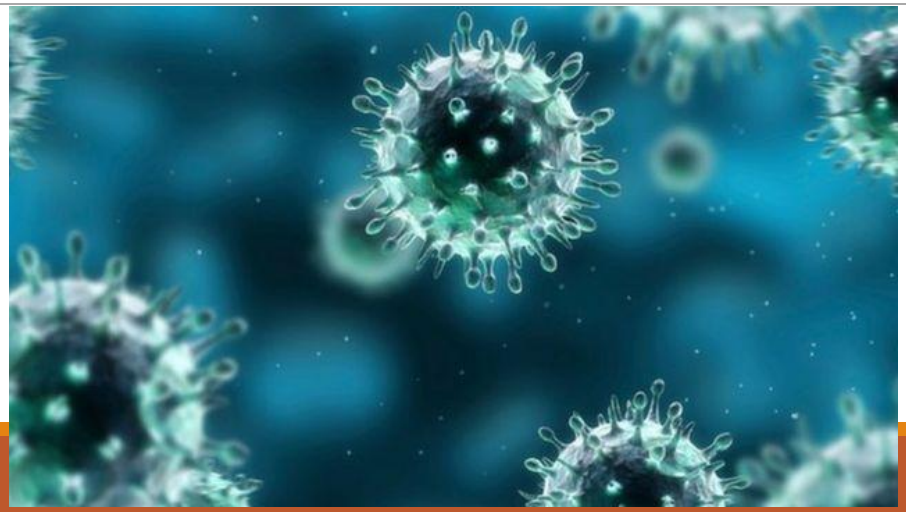
流感藥物治療進展與抗藥

成大醫院內科部感染科主治醫師

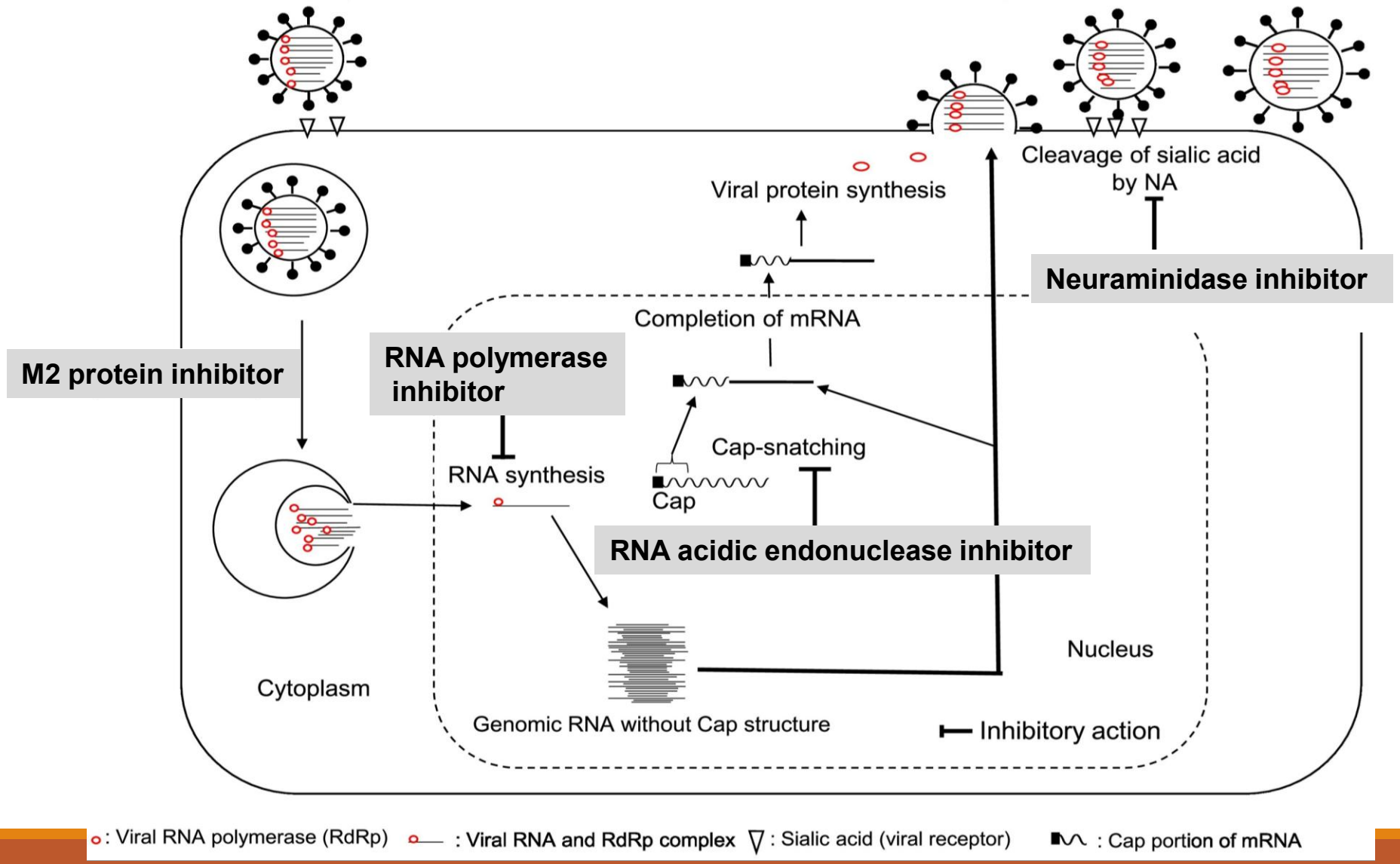
冉浩恩



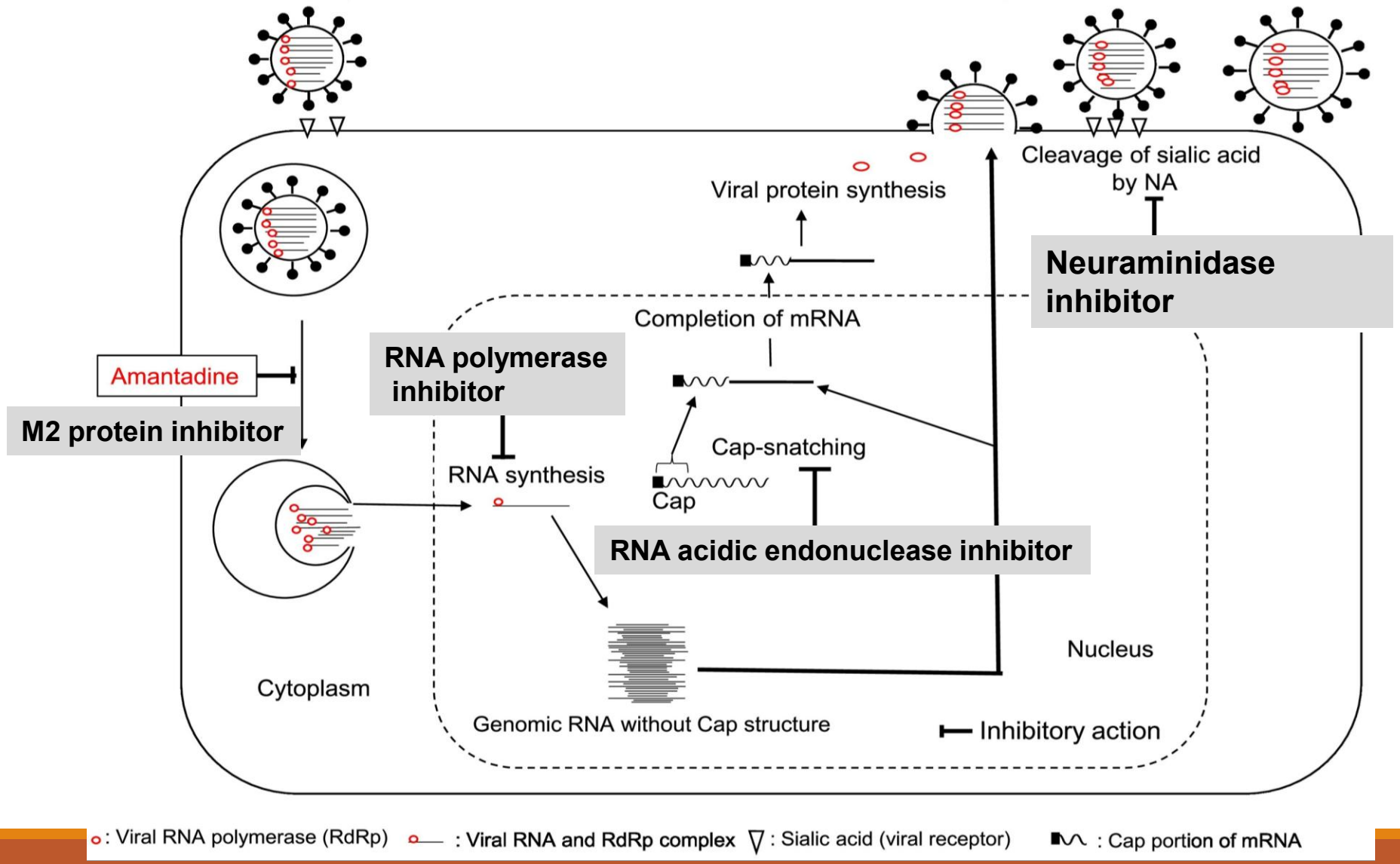
大綱

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

Influenza Virus



Influenza Virus

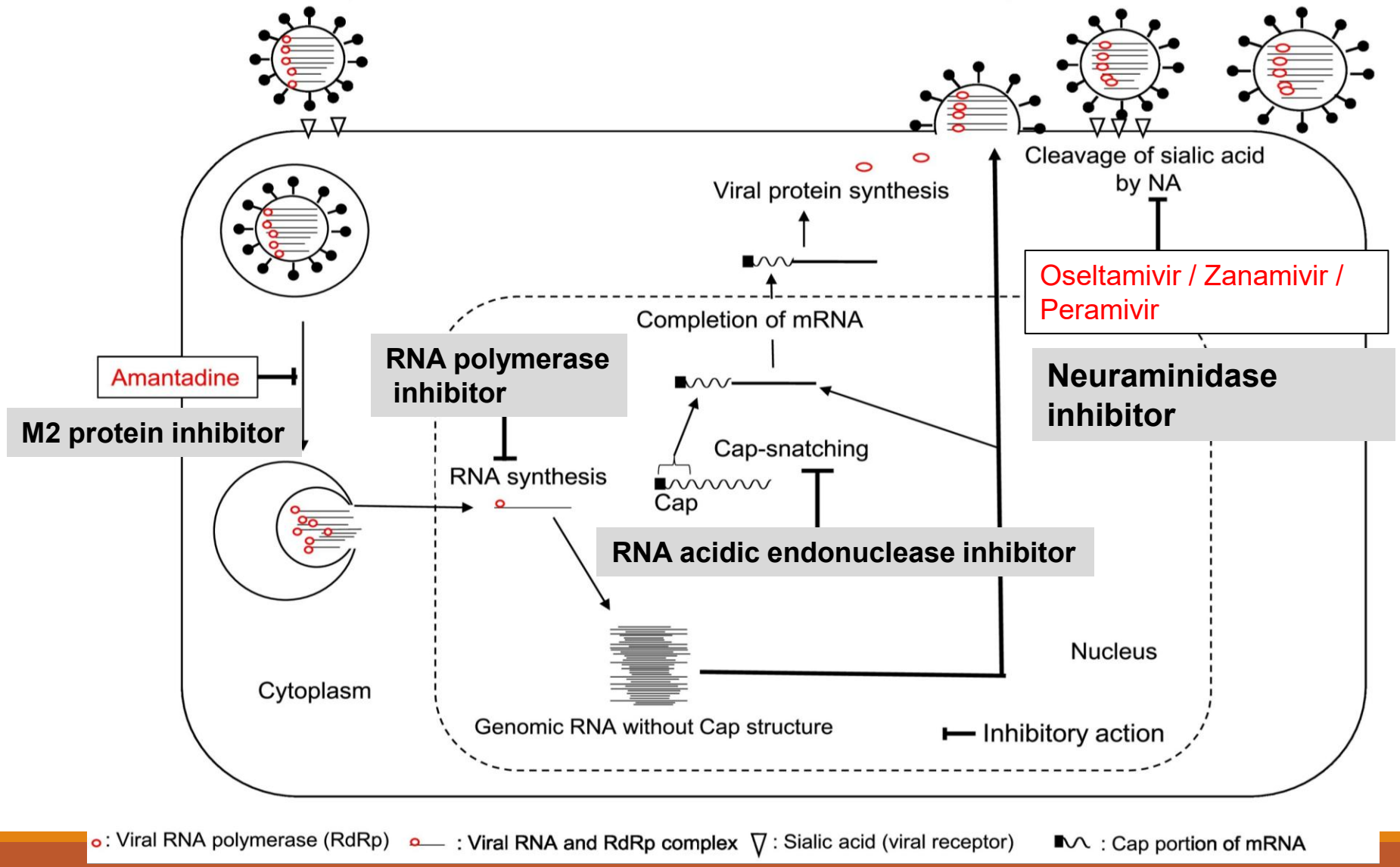


M2 protein inhibitor

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

已不建議使用於流感病毒感染治療

Influenza Virus



Neuraminidase inhibitor

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

目前抗病毒藥物主流

Cochrane Library
Trusted evidence.
Informed decisions.
Better health.

Title Abstract Ke

Cochrane Reviews | Trials | Clinical Answers | About | Help

Cochrane Database of Systematic Reviews

Neuraminidase inhibitors for preventing and treating influenza in adults and children

Cochrane Systematic Review - **Intervention** | Version publish

https://doi.org/10.1002/14651858.CD008965.pub4

Am score 756 View article information

Tom Jefferson | Mark A Jones | Peter Doshi | Chr
| Igho J Onakpoya | Kamal R Mahtani | David Nuna
View authors' declarations of interest

“ confirmed **or** **suspected exposure** ”

Time to first symptom alleviation. For the treatment of adults, oseltamivir reduced the time to first alleviation of symptoms by 16.8 hours (95% confidence interval (CI) 8.4 to 25.1 hours, P < 0.0001). This represents a reduction in the time to first alleviation of symptoms from 7 to 6.3 days. There was no effect in asthmatic children, but in otherwise healthy children there was (reduction by a mean difference of 29 hours, 95% CI 12 to 47 hours, P = 0.001). Zanamivir reduced the time to first alleviation of symptoms in adults by 0.60 days (95% CI 0.39 to 0.81 days, P < 0.00001), equating to a reduction in the mean duration of symptoms from 6.6 to 6.0 days. The effect in children was not significant. In subgroup analysis we found no evidence of a difference in treatment effect for zanamivir on time to first alleviation of symptoms in adults in the influenza-infected and non-influenza-infected subgroups (P = 0.53).

Hospitalisations. Treatment of adults with oseltamivir had no significant effect on hospitalisations: risk difference (RD) 0.15% (95% CI -0.78 to 0.91). There was also no significant effect in children or in prophylaxis. Zanamivir hospitalisation data were unreported.

Serious influenza complications or those leading to study withdrawal. In adult treatment trials, oseltamivir did not significantly reduce those complications classified as serious or those which led to study withdrawal (RD 0.07%, 95% CI -0.78 to 0.44), nor in child treatment trials; neither did zanamivir in the treatment of adults or in prophylaxis. There were insufficient events to compare this outcome for oseltamivir in prophylaxis or zanamivir in the treatment of children.

Pneumonia. Oseltamivir significantly reduced self reported, investigator-mediated, unverified pneumonia (RD 1.00%, 95% CI 0.22 to 1.49); number needed to treat to benefit (NNTB) = 100 (95% CI 67 to 451) in the treated population. The effect was not significant in the five trials that used a more detailed diagnostic form for pneumonia. There were no definitions of pneumonia (or other complications) in any trial. No oseltamivir treatment studies reported effects on radiologically confirmed pneumonia. There was no significant effect on unverified pneumonia in children. There was no significant effect of zanamivir on either self reported or radiologically confirmed pneumonia. In prophylaxis, zanamivir significantly reduced the risk of self reported, investigator-mediated, unverified pneumonia in adults (RD 0.32%, 95% CI 0.09 to 0.41); NNTB = 311 (95% CI 244 to 1086), but not oseltamivir.

主要分析2013年前臨床試驗，結論為
藥物可縮短病程 (16.8hr)，無降低住院風險

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

JAMA Internal Medicine | Original Investigation

Evaluation of Oseltamivir Used to Prevent Hospitalization in Outpatients With Influenza
A Systematic Review and Meta-analysis

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

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Emily G. McDonald, MD, MSc, Medicine, McGill University Health Centre, Office 3E.03, 5252 De Maisonneuve

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

RESULTS Of 2352 studies identified, 15 were included. The intention-to-treat infected (ITTi) population was comprised of 6295 individuals with 54.7% prescribed oseltamivir. Across study populations, 53.6% (5610 of 10 471) were female and the mean age was 45.3 (14.5) years. Overall, oseltamivir was not associated with reduced risk of hospitalization within the ITTi population (RR, 0.77; 95% CI, 0.47-1.27; RD, −0.14%; 95% CI, −0.32% to 0.16%). Oseltamivir was also not associated with reduced hospitalization in older populations (mean age ≥65 years: RR, 0.99; 95% CI, 0.19-5.13) or in patients considered at greater risk of hospitalization (RR, 0.90; 95% CI, 0.37-2.17). Within the safety population, oseltamivir was associated with increased nausea (RR, 1.43; 95% CI, 1.13-1.82) and vomiting (RR, 1.83; 95% CI, 1.28-2.63) but not serious adverse events (RR, 0.71; 95% CI, 0.46-1.08).

CONCLUSIONS AND RELEVANCE In this systematic review and meta-analysis among influenza-infected outpatients, oseltamivir was not associated with a reduced risk of hospitalization but was associated with increased gastrointestinal adverse events. To justify continued use for this purpose, an adequately powered trial in a suitably high-risk population is justified.

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

JAMA Intern Med . 2023 Jun 12;e230699.

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

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

Summary

Background Ne
evidence for th
data to investig
hospital with p

Oseltamivir 92%
Zanamivir 2.3%
Peramivir 0.3%

Findings

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

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

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

Original Contribution | Clinician's Corner

FREE

November 4, 2009

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

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

Article Information

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

Abstract

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

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

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

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

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

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

**Cornelia Adlhoch[1] , Co
Isabelle Thomas[5] , Jan
, Tanya Melillo[9] , Arian
Sonja J. Olsen[12]**

1. European Centre for
2. National Centre of E
3. Public Health Agenc
4. National Institute of Romania
5. Sciensano, Brussels
6. Department of Infec
7. National Influenza R
8. Center for Virology,
9. Infectious Disease p
10. National Institute f
11. Health Service Exec
12. WHO Regional Offic

Correspondence: Corn

TABLE 2

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

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

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

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

ERJ open research

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

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

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

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

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

Neuraminidase inhibitors 實證結論

	克流感/易剋冒 (Oseltamivir)	瑞樂沙 (Zanamivir)	瑞貝塔 (Peramivir)

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

Neuraminidase inhibitor

克流感(Oseltamivir)

瑞樂沙 (Zanamivir)

瑞貝塔 (Peramivir)

Open Forum Infectious Diseases

MAJOR ARTICLE

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

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

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

Background. Clinical studies comparing the different neuramini
have not been performed. To optimize such treatments, we assessed t
oral oseltamivir in treating seasonal influenza A or B virus infection.

Methods. A multicenter, randomized, controlled clinical trial w
patients infected with seasonal influenza. A total of 92 adult inpatien
by either a single intravenous infusion of peramivir (600 mg) or oral a

Results. The median times to clinical stability (time to reach <37°
and 37.8 hours (95% CI = 26.3–45.3) in the peramivir and oseltamivi
difference. The virus titer and change of mean total symptom scores
regression suggested that virus type was a significantly effective prog
(AEs) with peramivir and oseltamivir occurred in 2.2% (n = 1/46) and
was mild in all cases except 2 patients who showed pneumonia or CO

Conclusions. Intravenous peramivir was effective based on the re
show that peramivir is a useful option for the treatment of influenza-i

Keywords. high-risk patient; influenza; neuraminidase inhibitor;

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

Meta-analysis

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

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

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

Results

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

退燒時間、死亡率、住院時間、病毒量變化及副作用發生率兩者無差異

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

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Original Article

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

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

[a] Department of Internal Medicine, National Taiwan Univ
[b] Department of Internal Medicine, Taipei Veterans Gene

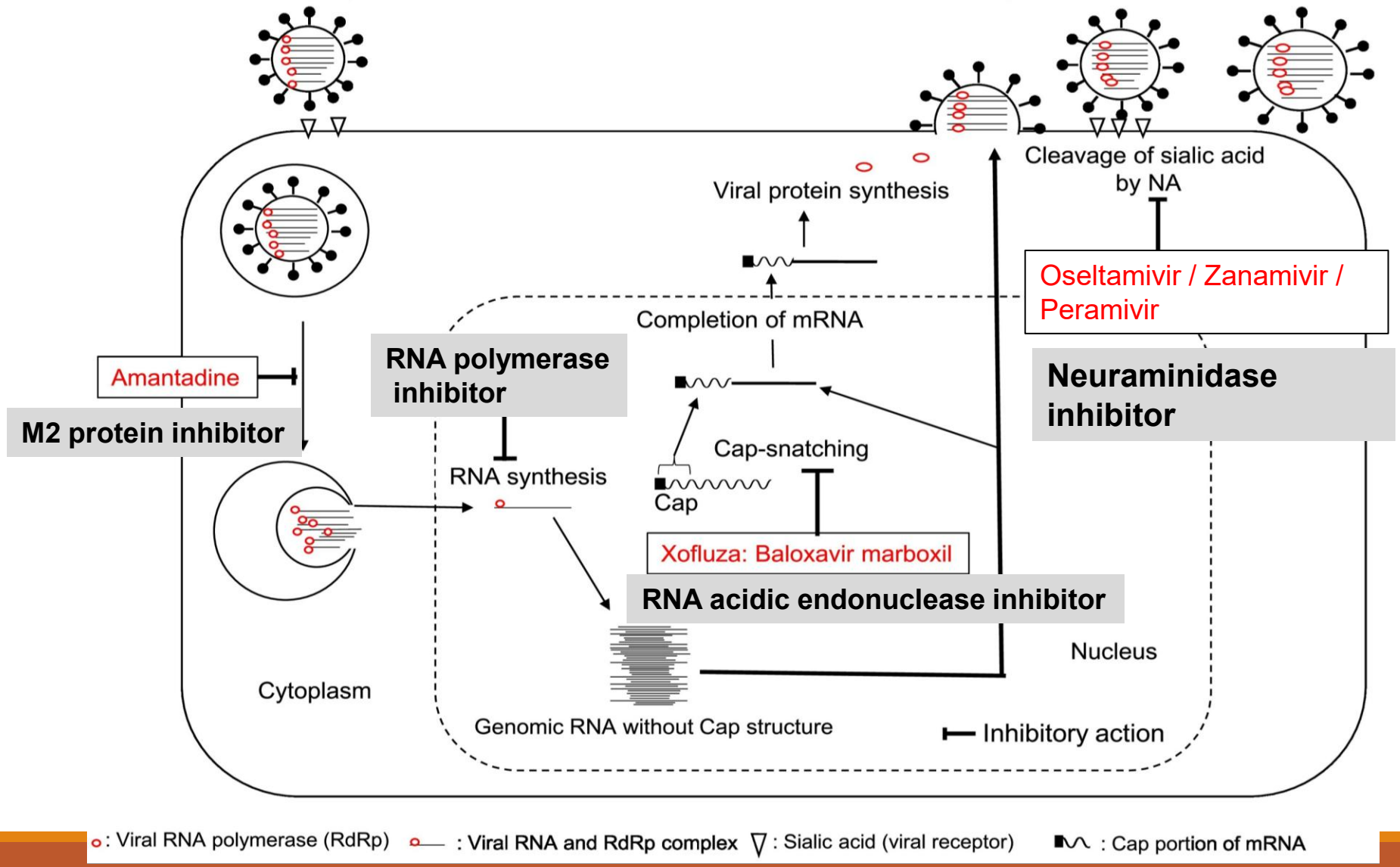
Abstract *Background:* Few studies have investigated patients with severe influenza who receive intravenous peramivir for salvage therapy.
Methods: We retrospectively analyzed data from 71 patients with severe influenza who received intravenous peramivir therapy in the intensive care units of three medical centers between 2012 and 2016. All patients received oseltamivir or zanamivir before the administration of peramivir.
Results: A total of 44 men and 27 women with a median age of 55 years were enrolled. Fifty-five (78%) had underlying comorbidities and 57 (80%) patients were infected with influenza type A. Forty-four (62%) patients survived and 27 (38%) died. Five patients (7%) had attributable adverse events, including elevated hepatic aminotransferase levels (n = 2), hyperbilirubinemia (n = 2), leukopenia (n = 1), and skin rash (n = 1). Multivariable logistic regression analysis revealed that initial bacteremia (odds ratio [OR], 27.59; 95% confidence interval

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

Neuraminidase inhibitors

	克流感/易剋冒 (Oseltamivir)	瑞樂沙 (Zanamivir)	瑞貝塔 (Peramivir)
劑型	口服	吸入	注射
使用對象	成人(含孕婦)及兒童（含足月新生兒） 公費/自費	成人(含孕婦)及五歲以上兒童 公費	成人(含孕婦)及兒童（含足月新生兒） 自費 (公費僅限於新型A型流感申請)
用法用量	每日2次，每次75mg，共5日	每日2次，每次吸2孔，共5日	單次 300mg
副作用	噁心、嘔吐	支氣管痙攣	腹瀉、血白球低下
腎功能調整	是	否	是
小兒劑量調整	是，依體重調整	否	是
注意事項	未成年病患需注意神經精神症狀	需特別注意支氣管痙攣及呼吸困難等症狀。如為平日使用吸入藥物病人，建議先使用支氣管擴張劑	因併發症等可能有惡化之虞的病患，可提高劑量至600mg，可依症狀連續多日反覆投與

Influenza Virus



Endonuclease inhibitor

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

潛在抗病毒藥物主流

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 6, 2018

CAPSTONE-1 study

Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents

Frederick G. Hayden, M.D., Norio Sugaya, M.D., Not

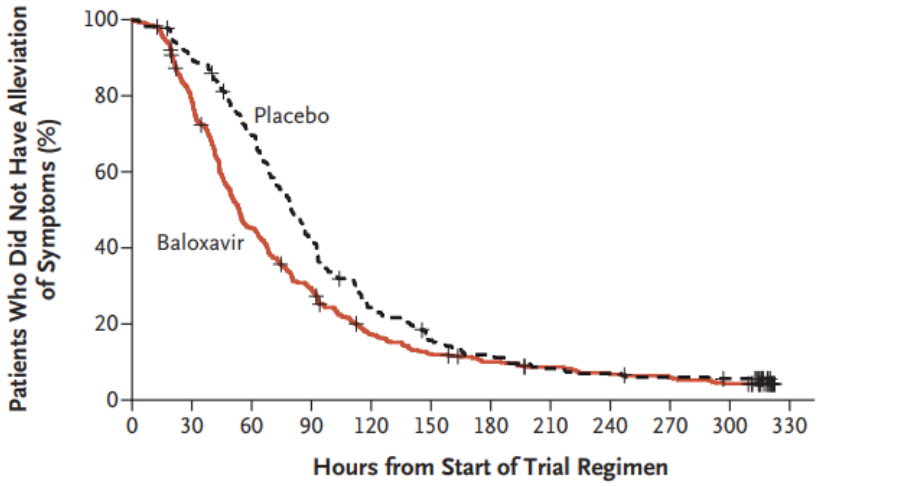
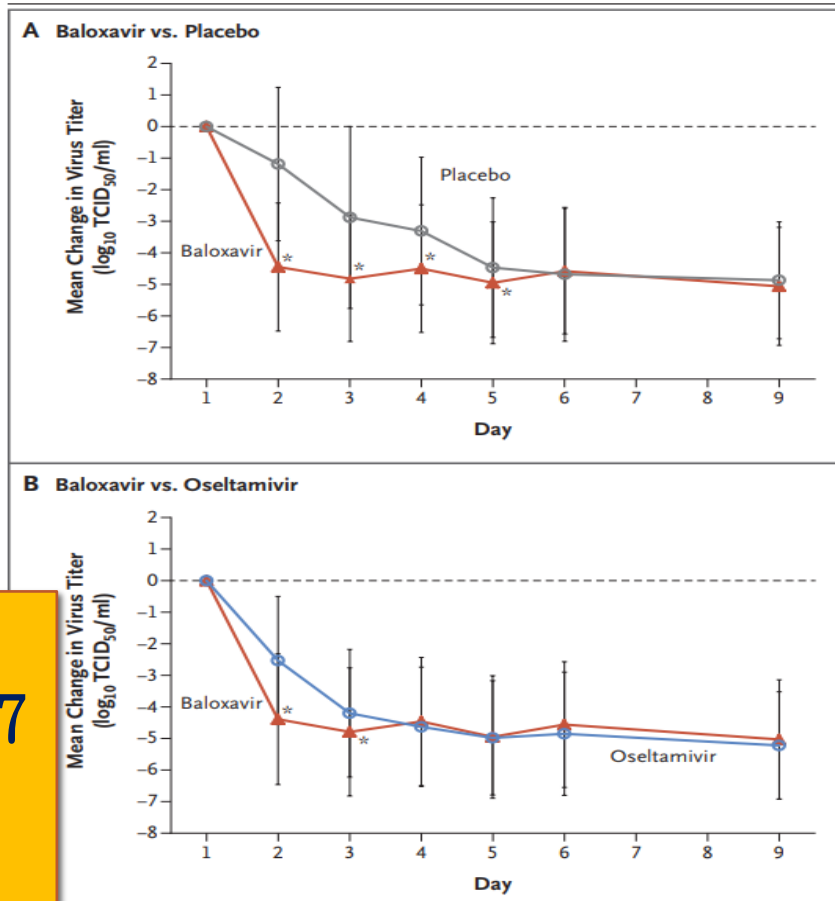


Figure 2. Kaplan–Meier Curves of the Time to Alleviation of Influenza



ure 3. Change from Baseline in Influenza Infectious Viral Load
er Time in the Phase 3
nel A shows the chang
tious viral load over time in the baloxavir group (427 patients) and placebo

隨機分派研究證據顯示在健康成人與placebo相比可縮短臨床症狀(53.7小時 vs 80.2小時)及減少病毒傳播與oseltamivir相比可減少病毒傳播(24小時 vs 72小時)

N Engl J Med. 2018;379(10):913-23

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

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

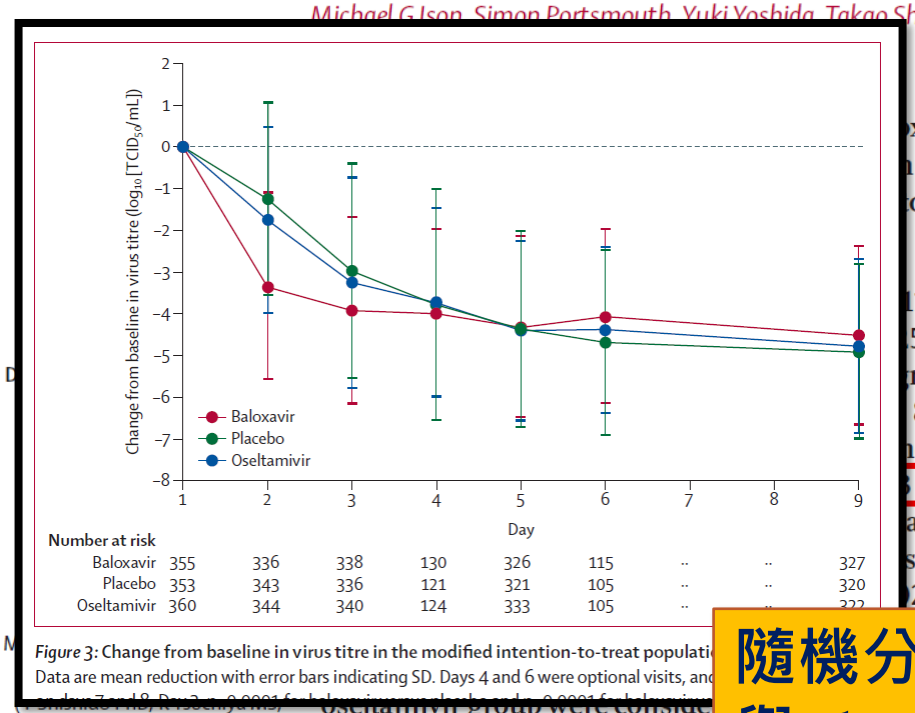


Figure 3: Change from baseline in virus titre in the modified intention-to-treat populati
Data are mean reduction with error bars indicating SD. Days 4 and 6 were optional visits, an

T Uehara PhD); and Division of
Infectious Diseases and

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

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

or Ile38Asn substitutions confe
assessed for amino acid substit

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

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

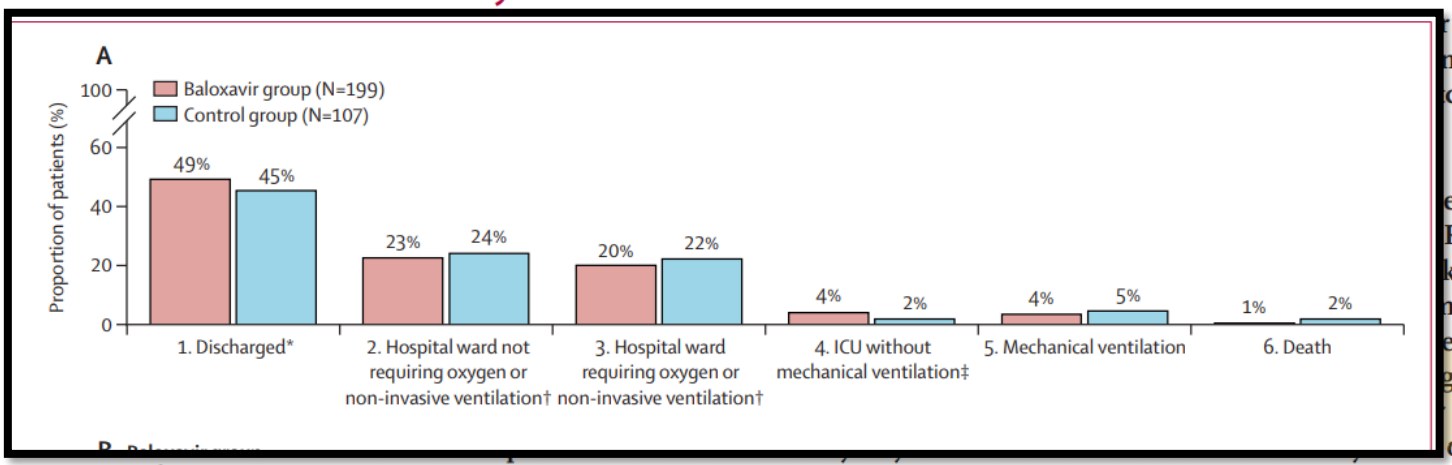
Lancet Infect Dis. 2020;20(10):1204-1214.

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, Steffe

Baloxavir治療劑量: 40mg on D1,D4 & D7

Summary



hospitalised patients with
nhibitor baloxavir marboxil
comes compared with NAI

eriority trial. Patients aged
R or a rapid test) and had a
k place in 124 centres across
n, patients were randomly
ebo plus NAIs (hereafter the
group assignment. Baloxavir
≥80 kg), and on day 7 if no
oseltamivir, zanamivir, and

(Prof M G Ison MD); **Groupe Hospitalier Paris Centre-Université de Paris, Cochin University Hospital, Medical Intensive Care Unit, Paris, France** (Prof J-P Mira MD); **Department of Pneumology and German Centre of Lung Research (DZL), Hannover Medical School, Hannover, Germany** (Prof T Welte MD);

peramivir, which were selected and administered according to local standard practice. The primary endpoint was time to clinical improvement, defined as time to a NEWS2 of 2 or lower for 24 h or hospital discharge, whichever came first, based o
The modified
received a do
assigned at r
least one dos
registered wit

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

J Antimicrob Chemother 2020;
doi:10.1093/jac/dkaa252 Adv

回溯性觀察研究證據顯示在住院流感病人baloxavir與oseltamivir相比,退燒時間、ICU住院天數及住院死亡率皆相當
Baloxavir較oseltamivir減緩缺氧時間
但baloxavir組較年輕（69歲 vs 77歲）

Clinical outc

Table 1. Demographics

	Baloxavir ($n = 359$)	Oseltamivir ($n = 431$)	P
Age (years), median (IQR)	69 (57–81)	77 (62–86)	<**0.001**[a]
Female, *n* (%)	184 (51.253)	232 (53.828)	0.471[b]
Active smoker, *n* (%)	61 (16.992)	64 (14.849)	0.411[b]

Table 3. Clinical outcomes

	Baloxavir ($n = 359$)	Oseltamivir ($n = 431$)	P
Hypoxia resolution, *n* (%)	*n* = 273 224 (82.051)	*n* = 348 263 (75.575)	0.052[a]
Hours from antiviral to hypoxia resolution, median (IQR)	*n* = 273 51.717 (25.3–89.317)	*n* = 348 71.95 (37.463–123)	<**0.001**[b]
Fever resolution, *n* (%)	*n* = 265 262 (98.868)	*n* = 314 306 (97.452)	0.241[c]
Hours from antiviral to fever resolution, median (IQR)	*n* = 265 25.067 (8.5–40.183)	*n* = 314 25.275 (11.204–41.492)	0.501[b]
LOS (days), median (IQR)	4 (3–6)	5 (3–6)	0.45[b]
ICU LOS (days), median (IQR)	*n* = 50 2 (1–4)	*n* = 52 3 (2–5)	0.44[b]
30 day all-cause mortality, *n* (%)	12 (3.343)	26 (6.032)	0.079[c]

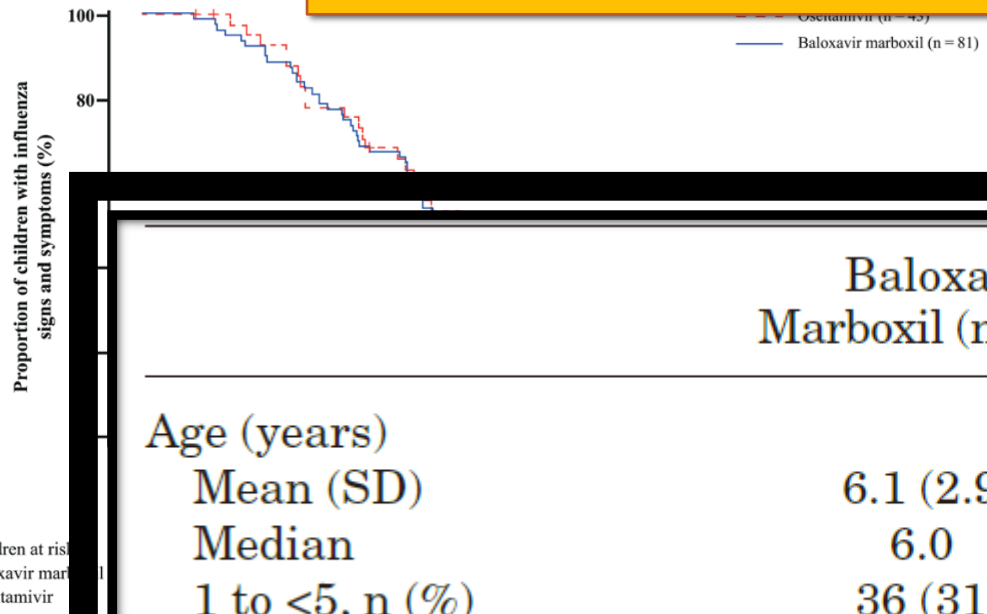
OPEN

Baloxavir Marboxil Single-dose Treatment in Influenza-infected Children

A Randomized, Double-blind, Active Controlled Phase 3 Safety and Efficacy Trial (miniSTONE-2)

Jeffrey Baker, ML … Steffen Wi… … PhD,‡

隨機分派研究證據顯示在小兒流感病人baloxavir與oseltamiir相比, 臨床預後相當baloxavir可縮短病毒傳播



and Virologic

	Baloxavir Marboxil (N = 81)	Oseltamivir (N = 43)
Efficacy		
Evaluable children (n)	80	43
Median TTASS*, hours	138.1 (116.6–163.2)	150.0 (115.0–165.7)

	Baloxavir Marboxil (n = 115)	Oseltamivir (n = 58)	All (N = 173)
Age (years)			
Mean (SD)	6.1 (2.9)	6.0 (3.2)	6.1 (3.0)
Median	6.0	6.0	6.0
1 to <5, n (%)	36 (31.3)	19 (32.8)	55 (31.8)
5 to <12, n (%)	79 (68.7)	39 (67.2)	118 (68.2)

Journal of Infection and Chemotherapy 30 (2024) 242–249

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

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

Original Article

Comparison of clinical efficacy and safety of baloxavir marboxil versus oseltamivir as the treatment for influenza virus infections: A systematic review and meta-analysis

Chihiro Shiraishi [a,b], Hideo Kato [a,b,c], Mao Hagihara [c,d], Nobuhiro Asai [c], Takuya Iwamoto [a,b], Hiroshige Mikamo [c,*]

[a] Department of Pharmacy, Mie University Hospital, Mie, Japan
[b] Department of Clinical Pharmaceutics, Division of Clinical Medical Science, Mie University Graduate School of Medicine, Mie, Japan
[c] Department of Clinical Infectious Diseases, Aichi Medical University, Aichi, Japan
[d] Department of Molecular Epidemiology and Biomedical Sciences, Aichi Medical University Hospital, Aichi, Japan

ARTICLE INFO

Keywords:
Meta-analysis
Baloxavir marboxil
Oseltamivir
Influenza virus

ABSTRACT

Introduction: Baloxavir marboxil (BXM), a newly developed cap-dependent endonuclease inhibitor, is widely used
sis included only out-
l symptoms. However,
versial. Therefore, we
of BXM versus oselta-
tically searched for ar-
, incidence of BXM- or
RNA load in patients

2篇RCT & 2篇Retrospective study 顯示baloxavir與oseltamivir相比,住院天數、副作用跟第2天病毒清除率較優

小結

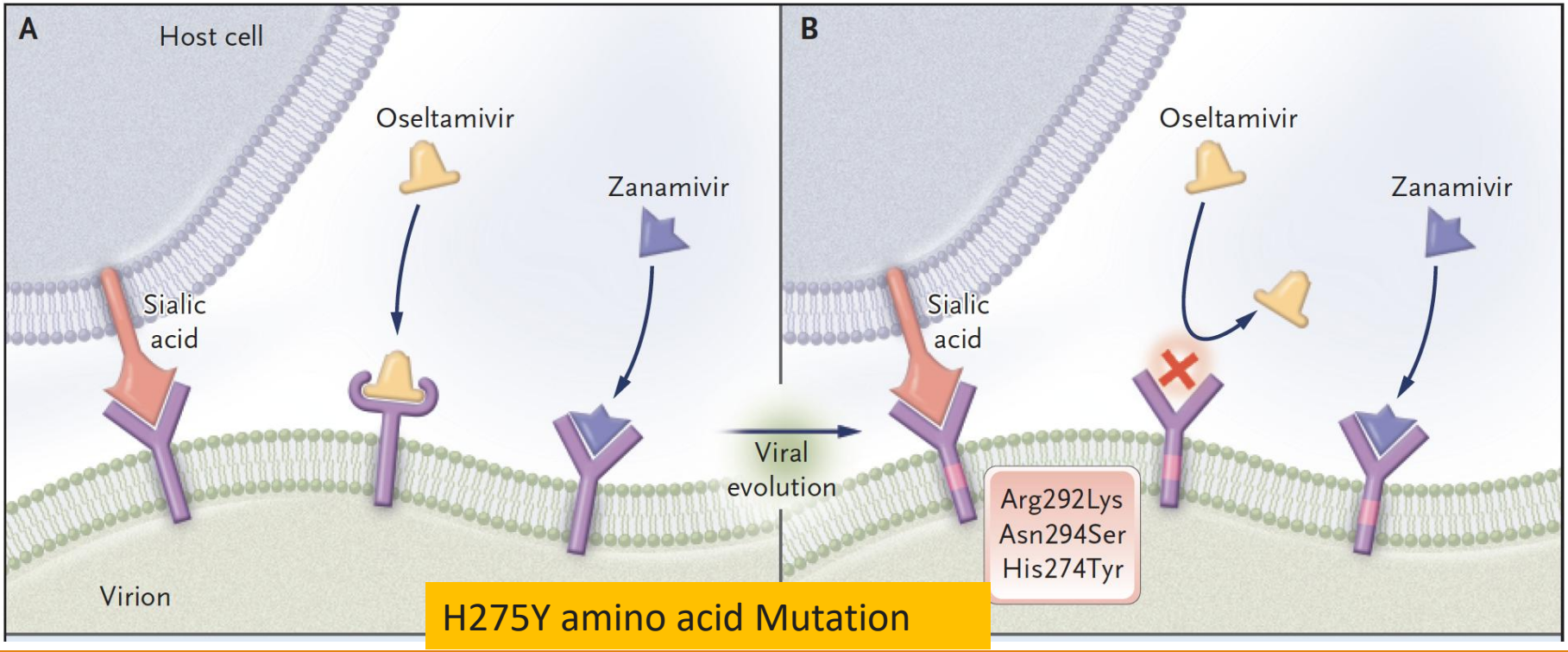
- 目前主流抗病毒藥物有：口服Oseltamivir五天、吸入劑Zanamivir五天、針劑Peramivir單次、口服Baloxavir單次
- 上述藥物於臨床實證皆可縮短臨床症狀時間及病毒傳播時間，但針對降低住院率及呼吸道感染相關併發症仍待更多實證。
- 口服Oseltamivir可改善流感重症病人預後、降低住院死亡率及住院天數及縮短呼吸器使用使間。
- 不建議常規combination, 但流感重症病人可視情況考慮oseltamivir/zanamivir合併peramivir針劑或是合併口服oseltamivir及口服baloxavir。需待更多臨床實證支持。
- 美國FDA通過baloxavir可用於5歲以上兒童。

大綱

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

警鐘響起—NAI抗藥性

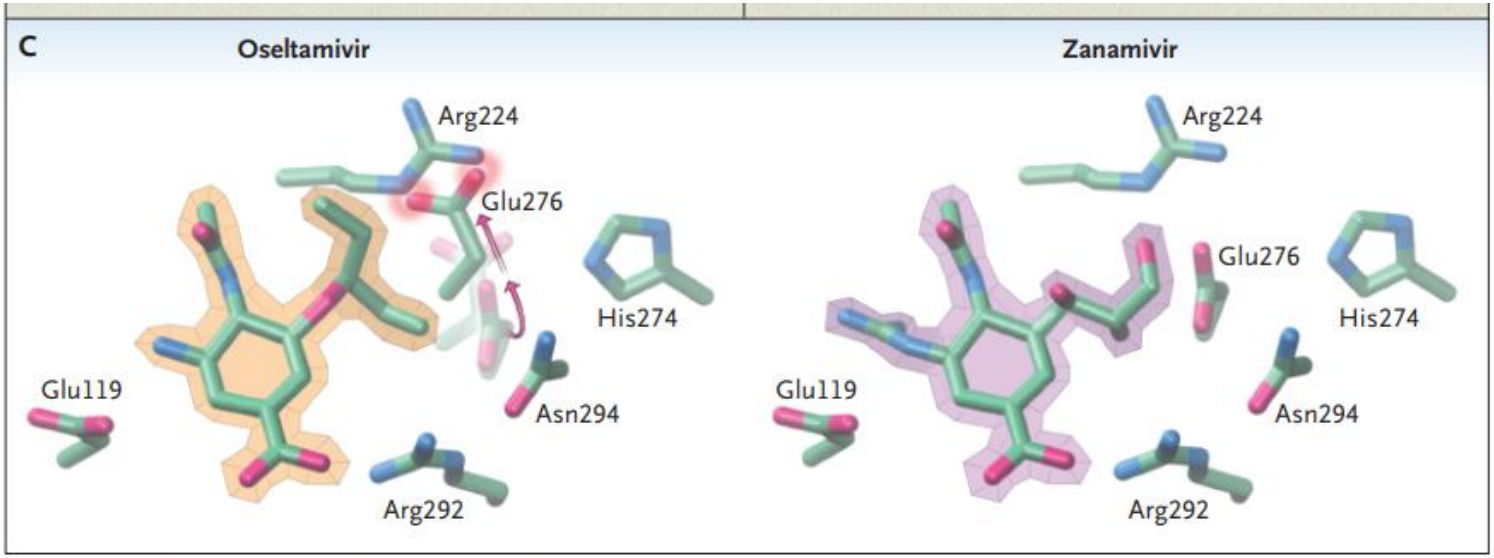
- 病毒基因突變：His274Tyr, Arg292Lys, Asn294Ser，改變病毒與NAI結合部位，使得oseltamivir不易與neuraminidase active site結合



N Engl J Med 2009; 360:953-6

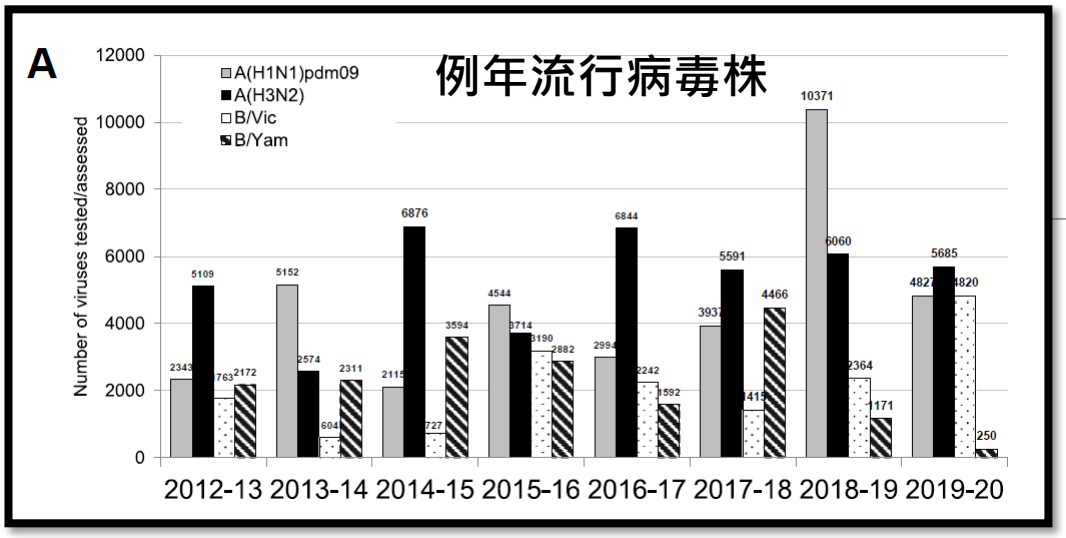
警鐘響起—NAI抗藥性

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



Mechanism of Development of Resistance to Oseltamivir.

Oseltamivir抗藥性病毒株近年監測結果



pdm09抗藥性病毒株比例

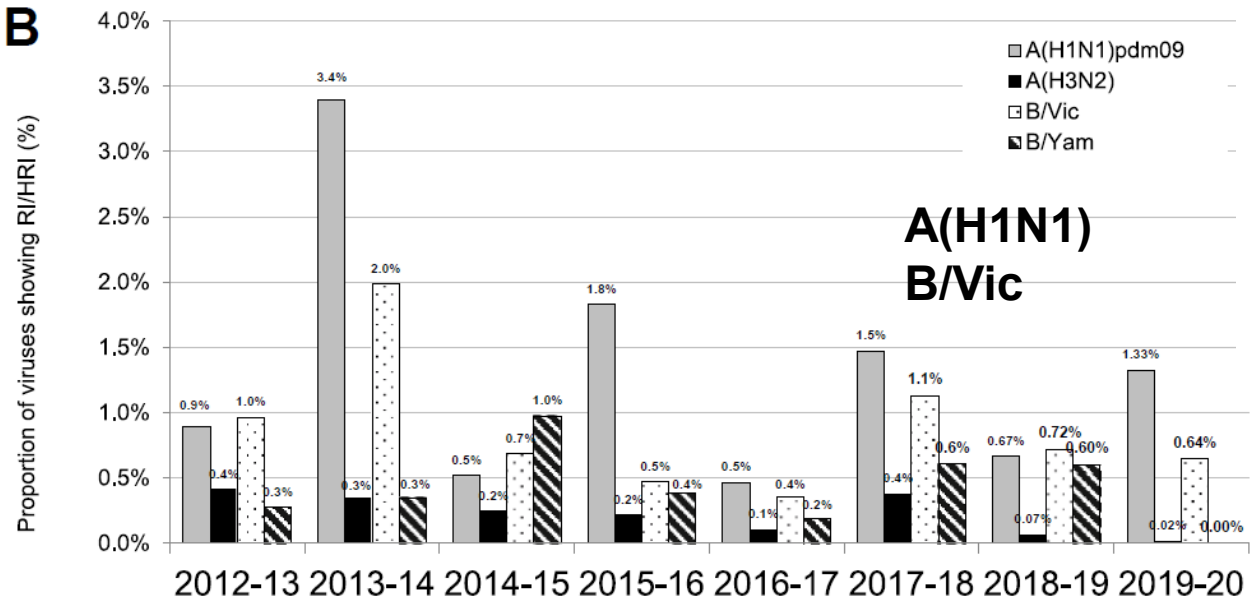
2019/20:1.33%

2018/19:0.67%

2017/18:1.5%

2016/17: 0.5%

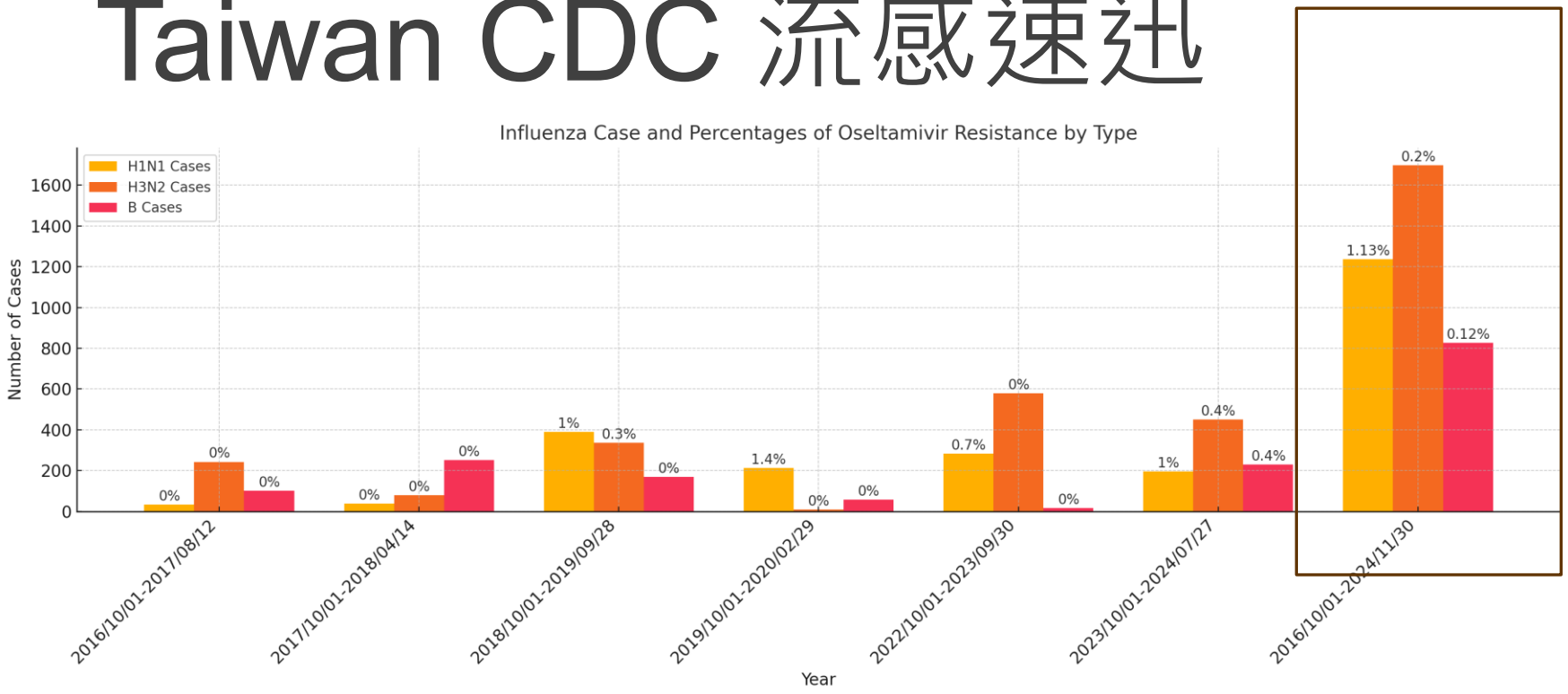
2015/16: 1.8%



Cross-resistant to peramivir

Antiviral Res. 2022;200:105281

Taiwan CDC 流感速迅



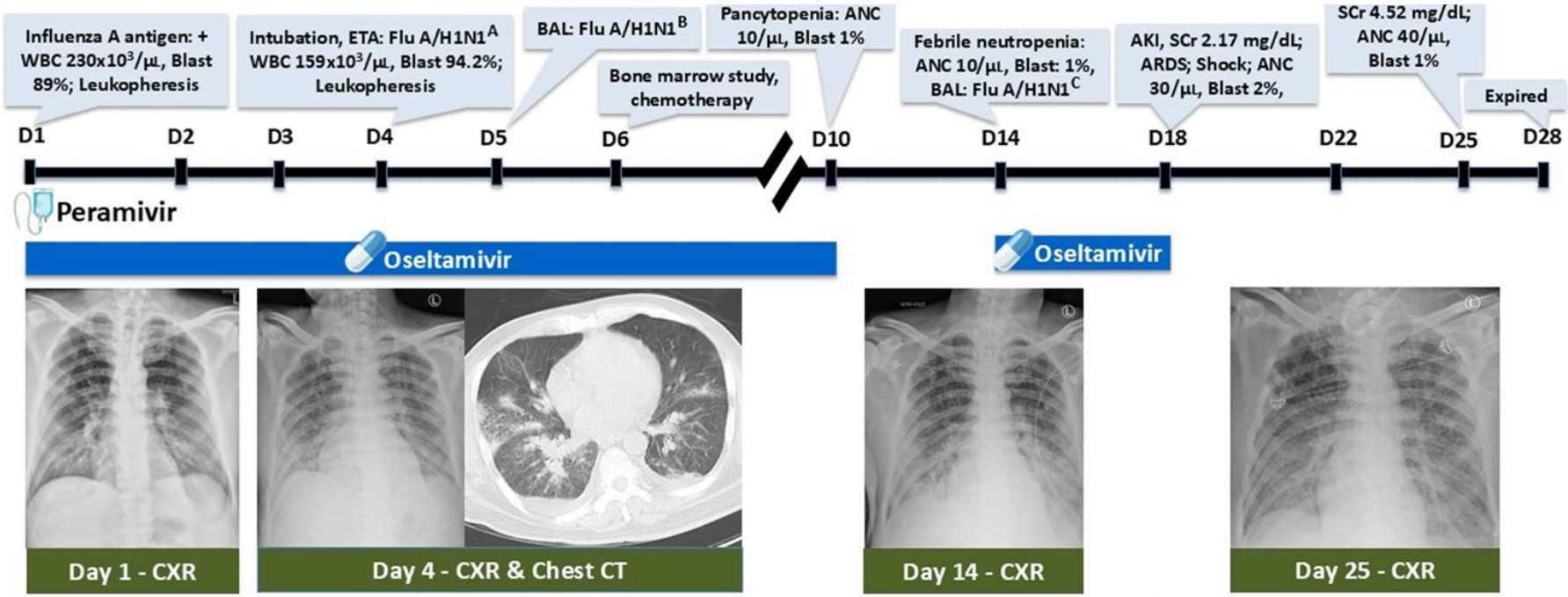
病毒抗藥性

2024-2025 流感季累積檢出克流感 (Oseltamivir) 抗藥性病毒株之分析結果如下表：

流感型別	檢驗數	病毒抗藥性, n (%)
A (H1N1)	332	7 (2.1%)
A (H3N2)	48	0 (0.0%)
B	51	0 (0.0%)

[2]病毒性感染症合約實驗室於 2024 年同步以病毒分離、培養與鑑定及分子生物學檢驗方式進行病原體檢測，為提升檢驗時效性，2024-2025 流感季調整呈現流感病毒分子生物學檢驗結果。

A case of oseltamivir- resistant



Isolate	Hospital day	Virus type/subtype	Clinical specimen	Fold change in oseltamivir IC_{50}	Oseltamivir susceptibility
A	D4	A/H1N1	Sputum	709	Highly reduced inhibition
B	D5	A/H1N1	Bronchoalveolar lavage	689	Highly reduced inhibition
C	D14	A/H1N1	Bronchoalveolar lavage	11	Reduced inhibition

Figure. Hospital course of an immunocompromised patient with bilateral pneumonia due to oseltamivir-resistant influenza A/H1N1 virus.

IC 50: half maximal inhibitory concentration

J Microbiol Immunol Infect. 2025;58(4):490-492

Baloxavir抗藥性病毒株監測結果

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

Virus (n)	n	EC_{50} fold-change as compared to reference median EC_{50} values	PA substitution[b]		Patient setting	Antiviral treatment	Immuno-compromised
			Virus isolate	Clinical specimen			
A(H1N1)pdm09 (14 of 984)	2	11.4–32.2	I38T	I38T/I mix	Community	Yes, baloxavir	No
	1	12.4	I38 T/F mix	I38T/F/I mix	Community	Yes, baloxavir	No
	2	36.9–49.5	I38S	I38S	Community	Yes, baloxavir	No
1.4%	3	3.0–3.7	I38V	I38V	Community	Yes, laninamivir	No
	1	2.5	I38F/I mix	I38F/I mix	Unknown	Unknown	Unknown
	1	6.9	E23G	E23G	Unknown	Unknown	Unknown
	1	7.4	E23K	E23K	Community	No	No
	2	1.6–4.7	K34R	K34R	Unknown	Unknown	Unknown
	1	2.9	E199G	E199G	Unknown	Unknown	Unknown
A(H3N2) (37 of 768) **4.8%**	21	64.3–614.0	I38T	I38T (10) I38T/I mix (9) I38T/K/I mix (1) Not available[c] (1)	Community (19) Hospital (2)	Yes, baloxavir (17) Yes, oseltamivir (1) No (3)	No (20) Unknown (1)
			I38T/I mix	I38T/I mix	Community	Yes, baloxavir	No
			I38 T/M/I mix	I38T/M/I mix	Community	Yes, baloxavir	No
			I38M	I38M	Community	Yes, baloxavir	No
			I38M/I mix	I38M/I mix (1)	Community (1)	Yes, baloxavir (1)	No (1)
				I38 (1)	Unknown (1)	Unknown (1)	Unknown (1)
			I38L	I38L	Unknown	Unknown	Unknown
			K34R	K34R	Unknown	Unknown	Unknown
	2	0.5–1.3	L28P	L28P (1) Not available (1)	Unknown	Unknown	Unknown
	1	0.9	I38V/I mix	Not available	Unknown	Unknown	Unknown
B/Victoria (2 of 425) **0.2%**	1	0.9	I38V	I38V	Unknown	Unknown	Unknown
	1	0.6	M34I	Not available	Unknown	Unknown	Unknown

全球抗藥性病毒株比例

2019/20:0.5%

2018/19:0.1%

In 2018-2019 Japan younger children (<12y/o)

But not persisted in 2019-2020

Antiviral Res. 2022;200:105281

何時監測抗藥性

- 免疫不全病人或流感重症病人使用抗病毒藥物後臨床狀況未改善(7~10天)且有持續病毒複製證據 (positive of RT-PCR or viral culture)
- 使用預防性抗流感藥物後仍出現臨床症狀且有病毒複製證據
- **Antiviral susceptibility patterns changed very little during 2020-2024**

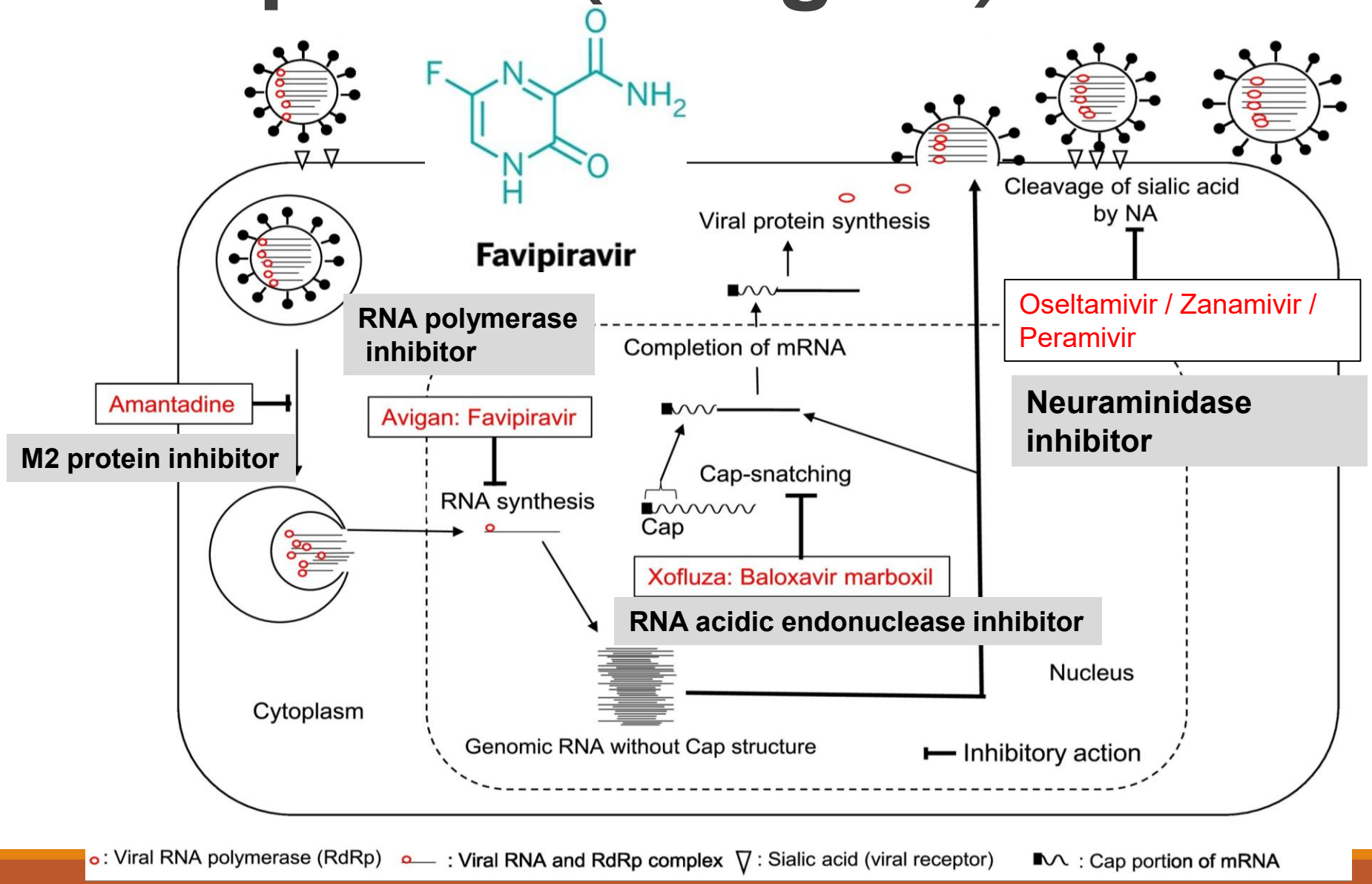
目前抗藥性病毒株並不常見，但仍需持續監測。
如當年流行病毒株為H1N1，需留意NAIs抗藥性。
如當年流行病毒株為H3N2，需留意Baloxavir抗藥性

(IDSA Influenza Clinical Guidelines 2018 • CID 2018)

大綱

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

Favipiravir（Avigan）



The Journal of Infectious Diseases

MAJOR ARTICLE

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

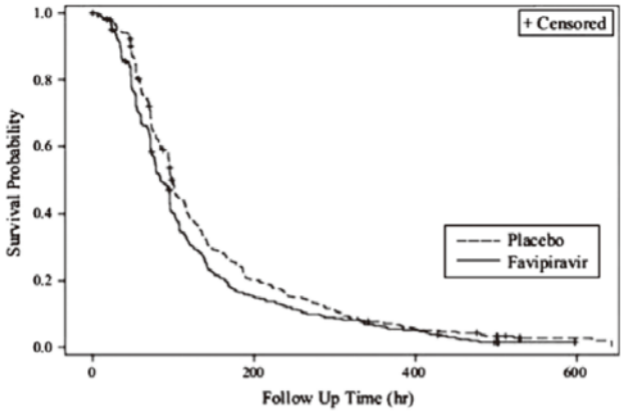
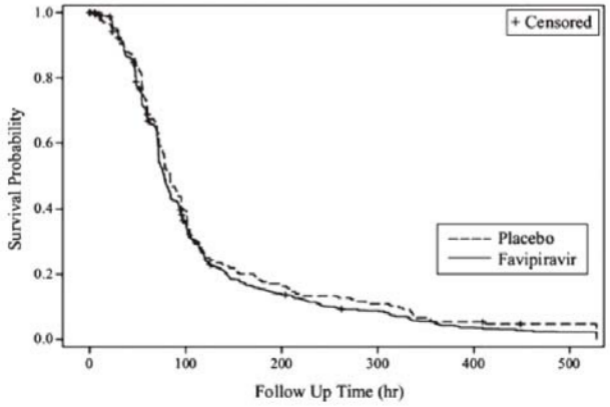


圖 3　以主要評估指標[註17]繪製 Kaplan-Meier Plot (ITTI 族群，試驗①)



[b] Catherine Oldham-Creamer,[2] Lih Lisa Kang,[2,c] and Carol Epstein[2,d]

ıf Medicine, University of Virginia School of Medicine, Charlottesville, Virginia, USA; and [2]Medivector, Inc, Boston,

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

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

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

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

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

Favipiravir 目前建議

- 專案進口藥物但無我國藥物許可證，提供在國內尚未取得藥物許可證，使用對象為符合疾病管制署公布之新型A型流感通報定義者，經使用oseltamivir及zanamivir等抗流感病毒藥劑治療無效，且經醫師評估及病患/家屬同意使用者
- 第 1 日每回服用 1600mg，每日2回。第 2 至 5 天每回 600mg，每日2回。總投藥期間為 5 天
- 本藥劑具致畸胎性， 兒童、已知/準備懷孕者及授乳者皆不可使用。
- 老人、痛風患者或有痛風病史者、高尿酸血症者、肝功能不良

或腎功能不良者，需慎重投藥。

大綱

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

流感病人治療國內外指引共識

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

公費抗流感病毒藥物適用對象定義及依據

9. 「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）

10. 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）

（二）Peramivir (Rapiacta)

符合新型A型流感通報定義，經醫師評估需使用，且經傳染
網區指揮官審核同意者。

註六、依防疫需要疾管署會定期更新，請至疾管署網站查閱最新公佈

5. 確診或疑似罹患流感住院（含急診待床）之病患

6. 具重大傷病、免疫不全（含使用免疫抑制劑者）或流感
疾病之類流感患者

7. 肥胖之類流感患者（BMI≧30 kg/m^2）

8. 類流感等群聚事件經疾病管制署各區管制中心防疫醫
藥者

新型 A 型流感傳染病病例定義暨防疫檢體採檢送驗事項

一、 臨床條件

同時具有以下二項條件:

(一)急性呼吸道感染[臨床症狀可能包括發燒(≧38℃)、咳嗽等]或急性結膜炎；

(二)臨床、放射線診斷或病理學上顯示肺部實質疾病。

二、 檢驗條件

具有下列任一個條件:

(一)臨床檢體培養分離及鑑定出新型 A 型流感病毒(非現行於人類流行傳播之 A(H1N1)、A(H3N2)季節性流感病毒)；

(二)臨床檢體新型 A 型流感病毒核酸檢測陽性；

(三)血清學抗體檢測呈現為最近感染新型 A 型流感。

三、 流行病學條件

發病前 10 日內，具有下列任一個條件:

(一)曾與出現症狀的極可能或確定病例有密切接觸，包括在無適當防護下提供照護、相處、或有呼吸道分泌物、體液之直接接觸；

(二)曾至有出現新型 A 型流感流行疫情地區之旅遊史或居住史；

(三)曾有禽鳥、豬暴露史或至禽鳥、豬相關場所；

(四)禽流感 A(H5N1)動物疫情接觸史；

(五)在實驗室或其他環境，無適當防護下處理動物或人類之檢體，而該檢體可能含有新型 A 型流感病毒。

肆、已上市之抗流感病毒藥物選擇

一、Oseltamivir (Tamiflu®, Eraflu®)

1. 適用於一個月大以上新生兒、兒童與成人流感之治療與預防。
2. 為孕婦及哺乳中婦女之首選藥物[9]。
3. Eraflu®為口服懸浮液。

二、Zanamivir (Relenza®)

1. 適用於5歲以上兒童與成人流感之治療與預防。
2. 下列情形原則上不建議要使用吸入型zanamivir治療病人：
   (1) 流感肺炎需住院治療者
   (2) 免疫不全病人流感快篩檢驗陽性
   (3) 預期無法配合正確使用吸入型者
   (4) 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）

三、Peramivir (Rapiacta®)

1. 靜脈注射投藥。
2. 適用於一個月大以上新生兒、兒童與成人流感之治療。
3. 因昏迷等原因致無法口服/吸入抗病毒藥劑，可考慮使用此藥。
4. 可作為懷疑或確定受 oseltamivir 抗藥性流感病毒株感染之病人治療之替代藥物。惟須注意曾有 oseltamivir 抗藥病毒株對peramivir感受性亦降低之報告。

四、Baloxavir Marboxil (Xofluza®)

1. 口服用藥。
2. 適用於5歲以上兒童與成人流感之治療與預防[10-12]。
3. 輕度或中度腎功能不全(CrCl>=30mL/min)的患者，不需要調整劑量[13]。

流感預防性用藥

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

結論

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

Thank you

Q&A

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

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

Summary

Background Despite widespread use, questions remain about the efficacy of oseltamivir in the treatment of influenza. Published Online
We aime
treatmen

Methods
trials of 7
illness in
Embase,
trials pu
intentior

Findings We included data from nine trials including 4328 patients. In the intention-to-treat infected population, we noted a 21% shorter time to alleviation of all symptoms for oseltamivir versus placebo recipients (time ratio 0·79, 95% CI 0·74–0·85; p<0·0001). The median times to alleviation were 97·5 h for oseltamivir and 122·7 h for placebo groups (difference –25·2 h, 95% CI –36·2 to –16·0). For the intention-to-treat population, the estimated treatment effect was attenuated (time ratio 0·85) but remained highly significant (median difference –17·8 h). In the intention-to-treat infected population, we noted fewer lower respiratory tract complications requiring antibiotics more than 48 h after randomisation (risk ratio [RR] 0·56, 95% CI 0·42–0·75; p=0·0001; 4·9% oseltamivir *vs* 8·7% placebo, risk difference –3·8%, 95% CI –5·0 to –2·2) and also fewer admittances to hospital for any cause (RR 0·37, 95% CI 0·17–0·81; p=0·013; 0·6% oseltamivir, 1·7% placebo, risk difference –1·1%, 95% CI –1·4 to –0·3). Regarding safety, oseltamivir increased the risk of nausea (RR 1·60, 95% CI 1·29–1·99; p<0·0001; 9·9% oseltamivir *vs* 6·2% placebo, risk difference 3·7%, 95% CI 1·8–6·1) and vomiting (RR 2·43, 95% CI 1·83–3·23; p<0·0001; 8·0% oseltamivir *vs* 3·3% placebo, risk difference 4·7%, 95% CI 2·7–7·3). We recorded no effect on neurological or psychiatric disorders or serious adverse events.

統合分析隨機分配試驗中4,328名病人
發現成年流感病人服用抗病毒藥劑能縮短症狀、
降低下呼吸道感染以及住院風險(0.6% vs 1.7%)

Lancet. 2015;385(9979):1729-37.

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

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

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

January 2016–March 2020

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

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

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

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

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

IJID. 2021;104:232-8.

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

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 6, 2018

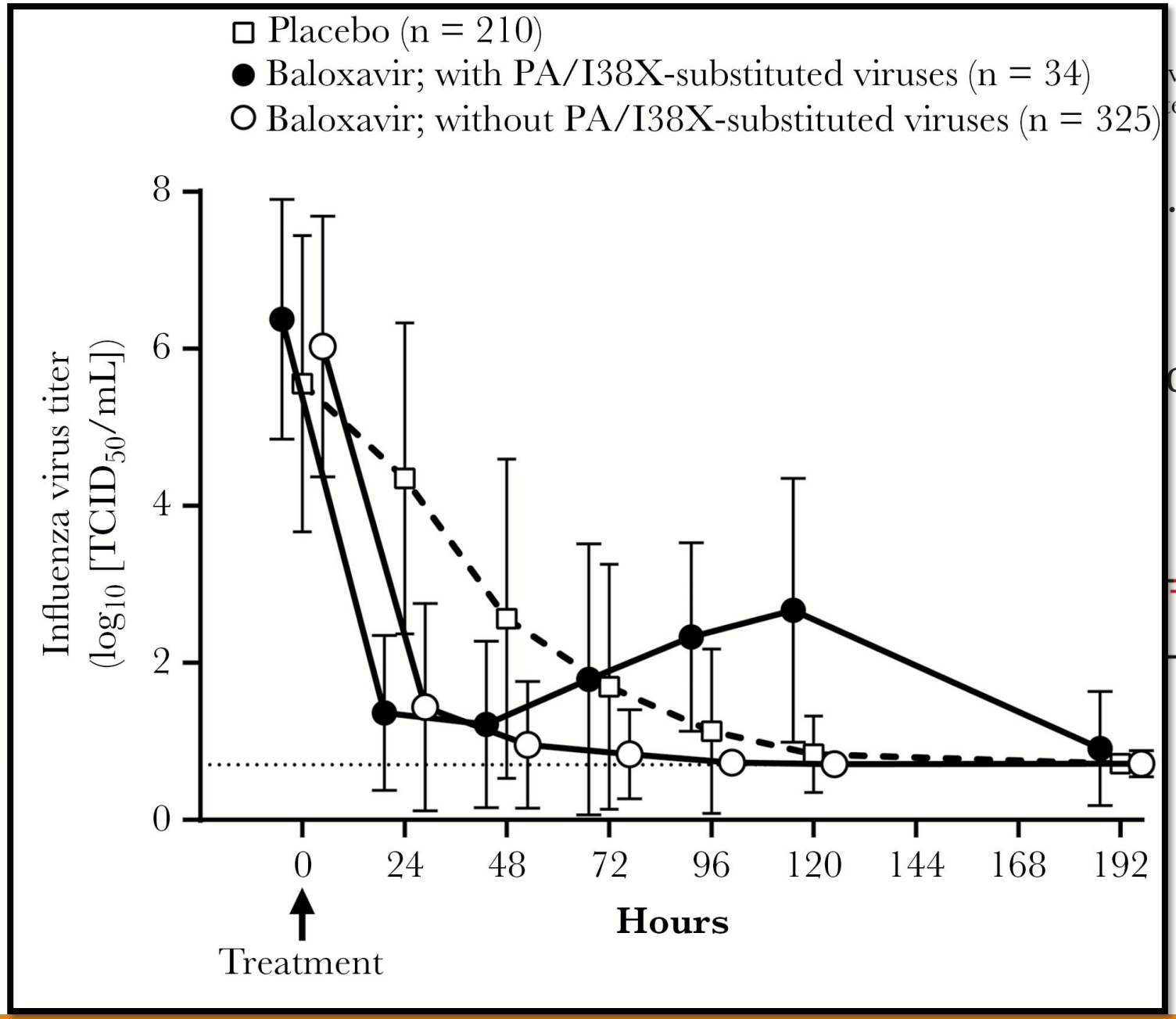
CAPSTONE-1 study

Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents

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

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

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



Proportion of unalleviated patients

viruses (n = 36)
ed viruses (n = 334)
.1
0)
312
336
360

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