

**NIH Recombinant DNA Advisory
Committee Presentation-
Antivirals for Influenza H5N1 Infections**

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Sources of Antiviral Information

- **Pre-clinical studies on H5N1 and other influenza viruses**
- **Clinical efficacy and effectiveness studies**
 - RCTs with adamantanes during 1968 pandemic and 1978 pandemic-like event
 - RCTs with NAIs in seasonal influenza
 - Observational reports from 2009 pandemic
 - Observational reports from H5N1-infected persons
- **Safety- RTC of long-term tolerability**

Antivirals for H5N1 Questions-1

- **What is known about the safety and efficacy of antivirals for treatment of H5N1?**
- **How critical is early intervention with antivirals for human infections with HPAI H5N1 and what are the mortality rates even when antivirals are initiated early?**
- **Is oseltamivir the only antiviral that we have significant clinical experience with for H5N1?**

Representative Anti-Influenza Agents with In Vivo Activity against H5N1

- **M2 inhibitors- amantadine, rimantadine (PO)**
- **Neuraminidase (NA) inhibitors**
 - **Oseltamivir (PO), zanamivir (topical, IV), peramivir (IV/IM)**
- **Polymerase inhibitors**
 - **Ribavirin (PO, IV); favipiravir/T-705 (PO)**
- **Conjugated sialidase- DAS181 (topical)**
- **Antibodies- convalescent plasma; neutralizing anti-HA monoclonals**
- **Interferons (topical)**

WHO Rapid Advice Guidelines for pharmacological management of sporadic human infection with avian influenza A (H5N1) virus

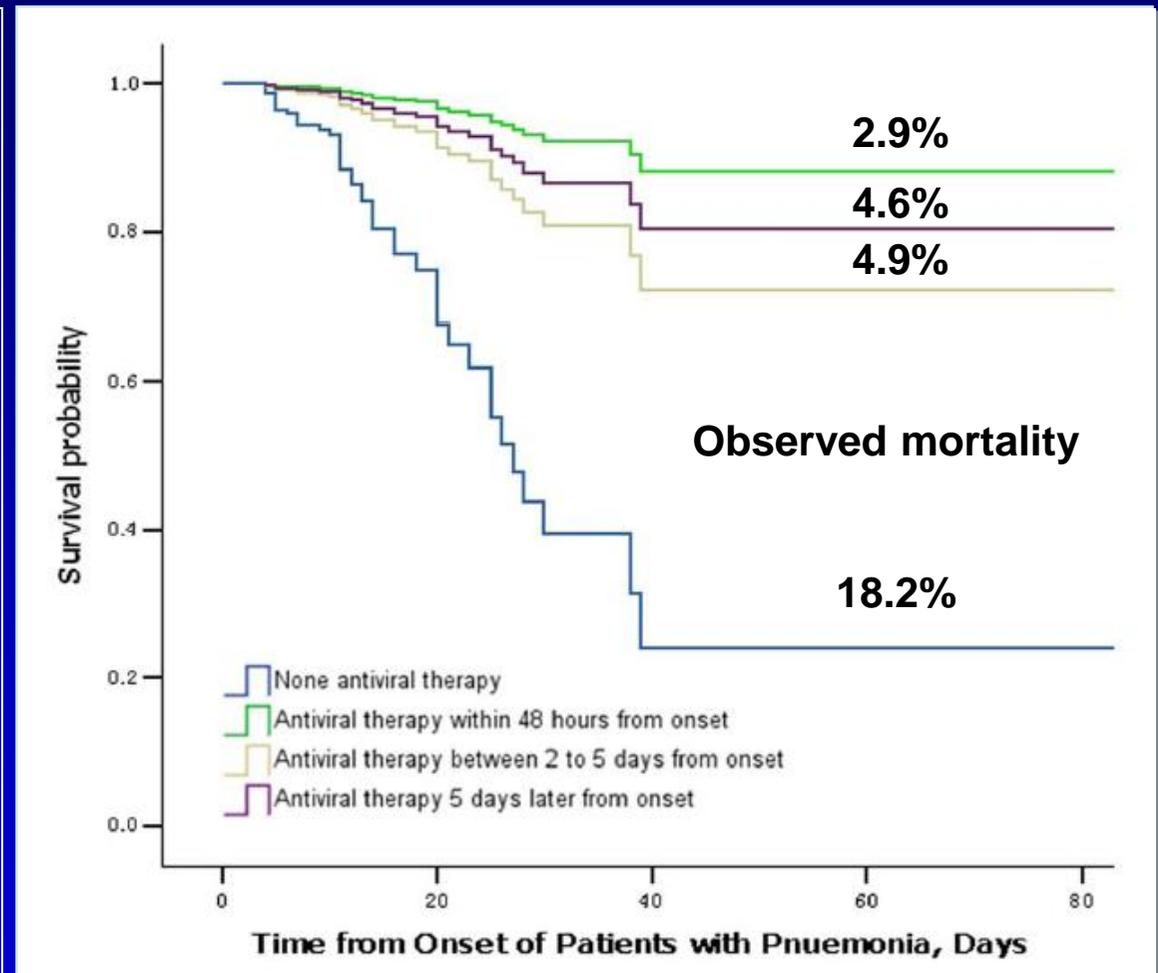
Holger J Schünemann, Suzanne R Hill, Meetal Kakad, Richard Bellamy, Timothy M Uyeki, Frederick G Hayden, Yazdan Yazdanpanah, John Beigel, Tawee Chotpitayasunondh, Chris Del Mar, Jeremy Farrar, Tran Tinh Hien, Bülent Özbay, Norio Sugaya, Keiji Fukuda, Nikki Shindo, Lauren Stockman, Gunn E Vist, Alice Croisier, Azim Nagjdaliyev, Cathy Roth, Gail Thomson, Howard Zucker, Andrew D Oxman, for the WHO Rapid Advice Guideline Panel on Avian Influenza

Recent spread of avian influenza A (H5N1) virus to poultry and wild birds has increased the threat of human infections with H5N1 virus worldwide. Despite international agreement to stockpile antivirals, evidence-based guidelines for their use do not exist. WHO assembled an international multidisciplinary panel to develop rapid advice for the pharmacological management of human H5N1 virus infection in the current pandemic alert period. A transparent methodological guideline process on the basis of the Grading Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to develop evidence-based guidelines. Our development of specific recommendations for treatment and chemoprophylaxis of sporadic H5N1 infection resulted from the benefits, harms, burden, and cost of interventions in several patient and exposure groups. Overall, the quality of the underlying evidence for all recommendations was rated as very low because it was based on small case series of H5N1 patients, on extrapolation from preclinical studies, and high quality studies of seasonal influenza. A strong recommendation to treat H5N1 patients with oseltamivir was made in part because of the severity of the disease. Similarly, strong recommendations were made to use neuraminidase inhibitors as chemoprophylaxis in high-risk exposure populations. Emergence of other novel influenza A viral subtypes with pandemic potential, or changes in the pathogenicity of H5N1 virus strains, will require an update of these guidelines and WHO will be monitoring this closely.

Lancet Infect Dis 2007;7: 21-31
Italian National Cancer Institute Regina Elena, INFORMA Unit, Department of Epidemiology, Istituto Regina Elena, Rome, Italy (Prof H J Schünemann MD); Health Technology and Pharmaceuticals, WHO, Geneva, Switzerland (S R Hill MD, H Zucker MD); Norwegian Knowledge Centre for the Health Services, Oslo, Norway (M Kakad MD, G E Vist PhD, A D Oxman MD); Department of Infection and Travel Medicine, James Cook University Hospital

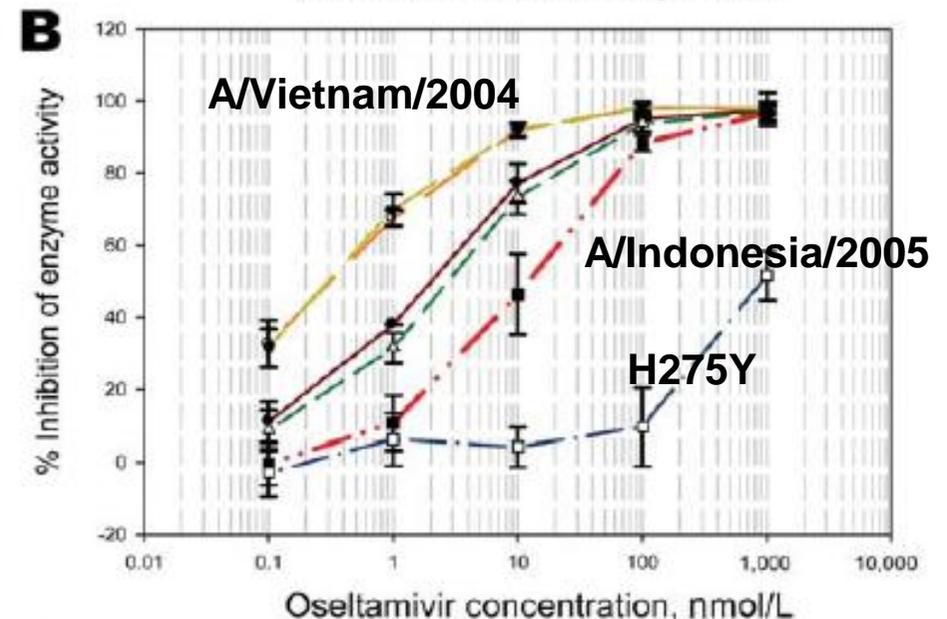
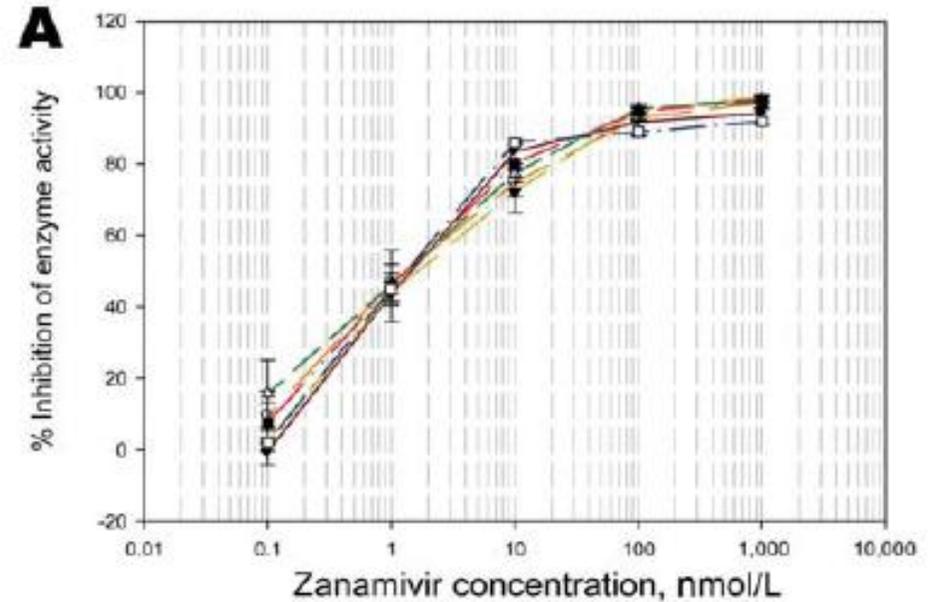
Survival in Influenza-Related Pneumonia: *Effect of Time to Oseltamivir Rx*

- 920 hospitalized adults with proven pH1N1 + pneumonia
 - No corticosteroids
 - 9.8% ventilated
- In-hospital mortality > 80% lower with oseltamivir ($P < 0.01$)
- No dose difference-standard vs higher



Oseltamivir Susceptibility of A(H5N1) Isolates

- Avian isolates (n = 26) tested by NAi assay
- 15 – 30 fold difference in oseltamivir IC₅₀s for clade 1 vs 2.1 viruses
- Clade 1 show ↑ oselt susceptibility
- No differences for zanamivir



Oseltamivir in H5N1: Time to Treatment Effect

Table 1. Relative Risk of Survival of Patients Treated with Oseltamivir, Compared with Patients Who Did Not Receive Antiviral Treatment (*N* = 221)

Treatment initiation from symptom onset, days	Oseltamivir treatment, survived/total (%)	No antiviral treatment, survived/total (%)	Difference in survival, %	Relative risk	95% CI	<i>P</i>
0-2	15/18 (83)	19/95 (20)	63	4.17	2.65-6.55	<.001
3-5	15/31 (48)	32/117 (27)	21	1.77	1.11-2.83	.032
6-8	16/32 (50)	31/108 (29)	21	1.74	1.10-2.75	.031
9-11	3/8 (38)	30/70 (43)	-5	0.88	0.34-2.23	.797
≥12	3/9 (33)	29/45 (64)	-31	0.52	0.20-1.34	.105
Any time	52/98 (53)	29/123 (24)	29	2.25	1.56-3.25	<.001

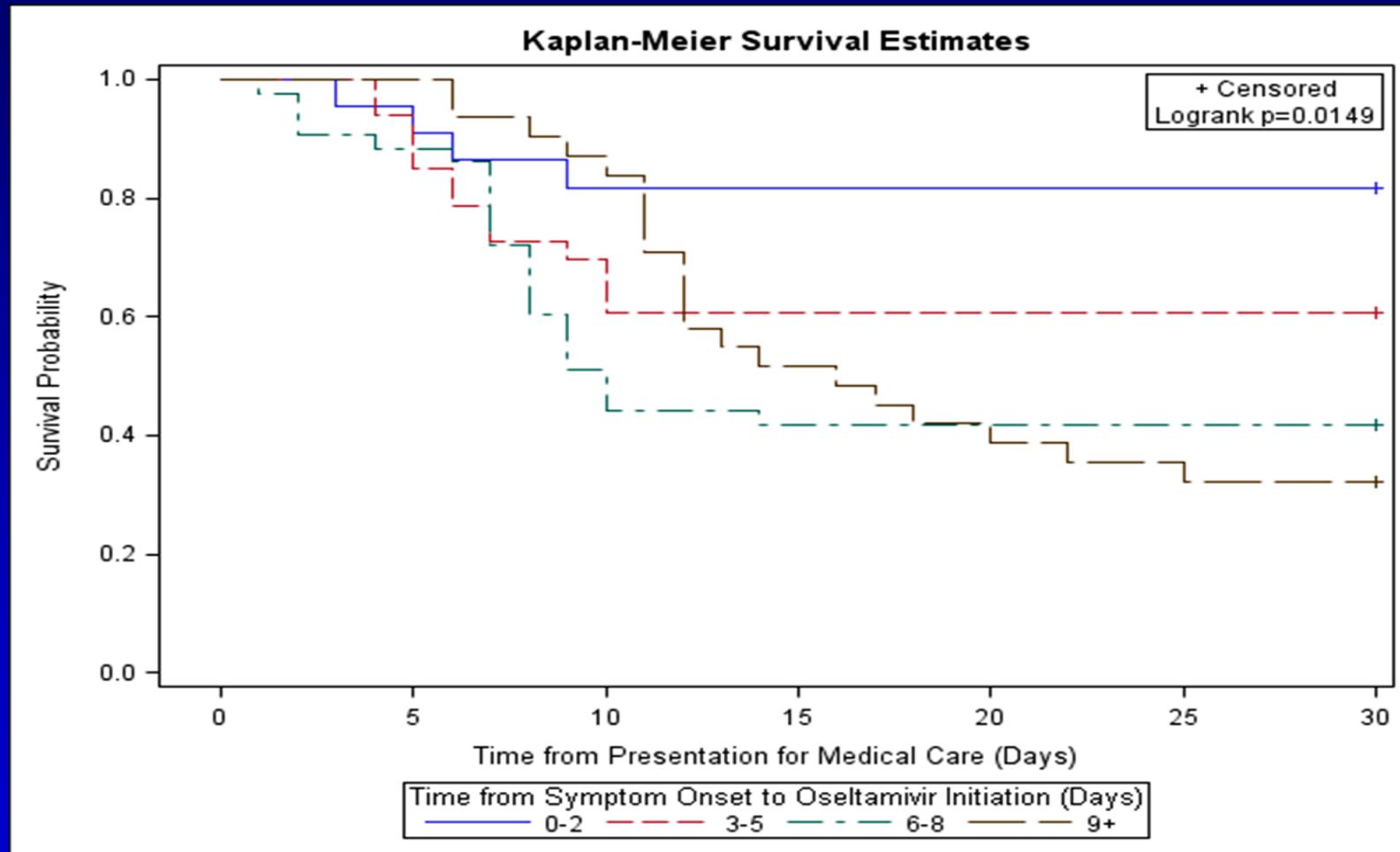
NOTE. Relative risk of survival by interval from symptom onset and first dose of oseltamivir, compared with risk of survival of individuals who presented for medical care during the interval, were alive in the interval, and did not receive any antiviral treatment during the interval. CI, confidence interval.

Table 3. Times to Presentation for Medical Care and Initiation of Treatment Among Patients Who Received Oseltamivir for Treatment of Influenza Virus A Subtype H5N1 Infection, by Patient Outcome

Variable	No. of Patients	Days, Median (Range)		<i>P</i>
		Patients Who Died (n = 100)	Patients Who Survived (n = 115)	
Time from symptom onset to				
To first presentation for medical care	92	1 (-2 to 10 ^a)	2 (0-20)	.039
To hospital admission	207	6 (0-20)	3 (0-20)	<.001
Time from symptom onset to treatment with				
Oseltamivir alone or in combination	151	7 (0-23)	5 (0-20)	<.001
Corticosteroid	28 ^b	6 (1-16)	7 (2-9)	.762
Antibiotic	65 ^b	5 (0-11)	4.5 (1-15)	.560
NSAID	31 ^b	4 (0-11)	3 (0-7)	.393

Abbreviation: NSAID, nonsteroidal antiinflammatory drug.

H5N1 Survival by Time of Initiation of Oseltamivir from Symptom Onset (n=129)



Antivirals for H5N1 Questions- 2

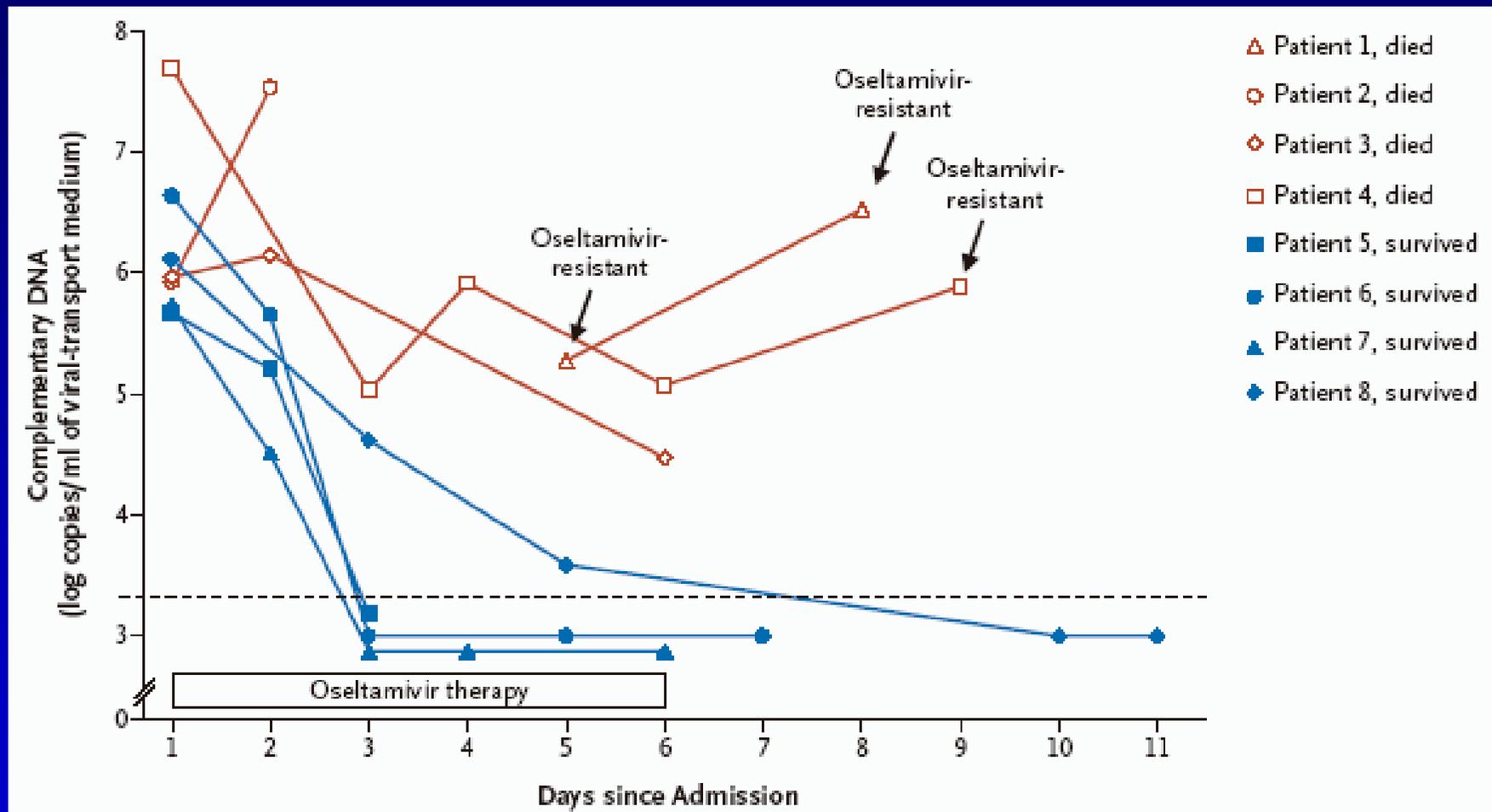
- **Are there certain mutations that confer selective resistance to oseltamivir but not zanamivir?**
- **Are there other mutations in influenza that confer resistance to both?**
- **Is zanamivir more difficult to correctly take given it is an inhaler?**
- **Are there groups that could not take it?**

N1 Mutations Associated with Reduced NAI Susceptibility in H5N1 Viruses

Mutation	Source	Fold decrease compared to wild-type	
		Oseltamivir	Zanamivir
H275Y	Human, in vitro	>300	1-2
N295S	Human, in vitro	10-81	1-4
D198G	In vitro	44	32
V116A	Chicken, in vitro	11-18	10-63
I117V	Chicken, in vitro	8-16	1-6
S246N	Chicken	24	2
Q136L	Ferret	26	~350
E119A	In vitro	4-56	>1,000

Mai Le et al., Nature 437:1108; 2005; Hurt et al., Antiviral Res 73: 228, 2007, AAC 53:4433, 2009, and Antiviral Res 87:361, 2010; Boltz et al., J Gen Virol 91: 949, 2010; Earhart et al., J Infect Pub Health 2:74, 2009; Ilyushina et al., PLoS Path 6:e1000933, 2010

Pharyngeal Viral Loads during Oseltamivir Treatment of H5N1



de Jong et al. NEJM 353:25, 2005

Antiviral Treatment for H5N1: *Comments*

- **Multiple potential reasons exist for treatment failure, but viral clearance → favorable prognosis.**
- **Oseltamivir is agent with most clinical experience.**
 - **Appropriate dose regimen and duration for H5N1 are uncertain. No obvious benefit from 2X dose.**
 - **Antiviral resistance (H275Y) and ↓ susceptibility (N295S) due to N1 mutations → IV zanamivir**
- **Majority of isolates resistant to M2 inhibitors**
 - **Combined NAI + M2 inhibitor therapy is reasonable if virus likely susceptible to both.**
 - **Rimantadine better CNS tolerability than amantadine**

Antivirals for H5N1 Questions- 3

- If antivirals are initiated upon exposure, how effective would we expect them to be in preventing disease with H5N1 and decreasing viral shedding?**
- What are the pros/cons to providing researchers with a 48 hr home supply of antivirals?**
- Would you be concerned about the safety of use of an antiviral beyond six weeks?**
- Might prophylaxis generating resistance in circulating influenza strains to which the lab worker was exposed or even leading to a resistant H5N1 if an exposure not recognized?**

Amantadine Prophylaxis During Pandemic Influenza

Protective efficacy

Pandemic	Influenza A illness	Seroconversion
1968 H3N2	59-100%	28-52%
1977 H1N1	31-71%	19-39%

Hayden. J Infect Dis 176:S56, 1997

Antiviral Post-Exposure Prophylaxis in Households

Antiviral (Study)	Season (Virus)	Adult dose regimen	Reduction in 2 influenza illness*
Amantadine (Galbraith et al, 1969)	1967-68 (A/H2N2)	100 mg bid for 10 d	100%
Rimantadine (Bricaire et al, 1990)	1988-89 (A/not stated)	200 mg qd for 10 d	70%+
Zanamivir (Hayden et al, 2000)	1998-99 (A/H3N2, B)	10 mg inhaled qd for 10 d	79%
Zanamivir (Monto et al, 2002)	2000-01 (A/H3N2, B)	10 mg inhaled qd for 10 d	82%
Oseltamivir (Welliver et al, 2001)	1998-99 (A/H3N2, B)	75 mg qd for 7 d	89%

*Laboratory proven influenza illness in contacts

+Clinical influenza

Oseltamivir Prophylactic Regimens Prevent H5N1 Influenza Morbidity and Mortality in a Ferret Model

David A. Boltz,¹ Jerold E. Rehg,² Jennifer McClaren,¹ Robert G. Webster,¹ and Elena A. Govorkova¹

¹Department of Infectious Diseases (Division of Virology) and ²Department of Pathology, St. Jude Children's Research Hospital, Memphis, Tennessee

- **Lethal clade 1 A/Vietnam/1203/04 infection**
- **Oseltamivir prophylaxis for 10 d starting 4 hr before inoculation**
 - **Once daily dosing @ 10 mg/kg oseltamivir → prevented death, ↓ illness + systemic spread, but pathology in internal organs.**
 - **Twice daily dosing @ 2.5 or 5 mg/kg → absence of illness, systemic virus spread, and organ pathology.**
 - **Only 5 mg/kg bid → no detectable virus in URT**

Boltz et al., J Infect Dis 197:1315, 2008

Oseltamivir and inhaled zanamivir as influenza prophylaxis in Thai health workers: a randomized, double-blind, placebo-controlled safety trial over 16 weeks

- **Parallel group, double-blinded, 2 (active drug): 1 (placebo) randomized trial of oral oseltamivir or inhaled zanamivir tolerability over 16 weeks in 390 healthy, Thai hospital staff**
 - **Symptoms, spirometry, EKGs, blood chemistry**
- **Primary endpoint - withdrawal from the study because of serious or grade ≥ 2 AEs that were possibly, probably or definitely drug related.**
- **No drug-related study withdrawals**

**Anekthananon, Pukritayakamee, et al., J Antimicrob Chemother 2013, in press.
Study by South East Asian Infectious Diseases Clinical Research Network**

Antiviral Home Access Considerations

- **Rapid access (emergency, unable to travel)**
- **Inappropriate use for non-influenza illness**
 - Drug side effects
- **Delay in presentation for care**
 - Failure to diagnose + treat other illnesses
 - Potential false negative H5N1 test results
 - If H5N1 transmission to contacts, delayed containment efforts
 - Need for rapid assessment + isolation
- **Inappropriate dosing, noncompliance**
 - Increased risk of resistance emergence

Antiviral Prophylaxis for H5N1: *Comments*

- **Oseltamivir use in persons at increased risk of H5N1 exposure (eg, family contacts, cullers, unprotected HCWs).**
- **Use of twice daily treatment regimen for post-exposure prophylaxis makes sense based on risks of incubating infection and possible resistance emergence.**
- **Little information on inhaled zanamivir or oral M2 inhibitors for H5N1 prevention.**
- **Daily oseltamivir or inhaled zanamivir to 16 weeks appears generally well-tolerated.**