

Pharmaceutical interventions for Rapid Containment



World Health
Organization

Learning Objectives

- List influenza-specific antivirals and the choice of drug for a rapid containment operation.
- Discuss their characteristics including benefits, contraindications and potential side-effects.
- Discuss the use of vaccines for an RC operation.
- Discuss options and feasibility of different monitoring approaches for compliance and adverse effects.

Session overview

- **Antiviral drugs for influenza**
 - Treatment and prevention
 - Precautions, contraindications and side effects
 - Antiviral resistance
- **Pharmaceutical interventions for rapid containment**
 - Role of vaccine and antivirals
 - Planning considerations
 - Practical issues

Pharmaceutical measures for prevention and control of Influenza

- **Pharmaceutical measures are influenza-specific**
 - Vaccines
 - Antivirals
- **Public health measures* are not specific to influenza**

Also called non-pharmaceutical interventions

Influenza vaccines

- **Primary means of preventing seasonal influenza**
- **Composition based on strains available to WHO Global Influenza Surveillance Network**
- **Safe -- serious adverse events are rare**
- **Proven efficacy / effectiveness to prevent infection, severe illness (hospitalization) and death**
- **Cost effective in many target groups**
- **Protective immunity lasts ~6 months**

Vaccine use during rapid containment (1)

- **May not be available or only in a small amount**
- **Slow immune response**
 - Two doses required
 - Sufficient response may take 2-4 weeks after 2nd dose
- **Uncertain efficacy/effectiveness**
- **Development of a pandemic vaccine**
 - Limited surge capacity
 - 6 months until large-scale production

Vaccine use during rapid containment (2)

- **Antivirals will be primary pharmaceutical intervention**
- **Vaccine should be used to supplement if**
 - **Available for newly identified pandemic virus**
 - **Stockpile available to WHO for rapid containment**
- **Inter-pandemic stockpiles of H5N1 vaccine being established**

Classes of influenza-specific antivirals

- 1. Neuraminidase inhibitors**
 - Oseltamivir
 - Zanamivir
- 2. M2 inhibitors (Adamantanes)**
 - Amantadine
 - Rimantadine

Use of influenza-specific antivirals

- **All 4 antiviral drugs can be effective for treatment and prophylaxis of susceptible viruses**
 - **Decrease uncomplicated infection by ~ 1- 2 days**
 - **Prophylaxis is 70% - 90% effective**
- **Neuraminidase inhibitors preferred for rapid containment**
 - **Amandatine and rimantadine: frequent resistance**
 - **Amandatine: neurotropic adverse effects**
 - **Oseltamivir and zanamivir: more tolerable; resistance less frequent**

Neuraminidase (NA) inhibitors

- Active against influenza A and B
 - Inhibitory for H5N1 and other avian viruses in laboratory
- Interfere with release of virus from infected cells and spread in respiratory tract
- Pharmacologic differences
 - Oseltamivir: oral drug - circulates systemically
 - Zanamivir: inhaled - local administration to respiratory tract

Oseltamivir: Adverse events (1)

- **Designed to fit into the active site of the virus**
 - No interaction with human cells
 - Adverse events due to other ingredients (e.g. gelatine)
- **GI problems (nausea, vomiting) likely drug-associated and can be reduced by taking food with drug**
- **Other frequently reported adverse events: headache, fatigue, cough, diarrhoea**
- **Expect reporting of adverse events during rapid containment**

Oseltamivir: Adverse Events (2)

- **Serious adverse events are very rare***
 - Allergic, anaphylactic reactions (e.g. swelling of the face or tongue)
 - Skin rash (sometimes severe)
 - Itching
 - Dizziness
 - Hepatitis
 - Seizure, bizarre behaviour, delirium
- **Important to monitor adverse events**

* Relation with use of oseltamivir has not been established



Oseltamivir Precautions

Pregnant or breastfeeding mothers

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

Liver disease

- Safety and efficacy not yet evaluated
- Use if expected benefit outweighs risk

Kidney disease

- Decrease dose if creatinine clearance ≤ 30 ml/min

H5N1 treatment with oseltamivir

- **Active against H5N1 viruses in the laboratory and animal models; limited human studies**
- **Early treatment likely reduces mortality**
- **Treatment also warranted at later stages of illness given prolonged virus replication**
- **Use same dosage as for seasonal influenza**
- **Consider modified regimens (e.g. doubled dose, longer duration, combination therapy) for pneumonia or progressive disease**
- **Limited evidence for prevention of H5N1 infection**

From: WHO Rapid Advice Guidelines on pharmacological management of humans infected with avian influenza A(H5N1) virus, Clinical management of human infection with avian influenza A(H5N1) virus, 2006.



Zanamivir overview

- **Orally inhaled powder (Diskhaler)**
- **Low systemic absorption**
 - ~7% - 21% of dose reaches lower airways
 - Possible choice for pregnant women, breast feeding mothers, renal/liver insufficiency
- **Adverse effects**
 - Bronchospasm, sometimes severe
 - Association with nausea, diarrhea, headache uncertain
- **Antiviral resistance rare to date**
- **No clinical data in human H5N1**

Role of antivirals

Avian influenza outbreaks in humans*:

- **Treat probable/confirmed cases**
- **Prophylax close contacts (e.g. household and family contacts)**
- **Monitor health status of persons with moderate/low exposure risk (e.g. health care and animal workers)**
 - **Treat if illness develops**

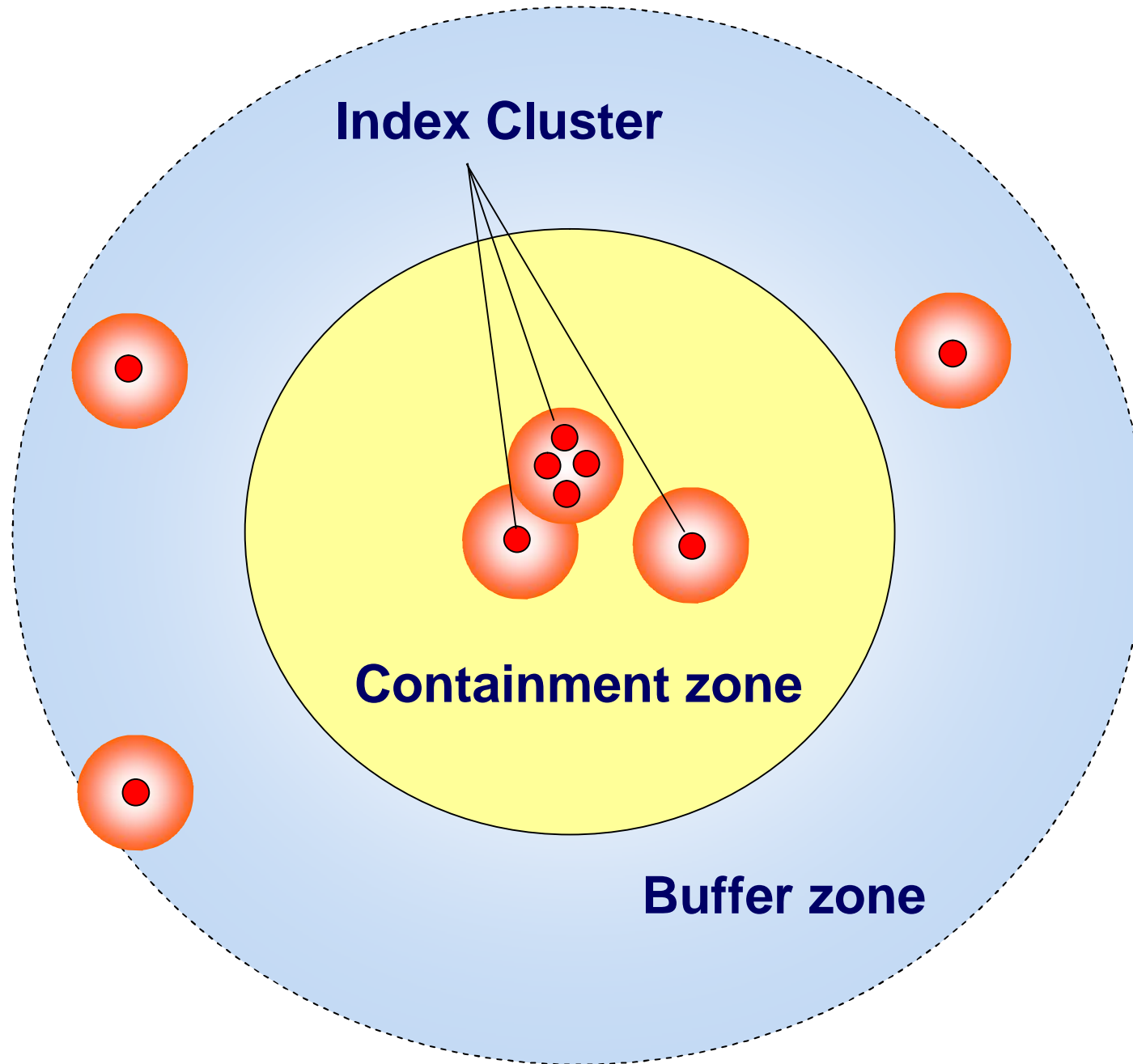
***WHO Rapid advice guidelines on pharmacological management of humans infected with avian influenza A(H5N1) virus**



Use of Antivirals during Rapid Containment

- **Index Cluster**
 - Treatment of ill cases
 - Prophylaxis of close contacts
- **Containment Zone (CZ)**
 - Treatment of ill cases
 - Prophylaxis of all persons (who are not ill) for 20 days
- **Buffer Zone (BZ)**
 - Treatment of symptomatic persons with Influenza-like illness while waiting for lab testing
 - Prophylaxis of their contacts

Use of antivirals during rapid containment



Antiviral prophylaxis in the CZ:

How long?

- **Prophylaxis for 20 days**
 - Increase the time most persons on prophylaxis or treatment at the same time
 - Uncertainty about the emerging virus; e.g. possibility of longer incubation period than seasonal influenza
 - Packaging considerations – blister pack of 10 tablets
- **If additional cases arise, assess exposure to ill persons and antiviral treatment history/ compliance**

Sources of antiviral supplies

- **WHO antiviral stockpile**
 - 3 million oseltamivir treatment courses
 - Reserved uniquely for containment of pandemic
- **Regional stockpiles (e.g. ASEAN-Japan)**
- **Assess local supplies**
 - Pharmacies
 - Manufacturing companies
 - Hospitals or private doctors
- **WHO stockpile will replenish national supplies if used for rapid containment**



Practical considerations for antivirals (1)

- **Pediatric administration / dose adjustment**
 - Scales needed to weigh children
 - Reconstitution of dry powder into a liquid formulation requires: training, safe water, measuring devices and sweet diluent to mask bitter taste
 - If only adult capsules available, manufacturer will provide preparation instructions
 - Refrigeration required

Practical considerations for antivirals (2)

- **Informed consent**
 - **Based on complete information about potential benefits and risks**
 - **Right to refuse**
 - **Special issues arise for use during pregnancy, breast feeding and infants < 1 year**



Monitoring antiviral use (1)

- **Needed to monitor compliance and adverse events**
- **Possible options**
 - Telephone surveys
 - Household visits
 - Incorporate into larger scheme to assess / deliver supplies
- **Factors to consider**
 - Size of population in Containment Zone
 - How antivirals distributed
 - Other logistical issues

Monitoring antiviral use (2)

● Compliance

- Achieve maximum benefit of antivirals
- Assess if new cases represent poor compliance, prophylaxis failure, antiviral resistance



● Adverse events

- Passive reporting system (e.g. telephone hotline) is minimum standard
- Active system with designated coordinator, reporting infrastructure desirable
- Advice on management of the event

Pharmaceutical Interventions

Supplementary slides if additional explanation is requested for the specific topics. These are NOT part of the presentation

Oseltamivir dose adjustment for renal impairment

Supplementary slide

Creatinine Clearance(CCr)	Treatment	Prophylaxis
> 30 ml/min	No dose adjustment required.	No dose adjustment required.
10-30 ml/min	75 mg once daily for 5 days	75 mg once every other day or 30 mg once a day
Endstage renal disease* (CCr < 10 ml/min)	A single dose of 75mg oseltamivir will deliver antiviral levels for up to 5 days	

*Patients undergoing routine hemodialysis or peritoneal dialysis treatment



Paediatric dose adjustment

Body Weight	Recommended dosage
≤ 15 kg	30 mg
15 < to 23 kg	45 mg
23 < to 40 kg	60 mg
40 kg <	75 mg

H5 vaccine development

As of April 2008

- 16 companies have candidate vaccines in development; > 40 clinical trials
- Types: inactivated (whole and split virus), virosomal, live-attenuated
- Routes: IM, intradermal, intranasal
- Adjuvants for inactivated: $\text{Al}(\text{OH})_3$, AlPO_4 , MF59, ASO_3
- Substrates for growth: eggs, Vero cells, MDCK cells, primary monkey cells

Oseltamivir: Adverse events

Supplementary slide

Adverse event	Treatment		Prophylaxis	
	Placebo N=716	Oseltamivir N=724	Placebo N=1688	Oseltamivir N=1790
Nausea	40 (6%)	72 (10%)	56 (3%)	129 (7%)
Vomiting	21 (3%)	68 (9%)	16 (1%)	39 (2%)
Diarrhoea	70 (10%)	48 (7%)	40 (2%)	50 (3%)
Headache	14 (2%)	13 (2%)	306 (18%)	326 (18%)
Cough	12 (2%)	9 (1%)	119 (7%)	94 (5%)

Data source: Roche