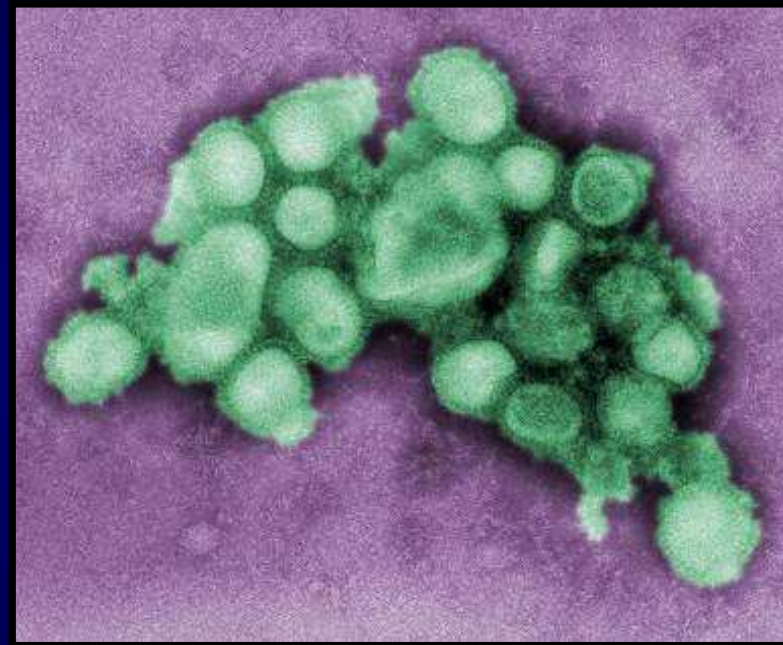


Antiviral Treatment and Chemoprophylaxis of Pandemic Influenza A (H1N1) Virus



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www.pandemicflu.gov

www.cdc.gov/flu



Antiviral Medications for Influenza

- **Two classes (Adamantanes, Neuraminidase Inhibitors)**
 - Monotherapy for treatment or chemoprophylaxis
 - Interfere with virus replication
- Differences in approved age groups, adverse effects, contraindications, routes of administration, metabolism, antiviral resistance, cost, availability



Adamantanes: Amantadine, Rimantadine

- Activity against influenza A viruses only
 - Orally administered (liquid, tablet)
 - Adverse effects: Gastrointestinal, CNS
- Treatment or chemoprophylaxis of influenza A in persons aged ≥ 1 year
- Resistance can develop rapidly during treatment of susceptible strains (10-30%), cross-resistance
- **Pandemic H1N1 virus is resistant to Amantadine and Rimantadine**



Neuraminidase Inhibitors

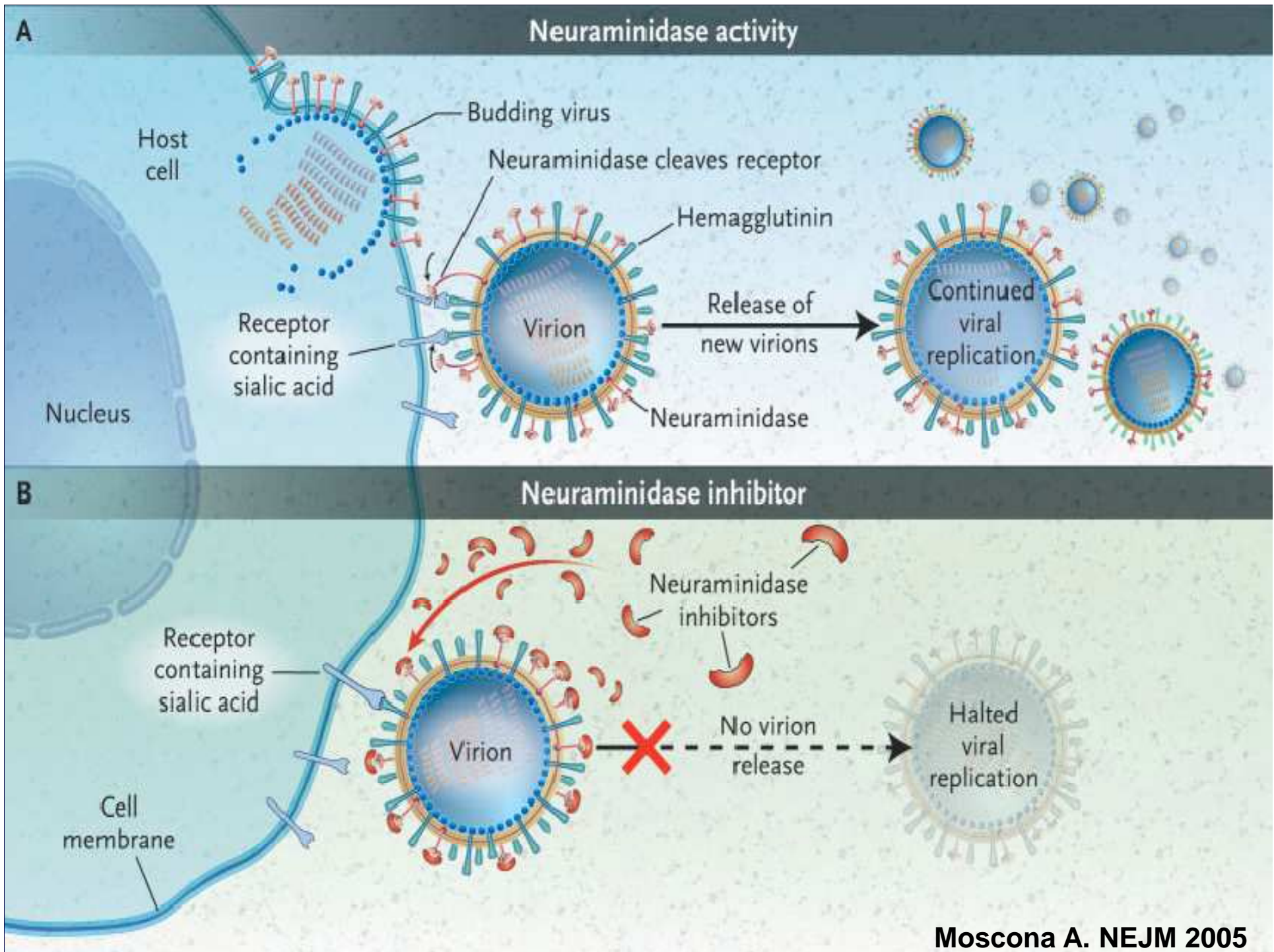
Oseltamivir (Tamiflu), Zanamivir (Relenza)

- **Activity against influenza A and B viruses**
- **Oseltamivir: Oral administration (liquid, capsule)**
 - Treatment or chemoprophylaxis of ≥ 1 year*
 - Adverse effects: Gastrointestinal, rare CNS sx. (adolescents)
- **Zanamivir: Orally inhaled powder (disk inhaler)**
 - Approved for treatment of ≥ 7 years
 - Approved for chemoprophylaxis of ≥ 5 years
 - Adverse effects: Bronchospasm, rare CNS sx.
 - Contraindicated in persons with chronic pulmonary disease, asthma



*Approval for use in children aged < 1 year; emergency use (U.S.)





Oseltamivir, Zanamivir

Treatment Efficacy - Seasonal Influenza

- **Efficacy of early treatment (<48 hours of onset) of uncomplicated illness (adult and pediatric outpatients):**
 - Reduce duration of symptoms by 1 day
 - Decrease frequency of mild to moderate complications
 - Otitis media, bronchitis, antibiotic use
 - May decrease viral shedding



Oseltamivir

Treatment Effectiveness: Seasonal Influenza

- Effectiveness of oseltamivir treatment of hospitalized patients (retrospective, uncontrolled):
 - Reduction of hospitalization duration in elderly when Oseltamivir started <48 hours of onset (Hong Kong)
 - Reduction of mortality within 15 days after onset in elderly, including Oseltamivir treatment >48 hours after onset (Canada)
 - Oseltamivir treatment associated with survival in hospitalized patients (Thailand; confirmed by RT-PCR)
 - No controlled clinical trial data available



Lee et al., Antiviral Therapy 2007; McGeer et al., CID 2007;
Hanshaworakul et al., PLoS ONE 2009



Oseltamivir

Treatment Effectiveness: H5N1 Influenza

- Effectiveness of Oseltamivir treatment of severely ill hospitalized patients with lower respiratory tract disease (retrospective, uncontrolled):
 - Treatment associated with survival (Vietnam; WHO)
 - Earlier treatment associated with survival (Indonesia)
 - No controlled data available
- WHO recommends considering higher dosing, longer duration of treatment for severely ill H5N1 patients



Nguyen et al. CID 2009; Kandun et al., Lancet 2008;
WHO. NEJM 2008



Neuraminidase Inhibitor

Chemoprophylaxis: Seasonal Influenza

- **70-80% efficacy in preventing illness after exposure (post-exposure chemoprophylaxis)**
 - **Oseltamivir and Zanamivir have similar efficacy in chemoprophylaxis**
 - **May not prevent asymptomatic virus infection - immune response may occur**
- **High effectiveness when chemoprophylaxis used to control outbreaks (e.g. nursing homes) with other measures**



Antiviral Resistance

- Oseltamivir resistance can develop infrequently during treatment of seasonal influenza and H5N1
- Public health concern: are Oseltamivir-resistant influenza viruses transmitted in the community?
- Global circulation of Oseltamivir-resistant seasonal influenza A (H1N1) virus, since 2007 (not associated with treatment)
 - Oseltamivir resistance associated with mutation in neuraminidase gene (H274Y) [*susceptible to Zanamivir*]
 - 99% of seasonal H1N1 virus strains in the U.S. resistant to Oseltamivir (2008-2009)
 - Susceptible to Zanamivir, Amantadine, Rimantadine



Antiviral Resistance

- **Pandemic H1N1 virus is resistant to Amantadine and Rimantadine**
- **Oseltamivir resistance reported in one patient with pandemic H1N1 in Denmark (mild illness)**
 - Patient was on Oseltamivir chemoprophylaxis
 - Resistance associated with H274Y mutation in neuraminidase gene [*susceptible to Zanamivir*]
- **Oseltamivir resistance in pandemic H1N1 virus reported in one case from Japan**
- **No Oseltamivir resistance detected in pandemic H1N1 virus strains in the U.S.**



Summary of Antiviral Resistance, U.S. 2008-09

	Influenza viruses			
Antiviral	Seasonal A (H1N1)	Seasonal A (H3N2)	Seasonal B	Pandemic H1N1
Adamantanes	Susceptible	Resistant	No activity	Resistant
Oseltamivir	Resistant	Susceptible	Susceptible	Susceptible
Zanamivir	Susceptible	Susceptible	Susceptible	Susceptible

Antiviral Treatment Recommendations

- **Priority: Hospitalized Patients with suspected or confirmed pandemic H1N1 virus infection**
 - Treatment recommended with Oseltamivir or Zanamivir
 - Treat patients as soon as possible (duration: 5 days)
- **Outpatients with suspected or confirmed pandemic H1N1 virus infection who are at high risk for complications**
 - Persons with chronic pulmonary, cardiac, renal, hepatic, metabolic, hematological disorders; immunosuppression, pregnant women, children <5 years; adults ≥65 years
 - Treatment recommended with Oseltamivir or Zanamivir
 - Treat patients as soon as possible (duration: 5 days)



Antiviral Treatment Considerations

- **Hospitalized patients with severe or progressive lower respiratory tract disease (ICU patients)**
 - **Oseltamivir or Zanamivir treatment**
 - **Consider higher dosing**
 - Potential for high viral levels in lower respiratory tract
 - Potential for reduced GI absorption
 - No indication of safety concerns
 - **Consider longer duration of treatment**
 - Potential for prolonged viral shedding

***Treatment of pregnant women, infants <1 year old is recommended in the U.S.**



Antiviral Chemoprophylaxis

- **Post-exposure chemoprophylaxis with Oseltamivir or Zanamivir can be considered:**
 - **Close contacts of cases who are at high risk for complications of influenza**
 - **Health care personnel, public health workers, first responders with unprotected close contact exposure to an ill person with pandemic H1N1 virus infection while in the infectious period**
 - **Chemoprophylaxis: 7-10 days after last known exposure**



Antiviral Questions

- **What is the clinical effectiveness of antiviral treatment?**
 - Early (<48 hours of onset) versus late treatment?
 - In critically ill patients with complications?
 - Reduction in clinical course, reduction in mortality?
- **What is the clinical benefit of higher antiviral dosing, longer duration of treatment?**
- **Clinical and virological data needed to inform antiviral treatment guidance**



Summary

- **Circulating pandemic H1N1 virus strains**
 - Resistant to Amantadine, Rimantadine
 - **Susceptible to Oseltamivir, Zanamivir**
- **Treatment of hospitalized patients and high-risk outpatients with pandemic H1N1 virus infection is recommended (limited data from seasonal and H5N1 influenza)**
- **Clinical and virological data are needed in patients treated with antivirals**
- **Post-exposure chemoprophylaxis can be considered for high-risk persons, health care personnel, first responders**
- **On-going monitoring for antiviral resistance is needed**



Thanks for your attention!

