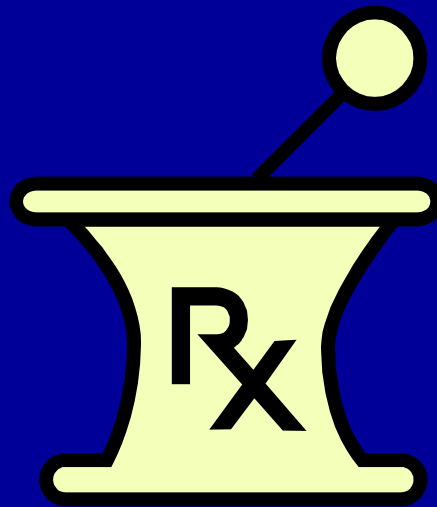


Interventions to Contain a Pandemic



Pharmaceutical Measures

Learning Objectives

- Describe the proper use of Oseltamivir for prophylaxis and treatment of influenza
- Recognize contraindications and potential side effects associated with Oseltamivir
- Explain pharmaceutical rapid response methods for a pandemic situation
- Understand the benefits and challenges of providing influenza vaccination

Session Overview

- **Antiviral medications for influenza**
 - Treatment and chemoprophylaxis
 - Contraindications and side effects
 - Indications for individual prophylaxis
 - Mass administration
- **Vaccines for influenza**
 - Seasonal versus pandemic vaccines
 - Potential use of pandemic vaccines
 - Prioritizing vaccine distribution

Influenza Public health interventions

- Antivirals
 - Vaccines
 - Non-pharmaceutical public health measures
- Pharmaceutical interventions
- Case or cohort isolation
 - Voluntary quarantine
 - Social distancing - school closure
 - Hand hygiene, cough etiquette
 - Respiratory protection (mask use)

Anti-viral Drugs: Classes of Influenza Specific Antivirals

1. Neuraminidase inhibitors

- Oseltamivir* (Tamiflu)
- Zanamivir (Relenza)

2. Adamantanes

- Amantadine
- Rimantadine

* Most relevant in treating human cases of avian influenza. ⁵

Influenza anti-virals

- All 4 antiviral drugs are effective for treatment and prophylaxis of susceptible viruses
 - Decrease the duration of uncomplicated influenza by ~ 1-2 days
 - Early neuraminidase inhibitor treatment reduces some complications
 - Prophylaxis is 70-90% effective
- Neuraminidase inhibitors active against influenza A and B
 - Against H5N1 and other AI viruses

Treatment with Oseltamivir

- Active against H5N1 viruses in the laboratory and in experimental animals
- No proof of effectiveness against human H5N1 disease
- Optimal dose and duration of treatment yet to be determined
- Use Oseltamivir dosing for seasonal influenza per WHO recommendations
- Oseltamivir:
 - Antiviral resistance may occur
 - Antiviral for pandemic containment
 - WHO has rapid response stockpile

http://www.who.int/csr/disease/avian_influenza/guidelines/pharmamanagement/en/index.html

Oseltamivir Administration and Treatment Regimen



Route of Administration

- Administer orally

For Treatment

- Administer within 48 hours of symptom onset

For Prophylaxis

- Give to close contacts within 48 hours of exposure
- **Adults:** 75 mg two times a day for 5 days
- Not approved for children less than 1 year of age
- **Children ≥ 1 year old:**

<15 kg:	30 mg twice daily
15 - <23 kg:	45 mg twice daily
23 - <40 kg:	60 mg twice daily
≥ 40 kg:	75 mg twice daily



Oseltamivir Oral Formulations

Capsules 75 mg each

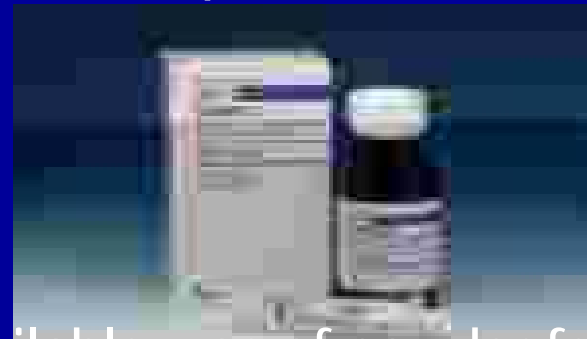
- 10 capsules per box
- Manufacturer: Roche
- Brand name—Tamiflu®
- Store at room temperature (15 - 30°C)



- When the paediatric suspension not available, use of powder from the capsules is an alternative.
- Capsule contents can be mixed in foods and beverages to mask taste.

Liquid Suspension

- White powder mixed with 23 mL of drinking water
- Fruit flavored
- Refrigeration required
- Use within 10 days
- Oral dispenser included



Oseltamivir

Chemoprophylaxis Doses*

Patient Age	Prophylactic Dose
≥ 13 years	1 capsule (75 mg) once a day
1 to 12 years	< 15 kg: 30 mg once a day 15-<23 kg: 45 mg once a day 23-<40 kg: 60 mg once a day ≥ 40 kg: 75 mg once a day

*Duration of prophylaxis depends on epidemiologic setting. Post-exposure use is typically for 7 to 10 days.

Oseltamivir Side Effects

- Headache (20%)*
- Nausea (10%)
- Vomiting (9%)
- Fatigue (8%)*
- Diarrhea (7%)
- Cough (6%)*
- Bronchitis, abdominal pain, dizziness (2%)
- Insomnia, vertigo (1%)

*In study of Oseltamivir as prophylaxis, treatment % is lower.

Oseltamivir Reactions

Serious Adverse Events*

Allergic reactions

Skin rash (sometimes severe)

Facial swelling

Dizziness

Hepatitis

*A causal relationship has not been established for many of these

Contraindications & Precautions

Pregnant or breastfeeding mothers

- No recognized birth defects in pre-clinical testing
- No human clinical studies demonstrating safety or efficacy
- Use if benefit outweighs risk

Liver disease

- Safety and efficacy not yet evaluated

Kidney disease

- Decrease dose based on creatinine clearance

Zanamivir Overview

- **Orally inhaled powder (Diskhaler)**
- **Low systemic absorption**
 - ~7-21% of dose reaches lower airways
- **Adverse effects**
 - Bronchospasm, sometimes severe
 - Uncertain relationship to drug: nausea, diarrhea, headache
- **Antiviral resistance rare to date**

Zanamivir Administration

- Treatment: 5 days
 - Age ≥ 7 years: 2 inhalations (5 mg each), twice daily
- Prophylaxis
 - Age ≥ 5 years: 2 inhalations (5 mg each) once daily
 - Duration of prophylaxis depends on clinical setting
- No dose reductions for age, renal insufficiency



Role of Antivirals in outbreak investigation

- Treatment of probable/ confirmed case
- Prophylaxis of close contacts* – individuals
 - Identification of close contacts by active case finding and contact tracing
 - Prophylaxis of household and family contacts,
 - Health monitoring of close contacts,
 - treatment when becomes symptomatic
- Implementation of non-pharmaceutical control measures

* WHO Rapid advice guidelines on pharmacological management of humans infected with avian influenza A(H5N1) virus

Rapid Response and Containment (RRC)

- Containment: Attempt to stop further spread of an emerging pandemic virus
- Goal of RRC:
“To ensure rapid detection and investigation of clusters of cases, closely related in time and place, and ensure immediate international intervention aimed at preventing the emergence of a fully transmissible pandemic virus or delaying its international spread.”
source WHO strategic action plan 2006-7
- When:
 - Signals suggest that the virus is acquiring the capacity for efficient human-to-human transmission
- Signals include
 - Epidemiological: clusters of human cases with acute lower respiratory illness, closely related in time and place, involving chains of transmission sustained over time
 - Virological: isolation of reassortant virus; virus with mutations indicative of human adaptation



Role of Antivirals in Rapid Response (Phase I)

- Treatment of suspected, probable and confirmed cases,
- Prophylaxis target groups based on risk assessment:
 1. Ring prophylaxis - to cover a specific geographic area.
i.e., prophylaxis of whole population in the neighborhood
 2. Layered approach - prophylaxis of exposed contacts
Family members, school, work place, etc. (e.g., socially targeted).

Role of Antivirals in Containment (Phase II)

- **Blanket approach**
 - Entire country or region
 - Enough drug to prophylax everyone for up to 3 weeks
 - à unfeasible
- **Geographically-defined chemoprophylaxis feasible if:**
 - in non-urban setting
 - Early intervention within 1-3 wks
 - Virus of low - moderate transmissibility ($R_0 < 1.8$)
 - Coverage of 80 - 90% of population
 - High compliance
 - Movement restrictions; social distancing
 - **Maximum of 1-3 million courses needed**
300,000 may be sufficient

Planning Considerations for Mass Chemoprophylaxis

- 1. Leadership roles**
- 2. Human resource needs**
- 3. Site of drug distribution: household, clinic, other facility (eg, school)**
- 4. Clinic layout and specifications**
- 5. Crowd management inside/outside of the facility**
- 6. Security of drug supplies**
- 7. Communication, advertising**

Sources of Antiviral Supplies

- **WHO antiviral stockpile**
 - 3 million oseltamivir courses
 - Reserved for containment of pandemic
- **Other national / international stockpiles**
- **Assess local supplies**
 - Pharmacies
 - Manufacturing companies
 - Hospitals or private doctors

Influenza Vaccines

Seasonal Vaccine

- **Primary means of preventing influenza**
 - proven efficacy / effectiveness to prevent infection, severe illness (hospitalization) and death
 - Cost effective in many target groups, Safe,
 - Generally safe
- **350 million* doses produced annually (5% of 6.7 billion population)**
- **Production and consumption highly localized.**
 - >95% produced in 9 countries (>65% in Europe)
 - 12% of population use 62% of vaccine
- **Production dependent on eggs**
 - Very little surge capacity

* 2006 estimate

Seasonal vaccine - Priority groups

1. Residents of institutions (elderly people and the disabled).
2. Elderly with chronic underlying conditions,
3. All individuals >6 months of age with chronic underlying conditions,
4. Elderly individuals,
5. Other groups (defined on the basis of national data and capacities), contacts of high-risk people, pregnant women, health-care workers and essential service providers, children 6–23 months of age.

WHO position paper, 2005

Influenza Vaccine Benefits

- Can match a seasonal vaccine with a circulating strain
- Can be highly effective for prevention of seasonal influenza
- **Vaccination of rapid responders reduces the risk of infection and prevents viral reassortment**

H5N1 Vaccines

- Human H5N1 vaccines are immunogenic in humans and generally well-tolerated.
- H5 hemagglutinin is a weak human immunogen.
 - Two doses and an adjuvant will likely be needed
- H5 viruses continue to change → antigenic match between vaccine and circulating strains of concern
 - 4-6 months time lag before a closely matching vaccine is produced

Pandemic vaccine

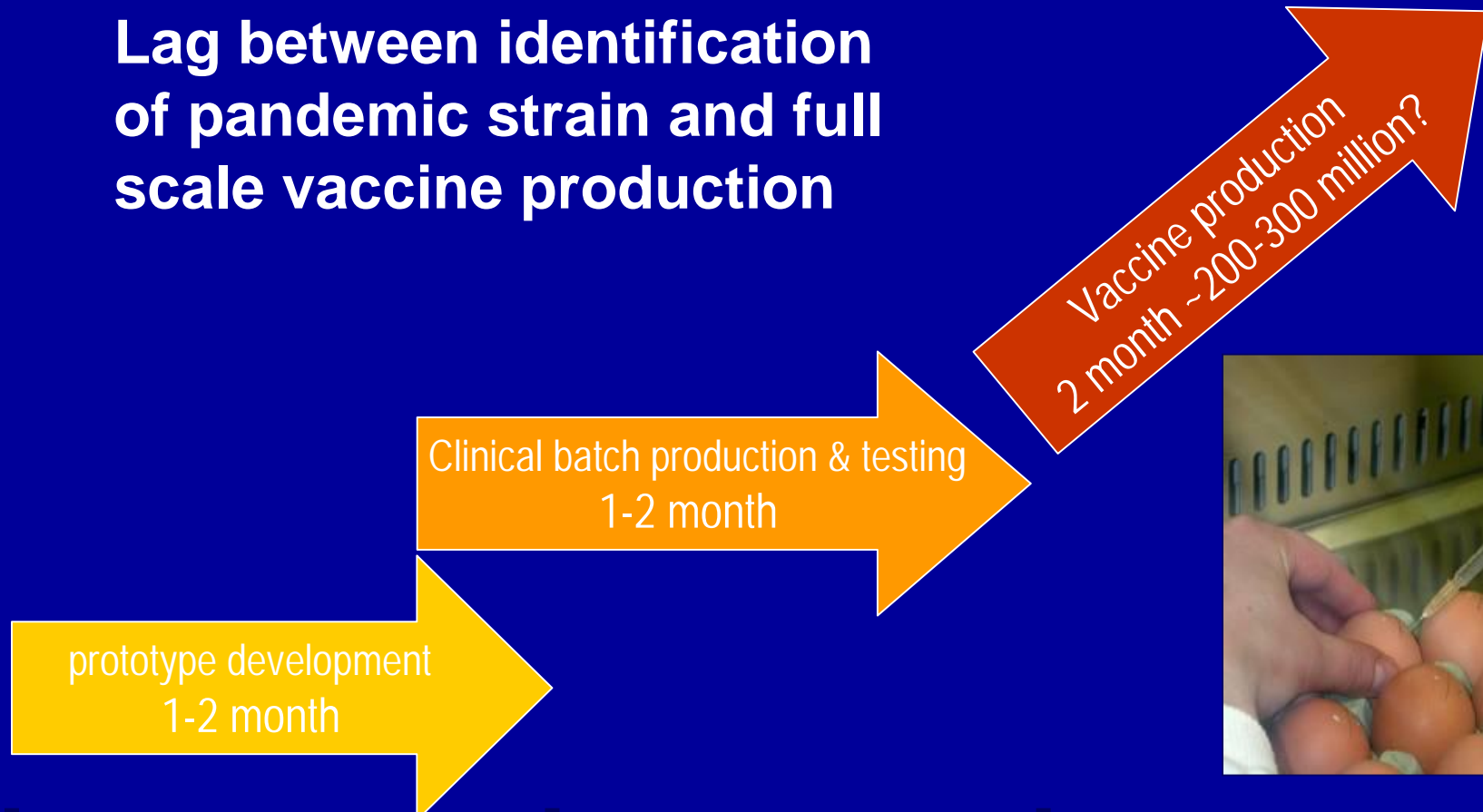
- **Priority groups will differ by country and depend on the goals**
 - **Maintain essential services**
 - **Reduce deaths and hospitalizations**
 - **Reduce morbidity**
- **Vaccine availability, population structure, and regional priorities**

Pandemic vaccine lessons from 1957, 1968, & 1977

- Unprimed subjects require second inoculation,
- Differences exist in immunogenicity between subtypes,
- Whole virus is usually more immunogenic but reactogenic,
 - Children have more side effects
- Adjuvants can spare antigen in unprimed persons,
- Efficacy/effectiveness are unpredictable.

Vaccine production timeline

Lag between identification of pandemic strain and full scale vaccine production



Vaccination Prioritization

- **After vaccine production begins, only enough for < 5% of world's population**
- **Priority groups differ by country, depending on:**
 - Vaccine availability
 - Infrastructure to administer vaccine
 - Population structure
- **Groups that provide essential services, such as health care workers, police**
- **Groups at high risk of death and hospitalization**
- **General population – persons without risk factors**

Role of vaccines in RRC

- Non-existent, stockpiling not possible
- or
- Poorly matched pre-pandemic vaccine in small amount
 - 2-4 weeks after inoculation
 - Second dose required
 - Uncertain efficacy / effectiveness
- Pandemic vaccine
 - 6 months until vaccine production
 - little surge capacity,



Reporting Adverse Events

- **Designate a coordinator**
 - Oversees the event
 - Reports the event
 - Provides education and letters
- **Establish a Reporting infrastructure**
 - Promotes efficient reporting
 - Promotes familiarity with reporting forms, procedures
- **Coordinate efforts**
 - Ensures public safety and well being
 - WHO hotlines and telephone surveys available
 - Provides technical assistance to the coordinator



Summary

- Oseltamivir is the neuraminidase inhibitor that is recommended for treatment and prophylaxis of potential avian influenza cases in humans.
- The best dosage of Oseltamivir is not yet known, and could change.
- Mass administration of drugs will depend upon the available drug supply and the local avian influenza situation.
- A vaccine against a pandemic strain of influenza is not yet available, and will only be available for high priority groups.
- Both drugs and vaccines have a risk of side effects and adverse events. Serious adverse events should be reported to the local public health system and the World Health Organization.

Glossary

Adamantanes

A class of anti-viral drugs, including Amantadine and Rimantadine, that is effective against influenza A. Adamantanes are not usually used against human infection with avian influenza because resistance may develop.

Adverse event

A negative, unintended physical reaction to the administration of a drug. An unwanted side effect.

Chemoprophylaxis

The administration of a drug to prevent disease from developing in someone who has been exposed, but is not yet ill.

Glossary

Contraindication

A specific circumstance when the use of a certain treatment could be harmful.

Neuraminidase inhibitors

A class of anti-viral drugs, including Oseltamivir and Zanamivir, that is effective against influenza A and B. Neuraminidase inhibitors are often used as prophylaxis or to treat human infection with avian influenza.

Ring prophylaxis

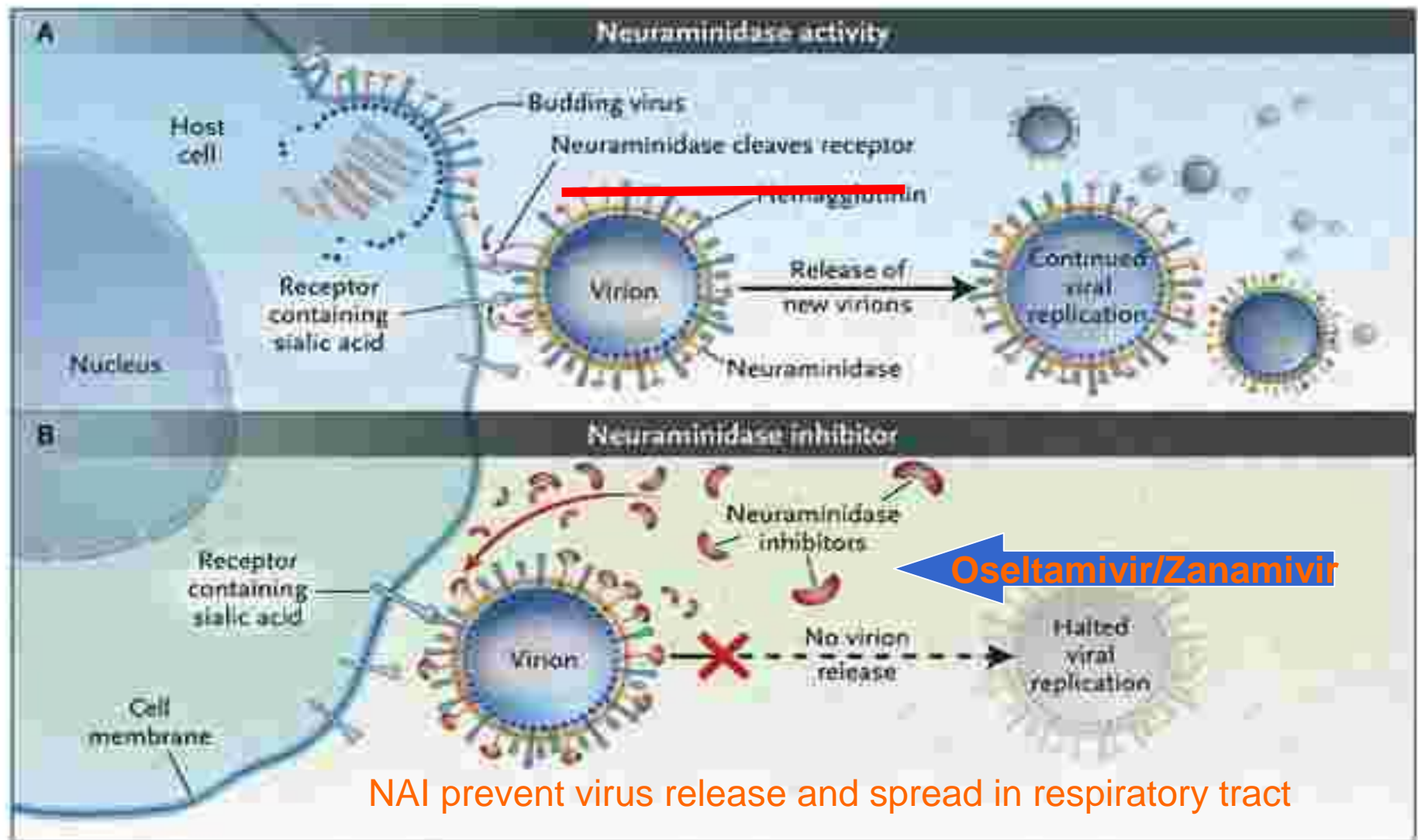
A disease containment strategy that calls for targeted containment of infected individuals within a geographic area

References and Resources

- de Jong et al. Fatal avian influenza A (H5N1) in a child presenting with diarrhea followed by coma N Engl J Med. 2005 Feb 17;352(7):686-91.
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- WHO Guidelines on the use of vaccines and antivirals during influenza pandemic. WHO/CDS/CSR/RMD/2004.8
http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_RMD_2004_8/en/

Appendix / Extra Slides

NA inhibitors Mechanism of Action



Oseltamivir Pharmacology



- Oseltamivir is pro-drug that is converted rapidly to active form in body
- Well-absorbed orally with over 80% bioavailability of active form
 - Absorption in critically ill ?
- Plasma half-life of active form averages 8-10 hours ® twice daily dosing for treatment and once daily for prophylaxis
- Renal excretion ® dose reduction for renal failure ($\text{CrCl} < 30 \text{ ml/mn}$)
- No important adverse drug interactions
 - Probenicid delays excretion