

GLI ANTIVIRALI IN PEDIATRIA

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PATOLOGIE E FARMACI ANTIVIRALI DI MAGGIOR USO IN PEDIATRIA

PATOLOGIE

- Influenza
- Infezioni da virus erpetici
- AIDS/Infezione da HIV
- Epatite B e C

FARMACI IN USO

- Inibitori della neuraminidasi
- Aciclovir, ganciclovir
- NRTI, NNRTI, PI, inibitori fusione, inibitori recettori chemochine
- Lamivudina, PEG Interferon, ribavirina

FARMACI ATTIVI CONTRO I VIRUS INFLUENZALI

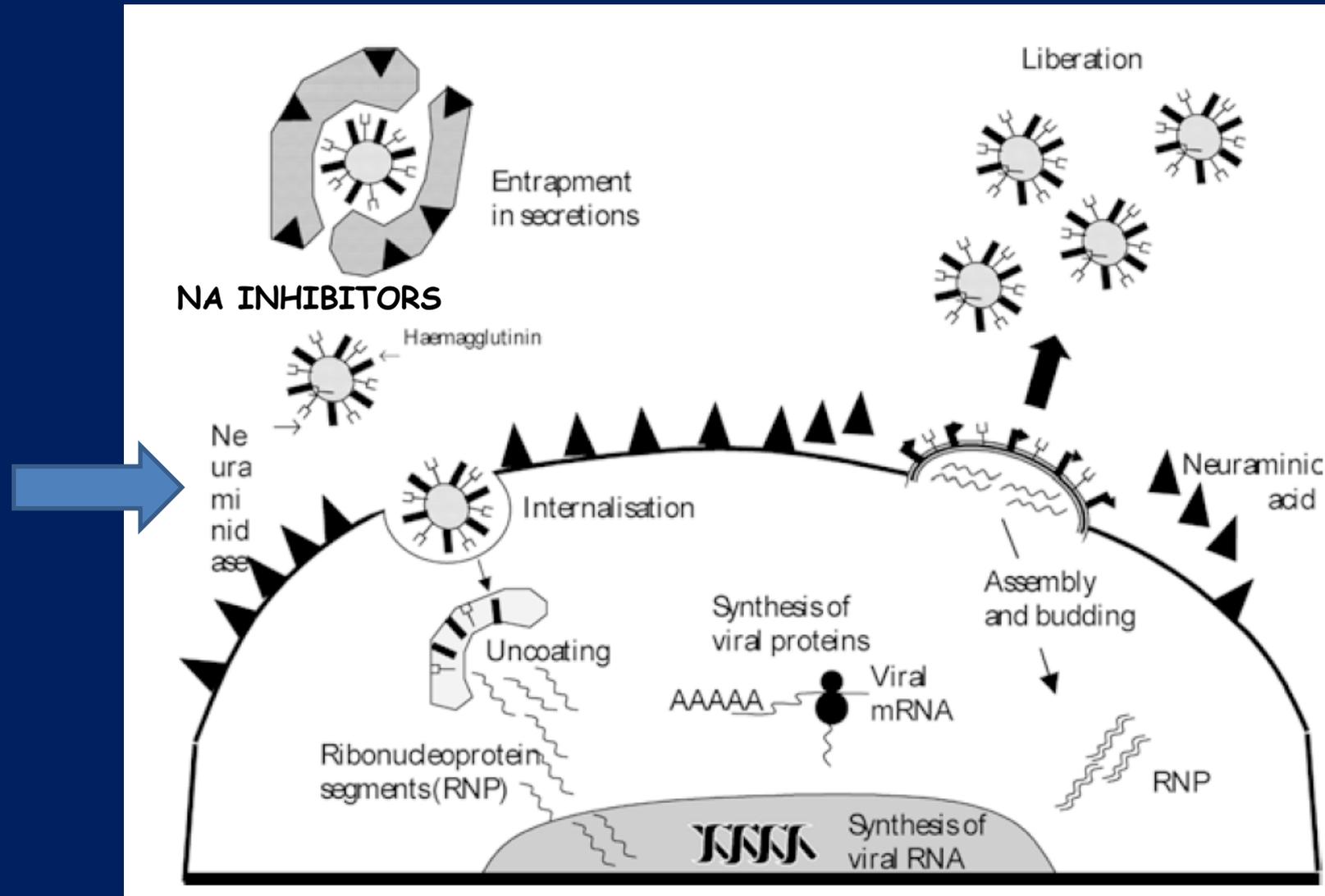
EFFICACI CONTRO LA
PROTEINA DI MEMBRANA M2
DEI VIRUS A

- Amantadina
- Rimantadina

INIBITORI DELLE
NEURAMINIDASI

- Oseltamivir
- Zanamivir

INFLUENZA VIRUS PENETRATION IN THE RESPIRATORY CELL: NA INHIBITORS ACTIVITY



Oseteltamivir (Tamiflu)

Prevenzione (per bocca)

- Da 1 a 12 anni: dosi uguali a quelle per il trattamento ma somministrate una sola volta al giorno
- ≥ 13 anni: 75 mg una volta al giorno

Trattamento (per bocca)

- Da somministrare per bocca
- Da 1 a 12 anni: ≤ 15 kg: 30 mg due volte al giorno
16-23 kg: 45 mg due volte al giorno
24-40 kg: 60 mg due volte al giorno
> 40 kg: 75 mg due volte al giorno
- ≥ 13 anni: 75 mg due volte al giorno

Zanamivir (Relenza)

Profilassi (per inalazione)

- ≥ 5 anni: 10 mg due volte al giorno per 10 giorni (prevenzione intrafamiliare) o per 28 (prevenzione comunitaria)

Trattamento (per inalazione)

- ≥ 5 anni: 10 mg due volte al giorno per 7 giorni

*In commercio in spinaler (rotadisk da 4 alveoli)
da 5 mg di polvere*

If possible, antiviral treatment should be started within 48 hours of influenza illness onset. The effectiveness of initiating antiviral treatment >48 hours after illness onset has not been established. Persons for whom antiviral treatment should be considered include:

- persons hospitalized with laboratory-confirmed influenza (limited data suggests benefit even for persons whose antiviral treatment is initiated >48 hours after illness onset);
- persons with laboratory-confirmed influenza pneumonia;
- persons with laboratory-confirmed influenza and bacterial coinfection;
- persons with laboratory-confirmed influenza infection who are at higher risk for influenza complications; and
- persons presenting to medical care with laboratory-confirmed influenza within 48 hours of influenza illness onset who want to decrease the duration or severity of their symptoms and transmission of influenza to others at higher risk for complications.

**Soggetti per i quali
può essere indicata
la chemioterapia
dell'influenza**

**Recommendations of the Advisory Committee
on Immunization Practices (ACIP), 2008**

MMWR, August 8, 2008

- Persons at high risk during the 2 weeks after influenza vaccination (after the second dose for children aged <9 years who have not previously been vaccinated), if influenza viruses are circulating in the community;
- Persons at high risk for whom influenza vaccine is contraindicated;
- Family members or health-care providers who are unvaccinated and are likely to have ongoing, close exposure to persons at high risk or unvaccinated persons or infants aged <6 months;
- Persons at high risk persons and their family members and close contacts, and health-care workers, when circulating strains of influenza virus in the community are not matched with vaccine strains;
- Persons with immune deficiencies or those who might not respond to vaccination (e.g., persons infected with human immunodeficiency virus or with other immunosuppressed conditions, or who are receiving immunosuppressive medications); and
- Unvaccinated staff and persons during response to an outbreak in a closed institutional setting with residents at high risk (e.g., extended-care facilities).

Soggetti per i quali può essere indicata la chemiopprofilassi dell'influenza

Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008

MMWR, August 8, 2008

EFFECTS OF TREATMENT WITH NA INHIBITORS ON INFLUENZA DISEASE

(From Shun-Shin M et al. BMJ 2009)

Study	Median days to resolution or alleviation of symptoms			Median days to resolution of illness*			Days to return to school/normal activities		
	Antiviral	Control	Difference (95%CI)	Antiviral	Control	Difference (95%CI)	Antiviral	Control	Difference (95%CI)
Confirmed influenza									
Zanamivir:									
NAI30009 ^{w2}	4.0	5.25	1.25 (0.5 to 2.0), P<0.001	—	—	—	NR	NR	1 day (NA), P=0.022
NAI30028 ^{w1}	5.0	5.5	0.5 (NA), P=NA	—	—	—	36% (62/172) at day 5	28% (25/89) at day 5	RD=0.08 (0.04 to 0.20), P=0.19
Oseltamivir:									
WV15758 ^{w3}	2.6	4.2	1.5 (NA) P<0.001	4.2	5.7	1.5 (0.3 to 2.5), P<0.001	NR	NR	NR
WV15759/ WV15871 ^{w4}	3.8	4.8	1.1 (NA), P=0.12	5.2	5.6	0.4 (NA), P=0.54	4.2†	4.8†	0.5 (NA), P=0.46
Clinical influenza									
Zanamivir:									
NAI30009 ^{w2}	4.5	5.0	0.5 (0.0 to 1.5), P=0.011	—	—	—	NR	NR	1 day (NA), P=0.019
NAI30028 ^{w1}	—	—	—	—	—	—	—	—	—
Oseltamivir:									
WV15758 ^{w3}	NR	NR	NR	4.4	5.3	0.9 (0.2 to 1.9), P<0.001	NR	NR	NR
WV15759/ WV15871 ^{w4}	NR	NR	NR	NR	NR	NR	NR	NR	NR

RD=risk difference; NR=outcome assessed in study but not results not reported; NA=not available.

*Defined as alleviation of symptoms + return to normal activities + afebrile.

†Median.

EFFICACIA DI OSELTAMIVIR IN PEDIATRIA

(Da Whitely RJ et al. *Pediatr Infect Dis J* 2001)

Event	Reduction
Illness duration until 'alleviation' (days)	1.5
Duration of fever (days)	1.1
Physician diagnosed complications requiring antibiotics (%)	40
Physician diagnosed otitis media (%)	44
Tympanometric confirmed otitis media (%)	50

Zanamivir for treatment of symptomatic influenza A and B infection in children five to twelve years of age: a randomized controlled trial

JAMES A. HEDRICK, MD, ASHER BARZILAI, MD, ULRICH BEHRE, MD, FREDERICK W. HENDERSON, MD, JANET HAMMOND, MD, PHD, LUCY REILLY, BSC AND OLIVER KEENE, MA, MS

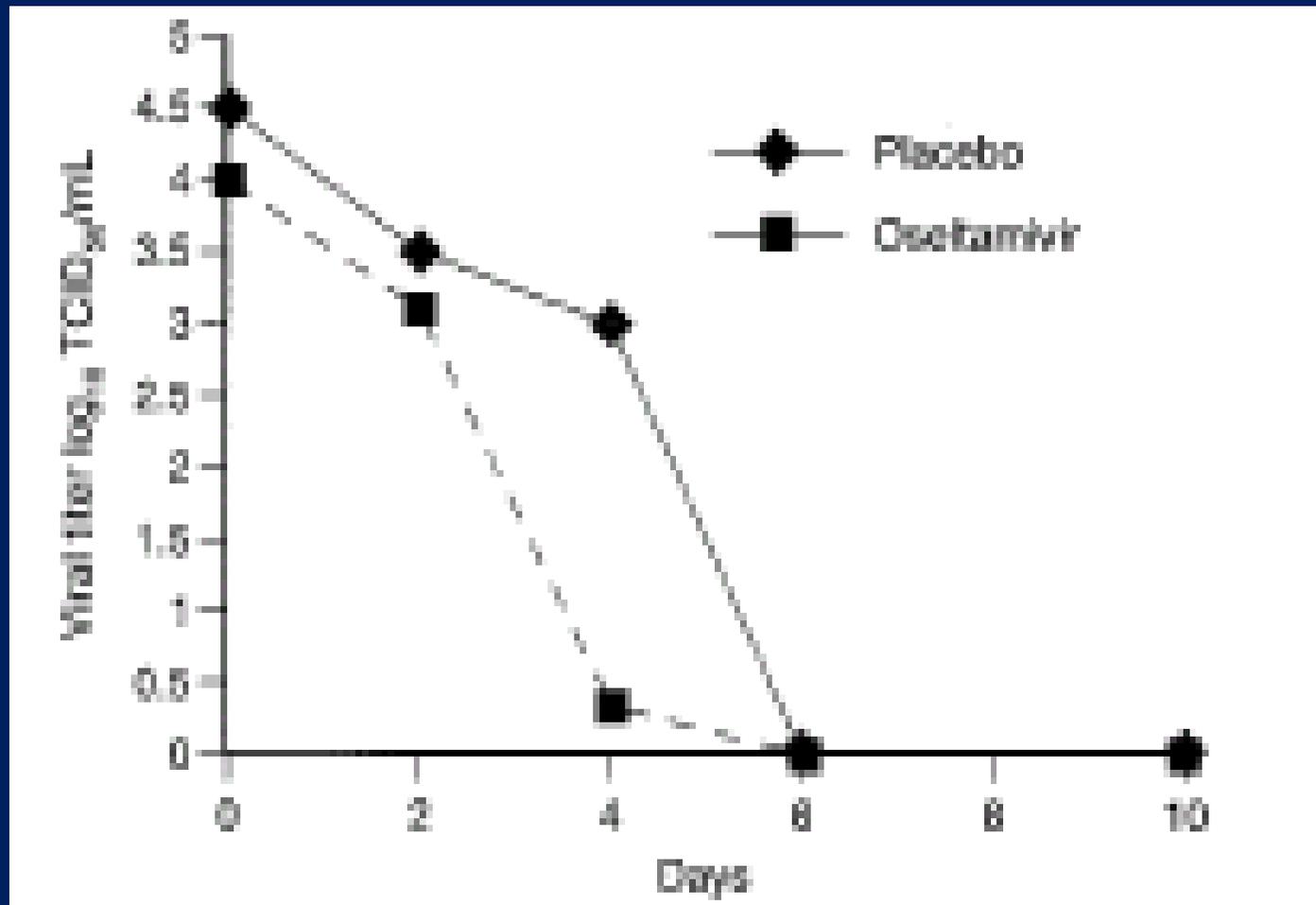
TABLE 2. Median time to alleviation of clinically significant symptoms regardless of use of relief medication and with no relief medication used

Group	Median Time (days) to Alleviation of Clinically Significant Symptoms				Difference in Alleviation (Days)*	95% Confidence Interval	P
	Placebo		Zanamivir				
	n	Median	n	Median			
Regardless of relief medication use							
Influenza-positive	182	5.25	164	4.0	1.25	(0.5, 2.0)	<0.001
Influenza A	120	5.0	106	4.0	1.0	(0.0, 1.5)	0.049
Influenza B	62	6.0	58	4.0	2.0	(1.0, 3.5)	<0.001
North America	105	5.0	96	4.0	1.0	(0.0, 1.5)	0.026
Europe	77	5.5	68	4.0	1.5	(0.5, 3.0)	0.004
Intent-to-treat	247	5.0	224	4.5	0.5	(0.0, 1.5)	0.011
Per protocol	172	5.0	159	4.0	1.0	(0.5, 2.0)	<0.001
No use of relief medication							
Influenza-positive	182	6.5	164	5.0	1.5	(0.5, 2.25)	<0.001
Influenza A	120	6.0	106	5.25	0.75	(-0.5, 2.0)	0.047
Influenza B	62	6.75	58	4.5	2.25	(1.0, 3.5)	<0.001
Intent-to-treat	247	6.0	224	5.0	1.0	(0.0, 1.75)	0.002

* Placebo minus zanamivir

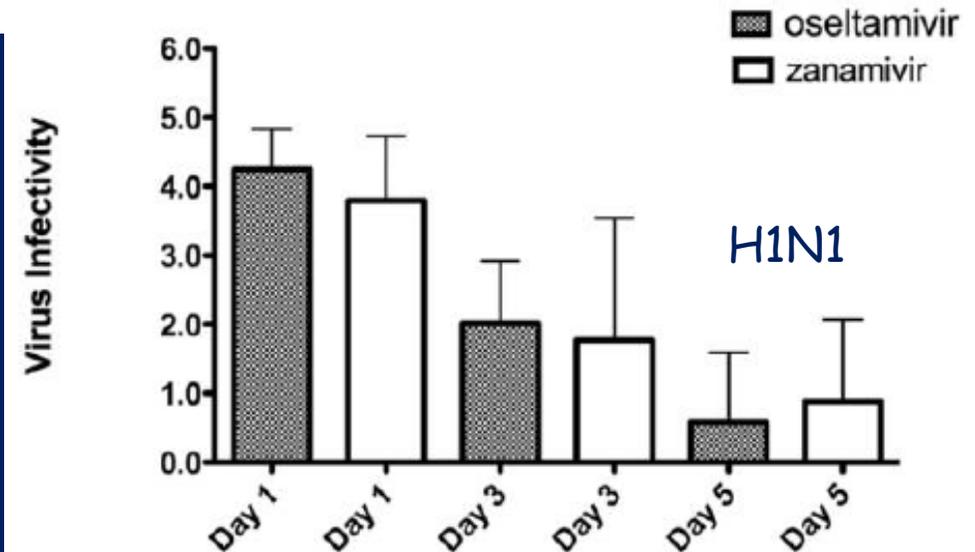
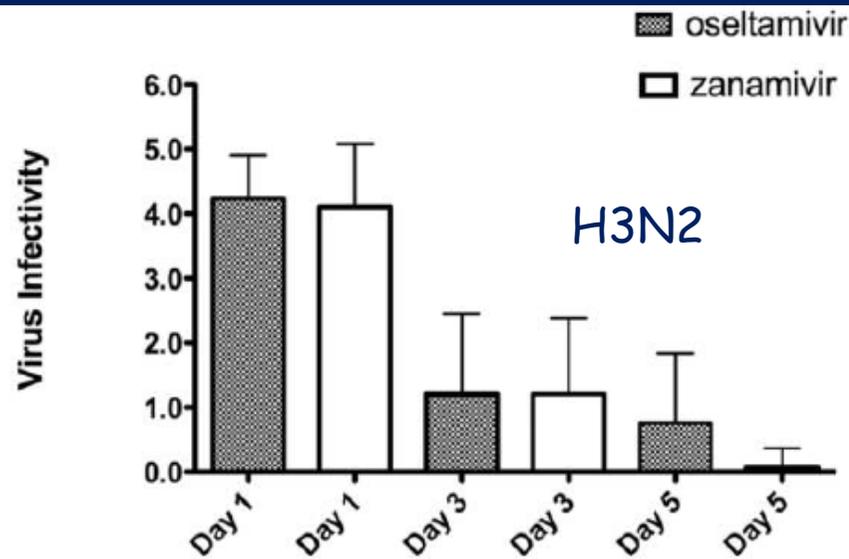
ELIMINAZIONE VIRALE

(Da Whitley et al. *Pediatr Infect Dis J* 2001)



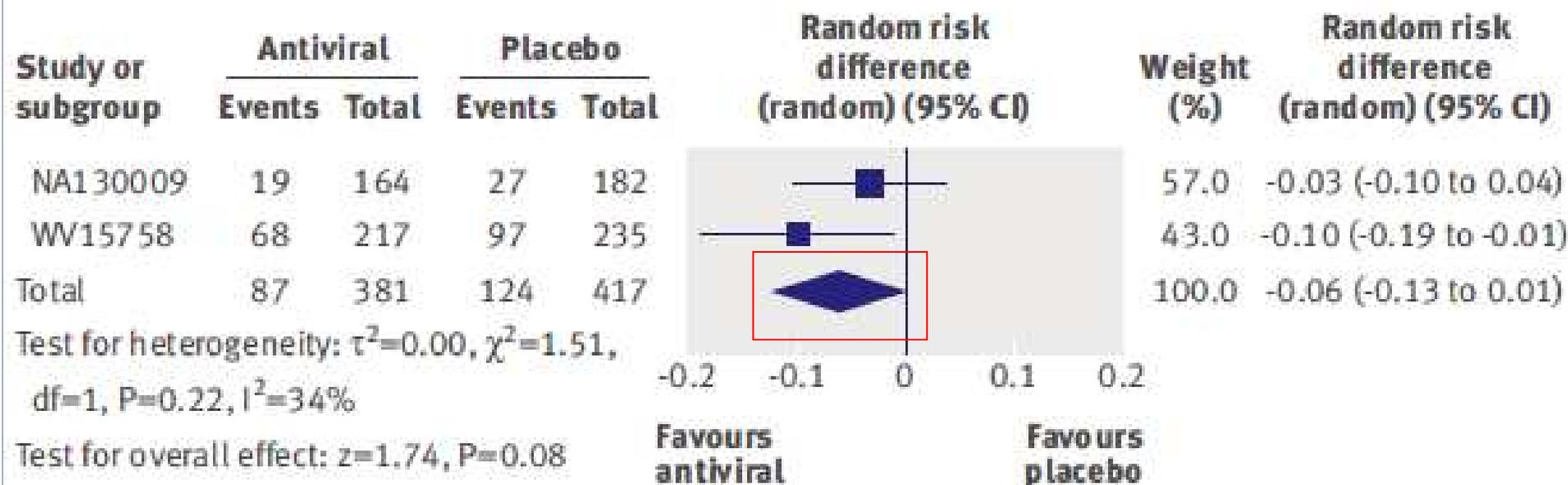
INIBITORI DELLE NEURAMINIDASI ED ELIMINAZIONE DEI VIRUS INFLUENZALI

(Da Sugaya N et al. Clin Infect Dis 2008)



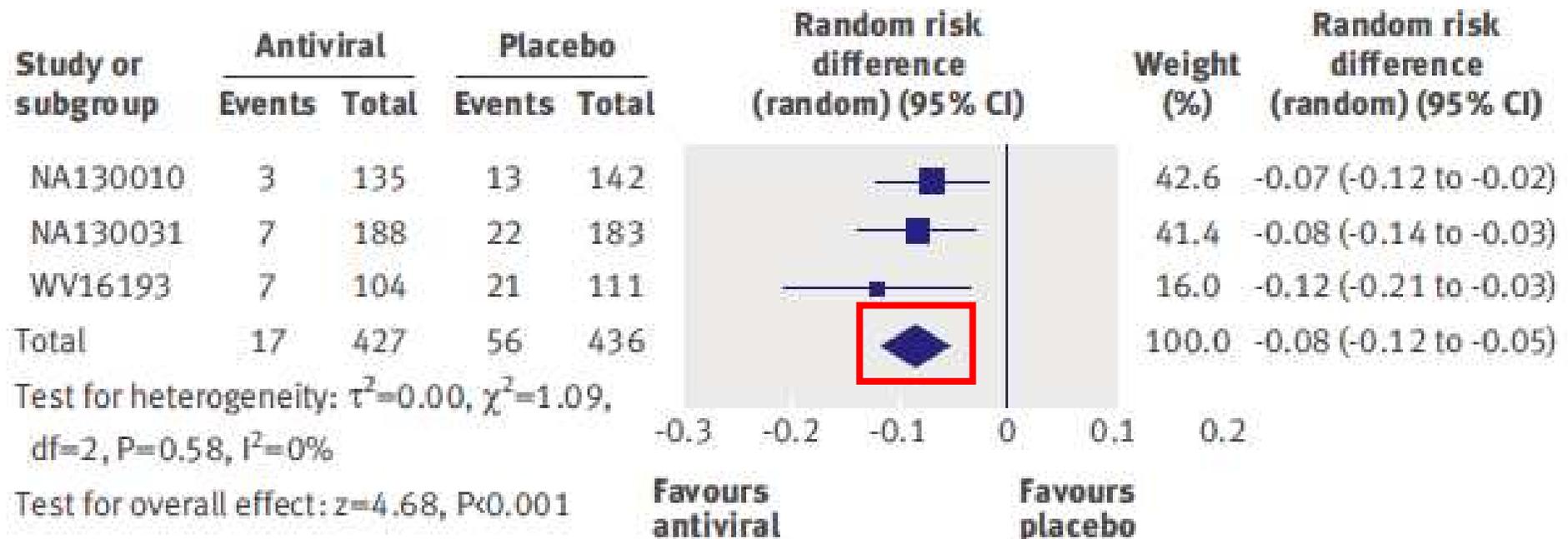
ADMINISTRATION OF NEURAMINIDASE INHIBITORS AND USE OF ANTIBIOTICS IN CHILDREN

(From Shun-Shim M et al. BMJ 2009)



INCIDENCE OF CONFIRMED INFLUENZA CASES IN CONTACTS OF CHILDREN WITH INFLUENZA AFTER PROPHYLAXIS WITH NA INHIBITORS

(From Shun-Shim M et al. BMJ 2009)



Cost/effectiveness of post exposure prophylaxis with oseltamivir in children 1-12 yrs

Data are based on an efficacy of 68% and are quite similar to those calculated for influenza vaccine

From Talbird SE, et al. Am J Prev Med 2009

Outcome	Payer perspective		Societal perspective	
	No PEP	PEP	No PEP	PEP
Cost per person exposed	49.36	138.40	121.02	218.03
Influenza cases per 100,000 ^a	18,919	6735	18,919	6735
Symptom days per person exposed	1.58	0.56	1.58	0.56
QALYs gained per person exposed ^b	0.0023		0.0023	
Cost per influenza case avoided	731		796	
Cost per symptom day avoided	87.30		95.11	
Cost per QALY gained	38,050		41,452	

^aBased on a placebo attack rate of 18.9% as observed in Hayden et al.²⁷

^bQALYs gained are computed from the reduced risk of influenza and include both the short-term effects for those children who survive the illness as well as the discounted QALYs lost due to premature mortality for those children who do not survive the illness.

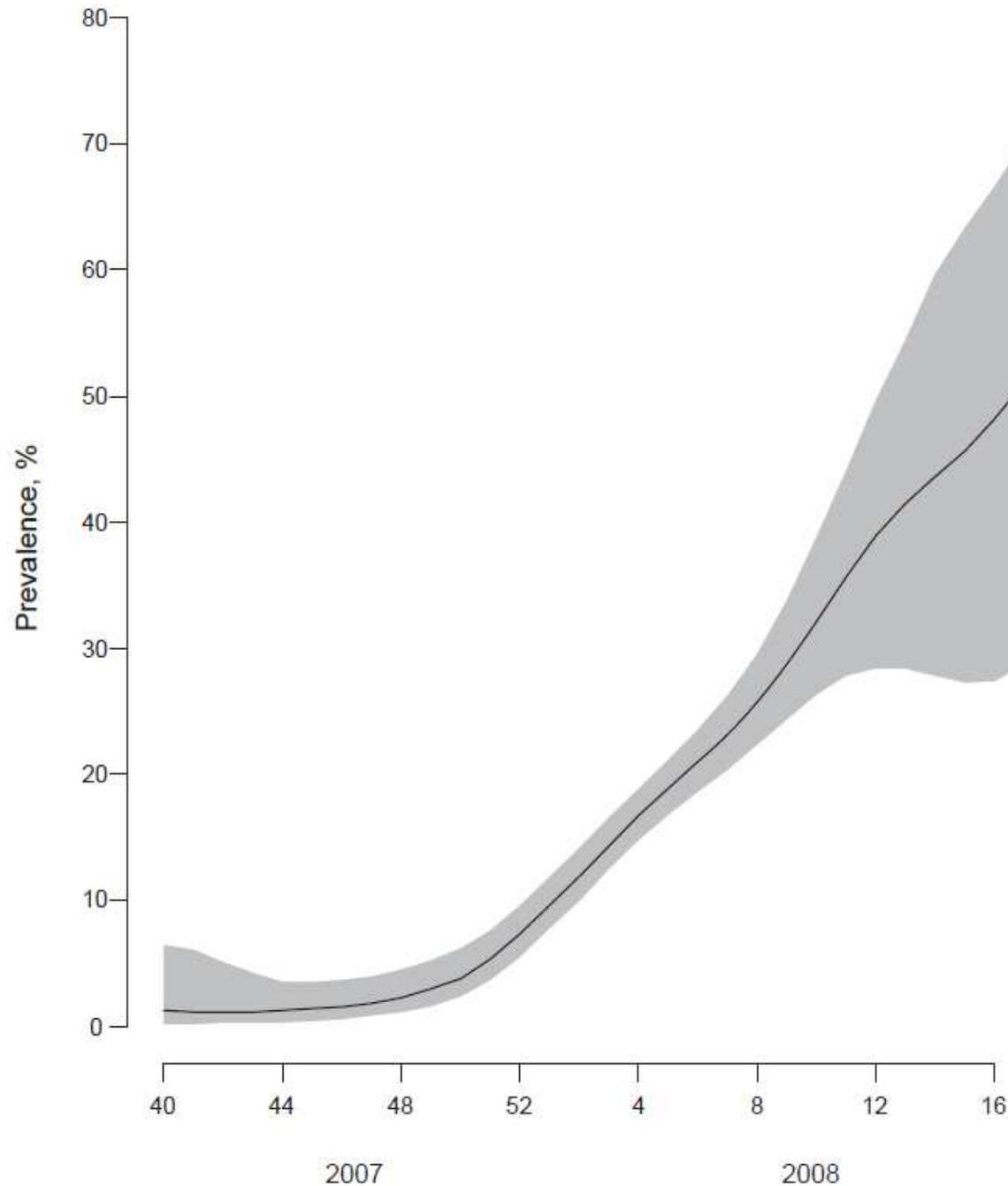
PEP, postexposure prophylaxis; QALY, quality-adjusted life-year

Catalytic and Framework mutations

Mutation	Obtention ^a	Select With	Subtype	NA Activity ^b	Inhibitor sensitivity ^c	
					Zanamivir	Oseltamivir
Catalytic residues						
R292K	In clinic	Oseltamivir	N2			R
	In vitro	Zanamivir	N2	<20%	R	R
	RG		N2	6%–29%	R	R
D151E	RG		B	6%	R	R
	RG		N2	2.2%	S	LowR
R152K	In clinic	Zanamivir	B	<3%–5%	R	R
	RG		B	77%	S	S
			N2	1.8%	S	S
R371K	RG		N2	2.5%	R	R
R118K	RG		N2	NoRescue	Nt	Nt
R224K	RG		N2	0.6%	R	R
E276D	RG		N2	3.3%	R	LowR
Framework residues						
E119V	In clinic	Oseltamivir	N2			R
	V	RG	N2	28%–81%	S	R
E119G	V	RG	B	72%	S	R
	In vitro	Zanamivir	N9		R	S
	G	In vitro	Zanamivir	B		R
	G	RG	B	72%	R	R
E119A/D	In vitro	Zanamivir	N2		R/R	I/S
E119A/D	RG		N2	1.1%/19%	Nt/R	Nt/S
E119A/D	RG		B	17.4%/29%	R/R	R/R
D198N	In clinic	Oseltamivir	B	100%	R	R
H274Y	In clinic	Oseltamivir	N1		S	R
	RG		N2	85%	S	S
	RG		N9	20%	S	R
N294S	In clinic	Oseltamivir	N2		Nt	lowR
	In clinic	Oseltamivir	N1		Nt	lowR
I222V	RG		N2	123%		LowR

Mutazioni che conferiscono resistenza agli inibitori delle neuraminidasi

Da Ferraris O, Lina B.
J Clin Virol 2008

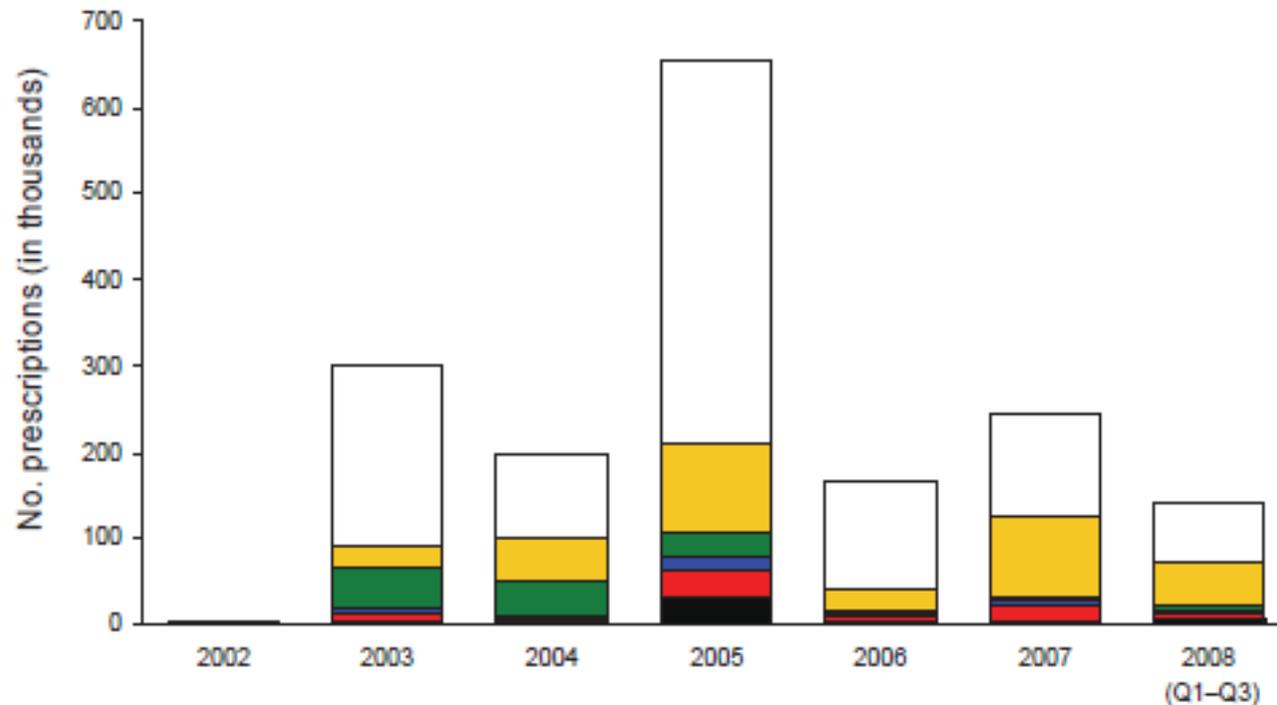


**Incremento
della resistenza
ad oseltamivir
del virus A/H1N1
nella stessa
stagione
invernale in
Europa**

Da Meijer A et al.
Emerg Infect Dis 2009

CICLI DI TERAPIA CON OSELTAMIVIR PRESCRITTI IN ALCUNI PAESI EUROPEI A MAGGIOR CONSUMO

(Da Meijer A et al. Emerg Infect Dis 2009)



	2002	2003	2004	2005	2006	2007	2008 (Q1-Q3)
Germany	4	211	100	442	128	121	71
France	0	27	49	104	24	93	50
Greece	0	45	41	30	4	2	4
Finland	0	9	2	15	3	7	2
Belgium	1	7	3	33	7	18	8
Austria	0	4	5	30	2	4	7

CLINICAL AND SOCIOECONOMIC IMPACT OF OSELTAMIVIR-RESISTANT SEASONAL A/H1N1 INFLUENZA VIRUS IN HEALTHY CHILDREN IN ITALY

(Esposito S et al. ESPID 2010)

- A total of 4,726 otherwise healthy children with influenza-like illness were tested for influenza viruses in the winters of 2007-2008 and 2008-2009 in Italy
- Among the A/H1N1 subtypes, the H275Y mutation was found in 2/126 samples taken in 2007-2008 (1.6%) and in all 17 samples (100%; $p < 0.0001$) taken in 2008-2009
- The clinical and socioeconomic impact of the mutated virus was similar to that of the wild-type virus

*Ministero del Lavoro, della Salute
e delle Politiche Sociali*

Ordinanza
30 sett 2009

Ordinanza: Misure urgenti in materia di protezione AHIN1v

3. L'uso degli inibitori delle neuraminidasi nei bambini e adolescenti deve essere limitato esclusivamente:

1. ai bambini con sintomi influenzali appartenenti ai gruppi a rischio per gravi complicanze (con alterazioni funzionali o strutturali dell'apparato respiratorio, ad esempio i nati gravemente pretermine, i bronco displasici, gli affetti da fibrosi cistica, o da condizioni che determinano una alterazione grave della ventilazione, ecc.), con patologie croniche (ad esempio malattie croniche polmonari [incluse l'iperreattività bronchiale grave e l'asma in trattamento], cardiache, epatiche, renali, ematologiche, neuromuscolari, metaboliche [compreso il diabete], malattie infiammatorie croniche e sindromi da malassorbimento intestinali, immunodepressione congenita o acquisita (HIV), malformazioni congenite, paralisi cerebrali, ecc.);
2. ai bambini senza fattori di rischio, ma ricoverati in ospedale per sintomi gravi attribuibili alla infezione con virus H1N1 (dispnea, ipossia, alterazioni del sensorio);
3. per la chemioprolifassi, ai bambini a rischio di gravi complicanze, sopra indicate, non vaccinati, che abbiano avuto stretti contatti con persone infette.

THE NATURAL VIRAL LOAD PROFILE OF CHILDREN WITH PANDEMIC 2009 A/H1N1 INFLUENZA VIRUS

(Esposito S et al.)

- A total number of 425 children (258 males; mean age \pm SD, 6.14 \pm 5.09 yrs) were positive for pandemic A/H1N1 influenza virus
- Mean duration of shedding was **11.58 \pm 3.16 (range, 3-28) days**
- Viral load was significantly higher in children whose enrollment occurred **in the first 2 days after the onset of symptoms** (mean cycle threshold - CT - \pm SD, 26.36 \pm 3.16 vs 28.19 \pm 4.22; $p < 0.05$) **and in those whose households suffered from a similar disease in the 7 days after enrollment** (CT 26.37 \pm 3.14 vs 28.49 \pm 3.63; $p = 0.0001$)
- **No correlation was found among viral load and duration of shedding, age, severity of respiratory involvement, presence of an underlying chronic disease and use of antivirals**

SENSIBILITÀ DEI CEPPI DI A/H1N1 PANDEMICI AGLI INIBITORI DELLE NEURAMINIDASI IN EUROPA

(Da ECDC 2010)

Table 4: Antiviral resistance by influenza virus type and subtype, weeks 40/2009–10/2010

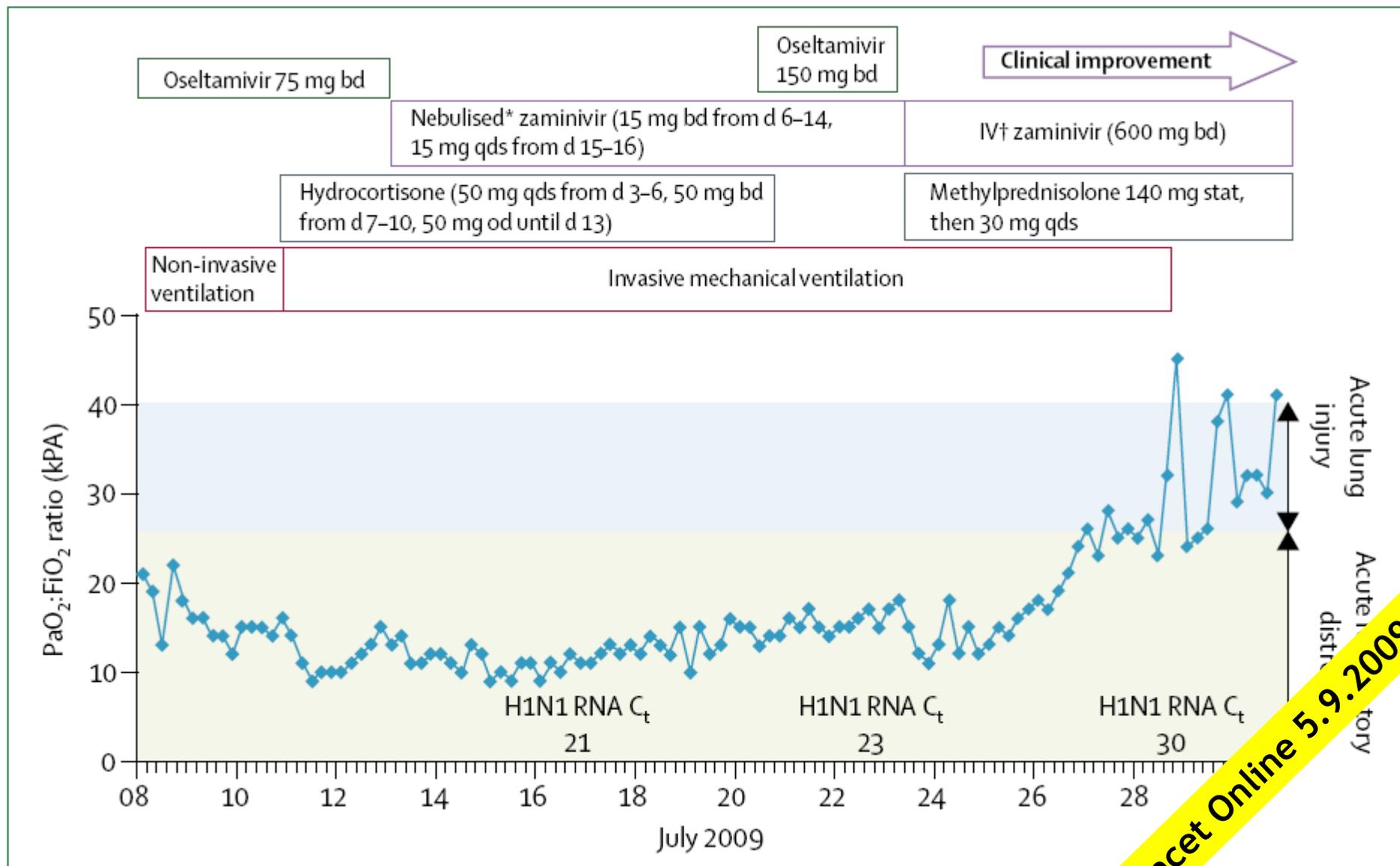
Virus type and subtype	Resistance to neuraminidase inhibitors				Resistance to M2 inhibitors	
	Oseltamivir		Zanamivir		Isolates tested	Resistant n (%)
	Isolates tested	Resistant n (%)	Isolates tested	Resistant n (%)		
A(H3N2)	0	0	0	0	0	0
A(H1N1)	0	0	0	0	0	0
A(H1N1)v	1453	37 (2.5)	1447	0	205	205 (100)
B	0	0	0	0	NA	NA

CLINICAL AND LABORATORY FINDINGS IN A 8-YEAR OLD BOY WITH CYSTIC FIBROSIS AND OSELTAMIVIR-INDUCED RESISTANT PANDEMIC INFLUENZA A VIRUS (Esposito S et al. J Clin Virol 2010)

Characteristic	T day 0	T day 3	T day 5	T day 7	T day 10
Axillary temperature (°C)	37.7	36.8	36.6	36.6	36.6
Respiratory rate, breaths (min)	24	26	28	25	22
SpO ₂ in room air (%)	97	94	88	96	98
Chest radiography	Worsening of pleuroparenchymal findings in comparison with previous chest radiograph	n.e.	Atelectasis with pleural effusion in the lower part of right lung	n.e.	n.e.
White blood cell counts, cells (μL)	8100	27,520	32,700	12,500	7300
Neutrophils (%)	66.8	79.7	81.0	73.3	65.6
CRP (mg/dL)	0.7	<0.03	<0.03	<0.03	<0.03
Antiviral therapy	Oseltamivir	Oseltamivir	Oseltamivir → zanamivir	Zanamivir	Zanamivir
Antibiotic therapy	Ceftazidime + tobramycin	Ceftazidime + tobramycin	Ceftazidime + tobramycin + vancomycin	Ceftazidime + tobramycin + vancomycin	Ceftazidime + tobramycin + vancomycin
Supportive therapy	PEP physiotherapy	PEP physiotherapy	PEP physiotherapy, oxygen therapy	PEP physiotherapy	PEP physiotherapy
Pandemic A/H1N1 virus detection in nasopharyngeal swab					
CT value	17.5	30.9	29.4	Negative	Negative
H275Y substitution	Absent	Absent	Present	n.e.	n.e.
Bacterial findings in sputum	<i>Pseudomonas aeruginosa</i>	n.e.	Negative	n.e.	n.e.

Peripheral oxygen saturation, SpO₂; CRP, C reactive protein; PEP, positive expiratory pressure; n.e., not evaluated.

Antiviral use in ICU



Lancet Online 5.9.2009



PERSPECTIVES ON INFLUENZA AND ANTIVIRALS

- To use carefully antivirals
- To continue to monitor the circulation of oseltamivir resistance among different influenza strains and its impact in the community
- To clarify the mechanism of oseltamivir resistance (spontaneous, drug-induced?)
- To understand whether the reduction in host defences due to underlying condition favour prolonged viral shedding and the development of resistance
- To analyse whether in cases with a negative evolution the H275Y mutation may be associated with one or more other genetic mutations

Congenital CMV Infection



Congenital CMV Infection



Congenital CMV Infection

Symptomatic Neonates

Abnormality	Positive/Total Examined (%)
Prematurity (< 38 wks)	36/106 (34)
Small for Gestational Age	53/106 (50)
Reticuloendothelial	
Petechiae	80/106 (76)
Jaundice	69/103 (67)
Hepatosplenomegaly	63/105 (60)
Purpura	14/105 (13)

Congenital CMV Infection Symptomatic Neonates

Abnormality	Positive/Total Examined (%)
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Neurologic

One or more of the following:	72/106 (68)
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Microcephaly	54/102 (53)
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Lethargy/hypotonia	28/104 (27)
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Poor suck	20/103 (19)
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Seizures	7/105 (7)
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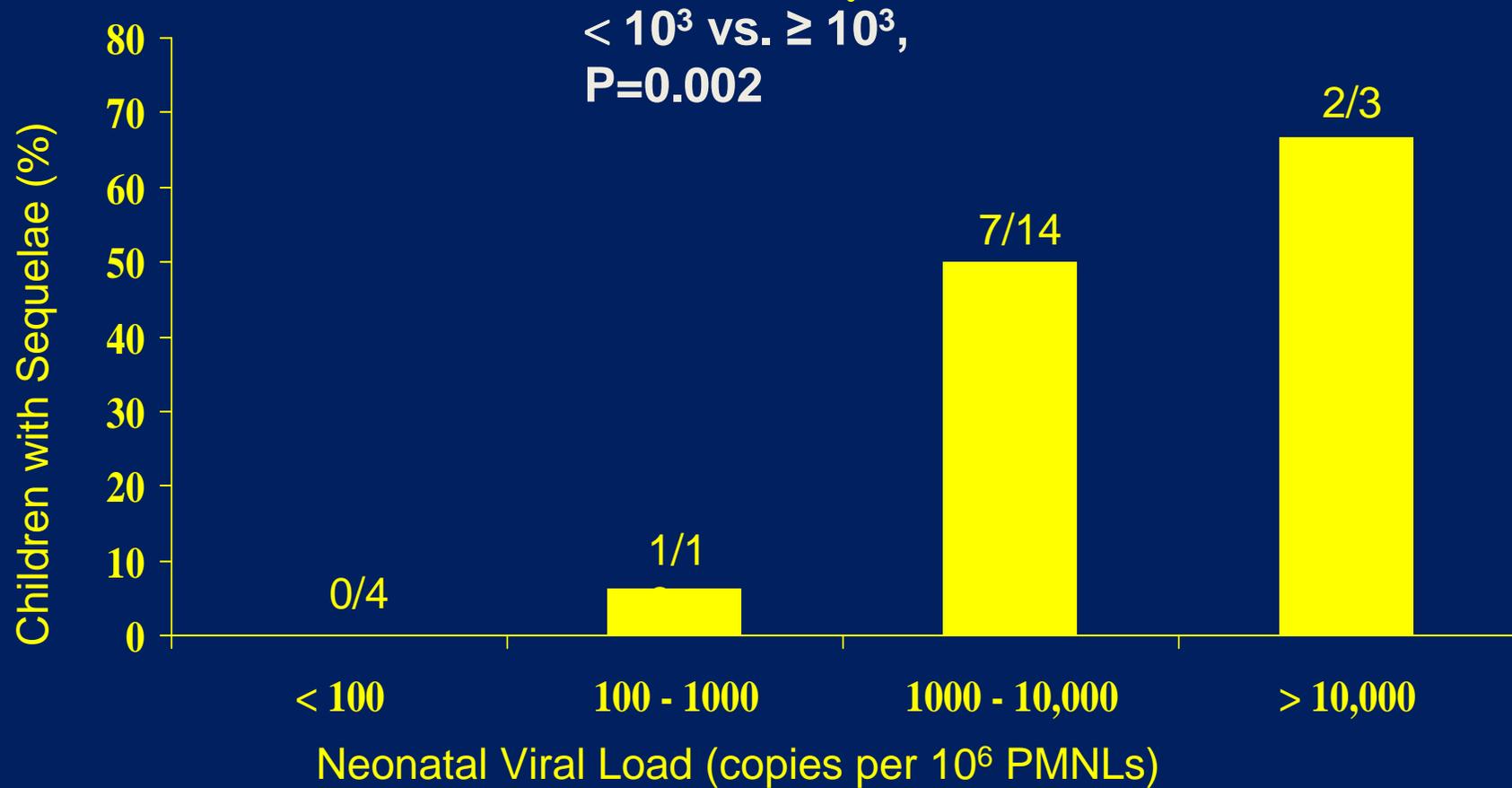
Congenital CMV Infection Symptomatic Neonates

Abnormality	Positive/Total Examined (%)
Elevated ALT (> 80 units/liter)	46/58 (83)
Thrombocytopenia	
< $100 \times 10^3/\text{mm}^3$	62/81 (77)
< $50 \times 10^3/\text{mm}^3$	43/81 (53)
Conjugated hyperbilirubinemia	
Direct > 2 mg/dL	55/68 (81)
Direct > 4 mg/dL	47/68 (69)
Hemolysis	37/72 (51)
Increased CSF protein (> 120 mg/dL)	24/52 (46)

Congenital CMV Infection Sequelae Following Fetal Infection/Disease

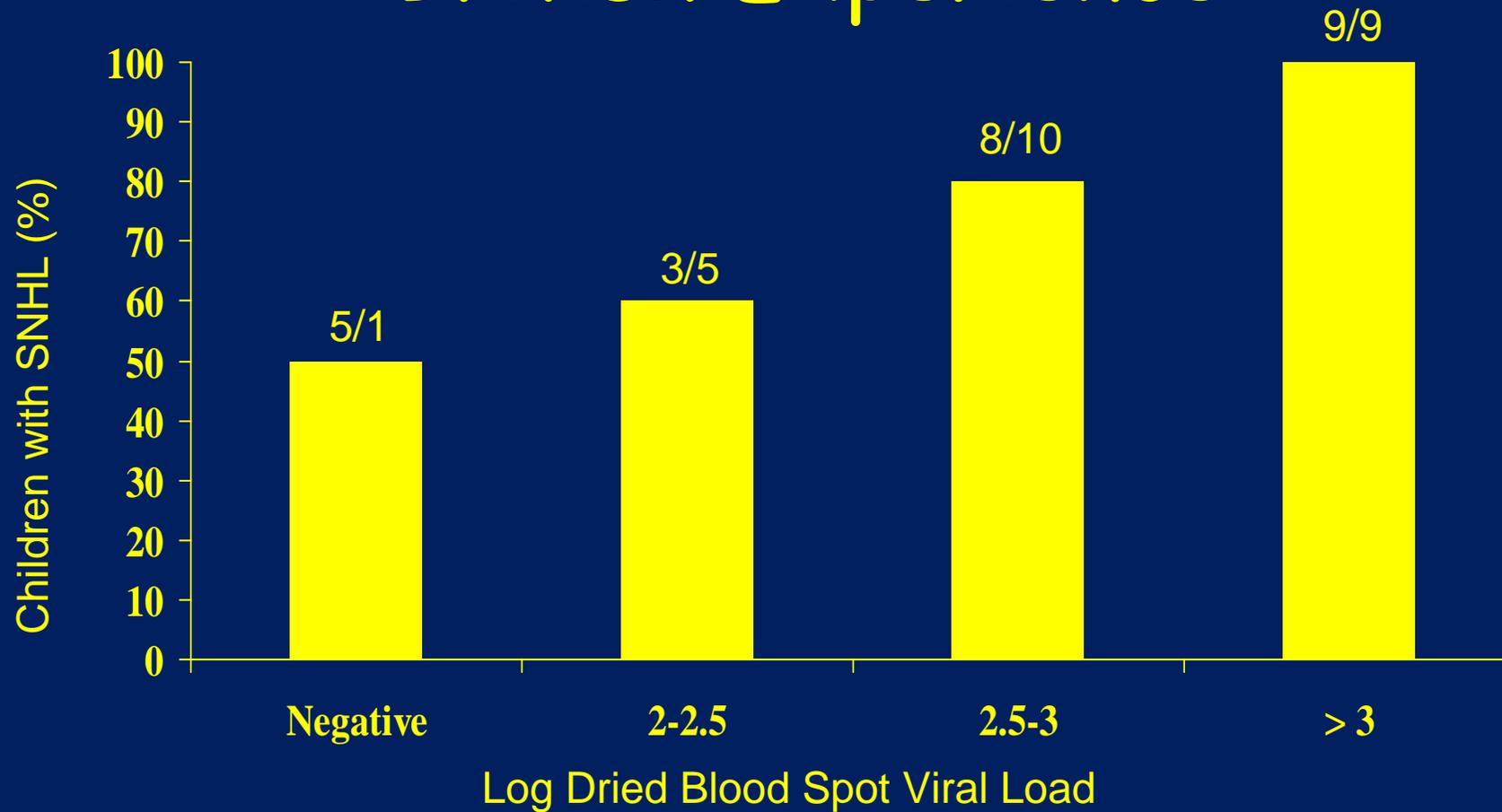
<u>Sequelae</u>	<u>Symptomatic</u>	<u>Asymptomatic</u>
Sensorineural hearing loss	58%	7.4%
Bilateral hearing loss	37%	2.7%
Speech threshold moderate to profound (60 to 90 dB)	27%	1.7%
Chorioretinitis	20.4%	2.5%
IQ < 70	55%	3.7%
Microcephaly, seizures, or paresis/paralysis	51.9%	2.7%

Correlation of Viral Load with Sequelae Italian Experience



Correlation of Viral Load with SNHL

British Experience



Arch Dis Child Fetal Neonatal Ed 2008;93:F280–F285

PERIPHERAL BLOOD VIRAL LOAD AND HEARING OUTCOMES IN ASYMPTOMATIC CONGENITAL CMV

Age	PB VL (ge/mL)	SNHL	Normal	PPV (CI)	NPV (CI)
< 2 mo	≤ 3,500	2	34	7.9% (1.6-21.4)	94.4% (81.3-99.3)
	> 3,500	3	35		
2-12 mo	≤ 3,500	0	26	7.7% (0.95, 25.1)	100% (86.8, 100)
	> 3,500	2	24		
12-36 mo	≤ 3,500	0	25	11.8% (1.5, 6.4)	100% (86.3, 100)
	> 3,500	2	15		

PERIPHERAL BLOOD VIRAL LOAD AND HEARING OUTCOMES IN SYMPTOMATIC CONGENITAL CMV

Age	PB VL (ge/mL)	SNHL	Normal	PPV (CI)	NPV (CI)
< 2 mo	≤ 3,500	1	2	50.0% (23.0-77.0)	66.7% (9.4-99.2)
	> 3,500	7	7		
2-12 mo	≤ 3,500	1	5	60.0% (14.7, 94.7)	83.3% (35.9, 99.6)
	> 3,500	3	2		
12-36 mo	≤ 3,500	1	3	0.0% (0.0, 84.2)	75.0% (19.4, 99.4)
	> 3,500	0	2		

TERAPIA DELL'INFEZIONE CONGENITA DA CMV (I)

- IL VIRUS RIMANE LATENTE PER TUTTA LA VITA CON PERIODICHE RIACUTIZZAZIONI
- TRATTAMENTI BREVI PORTANO SOLO UNA TRANSITORIA RIDUZIONE DELLA VIREMIA
- OGGI SI E' SEMPRE PIU' ORIENTATI VERSO TERAPIE MOLTO PROTRATTE

TERAPIA INFEZIONE CONGENITA DA CMV (II)

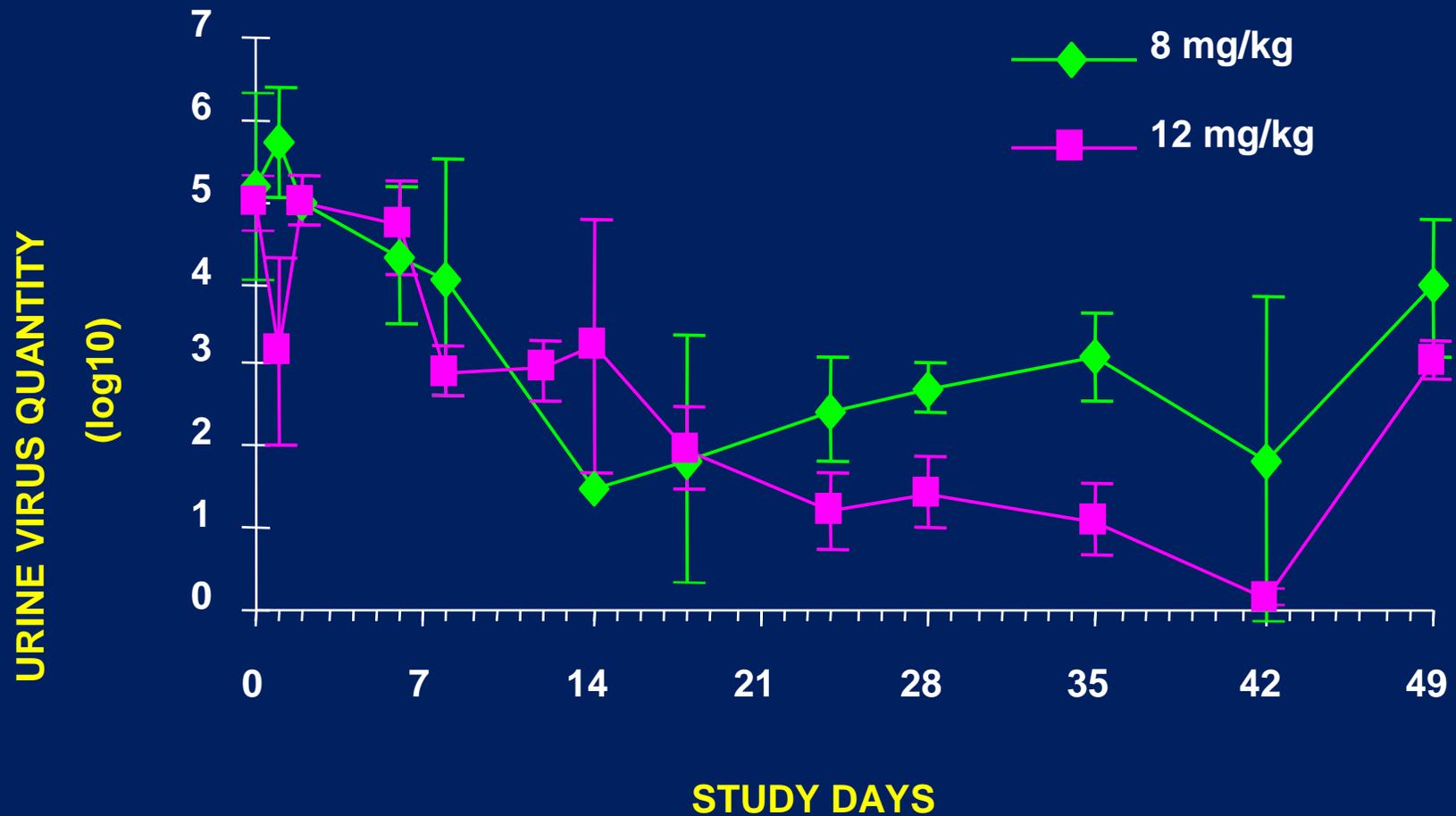
- NON SONO DISPONIBILI LINEE GUIDA UFFICIALI
- VI SONO SPORADICI TENTATIVI CON GANCICLOVIR CON SCHEMI DIVERSI E CON RISULTATI DIVERSI
- I DATI RACCOLTI SI RIFERISCONO QUASI ESCLUSIVAMENTE A SOGGETTI CON ALTERAZIONI DEL SNC GIÀ PRESENTI ALLA NASCITA
- NON SI SA QUALE PUÒ ESSERE IL RISULTATO DEL TRATTAMENTO DI SOGGETTI CHE SVILUPPANO SUCCESSIVAMENTE I SINTOMI

SVILUPPO UDITIVO E NEUROLOGICO IN 9 BAMBINI CON INFEZIONE CONGENITA DA CMV TRATTATI CON GANCICLOVIR

(Da Michaels et al. *Pediatr Infect Dis J* 2003)

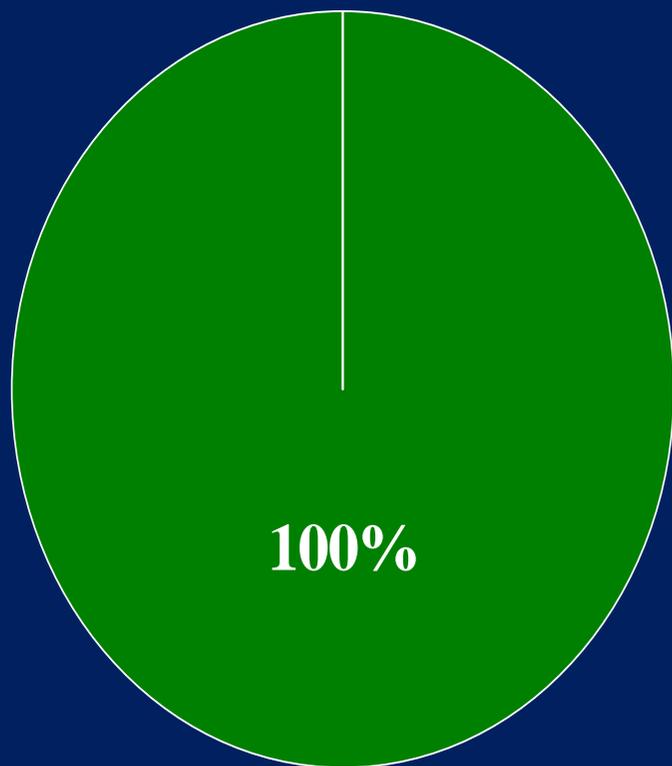
Patient	Age at Start of iv GCV	Duration of iv GCV (mo)	Duration of Oral GCV (mo)	Hearing Assessment at Time of Starting GCV	Age at Follow-up (yr)	Hearing Assessment at Follow-up	Hearing Change from Baseline to Most Recent Test*	Abnormal Development† at Initiation of Treatment	Abnormal Development† at Follow-up
1	11 mo	18	12	L-severe R-mild	7	L-severe R-normal	No change Improved	Yes	Yes
2	7 mo	15	36	L-normal R-severe	6	L-normal R-severe	No change No change	Yes	Yes
3	4.5 mo	12	10	L-severe R-normal	7	L-severe R-normal	No change No change	Yes	No
4	3 mo	12	12	L-moderate R-abnormal‡	2	L-mild R-normal	Improved No change	Yes	Yes
5§	10 days	6	6	L-passed R-passed	2	L-normal R-normal¶	No change No change	Yes	No
6§	4 days	12	24	L-passed R-passed	4	L-normal R-normal	No change No change	Yes	Yes
7§	3 days	12	10	L-failed R-passed**	2	L-mild-middle range Moderate-at low and high frequencies R-normal-middle range Mild-at high and low frequencies**	No change No change**	Yes	Yes
8§	10 days	9	10	L-passed†† R-passed	1.75	L-normal R-normal	No change No change	Yes	Yes
9§	7 days	5.5	6	L-passed R-passed	1	L-normal R-normal¶	No change No change	Yes	No

CASG Phase II Ganciclovir Study Virologic Response

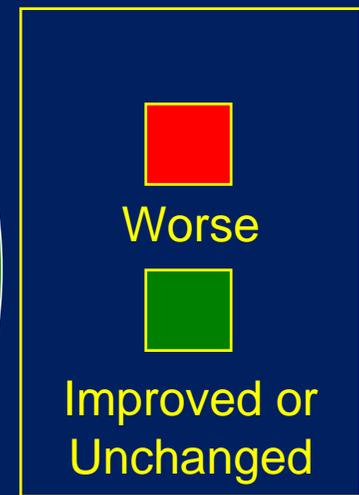
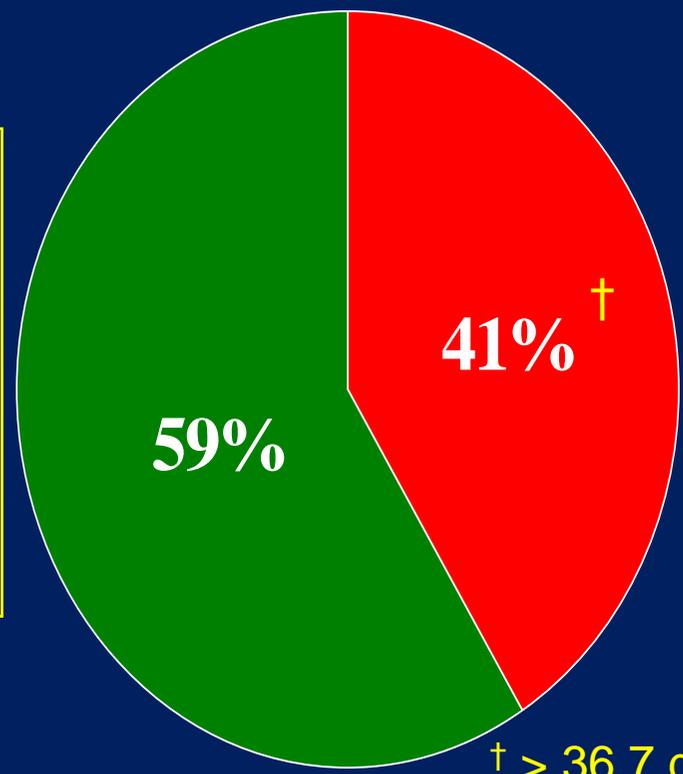


CASG PHASE III GANCICLOVIR STUDY CHANGE IN HEARING BETWEEN BIRTH AND 6 MOS.

Ganciclovir Recipients



No Treatment Group

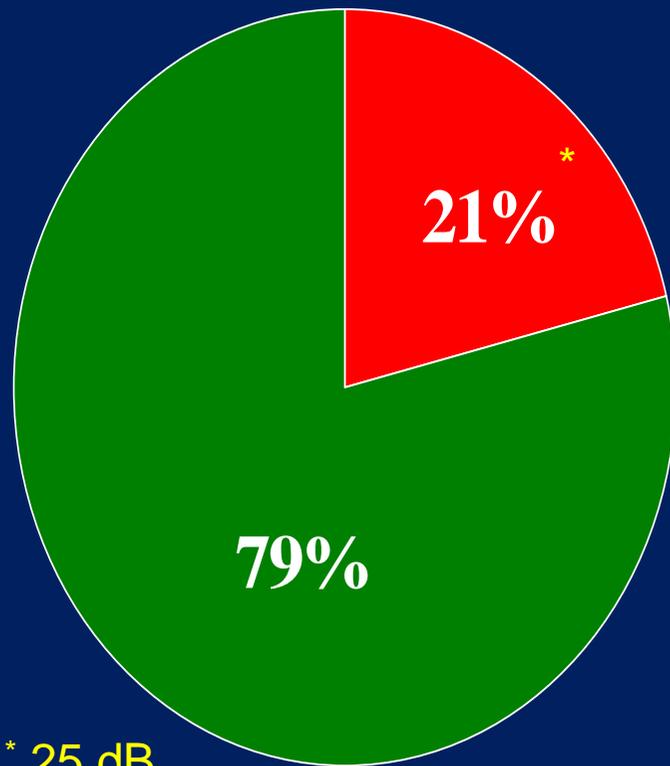


P < 0.01

J Pediatr 2003;143:16-25

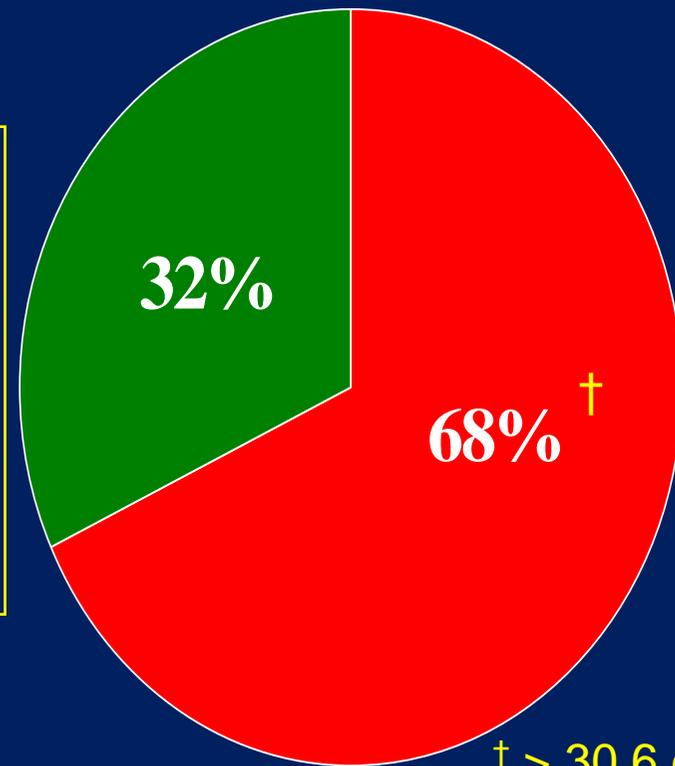
CASG PHASE III GANCICLOVIR STUDY CHANGE IN HEARING BETWEEN BIRTH AND ≥ 1 YR.

Ganciclovir Recipients

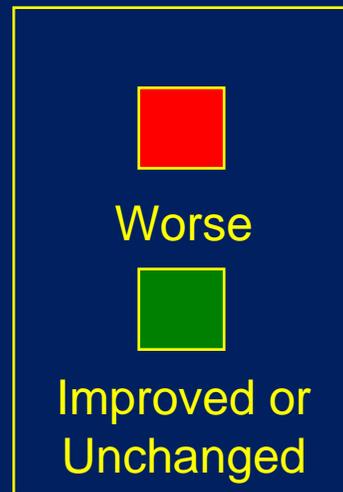


* 25 dB

No Treatment Group



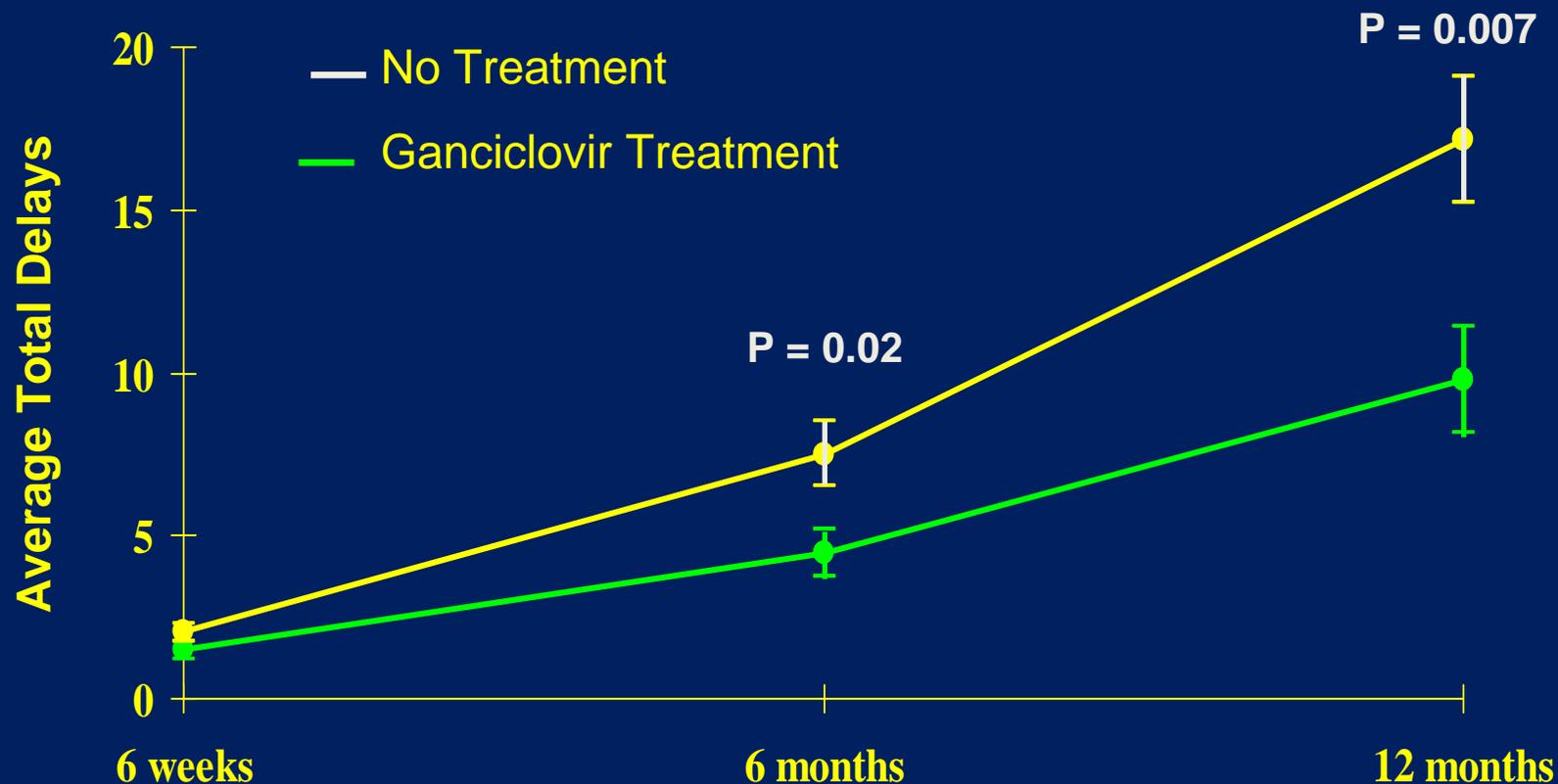
† > 30.6 dB



P < 0.01

J Pediatr 2003;143:16-25

CASG PHASE III GANCICLOVIR STUDY AVERAGE TOTAL DELAYS PER SUBJECT



APS/SPR Annual Meeting, San Francisco, April 29, 2006;
Abstract # 752908 J Clin Virol, 2009, In Press

CASG PHASE III GANCICLOVIR STUDY DEVELOPMENT OF NEUTROPENIA DURING THERAPY

	Treatment Group		
	Ganciclovir (n=47)	No Treatment (n=50)	
Grade 3-4 Neutropenia	29/46 (63%)	9/43 (21%)	<i>P</i> = 0.0001
Grade 3 ANC	18/46 (39%)	8/43 (19%)	
Grade 4 ANC	11/46 (24%)	1/43 (2%)	

TERAPIA DELL'INFEZIONE CONGENITA DA CMV

- LA TERAPIA CON GANCICLOVIR NEI SOGGETTI GIA' SINTOMATICI DA' RISULTATI MODESTI
- IL TRATTAMENTO MOLTO PROTRATTO NON E' BENE ACCETTO
- GLI EFFETTI COLLATERALI (COMPLICANZE DA CATETERE CENTRALE, NEUTROPENIA) SONO FREQUENTI
- MOLTO SI SPERA DAL VALGANCICLOVIR

CASG 109 (VERSION 2.0/3.0)

PK RESULTS

ORAL VALGANCICLOVIR DOSING

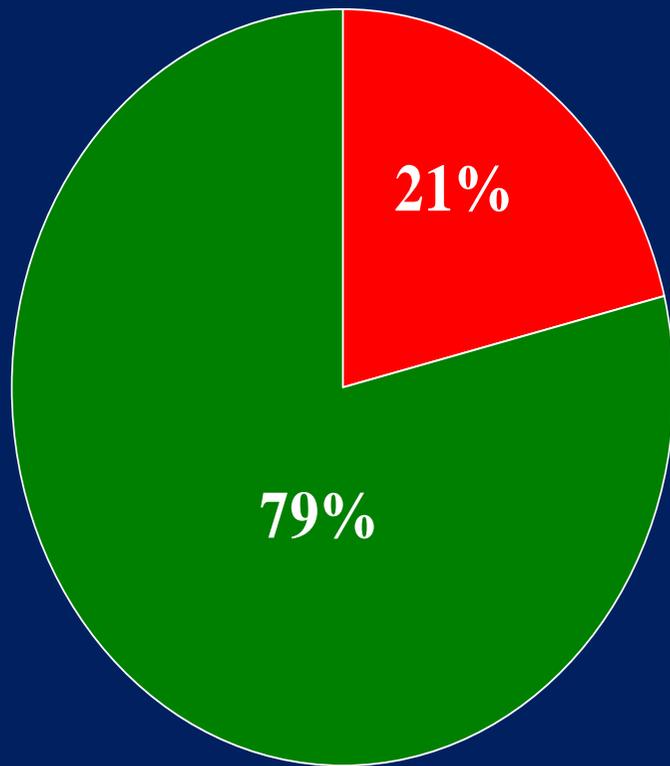
	Dose (mg/kg)	T _{1/2} (hr)	T _{max} (hr)	C _{max} (mg/L)	T _{last} (hr)	C _{last} (mg/L)	AUC ₁₂ (hr*mg/L)	V/F (L/kg)	CL/F (L/hr/kg)	CL/F (mL/min/kg)
Mean	15.85	2.98	3.39	5.44	10.45	1.06	30.10	2.17	0.56	9.26
GM	15.62	2.76	2.90	4.73	10.44	0.80	27.35	2.04	0.51	8.55
SD	2.88	1.26	1.82	4.05	0.54	0.86	15.10	0.60	0.23	3.75
CV	18.19	42.12	53.77	74.36	5.21	81.41	50.19	27.75	40.49	40.49
Min	14.00	1.18	1.11	1.98	10.00	0.28	12.63	0.46	0.25	4.11
Median	14.00	2.81	2.50	4.40	10.37	0.71	23.97	2.06	0.54	9.00
Max	20.00	5.79	5.87	20.92	12.00	3.46	72.91	3.02	1.06	17.67

IV GANCICLOVIR DOSING

	Dose (6 mg/kg)	T _{1/2} (hr)	T _{max} (hr)	C _{max} (mg/L)	T _{last} (hr)	C _{last} (mg/L)	AUC ₁₂ (hr*mg/L)	Vd (L/kg)	CL (L/hr/kg)	CL (mL/min/kg)
Mean		2.52	1.20	12.91	10.50	0.80	38.18	1.14	0.37	6.12
GM		2.47	1.10	7.09	10.49	0.42	25.45	0.80	0.22	3.74
SD		0.55	0.52	21.51	0.59	0.88	42.74	1.27	0.54	8.92
CV		21.73	43.22	166.64	5.62	110.51	111.97	112.00	145.73	145.73
Min		1.69	0.23	0.70	10.00	0.02	2.45	0.14	0.03	0.49
Median		2.40	1.08	5.95	10.30	0.52	25.49	0.88	0.22	3.74
Max		3.90	2.92	93.02	12.00	2.92	191.00	5.91	2.43	40.44

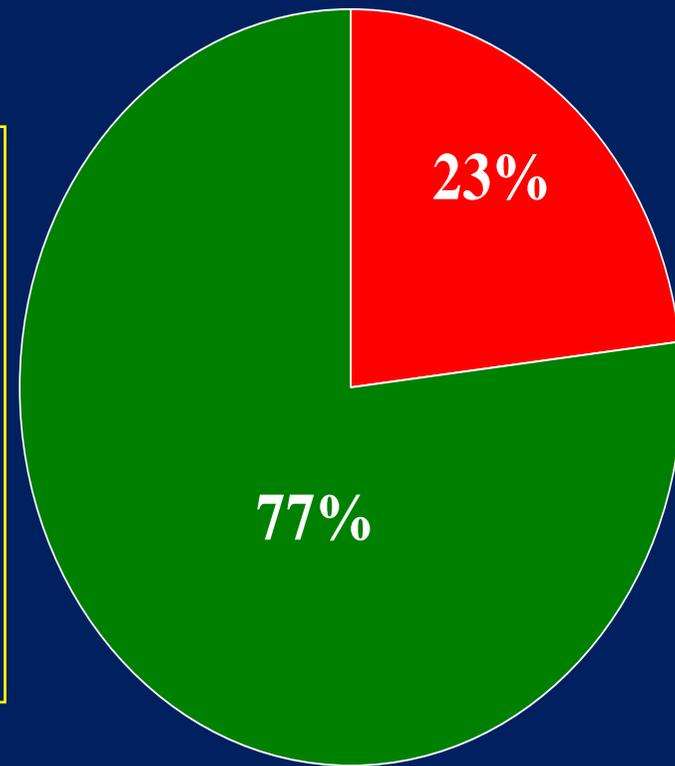
CHANGE IN HEARING BETWEEN BIRTH AND ~ 2 YR.

CASG 102 Ganciclovir Recipients



J Pediatr 2003;143:16-25

CASG 109 Valganciclovir Recipients

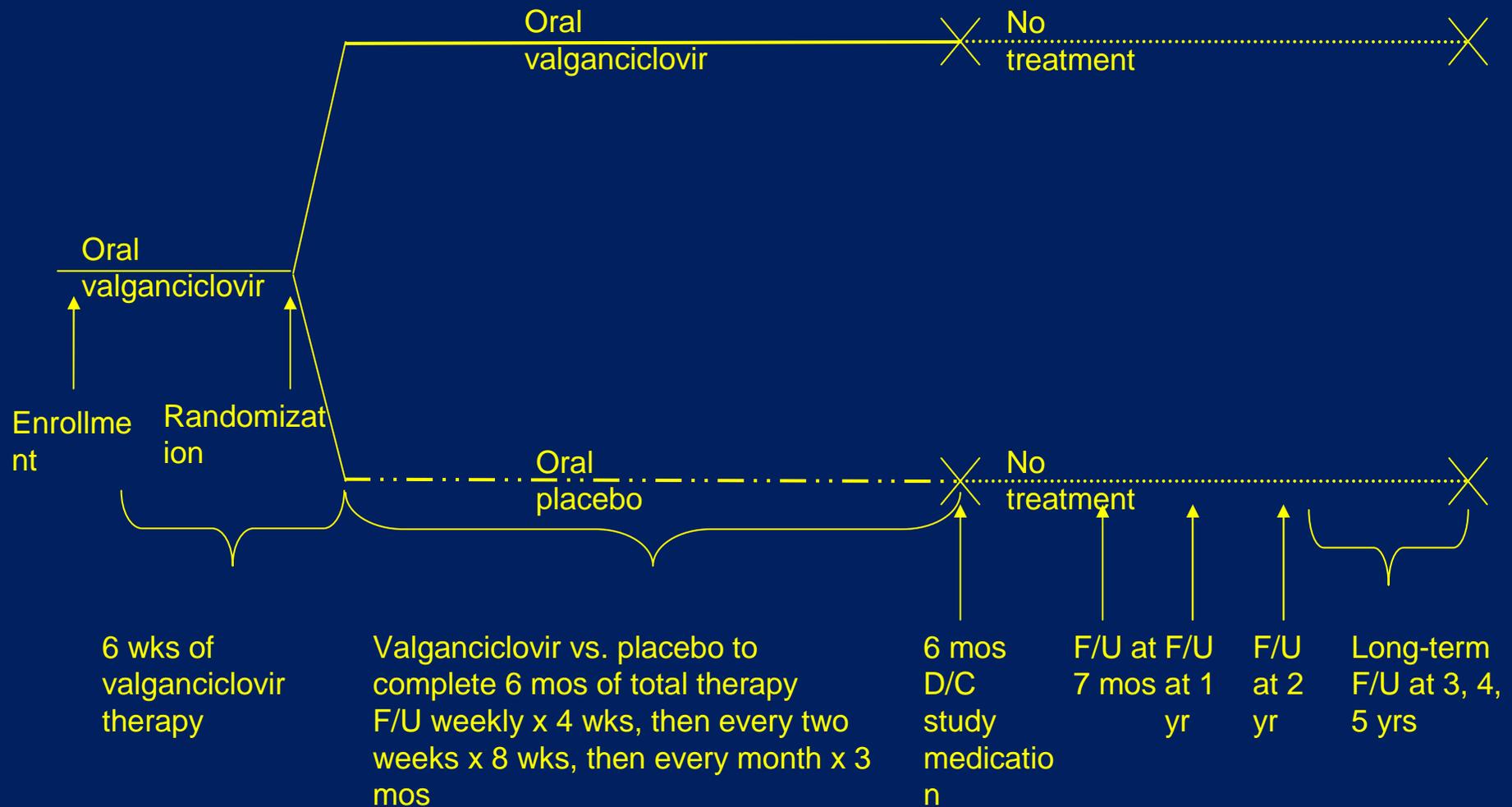


J Infect Dis 2008;197:836-845



CASG 112

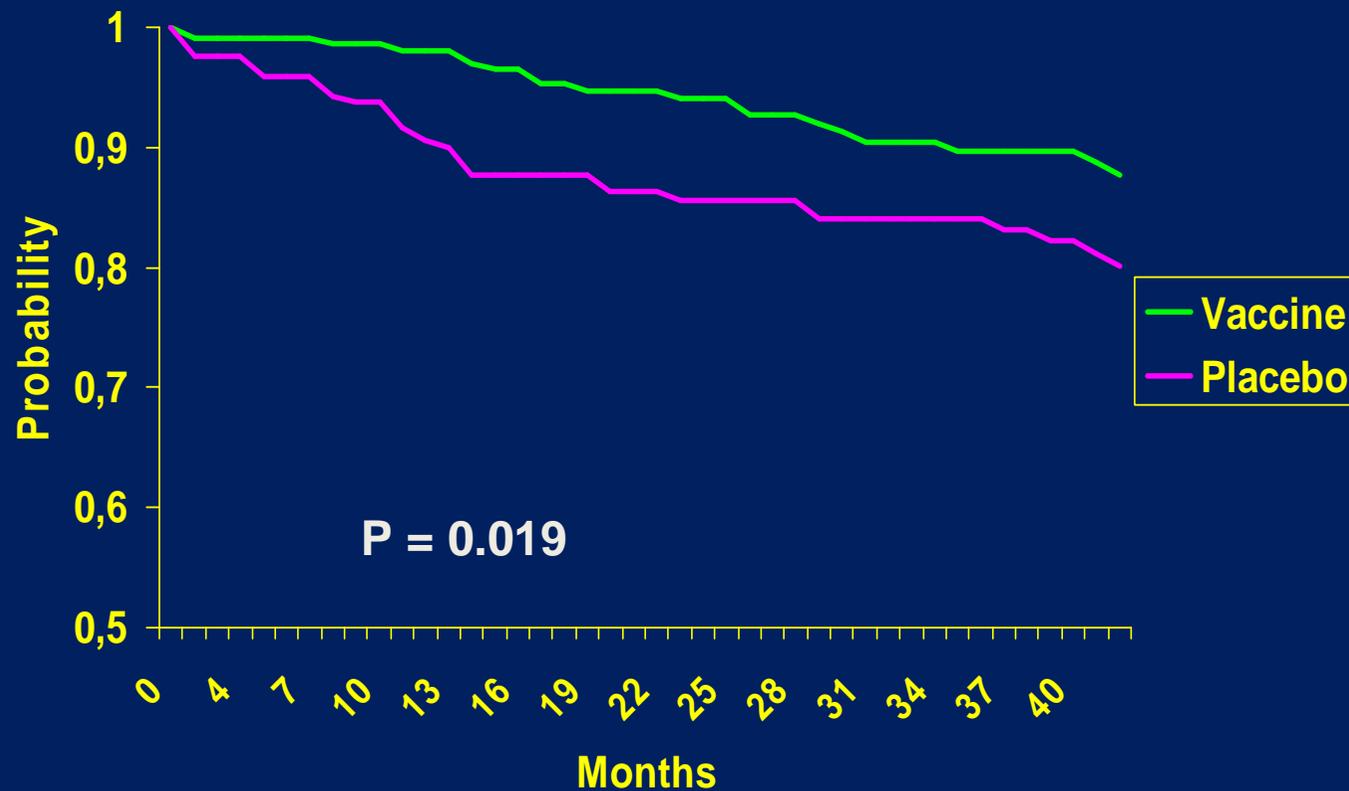
SCHEMATIC OF STUDY DESIGN



UAB Phase II Efficacy Trial of gB Vaccine

- Vaccines:
 - CMV gB, 20 μ g (Sanofi Pasteur) with MF59 (Novartis)
 - Saline placebo
 - Schedule: 0, 1, and 6 months
- Population: Healthy CMV seronegative women within 12 months of birth of a newborn
- Screening on post-partum wards
- Study sites:
 - UAB, Birmingham
 - UA College of Community Health Sciences, Tuscaloosa

UAB Phase II Efficacy Trial of gB Vaccine Probability of Remaining CMV Negative



NEJM 2009;360:1191-1199

UAB Phase II Efficacy Trial of gB Vaccine Preliminary Vaccine Efficacy Data

- Infection rates per 100-person years (over 42 months)
 - Vaccine, 3.3
 - Placebo, 6.6
 - Efficacy = 50%
- Cox proportional hazards, only regimen (CMVgB vs placebo) statistically significant
- Multivariate analysis: regimen, age, race, height
 - Only regimen significant, $P = 0.024$
 - Hazard ratio 0.51

IL FUTURO DELLA TERAPIA ANTIVIRALE

- Maggiore spazio per la prevenzione vaccinale invece che per farmaci antivirali
- Identificazione dei fattori immunogenetici associati a maggiore gravità delle malattie infettive virali
- Individualizzazione del trattamento da effettuare solo in casi selezionati