流感流行病學與疫苗

2023.8.5

成大醫院感染科 李明吉

流感重症+23、死亡+3 病程最短當日死亡、最長達9天

葉立斌 報導

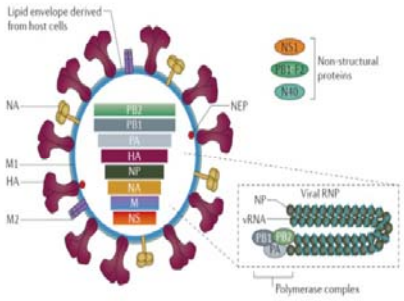
2023年8月1日 週二 下午5:56

https://tw.sports.yahoo.com/news/%E6%B5%81%E6%84%9F%E9%87%8D%E7%97%87-23-%E6%AD%BB%E4%BA%A1-3-%E7%97%85%E7%A8%8B%E6%9C%80%E7%9F%AD%E7%95%B6%E6%97%A5%E6%AD%BB%E4%BA%A1-095627474.html

流感病毒

流感病毒介紹

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



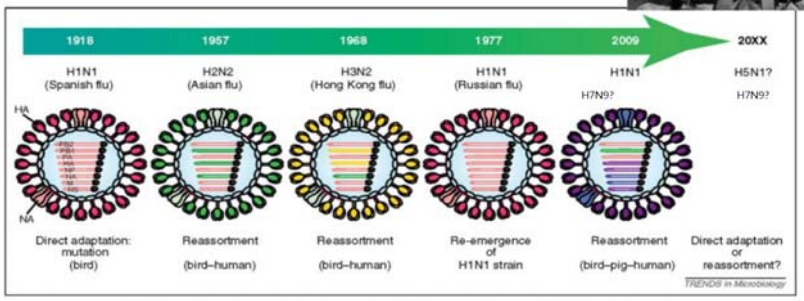
圖片來源：Nature Reviews Microbiology 9, 590-603 (August 2011)

3

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

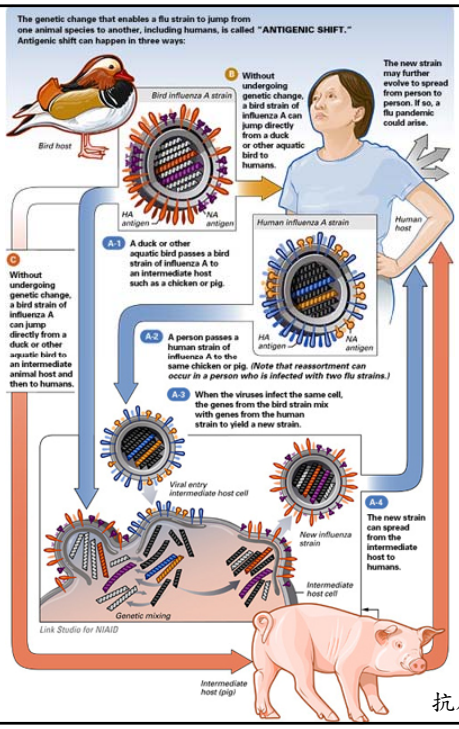
流感大流行的歷史

百年間主要之全球性大流行：



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)

5

流感病毒

流感病毒的變異

- 流感病毒的抗原變異主要分為下列二種
  - 抗原微變(Antigenic drift)：
    - 連續變異
    - 與地區性流行有關
    - HA(H1-18)或NA(N1-11)基因突變
  - 抗原移型(Antigenic shift)：
    - 不連續變異
    - 不同病毒株引發的基因重組, 不常發生
    - 與全球大流行有關
- 新型流感病毒株則是由突變和基因重組（Reassortment）產生

6

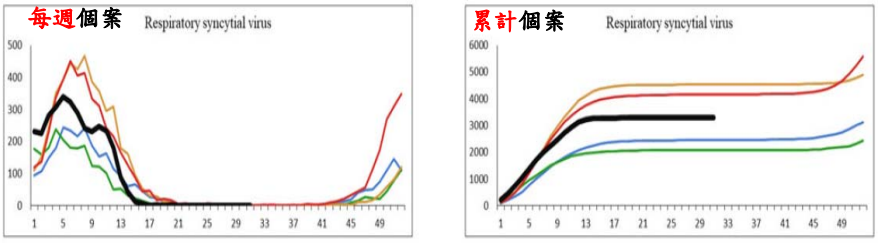
流行情形

- 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。
- 通常具有週期性，而臺灣雖然一年四季均有病例發生，但仍以秋、冬季較容易發生流行，高峰期多自12月至隔年3月
- 自2019年底COVID-19大流行後，南北半球國家均發現流感活動度顯著下降。在美國2020-21流感季節累計住院率為0.8例/10萬人口，2021-22流感季則為17例/10萬人口，但65歲以上長者及年齡小於5歲孩童仍為住院率較高族群。

疾病管制署 季節性流感防治工作手冊 2022 12月修訂

7

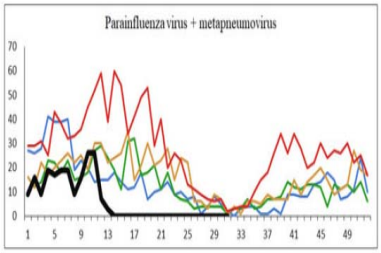
COVID-19 preventive measures coincided with a marked decline in other infectious diseases in Denmark, spring 2020

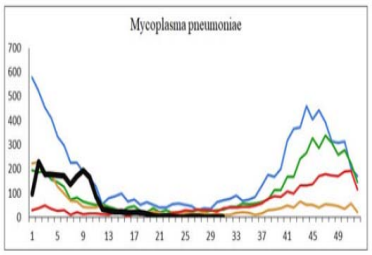


黑色：2020 其他色：2016~2019

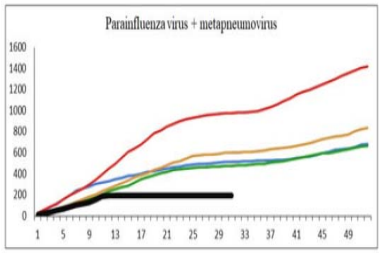
8

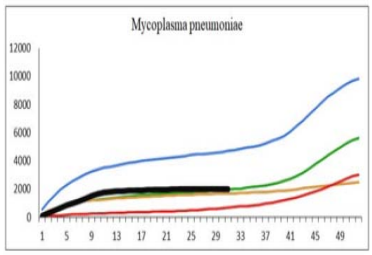
每週個案





累計個案

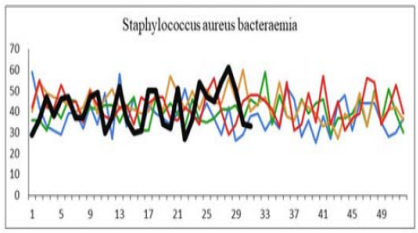


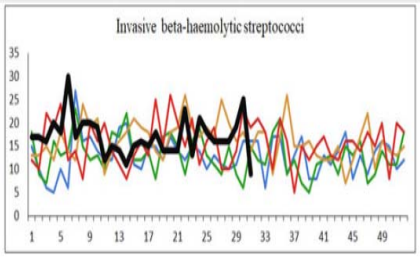


Epidemiol Infect 2022 Jul 28;150:e138

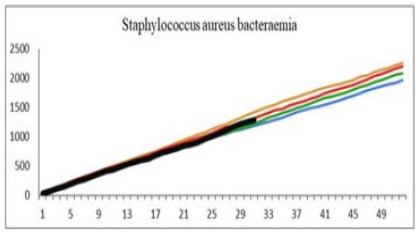
9

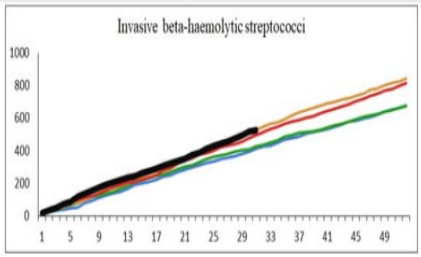
每週個案





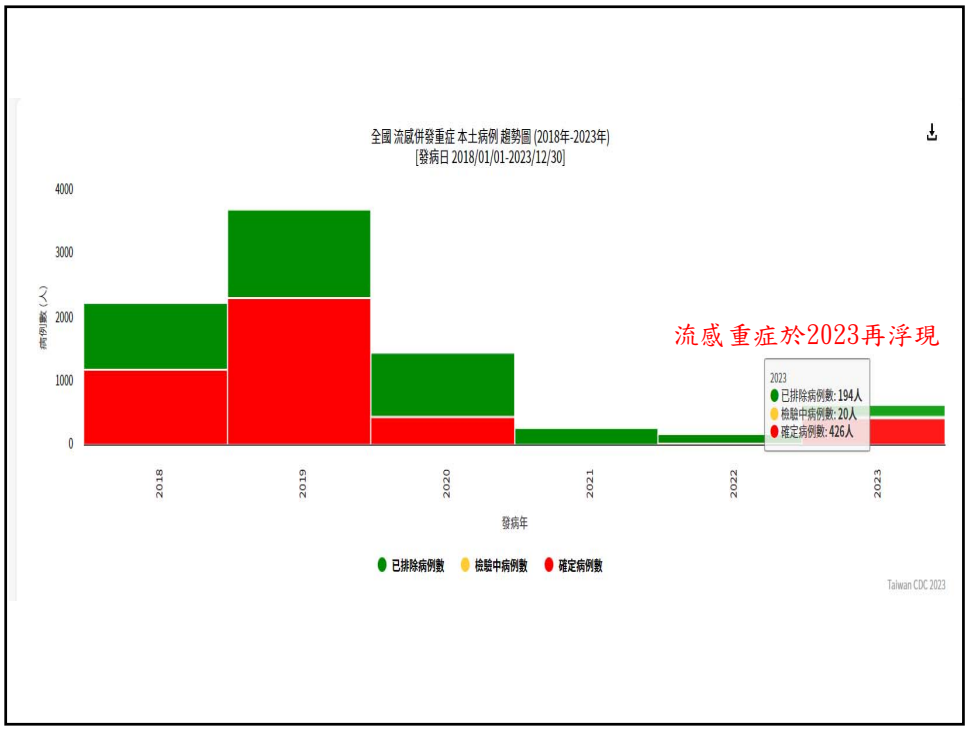
累計個案



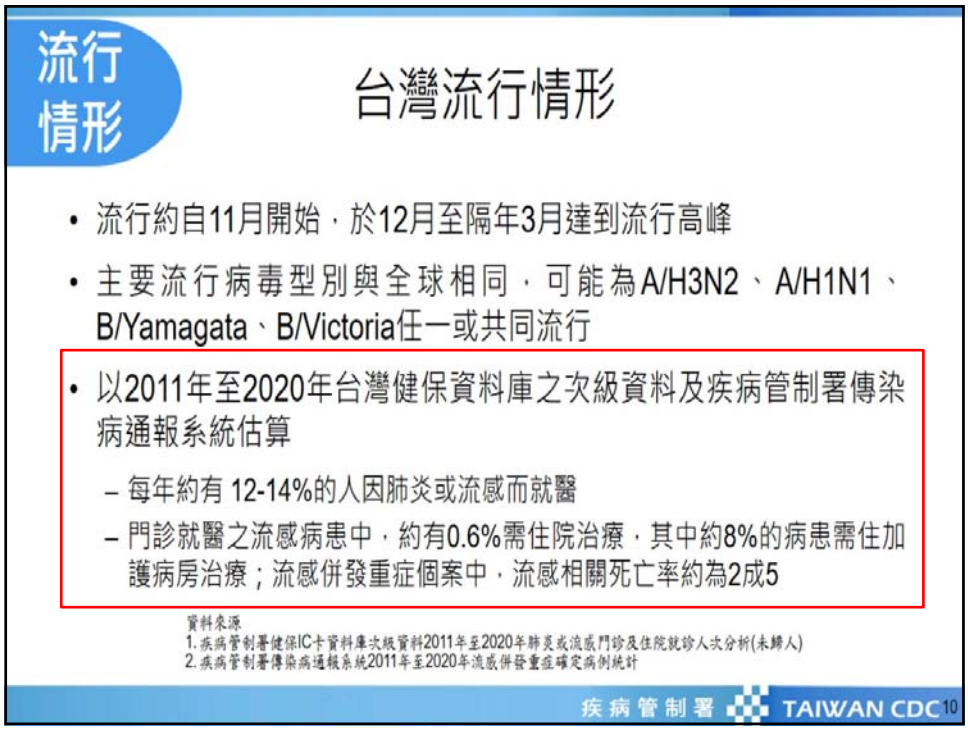


Epidemiol Infect 2022 Jul 28;150:e138

10


全國流感併發重症本土病例趨勢圖(2018年-2023年)
[發病日 2018/01/01-2023/12/30]
4000
3000
2000
1000
0
病例數（人）
2018
2019
2020
2021
2022
2023
發病年
2023
已排除病例數: 194人
檢驗中病例數: 20人
確定病例數: 426人
已排除病例數
檢驗中病例數
確定病例數
Taiwan CDC 2023
流感重症於2023再浮現

11


流行情形
台灣流行情形
• 流行約自11月開始，於12月至隔年3月達到流行高峰
• 主要流行病毒型別與全球相同，可能為A/H3N2、A/H1N1、B/Yamagata、B/Victoria任一或共同流行
• 以2011年至2020年台灣健保資料庫之次級資料及疾病管制署傳染病通報系統估算
– 每年約有12-14%的人因肺炎或流感而就醫
– 門診就醫之流感病患中，約有0.6%需住院治療，其中約8%的病患需住加護病房治療；流感併發重症個案中，流感相關死亡率約為2成5
資料來源
1. 疾病管制署健保IC卡資料庫次級資料2011年至2020年肺炎或流感門診及住院就診人次分析(未歸人)
2. 疾病管制署傳染病通報系統2011年至2020年流感併發重症確定病例統計
疾病管制署 TAIWAN CDC
10

12

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

13

14

衛生福利部疾病管制署

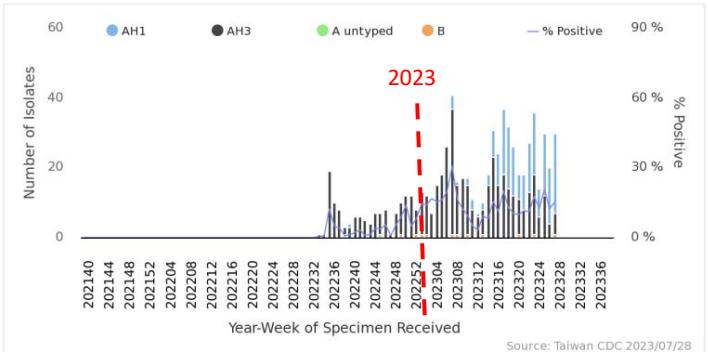
台灣流感速訊

2023年第30週 (2023/7/23－2023/7/29)

病毒性感染症合約實驗室監測

2023 年第 28 週流感病毒陽性率為 15.3%，近四週(2023 年第 25 週至第 28 週)流感病毒分離株型別及占比以 A/H1N1 (69.1%)為多，A/H3N2 (29.8%)次之。每週資料可參閱網站：傳染病統計資料查詢系統。

病毒性感染症合約實驗室 - 流感病毒分型趨勢



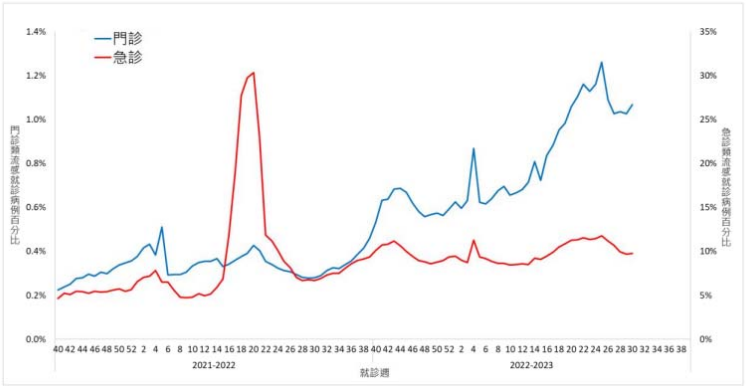
15

衛生福利部疾病管制署

台灣流感速訊

2023年第30週 (2023/7/23－2023/7/29)

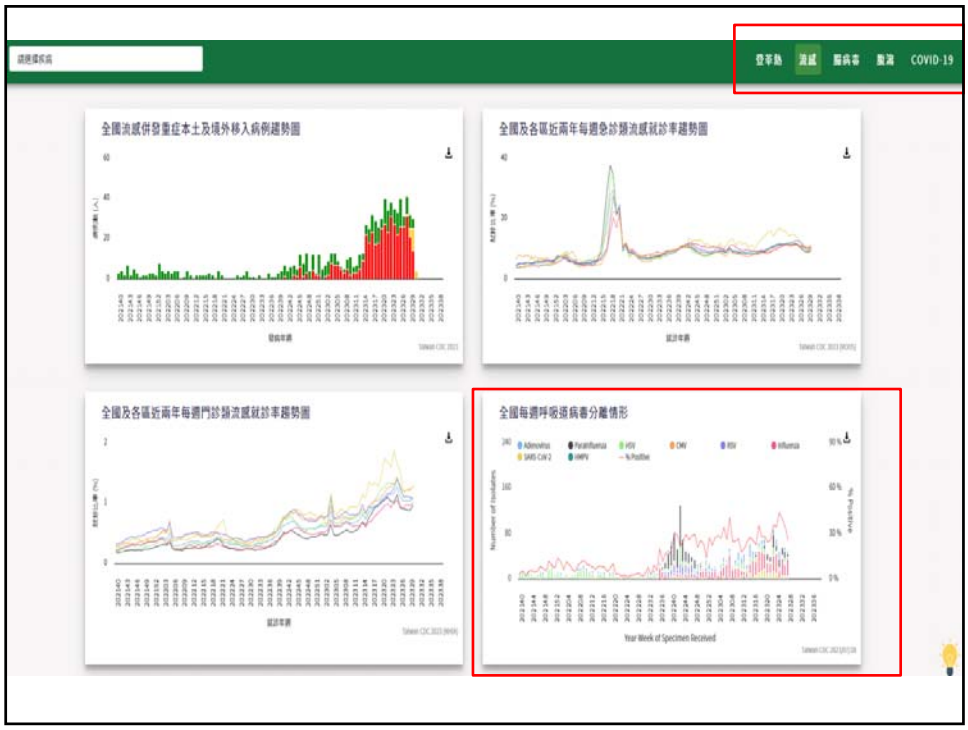
門診及急診類流感就診病例占比



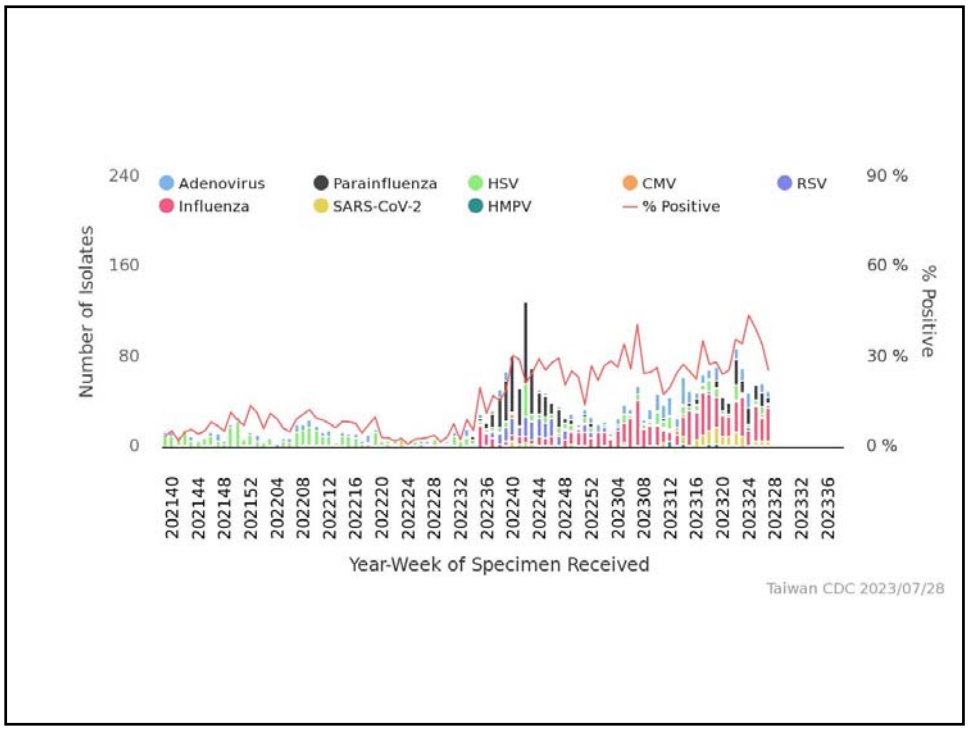
16


衛生福利部疾病管制署
關於CDC
傳染病與防疫專題
預防接種
國際旅遊與健康
通報
檢驗
宣導
統計專區
申請
«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
疫情監測速訊
愛滋病統計資料
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
疫情監測速訊
愛滋病統計資料

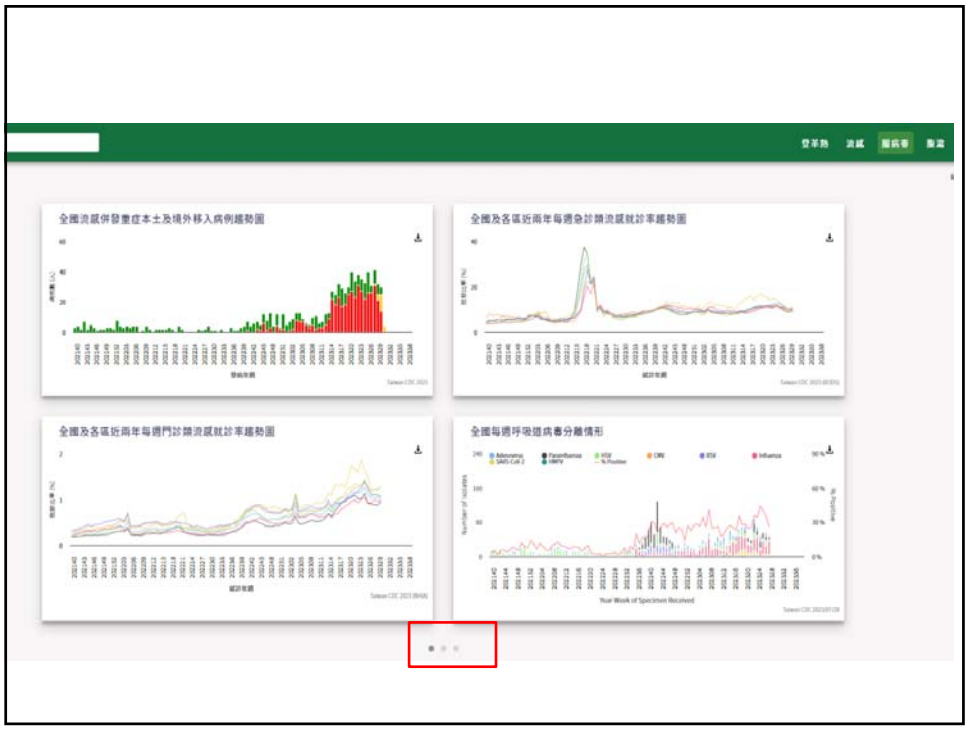
17


登革熱
流感
腸病毒
腸道
COVID-19
全國流感併發重症本土及境外移入病例趨勢圖
全國及各區近兩年每週急診類流感就診率趨勢圖
全國及各區近兩年每週門診類流感就診率趨勢圖
全國每週呼吸道病毒分離情形

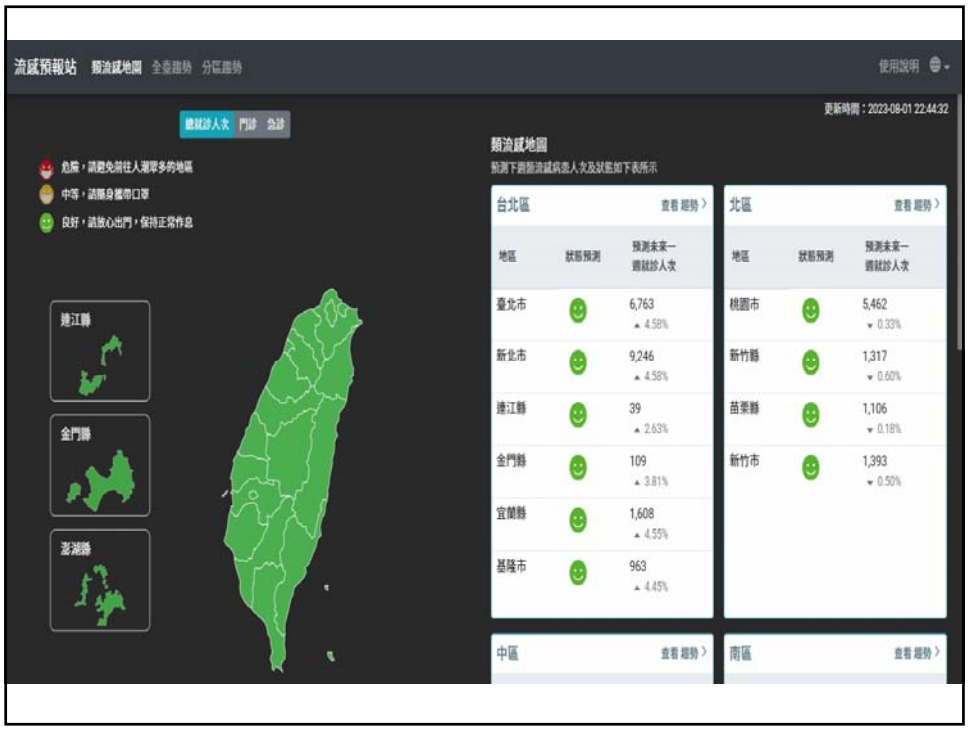
18


240
160
80
0
90 %
60 %
30 %
0 %
Adenovirus
Parainfluenza
HSV
CMV
RSV
Influenza
SARS-CoV-2
HMPV
% Positive
Number of Isolates
% Positive
202140
202144
202148
202152
202204
202208
202212
202216
202220
202224
202228
202232
202236
202240
202244
202248
202252
202304
202308
202312
202316
202320
202324
202328
202332
202336
Year-Week of Specimen Received
Taiwan CDC 2023/07/28

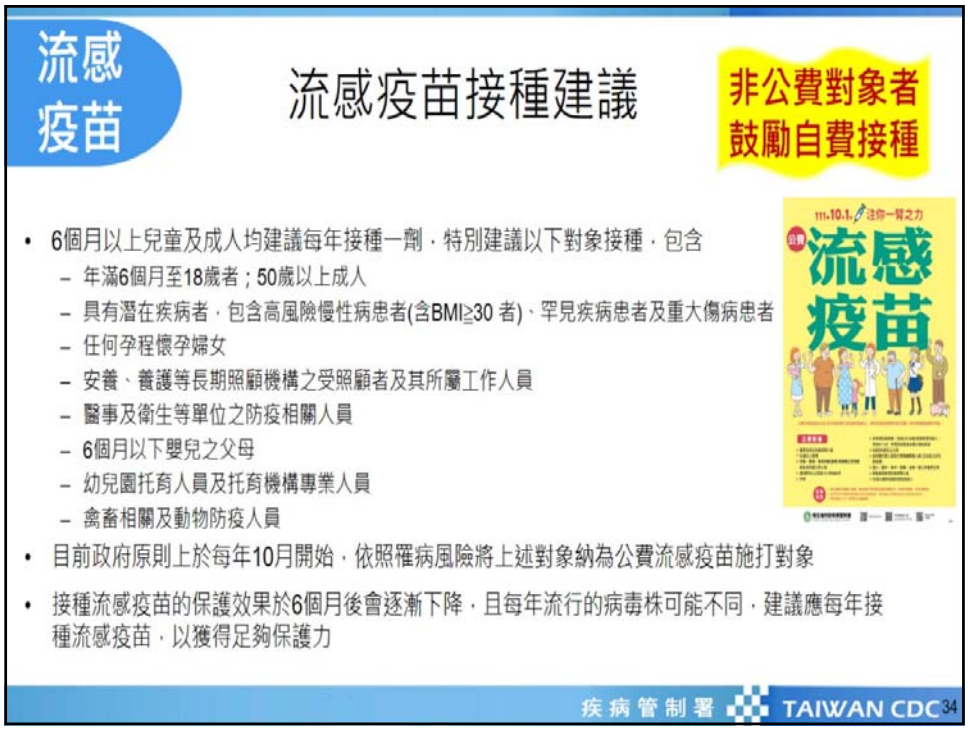
19


全國流感併發重症本土及境外移入病例趨勢圖
全國及各區近兩年每週急診類流感就診率趨勢圖
全國及各區近兩年每週門診類流感就診率趨勢圖
全國每週呼吸道病毒分離情形

20


流感預報站
類流感地圖
全臺趨勢
分區趨勢
使用說明
更新時間：2023-08-01 22:44:32
總就診人次
門診
急診
危險，請避免前往人潮眾多的地區
中等，請隨身攜帶口罩
良好，請放心出門，保持正常作息
連江縣
金門縣
澎湖縣
類流感地圖
預測下週類流感病患人次及狀態如下表所示
台北區
查看 趨勢
地區
狀態預測
預測未來一週就診人次
臺北市 6,763 ▲ 4.58%
新北市 9,246 ▲ 4.58%
連江縣 39 ▲ 2.63%
金門縣 109 ▲ 3.81%
宜蘭縣 1,608 ▲ 4.55%
基隆市 963 ▲ 4.45%
北區
查看 趨勢
地區
狀態預測
預測未來一週就診人次
桃園市 5,462 ▼ 0.33%
新竹縣 1,317 ▼ 0.60%
苗栗縣 1,106 ▼ 0.18%
新竹市 1,393 ▼ 0.50%
中區
查看 趨勢
南區
查看 趨勢

21


流感疫苗
流感疫苗接種建議
非公費對象者
鼓勵自費接種
• 6個月以上兒童及成人均建議每年接種一劑，特別建議以下對象接種，包含
– 年滿6個月至18歲者；50歲以上成人
– 具有潛在疾病者，包含高風險慢性病患者(含BMI≥30 者)、罕見疾病患者及重大傷病患者
– 任何孕程懷孕婦女
– 安養、養護等長期照顧機構之受照顧者及其所屬工作人員
– 醫事及衛生等單位之防疫相關人員
– 6個月以下嬰兒之父母
– 幼兒園托育人員及托育機構專業人員
– 禽畜相關及動物防疫人員
• 目前政府原則上於每年10月開始，依照罹病風險將上述對象納為公費流感疫苗施打對象
• 接種流感疫苗的保護效果於6個月後會逐漸下降，且每年流行的病毒株可能不同，建議應每年接種流感疫苗，以獲得足夠保護力
111.10.1. 注你一臂之力
公費
流感疫苗
疾病管制署
TAIWAN CDC
34

22

流感高危險族群 與 高傳播族群

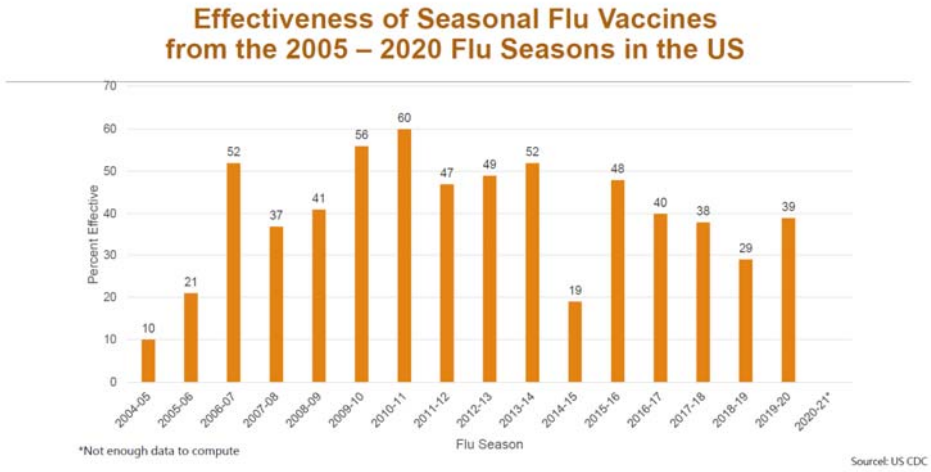
- 高危險族群係因自身免疫力關係，比非高危險族群有較多機會感染流感及出現嚴重併發症，包括有65歲以上長者、嬰幼兒、孕婦、免疫功能不全者，以及罹患氣喘、糖尿病、心血管、肺臟、肝臟、腎臟等疾病或BMI≧30者等。

- 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

23

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



24

流感疫苗

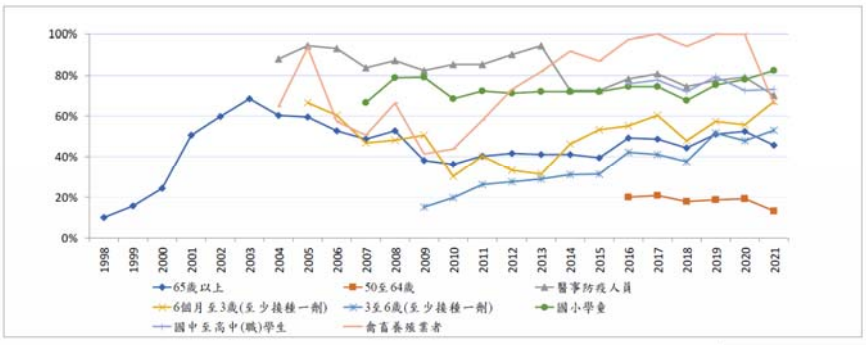
- 流感疫苗的保護力約6個月後會逐漸下降，必須每年接種1次。完整接種後至少約需2星期的時間可產生保護力。
- 對18歲以上成人需入住加護病房的流感重症保護力則可達82%。
- 6個月至未滿18歲兒童青少年族群接種流感疫苗之保護力與成人相仿，流感疫苗對健康兒童青少年因流感死亡的保護力約65%

疾病管制署 季節性流感防治工作手冊 2022 12月修訂

25

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

14

26

是否可和COVID-19疫苗一同接種？

- 流感疫苗是不活化疫苗，可以和其他疫苗同時接種於不同部位，或間隔任何時間接種。
  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。
  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

27

- 6個月以上接種劑量為0.5 mL（各家廠牌適用年齡不同，詳見仿單「產品說明書」）。
  未滿9歲兒童，若是初次接種，應接種2劑，2劑間隔4週以上每次接種0.5mL；若過去曾接種過季節性流感疫苗（不論1劑或2劑），今年接種1劑即可。
- 109年7月6日衛生福利部傳染病防治諮詢會預防接種組會議討論決議，需接種2劑之兒童，2劑可接種不同廠牌疫苗。

28

衛生福利部疾病管制署
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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

29

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

「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

30

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

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

31

衛生福利部疾病管制署
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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

32

衛生福利部疾病管制署
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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**

33

衛生福利部疾病管制署
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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**。

34

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

35

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

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

36

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

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)

37

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

38

醫療院所預防接種紀錄查詢子系統

39

CDC網站：流感疫苗資訊

40

結論

- 我國季節性流感高峰期：12月到隔年3月(近年常見流感型別：A/H3N2，2009A/H1N1，B)
- 可利用疾管署的資料查詢現今流感概況
- 流感病毒可感染各年齡層，疫苗為預防流感重症的最佳方式。

流感臨床診斷與檢驗

成大醫院 感染科
羅景霳

1

流感臨床診斷與檢驗

- 臨床表現
- 診斷工具
- 鑑別診斷

2

Case

80 years old

Fever with general weakness

- Runny nose
- Dry cough
- Mild dyspnea

3

Case

80 years old

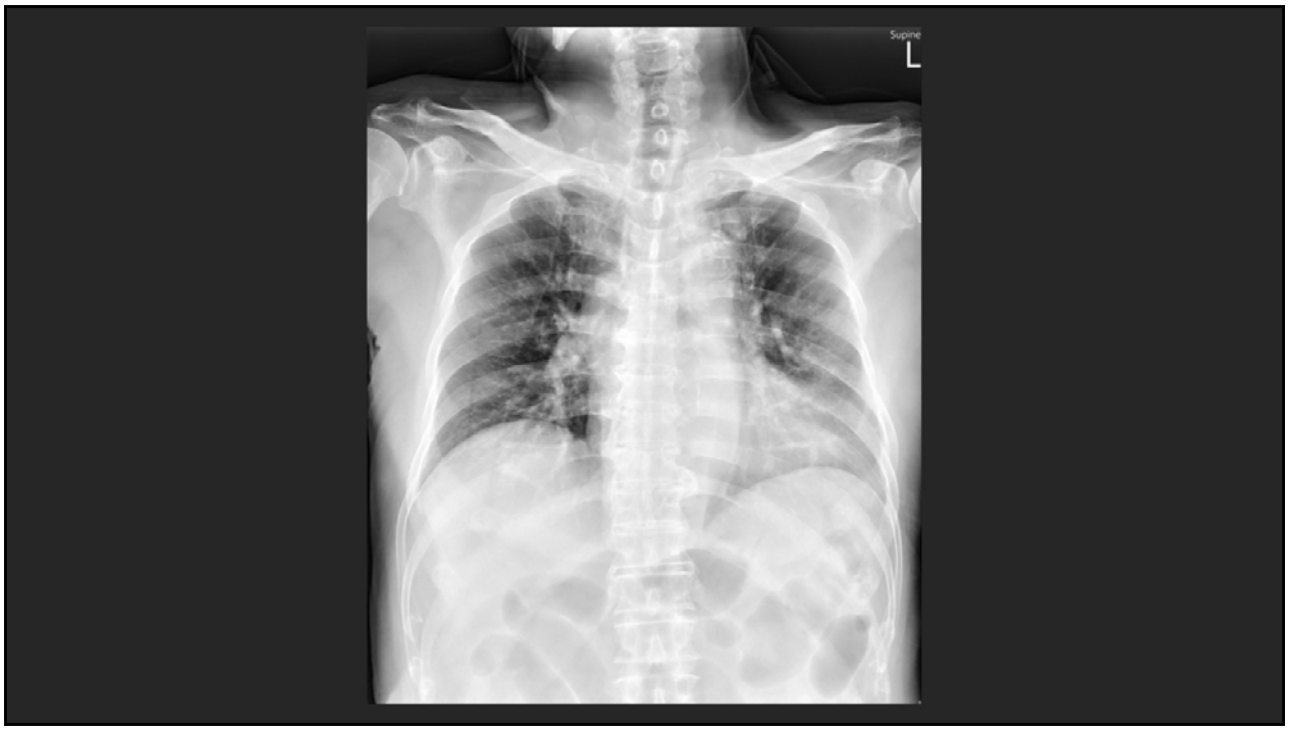
CBC

WBC	6200
Seg	73
Eos	0
Baso	0
Mono	19
Lymph	8
Hb	10.7
Plt	117000

BCS

Crea	1.18
Na	139
K	3.6
AST	67
ALT	66

4



5

是不是流感？

6

流感臨床表現

- Uncomplicated
- Complication

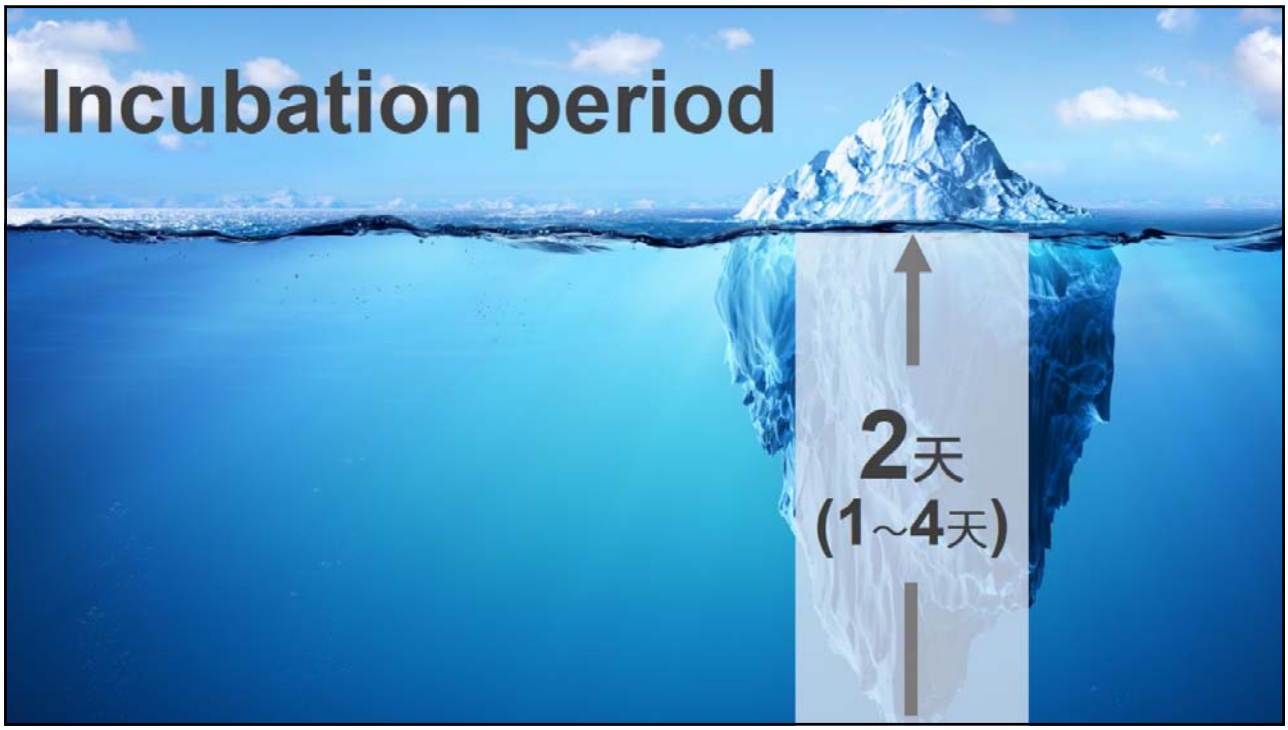
7

Uncomplicated influenza

Onset

Incubation | Disease period

8



9

Uncomplicated influenza

Onset

Incubation	Disease period
2天	3天 +數天

10

講到流感症狀

你會想到什麼?

11

Symptom — Uncomplicated influenza

- **Systemic symptom**
- Respiratory symptom

12

Systemic symptom

Uncomplicated influenza

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

13

Systemic symptom

Uncomplicated influenza

- Fever
  - Abrupt onset
  - 知道明確時間

14

Systemic symptom

Uncomplicated influenza

- Fever
  - 37.8~40.0°C

15

Systemic symptom

Uncomplicated influenza

- Fever
  - 37.8~41.1°C

16

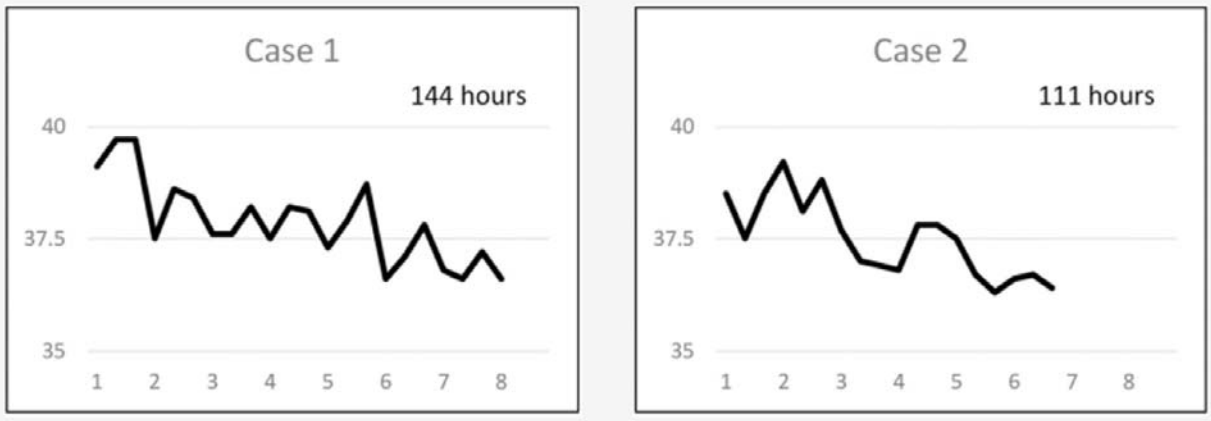
Systemic symptom

Uncomplicated influenza

- Fever
  - Highest on D1
  - 0.3~0.6°C lower afterward

17

Fever curve of influenza



PLoS ONE 14(11): e0224683

18

Systemic symptom

Uncomplicated influenza

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

19

Systemic symptom

Uncomplicated influenza

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

20

Systemic symptom

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

21

Respiratory symptom

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

22

Respiratory symptom

Uncomplicated influenza

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

不是變嚴重

23

Atypical Symptom

Uncomplicated influenza

- Age > 65 years old
- Immunocompromised

24

Atypical Symptom

Uncomplicated influenza

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

25

Atypical Symptom

Uncomplicated influenza

- Older adults
  - Altered mental status

26

流感和一般感冒差別

是較容易有併發症

27

Risk of complication

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

28

Risk of complication — Medical condition

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

29

Complication of influenza

- Respiratory
- Extrapulmonary

30

Respiratory complication

- Pneumonia

31

Symptom of pneumonia

- Cough with dyspnea
- Tachypnea
- Hypoxia
- Fever

32

Types of pneumonia

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

33

Types of pneumonia

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

34

Types of pneumonia

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

35

Types of pneumonia

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

36

Extrapulmonary complication

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

37

Extrapulmonary complication

- Cardiac
  - Myocardial infarction
  - Myocarditis/Pericarditis

38

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)

39

Case

80 years old

Fever with general weakness

- Runny nose
- Dry cough
- Mild dyspnea

40

Case

Influenza virus type A antigen Negative
Influenza virus type B antigen Negative

SARS-CoV-2 Ag（公費快篩-有症狀/醫用）
Negative

41

Case

Viral antigen detection-Dengue virus NS1Ag(登革熱病毒NS1抗原)
Positive

Dengue virus nucleic acid qualitative amplification test
Positive

DENV typing(登革熱病毒核酸)
Dengue virus type 1 detected

42

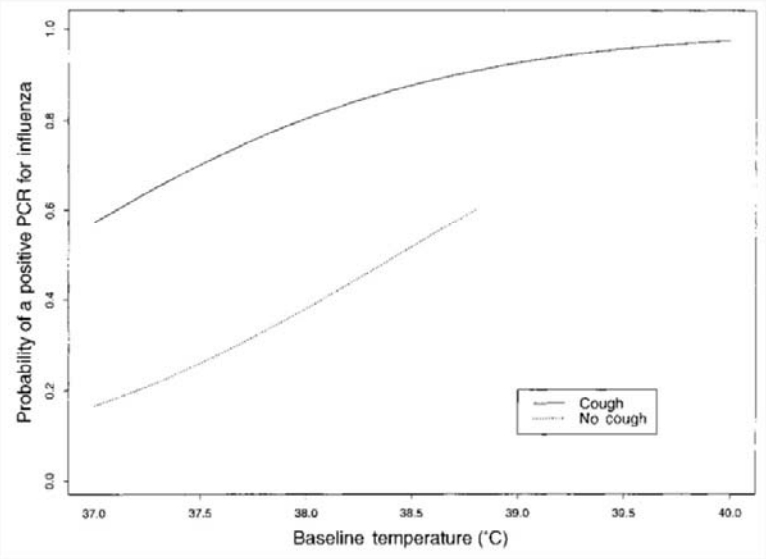
我去年是這麼提到

43

44

病史詢問與流感診斷

核酸陽性預測值



發燒
咳嗽

45

一年之後

我覺得是有前提的

46

只有流感在流行的前提

47

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

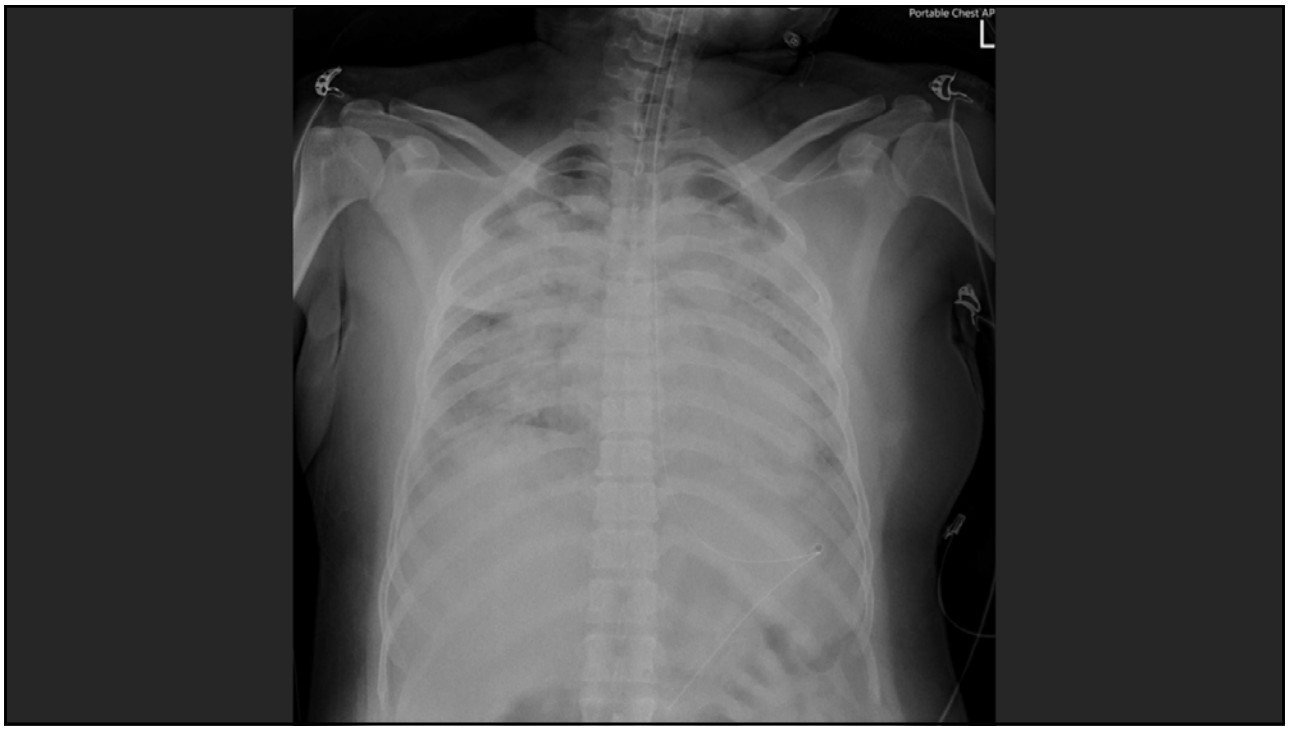
48

Case

42 years old

Cough with sputum and rhinorrhea for one week
Fever with chillness for 4 days
- Diarrhea

49



50

Case

42 years old

法定傳染病通報送檢檢驗報告
通報疾病: SARS-CoV-2病毒檢測
檢體種類: 鼻咽拭子/咽喉拭子
病原體檢驗方法:螢光定量聚合酶連鎖反應(real-time PCR)
檢驗結果: 陰性
綜合檢驗結果: 陰性
檢驗單位：國立成功大學醫學院附設醫院

Influenza virus type A+B antigen(酵素免疫法)(快診-流行感冒病毒A+B型抗原檢驗(酵素免疫法))
Influenza virus type A antigen Negative
Influenza virus type B antigen Negative

51

是不是流感？

52

診斷工具

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

53

什麼狀況下

你會想要做流感檢驗

54

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

55

Whom to test

原則

- If result will influence management
- Public health activity

56

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

57

Whom to test

原則

- Public health activity
  - Interventions for outbreak management

58

Whom to test

不同背景

- Influenza is circulating
- Influenza is not circulation

59

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

60

流行期間

有風險/症狀惡化可檢驗

61

Whom to test 不同背景

- Influenza is circulating
- Influenza is not circulation

62

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

63

非流行期間

要有曝觸才要驗

64

診斷工具

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

65

What to test

- Molecular assay
- Antigen detection assay
- Others

66

Molecular assay

What to test

- High sensitivity
- High specificity

67

Molecular assay

What to test

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

68

Conventional RT-PCR

Molecule

- Distinguish influenza A and B
- Influenza A subtype

- Turnaround time: 1-8 hours

69

Multiplex RT-PCR

Molecule

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

70

Filmarray respiratory panel

- Adenovirus
- Human Rhinovirus/ Enterovirus
- Influenza virus
- Respiratory syncytial virus
- Parainfluenza
- Human metapneuovirus
- Coronavirus
  - SARS-CoV-2
- Chlamydia pneumoniae
- Bordetella pertussis
- Bordetella parapertussis
- Mycoplasma pneumoniae

71

Rapid molecular tests — Molecule

- Distinguish influenza A and B
- No influenza A subtype

- Turnaround time: 15~30 min

72

What to test

- Molecular assay
- Antigen detection assay
- Others

73

Antigen detection assay

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

74

Antigen detection assay

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

75

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

76

What to test

- Molecular assay
- Antigen detection assay
- Others

77

Others

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

78

診斷工具

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

79

80

How to test

- 檢測時間點
- 採哪裡
- 用什麼採檢

81

檢測時間點

- Within four days of symptom onset

82

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

83

採哪裡

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

84

用什麼採

- Flocked swab

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

85

Case

42 years old

Rapid molecular test-Flu A
Positive

Viral nucleic acid detection-influenza A virus(病毒核酸檢驗-A型流感病毒)
Positive (H1),請確認是否通報流感併發重症

86

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

87

流感臨床診斷與檢驗

臨床表現

診斷工具

鑑別診斷

88

Case

26 years old

- Rheumatoid arthritis

89

Case

26 years old

Cough since last night

90

Case

26 years old

Cough since last night
- Fever
- Headache
- Chest pain
- Nausea/vomiting, diarrhea

91

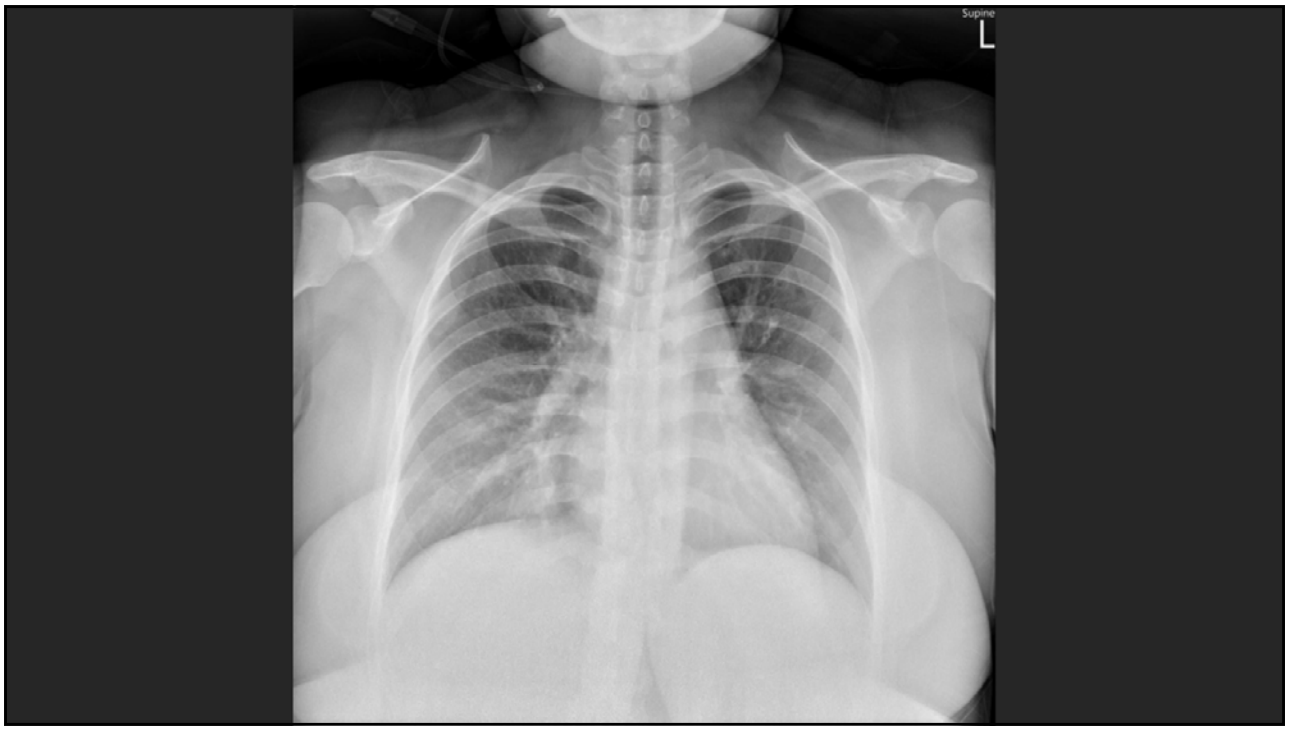
Case

26 years old

Cough since last night
- Fever
- Headache
- Chest pain
- Nausea/vomiting, diarrhea

Dyspnea with desaturation

92



93

是不是流感？

94

鑑別診斷

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

95

Respiratory viral infection

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

96

COVID-19

鑑別診斷

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

97

COVID-19

鑑別診斷

- Diagnosed by antigen / PCR

98

Respiratory syncytial virus — 鑑別診斷

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

99

Respiratory syncytial virus — 鑑別診斷

- Diagnosed by PCR

100

Common cold

鑑別診斷

- Several virus
  - Rhinovirus
  - Parainfluenza
  - Common cold coronavirus

101

Common cold

鑑別診斷

- Mild symptom than influenza
- Nasal congestion milder

102

Common cold

鑑別診斷

- Diagnosis by clinical manifestation

103

MERS-CoV

鑑別診斷

- History of Arabian peninsula

104

MERS-CoV

鑑別診斷

- Diagnosis by PCR

105

Novel influenza A virus

鑑別診斷

- Symptom not distinguish from seasonal influenza A

106

Novel influenza A virus 鑑別診斷

- Exposure history
- Travel history

107

Novel influenza A virus 鑑別診斷

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

108

Novel influenza A virus 鑑別診斷

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

109

Novel influenza A virus 鑑別診斷

- Diagnosis by PCR

110

Bacterial pneumonia

鑑別診斷

- Complication of influenza
- Infection alone

111

Bacterial pneumonia

鑑別診斷

- Complication of influenza
  - initial improvement
  - relapse of fever and productive cough

112

Bacterial pneumonia

鑑別診斷

- Fever
- Dyspnea
- Cough
- Sputum production

113

Case

26 years old

Influenza virus type A+B antigen(酵素免疫法)(快診-流行感冒病毒A+B型抗原檢驗(酵素免疫法))
Influenza virus type A antigen Positive
請確認是否通報流感併發重症
Influenza virus type B antigen Negative

SARS-CoV-2 Ag（公費快篩-有症狀/醫用）
Positive

114

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

115

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。

116

COVID-19 疫情下針對流感等呼吸道重症之照護

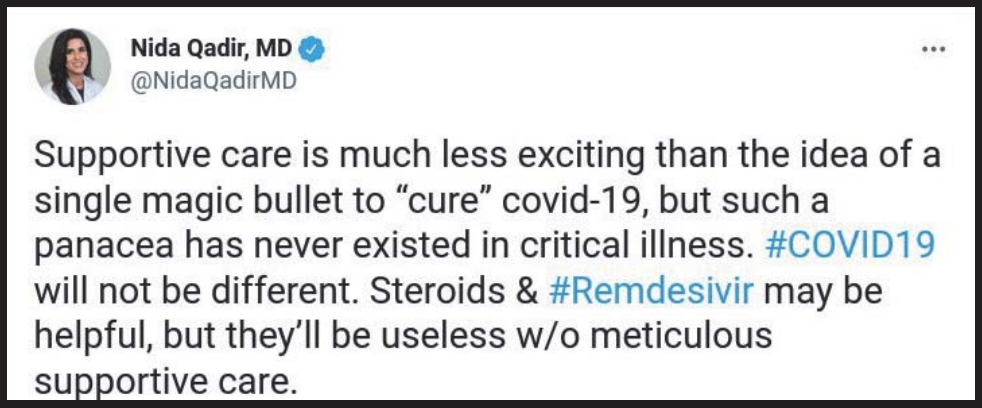
謝宗達

成大醫院 重症加護科 / 感染管制中心

Aug 05, 2023

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 24 版 . 2023-07-28.

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

Rapid antigen test 敏感度 60-90% ，
如陰性但臨床有仍有懷疑請驗核酸。

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

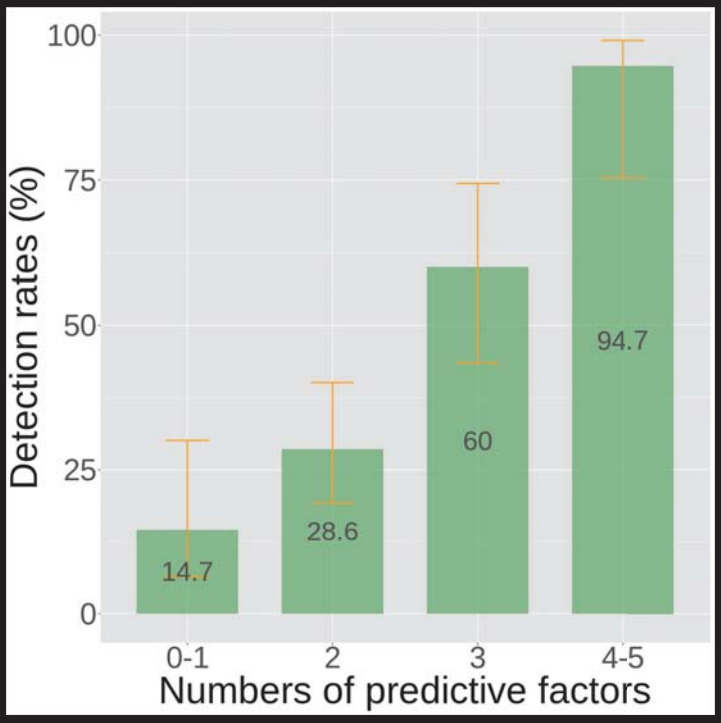
Site of Virus Detection	SARI, *n* = 45 (%)	Non-SARI, *n* = 213 (%)
Nasopharyngeal swab	32 (71)	133 (62)
TA	36 (80)	136 (64)
Exclusive nasopharyngeal	9 (20)	77 (36)
Both nasopharyngeal/TA	23 (51)	56 (26)
Exclusive TA	13 (29)	80 (38)

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？

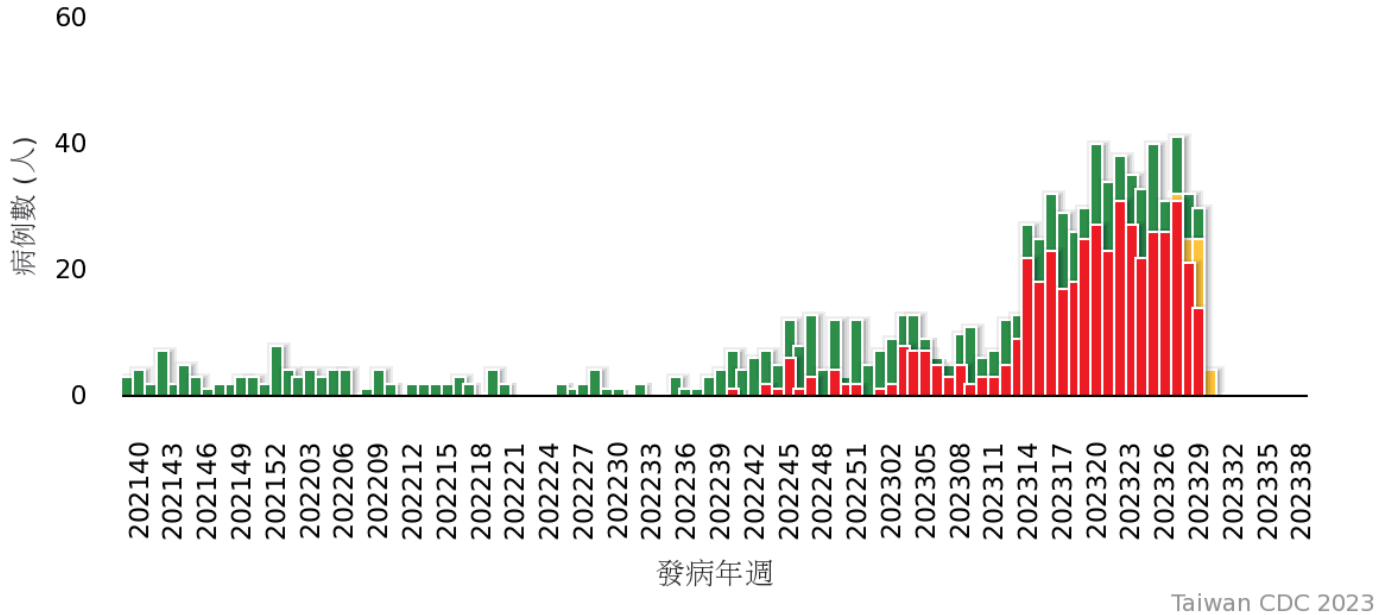
Predictive factor	Odds Ratio
Age < 65 years	3.98
Clustered URI	3.93
Fever	2.89
Cough and sputum production	3.24
Sore throat	3.70



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

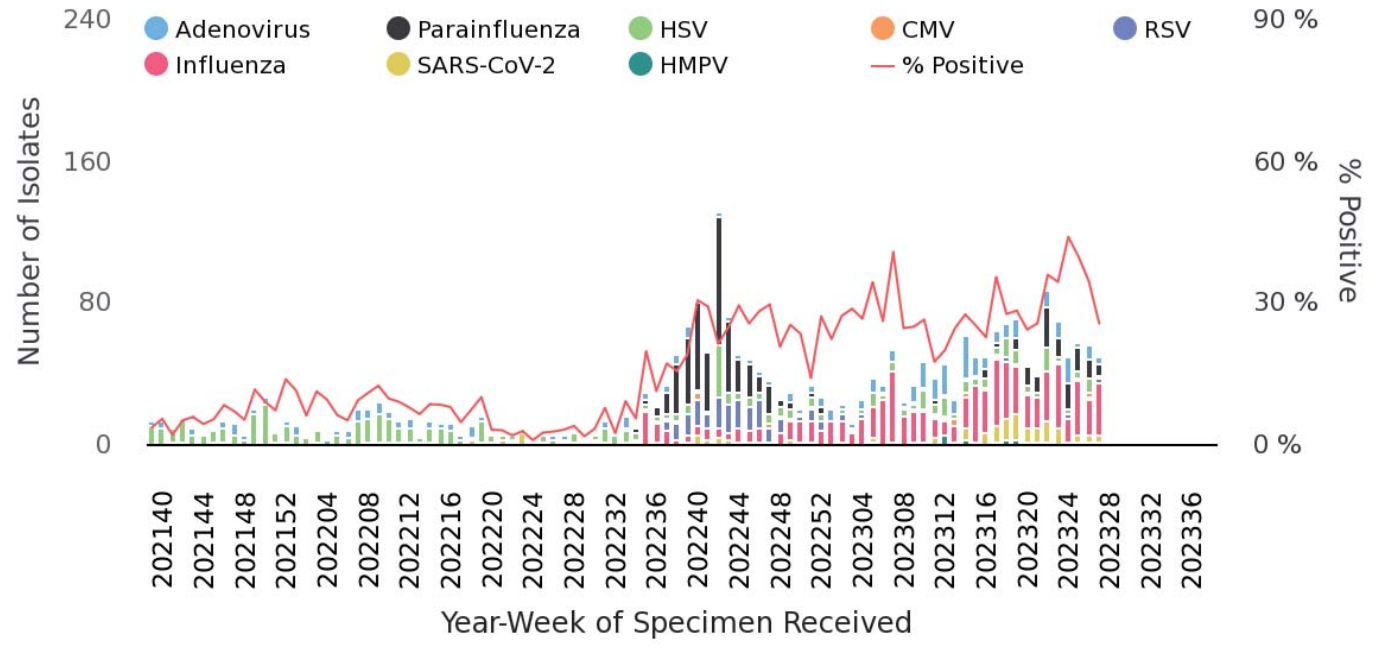
感染症：流行什麼很重要

流感併發重症今年已經不少



Taiwan CDC 2023

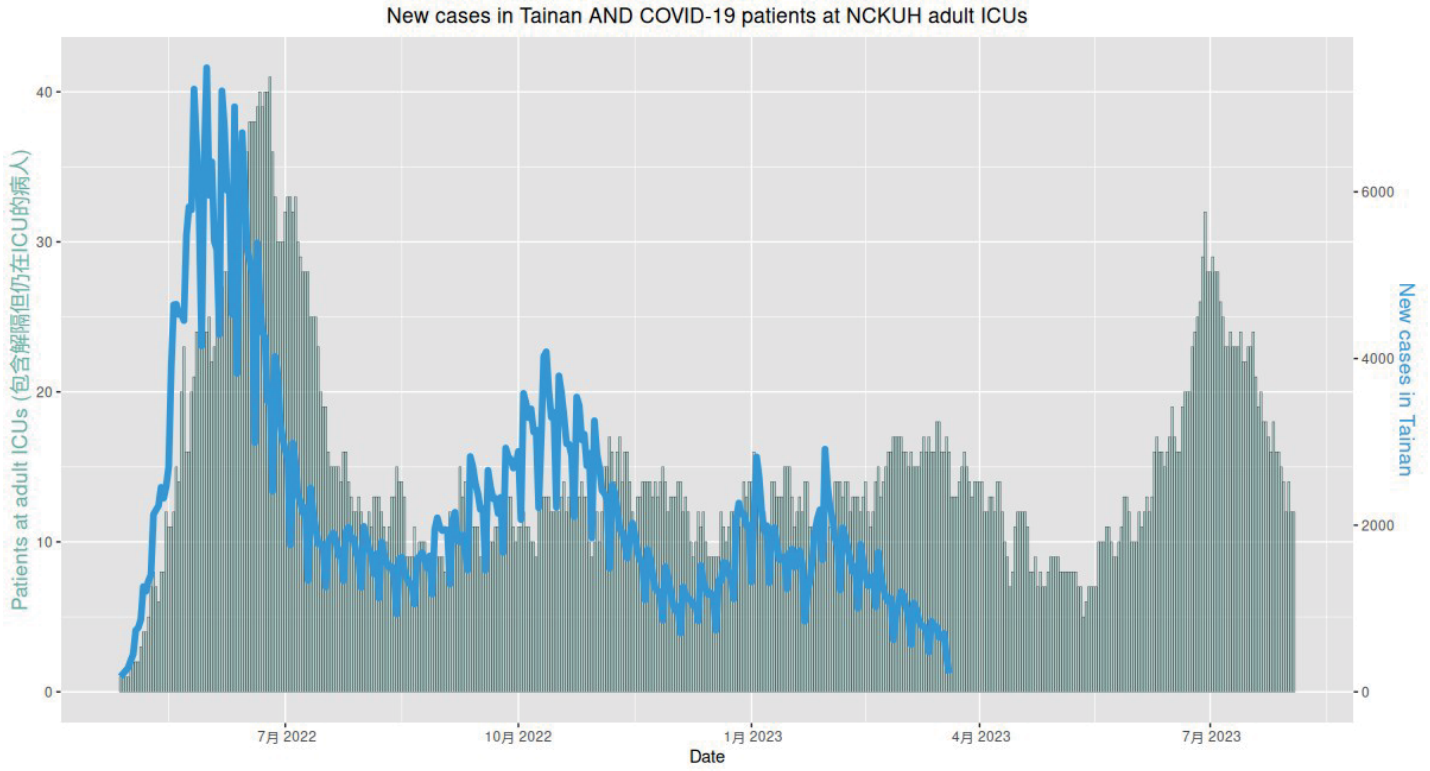
https://nidss.cdc.gov.tw/



Taiwan CDC 2023/07/28

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

台南與成大醫院 ICU COVID-19 人數

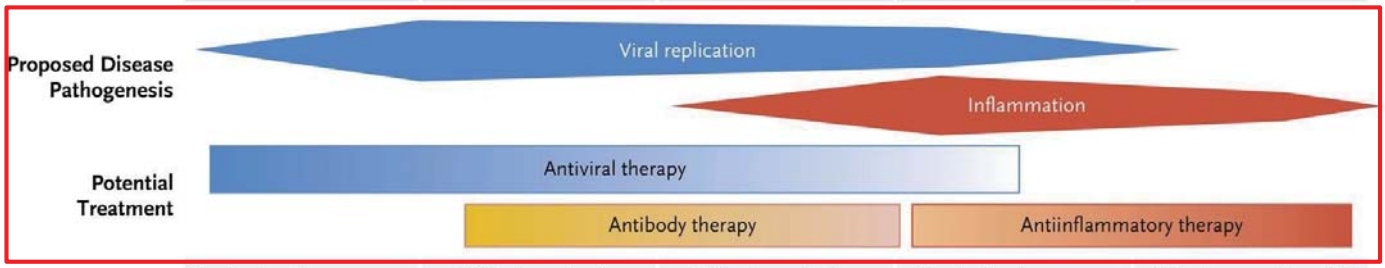


Cia CT.

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



	Asymptomatic or Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical Illness
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)

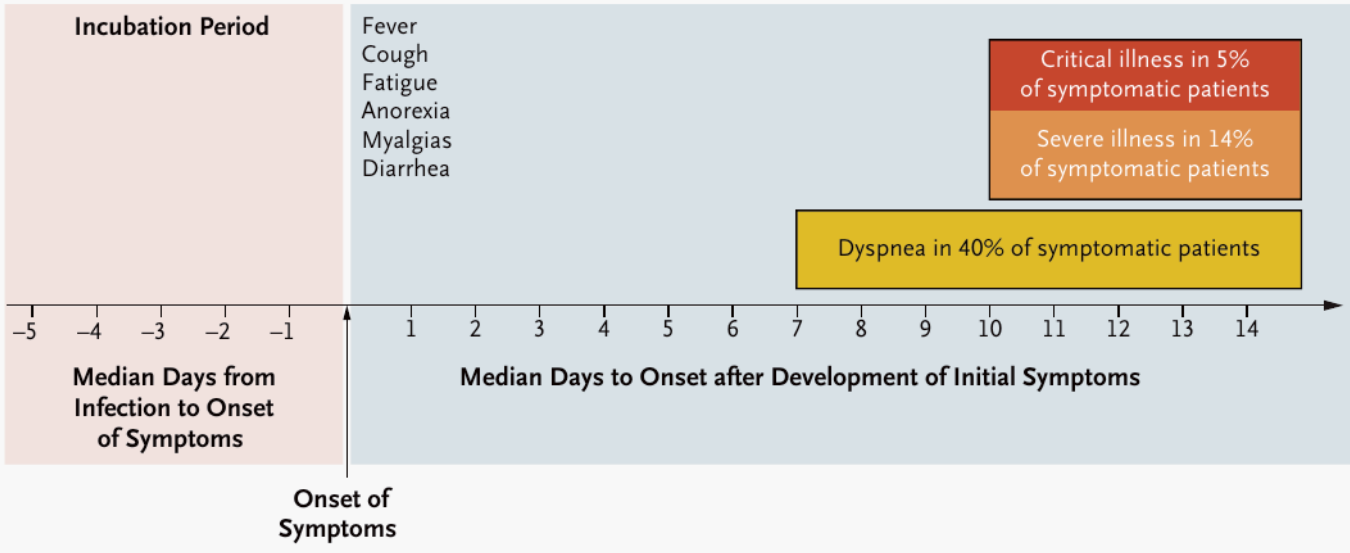
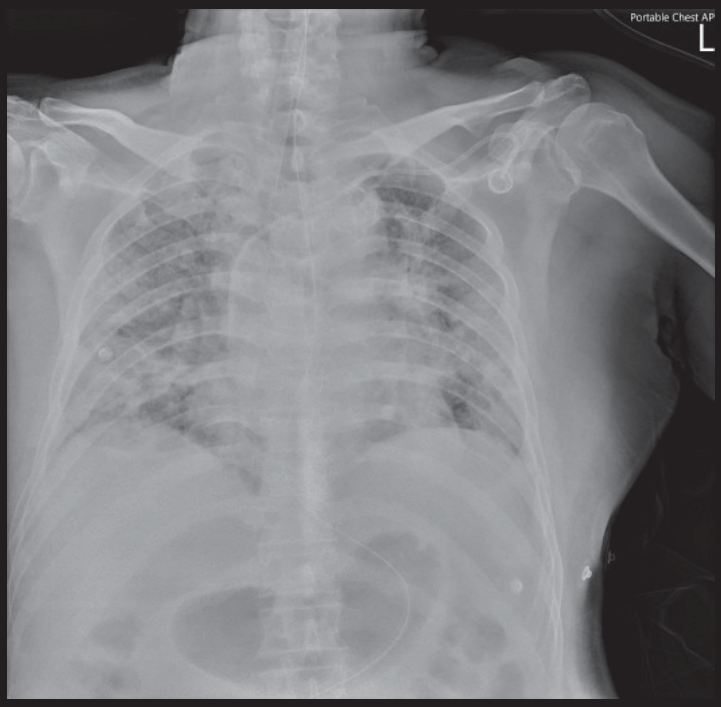


Figure 1. Timeline of Symptoms of Severe Coronavirus Disease 2019 (Covid-19).

~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.

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 台灣插管重症病人樣態
TSCCC study – 24 間醫院 , n=609

- Mean age 66.8 y
- Male sex 66%
- DM 35.7%
- HTN 54.0%
- Vasopressor 62.7%
- RRT 12.4%
- Prone position 23.5%
- ECMO 2.3%
- ARDS 77%
- AKI 36.1%
- Pul. embolism 2.8%
- Myocarditis 0.5%
- 28-d mortality 26.9%
- In-hospital mortality 36.8%
- MV duration 17.3 d

Kao KC. TSCCC study results (unpublished). https://www.youtube.com/watch?v=YACvQb9FQV0

A study at 20 French ICUs, 2021-2022 Omicron variant, n = 148 (Delta n = 111)

- Mean age 63.9 y*
- Male sex 71.6%
- DM 34.7%
- HTN 51.4%
- Immunosuppresion 43.2%*
- Bacterial co-infection 12.5%
- Pulmonary embolism 4.8%
- Vasopressor 40.4%
- RRT 16.9%
- Invasive MV 46.62%
- Prone positioning 36.8%
- ECMO 6.08%
- MV duration 12.5 d*
- D-28 mortality 35.1%
- ICU stay 11 d

de Prost N. *Nat Commun*. 2022;13(1):6025.

ICUs of the APHP, France, 2021-2022 Omicron variant n=229 (Delta n = 400)

- Median age 63 y; Male sex 67.2%
- Immunocompromised 34.5%*
- Onset to ICU < 5d 22.7%
- Pneumonia 67.2%*
  - Vaccinated 62.1%
  - Unvaccinated 80.7%
- Invasive MV 41.0%*
- In-ICU mortality 20%

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

OVID-19 omicron variant
重症病人死亡率

法國 AP-HP ICUs	成大醫院 2022.05-2023.04
n = 229	n = 357
Median age 63 y	Median age 74 y
Mechanical ventilatoin 41%	Mechanical venilation 64%
ICU mortality	ICU mortality
20.0%	17.1%

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

插管使用侵入式呼吸器 (IMV) 病人
Alpha v.s. Omicron variant in Taiwan

台灣 TSCCC 2021	成大醫院 2022.04-2023.05
Alpha variant	Omicron variant
Mean age 66.8 y	Mean age 72.4 y
In-hospital mortality	In-hospital mortality
36.8%	33.9%

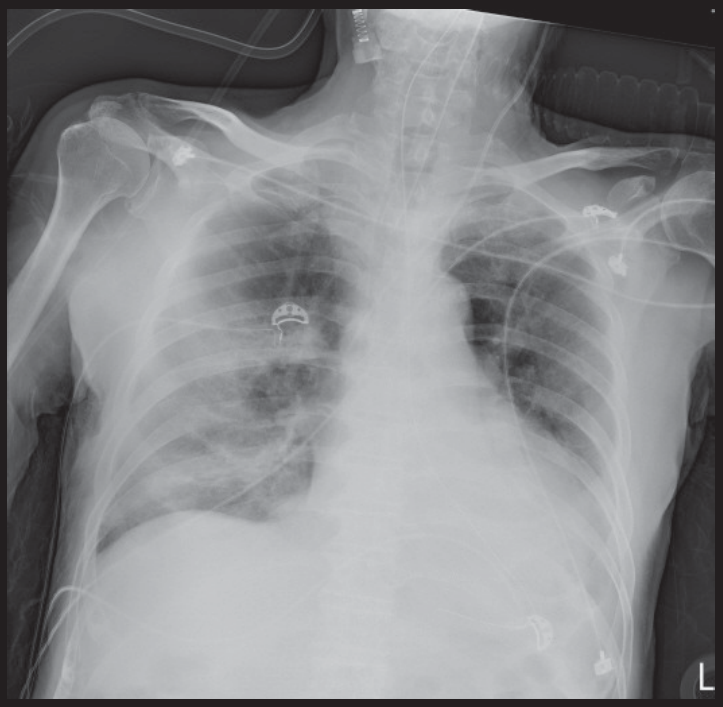
Kao KC. TSCCC study results (unpublished). https://www.youtube.com/watch?v=YACvQb9FQV0
Cia CT. Unpublished data.

Characters of critically ill adults with COVID-19 at NCKUH, Apr-Aug 2022, n = 204

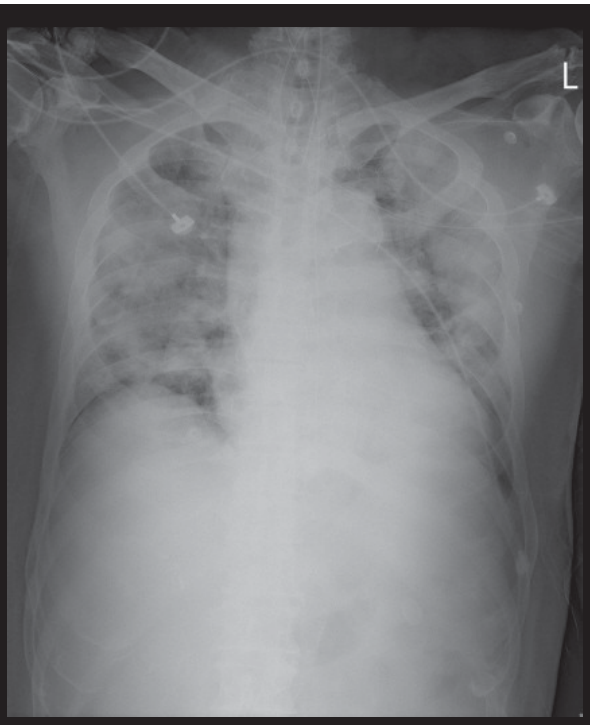
Pneumonia upon ICU admission	108	(52.9%)
Typical COVID-19 pneumonia	40	(19.6%)
Acute decompensated heart failure	49	(24.0%)
Acute coronary syndrome	16	(7.8%)
Acute exacerbation of COPD or asthma	9	(4.4%)
ICU admission due to other causes	52	(25.5%)

Cia CT. Unpublished data.

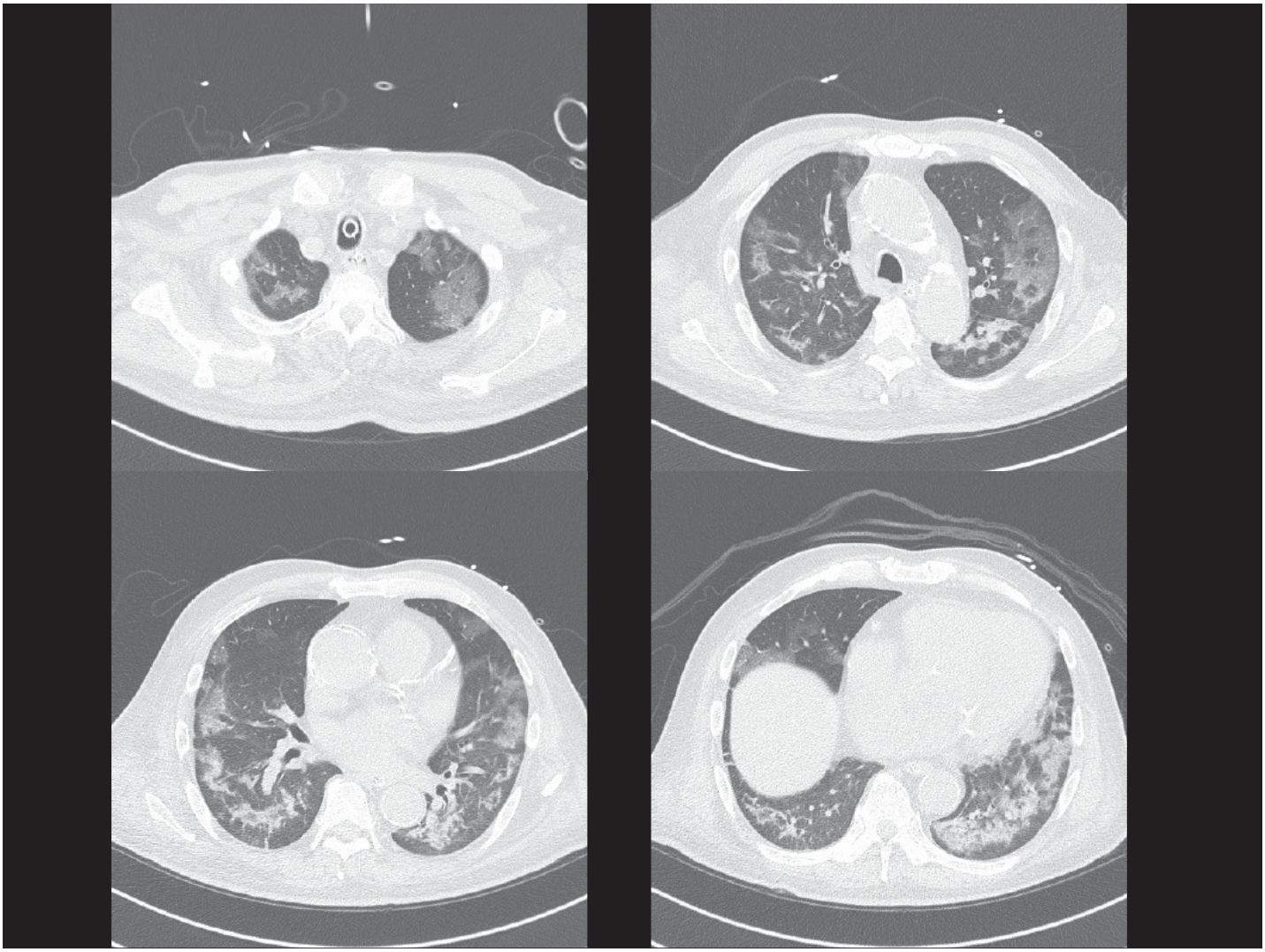
典型的武漢肺炎

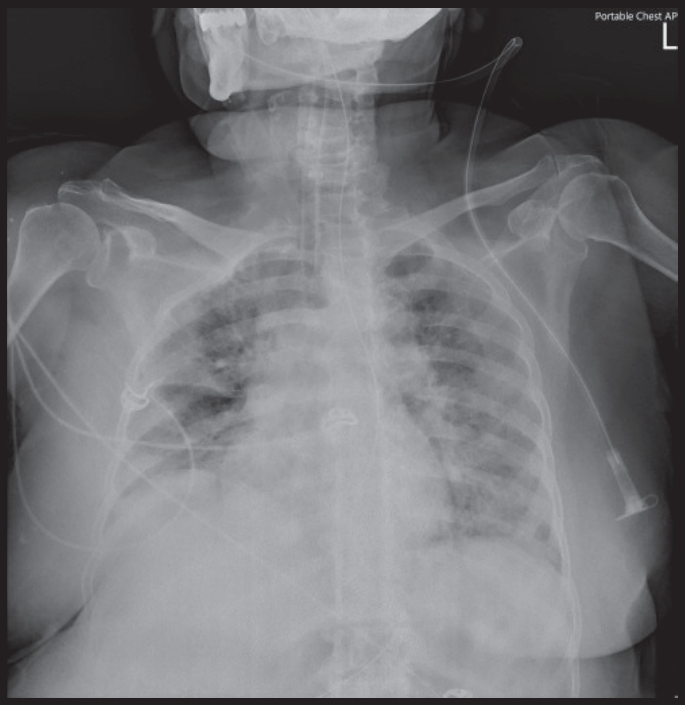


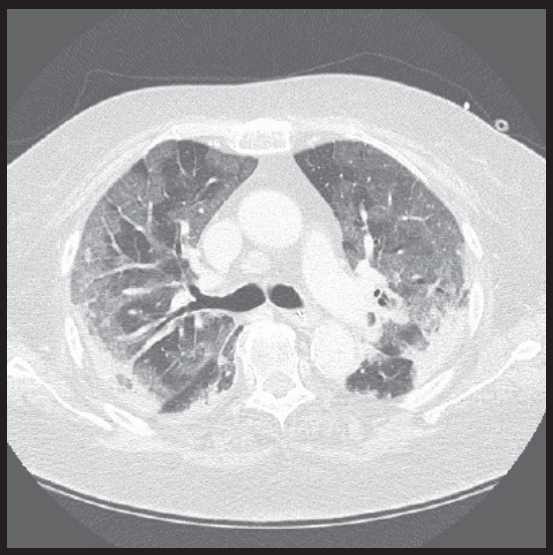
78M. HTN. CKD. Old SAH. Vaccine x0
SARS-CoV-2 Ag+ on 5/21. Dyspnea on 5/29.



69M. ESRD on HD. HTN. DM. Vaccine x0
Chest tightness. Dyspnea. STEMI.
COVID-19 pneumonia.







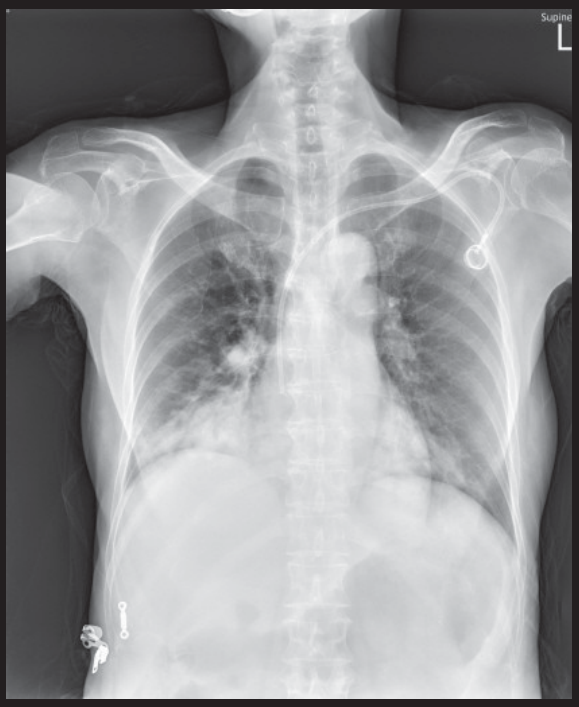
76F. CKD. HTN. DM. Dyslipidemia. Vaccine x1. Sore throat initially. Dypsnea & weakness one week later. Worse respiration for two days. SARS-Cov-2 Ag-, ETA Ct 27.5

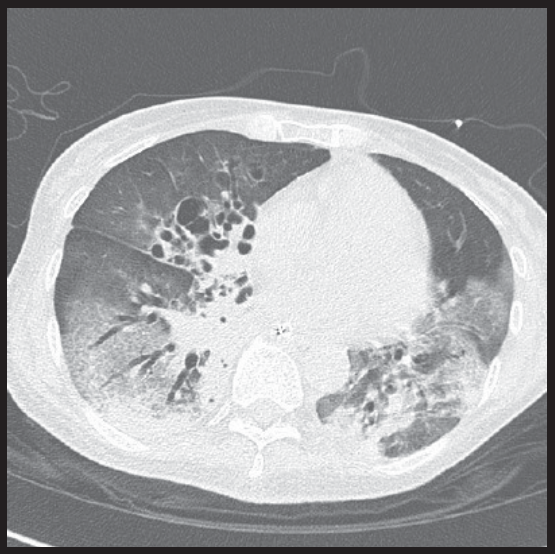
Typical presentation of COVID-19 pneumonia on CXR

- 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%).

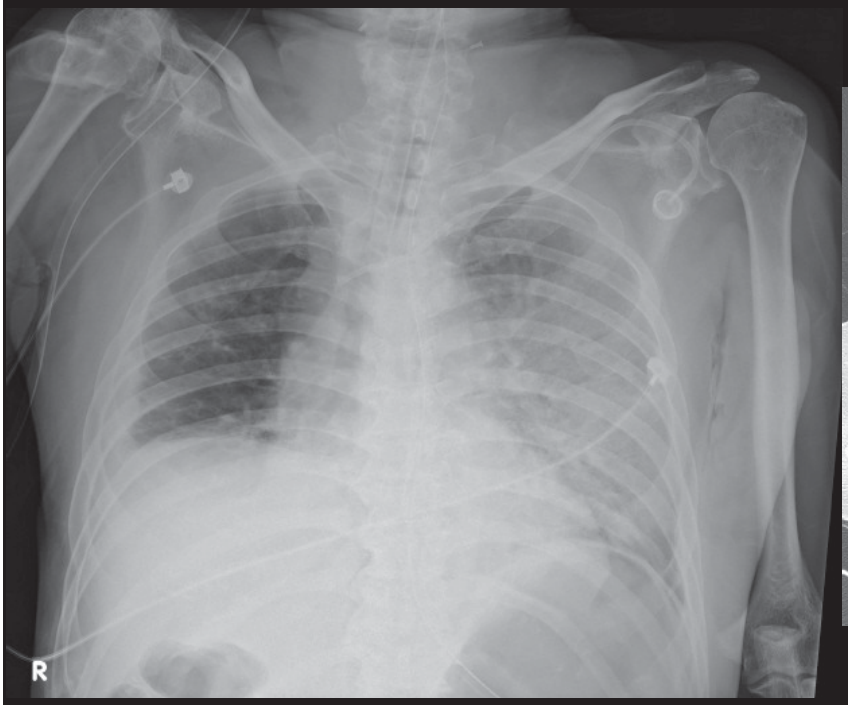
https://radiopaedia.org/articles/covid-19-4

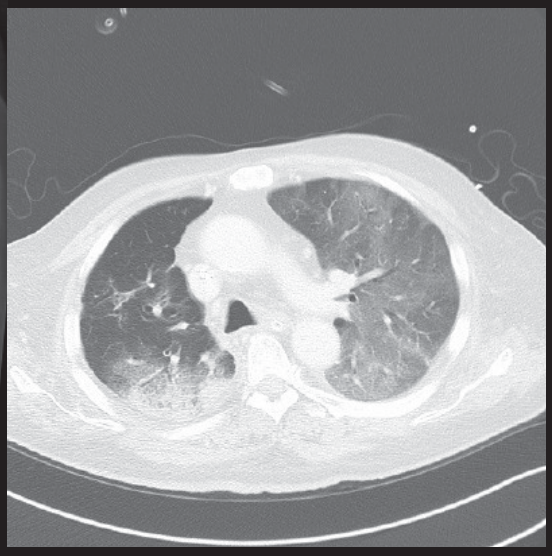
COVID-19 合併其他肺部感染





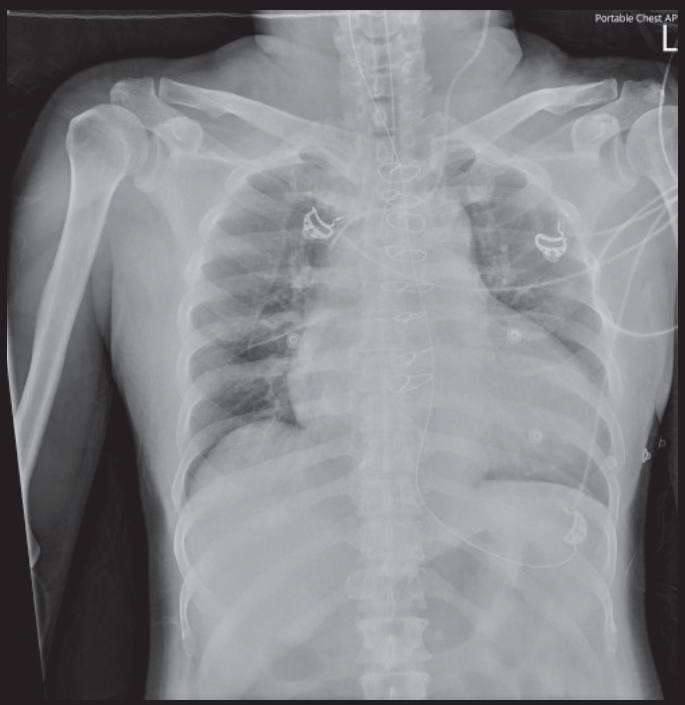
60 F. Cervical ca. DM. Depression.
Fever. Dyspnea.
SARS-CoV-2 & *Streptococcus pneumoniae* pneumonia





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

Prevalence of cardiovascular manifestations among patients with COVID-19

- Myocardial injury
  - 住院病人 15-42%
  - Associated with death
- Acute coronary syndrome
  - Case series
  - Cohort study including 924 patients with STEMI
  - 3% in pts having TTE
- Arrythmias
  - 住院病人 10-30%
  - ICU 病人 30-50%
- Cardiomyopathy / AHDF
  - 住院病人 23-25%
  - TTE: LV 39%, RV 33%, myocarditis 3%, takotsubo 2%

Fauvel C. *Respir Med Res*. 2022;81:100904.
Maitz T. *Curr Probl Cardiol*. 2022;101186.
Dweck MR. *Eur Heart J Cardiovasc Imaging*. 2020;21(9):949-958.

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，藥物交互作用多
- Molnupiravir (Lagevrio®)
  - 口服 5 天，效果較差
  - 腎臟不好可用
- Remdesivir (Veklury®)
  - 靜脈注射 x3 天
  - 腎臟不好可用
- 單株抗體：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 + baricitinib OR tocilizumab

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

請先確定真的是武漢肺炎

- 典型的 COVID-19 pneumonia 發生在開始有症狀之後的第 2 週，所以剛發病沒幾天就來住 ICU 的，不是 COVID-19 pneumonia 。
- COVID-19 pneumonia 專屬的治療 (dexamethasone, tocilizumab, baricitinib) ，都真的是在處理第 2 週以發炎為主的 COVID-19 pneumonia ，還沒發生或根本沒有 COVID-19 pneumonia 就用，只是讓病人增加併發症的風險而沒有好處。

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

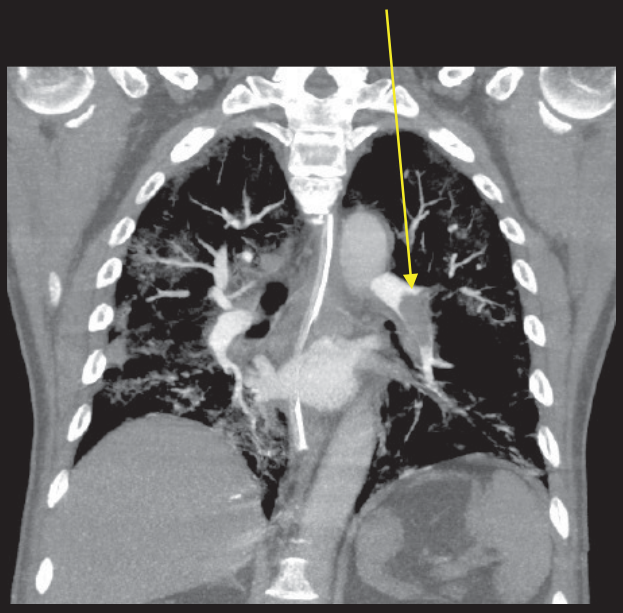
- 肺炎但不像武漢肺炎
  - 太早 (5 日內) 出現
  - 黃痰
  - 影像不典型
- 休克需使用高劑量生壓劑，須懷疑非呼吸道感染

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

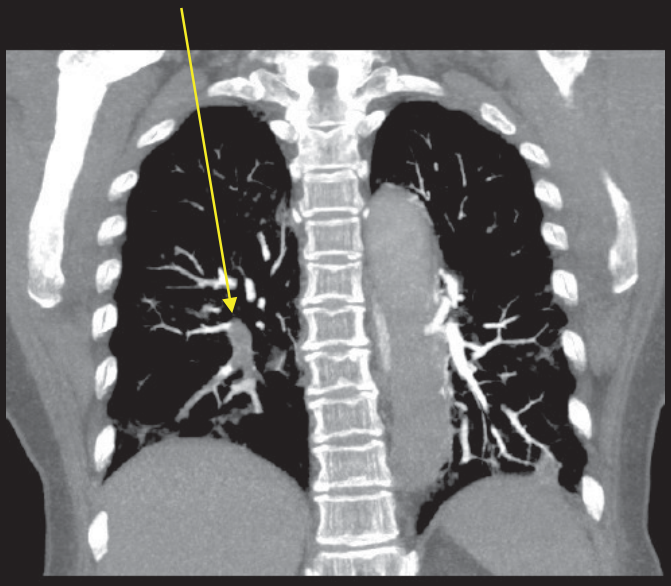
All VTE	Pulmonary embolism
14.3 –27.9%	8.6–24.7%

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 with pulmonary embolism



66M. HTN.
CAPA+



70F. HTN.
CAPA+

如果要做 chest CT ，就直接排 CT angiogram 吧

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.

VAP after COVID-19 is very common in french ICUs

Number of VAP episodes	All patients (n=259)	Delta (n=111)	Omicron (n=148)
0	42 (33.07%)	16 (26.67%)	26 (38.81%)
1	42 (33.07%)	22 (36.67%)	20 (29.85%)
2	28 (22.05%)	10 (16.67%)	18 (26.8%)
3	15 (11.81%)	11 (10.09%)	3 (4.48%)
CAPA	18 (7.06%)	11 (10.09%)	7 (4.79%)

CAPA: COVID-19 associated pulmonary aspergillosis

de Prost N. *Nat Commun*. 2022;13(1):6025.

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).

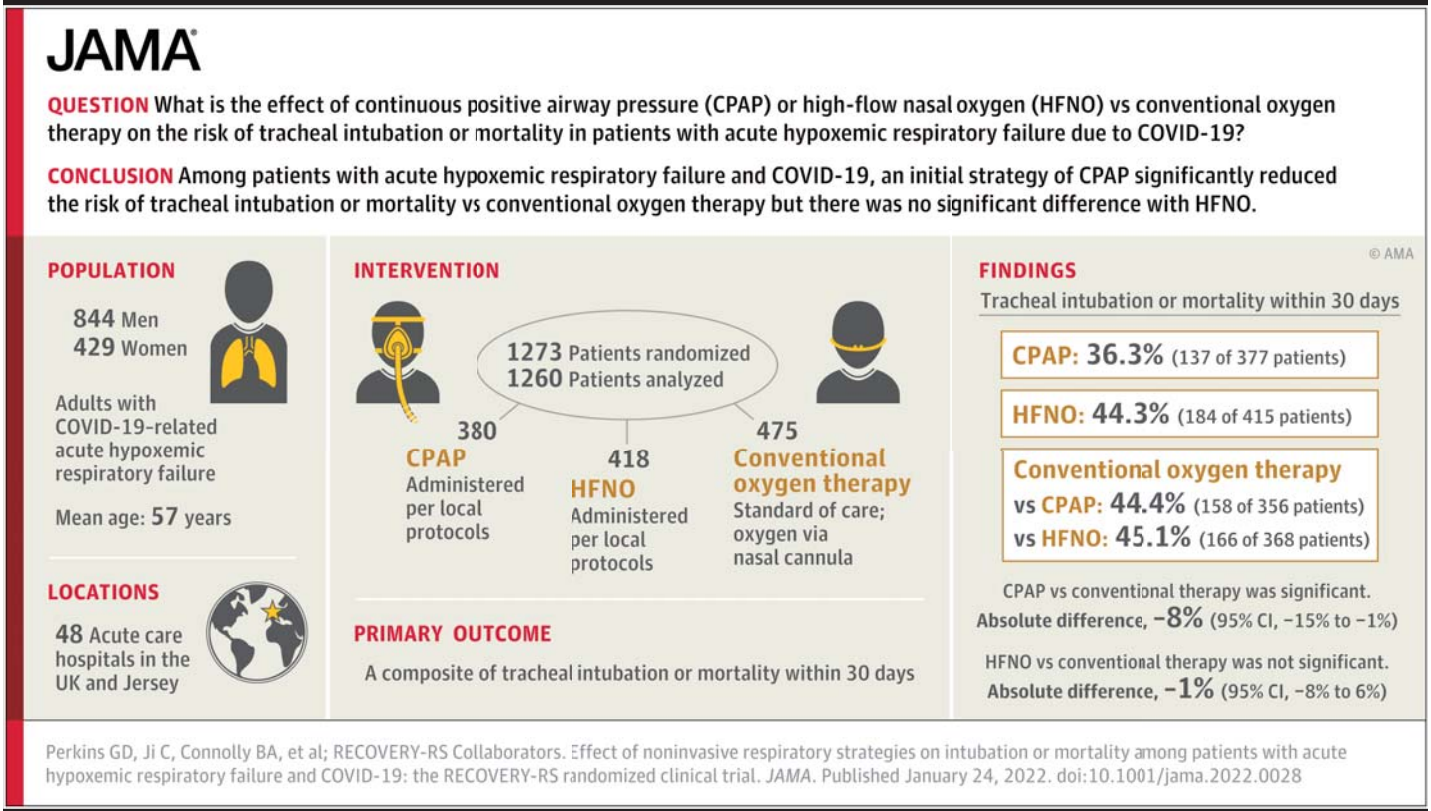
NIH. COVID-19 Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/

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.

NIV v.s. HFNC v.s. 一般給氧 (COVID-19)



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*. 2023;78(4):354-361.

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

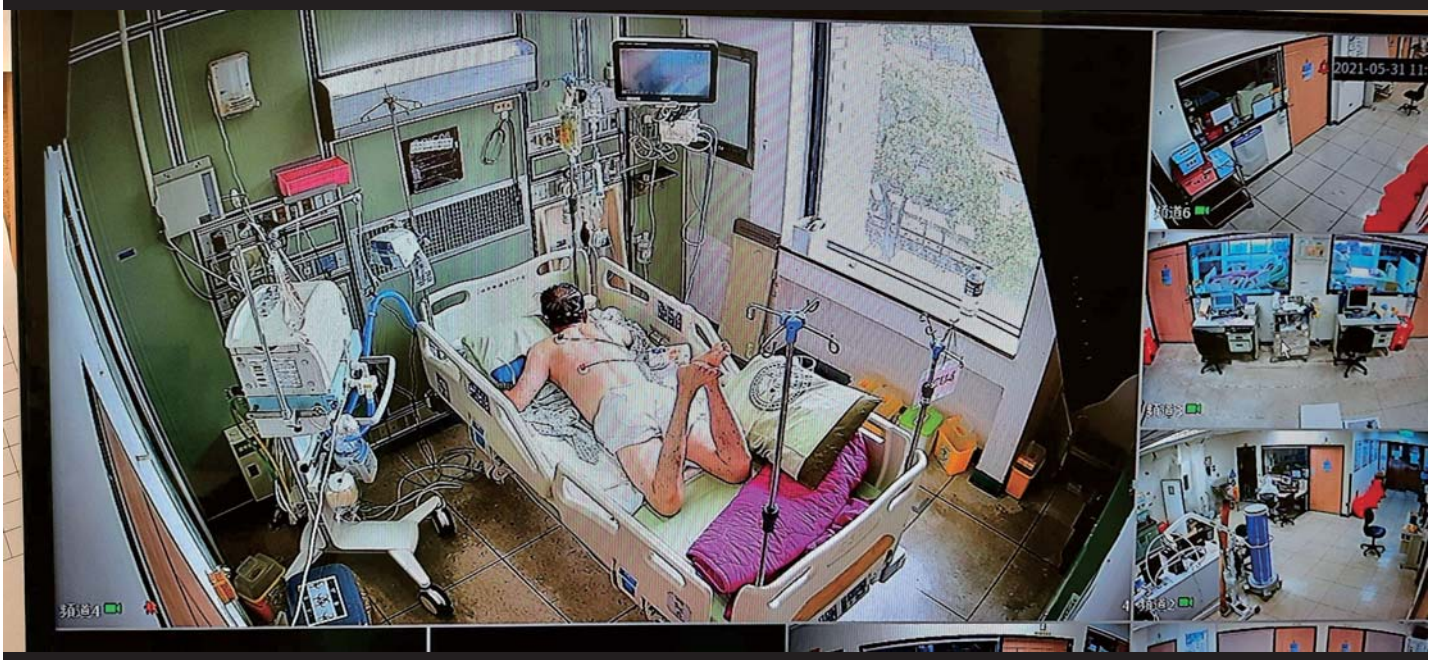
NIH 建議：還沒面臨插管的病人可嘗試

Ehrmann S. *Lancet Respir Med*. 2021;9(12):1387-1395.

Alhazzani W. *JAMA*. 2022;327(21):2104-2113.

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 病人通氣策略和一般重症病人相同

- 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)
- 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。
- 中度或重度 ARDS 患者，建議使用較高的 PEEP ，不建議常規使用 NMBA 持續輸注。
- 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。

新型冠狀病毒 (SARS-CoV-2) 感染臨床處置指引 . 第 24 版 . 2023-07-28.

之前的 PPE

2021

2022

2023 的 COVID-19 PPE

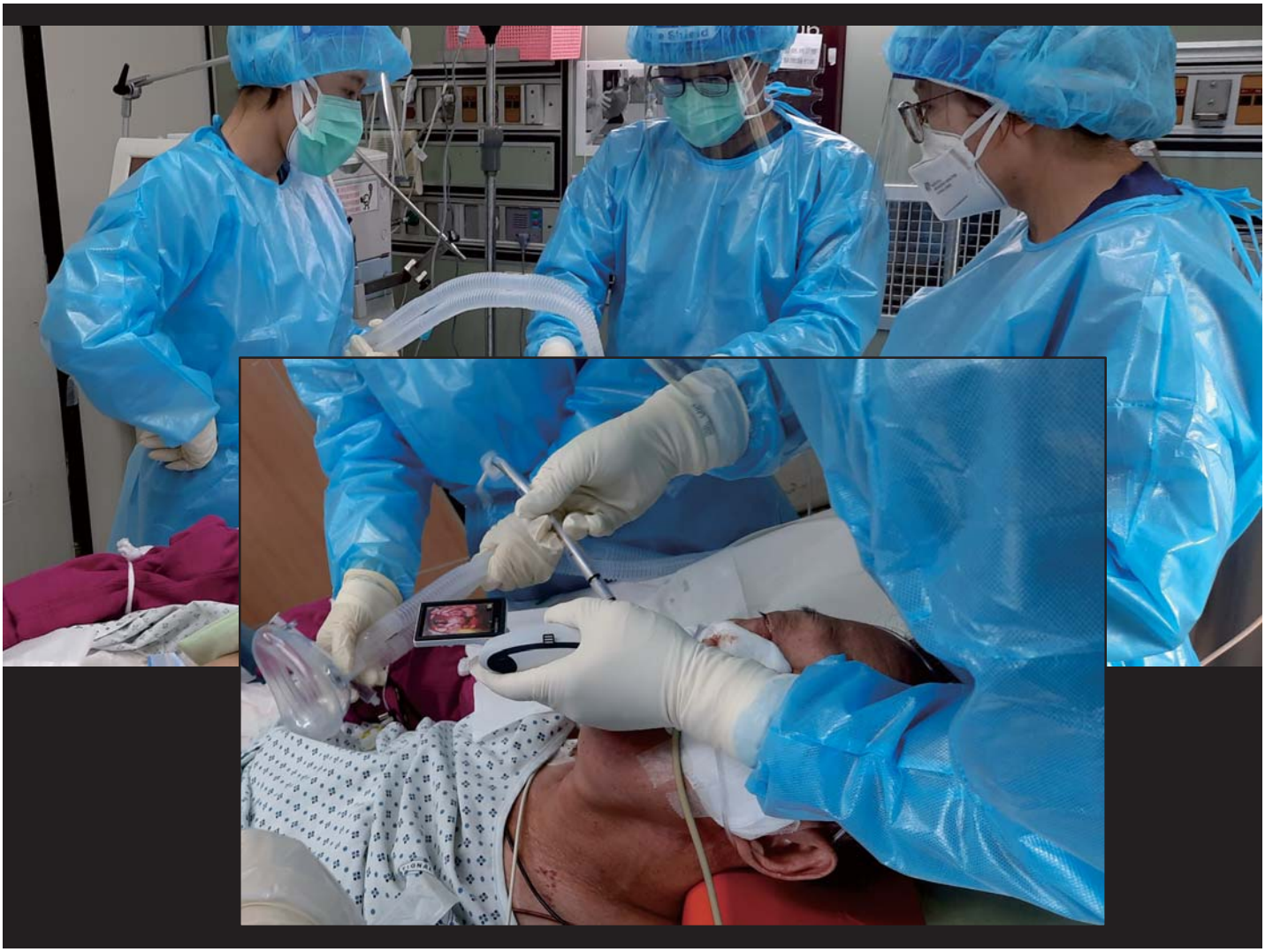
一般接觸病人的醫療照護[註2] 口罩、手套	接觸血體液/分泌物風險之醫療照護 、呼吸道檢體採檢、環境清潔 口罩、手套、防水隔離衣	引發飛沫微粒醫療處置 N95、手套、防水隔離衣、護目裝備
		

成大醫院感染管制中心

Tracheal intubation

- 防水隔離衣
- 面罩 + N95 or PAPR
- 負壓環境（如有）
- 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
疾病管制署 . 醫療機構因應 COVID-19 感染管制措施指引 . 2023/06/20.



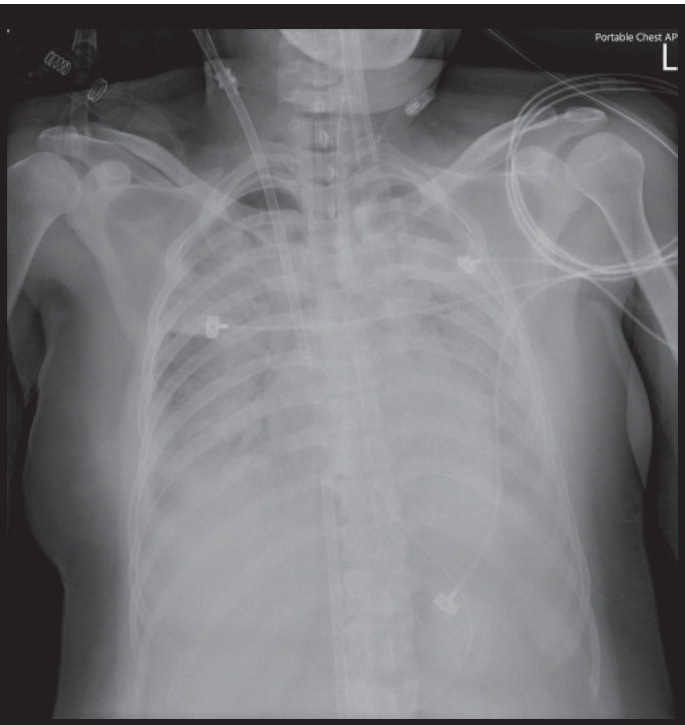
流感併發重症

Severe influenza in Taiwan, 2016

Taiwan Severe Influenza Research Consortium

- 336 patients admitted to ICUs in 8 hospitals
  - Age 61.4 y; Male 62.8%
  - IMV 288 (85.7%); ARDS in 263; ECMO in 50 pts
- Mortality ~ 18.6%
- Predictors of better survival
  - negative day 1-4 cumulative fluid balance
- Associated with worse survival
  - high driving pressure; high tidal volume
  - Earlier treatment and higher dose corticosteroid

Chao WC. PLoS One. 2018;13(1):e0190952.
Chan MC. J Formos Med Assoc. 2019;118:378-385.
Tsai MJ. Ann Intensive Care. 2020;10(1):26.
Kao KC. Ann Intensive Care. 2018;8(1):94.



42 F. no known chronic disease.
Productive cough and rhinorrhea for one week.
Fever and chills for 4 days.
Severe Influenza A (H1).
Severe ARDS. s/p V-V ECMO

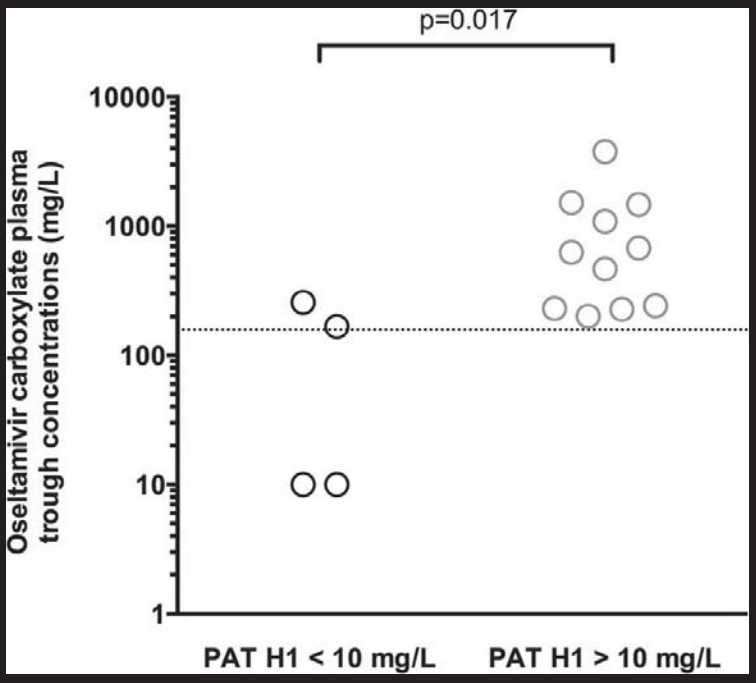
Influenza 重症病人處置

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.

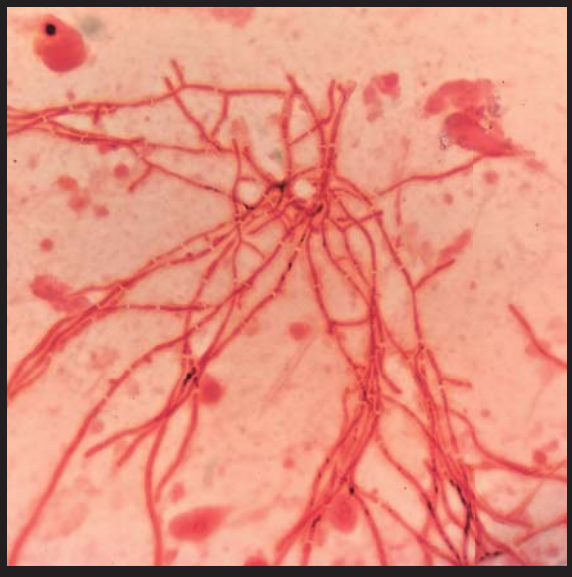
Co-pathogens in Taiwan

- 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.

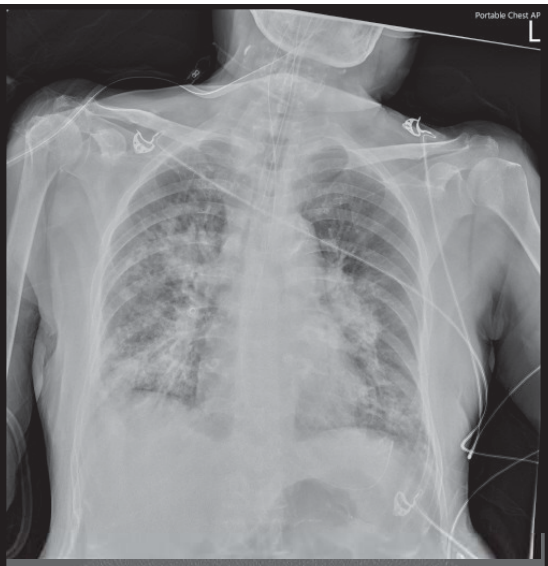
Influenza-associated pulmonary aspergillosis

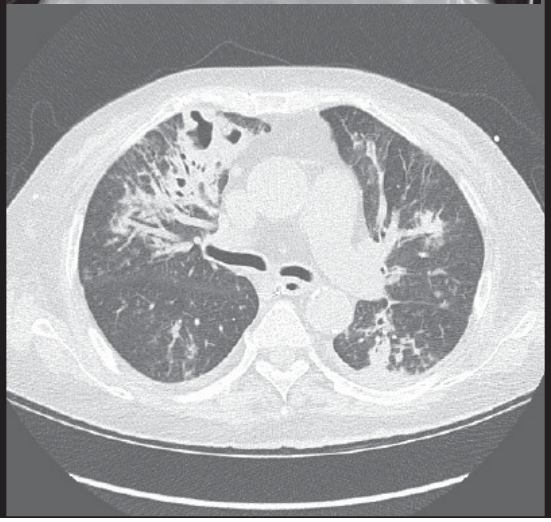
- Prevalence 5-19% among critically ill patients with influenza
- Short interval from diagnosis of influenza to pulmonary apergillosis
  - Prophylaxis not praticable
- Associated with high mortality: 49-61%



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.





- 76-year-old woman
- ESRD s/p kidney transplantation, DM
- Influenza A (H1)

- Concurrent infections
  - *Staphylococcus aureus*
  - *Klebsiella pneumoniae*
  - *Aspergillus tereus* complex
  - *Cunninghamella* spp.
  - Cytomegalovirus

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. 2018;154:84-90.

rhinovirus

influenza A

RSV

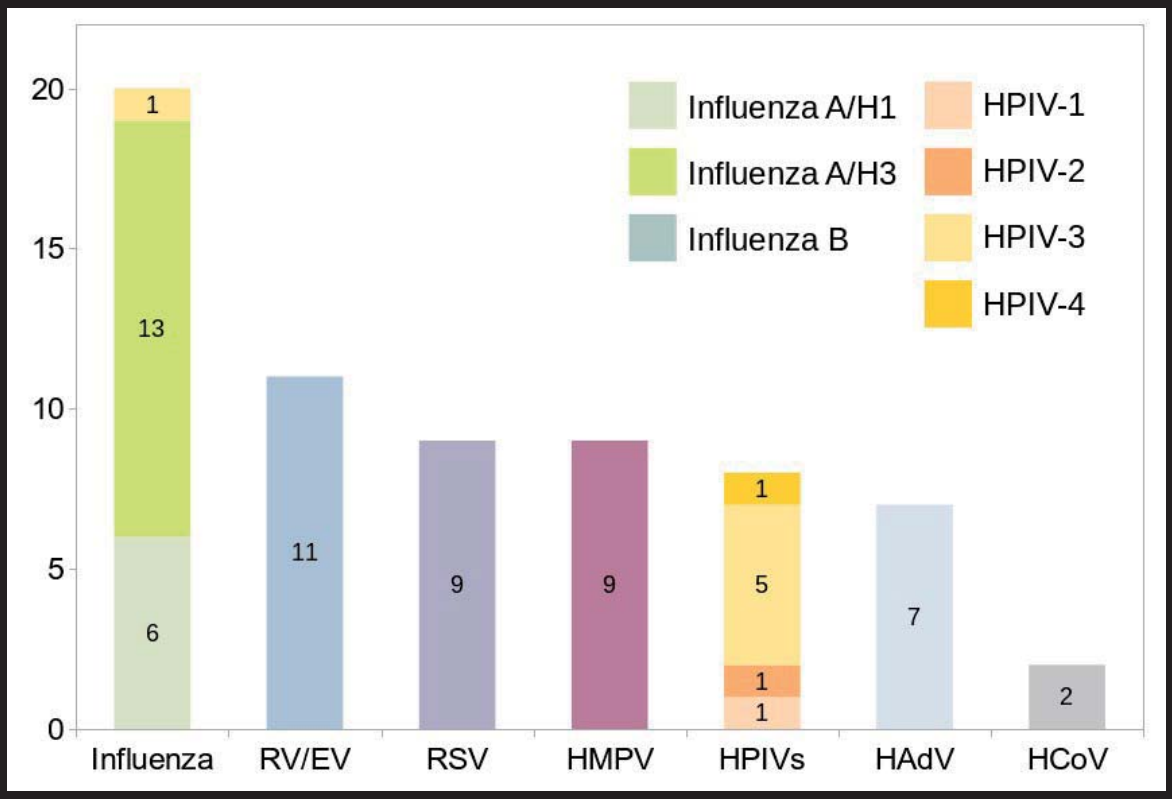
Crit Care Med 2018;46:29–36

parainfluenza virus 3

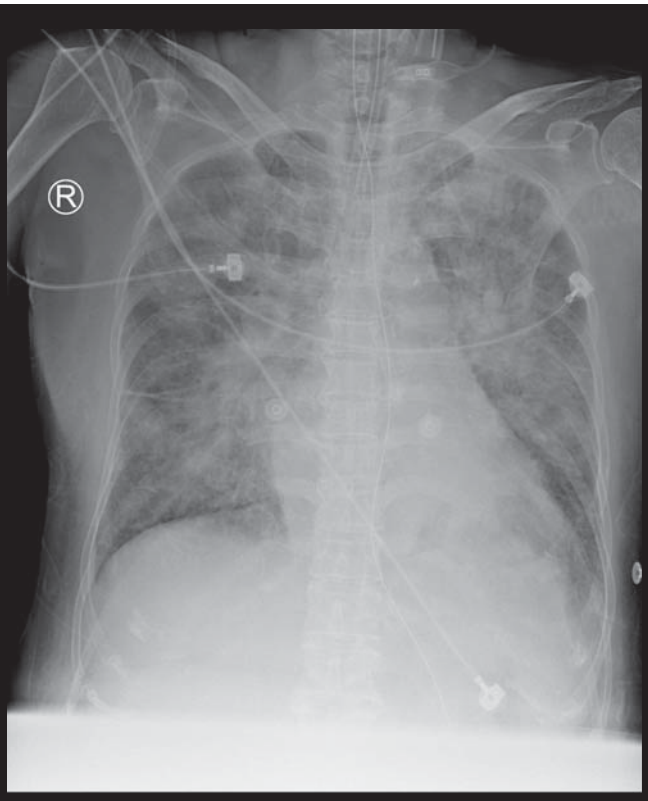
rhinovirus

coronavirus

在台灣 ICU 也不少見



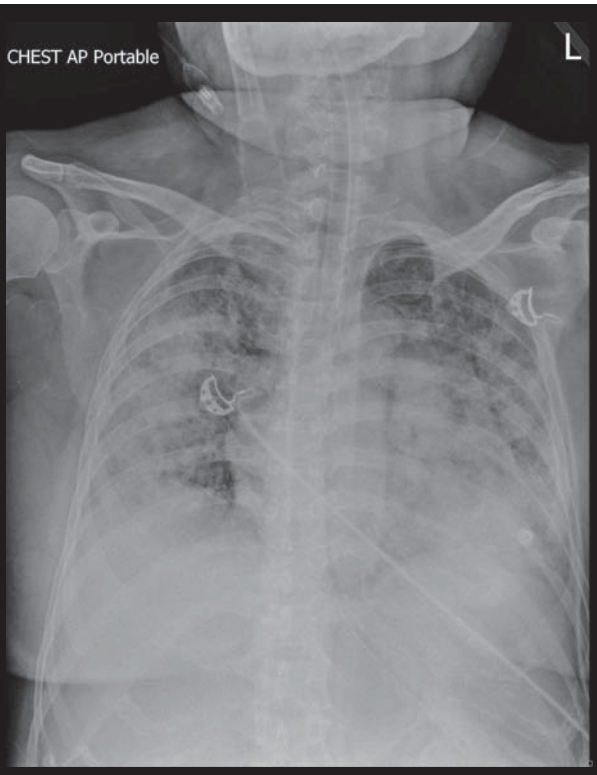
Cia CT. *Sci Rep*. 2021;11(1):20058.



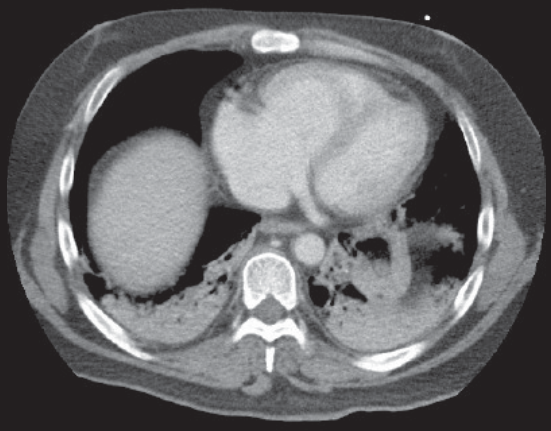
63 F. HTN. HFpEF. Dyslipidemia

Upper airway symptom for 3 days. Dyspnea.

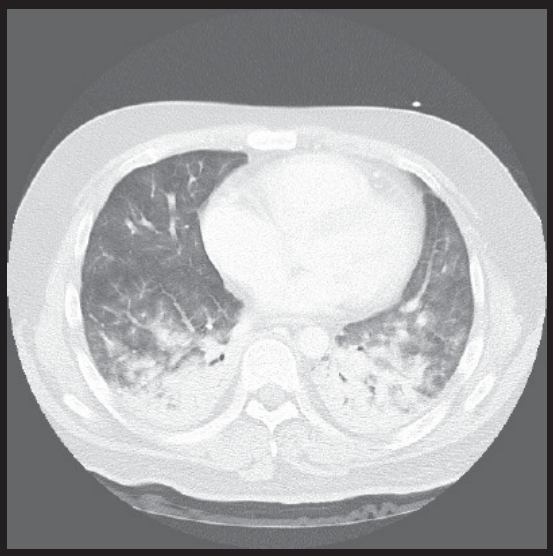
Parainfluenza virus 3 pneumonia



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.

- 402 patients, 26 admitted to ICU
- in-hospital mortality 30.8%

Kapandji N. *Ann Intensive Care*. 2023;13(1):21.

其他呼吸道病毒感染也可以很嚴重
RSV

- IMV 36.6%, In-hospital mortality 23.9%
- No difference from severe influenza in ICUs

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

- Septic shock 51%, IMV 89%
- Bacterial co-infeciton 28.3%
- 30d mortality 26.1%, in-hospital mortality 43.5%
- comparable to influenza-associated pneumonia.

Kim T. *Open Forum Infect Dis*. 2023;10(4):ofad131.

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

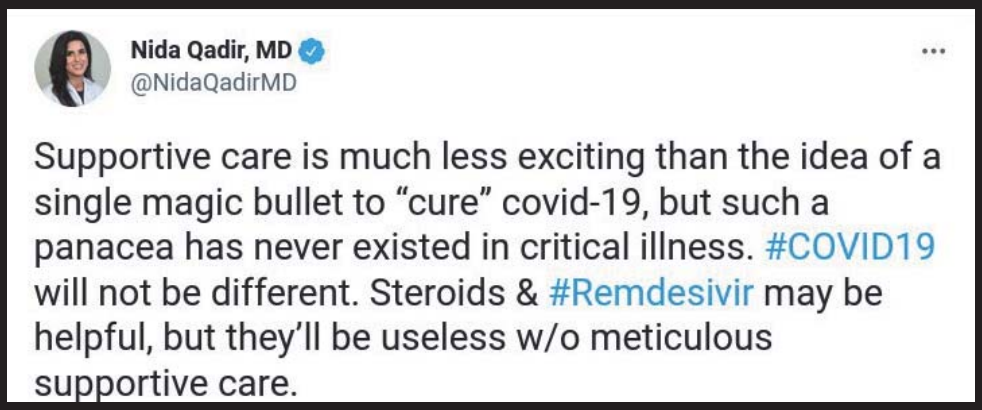
Favipiravir

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

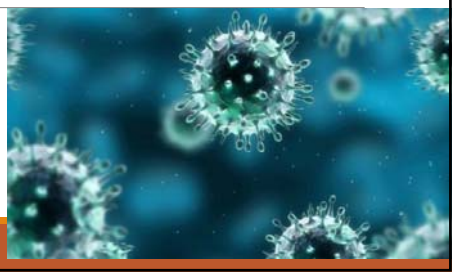
Take Home Messages

- 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



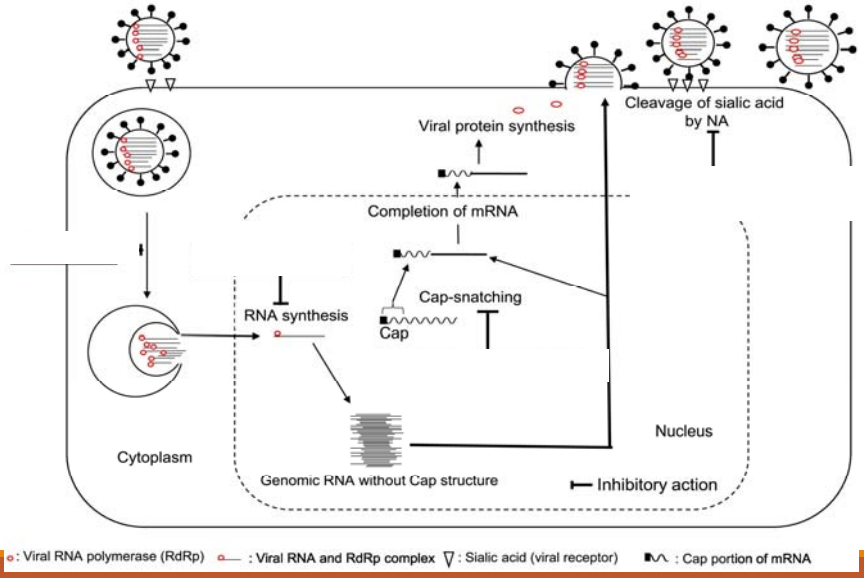
1

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

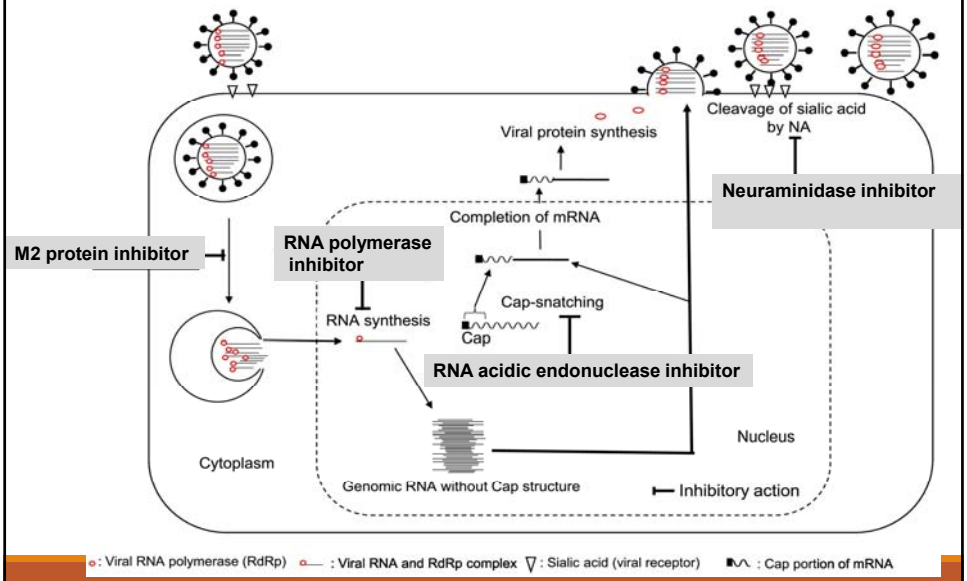
Influenza Virus



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 inhibitor

克流感(Oseltamivir)

瑞樂沙 (Zanamivir)

瑞貝塔 (Peramivir)

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

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“ 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年前臨床試驗，結論為
藥物可縮短病程 (16.8hr)，無降低住院風險

Cochrane Database Syst Rev. 2014 Apr 10;2014(4):CD008965.

9

JAMA Internal Medicine | Original Investigation

Evaluation of Oseltamivir Used to Prevent Hospitalization in Outpatients With Influenza

A Systematic Review and Meta-analysis

Ryan Hanula, BSc; Émilie Bortolussi-Courval, NClin; Arielle Mendel, MD, MSc; Brian J. Ward, MSc, MDCM; Todd C. Lee, MD, MPH; Emily G. McDonald, MD, MSc

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JAMA Intern Med. doi:10.1001/jamainternmed.2023.0699
Published online June 12, 2023.

RESULTS Of 2352 studies identified, 15 were included. The intention-to-treat infected (ITTi) population was comprised of 6295 individuals with 54.7% prescribed oseltamivir. Across study populations, 53.6% (5610 of 10 471) were female and the mean age was 45.3 (14.5) hospitalization within the 0.32% to 0.16%). older populations (mean ed at greater risk of pulation, oseltamivir was vomiting (RR, 1.83; 95% CI, 1.08). analysis among h a reduced risk of adverse events. To justify itably high-risk population

Figure 2. Random Effects Meta-analysis on the Outcome of Hospitalization Within the ITTi Population Aged 12 Years and Older

Study	Oseltamivir Yes	Oseltamivir No	Control Yes	Control No	RR (95% CI)	Weight, %
Beigel et al,[12] 2020	4	276	2	277	2.01 (0.37-10.91)	8.65
Hayden et al,[15] 2018	1	376	0	231	1.84 (0.08-45.01)	2.42
Ison et al,[14] 2020	4	385	5	381	0.79 (0.21-2.93)	14.45
Lin et al,[28] 2006	2	25	5	24	0.43 (0.09-2.03)	10.23
Roberts et al,[29] 2019	0	7	0	7	1.00 (0.02-44.50)	1.71
Dorkings,[31] 1998	0	158	0	161	1.02 (0.02-51.03)	1.61
Dorkings,[32] 1999	0	124	0	129	1.04 (0.02-52.02)	1.61
McGarty,[10] 2000	3	699	4	357	0.39 (0.09-1.71)	11.10
Grosse,[33] 1999	1	5	1	5	1.00 (0.08-12.56)	3.86
McCarvil,[34] 2000	2	129	4	132	0.52 (0.10-2.79)	8.74
Roche WV15819, WV15876, WV15978,[35] 2000	3	246	8	253	0.39 (0.11-1.46)	14.27
Roche WV16277,[16] 2003	0	119	0	109	0.92 (0.02-45.80)	1.61
Dorkings,[37] 1999	0	19	0	19	1.00 (0.02-47.97)	1.65

Favors oseltamivir | Favors control

統合分析1999-2020年間隨機臨床試驗
結果顯示 克流感使用無降低住院風險

JAMA Intern Med . 2023 Jun 12:e230699.

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

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, Zhan, Xiaoyun Hu, Quazi, Ilija Kuzman, Arthu, Elga Mayo-Montero, Pagbajabyn Nymad, Elena B Sarrouf, An, Kelvin K W To, Anto, Paul Zarogoulidis, F

Oseltamivir 92%
Zanamivir 2.3%
Peramivir 0.3%

Summary

Background N
evidence for th
data to investig
hospital with p

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).

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.

11

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.

12

SURVEILLANCE

Effect of neuraminidase inhibitor (oseltamivir) treatment on outcome of hospitalised influenza patients, surveillance data from 11 EU countries, 2010 to 2020

Cornelia Adlhoch[1], Co
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, Tanya Melillo[9], Arian
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3. Public Health Agenc
4. National Institute of
Romania
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6. Department of Infec
7. National Influenza R
8. Center for Virology,
9. Infectious Disease
10. National Institute f
11. Health Service Exe
12. WHO Regional Offi
Correspondence: Corn

TABLE 2

Risk of death in hospitalised influenza cases by age group, sex, influenza subtype, timing of antiviral treatment, intensive care unit admission status, timing of hospitalisation and vaccination status, 11 European Union countries, influenza seasons 2010/11–2019/20

Variable	0–19 years		20–39 years		40–59 years		60–79 years		≥ 80 years	
	aOR	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI
Female sex	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Male sex	0.81	0.45–1.46	1.16	0.73–1.83	1.06	0.84–1.33	1.16[a]	1.00–1.33	1.02	0.89–1.16
Influenza virus										
Type B	Ref.		Ref.		Ref.		Ref.		Ref.	
A(H1N1)pdm09	2.65[a]	1.24–5.66	1.23	0.59–2.57	2.09[b]	1.40–3.13	1.18	0.95–1.45	1.13	0.90–1.42
A(H3N2)	0.41	0.11–1.54	1.07	0.41–2.81	1.48	0.89–2.45	0.91	0.73–1.14	1.01	0.84–1.22
A unsubtyped	1.05	0.38–2.89	0.89	0.38–2.09	1.38	0.89–2.11	0.81[a]	0.66–0.99	0.85	0.72–1.02
Timing of AV treatment										
No treatment	Ref.		Ref.		Ref.		Ref.		Ref.	
Within 2 days	1.27	0.55–2.93	1.38	0.58–3.29	0.43[b]	0.28–0.66	0.50[b]	0.39–0.63	0.51[b]	0.42–0.63
3–4 days	1.13	0.46–2.80	1.15	0.48–2.75	0.62[a]	0.42–0.92	0.52[b]	0.41–0.65	0.60[b]	0.49–0.73
5–7 days	1.08	0.36–3.18	1.55	0.64–3.78	0.64[a]	0.43–0.94	0.59[b]	0.47–0.75	0.65[b]	0.52–0.81
>7 days	2.90	0.99–8.55	3.02[a]	1.05–8.68	1.16	0.75–1.82	1.07	0.81–1.41	0.72[a]	0.54–0.96
Non-ICU admission	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.

歐盟多國觀察性研究分析近2萬名在2009/2010及2019/2020年流感流行期間住院的病人發現(越早)服用抗病毒藥劑能減少死亡風險

Euro Surveill . 2023 Jan;28(4):2200340.

13

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.

14

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

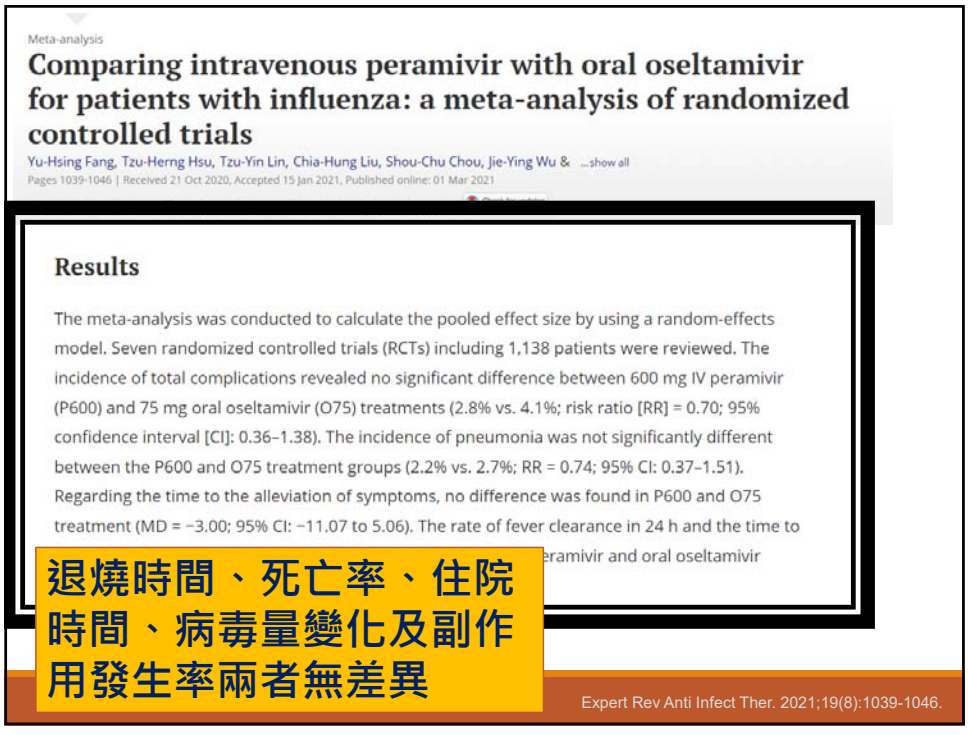
Results. The median times to clinical stability (time to reach <37°
and 37.8 hours (95% CI = 26.3–45.3) in the peramivir and oseltamivi
difference. The virus titer and change of mean total symptom scores
regression suggested that virus type was a significantly effective prog
(AEs) with peramivir and oseltamivir occurred in 2.2% (n = 1/46) an
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-

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

15



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

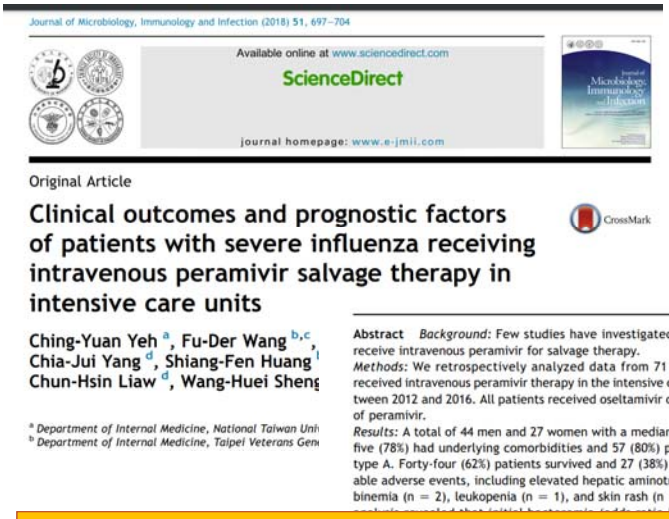
The meta-analysis was conducted to calculate the pooled effect size by using a random-effects model. Seven randomized controlled trials (RCTs) including 1,138 patients were reviewed. The incidence of total complications revealed no significant difference between 600 mg IV peramivir (P600) and 75 mg oral 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.

16



Journal of Microbiology, Immunology and Infection (2018) 51, 697–704

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Original Article

Clinical outcomes and prognostic factors of patients with severe influenza receiving intravenous peramivir salvage therapy in intensive care units

Ching-Yuan Yeh [a], Fu-Der Wang [b,c], Chia-Jui Yang [d], Shiang-Fen Huang [], Chun-Hsin Liaw [d], Wang-Huei Sheng

[a] Department of Internal Medicine, National Taiwan Uni
[b] Department of Internal Medicine, Taipei Veterans Gen

Abstract *Background:* Few studies have investigated patients with severe influenza who receive intravenous peramivir for salvage therapy.
Methods: We retrospectively analyzed data from 71 patients with severe influenza who received intravenous peramivir therapy in the intensive care units of three medical centers between 2012 and 2016. All patients received oseltamivir or zanamivir before the administration of peramivir.
Results: A total of 44 men and 27 women with a median age of 55 years were enrolled. Fifty-five (78%) had underlying comorbidities and 57 (80%) patients were infected with influenza type A. Forty-four (62%) patients survived and 27 (38%) died. Five patients (7%) had attributable adverse events, including elevated hepatic aminotransferase levels (n = 2), hyperbilirubinemia (n = 2), leukopenia (n = 1), and skin rash (n = 1). Multivariable logistic regression

北部醫中聯合研究 71位流感重症入住ICU 使用口服oseltamivir或吸入zanamivir再使用iv peramivir為救援治療,62%存活率

J Microbiol Immunol Infect . 2018 Dec;51(6):697-704.

17

Neuraminidase inhibitors 實證結論

	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	成人(含孕婦)及	成人(含孕婦)及兒童

實證顯示針對易併發重症之高風險對象(老人、幼兒、慢性疾病、孕婦)，不論發病時間，均應立刻給予抗病毒藥物治療，以降低死亡風險

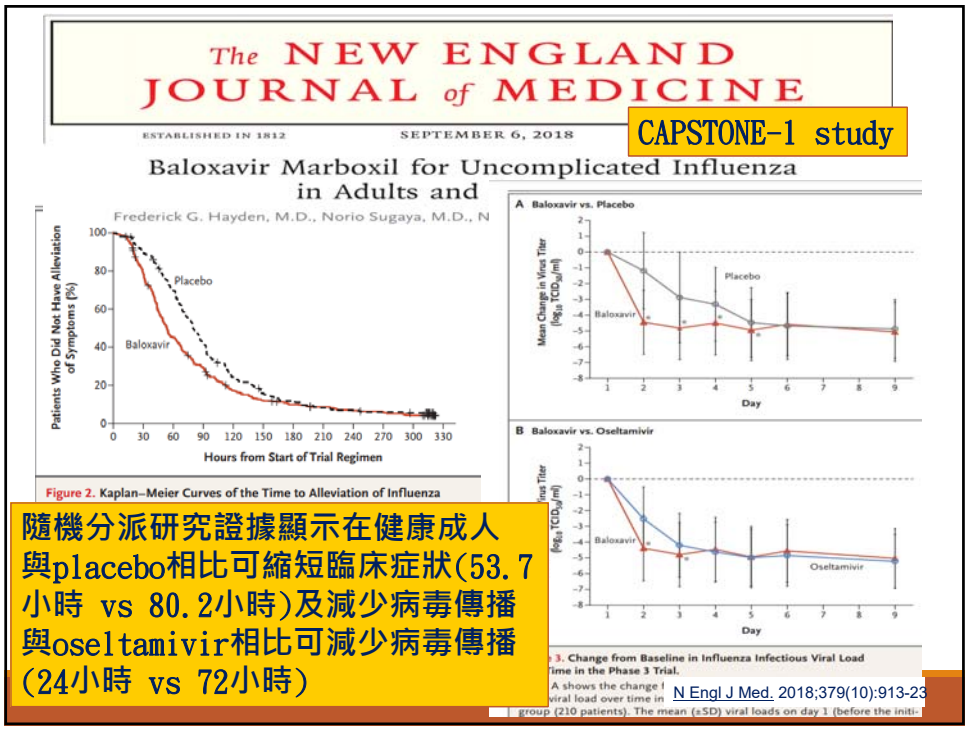
18

Endonuclease inhibitor

- Mechanism : inhibiting the initiation of mRNA synthesis
- Drug : Baloxavir (single dose regimen)
- Active against influenza A and B

潛在抗病毒藥物主流

19



20

Early treatment with baloxavir marboxil in high-risk adolescent and adult outpatients with uncomplicated influenza (CAPSTONE-2): a randomised, placebo-controlled, phase 3 trial

Michael G Ison, Simon Portsmouth, Yuki Yoshida, Takao Shishido, Melissa Mitchener, Kenji Tsuchiya, Takeki Uehara, Frederick G Hayden

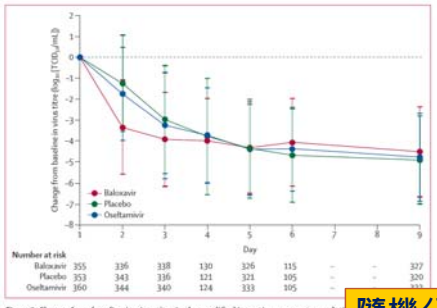


Figure 3: Change from baseline in virus titre in the modified intention-to-treat populati
Data are mean reduction with error bars indicating SD. Days 4 and 6 were optional visits, ar

oxavir), a selective inhibitor of influenza cap-dependent endonuclease, n for the treatment of uncomplicated influenza in otherwise healthy to study the efficacy of baloxavir in outpatients at high risk of developing

11, 2017, to March 30, 2018, and randomly assigned to receive baloxavir 25). The modified intention-to-treat population included 1163 patients: group, and 389 in the oseltamivir group. 557 (48%) of 1163 patients had . 80 (7%) had influenza A H1N1, 14 patients had a mixed infection, and he median TTIIS was shorter in the baloxavir group (73·2 h [95% CI 3 h [92·7 to 113·1]; difference 29·1 h [95% CI 14·6 to 42·8]; p<0·0001). as 81·0 h (95% CI 69·4 to 91·5), with a difference from the baloxavir s were reported in 183 (25%) of 730 patients in the baloxavir group, 02 (28%) of 721 in the oseltamivir group. Serious adverse events were

oseltamivir group were conside
or Ile38Asn substitutions conf
assessed for amino acid substit

Interpretation Single-dose balox
influenza symptoms in high-ri
early therapy for patients at high

隨機分派研究證據顯示在高風險族群與placebo相比可縮短臨床症狀(73.2小時 vs 102.3小時)及減少病毒傳播與oseltamivir相比可縮短病毒傳播

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

21

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

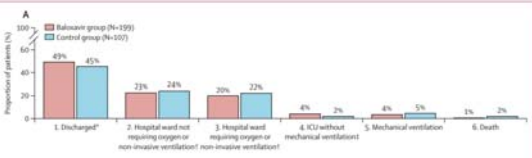
Deepali Kumar, Michael G Ison, Jean-Paul Mira, Tobias Welte, Jick Hwan Ha, David S Hui, Nanshan Zhong, Takefumi Saito, Laurie Katugampola, Neil Collinson, Sarah Williams, Steffen Wildum, Andrew Ackrill, Barry Clinch, Nelson Lee

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 uded. Recruitment took place in 124 centres across ictive response system, patients were randomly aloxavir 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 d 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 wi

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, Germany (Prof T Welte MD);

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.

22

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及病毒傳播時間，但針對降低住院率及呼吸道感染相關併發症(除oseltamivir外)仍待更多實證
- 口服Oseltamivir可改善流感重症病人預後、降低住院死亡率及住院天數及縮短呼吸器使用使間。
- 流感重症病人可考慮oseltamivir/zanamivir合併peramivir針劑或是合併口服oseltamivir及口服baloxavir。需待更多臨床實證
- 美國FDA已通過baloxavir可用於5歲以上兒童

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

23

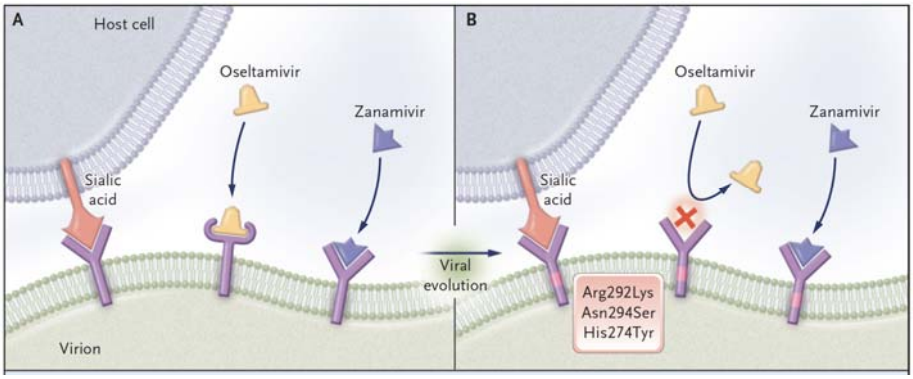
大綱

- 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

24

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

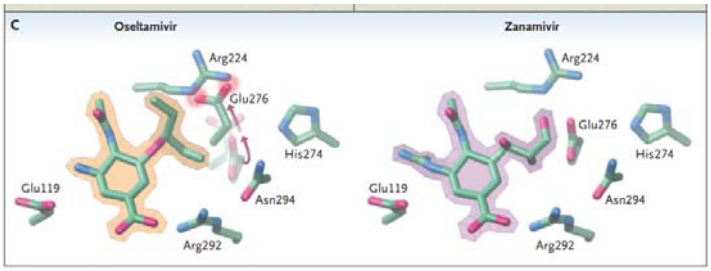


N Engl J Med 2009; 360:953-6

25

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

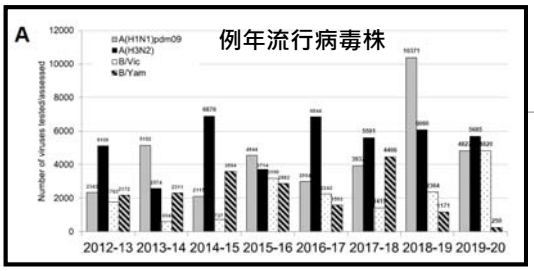


Mechanism of Development of Resistance to Oseltamivir.

N Engl J Med 2009; 360:953-6

26

Oseltamivir抗藥性病毒株近年監測結果



pdm09抗藥性病毒株比例

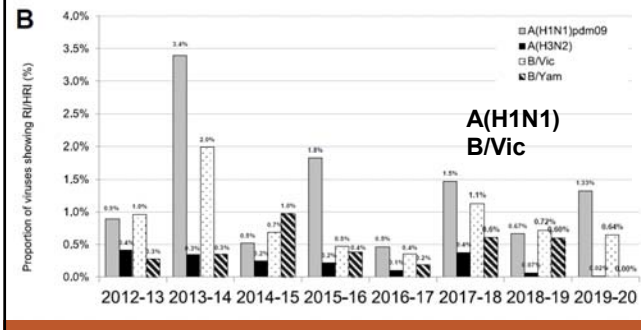
2019/20:1.33%

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

27

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)	Hospital (2)	Yes, oseltamivir (1)	Unknown (1)
				I38T/K/I mix (1)		No (3)	
				Not available[c] (1)			
	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%

全球抗藥性病毒株比例

2019/20:0.5%

2018/19:0.1%

0.2%

28

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
- Antiviral susceptibility patterns changed very little during 2020-2022

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)

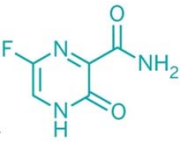
29

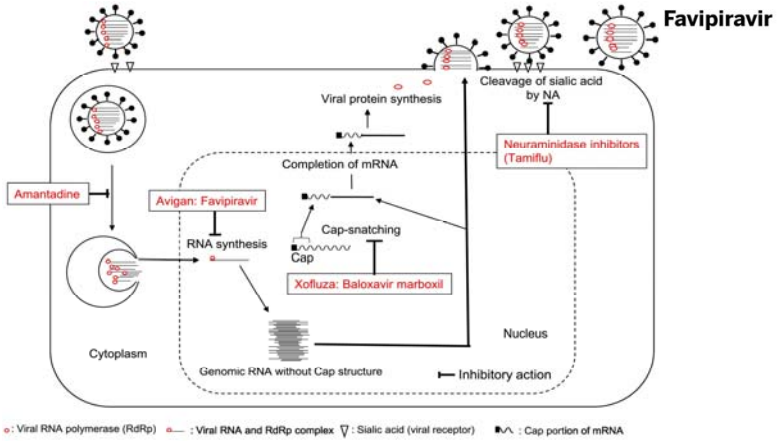
大綱

- 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

30

Favipiravir（Avigan）





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

31

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

[b] 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,

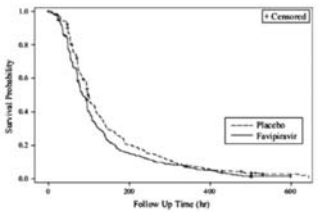
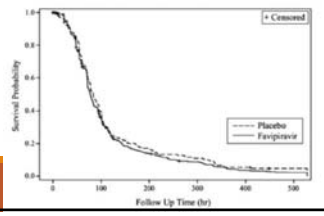


圖 3　以主要評估指標[17]繪製 Kaplan-Meier Plot (ITT1 族群，試驗1)



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

ıfluenza-like symptoms and fever of ≤48 hours were randomized to favipiravir BID on days 2–5) or placebo tablets (1:1 in US316; 3:1 in US317). The primary tion when 6 influenza symptoms were self-rated as absent or mild and fever was ted participants.

acebo), favipiravir was associated with a 14.4-hour reduction (median, 84.2 vs ıtion vs placebo. In US317 (526 favipiravir, 169 placebo), favipiravir did not

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

32

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

33

其它機轉抗病毒藥物

藥物	特色	上市
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

仍在持續研發中

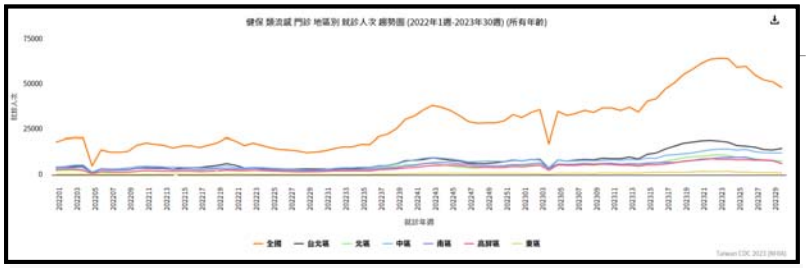
34

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

35

流感速訊- 社區流行 A/H1N1



全國流感併發重症本土病例及境外移入病例統計表-依發病日

https://pidss.cdc.gov.tw/Home/Index?op=2

36

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)

37

抗病毒藥劑

公費抗病毒藥劑使用對象

治療性用藥	
• 符合「流感併發重症」通報病例(需通報於傳染病通報系統)	• 符合「新型A型流感」通報定義者(需通報於傳染病通報系統)
• 孕婦經評估需及時用藥者	• 肥胖之類流感患者(BMI>=30)
• 未滿5歲及65歲以上之類流感患者	• 確診或疑似罹患流感住院(含急診待床)之病患
• 重大傷病、免疫不全(含使用免疫抑制劑者)或流感高風險慢性疾病之類流感患者	• 流行高峰期擴大用藥(有發燒之類流感患者，且家人/同事/同班同學有類流感發病者)

預防性用藥

- 類流感等群聚事件經疾病管制署各區管制定需用藥者
- 動物流感發生場所撲殺清場工作人員(接判需給藥者)

流感併發重症病例數未明顯下降，擴大公費流感抗病毒藥劑使用對象「有類流感症狀，且家人/同事/同班同學有類流感發病者」適用期限再延長至112年8月31日止，籲請醫師善用公費藥劑，共同防治流感(疾病管制署致醫界通函第517號)

流感併發重症
(Severe Complicated Influenza)

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

38

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/

39

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

N Engl J Med 2020; 383:309-320

40

結論

- 易併發重症之高風險對象或住院病人，應即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

41

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

42

Q&A

43

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

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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.

44

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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

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45

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

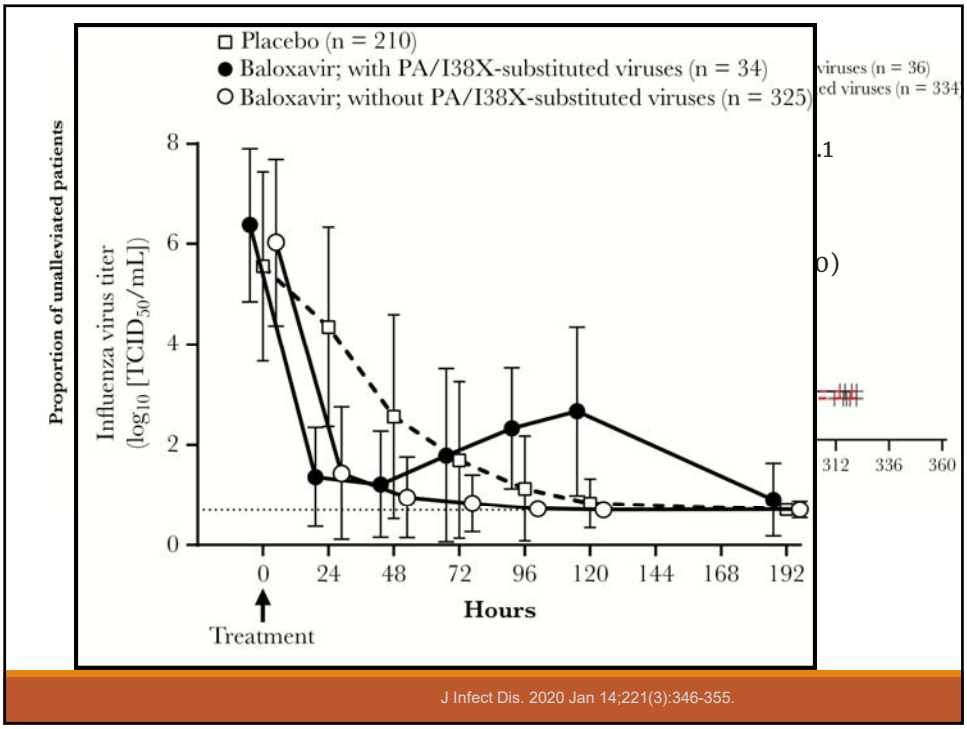
Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents

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

46



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