



# Osetamivir para tratamento de influenza funciona?

## SIM

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# Argumentos

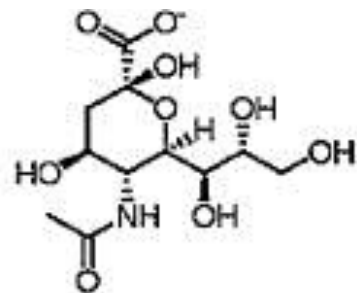
1. Droga moderna – “sob medida”
2. Evidência em estudos com animais
3. Evidência laboratorial
  1. Queda da carga viral
  2. Diminuição dos mediadores inflamatórios
4. Evidência em estudos clínicos controlados
5. Evidência de redução de sintomas
6. Tratamento do H5N1



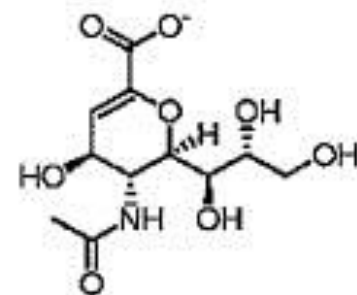
# 1. Droga moderna

## Drogas modernas

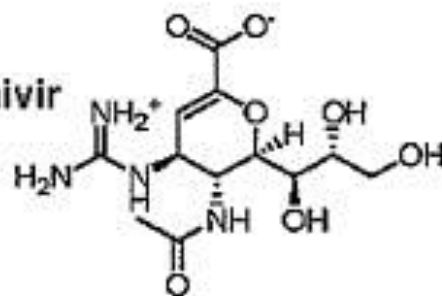
1 - Sialic acid



2 - DANA

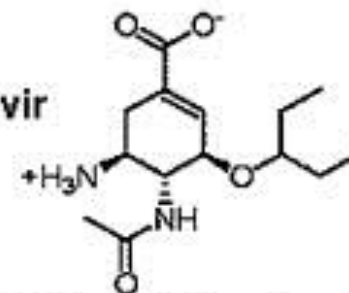


3 - Zanamivir



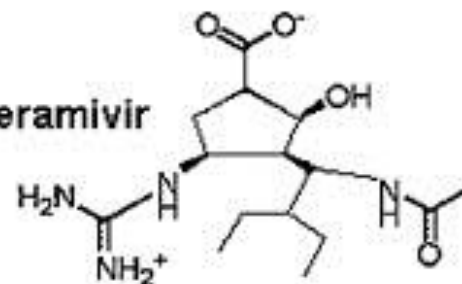
GG167

4 - Oseltamivir



GS4104 the estyl ester (prodrug),  
GS4071 (active drug)

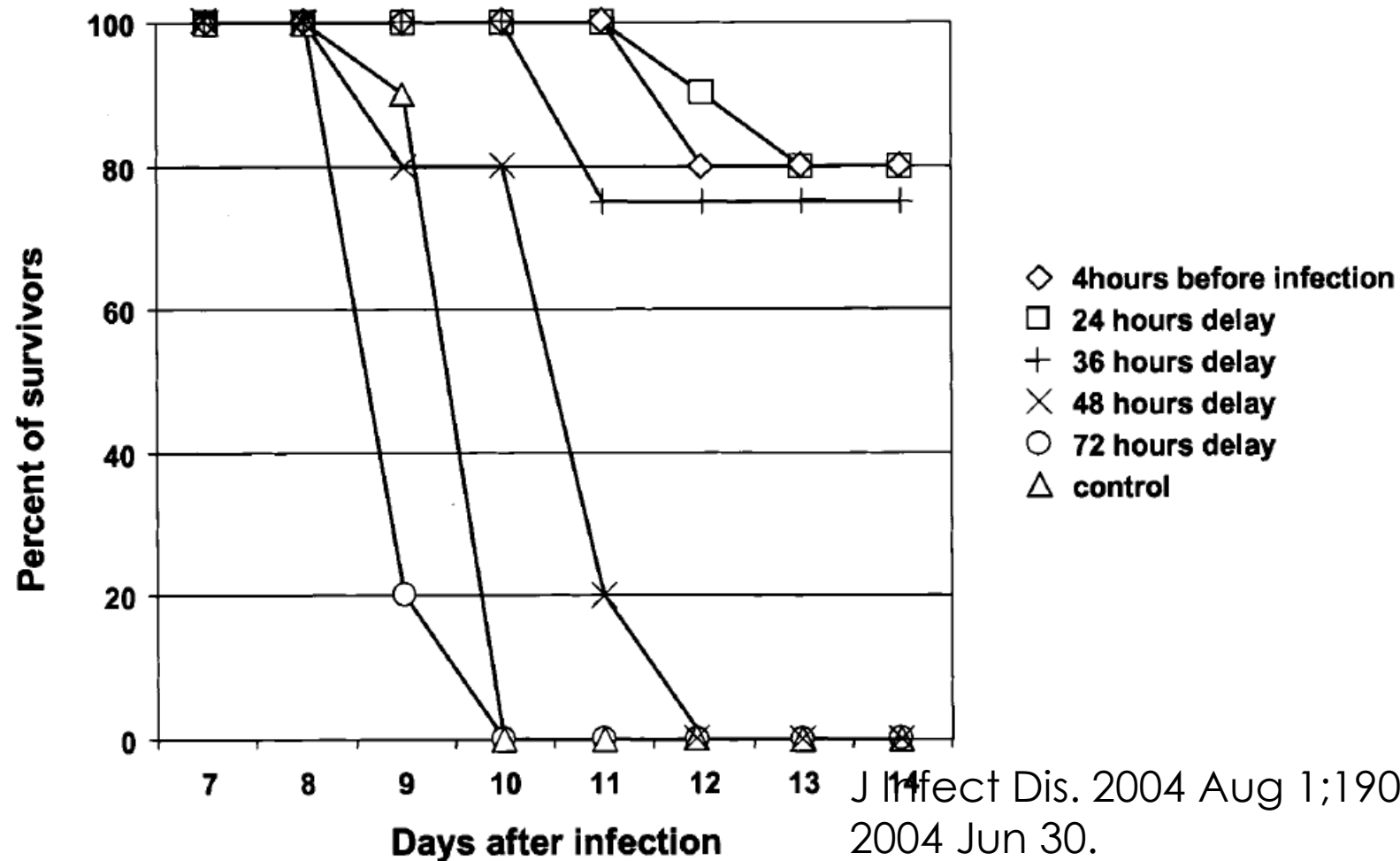
5 - Peramivir





## 2. Experimentos com animais

# Mortalidade em experimentos com ratos



J Infect Dis. 2004 Aug 1;190(3):519-26. Epub 2004 Jun 30.



### 3. Evidência laboratorial

# Viral Loads and Duration of Viral Shedding in Adult Patients Hospitalized with Influenza

Nelson Lee,<sup>1,3</sup> Paul K. S. Chan,<sup>2,3</sup> David S. C. Hui,<sup>1,3</sup> Timothy H. Rainer,<sup>4</sup> Eric Wong,<sup>5</sup> Kin-Wing Choi,<sup>1</sup> Grace C. Y. Lui,<sup>1</sup> Bonnie C. K. Wong,<sup>1</sup> Rita Y. K. Wong,<sup>1</sup> Wai-Yip Lam,<sup>2</sup> Ida M. T. Chu,<sup>2</sup> Raymond W. M. Lai,<sup>2</sup> Clive S. Cockram,<sup>1</sup> and Joseph J. Y. Sung<sup>1,3</sup>

Departments of <sup>1</sup>Medicine and Therapeutics, and <sup>2</sup>Microbiology, <sup>3</sup>Stanley Ho Centre for Emerging Infectious Diseases, <sup>4</sup>Trauma and Emergency

- Prospectivo observacional
- Carga viral no diagnóstico e todo dia por 1 semana
- 147 pacientes

scores and was significantly higher than that among time-matched outpatients (control subjects). Patients with major comorbidities had high viral RNA concentration even when presenting >2 days after symptom onset (mean  $\pm$  standard deviation,  $5.06 \pm 1.85$  vs  $3.62 \pm 2.13$  log<sub>10</sub> copies/mL;  $P = .005$ ;  $\beta$ ,  $+0.86$  [95% confidence interval,  $+0.03$  to  $+1.68$ ]). Viral RNA concentration demonstrated a nonlinear decrease with time; 26% of oseltamivir-treated and 57% of untreated patients had RNA detected at 1 week after symptom onset. Oseltamivir started on or before symptom day 4 was independently associated with an accelerated decrease in viral RNA concentration (mean  $\beta$  [standard error],  $-1.19$  [0.43] and  $-0.68$  [0.33] log<sub>10</sub> copies/mL for patients treated on day 1 and days 2–3, respectively;  $P < .05$ ) and viral RNA clearance at 1 week (odds ratio, 0.10 [95% confidence interval, 0.03–0.35] and 0.30 [0.10–0.90] for patients treated on day 1–2 and day 3–4, respectively). Conversely, major comorbidities and systemic corticosteroid use for asthma or chronic obstructive pulmonary disease exacerbations were associated with slower viral clearance. Viral RNA clearance was associated with a shorter hospital stay (7.0 vs 13.5 days;  $P = .001$ ).

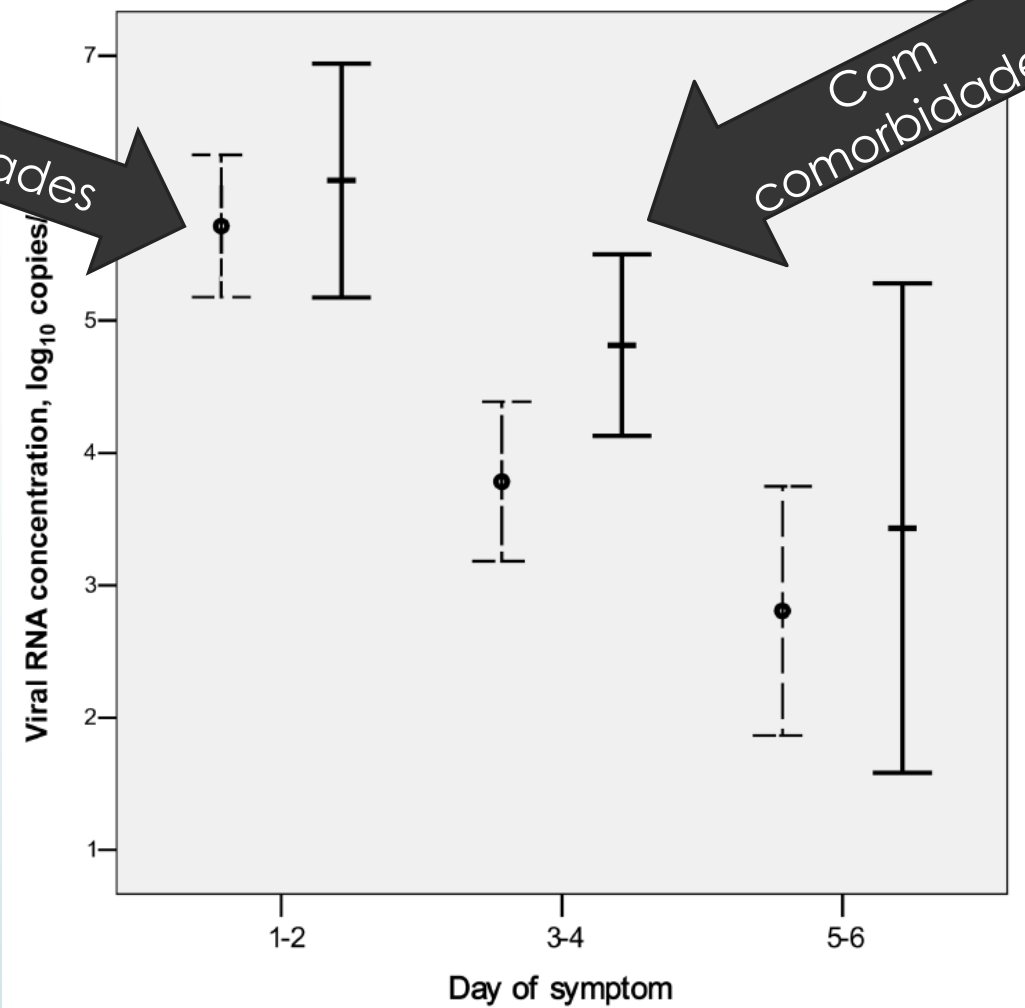
**Conclusion.** Patients hospitalized with severe influenza have more active and prolonged viral replication. Weakened host defenses slow viral clearance, whereas antivirals started within the first 4 days of illness enhance viral clearance.



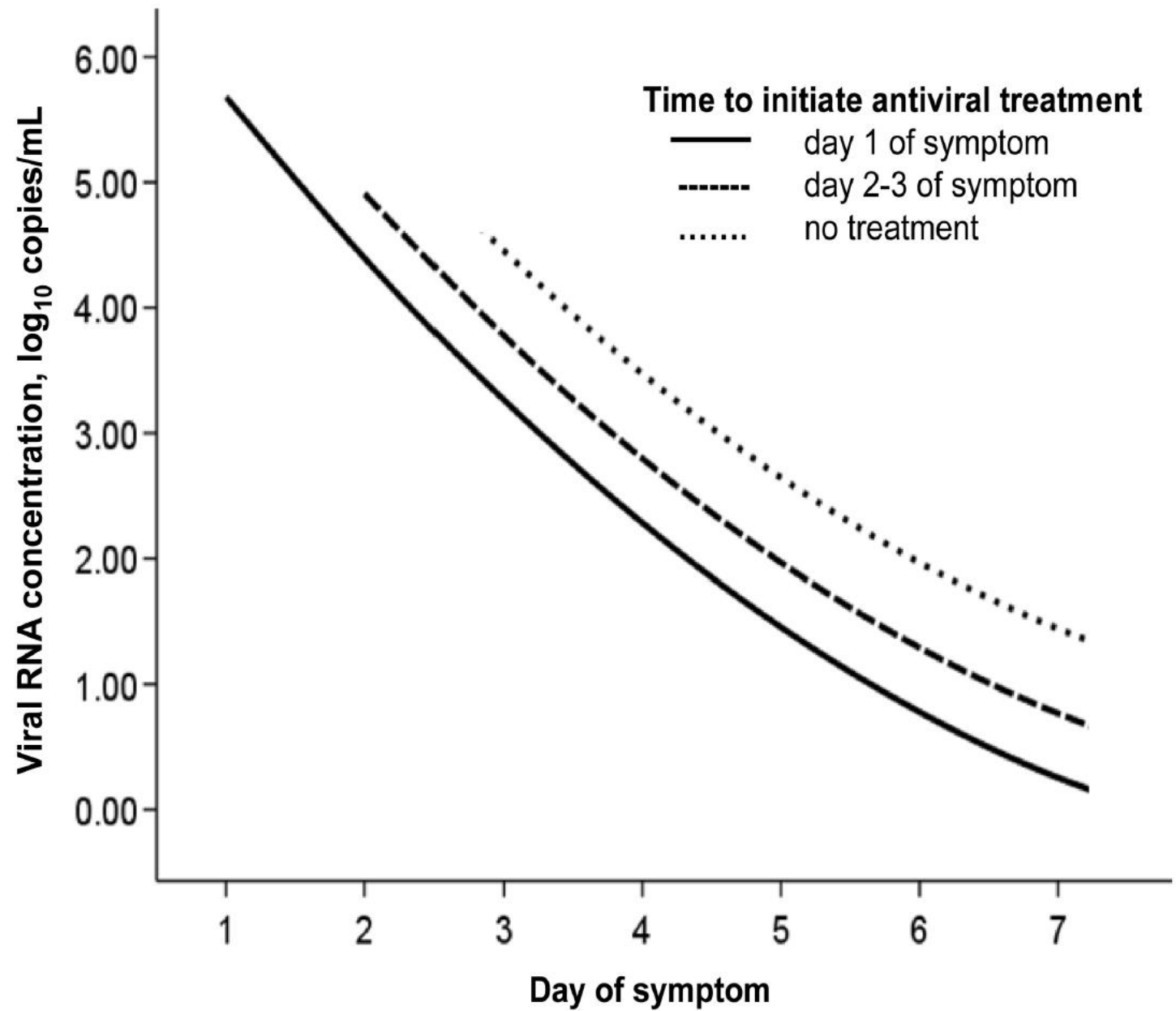
Carga viral e  
comorbidades

Sem comorbidades

Com  
comorbidades



**Figure 1.** Influenza A viral RNA concentration at time of presentation shown according to day of symptom in patients with (*solid lines*) or without (*hatched lines*) major comorbidities. Error bars represent the standard error of the mean. Major comorbidity refers to chronic systemic medical illnesses, including congestive heart failure; cerebrovascular, neoplastic, chronic liver and renal diseases; and use of immunosuppressants (table 1).



**Table 6. Factors Associated with Viral Clearance at 1 Week After Illness Onset in a Final Multiple Logistic Regression Model**

Variable associated with viral clearance	Adjusted OR (95% CI)	<i>P</i>
Age >65 years (vs ≤65 years)	5.87 (1.32–26.00)	.020
Comorbidity, major (yes vs no)	2.78 (1.03–7.48)	.043
Influenza B (vs influenza A)	5.83 (1.30–26.10)	.021
Systemic corticosteroid (yes vs no)	5.44 (1.86–15.89)	.002
Oseltamivir started on symptom day 1–2 <sup>a</sup>	0.10 (0.03–0.35)	<.001
Oseltamivir started on symptom day 3–4 <sup>a</sup>	0.30 (0.10–0.90)	.031

**NOTE.** Refer to the footnotes of table 1 for an explanation of clinical variables. CI, confidence interval; OR, odds ratio.

<sup>a</sup> Versus no antiviral treatment within 4 days.



## 4. Estudo clínico controlado

- 117 voluntários inoculados com H1N1
- Tratamento – 28 horas após inoculação
- Profilaxia em um grupo separado

enza

## Randomized Controlled Trials for Prevention and Treatment

Frederick G. Hayden, MD

John J. Treanor, MD

R. Scott Fritz, PhD

Monica Lobo, MD

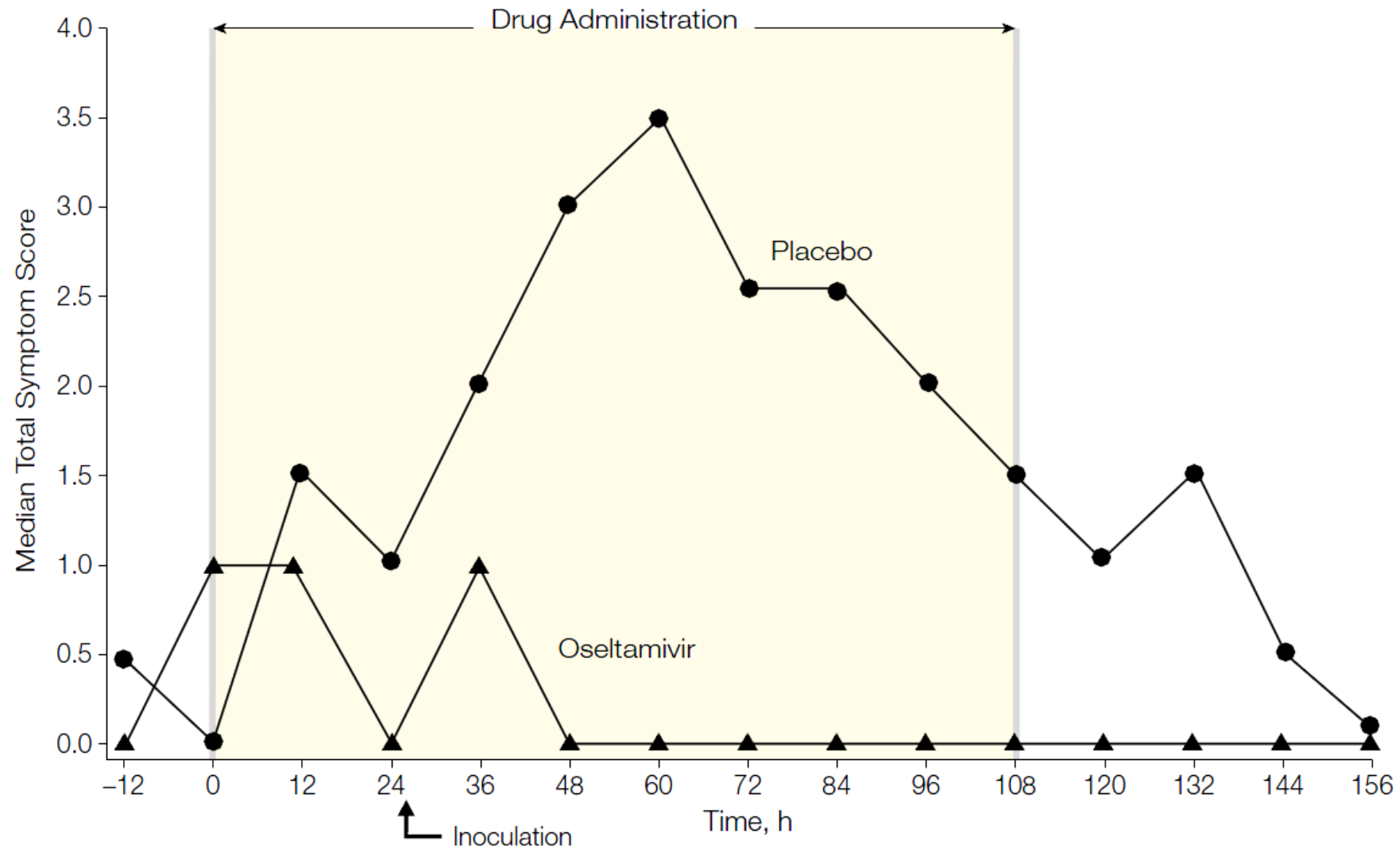
Robert F. Betts, MD

Madeline Miller, DVM

**Context** Influenza virus neuraminidase is thought to be essential for virus replication in humans; however, to date, available neuraminidase inhibitors are limited to zanamivir, which is topically administered.

**Objective** To determine the safety, tolerability, and antiviral activity of oral neuraminidase inhibitor oseltamivir (GS4104/Ro64-0796) for prevention and the early treatment of influenza in experimentally infected humans.

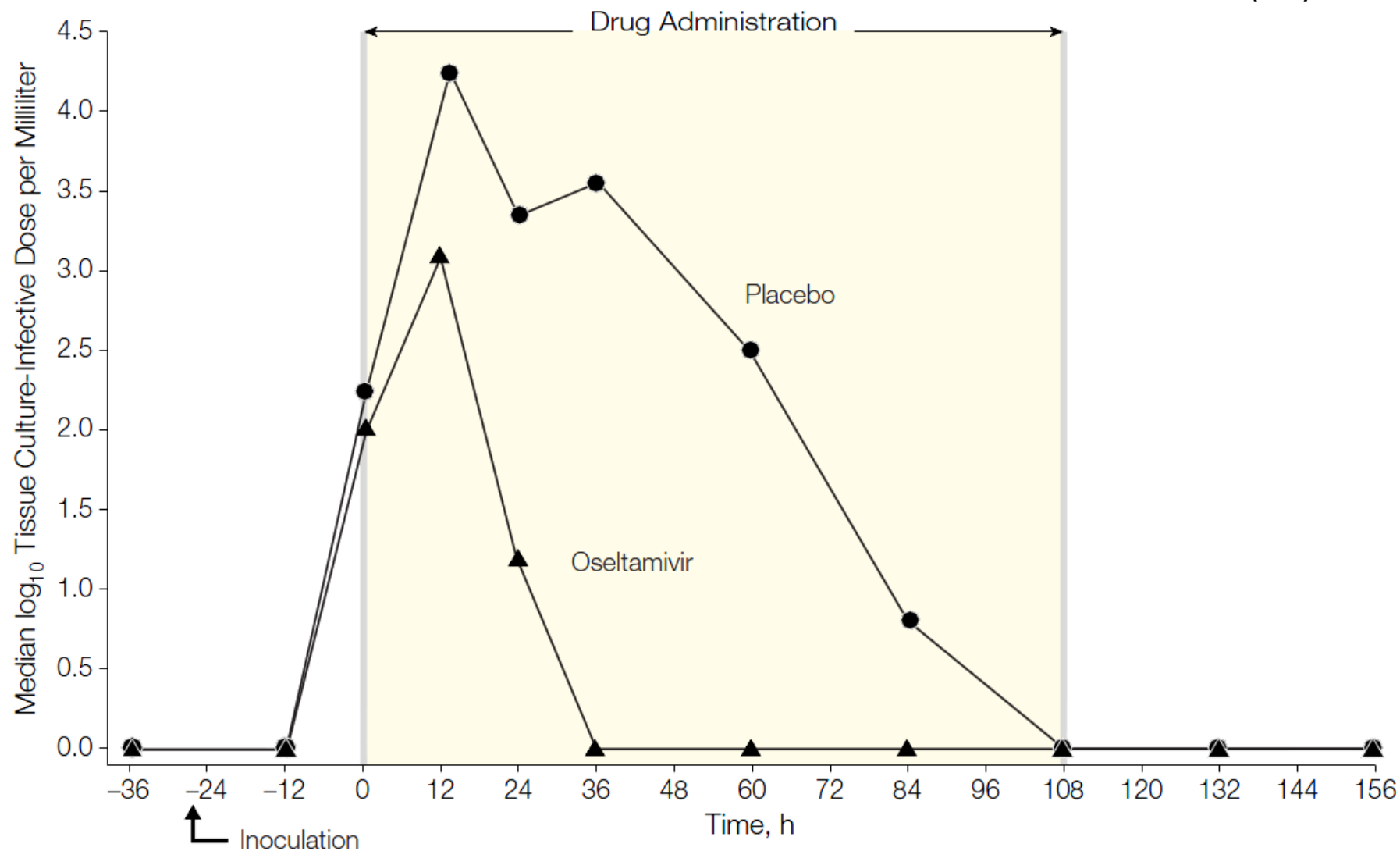
**Design** Two randomized, double-blind, placebo-controlled trials conducted between June and July 1997



The total symptom score area under the curve value was lower in the combined oseltamivir groups ( $n = 21$ ) compared with placebo ( $n = 12$ );  $P = .02$ . Fourteen symptoms related to influenza were included in the score.

**Figure 3.** Effect of Oral Oseltamivir Treatment on Viral Titers in Nasal Lavages Following Experimental Influenza A/Texas/36/91(H1N1) Infection

*JAMA.* 1999;282(13):1240-1246.



The viral titer area under the curve value was lower in the combined oseltamivir group (n = 56) compared with placebo (n = 13);  $P = .02$ .



## 5. Estudo multicêntrico, randomizado, caso controle



# EFFICACY AND SAFETY OF THE NEURAMINIDASE INHIBITOR ZANAMIVIR IN THE TREATMENT OF INFLUENZAVIRUS INFECTIONS

FREDERICK G. HAYDEN, M.D., ALBERT D.M.E. OSTERHAUS, D.V.M., PH.D., JOHN J. TREANOR, M.D.,  
DOUGLAS M. FLEMING, F.R.C.G.P., PH.D., FRED Y. AOKI, M.D., KARL G. NICHOLSON, M.D., ARTHUR M. BOHNEN, M.D.,  
HILARY M. HIRST, OLIVER KEENE, M.A., M.S., AND KEVIN WIGHTMAN, B.S., FOR THE GG167 INFLUENZA STUDY GROUP\*

## ABSTRACT

**Background** The sialic acid analogue zanamivir (GG167) is a selective inhibitor of influenza A and B virus neuraminidases. These viral enzymes are essential for the release of virus from infected cells, and they may also reduce the inactivation of virus by res-

tiveness in severe influenza or in preventing complications, side effects, and the emergence of drug-resistant variants.<sup>2</sup> Consequently, there is a continuing need for more effective antiviral agents to manage influenza infections.

The sialic acid analogue zanamivir (GG167) is a

38 centros no EUA e 32 na Europa  
417 pacientes foram randomizados  
em 3 grupos  
68% realmente tinham influenza  
Na média levaram 31 horas para  
iniciar tratamento

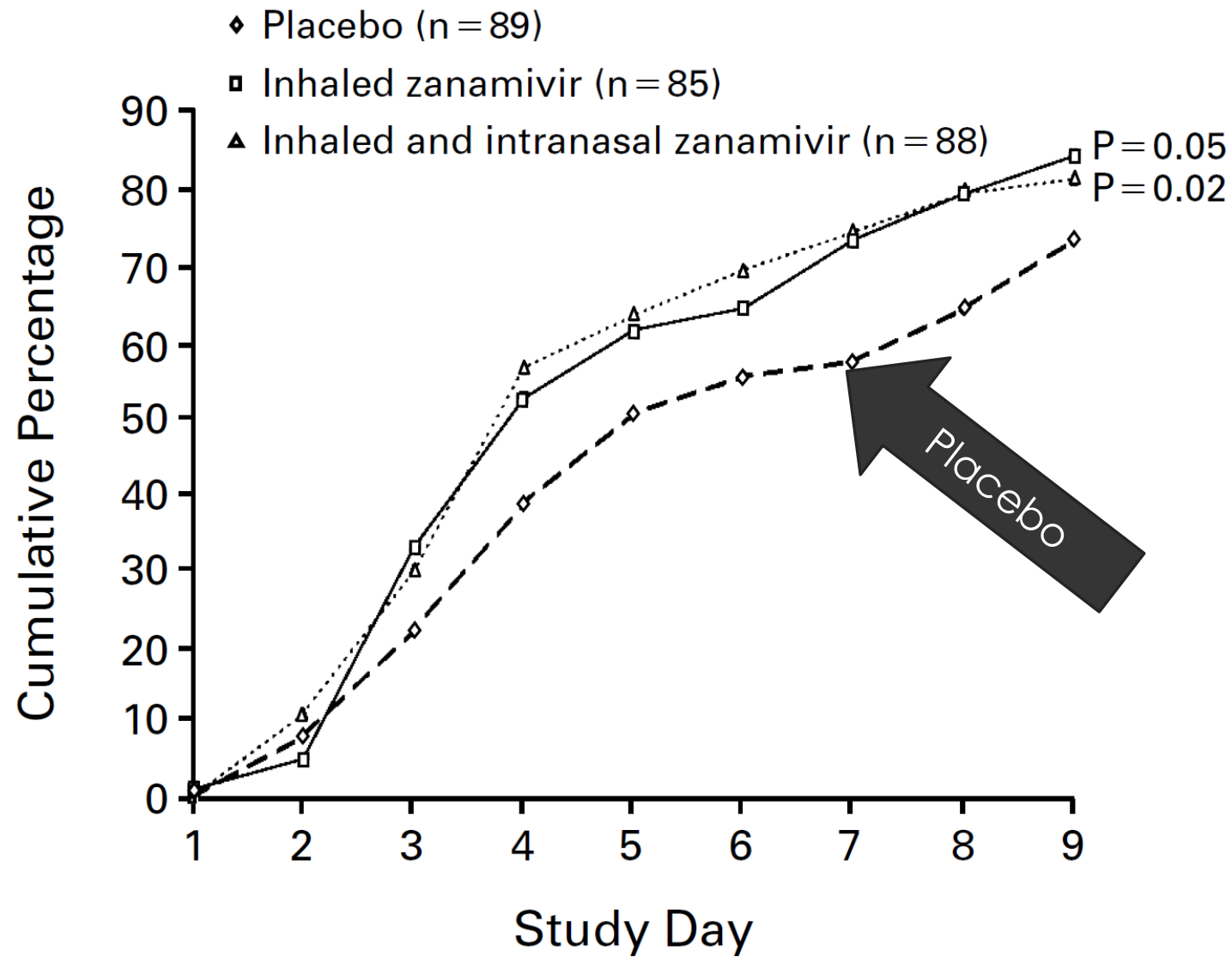
zanamivir alone ( $P=0.05$ ) than in the 89 patients given placebo. Among the infected patients who were febrile at enrollment and among those who began treatment within 30 hours after the onset of symptoms, the median time to the alleviation of major symptoms was four days in both zanamivir groups and seven days in the placebo group ( $P\leq 0.01$ ). Viral titers of nasal washings in the group given inhaled and intranasal zanamivir were significantly lower than those in the placebo group. The topically administered zanamivir was well tolerated.

in the treatment of naturally occurring acute influenza. Because influenza commonly involves the lower respiratory tract,<sup>1,2</sup> both intranasal and inhaled forms of the drug were tested.

## METHODS

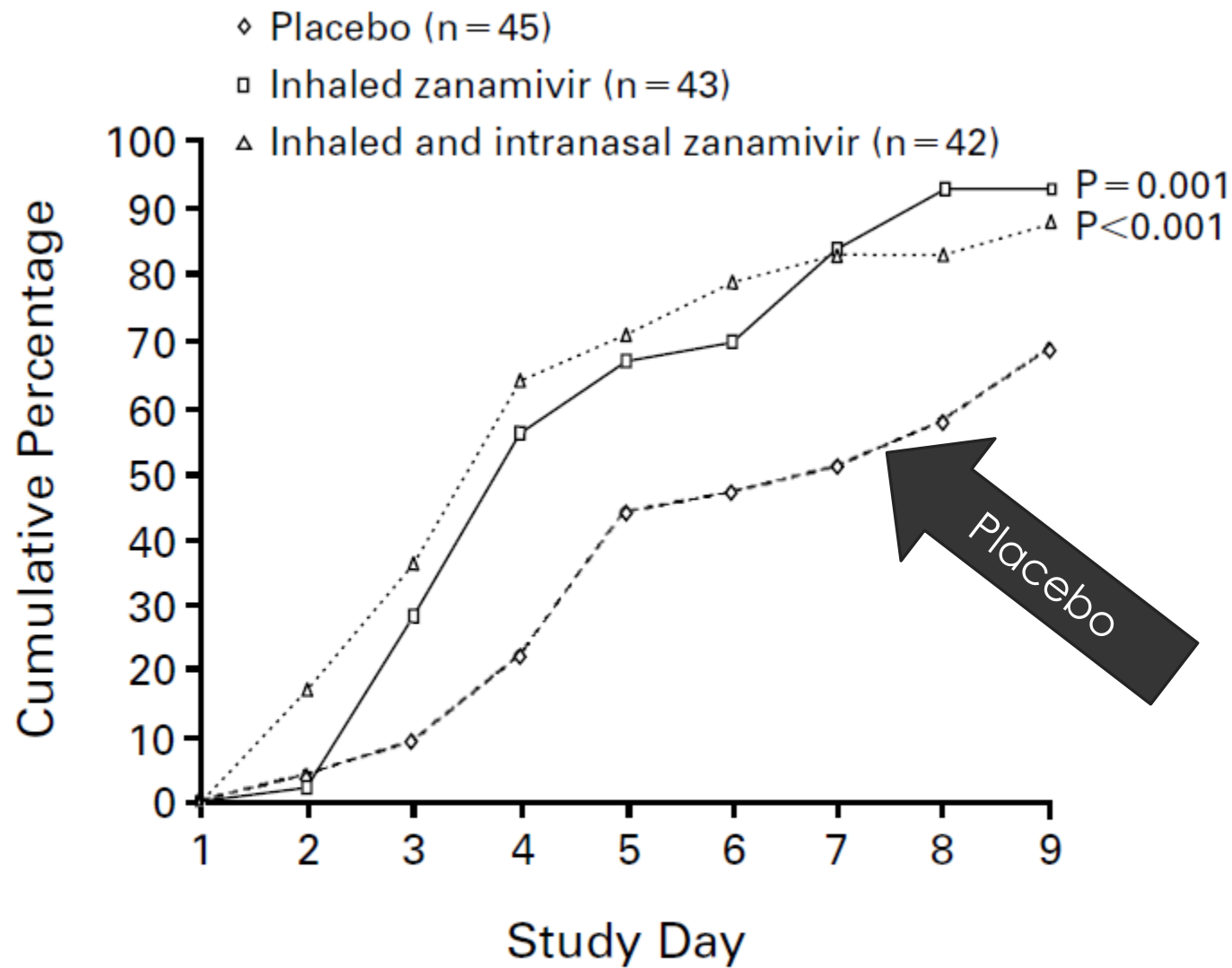
Two parallel multicenter trials were conducted in North America (38 centers) and Europe (32 centers) during the 1994–1995 influenza season. Both were randomized, double-blind, and placebo-controlled in design and tested the same regimen of drug treatment.





Efficacy and  
Safety of the  
Neuraminidase  
Inhibitor Zanamivir  
in the Treatment  
of Influenzavirus  
Infections  
Frederick G.  
Hayden, Influenza  
Study Group N  
Engl J Med 1997;  
337:874-880

**Figure 1.** Alleviation of Symptoms in Patients Infected with Influenza A or B Virus Who Were Treated with Inhaled Zanamivir, Intranasal and Inhaled Zanamivir, or Placebo.



**Figure 2.** Alleviation of Symptoms in Patients Infected with Influenza A or B Virus Who Were Treated within 30 Hours after the Onset of Symptoms with Inhaled Zanamivir, Inhaled and Intranasal Zanamivir, or Placebo.

Efficacy and Safety of the Neuraminidase Inhibitor Zanamivir in the Treatment of Influenzavirus Infections  
Frederick G. Hayden, Influenza Study Group N Engl J Med 1997; 337:874-880



## 6. Tratamento do H5N1

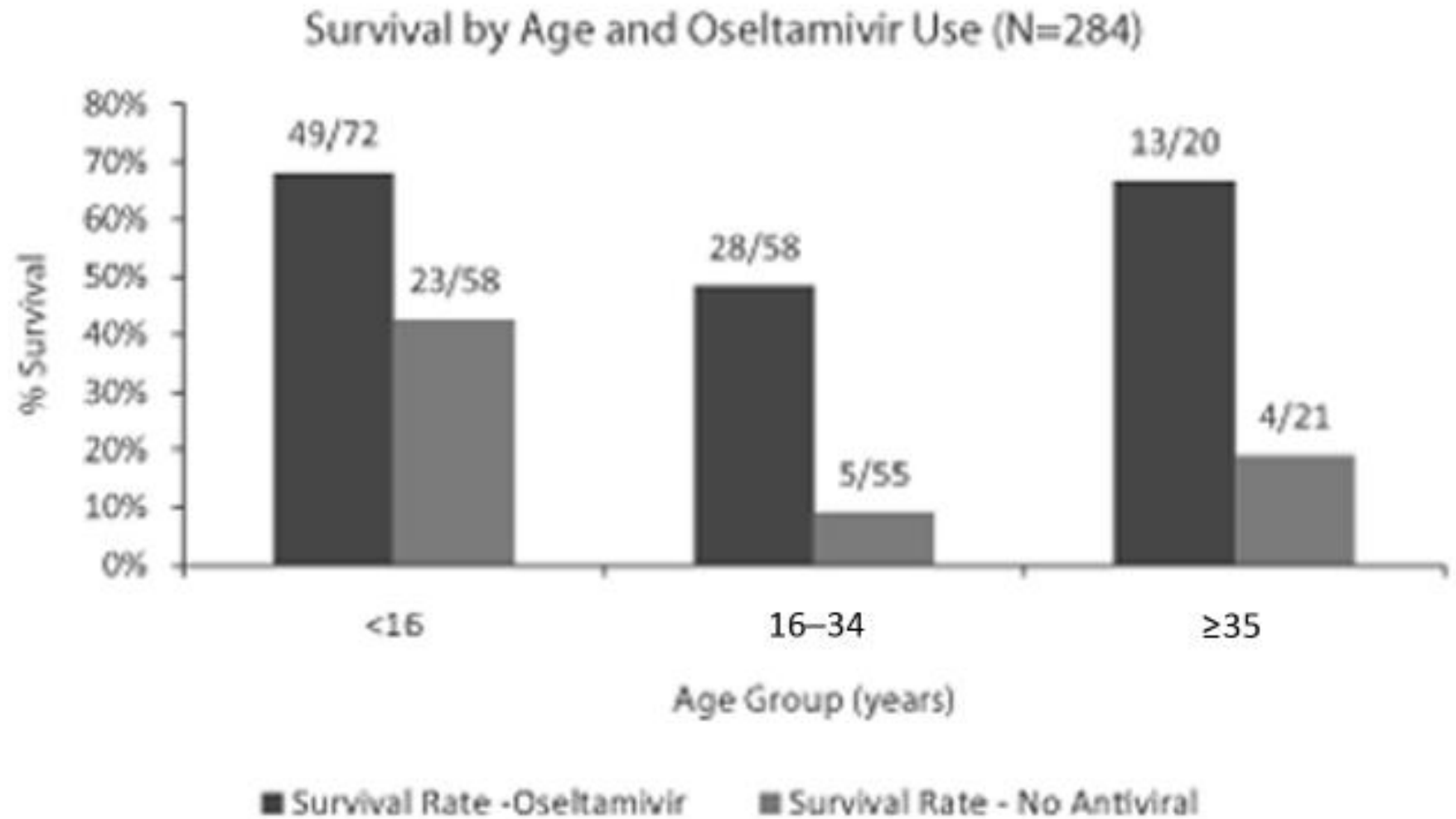


# Effectiveness of Antiviral Treatment in Human Influenza A(H5N1) Infections: Analysis of a Global Patient Registry

Wiku Adisasmito,<sup>1</sup> Paul K. S. Chan,<sup>2</sup> Nelson Lee,<sup>2</sup> Ahmet Faik Oner,<sup>3</sup> Viktor Gasimov,<sup>5</sup> Faik Aghayev,<sup>6</sup> Mukhtiar Zaman,<sup>7</sup> Ebun Bamgboye,<sup>8</sup> Nazim Dogan,<sup>4</sup> Richard Coker,<sup>10</sup> Kathryn Starzyk,<sup>9</sup> Nancy A. Dreyer,<sup>9</sup> and Stephen Toovey<sup>11</sup>

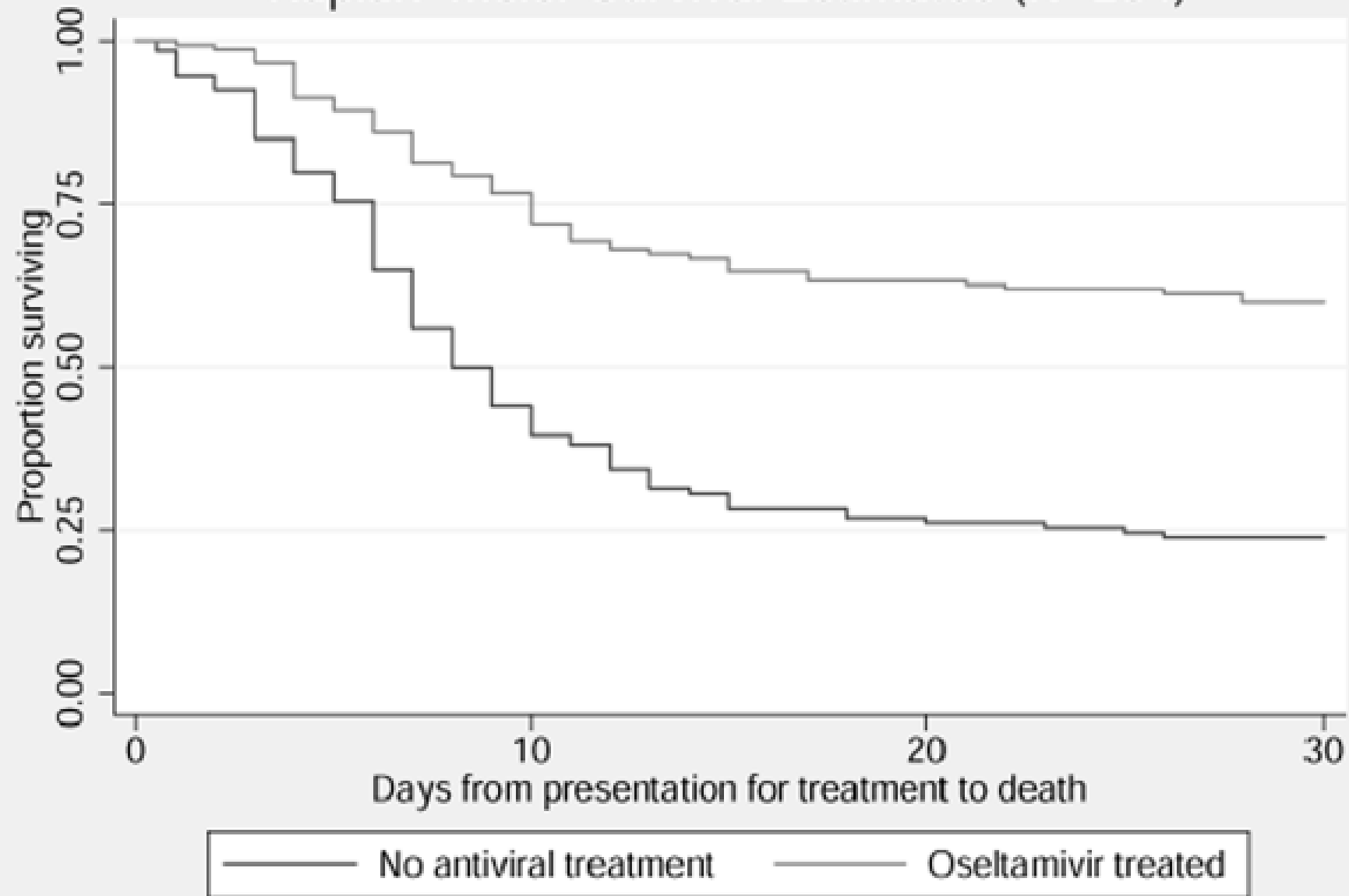
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1154 • JID 2010:202 (15 October) • Adisasmito et al



**Figure 2.** Survival rates by age and receipt of oseltamivir for 3 age groups.

Kaplan-Meier Survival Estimates (N=284)





# Origem da controvérsia



## RESEARCH

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



OPEN ACCESS

Tom Jefferson *reviewer*<sup>1</sup>, Mark Jones *senior research fellow (biostatistics)*<sup>2</sup>, Peter Doshi *assistant professor*<sup>3</sup>, Elizabeth A Spencer *nutritional epidemiologist*<sup>4</sup>, Igbo Onakpoya *research fellow in evidence-based practice and pharmacovigilance*<sup>4</sup>, Carl J Heneghan *professor*<sup>4</sup>

<sup>1</sup>Cochrane Acute Respiratory Infections Group, Via Puglie 23, 00187 Rome, Italy; <sup>2</sup>School of Population Health, University of Queensland, Brisbane, Australia; <sup>3</sup>Department of Pharmaceutical Health Services Research, University of Maryland School of Pharmacy, Baltimore, MD 21201, USA;

<sup>4</sup>Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

# Selection of studies

## *Types of studies*

We included randomised controlled trials testing the effects of oseltamivir for treatment, prophylaxis, and post-exposure prophylaxis of influenza. Treatment was the use of oseltamivir in people showing signs of influenza-like illness that might be caused by influenza A and B viruses. Prophylaxis was the mode of use of oseltamivir when there was expectation of possible exposure to influenza in the near future. Post-exposure prophylaxis was the use of oseltamivir after probable exposure to influenza but before symptoms developed. Studies which were open label, and those not involving naturally occurring influenza were excluded.

Because of discrepancies between published and unpublished reports of the same trials, we decided to include only those trials for which we had unabridged clinical study reports. Two authors (PD and TJ) reapplied inclusion criteria for the full clinical study reports received in 2013 and resolved disagreements through discussion.

the mode of action of the drug and incompatibility of the two contrasting claims on its activity against antibody production. If oseltamivir does not interfere with antibody production (see for example web extra on Roche statements and reference 23<sup>23</sup>), why do recipients of oseltamivir with influenza-like illness receiving treatment have such a consistently reduced odds of being classified as influenza infected? We have presented evidence clearly fitting a mode of action affecting several body systems (central nervous system, gastrointestinal, renal, immune, and metabolic).

## Conclusions

Given that oseltamivir is now recommended as an essential medicine for the treatment of seriously ill patients or those in higher risk groups with pandemic influenza,<sup>4 5</sup> the issues of mode of action, lack of sizeable benefits, and toxicity are of concern. This is made worse by the record and stated intentions of governments to distribute oseltamivir to healthy people to prevent complications and interrupt transmission on the basis of a published evidence base that has been affected by reporting bias, ghost authorship, and poor methods.

We believe these findings provide reason to question the stockpiling of oseltamivir, its inclusion on the WHO list of essential drugs, and its use in clinical practice as an anti-influenza drug.

workers in Canada. In 1997-99 TJ acted as consultant for Roche, in 2001-02 for GSK, and in 2003 for Sanofi-Synthelabo for pleconaril (an antirhinoviral that did not get approval from FDA). TJ is a consultant for IMS Health. PD received €1500 (£1241; \$2052) from the European Respiratory Society in support of his travel to the society's September 2012 annual congress in Vienna, where he gave an invited talk on oseltamivir. PD is an associate editor of the *BMJ*. TJ, MJ, CJH, and PD are co-recipients of a UK National Institute for Health Research grant (HTA—10/80/01 Update and amalgamation of two Cochrane reviews: neuraminidase inhibitors for preventing and treating influenza in healthy adults and children [www.nets.nihr.ac.uk/projects/hta/108001](http://www.nets.nihr.ac.uk/projects/hta/108001)). CJH receives payment for running educational courses at the University of Oxford and University of Oxford ISIS consulting services for external teaching and training. He also receives royalties for books (*Evidence Based Toolkit* series by Blackwell BMJ Books). MJ, IO, and EAS have no additional interests to disclose.

Ethical approval: Ethical approval and patient consent forms are not provided as they are not necessary for a Cochrane review.

Data sharing: All clinical study reports will shortly be available through the Dryad repository ([www.datadryad.org](http://www.datadryad.org)).

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the synthesis of the clinical study reports in the review; that no important aspects of the included clinical study reports have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.



Obrigado!

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