流行性感冒之
抗病毒藥物治療及疫苗預防

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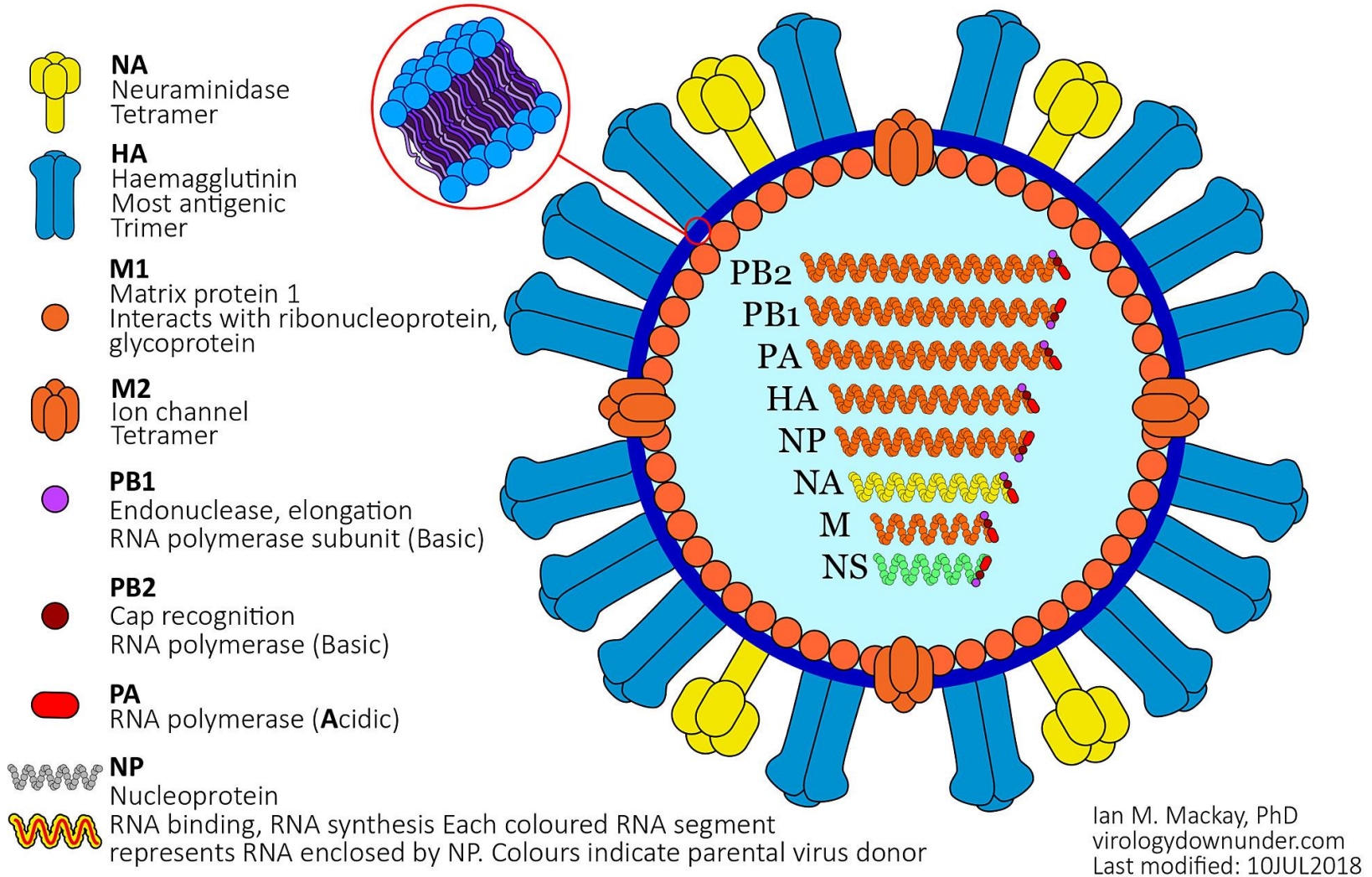
Outline

- 抗病毒藥物介紹
- 抗病毒藥物的成效及給予時機
- 流感疫苗的介紹
- 流感疫苗的政策與展望

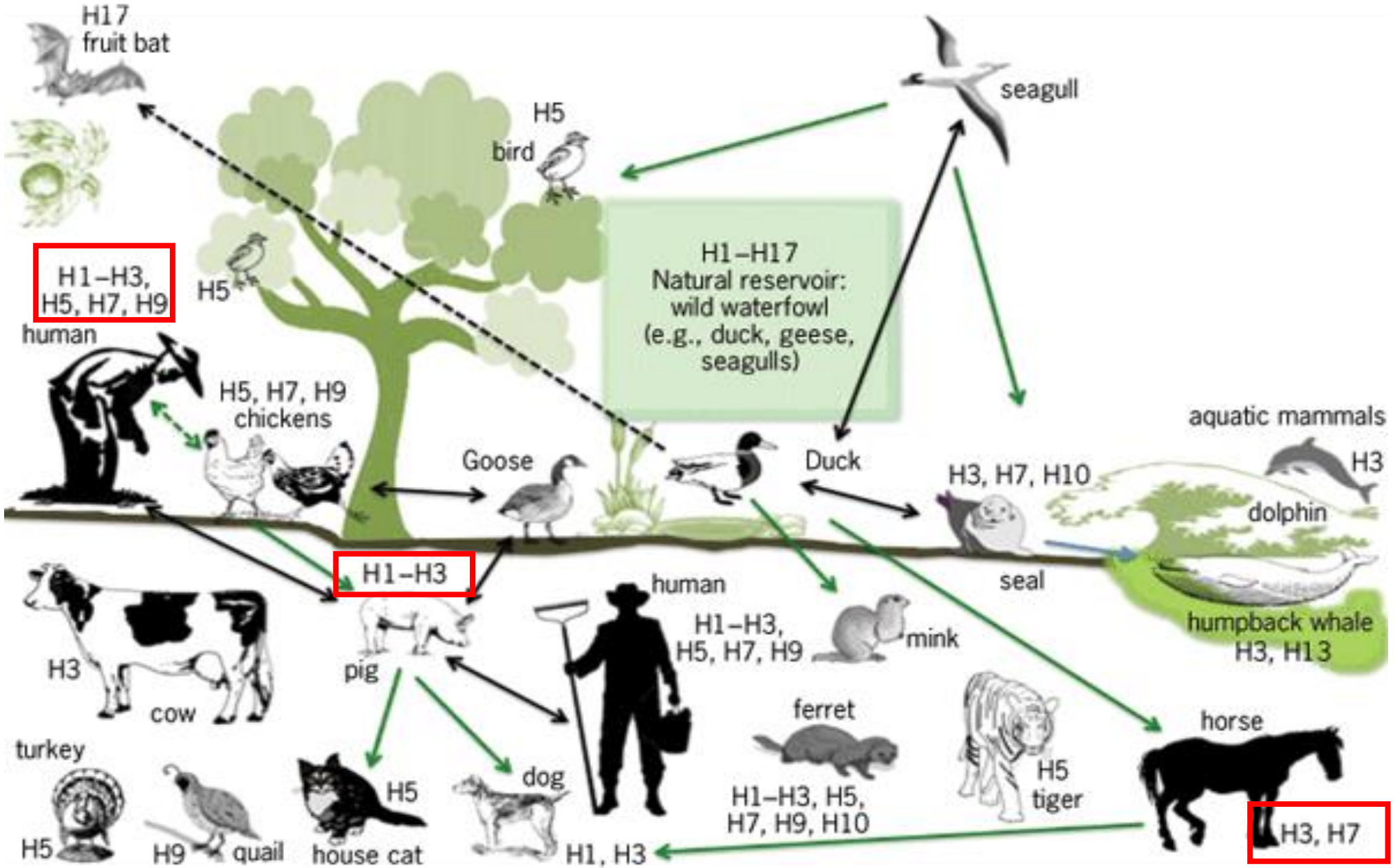
病毒結構



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

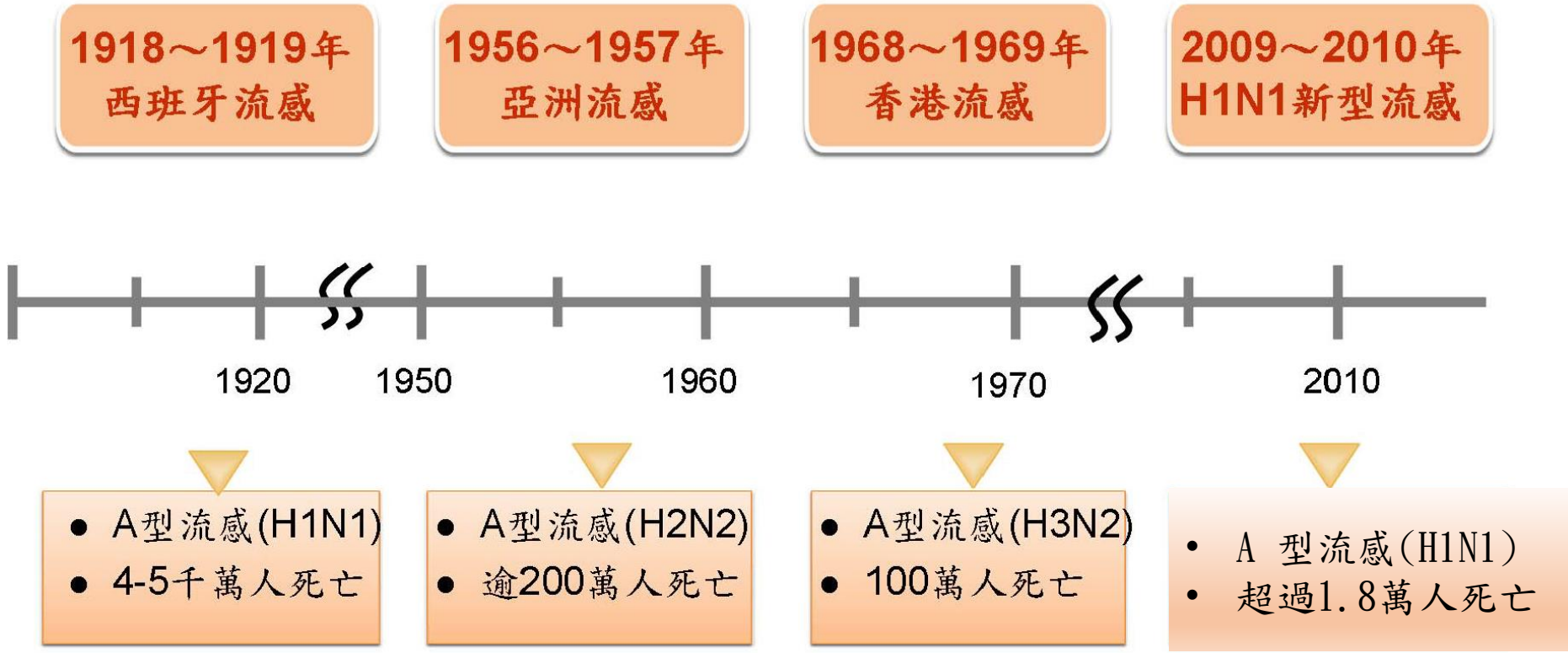
流感病毒的基本構造及分型

- **正黏液病毒科(Orthomyxoviridae)**
- **基因體含8段(A、B型)或7段(C、D型)單股RNA**
- **依NP及M蛋白可分為A型、B型、C型及D型**
  - **A型：人畜共通，會感染人類、哺乳動物與鳥類**
  - B型：只會感染人類
  - C型：感染人類後不造成明顯臨床症狀
  - D型：目前僅主要感染牛隻，對人類是否有致病性仍未知
- **A型流感又可依外套膜上的HA與NA 2種醣蛋白分為各種分型**
- 血球凝集素(Hemagglutinin, HA)，共有18種
- 神經胺酸酶(Neuraminidase, NA)，共有11種



http://www.accessscience.com/search.aspx?rootID=802694

二十世紀歷史上流感的大流行 (Influenza pandemics)

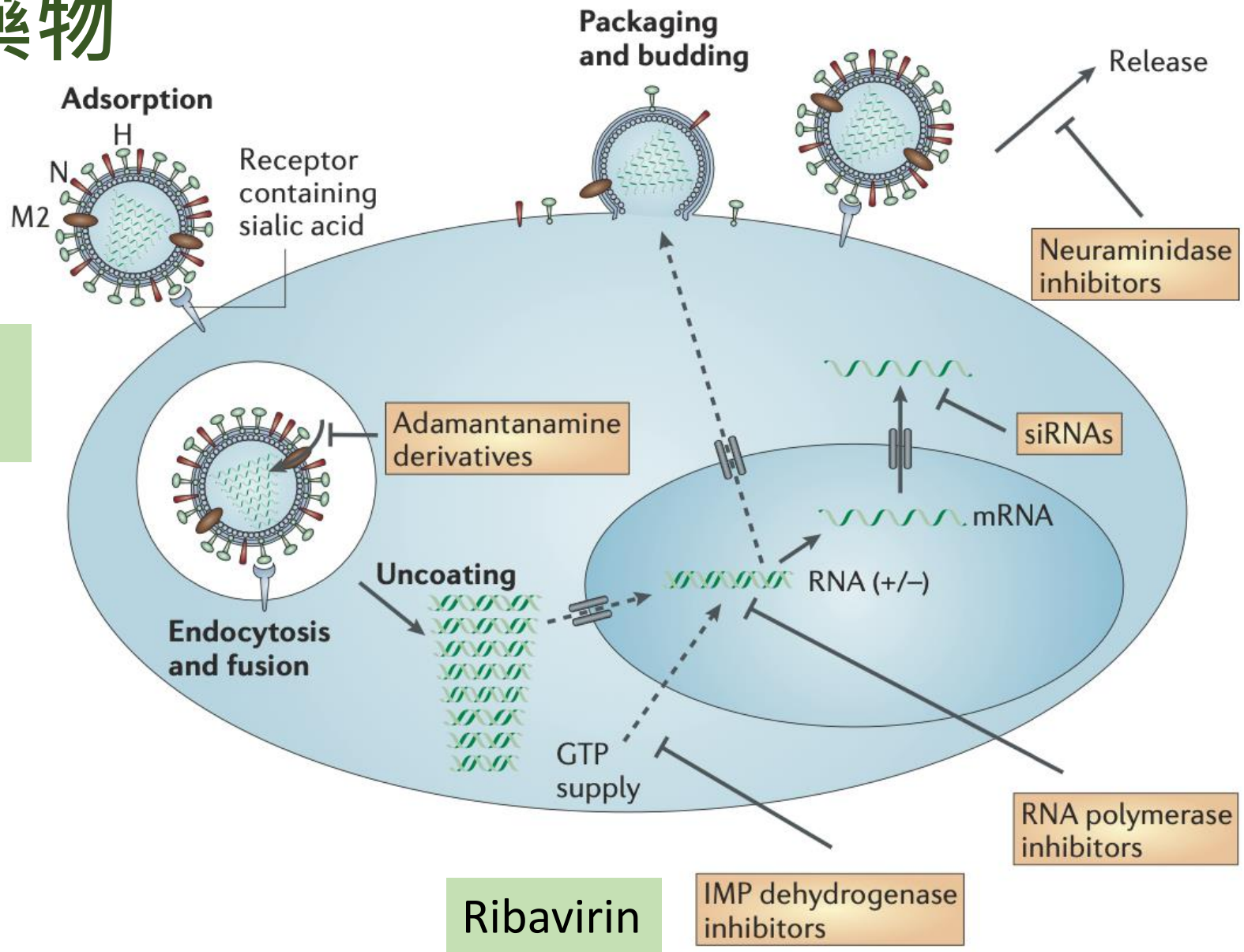


Year	Subtype	Estimate Death (million)	Origin of gene						
			NA	PA	PB1	PB2	NP	M	NS
1918	H1N1	50~100							
1957	H2N2	1~4							
1968	H3N2	1							
2009	H1N1	~0.018							

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

抗病毒藥物介紹

抗病毒藥物



Amantadine
Rimantadine

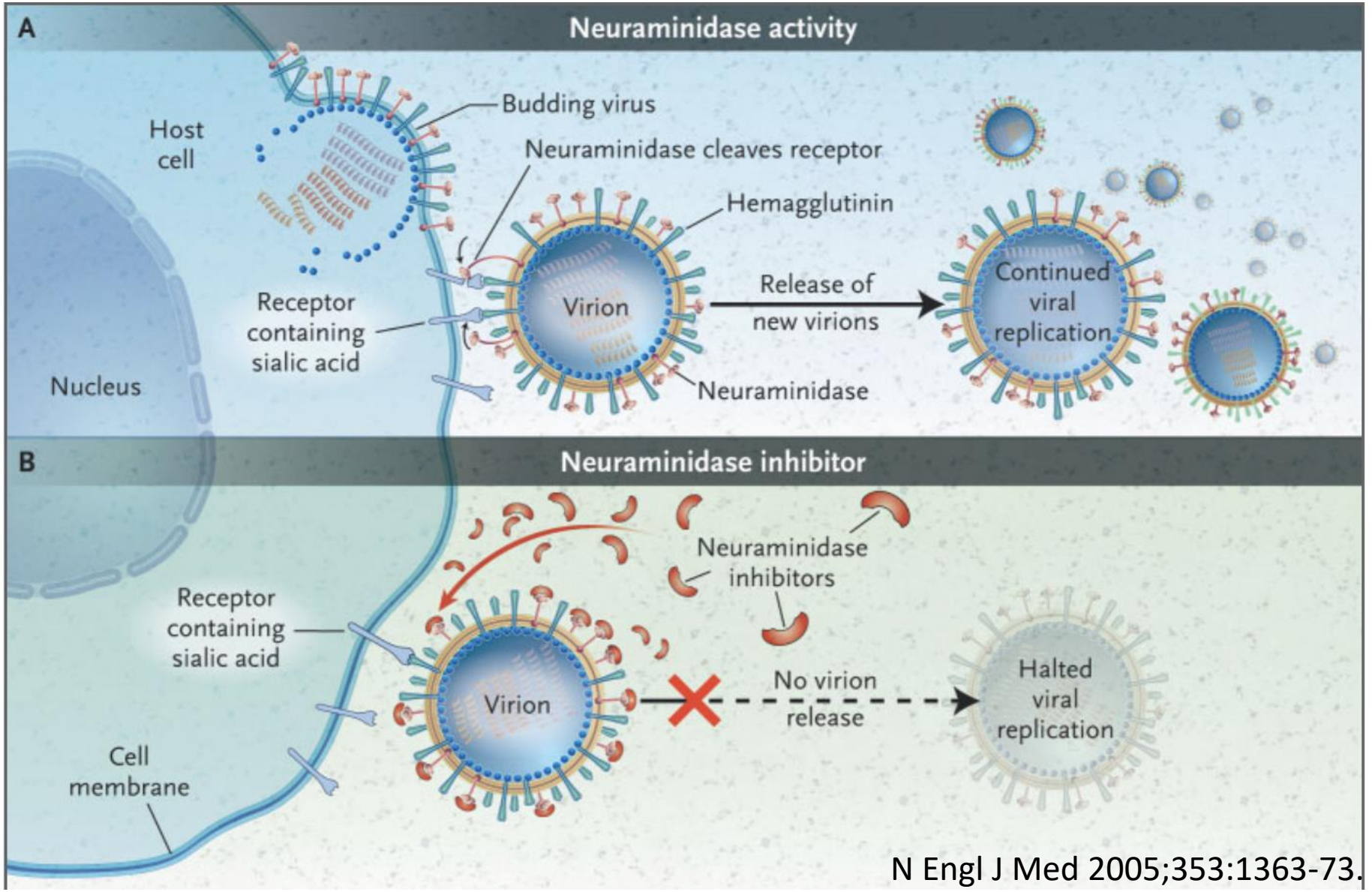
Zanamivir
Oseltamivir
Peramivir

Favipiravir

Ribavirin

De Clercq E. Nat Rev Drug Discov. 2006.

Mechanism of Neuraminidase Inhibitor



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

抗病毒藥物

- **M2 protein inhibitor**
  - Amantadine/Rimantadine
  - 抗藥性問題嚴重，目前不適用
- **Neuraminidase inhibitor**
  - Oseltamivir (oral) / zanamivir (INH) / peramivir (IV)
  - 流感抗病毒藥物主流
  - 抑制病毒表面之神精氨酸酶，阻止複製完成之病毒自宿主細胞內釋出
  - 預防疾病、減輕症狀、縮短病程

- **RNA polymerase inhibitor**
  - Favipiravir (Avigan)
  - 干擾RNA病毒的複製過程，抑制感染細胞內的病毒基因複製以防止繁殖
  - 用於治療新型流感（限於其他抗流感病毒藥物無效）
  - 日本藥政許可
- **Polymerase Acidic Endonuclease inhibitor**
  - Baloxavir marboxi (Xofluza)
  - 作用於流感病毒複製過程所必需的Cap-snatching mechanism，可抑制流感病毒的複製增生，亦可阻斷流感病毒的傳播
  - 108年藥證許可

流感抗病毒藥劑種類

學名	Oseltamivir	Zanamivir	Peramivir	Favipiravir	Baloxavir marboxil
商品名	克流感/易剋冒	Relenza	Rapiacta	Avigan	Xofluza
包裝	75毫克膠囊	碟型吸入器x1 4孔間隔之泡囊x5	點滴用注射袋300mg	淡黃色膜衣錠，每錠200mg	20毫克膜衣錠
使用方式	口服	吸入	注射	口服	口服
對象	>=1個月	>=5歲	>=1個月	成人	>=12歲且體重>=40kg
劑量	75mg BID，5 days 2-3mg/kg BID	2孔 BID，5 days	成人：300mg（max 600mg） 兒童：10mg/kg	1600mg BID，1 day 600mg BID，4day	40-80公斤：口服單次40mg；大於80公斤：口服單次80mg
腎功能調整劑量	是	否	是	是	否

Baloxavir(Xofluza®)

□2018年2月在日本核准上市

- 適用於體重10公斤以上孩童及成人
- 上市後迅速成為日本市佔率第一的流感抗病毒藥劑

□2018年10月於美國核准上市

- 適用於12歲以上孩童及成人，發病後48小時內

□2019年取得我國藥證

- 適應症
  - 1. 治療成人及12歲以上兒童之A型及B型流行性感冒病毒急性感染
  - 2. 成人及12歲以上兒童密切接觸流感病人後預防流行性感冒
  - 用法用量：
    - 40-80公斤成人單次20 mg錠2錠 / 80公斤以上成人單次20mg錠4錠
    - 無健保給付

https://www.xofluza.com/hcp/why-xofluza/mechanism-of-action.html

公費流感抗病毒藥劑儲備目的

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

公費流感抗病毒藥劑使用對象

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

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

公費流感抗病毒藥劑擴大使用對象

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

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

抗病毒藥物的成效及給予時機

BMJ

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

RESEARCH

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

OPEN ACCESS

...fellow (biostatistics)[2], Peter Doshi *assistant*
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...rd, UK

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

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

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

Summary

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

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

Lancet Infect Dis 2014; 14: 109–18

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

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

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

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

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

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

Summary

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

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

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

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

Lancet 2015; 385: 1729–37

Published Online
January 30, 2015
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This online publication has been corrected. The corrected version first appeared at thelancet.com on February 2, 2015

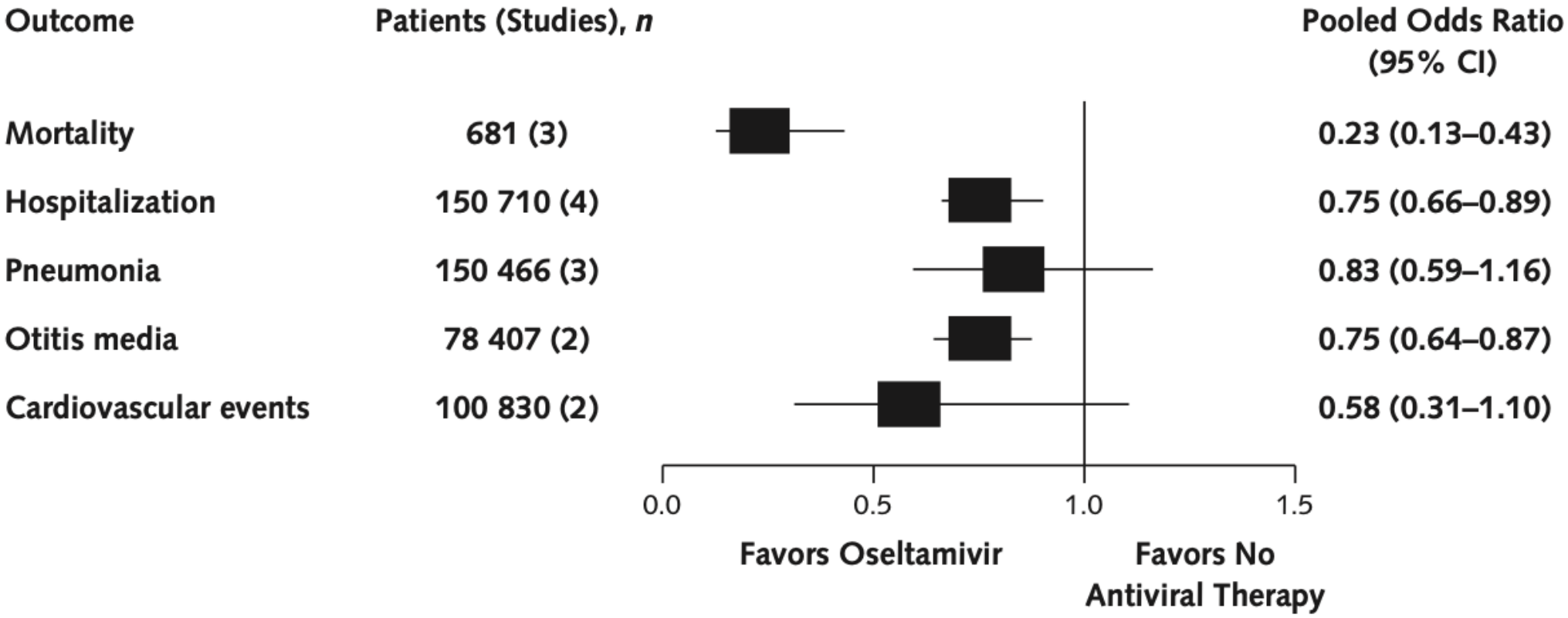
See Comment page 1700

Department of Medical Statistics, London School of

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

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

Efficacy of Oseltamivir



Evidence summary for Oseltamivir

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

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

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

Zanamivir

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

Figure 1. Parts of the DISKHALER

Evidence summary for Zanamivir

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

Zanamivir：uncertain
死亡風險、住院風險、重症插管風險

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

Peramivir

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

Favipiravir

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

Baloxavir marboxil

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

Use of Ribavirin to Treat Influenza

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

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

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

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

N Engl J Med 2009; 361:1713-1714

Combination therapy

Oseltamivir, amantadine, and ribavirin vs. Oseltamivir

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

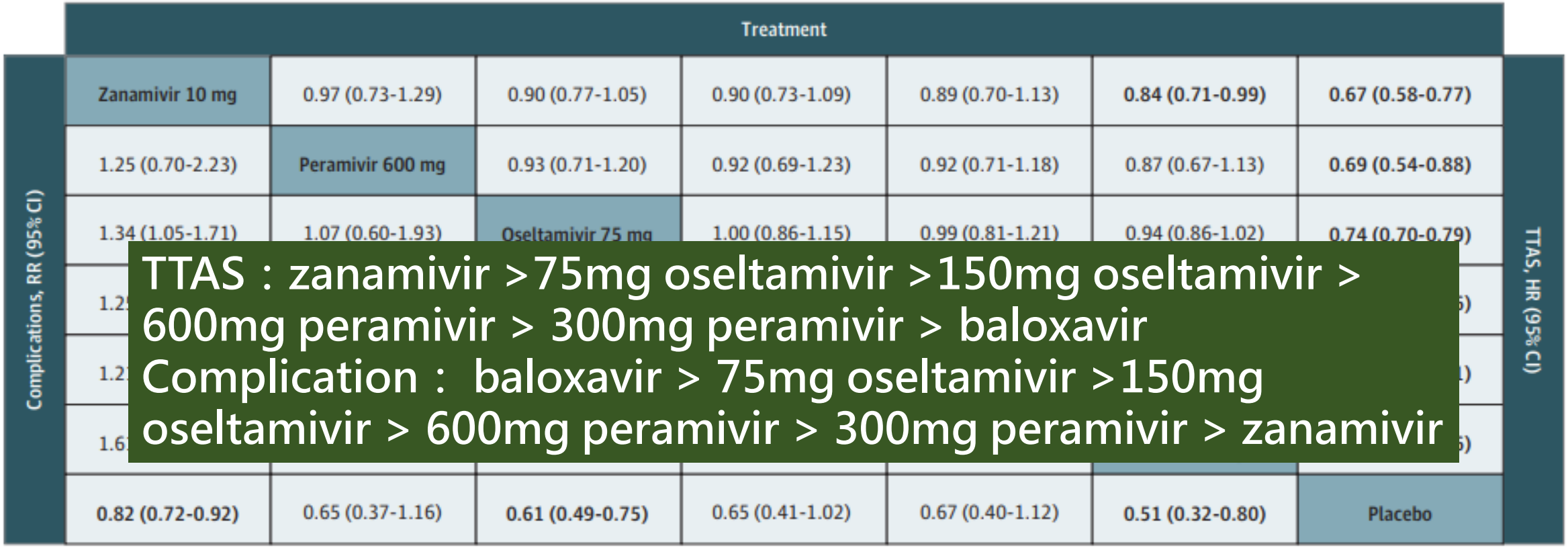
	Total (n=454)	Combination group (n=230)	Monotherapy group (n=224)	p value
Day 0	454	230	224	..
Median viral count, log_{10} copies/mL	6·5 (5·4–7·4)	6·4 (5·6–7·2)	6·7 (5·1–7·7)	..
≥LLOQ	421 (93%)	221 (96%)	200 (89%)	..
≥LOD, < LLOQ	13 (3%)	4 (2%)	9 (4%)	..
<LOD	20 (4%)	5 (2%)	15 (7%)	..
Day 3	437	221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

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

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

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

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



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

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

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

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

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

	Crude			Propensity Score–Weighted			
Principal Diagnosis for Hospitalization or Death	Number of Events	Total Person- Days	Incidence Rate	Number of Events	Total Person-Days	Incidence Rate	Adjusted Hazard Ratio (95% Confidence Interval)
Influenza, influenza-like illness, or pneumonia[b]							
Zanamivir	10 840	579 476	0.019	14 998	579 461	0.026	1
Oseltamivir	6557	250 909	0.026	6557	250 901	0.026	1.01 (.96–1.06)
Influenza[c]							
Zanamivir	7229	579 949	0.012	10 156	579 943	0.018	1
Oseltamivir	4220	251 588	0.017	4220	251 557	0.017	0.96 (.90–1.02)
Influenza-like illness[d]							
Zanamivir							1
Oseltamivir							1.01 (.96–1.06)

Zanamivir與oseltamivir效果無統計顯著差異

COVID-19 流行期間對流感治療的建議

- COVID-19與流感無法單純以症狀區分
- 即使已確診COVID-19，仍不能排除流感感染的可能性。病患有可能是流感、COVID-19，或共同感染(co infection)
- 需經**檢驗**才能分辨COVID-19與流感感染
- 若COVID-19患者有接受**類固醇**治療又同時有流感病毒感染，可能延長病毒排出時間
- COVID-19疫情期間，對流感檢驗和治療的建議並未改變

輕症門診病患之治療

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

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

並非所有輕症病患都需要抗病毒藥物治療

住院/重症病患之治療

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

住院/重症病患，不需等待確診，不論發病時間，均應立即給予抗病毒藥物治療

預防性投藥

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

並非所有輕症病患都需要抗病毒藥物治療

疫苗

流感疫苗的介紹

流感的預防

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

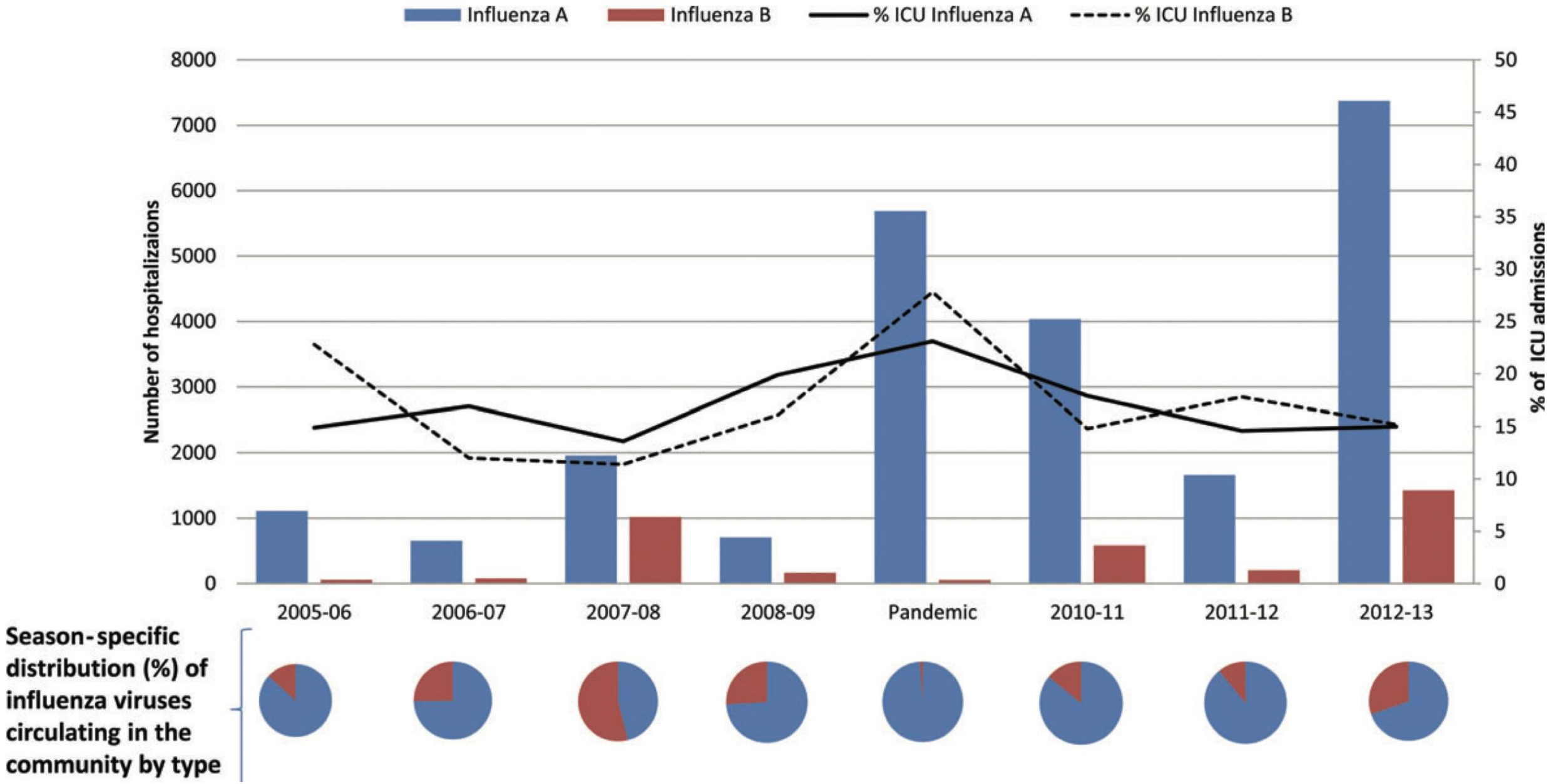
現行流感疫苗種類

分類	說明
疫苗株組成	三價(TIV，2A1B)、四價(QIV，2A2B)
製程	雞胚胎蛋培養、細胞培養、重組疫苗
疫苗病毒活性	不活化疫苗(IIV)、活性減毒疫苗(LAIV)
接種方式	肌肉注射、鼻噴劑、皮內注射
其他	高劑量疫苗(HD)、含佐劑疫苗(A)

Influenza vaccine in 2020-21 in UK

Age Group	Recommended Vaccine	Live vaccine?	Types of flu strains protected	Reason for recommendation
Children aged 6 months to 2 years	Egg-grown quadrivalent vaccine (QIVe)	**No**	**Four**	LAIV is not suitable for children under two
Children aged 2 – 17 years	Live attenuated influenza vaccine (LAIV)	**Yes**	**Four**	Nasal vaccine helps to reduce spread of flu virus in children
Adults aged 18 – 64 years	Quadrivalent influenza vaccine: Egg-grown (QIVe) Cell-based (QIVc)	**No**	**Four**	Quadrivalent vaccines protect against four types of flu strain
Adults aged 65 or over	Adjuvanted trivalent influenza vaccine (aTIV)	**No**	**Three**	"Adjuvant" is added to the vaccine to make it more effective in older people

https://vk.ovg.ox.ac.uk/vk/inactivated-flu-vaccine



Clin Infect Dis 2014 July 15

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

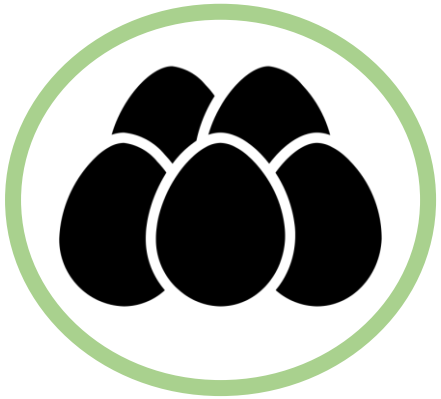
Season	Vaccine B Lineage	Circulating B Lineages	Lineage-Level Vaccine Match, %	Lineage-Level Vaccine Mismatch, %
1999–2000	Yamagata	Yamagata (100%)	100	0
2000–2001	Yamagata	Yamagata (100%)	100	0
2001–2002	Yamagata	Yamagata (100%)	100	0
2002–2003	Victoria	Victoria (90%), Yamagata (10%)	90	10
2003–2004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

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

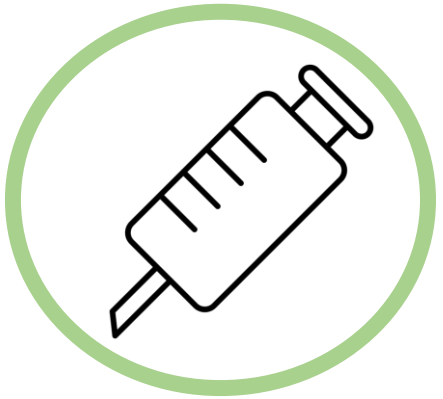
流感疫苗

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

Disadvantages of egg-based vaccine



Supply of eggs
Egg allergies



Haemagglutinin proteins mutation
H3N2

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

Cell - based influenza vaccine

18-49yrs	TIVc/TIVe Phase 3, randomized, placebo-controlled, multicenter study (2007-2008) in the US, Finland, and Poland
18-64 yrs/ >65yrs	TIVc/QIVc Phase 3, randomized, double blind, multicenter study (2013-2014) in the United States
4-17 yrs	TIVc/QIVc Phase 3, randomized, double blind, multicenter study (2013-2014) in the United States
2/3-17 yrs	Phase 3, randomized, observer blind, multicenter study (2017-2019) in EUR, South America, AST, ASIA
6m-2 yrs	Post-marketing study, randomized, observer blind, multicenter study (2017-2019)

Frey S et al. *Clin Infect Dis.* 2010;51:997-1004
Bart S et al. *Hum Vaccin Immunother.* 2016;12(9):2278-2288
Hartvickson R et al. *Int J Infect Dis.* 2015;41:65-72

2022-2023年流感疫苗選株

- 雞胚胎疫苗
  - A/Victoria/2570/2019 (H1N1)pdm09
  - A/Darwin/9/2021 (H3N2)
  - B/Austria/1359417/2021 (B/Victoria)
  - B/Phuket/3073/2013 (B/Yamagata)
- 細胞培養疫苗
  - A/Wisconsin/588/2019 (H1N1)pdm09
  - A/Darwin/6/2021 (H3N2)
  - B/Austria/1359417/2021 (B/Victoria)
  - B/Phuket/3073/2013 (B/Yamagata)

流感疫苗的有效性

Vaccine Efficacy 效力 / Effectiveness 有效性

Efficacy

(1 - relative risk) x 100

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

Effectiveness

1 – adjusted odds ratio [aOR] × 100

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

Drugs (2019) 79:1337–1348

Vaccine Effectiveness: How Well Do the Flu Vaccines Work?

Questions & Answers

疫苗株與當季流行病毒株吻合時，流感疫苗降低疾病的風險只有40-60%

Español | Other Languages

How effective is the flu vaccine?

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

FLU vaccine effectiveness varies by type or subtype

Pooled VE for all study participants irrespective of age.

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

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

Vaccine 39 (2021) 1225–1240

流感疫苗的保護效果

Pooled VE for all study participants irrespective of age.

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

VE = vaccine effectiveness; NA = not applicable.

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

Vaccine 39 (2021) 1225–1240

2019–20 Seasonal Influenza Vaccine Effectiveness — United States,

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

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

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

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

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

The Journal of Infectious Diseases

MAJOR ARTICLE

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

Mark W. Tenforde,[1] H. Keipp Talbot,[2] Christopher H. Trabue,[3] Manjusha Gaglani,[4] Tresa M. McNeal,[4] Arnold S. Monto,[5] Emily T. Martin,[5] Richard K. Zimmerman,[6] Fernanda P. Silveira,[6] Donald B. Middleton,[6] Samantha M. Olson,[1] Rebecca J. Garten Kondor,[1] John R. Barnes,[1] Jill M. Ferdinands,[1] and Manish M. Patel[1]; for the Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN) Investigators

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

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

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

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

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

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

Clinical Infectious Diseases

MAJOR ARTICLE

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

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

Methods. We conducted a test-negative study in an intensive care unit (ICU) network at 10 US hospitals to evaluate VE for preventing influenza-associated severe acute respiratory infection (SARI) during the 2019–2020 season, wh
drifted A/H1N1 and B-lineage viruses. Cases were adults hospitalized in the ICU and a targete
spectrum of severity) with laboratory-confirmed, influenza-associated SARI. Test-negative con
hospital, timing of admission, and care location (ICU vs non-ICU). Estimates were adjusted for ag

Results. Among 638 patients, the median (interquartile) age was 57 (44–68) years; 286 (4
and 42 (6.6%) died during hospitalization. Forty-five percent of cases and 61% of controls
overall VE of 32% (95% CI: 2–53%), including 28% (−9% to 52%) against influenza A and 5
was higher in adults 18–49 years old (62%; 95% CI: 27–81%) than those aged 50–64 years (
(−3%; 95% CI: −97% to 46%) (P = .0789 for interaction). VE was significantly higher against influenza-associated death (86%, 95% CI: 4–96%) than nonfatal influenza illness.

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

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

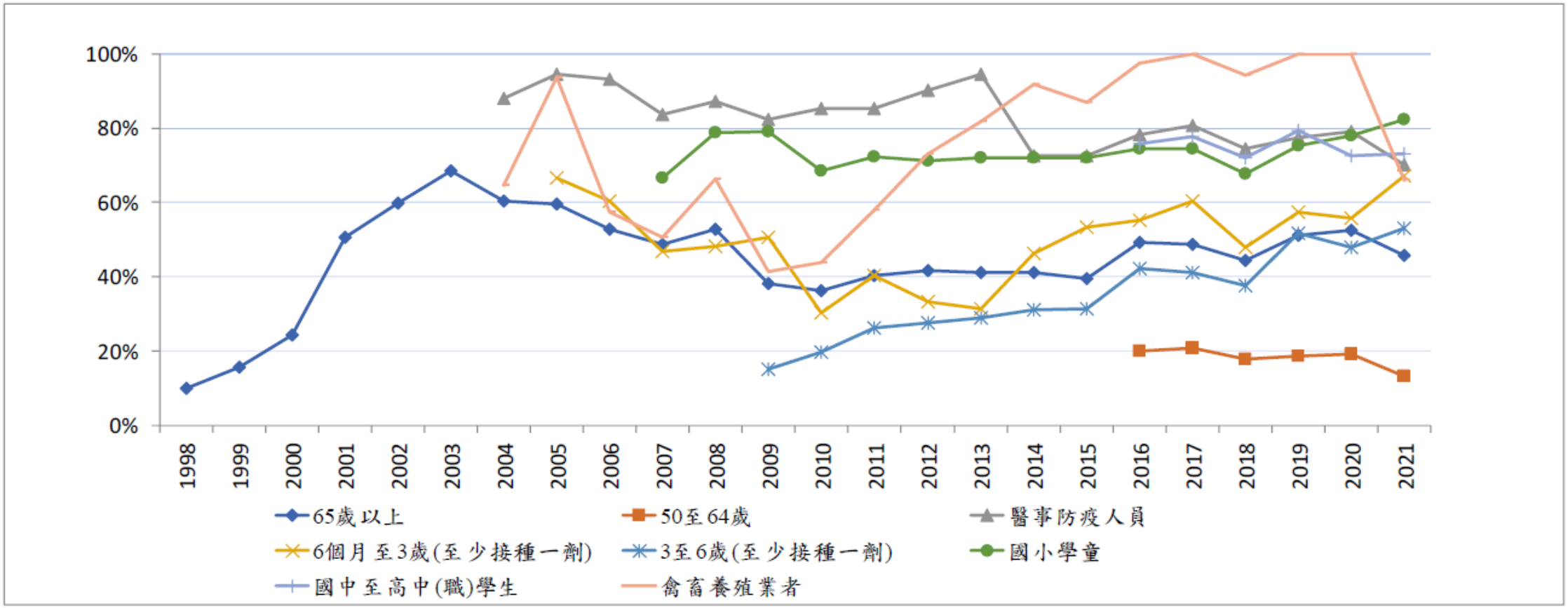
2019-2020年美國流感季流感疫苗效果
降低32%流感重症風險。
在18-49歲族群中成效最好。

流感疫苗的政策與展望

公費流感接種對象

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

歷年各類對象流感疫苗接種率



109年度流感疫苗接種計畫成果

統計日期：110/8/31

接種對象	應接種數	接種數	接種率
65歲以上長者/機構對象*	3,722,162	1,958,073	52.6%
50-64歲成人	5,304,229	1,018,139	19.2%
醫事執登人員	335,121	245,196	73.2%
防疫人員及醫院非執登工作人員	153,882	142,318	92.5%
禽畜養殖業等及動物防疫人員	10,202	10,202	100.0%
國小、國中、高中、高職、五專1至3年級學生	2,443,880	1,840,090	75.3%
3歲以上至入學前幼童--曾接種過	431,360	285,792	66.3%
3歲以上至入學前幼童--未曾接種過(第1劑)	222,842	27,168	12.2%
3歲以上至入學前幼童--未曾接種過(第2劑)		11,162	5.0%
罕見疾病/重大傷病患者		57,423	
19-49歲高風險慢性病人			
孕婦及6個月內嬰兒之父母	-	79,194	-
托育人員及托育機構專業人員	63,122	19,328	30.6%
6個月以上3歲以下幼兒--曾接種過	162,360	162,360	100.0%
6個月以上3歲以下幼兒--未曾接種過(第1劑)	340,333	111,225	32.7%
6個月以上3歲以下幼兒--未曾接種過(第2劑)		81,760	24.0%
擴大對象**	-	101,199	-

近5 年醫事人員流感接種率：66-74%

*為安養等機構之住民及所屬直接照顧工作人員

**自110年1月30日起，除原計畫對象外，擴大至全國出生滿6個月以上尚未接種之民眾

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

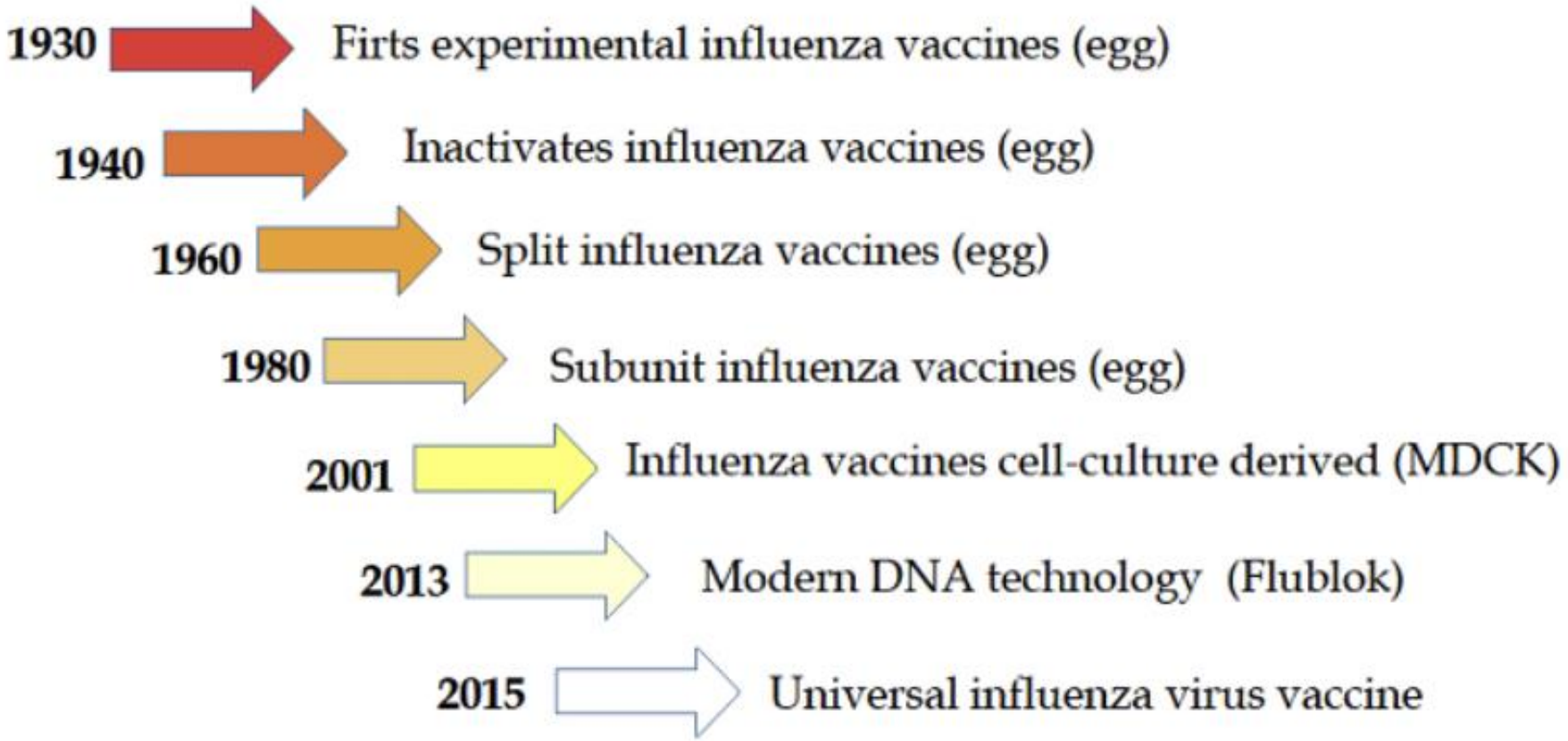
立即型過敏

- 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

30201.

- **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

Historical path of the development of influenza vaccine



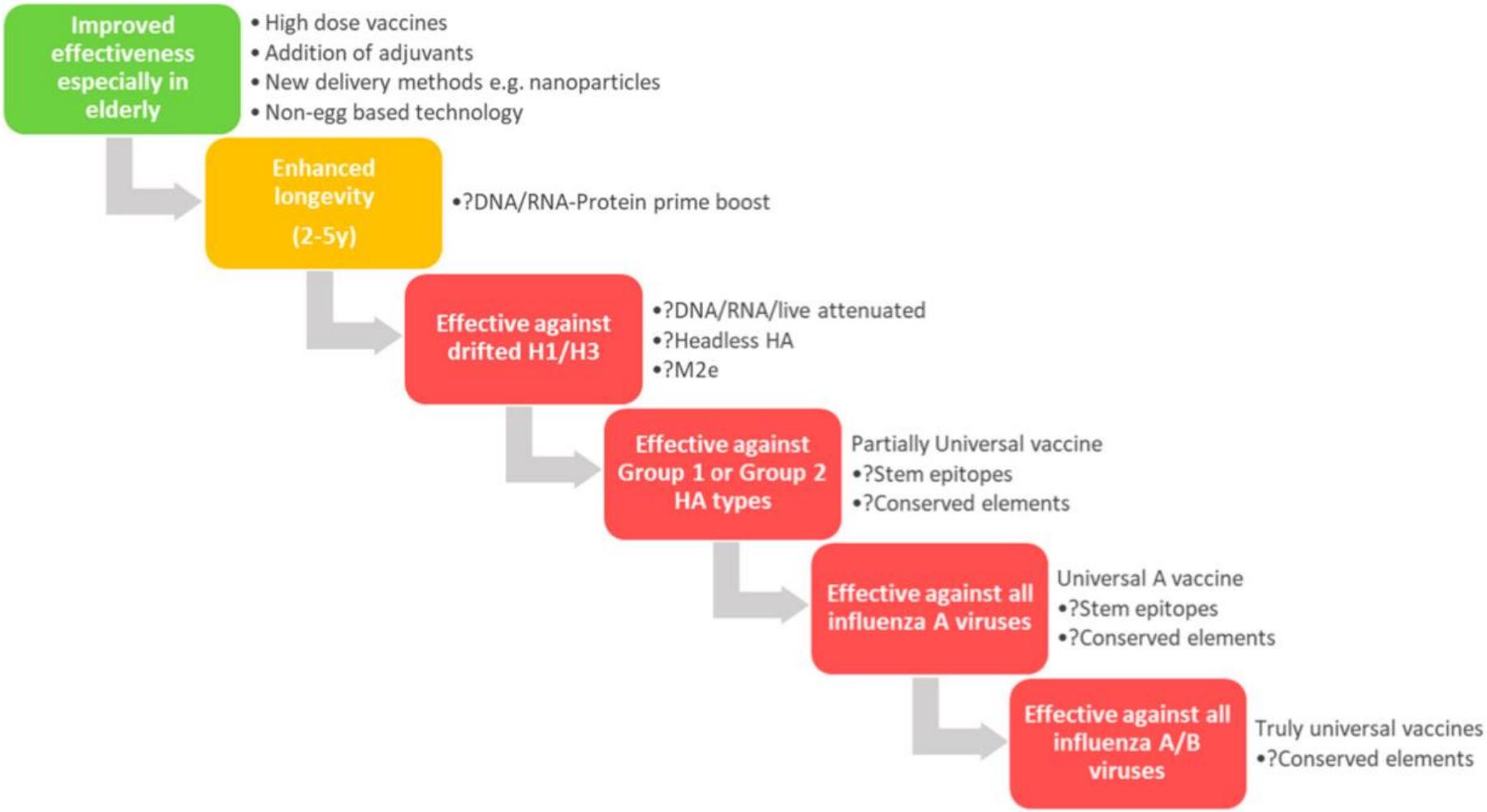
Vaccines 2017, 5, 18

Non-egg-based Influenza Vaccines

Company	Phase	Administration	Reference
Recombinant			
BiondVax	Phase III	Oral	[19]
Imutex	Phase II	SC	[20]
Recombinant—VLP			
Novavax	Phase III	IM	[21]
Osivax	Phase II	IM	[22]
Medicago	Phase III/discontinued	IM	[23]
Medigen	Phase II	IM	[24]
Recombinant—H5 protein fragment			
Generex	Phase I	Oral	[25]
Live attenuated			
Codagenix	Phase I	Nasal	[26]
FluGen	Phase II	Nasal	[27]
Vivaldi	Phase II	Nasal	[28]
Polymun	Phase I	Nasal	[29]
Vector—adenovirus			
Vaccitech	Phase II	IM	[30]
Vaxart	Phase II	Oral	[31]
Altimmune	Phase II	Nasal	[32]
Vector—alphavirus			
AlphaVax	Phase II	IM	[33]

Company	Phase	Administration	Reference
Adjuvant—novel			
BlueWillow	Phase I	Nasal	[34]
Nitto Denko	Phase I	Sublingual	[35]
Mercia	Phase II	IM	[36]
Adjuvant—toxin			
Mucosis	Phase I	Nasal	[37]
Eurocine	Phase I/II	Nasal	[38]
Advagene	Phase II	Nasal	[39]
mRNA			
Moderna Therapeutics	Phase I	IM	[40]
DNA vaccine			
Inovio	Phase I	IM	[41]
Virosomes			
Mymetics	Phase II	Nasal	[42]
Dendritic cells			
CEL-SCI	Phase I	IM	[43]

Potential steps and technologies to improve influenza vaccines



Microorganisms **2020**, *8*, 1745

總結

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

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


THANK YOU