

流感臨床處置

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大綱

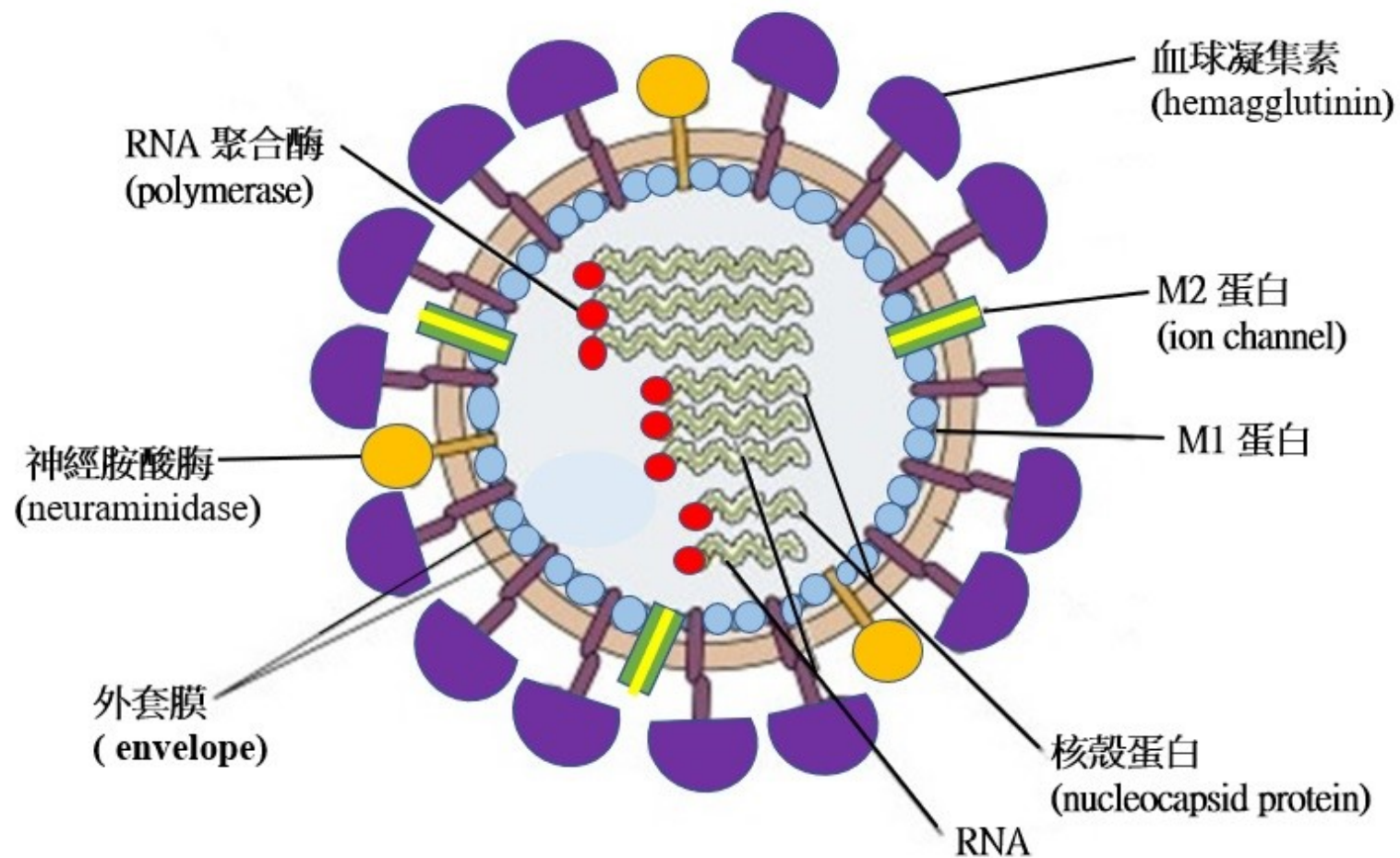
- 流感與併發症
- 流感藥物介紹
- 合併療法與類固醇在流感嚴重肺部併發症之角色

流感與併發症

流感病毒的介紹

- **Orthomyxoviridae** 正黏液病毒科，**Influenzavirus** 流感病毒屬
 - RNA病毒
 - 依照nucleoprotein核蛋白、membrane protein膜蛋白的差異，可以分成4型：A, B, C, D
 - 病毒外層有兩種重要抗原（醣蛋白）：Hemagglutinin (HA, 血球凝集素)、Neuraminidase (NA, 神經氨酸酶)
 - HA負責讓流感病毒接上受器
 - NA負責讓病毒釋放，增加病毒感染力
 - A型病毒再依不同的HA及NA區分亞型；B型、C型及D型流感病毒則不區分亞型，但B型流感病毒可依抗原性不同再分為 B/Yamagata/山形株 及 B/Victoria/維多利亞株 兩個種系 (lineage)，兩個種系可能共同或交互流行

流感病毒的介紹



臨床症狀

- 流感為急性病毒性呼吸道疾病，常引起發燒、咳嗽、頭痛、肌肉痠痛、疲倦、流鼻水及喉嚨痛等。
- 10%的人有噁心、嘔吐及腹瀉等腸胃道症狀伴隨呼吸道症狀而來。
- 多數人通常約可在1週內康復。
- 研究指出感染A型流感病毒患者出現頭痛、流鼻水、關節痛及熱痙攣等臨床症狀較感染B型流感病毒明顯，且平均體溫較高；肌肉痠痛、小腿痛及腸胃道症狀則是B型流感較A型流感發生機率高。

流感

一燒（發燒）

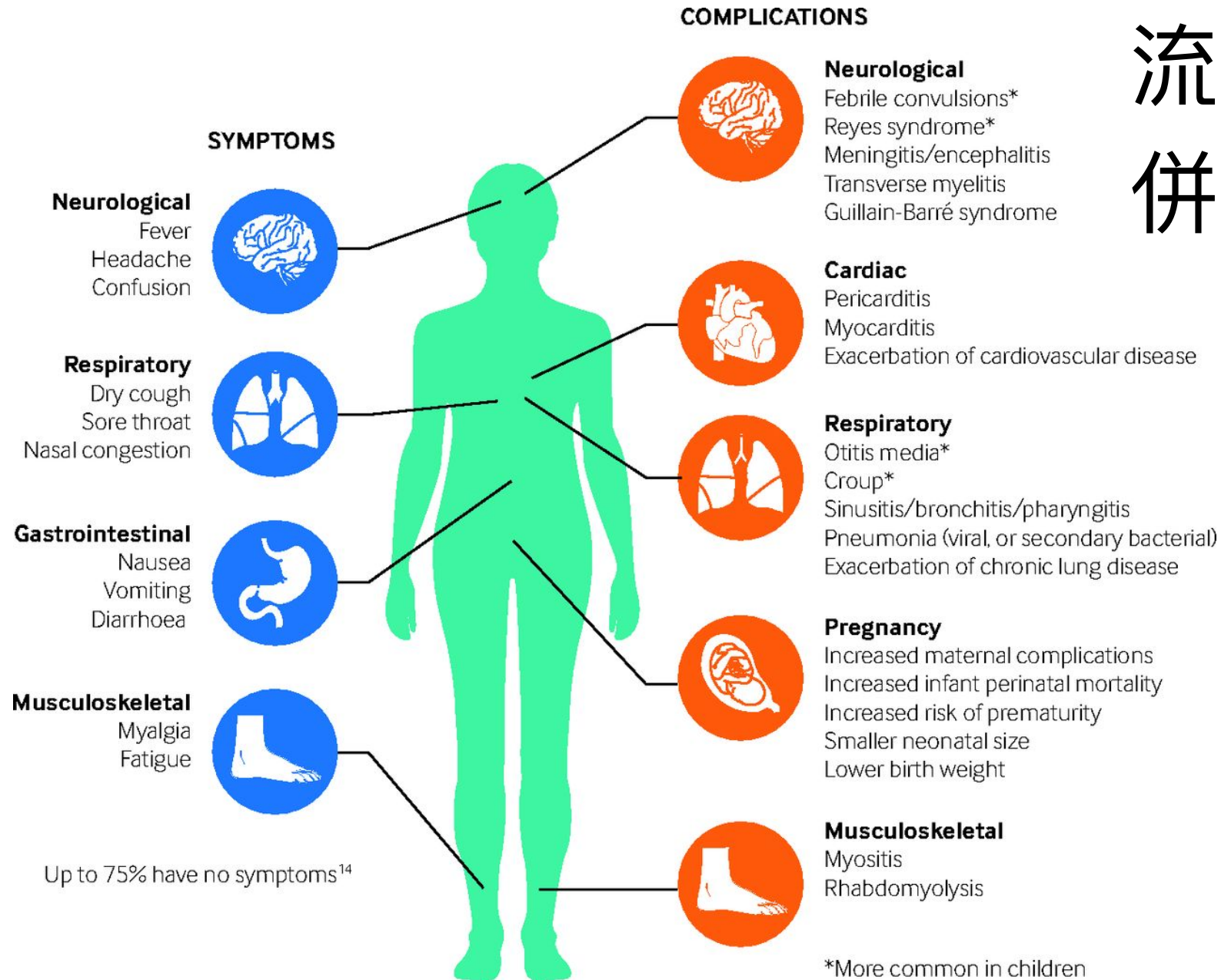
二痛（頭痛、明顯肌肉酸痛）

三疲倦

項目	流感	一般感冒
致病原	流感病毒	大約有200多種病毒可引起，常見的有鼻病毒、呼吸道融合病毒、腺病毒等
影響範圍	全身性	呼吸道局部症狀為主
發病速度	突發性	突發/漸進性
主要臨床症狀	發燒、咳嗽、肌肉酸痛、倦怠、流鼻水、喉嚨痛	喉嚨痛、打噴嚏、鼻塞、流鼻水
發燒	高燒3-4天	少發燒，僅體溫些微升高
病情	嚴重、無法工作/上課	較輕微
病程	約1-2週	約2-5天
併發症	肺炎、心肌炎、腦炎及其他嚴重之繼發性感染或神經症狀(雷氏症候群)等	少見(中耳炎或肺炎)
傳染性	高傳染性	傳染性不一

流感

流感併發症



流感併發症

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

流感併發重症 通報定義

一、臨床條件

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

二、檢驗條件

具有下列任一個條件：

- (一) 呼吸道臨床檢體(咽喉擦拭液等)分離並鑑定出流感病毒(Influenza virus)。
- (二) 臨床檢體分子生物學核酸檢測陽性。
- (三) 臨床檢體抗原檢測陽性。
- (四) 臨床檢體血清學抗體檢測陽性：急性期與恢復期流感病毒血清抗體效價 ≥ 4 倍上升。

三、流行病學條件

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

四、通報定義

符合臨床條件。

五、疾病分類

- (一) 可能病例：
符合臨床條件。
- (二) 極可能病例：
符合臨床條件及流行病學條件。
- (三) 確定病例：
符合臨床條件及檢驗條件。

流感併發重症

- 流感併發重症（此為第四類法定傳染病，需1週內通報）
 - 有些人感染流感病毒後可能引起肺炎、腦炎、心肌炎及其他嚴重之繼發性感染或神經系統疾病等嚴重併發症，而需住院治療，甚至導致死亡，稱之為流感併發重症
- 可能併發重症之高危險群
 - 老年人、嬰幼兒、孕婦
 - 患有氣喘、糖尿病、心血管、肺臟、肝臟、腎臟等慢性疾病
 - 免疫功能不全者
 - 肥胖(身體質量指數BMI $\geq$ 30)

流感普通症狀

發燒、頭痛、
喉嚨痛、咳嗽、
肌肉酸痛

危險徵兆

呼吸困難、呼吸急促、發紺(缺氧)、
血痰或痰液變濃、胸痛、意識改變、
低血壓或高燒持續72小時

65歲以上長者或有潛在疾病者，應提高警覺

112年流感疫苗QA問答集

儘速轉診
至大醫院

門診就醫

(約1%需住院)

流感病毒



潛伏期1-4天
(平均2天)

上呼吸道
感染

(1-2週內)

流感併發症

(佔流感住院病人10-25%)

病毒性併發症

(如：肺炎、心肌炎、腦炎)

細菌感染

(如：肺炎鏈球菌、金黃色葡萄球菌)

加重高風險族群

本身潛在性疾病嚴重度

(如：心血管疾病、慢性肺炎、

嚴重併發症

(佔流感併發症
1%-4%，如：呼吸衰
竭或敗血症等)

死亡

(嚴重併發症者中
約一半會死亡¹²)

流感藥物介紹

2022 U.S. CDC Summary of Influenza Antiviral Treatment Recommendations

Early antiviral treatment can

Shorten the duration of fever and illness symptoms, and may reduce the risk of complications from influenza (e.g., otitis media)

Reduce death for hospitalized patients

Shorten the duration of hospitalization in hospitalized children

Antiviral treatment is recommended as early as possible for patients with confirmed or suspected influenza who:

is
hospitalized

has severe,
complicated, or
progressive
illness

is at higher risk
for influenza
complications

Antiviral treatment also can be considered for

any previously healthy, symptomatic outpatient not at high risk with confirmed or suspected influenza on the basis of clinical judgment

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Clinical benefit is greatest when antiviral treatment is administered early, especially within **48 hours** of influenza illness onset

全年
適用

公費流感抗病毒藥劑使用對象一覽表

適用日期：114年8月1日起



除法定傳染病外，應為本國籍人士或持有居留證
【18歲(含)以下孩童其父母需一方為本國籍或持有居留證】

治療性用藥條件 經醫師評估符合條件者，

無須快篩陽性

法定傳染病

需通報於法定傳染病通報系統及填寫法傳編號

- 「流感併發重症」通報病例
- 「新型A型流感」通報病例

住院病患

• 確診或疑似罹患流感住院(含急診待床)之病患

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」或「急診待床紀錄」

門急診病患

- 未滿5歲及65歲以上之類流感患者
- 孕婦及產後兩週內之婦女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
- 肥胖之類流感患者(BMI $\geq$ 30或未滿18歲兒童青少年BMI超過同齡第95百分位)
未滿18歲兒童青少年BMI第95百分位一覽表詳如附件
- 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
 - 1.重大傷病：IC卡註記為重大傷病或持有重大傷病證明紙卡者
 - 2.流感高風險慢性疾病之ICD CODE：B20, Z21, D80-84, D86, D89, E08-13, E66, E85, G09, G20, G30-32, G35-37, G40, G45-46, G65, G70, G72, I00-02, I05-09, I11-13, I20-22, I24-25, I27-28, I34-37, I42-43, I44-45, I47-49, I50-51, I60-62, I63, I67-69, I70, I71, I72, I73-74, I77, I79, J40-45, J47, J60-70, J82, J84, J96, J98, J99, K70-72, K73-76, B18-19, M05-06, M30-31, M32-34, M35, M94.1, N00-01, N03, N05, N04, N18-19, N26-27, Q89.01, Z90.81

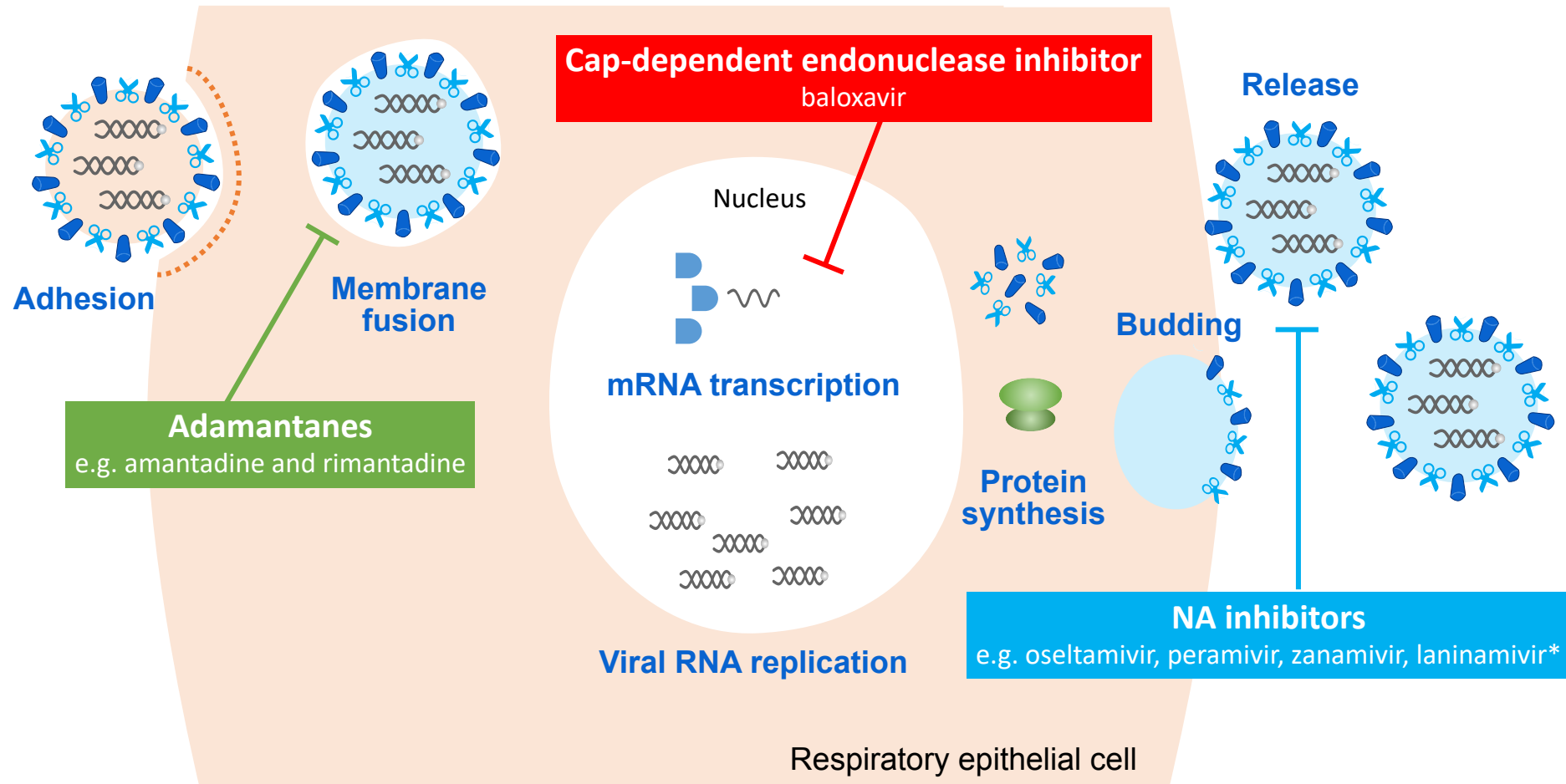
預防性用藥條件

需通報並經審核

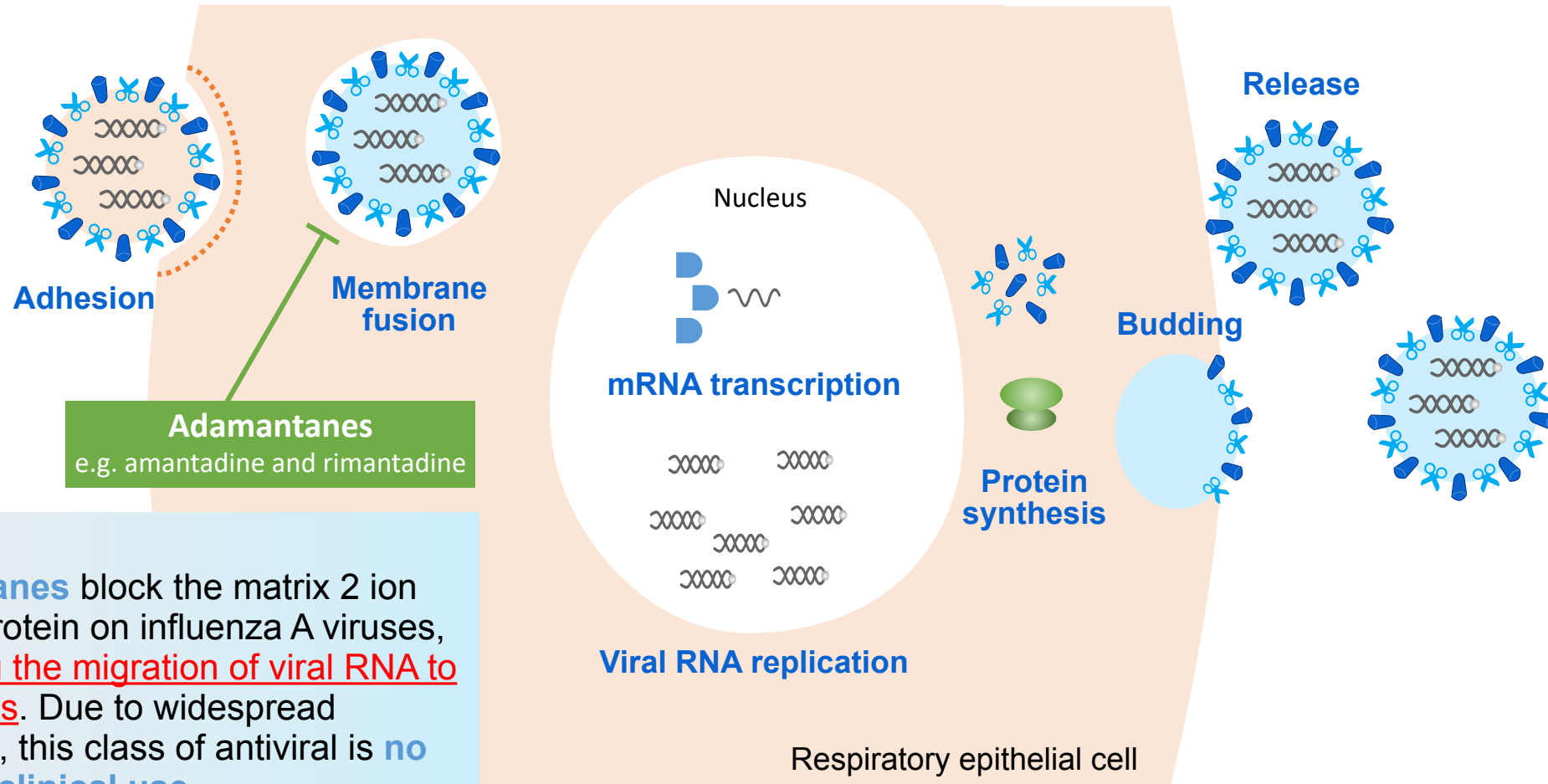
需通報衛生局進行疫情調查，並經疾病管制署各區管制中心防疫醫師或傳染病防治醫療網區正/副指揮官或其授權人員同意後始可用藥

- 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
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;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；需填寫禽畜場名稱或編號

各流感藥物作用機轉

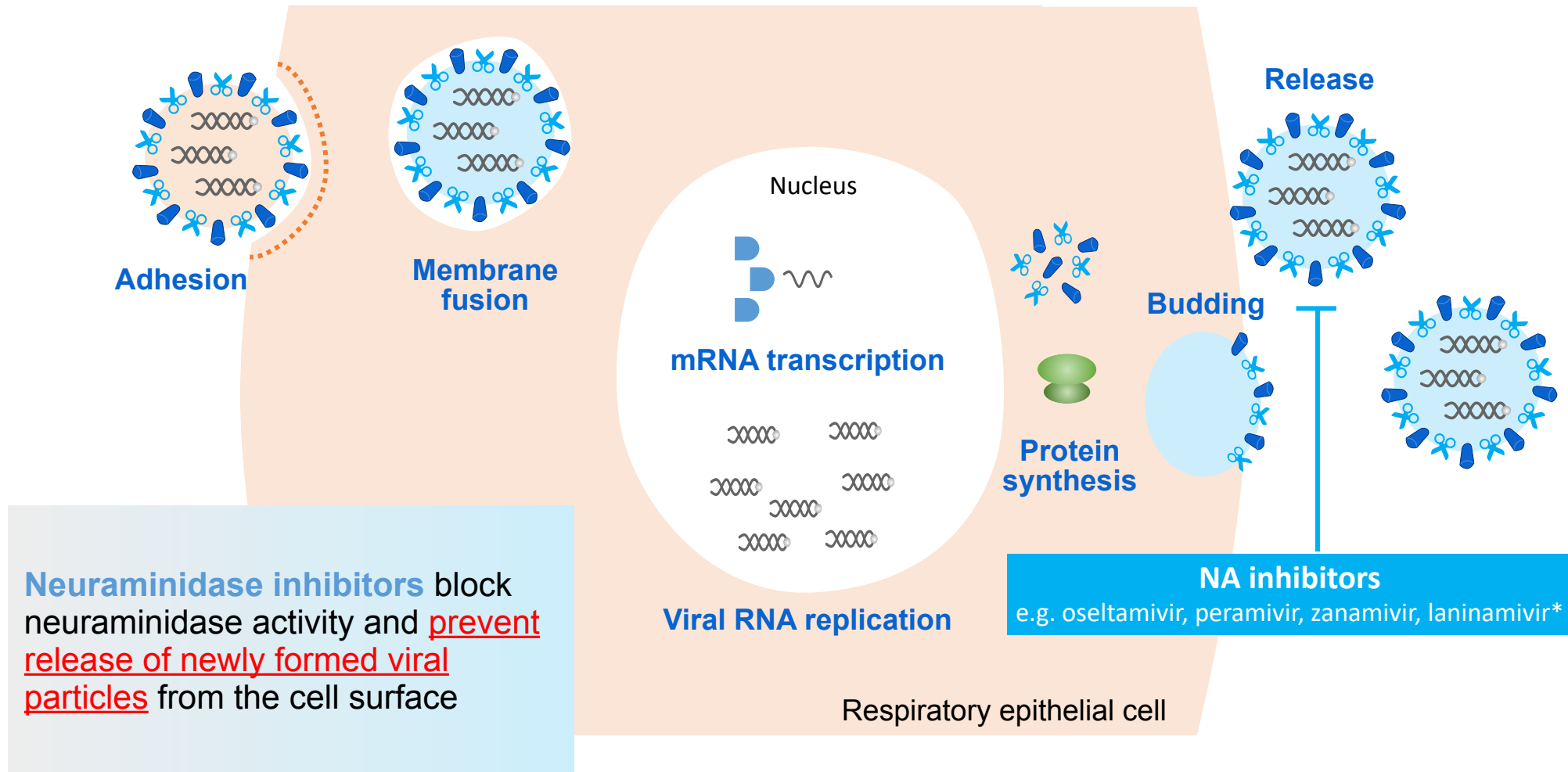


各流感藥物作用機轉

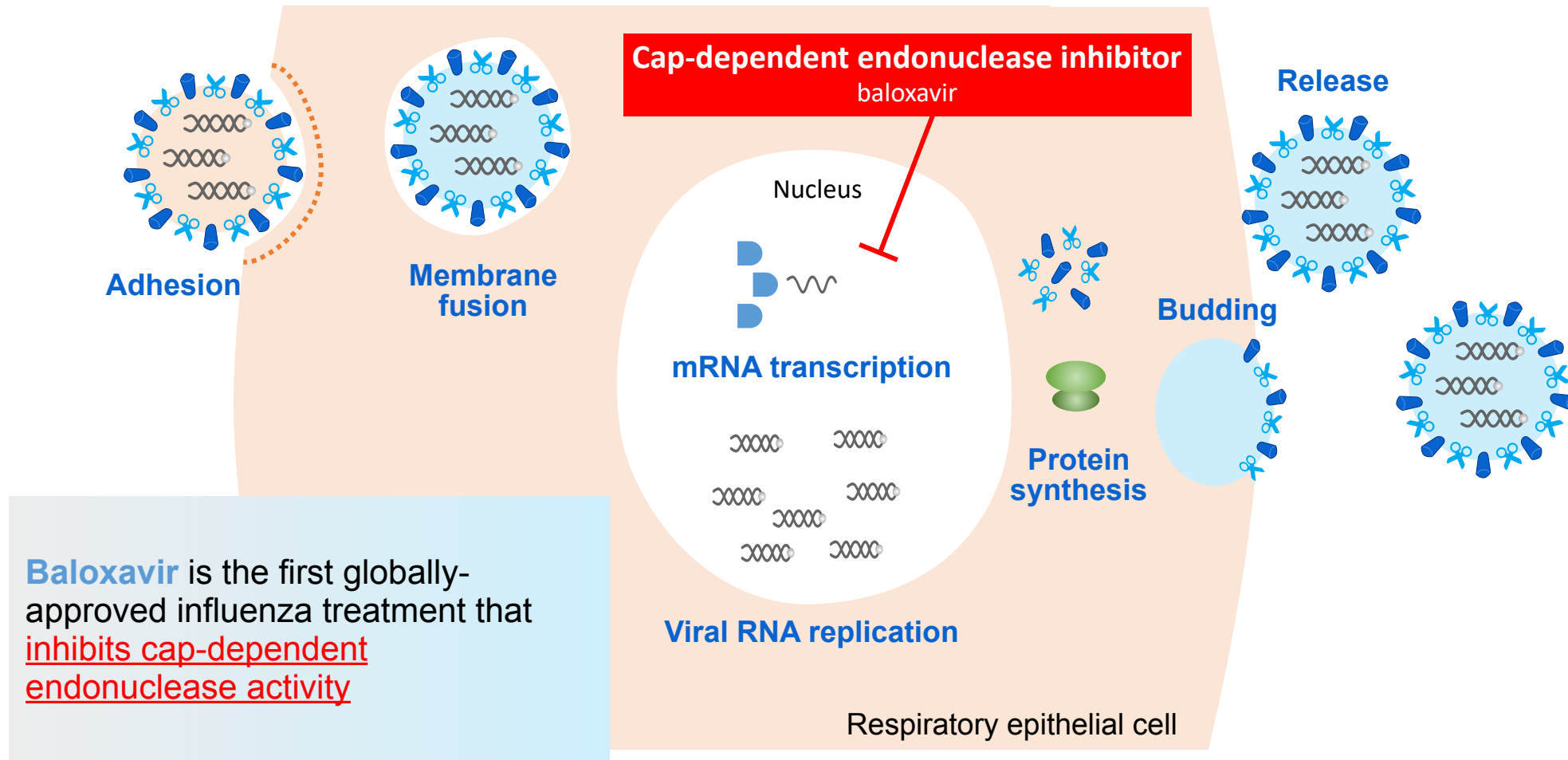


Adamantanes block the matrix 2 ion channel protein on influenza A viruses, preventing the migration of viral RNA to the nucleus. Due to widespread resistance, this class of antiviral is **no longer in clinical use**

各流感藥物作用機轉



各流感藥物作用機轉



流感抗病毒藥物

季節性流感防治工作手冊2023年修訂

	M2 蛋白抑制劑 (M2 protein inhibitor)		神經胺酸酶抑制劑 (Neuraminidase inhibitor)			核酸內切酶抑制劑 (Endonuclease inhibitor)
藥物學名	Amantadine	Rimantadine	Oseltamivir	Zanamivir	Peramivir	Baloxavir
商品名	Amantadin Amandin Amanta Amandine Zneil 等	Flumadine	Tamiflu, Eraflu	Relenza	Rapiacta	Xofluza
對抗流感型別	A	A	A及B	A及B	A及B	A及B
預防	可	可	可	可	非適應症	可
治療	不建議	不建議	可	可	可	可
病程縮短	約1天	約1天	約1-1.5天	約1-1.5天	約1天	約1天
常見副作用	噁心、頭暈、失眠(5-10%)	噁心、頭暈、失眠(1-3%)	噁心(10%)、嘔吐(8%)、頭痛(2%)	噁心、腹瀉、 <u>鼻竇炎(3%)</u>	腹瀉(5-10%)、噁心、嘔吐(5%)	腹瀉(3%)、氣管炎(2%)
抗藥性	廣泛	廣泛	曾有報告	曾有報告	曾有報告	曾有報告
國內許可證	有	無	有	有	有	有

流感抗病毒藥物

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對抗流感型別	A	A	A及B	A及B	A及B	A及B
預防	可	可	可	可	可	可
治療	不建議	不建議	可	可	可	可
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抗藥性	廣泛	廣泛	曾有報告	曾有報告	曾有報告	曾有報告
國內許可證	有	無	有	有	有	有

M2 protein抑制劑

抗藥性問題嚴重

已不建議用來治療流感

流感抗病毒藥物

季節性流感防治工作手冊2023年修訂

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對抗流感型別	A	A	A及B	A及B	A及B	A及B
預防	可	可	可	可	非適應症	可
治療	不建議	不建議	可	可	可	可
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抗藥性	廣泛	廣泛	曾有報告	曾有報告	曾有報告	曾有報告
國內許可證	有	無	有	有	有	有

神經胺酸酶抑制劑

目前治療主流

流感抗病毒藥物

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對抗流感型別	A	核酸內切酶抑制劑			A及B	A及B
預防	可	可	可	可	非適應症	可
治療	不建議	不建議	可	可	可	可
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抗藥性	廣泛	廣泛	曾有報告	曾有報告	曾有報告	曾有報告
國內許可證	有	無	有	有	有	有

流感抗病毒藥物

季節性流感防治工作手冊2023年修訂

	M2 蛋白抑制劑 (M2 protein inhibitor)		神經胺酸酶抑制劑 (Neuraminidase inhibitor)			核酸內切酶抑制劑 (Endonuclease inhibitor)
藥物學名	Amantadine	Rimantadine	Oseltamivir	Zanamivir	Peramivir	Baloxavir
商品名	Amantadin Amandin Amanta Amandine Zneil 等	Flumadine	Tamiflu, Eraflu	Relenza	Rapiacta	Xofluza 口服
對抗流感型別	A	核酸內切酶抑制劑			A及B	A及B
預防	可	可	可	可	非適應症	可
治療	不建議	不建議	可	可	可	可
病程縮短	約1天	約1天	約1-1.5天	約1-1.5天	約1天	約1天
常見副作用	噁心、頭暈、失眠(5-10%)	噁心、頭暈、失眠(1-3%)	噁心(10%)、嘔吐(8%)、頭痛(2%)	噁心、腹瀉、 <u>鼻竇炎</u> (3%)	腹瀉(5-10%)、噁心、嘔吐(5%)	腹瀉(3%)、氣管炎(2%)
抗藥性	廣泛	廣泛	曾有報告	曾有報告	曾有報告	
國內許可證	有	無	有	有	有	

支持療法-
醫師評估投以症狀緩解藥物

台灣感染症醫學會-抗流感病毒藥物使用建議

抗流感藥物使用對象、劑量與療程



藥物	Oseltamivir Capsule		Oseltamivir Oral Suspension		Zanamivir		Peramivir		Baloxavir Marboxil	
使用方式	吞服/無法吞服者（如需使用鼻胃管者）則打開膠囊泡水或糖漿服用 懷孕哺乳首選		經調配後服用		經口吸入 懷孕哺乳：利>弊投予		單次點滴靜脈注射15 分鐘以上 懷孕哺乳：利>弊投予		單次口服 可以磨粉 懷孕哺乳不建議	
適用年齡	成人及兒童（含一個月大新生兒）		成人及兒童（含一個月大新生兒）		5 歲(含)以上		小兒(早產兒及新生兒除外)及成人		成人及兒童（5 歲以上）	
標準治療劑量	輕症	重症	輕症	重症	輕症	重症	輕症	重症	輕症	重症
	13歲以下依體重調整劑量； 13歲(含)以上或體重40kg以上者75mg BID		40kg以下兒童依體重調整劑量； 40kg以上兒童或成年人及青少年為75mg BID		10mg BID	不建議使用	成人300mg; 小兒10-12 mg/kg	成人600mg QD	<20kg單次服用20mg ≥20 至 <80kg 單次服用 40mg ≥80kg 單次服用 80mg	現無臨床數據
標準療程	5天	5天	5天	現無臨床數據	5天		單次	可依症狀連續多日反覆投予	單次	

台灣感染症醫學會-抗流感病毒藥物使用建議

預防性抗流感藥物使用對象、劑量與療程

藥物	Oseltamivir Capsule	Zanamivir	Baloxavir Marboxil
使用方式	吞服；無法吞服者（如需使用鼻胃管者）則打開膠囊泡水或糖漿服用	經口吸入	口服 可以磨粉
適用年齡	成人及兒童 (含一個月大新生兒)	5 歲(含)以上	成人及兒童 (5 歲以上)
建議療程	• 非群突發狀況下,建議使用七天 • 群突發狀況下建議使用14 天或直至最後一位病患發生症狀起七天後	• 非群突發狀況下,建議使用七天 • 群突發狀況下建議使用14 天或直至最後一位病患發生症狀起七天後	單次口服
建議劑量	13 歲以下依體重調整劑量； 13 歲(含)以上或體重40kg 以上者75mg QD 減半劑量	10mg QD	<20kg單次服用20mg; ≥20 至 <80kg 單次服用 40mg ； ≥80kg 單次服用 80mg

公費流感抗病毒藥劑種類

RNA polymerase inhibitor

藥物學名	Oseltamivir	Zanamivir	Peramivir	Favipiravir
商品名	克流感/易剋冒	Relenza 瑞樂沙	Rapiacta	Avigan
包裝	75 毫克膠囊 10 入之盒裝	盒裝有碟型吸入器 1 枚，及含 4 孔規則間隔之泡囊 5 入	點滴用注射袋 300mg	淡黃色膜衣錠，每錠200mg
使用方式	口服	吸入	注射	口服
使用對象	成人及兒童（含足月新生兒）	五歲以上	成人及一個月大以上兒童	成人
用法用量	每日2次，每次75mg，共5日	每日2次，每次吸 2 孔，共5日	每日 300mg	每日2次，第1日每次服用 1600mg。第2日起每次服用600mg，共5日
小兒是否需調整劑量	是	否	是	本藥劑具致畸胎性，禁使用於兒童，且無小兒投藥經驗
腎功能不佳是否調整劑量	是	否	是	是
備註	可能出現輕微噁心及嘔吐，未成年病患需注意神經精神症狀	用於慢性呼吸系統病患時需特別注意支氣管痙攣及呼吸困難等症狀	提供新型A型流感通報病例使用，且需由醫院申請並經醫療網指揮官同意	無我國藥物許可證，提供新型A型流感通報病例使用（限於其他抗流感病毒藥物無效或效力不足的情況），且需由醫院向區管中心申請並經醫療網指揮官同意。本藥劑具致畸胎性，孕婦及有懷孕可能的婦人禁止使用

Oseltamivir (Tamiflu® , Eraflu®)

Oseltamivir in seasonal influenza: cumulative experience in low- and high-risk patients

Regina Dutkowski*

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2003~2008

Oseltamivir significantly reduces the frequency of secondary illness and exacerbation of underlying conditions; survival is also significantly improved in seriously ill patients who are hospitalized with severe influenza.

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 effectiveness of oseltamivir for the treatment of seasonal influenza in adults regarding safety and efficacy.

Methods We included all published and unpublished randomised controlled trials of 75 mg twice a day oseltamivir in adults. Trials were included if they reported on efficacy, safety, or both in adults reporting at least one of the study outcomes. We searched Embase, the Cochrane Central Register of Controlled Trials, and PubMed for trials published before Jan 1, 2014 (search last updated May 1, 2015). We included all randomised controlled trials published before Jan 1, 2014 (search last updated May 1, 2015). We included all randomised controlled trials published before Jan 1, 2014 (search last updated May 1, 2015).

Findings We included data from nine trials including 4328 patients. In the intention-to-treat infected population, we noted a 21% shorter time to alleviation of all symptoms for oseltamivir versus placebo recipients (time ratio 0.79, 95% CI 0.74–0.85; $p < 0.0001$). The median times to alleviation were 97.5 h for oseltamivir and 122.7 h for placebo groups (difference -25.2 h, 95% CI -36.2 to -16.0). For the intention-to-treat population, the estimated treatment effect was attenuated (time ratio 0.85) but remained highly significant (median difference -17.8 h). In the intention-to-treat infected population, we noted fewer lower respiratory tract complications requiring antibiotics more than 48 h after randomisation (risk ratio [RR] 0.56, 95% CI 0.42–0.75; $p = 0.0001$; 4.9% oseltamivir vs 8.7% placebo, risk difference -3.8%, 95% CI -5.0 to -2.2) and also fewer admittances to hospital for any cause (RR 0.37, 95% CI 0.17–0.81; $p = 0.013$; 0.6% oseltamivir, 1.7% placebo, risk difference -1.1%, 95% CI -1.4 to -0.3). Regarding safety, oseltamivir increased the risk of nausea (RR 1.60, 95% CI 1.29–1.99; $p < 0.0001$; 9.9% oseltamivir vs 6.2% placebo, risk difference 3.7%, 95% CI 1.8–6.1) and vomiting (RR 2.43, 95% CI 1.83–3.23; $p < 0.0001$; 8.0% oseltamivir vs 3.3% placebo, risk difference 4.7%, 95% CI 2.7–7.3). We recorded no effect on neurological or psychiatric disorders or serious adverse events.

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

Lancet. 2015 May 2;385(9979):1729-1737.

Guidelines for the clinical management of severe illness from influenza virus infections

3.1 Oseltamivir (oral)

March 2022, WHO



RECOMMENDATION 1

In persons with suspected or confirmed influenza virus infection with or at risk of severe illness (i.e. including seasonal influenza, pandemic influenza and zoonotic influenza), **we suggest administering oseltamivir as soon as possible (vs not administering oseltamivir)** (conditional recommendation, low-quality evidence).

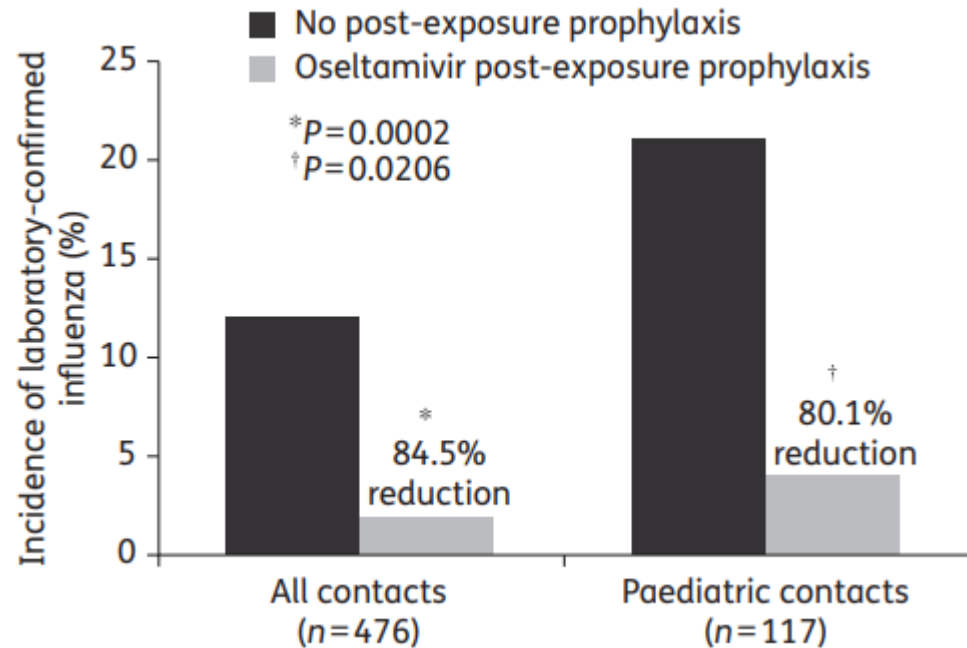
根據現有證據，有重症風險因子之疑似或確診流感病患，建議及早給予oseltamivir治療

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 confidence.

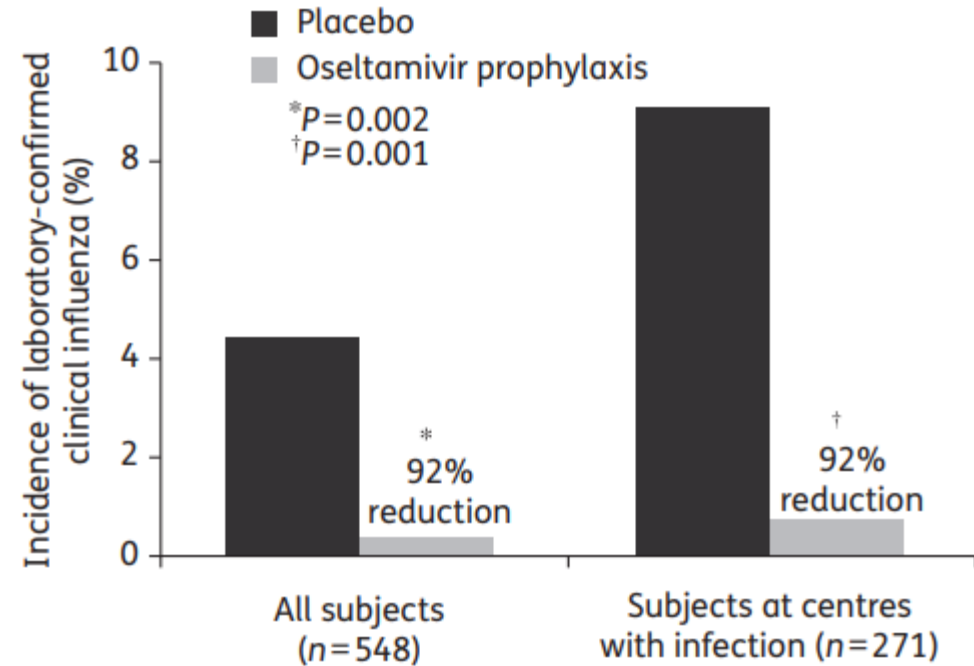
觀察性研究顯示可降低62%死亡風險

觀察性研究顯示可降低36%住院風險
但隨機對照研究結果則無顯著差異

Prophylaxis with Oseltamivir in seasonal influenza



Household contacts



Elderly nursing home residents



Oseltamivir phosphate (Tamiflu®)

成人及青少年(≥ 13 歲)

CCr	>60	30-60	10-30	≤ 10	HD	CAPD
Treatment dose	75mg BID	30mg BID	30mg QD	X	30mg stat, then 30mg after every HD	30mg stat, single dose
Prophylaxis dose	75mg QD	30mg QD	30mg QOD	X	30mg stat, then 30mg after alternate HD	30mg stat, then QWK

Oseltamivir phosphate (Tamiflu®)

1 歲或以上兒童

體重	建議劑量，為期 5 天	藥局調製口服懸浮液的容量 (6 mg/mL)	HD
≤15 公斤	30 毫克，每天 2 次	5.0 毫升，每天 2 次	7.5mg every HD
> 15 - 23 公斤	45 毫克，每天 2 次	7.5 毫升，每天 2 次	10mg every HD
> 23 - 40 公斤	60 毫克，每天 2 次	10.0 毫升，每天 2 次	15mg every HD
> 40 公斤	75 毫克，每天 2 次	12.5 毫升，每天 2 次	30mg every HD

Oseltamivir phosphate (Tamiflu®)

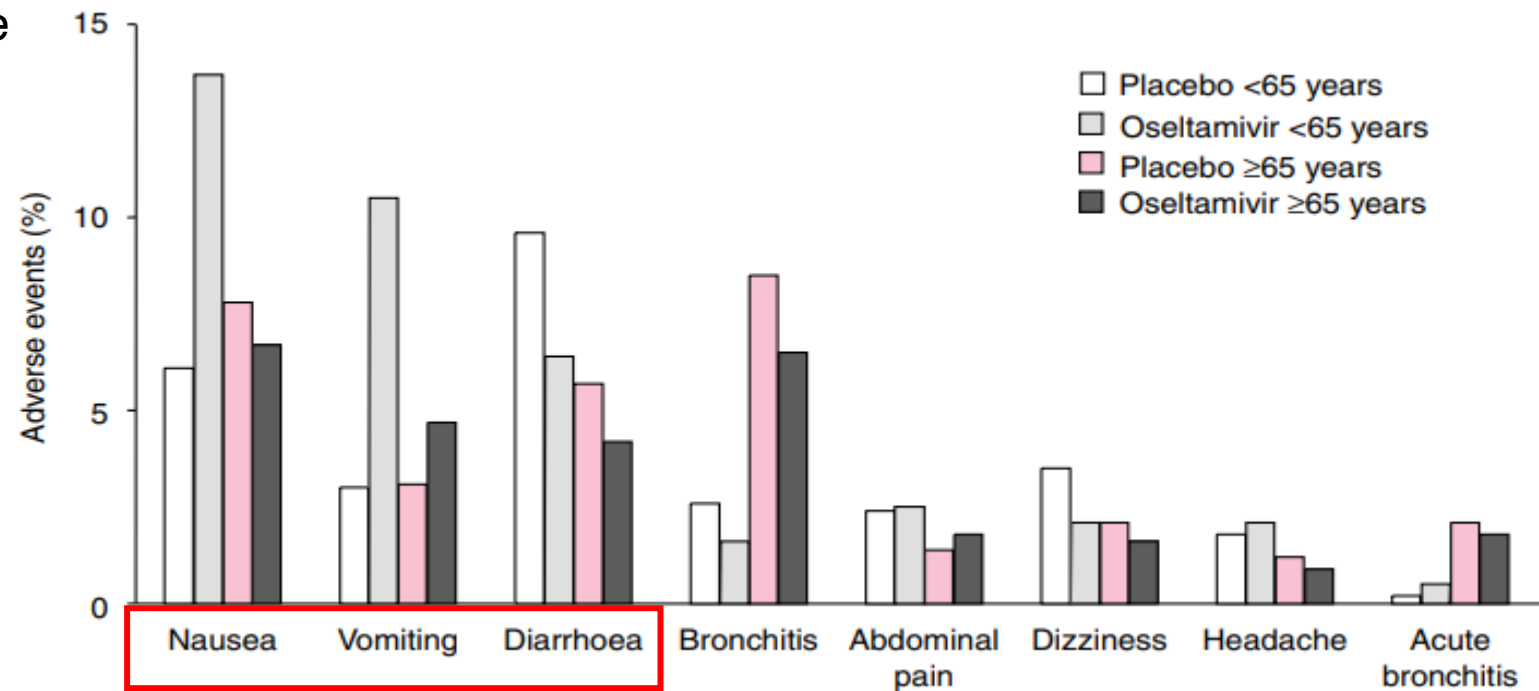
未滿1歲兒童 (3mg/kg)

此建議劑量不適用於胎齡未滿 36 週的嬰兒

體重	建議劑量，為期 5 天	藥局調製口服懸浮液的容量 (6 mg/mL)
3 公斤	9 毫克，每天 2 次	1.5 毫升，每天 2 次
4 公斤	12 毫克，每天 2 次	2.0 毫升，每天 2 次
5 公斤	15 毫克，每天 2 次	2.5 毫升，每天 2 次
6 公斤	18 毫克，每天 2 次	3.0 毫升，每天 2 次
7 公斤	21 毫克，每天 2 次	3.5 毫升，每天 2 次
8 公斤	24 毫克，每天 2 次	4.0 毫升，每天 2 次
9 公斤	27 毫克，每天 2 次	4.5 毫升，每天 2 次
10 公斤	30 毫克，每天 2 次	5.0 毫升，每天 2 次

Safety

- North America, Europe and the Southern Hemisphere
- N=11675
- Including healthy adults, elderly/ high-risk subjects, and children aged 1–12 years
- Oseltamivir 5 days course



Safety

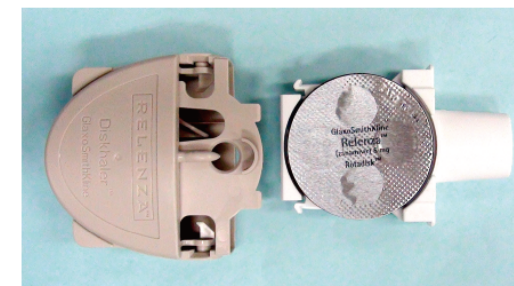
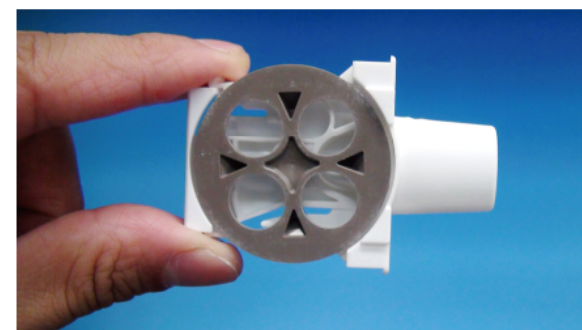
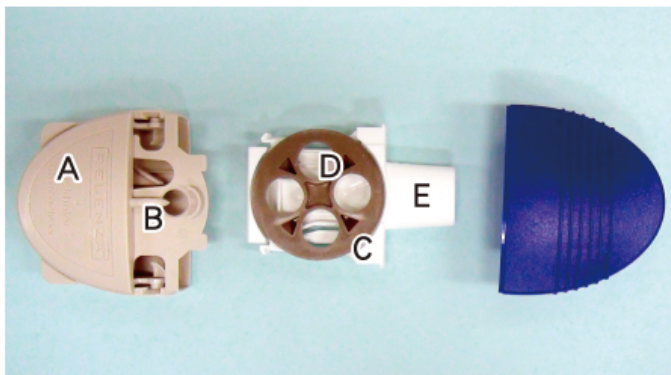
系統器官類別 藥物不良反應	治療研究		預防性治療		發生頻率類別 ^a
	Oseltamivir (75 毫克每天 兩次) N=2647	安慰劑 N=1977	Oseltamivir (75 毫克每天 一次) N=1945	安慰劑 N=1588	
胃腸道疾患					
噁心	10%	6%	8%	4%	極常見
嘔吐	8%	3%	2%	1%	常見
神經學與神經系統疾患					
頭痛	2%	1%	17%	16%	極常見
全身性疾患					
疼痛	<1%	<1%	4%	3%	常見

Zanamivir (Relenza®)

Zanamivir

裝置說明

- A. 上蓋：掀開可將刺針刺破含藥泡殼。
- B. 刺針：刺破含藥泡殼準備上藥。
- C. 指握部分（按壓）：將滑盤從主體取出。
- D. 轉盤：置入含藥泡殼（一片四個泡殼）。
- E. 吸嘴：兩側各有一個氣孔。



Zanamivir

作用

治療及預防成人及兒童（>5歲）之A型及B型流行性感冒。

用法

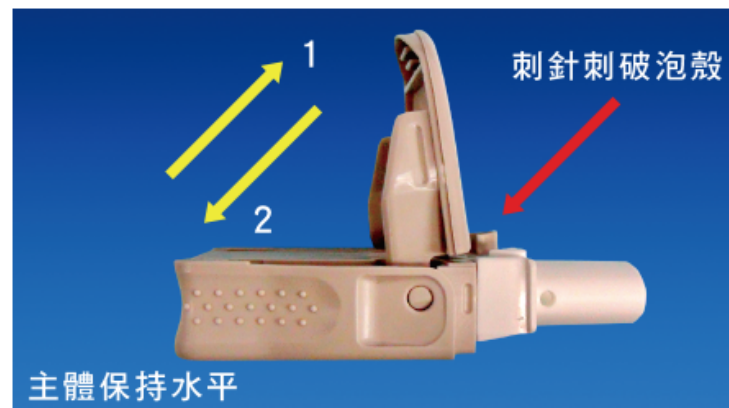
1. 請遵照醫師處方之用法及劑量服用。
2. 治療流行性感冒：每日二次，每次二個劑量（10毫克），連續五天。
3. 預防流行性感冒：每日一次，每次二個劑量（10毫克），連續十天。

吸入藥物

1. 輕吐氣（勿對藥物吸嘴處吐氣）。
2. 吸嘴置入齒間(勿啃咬吸嘴)，緊閉雙唇包住吸嘴（請勿阻塞吸嘴側邊的氣孔）。
3. 快速深吸一口氣，憋氣數秒可將吸嘴由口中移開，但仍維持屏息狀態，以舒適範圍內盡可能延長憋氣時間，正常呼吸。
4. 完成吸入完整劑量後，請以紙巾擦拭吸嘴，並將藍色外蓋裝回原位。

奇美醫院藥劑部衛教資訊網站

https://www.chimei.org.tw/main/cmh_department/59012/info/5500/A5500265.html



26 RCT, N= 11897

雖然說 Zanamivir 效果最好 (HR:0.67),但所有藥物 (Tamiflu, rapiacta, Xofluza)的HR都約在0.7左右

Original Investigation | Infectious Diseases

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

A Systematic Review and Network Meta-analysis

Jen-Wei Liu, MS; Shen-Hua Lin, BS; Lin-Chien Wang, MS; Hsiao-Yean Chiu, PhD; Jen-Ai Lee, PhD

Abstract

IMPORTANCE Antiviral treatment of influenza is recommended for patients with influenza-like illness during periods of community cocirculation of influenza viruses and SARS-CoV-2; however, questions remain about which treatment is associated with the best outcomes and fewest adverse events.

OBJECTIVE To compare the efficacy and safety of neuraminidase inhibitors and the endonuclease inhibitor for the treatment of seasonal influenza among healthy adults and children.

DATA SOURCES Medline, Embase, and the Cochrane Register of Clinical Trials were searched from inception to January 2020 (the last search was updated in October 2020).

STUDY SELECTION Included studies were randomized clinical trials conducted among patients of all ages with influenza treated with neuraminidase inhibitors (ie, oseltamivir, peramivir, zanamivir, or laninamivir) or an endonuclease inhibitor (ie, baloxavir) compared with other active agents or placebo.

DATA EXTRACTION AND SYNTHESIS Two investigators identified studies and independently abstracted data. Frequentist network meta-analyses were performed; relative ranking of agents was conducted using P-score probabilities. Quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations criteria. Data were analyzed in October 2020.

MAIN OUTCOMES AND MEASURES The time to alleviation of influenza symptoms (TTAS), complications of influenza, and adverse events (total adverse events, nausea, and vomiting).

RESULTS A total of 26 trials were identified that investigated antiviral drugs and these trials included 11 897 participants, among whom 6294 (52.9%) were men and the mean age was 32.5 (16.9) years. Of all treatments comparing with placebo in efficacy, quality evidence indicated that zanamivir was associated with the shortest TTAS (HR, 0.67; 95% CI, 0.58-0.77), while baloxavir was associated with the lowest risk of influenza complications (risk ratio [RR], 0.51; 95% CI, 0.32-0.80) based on moderate-quality evidence. For safety outcomes, baloxavir was associated with the lowest risk of total adverse events (RR, 0.74-0.96) compared with placebo based on moderate-quality evidence. There was strong evidence of associations with risk of nausea or vomiting among all comparisons. Compared with placebo, oseltamivir was associated with greater occurrence of nausea (RR, 1.88; 95% CI, 1.47-2.41) and vomiting (RR, 1.88; 95% CI, 1.47-2.41).

Abstract (continued)

CONCLUSIONS AND RELEVANCE In this systematic review and network meta-analysis, all antiviral agents assessed were associated with shortening TTAS; zanamivir was associated with the shortest TTAS, and baloxavir was associated with reduced rate of influenza-related complications.

Key Points

Question What antiviral agents for treating seasonal influenza are associated with the most safety and best outcomes among healthy adults and children?

Findings This network meta-analysis of 26 randomized clinical trials, including 11 897 patients, found that antiviral agents were associated with significantly greater efficacy than placebo.

依系統性文獻回顧及網絡統合分析結果，發現抗病毒藥物皆可縮短病程，其中zanamivir效果最好。另針對容易併發重症的高風險族群，可考慮使用baloxavir。

Inhaled Zanamivir vs Oral Oseltamivir to Prevent Influenza-related Hospitalization or Death: A Nationwide Population-based Quasi-experimental Study 台灣本土研究

- ❑ 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

Principal Diagnosis for Hospitalization or Death 主診斷	Crude			Propensity Score-Weighted			Adjusted Hazard Ratio (95% Confidence Interval)
	Number of Events	Total Person-Days	Incidence Rate	Number of Events	Total Person-Days	Incidence Rate	
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	10 083	579 564	0.017	13 878	579 539	0.024	1
Oseltamivir	6072	251 053	0.024	6070	250 995	0.024	1.01 (.96–1.06)

Zanamivir與oseltamivir
效果無統計顯著差異

不適用吸入型 Zanamivir 的情況

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

Peramivir (Rapiacta®)

Chemotherapy 2013;59:373–378

DOI: [10.1159/000362436](https://doi.org/10.1159/000362436)

Received: November 19, 2013

Accepted after revision: March 25, 2014

Published online: May 10, 2014

Clinical Effects of Oseltamivir, Zanamivir, Laninamivir and Peramivir on Seasonal Influenza Infection in Outpatients in Japan during the Winter of 2012–2013

Yuji Takemoto^a Teizaburo Asai^d Itsuo Ikezoe^b Takako Yano^e

Masahiro Ichikawa^c Shogo Miyagawa^f Jun Matsumoto^g

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^eMori-Yano Clinic, ^fMiyagawa Clinic, and ^gMatsumoto Clinic, Osaka, Japan

試驗概要-第四期上市後的觀察性試驗

試驗目的: 評估各抗病毒藥物治療門診流感病患之效果

試驗組別 : Peramivir 成人: 300mg; 兒童: 10mg/kg IV Infusion over 15-30min **once**

Oseltamivir 兒童 > 37.5 kg及成人: **150mg BID** PO 5 days;

兒童 < 37.5kg: 4mg/kg/day PO 5 days

Zanamivir > 5歲兒童及成人: **20mg BID** INH 5 days

Laninamivir > 10歲兒童及成人 40mg or 20mg INH once

共191例 (Open Label) (6m - 95y)

Influenza Onset < 48hr
尚未接受任何治療
無其他疾病

peramivir 53例

laninamivir 44例

oseltamivir 51(47*)例

zanamivir 39例

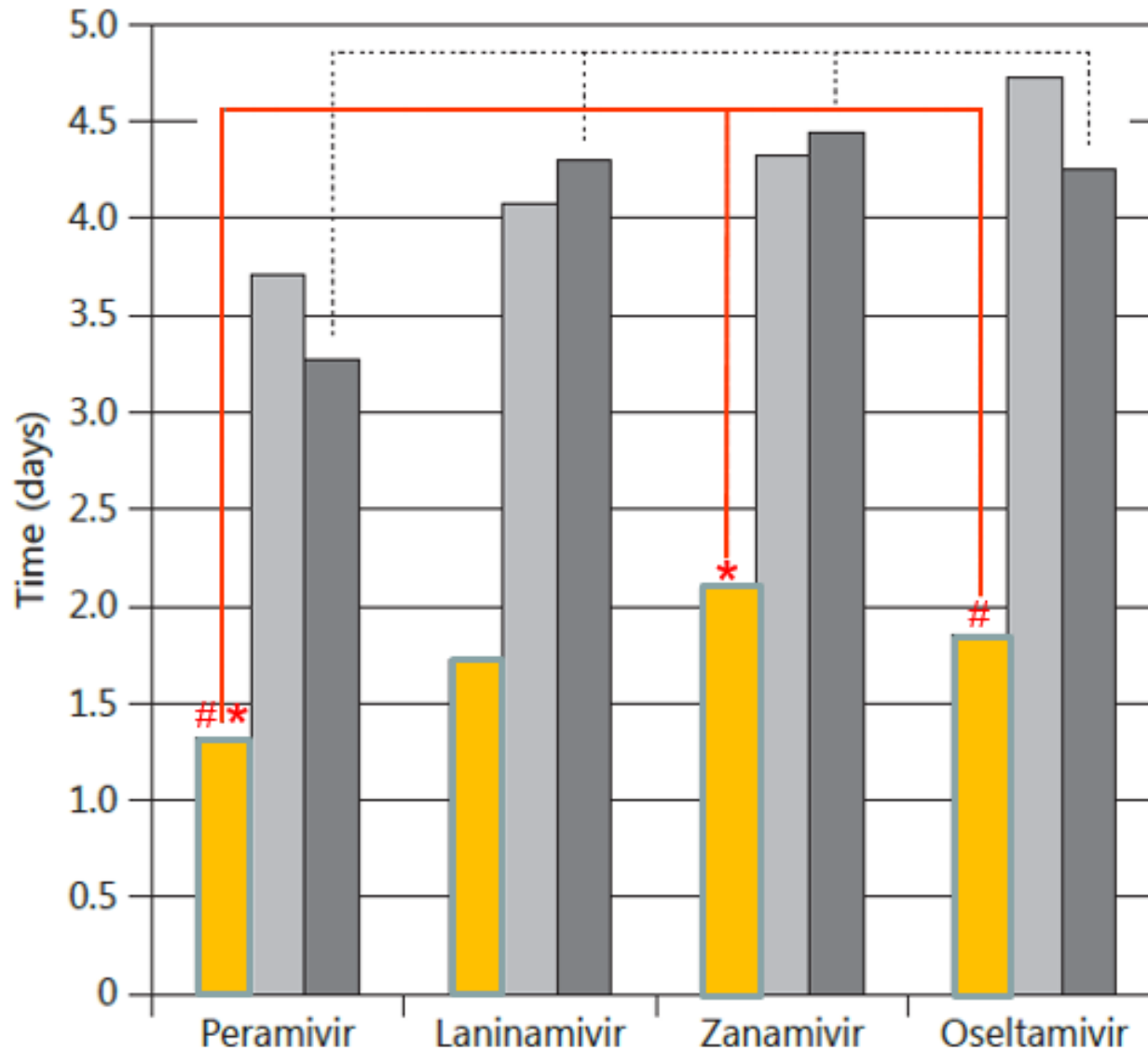
*No records were available for 4 patients.

療效指標 :

1. Time to alleviate fever (from > 37.5°C to < 37°C)
2. Time to alleviate symptoms (cough, rhinorrhea, arthralgia, general malaise)
3. Time to eliminate the influenza virus

試驗國家: Japan (November 2012 to March 2013)

Time to alleviate fever



Peramivir tended to reduce fever duration

Peramivir: 1.32 ± 0.79 days
Laninamivir: 1.72 ± 1.03 days
Zanamivir: 2.10 ± 1.12 days
Oseltamivir: 1.86 ± 1.02 days

* $p=0.002$

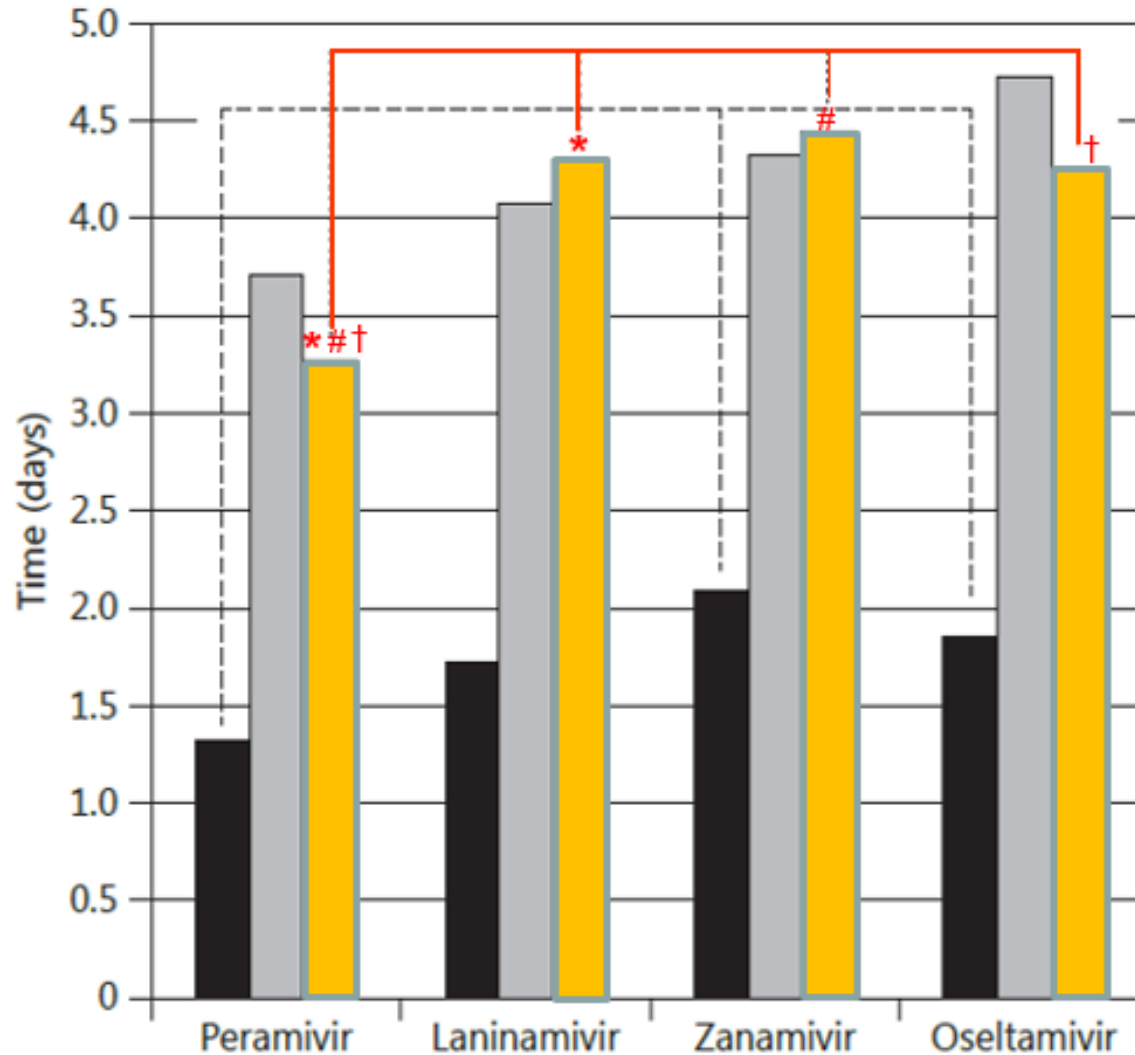
$p=0.0059$

Fever duration

Elimination of influenza

Symptoms

Recover from symptoms



Peramivir rapidly alleviated clinical symptoms

Peramivir: 3.28 ± 1.35 days
Laninamivir: 4.31 ± 0.92 days
Zanamivir: 4.46 ± 0.84 days
Oseltamivir: 4.27 ± 1.08 days

* $p=0.002$

$p<0.001$

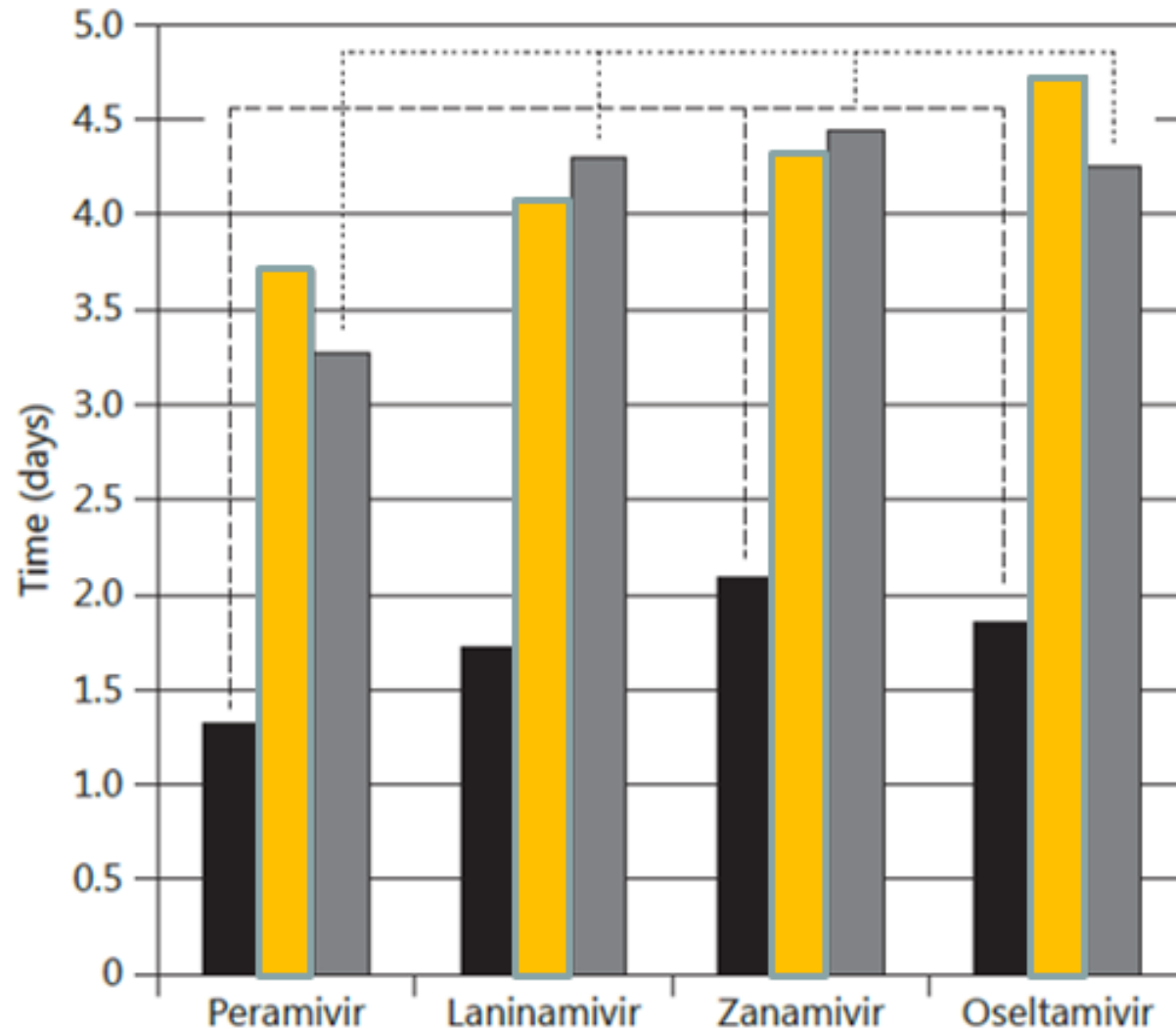
† $p=0.002$

■ Fever duration

■ Elimination of influenza

■ Symptoms

Eliminate the Influenza Virus



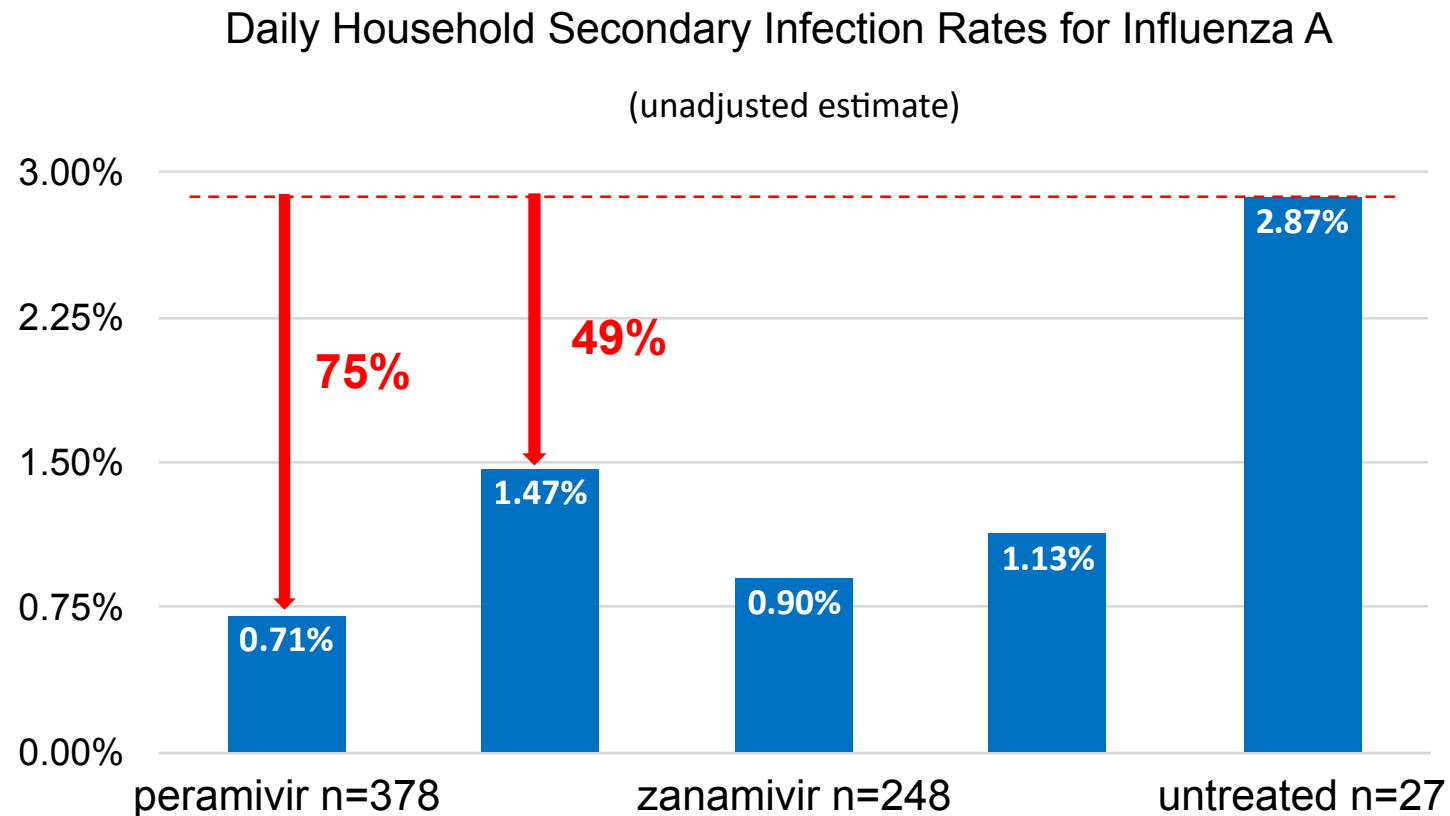
Peramivir tended to eliminate the virus sooner

Peramivir: 3.71 ± 1.38 days
Laninamivir: 4.09 ± 1.23 days
Zanamivir: 4.33 ± 1.38 days
Oseltamivir: 4.75 ± 1.47 days

■ Fever duration
■ Elimination of influenza
■ Symptoms

Daily Household Secondary Infection Rate

- Compared with no treatment, all NAIs reduced the daily SIR of influenza A, with the extent of **daily SIR reduction** ranging from **49%** with **oseltamivir** to **75%** with **peramivir**.

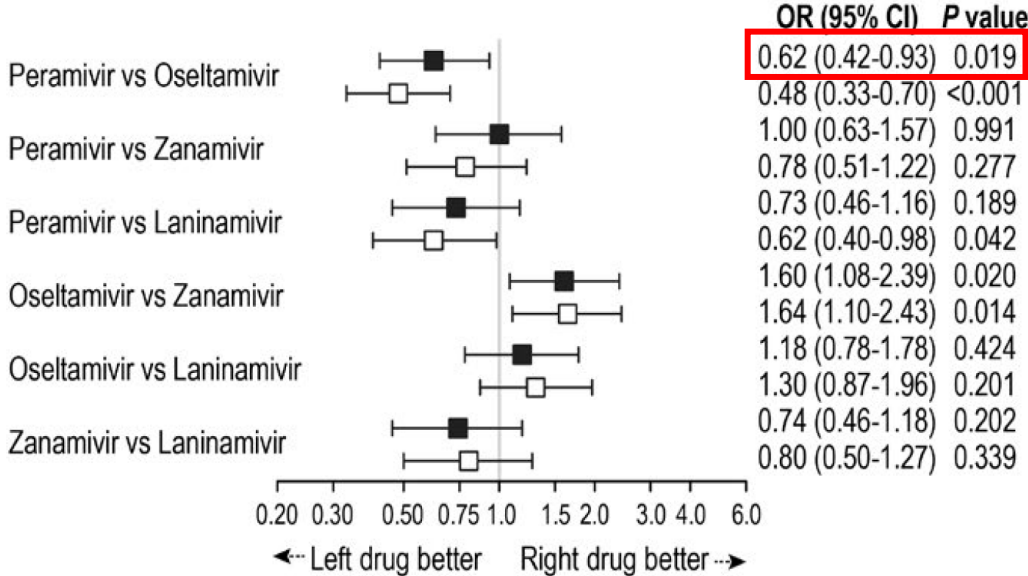


相較於未使用抗病毒藥物治療者，Rapiacta較Oseltamivir降低 38%每天傳染給家人的機會

Daily Household Secondary Infection Rate

Type A

Daily secondary infection rate	Peramivir n = 378	Oseltamivir n = 323	Zanamivir n = 248	Laninamivir n = 170	Untreated n = 27
Unadjusted estimate	0.71%	1.47%	0.90%	1.13%	2.87%
95% CI	0.53-0.96	1.18-1.83	0.66-1.24	0.81-1.58	2.32-3.54



■ adjusted □ unadjusted

Adjusting for the following covariates of patients with infectious ability in a household using the logit link function: age, time from onset to start of treatment, and influenza vaccine in the same season

Rapiacta®適應症及用法用量

適應症：治療成人及一個月大以上兒童之A型及B型
流感病毒急性感染

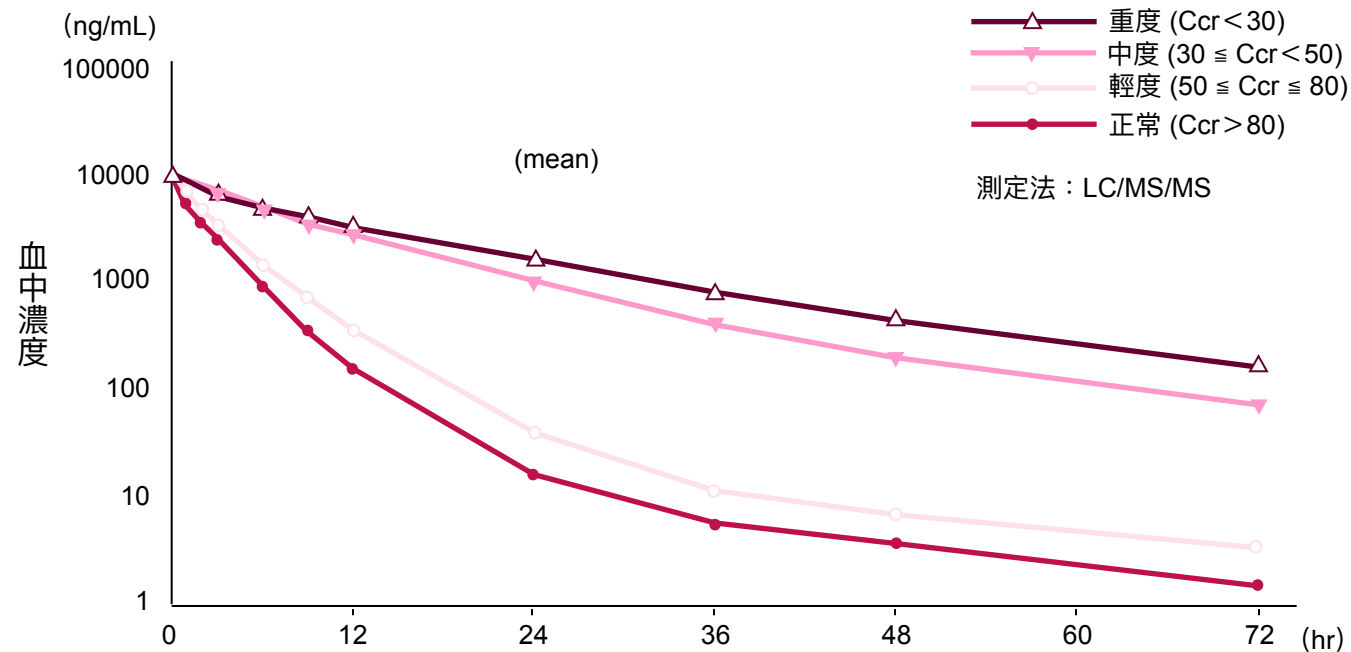


<本藥限由醫師使用>

- 宜於症狀發生後48小時內使用本藥。
- 成人建議劑量為300 mg，每次最多不得超過600 mg，15分鐘以上。
- 單次點滴靜脈注射。
- 兒童建議劑量為10 mg/kg，每次最多不得超過600 mg，15分鐘以上單次點滴靜脈注射。
- 連續投予之經驗有限。
- 腎功能不全病人：請依腎功能情況調整投予劑量，血液透析病人請於透析後投予。

Rapiacta® 瑞貝塔®仿單

Rapiacta[®] 腎功能不全患者之血中濃度及建議劑量



腎功能不全患者之建議劑量

Ccr (mL/min)	1 次投與量
	一般情形
Ccr ≥ 50	300 mg
30 ≤ Ccr < 50	100 mg
10* ≤ Ccr < 30	50 mg

Ccr: Creatinine clearance (肌酐清除率)

*Creatinine clearance < 10 mL/min 及接受血液透析的病患，請審慎調整投與量。Peramivir 會因血液透析而快速自血中清除。

Rapiacta® 不良反應

- 主要不良反應：
 - 腹瀉(5.8%)、嗜中性白血球減少(2.8%)、蛋白尿(2.5%)
- 其他不良反應：

不良反應類別	發生頻率 $\geq 1\%$
消化道	噁心、嘔吐
肝臟	AST(GOT)、ALT(GPT)上升
腎臟	蛋白尿、尿中 β_2 微球蛋白 (β_2 -microglobulin)上升、NAG上升
血液	淋巴球增加
其他	血中葡萄糖增加

Highlight of Adverse Events

Incidence of all adverse events for peramivir was **comparable to that for placebo**.
Adverse events were generally mild to moderate.

	Peramivir		Placebo
	300 mg QD N=99	600 mg QD N=99	N=100
No. (%) of patients with ≥ 1 event	87 (87.9)	90 (90.9)	91 (91.0)
Adverse events ($\geq 6\%$ in either group) [n (%) of patients]			
Monocyte % increased	20 (20.2)	18 (18.2)	31 (31.0)
Blood glucose increased	18 (18.2)	17 (17.2)	18 (18.0)
Diarrhea	14 (14.1)	15 (15.2)	17 (17.0)
Lymphocyte % increased	14 (14.1)	14 (14.1)	5 (5.0)
Proteinuria present	9 (9.1)	11 (11.1)	18 (18.0)
$\beta 2$ Microglobulin in urine increased	14 (14.1)	8 (8.1)	11 (11.0)
Blood bilirubin increased	7 (7.1)	8 (8.1)	7 (7.0)
Alanine aminotransferase increased	4 (4.0)	7 (7.1)	8 (8.0)
Aspartate aminotransferase increased	1 (1.0)	7 (7.1)	6 (6.0)
Nausea	3 (3.0)	6 (6.1)	1 (1.0)
β -N-Acetyl-D-glucosaminidase	9 (9.1)	5 (5.1)	5 (5.0)

與安慰劑組相比，副作用發生比率不管是使用
Peramivir 300mg或600mg皆與安慰劑相當

Rapiacta®不良事件(AE)與藥物不良反應(ADR)

	Number of Patients (%)		
	Peramivir 300 mg (N=364)	Peramivir 600 mg (N=364)	Oseltamivir 75 mg (N=365)
≥ 1 AEs	170 (46.7)	174 (47.8)	178 (48.8)
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)		
Urine positive for WBCs	14 (3.8)		
Nausea	8 (2.2)		
Vomiting	2 (0.5)	6 (1.6)	15 (4.1)

藥物不良反應發生率，於Peramivir 300mg組為14.0% (p=0.0382) ，顯著低於oseltamivir組的20.0%，Rapiacta的安全性應當比Tamiflu高

(*p=0.0382)

≥ 1 ADRs	51 (14.0)*	66 (18.1)	73 (20.0)
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)

AEs, adverse events; ADRs, adverse drug reactions; WBCs, white blood cells

Data are shown only for AEs or ADRs that occurred at a frequency of 3% in any of the three groups

Post-marketing evaluation - 門診病人(包含兒童) ADRs

- The most frequently reported ADRs were **diarrhea**, **vomiting**, and **nausea** (1.87%, 0.68% and 0.85%).
- No ADR** was reported as **serious**.
- Of 78 ADRs, 47.4% (37 events) developed on the day of administration, 29.5% (23 events) on the following day, and 14.1% (11 events) at **2 days** after administration.
- Apart from the one event whose outcome was unknown, **all ADRs resolved or improved without after effects**.
- Resolution was swift in most cases and noted on the day of onset (12 events, 15.4%) or 1 day (33 events, 42.3%), 2 days (15 events, 19.2%), 3 days (2 events, 2.6%), or 4-7 days after onset (13 events, 16.7%), i.e., mostly within **7 days** after onset (75 events, **96.2%**).

Number of patients evaluated for safety	1174
Number of patients with ADRs	51
Number of ADRs	78
Incidence of ADRs	4.34%
Type of ADRs	Incidence of ADRs [number (%)]
Metabolism and nutrition disorders	3 (0.26)
Decreased appetite	3 (0.26)
Psychiatric disorders	6 (0.51)
Abnormal dreams	1 (0.09)
Insomnia	5 (0.43)
Nervous system disorder	9 (0.77)
Dizziness	5 (0.43)
Headache	4 (0.34)
Respiratory, thoracic, and mediastinal disorders	1 (0.09)
Nasal congestion	1 (0.09)
Gastrointestinal disorders	37 (3.15)
Abdominal discomfort	4 (0.34)
Abdominal pain	4 (0.34)
Diarrhea	22 (1.87)
Nausea	8 (0.68)
Vomiting	10 (0.85)
Skin and subcutaneous tissue disorders	4 (0.34)
Pruritus	2 (0.17)
Rash	2 (0.17)
Urticaria	2 (0.17)
General disorders and administration site conditions	4 (0.34)
Asthenia	1 (0.09)
Fatigue	1 (0.09)
Pyrexia	2 (0.17)
Investigations	1 (0.09)
Lymphocyte count increased	1 (0.09)

Baloxavir (Xofluza®)

Baloxavir marboxil (Xofluza) 紓伏效

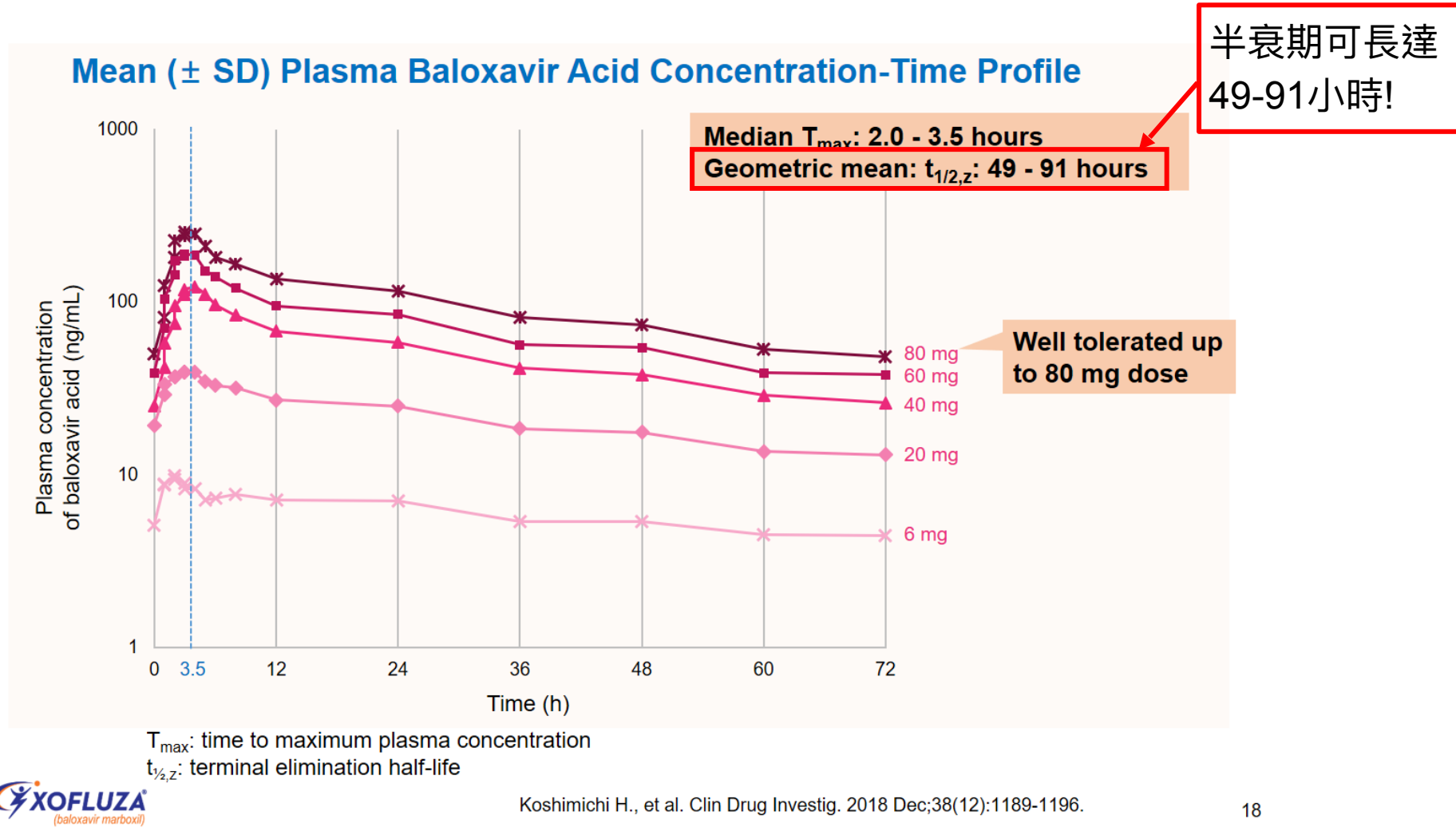
- 口服劑型 (20mg/tab)，僅需服用單次劑量
- 於2018年在日本及美國先後取得許可證上市的 Baloxavir，藉由抑制流感病毒的 Cap 依賴型核酸內切酶 (Cap dependent endonuclease) 破壞病毒在人體複製機制
- 適用成人及5歲以上兒童
- 副作用: 腹瀉，噁心
- 肝腎功能: CCr>30, Child A-B無需調整劑量

• 使用:	<20kg	單次服用 20mg (1 tab)
	20~<80kg	單次服用 40mg (2 tab)
	>=80kg	單次服用 80mg (4 tab)



- 服藥時，可與或不與食物併服，但應避免和乳製品、高鈣飲品、含多價陽離子緩瀉劑、抗酸劑或口服補充劑(例如：鈣、鐵、鎂、硒或鋅) 併服。

Baloxavir藥物動力學特性支持單次口服使用



Xofluza針對門診流感病患的效果及安全性 (CAPSTONE-1 Study)

Phase III, randomised, double-blind study of baloxavir vs placebo or oseltamivir in otherwise healthy adults and adolescents with influenza

N= 1436 (B-612, P-310, O-514), 2016-2017, 12-64yr

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

SEPTEMBER 6, 2018

VOL. 379 NO. 10

Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents

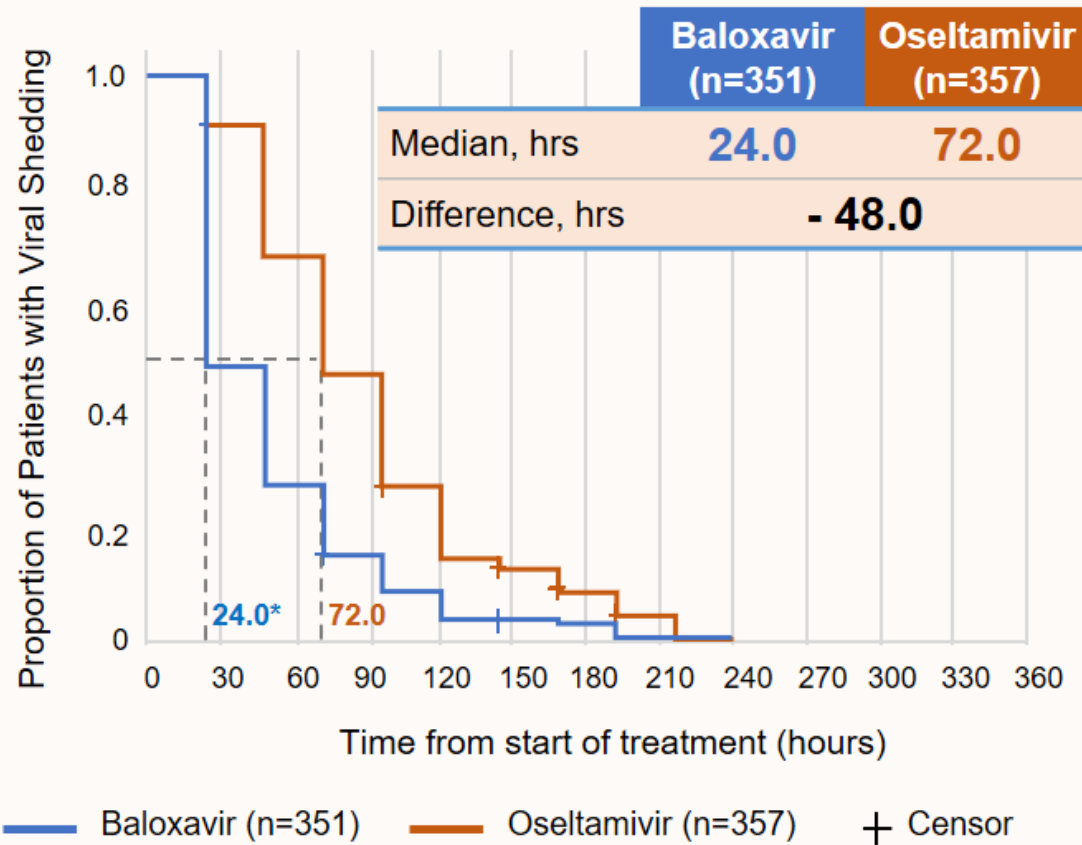
Frederick G. Hayden, M.D., Norio Sugaya, M.D., Nobuo Hirotsu, M.D., Ph.D., Nelson Lee, M.D.,
Menno D. de Jong, M.D., Ph.D., Aeron C. Hurt, Ph.D., Tadashi Ishida, M.D., Ph.D., Hisakuni Sekino, M.D., Ph.D.,
Kota Yamada, M.D., Simon Portsmouth, M.D., Keiko Kawaguchi, M.Sc., Takao Shishido, Ph.D.,
Masatsugu Arai, M.Sc., Kenji Tsuchiya, M.Sc., Takeki Uehara, Ph.D., and Akira Watanabe, M.D., Ph.D.,
for the Baloxavir Marboxil Investigators Group*

Baloxavir停止排出病毒及降低病毒量較Oseltamivir快

Hayden et al. N Engl J Med. 2018 Sep 6;379(10):913-923

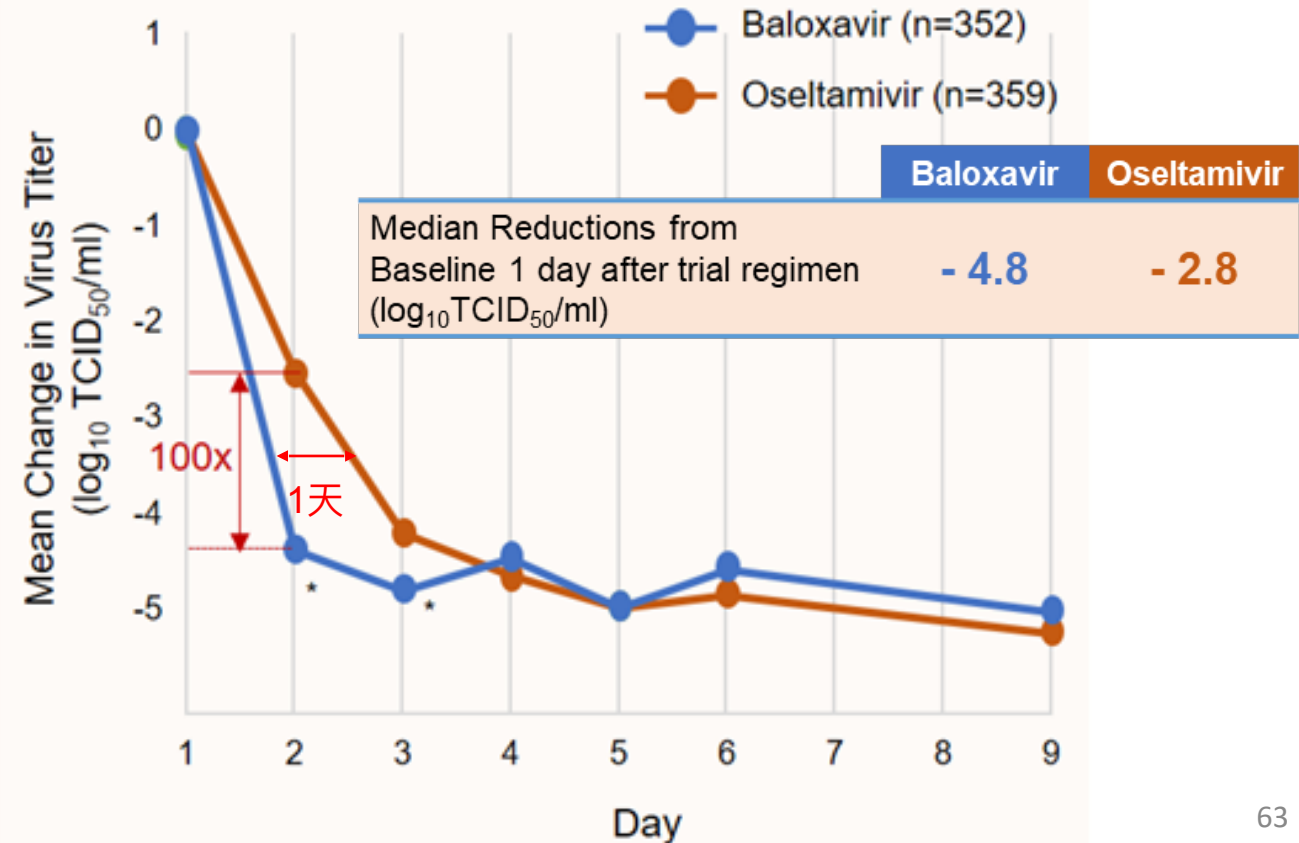
Baloxavir較Oseltamivir快3倍時間停止排出病毒

**Time to Cessation of Infectious Virus Detection:
Baloxavir vs Oseltamivir[§]**



Baloxavir使用24小時即能較Oseltamivir多降低100倍的病毒量

Baloxavir vs Oseltamivir[†]



Baloxavir提早緩解流感症狀及退燒

Baloxavir較Placebo快一天緩解症狀

跟Oseltamivir沒有差別

	Baloxavir (n=455)	Placebo (n=230)
Median (95% CI), hours	53.7 (49.5, 58.5)	80.2 (72.6, 87.1)
Difference (95% CI), hours	-26.5 (-35.8, -17.8)	
P-value*	<0.001	

Baloxavir較Placebo快一天退燒

	Baloxavir	Placebo	p value
Median Time to Resolution of Fever*	24.5 hrs	42.0 hrs	P < 0.001

Xofluza針對家內傳播預防

- Multicenter, double-blind, randomized, placebo-controlled trial
- 2018–2019 season in Japan
- 374 in the baloxavir group and 375 in the placebo group

The logo for The New England Journal of Medicine, featuring the text "The NEW ENGLAND JOURNAL of MEDICINE" in a red serif font, with "The" and "of" in italics. The text is centered within a light yellow rectangular box with a thin black border.

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JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

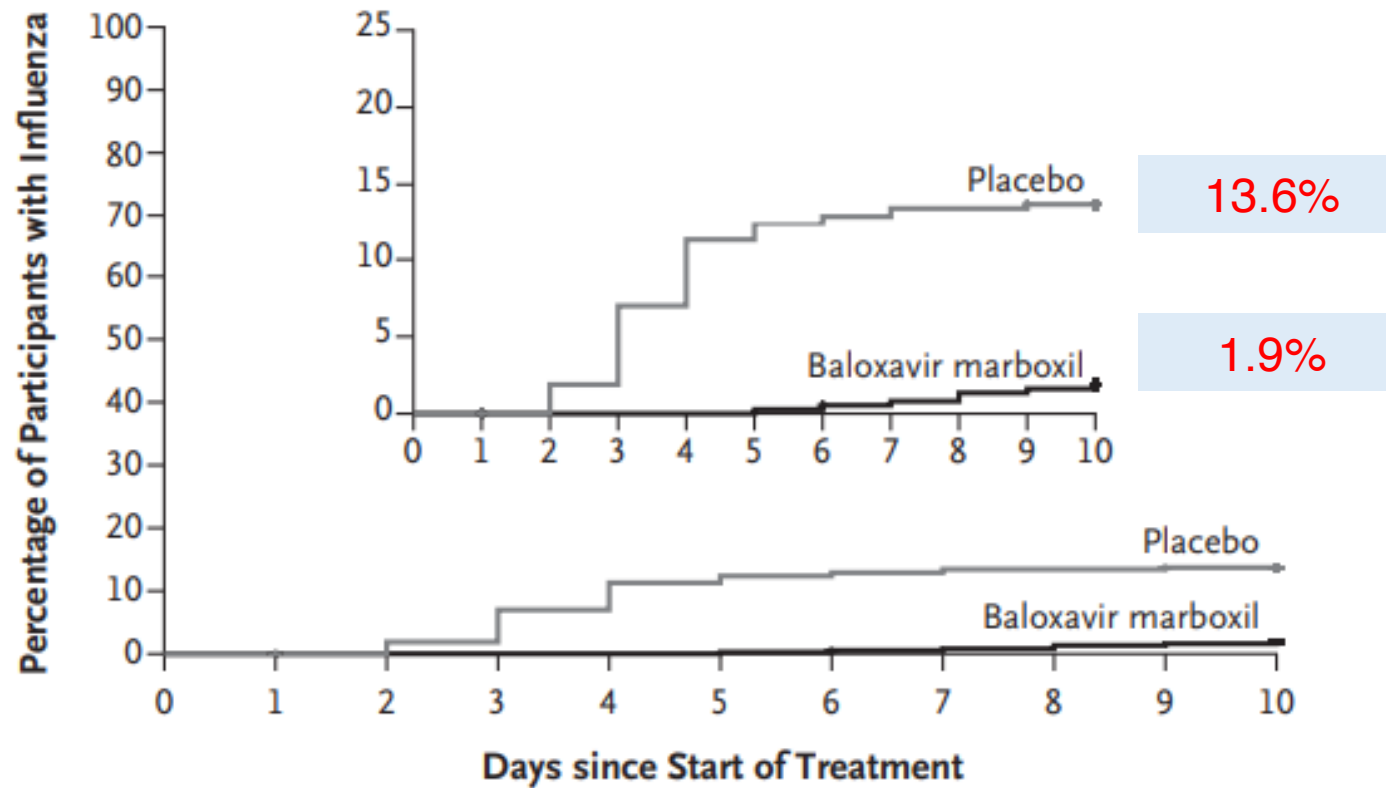
JULY 23, 2020

VOL. 383 NO. 4

Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts

Hideyuki Ikematsu, M.D., Frederick G. Hayden, M.D., Keiko Kawaguchi, M.S., Masahiro Kinoshita, M.Pharm.,
Menno D. de Jong, M.D., Nelson Lee, M.D., Satoru Takashima, M.S., Takeshi Noshi, M.S., Kenji Tsuchiya, M.S.,
and Takeki Uehara, Ph.D.

Xofluza可減少家內傳播發生



Adjusted risk ratio, **0.14**
95% confidence interval (0.06 to 0.30; $P < 0.001$)

Baloxavir 特點

一般流感病患 ¹	流感高危險群病患 ²	流感預防 ³
• 單次口服即完成療程 • 快速停止排出病毒及降低病毒量 • 快速緩解流感症狀及退燒 • 安全性與安慰劑相當	• 症狀改善所需時間與Oseltamivir相當 • 顯著較Oseltamivir快2天停止排出病毒 • 顯著較安慰劑降低流感併發症發生率 • 安全性與安慰劑相當	• 可預防暴露後罹患流感風險達86% • 對兒童、成人、是否具高危險因子、是否接種過疫苗，預防流感之效果皆相當 • 安全性與安慰劑相當

重症目前沒有足夠證據支持使用

1. Hayden et al. N Engl J Med. 2018 Sep 6;379(10):913-923

2. Ison MG et al. Lancet Infect Dis. 2020 Oct;20(10):1204-1214.

3. Ikematsu H, et al. N Engl J Med. 2020 doi: 10.1056/NEJMoa1915341.

Combination therapy in severe Influenza

Influenza A-associated severe pneumonia in hospitalized patients: Risk factors and NAI treatments

- combination therapy (oseltamivir-peramivir vs. monotherapy) showed **no differences in 60-day mortality**

Variables	Oseltamivir (n=122)	Peramivir (n=40)	Oseltamivir + Peramivir (n=29)	P values
Demographics				
Age	64 (48.8-77)	67 (46.3-72.8)	66 (57-73)	.839
Male (%)	81 (66.4)	32 (80.0)	18 (62.1)	.196
Comorbidity (%)	84 (68.9)	26 (65.0)	18 (62.1)	.748
Oseltamivir administered ≤48h (%)	6 (4.9)	1 (2.5)	0 (0)	.243
SOFA score	7 (6-8)	7 (6-8.5)	7 (7-8.5)	.574
Outcomes				
60-day mortality, n (%)	49 (40.2)	15 (37.5)	9 (31.0)	.658

Combination treatment with the cap-dependent endonuclease inhibitor baloxavir marboxil and a neuraminidase inhibitor in a mouse model of influenza A virus infection

Combination treatment with baloxavir acid and oseltamivir acid in vitro and baloxavir marboxil and oseltamivir phosphate in mice produced **synergistic responses** against influenza virus infections, suggesting that treating humans with the combination may be beneficial.

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

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

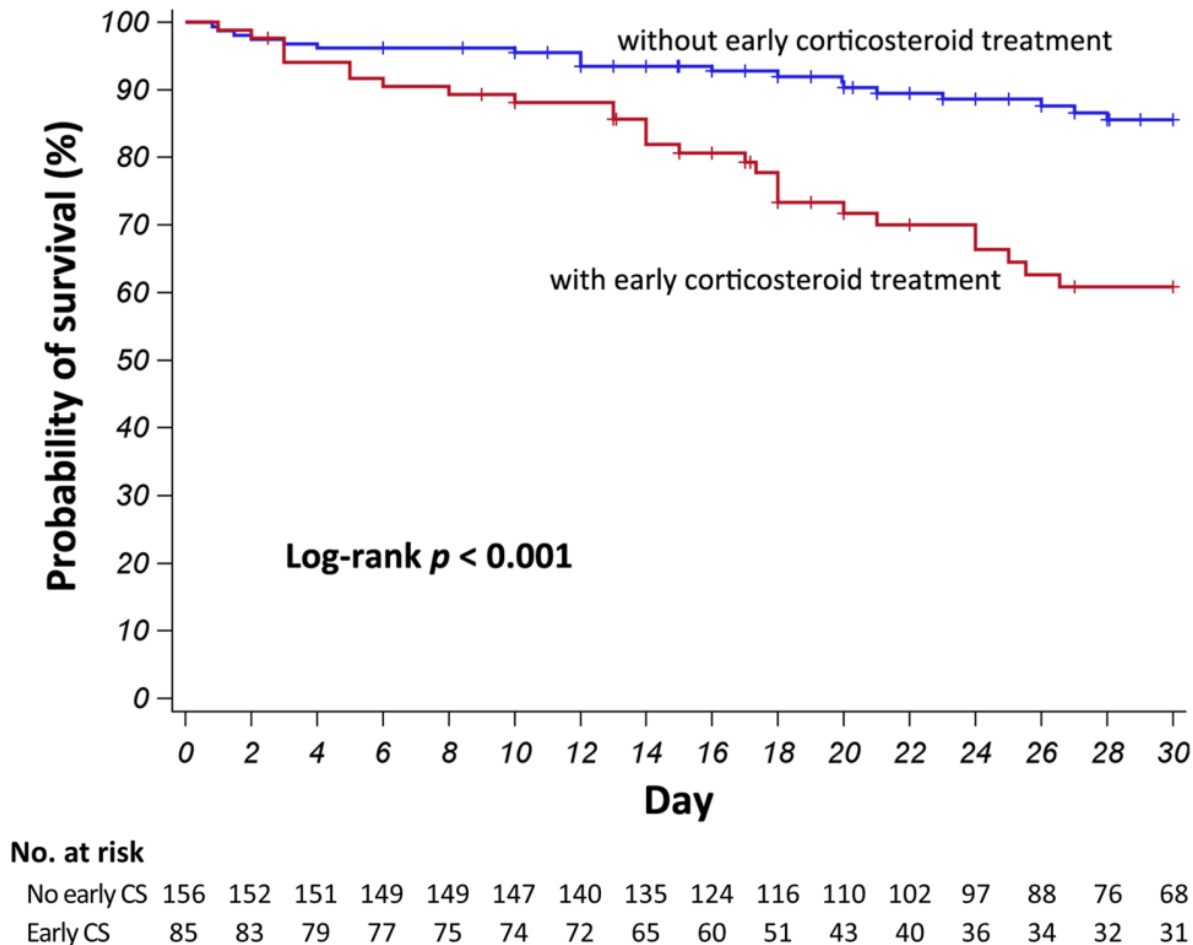
Lancet Infect dis.

2022 May;22(5):718-730. doi: 10.1016/S1473-3099(21)00469-2. Epub 2022 Jan 24.

- Double blind RCT, 124 centres across 25 countries, Jan 8, 2019 ~March 16, 2020
- Patients aged 12 years or older, hospitalization
- National Early Warning Score ≥ 2
- Baloxivir + NAIs (241) VS. Placebo + NAIs (125)
 - Baloxavir was administered orally on day 1 and day 4 (40 mg for bodyweight <80 kg, or 80 mg for ≥ 80 kg), and on day 7 if no clinical improvement had occurred by day 5.
 - The NAIs included in this study were oseltamivir, zanamivir, and peramivir.
- Aim: Median time to clinical improvement
- Median time to clinical improvement was 97.5 h (95% CI 75.9 to 117.2) in the baloxavir group and 100.2 h (75.9 to 144.4) in the control group (median difference -2.7 h [95% CI -53.4 to 25.9], $p=0.467$).
- **Combining baloxavir with NAIs did not result in superior clinical outcomes compared with NAIs alone.**

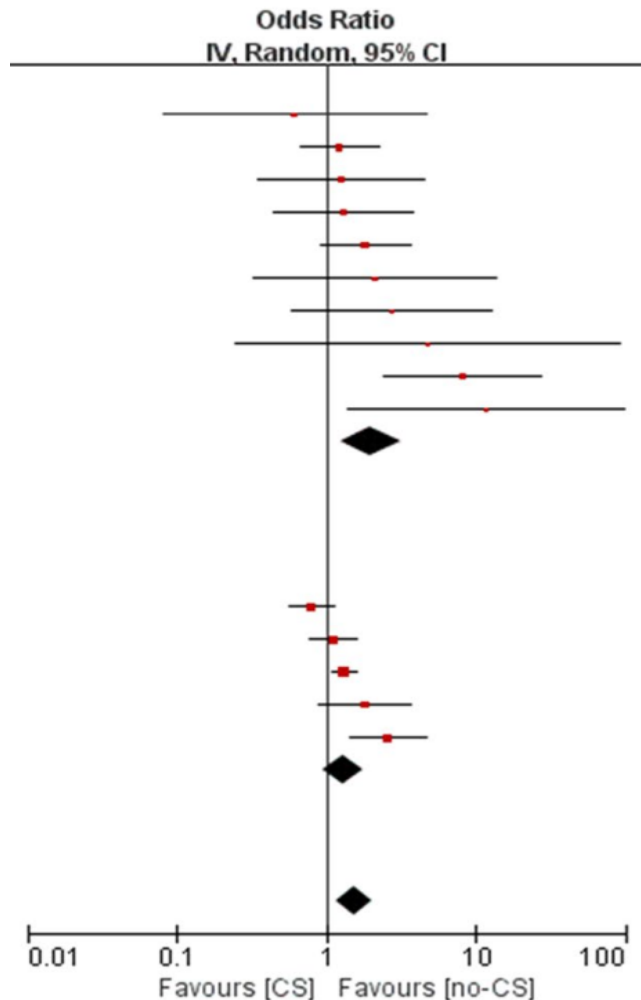
Adjunctive steroids in severe Influenza

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



- Taiwan, Multicenter, retrospective cohort study
- 241 patients, October 2015-March 2016, 8 centers
- Early corticosteroid treatment** was associated with a significantly **increased hospital mortality** in adult patients with influenza-associated ARDS.
 - early corticosteroid treatment: ≥ 200 mg hydrocortisone equivalent dose within 3 days after ICU admission
- hospital mortality: with early corticosteroid treatment vs. without [43.5% (37/85) vs. 19.2% (30/156), $p < 0.001$]
- [adjusted odds ratio (95% CI) = 5.02 (2.39–10.54), $p < 0.001$]

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



- 15 Studies, N= 6427, 2010-2018
- The meta-analysis results showed that corticosteroid therapy was associated with significantly **higher mortality** (OR 1.53, 95% CI [1.16, 2.01]) and **incidence of nosocomial infection** (OR 3.15, 95% CI [1.54, 6.45])
- Current data do **not support the routine use of corticosteroids** in patients with influenza severe pneumonia or ARDS.

In Summary...

- EARLY antiviral agent can shorten the course of influenza and reduce complication
- The benefit of antiviral agent combination therapy is controversial in severe influenza
- The routine use of steroid in influenza-associated acute respiratory distress syndrome and severe pneumonia is not recommended

台灣感染症醫學會-抗流感病毒藥物使用建議

抗流感藥物使用對象、劑量與療程



藥物	Oseltamivir Capsule		Oseltamivir Oral Suspension		Zanamivir		Peramivir		Baloxavir Marboxil	
使用方式	吞服/無法吞服者（如需使用鼻胃管者）則打開膠囊泡水或糖漿服用		經調配後服用		經口吸入		單次點滴靜脈注射15 分鐘以上		單次口服 可以磨粉	
	懷孕哺乳首選				懷孕哺乳: 利>弊投予		懷孕哺乳: 利>弊投予		懷孕哺乳不建議	
適用年齡	成人及兒童 (含一個月大新生兒)		成人及兒童 (含一個月大新生兒)		5 歲(含)以上		小兒(早產兒及新生兒除外)及成人		成人及兒童 (5 歲以上)	
標準治療劑量	輕症	重症	輕症	重症	輕症	重症	輕症	重症	輕症	重症
	13歲以下依體重調整劑量； 13歲(含)以上或體重40kg以上者75mg BID		40kg以下兒童依體重調整劑量； 40kg以上兒童或成年人及青少年為75mg BID		10mg BID	不建議使用	成人300mg; 小兒10-12 mg/kg	成人600mg QD	<20kg單次服用20mg ≥20 至 <80kg 單次服用 40mg ≥80kg 單次服用 80mg	現無臨床數據
標準療程	5天	5天	5天	現無臨床數據	5天		單次	可依症狀連續多日反覆投予	單次	