molecule

- Distinguish influenza A and B
- No influenza A subtype

104

Rapid molecular tests — Molecule

- Distinguish influenza A and B
- No influenza A subtype

- Turnaround time: 15~30 min

105

What to test

Molecular assay

Antigen detection assay

Others

106

Antigen detection assay

- Low to moderate sensitivity
- High specificity

107

Antigen detection assay

- Low to moderate sensitivity 50~70%
- High specificity

108

Antigen detection assay

- Interpret with caution
  - False negative result are common
  - Not used for hospitalized

Antigen detection assay

- Molecular test recheck

Antigen detection assay

- Molecular test recheck
  - Negative Ag in high community influenza, and indication for confirmation
  - Positive Ag in low community influenza
  - Recent exposure to pigs or poultry

What to test

Molecular assay

Antigen detection assay

Others

Others

- Viral culture
- Serological tests

113

Others

- Viral culture: public surveillance
- Serological tests: not routine test

114

診斷工具

- Whom to test
- What to test
- How to test

115

How to test

- 檢測時間點
- 採哪裡
- 用什麼採檢

116

檢測時間點

- Within four days of symptom onset

117

採哪裡

- 首選為Nasopharynx

118

採哪裡

- 首選為Nasopharynx
- 其次是Nasal加上Throat swab

採哪裡

- 首選為Nasopharynx
- 其次是Nasal加上Throat swab
  - 若非要選一個，就選nasal swab

採哪裡

- For ventilated patients with negative upper respiratory tract

121

採哪裡

- For ventilated patients with negative upper respiratory tract
  - Endotracheal aspirate
  - Bronchoalveolar lavage fluid

122

採哪裡

- For ventilated patients with negative upper respiratory tract
  - Endotracheal aspirate
  - Bronchoalveolar lavage fluid
- Greater and prolonged respiration in lower respiratory tract

123

用什麼採

124

用什麼採

- Flocked swab

125

用什麼採

- Flocked swab

https://www.thermofisher.com/order/catalog/product/R12566

126

診斷工具

- 當檢驗結果會影響後續決策或是要進行流病調查時，才需要進行流感的檢測
- 流感診斷以核酸檢測為原則，若是用抗原檢測，則需要小心判讀
- 在病程早期進行檢測的陽性率較高，最好是取鼻咽的檢體

127

流感臨床診斷與檢驗

臨床表現

診斷工具

鑑別診斷

128

鑑別診斷

- Respiratory viral infection
- Novel influenza A virus infection
- Bacterial pneumonia

129

鑑別診斷

- Respiratory viral infection
- Novel influenza A virus infection
- Bacterial pneumonia

130

Respiratory viral infection

- COVID-19
- Respiratory syncytial virus
- Common cold
- MERS-CoV

131

COVID-19

鑑別診斷

- Difficult to distinguish

132

COVID-19

鑑別診斷

- Difficult to distinguish
- More common in COVID-19
  - Fatigue
  - Diarrhea
  - Olfactory disorders
  - Taste disorders

133

COVID-19

鑑別診斷

- Diagnosed by antigen / PCR

134

Respiratory syncytial virus — 鑑別診斷

- More common in children

135

Respiratory syncytial virus — 鑑別診斷

- More common in children
- Also important in
  - Older adults
  - Immunocompromised

136

Respiratory syncytial virus

鑑別診斷

- Diagnosed by PCR

137

Common cold

鑑別診斷

- Several virus

138

Common cold

鑑別診斷

- Several virus
  - Rhinovirus
  - Parainfluenza
  - Common cold coronavirus

139

Common cold

鑑別診斷

- Mild symptom than influenza
- Nasal congestion milder

140

Common cold

鑑別診斷

- Diagnosis by clinical manifestation

141

MERS-CoV

鑑別診斷

- History of Arabian peninsula

142

MERS-CoV

鑑別診斷

- Diagnosis by PCR

143

Novel influenza A virus

鑑別診斷

144

Novel influenza A virus 鑑別診斷

- Symptom not distinguish from seasonal influenza A

145

Novel influenza A virus 鑑別診斷

- Exposure history
- Travel history

146

Novel influenza A virus 鑑別診斷

- Exposure to
  - Poultry
  - Pigs
  - Ill person with animal associated influenza

147

Novel influenza A virus 鑑別診斷

- Travel to region with local transmission
  - H7N9: China
  - H5N1: Asia, Middle east

148

Novel influenza A virus

鑑別診斷

- Diagnosis by PCR

149

Bacterial pneumonia

鑑別診斷

- Fever
- Dyspnea
- Cough
- Sputum production

150

鑑別診斷

- 各種會造成呼吸道感染的病原體都要考慮
  - Common cold以臨床診斷就可以
  - MERS-CoV和新型A型流感則需要利用核酸作診斷
- 除了病毒，細菌性肺炎也是需要思考

151

Take home message

- 在流感流行期，臨床診斷的正確率可達80~90%
- 流感除了呼吸道症狀，全身性的症狀會特別明顯，像是發燒、頭痛、痠痛等
- 在流感非流行期，有相關的曝露史，再進行流感相關檢測
- 流感的檢測以核酸為原則，使用抗原時要謹慎解讀
- 除了流感，呼吸道相關的感染症也要考慮。

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COVID-19 疫情下針對流感等呼吸道重症之照護

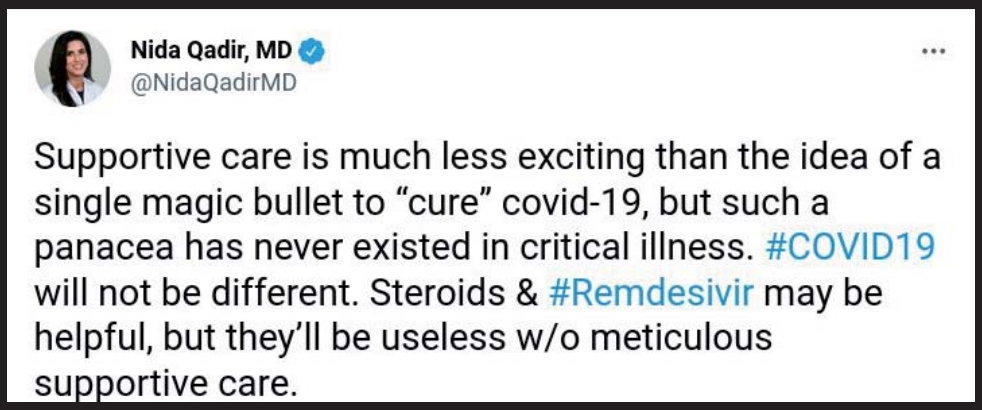
謝宗達

成大醫院 重症加護科 / 感染管制中心

Aug 20, 2022

I have no conflict of interest.

重症照護 = 嚴謹的支持性治療



https://twitter.com/NidaQadirMD/status/1287443875167051776

- 密切監測
  - 心律 / 血壓 / 血氧
  - 動脈導管 / 心輸出
  - 隨時有人看
- 器官支持
  - 氧氣 / 呼吸器 / 俯臥
  - 升壓劑 / 強心劑
  - IABP / ECMO
  - 腎臟替代療法

呼吸道病毒感染的症狀

- Respiratory symptoms
  - Cough
  - Sputum production
  - Nasal discharge
  - Sore throat
- Other symptoms
  - Photophobia
  - Conjunctivitis
  - Anosmia (COVID-19)
- Systemic symptoms
  - Fever / chills
  - Headache
  - Myalgia
  - Malaise / anorexia
  - Dyspnea
  - Altered mental status

Paules C. *Lancet*. 2017;390:697-708.
https://www.cdc.gov/flu/about/qa/coldflu.htm
新型冠狀病毒 (SARS-CoV-2) 感染臨床處置指引 . 第十九版 . 2022-05-26.

呼吸道病毒的診斷工具

TABLE 3 Sensitivity of respiratory viral detection from different specimen types[a]

Specimen type	Sensitivity of detection[b] of: FLUA/B[c]	RSV	RV/EV	ADV	hMPV	PIVs	CoVs[c]
NPS	++	++	++	++	++	+++	++
NPA	+++	+++	+++	+++	+++	+++	+++
OPS	++(+)[d]	++	+	++	+	+	+
TS	++	++	+	++	+	++	++
Sputum[f]	+++	+++	+++	+++	++	+(+)	++(+)[e]
BAL fluid	+++	+++	++	++	++	+(+)	++
Lung biopsy specimen	++	++	+	+	+	o	+++

- Nucleic acid detection
- Rapid antigen tests
- DFA/IFA assays
- Cell culture

Charlton CL. *Clin Microbiol Rev*. 2018;32(1):e00042-18.

只採檢鼻咽或下呼吸道
會漏掉 20-30% 的呼吸道病毒感染

TABLE 2. Site of Virus Detection

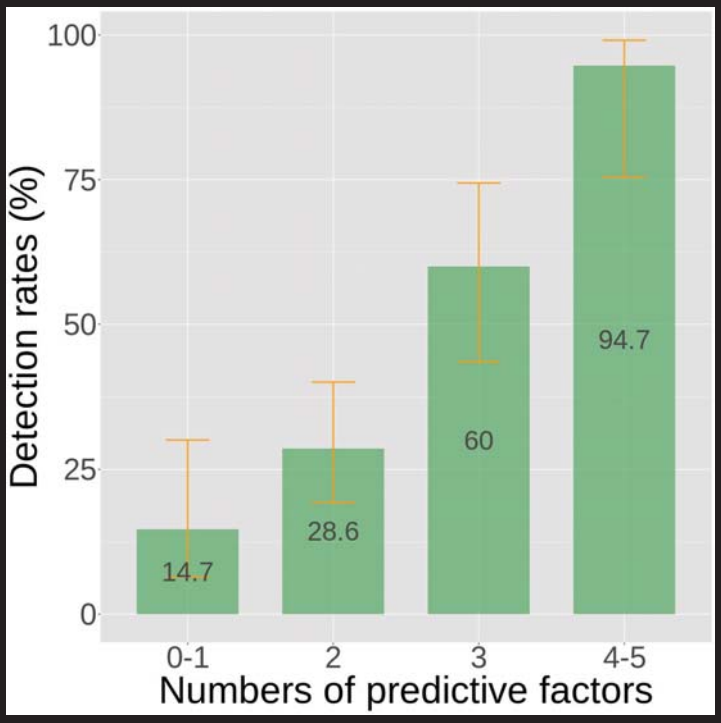
Site of Virus Detection	SARI, *n* = 45 (%)	Non-SARI, *n* = 213 (%)
Nasopharyngeal swab	32 (71)	133 (62)
TA	36 (80)	136 (64)
Exclusive nasopharyngeal	9 (20)	77 (36)
Both nasopharyngeal/TA	23 (51)	56 (26)
Exclusive TA	13 (29)	80 (38)

SARI = severe acute respiratory infection (at ICU admission), TA = tracheobronchial aspirate.

van Someren Gréve. *Crit Care Med*. 2018;46(1):29-36.

哪些重症病人比較驗得到呼吸道病毒？

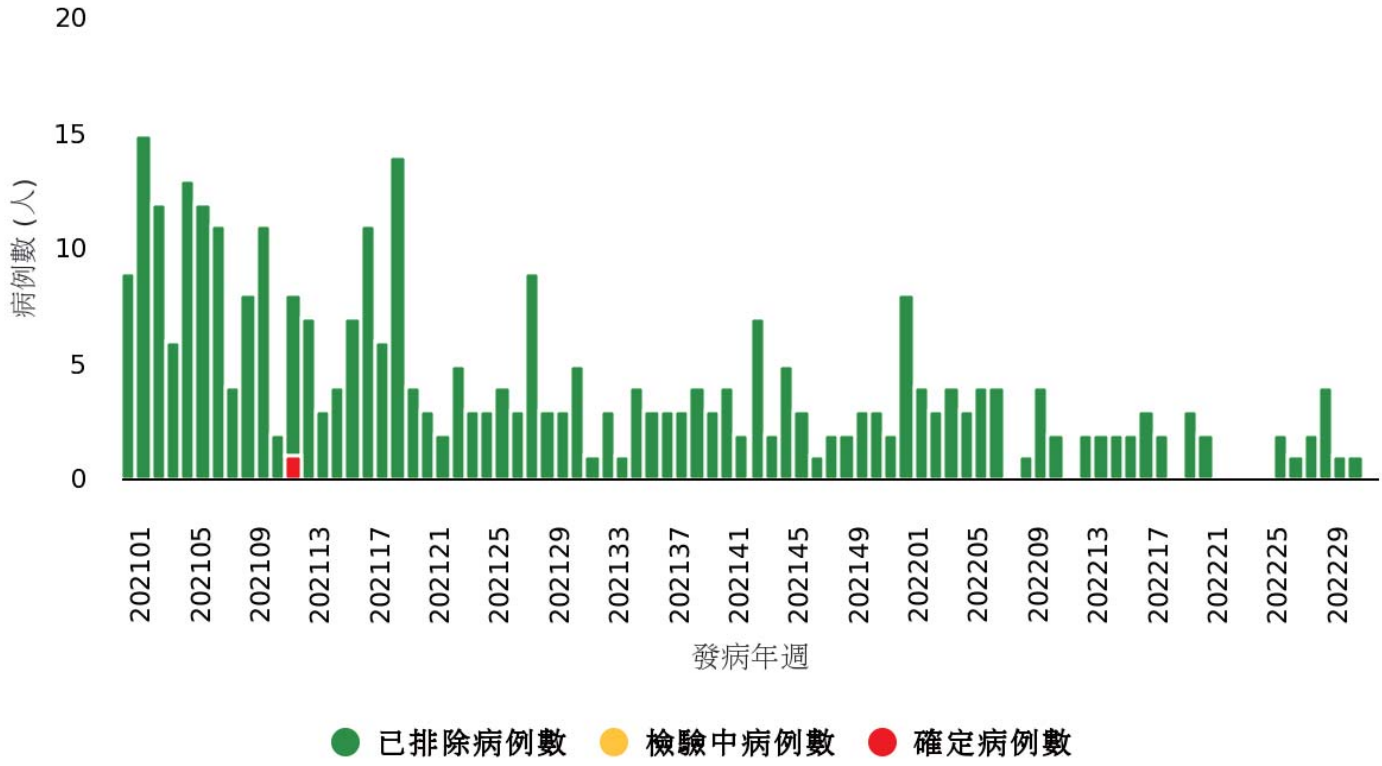
Predictive factor	Odds Ratio
Age < 65 years	3.98
Clustered URI	3.93
Fever	2.89
Cough and sputum production	3.24
Sore throat	3.70



Cia CT. *Sci Rep*. 2021;11(1):20058.

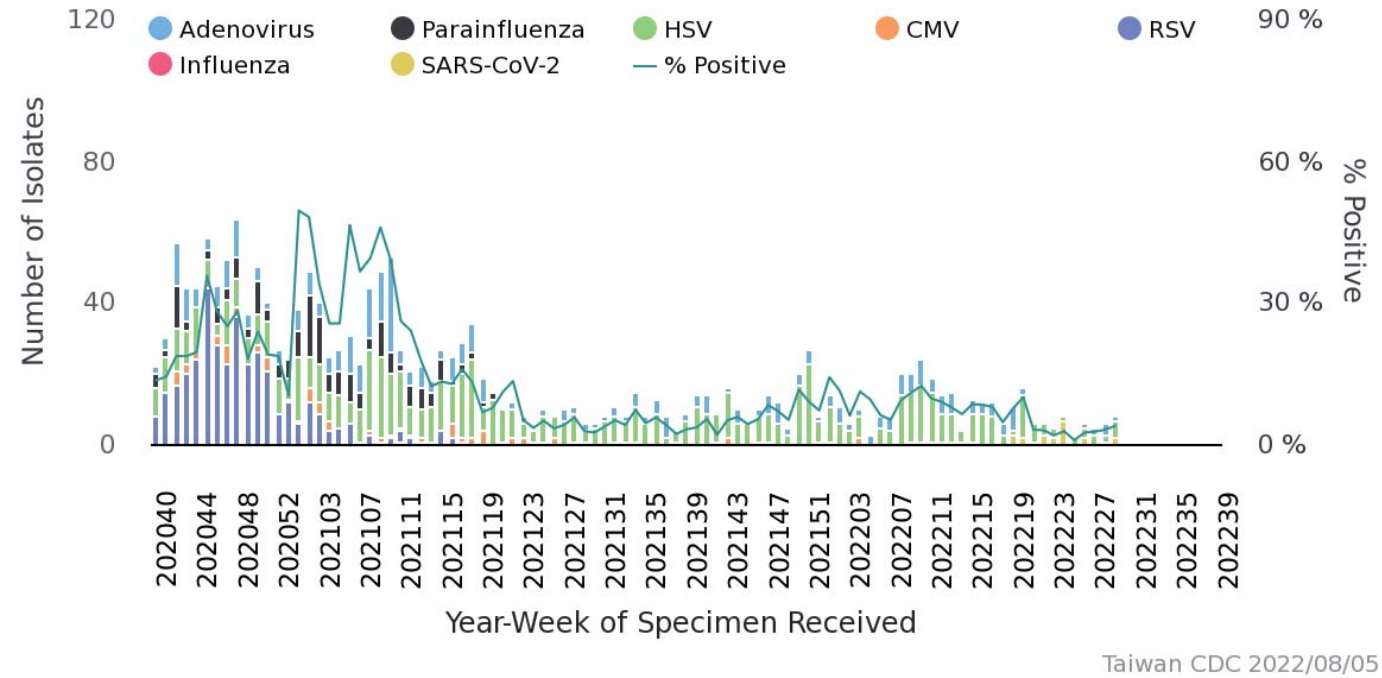
感染症：流行什麼很重要

全國 流感併發重症 本土病例及境外移入病例 趨勢圖 (2021年1週-2022年32週)
[發病日 2021/01/03-2022/08/13]



Taiwan CDC 2022

https://nidss.cdc.gov.tw/



Taiwan CDC 2022/08/05

https://nidss.cdc.gov.tw/

COVID-19 重症和其他呼吸道病毒重症不同的地方

Stages / severities of COVID-19

	Asymptomatic or Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical Illness
Features	Positive SARS-CoV-2 test; no symptoms	Mild symptoms (e.g., fever, cough, or change in taste or smell); no dyspnea	Clinical or radiographic evidence of lower respiratory tract disease; oxygen saturation ≥94%	Oxygen saturation <94%; respiratory rate ≥30 breaths/min; lung infiltrates >50%	Respiratory failure, shock, and multiorgan dysfunction or failure
Testing	Screening testing; if patient has known exposure, diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing
Isolation	Yes	Yes	Yes	Yes	Yes
Proposed Disease Pathogenesis	Viral replication; Inflammation				
Potential Treatment	Antiviral therapy; Antibody therapy; Antiinflammatory therapy				
Management Considerations	Monitoring for symptoms	Clinical monitoring and supportive care	Clinical monitoring; if patient is hospitalized and at high risk for deterioration, possibly remdesivir	Hospitalization, oxygen therapy, and specific therapy (remdesivir, dexamethasone)	Critical care and specific therapy (dexamethasone, possibly remdesivir)

Gandhi RT. *N Engl J Med*. 2020;383(18):1757-1766.

Critical COVID-19 (before omicron)

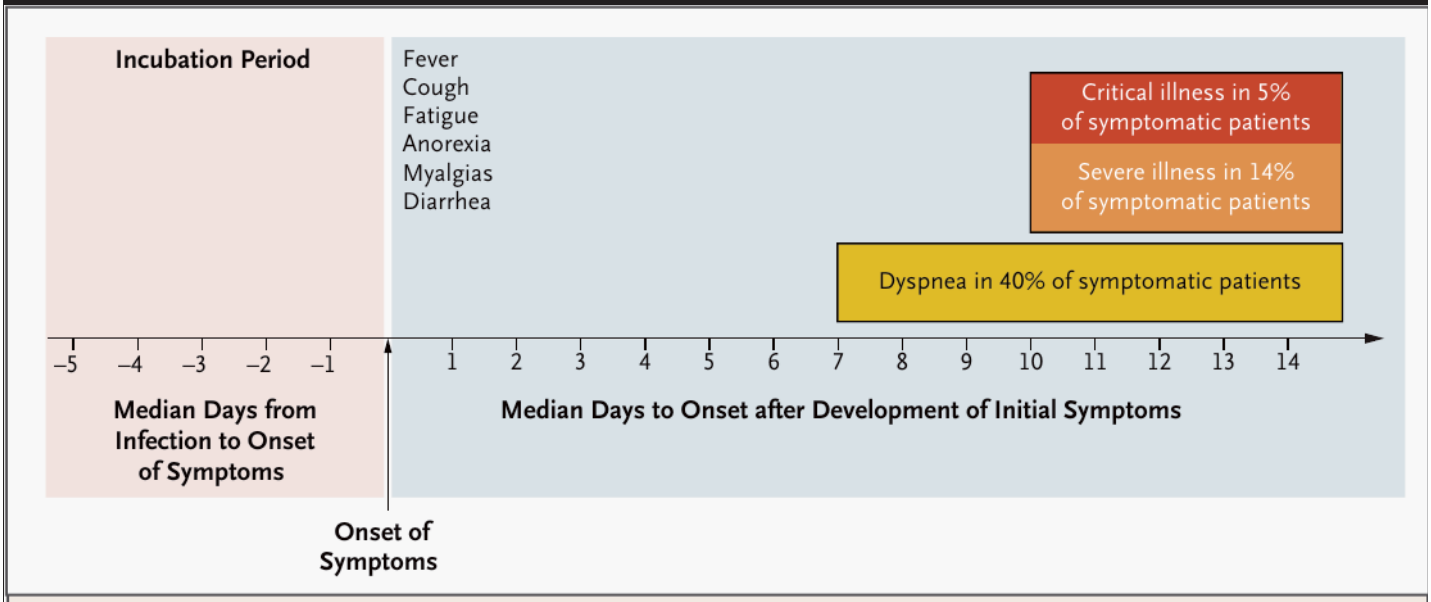
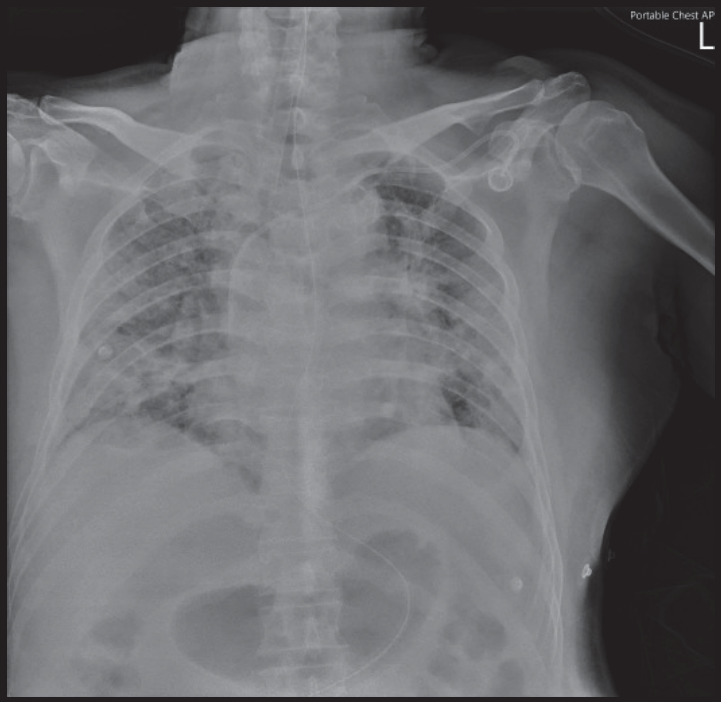


Figure 1. Timeline of Symptoms of Severe Coronavirus Disease 2019 (Covid-19).

~10 days after symptom onset

Inflammation >> viral replication

Berlin DA. *N Engl J Med*. 2020;383(25):2451-2460.



69 y/o M. Lung SqCC on chemotherapy.
DM. CKD. HTN. Independent ADL.
COVID-19 Ag+ on 7/20. Cough with sputum
Dyspnea 7/29-. Respiratory failure on 8/05

RV study at NCKUH ICU 2017-2018
From symptom onset to ICU admission

Median: **3 days**

(1st & 3rd quartile: 2 & 5 days)

Cia CT. *Sci Rep*. 2021;11(1):20058.

COVID-19 病人死亡率

2020 國外
住院病人死亡率

15 – 20%

2020-2021 台灣
通報個案死亡率

4.99%

英國 omicron 感染的
死亡風險為 delta 的

0.31 倍

2022 台灣
通報個案死亡率

0.17%

Wiersinga WJ. *JAMA*. 2020. 2020;324(8):782-793.
中央流行疫情指揮中心 . 2022/01/01新聞稿.
Nyberg T. *Lancet*. 2022;399(10332):1303-1312.
中央社 . 台灣 COVID-19 疫情總覽 https://www.cna.com.tw/topic/newstopic/3829.aspx

2020 COVID-19 重症病人樣態

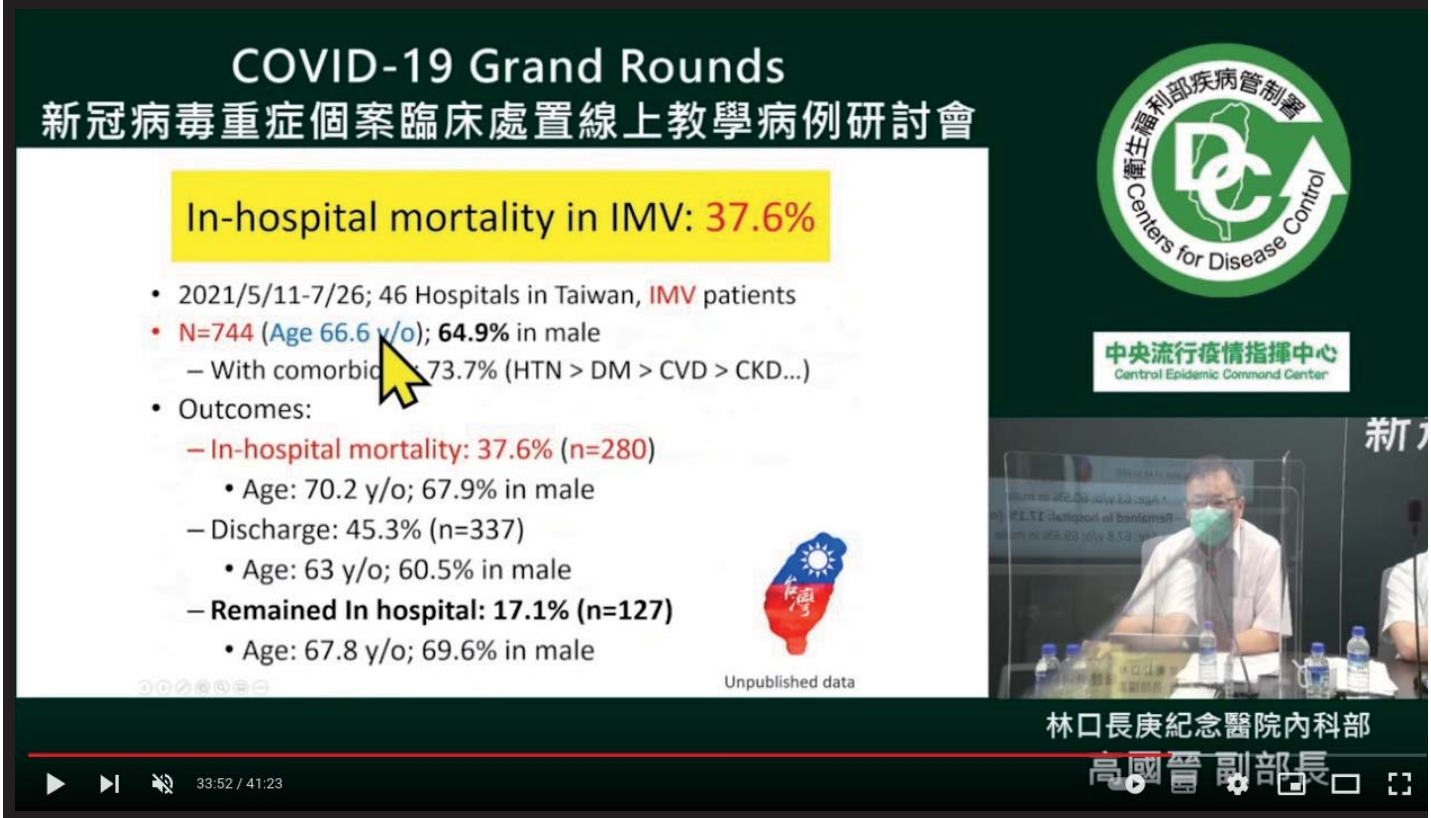
- 平均年齡 62.6 歲
- 男性佔 65.6%
- HTN 49.5%
- DM 26.6%
- 使用升壓劑 65.9%
- 腎臟替代療法 16.9%
- ARDS 比率 76.1%
- 侵入式呼吸器 67.6%
- EMCO 6.4%
- ICU 停留 10.8 天
- 住院天數 19.1 天
- 院內死亡率 28.1%

Tan E. *Chest*. 2021;159(2):524-536.

2021 年台灣北部某醫學中心 COVID-19 重症病人樣態

- 年齡中位數 66 歲
- 男性佔 65%
- DM 35%
- 腎臟透析治療 8%
- 侵入式呼吸器 67%
- Prone positioning 24%
- ECMO 6%
- ICU 停留 17 天
- 住院天數 31 天
- 院內死亡率 19%

Huang JR. *J Formos Med Assoc*. 2022; doi: 10.1016/j.jfma.2022.07.006



衛生福利部疾病管制署 https://www.youtube.com/watch?v=eONkG9-SkXo

OVID-19 omicron variant
重症病人死亡率

本院確診重症病人
使用呼吸器 56.7%

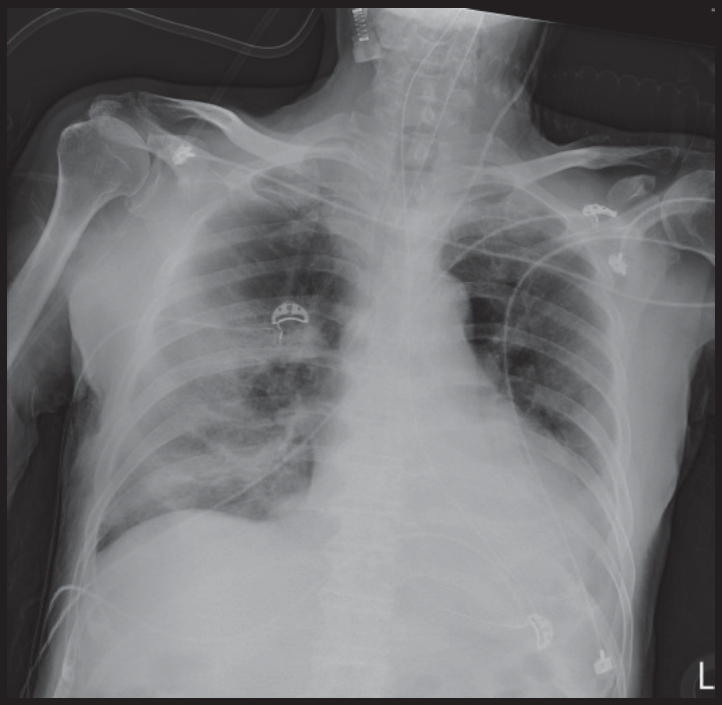
ICU 死亡率
17.7%

法國 AP-HP 體系 ICU
使用呼吸器 41%

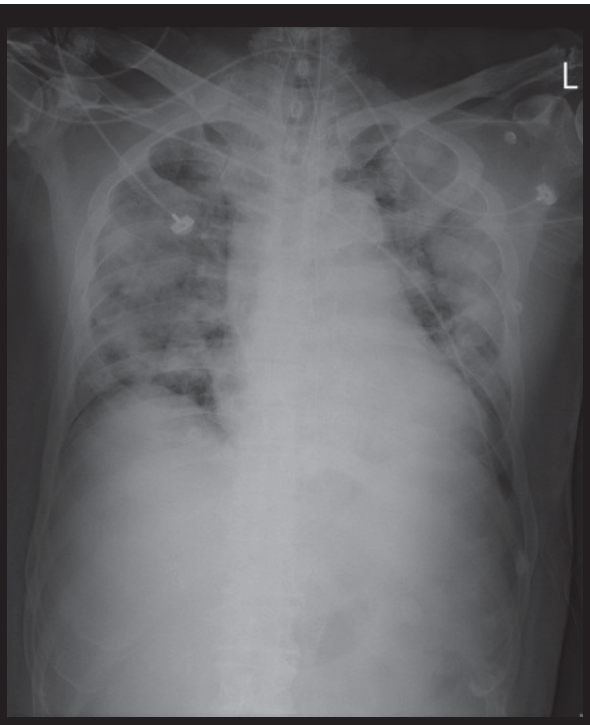
ICU 死亡率
20.0%

Vieillard-Baron A. Am *J Respir Crit Care Med*. 2022;206(3):349-363.

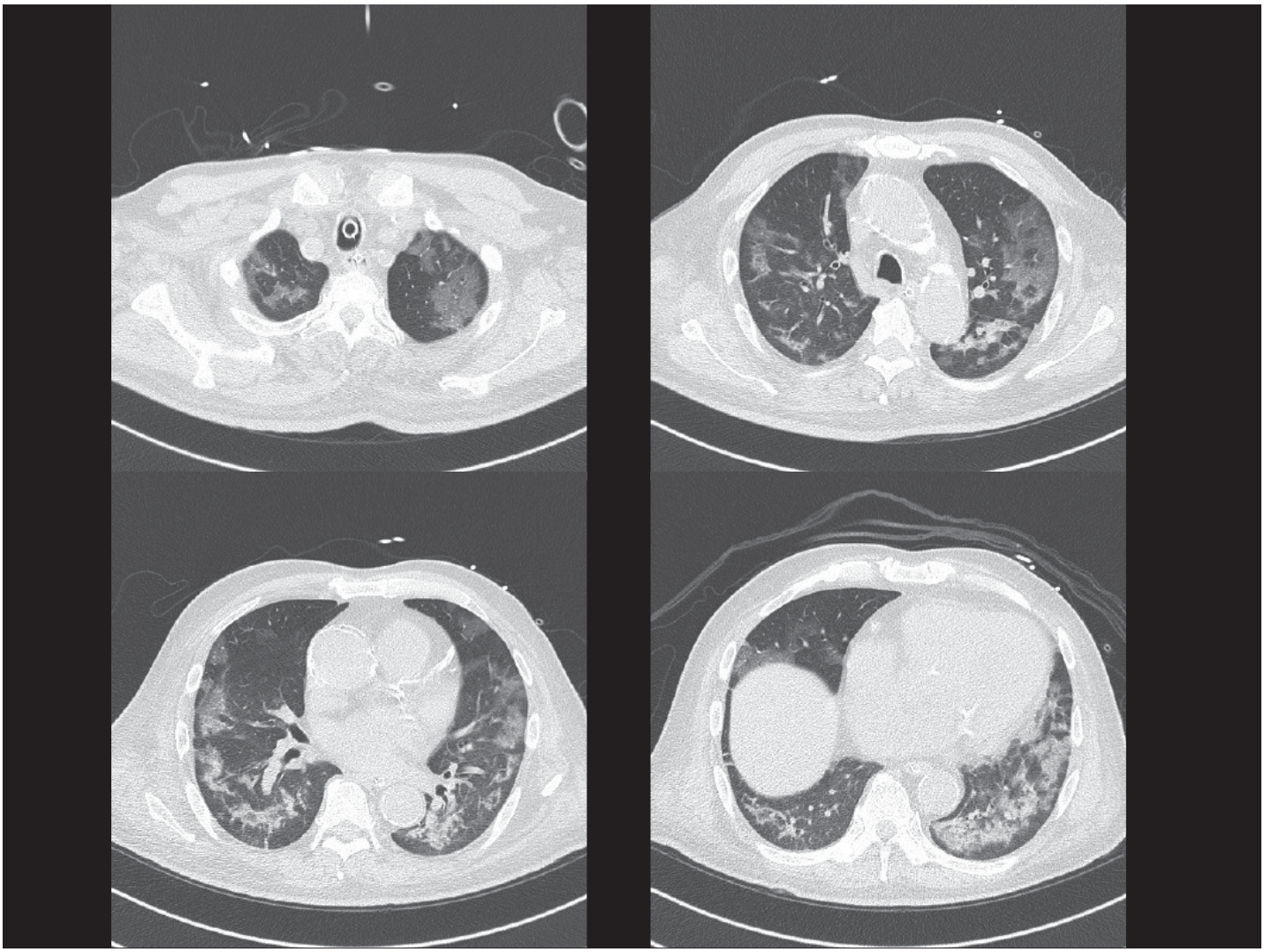
典型的武漢肺炎

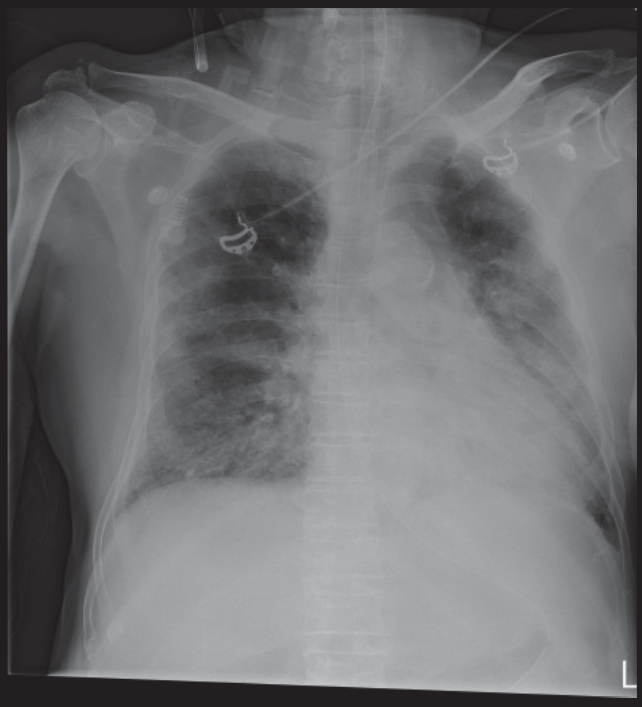


78M. HTN. Dyslipidemia. CKD. Old SAH.
COVID-19 pneumonia
SARS-CoV-2 Ag+ on 5/21. Dyspnea on 5/29.



69M. ESRD on HD. HTN. DM.
Chest tightness. Dyspnea. STEMI.
COVID-19 pneumonia.





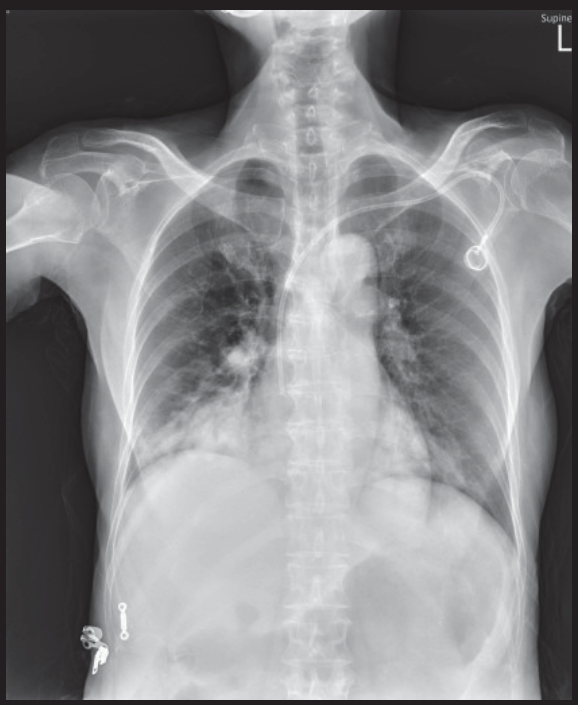
68M. DM. HTN. CAD.
Dyspnea for one day.
COVID-19 pneumonia.

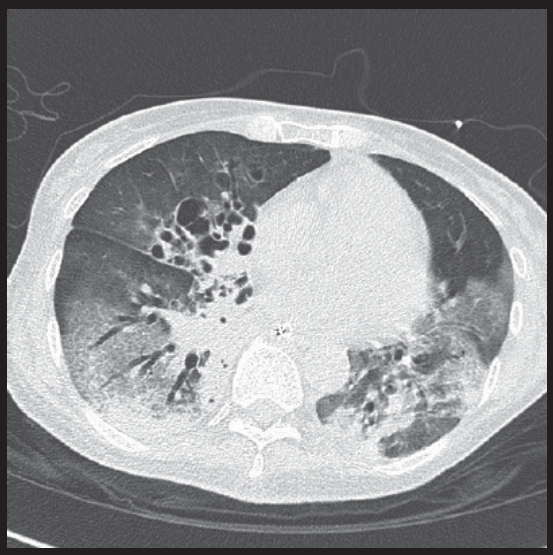
Typical presentation of COVID-19 pneumonia on CXR

- airspace opacities, whether described as consolidation or, less commonly, GGO.
- Distribution: often bilateral, peripheral, and lower zone predominant.
- In contrast to parenchymal abnormalities, pleural effusion is rare (3%).

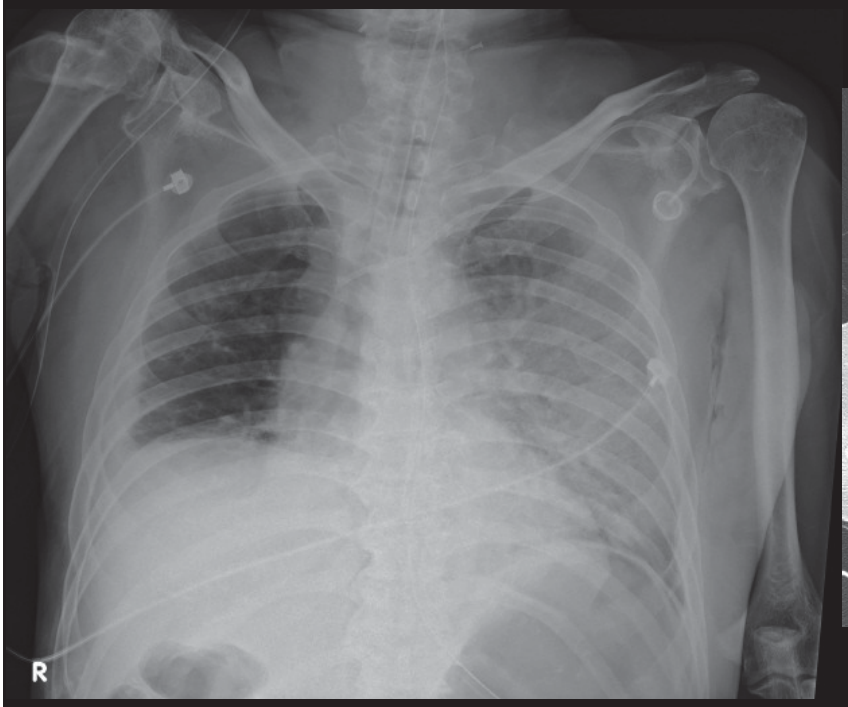
https://radiopaedia.org/articles/covid-19-4

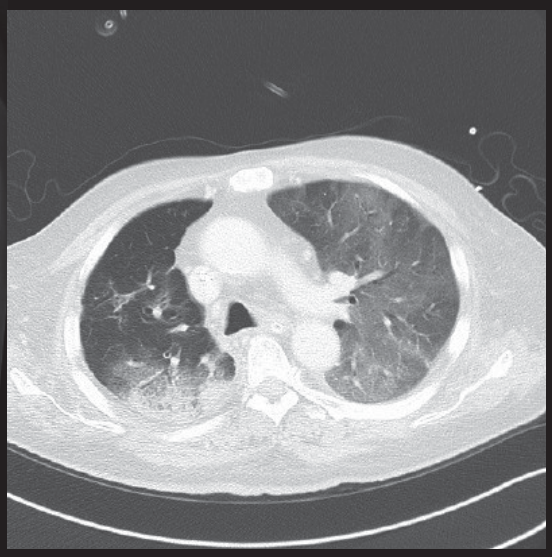
COVID-19 合併其他肺部感染





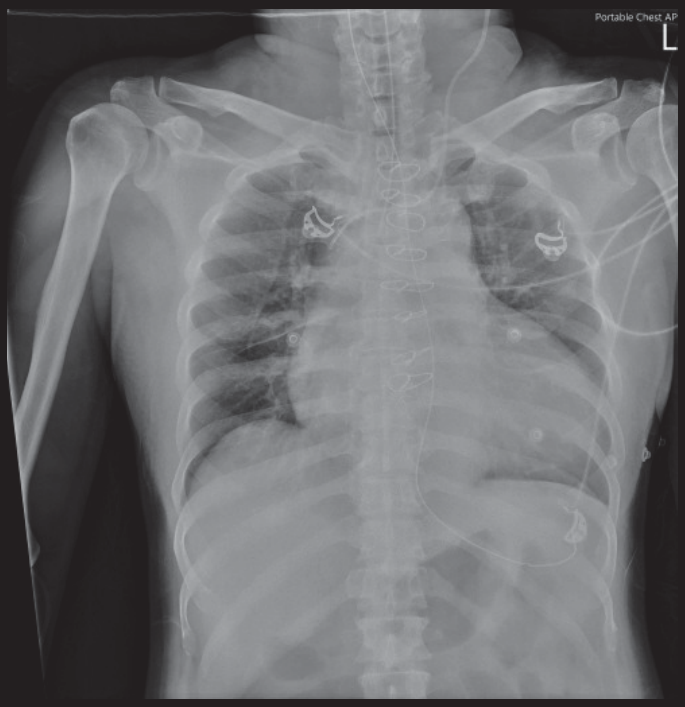
60 F. Cervical ca. DM. Depression.
Fever. Dyspnea.
SARS-CoV-2 & *Streptococcus pneumoniae* pneumonia



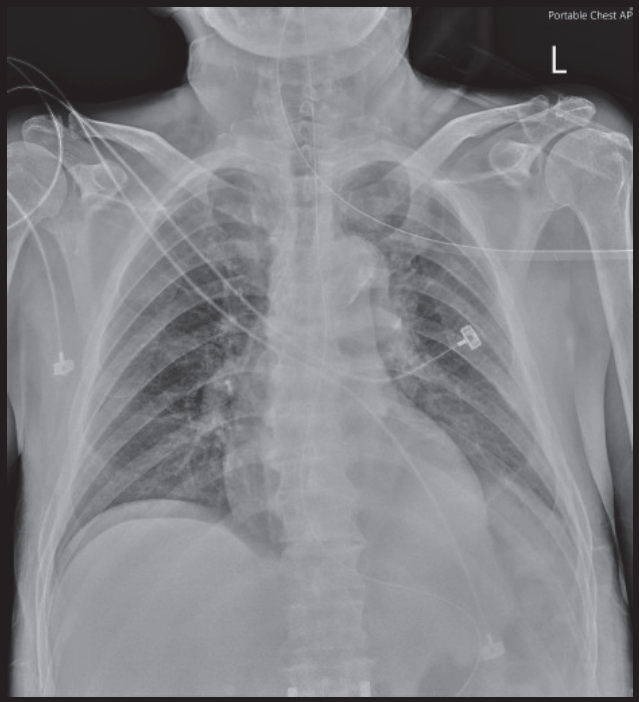


60 F. Lung ca. CKD. HTN.
Dyspnea for 2 days.
SARS-CoV-2, *Staphylcococcus aureus*, and *Pneumocysitis jiroveci* pneumonia

COVID-19 引起慢性疾病恶化



68 M. CAD. HFrEF. DM. Dyslipidemia. CKD.
Fever and altered mental status.
Acute decompensated heart failure related to COVID-19



68 M. COPD. ESRD on HD. Alcoholism.
Admission due to OHCA related to AECOPD.
Got COVID-19 during the ICU stay.
AECOPD, worse respiration requiring all-day NIV

所有呼吸道病毒都會引起慢性疾病惡化導致重症

Chronic disease with acute exacerbation	Proportion of respiratory virus detection
Heart failure	46.8% (22/47)
COPD	29.2% (7/24)
Asthma	50% (2/4)

此研究納入無明顯細菌感染的重症病人

Cia CT. *Sci Rep*. 2021;11(1):20058.

COVID-19 重症病人處置

COVID-19 藥物治療：預防重症
需在發病後 5 天內給予

- Nirmatrelvir/ritonavir (Paxlovid®)
  - 口服 5 天
  - 腎臟不好不可用，不可管灌，藥物交互作用多
- Molnupiravir (Lagevrio®)
  - 口服 5 天
  - 腎臟不好可用，可管灌
- Remdesivir (Veklury®)
  - 靜脈注射 x3 天
- 單株抗體：常常新變種出來就沒效了

COVID-19 肺炎住院病人藥物治療

住院不用氧氣	不需要給類固醇或抗病毒藥
使用一般氧氣設備	Dexamethasone + remdesivir +/- tocilizumab OR baricitinib
使用 HFNC 或是 NIV	Dexamethasone + remdesivir + baricintinib OR tocilizumab
插管 IMV	Dexamethasone + tocilizumab

NIH. COVID-19 Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/

COVID-19 重症病人
Bacterial co-infection rate

5.5 – 28%

研究多為 2020-2021, omicron 未出現

Lansbury L. *J Infect*. 2020;81(2):266-275.
Kreitmann L. *Intensive Care Med*. 2020;46(9):1787-1789.
Contou D. *Ann Intensive Care*. 2020;10(1):119.
Elabbadi A. *Infection*. 2021;49(3):559-562.
Saade A. *Ann Intensive Care*. 2021;11(1):83.
Baskaran V. *J Med Microbiol*. 2021;70(4):001350.
Musuuza JS. *PLoS One*. 2021;16(5):e0251170.
Morris AC. *Crit Care*. 2022;26(1):236.

COVID-19 重症病人
要不要用抗生素？個人作法

不用

- 典型 COVID-19 肺炎
  - 發病後 7-14 天呼吸喘
  - 沒有黃痰
  - 影像典型 (週邊 GGO)
- 單純 COVID-19 引起慢性病急性惡化

用

- 肺炎但不像武漢肺炎
  - 太早 (5 日內) 出現
  - 黃痰
  - 影像不典型
- 休克需使用高劑量生壓劑，須懷疑非呼吸道感染

COVID-19 重症病人靜脈血栓發生率高
如無出血，建議給抗凝血劑

All VTE	Pulmonary embolism
14.3 –27.9%	8.6–24.7%

Suh YJ. *Radiology*. 2021;298(2):E70-E80.
Porfidia A. *Thromb Res*. 2020;196:67-74.
Tan BK. *Thorax*. 2021;76(10):970-979.
Ng JJ. *J Intensive Care*. 2021;9(1):20.
Fujiwara S. *J Infect Chemother*. 2021;27(6):869-875.

COVID-19 重症病人院內感染機會大
住院過程需小心處理

呼吸器相關肺炎	血流感染
26 – 50%	15 – 26%

Rouzé A. *Intensive Care Med*. 2021;47(2):188-198.
Ferreira FC. *Ann Intensive Care*. 2021;11(1):92.
Giacobbe DR. *J Clin Med*. 2021;10(4):555.
Ferrando C. *Rev Esp Anestesiol Reanim (Engl Ed)*. 2020;67(8):425-437.
Buetti N. *Intensive Care Med*. 2021;47(2):180-187.
Grasselli G. *Chest*. 2021;160(2):454-465.

COVID-19 病人使用 HFNC 及 NIV

- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends starting therapy with HFNC oxygen; if patients fail to respond, NIV or intubation and mechanical ventilation should be initiated (BIIa).
- For adults with COVID-19 and acute hypoxemic respiratory failure who do not have an indication for endotracheal intubation and for whom HFNC oxygen is not available, the Panel recommends performing a closely monitored trial of NIV (BIIa).

NIH. COVID-19 Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/

A systematic review & meta-analysis before the COVID-19 era

- HFNC decreased tracheal intubation
  - OR 0.62 (compared to conventional O2 therapy)
  - OR 0.48 (compared to NIV)
- HFNC decreased ICU mortality
  - OR 0.47 (compared to conventional O2 therapy)
  - OR 0.36 (compared to NIV)
- No effect on ICU length of stay (LOS)

Ni YN. *Am J Emerg Med*. 2018;36(2):226-233.

全罩式 NIV v.s. HFNC (COVID-19)

JAMA Network

QUESTION Among patients in the intensive care unit with COVID-19–induced moderate to severe hypoxemia, does early continuous treatment with helmet noninvasive ventilation increase the number of days free of respiratory support at 28 days vs high-flow nasal oxygen?

CONCLUSION This randomized trial found that in patients with COVID-19–induced moderate to severe hypoxemia, helmet noninvasive ventilation, vs high-flow nasal oxygen, resulted in no significant difference in the number of days free of respiratory support within 28 days.

POPULATION

88 Men
21 Women

Adults in the intensive care unit with COVID-19 and moderate to severe hypoxemic respiratory failure

Median age: **65** years

LOCATIONS

4
ICUs in Italy

INTERVENTION

109 Patients analyzed

54
Helmet ventilation
Continuous treatment with helmet noninvasive ventilation for at least 48 hours followed by high-flow nasal oxygen

55
High-flow oxygen
High-flow nasal oxygen alone

PRIMARY OUTCOME

Median number of days free of respiratory support within 28 days after enrollment

FINDINGS

Median respiratory support-free days

Helmet ventilation

Day 0 — **20 Days** (IQR, 0-25) — Day 28
Respiratory support-free

High-flow oxygen

Day 0 — **18 Days** (IQR, 0-22) — Day 28
Respiratory support-free

Mean between-group difference was not statistically significant:
2 days (95% CI, −2 to 6)

Grieco DL, Menga LS, Cesarano M, et al; COVID-ICU Gemelli Study Group. Effect of helmet noninvasive ventilation vs high-flow nasal oxygen on days free of respiratory support in patients with COVID-19 and moderate to severe hypoxemic respiratory failure. *JAMA*. Published March 25, 2021. doi:10.1001/jama.2021.4682

NIV v.s. HFNC v.s. 一般給氧 (COVID-19)

JAMA

QUESTION What is the effect of continuous positive airway pressure (CPAP) or high-flow nasal oxygen (HFNO) vs conventional oxygen therapy on the risk of tracheal intubation or mortality in patients with acute hypoxemic respiratory failure due to COVID-19?

CONCLUSION Among patients with acute hypoxemic respiratory failure and COVID-19, an initial strategy of CPAP significantly reduced the risk of tracheal intubation or mortality vs conventional oxygen therapy but there was no significant difference with HFNO.

POPULATION

844 Men
429 Women

Adults with COVID-19–related acute hypoxemic respiratory failure

Mean age: **57** years

LOCATIONS

48 Acute care hospitals in the UK and Jersey

INTERVENTION

1273 Patients randomized
1260 Patients analyzed

380
CPAP
Administered per local protocols

418
HFNO
Administered per local protocols

475
Conventional oxygen therapy
Standard of care; oxygen via nasal cannula

PRIMARY OUTCOME

A composite of tracheal intubation or mortality within 30 days

FINDINGS

Tracheal intubation or mortality within 30 days

CPAP: 36.3% (137 of 377 patients)

HFNO: 44.3% (184 of 415 patients)

Conventional oxygen therapy
vs CPAP: **44.4%** (158 of 356 patients)
vs HFNO: **45.1%** (166 of 368 patients)

CPAP vs conventional therapy was significant.
Absolute difference, −8% (95% CI, −15% to −1%)

HFNO vs conventional therapy was not significant.
Absolute difference, −1% (95% CI, −8% to 6%)

Perkins GD, Ji C, Connolly BA, et al; RECOVERY-RS Collaborators. Effect of noninvasive respiratory strategies on intubation or mortality among patients with acute hypoxemic respiratory failure and COVID-19: the RECOVERY-RS randomized clinical trial. *JAMA*. Published January 24, 2022. doi:10.1001/jama.2022.0028

HFNC v.s. 一般給氧 (COVID-19)

- A RCT including 220 patients with P/F < 200.
  - Lower intubation rate in the HFNC group

    34.3% v.s. 51.0%, HR 0.62 (0.39 – 0.96)
  - Shorter median time to recovery

    11 days v.s. 14 days, HR 1.39 (1.00 – 1.92)

Ospina-Tascón GA. *JAMA*. 2021;326(21):2161-2171.

- A RCT including 364 patients with SpO2 ≤ 92%
  - No significant difference in escalation of oxygen device, clinical recovery, ICU admission, LOS.

Crimi C. *Thorax*. 2022 May. doi: 10.1136/thoraxjnl-2022-218806.

用這些高流量設備 會產生可能具感染性的氣溶膠嗎？

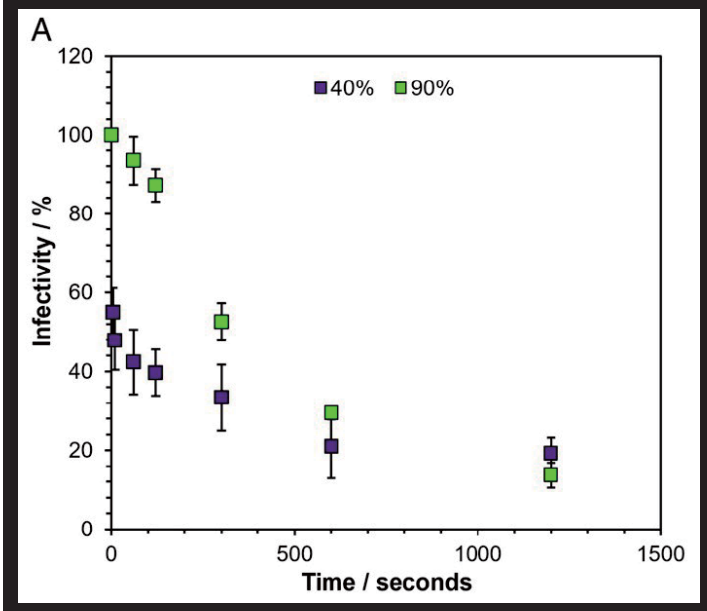
- 觀察性研究：在病人口腔前後 50 公分處採空氣進行核酸檢測。
- 75 位病人， 8 人附近空氣陽性， 67 人陰性。
- 病人 PCR 的 Ct 值 22 v.s. 26, p = 0.02
- 使用 nasal cannula 比較容易偵測到病毒， HFNC 風險不特別高。

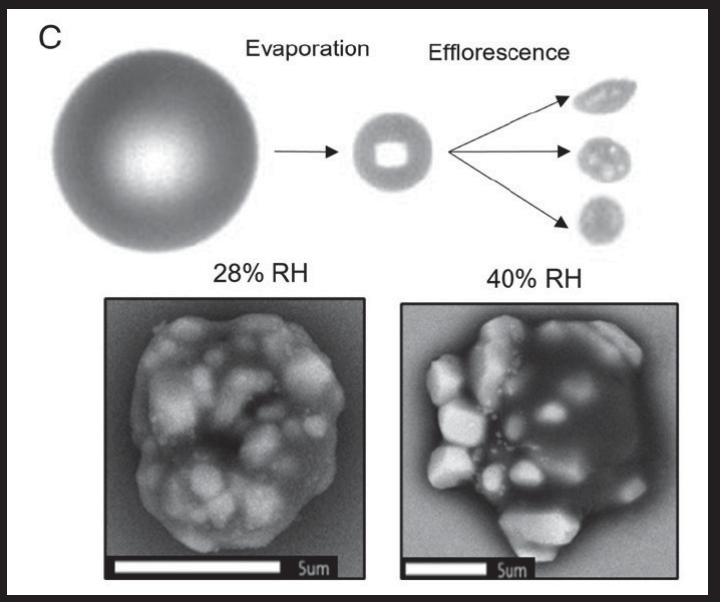
Table III
Air sample positivity risk: comparison between oxygen-delivery systems

	Odds ratio[†]	95% CI	P*
HFNC (*N*=39) vs. non-HFNC (*N*=36)	0.52	0.11–2.34	0.39
HFNC (*N*=39) vs. nasal cannula (*N*=20)	0.25	0.05–1.18	0.11
HFNC (*N*=39) vs. air-entrainment/NRM (*N*=13)	–	–	0.55
Nasal cannula (*N*=20) vs. non-nasal cannula (*N*=55)	5.78	1.24–27.01	0.03
Nasal cannula (*N*=20) vs. air-entrainment/NRM (*N*=13)	–	–	0.05
Air-entrainment/NRM (*N*=13) vs. non-air-entrainment/NRM (*N*=62)	–	–	0.19
ICU (*N*=23) vs. non-ICU environment (*N*=52)	0.73	0.14–3.92	0.14
HFNC: ICU (*N*=21) vs. non-ICU (*N*=18)	1.79	0.15–21.54	0.64

Janssen ML. *J Hosp Infect*. 2022;123:87-91.

PCR 陽性 =/= 具傳染力
氣溶膠傳染的環境條件





Oswin HP. *Proc Natl Acad Sci U S A*. 2022;119(27):e2200109119.

清醒俯臥 (awake self proning)

2020 年起 COVID-19 疫情時開始流行

血氧會上升

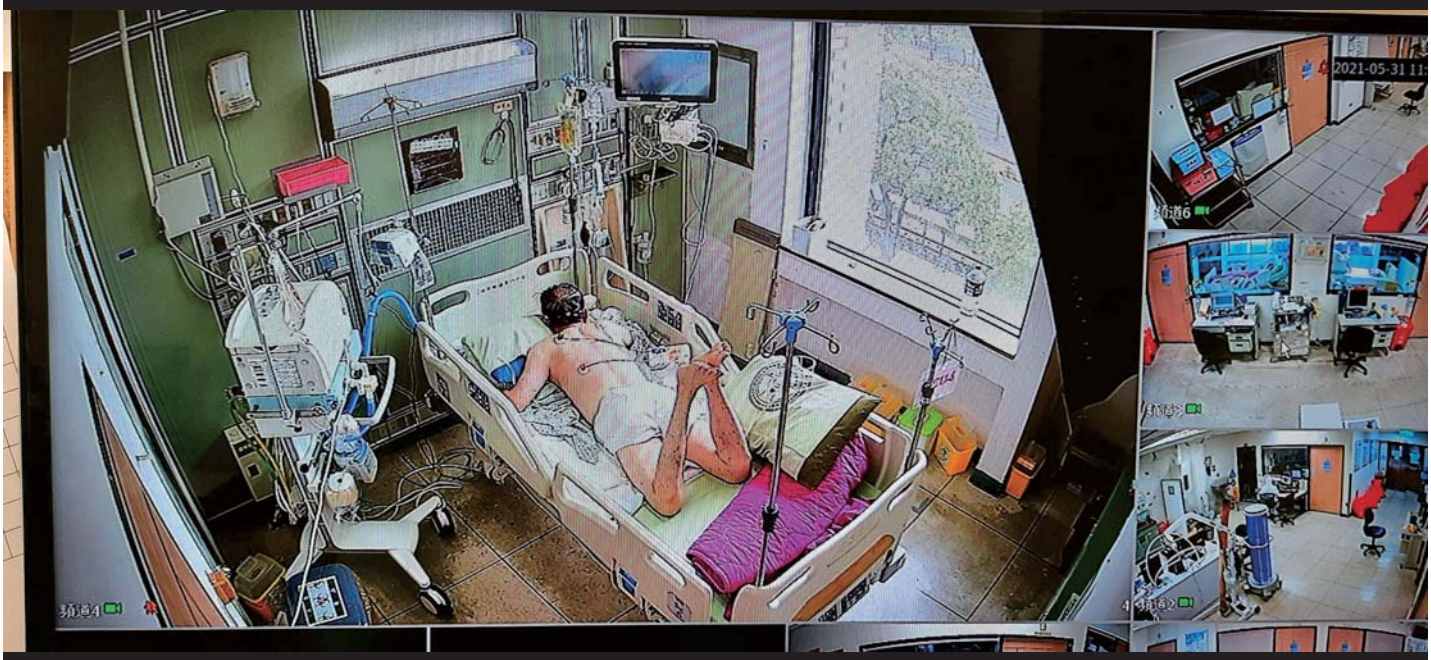
可以減少一點插管 (↓6%)

死亡率沒差

NIH 建議：還沒面臨插管的病人可嘗試

Ehrmann S. *Lancet Respir Med*. 2021;9(12):1387-1395.
Alhazzani W. *JAMA*. 2022; doi: 10.1001/jama.2022.7993.
NIH. COVID-19 Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/

A patient on HFNC, awake prone positioning, up to 13.5 hr/d



COVID-19 病人通氣策略 1

- 使用較低的潮氣量 (4–8 ml / kg PBW) 和較低的吸氣高原壓力 (plateau pressure < 30 cmH2O) 進行機械通氣輔助。
  - 最初的潮氣量建議為 6 ml/kg PBW 。 如果發生不良反應 (例如 , 病患與呼吸器不同步、 pH < 7.15), 則允許調升使用潮氣量至 8 ml/kg PBW, 亦可以容許高二氧化碳血症 (permissive hypercapnia)
- 對於重度 ARDS 的成人患者 , 建議每天應進行至少 12-16 小時俯臥式通氣 (prone ventilation)
- 對沒有組織灌注不足的 ARDS 患者使用保守性的液體管理策略。

新型冠狀病毒 (SARS-CoV-2) 感染臨床處置指引 . 第十九版 . 2022-05-26.

COVID-19 病人通氣策略 2

- 在中度或重度 ARDS 患者中 , 建議使用較高的 PEEP 而不是較低的 PEEP 。
- 對於中度至重度 ARDS(PaO2 / FiO2 < 150) 的患者，不建議常規使用神經肌肉阻斷劑持續輸注。
- 對肺部保護性通氣後仍有低血氧症的患者，是否需使用 ECMO ，應由具有相關醫療專業的團隊評估。
- 建議使用密閉式抽痰管，並在需要斷開呼吸管路時 , 須在氣管內管連結高效能氣體過濾器。

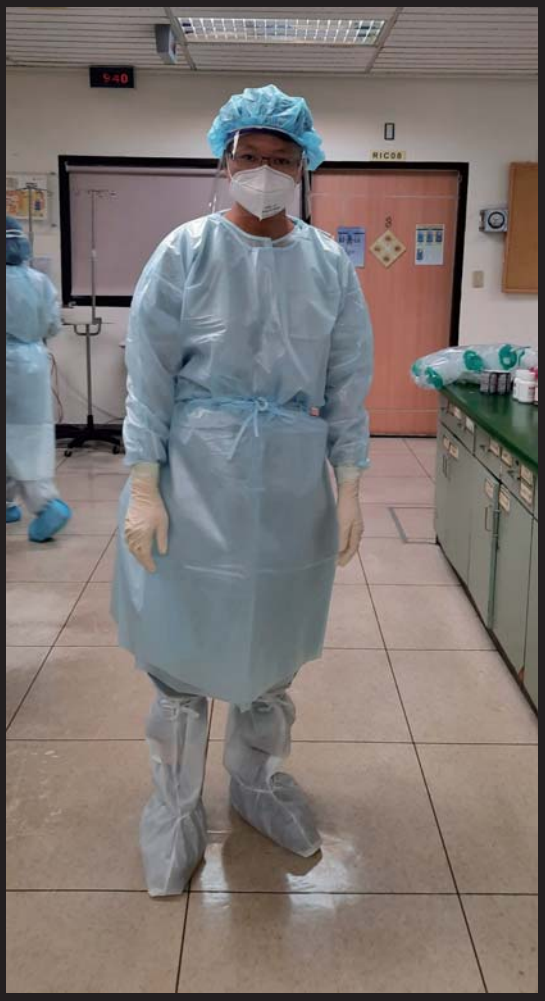
新型冠狀病毒 (SARS-CoV-2) 感染臨床處置指引 . 第十九版 . 2022-05-26.

PPE 選擇

CDC 的規定

場所	處置項目	呼吸防護		手套	隔離衣		護目裝備 (A 護目鏡 B 全面罩)	髮帽
		醫用/外科口罩	N95 或相當等級(含)以上口罩		一般隔離衣	防水隔離衣		
公共區域	入口服務人員、掛號、批價、傳送等	V						
一般門診	詢問相關主訴及 TOCC	V						
急診檢傷區	詢問相關主訴及 TOCC	V						
病人轉送	病室到院內其他單位		V	V	V			
分流看診區或收治病室（如：具負壓或獨立檢查室）	一般性接觸病人之醫療照護行為（如：量體溫、血壓、照 X 光）		V	V	V [※1]		V(A)	~~V~~
	執行發藥、更換輸液等未直接接觸病人之醫療照護行為		V	V	V [※1]		V(A)	~~V~~
	接觸病人血液、體液、排泄物等風險之醫療照護行為		V	V		V	V(B)	V
	呼吸道檢體採集(如：咽喉拭子)		V	V		V	V(B)	V
	執行可能產生飛沫微粒 (aerosol)的醫療處置		V	V		V	V(B)	V
	環境清潔消毒		V	V		V	V(B)	V

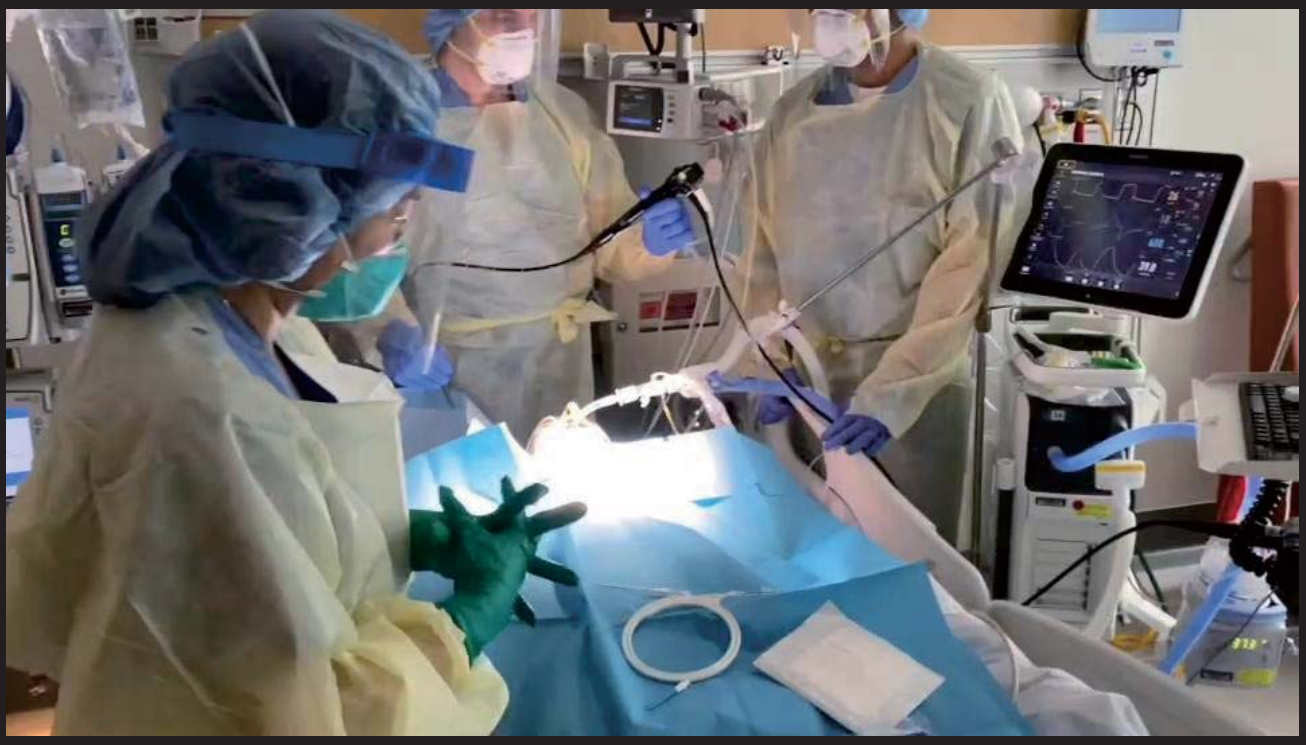
https://www.cdc.gov.tw/Uploads/e053a14c-7d9e-4b7f-9d89-f5383cee2dc7.pdf



個人在專責 ICU 使用的 PPE（插管時相同）

Dr. Zafia Anklesaria, 35, who is seven months pregnant, attends to a COVID-19 patient. California, U.S., May 18, 2020.

https://www.cnbc.com/2020/10/27/covid-hospitalizations-rising-in-36-states-as-us-hits-another-record-for-average-new-cases.html

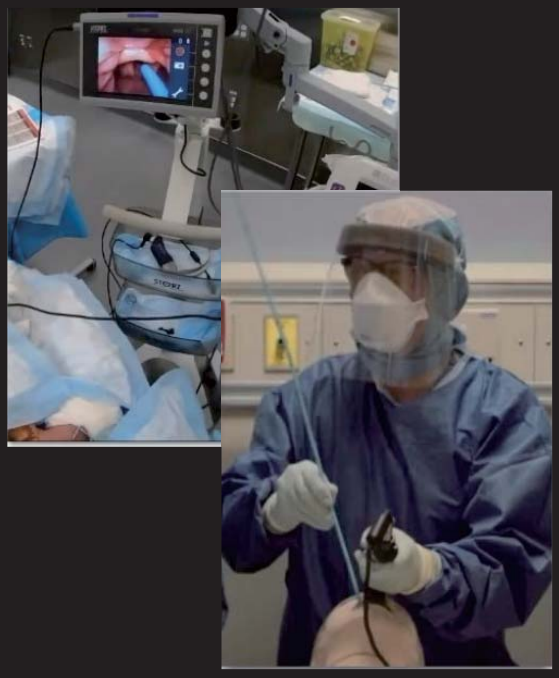


"Percutaneous dilational tracheostomy for patients with COVID-19"
Early tracheostomy (7-12d) ~ discontinuation from MV & lower mortality

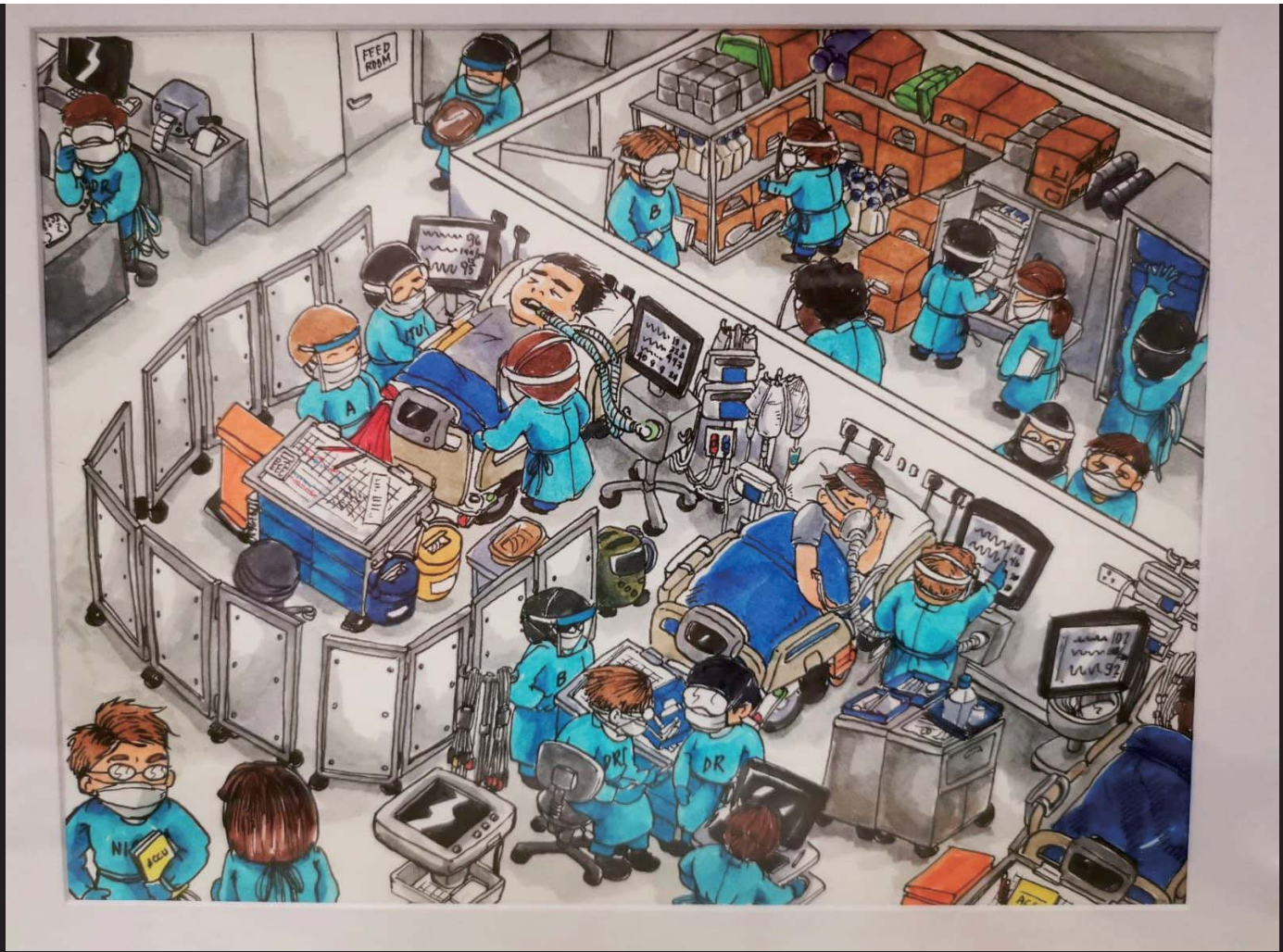
Angel LF. *Crit Care Med*. 2021;49(7):1058-1067.

Tracheal intubation

- 防水隔離衣
- 面罩 + N95 or PAPR
- 負壓環境
- 儘量避免手動通氣
  (請成功率最高者上場)
- Paralytics
- 影像式喉頭鏡
- 使用 EtCO2 偵測器確認位置
- 備妥 SGA 及 FONA



台灣麻醉醫學會 . https://www.anesth.org.tw/news/content.asp?ID=684
George Kovacs. https://www.youtube.com/watch?v=pv_xyMolazA
https://www.cdc.gov.tw/Uploads/e053a14c-7d9e-4b7f-9d89-f5383cee2dc7.pdf



https://twitter.com/lucenamaros/status/1375582495534678016

https://twitter.com/rupert_pearse/status/1476821951171731459

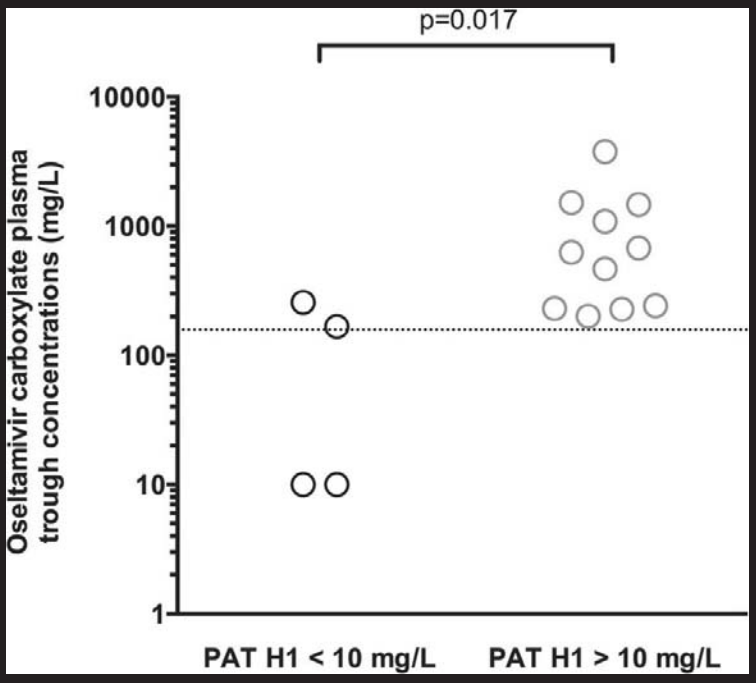
Influenza 重症病人處置

流感重症病人使用抗病毒藥物

- 首選：口服 osetlmamivir
  - 資料最多（但無 v.s. placebo 的 RCT)
  - meta-analysis 顯示住院及重症病人死亡率下降
    OR 0.81 (0.70-0.93) 及 0.72 (0.56-0.94)
  - 多數重症病人腸道吸收血中藥物濃度和一般病人接近
- 消化功能明顯不良的病人： permamivir (IV)
  - 療效和副作用與口服 oseltamivir 無差異

Muthuri SG. *Lancet Respir Med*. 2014;2(5):395-404.
Ariano RE. *CMAJ*. 2010;182(4):357-63.
Nakamura S. *Open Forum Infect Dis*. 2017;4(3):ofx129.

用 acetaminophen 來測 oseltamivir 吸收效果



口服 acetaminophen 一小時候抽血中濃度超過 10 mg/L

oseltamivir 血中濃度就會達到治療標準

May F. *Intensive Care Med*. 2019;45(10):1484-1486.

No routine corticosteroid use for critically ill patients with influenza

- IDSA guideline 2018: Clinicians should not administer corticosteroid adjunctive therapy for the treatment of adults or children with suspected or confirmed seasonal influenza, influenza-associated pneumonia, respiratory failure, or ARDS, unless clinically indicated for other reasons (A-III).
- No RCT, but nearly all observational study show possible harm.

Chow EJ. *Crit Care*. 2019;23(1):214.
Lansbury L. *Cochrane Database Syst Rev*. 2019;2(2):CD010406.
Tsai MJ. *Ann Intensive Care*. 2020;10(1):26.

Bacterial co-infections in influenza

- 0.5% in young healthy individuals
- At least 2.5% in older individuals and those with predisposing conditions
- 34% of ICU patients
- High risk patients
  - Age ≥ 65 y or < 5 y
  - Pregnant woman
  - Morbid obesity
  - Pre-existing medical conditions

Metersky ML. *Int J Infect Dis*. 2012;16(5):e321-31.
Chertow DS. *JAMA*. 2013;309(3):275-82.

Co-pathogens in the US

- 2003-04
  - 959 adults with influenza
  - 125 needed intubation
  - 97 with co-infection
    - *S. aureus* 31
      MRSA 24
    - *S. pneumoniae* 16
    - *S. pyogenes* 2
    - Other 4
- 2009-10
  - Bacterial infection in 13 – 55% fatal cases
  - 77 lung tissue specimens
    - *S. pneumoniae* 10
    - *S. aureus* 7
      MRSA 5
    - *S. pyogenes* 6
    - *S. mitis* 2
    - Other 5

Metersky ML. *Int J Infect Dis*. 2012;16(5):e321-31.

Co-pathogens in Spainish ICUs

- 2009 – 2015, 184 ICUs in Spain, 2901 patients
- Patients with co-infections: 482 (16.6%)

Streptococcus pneumoniae	246	51.0%
Pseudomonas aeruginosa	55	11.4%
MSSA	42	8.7%
Aspergillus spp	35	7.2%
Haemophilus influenzae	17	3.5%
Acinetobacter baumannii	14	2.9%
MRSA	12	2.4%
Klebsiella pneumoniae	12	2.4%

Martin-Loeches I. *Intensive Care Med*. 2017;43(1):48-58.

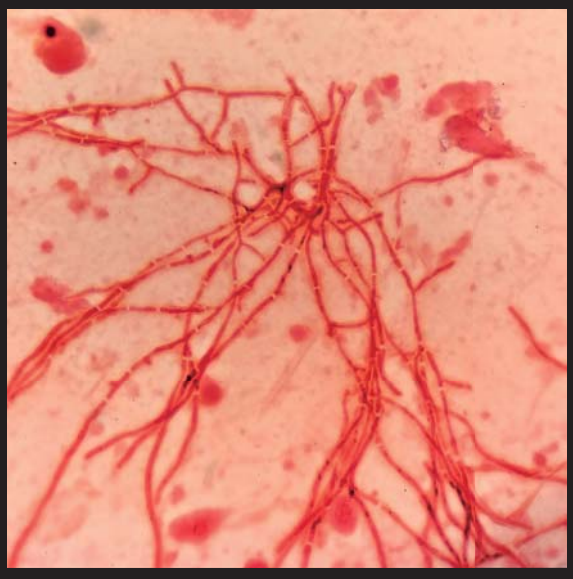
Co-pathogens in Taiwan

- 7 centers, 2016/01 – 03: 39%
  - Methicillin-sensitive *Staphylococcus aureus* 12
- Chi-Mei H 2015/01 – 2016/03: 31% within 48h
  - *Klebsiella pneumoniae* 14 *Pseudomonas aeruginosa* 12
  - *Staphylococcus aureus* 12 (MRSA: 9)
  - *Aspergillus* spp 21 (beyond 48 h)
- NCKUH 2017/01 – 2018/06: 43% within 7 days.
  - *Klebsiella pneumoniae* 12 *Aspergillus* spp 8
  - *Staphylococcus aureus* 8 (MRSA: 4)
  - *Pseudomonas aeruginosa* 5

Chen WC. *Am J Respir Crit Care Med*. 2017;195:A6066.
Ku YH. *J Formos Med Assoc*. 2017;116(9):660-670.
CT Cia. Unplished data.

Influenza-associated pulmonary aspergillosis

- Prevalence 5-19% among critically ill patients with influenza
- Short interval from diagnosis of influenza to pulmonary apergillosis
  - Prophylaxis not praticable
- Associated with high mortality: 49-61%



endotracheal aspirate, Gram stain. 1,000x

Wu CJ. *J Fungi* (Basel). 2022;8(1):49.
Vanderbeke L. *Intensive Care Med*. 2021;47(6):674-686.

流感病人有肺炎
建議經驗性抗生素需涵蓋

Methicillin-sensitive *Staphylococcus aureus*

Streptococcus pneuomniae

Klebsiella pneumoniae

部份病人需考慮，應努力尋找相關證據

MRSA, *P. aeruginosa*, *Aspergillus* spp

通氣策略

同 COVID-19

Extrapulmoary complications of influenza

- Cardiac
  - Myocarditis and cardiomyopathy
  - Heart failure
  - Pericadial effusion
  - Myopericarditis
  - Arrythmia
- Neurologic
  - Encephalopathy, encephalitis, meningitis
  - Seizure
  - Guillains–Barre syndrome
- Other
  - Rhabdomyolysis
  - Acute kidney injury
  - Miscellaneous

Sarda C. *Curr Opin Crit Care*. 2019;25(5):449-457.

其他呼吸道病毒

- Respiratory syncitial virus (RSV)
  - A & B
- Human metapneumovirus
  - A & B
- Enterovirus
- Rhinovirus
- Adenovirus
- Parainfluenza virus
  - 1-4
- Coronavirus
  - SARS, MERS
  - NL63, OC43, HKU1, 229E
- Bocavirus

在國外的 ICU 比 influenza 多

Clin Infect Dis. 2014;59:62-70.

rhinovirus

adenovirus

coronavirus

Critical Care. 2016;20:375

influenza virus

rhinovirus

coronavirus

Chest. 2017 Dec 21.

rhinovirus

influenza A

RSV

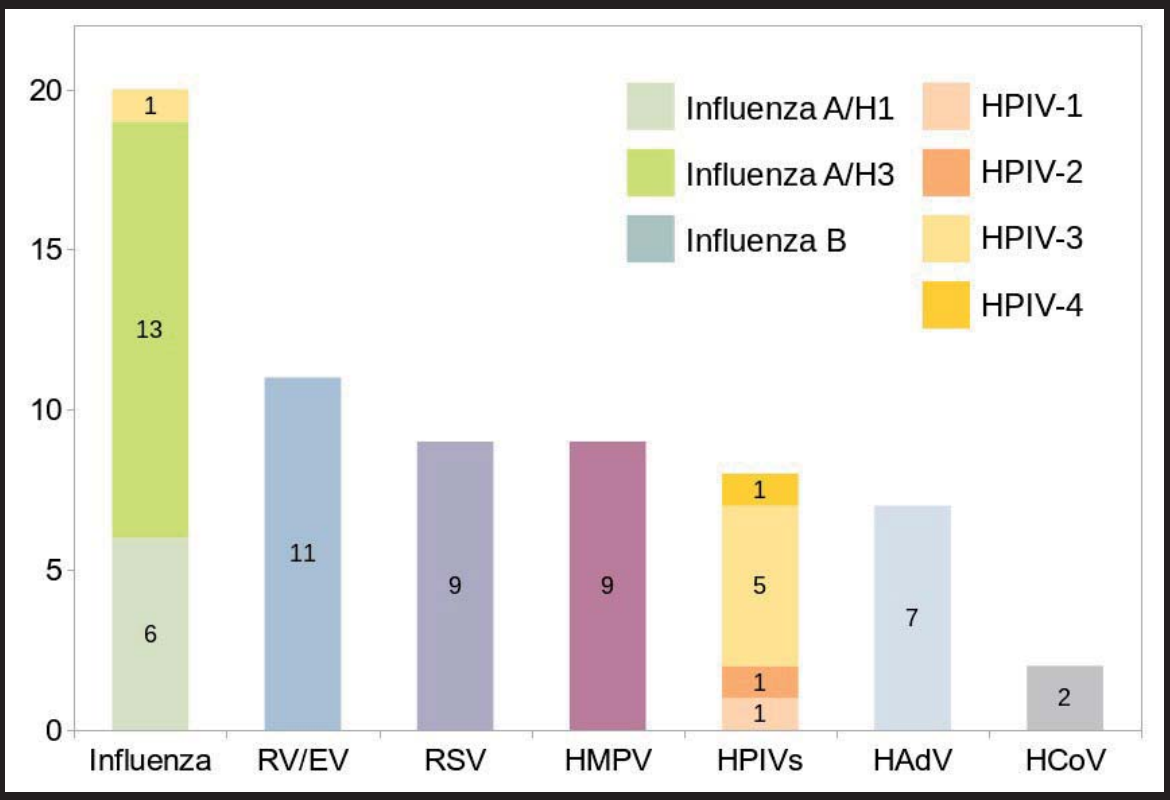
Crit Care Med 2018;46:29–36

parainfluenza virus 3

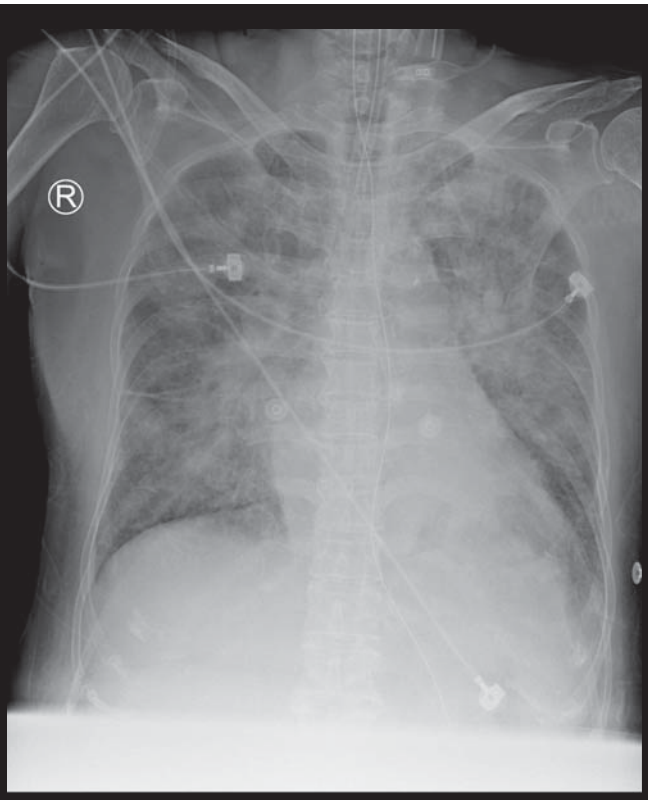
rhinovirus

coronavirus

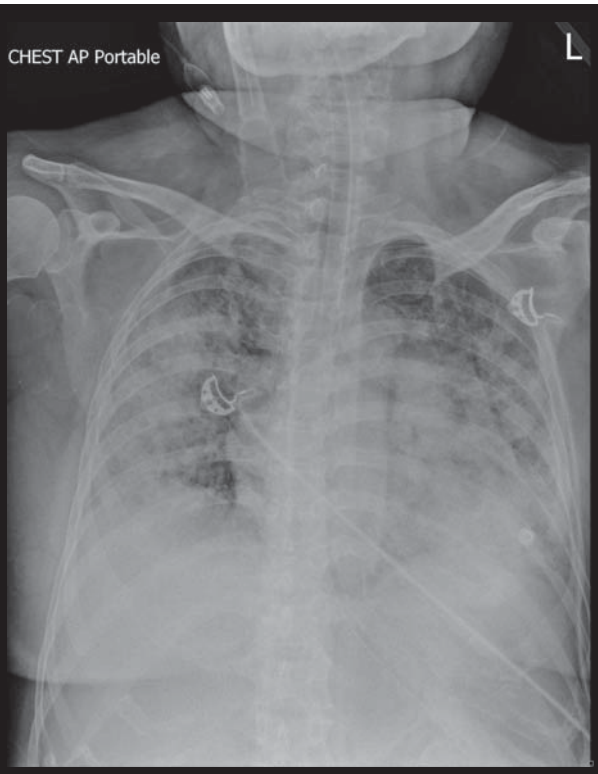
在台灣 ICU 也不少見



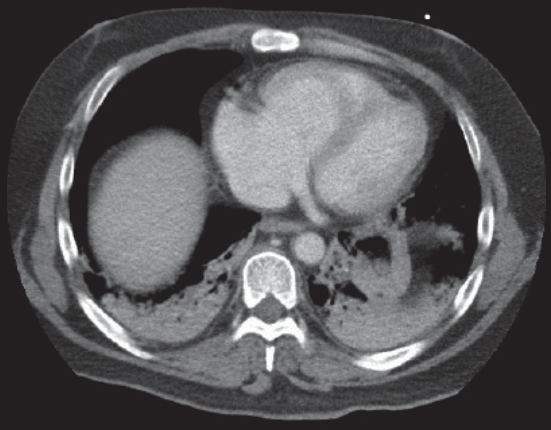
Cia CT. *Sci Rep*. 2021;11(1):20058.



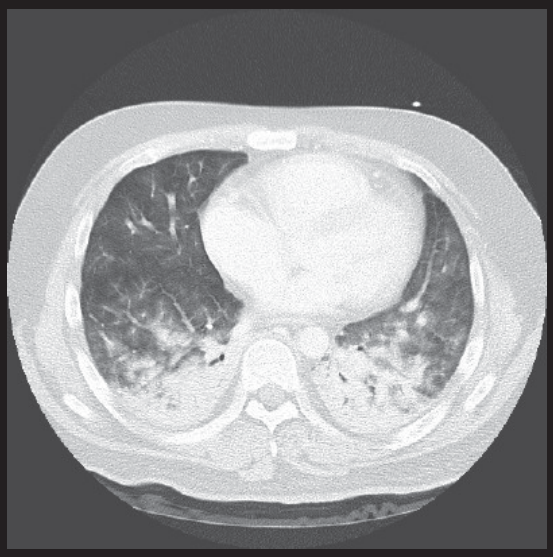
63 F. HTN. HFpEF. Dyslipidemia
Upper airway symptom for 3 days. Dyspnea.
Parainfluenza virus 3 pneumonia



55 F. DM. IDA. Dyslipidemia.
Fever and URI symptom for 5 days. Dyspnea.
Human metapneumovirus pneumonia



Dilated RA, RV



Bilateral GGOs
BLL consolidatoin

30 M. No chronic disease.
URI symptom for 4 days. Dyspnea.
IHCA at ED. Withdrawal of ECMO on D9.
RSV pneumonia

其他呼吸道病毒感染也可以很嚴重

- Human metapneumovirus
  - Shock 60.7%, IMV 50% MV, ICU mortality 14.3%

    Vidaur L. *Ann Intensive Care*. 2019;9(1):86.
  - Pressor use 23%, IMV 55%, mortaility 18%

    Hasvold J. *J Crit Care*. 2016;31(1):233-7.
- RSV
  - IMV 36.6%, In-hospital mortality 23.9%
  - No difference from severe influenza in ICUs

    Coussement J. *Chest*. 2022;161(6):1475-1484.

其他呼吸道病毒感染
抗病毒藥物有限，資料也少

RSV

ribavirin

adenovirus

cidofovir

RNA viruses

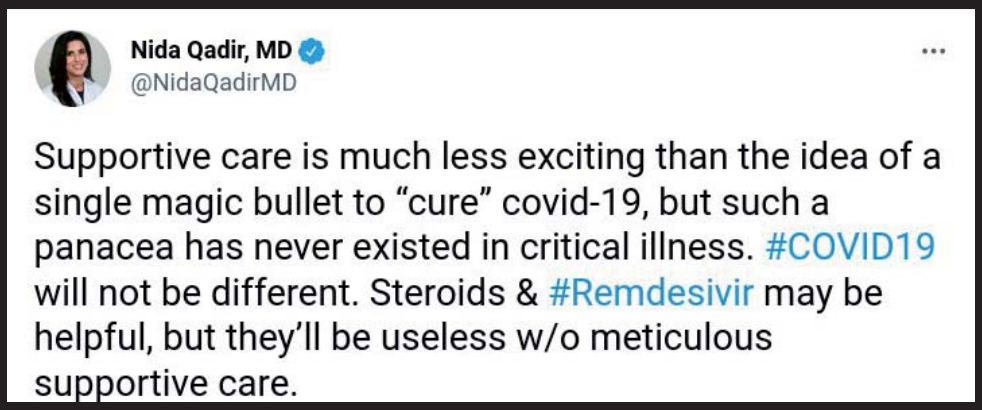
Favipiravir

Arabi YM. *Intensive Care Med*. 2020;46(2):315-328.

血液動力
呼吸照護
俯臥通氣
ECMO 時機
與一般重症及 COVID-19 相同

Arabi YM. *Intensive Care Med*. 2020;46(2):315-328.

重症照護 = 嚴謹的支持性治療



https://twitter.com/NidaQadirMD/status/1287443875167051776

- 密切監測
  - 心律 / 血壓 / 血氧
  - 動脈導管 / 心輸出
  - 隨時有人看
- 器官支持
  - 氧氣 / 呼吸器 / 俯臥
  - 升壓劑 / 強心劑
  - IABP / ECMO
  - 腎臟替代療法

Take Home Messages

- 呼吸道病毒感染的重症照護，最重要的是嚴謹的支持性療法
- 流行季、接觸史、上呼吸道症狀是重要線索，查不到原因的呼吸道重症也該檢驗呼吸道病毒
- 典型 COVID-19 肺炎是在發病後第二週出現，發炎成份明顯，除了抗病毒藥之外也需使用類固醇/tocilizumab / bacricinitib 等免疫抑制劑
- 其他呼吸道病毒感染目前不建議常規使用類固醇
- 要小心 co-infection ，也不要因此濫用抗生素

流感藥物治療進展與抗藥

成大醫院內科部感染科主治醫師
薛伶珊

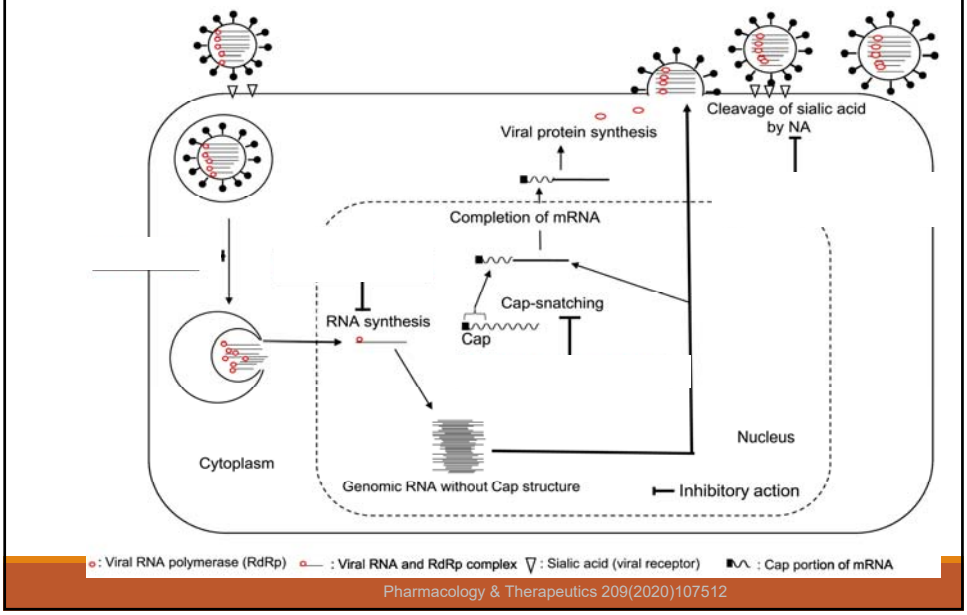
1

大綱

- 抗流感病毒藥物機轉及實證
- 抗流感病毒藥物抗藥性現況
- 新機轉抗病毒藥物
- 流感藥物治療準則及建議

2

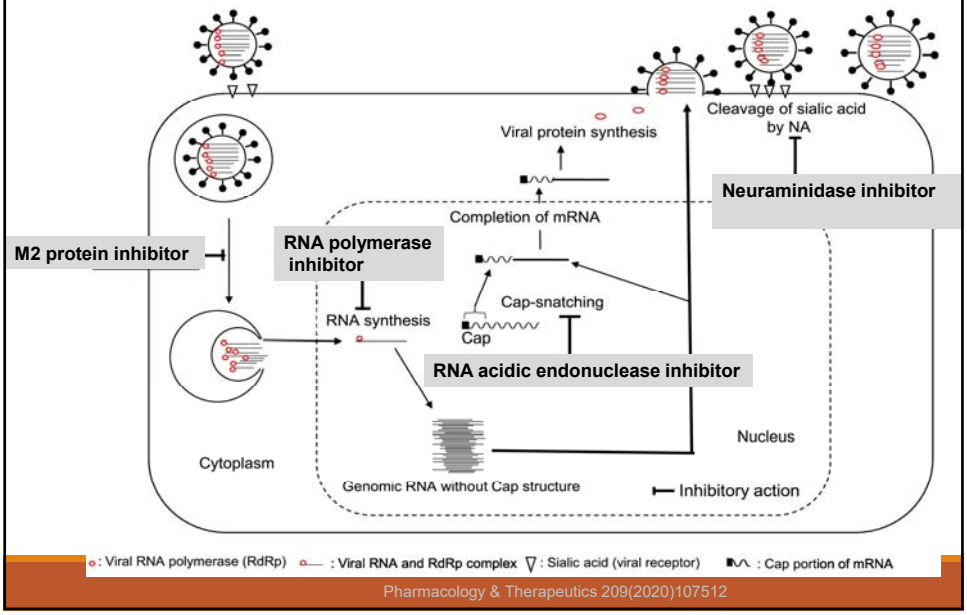
抗流病毒



Pharmacology & Therapeutics 209(2020)107512

3

抗流感藥物機轉



Pharmacology & Therapeutics 209(2020)107512

4

M2 protein inhibitor

- Mechanism : Inhibit viral uncoating
- Drug : Amantadine / Rimantadine
- Only active against influenza A
- Resistance rapidly increasing

已不建議使用於流感病毒感染治療

5

Neuraminidase inhibitor

- Mechanism : inhibiting viral release
- Drug : Oseltamivir、Zanamivir、Peramivir
- Active against influenza A and B

目前抗病毒藥物主流

6

Neuraminidase inhibitors

	克流感/易剋冒 (Oseltamivir)	瑞樂沙 (Zanamivir)	瑞貝塔 (Peramivir)
劑型	口服	吸入	注射
使用對象	成人(含孕婦)及兒童（含足月新生兒）	成人(含孕婦)及五歲以上兒童	成人(含孕婦)及兒童（早產兒與新生兒除外）
用法用量	每日2次，每次75mg，共5日	每日2次，每次吸2孔，共5日	單次 300mg
副作用	噁心、嘔吐	支氣管痙攣	腹瀉、血白球低下
腎功能調整	是	否	是
小兒劑量調整	是，依體重調整	否	是
注意事項	未成年病患需注意神經精神症狀	用於慢性呼吸系統病患時需特別注意支氣管痙攣及呼吸困難等症狀	因併發症等可能有惡化之虞的病患，可提高劑量至600mg，可依症狀連續多日反覆投與

7

Neuraminidase inhibitor

克流感(Oseltamivir)

瑞樂沙 (Zanamivir)

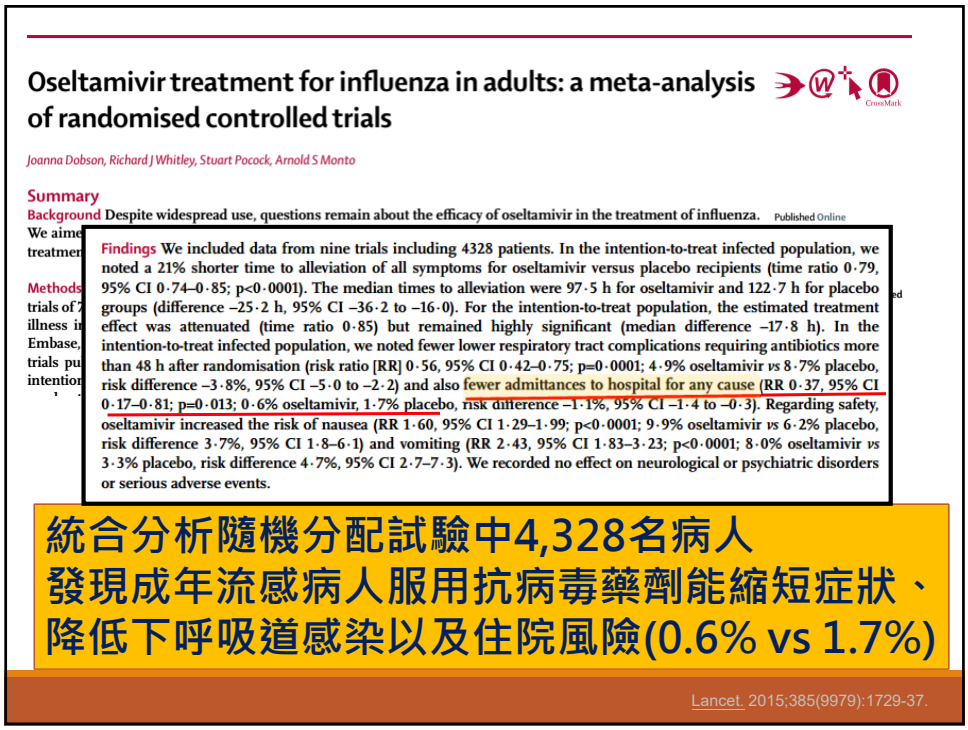
瑞貝塔 (Peramivir)

8

8


Cochrane Library
Trusted evidence.
Informed decisions.
Better health.
Title Abstract Ke
Cochrane Reviews
Trials
Clinical Answers
About
Help
Cochrane Database of Systematic Reviews
" confirmed or suspected exposure "
Neuraminidase inhibitors for preventing and treating influenza in adults and children
Cochrane Systematic Review - Intervention | Version publish
https://doi.org/10.1002/14651858.CD008965.pub4
Am score 756
View article information
Tom Jefferson | Mark A Jones | Peter Doshi | Chr
| Igho J Onakpoya | Kamal R Mahtani | David Nuna
View authors' declarations of interest
Time to first symptom alleviation. For the treatment of adults, oseltamivir reduced the time to first alleviation of symptoms by 16.8 hours (95% confidence interval (CI) 8.4 to 25.1 hours, P < 0.0001). This represents a reduction in the time to first alleviation of symptoms from 7 to 6.3 days. There was no effect in asthmatic children, but in otherwise healthy children there was (reduction by a mean difference of 29 hours, 95% CI 12 to 47 hours, P = 0.001). Zanamivir reduced the time to first alleviation of symptoms in adults by 0.60 days (95% CI 0.39 to 0.81 days, P < 0.00001), equating to a reduction in the mean duration of symptoms from 6.6 to 6.0 days. The effect in children was not significant. In subgroup analysis we found no evidence of a difference in treatment effect for zanamivir on time to first alleviation of symptoms in adults in the influenza-infected and non-influenza-infected subgroups (P = 0.53).
Hospitalisations. Treatment of adults with oseltamivir had no significant effect on hospitalisations: risk difference (RD) 0.15% (95% CI -0.78 to 0.91). There was also no significant effect in children or in prophylaxis. Zanamivir hospitalisation data were unreported.
Serious influenza complications or those leading to study withdrawal. In adult treatment trials, oseltamivir did not significantly reduce those complications classified as serious or those which led to study withdrawal (RD 0.07%, 95% CI -0.78 to 0.44), nor in child treatment trials; neither did zanamivir in the treatment of adults or in prophylaxis. There were insufficient events to compare this outcome for oseltamivir in prophylaxis or zanamivir in the treatment of children.
Pneumonia. Oseltamivir significantly reduced self reported, investigator-mediated, unverified pneumonia (RD 1.00%, 95% CI 0.22 to 1.49; number needed to treat to benefit (NNTB) = 100 (95% CI 67 to 451) in the treated population. The effect was not significant in the five trials that used a more detailed diagnostic form for pneumonia. There were no definitions of pneumonia (or other complications) in any trial. No oseltamivir treatment studies reported effects on radiologically confirmed pneumonia. There was no significant effect on unverified pneumonia in children. There was no significant effect of zanamivir on either self reported or radiologically confirmed pneumonia. In prophylaxis, zanamivir significantly reduced the risk of self reported, investigator-mediated, unverified pneumonia in adults (RD 0.32%, 95% CI 0.09 to 0.41; NNTB = 311 (95% CI 244 to 1086), but not oseltamivir.
主要分析2013年前克流感相關臨床試驗結果，
結論為藥物可縮短病程，但效果有限
Cochrane Database Syst Rev 2014; CD008965.

9


Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials
Joanna Dobson, Richard J Whitley, Stuart Pocock, Arnold S Monto
Summary
Background Despite widespread use, questions remain about the efficacy of oseltamivir in the treatment of influenza.
Published Online
We aime
treatmer
Methods
trials of
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Findings We included data from nine trials including 4328 patients. In the intention-to-treat infected population, we noted a 21% shorter time to alleviation of all symptoms for oseltamivir versus placebo recipients (time ratio 0·79, 95% CI 0·74–0·85; p<0·0001). The median times to alleviation were 97·5 h for oseltamivir and 122·7 h for placebo groups (difference −25·2 h, 95% CI −36·2 to −16·0). For the intention-to-treat population, the estimated treatment effect was attenuated (time ratio 0·85) but remained highly significant (median difference −17·8 h). In the intention-to-treat infected population, we noted fewer lower respiratory tract complications requiring antibiotics more than 48 h after randomisation (risk ratio [RR] 0·56, 95% CI 0·42–0·75; p=0·0001; 4·9% oseltamivir vs 8·7% placebo, risk difference −3·8%, 95% CI −5·0 to −2·2) and also fewer admittances to hospital for any cause (RR 0·37, 95% CI 0·17–0·81; p=0·013; 0·6% oseltamivir, 1·7% placebo, risk difference −1·1%, 95% CI −1·4 to −0·3). Regarding safety, oseltamivir increased the risk of nausea (RR 1·60, 95% CI 1·29–1·99; p<0·0001; 9·9% oseltamivir vs 6·2% placebo, risk difference 3·7%, 95% CI 1·8–6·1) and vomiting (RR 2·43, 95% CI 1·83–3·23; p<0·0001; 8·0% oseltamivir vs 3·3% placebo, risk difference 4·7%, 95% CI 2·7–7·3). We recorded no effect on neurological or psychiatric disorders or serious adverse events.
統合分析隨機分配試驗中4,328名病人
發現成年流感病人服用抗病毒藥劑能縮短症狀、
降低下呼吸道感染以及住院風險(0.6% vs 1.7%)
Lancet. 2015;385(9979):1729-37.

10

Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data

Oseltamivir 92%
Zanamivir 2.3%
Peramivir 0.3%

Stella G Muthuri*, Sudhir Venkatesan*, Puja R Myles, Jo Leonardi-Bee, Tariq S A Al Khuwaitir, Adbullah Al Mamun, Ashish P Anovadiya, Eduardo Azziz-Baumgartner, Clarisa Báez, Matteo Bassetti, Bojana Beovic, Barbara Bertisch, Isabelle Bonmarin, Robert Booy, Victor H Borja-Aburto, Heinz Burgmann, Bin Cao, Jordi Carratalà, Justin T Denholm, Samuel R Dominguez, Benigno A D Duarte, Gal Dubnov-Raz, Marcela Echavarria, Sergio Fanella, Zha
Xiaoyun Hu, Quazi
Ilija Kuzman, Arthu
Elga Mayo-Monter
Pagbajabyn Nymad
Elena B Sarrouf, An
Kelvin K W To, Anto
Paul Zarogoulidis, F

Findings

We included data for 29 234 patients from 78 studies of patients admitted to hospital between Jan 2, 2009, and March 14, 2011. Compared with no treatment, neuraminidase inhibitor treatment (irrespective of timing) was associated with a reduction in mortality risk (adjusted odds ratio [OR] 0·81; 95% CI 0·70–0·93; p=0·0024). Compared with later treatment, early treatment (within 2 days of symptom onset) was associated with a reduction in mortality risk (adjusted OR 0·48; 95% CI 0·41–0·56; p<0·0001). Early treatment versus no treatment was also associated with a reduction in mortality (adjusted OR 0·50; 95% CI 0·37–0·67; p<0·0001). These associations with reduced mortality risk were less pronounced and not significant in children. There was an increase in the mortality hazard rate with each day's delay in initiation of treatment up to day 5 as compared with treatment initiated within 2 days of symptom onset (adjusted hazard ratio [HR 1·23] [95% CI 1·18–1·28]; p<0·0001 for the increasing HR with each day's delay).

Summary

Background N
evidence for th
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觀察性研究統合分析近3萬名在2009年H1N1流感大流行期間住院的病人，發現流感住院病人服用抗病毒藥劑能減少死亡風險

Lancet Respir Med. 2014;2(5):395-404.

Original Contribution | Clinician's Corner

FREE

November 4, 2009

Factors Associated With Death or Hospitalization Due to Pandemic 2009 Influenza A(H1N1) Infection in California

Janice K. Loule, MD, MPH; Meileen Acosta, MPH; Kathleen Winter, MPH; et al

Article Information

JAMA. 2009;302(17):1896-1902. doi:10.1001/jama.2009.1583

Abstract

Table 2. Comorbid Conditions of Reported Hospitalized and Fatal Cases of Pandemic 2009 Influenza A(H1N1) Infections in California, April 23 Through August 11, 2009

	All Cases (N = 1088)	Cases Aged 0-17 Years		Cases Aged ≥18 Years	
		Fatal (n = 8)	Nonfatal (n = 336)	Fatal (n = 110)	Nonfatal (n = 634)
Chronic comorbid illness associated with severe influenza[a]	741 (68)	6 (75)	199 (59)	83 (75)	453 (71)
Chronic lung disease	403 (37)	3 (38)	126 (38)	45 (41)	229 (36)
Asthma	257 (24)	1 (13)	99 (29)	18 (16)	139 (22)
Other/unknown[b]	146 (13)	2 (25)	27 (8)	27 (25)	90 (14)
Chronic cardiac disease[c]	167 (15)	2 (25)	25 (7)	25 (23)	115 (18)
Metabolic disease	223 (20)	2 (25)	23 (7)	38 (35)	160 (25)
Diabetes mellitus	116 (11)	0	4 (1)	20 (18)	92 (14)
Renal disease	72 (7)	0	8 (2)	18 (16)	46 (7)
Other/unknown[d]	59 (5)	2 (25)	11 (3)	7 (6)	39 (6)
Immunosuppressive conditions	205 (19)	3 (38)	55 (16)	36 (33)	111 (18)
Cancer/transplant/immunosuppressive drugs[e]	155 (14)	2 (25)	42 (13)	29 (26)	82 (13)
HIV/AIDS	22 (2)	0	0	4 (4)	18 (3)
Other/unknown	31 (3)	1 (13)	13 (4)	4 (4)	13 (2)
Neuromuscular disorder[f]	115 (11)	4 (50)	45 (13)	14 (13)	52 (8)
Pregnancy[g]	97/1012 (10)	0	5 (2)	6/104 (6)	86/587 (15)
Other chronic comorbid illness[a]	370 (34)	2 (25)	45 (13)	69 (63)	254 (40)
Obesity[g,h]	172/361 (48)	0	15 (19)	46/68 (66)	111/212 (52)
BMI 30-34.9	55 (35)			11 (24)	44 (40)
BMI 35-39.9	34 (22)			12 (26)	22 (20)
BMI ≥40	67 (43)			23 (50)	44 (40)
Gastrointestinal tract	109 (10)	2 (25)	29 (9)	12 (11)	66 (10)
GERD	34 (3)	1 (13)	5 (2)	4 (4)	24 (4)
Other/unknown[i]	75 (7)	1 (13)	24 (7)	8 (7)	42 (7)
Hyperlipidemia	33 (3)	0	0	2 (2)	31 (5)
Hypertension	176 (16)	0	2 (<1)	27 (25)	147 (23)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; GERD, gastroesophageal reflux disease; HIV, human immunodeficiency virus.

高危險族群：
2歲以下幼兒
65歲以上老人
慢性疾病 (心血管疾病、肺部疾病、糖尿病、肝腎疾病)
免疫功能不全 (移植及癌症及HIV病人)
孕婦或最近兩週內生產的產婦
病態肥胖

JAMA. 2009;302(17):1896-1902.

ERJ open research

Early oseltamivir treatment improves survival in critically ill patients with influenza pneumonia

Background: The relationship between early oseltamivir treatment (within 48 h of symptom onset) and mortality in patients admitted to intensive care units (ICUs) with severe influenza is disputed. This study aimed to investigate the association between early oseltamivir treatment and ICU mortality in critically ill patients with influenza pneumonia.

Methods: This was an observational study of patients with influenza pneumonia admitted to 184 ICUs in Spain during 2009–2018. The primary outcome was to evaluate the association between early oseltamivir treatment and ICU mortality compared with later treatment. Secondary outcomes were to compare the duration of mechanical ventilation and ICU length of stay between the early and later oseltamivir treatment groups. To reduce biases related to observational studies, propensity score matching and a competing risk analysis were performed.

Results: During the study period, 2124 patients met the inclusion criteria. All patients had influenza pneumonia and received oseltamivir before ICU admission. Of these, 529 (24.9%) received early oseltamivir treatment. In the multivariate analysis, early treatment was associated with reduced ICU mortality (OR 0.69, 95% CI 0.51–0.95). After propensity score matching, early oseltamivir treatment was associated with improved survival rates in the Cox regression (hazard ratio 0.77, 95% CI 0.61–0.99) and competing risk (subdistribution hazard ratio 0.67, 95% CI 0.53–0.85) analyses. The ICU length of stay and duration of mechanical ventilation were shorter in patients receiving early treatment.

西班牙多中心ICU觀察性研究2124位流感重症病人,oseltamivir使用可降低ICU住院死亡率、ICU留滯天數及呼吸器使用天數

ERJ Open Res. 2021;7(1):00888-2020.

13

International Journal of Infectious Diseases 104 (2021) 232–238

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Effectiveness of Oseltamivir in reducing 30-day readmissions and mortality among patients with severe seasonal influenza in Australian hospitalized patients

January 2016–March 2020

Yogesh Sharma[a,b,*], Chris Horwood[c], Paul Hakendorf[c], Campbell Thompson[d]

Table 2
Outcomes using propensity score matching in influenza patients who received Oseltamivir compared to the group who did not receive this treatment.

Outcome variable	Delayed/no treatment (n = 245)	Prompt treatment (n = 245)	Difference	Odds ratio	95% CI	P-value
In-hospital mortality n (%)	7 (2.9)	4 (1.6)	3 (1.2)	0.24	0.05–1.17	0.07
30-day mortality n (%)	11 (4.5)	11 (4.5)	0	0.84	0.34–2.10	0.714
30-day readmissions n (%)	38 (15.5)	24 (9.7)	14 (5.7)	0.56	0.32–0.98	0.03
[a]Composite outcome n (%)	49 (20)	33 (13.4)	16 (6.5)	0.56	0.34–0.92	0.02
LOS median (IQR)	4 (6)	3 (3)	1 (3)	−2.32[b]	−4.0 to −0.56	0.010

CI, confidence interval; LOS, length of hospital stay; IQR, interquartile range.
[a] 30-day readmission or death.
[b] Coefficient.

澳洲多家醫學中心觀察性研究490位流感住院病人,oseltamivir早期使用可降低住院死亡率、住院併發症及住院天數

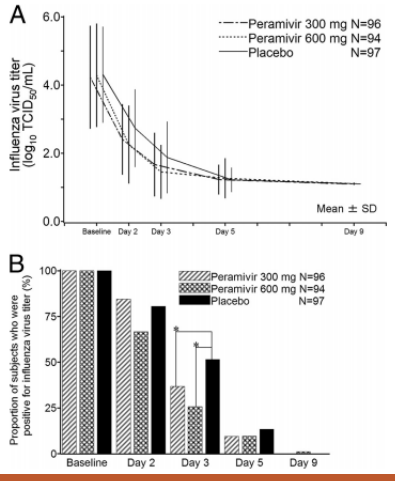
IJID. 2021;104:232-8.

14

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2010, p. 4568–4574 Vol. 54, No
0066-4804/10/$12.00 doi:10.1128/AAC.00474-10

Efficacy and Safety of Intravenous Peramivir for Treatment of Seasonal Influenza Virus Infection▽†

Shigeru Kohno,[1]* Hiroshi Kida,[2] Masashi Mizuguchi,[3] and Jingoro Shimada[4]
for the S-021812 Clinical Study Group



隨機分派研究證據顯示在成年流感病人使用Peramivir可縮短病程，減少病毒傳播

Antimicrob Agents Chemother. 2010;54(11):4568-74

15

Open Forum Infectious Diseases
MAJOR ARTICLE

Efficacy and Safety of Intravenous Peramivir Compared With Oseltamivir in High-Risk Patients Infected With Influenza A and B Viruses: A Multicenter Randomized Controlled Study

Shigeki Nakamura,[1,6] Taiga Miyazaki,[1,2] Koichi Izumikawa,[2] Hiroshi Kakeya,[3] Yutaka Saisho,[4] Katsunori Yanagihara,[5] Yoshitsugu Miyazaki,[6] Hiroshi Mukae,[1] and Shigeru Kohno[1]

[1]Department of Respiratory Diseases, Nagasaki University Hospital, [2]Department of Infectious Diseases, Nagasaki University Graduate School of Biomedical Sciences, [3]Department of Infection Control Science, Graduate School of Medicine, Osaka City University, [4]Medical Affairs, Shionogi & Co, Ltd, Osaka, [5]Department of Laboratory Medicine, Nagasaki University Graduate School of Biomedical Sciences, and [6]Department of Chemotherapy and Mycoses, National Institute of Infectious

Background. Clinical studies comparing the different neuramini
have not been performed. To optimize such treatments, we assessed t
oral oseltamivir in treating seasonal influenza A or B virus infection.
Methods. A multicenter, randomized, controlled clinical trial w
patients infected with seasonal influenza. A total of 92 adult inpatien
by either a single intravenous infusion of peramivir (600 mg) or oral a
Results. The median times to clinical stability (time to reach <37°
and 37.8 hours (95% CI = 26.3–45.3) in the peramivir and oseltamivi
difference. The virus titer and change of mean total symptom scores
regression suggested that virus type was a significantly effective prog
(AEs) with peramivir and oseltamivir occurred in 2.2% (n = 1/46) and
was mild in all cases except 2 patients who showed pneumonia or CO
Conclusions. Intravenous peramivir was effective based on the re
show that peramivir is a useful option for the treatment of influenza-i
Keywords. high-risk patient; influenza; neuraminidase inhibitor;

隨機分派研究證據顯示在高危險族群流感病人使用oseltamivir或peramivir治療，兩者退燒時間及病毒量下降變化無差異

16

Meta-analysis

Comparing intravenous peramivir with oral oseltamivir for patients with influenza: a meta-analysis of randomized controlled trials

Yu-Hsing Fang, Tzu-Herng Hsu, Tzu-Yin Lin, Chia-Hung Liu, Shou-Chu Chou, Jie-Ying Wu & ...show all

Pages 1039-1046 | Received 21 Oct 2020, Accepted 15 Jan 2021, Published online: 01 Mar 2021

Results

The meta-analysis was conducted to calculate the pooled effect size by using a random-effects model. Seven randomized controlled trials (RCTs) including 1,138 patients were reviewed. The incidence of total complications revealed no significant difference between 600 mg IV peramivir (P600) and 75 mg oral oseltamivir (O75) treatments (2.8% vs. 4.1%; risk ratio [RR] = 0.70; 95% confidence interval [CI]: 0.36–1.38). The incidence of pneumonia was not significantly different between the P600 and O75 treatment groups (2.2% vs. 2.7%; RR = 0.74; 95% CI: 0.37–1.51). Regarding the time to the alleviation of symptoms, no difference was found in P600 and O75 treatment (MD = −3.00; 95% CI: −11.07 to 5.06). The rate of fever clearance in 24 h and the time to

eramivir and oral oseltamivir

退燒時間、死亡率、住院時間、病毒量變化及副作用發生率兩者無差異

Expert Rev Anti Infect Ther. 2021;19(8):1039-1046.

17

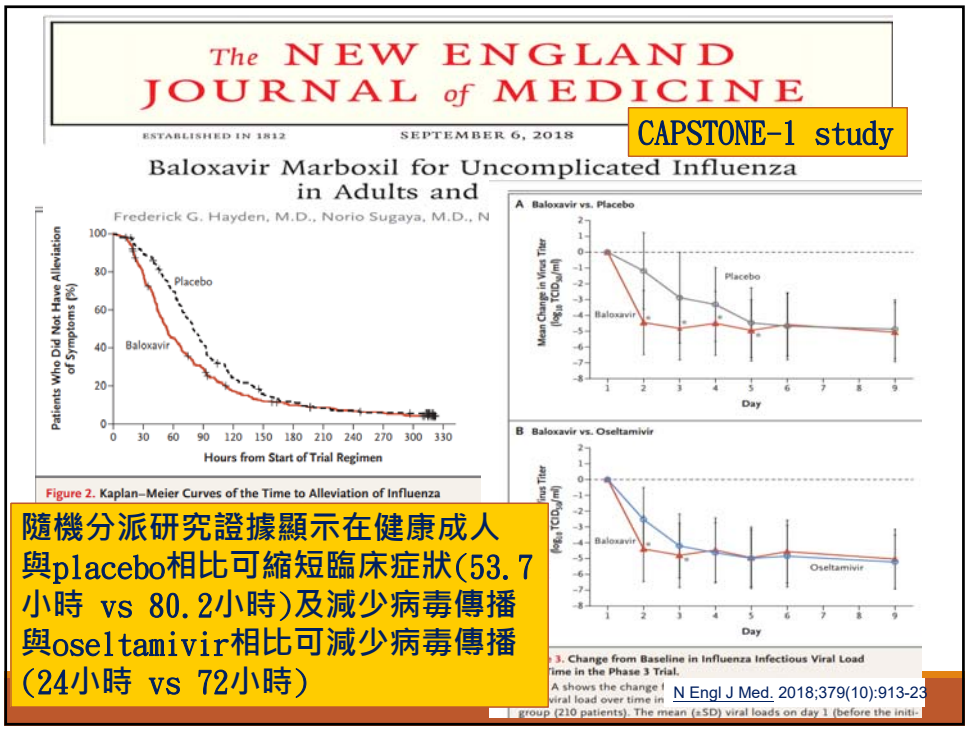
Endonuclease inhibitor

- Mechanism : inhibiting the initiation of mRNA synthesis
- Drug : Baloxavir

  (40 mg PO as a single dose; ≥80 kg: 80 mg PO as a single dose)
- Active against influenza A and B

未來抗病毒藥物主流

18



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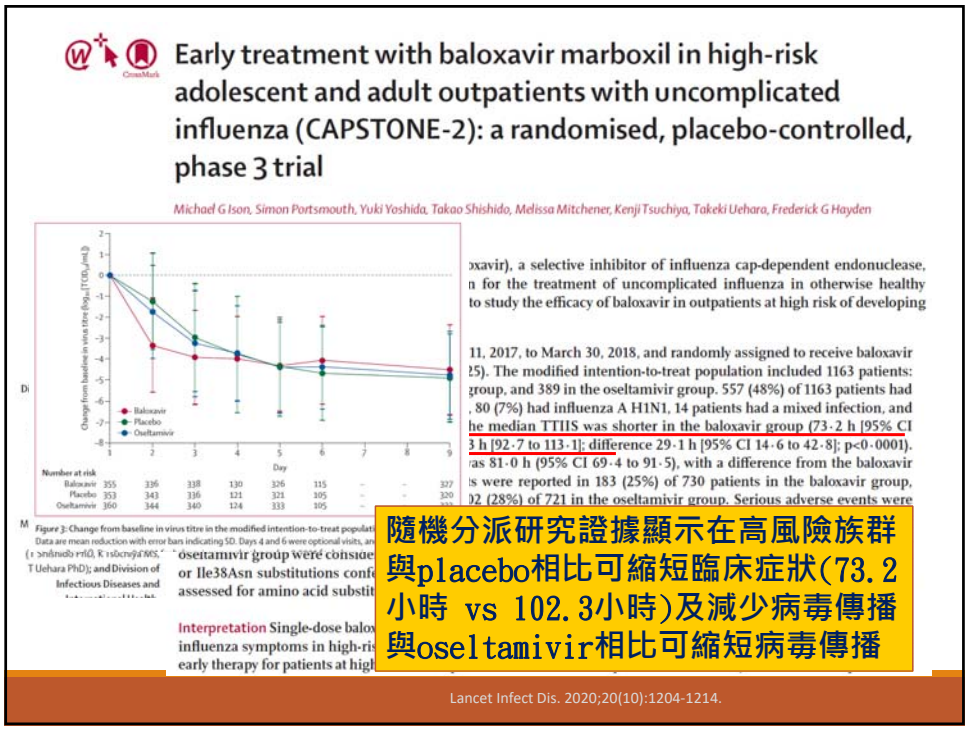

Lancet Infect Dis. 2020;20(10):1204-1214.

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

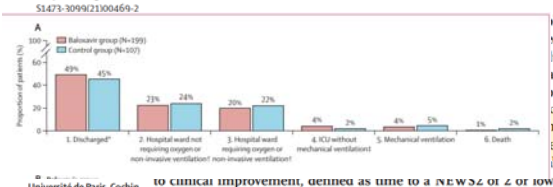
Deepali Kumar, Michael G Ison, Jean-Paul Mira, Tobias Welte, Neil Collinson, Sarah Williams, Steffen Wildum, Andrew Ack

Baloxavir治療劑量: 40mg on D1,D4&D7

Lancet Infect Dis 2022; 22: 718–30
Published Online January 24, 2022
https://doi.org/10.1016/S1473-3099(21)00469-2

Summary

Background Neuraminidase inhibitors (NAIs) are considered the standard of care for hospitalised patients with influenza. We aimed to test whether combining the cap-dependent endonuclease inhibitor baloxavir marboxil (hereafter baloxavir) with standard-of-care NAIs would result in improved clinical outcomes compared with NAI monotherapy in hospitalised patients with severe influenza.



placebo-controlled, superiority trial. Patients aged d influenza (by RT-PCR or a rapid test) and had a luded. Recruitment took place in 124 centres across active response system, patients were randomly baloxavir group) or placebo plus NAIs (hereafter the comes were masked to group assignment. Baloxavir t <80 kg, or 80 mg for ≥80 kg), and on day 7 if no ed in this study were oseltamivir, zanamivir, and l standard practice. The primary endpoint was time to clinical improvement, defined as time to a NEWS2 of 2 or lower for 24 h or hospital discharge, whichever came first, based on daily assessments over the study duration of 35 days. Secondary endpoints included safety analyses. The modified received a do assigned at r least one dos registered wit

Université de Paris, Cochin University Hospital, Medical Intensive Care Unit, Paris, France (Prof J-P Mira MD); Department of Pneumology and German Centre of Lung Research (DZL), Hannover Medical School, Hannover,

隨機分派研究證據顯示在流感重症病人baloxavir合併NAIs與NAIs相比, 臨床預後相當但NAIs合併baloxavir可縮短病毒傳播

Lancet Infect Dis. 2022;22(5):718-730.

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JAMA Network | Open

Original Investigation | Infectious Diseases

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

A Systematic Review and Network Meta-analysis

Figure 3. Network Meta-analysis Estimates of Time to Alleviation of Influenza Symptoms (TTAS) and Complications

Complications, RR (95% CI) \ Treatment	Zanamivir 10 mg	Peramivir 600 mg	Oseltamivir 75 mg	Oseltamivir 150 mg	Peramivir 300 mg	Baloxavir 40 or 80 mg	Placebo
Zanamivir 10 mg	0.97 (0.73-1.29)	0.90 (0.77-1.05)	0.90 (0.73-1.09)	0.89 (0.70-1.13)	0.84 (0.71-0.99)	0.67 (0.58-0.77)
1.25 (0.70-2.23)	Peramivir 600 mg	0.93 (0.71-1.20)	0.92 (0.69-1.23)	0.92 (0.71-1.18)	0.87 (0.67-1.13)	0.69 (0.54-0.88)
1.34 (1.05-1.71)	1.07 (0.60-1.93)	Oseltamivir 75 mg	1.00 (0.86-1.15)	0.99 (0.81-1.21)	0.94 (0.86-1.02)	0.74 (0.70-0.79)
1.25 (0.79-2.00)	1.01 (0.49-2.07)	0.94 (0.59-1.48)	Oseltamivir 150 mg	0.99 (0.78-1.26)	0.94 (0.80-1.10)	0.75 (0.65-0.86)
1.21 (0.72-2.05)	0.97 (0.47-2.00)	0.91 (0.52-1.57)	0.97 (0.49-1.92)	Peramivir 300 mg	0.95 (0.77-1.17)	0.75 (0.62-0.91)
1.61 (1.01-2.58)	1.29 (0.63-2.67)	1.20 (0.75-1.92)	1.29 (0.68-2.42)	1.33 (0.67-2.64)	Baloxavir 40 or 80 mg	0.79 (0.73-0.86)
0.82 (0.72-0.92)	0.65 (0.37-1.16)	**0.61 (0.49-0.75)**	0.65 (0.41-1.02)	0.67 (0.40-1.12)	**0.51 (0.32-0.80)**	Placebo

TTAS, HR (95% CI)

Effect sizes presented on the upper triangle TTAS between the row and columns (eg, th placebo is 0.67 [0.58-0.77]); On the lower

tiviral age ifluenza a most saf ealthy ad work meta ical trials, nd that a

統合分析隨機分配試驗證據顯示流感病人使用NAIs或baloxavir，與placebo相比，皆可縮短臨床症狀及降低呼吸道感染併發症

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

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小結

- 目前主流抗病毒藥物有：口服Baloxavir單次、口服Oseltamivir五天、吸入劑Zanamivir五天、針劑Peramivir單次
- 上述藥物於臨床實證皆可縮短臨床症狀時間、降低住院率及呼吸道感染相關併發症

Antiviral Drug Options

- For hospitalized patients with suspected or confirmed influenza, initiation of antiviral treatment with oral or enterically-administered oseltamivir is recommended as soon as possible.
- For outpatients with complications or progressive disease and suspected or confirmed influenza (e.g., pneumonia, or exacerbation of underlying chronic medical conditions), initiation of antiviral treatment with oral oseltamivir is recommended as soon as possible.
- For outpatients with suspected or confirmed uncomplicated influenza, oral oseltamivir, inhaled zanamivir, intravenous peramivir, or oral baloxavir may be used for treatment, depending upon approved age groups and contraindications. In one randomized controlled trial, baloxavir had greater efficacy than oseltamivir in adolescents and adults with influenza B virus infection (Ison, 2020).

Pediatr Infect Dis J. 2020;39(8):700-5 https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm

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大綱

- 抗流感病毒藥物機轉及實證
- 抗流感病毒藥物抗藥性現況
- 新機轉抗病毒藥物
- 流感藥物治療準則及建議

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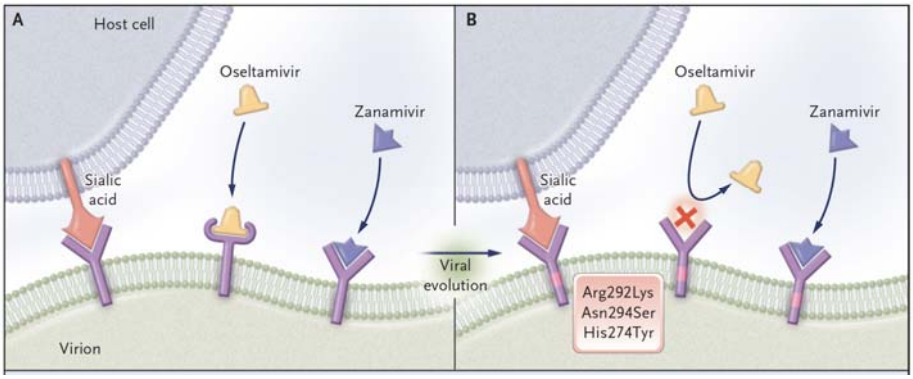
警鐘響起—NAI抗藥性

- 病毒基因突變：His274Tyr, Arg292Lys, Asn294Ser，改變病毒與NAI結合部位，使得oseltamivir不易與neuraminidase active site結合



N Engl J Med 2009; 360:953-6

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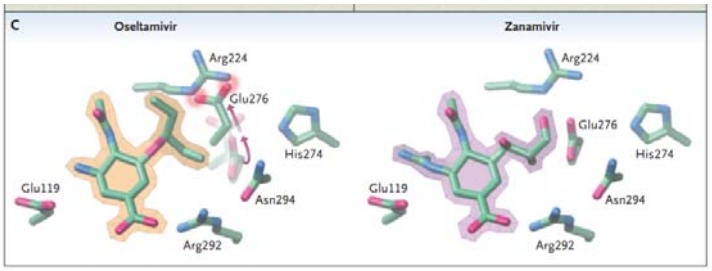
警鐘響起—NAI抗藥性

- 病毒突變株並不會降低病毒的生存能力(fitness)及傳染力(transmissibility)
- 2007-2008 H1N1流行於北半球的病毒株帶有神經胺酸酶突變的比例為10%~70%, 2008-2009年美國H1N1突變比例高達98%
- 當次流行病毒株對於zanamivir仍具有感受性



Mechanism of Development of Resistance to Oseltamivir.

N Engl J Med 2009; 360:953-6

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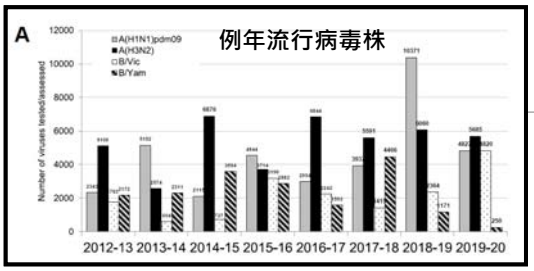
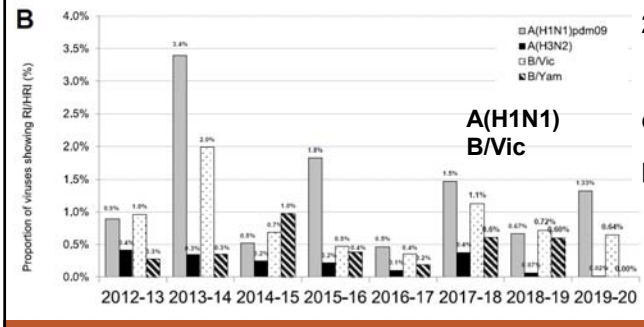
Oseltamivir抗藥性病毒株近年監測結果





pdm09抗藥性病毒株比例

2019/20:1.33%

2018/19:0.67%

2017/18:1.5%

2016/17: 0.5%

2015/16: 1.8%

A(H1N1)
B/Vic

cross resistant to peramivir

Antiviral Res. 2022;200:105281

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Polymerase acid (PA) amino acid substitutions in CAPSTONE-1 studt

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 6, 2018

CAPSTONE-1 study

Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents

PA/I38X amino acid substitutions detected in **9.7%** baloxavir recipients (mainly **influenza A(H3N2)** infection) after baloxavir treatment

The median time to alleviation of symptoms was longer in baloxavir recipients with PA/I38X substitutions than in those without variants (**63.1 hours vs. 49.6 hours**)

91% of baloxavir recipients with PA/I38X substitutions detected virus on Day 5; 17% detected virus on Day 9

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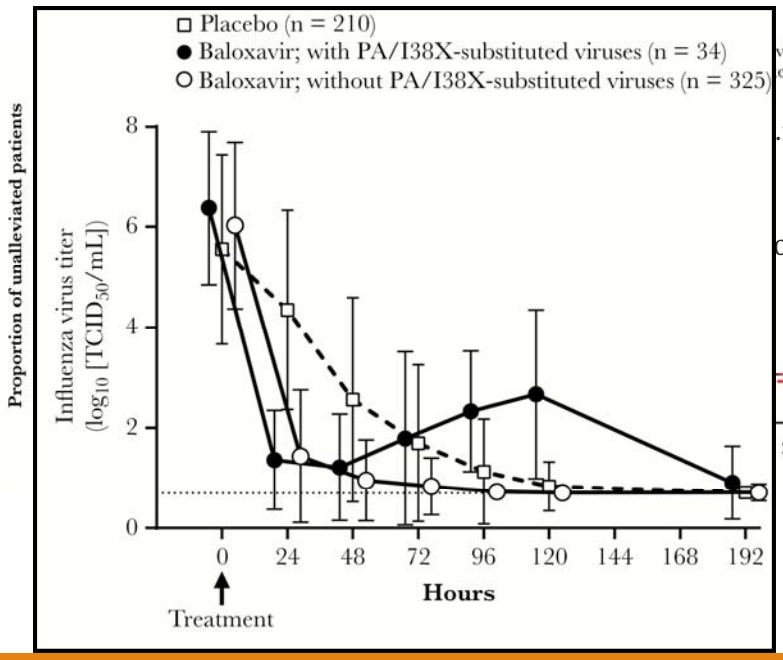

J Infect Dis. 2020 Jan 14;221(3):346-355.

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Baloxavir抗藥性病毒株監測結果

2018-19 Atlanta and Tokyo

Table 3
Virus and patient characteristics for type A and B influenza viruses (n = 53) containing PA amino acid substitutions of concern and phenotypically tested by WHO CCs for baloxavir susceptibility.[a]

Virus (n)	n	EC_{50} fold-change as compared to reference median EC_{50} values	PA substitution[b]		Patient setting	Antiviral treatment	Immuno-compromised
			Virus isolate	Clinical specimen			
A(H1N1)pdm09 (14 of 984)	2	11.4-32.2	I38T	I38T/I mix	Community	Yes, baloxavir	No
	1	12.4	I38 T/F mix	I38T/F/I mix	Community	Yes, baloxavir	No
	2	36.9-49.5	I38S	I38S	Community	Yes, baloxavir	No
	3	3.0-3.7	I38V	I38V	Community	Yes, laninamivir	No
	1	2.5	I38F/I mix	I38F/I mix	Unknown	Unknown	Unknown
	1	6.9	E23G	E23G	Unknown	Unknown	Unknown
	1	7.4	E23K	E23K	Community	No	No
	2	1.6-4.7	K34R	K34R	Unknown	Unknown	Unknown
	1	2.9	E199G	E199G	Unknown	Unknown	Unknown
A(H3N2) (37 of 768)	21	64.3-614.0	I38T	I38T (10)	Community (19)	Yes, baloxavir (17)	No (20)
				I38T/I mix (9)			Unknown (1)
				I38T/K/I mix (1)	Hospital (2)	Yes, oseltamivir (1)	
				Not available[c] (1)		No (3)	
	7	5.6-250.0	I38T/I mix	I38T/I mix	Community	Yes, baloxavir	No
	1	25.6	I38 T/M/I mix	I38T/M/I mix	Community	Yes, baloxavir	No
	1	23.7	I38M	I38M	Community	Yes, baloxavir	No
	2	1.0-91.8	I38M/I mix	I38M/I mix (1)	Community (1)	Yes, baloxavir (1)	No (1)
				I38 (1)	Unknown (1)	Unknown (1)	Unknown (1)
	1	4.1	I38L	I38L	Unknown	Unknown	Unknown
	1	4.1	K34R	K34R	Unknown	Unknown	Unknown
	2	0.5-1.3	L28P	L28P (1)	Unknown	Unknown	Unknown
				Not available (1)			
	1	0.9	I38V/I mix	Not available	Unknown	Unknown	Unknown
B/Victoria (2 of 425)	1	0.9	I38V	I38V	Unknown	Unknown	Unknown
	1	0.6	M34I	Not available	Unknown	Unknown	Unknown

1.4%

4.8%

0.2%

全球抗藥性病毒株比例

2019/20:0.5%

2018/19:0.1%

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何時監測抗藥性

- 免疫不全病人或流感重症病人使用抗病毒藥物後臨床狀況未改善(7~10天)且有持續病毒複製證據 (positive of RT-PCR or viral culture)
- 使用預防性抗流感藥物後仍出現臨床症狀且有病毒複製證據

目前抗藥性病毒株並不常見，但仍需持續監測。
如當年流行病毒株為H1N1，需留意NAIs抗藥性。
如當年流行病毒株為H3N2，需留意Baloxavir抗藥性

(IDSA Influenza Clinical Guidelines 2018 • CID 2018)

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大綱

- 抗流感病毒藥物機轉及實證
- 抗流感病毒藥物抗藥性現況
- **新機轉抗病毒藥物**
- 流感藥物治療準則及建議

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其它機轉抗病毒藥物

藥物	特色	上市
Falvipiravir (T-705)	**抑制病毒RNA polymerase**	Y
1,3-dihydroxy-6-benzo [c] chromene (D715-2441)	抑制病毒RNA polymerase	N
Fludase (DAS181)	切除呼吸道上皮細胞的silic acid receptor	N
FA-6005	抑制病毒vRNP complex活性，阻斷RNPs合成	N
Cynovirin-N	Hemagglutinin inhibitor	N
siRNAs	short interfering RNAs	N

Environ. Res. Public Health 2022, 19, 3018.

N Engl J Med 2009; 360:953-6

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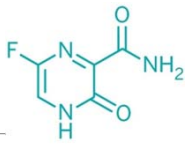
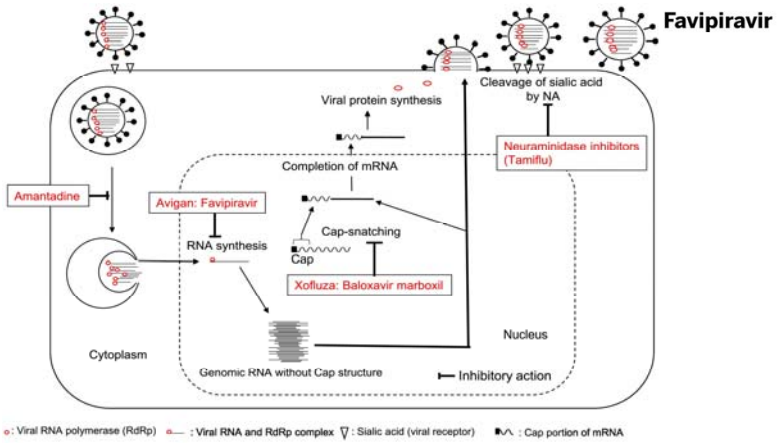
Favipiravir（Avigan）





https://www.toyama-chemical.co.jp/en/rd/area/infection.html

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The Journal of Infectious Diseases
MAJOR ARTICLE

Favipiravir Treatment of Uncomplicated Influenza in Adults: Results of Two Phase 3, Randomized, Double-Blind, Placebo-Controlled Trials

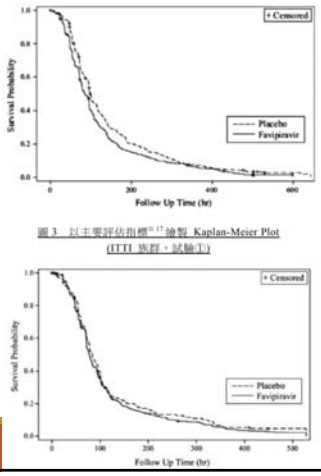

圖 3　以主要評估指標[17]繪製 Kaplan-Meier Plot (ITTI 族群，試驗 1)

Catherine Oldham-Creamer,[2] Lih Lisa Kang,[2,c] and Carol Epstein[2,d]
f Medicine, University of Virginia School of Medicine, Charlottesville, Virginia, USA; and [2]Medivector, Inc, Boston,

placebo-controlled trials assessing the efficacy and tolerability of favipiravir in acute

nfluenza-like symptoms and fever of ≤48 hours were randomized to favipiravir BID on day primary tion when fever was ted particip acebo), favi , 84.2 vs ation vs pla did not , 77.8 vs 8 ced viral ys 1–5, and ide from ferences in n demonst iation in es and anti NA viral

隨機分派研究證據顯示在成年流感病人使用與placebo相比無差異與oseltamivir相比亦未顯示有效性（63.1小時 vs 51.2小時）

JID. 2022; jiac135, https://doi.org/10.1093/infdis/jiac135

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Favipiravir 目前建議

- 專案進口藥物但無我國藥物許可證，提供新型A型流感通報病例使用（限於其他抗流感病毒藥物無效或效力不足的情況）
- 第 1 日每回服用 1600mg，每日2回。第 2 至 5 天每回 600mg，每日2回。總投藥期間為 5 天
- 本藥劑具致畸胎性，禁使用於兒童，且無小兒投藥經驗

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其它機轉抗病毒藥物

藥物	特色	上市
Falvipiravir (T-705)	**抑制病毒RNA polymerase**	Y
siRNAs	short interfering RNAs	N

仍在持續研發中

Environ. Res. Public Health 2022, 19, 3018.

N Engl J Med 2009; 360:953-6

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流感病人治療國內外指引共識

- 非屬重症高風險或高傳播族群之輕症病患，以支持性療法為主。大多數人可自行痊癒，而不需使用抗病毒藥物
- 易併發重症之高風險對象，出現危險徵兆者或重症住院病患，不需等待確診，不論發病時間，均應立刻給予抗病毒藥物治療 (NAIs, Baloxavir)

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流感抗病毒藥劑種類

藥物學名	Oseltamivir	Zanamivir	Peramivir	Baloxavir	Favipiravir
商品名	克流感/易剋冒	Relenza 瑞樂沙	Rapiacta 瑞貝塔	Xofluza紓伏效	Avigan
包裝	75 毫克膠囊 10 入之盒裝 公費自費	盒裝有碟型吸入器 1 枚，及含 4 孔規則間隔之泡囊 5 入 公費	點滴用注射袋 300mg 公費自費	20mg/tab 白色錠劑 自費	200mg，淡黃色膜衣錠 公費
使用方式	口服	吸入	注射	口服	口服
使用對象	成人及兒童（含足月新生兒）	成人及5歲以上可配合兒童	小兒（早產兒與新生兒除外）與成人	成人及5歲以上兒童	成人
用法用量	每日2次，每次75mg，共5日	每日2次，每次吸 2 孔，共5日	單次注射300mg，可依症狀提高劑量或連續投與	40mg 單次投予。80kg上：80mg 單次投予	每日2次，第1日每次服用 1600mg。第2日起每次服用600mg，共5日
小兒是否需調整劑量	是	否	是	是	本藥劑具致畸胎性，禁使用於孕婦、兒童
腎功能不佳是否需調整	是	否	是	否 50 mL/min以下：未有資料	否 腎功能不佳未有資料
備註	可能出現輕微噁心及嘔吐，未成年病患需注意神經精神症狀 自費 114元/顆	用於慢性呼吸系統病患時需特別注意支氣管痙攣及呼吸困難等	公費使用僅提供新型A型流感通報病例使用 自費使用 (1760元/劑)	避免與乳製品、含多價陽離子緩瀉劑、制酸劑併服 自費使用 (960元/顆)	無我國藥物許可證，提供新型A型流感通報病例使用需經醫療網指揮官同意

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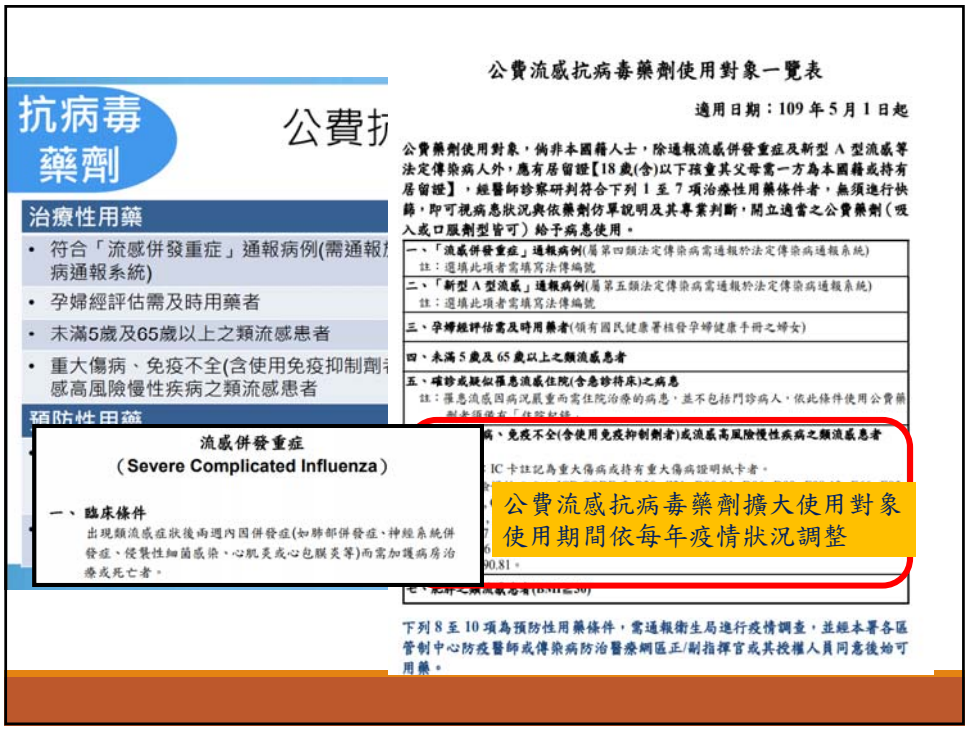

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流感預防性用藥

- 目前無建議流感暴觸後例行使用流感預防性用藥
- 針對特定單位(如長照機構)流感群聚或新型A型流感接觸者可考慮流感預防性用藥
- 流感預防性用藥以oseltamivir或zanamivir為主，至少使用7天或Baloxavir 單次使用

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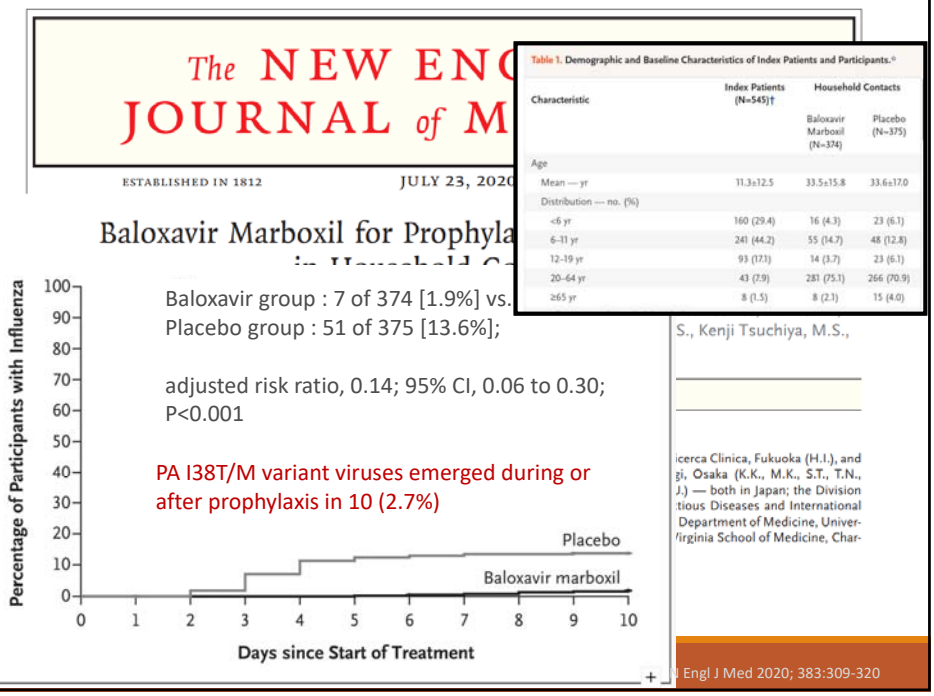

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Co-circulation of Influenza Viruses and SARS-CoV-2

- 流感病毒與新冠病毒同時流行
- 抗病毒藥同時使用，無藥物交互作用
- steroid 及immunomodulatory therapies使用需小心謹慎評估

https://www.covid19treatmentguidelines.nih.gov/special-populations/influenza/

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結論

- 易併發重症之高風險對象或住院病人，應早期診斷並及早使用有效抗病毒藥物：oseltamivir、zanamivir、peramivir、baloxavir
- 目前抗藥性病毒株並不常見，但仍需持續監測。如當年流行病毒株為H1N1，需留意NAIs抗藥性。如當年流行病毒株為H3N2，需留意Baloxavir抗藥性。
- 如出現抗藥性病毒株，可考慮新機轉抗病毒藥物或合併不同機制抗病毒藥物
- 流感疫苗注射才是最好的預防方法

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Q&A