
Influenza: Unmet Needs and Future Approaches

Richard Whitley
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Considerations

- Therapeutic Approaches
 - Treatment of Disease
 - Post-exposure prophylaxis (PEP)
- High Risk Populations
 - Children
 - Pregnant Women
 - Immunocompromised Hosts
- Potential Toxicity
- Resistance
- Future Therapeutic Approaches

Current Antivirals for Influenza

- Oseltamivir
 - Treatment of influenza in persons ≥ 1 yoa
 - Prophylaxis of influenza in persons ≥ 1 yoa
- Zanamivir
 - Treatment of influenza in persons ≥ 7 yoa
 - Prophylaxis of influenza in persons ≥ 5 yoa
- Amantadine
 - Influenza A strains only
 - High levels of resistance \rightarrow since 2006, not recommended for use in U.S.
- Rimantadine
 - Influenza A strains only
 - High levels of resistance \rightarrow since 2006, not recommended for use in U.S.

Neurotoxicity: Is it Real?

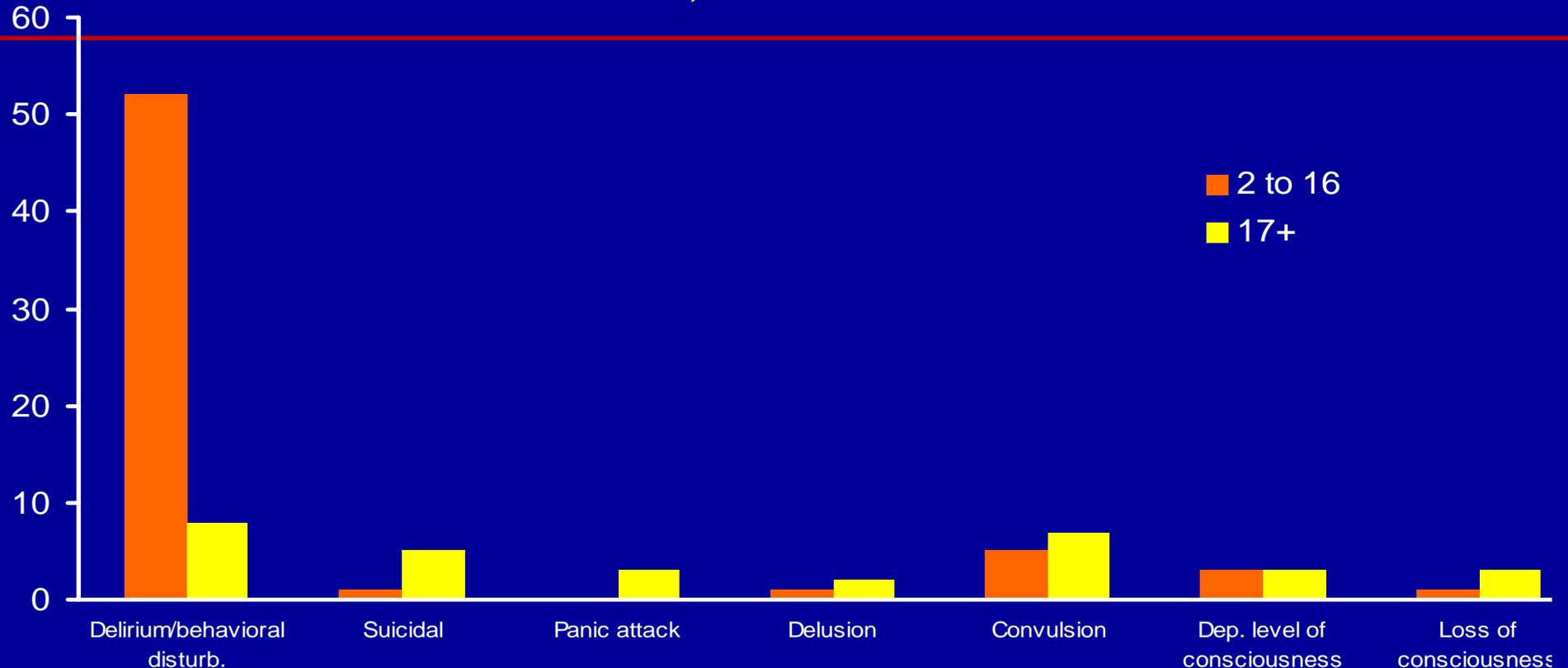
Juvenile Toxicology Studies in Rats

- Oseltamivir metabolism in rats is substantially different than in humans
 - In humans, majority of prodrug is converted to carboxylate metabolite on first pass through liver
 - In rats, conversion to metabolite is much slower and does not occur in liver
 - Plasma half-life of prodrug in rats is ~ 5 times longer than in man
- Four retrospective studies of oseltamivir in human infants and children
 - Japan, n=103
 - Japan, n=771
 - Japan, n=1,674
 - U.S., n=180 (CASG 113)
 - No evidence of encephalopathy seen in these retrospective studies

Oseltamivir and Behavioral Concerns

- 103 neuropsychiatric adverse events
 - 67% in patients under 18 yoa
 - 95% foreign (Japan)
 - 10-times the use of oseltamivir c/w U.S.
 - Half the population of U.S.
 - Eight categories
 - Delirium with prominent behavioral disturbances
 - Suicidal events
 - Panic attack
 - Delusions
 - Convulsions
 - Depressed level of consciousness
 - Loss of consciousness
 - Miscellaneous

Number of AERS Neuropsychiatric Reports by age Group and Category, Oseltamivir, 8/05-7/06, Worldwide



FDA Review Oseltamivir Safety Neuropsychiatric Events

- 129 AERS reports returned
- 26 excluded
 - Narrative did not support
 - Medication errors
 - Confounded by concurrent medical or psychiatric disorders
- 103 cases included in review
 - 95 from Japan, 5 from U.S., 3 from other countries
 - Median age = 12 yrs (range 1½ - 90)
 - Only 3 involved prophylactic use
 - 69 M, 32 F

Oseltamivir and Behavioral Concerns

- Real vs. artifact?
- Influenza vs. oseltamivir?
- Genetic predisposition vs. high use of drug?
- FDA modified label on November 13, 2006
 - Precautions section of PI now has Neuropsychiatric Events subheading:
“There have been postmarketing reports (mostly from Japan) of self-injury and delirium with the use of TAMIFLU in patients with influenza. The reports were primarily among pediatric patients. The relative contribution of the drug to these events is not known. Patients with influenza should be closely monitored for signs of abnormal behavior throughout the treatment period.”

*A Retrospective Chart Review to Assess the Safety
of Oseltamivir (Tamiflu[®]) Compared to Alternate
Antiviral Therapy (Amantadine or Rimantadine)
Administered to Children Less Than 12 Months of
Age with Diagnosed or Suspected Influenza*

Characteristics by Treatment Group

	Oseltamivir n=115	Rimantadine or Amantadine n=65	Total n=180	P-value
Hospitalization				
Inpatient	105 (91.3%)	52 (80%)	157 (87.2%)	0.0369
Outpatient	10 (8.7%)	13 (20%)	23 (12.8%)	
Virus				
Type A	77 (83.7%)	51 (100%)	128 (89.5%)	0.0011
Type B	15 (16.3%)	0 (0%)	15 (10.5%)	
Term vs. Preterm				
Preterm	7 (9.9%)	9 (29%)	16 (15.7%)	0.0348
Term	63 (88.7%)	22 (71%)	85 (83.3%)	
Neonatal Course				
Normal	48 (50%)	25 (48.1%)	73 (49.3%)	0.8644
Abnormal	48 (50%)	27 (51.9%)	75 (50.7%)	

Abnormalities During Therapy

	Oseltamivir n=115	Rimantadine or Amantadine n=65	P-value
Neurologic	21 (18.26%)	17 (26.15%)	0.25
Pulmonary	60 (52.17%)	30 (46.15%)	0.53
Gastrointestinal	28 (24.34%)	14 (21.53%)	0.72
Cardiovascular	5 (4.34%)	5 (7.69%)	0.50
HEENT	2 (1.73%)	10 (15.38%)	< 0.01
Dermatologic	5 (4.34%)	4 (6.15%)	0.72
Body as a whole	5 (4.34%)	4 (6.15%)	0.72
Genitourinary	4 (3.47%)	2 (3.07%)	1.00
Musculoskeletal	2 (1.73%)	0 (0%)	0.54
Hematologic/Lymphatic	7 (6.08%)	2 (3.07%)	0.49
Hepatobiliary/Pancreatic	4 (3.47%)	0 (0%)	0.30
Endocrine/Metabolic	0 (0%)	1 (1.53%)	0.36

Neurologic Abnormalities During Therapy

	Oseltamivir n=115	Rimantadine or Amantadine n=65
Agitated	1	0
Cerebral edema	1	0
Hydrocoele	0	1
Hypertonia	1	0
Hyporeflexia	0	1
Hypotonia	2	1
Irritable	13	13
Left hemiparesis	1	0
Sedated	2	1
Seizure	2	2
Tone	1	0

Tricare Retrospective Chart Review

- Tricare military electronic data base review
 - Oct 1, 2006 to Sept 30, 2007
- 18,109 charts reviewed (confirmed influenza)
 - 7,798 received oseltamivir
 - 10,411 did not receive antiviral therapy
- 628 (3.5%) received a neuropsychiatric diagnosis
 - 3.0% in the oseltamivir group
 - 3.8% in the no treatment group

Odds Ratio of a Neuropsychiatric Event

	OR	95% CI
Oseltamavir Rx	0.82	(0.69, 0.96)
Gender		
Male	1.06	(0.91, 1.25)
Female	*	*
Age (years)		
1-4	0.71	(0.54, 0.94)
5-8	*	*
9-12	1.15	(0.90, 1.49)
13-16	1.98	(1.56, 2.52)
17-21	2.58	(2.05, 3.25)
* Reference value		

Do We Know How to Treat Infants?

A Pharmacokinetic/Pharmacodynamic and Safety
Evaluation of Oseltamivir (Tamiflu[®]) for the
Treatment of Children Less Than 24 Months of Age
with Confirmed Influenza Infection

Study Objectives

- Primary
 - To define the pharmacokinetics of oseltamivir and oseltamivir carboxylate in children with confirmed influenza less than two years of age.
- Secondary
 - To describe the frequency of all adverse events, including neurologic adverse events, among treated children.
 - To assess the clearance of virus (culture) and viral RNA (PCR) as a function of drug pharmacokinetics.
 - To determine the potential for the development of resistance to oseltamivir as a function of pharmacokinetics and age.

Inclusion Criteria

- Signed informed consent from parent(s) or legal guardian(s)
- Age:

Cohort I	12 – 23 mos.	Enrolled (12 pts)
Cohort II	9 – 11 mos.	Enrolling (7/12 pts)
Cohort III	6 – 8 mos.	Enrolled (12 pts)
Cohort IV	3 – 5 mos.	Open to Enrollment
Cohort V	0 – 2 mos.	
- Confirmed laboratory diagnosis of influenza by viral culture or rapid influenza diagnostic test within 96 hours prior to study enrollment
- Duration of influenza symptoms \leq 96 hours

Resistance

Prevalence of resistance to existing antivirals

Global Prevalence of Resistance to Adamantanes 2005-2006

Subtype	Prevalence
H3N2	90.6%
H1N1	15.6%

Deyde et al., J Infect Dis. 2007, 196:249.

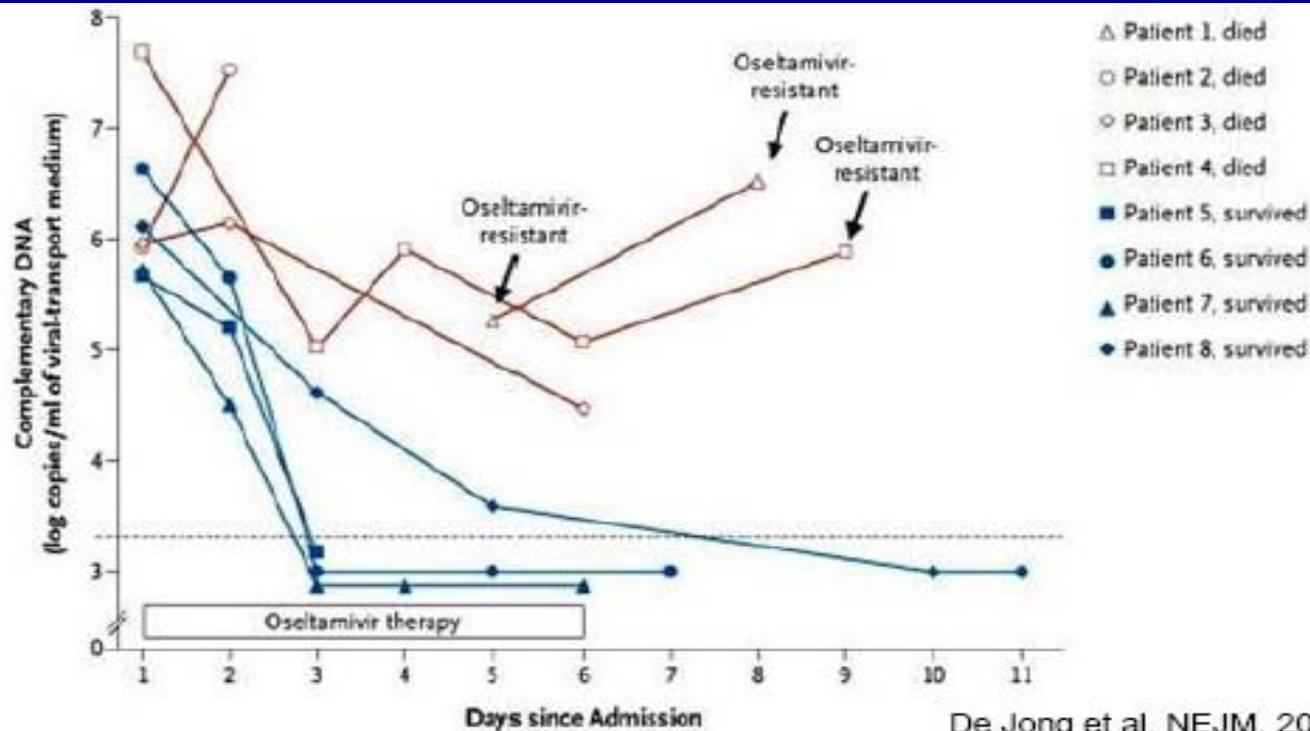
Prevalence of Resistance to Oseltamivir (H1N1) 2008

Region	Prevalence
Africa	88%
Americas	29%
Europe	55%
Asia & Oceania	23%

WHO, 14 October 2008

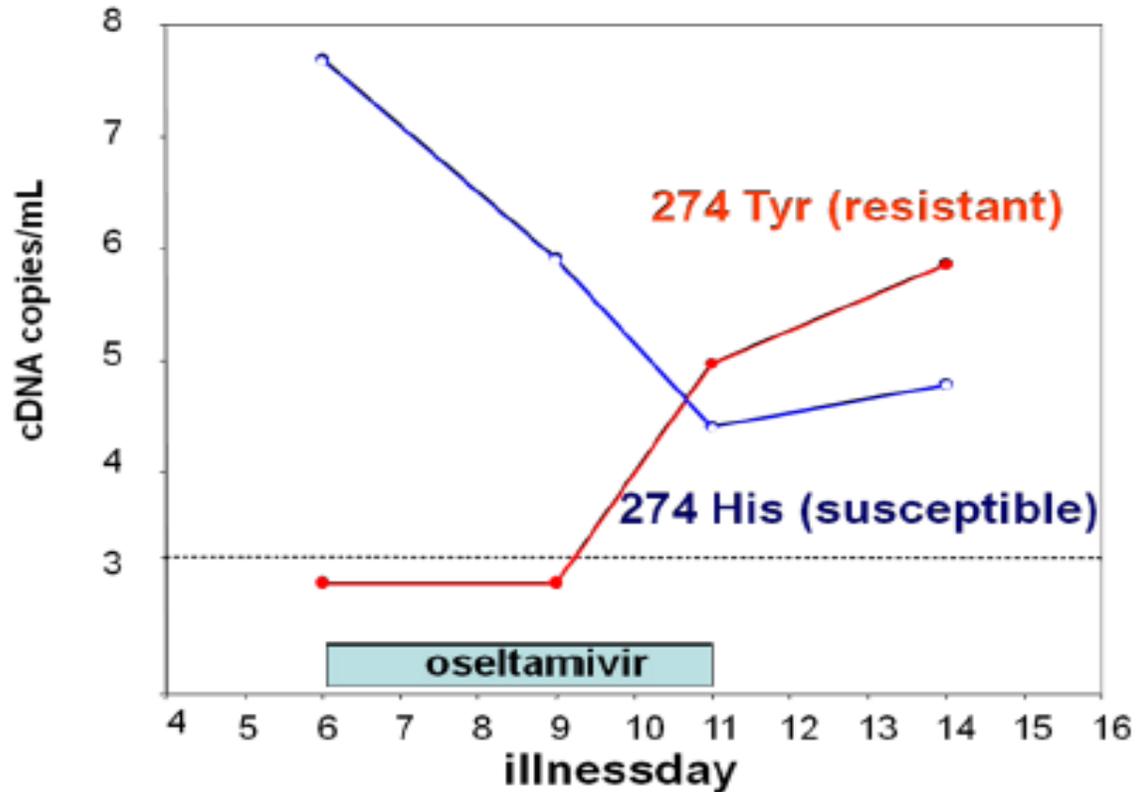
What is the need today for treatment of severe influenza.....

We have seen multidrug-resistant H5N1 emerge



De Jong et al. NEJM, 2005, 353: 2667;
Endpoint genotype by Sanger Sequencing

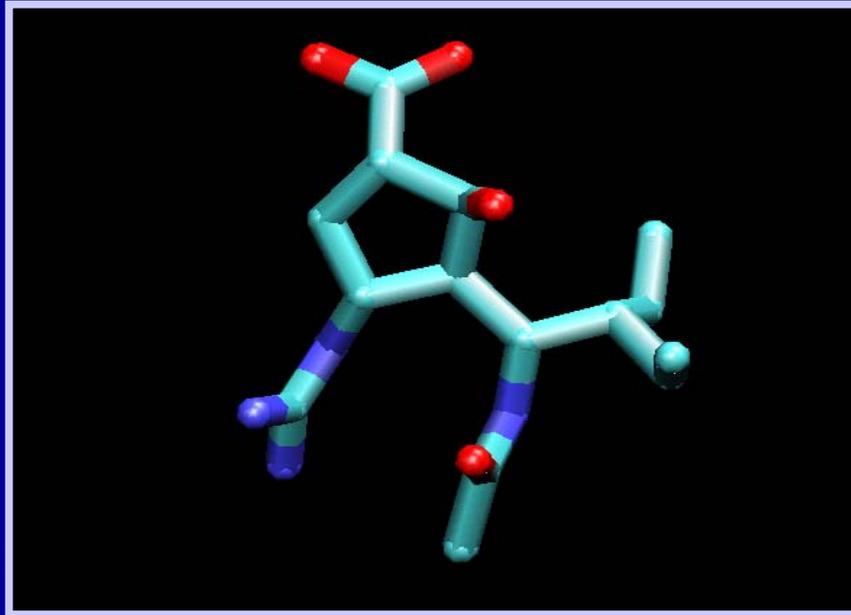
What is the need today for treatment of severe influenza?and it emerges quickly



Menno De Jong, Tran Tan Thanh
Pyrosequencing, 150 clone Sanger Sequencing

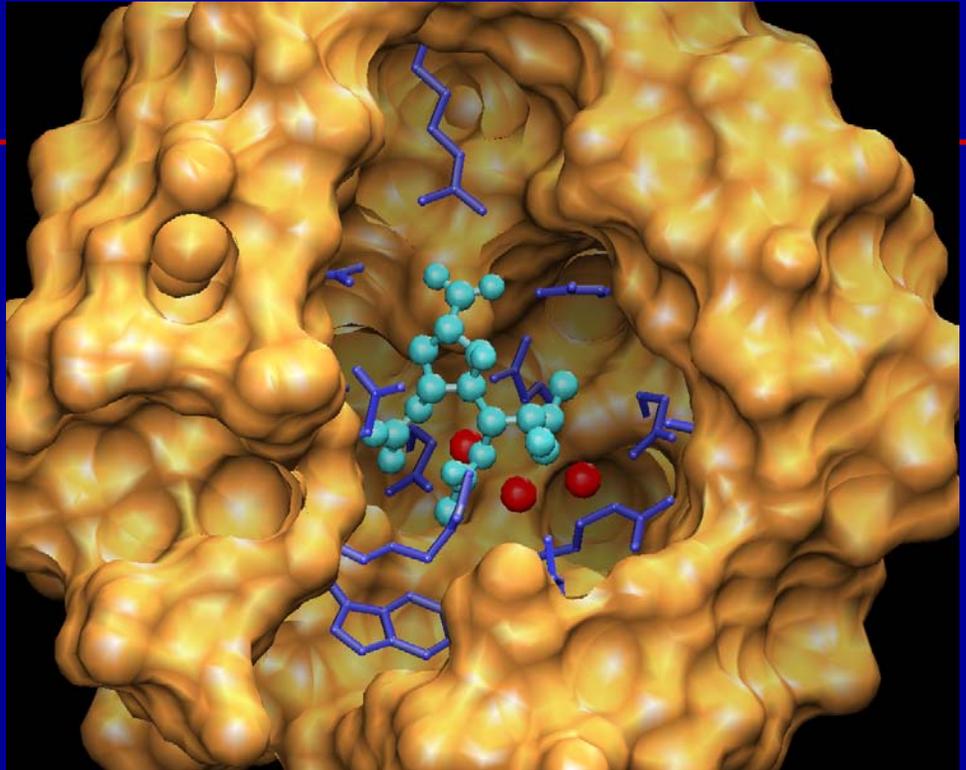
New Approaches

Peramivir



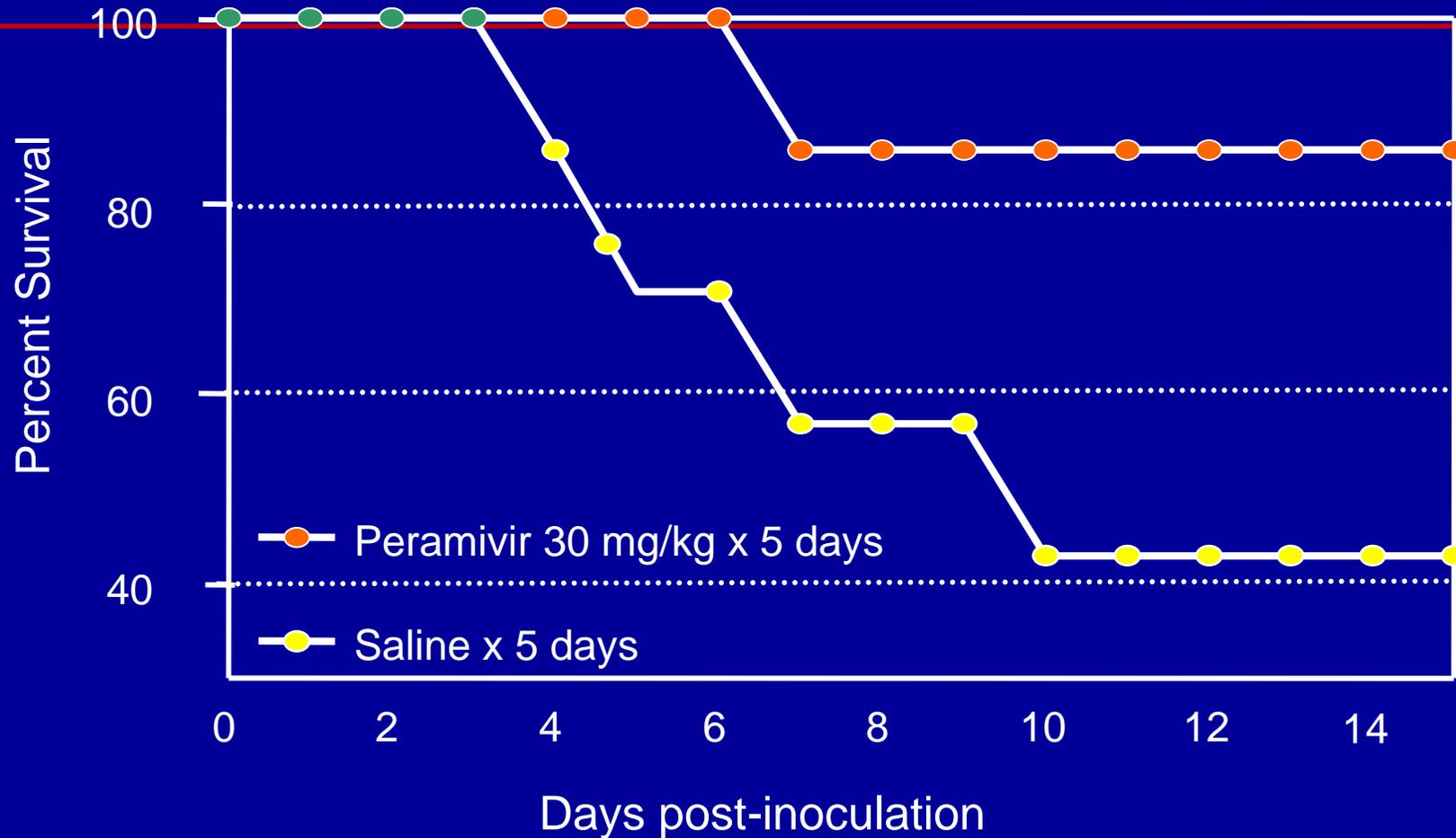
Peramivir: Drug Profile

- Broad spectrum activity against multiple strains of influenza A & B, including avian viruses
- A single IM or IV injection is efficacious in the mouse model including (H5N1)
- Rapid onset of activity
- Low tendency for viral resistance



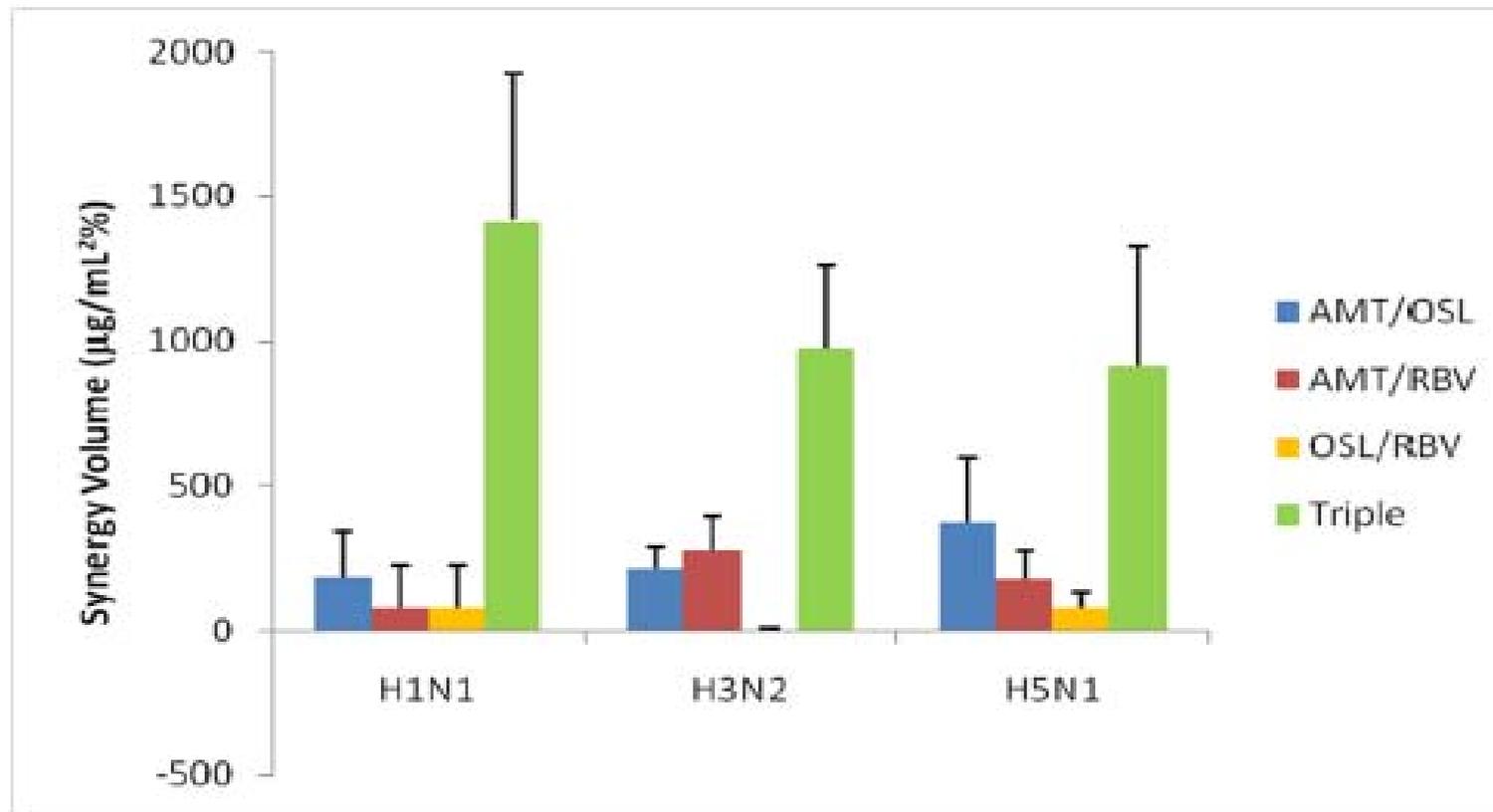
Peramivir in the neuraminidase active site

Intramuscular Peramivir Injections Promote Survival in Highly Pathogenic A/Vietnam/1203/04 (H5N1) Ferret Model



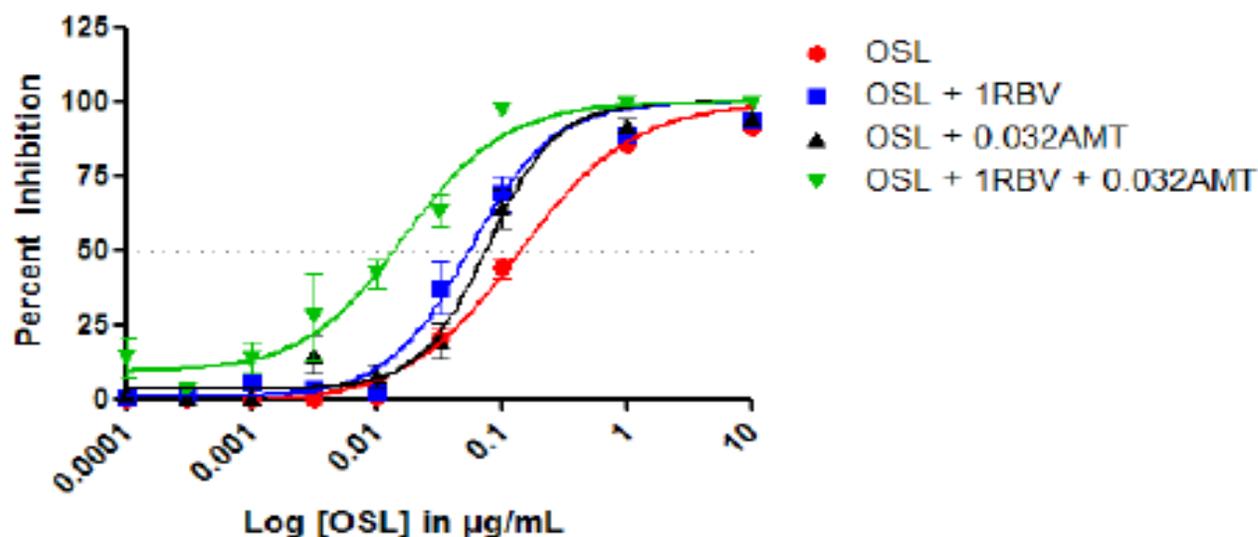
Combination Therapies

Triple combination displays greater synergy than all double combinations against all three subtypes (wildtype)



Triple combination at 0.1 $\mu\text{g}/\text{mL}$ amantadine

Effectiveness of oseltamivir is enhanced 10-fold in triple combination against A/New Calenonia/20/99 (H1N1)



Drug	EC ₅₀ (µg/mL)	P-Value (OSL alone)	P-Value (OSL + RBV)	P-Value (OSL + AMT)
OSL alone	0.14	-	-	-
OSL + 1 RBV	0.055	<0.0001	-	-
OSL + 0.032 AMT	0.076	0.0002	-	-
OSL + 1 RBV + 0.032 AMT	0.016	<0.0001	<0.0001	<0.0001

Unmet Antiviral Needs

New Drugs with Different Mechanisms of
Action

Investigational Anti-Influenza Agents

- Neuraminidase (NA) inhibitors
 - Peramivir (IV/IM), zanamivir (IV), A-315675 (oral)
- Long-acting NA inhibitors (LANI)
 - CS8958/R-118958 (topical), Flunet[®](topical)
- Conjugated sialidase: DAS181 (topical)
- HA inhibitors: cyanovirin-N, sialyl-glycopolymer, entry blocker
- Polymerase inhibitors: ribavirin, viramidine, siRNA, T-705
- Protease inhibitor: aprotinin

Investigational Agents in Clinical Development

Agent	Target	Sponsor	Route	Development Phase
Zanamivir	NA	GSK	IV	Phase 1
Peramivir	NA	BioCryst	IV, IM	Phase 2
CS8958	NA	Sankyo, Biota	Topical	Phase 2
T-705	Polymerase	Toyama	Oral	Phase 1
DAS181	HA receptor	NexBio	Topical	Pending