



Towards the Ideal Anti-Influenza Drugs ?



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Introduction

- Influenza is an important disease
- Old antiviral drugs (amantadine, rimantadine) have drawbacks in terms of
 - spectrum of activity limited to influenza A
 - emergence of resistance
 - side effects
- Neuramidinase inhibitors (NAI) are a new class of antiviral agents developed to inhibit specifically influenza viruses neuramidinase

The different steps towards ideal anti-influenza drugs

- *In vitro* antiviral activity
- Animal studies
- Pharmacokinetics in humans :
 - Absorption, distribution, metabolism, elimination
- Clinical efficacy
 - Experimental human influenza
 - Treatment : healthy and at risk adult patients, children
 - Prophylaxis : post contact prophylaxis, seasonal prophylaxis, in adults
- Viral resistance
- Safety and tolerance

In vitro activity

Animal studies

Pharmacokinetic characteristics

In vitro antiviral activity

Virus	median (range) IC50 (nM)	
	oseltamivir carboxylate	zanamivir
<i>Sidwell RW 1998</i>		
H1N1	26.0	60.0
H3N2	0.2	0.4
H3N2	1.8	10.0
B	2.3	1.2
<i>Mendel DB 1998</i>		
H1N1	0.02	0.02
H1N1	0.02	0.02
H3N2	0.0006	0.004
B	0.12	0.09
B	0.16	0.15

McClellan Drugs 2000;60

Animal studies

Oseltamivir

- Mice model
 - Mendel DB AAC 1998
 - Sidwell RW Antiviral Res 1998
- Ferret model
 - Mendel DB
 - Roberts NA
 - Data Hoffmann-La Roche, 1999

Zanamivir

- Mice model
 - Von Itzstein M Nature 1993
 - Gubareva LV JID 1998
 - Ryan DM AAC 1994
 - Fenton RJ AAC 1999
- Ferret model
 - Von Itzstein M Nature 1993
 - Ryan DM AAC 1995

Pharmacokinetic characteristics of zanamivir and oseltamivir (1)

	zanamivir	oseltamivir
Absorption	4%-17% of inhaled dose	rapidly absorbed : 75%
Distribution	<10% plasma protein bound	Os. carboxylate : 3% Os. phosphate : 43% plasma protein bound

Pharmacokinetic characteristics of zanamivir and oseltamivir (2)

	zanamivir	oseltamivir
Metabolism	no hepatic Mb >90% eliminated unchanged	hepatic esterases cytochrome P450 >90% metabolized to Os carboxylate
Elimination	renal excretion unabsorbed drug : feces	renal excretion tubular secretion may occur
Half life	2.5-5.1 hours	6-10 hours

Dreitlein WB, Clin Ther 2001;23:327-355

Clinical efficacy :
Experimental influenza

Experimental human influenza

Oseltamivir

Prophylaxis or treatment of human influenza A or B

- Hayden FG JAMA 1999
- Hayden FG CID 1999
[abstract]
- Hayden FG Antiviral Therapy 2000
- Jennings L 11th IC of virology
[abstract]

Zanamivir

Prophylaxis or treatment of human influenza A or B

- Hayden FG, JAMA 1996
- Hayden FG, Elsevier Science 1996

Oseltamivir in prevention of experimental human influenza

- Susceptible volunteers (n=37)
 - randomized to receive placebo or oseltamivir (100 mg od or bid) for 5d,
 - Treatment was started 26 h prior to intranasal inoculation with A/Texas/36/91 (H1N1)
- Oseltamivir reduced
 - Infection from 67% to 38%, efficacy 61%, $p = .16$
 - Respiratory illness from 33% to 0%, $p < .01$
 - Viral shedding from 50% to 0%, $p < .001$

Oseltamivir in treatment of experimental human influenza

- Healthy (18-40 year old) volunteers
 - Intranasally inoculated A/Texas/36/91 (H1/N1)
 - Randomized 28h later to receive placebo *versus* oseltamivir (one of four doses ranging from 20-200 mg bid for 5 days)
- Oseltamivir reduced
 - symptoms scores
 - Inflammatory cytokines levels in nasal washings
 - Viral titre AUC ($p = .02$)
 - Median duration of viral shedding from 107 to 58 h ($p = .003$)

Zanamivir in human experimental influenza

- Zanamivir administered by intranasal route in volunteers
- Influenza A : A/Texas/91 (H1N1)
 - Prophylaxis (beginning 4h before inoculation)
 - 82% effective in preventing laboratory-confirmed infection ($p < .01$)
 - 95% effective in preventing febrile illness ($p < .01$)
 - Early or delayed treatment (1-2 days after)
 - Reduced peak viral shedding by $2.0 \log_{10}$ ($p < .05$)
 - Reduced mean duration of viral shedding by 3 days ($p < .05$)
- Influenza B : B/Yamagata/88
 - 32% protective efficacy against infection
 - 60% protective efficacy against viral shedding

Hayden JAMA 1996;275:295-299 and Elsevier Science 1996

Clinical efficacy :
Treatment of acute influenza

Efficacy of NAIs for treatment of acute influenza : methodology used in main studies (adults)

- Randomized, double-blind, placebo-controlled trials
- During circulating period of virus
- Relief medication authorized
- Inclusion criteria :
 - Healthy individuals aged ≥ 12 years
 - Influenza-like illness of 36h or less
 - Fever, feverishness or both
 - And respiratory, and constitutional symptoms

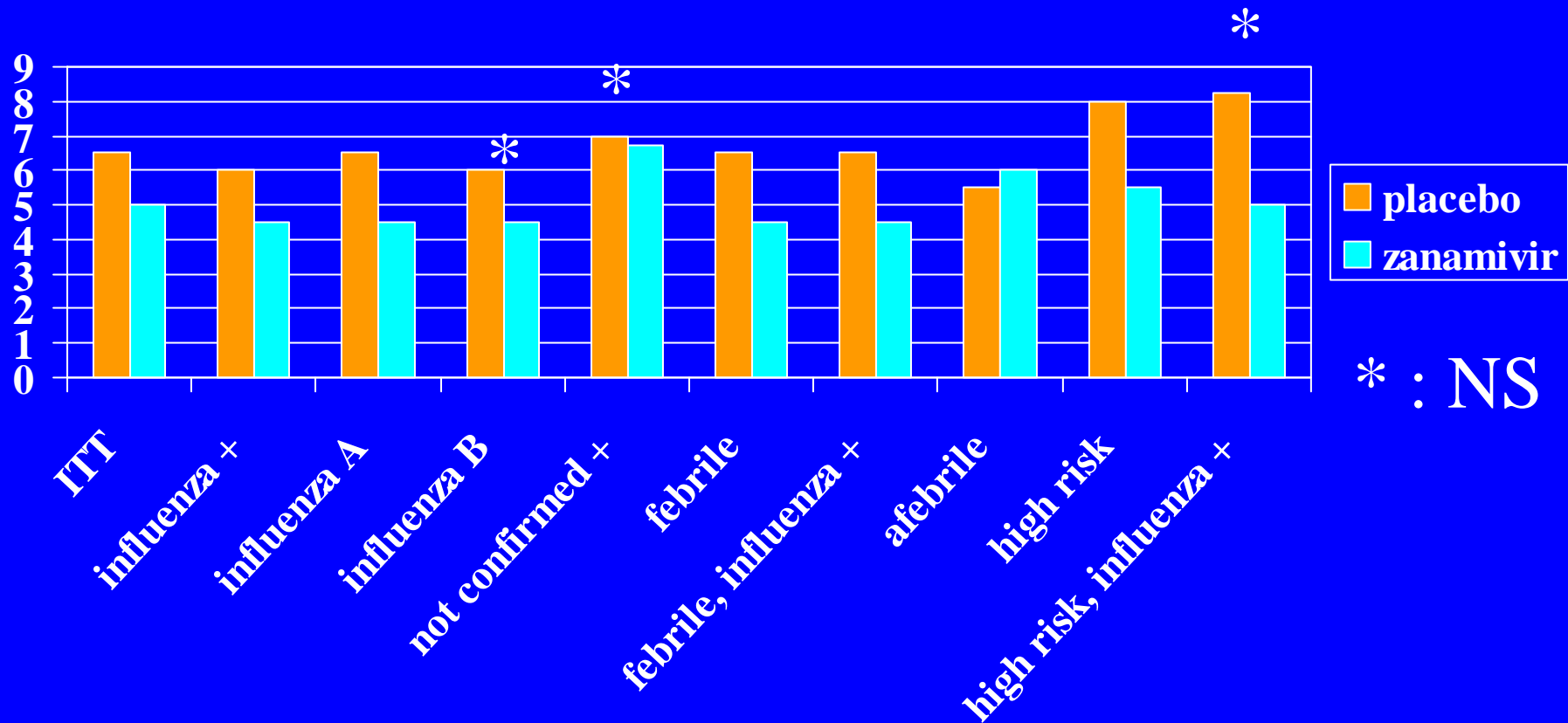
Efficacy of NAIs for treatment of acute influenza : methodology used of main studies (adults)

- Primary end point : length of time to alleviation of clinically important symptoms, using a symptom score
- Secondary endpoints (depending upon studies) :
 - measure of individual symptoms : T, cough...
 - time to return to normal activities
 - physician's global assessment of symptoms
 - use of relief medication
 - complications/antibiotic use
 - viral shedding....

Zanamivir Relenza[®]

Efficacy and safety of inhaled zanamivir in treatment of influenza

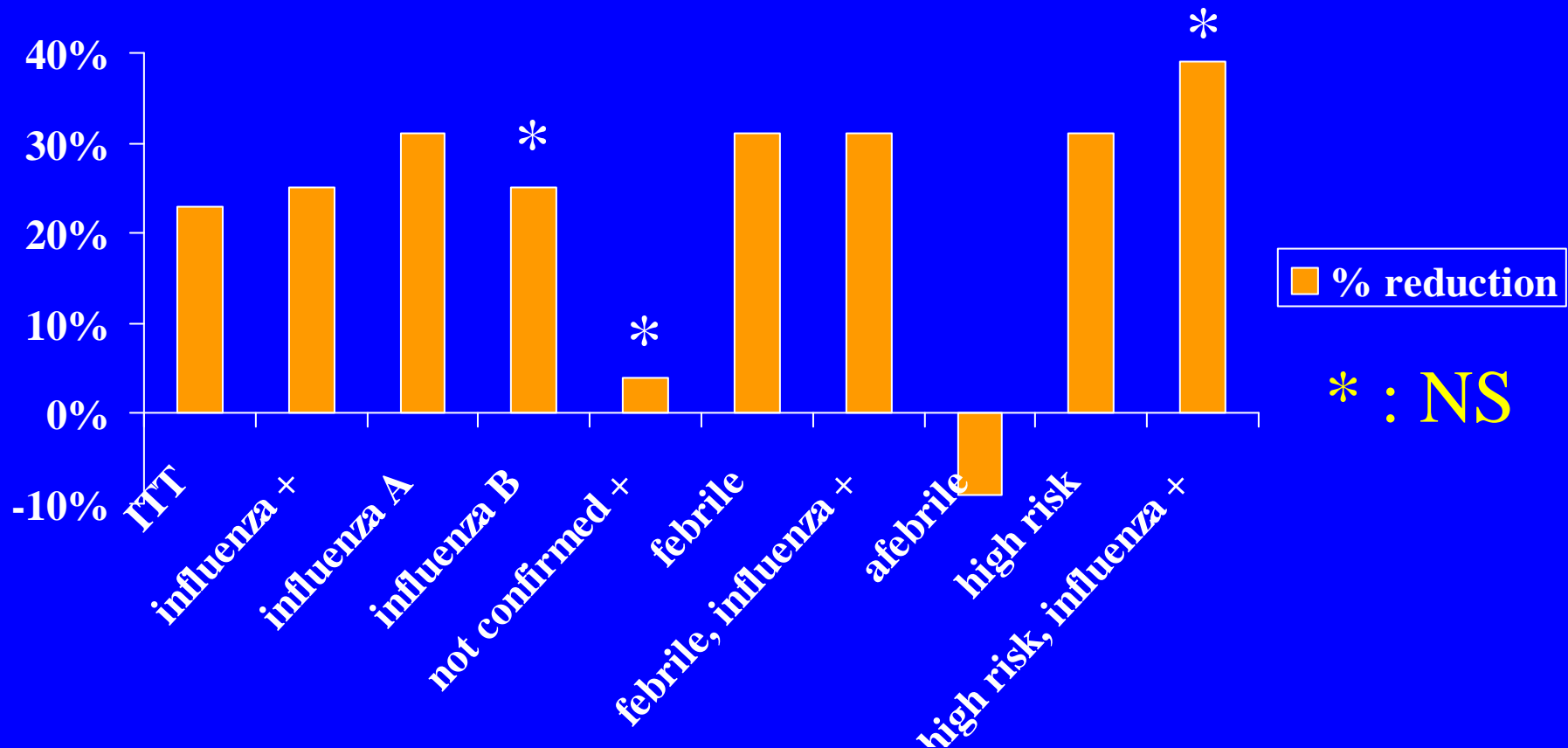
Median time (days) to alleviation of clinically important syndrome



MIST Study, Lancet 1998;352:1877-1881

Efficacy and safety of inhaled zanamivir in treatment of influenza

Difference in alleviation (%) of clinically important syndrome



MIST Study, Lancet 1998;352:1877-1881

Efficacy and safety of inhaled zanamivir in treatment of influenza (1)

Median time (days) to alleviation of clinically important syndrome

	placebo	zanamivir	difference (95% CI)	p	difference (%)
ITT	6.5	5.0	1.5[0.5 to 2.25]	.011	23
Influenza +	6.0	4.5	1.5[0.5 to 2.25]	.004	25
Influenza A	6.5	4.5	2.0[0 to 3.0]	.015	31
Influenza B	6.0	4.51	1.5[0 to 3.0]	.12	4
Not confirmed +	7.0	6.75	0.25[-2.25 to 3.25]	.486	4

MIST Study, Lancet 1998;352:1877-1881

Efficacy and safety of inhaled zanamivir in treatment of influenza (2)

Median time (days) to alleviation of clinically important syndrome

	placebo	zanamivir	difference (95%CI)	p	difference (%)
Febrile	6.5	4.5	2.0[1.0 to 4.0]	<.001	31
Febrile influenza +	6.5	4.5	2.0[1.25 to 4.5]	<.001	31
Afebrile	5.5	6.0	0.5[-2.0 to 1.5]	.932	-9
High risk	8.0	5.5	2.5[-1.0 to 8.0]	.048	31
High risk, Influenza +	8.25	5.0	3.25[-1.75 to 8.50]	.161	39

MIST Study, Lancet 1998;352:1877-1881

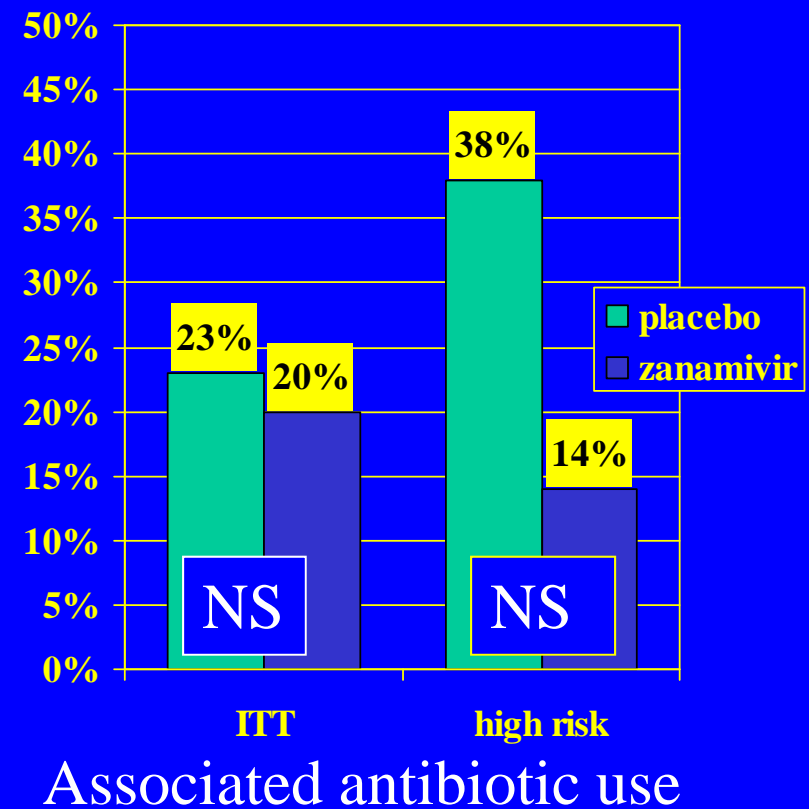
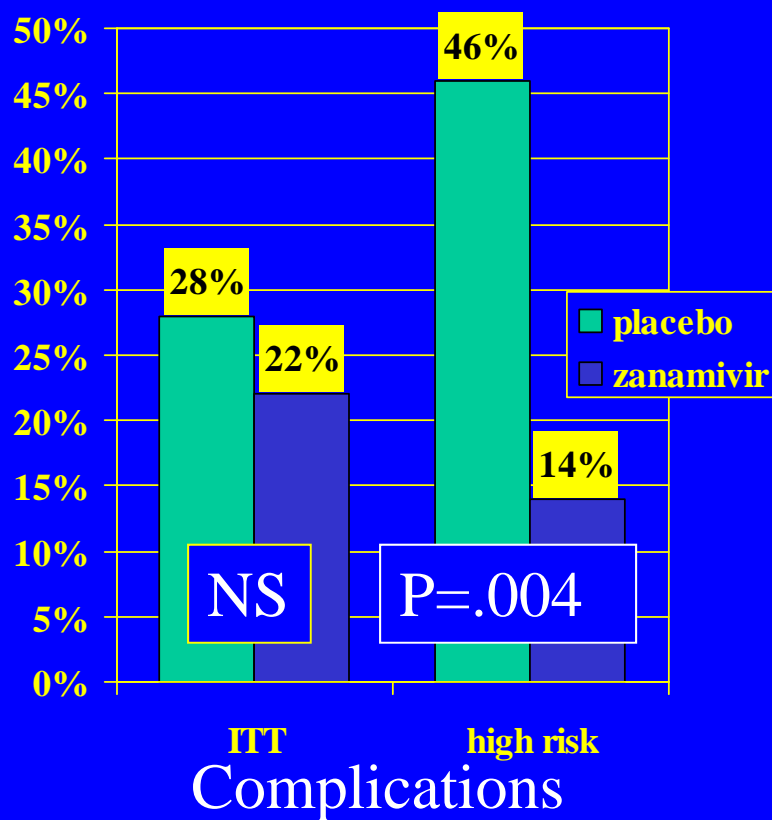
Efficacy and safety of inhaled zanamivir in treatment of influenza

	placebo	zanamivir	difference (95% CI)	p
Return to normal activities (days)				
ITT	9.0	<7.0	2.0[0 to 4.0]	<.001
Influenza +	9.0	<7.0	2.0[0.25 to 4.0]	<.001
Sleep disturbances (days of 13)				
ITT	3.0	3.0	0[-1.0 to 1.0]	.088
Influenza +	3.0	2.0	1.0[0 to 1.5]	.047
# paracetamol tablets (days 1-4)				
ITT	12	14	-2[-6 to 0]	.291
Influenza +	13	14	-1[-5 to 2]	.854
# cough mixture spoonfuls (days 1-14)				
ITT	9	7.0	2[-3 to 5]	.738
Influenza +	12	7.0	5[-1 to 9]	.045

MIST Study, Lancet 1998;352:1877-1881

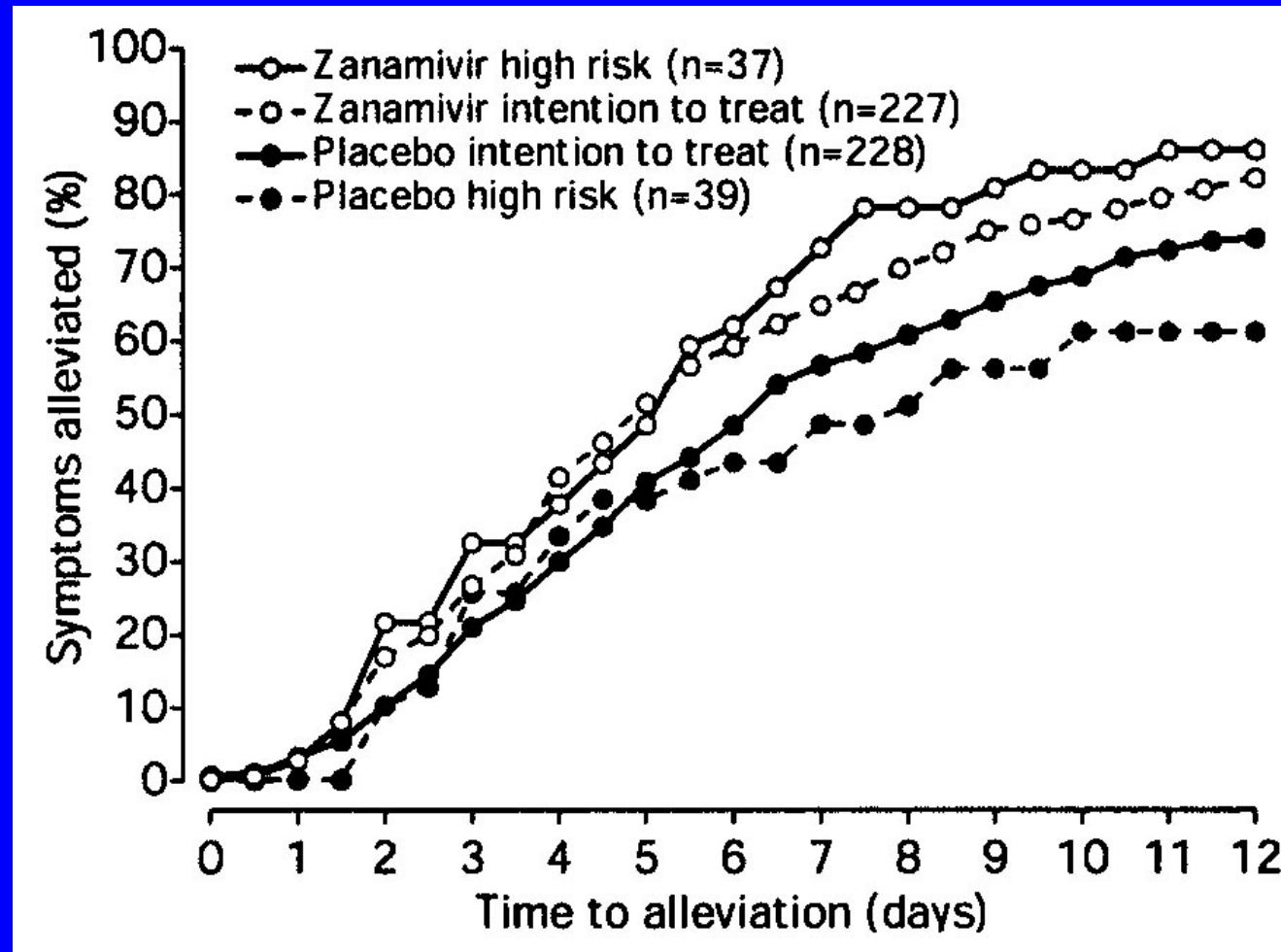
Efficacy and safety of inhaled zanamivir in treatment of influenza

complications and associated antibiotic use in ITT and high risk patients



MIST Study, Lancet 1998;352:1877-1881

Cumulative percentage alleviation of clinically significant symptoms ITT and high risk population



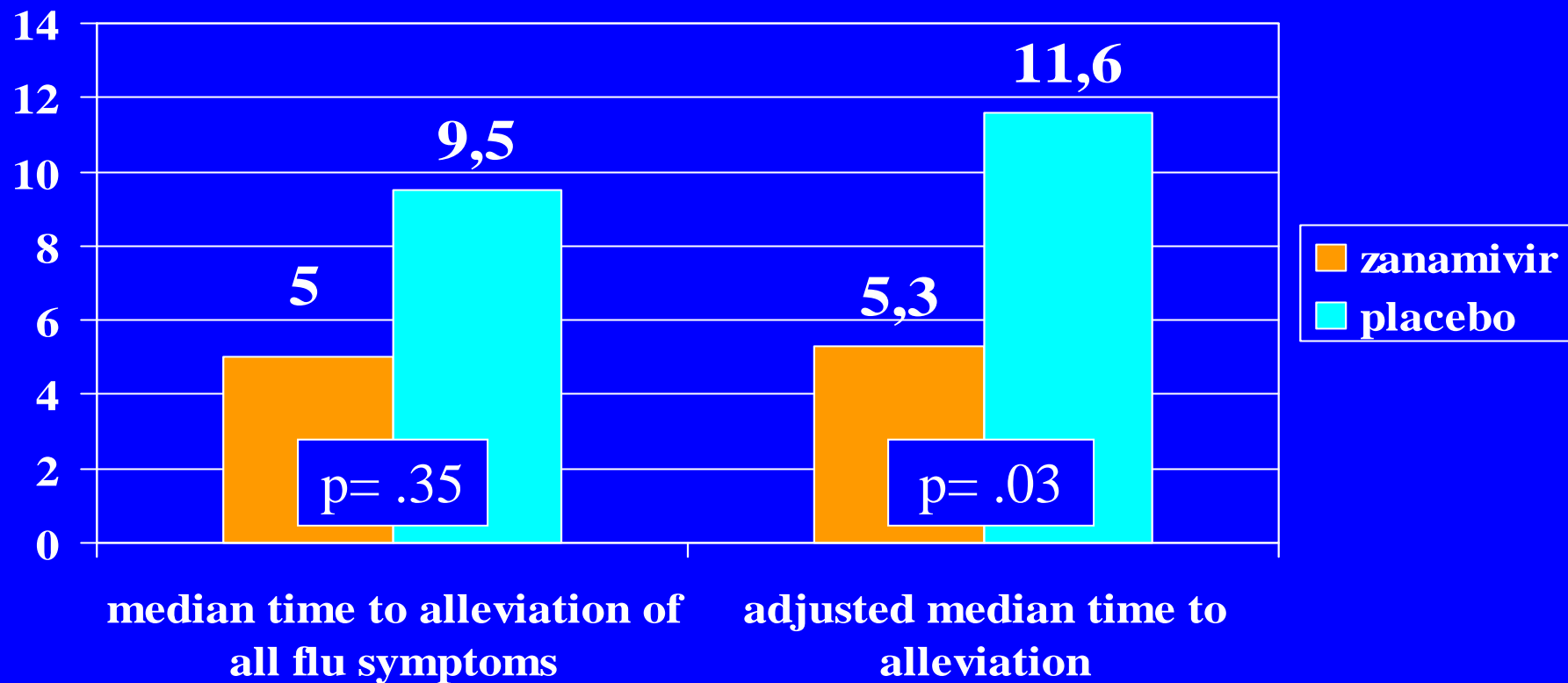
MIST Study, Lancet 1998;352:1877-1881

Zanamivir in the treatment of naturally occurring influenza in otherwise healthy adults

- 35 pts enrolled
- 27 (77%) : laboratory confirmed infection (culture and PCR), Influenza virus H3
- 10 (37%) : placebo
- 17 (63%) : zanamivir

Zanamivir in the treatment of naturally occurring influenza in otherwise healthy adults

Clinical efficacy of zanamivir (35 pts enrolled)



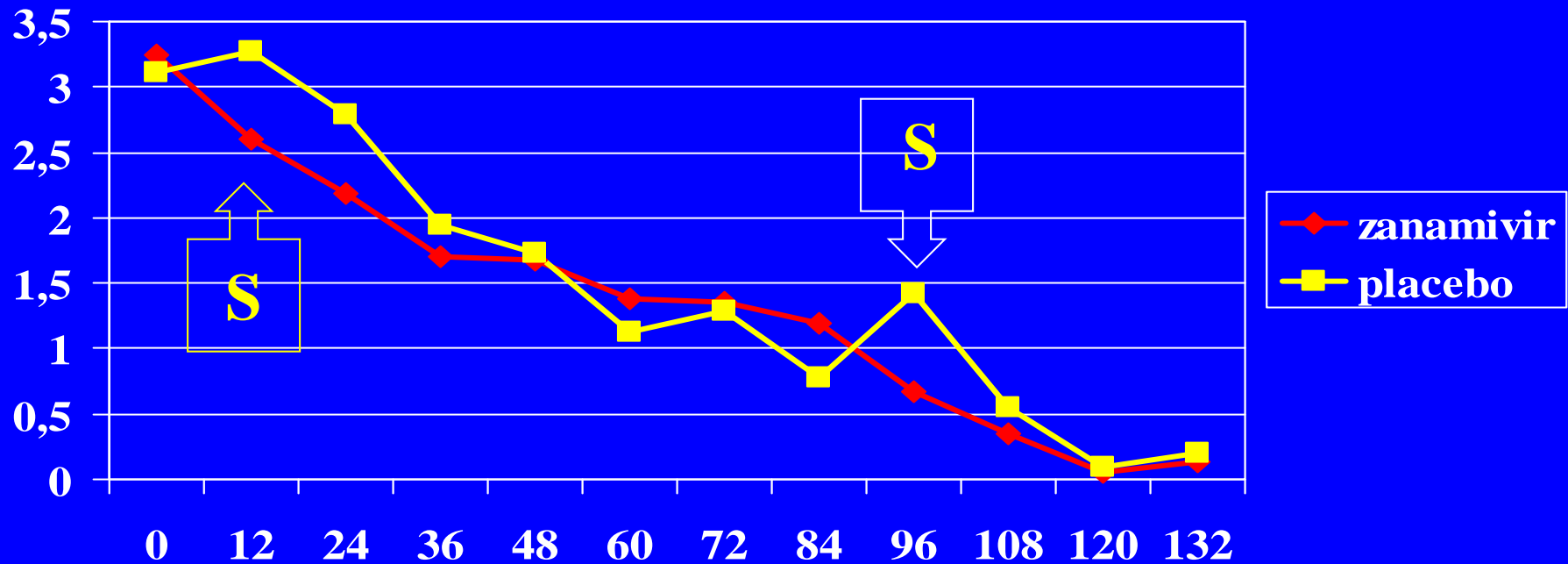
Boivin J Infect Dis 2000;181:1471-4

Zanamivir in the treatment of naturally occurring influenza in otherwise healthy adults

- Mean influenza virus titers in zanamivir and placebo recipients by time
- Zanamivir group : trend towards
 - Lower viral load, but significant difference only at 96h
 - Lower mean AUC of virus titers
- Zanamivir reduced the median time to the last positive culture by 18h, positive PCR by 12h
- Zanamivir exhibited no evidence of resistance by use of either phenotypic or genotypic assay

Zanamivir in the treatment of naturally occurring influenza in otherwise healthy adults

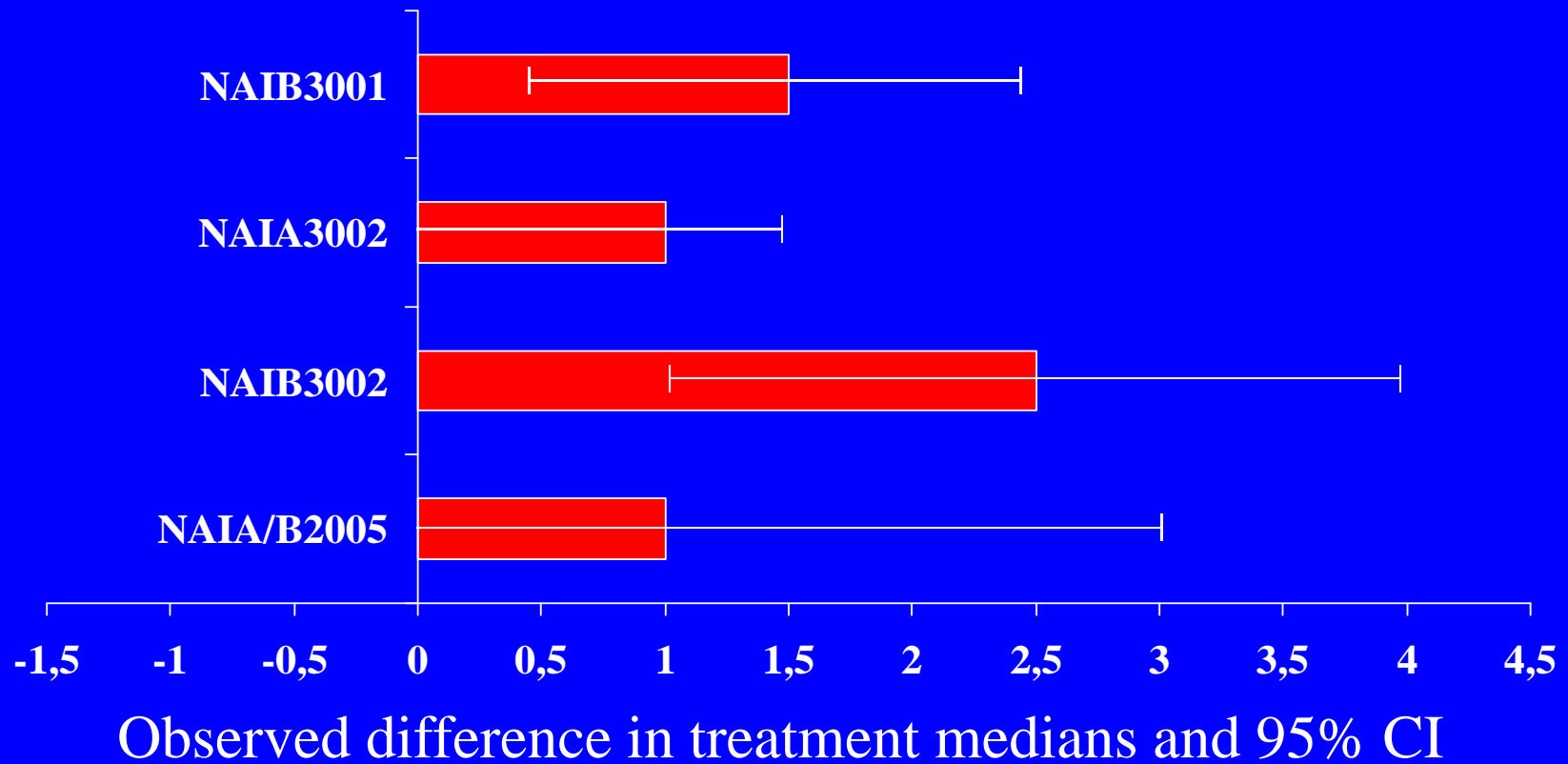
Antiviral effect of zanamivir (35 pts enrolled)
mean influenza virus titers



Zanamivir in the treatment of influenza A and B : pooled efficacy analysis

- 4 phase II studies : NAIA2005, NAIB2005, NAIB2007, ANAI/B2008
- 3 phase III studies : NAIB3001, NAIA3002, ANIB3002
- Randomized, double-blind, placebo-controlled, parallel-group design
- Zanamivir 10 mg inhaled bid *vs* placebo, 5 days

Difference in days to alleviation of influenza symptoms : IP population

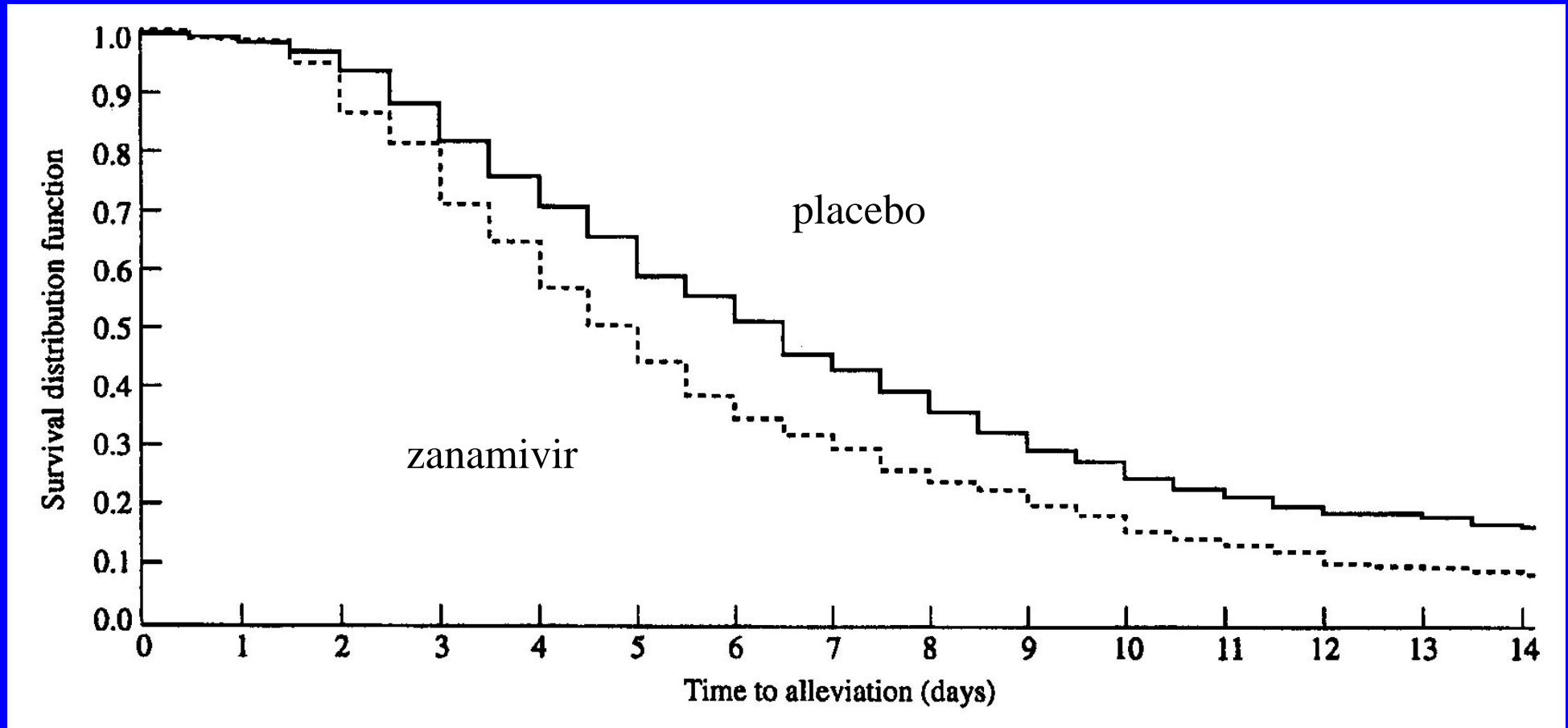


Monto AS JAC 1999;44:23-29

Zanamivir in the treatment of influenza A and B : pooled efficacy analysis

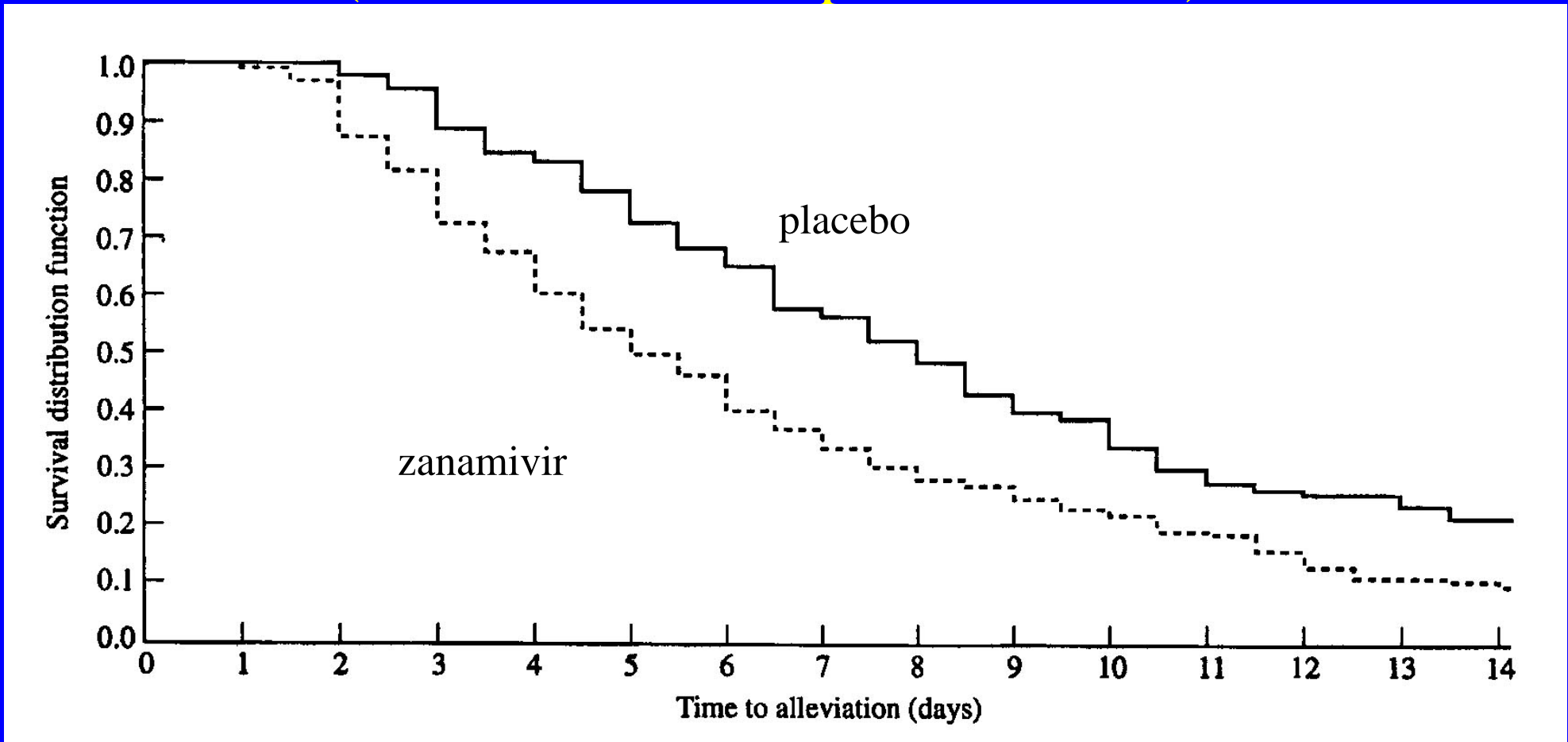
	placebo	zanamivir	Δ (days)	p
ITT	6.0 (1102)	5.0 (1133)	1.0	<.001
Influenza + Febrile	6.0 (765)	5.0 (807)	1.0	<.001
Not severe	6.5 (595)	5.0 (630)	1.5	<.001
Severe	5.5 (543)	4.5 (555)	1.0	<.001
< 50y	8.0 (222)	5.0 (252)	3.0	<.001
>50y	6.0 (619)	5.0 (690)	1.0	<.001
High-risk	8.0 (106)	5.5 (89)	2.5	.114

Time to alleviation of clinically significant symptoms : febrile IP population (zanamivir : 630, placebo : 595)



Monto AS JAC 1999;44:23-29

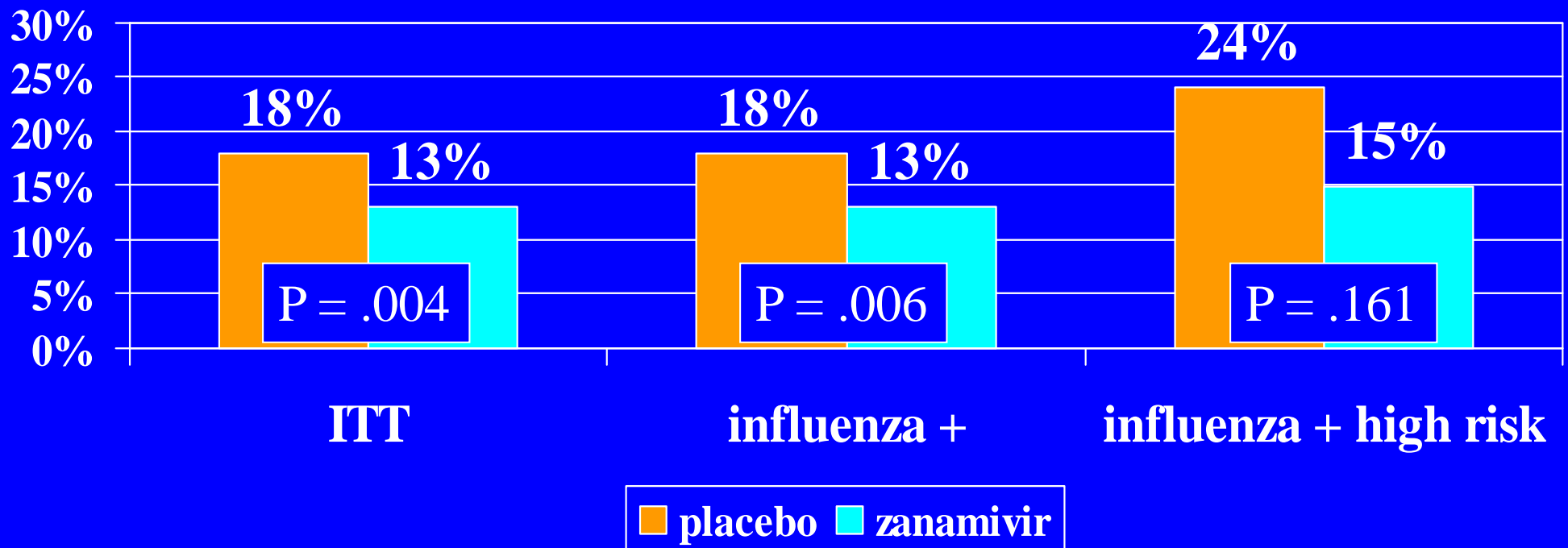
Time to alleviation of clinically significant symptoms
patients with severe disease at baseline
(zanamivir : 252, placebo : 222)



Monto AS JAC 1999;44:23-29

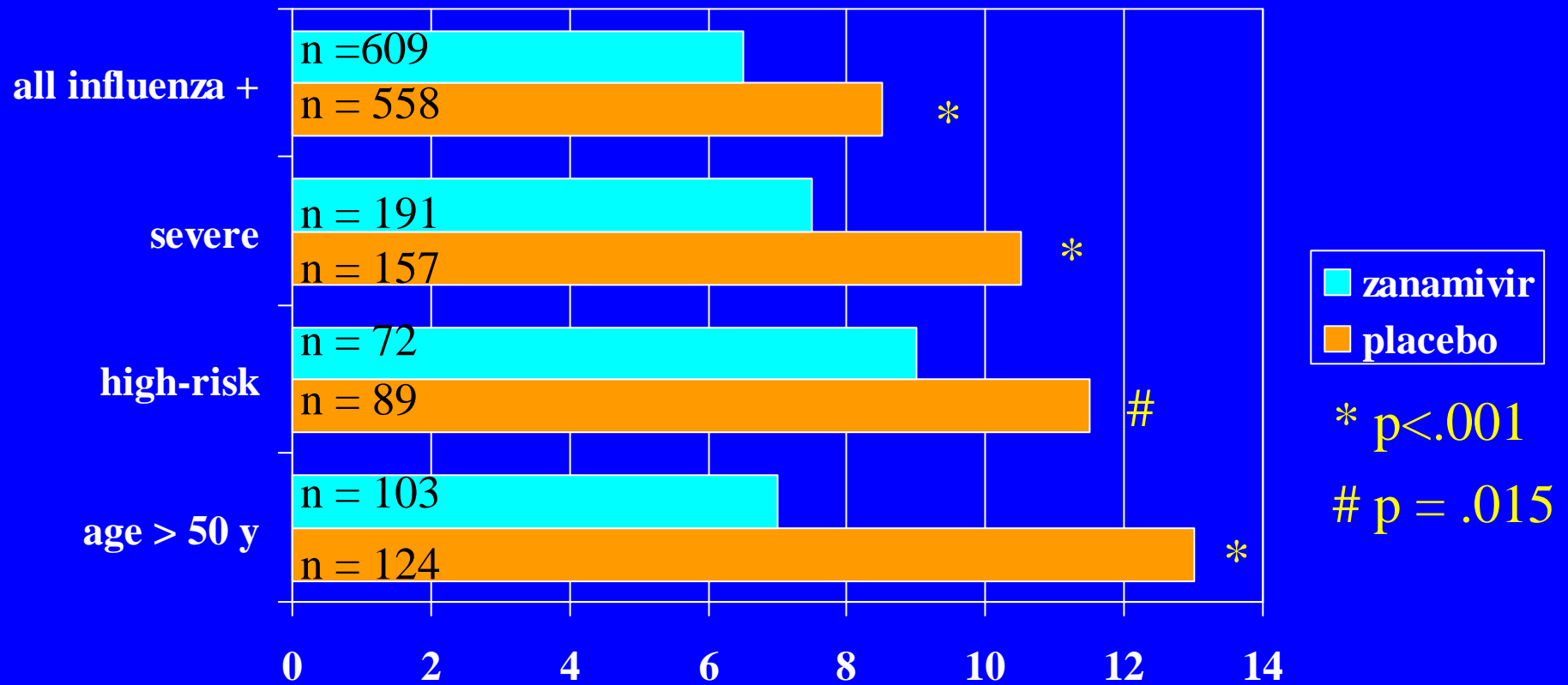
Zanamivir in the treatment of influenza A and B : pooled efficacy analysis

use of antibiotic for complications in placebo and zanamivir patients



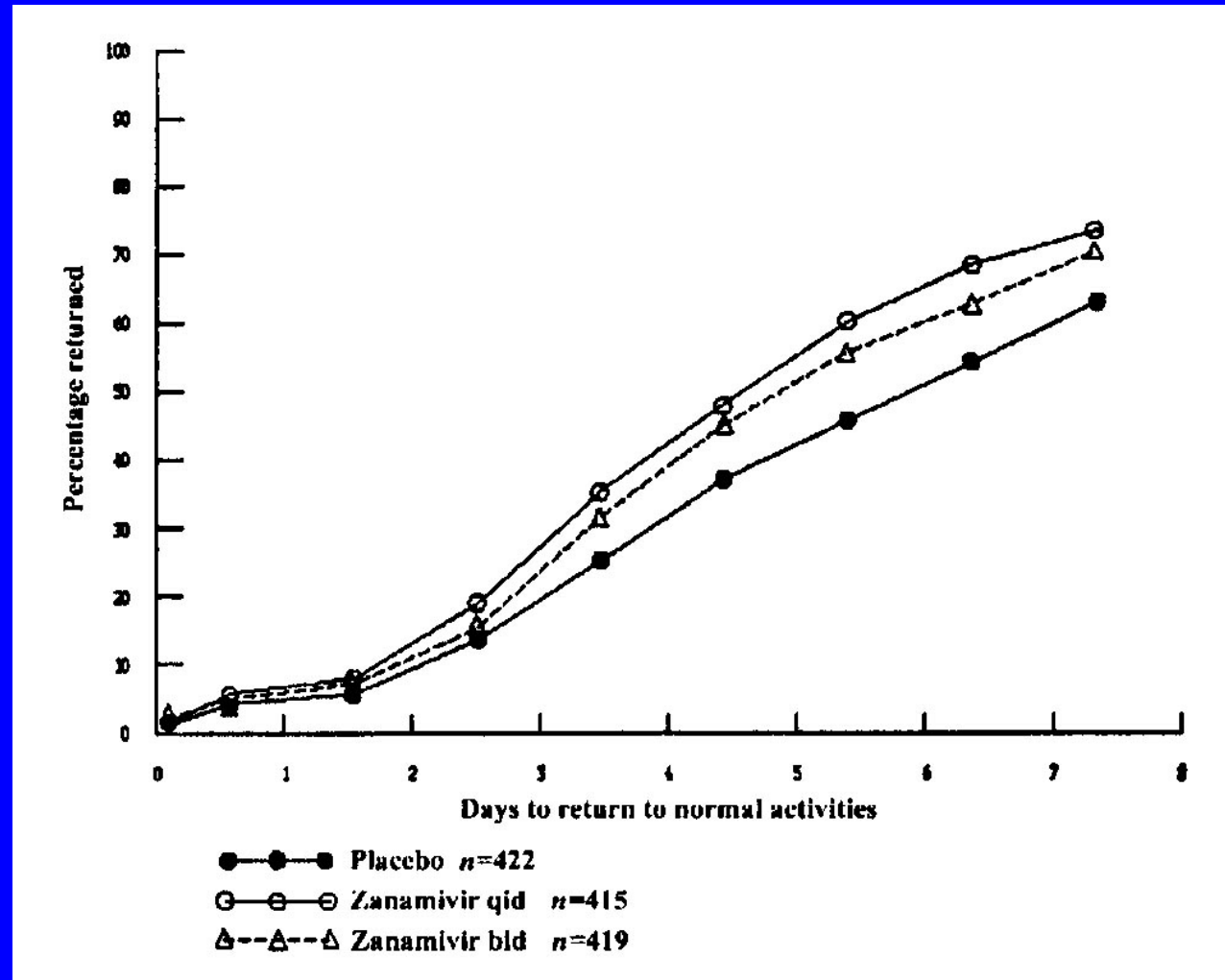
Effect of zanamivir on influenza symptoms

time to alleviation of clinically significant symptoms



Monto AS Clinical Therapeutics 2000;22:1294-1305

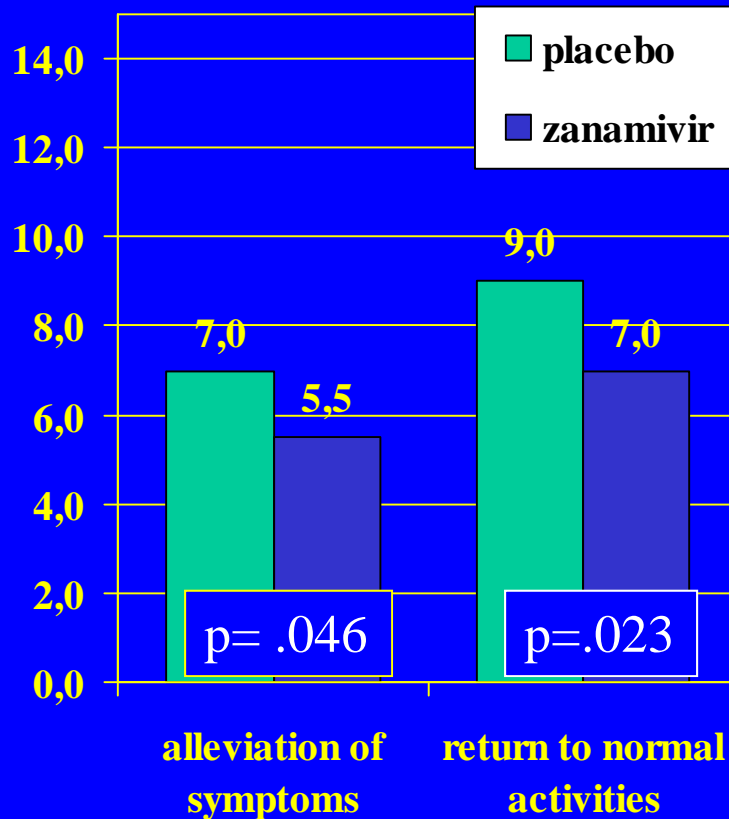
Zanamivir in the treatment of influenza : time to return to normal activities



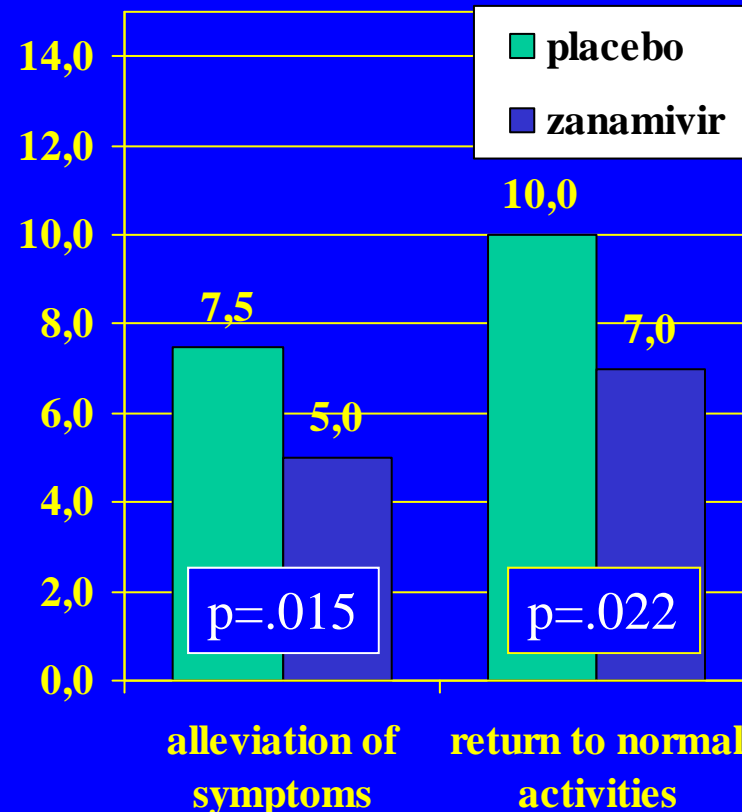
Zanamivir for the treatment of influenza A and B in high-risk patients

- Retrospective pooled analysis of studies 1998-99
- High-risk pts with influenza-like illness :
 - chronic respiratory disease,
 - cardiovascular disease,
 - elderly (≥ 65 y)
- Zanamivir 10 mg bid
- 312/2751 (12%) considered as high-risk and 154 received zanamivir

Zanamivir for the treatment of influenza A and B in high-risk patients

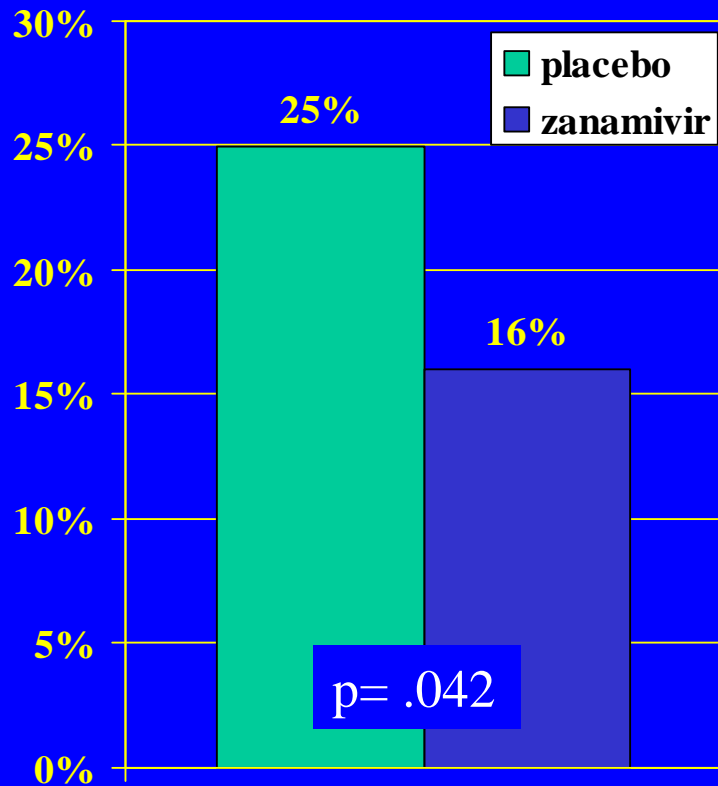


ITT

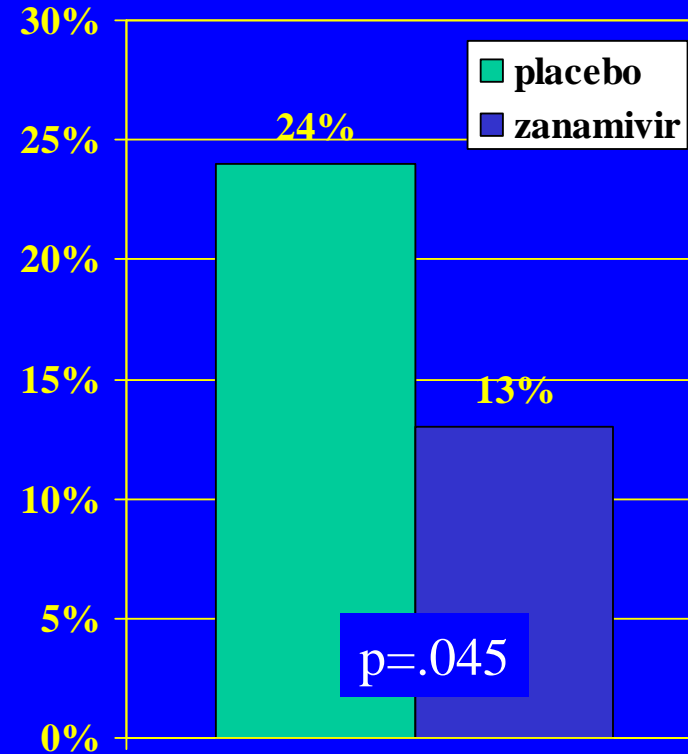


Influenza positive population

Incidence of complications requiring antibiotics in high-risk patients

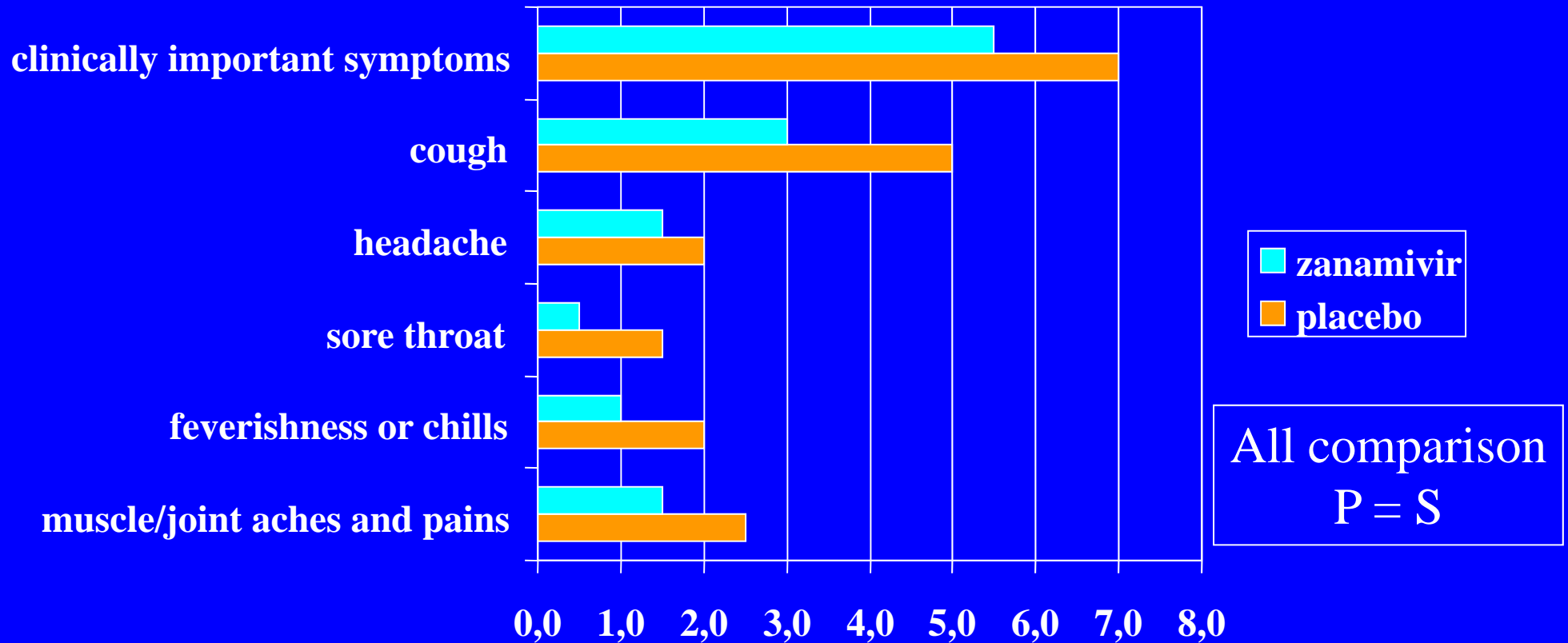


ITT



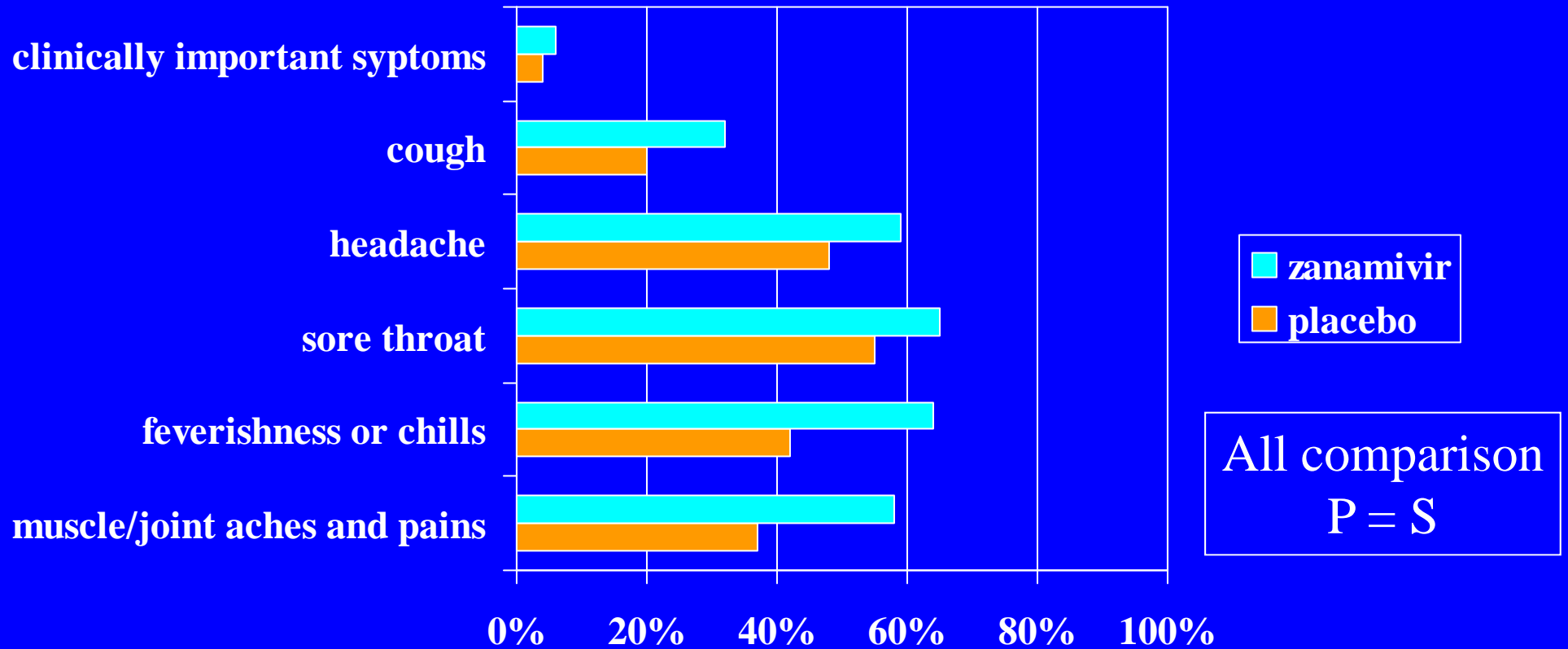
Influenza positive population

Patients with asthma or COPD : Median number of days to alleviation (influenza positive population)



Murphy KR Clin Drug Invest 2000;20:337-349

Patients with asthma or COPD : patients (%) alleviated within 36 hours (influenza positive population)

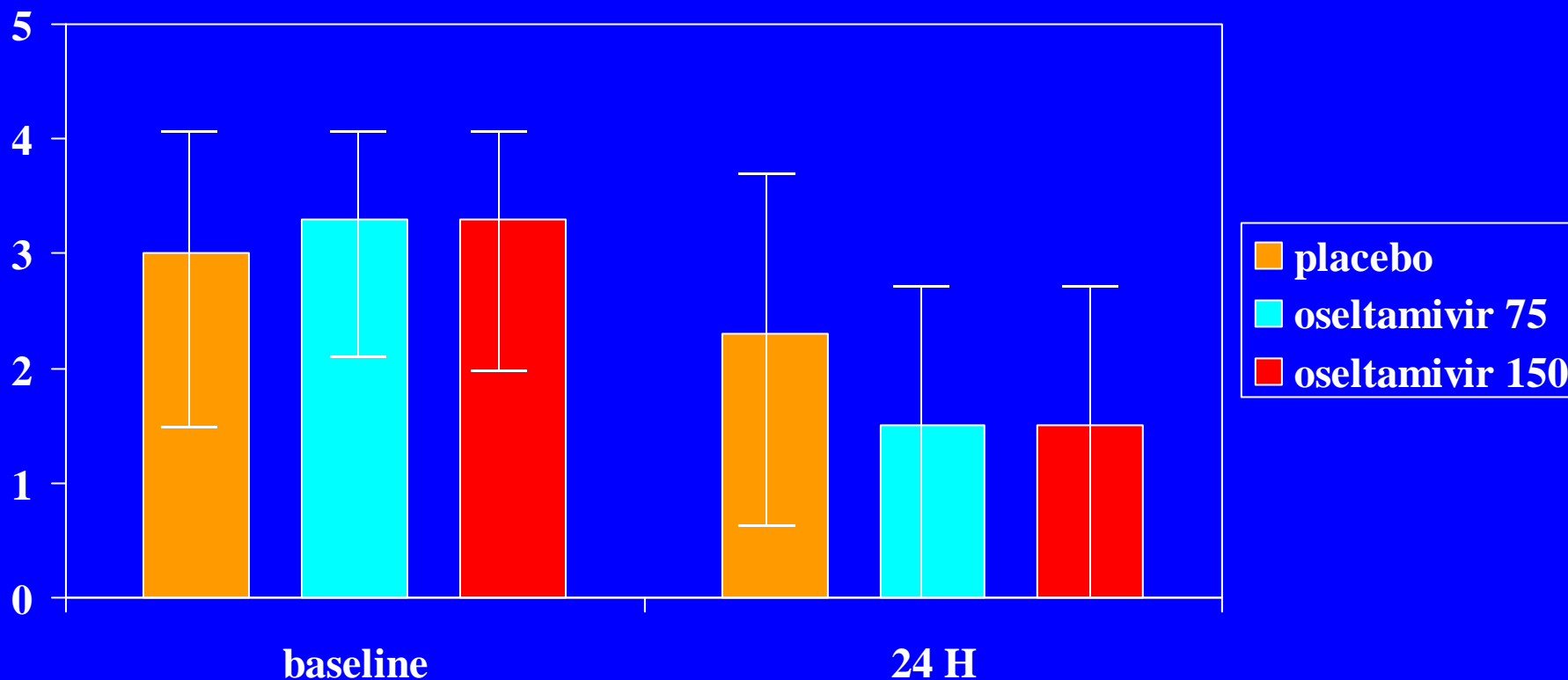


Summary zanamivir

- Zanamivir can reduce duration of influenza by 1 to 1,5 days in healthy adults
- Zanamivir can reduce duration of illness of influenza in high-risk patients
- Zanamivir may reduce complications and antibiotic use, but statistical significance is not obtained for all studies

Oseltamivir Tamiflu®

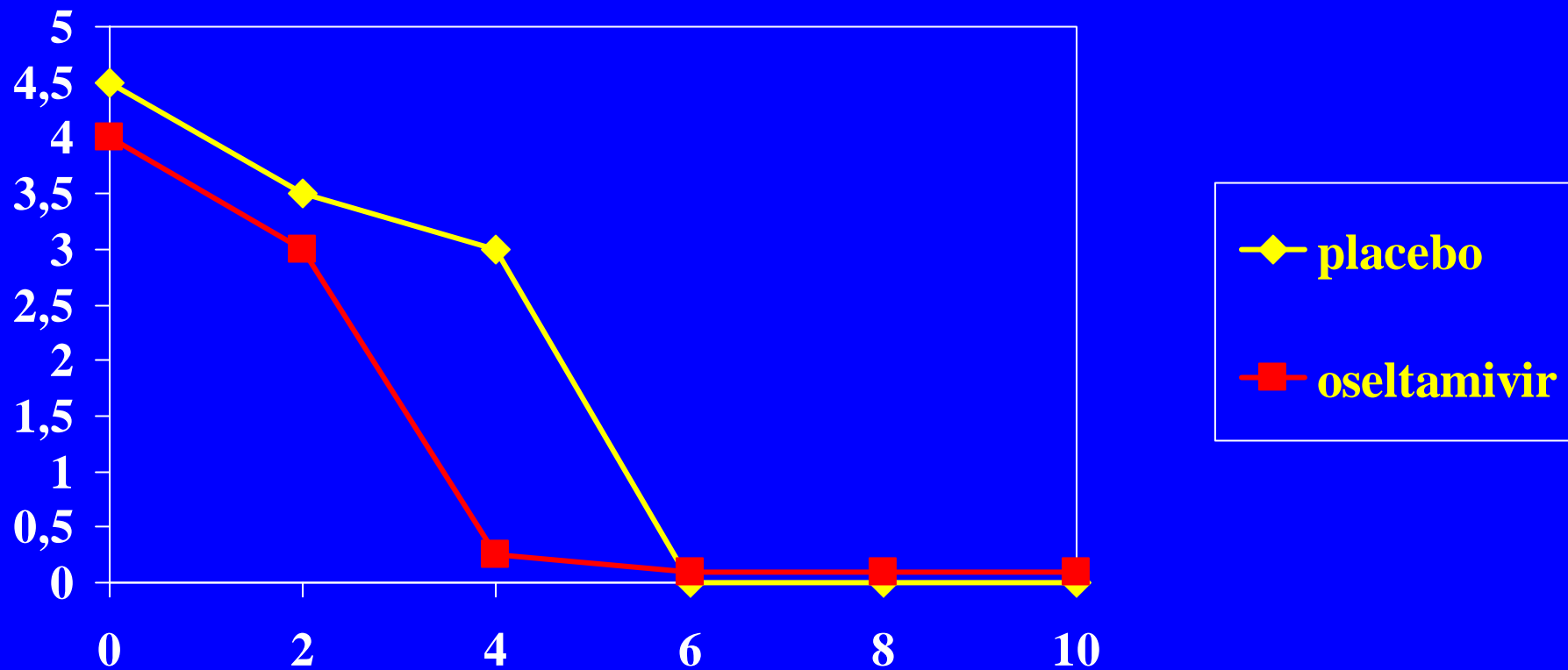
Efficacy of oseltamivir in treating acute influenza median virus titer (log₁₀ TCID₅₀/mL)



Os 75 mg *vs* placebo, $p = .0004$, Os 150mg *vs* placebo, $p=.0003$

Nicholson Lancet 2000;355:1845-50

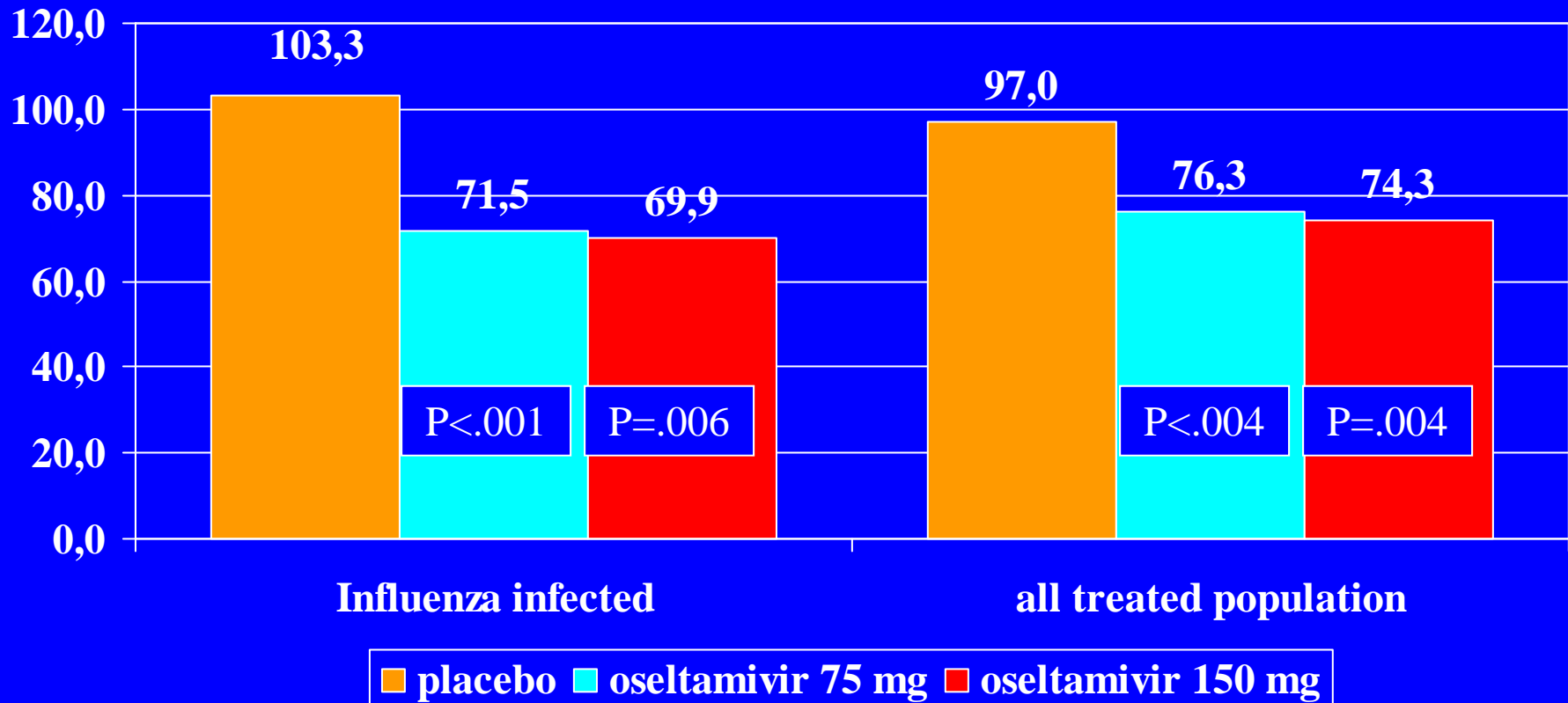
Oseltamivir treatment of influenza in children median viral titers over time (ITT infected population)



Withley R, Pediatr Infect Dis J 200;20:127-33

Efficacy of oseltamivir in treating acute influenza : median duration of illness (hours)

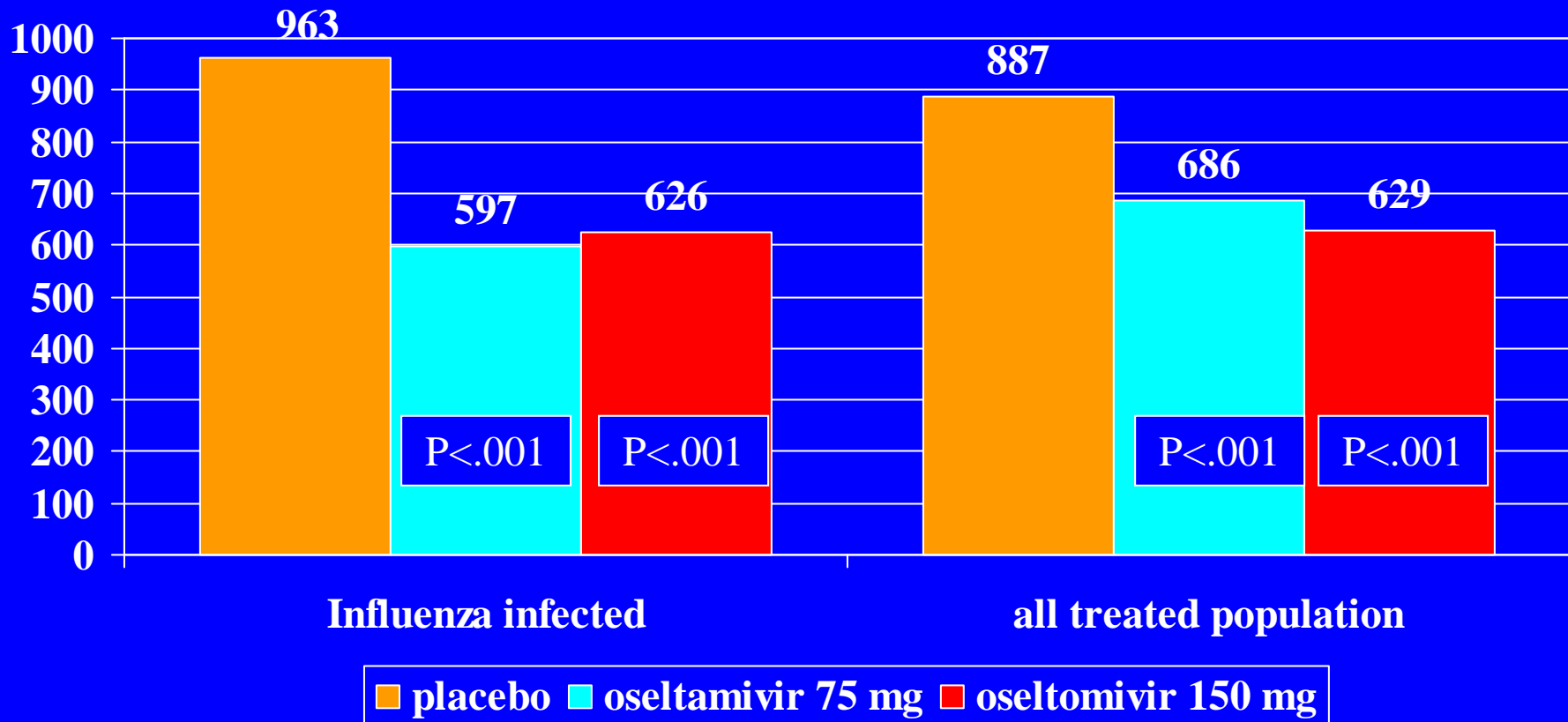
Overall, oseltamivir treatment reduced the median duration of illness by over 30% ($P=0.006$).



Treanor JJ JAMA 2000;283:1016-1024

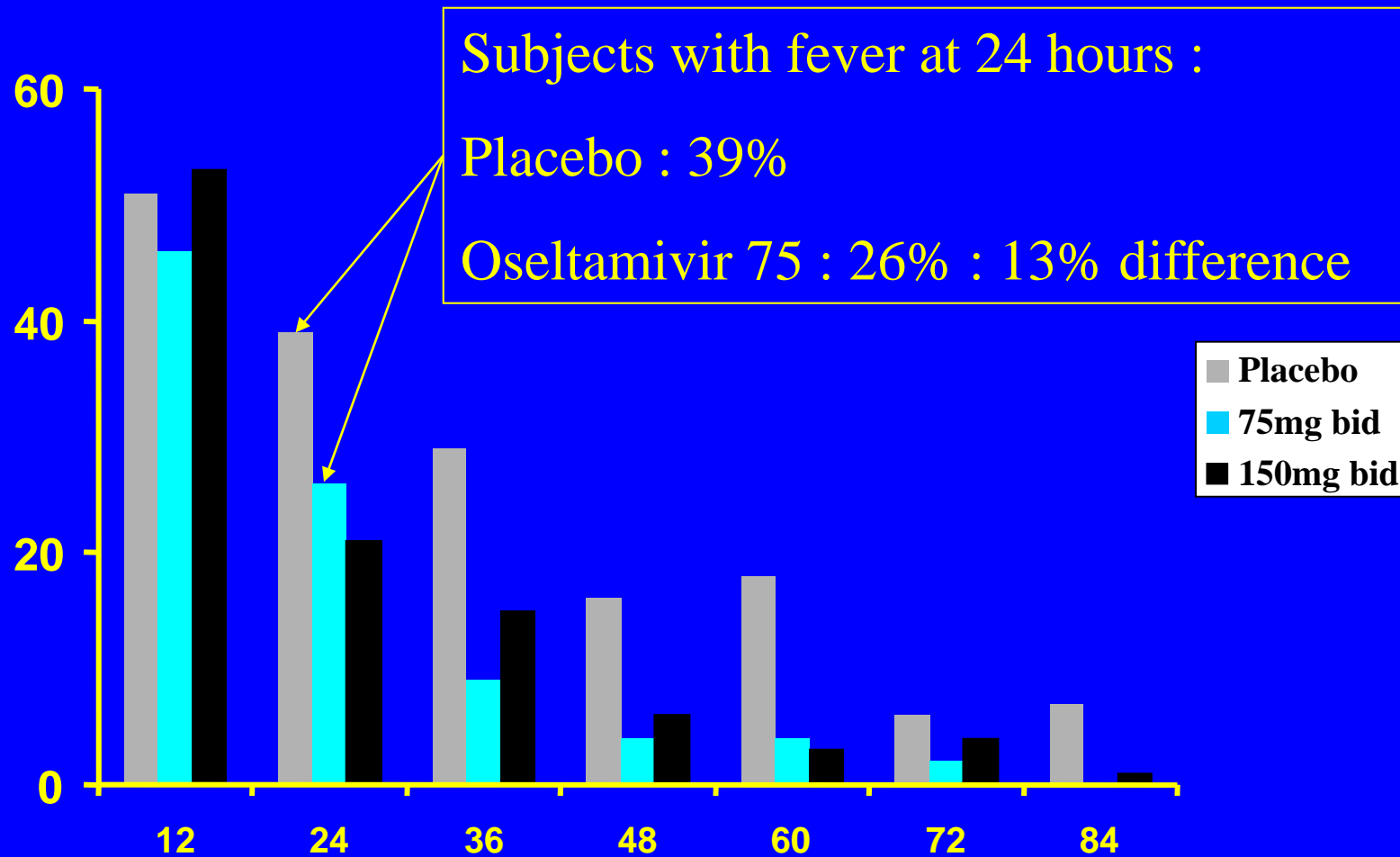
Efficacy of oseltamivir in treating acute influenza : median score of severity

38% reduction in median symptom score AUC (n=129; $P<0.001$).



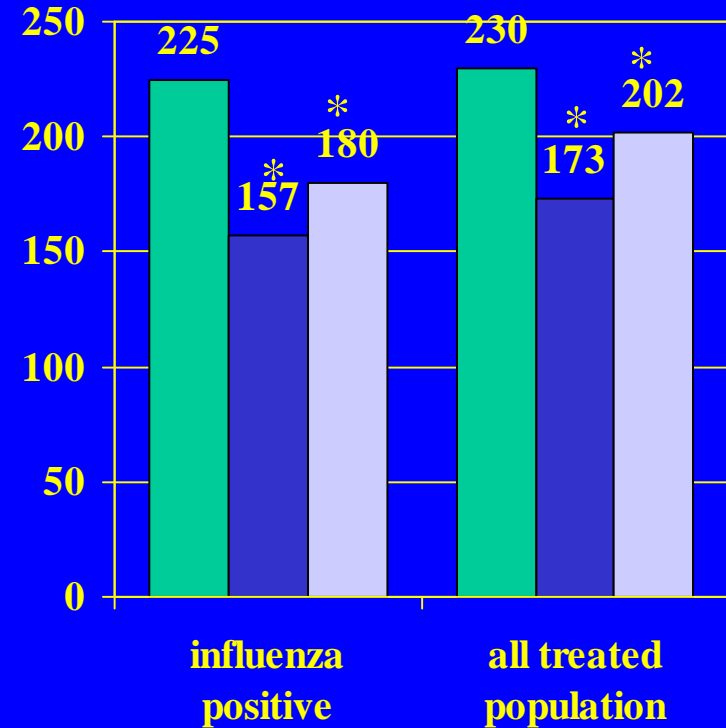
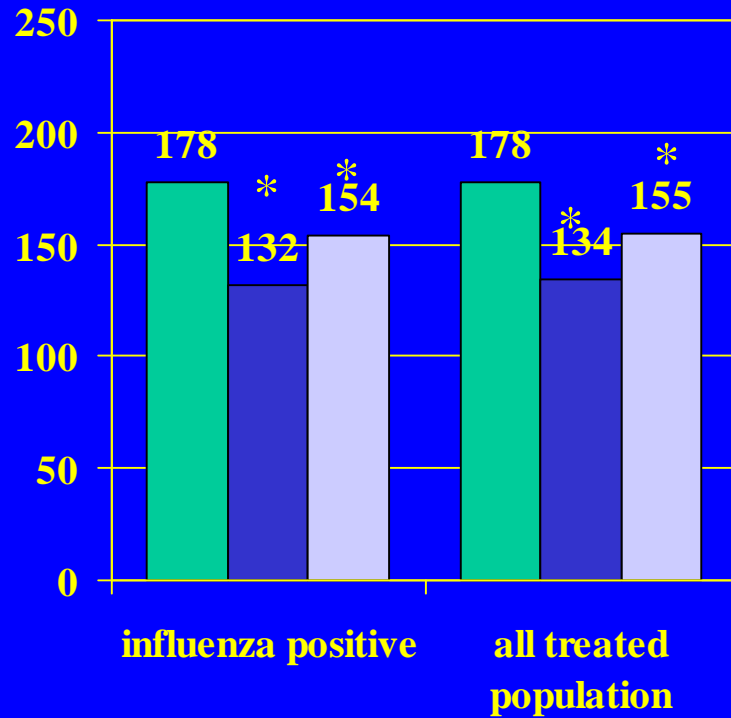
Treanor JJ JAMA 2000;283:1016-1024

Efficacy of oseltamivir in treating acute influenza : Proportion of subjects reporting fever



Treanor JJ JAMA 2000;283:1016-1024

Efficacy of oseltamivir in treating acute influenza : return to normal health and activities



■ placebo ■ oseltamivir 75 ■ oseltamivir 150

■ placebo ■ oseltamivir 75 ■ oseltamivir 150

* vs placebo
P = S

Return to normal health

Return to normal activities

Treanor JJ JAMA 2000;283:1016-1024

Oseltamivir treatment of influenza in children. clinical outcome in the ITT population

	placebo	oseltamivir	p	Δ h
Median duration of illness	137	101	<.0001	36 (26)
≤ 2yr	161	139		23 (14)
2-≤5yr	137	99		38 (28)
> 5yr	125	90		35 (28)
Median duration of individuals CARIFS* symptoms (h)				
Fever	68	44	<.0001	25 (36)
Cough	71	39	=.0008	32 (45)
Coryza	66	43	=.0008	23 (34)

*CARIFS : Canadian Acute Respiratory Infection and Flu Scale

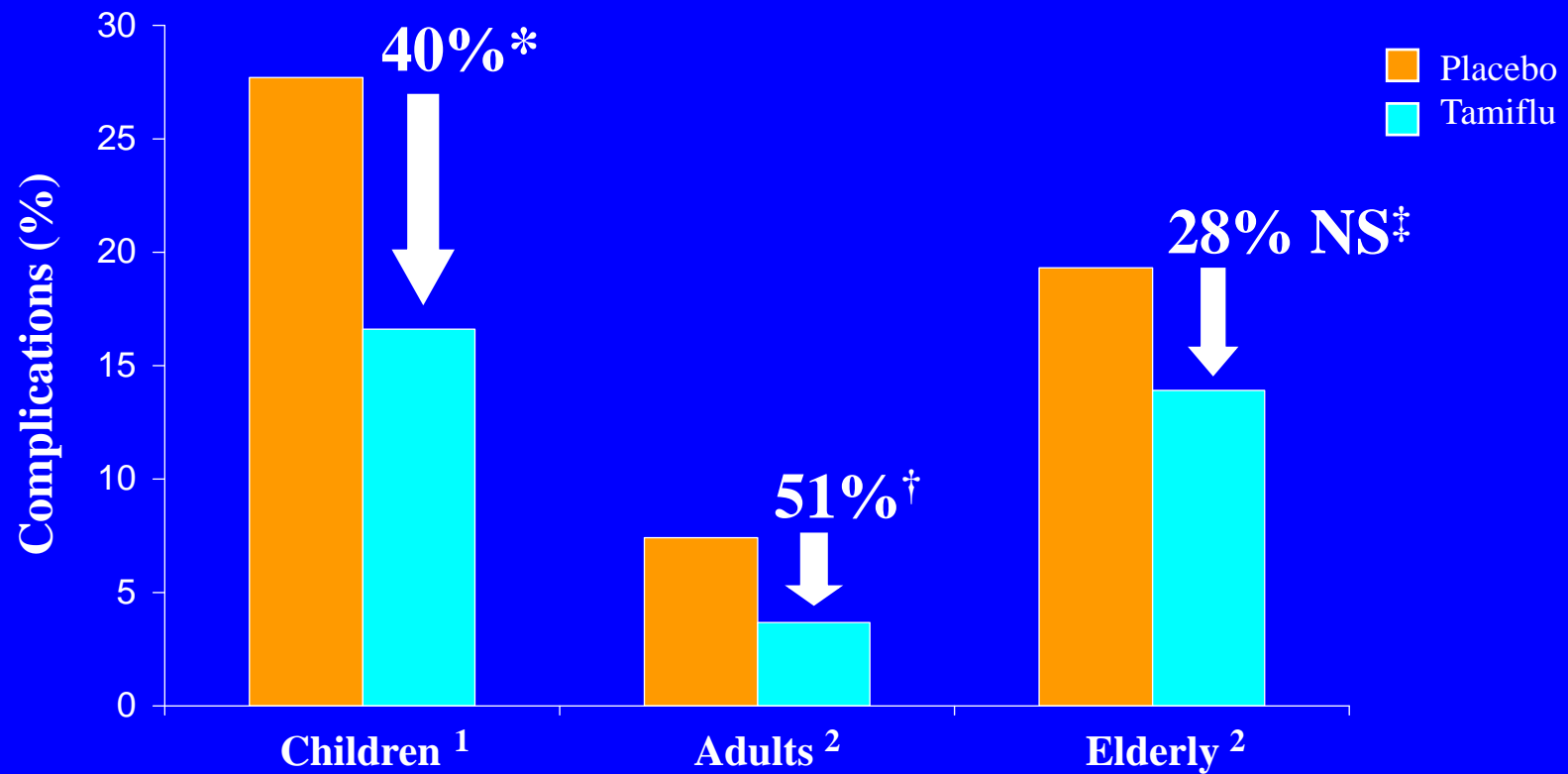
Withley R, Pediatr Infect Dis J 2001;20:127-33

Oseltamivir treatment of influenza in children. clinical outcome in the ITT population

	placebo	oseltamivir	p	Δ h
CARIFS symptoms median duration (h)	100	63	<.0001	36 (36)
Median AUC symptom scores, score.h	1358	960	<.0001	
Median AUC virus titer Log10 TCID50.h/mL	303	243	= .04	

Withley R, Pediatr Infect Dis J 200;20:127-33

Oseltamivir reduces secondary complications in all age groups



* $P = 0.005$

† $P = 0.05$

‡ $P = 0.14$

1. Whitley RJ, et al. *Pediatr Infect Dis J.* 2001;20:127-133; 2. Wood M, et al. Presentation at World Organization for Family Doctors. Durban, South Africa, 2001.

Efficacy of oseltamivir in treating acute influenza : complications and antibiotic use among influenza-infected patients

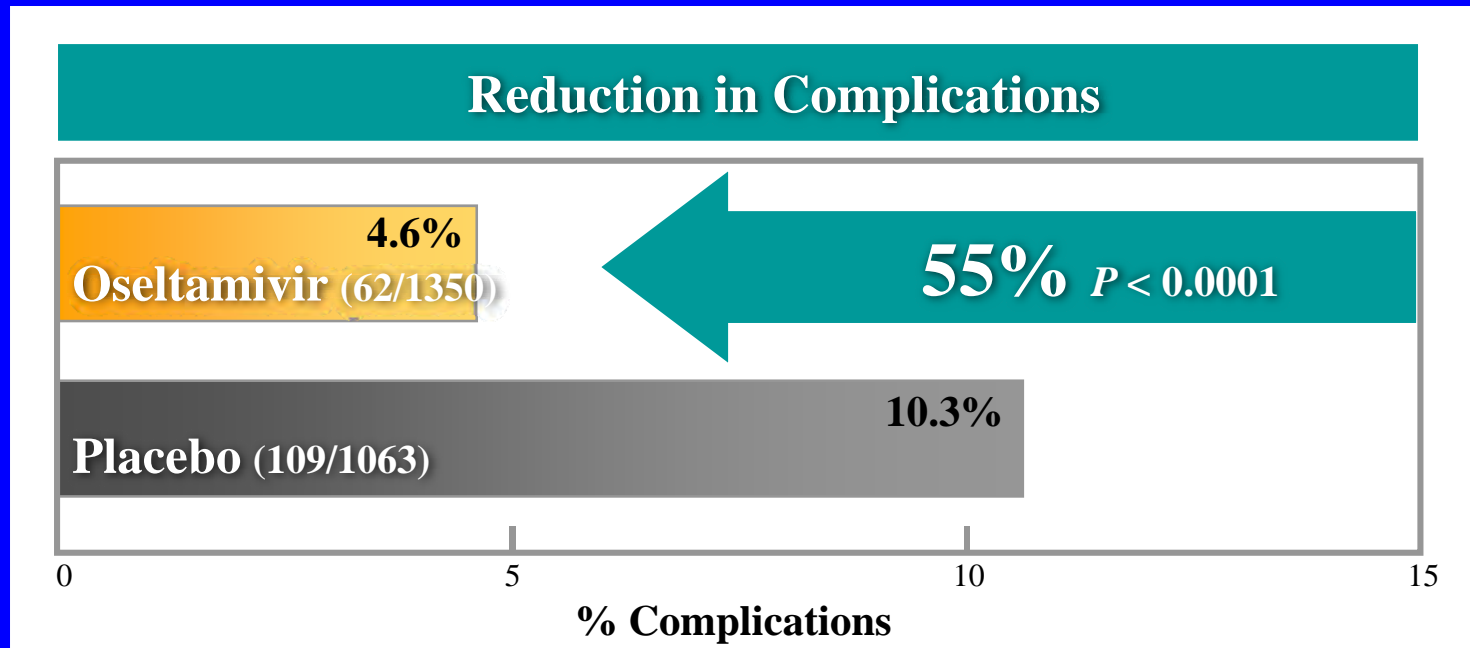
	placebo n=129	oseltamivir, 75 n=124	oseltamivir, 150 n=121
Otitis media	1	0	0
Sinusitis	11	6	4
Bronchitis	8	5	2
Pneumonia	1	0	0
Any complication (%)	19 (15)	11 (9)*	6 (5)*
Antibiotic use (%)	14 (11)	8 (6)‡	4 (3)‡

* Combined oseltamivir results *versus* placebo, p = .03

‡ Combined oseltamivir results *versus* placebo, p = .05

Oseltamivir treatment studies: secondary complications

Significant reduction in secondary complications

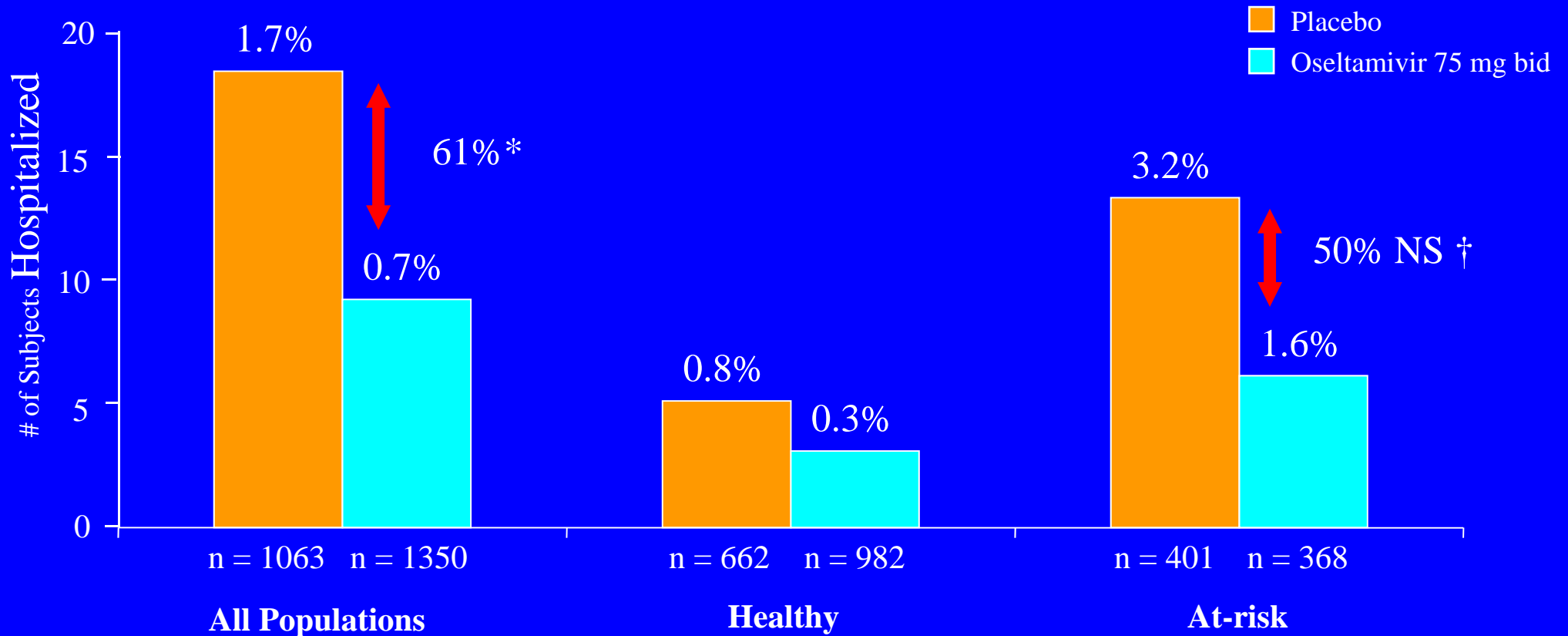


- Incidence of secondary complications cut by over half
- Influenza complications include bronchitis, otitis media, and pneumonia

Data on file. F. Hoffmann-La Roche Ltd. Basel, Switzerland.

Influenza-related hospitalizations

Confirmed Influenza Illness



* $P = 0.019$.

† $P = 0.169$.

Data on file. F. Hoffmann-La Roche Ltd. Basel, Switzerland.

Secondary complications – pooled studies

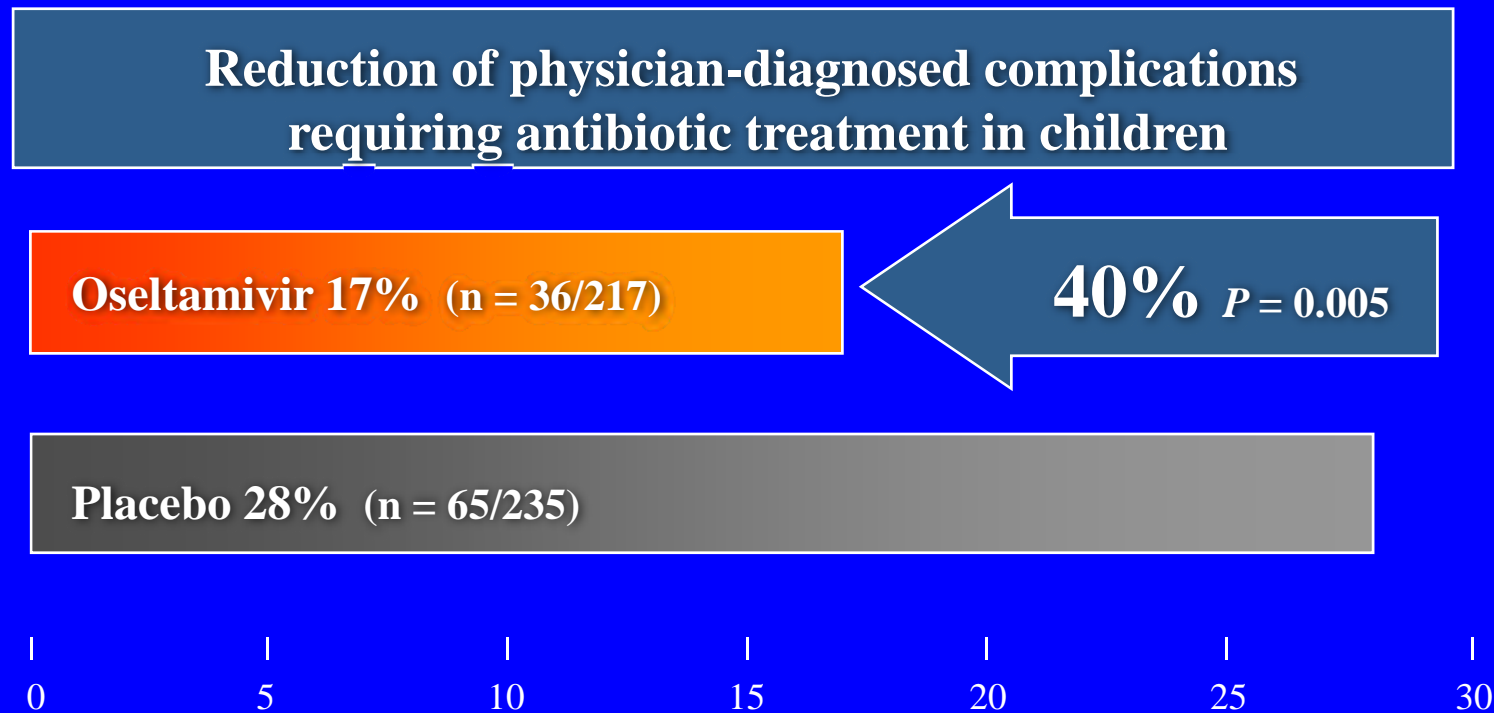
Summary of Specified Secondary Illnesses With Associated Antibiotics (ITT-Infected Population)

Specified Secondary Illness*	Placebo		Tamiflu™ (oseltamivir)
	(N = 1063)		75 mg bid (N = 1350)
Bronchitis	87 (8%)		53 (4%)
Lower respiratory tract infection	4 (0%)		1 (0%)
Otitis media	5 (0%)		12 (1%)
Pneumonia	19 (2%)		9 (1%)
Sinusitis	27 (3%)	P value 95%	49 (4%)
Any specified secondary illness*	135 (13%)	0.0012	116 (9%)

*Secondary illness preferred term of bronchitis, lower respiratory tract infection, otitis media, pneumonia, or sinusitis commencing on or after study day 3 or at least 48 hours after first study drug intake.

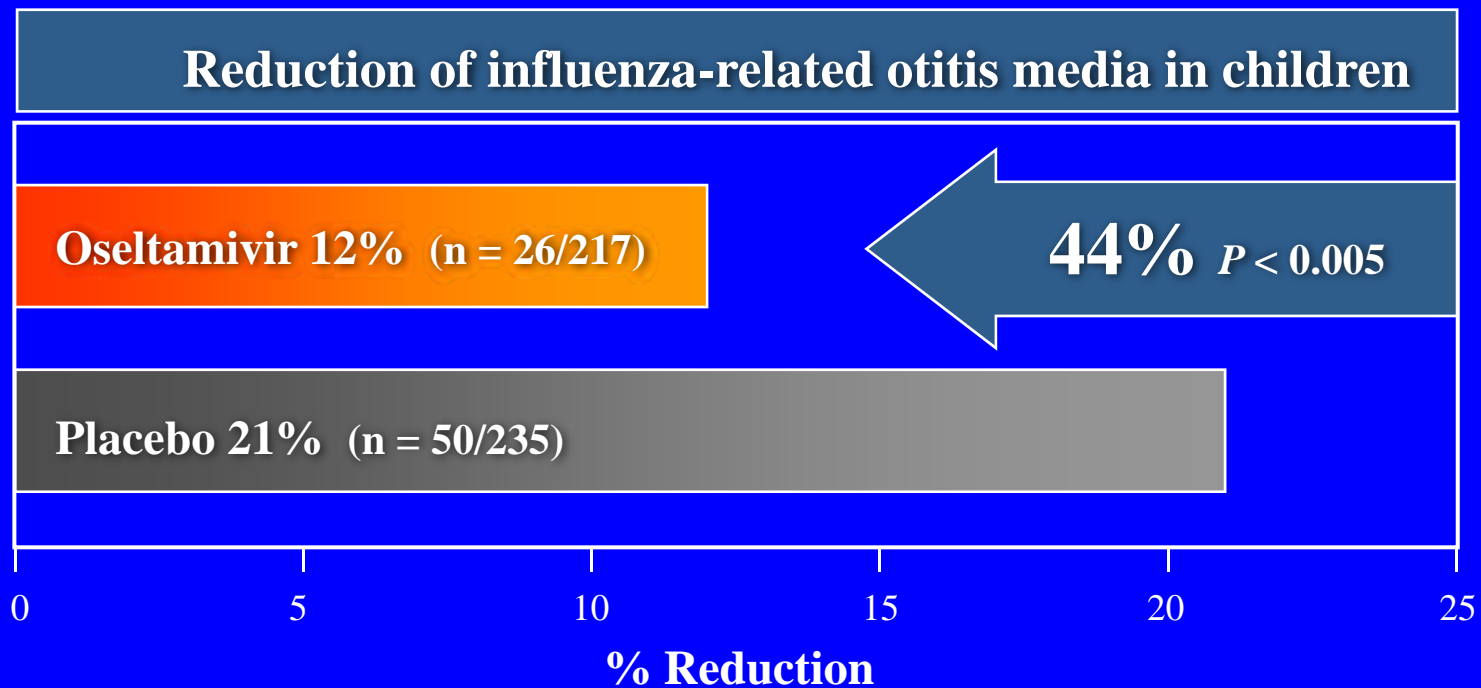
Percentages use number of subjects (per treatment) in ITT-infected population as denominator. Subjects may record more than one of the specified secondary illnesses.

Oseltamivir significantly reduced incidence of influenza-related complications requiring antibiotics in children



Oseltamivir significantly reduced risk of otitis media

- Oseltamivir significantly reduced risk of developing otitis media in children



Oseltamivir significantly reduced risk of otitis media

- Otitis media (OM) most common secondary complication in both study groups
- 44% reduced risk of OM with oseltamivir (12%, 26/217) vs placebo (21%, 50/235)
- 50% risk reduction in tympanometrically confirmed OM in oseltamivir group, 9.3% (17/183) vs 18.5% (37/200) in placebo group
- Associated with significantly less antibiotic usage in oseltamivir subjects than in placebo subjects

Clinical efficacy : Prevention of
influenza

Effectiveness of oseltamivir in preventing influenza in household contacts

- Two double-blind, randomized, parallel-group, placebo-controlled studies in healthy volunteers aged 18-65 yrs
- Oseltamivir 75, or 150 vs placebo over a 6 weeks period during circulating period of virus
- Primary end point : incidence of laboratory-confirmed influenza-like illness during the 6 weeks period

Hayden FG, N Engl J Med 1999;341:1336-43

Incidence of laboratory-confirmed influenza-like illness

	oseltamivir			placebo
	od	bid	combined	
N° subjects	520	520	1040	519
Laboratory-confirmed clinical influenza	6 (1.2)	7 (1.3)	13 (1.3)	25 (4.8)
Protective efficacy %	76	72	74	
P	<.001	<.001	<.001	

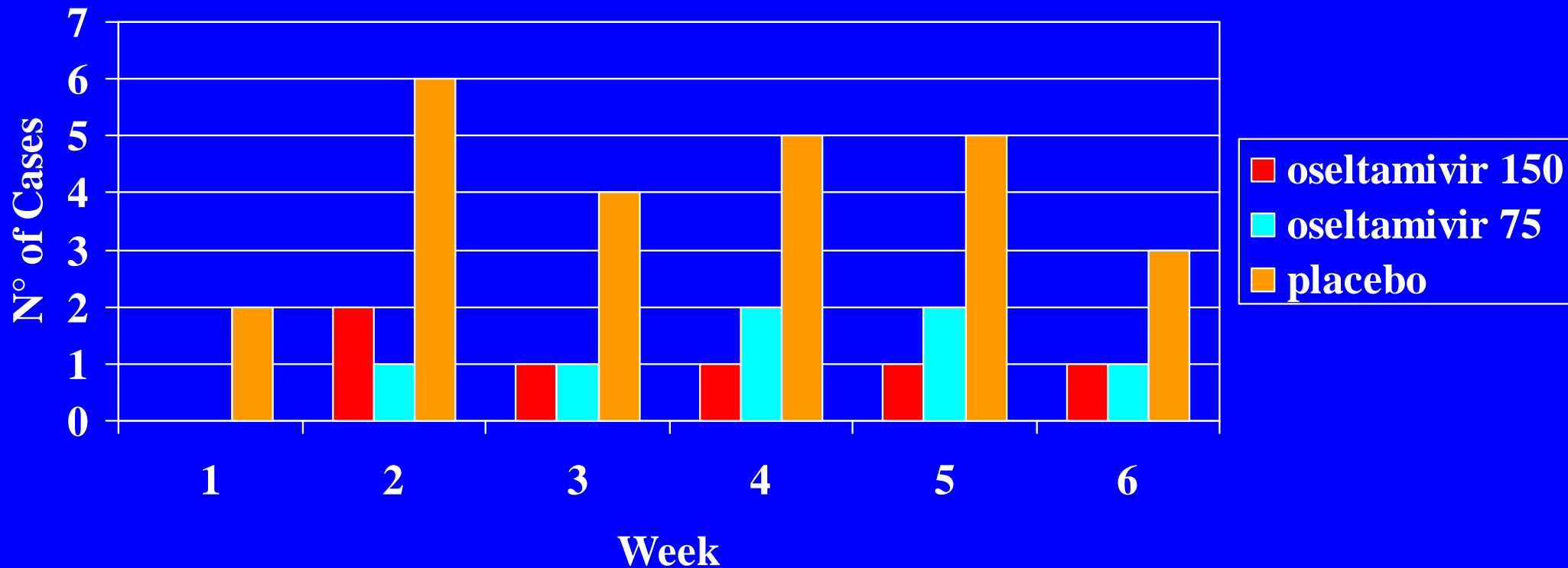
Hayden FG, N Engl J Med 1999;341:1336-43

Incidence of influenza and influenza-like illness

	oseltamivir			placebo
	od	bid	combined	
N° subjects	520	520	1040	519
Culture-proved influenza-like illness	0	4(0.8)	4(0.4)	15(2.9)
Protective efficacy %	100 %	73 %	87 %	
P	<.001	.011	<.001	
Lab-confirmed influenza, T ≥ 37.8° C	2(0.4)	5(1.0)	7(0.7)	19(3.7)
Protective efficacy	90 %	74 %	82 %	
P	<.001	.004	<.001	
Lab-confirmed infection	28(5.4)	27(5.2)	55(5.3)	55(10.6)
Protective efficacy	49 %	51 %	50 %	
P	.002	.001	<.001	

Effectiveness of oseltamivir in preventing influenza in household contacts

Incidence of laboratory-confirmed influenza-like illness



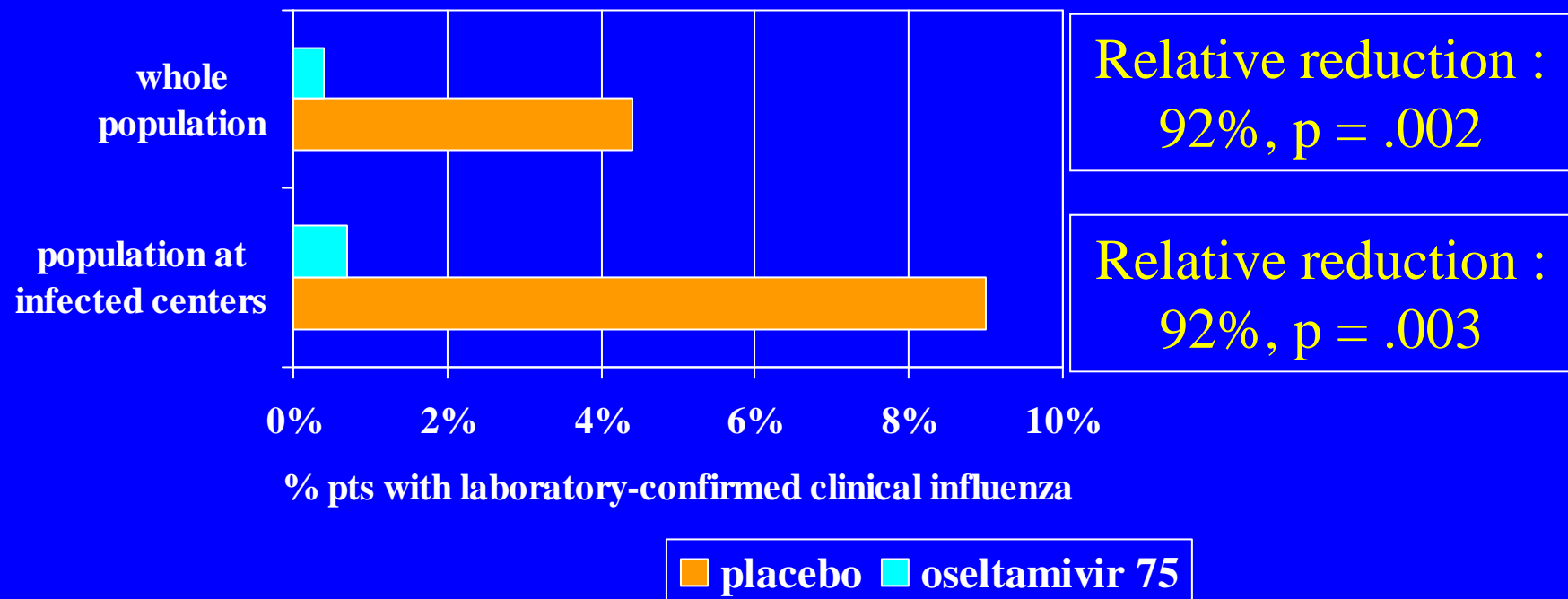
Hayden FG, N Engl J Med 1999;341:1336-43

Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population

- Double-blind, randomized, parallel-group, placebo-controlled, multicenter study
- All subjects older (≥ 65 yrs) and occupants of residential homes
- Oseltamivir 75 mg *vs* placebo over a 6 weeks when local influenza activity was detected
- Primary end point : incidence of laboratory-confirmed clinical influenza during the 6 week period

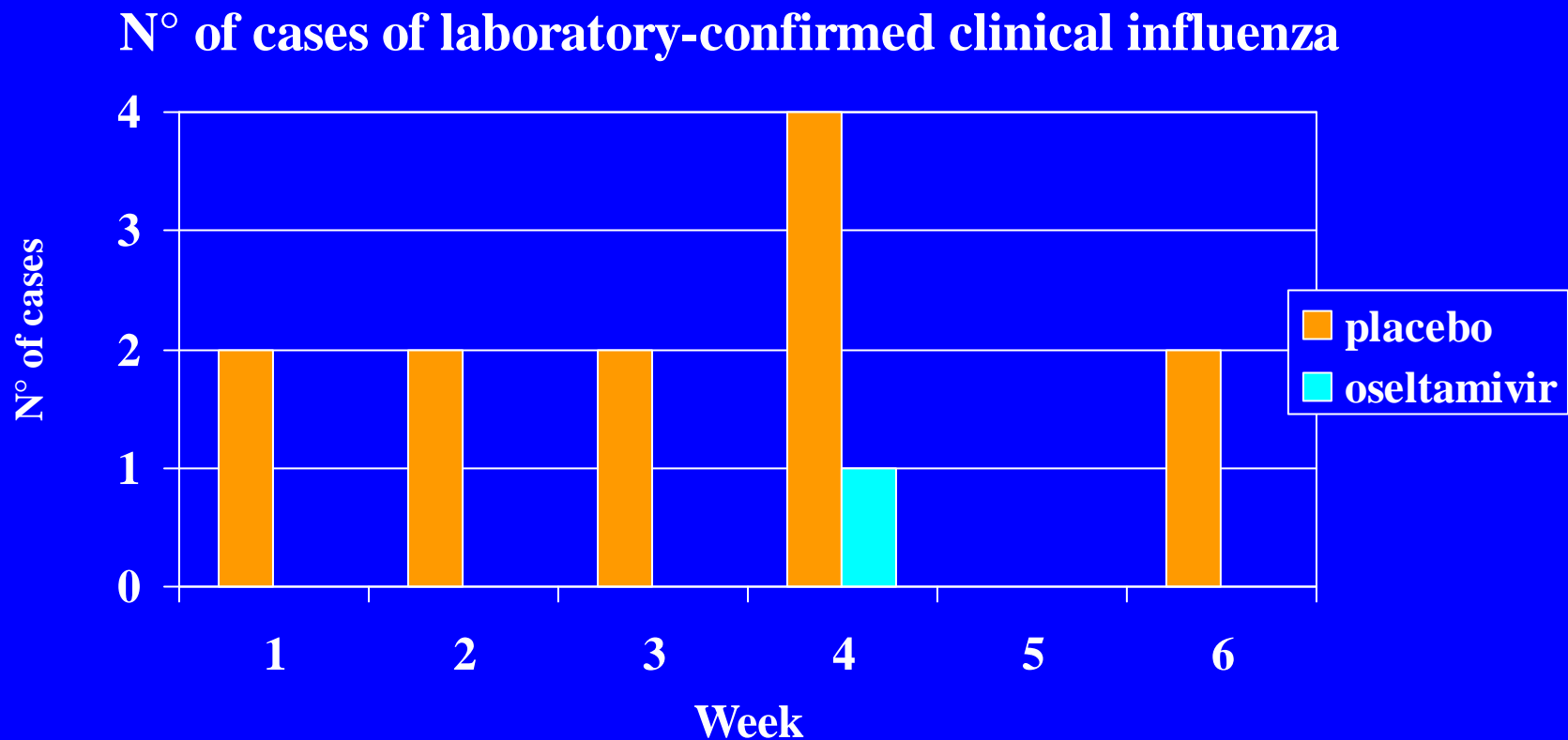
Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population

Incidence of laboratory-confirmed clinical influenza



Peters PH, J Am Geriatr Soc 2001;49:1025-1031

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Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population

Nº . (%) of patients with secondary influenza complications

	placebo (n : 272)	oseltamivir 75 mg (n : 276)	treatment effect
<hr/>			
All complications			
Population as a whole	7(2.6)	1(0.4)	86% (p=.037)
Lab-confirmed			
Infected population	7/23(30.4)	1/15(6.7)	78% (p=1.14)
<hr/>			
Types of complications			
Bronchitis	4(1.5)	1(0.4)	
Pneumonia	3(1.1)	0	
Sinusitis	1(0.4)	0	
<hr/>			

Effectiveness of oseltamivir in preventing influenza in household contacts

- Randomized, double-blind, placebo-controlled study
- 76 centers in North America and Europe, 1998-99
- Participants were :
 - Index cases (n = 377, 43% laboratory-confirmed influenza)
 - Household contacts (n = 955, 415 contacts of influenza positive ICs)
- Household contacts were randomly assigned by household cluster to take 75 mg oseltamivir od (n=462) or placebo (n=493), for 7 days within 48h of symptoms onset in the ICs.
- Main outcome measure : clinical influenza in contacts of influenza positive ICs

Effectiveness of oseltamivir in preventing influenza in household contacts

	protective efficacy % (95% CI)	p
<hr/>		
Contacts of all ICs		
Individuals	89% (71-96)	<.001
Affected households	86% (60-95)	<.001
<hr/>		
Contacts of an influenza-positive ICs		
Individuals	89% (67-97)	<.001
Affected households	84% (49-95)	<.001
<hr/>		
Contacts of an influenza-negative ICs		
Individuals	89% (10-99)	.009
Affected households	89% (10-99)	.01
<hr/>		

Zanamivir for prophylaxis of influenza in the community or in family groups

- Zanamivir 10 mg inhaled od for 4 weeks
- Double-blind trial in 2 universities communities

Effectiveness in prevention

Laboratory-confirmed

influenza A

67%

$p \leq .001$

Laboratory-confirmed

illness with fever

84%

$p = .001$

Zanamivir for prophylaxis of influenza : post contact prevention in family settings

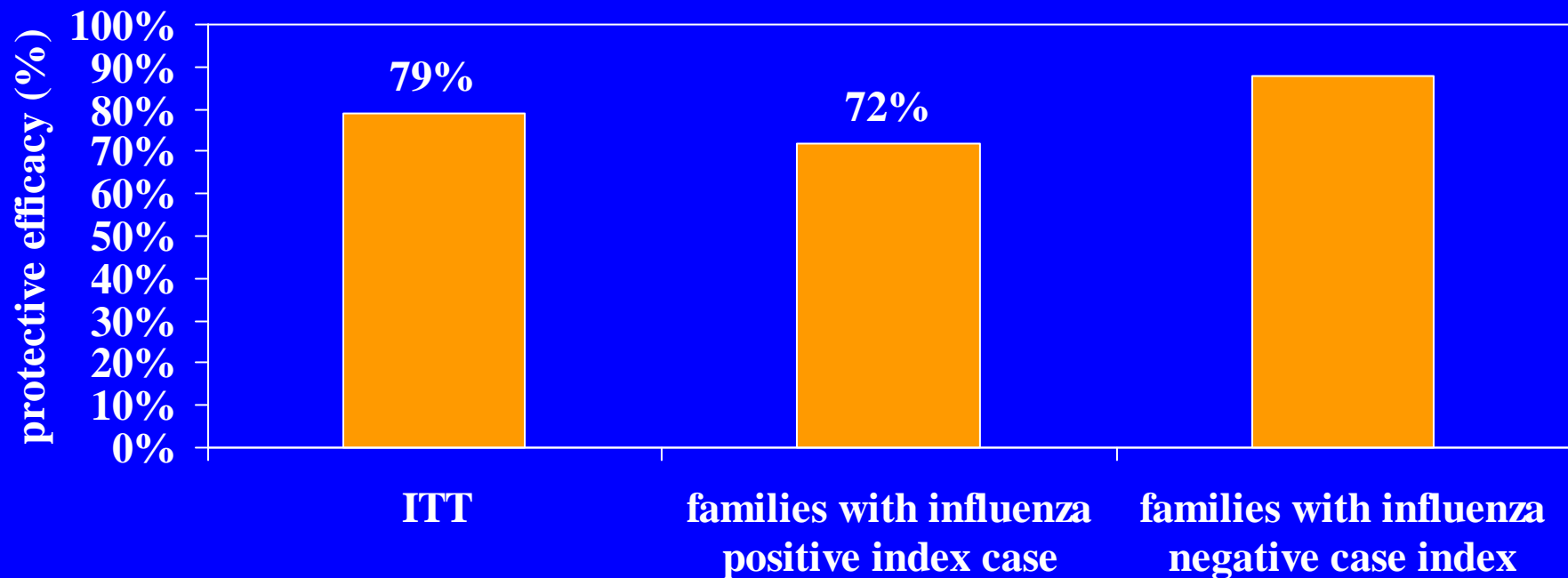
Families with at least one household contact who developed influenza (zanamivir 10 mg od for 10 days post contact)

	placebo	zanamivir	p
ITT	19%	4%	<.001
Laboratory-confirmed			
Index influenza	29%	8%	<.001
Not influenza	8%	1%	= .04

Hayden FG, N Engl J Med 2000;343:1282-9

Zanamivir for prophylaxis of influenza : post contact prevention in family settings

Relative protective efficacy in families



Hayden FG, N Engl J Med 2000;343:1282-9

Zanamivir for prophylaxis of influenza in long-term care facilities

- Zanamivir vs rimantadine in elderly volunteers in nursing home, during outbreak of influenza A

Schilling M 1998

Gravenstein S [abstr. 1155] ICAAC 2000

- Limited non comparative trials

- in nursing home

Lee C Infect Control Hosp Epidemiol 2000

McGeer, Clin Infect Dis 2000

- In rehabilitation institution

Hirji Z, Can Commun Dis Rep Health Canada 2000

Cheer SM, Drugs 2002;62:71-106

Viral resistance

Resistance to NAIs

- Documented *in vitro*, appears to be uncommon in treated pts
 - *MMWR 1999, Barnett J, AAC 2000, Gubareva L, J Infect Dis 2001*
- Mediated either by mutations in the neuramidinase or HA proteins or both
 - *McKimm-Breschkin J, Antiviral Res 2000, Barnett J, AAC 2000*
- Detection of NAI resistance is technically difficult
 - *McKimm-Breschkin J, Antiviral Res 2000*
- Infectivity of resistant strains
 - Frequently reduced in ferrets
 - Unknown in humans

Safety and tolerance of NAIs

Safety and tolerance : Oseltamivir

	oseltamivir	placebo
<hr/>		
Adults		
nausea	10%	6%
vomiting	9%	3%
<hr/>		
Children		
vomiting	14,3%	8,5%
<hr/>		

Safety, Tolerance : zanamivir and underlying airway diseases (1)

- Inhaled zanamivir after B2-agonist in pts with asthma or COPD :
 - >20% decline in FEV1
 - In 13% of pts receiving zanamivir
 - In 14% of pts receiving placebo
- Post marketing surveillance : cases of respiratory function deterioration after inhalation of zanamivir, certain pts had underlying airway diseases

Safety and tolerance : zanamivir and underlying airway diseases (2)

- Zanamivir is generally not recommended for pts with underlying airway diseases
 - Because of the risk for serious adverse events
 - Because the efficacy has not been demonstrated among this population
- In case of prescription,
 - Potential risks and benefits must be carefully considered
 - Drug should be used with caution under conditions of proper monitoring and supporting care, including the availability of short-acting bronchodilators

Are the NAIs the ideal anti-influenza drugs ?

Conclusion 1

- **Value in Influenza Management :**
 - NAI shorten time to resolution of illness significantly : duration and severity of symptoms
 - but they must be taken as soon as possible after symptoms onset.
- **Interest in prevention of secondary complications requiring antibiotics :**
 - Oseltamivir significantly reduces risk of developing otitis media in children by 44%
 - Low respiratory tract complications requiring antibiotics are reduced by half in adults

Conclusion 1 (cont ')

- **Strong value in Prophylaxis :**
- When influenza virus is circulating in the community
- But NAIs are not a substitute for vaccination
- Both drugs are similarly effective in preventing, laboratory-confirmed illness in healthy adults :
 - Oseltamivir reduces significantly the incidence of clinical influenza illness occurring in the contacts of confirmed influenza by 92%
- **Good safety profile**

Conclusion 2

But...More data are still needed :

- No strong demonstration of effectiveness in preventing serious influenza-related complications : bacterial or viral pneumonia, exacerbation of chronic diseases in healthy adults and at risk patients.
- Data are limited and inconclusive concerning the effectiveness for treatment among persons at high risk for serious complications of influenza
- Experience with prophylactic use of NAI in institutional settings or among patients with chronic medical conditions is limited
- Reduction of mortality not still available

Conclusion 3

- Future prospects with NAIs use :
 - Reduction of antibiotic misuse
 - Alleviation of socioeconomic impact of influenza
 - Reduction of hospitalizations and mortality

and....

 - The only immediate therapeutic response in a pandemic situation....