流行性感冒歷史、流行病學、臨床表徵、診斷、與抗病毒藥物治療

(Epidemiology, clinical manifestations, laboratory diagnosis, and treatment of influenza)

中山醫學大學醫學系

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講授大綱

1. 流行性感冒的歷史與流行病學 (History and Epidemiology of Influenza)。
2. 流行性感冒 (傳統與新型流行性感冒) 的臨床表現 (Clinical Manifestations of Influenza)。
3. 流行性感冒的實驗室診斷方法 (Laboratory Diagnostic Methods of Influenza)。
4. 流行性感冒的治療藥物(Treatment Regimens of Influenza)。
5. 預防流行性感冒的疫苗注射 (Influenza Vaccine)。
6. 結論 (Conclusion)。

1. 流行性感冒的歷史與流行病學 (History and Epidemiology of Influenza)

流行性感冒 (Influenza) 大流行的歷史

1918-1919年: 被稱為 “西班牙流感”, 為A型流感病毒 (H1N1) 感染,為已知感冒引起死亡數目最多的一次流行,美國有50多萬人死亡, 全世界可能有2千萬至5千萬人死亡,許多人在感染後頭幾天內死亡,其他人則很快死於併發症,死去的人幾乎一半是年輕,健康成人

CDC, January 15, 2004

流行性感冒 (Influenza) 大流行的歷史

1957-1958年:被稱為 “亞洲流感”,為A型流感病毒 (H2N2) 感染,最初在1957年2月下旬于中國發現, 1957年6月傳至美國,在美國大約引起7萬人死亡

1968-1969年: 被稱為 “香港流感”, 為A型流感病毒 (H3N2) 感染,最初在1968年于香港發現,當年晚些時後傳到美國,在美國大約引起3萬4千人死亡; A型 (H3N2) 病毒現在仍在傳播

CDC, January 15, 2004

禽類流行性感冒 – 定義

為流行於鳥類 (常見) 與豬 (少見) 中的動物性傳染性疾病

所有鳥類對禽類流行性感冒病毒 (禽流感病毒) 均有感受性

畜養的家禽比野生禽類更易感染禽流感病毒,並造成大規模的疫情

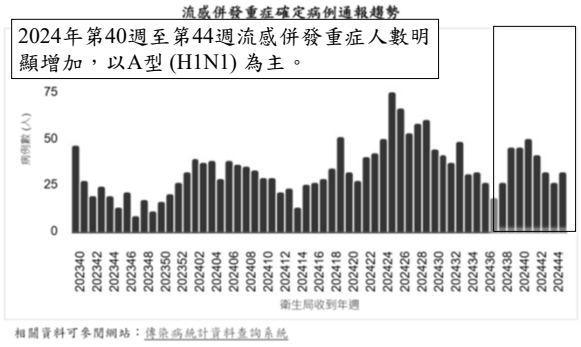
2024年第30週台灣地區流行性感冒疫情摘要

國內疫情摘要

類流感疫情已脫離流行期，惟流感併發重症病例數及死亡數仍高，須持續留意疫情變化及重症病例發生風險。

- 類流感門急診就診人次呈下降趨勢，急診就診病例百分比連續兩週低於流行閾值，研判疫情脫離流行期，惟仍須觀察後續疫情變化。
- 近四週社區合約實驗室監測顯示，流感病毒中 A 型占 86.8%，B 型占 13.2%。
- 本流感季(自 2023 年 10 月 1 日起)累計 1,433 例流感併發重症病例，其中 297 例死亡。

CDC, Taiwan. Aug 20th, 2024



CDC, Taiwan. Nov 10th, 2024

2024-2025流行性感冒季節 (2024年10月1日開始) 台灣地區流感併發重症/死亡病例

2024-2025年流感季節流感合併重症發生率依序為65歲以上和50-64歲和3-6歲族群居多，死亡率以65歲以上族群最高。

2024-2025 流感季

年齡別	病例數	死亡數	每十萬人口累積發生率	每十萬人口累積死亡率
小於 3 歲	0	0	0.00	0.00
3-6 歲	1	0	0.13	0.00
7-18 歲	2	0	0.08	0.00
19-24 歲	0	0	0.00	0.00
25-49 歲	20	3	0.23	0.03
50-64 歲	56	8	1.06	0.15
65 歲以上	123	15	2.94	0.36
總計	202	26	0.86	0.11

CDC, Taiwan. Nov 10th, 2024

H7N9A型流行性感冒 – Q&A (XI)

14. 醫療人員有感染此種A型流感 (H7N9) 的風險嗎？

答案：醫療從業人員的確是需要經常與傳染病患接觸，因此世界衛生組織建議，醫療相關機構應持續的實施感染預防及控制措施，同時其內部醫療從業人員的健康狀況也應密切監控。除了基本注意事項外，照護疑似或確診A型流感 (H7N9) 病例的醫療從業人員還必須遵從一些額外的注意事項。
(http://www.who.int/csr/resources/publications/swineflu/WHO_CDS_EPR_2007_6/en/index.html)

WHO, April 5th, 2013

Seminar

Influenza

Catharine Paules, Kanta Subbarao

內容摘要：流行性感冒是一種急性呼吸道感染，依病原可分為A、B，和C型三種型別，可在局部地區引起群突發或季節性大規模流行。臨床表現為在接觸後於極短潛伏期 (1-5日) 產生無症狀至嚴重的症狀，這取決於病毒與宿主的特性。當新型病毒自動物宿主因某些原因感染人類族群，A型流感可引起偶發性或全球大流行感染，針對季節流感和全球流感的預防和治療的新策略有其急迫性。本篇論文討論季節流感的臨床表現、傳染途徑、診斷方法、治療模式，和預防方法，並討論動物與人類之間流感傳遞模式，與聚焦於全球大流行的威脅。

Paules C and Subbarao K. Lancet. 2017;390:696-708.

表. 增加流行性感冒的罹病率與死亡率相關因子 - (I)

Panel: Factors associated with increased morbidity and mortality from influenza[1,4,9,12-19]

年齡：
1. 流感在大於65歲的老年族群增加死亡與住院比率的風險。
2. 大規模流感流行在年輕族群 (20-40歲) 增加死亡率的風險。
3. 流感在小於5歲 (特別小於2歲) 兒童族群增加住院率風險。

懷孕：
1. 在懷孕第三期時罹患流感的罹病率 (嚴重程度) 最高。
2. 在1918年和1957年全球流感大流行時懷孕病人族群死亡率最高。
3. 在2009年全球流感大流行和流行間隔期孕婦罹患流感增加住院比率。
4. 孕婦因罹患流感住院時對胎兒預後不佳。

表. 增加流行性感冒的罹病率與死亡率相關因子 - (II)

免疫功能低下族群：
1. 流感在幹細胞移植、實體器官移植，和接受化學治療的病人族群增加死亡風險。
2. 流感在人類免疫不全病毒感染 (HIV) 族群且CD4 細胞數量降低且未接受抗反轉錄病毒藥物 (HAART) 增加死亡風險。
3. 流感在接受免疫功能調節藥物族群 (決定於免疫功能抑制程度) 增加死亡風險。

合併原有疾病：
1. 包括神經肌肉疾病、認知障礙、肺部疾病、心血管疾病、腎臟疾病、肝臟疾病、糖尿病、重度酒精濫用，和肥胖病人族群增加死亡風險。
2. 因其他疾病合併流感亦增加住院率和死亡風險。
4. 孕婦因罹患流感住院時對胎兒預後不佳。

基因的易感受性：
1. 具特定基因 (干擾素誘發經膜蛋白 - IFITM3) 序列增加因流感住院風險。

interferon-stimulated gene

Paules C and Subbarao K. Lancet. 2017;390:696-708.

A型流行性感冒病毒 (Influenza Virus A)

可感染多種動物,包括鳥,豬,馬,海豹,和鯨

依表面蛋白質 (血凝素 hemagglutinin – HA 和神經氨酸 neuraminic acid – NA) 分型,分15種HA亞型 (H1 – H15) (在鳥類可全部發現)

目前已知只有3種HA亞型 (H1, H2, and H3) 和2種NA亞型 (N1 and N2) 在人類廣泛傳佈

禽類流行性感冒病毒通常不會使野鳥生病 (或病情較輕微) ,但可使家禽得重病致死

CDC, January 15, 2004

新型A型流感比較表

	H5N6流感	H7N9流感
傳染途徑	均為禽傳人 人傳人尚無案例	絕大多數為禽傳人 人傳人罕見，僅零星案例
禽鳥案例流行地區	韓國、日本、中國大陸	中國大陸
人類病例感染地區	中國大陸	中國大陸
對禽鳥致病性	高致病性，可引起禽鳥大量死亡	原本為低致病性，但近日已發現高致病性突變株可引起禽鳥大量死亡
人類病例總數	17例（含12死）	1307例（含380死）
致死率	約70%	約30-40%
症狀	初期為類流感症狀，發展為嚴重肺炎，可引發多重器官衰竭	初期為類流感症狀，發展為嚴重肺炎，可引發多重器官衰竭
治療	抗病毒藥物、重症加護治療	抗病毒藥物、重症加護治療

CDC, Taiwan. March 14th,

2. 流行性感冒 (傳統與新型流行性感冒) 的臨床表現 (Clinical Manifestations of Influenza)

流行性感冒症狀: 高燒、咽喉疼痛、頭痛、肌肉關節酸痛、鼻塞和流鼻水 (少見)、嘔吐 (少見)，腹瀉 (少見)、

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CURRENT CONCEPTS

Update on Avian Influenza A (H5N1) Virus Infection in Humans

Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus*

內容摘要：H5N1 A型新型流感 (前稱禽流感) 於1997年開始以史無前例的方式自鳥類有效傳遞至人類族群，引起高死亡率和具有造成全世界大流行的風險。本篇論文整理2005年H5N1 A型流感的最新資訊，包含通報疫情與第二次世界衛生組織 (WHO) 的人類感染H5N1 A型流感臨床表現諮詢會議內容。

World Health Organization. N Engl J Med. 2008;358:261-273.

表一. 根據H5N1 A型新型流感病毒的基因分型 (含亞型) 和所在國家和地區的人類病例死亡率與症狀出現至住院和死亡的中位數日期

Table 1. Case Fatality Proportion According to Clade or Subclade and Median Time from Onset of Illness to Hospitalization or Death in Patients with Confirmed Influenza A (H5N1) Illness.

流行的國家和地區 / Country	病毒基因分型（含亞型） / Predominant Clade or Subclade*	死亡人數和死亡率 / Case Fatality Proportion	症狀出現至住院間隔 / Onset of Illness to Hospitalization		症狀出現至死亡間隔 / Onset of Illness to Death	
		no. of patients/ total no. (%)	*days*	*no. of patients*	*days*	*no. of patients*
Cambodia, Thailand, Vietnam†	1	66/123 (54)	4	109	9	65
Indonesia	2.1	76/96 (79)	5	64	9	72
Azerbaijan, Djibouti, Egypt, Iraq, Nigeria, Turkey	2.2	26/59 (44)	3	36	9	24
China, Laos	2.3	17/26 (65)	5	16	10	17

World Health Organization. N Engl J Med. 2008;358:261-273.

表二. 依據發生國家和地區的人類感染病例H5N1 A型新型流感病例的基本資料與臨床表現 - (I)

Table 2. Clinical and Common Laboratory Features of Influenza A (H5N1) Disease at Hospital Admission.*

Variable	Vietnam, Thailand, Cambodia, 2004–2005, Clade 1†	Indonesia, 2005–2006, Clade 2.1‡	China, 2005–2006, Clade 2.3§	Egypt, 2006–2007, Clade 2.2¶	Turkey, Azerbaijan, 2006, Clade 2.2‖
Age — yr					
Median	14–22	18.5	30	12.5	16.5–10.0
Range	2–58	1.5–45.0	12–41	1–75	5–20
Male sex — no./total no. (%)	19/41 (46)	33/54 (61)	3/8 (38)	12/38 (32)	9/16 (56)
Contact with poultry within previous 2 weeks — no./ total no. (%)	31/36 (86)	41/54 (76)	8/8 (100)**	31/38 (82)	8/8 (100)††
Time from onset of symptoms to hospitalization — days					
Median	6–8	5	6	3	5–6
Range	3–8	1–14	3–11	0–14	1–12
Clinical presentation — no./ total no. (%)					
Fever	41/41 (100)	54/54 (100)	8/8 (100)	34/38 (89)	15/16 (94)
Dyspnea	33/37 (89)	51/54 (94)	4/8 (50)	14/38 (37)	7/16 (44)
Cough	40/41 (98)	50/54 (93)	7/8 (88)	27/38 (71)	12/15 (80)
Pneumonia	41/41 (100)	54/54 (100)	8/8 (100)	23/38 (61)‡‡	14/16 (88)
Coryza	9/27 (33)	NR	NR	NR	2/14 (14)
Sore throat	13/41 (32)	NR	NR	26/38 (68)	14/16 (88)
Vomiting	5/31 (16)	6/54 (11)	NR	3/37 (8)	0/7 (0)
Diarrhea	16/31 (52)	6/54 (11)	NR	2/37 (5)	4/14 (29)

World Health Organization. N Engl J Med. 2008;358:261-273.

表二. 依據發生國家和地區的人類感染病例H5N1 A型新型流感病例的基本資料與臨床表現 - (II)

Table 2. Clinical and Common Laboratory Features of Influenza A (H5N1) Disease at Hospital Admission.*

Variable	Vietnam, Thailand, Cambodia, 2004–2005, Clade 1†	Indonesia, 2005–2006, Clade 2.1‡	China, 2005–2006, Clade 2.3§	Egypt, 2006–2007, Clade 2.2¶	Turkey, Azerbaijan, 2006, Clade 2.2‖
Depressed consciousness	NR	NR	NR	3/38 (8)	4/8 (50)
Seizures	NR	1/54 (2)	NR	NR	2/7 (29)
Headache	5/14 (36)	7/54 (13)	NR	19/38 (50)	7/15 (47)
Conjunctivitis	0/22 (0)	NR	NR	14/38 (37)	1/8 (12)
Myalgia	11/37(30)	7/54 (13)	NR	17/38 (45)	4/15 (27)
Leukopenia	17/22 (77)	41/49 (84)	NR	10/37 (27)	11/15 (73)
Lymphopenia	16/24 (67)	16/29 (55)	NR	4/25 (16)	7/13 (54)
Thrombocytopenia	13/24 (54)	29/45 (64)	NR	8/26 (31)	9/13 (69)
Increased aminotransferase levels	20/28 (71)	NR	NR	15/27 (56)	6/8 (75)
Deaths — no./ total no. (%)	32/41 (78)	41/54 (76)	7/8 (88)	15/38 (39)	9/16 (56)
Time from onset of symptoms to death — days					
Median	8–12	9	9	11.5	10–13
Range	4–30	5–19	8–19	6–32	9–17

World Health Organization. N Engl J Med. 2008;358:261-273.

表三. 在印尼和泰國實驗室確認感染H5N1 A型新型流感人類病例的初始診斷種類與個案數

Table 3. Initial Diagnosis in Patients with Confirmed Influenza A (H5N1) Virus Infection.*

Diagnosis	Indonesia (N=52)	Thailand (N=25)
	number (percent)	
Pneumonia	24 (46)	11 (44)
Dengue virus infection	6 (12)	4 (16)
Typhoid fever	2 (4)	0 (0)
Upper respiratory illness	14 (27)	4 (16)
Avian influenza	6 (12)	2 (8)
Other	0 (0)	4 (16)†

World Health Organization. N Engl J Med. 2008;358:261-273.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Human Infection with a Novel Avian-Origin Influenza A (H7N9) Virus

Rongbao Gao, M.D., Bin Cao, M.D., Yunwen Hu, M.D., Zijian Feng, M.D., M.P.H., Dayan Wang, M.D., Wanfu Hu, M.D., Jian Chen, M.D., Zhijun Jie, M.D., Haibo Qiu, M.D., Ph.D., Ke Xu, M.D., Xuewei Xu, M.D., Hongzhou Lu, M.D., Ph.D., Wenfei Zhu, M.D., Zhancheng Gao, M.D., Nijuan Xiang, M.D., Yinzhong Shen, M.D., Zebao He, M.D., Yong Gu, M.D., Zhiyong Zhang, M.D., Yi Yang, M.D., Ph.D., Xiang Zhao, M.D., Lei Zhou, M.D., Xiaodan Li, M.D., Shumei Zou, M.D., Ye Zhang, M.D., Xiyan Li, M.D., Lei Yang, M.D., Junfeng Guo, M.D., Jie Dong, M.D., Qun Li, M.D., Libo Dong, M.D., Yun Zhu, M.D., Tian Bai, M.D., Shiwen Wang, M.D., Pei Hao, M.D., Weizhong Yang, M.D., Yanping Zhang, M.D., Jun Han, M.D., Hongjie Yu, M.D., Dexin Li, M.D., George F. Gao, Ph.D., Guizhen Wu, M.D., Yu Wang, M.D., Zhenghong Yuan, Ph.D., and Yuelong Shu, Ph.D.

Gao R et al. N Engl J Med April 11th, 2013 DOI:10.1056/NEJMoa1304459

表一. 3名新型H7N9流感病毒感染病人的基本資料、流行病學、病毒學特性、併發症、治療藥物，和臨床預後資料 – (I)

Table 1. Demographic, Epidemiologic, and Virologic Characteristics and Complications, Treatment, and Clinical Outcomes of Three Patients Infected with Avian-Origin Influenza A (H7N9) Virus.*

Characteristic	Patient 1	Patient 2	Patient 3
Age (yr)	87	27	35
Sex	Male	Male	Female
Occupation	Retired	Butcher	Housewife
Underlying conditions	COPD, hypertension	Hepatitis B	Depression, hepatitis B, obesity
Area of origin	Shanghai	Shanghai	Anhui
Exposure to chicken market in past 7 days	No	Yes	Yes
Date of illness onset	February 18, 2013	February 27, 2013	March 13, 2013
Date of admission	February 25, 2013	March 4, 2013	March 19, 2013
Admission to ICU	None	March 6, 2013	March 20, 2013
Date of specimen collection	February 26, 2013	March 5, 2013	March 20, 2013
Date of laboratory confirmation of virus	March 30, 2013	March 30, 2013	March 30, 2013
Viral isolation	A/Shanghai/1/2013 (H7N9)	A/Shanghai/2/2013 (H7N9)	A/Anhui/1/2013 (H7N9)

Gao R et al. N Engl J Med April 11th, 2013
DOI:10.1056/NEJMoa1304459

ORIGINAL ARTICLE

Clinical Findings in 111 Cases of Influenza A (H7N9) Virus Infection

研究方法與目的：自2013年的春天開始，中國大陸開始在人群流行新型H7N9禽類流行性感冒感染，有關此類新型禽流感病毒感染的臨床表現並無文獻報告。
研究方法：自醫療病歷收集自2013年5月開始的111名實驗室檢驗確定診斷新型H7N9禽流感病人的臨床資訊。
研究結果：在111名實驗室檢驗確定H7N9禽類流感病毒感染病人中，有76.6%病人收治加護病房治療，其中27.0%病人死亡。病人年齡中位數為61歲，其中42.3%病人的年齡超過65歲，且61.3%病人具有一種以上的原有疾病。發燒與咳嗽是最常見的症狀，住院時發現有108名病人有肺炎表現。、

Gao H-N et al. N Engl J Med 2013;368:2277-2285.

表一. 中國大陸確認感染H7N9流感病毒的111名病人的基本資料與流行病學資料 – (I)

Table 1. **Demographic and Epidemiologic Characteristics of 111 Patients Infected with H7N9 Virus in China.**

Characteristic	Value
Age	
Median (range) — yr	61 (3–88)
Subgroup — no. (%)	
0–4 yr	1 (0.9)
5–14 yr	1 (0.9)
15–49 yr	28 (25.2)
50–64 yr	34 (30.6)
≥65 yr	47 (42.3)
Female sex — no. (%)	35 (31.5)

大部分感染H7N9流感的病人為成年男性病人

Gao H-N et al. N Engl J Med 2013;368:2277-2285

表一. 中國大陸確認感染H7N9流感病毒的111名病人的基本資料與流行病學資料 – (II)

Coexisting condition — no. (%)	
Any	68 (61.3)
Hypertension	51 (45.9)
Diabetes	18 (16.2)
Coronary heart disease	11 (9.9)
Immunosuppression*	10 (9.0)
Chronic obstructive pulm	
Cancer†	
Cerebrovascular disease	
Hepatitis B infection‡	
Chronic renal disease	
Pregnancy	
Current smoker — no. (%)	27 (24.3)
Exposure to live poultry	
In previous 14 days — no. (%)	62 (55.9)
Median incubation time since exposure (interquartile range) — days	5 (2–8)
Hospitalization — no. (%)	109 (98.2)

多數感染H7N9流感的病人具有原有疾病、有1/4病人抽煙、超過半數病人於發病前14天內有禽鳥接觸史，幾乎所有病人接受住院診斷治療。

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表二. 中國大陸確認感染H7N9流感病毒的111名病人的臨床表現和實驗室檢查結果 – (I)

Table 2. **Clinical Characteristics and Selected Laboratory Abnormalities of 111 Patients Infected with H7N9 Virus ***

Characteristic 臨床表現	Value 數值
Fever	
Any — no. (%)	111 (100.0)
Maximal temperature — °C	39.2±0.8
Subgroup — no. (%)	
37.3–38.0°C	11 (9.9)
38.1–39.0°C	43 (38.7)
>39.0°C	57 (51.4)
Fatigue — no. (%)	40 (36.0)
Conjunctivitis — no. (%)	0
Cough — no. (%)	100 (90.1)
Sputum production — no. (%)	62 (55.9)
Hemoptysis — no. (%)	27 (24.3)
Shortness of breath — no. (%)	62 (55.9)
Diarrhea or vomiting — no. (%)	15 (13.5)

多數感染H7N9流感病人多有高燒和咳嗽有痰等症狀

Gao H-N et al. N Engl J Med 2013;368:2277-2285

表二. 中國大陸確認感染H7N9流感病毒的111名病人的臨床表現和實驗室檢查結果 – (II)

實驗室檢查項目	數值
White cells	
Median — per mm³	4450
Interquartile range — p	2900–6230
Subgroup — no. (%)	
>10,000 per mm³	5 (4.5)
<4000 per mm³	51 (45.9)
Lymphocytes — per mm³	
Median	460
Interquartile range	320–700
Lymphocytopenia — no. (%)	98 (88.3)
Hemoglobulin — g/dl	12.9±3.1
Platelets — per mm³	
Median	115,500
Interquartile range	82,000–149,500
Thrombocytopenia — no. (%)	81 (73.0)
C-reactive protein >10 mg/liter — no. (%)	85 (76.6)
Procalcitonin >0.5 ng/ml — no. (%)	28 (37.3)

多數的感染H7N9流感病人血液的白血球小於4,000 cells/mm3 、淋巴球數目低下、 血小板數目低下，和發炎指數上升等異常實驗室檢查結果

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表二. 中國大陸確認感染H7N9流感病毒的111名病人的臨床表現和實驗室檢查結果 – (III)

實驗室檢查項目	數值
Aspartate aminotransferas	73 (65.8)
Creatinine >133 μmol/liter	10 (9.0)
Lactate dehydrogenase >2	91 (82.0)
Creatine kinase >200 U/lit	49 (44.1)
Myoglobulin >80 μg/ml —	16 (55.2)
PaO_2:FiO_2	
Median	144.0
Interquartile range	107.1–226.9
Potassium — mmol/liter	3.8±0.5
Sodium — mmol/liter	136.8±6.0
D-dimer >0.5 mg/liter — no. (%)	47 (90.4)
Chest radiologic findings — no. (%)	
Involvement of both lungs	60 (54.1)
Ground-glass opacity	62 (55.9)
Consolidation	99 (89.2)

多數的感染H7N9流感病人血液的肝功能、乳酸去氫酶、肌酐激酶，和肌肉球蛋白數值上升，血氧濃度與氧氣分壓比值下降，和D-dimer數值上升；胸部影像學檢查發現多為兩側肺部病灶、堅實化病變，和毛玻璃病變

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表三. 中國大陸確認感染H7N9流感病毒的111名病人的併發症、治療模式，和預後 – (I)

感染H7N9流感病人多出現肺炎、急性呼吸窘迫症候群，和休克等併發症；有四分之一的病人的檢體培養出細菌，絕大多數的病人接受抗流感藥物

Table 3. Complications, Treatment, and Clinical Outcomes in 111 Patients Infected with H7N9 Virus.*

Variable 併發症種類	Value 人數 (%)
	no. of patients (%)
Complications	
Pneumonia	108 (97.3)
Acute respiratory distress syndrome	79 (71.2)
Shock	29 (26.1)
Acute kidney injury	18 (16.2)
Rhabdomyolysis	11 (9.9)
Treatment 治療模式種類	
Bacteria isolation from culture	29 (26.1)
Administration of oseltamivir or peramivir	108 (97.3)

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表三. 中國大陸確認感染H7N9流感病毒的111名病人的併發症、治療模式，和預後 – (II)

感染H7N9流感病人多數於症狀出現3天後才開始接受抗流感藥物，超過8成的病人使用呼吸器，約四分之一病人需要接受血液透析治療，合併使用抗生素的病人超過7成

治療模式種類	
Timing from onset of illn… of antiviral therap…	
0–2 days	…
3–5 days	32 (28.8)
≥6 days	65 (58.6)
Oxygen therapy	111 (100)
Mechanical ventilation	
Noninvasive	31 (27.9)
Invasive	65 (58.6)
Admission to an intensive care unit	85 (76.6)
Extracorporeal membrane oxygenation	20 (18.0)
Continuous renal-replacement therapy	29 (26.1)
Artificial-liver-support-system therapy*	17 (15.3)
Antibiotics	79 (71.2)

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表三. 中國大陸確認感染H7N9流感病毒的111名病人的併發症、治療模式，和預後 – (III)

感染H7N9流感病人死亡率為27%，且死因多為頑固性低血氧症

治療模式種類	人數 (%)
Antifungal drugs	1 (0.9)
Glucocorticoids	69 (62.2)
Intravenous immune globulin	59 (53.2)
Clinical outcome 臨床預後	
Death	30 (27.0)
Cause of death	
Refractory hypoxemia	22 (73.3)
Shock	1 (3.3)
Acute heart failure	2 (6.7)
Secondary bacterial or fungal infection	3 (10)
Arrhythmia	2 (6.7)
Discharge from hospital†	49 (44.1)

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表四. 中國大陸確認感染H7N9流感病毒的97名病人與急性呼吸窘迫症候群相關的危險因子 (多變數分析)

Table 4. Multivariate Analysis of Risk Factors for the 79 Patients with the Acute Respiratory Distress Syndrome.

感染H7N9流感病人合併急性呼吸窘迫症候群與病人具有原發性疾病有密切相關

Risk Factor	Odds Ratio (95% CI)*	P Value
Age ≥65 yr	1.01 (0.99–1.03)	0.30
Coexisting medical condition	3.42 (1.21–9.70)	0.02
Lymphocyte count <1000 cells/mm³	2.73 (0.60–12.52)	0.20
Aspartate aminotransferase level >40 U/liter	1.37 (0.42–4.43)	0.60
Creatine kinase level >200 U/liter	1.80 (0.59–5.48)	0.30
Time from symptom onset to initiation of antiviral therapy >3 days	2.42 (0.49–11.99)	0.28

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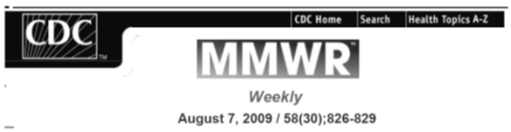
3. 流行性感冒的實驗室診斷方法 (Laboratory Diagnostic Methods of Influenza)



Evaluation of Rapid Influenza Diagnostic Tests for Detection of Novel Influenza A (H1N1) Virus --- United States, 2009

TABLE 1. Comparison of the number of positive influenza A test results from three RIDTs* with the number of positive results from rRT-PCR† assay, by influenza A type and cycle threshold (Ct) interval — United States, 2009

對H1N1 swine flu 的敏感性只有 40-69%

RIDT	Influenza A virus type	No. of specimens positive by RIDT/ No. positive by rRT-PCR Ct interval§ (<20)	(20 to <25)	(25–30)	(>30)	Total no. of specimens positive by RIDT/ Total no. positive by rRT-PCR (%)
BinaxNOW Influenza A&B	Novel H1N1	8/9	7/17	2/13	1/6	18/45 (40)
	Seasonal H1N1	---¶	2/3	1/2	---	3/5 (60)
	Seasonal H3N2	---	10/10	2/4	0/1	12/15 (80)
Directigen EZ Flu A+B	Novel H1N1	8/9	10/16	2/12	1/6	21/43** (49)
	Seasonal H1N1	---	2/2	1/2	---	3/4** (75)
	Seasonal H3N2	---	8/8	2/3	0/1	10/12** (83)
QuickVue A+B	Novel H1N1	9/9	13/17	6/13	3/6	31/45 (69)
	Seasonal H1N1	---	2/3	2/2	---	4/5 (80)
	Seasonal H3N2	---	10/10	2/4	0/1	12/15 (80)

* Rapid influenza A diagnostic tests.

MMWR 2009;58(30):826-829

World Health Organization

Real-time RT-PCR Protocol for the Detection of A(H7N9) Influenza Virus

使用分子生物學 (即時聚合酶連鎖反應 – real time PCR) 對咽喉拭子檢體檢驗H7N9流感病毒的血凝素 (hemaglutinin – HA) 和神經激胺酶 (neuramidase – NA) 的支配基因 (H7和N9)。

The WHO Collaborating Center for Reference and Research on Influenza at the Chinese National Influenza Center, Beijing, China, has made available attached real-time RT-PCR protocol for influenza A(H7N9).

WHO, April 8th 2013

使用即時聚合酶連鎖反應 (Real-Time PCR) 偵測H7N9流感病毒的實驗設備與材料

2.1 Real-time fluorescence quantitative PCR analysis system

2.2 Bench top centrifuge for 1.5mL Eppendorf tubes

2.3 10, 200, 1000μL pipettors and plugged tips

2.4 Vortex

2.5 QIAGEN RNeasy Mini Kit

2.6 AgPath one-step RT-PCR kit

2.7 The specific primers and probes for the H7and N9 genes are summarized in the table below. In addition, the use of a primer and probe targeted M gene and house-keeping gene such a RNP is recommended for typing all influenza A virus and internal control in the tests.

WHO, April 8th 2013

使用即時聚合酶連鎖反應 (Real-Time PCR) 偵測H7N9流感病毒所需的探針核苷酸序列

Table of PCR primers and probes

ID	Sequence	Note
H7		
CNIC-H7F	5'-AGAAATGAAATGGCTCCTGTCAA-3'	Primer
CNIC-H7R	5'-GGTTTTTTTCTTGTATTTTTATATGACTTAG-3'	Primer
CNIC-H7P	5'FAM-AGATAATGCTGCATTCCCGCAGATG-BHQ1-3'	Probe
N9		
CNIC-N9	5′ TGGCAATGACACACACTAGTCAGT 3′	Primer
CNIC-N9R	5′ ATTACCTGGATAAGGGTCGTTACACT 3′	Primer
CNIC-N9P	5'FAM- AGACAATCCCCGACCGAATGACCC -BHQ1-3′	Probe
FluA		
InfA Forward	5′ GACCRATCCTGTCACCTCTGA C 3′	Primer
InfA Reverse	5′ AGGGCATTYTGGACAAAKCGTCTA3′	Primer
InfA Probe1	5′ FAM-TGC AGT CCT CGC TCA CTG GGC ACG-BHQ1-3′	Probe
RnaseP		
RnaseP Forward	5′ AGATTTGGACCTGCGAGCG 3′	Primer
RnaseP Reverse	5′ GAGCGGCTGTCTCCACAA GT3′	Primer
RnaseP Probe1	5'FAM-TTCTGACCTGAA GGCTCTGCGCG-BHQ1-3′	Probe

Note: FluA and RNase primer/probe sets were from published WHO protocol provided by CDC, Atlanta.

WHO, April 8th 2013

使用即時聚合酶連鎖反應 (Real-Time PCR) 偵測H7N9流感病毒所需的各項實驗材料與劑量

Components	volume（μL）
2× RT-PCR Master Mix	12.5
primer-forward（40μM）	0.5
primer-reverse（40μM）	0.5
Probe （20 μM）	0.5
QuantiTect RT Mix	1
Template RNA	5.0
RNase Free H_2O	5
Total	25

WHO, April 8th 2013

偵測H7N9流感病毒使用即時聚合酶連鎖反應 (Real-Time PCR) 的反應條件與判讀結果標準

The results are determined if the quality controls work.

(1) The specimen is negative if the value of Ct is undetectable,

(2) The specimen is positive if Ct value is ≤38.0.

(3) It is suggested that specimens with a Ct higher than 38 are repeated. The specimen can be considered positive if the repeat results are the same as before i.e. Ct is higher than 38. If the repeat Ct is undetectable, the specimen is considered negative.

WHO, April 8th 2013

Journal of Clinical Microbiology®
VIROLOGY

Multicenter Evaluation of BioFire FilmArray Respiratory Panel 2 for Detection of Viruses and Bacteria in Nasopharyngeal Swab Samples

研究背景：多重引子聚合酶反應 - 呼吸道感染模組 (Filmarray Respiratory Panel 2 – RP2) 是經美國食品藥物管理局審核通過的快速檢驗 (約需22分鐘) 鼻咽拭子 (nasopharyngeal swab – NPS) 的22種常見呼吸道感染微生物的檢驗方法，包括更新先前的RP1.7版內容並加速檢驗時間，檢驗項目包括腺病毒、冠狀病毒229E、冠狀病毒HKU1、冠狀病毒NL63、冠狀病毒OC43、人類間質性肺炎病毒 (metapneumovirus)、人類鼻病毒/腸病毒、A型流感病毒、A型流感病毒H1、2009年A型流感病毒H1 (株流感病毒)、A型流感病毒H3、 B型流感病毒、副流感病毒 (1, 2, 3型)、呼吸道融合病毒 (RSV)、百日咳菌 (*Bordetella pertussis*)、

Leber A L. et al. J Clin Microbiol. 2018;56(6):e01945-17.

Journal of Clinical Microbiology®
VIROLOGY

Multicenter Evaluation of BioFire FilmArray Respiratory Panel 2 for Detection of Viruses and Bacteria in Nasopharyngeal Swab Samples

研究背景 (續)：肺炎披衣菌 (*Chlamydia pneumoniae*)、黴漿菌 (*Mycoplasma pneumoniae*)、中東呼吸道冠狀病毒 (Middle East respiratory syndrome coronavirus – MERS-CoV) (新)，和副百日咳菌 (*Bordetella parapertussis*) (新)。
研究方法：屬於前瞻性研究，收集多中心共1,612個NPS檢體，實驗組為 FilmArray RP2，對照組為RP、其他PCR，和核苷酸定序 (sequencing)。
研究結果：實驗組和對照組的整體實驗符合度 (agreement) 為99.2%。除冠狀病毒OC43、百日咳菌，和副百日咳菌外，RP2對偵測微生物的陽性實驗符合度≥ 91.7%，對所有偵測微生物

Leber A L. et al. J Clin Microbiol. 2018;56(6):e01945-17.

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VIROLOGY

Multicenter Evaluation of BioFire FilmArray Respiratory Panel 2 for Detection of Viruses and Bacteria in Nasopharyngeal Swab Samples

研究結果 (續)：的陰性實驗符合度均≥ 93.8%。RP2可以偵測所有腺病毒的基因型，並且試驗的敏感度較對照組提昇。
結論： FilmArray RP2 較先前版本 FilmArray RP 對於常見呼吸道感染微生物的偵測有較高的敏感度和特異度，並且檢驗時間縮短，這對於不同情境 (如門診和住院與加護病房肺炎病人)的呼吸道感染症提供快速和可信賴的檢驗結果。

Leber A L. et al. J Clin Microbiol. 2018;56(6):e01945-17.

表一. 使用 FilmArray RP2 診斷呼吸道感染的標的 (病毒與細菌) 種類和舊版 (FilmArray RP) 的相異

TABLE 1 Analytes detected by the FilmArray RP2

Analyte	Change relative to RP[a]
Viruses	
Adenovirus	Updated primers[b], additional assays
Coronavirus 229E	Updated primers
Coronavirus HKU1	Not modified
Coronavirus NL63	Not modified
Coronavirus OC43	Updated primers
Human metapneumovirus	Updated primers
Human rhinovirus/enterovirus	Updated primers
Influenza A virus	Updated primers
H1	Updated primers
H1-2009	Not modified
H3	Updated primers
Influenza B virus	Not modified
Middle East respiratory syndrome coronavirus (MERS-CoV)	New
Parainfluenza virus 1	Updated primers
Parainfluenza virus 2	Updated primers
Parainfluenza virus 3	Updated primers
Parainfluenza virus 4	Updated primers
Respiratory syncytial virus	Updated primers
Bacteria	
Bordetella parapertussis (IS*1001*)	New
Bordetella pertussis (*ptxP*)	Not modified
Chlamydia pneumoniae	Not modified
Mycoplasma pneumoniae	Updated primers

[a]General pouch chemistry improvements led to increased sensitivity overall.
[b]Assay modified for broader inclusivity.

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表三. 使用 FilmArray RP2 診斷呼吸道感染的標的 (病毒與細菌) 種類和整體與各年齡層的陽性率

TABLE 3 Prevalence of FilmArray RP2-detected analytes stratified by age group

	Prevalence of analyte in indicated subject group									
	Overall (*n* = 1,612)		≤5 yrs (*n* = 885)		6–21 yrs (*n* = 331)		22–49 yrs (*n* = 128)		≥50 yrs (*n* = 268)	
Analyte	No.	%	No.	%	No.	%	No.	%	No.	%
Viruses										
Adenovirus	118	7.3	96	10.8	18	5.4	2	1.6	2	0.7
Coronavirus 229E	16	1.0	3	0.3	7	2.1	1	0.8	5	1.9
Coronavirus HKU1	55	3.4	37	4.2	9	2.7	2	1.6	7	2.6
Coronavirus NL63	50	3.1	41	4.6	6	1.8	2	1.6	1	0.4
Coronavirus OC43	38	2.4	28	3.2	7	2.1	0	0	3	1.1
Human metapneumovirus	81	5.0	60	6.8	12	3.6	3	2.3	6	2.2
Human rhinovirus/enterovirus	502	31.1	379	42.8	88	26.6	16	12.5	19	7.1
Influenza virus A	78	4.8	29	3.3	20	6.0	13	10.2	16	6.0
H1	0	0	0	0	0	0	0	0	0	0
H1-2009	74	4.6	26	2.9	19	5.7	13	10.2	16	6.0
[illegible]	[illegible]									
Influenza B	16	1.0	7	0.8	7	2.1	1	0.8	1	0.4
Middle East respiratory syndrome coronavirus (MERS-CoV)	0	0	0	0	0	0	0	0	0	0
Parainfluenza virus 1	10	0.6	9	1.0	0	0	1	0.8	0	0
Parainfluenza virus 2	54	3.3	39	4.4	10	3.0	1	0.8	4	1.5
Parainfluenza virus 3	53	3.3	44	5.0	6	1.8	2	1.6	1	0.4
Parainfluenza virus 4	16	1.0	13	1.5	1	0.3	0	0	2	0.7
Respiratory syncytial virus	199	12.3	168	19.0	10	3.0	8	6.3	13	4.9
Bacteria										
Bordetella parapertussis (IS*1001*)	6	0.4	4	0.5	2	0.6	0	0	0	0
Bordetella pertussis (*ptxP*)	3	0.2	0	0	3	0.9	0	0	0	0
Chlamydia pneumoniae	6	0.4	1	0.1	4	1.2	1	0.8	0	0
Mycoplasma pneumoniae	28	1.7	10	1.1	14	4.2	3	2.3	1	0.4

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表四. 使用 FilmArray RP2 和對照組相比的陽性結果符合度 (positive percent agreement – PPA) 與陰性結果符合度 (negative percent agreement – NPA)

TABLE 4 Performance summary and characteristics of FilmArray RP2 versus those of the comparator assays[a]

	PPA[b]			NPA		
Analyte	TP/(TP + FN)	%	95% CI	TN/(TN + FP)	%	95% CI
Viruses						
Adenovirus	70/74	94.6	86.9–97.9	1,490/1,538	96.9	95.9–97.6
Coronavirus 229E	11/12	91.7	64.6–98.5	1,595/1,600	99.7	99.3–99.9
Coronavirus HKU1	43/43	100	91.8–100	1,557/1,569	99.2	98.7–99.6
Coronavirus NL63	40/40	100	91.2–100	1,562/1,572	99.4	98.8–99.7
Coronavirus OC43	33/41	80.5	66.0–89.8	1,566/1,571	99.7	99.3–99.9
Human metapneumovirus	73/75	97.3	90.8–99.3	1,529/1,537	99.5	99.0–99.7
Human rhinovirus/enterovirus	425/436	97.5	95.5–98.6	1,099/1,176	93.5	91.9–94.7
Influenza virus A	78/78	100	95.3–100	1,531/1,531	100	99.7–100
H1	0/0			1,609/1,609	100	99.8–100
H1-2009	74/74	100	95.1–100	1,535/1,535	100	99.8–100
H3	4/4	100	51.0–100	1,605/1,605	100	99.8–100
Influenza virus B	14/14	100	78.5–100	1,596/1,598	99.9	99.5–100
Middle East respiratory syndrome coronavirus (MERS-CoV)	0/0			1,612/1,612	100	99.8–100
Parainfluenza virus 1	9/9	100	70.1–100	1,602/1,603	99.9	99.6–100
Parainfluenza virus 2	46/47	97.9	88.9–99.6	1,557/1,565	99.5	99.0–99.7
Parainfluenza virus 3	43/45	95.6	85.2–98.8	1,557/1,567	99.4	98.8–99.7
Parainfluenza virus 4	9/9	100	70.1–100	1,596/1,603	99.6	99.1–99.8
Respiratory syncytial virus	175/176	99.4	96.9–99.9	1,412/1,436	98.3	97.5–98.9
Bacteria						
Bordetella parapertussis (IS*1001*)	6/7	85.7	48.7–97.4	1,605/1,605	100	99.8–100
Bordetella pertussis (*ptxP*)	2/3	66.7	20.8–93.9	1,608/1,609	99.9	99.6–100
Chlamydia pneumoniae	5/5	100	56.6–100	1,606/1,607	99.9	99.6–100
Mycoplasma pneumoniae	23/24	95.8	79.8–99.3	1,583/1,588	99.7	99.3–99.9

[a]These data are presented based on a comparator assay only and do not reflect any discordant analysis.
[b]The terms PPA (positive percent agreement) and NPA (negative percent agreement) are used instead of sensitivity and specificity to indicate that a non-gold standard comparator (e.g., PCR) was used for the analysis.

Leber A L. et al. J Clin Microbiol. 2018;56(6):e01945-17.

表一. 上市的次世代定序 (next generation sequencing – NGS) 平台的基本資料 [包含公司名稱、使用設備、定序資料輸出量 (Gb/次)、序列片段讀取長度 (bp)、讀取產物股數，和執行時間]

Table 1
Properties of current NGS platforms.

Company	Equipment	Output/run (Gb)	Maximum read length (bp)	Reads ($x10^6$)	Running time
Illumina	MiniSeq	0.6–7.5	2 × 150	25	4–24 h
Illumina	Miseq	0.3–15	2 × 300	25	5–55 h
Illumina	NextSeq	20–120	2 × 150	130/400	12–30 h
Illumina	HiSeq 3000	125–700	2 × 150	2500	<1–3.5 days
ThermoFisher	Ion PGM™	0.03–2	200–400	0.4–5.5	2–7 h
ThermoFisher	Ion S5™	0.6–15	200–400	3–80	2.5–4 h
ThermoFisher	Ion S5™ XL	0.6–15	200–400	3–80	<24 h
Oxford Nanopore	MinION	21–42	230,000–300,000	2.2–4.4	1 min–48 h
Pacific Biosciences[a]	Sequel	0.75–1.25	>20,000	370,000	30 min–6 h
Pacific Biosciences[a]	RSII	0.5–1	>20,000	55,000	30 min–4 h

[a] The Pacific Biosciences data are per smart cell; both the Sequel and the RSII can run 1–16 smart cells in one run.

Deurenberg RH. et al. J Biotechnol. 2017;243:16-24.

表一. 比較不同方法診斷流行性感冒的敏感度與優缺點

診斷方法種類 敏感度 診斷所需時間 優點 缺點

	Sensitivity	Turnaround time	Advantages	Disadvantages
Viral culture 傳統病毒培養	Close to 100%	3–10 days	High sensitivity and specificity; virus available for characterisation (recovery of new and divergent strains); ability to recover other viruses	Poor specimen quality might affect yield; results not available in time to inform clinical decision making; time and labour intensive; specialised laboratory facilities required
Rapid viral culture* 快速病毒培養	70–90%	1–3 days	Faster than traditional viral culture; less expertise needed than for traditional cell culture	Less sensitive than traditional viral culture; might miss divergent influenza viruses; specialised laboratory facilities required
Rapid antigen detection: direct fluorescent antibody 快速抗原檢測 – 螢光抗體法	70–90%	1–4 h	Rapid turnaround; can identify additional pathogens (different staining methods); can assess sample quality	Sensitivity and specificity dependent on expertise of technician; specialised equipment required; virus is not available for characterisation of antigenicity
Rapid antigen detection: 快速抗原檢測 – 免疫色層法 immunochromatogenic assay	59–93%	<30 min	No specialised equipment or technical skill required; specialised specimen transport not required; rapid results	Least sensitive method; virus is not available for characterisation of antigenicity
RT-PCR 反轉錄病毒聚合酶反應	Close to 100%	1–8 h	High sensitivity and specificity; specimen quality and handling have less impact on sensitivity; typing, subtyping, and sequencing possible; can be combined with multiplex technology	Expensive; specialised equipment and trained personnel required; potential for cross-contamination; might miss divergent strains (dependent on primers)

*This technique is a modification of conventional viral culture, where the clinical specimen is inoculated onto a cell monolayer and centrifuged before incubation. Specimens are then stained and examined by immunofluorescence.

***Table 1*: Comparison of methods for diagnostic testing of influenza**[2,11,49,53,59]

Paules C and Subbarao K. Lancet. 2017;390:696-708.

4. 流行性感冒的治療藥物 (Treatment Regimens of Influenza)

表2.5.2. 社區肺炎感染的病史與病原菌的相關性 – (III)

特定旅遊特定旅遊便或是群聚史	
美國西南部	• 球衣菌屬 *(Coccidioides* species) • 漢他病毒 (Hantavirus)
東南亞	• 類鼻疽伯克氏 *(Burkholderia pseudomallei)* • 流行性感冒病毒 (influenza virus) • 禽流感病毒(avian influenza virus) • 新型冠狀病毒 (SARS coronavirus)
流感盛行社區	• 流行性感冒病毒 (influenza virus) • 肺炎鏈球菌 *(S. pneumoniae)* • 金黃色葡萄球菌 *(S. aureus)* • 流感嗜血桿菌 *(H. influenzae)*
接觸到咳嗽大於兩天合併呼哮性咳嗽以及咳嗽後嘔吐現象或有群聚史	• 百日咳博德特氏菌 *(Bordetella pertussis)*
生化恐攻	• 炭疽桿菌*(Bacillus anthracis*，引起炭疽病anthrax) • 鼠疫桿菌 *(Yersinia pestis* 引起鼠疫 plague) • 土倫法蘭西斯氏菌*(Francisella tularensis*，引起兔熱病 tularemia)
冷卻水塔相關之群聚	退伍軍人桿菌屬 *(Legionella* species)

台灣肺炎診治指引, 2018.

表2.7.3.1. 流感肺炎建議用藥、劑量與療程

	首選	另選
藥物名稱	Oseltamivir[b] (1C)	Peramivir[c] (2D)
建議劑量	75mg PO BID[d]	600mg IV QD[f]
建議療程[e]	5天	5天

• a. 抗流感病毒藥物使用時機

1. 感染流感病毒後，大多數人可自行痊癒；流感併發症病人之治療除了支持療法，必要時可給予抗病毒藥劑治療。
2. 針對已出現流感危險徵兆（包括呼吸急促、呼吸困難、發紺、血痰、胸痛、意識改變、低血壓），或流感併發症高風險病人出現類流感症狀，應考慮給予抗流感病毒治療。
3. 當決定給予抗病毒藥劑治療，就應儘快給予，不需等到檢驗確診才給藥。
4. 研究顯示症狀開始後 48 小時內開始治療，療效最佳。然而有些研究顯示對住院病人症狀超過 48 小時才投予 oseltamivir 仍有縮短住院天數或減低死亡率的助益 [31]。

台灣肺炎診治指引, 2018.

表一. 治療流感的神經激胺酶抑制劑 (Neuraminidase Inhibitor – NI) 的種類適用年齡建議劑量和依原有疾病 (如肝臟與腎臟疾病) 執行劑量調整

Table 1. **Dosing Schedule of Neuraminidase Inhibitors for the Treatment and Prevention of Influenza, According to Patient's Age and Coexisting Illnesses.***

Antiviral Drug	Recommended Dose According to Age				Coexisting Illness	
	1–6 yr	7–12 yr	13–64 yr	≥65 yr	Renal Disease	Hepatic Disease
Treatment						
Zanamivir	NA	10 mg (equivalent to 2 inhalations) twice daily for 5 days	10 mg (equivalent to 2 inhalations) twice daily for 5 days	10 mg (equivalent to 2 inhalations) twice daily for 5 days	10 mg (equivalent to 2 inhalations) twice daily for 5 days	—
Oseltamivir	Weight <15 kg: 30 mg twice daily for 5 days; 15–23 kg: 45 mg twice daily for 5 days; >23–40 kg: 60 mg twice daily for 5 days; >40 kg: 75 mg twice daily for 5 days	Weight <15 kg: 30 mg twice daily for 5 days; 15–23 kg: 45 mg twice daily for 5 days; >23–40 kg: 60 mg twice daily for 5 days; >40 kg: 75 mg twice daily for 5 days	75 mg twice daily for 5 days	75 mg twice daily for 5 days	For adults, reduce dose if creatinine clearance is ≤30 ml/min; if creatinine clearance is 10–30 ml/min, 75 mg once daily†	Not evaluated
Prevention						
Oseltamivir	NA	NA	75 mg once daily for >7 days (up to 6 wk)	75 mg once daily for >7 days (up to 6 wk)	If creatinine clearance is 10–30 ml/min, 75 mg every other day†	Not evaluated

* The doses listed are those currently approved in the United States. NA denotes not applicable.
† No regimen is available for patients with end-stage renal disease.

Moscona A. N Engl J Med. 2005;353:1363-1373.

表二. 治療流感神經激胺醯抑制劑 (Neuraminidase Inhibitor – N 時間)

使用神經激胺酶抑制劑治療流感，可以減少症狀時間為0.5 - 4.1日 (平均 1-2日)。

Table 2. Selected Treat

Study	No. of Patients	Characteristics of Patients*	Time from Onset of Symptoms to Start of Therapy	Reduction in Length of Illness†
Zanamivir				
Hayden et al.,[13] Cooper et al.,[13] Monto et al.,[14] Makela et al.,[15] MIST Study Group,[16] Matsumoto et al.[17]	2600 (pooled number)	Healthy adults	36–48 hr	1.0–2.0 days
Cooper et al.[13]	Pooled number(meta-analysis)	Elderly and high-risk patients	36–48 hr	2.0 days
Hedrick et al.[21]	471	Children 5–12 yr	36–48 hr	1.0 day
Oseltamivir				
Cooper et al.[13]	Pooled number	Healthy adults with laboratory-confirmed influenza	<48 hr	1.4 days
Treanor et al.[18]	629	Healthy adults with laboratory-confirmed influenza	<36 hr	1.3 days
Nicholson et al.[19]	726	Healthy adults with laboratory-confirmed influenza	24–36 hr	1.0–2.0 days
Aoki et al.[23]	1426 (total)	Healthy adults (12–70 yr) with laboratory-confirmed influenza	0–6 hr	4.1 days‡
Aoki et al.[23]	1426 (total)	Healthy adults (12–70 yr) with laboratory-confirmed influenza	6–12 hr	3.1 days‡
Cooper et al.,[13] Kaiser et al.[24]	Pooled number from compiled studies	Elderly and high-risk patients with laboratory-confirmed influenza	36–48 hr	0.5 day§
Whitley et al.[22]	695	Children (1–12 yr) with influenza-like illness (65% with laboratory-confirmed influenza)	<48 hr	1.5 days¶

Moscona A. N Engl J Med. 2005;353:1363-1373.

表三. 接觸後預防流感神經激胺酶抑制劑 (Neuraminidase Inhibitor – NI) 的臨床

接觸流感病人後使用神經激胺酶抑制劑預防流感，平均預防率為68-92%。

Table 3. Selected Trials of Prophylaxis with the

Study and Drug	No. of Patients	Characteristics of Patients	Setting of Prophylaxis	Reduction in Incidence of Influenza*
Zanamivir				
Monto et al.[31]	1107	Healthy adults	Seasonal prophylaxis in the community	69% (laboratory-confirmed influenza)
Cooper et al.[13]	Pooled number	Healthy adults	Prophylaxis after exposure in household	81%
Oseltamivir				
Hayden et al.[32]	1559	Healthy adults	Seasonal prophylaxis in the community	87% (laboratory-confirmed influenza); 74% (influenza-like illness)
Welliver et al.[30]	955	Teenagers and adults (>12 yr)	Prophylaxis after exposure in household	89% (laboratory-confirmed influenza); 84% (disease in the household)
Hayden et al.[29]	812	All ages (including children >1 yr)	Prophylaxis after exposure in household	68% (laboratory-confirmed influenza) (85%, excluding patients who tested positive at start of prophylaxis); children, 55% (80%, excluding patients who tested positive at start of prophylaxis)†
Peters et al.[26]	548	Elderly persons (>80% vaccinated against influenza)	Seasonal prophylaxis in institutional setting	92% (laboratory-confirmed influenza)

Moscona A. N Engl J Med. 2005;353:1363-1373.

Zanamivir 與 Oseltamivir 的作用機轉

N-acetylneuraminic acid 為呼吸道分泌物中黏液蛋白的成分之一,病毒與黏液相結合,而神經激氨脢可液化黏液,使得病毒可通過宿主細胞表面

神經激氨脢亦是讓感染病毒的宿主細胞釋放病毒表面所需物質,可加強病毒的散播和感染的強度,因此神經激氨脢抑制劑可以疾病發生的可能性和降低疾病的嚴重度

Lamb et al *Orthomyxoviridae*: the viruses and their replication. In: Fields BM, Knipe DM, Howley PM, eds. Fields virology. 3rd ed. Vol 1. Philadelphia: Lippincott-Raven, 1999:1353-95

Zanamivir 與 Oseltamivir 的作用機轉

Zanamivir 與 Oseltamivir 為相關藥物,具類似的機轉,可預防和治療A型和B型流行性感冒二者皆是 *N*-acetylneuraminic acid (*N*基乙醯神經氨酸,為宿主細胞表面讓流行性感冒病毒進入的受體 - receptor) 的同類物質,可抑制神經激氨脢 (neuraminidase ,為三級結構)

Kim et al J Am Chem Soc 1997;119:681-90
von Itzstein et al Nature 1993;363:418-23
Varghese et al Nature 1983;303:35-40

Zanamivir 的藥物動力學

利用高流量氣流將 zanamivir 自口腔吸入,使用核子醫學放射線同位素研究發現,有78%的藥物存留在口咽腔,只有15%經氣管支氣管到達肺部,因此生物可利用率為10%至20%

流行性感冒病毒的MIC_{90}在0.05 to≧100 *u*M

吸入的藥物以原型自尿液中排洩

Cass et al Clin Pharmacokinet 1999;36:Suppl 1:21-31
Cass et al Clin Pharmacokinet 1999;36:Suppl 1 1-11

Oseltamivir 的藥物動力學

Oseltamivir 以口服方式給藥,經由肝臟代謝後約有75%轉化為 oseltamivir carboxylate 進入心臟血管系統

Oseltamivir 在病人腎功能 (CCr) 小於30 ml/min 以下才需劑量調整,但是目前並無確定準則適用於 oseltamivir 的劑量調整

Tamiflu (oseltamivir phophate) capsules. Nutley, N.J.: Roche Laboratories, 2000 (package insert)

EXPERT REVIEWS

Peramivir for the treatment of influenza

Expert Rev. Anti Infect. Ther. 10(2), 123–143 (2012)

摘要：新型神經激胺酶抑制劑瑞貝塔 (Peramivir, Rapiacta®, BioCryst Pharmaceuticals) 是新研發靜脈注射有效治療A型和B型流行性感冒的抗病毒藥物，結構以 cyclopentane 為骨架，加入帶正電的 guanidinyl 官能基和親脂性旁鏈。Peramivir 為美國緊急新藥研發條例核定使用，並於2009年H1N1新型流感全球性大流行時，經由緊急授權法律，使用於疑似或確認流感的住院病人。在可行動的成人病人的研究，靜脈注射瑞貝塔是安全的，該藥品已經美國、臺灣、日本，和南韓核准使用。對於瑞貝塔抗藥性機轉目前未明，需要持續追蹤。基於流感對於各年齡層人群具有嚴重威脅，並且施打流感疫苗有其限制，瑞貝塔可作為罹患嚴重流感病人的有限治療用藥的選擇。

Shetty A. K. and Peek L. A. Expert Rev Anti Infect Ther. 2012;10(2):123-143.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2011, p. 5267–5276 Vol. 55, No. 11
0066-4804/11/$12.00 doi:10.1128/AAC.00360-11

Phase III Randomized, Double-Blind Study Comparing Single-Dose Intravenous Peramivir with Oral Oseltamivir in Patients with Seasonal Influenza Virus Infection▽†

研究背景和目的：治療A型流行性感冒 (Influenza A virus – IAV) 的抗病毒藥物是控制流感流行的有效工具。本篇論文比較使用新型神經激胺酶抑制劑瑞貝塔 (peramivir) 和傳統治療流感的克流感 (oseltamivir) 於治療季節流感的療效。
研究方法：本篇論文為多國、多中心、雙盲、隨機，和具對照組研究，納入研究族群為罹患A型或B型流行性感冒的成人病人 (>= 20歲)，被隨機分配至接受單一劑量靜脈注射瑞貝塔 (300 mg 或 600 mg) (實驗組)，和口服克流感 (75 mg) 一天兩次共5日 (對照組)。利用危險係數分析模式與效能不低下邊緣閾值0.170，比較瑞貝塔和克流感於緩解流感症狀所需時間差別。計畫納入1,050名病人 (病人族群來自日本、臺灣，和南韓)。

Kohno S. et al. Antimicrob Agents Chemother. 2011;55(11):5267-5276.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 2011, p. 5267–5276 Vol. 55, No. 11
0066-4804/11/$12.00 doi:10.1128/AAC.00360-11
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Phase III Randomized, Double-Blind Study Comparing Single-Dose Intravenous Peramivir with Oral Oseltamivir in Patients with Seasonal Influenza Virus Infection▽†

研究結果：在意欲治療族群 (intention-to-treat - ITT：至少接受過一劑藥物) 共有1,091名病人 (364名接受300 mg 瑞貝塔靜脈輸注、362名接受600 mg 瑞貝塔靜脈輸注，和365名接受口服克流感藥物)，流感症狀持續時間在300 mg 瑞貝塔靜脈輸注、362名接受600 mg 瑞貝塔靜脈輸注，和365名接受口服克流感藥物分別為 78.0小時、81.0小時，81.8小時。危險係數與對照組 (口服克流感藥物) 相比為300 mg 瑞貝塔靜脈輸注 0.946 (97.5% C.I.: 0.793-1.129) 和600 mg 瑞貝塔靜脈輸注0.970 (97.5% C.I.: 0.814-1.157)，兩種瑞貝塔靜脈輸注劑型效果均不亞於口服克流感藥物 (97.5% C.I.: <1.170)，藥物不良反應率在300 mg 瑞貝塔靜脈輸注組有明顯降低，

Kohno S. et al. Antimicrob Agents Chemother. 2011;55(11):5267-5276.

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Phase III Randomized, Double-Blind Study Comparing Single-Dose Intravenous Peramivir with Oral Oseltamivir in Patients with Seasonal Influenza Virus Infection▽†

研究結果 (續)：但嚴重藥物不良反應比率在兩組不同劑量的靜脈輸注瑞貝塔病人族群和對照組 (口服克流感藥物病人) 無明顯差異。
結論：對於季節性流感病人，單一使用靜脈輸注瑞貝塔，效果與口服克流感藥物5日類似 (可作為替代藥物)。

Kohno S. et al. Antimicrob Agents Chemother. 2011;55(11):5267-5276.

圖一. 納入單一劑量300 mg 靜脈輸注瑞貝塔、單一劑量600 mg 靜脈輸注瑞貝塔，和口服克流感 (75 mg BID 5日) 的病人數目

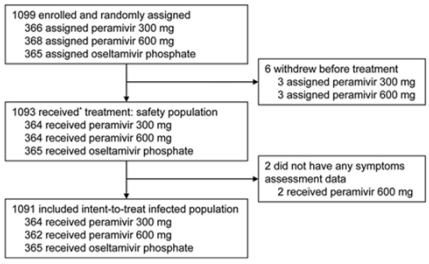

FIG. 1. Study profiles. *, One patient assigned to the 600-mg-peramivir group received 300 mg peramivir. This patient's data were included in the analyses according to the treatment actually administered.

Kohno S. et al. Antimicrob Agents Chemother. 2011;55(11):5267-5276.

表一. 納入研究 (日本、臺灣，和南韓) 的1,091名意欲治療族群 (ITT) 的病人的基本資料 – (I)

TABLE 1. Baseline characteristics for the intent-to-treat infected population

Characteristic[a]	Value for group receiving: Peramivir 300 mg (*n* = 364)	Peramivir 600 mg (*n* = 362)	Oseltamivir (*n* = 365)
Region/country[b] 病人所屬國家			
Japan	247 (67.9)	249 (68.8)	246 (67.4)
Taiwan	81 (22.3)	79 (21.8)	84 (23.0)
South Korea	36 (9.9)	34 (9.4)	35 (9.6)
Male sex 男性所占比率	180 (49.5)	198 (54.7)	184 (50.4)
Age (yr)			
Mean ± SD	34.9 ± 11.7	35.9 ± 12.0	34.6 ± 11.7
Range	20–78	20–78	20–80
Wt (kg) 體重			
Mean ± SD	61.50 ± 13.04	62.69 ± 13.05	61.59 ± 13.09
Range	39.5–120.0	33.4–104.7	40.0–140.1
Smoking[b] 抽煙	113 (31.0)	111 (30.7)	112 (30.7)
Coexisting disease at baseline 原有疾病	127 (34.9)	146 (40.3)	132 (36.2)
Receipt of drugs from onset of influenza to randomization 出現至藥物給予時間間隔	206 (56.6)	212 (58.6)	211 (57.8)
Influenza vaccination 流感疫苗注射	64 (17.6)	56 (15.5)	63 (17.3)
Duration of influenza 流感症狀持續時間			
0–12 h	33 (9.1)	24 (6.6)	30 (8.2)
>12–24 h	129 (35.4)	117 (32.3)	131 (35.9)
>24–36 h	94 (25.8)	114 (31.5)	107 (29.3)
>36–48 h	108 (29.7)	106 (29.3)	95 (26.0)
>48 h	0 (0.0)	1 (0.3)	2 (0.5)

Kohno S. et al. Antimicrob Agents Chemother. 2011;55(11):5267-5276.

表一. 納入研究 (日本、臺灣，和南韓) 的1,091名意欲治療族群 (ITT) 的病人的基本資料 – (II)

TABLE 1. Baseline characteristics for the intent-to-treat infected population

Characteristic[a]	Value for group receiving: Peramivir 300 mg (n = 364)	Peramivir 600 mg (n = 362)	Oseltamivir (n = 365)
Composite symptom score (mean ± SD)[b] 綜合症狀評分	12.5 ± 3.4	12.5 ± 3.3	12.5 ± 3.2
Body temp (°C) (mean ± SD) 體溫	38.53 ± 0.49	38.48 ± 0.49	38.56 ± 0.52
Result of rapid antigen test[b] 流感快篩檢驗			
A	335 (92.0)	333 (92.0)	338 (92.6)
B	27 (7.4)	29 (8.0)	25 (6.8)
A and B	2 (0.5)	0 (0.0)	2 (0.5)
Influenza virus subtype 流感病毒亞型			
A/H1	197 (54.1)	200 (55.2)	201 (55.1)
A/H1, H3	0 (0.0)	0 (0.0)	1 (0.3)
A/H3	112 (30.8)	108 (29.8)	108 (29.6)
A/–	21 (5.8)	15 (4.1)	17 (4.7)
B	21 (5.8)	26 (7.2)	23 (6.3)
Unknown	13 (3.6)	13 (3.6)	15 (4.1)

[a] Unless otherwise indicated, each value is the number (percentage) of patients with the characteristic.
[b] Randomization ensured balance for this factor.

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表二. 依據流感病毒亞型和使 經激胺酶抑制劑 (NI) 的抑制50%病毒的藥 與中位數

A/H1和B型流感病毒對各種NI具有較高的 IC_{50} (藥物不敏感度)

TABLE 2. IC_{50} in NA inhibiti to-treat infected population[a]

Influenza virus subtype (n) and treatment group	IC_{50} (nM) Mean ± SD	Median (range)[b]
A/H1 (593)		
Peramivir	22.25 ± 4.37	21.59 (0.41–100.00)
Oseltamivir	87.70 ± 16.38	100.00 (0.66–100.00)
Zanamivir	1.35 ± 0.18	1.34 (0.97–3.41)
A/H3 (323)		
Peramivir	0.83 ± 0.17	0.82 (0.45–2.13)
Oseltamivir	0.63 ± 0.17	0.62 (0.27–1.84)
Zanamivir	1.97 ± 0.37	1.91 (1.46–5.93)
B (70)		
Peramivir	3.51 ± 0.39	3.58 (2.18–4.33)
Oseltamivir	16.53 ± 2.30	16.77 (8.77–22.33)
Zanamivir	9.74 ± 1.10	9.79 (5.92–12.17)

[a] The reliability of each assay was confirmed by the observation that the IC_{50} of peramivir ranged from 0.2 to 2 nM for the standard strain (A/PR/8/34).
[b] Minimum to maximum IC_{50}. The upper limit of the IC_{50} was 100.0 nM.

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TABLE 3. Time to alleviation of symptoms for the intent-to-treat infected population

Population and treatment (n)	Median time to alleviation (h) (95% CI)	Hazard ratio (97.5% CI)[a]
Overall		
Peramivir		
300 mg (364)	78.0 (68.4, 88.6)	0.946 (0.793, 1.129)[b]
600 mg (362)	81.0 (72.7, 91.5)	0.970 (0.814, 1.157)[b]
Oseltamivir (365)	81.8 (73.2, 91.1)	
A/H1		
Peramivir		
300 mg (197)	80.2 (69.3, 90.6)	0.854 (0.672, 1.085)
600 mg (200)	83.6 (72.7, 101.9)	0.927 (0.730, 1.176)
Oseltamivir (201)	88.8 (73.1, 102.2)	
A/H3		
Peramivir		
300 mg (112)	69.9 (54.4, 97.1)	1.039 (0.745, 1.448)
600 mg (108)	70.6 (47.7, 91.9)	0.958 (0.687, 1.335)
Oseltamivir (108)	75.1 (63.4, 92.6)	
B		
Peramivir		
300 mg (21)	55.3 (43.9, 86.4)	0.445 (0.202, 0.982)
600 mg (26)	92.8 (57.4, 116.1)	0.706 (0.341, 1.460)
Oseltamivir (23)	92.7 (70.2, 138.5)	

[a] Hazard ratios compared to the oseltamivir group were estimated using Cox proportional-hazards models, which were adjusted for current smoking behavior, composite symptom score at baseline, country/region, influenza virus type, sex, complications, and previous therapy.
[b] Both peramivir groups were noninferior to the oseltamivir group, with a noninferiority margin of 0.170.

表三. 所有病毒和各種流感病毒亞型和使用藥物種類對於各種神經激胺酶抑制劑 (Peramivir 300 mg and 600 mg IVD stat and Oseltamivir 75 mg PO BID for 5 days) 的症狀緩解所需時間和

在所有流感病人和各亞型流感病毒感染病人族群使用2種靜脈注射劑型 peramivir 和口服 oseltamivir 的流感症狀緩解時間無統計學差異

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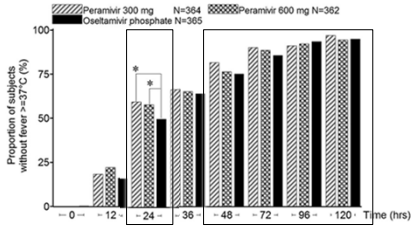
圖二. 在意欲治療族群 (ITT) 使用各種神經激胺酶抑制劑於各別觀察時間間隔體溫恢復正常比率



接受神經激胺酶抑制劑治療的病人超過75%以上在48小時內體溫恢復正常，在使用藥物24小時接受2種靜脈注射劑型 peramivir 體溫恢復正常比率優於口服 oseltamivir (具統計學差異)。

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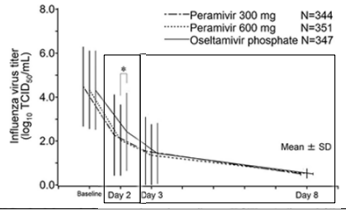
圖三.在意欲治療族群 (ITT) 使用各種神經激胺酶抑制劑於各別觀察時間間隔病毒量下降趨勢比較



接受各種神經激胺酶抑制劑治療的病人其體內病毒量在72小時均可有效被抑制，在使用藥物48小時接受2種靜脈注射劑型 peramivir 體溫抑制宿主體內病毒的能力優於口服 oseltamivir (具統計學差異)。

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表四. 在意欲治療族群 (ITT) 使用各種神經激胺酶抑制劑於各別觀察時間間隔病毒下降量比較 (實驗組 vs. 對照組)

TABLE 4. Time-weighted change from baseline in virus titer for the intent-to-treat infected population

Population and time interval	Value for group receiving: Peramivir (300 mg) No. of patients tested	Change in virus titer[a]	P^b	Peramivir (600 mg) No. of patients tested	Change in virus titer[a]	P^b	Oseltamivir No. of patients tested	Change in virus titer[a]
Overall								
From day 1 to day 2	201	−1.10 ± 0.90	0.4278	192	−1.08 ± 0.82	0.2252	195	−1.04 ± 0.84
From day 1 to day 3	338	−1.71 ± 1.21	0.1337	349	−1.71 ± 1.10	0.1778	343	−1.63 ± 1.11
From day 1 to day 8	323	−2.97 ± 1.53	0.0674	338	−2.91 ± 1.44	0.2066	331	−2.82 ± 1.49
A/H1								
From day 1 to day 2	115	−1.18 ± 0.95	0.6244	117	−1.15 ± 0.90	0.4678	111	−1.06 ± 0.97
From day 1 to day 3	190	−1.79 ± 1.26	0.5092	198	−1.81 ± 1.19	0.5204	195	−1.71 ± 1.22
From day 1 to day 8	182	−3.20 ± 1.55	0.1735	191	−3.17 ± 1.42	0.4007	187	−3.04 ± 1.57
A/H3								
From day 1 to day 2	58	−1.23 ± 0.68	0.0386	54	−1.12 ± 0.52	0.3129	60	−1.01 ± 0.60
From day 1 to day 3	106	−1.87 ± 0.91	0.0218	105	−1.68 ± 0.71	0.2434	107	−1.58 ± 0.76
From day 1 to day 8	102	−2.86 ± 1.28	0.0644	103	−2.57 ± 1.05	0.5459	103	−2.48 ± 1.01
B								
From day 1 to								−1.21 ± 0.73
From day 1 to								−2.08 ± 1.00
From day 1 to								−3.99 ± 1.24

[a] Expressed as log
[b] Determined by t

接受實驗組與對照組的神經激胺酶抑制劑治療的病人族群均有極佳抑制病毒量的能力，在A/H3的病人族群在使用靜脈注射劑型 peramivir 300 mg 於使用第1-3日抑制病毒能力優於口服 oseltamivir (具統計學差異)。

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TABLE 5. Summary of adverse events and adverse drug reactions (safety population)

Parameter[a]	Value for group: Peramivir 300 mg (n = 364)	Peramivir 600 mg (n = 364)	Oseltamivir (n = 3
AEs			
Total			
No. of AEs	272	288	297
No. (% [95% CI]) of patients with ≥1	170 (46.7 [41.5, 52.0])	174 (47.8 [42.6, 53.1])	178 (48.8 [43.5, 54
P	0.6040	0.8242	
Mild			
No. of mild AEs	90	90	95
No. (%) of patients with ≥1	69 (19.0)	66 (18.1)	74 (20.3)
Moderate			
No. of moderate AEs	161	166	177
No. (%) of patients with ≥1	119 (32.7)	116 (31.9)	121 (33.2)
Severe			
No. of severe AEs	21	32	25
No. (%) of patients with ≥1	19 (5.2)	30 (8.2)	24 (6.6)
ADRs			
Total			
No. of ADRs	80	99	104
No. (% [95% CI]) of patients with ≥1	51 (14.0 [10.6, 18.0])	66 (18.1 [14.3, 22.5])	73 (20.0 [16.0, 24.5])
P	0.0302	0.5718	
Mild			
No. of mild ADRs	40	42	48
No. (%) of patients with ≥1	29 (8.0)	32 (8.8)	40 (11.0)
Moderate			
No. of moderate ADRs	37	47	47
No. (%) of patients with ≥1	29 (8.0)	34 (9.3)	37 (10.1)
Severe			
No. of severe ADRs	3	10	9
No. (%) of patients with ≥1	3 (0.8)	10 (2.7)	9 (2.5)
No. (%) of patients with the following AE[b]:			
Neutrophil count decreased	39 (10.7)	38 (10.4)	34 (9.3)
Diarrhea	24 (6.6)	30 (8.2)	27 (7.4)
Protein present in urine	17 (4.7)	16 (4.4)	22 (6.0)
Blood glucose increased	11 (3.0)	14 (3.8)	12 (3.3)
Urine positive for WBCs	14 (3.8)	8 (2.2)	16 (4.4)
Nausea	8 (2.2)	8 (2.2)	20 (5.5)
Vomiting	2 (0.5)	6 (1.6)	15 (4.1)
No. (%) of patients with the following ADR[c]:			
Diarrhea	14 (3.8)	20 (5.5)	19 (5.2)
Neutrophil count decreased	9 (2.5)	14 (3.8)	13 (3.6)
Nausea	2 (0.5)	7 (1.9)	16 (4.4)

[a] AEs, adverse events; ADRs, adverse drug reactions; WBCs, white blood cells. P values were calculated by intergroup comparison between the peramivir and oseltamivir groups using Fisher's exact test.
[b] Data are shown only for AEs or ADRs that occurred at a frequency of >3% in any of the three groups.

接受實驗組與對照組的神經激胺酶抑制劑治療的病人族群的藥物副作用與藥物不良反應的嚴重程度無明顯差異，且嚴重藥物不良反應個案極少 (安全度極佳)。

days) 通報藥物副作用與藥物不良反應種類與比率

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表六. 在第二期和第三期臨床試驗中病人的中性白血球最低數值屬於嚴重層級 (第三級至第四級)

接受實驗組與對照組的神經激胺酶抑制劑治療的病人族群其中性白血球低下的人數不高，且嚴重中性白血球低下的副作用病人 (第3級至第4級) 比率極低。

TABL

Grade (no. of neutrophils/μl)	Phase II study[a] Peramivir (n = 198)	Phase II study[a] Placebo (n = 100)	Phase III study[b] Peramivir (n = 723)	Phase III study[b] Oseltamivir (n = 363)
Grade 0 (≥1,300/μl)	151 (76.3)	89 (89.0)	557 (77.0)	288 (79.3)
Grade 1 (≥1,000 and <1,300/μl)	29 (14.6)	7 (7.0)	93 (12.9)	41 (11.3)
Grade 2 (≥750 and <1,000/μl)	14 (7.1)	3 (3.0)	60 (8.3)	25 (6.9)
Grade 3 (≥500 and <750/μl)	3 (1.5)	1 (1.0)	10 (1.4)	7 (1.9)
Grade 4 (<500/μl)	1 (0.5)	0 (0.0)	3 (0.4)	2 (0.6)

[a] A placebo-controlled randomized study (12).
[b] An oseltamivir-controlled randomized study (our present study).

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表七. 在第二期和第三期臨床試驗病人的中性白血球最低數值屬於嚴重層級 (第二級至第四級) 緩解 (至第一級或零級) 所需時間

TABLE 7. Summary of time (duration) to recovery from grade 2 or more-severe neutropenia to grade 1 or less (safety population)

Duration (days) of ≥grade 2 neutropenia[a]	No. (%) of patients: Phase II study[b] Peramivir (n = 198)	Phase II study[b] Placebo (n = 100)	Phase III study[c] Peramivir (n = 723)	Phase III study[c] Oseltamivir (n = 363)
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2–3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4–9	0 (0.0)	0 (0.0)	66 (90.4)	25 (73.5)
10–14	14 (77.8)	2 (50.0)	4 (5.5)	6 (17.6)
≥15	4 (22.2)	2 (50.0)	3 (4.1)	1 (2.9)
No recovery	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.9)[d]
Total	18	4	73	34

多數使用神經激胺酶抑制劑治療的流感病人其中性白血球低下恢復正常所需時間多位於4-9日，極少病人需10-14日。

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表二. 於成年人給予一劑600 mg Peramivir 的各項藥物動力學資料

Table 2. Pharmacokinetic parameters for peramivir following administration of a single 600 mg dose in adults.

Parameter	Normal renal function
Route	Intravenous[a]
Dose	600 mg
Kinetics	Linear
Protein binding	<30%
C_{max} (ng/ml)	34,100
C_{min} (ng/ml)	
AUC (μg·h/ml)	
System	
System	
Plasma	
Vd (l/kg)[a]	NA
Metabolism	Minimal
Excretion	Renal (90%)
Dose adjustment for renal insufficiency	Yes
Dose adjustment for hepatic insufficiency	None

[a]Investigational (drug not approved in the USA).
[b]Dose range 0.5–8 mg/kg as a single dose or 4 mg/kg twice daily for 1 day.
$T_{1/2}$: Terminal half-life; Vd: Volume of distribution.
Data taken from [202].

與血漿蛋白質結合率較低 (30%)，且多數藥物自腎臟代謝 (腎臟功能不全病人使用時需要調整劑量)。

Shetty A. K. and Peek L. A. Expert Rev Anti Infect Ther. 2012;10(2):123-143.

表三. 在各種罹患流感的成年病人族群使用靜脈或肌肉注射 Peramivir 的各種臨床試驗效果 – (I)

Table 3. Clinical efficacy of peramivir: randomized controlled trials of intravenous or intramuscular peramivir in adults.

Author/ company (year)	Location/ sponsor/trial ID	Design	Population	Regimen	Results	Ref.
Ambulatory patients with acute uncomplicated influenza (normal hosts) 可以行動且無併發症的成年流感病人族群						
Biocryst (2007)	USA, Canada/ Biocryst	Phase II, randomized, double-blind, placebo-controlled, multicenter	Adults with positive RAT test for influenza	Peramivir 150 mg, 300 mg, or placebo as im. single dose within 48 h of symptom onset	Completed (n = 344) No statistically significant differences between treatment groups for time to alleviation of symptoms (primary end point) Improvement over placebo was 22.9 h with 150-mg dose (p = 0.284) and 21.1 h with the 300-mg dose (p = 0.152)	[203]
Biocryst (2008)	USA, Australia, New Zealand, South Africa/ Biocryst	Phase II randomized, double-blind, placebo-controlled, multicenter	Adults with positive influenza A or B (by RAT) with symptom duration ≤48 h	Peramivir 600 mg vs placebo as im. single dose	Completed (n = 402, n = 334 efficacy analyses) No statistically significant differences between treatment groups for time to alleviation of symptoms (primary end point) Median time to alleviation 91.1 h for 600 mg im. injection of peramivir and 106.1 h for placebo. Peramivir compared safe and well-tolerated	[67]
Kohno *et al.* (2011)	Japan/ Shionogi/ 08151T0631	Phase III randomized, double-blind, double-dummy controlled, multicenter	Adults aged >20 years with with influenza's symptoms and positive influenza A or B (by RAT)	Peramivir 300 mg or 600 mg iv. single dose vs oral oseltamivir 75 mg b.i.d. x 5 days	Completed (n = 1093, n = 1091 efficacy analyses) Similar time to symptom alleviation (primary end point) for all three treatment groups (78 h for 300 mg peramivir, 81 h for 600 mg peramivir and 81.8 h for oseltamivir). The hazard ratios of the 300- and 600-mg groups compared with the oseltamivir group were 0.946 (95.5% CI: 0.793–1.129) and 0.970 (95.5% CI: 0.814–1.157), respectively. Both peramivir groups were noninferior to the oseltamivir group (97.5% CI: <1.170).	[45]
Kohno *et al.* (2010)	Japan/ Shionogi/ 0722T0621	Phase II randomized, double-blind, placebo-controlled multicenter	Adults 20–64 years of age with influenza symptoms and positive influenza A or B (by RAT)	Peramivir 300 or 600 mg iv. single dose vs placebo within 48 h of onset of symptoms	Completed (n = 300, n = 296 efficacy analyses) Statistically significant difference for both doses of peramivir compared with placebo for time to symptom alleviation (hazard ratio: 0.681 [p = 0.0092] in 300-mg group and 0.666 [p = 0.0092] in the 600-mg group compared with placebo; adjusted p-value 0.0092 for both comparisons). The median time to alleviation of symptoms was 59.1 h after 300 mg peramivir, 59.9 h after 600 mg peramivir compared with 82 h for placebo	[44]

[a]Uncontrolled diabetes, chronic pulmonary disorders, patients on immunosuppressive therapy.
b.i.d.: Twice daily; DHHS: Department of Health and Human Services; im.: Intramuscular; ITT: Intent-to-treat infected; iv.: Intravenous; NP: Nasopharyngeal; q.d.: Once a day; RAT: Rapid antigen test.

Shetty A. K. and Peek L. A. Expert Rev Anti Infect Ther. 2012;10(2):123-143.

表三. 在各種罹患流感的成年病人族群使用靜脈或肌肉注射 Peramivir 的各種臨床試驗效果 – (II)

Table 3. Clinical efficacy of peramivir: randomized controlled trials of intravenous or intramuscular peramivir in adults (cont.).

Author/ company (year)	Location/ sponsor/trial ID	Design	Population	Regimen	Results	Ref.
High-risk ambulatory patients with acute uncomplicated influenza 可以行動且無併發症的但有高風險成年流感病人族群						
Kohno *et al.* (2011)	Japan/ Shionogi/ 08161T0632	Phase III, randomized, double-blind, uncontrolled, multicenter	High risk patients' with influenza symptoms and positive influenza A or B (by RAT)	Peramivir 300 mg or 600 mg iv. x 1–5 days	Completed (n = 37 efficacy analyses) The median time to symptom alleviation was 68.6 h (90% CI: 41.5–113.4 h) in all patients. The duration of influenza illness was significantly shorter (hazard ratio: 0.497; 90% CI: 0.25–0.984) in the 600-mg group than in the 300-mg group. Patients who received multiple doses of peramivir showed more rapid symptom alleviation compared with those who received single doses	[47]
Hospitalized patients with influenza 成年流感住院病人族群						
Ison *et al.* (2009)	USA, Australia, Canada, Hong Kong, New Zealand, Singapore, South Africa/ Biocryst/ NCT00453999	Phase II randomized, double-blind, double-dummy placebo-controlled, multicenter	Hospitalized patients with acute serious or potentially life-threatening influenza	Peramivir 200 mg, 400 mg, or placebo iv. q.d. x 5 days plus either oseltamivir oral suspension or placebo 75 mg b.i.d. x 5 days	Completed (n = 137, n = 122 efficacy analyses) No significant differences in the time to clinical stability (primary end point) or time to resumption of normal activities and change in vital titers at 48 h (secondary end points) between any of the treatment groups Peramivir was noninferior to oseltamivir in hospitalized patients with acute influenza and demonstrated similar tolerability. No significant difference in dose response among the peramivir groups	[69]
US NIH (2009)	USA, Australia, Canada, New Zealand, Mexico, Puerto Rico/ Biocryst & US DHHS/ NCT00957996	Phase II randomized, open-label	Hospitalized adults and adolescents (14–92 years of age) with confirmed or suspected 2009 pandemic influenza (H1N1)	Peramivir 300 mg iv. b.i.d. or 600 mg iv. q.d.	Completed (n = 234) Primary outcome: similar reduction in influenza virus titer in NP samples over the first 48 h for both groups (−1.66 [95% CI: −2.32, −0.61] for 300 mg peramivir twice daily and −1.47 [95% CI: −1.89, −0.75] for 600 mg peramivir once daily). The analysis of the combined ITT population showed median time to resolution of fever was 25.3 h; time to clinical resolution, 92.0 h; time to alleviation of symptoms, 145 h; and time to resumption of usual activities, 26.8 days	[269,204]
US NIH (2009)	North and South America, Europe, South Africa/ Biocryst & US DHHS/ NCT00958776	Phase III randomized, double-blind, controlled, multicenter	Hospitalized adolescents and adults (≥12 years of age) who have suspected or confirmed influenza as shown by positive influenza A or B (by RAT)	Adults: peramivir 600 mg iv. q.d. Adolescents: peramivir 10 mg/kg (max. 600 mg) q.d.	Currently recruiting patients Primary outcome: time to clinical resolution at day 5 Secondary outcome: change in influenza virus titer at day 5	[269]

[a]Uncontrolled diabetes, chronic pulmonary disorders, patients on immunosuppressive therapy.
b.i.d.: Twice daily; DHHS: Department of Health and Human Services; im.: Intramuscular; ITT: Intent-to-treat infected; iv.: Intravenous; NP: Nasopharyngeal; q.d.: Once a day; RAT: Rapid antigen test.

Shetty A. K. and Peek L. A. Expert Rev Anti Infect Ther. 2012;10(2):123-143.

表四. 在2009年H1N1新型流感全球大流行期間於兒童、懷孕或產婦，以及成年病人族群使用 Peramivir 的個案資訊與預後 – (I)

Table 4. Case series of peramivir use in children, pregnant or postpartum women, and in adult patients infected with 2009 H1N1 severe pandemic influenza.

Year	Age/sex	Host characteristics/underlying medical condition	Clinical syndrome	Complications/critical care support	Antiviral drug therapy dose/duration	Outcome	Ref.
Pediatric patients							
2011	3 mo/F	Immunocompetent	Pneumonia, myocarditis	Multiorgan failure requiring ECMO and CVVH, intracranial hemorrhage, CVC sepsis (Candida spp. CA-MRSA)	Peramivir 2.2 mg/kg Dose adjusted by TDM HD 2–12	Survived	[79]
2011	5 y/M	Immunocompetent	Pneumonia	Respiratory failure, intubation, mechanical ventilation HD 5, ECMO, heart failure, coma	Peramivir 10 mg/kg HD 16–26	Died	[79]
2011	8 y/M	Noonan syndrome, CHD, pulmonary hypertension, scoliosis s/p spinal fusion	Pneumonia	Respiratory failure mechanical ventilation, ECMO, cardiac arrest, diffuse cerebral ischemia	Peramivir 10 mg/kg HD 10–18	Died	[79]
2011	10 y/M	Immunocompromised renal failure s/p renal transplant	Pneumonia	ARDS, respiratory failure, ECMO mechanical ventilation, renal failure requiring CVVH, hypotension requiring inotropes	Peramivir 2.2–5.4 mg/kg dose adjusted by TDM, HD 8–22; 2009 discontinuation of immunosuppressant drugs; H1N1 isolate with H275Y mutation and oseltamivir resistance	Survived	[79]
2011	11 y/F	Previously healthy	Pneumonia	Respiratory failure, intubation, mechanical ventilation	Peramivir 10 mg/kg HD 2–12	Survived	[79]
2011	13 y/M	Previously healthy	Pneumonia	Respiratory failure, intubation, mechanical ventilation, vasopressor support	Peramivir 10 mg/kg HD 2–10	Survived	[79]
2011	13 y/M	Asthma	Pneumonia	Respiratory failure, intubation, mechanical ventilation, ECMO, vasopressor support	Peramivir 600 mg/day HD 16–25	Died	[79]
2011	14 y/F	Asthma, chronic renal failure	Pneumonia	Respiratory failure, intubation, mechanical ventilation and HFO, vasopressor support	Peramivir 10 mg/kg HD 14–20	Died	[79]
2011	15 y/M	Previously healthy	Pneumonia, myocarditis	Respiratory failure, CHF, ECMO, mechanical ventilation, vasopressor support	Peramivir 600 mg/day HD 6–16	Survived	[79]
2011	15 y/F	Previously healthy	Pneumonia	Mechanical ventilation, vasopressor support, ECMO	Peramivir 600 mg/day HD 6–7	Survived	[79]
2011	17 y/M	Previously healthy	Pneumonia	Respiratory failure, intubation, mechanical ventilation, vasopressors, renal failure	Peramivir 600 mg/day HD 3–8	Survived	[79]

ARDS: Acute respiratory distress syndrome; CA-MRSA: Community-associated MRSA; CHD: Congenital heart defect; CHF: Congestive heart failure; CVC: Central venous catheter; CVVH: Continuous veno-venous hemofiltration; CVVHDF: Continuous veno-venous hemodiafiltration; CRRT: Continuous renal replacement therapy; ECMO: Extracorporeal membrane oxygenation; F: Female; HD: Hospital day; HFO: High frequency oscillatory; HSCT: Hematopoietic stem cell transplantation; M: Male; Mo: Month; s/p: Status post; TDM: Therapeutic drug monitoring; y: Year.

Shetty A. K. and Peek L. A. Expert Rev Anti Infect Ther. 2012;10(2):123-143.

表四. 在2009年H1N1新型流感全球大流行期間於兒童、懷孕或產婦，以及成年病人族群使用 Peramivir 的個案資訊與預後 – (II)

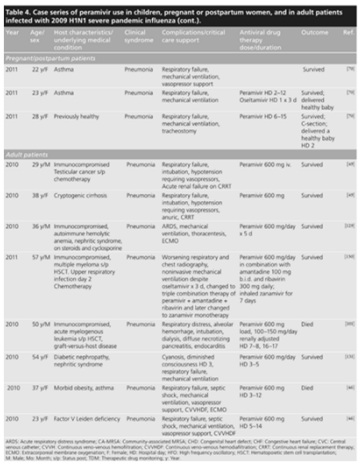


Table 4. Case series of peramivir use in children, pregnant or postpartum women, and in adult patients infected with 2009 H1N1 severe pandemic influenza (cont.).

Year	Age/sex	Host characteristics/underlying medical condition	Clinical syndrome	Complications/critical care support	Antiviral drug therapy dose/duration	Outcome	Ref.
Pregnant/postpartum patients							
2011	22 y/F	Asthma	Pneumonia	Respiratory failure, mechanical ventilation, vasopressor support		Survived	[79]
2011	23 y/F	Asthma	Pneumonia	Respiratory failure, mechanical ventilation	Peramivir HD 2–12 Oseltamivir HD 1 x 3 d	Survived; delivered healthy baby	[79]
2011	28 y/F	Previously healthy	Pneumonia	Respiratory failure, mechanical ventilation, tracheostomy	Peramivir HD 6–15	Survived; C-section; delivered a healthy baby HD 2	[79]
Adult patients							
2010	29 y/M	Immunocompromised Testicular cancer s/p chemotherapy	Pneumonia	Respiratory failure, intubation, hypotension requiring vasopressors, Acute renal failure on CRRT	Peramivir 600 mg iv.	Survived	[69]
2010	38 y/F	Cryptogenic cirrhosis	Pneumonia	Respiratory failure, intubation, hypotension requiring vasopressors, anuric, CRRT	Peramivir 600 mg	Survived	[69]
2010	36 y/M	Immunocompromised, autoimmune hemolytic anemia, nephritic syndrome, on steroids and cyclosporine	Pneumonia	ARDS, mechanical ventilation, thoracentesis, ECMO	Peramivir 600 mg/day x 5 d	Survived	[119]
2011	57 y/M	Immunocompromised, multiple myeloma s/p HSCT. Upper respiratory infection day 2 Chemotherapy	Pneumonia	Worsening respiratory and chest radiography, noninvasive mechanical ventilation despite oseltamivir x 3 d, changed to triple combination therapy of peramivir + amantadine + ribavirin and later changed to zanamivir monotherapy	Peramivir 600 mg/day in combination with amantadine 100 mg b.i.d. and ribavirin 300 mg daily; inhaled zanamivir for 7 days	Survived	[130]
2010	50 y/M	Immunocompromised, acute myelogenous leukemia s/p HSCT, graft-versus-host disease	Pneumonia	Respiratory distress, alveolar hemorrhage, intubation, dialysis, diffuse necrotizing pancreatitis, endocarditis	Peramivir 600 mg load, 100–150 mg/day renally adjusted HD 7–8, 16–17	Died	[84]
2010	54 y/F	Diabetic nephropathy, nephritic syndrome		Cyanosis, diminished consciousness HD 3, respiratory failure, mechanical ventilation	Peramivir 600 mg/day HD 3–5	Survived	[131]
2010	37 y/F	Morbid obesity, asthma	Pneumonia	Respiratory failure, septic shock, mechanical ventilation, vasopressor support, CVVHDF, ECMO	Peramivir 600 mg HD 3–12	Died	[46]
2010	23 y/F	Factor V Leiden deficiency	Pneumonia	Respiratory failure, septic shock, mechanical ventilation, vasopressor support, CVVHDF	Peramivir 600 mg HD 5–14	Survived	[46]

ARDS: Acute respiratory distress syndrome; CA-MRSA: Community-associated MRSA; CHD: Congenital heart defect; CHF: Congestive heart failure; CVC: Central venous catheter; CVVH: Continuous veno-venous hemofiltration; CVVHDF: Continuous veno-venous hemodiafiltration; CRRT: Continuous renal replacement therapy; ECMO: Extracorporeal membrane oxygenation; F: Female; HD: Hospital day; HFO: High frequency oscillatory; HSCT: Hematopoietic stem cell transplantation; M: Male; Mo: Month; s/p: Status post; TDM: Therapeutic drug monitoring; y: Year.

Shetty A. K. and Peek L. A. Expert Rev Anti Infect Ther. 2012;10(2):123-143.

表五. 在不同年齡與腎功能等級的病人族群建議使用 Peramivir 的劑量

Table 5. Dosing of intravenous peramivir treatment in pediatric and adult patients based on renal function.

CrCl (ml/min)[1]	Age range					
	0–30 days	*31–90 days*	*91–80 days*	*81 days–5 years*	*6–17 years*[4]	*Adult*
>50	6 mg/kg/day	8 mg/kg/day	10 mg/kg/day	12 mg/kg/day	10 mg/kg/day	600 mg/day
31–49	1.5 mg/kg/day	2 mg/kg/day	2.5 mg/kg/day	3 mg/kg/day	2.5 mg/kg/day	150 mg/day
10–30	1 mg/kg/day	1.3 mg/kg/day	1.6 mg/kg/day	1.9 mg/kg/day	1.6 mg/kg/day	100 mg/day
<10 and not on HD or CRRT	1 mg/kg (d1)	1.3 mg/kg (d1)	1.6 mg/kg (d1)	1.9 mg/kg (d1)	1.6 mg/kg (d1)	100 mg (d1)
	Then	Then	Then	Then	Then	Then
	0.15 mg/kg/day	0.2 mg/kg/day	0.25 mg/kg/day	0.3 mg/kg/day	0.25 mg/kg/day	15 mg
ESRD on intermittent HD	1 mg/kg (d1)	1.3 mg/kg (d1)	1.6 mg/kg (d1)	1.9 mg/kg (d1)	1.6 mg/kg (d1)	100 mg (d1)
	Then	Then	Then	Then	Then	Then
	1 mg/kg 2 h	1.3 mg/kg	1.6 mg/kg	1.9 mg/kg	1.6 mg/kg	100 mg 2 h
	After each HD session on dialysis days only	After each HD session on dialysis days only	After each HD session on dialysis days only	After each HD session on dialysis days only	After each HD session on dialysis days only	After each HD session on dialysis days only

[1]CrCl based on Cockcroft-Gault equation.
[4]Not to exceed the adult dose.
CrCl: Creatinine clearance; CRRT: Continuous renal replacement therapy; d: Day; ESRD: End-stage renal disease; HD: Hemodialysis; y: Years.
Data taken from [202].

Shetty A. K. and Peek L. A. Expert Rev Anti Infect Ther. 2012;10(2):123-143.

表一. 各種已進入臨床第二期和第三期人體試驗階段治療流感病毒的藥物 (病毒標的、學名或編號、作用機轉、特定目標、使用途徑、臨床試驗階段，和製造藥廠)

TABLE 1 Summary of influenza antivirals currently in phase II or III clinical trials

Host/Viral targeted	Name	Type of antiviral	Specific target			
Host targeting	DAS181–F03/F04[a]	Sialidase	Neu5Ac α(2,3)- and Neu5Ac α(2,6)-Gal linkages of sialic acid			
	Nitazoxanide	Thiazolide	Haemagglutinin maturation			
Viral targeting	JNJ-63623872	PB2 Inhibitor	Small molecule inhibitor of PB2	Oral, tablet	I, II	Janssen, Belgium
	T705	RNA-dependent RNA polymerase	Purine pseudobase (incorporates in viral RNA)	Oral, tablet	II, III	Toyama, Japan
	S-033188	Cap-dependent endonuclease inhibitor	Small molecule inhibitor of cap-dependent endonuclease	Oral, tablet	III	Shionogi, Japan
	CR6261	Monoclonal antibody	HA stem			
	CR8020	Monoclonal antibody	HA stem			
	MEDI8852	Monoclonal antibody	HA stem			
	MHAA4549A	Monoclonal antibody	HA stem			
	VIS410	Monoclonal antibody	HA stem	Intravenous	II	Visterra, USA

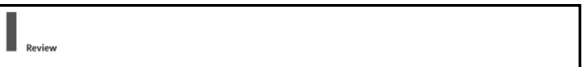
[a]F03 and F04 refer to formulations of DAS181. DAS181-F03 and DAS181-F04 are 10 μm particles, however, F04 differs via the addition of $MgSO_4$.

Avigan®, 1,600 mg BID for one day and 600 mg PO BID for another 4 days (contraindication for pregnant women), licensed in Japan and Taiwan since 2015.

Baloxavir (Xofluza®), 10/20 mg single dose only, licensed in Japan on February 23rd, 2018.

Koszalka P. et al. Influenza Other Respir Viruses. 2017;11(3):240-246.

5. 預防流行性感冒的疫苗注射 (Influenza Vaccine)



Review

Mortality benefits of influenza vaccination in elderly people: an ongoing controversy

摘要：在高收入已開發國家對年齡大於65歲的老年族群實施流感疫苗接種，其目的為降低因為流感造成的死亡風險和負擔，但是效果眾說紛云。雖然在隨機具對照組的研究顯示，流感疫苗在年青族群的效果顯著，但少有研究針對老年族群，特別是年齡超過70歲以上，佔了所有流感有關死亡原因的四分之三。於1980年後的研究，即使疫苗覆蓋率自15%上升至65%，亦無法證實可以有效降低與流感有關的死亡率。矛盾在於先前研究歸因流感佔5%的冬季死亡人數，但是文獻結論為流感疫苗可以有效降低50%與流感有關的死亡風險，這是十倍於流感死亡風險降低的利益。晚近的研究發現先前的集合式個案研究有潛在

Simonsen L. et al. Lancet Infect Dis. 2007;7:658-666.

Review

Mortality benefits of influenza vaccination in elderly people: an ongoing controversy

摘要 (續)：未經校正的選擇性誤差 (selection bias)，本篇文章作者提供分析性結構方法以偵測研究可能存在的誤差。本篇文章結論為脆弱的選擇性誤差和不具高特異性的研究目標 (如所有原因死亡率等) 可以導致集合式研究過度誇大疫苗效果。目前的證據醫學資料不足以有效證實流感疫苗對於老年人納入流感疫苗注射計畫後降低死亡率的影響程度。

Simonsen L. et al. Lancet Infect Dis. 2007;7:658-666.

圖一. 美國於1980年至2001年年齡大於65歲以上族群死亡率 (每十萬人口死亡率) 的月份趨勢圖 (含流感有關死亡率)

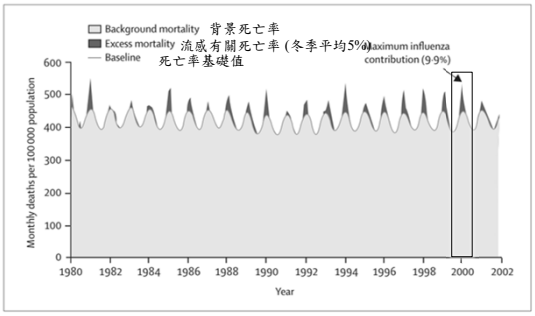


Figure 1: **Monthly national all-cause mortality rates in all US elderly people aged 65 years or more, 1980–2001**
The total winter-seasonal fraction of mortality attributed to influenza in national excess mortality studies averaged 5%, and was always less than 10%. Based on data from Simonsen et al.[4]

Simonsen L. et al. Lancet Infect Dis. 2007;7:658-666.

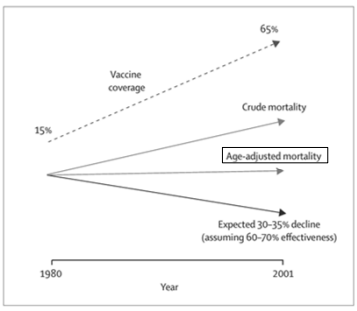


Figure 2: **Crude and age-adjusted trends in vaccination and national excess pneumonia and influenza mortality in US elderly people aged 65 years or more**

疫苗覆蓋率自15%上昇至65%，但經校正年齡後併發肺炎和死亡的比率無任何明顯變化。

powered to exclude the possibility of more limited mortality benefits.

圖二.美國於1980年至2001年流行性感冒疫苗包覆率 (虛線) 和流感併發肺炎和死亡率趨勢圖 (粗死亡率 – 藍線；經校正年齡因素後死亡率 – 紫線；和預期死亡率曲線 - 紅線)

Simonsen L. et al. Lancet Infect Dis. 2007;7:658-666.

重點. 使用五種分析性結構方法以減少可能存在的研究誤差於老年族群接種流感疫苗後評估效果的理由 – (I)

Panel: Expectations when applying the five framework criteria given in table 3

Seasonality

Expect no difference in risk (RR=1·0) during pre-influenza periods between the vaccinated and unvaccinated groups

Because the underlying heterogeneity in mortality rates in vaccinated and unvaccinated elderly people fades substantially with time (figure 3), the pre-influenza period should be used to assess the presence and magnitude of bias.

Vaccine match

社區流感流行程度：當大規模流感流行時，預期在施打流感疫苗的族群罹患流感合併肺炎與死亡風險 (RR) 大幅低於小規模流行時期。

match for each season and location studied, but this is not always done.[28]

Severity

Expect the measured RR reduction to be least pronounced for seasons with low national excess mortality and most pronounced for severe seasons with high excess mortality

Mild seasons are usually dominated by less virulent influenza A (H1N1) and influenza B viruses, and severe seasons by influenza A (H3N2) viruses. Cohort studies tend to find similar RR estimates for seasons dominated by different subtypes of influenza viruses,[29,30] again suggesting the presence of unadjusted bias.

季節：在流感流行季節前，預期在施打與不施打流感疫苗的族群的罹患流感合併肺炎與死亡的風險 (risk ratio – RR) 無明顯差異。

疫苗病毒株預測正確與否：當疫苗病毒株和流行的流感病毒株有明顯差異 (severely mismatched)，預期在施打流感疫苗的族群的罹患流感合併肺炎與死亡的風險 (RR) 大幅低於病毒株預測正確組。

重點. 使用五種分析性結構方法以減少可能存在的研究誤差於老年族群接種流感疫苗後評估效果的理由 – (II)

Panel: Expectations when applying the five framework criteria given in table 3

Age

Expect the RR reduction measured in the oldest groups of elderly people to be less pronounced than that of younger age-groups, because of immune senescence

One cohort study reported no mortality benefit in elderly people aged 65–74 years (RR=0·98), whereas those aged ≥80 years accounted for most of the benefits observed (RR=0·69),[31] a finding almost certainly indicative of residual bias. Similarly, Cochrane reviews found similar vaccine effectiveness in elderly people and younger age-groups, further suggesting the presence of bias.[28,32]

Endpoint specificity

Expect the measured RR to be most pronounced for clinical endpoints with higher specificity, and less pronounced for low-specificity outcomes

This follows because the proportion of the outcome that is attributable to influenza and therefore preventable with influenza vaccine increases with higher specificity. For a perfect (100% efficacious) vaccine, the measured vaccine effectiveness would be about 5% for an outcome with about 5% specificity, such as all-cause mortality, and about 90–100% for a laboratory-confirmed outcome. When the true effectiveness of a vaccine is known, the risk reduction for a moderately specific outcome (such as pneumonia deaths or pneumonia hospital admissions) is a useful measure of the vaccine-preventable proportion of an outcome of interest. But when the true effectiveness is not known—as is the case for influenza vaccine in older elderly people—the measured risk reduction can be difficult to interpret. The current cohort study evidence base for elderly people does not pass the specificity test, because the vaccine effectiveness estimates are highest

年齡：由於免疫功能衰退，預期在施打流感疫苗的老年族群中年齡最大的族群罹患流感合併肺炎與死亡風險 (RR) 影響效果不顯著。

選擇的預後目標：若是選擇高特異性的預後目標 (額外所有原因死亡率等)，預期在施打流感疫苗的族群的罹患流感合併肺炎與死亡的風險 (RR) 降低效果較選擇低特異性的預後目標 (如所有原因死亡率等) 顯著。

大眾對於H1N1A型流感疫苗的情緒反應

The Emotional Epidemiology of H1N1 Influenza Vaccination

Danielle Ofri, M.D., Ph.D.

民眾陷入恐慌

Last spring, when 2009 H1N1 influenza first came to our attention, my patients were in a panic. Our clinic was flooded with calls and walk-in patients, all with the same question: "When will there be a vaccine?"

It was all so new then, and we didn't have an answer. That lack of answer seemed to fuel anxiety to a fever pitch. A substantial cohort of my patients continued calling, almost on a weekly basis, to ask about the vaccine.

These, of course, were the same patients who routinely refused the seasonal flu vaccine. Each year when they demanded the H1N1 vaccine last spring, I reminded them of their reluctance over the seasonal flu shot. "Oh, that's different," they said.

Six months have passed. Flu season is now here. After repeated delays, H1N1 vaccine finally arrived in our clinic earlier this month to the uniform relief of the medical staff. But my formerly desperate patients were now leery. "It's not tested," they said. "Everyone knows there are problems with the vaccine." "I'm not putting that in my body."

I was unprepared for this reod. It seems to reflect a sort of psychological contagion of myth and suspicion.

Just as there are patterns of infection, there seem to be patterns of emotional reaction ("emotional epidemiology") associated with new illnesses. When 2009 H1N1 influenza was first detected, it fit a classic pattern that Priscilla Wald recently outlined in her book *Contagious*[1]: It was novel and mysterious; it emerged from a teeming third-world city, and it was now making its insidious — and seemingly unstoppable — way toward the "civilized" world.

新型神秘的疾病來自第三世界的城市，未能察覺且無法停止地散播到文明世界

Ofri D. N Engl J Med 2009;361(27):2594-2595

世界衛生組織建議2024-2025年北半球流行性感冒流行季節使用流行性感冒疫苗 (3價) 的成分 (雞胚蛋白疫苗)

1. an A/Victoria/4897/2022 (H1N1)pdm09-like virus;
2. an A/Thailand/8/2022 (H3N2)-like virus; and
3. a B/Austria/1359417/2021 (B/Victoria lineage)-like virus.

World Health Organization. Feb. 23rd, 2024.

若無禁忌症，建議老年族群和慢性病人與免疫功能低下病人與易感受族群(如醫療人員等)廣泛施打流行性感冒病毒疫苗。

世界衛生組織建議2024-2025年北半球流行性感冒流行季節使用流行性感冒疫苗 (3價) 的成分 (細胞培養或基因重組疫苗)

1. an A/Wisconsin/67/2022 (H1N1)pdm09-like virus;
2. an A/Massachusetts/18/2022 (H3N2)-like virus; and a B/Austria/1359417/2021 (B/Victoria lineage)-like virus.

World Health Organization. Feb. 23rd, 2024.

若無禁忌症，建議老年族群和慢性病人與免疫功能低下病人與易感受族群(如醫療人員等)廣泛施打流行性感冒病毒疫苗。

世界衛生組織建議2024-2025年北半球流行性感冒流行季節使用流行性感冒疫苗 (4價) 的成分 (雞胚蛋

若無禁忌症，建議老年族群和慢性病人與免疫功能低下病人與易感受族群(如醫療人員等)廣泛施打流行性感冒病毒疫苗。

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2. an A/Thailand/8/2022 (H3N2)-like virus;
3. B/Austria/1359417/2021 (B/Victoria lineage)-like virus; and a
4. B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

World Health Organization. Feb. 23rd, 2024.

世界衛生組織建議2024-2025年北半球流行性感冒流行季節使用流行性感冒疫苗 (4價) 的成分 (細胞培

若無禁忌症，建議老年族群和慢性病人與免疫功能低下病人與易感受族群(如醫療人員等)廣泛施打流行性感冒病毒疫苗。

1. an A/Wisconsin/67/2022 (H1N1)pdm09-like virus;
2. an A/Massachusetts/18/2022 (H3N2)-like virus;
3. B/Austria/1359417/2021 (B/Victoria lineage)-like virus; and a
4. B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

World Health Organization. Feb. 23rd, 2024.

6. 結論 (Conclusion)

流行性感冒感染 – 結論

1. 流行性感冒病毒的基因經常突變，在冬季和春季造成地區性 (endemic) 和全球性 (pandemic) 感染。
2. 流行性感冒病毒非常容易經由飛沫和接觸造成高度人傳人傳染，臨床表現包括發燒、全身肌肉關節酸痛、咳嗽、咽喉疼痛，和/或呼吸困難等。
3. 診斷方法，流行期多以抗原快速篩檢和RT-PCR診斷。
4. 治療藥物以神經激胺酶受體抑制劑 (如 oseltamivir) 為主，但新型抗流感藥物如內切酶抑制劑 (如baloxavir) 亦有極佳療效和極低抗藥性。
5. 預防流行性感冒仍以每年疫苗注射有極高成本效益 (降低罹病率/死亡率和減少相關醫療/社會支出成本)。

流行性感冒是每年都會流行的大規模傳染病，早期診斷和早期治療可以有效減少罹病率和死亡率，每年注射流感疫苗是最有效的預防方法。

感謝參加並歡迎提出問題討論。

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