Outbreak and Pandemic Response: Role of Antivirals

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World Health Organization
WHO Emergency Reform

WHE = WHO's Health Emergency (WHE) Programme
WHO Health Emergencies Programme

Dr. Peter Salama
ExD, WHE

WHO Health Emergencies Programme (WHE)

- Infectious Hazard Management (IHM)
  - High Threat Pathogens (PAT)
  - Experts Networks & Interventions (ENI)
  - PIP Secretariat (PIP)
- Country Health Emergency Preparedness & IHR (CPI)
  - Core Capacity Assessment, Monitoring & Evaluation (CME)
  - Preparedness, Readiness & Core Capacity Building (PCB)
  - IHR Global Functions (IHR)
- Health Emergency Information & Risk Assessment (HIM)
  - Detection, Verification & Risk Assessment (DVA)
  - Health Ops Monitoring & Data Collection (MDC)
  - Data Management, Analytics & Products (MAP)
- Emergency Operations (EMO)
  - Emergency Management & Support (OPM)
  - Operational Partnerships (OPR)
  - Operations Support & Logistics (OSL)
- Management & Administration (MGA)
  - Workplanning, Budgets & Finance (WBF)
  - HR, Security & Staff Wellbeing (HSW)
  - Grant Management & Reporting (GMR)
  - Continuous Business Improvement (CBI)

Office of the Executive Director (HEO)

- External Relations (EXR)
- Communications (COE)
- Advocacy (ADV)
- Resource Mobilisation (RMB)
Infectious Hazard Management
(Department)

Pandemic Influenza Preparedness (PIP) Framework

Global Influenza Programme

MERS CoV

Job vacancies:
http://www.who.int/employment/vacancies/en/
## Infectious Hazard management activities

### Diseases
- Cholera
- Emerging diseases
- Hendra virus infection
- Influenza (avian, seasonal, pandemic)
- Leptospirosis
- Meningitis
- Nipah virus infection
- Plague
- Rift Valley fever
- SARS and MERS coronavirus infections
- Smallpox and human monkeypox
- Tularemia
- Viral Haemorrhagic fevers (Ebola, Marburg, Lassa, CCHF)
- Yellow fever, ZIKA

### Cross-cutting initiatives and networks
- Battle against Respiratory Viruses (BRaVe) initiative
- Communicable Disease Control in Humanitarian Emergencies (DCE)
- Emerging and Dangerous Pathogens Laboratory Network (EDPLN)
- Emerging Disease Clinical Assessment and Response Network (EDCARN)
- International Coordinating Group (ICG) for yellow fever, meningitis and cholera
- Global Infection Prevention and Control Network (GIPCN)
- Global Influenza Surveillance and Response System (GISRS)
- Global Leptospirosis Environmental Action Network (GLEAN) and Meningitis Environmental Risk Information Technologies (MERIT) project
- Pandemic Influenza Preparedness framework (PIP)
Addressing the public health burden of respiratory viruses: the Battle against Respiratory Viruses (BRaVe) Initiative

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Future Virol. (2013) 8(10), 953–968
Ensuring WHO’s capacity to prepare for and respond to future large-scale and sustained outbreaks and emergencies
Pandemic Response Tools

PH measures (i.e. school closures, mask, mass gathering)

Medical countermeasures/Good clinical management

Non-pharmaceutical interventions

Inactivated Influenza Vaccine (IIV) (1944)

Improved IIV (1960 purified)

LAIV (live-attenuated, 1960, Russia)

GISN (1952)

IIV (1968 fragmented)

II (1980 sub-unit)

Adjuvanted IIV (1997)

LAIV (2003, USA)

Cell-based IIV (2007)

1918 Spanish flu pandemic

1957 Asian flu pandemic

1968 Hong Kong flu pandemic

1997 H5N1 Hong Kong SAR

2003 H5N1 Asia

2009 A (H1N1) 2009 pandemic

2013 H7N9 China

Vaccines

Introduction of other classes of antibiotics

Antibiotics

Antivirals

Rimatadane (1993)

Neuraminidase inhibitor Favipiravir (2009)

Amatadane for influenza (1966)

Rimadane for influenza (1966)

Aminoglycosides (1943)

Sulfonamides (1939)

Penicillin (1945)

Erythromycin (1952)

Cephalosporins (1964)

Medical countermeasures/Good clinical management

PH measures (i.e. school closures, mask, mass gathering)
We have imperfect vaccines, and imperfect antivirals.

Role of antivirals?
Development of WHO Standard Guideline on Clinical Management of Influenza Virus Infection
Scope

Clinical management of severe influenza disease

- Treatment of severe influenza e.g. viral pneumonia, ARDS, multiple organ failure, septic shock;

- Pharmacological interventions for treatment, including influenza antiviral drugs, anti-inflammatory drugs and adjunctive therapies;

- Non-pharmacological clinical interventions, such as mechanical ventilation, oxygen and fluid management.

- Preventing development of severe influenza; including treatment of patients at higher risk of progression to severe disease and prevention of infection in highest risk patients
Formulating questions and choosing outcomes based on the PICOT framework

| Population                        | All patients presenting with severe or deteriorating influenza illness  
|                                  | All patients in groups defined as at higher risk of severe or complicated disease |
| Intervention                     | Influenza antivirals (including investigational products)  
|                                  | Adjunctive therapies, such as immunomodulators, serum or plasma products  
|                                  | Other pharmacological and non-pharmacological clinical interventions |
| Comparator                       | There are currently few established standards; comparator is generally no intervention or placebo |
| Outcome                          | Prevention of infection (in higher risk individuals)  
|                                  | Prevention of disease progression  
|                                  | Time to resolution of severe illness  
|                                  | Reduction in hospital or ICU admission or length of hospital stay  
|                                  | Reduction in mortality  
| Time                             | Short term (to resolution of illness) |
Process

In accord with WHO standard for guideline development; requires substantial evidence review and assessment.

Commissioning of systematic reviews and GRADE assessments

Followed by panel review with good regional representation

http://www.who.int/kms/guidelines_review_committee/en/index.html
http://www.gradeworkinggroup.org/index.htm
GRADE

- Grading of Recommendations, Assessment, Development and Evaluations

- Systematic method of linking evidence quality evaluations to clinical recommendations
Introduction

- Licensed influenza antivirals
  - M2-inhibitor (M2I): amantadine, rimantadine,
  - Neuraminidase inhibitors (NAI): zanamivir, oseltamivir, laninamivir, peramivir
  - Other mechanisms: not licensed or extremely limited availability

- All currently circulating human influenza viruses are resistant to M2Is. NAI resistance is rare.

- Oseltamivir is licensed in >80 countries for prophylaxis and treatment for influenza virus infection; only antiviral suitable for use in children<5, US FDA approval lowered to 2 weeks of age in December 2012.
Future prospects

- Inhaled Laninamivir
- IV Peramivir
- Oral Favipiravir
- IV Zanamivir
- Novel PB2 and PA inhibitors
- Antibodies
Regional and other antivirals

- Arbidol
- Ingavirin
- Ribavirin
- Others.....
Evidence

- Clinical trial data

- Observational data
  - Hsu et al. 2012
  - Muthuri et al. 2013
  - MUGAS 2015
  - PRIDE 2015

- Public Health observations
  - Canada, Japan, Argentina
  - Miller et al. 2012
Supply of Neuraminidase Inhibitors Related to Reduced Influenza A (H1N1) Mortality during the 2009–2010 H1N1 Pandemic: An Ecological Study

Paula Miller, Aksharananda Rambachan, Roderick Hubbard, Jiabai Li, Alison Meyer, Peter Stephens, Anthony W. Mounts, Melissa Rolfes, Charles Penn
Policy case study: Argentina 2009

Number of H1N1 cases among pregnant women, 2009 by day according to date of symptom onset. Argentina Year 2009 (n = 243 *)

SARI-only Treatment

Leave for pregnancy

Treat all ILI
Figure 9: Antivirals Prescribed Compared to ICU and Ventilation Admissions (by Admit Date), April to December 2009
Public health aim

- To mitigate severe or complicated illness
- Reduce hospitalization (incidence, duration)
- Prevent death

- NOT to shorten self limiting, uncomplicated illness
Existing WHO Guidelines

- 2006 Rapid Advice Guidelines in Pharmacological Management of Humans Infected with Avian Influenza A (H5N1) Virus

- Rapid advice guidelines for the treatment of pandemic H1N1 influenza (H1N1pdm09)
  - First published in August 2009, and revised in February 2010.
  - 2010-12, WHO reviewed its guidelines for clinical management of severe influenza and developed a set of Standard Guidelines that include use of influenza antivirals. These standard guidelines are in the final stage of completion, following a full review of evidence and expert consultation.

- 2014 Emergency guidance for avian influenza A(H7N9) virus
  - Post-exposure antiviral chemoprophylaxis of close contacts of a patient with confirmed H7N9 virus infection and/or high risk poultry / environmental exposures.
**Recommendations**

- Use of oseltamivir for treatment of severe or complicated influenza, and for treatment of influenza in patients at higher risk of developing severe disease.

- Prophylactic use of oseltamivir for persons with a high risk of exposure to avian influenza H5N1 to prevent illness that has a high case fatality rate.

- WHO does not recommend prophylactic use for seasonal influenza nor for the recent pandemic virus (H1N1pdm09).

- Antiviral chemoprophylaxis following exposure to H7N9 virus is generally not recommended. Symptomatic individuals with exposure to H7N9 virus should receive prompt antiviral treatment with a neuraminidase inhibitor.
Increasing accessibility

- Qualified inclusion on model list of Essential Medicines (in the context of influenza pandemic)
- Rapid deployment (donations) from a global stockpile
- Prequalified products
- Guidelines for use
  - Does not displace vaccination
Relevant WHO work

- Oseltamivir is on EML since 2010

- WHO has prequalified oseltamivir formulations from several companies to facilitate equitable access to the medicine.

- WHO Prequalified products for influenza
  [http://apps.who.int/prequal/query/ProductRegistry.aspx](http://apps.who.int/prequal/query/ProductRegistry.aspx)

- Antivirals as one of 'benefits' along with vaccines and surveillance/diagnostics capacity of the PIP Framework
WHO global strategic antiviral stockpiles

**Tamiflu™**

- Rapid response stockpile (3.65M*, 3M adult, .65M* paediatric)
  - Draft SOP ready for expert review (scenario-based)
  - MS to request deployment
  - Deploy, not deploy or continue preparatory actions to be decided based on technical, operational and legal/policy information

- Regional stockpile – for LMIC (2M*)
  ROs to work with MS on risk / needs assessment
  - To control outbreaks caused by human and non-human influenza,
  - To control severe influenza epidemics,
  - For potential pandemic or pandemic response

**Relenza™** (2M* donation+8M* affordable prices), SMTA2. SOP, deployment details to be determined.
2009 (H1N1) pandemic Antiviral deployment

72 countries Global + 46 countries AFRO + 20 countries EURO stockpiles

Delivery within 21 days (ahead planning & tool, good coordination with Roche)
WHO antiviral deployment

- Continued support after 2009-10 Influenza pandemic: up & running
- Tamiflu™ adult and paediatric formulations
- Total 13 deployment in response to human and poultry outbreak responses
- **Providing clinical support/training as a package. (WHO Training → See Poster presentation)**

Courses*: treatment courses – 10 capsules of 75/45/30 mg oseltamivir phosphate

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<thead>
<tr>
<th>Year</th>
<th>Country</th>
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<tbody>
<tr>
<td>2011</td>
<td>Bhutan</td>
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<tr>
<td>2013</td>
<td>Iraq</td>
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Antiviral WHO Stockpile deployment

- Under PIP Framework (2011)
- Standard Operating Procedure (SOP) currently under development
  - Scenario-based deployment plans: 12 scenarios, including containment operation
  - Identification of variables to characterise and plan for deployment (R0, clinical attack rate, generation interval, etc)

SOP and scenario ready for expert review (contact: shindon@who.int)

- Deployment drills to be conducted
Need for research
Research agenda progress review

- Literature reviews conducted for high priority research topics.
- Over 4,000 articles reviewed in more than 200 journals.
- Work related to H1N1pdm09 dominated the body of work.
- Increased knowledge in some topics.
- WHO-lead approach needs evaluation.

http://www.who.int/influenza/resources/research/en/
Thank you