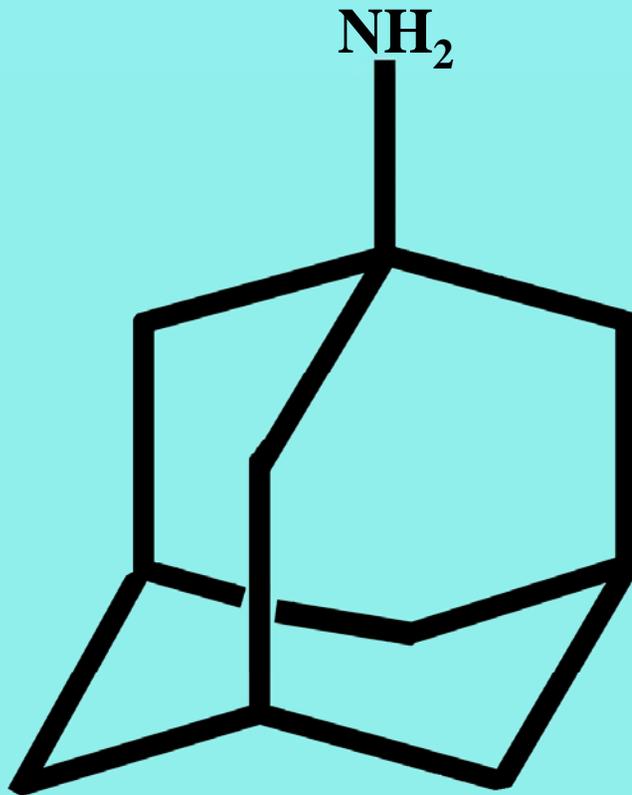
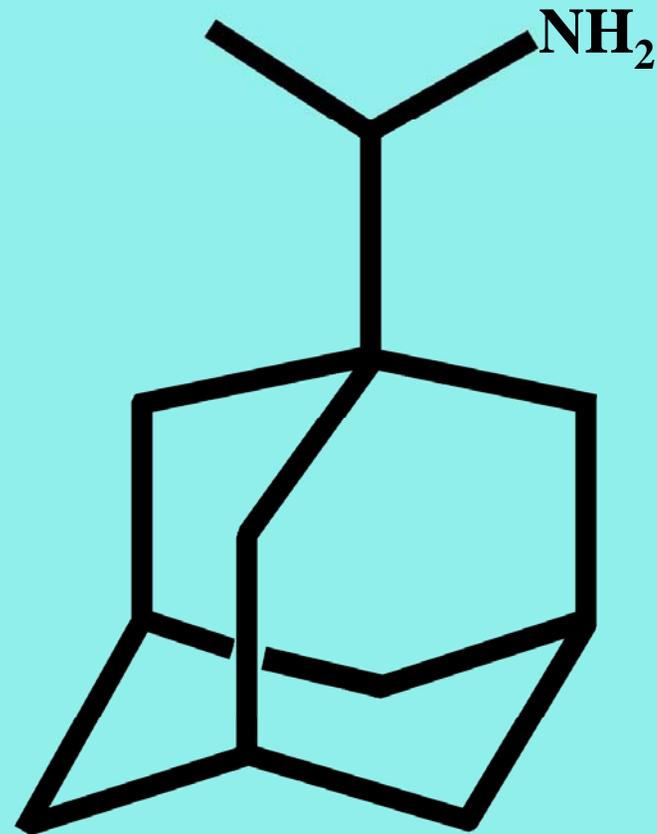

Safety and Efficacy of Antivirals for Influenza

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Amantadine and Rimantadine Structures



Amantadine

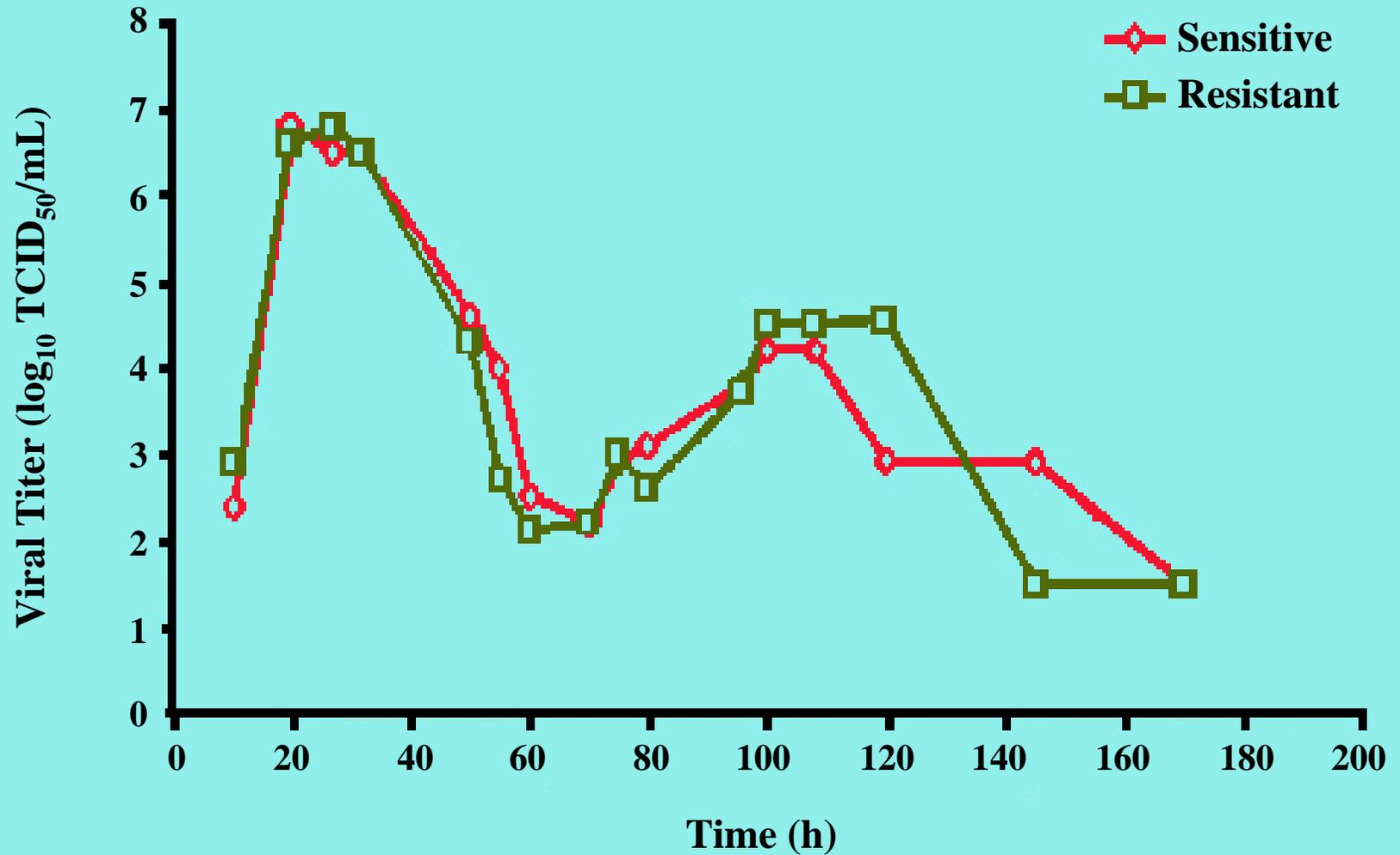


Rimantadine

Efficacy of Amantadine in Seasonal Prophylaxis of Type A (H1N1) Influenza and Frequency of Withdrawal

	Placebo	Amantadine
Symptomatic Lab-Confirmed Influenza	28/139 (20%)	8/136 (6%)
Efficacy \cong 70% (38–86% $P=0.01$)		
Influenza With/Without symptoms	42/139 (30%)	26/142 (18%)
Efficacy \cong 39% (7–61%) $P=0.028$		
Withdrawals	3/142 (2%)	12/144 (8%)
Risk Difference = 6%		

Amantadine-Resistant Influenza A Replication in Ferrets



Neuraminidase Inhibitors (NAIs)

- Active *in vitro* and in animal models against both influenza A and B viruses. More active against type A viruses than type B.
- Active against neuraminidases of all influenza A viruses tested (N1-N9)
- Zanamivir (GG167) *Relenza*
 - topically applied sialic acid analog
- Oseltamivir (GS4104, Ro 04-0796) *Tamiflu*
 - oral prodrug of GS4071, transition state analog

Population Characteristics

Characteristic	Placebo n=554	Zanamivir n=553
Non-vaccinated	86%	86%
Female	60%	59%
Age (mean)	28.6	29.0
Race:		
White	83%	82%
Black	7%	8%
Asian	5%	6%
Hispanic	2%	1%
Other	4%	3%
Site:		
Michigan	51%	52%
Missouri	49%	48%

Prevention of Laboratory-Confirmed Clinical Influenza

	<u>Placebo</u>	<u>Zanamivir</u>
	n=554	n=553
Illness		
Frequency:	34 (6%)	11 (2%)
Relative Risk (95% CI) \cong	0.33 (0.17-0.61)	
p<	0.001	
Efficacy \cong	67% (39-83%)	

Prevention of Febrile Influenza and Total Influenza Infections

	<u>Placebo</u>	<u>Zanamivir</u>
	n=554	n=553
<u>Lab-Confirmed Febrile</u>		
frequency:	19 (3%)	3 (<1%)

Efficacy = 84% (55-94%)

<u>All Influenza infections</u>		
frequency:	77 (14%)	53 (10%)

Efficacy = 31% (4-50%)

Adverse Events

	<u>Placebo</u>	<u>Zanamivir</u>
	n=554	n=553
<u>Event:</u>		
Possibly related	27 (5%)	30 (5%)
Any serious event	1 (<1%)	1 (<1%)
Withdrawal		
- any	17 (3%)	10 (2%)
- related to adverse event	6 (1%)	4 (<1%)

Prevention of Confirmed Clinical Influenza (Temperature ≥ 37.2) with Oseltamivir Over 6 Weeks

	Placebo	75 mg qd	75 mg bid	Combined prophylaxis groups
All sites	25/519 (4.8%)	6/520 (1.2%)	7/520 (1.3%)	13/1040 (1.3%)
Efficacy % (95% CI)	—	76 (46 to 91)	72 (40 to 89)	74 (53 to 88)
Virginia	19/268 (7.1%)	3/268 (1.1%)	4/267 (2.3%)	7/535 (1.3%)
Efficacy % (95% CI)	—	84 (53 to 96)	79 (45 to 94)	82 (60 to 93)
Texas & Kansas	6/251 (2.4%)	3/252 (1.2%)	3/253 (1.2%)	6/502 (1.2%)
Efficacy % (95% CI)	—	50 (-55 to 94)	50 (-54 to 94)	50 (-23 to 93)

*Modified from Hayden et al. NEJM 1999; 341:1336-43.

Prevention of Laboratory-Confirmed Clinical Influenza with Fever & Total Influenza Infections with Oseltamivir Over 6 Weeks

	Placebo	Once Daily	Twice Daily	Combined
Laboratory-Confirmed:				
Influenza with fever (≥ 37.8)	19/519 (2.9%)	2/520 (0.4%)	5/520 (1.0%)	7/1040 (0.7%)
Efficacy (95% CI)	—	90 (61 to 98)	74 (37 to 91)	82 (60 to 93)
Influenza Infections	55/519 (10.6%)	28/520 (5.4%)	27/520 (5.2%)	55/1040 (5.3%)
Efficacy (95% CI)	—	49 (24 to 69)	51 (26 to 70)	50 (31 to 67)

*Modified from Hayden et al. NEJM 1999; 341:1336-43.

Adverse events occurring at > 1% in phase III studies of oseltamivir

Number of subjects (%) experiencing event in following groups

	Tamiflu 75 mg bid (n=724)	Placebo (n=716)
Nausea (no vomiting)	72 (9.9)	40 (5.6)
Vomiting	68 (9.4)	21 (2.9)
Bronchitis	17 (2.3)	15 (2.1)
Insomnia	8 (1.1)	6 (0.8)
Vertigo	7 (1.0)	3 (0.4)

Population (N=1440) included 945 healthy young adults and 495 “at-risk” patients (elderly patients and patients with chronic cardiac or respiratory disease).

*Includes only adverse events occurring with a greater frequency in patients taking Tamiflu compared with the placebo group.

Potential Upper Gastrointestinal Side Effects

	Placebo % n = 519	75 mg qd % n = 520	75 mg bid % n = 520
Nausea	7.1	12.1	14.6
Difference (95% CI)	—	5.0 (1.4 to 8.6)	7.5 (3.7 to 11.2)
Vomiting	0.8	2.5	2.7
Difference (95% CI)	—	1.7 (0.2 to 3.3)	1.9 (0.3 to 3.5)

*Modified from Hayden et al. NEJM 1999; 341:1336-43.

Influenza Prophylaxis in Vaccinated Frail Elderly: Study Design

- Double-blind, placebo-controlled randomized, multicenter study
- Elderly (≥ 65 y) occupants of residential homes
- Subjects pre-screened for eligibility and to obtain consent
- Prophylaxis started when local influenza activity detected by surveillance
- Subjects randomized to receive placebo or oseltamivir 75mg once daily over a 6 week period, plus 2 weeks follow-up period

Influenza Prophylaxis in Vaccinated Frail Elderly: Primary Endpoint

A total of 13 laboratory-confirmed clinical influenza cases were identified in 9 outbreaks.

N	Placebo	Oseltamivir 75 mg q.d.	Protective Efficacy
ITT population	12 (9%)	1 (0.7%)*	92%

* p = 0.002 compared with placebo

Post-Exposure Prophylaxis

Zanamivir

- Index case treated
- Size of household: 2-5 persons
- Children < 5 years of age excluded as contacts
- Zanamivir 10 mg twice daily for 5 days for therapy
Zanamivir 10 mg once daily for 10 days for prophylaxis
- First dose within 36 hours of first symptoms in IC
- All household members receive same drug or placebo

Relative Risk of Laboratory-confirmed Influenza in Household Contacts (Zanamivir Study)

Laboratory-Confirmed Influenza in Contact	Placebo	Zanamivir	Relative Risk (95% CI)	P Value	Protective Efficacy (95% CI)
	No. of families/total no. (%)				%
All symptomatic cases					
Intention-to-treat analysis	32/168 (19.0)	7/169 (4.1)	0.21 (0.11-0.43)	<0.001	79 (57-89)
Influenza-positive index case	25/87 (28.7)	6/78 (7.7)	0.28 (0.13-0.58)	<0.001	72 (42-87)
Influenza A	15/58 (25.9)	3/52 (5.8)	0.23 (0.08-0.64)	0.009	77 (36-92)
Influenza B	10/29 (34.5)	3/26 (11.5)	0.32 (0.10-1.00)	0.099	68 (0-90)
Influenza-negative index case	7/83 (8.4)	1/89 (1.1)	0.13 (0.02-0.72)	0.04	87 (28-98)
Onset of symptoms =1 day after start of prophylaxis					
Intention-to-treat analysis	25/168 (14.9)	4/169 (2.4)	0.16 (0.06-0.38)	<0.001	84 (62-94)
All cases (symptomatic and asymptomatic)					
Intention-to-treat analysis	47/168 (28.0)	22/169 (13.0)	0.47 (0.30-0.73)	0.001	53 (27-70)
Influenza-positive index case	33/87 (37.9)	15/78 (19.2)	0.52 (0.32-0.85)	0.014	48 (15-68)

In five families with influenza-positive index cases (four families in the placebo group and one in the zanamivir group), household contacts had influenza of a different type from that of the index case.

*Hayden et al. Inhaled zanamivir for the prevention of influenza in families. NEJM. 2000;343:1282-9.

Post-Exposure Prophylaxis

Oseltamivir

- Index case not treated
- Size of household: 2 to 8 contacts
- Children < 12 years excluded as contacts
- Oseltamivir 75 mg or placebo for 7 days
- First dose within 48 hours of first symptoms in Index Case (IC)
- All household members receive drug or placebo

Number of Contracts Receiving Oseltamivir 75 Mg Once Daily or Placebo With Laboratory-confirmed Clinical Influenza During the Prophylaxis Period

	Placebo	Oseltamivir	Protective efficacy [95% CI]	P value
ITT population				
Individuals	34/462 (7.4%)	4/493 (0.8%)	89% [71%-96%]	.000003
Affected households	26/178 (14.6%)	4/193 (2.1%)	86% [60%-95%]	<.0001
Contacts of an influenza positive IC				
Individuals	26/206 (12.6%)	3/209 (1.4%)	89% [67%-97%]	.00009
Affected households	18/79 (22.8%)	3/84 (3.6%)	84% [49%-95%]	.0003
Contacts of an influenza negative IC				
Individuals	8/256 (3.1%)	1/284 (0.4%)	89% [10%-99%]	.009
Affected households	8/99 (8.1%)	1/109 (0.9%)	89% [10%-99%]	.015

*Welliver R et al. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. JAMA. 2001;In press.

Influenza Prevention in Household Studies with NAI's

Antiviral (Study)	Season (Virus)	Reduction in Secondary Cases %	Resistance Transmission
<u>No Treatment of Index</u>			
Zanamivir* (Monto et al, 2002)	2000-01 (A/H3N2, B)	81%	—
Oseltamivir (Welliver et al, 2001)	1998-99 (A/H3N2, B)	89%	—
<u>With Treatment of Index</u>			
Zanamivir* (Hayden et al, 2000)	1998-99 (A/H3N2, A/H1N1)	79%	No
†Oseltamivir (Hayden et al, 2004)	2000-01 (A/H3N2, B)	85%	No

*Prophylaxis is given ≥ 5 years.

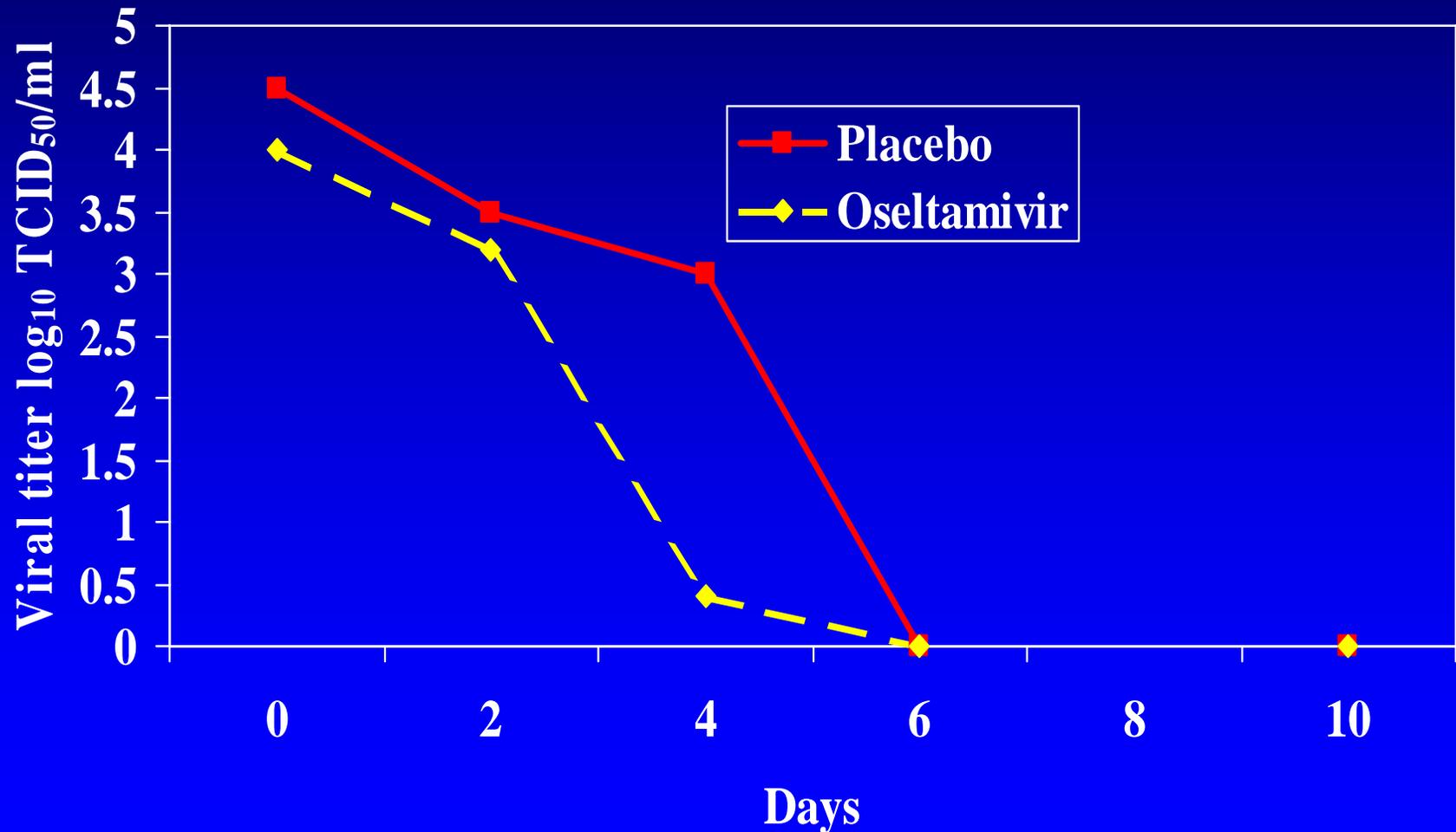
†Excludes contacts positive for influenza prior to prophylaxis.

Demographic Characteristics of the Intent to Treat Population

Demographic Characteristic	Placebo (n = 351)	Oseltamivir (n = 344)
Sex (males)	179 (51)*	171 (50)
Median age, yr (range)	5 (1-12)	5 (1-12)
Median wt, kg (range)	20 (8-85)	20 (8-69)
Race		
Caucasian	229 (65)	222 (65)
Hispanic	61 (17)	62 (18)
Black	39 (11)	37 (11)
Oriental	6 (2)	7 (2)
Other	16 (5)	16 (5)

*Numbers in parentheses, percent unless otherwise stated.

Median Viral Titers Over Time

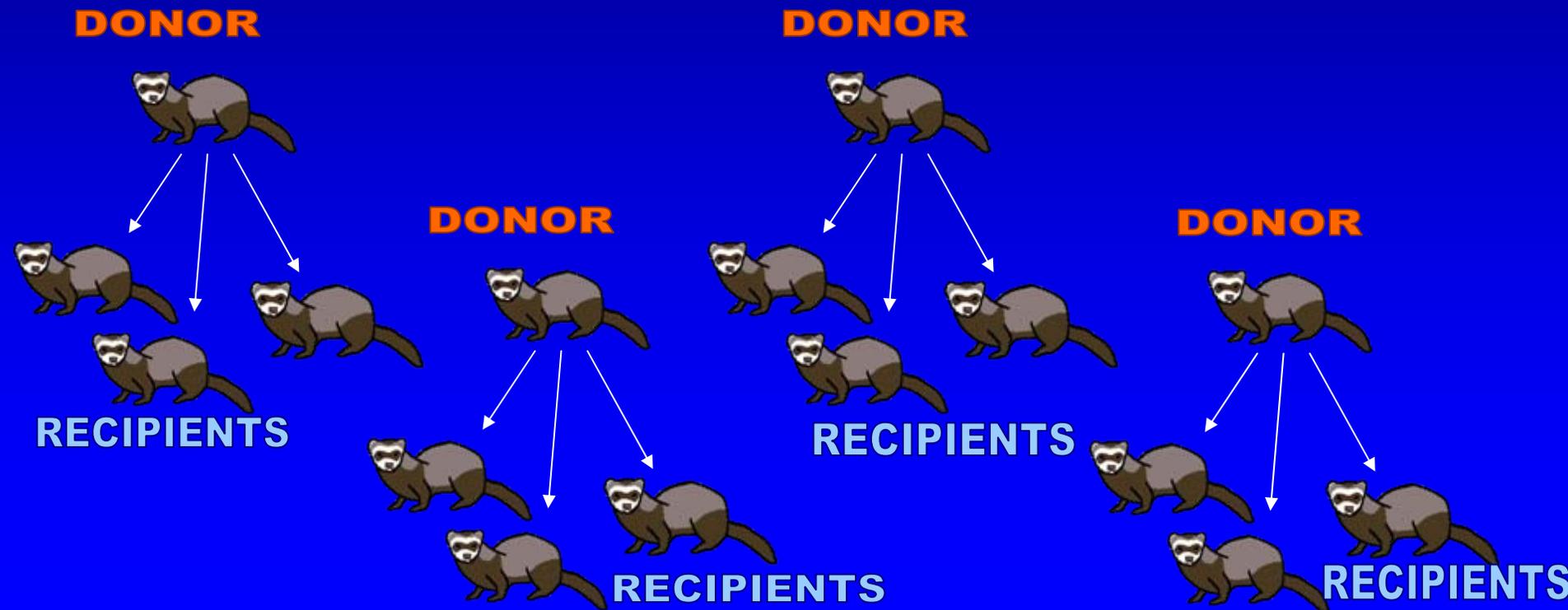


Current Situation with the A(H1N1) resistance

- Outbreak in Europe during 2007-2008 mainly H1N1
- Resistance (H274Y) high in certain countries: Norway, 67%, Belgium 53%, France and Russia 45%
- Other countries much lower: UK 11%
- No correlation with use of oseltamivir – Japan = 3%, USA 12%
- Now, 100% of isolates in South Africa are resistant. Variable in other countries.

Ferret Transmission Model

- Four donors and 12 recipients each for wt and mt
- Groups of four housed together in cage



Comparisons of Infectivity and Transmissibility of WT and MUT Pairs for NA Genotypes Isolated During Treatment Studies

Wild type [WT] and Mutant [MUT] pairs isolated from pre- and follow-up specimens from the same subject	Infectious dose	Donor infection status	Recipient infection status	Sequence confirmation of WT or MUT NA genotype
A/Sydney/5/97-like (H3N2) R292 - WT	2.3 TCID ₅₀ /0.5 ml	4 of 4	12 of 12	WT
R292K – MUT	Same	2 of 4	3 of 6	*Reversion to WT
A/Wuhan/359/95-like (H3N2) E119 - WT	1.0 x 10 ⁻⁶ Dilution of stock	4 of 4	11 or 11	WT
E119V - MUT	1.0 x 10 ⁻⁶ Dilution of stock	4 of 4	11 or 11	MUT
A/New Calendonia (H1N1) H274 – WT	1.5 x 10 ⁻⁶ Dilution of stock	4 of 4	12 or 12	WT
H274Y – MUT	1.5 x 10 ⁻⁵ Dilution of stock	0 of 4 @ day 7	0 of 12 @ day 7	
	1.5 x 10 ⁻³ Dilution of stock	4 of 4	12 of 12	MUT

Summary

- Adamantanes prevent type A influenza illness and infection. Rimantadine has fewer side effects. Resistance common in treatment and resistant viruses are fit.
- Zanamavir and oseltamivir equally prevent influenza illness and infection in seasonal prophylaxis. Low level GI side effects documented with oseltamivir.
- Efficacy in post-exposure studies of both drugs is similar. Some early transmission may take place.
- Resistance to the NAIs was thought to be of low frequency and produced by drug pressure in treatment. Some resistant variants were found to be fit, others not. There is no clear relation of the current A(H1N1) situation to drug pressure.