Antivirals: What can they do to slow down a possible flu pandemic?

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Role of antivirals in a pandemic

- **Antivirals**
  - "Once a pandemic has been declared…the role of antiviral drugs is unquestionable"
  - "Pending the availability of vaccines, antiviral drugs will be the principle medical intervention for reducing morbidity and mortality"

Avian influenza: assessing the pandemic threat. WHO January 2005

Influenza Antivirals

M2 Inhibitors: amantadine and rimantadine

- Block the M2 ion channel of influenza A
- Resistance reported in many of the currently circulating H5N1 viruses

Neuraminidase inhibitors:

- Bind to the highly conserved active site of the influenza virus neuraminidase
- Prevent release of the virus from the cell, reducing spread
- Indicated in treatment and prevention of influenza
  - Tamiflu (oseltamivir); delivered orally, suitable for age ≥ 1 year
  - Relenza (zanamivir); delivered by inhalation, suitable for age ≥ 5 years
  - [peramivir - investigational]

Neuraminidase inhibitors: use in a pandemic setting

- Are effective for both early treatment and chemoprophylaxis of seasonal influenza infections
- Likely to be the only virus-specific interventions available during the initial pandemic response, as a suitable vaccine is unlikely to be available for at least 6-8 months
- Have shown activity against a range of avian influenza virus types

Oseltamivir and Zanamivir: clinical efficacy

- Studied in usual seasonal epidemics of influenza A (H3N2, H1N1) and influenza B
- Effective in prevention of influenza illness
  - Reduces risk of illness by ~ 80-90%
- Effective in treatment of influenza, given within 2 days of symptom onset, 5 day course
  - reduces duration of symptoms by ~ 1.5 days
  - reduces incidence of complications requiring antibiotics by ~ 30%

Antiviral resistance

- Resistance to M2 inhibitors reported in currently circulating H5N1 strains
- Resistance to NI may emerge
  - Resistance infrequent compared with M2 inhibitors
  - May be associated with lower pathogenicity and/or transmissability
  - Not all mutant strains are cross-resistant to other NIs
- Surveillance ongoing
- Clinical significance currently unknown

Activity of antivirals against H5N1
Gubareva, L.V., *et al.,* 1998

- In 1997, influenza A:Hong Kong:156:97 virus transmitted directly to humans and killed six of the 18 people infected

- Zanamivir administered intranasally has been shown to be effective in treating mice infected with A:HK:156:97 (H5N1) influenza virus
  - protected mice from lethal infection with H5N1 virus
  - significantly reduced virus titers in mouse lungs and prevented the spread of virus to the brain

Gubareva, L.V., et al., 1998. Characterization of influenza A:Hong Kong:156:97 (H5N1) virus in mouse model and protective effect of zanamivir on H5N1 infection in mice. J. Infect. Dis. 178, 1592–1596

Activity of antivirals against H5N1
Govorkova et al. 2001

- Neuraminidase inhibitors oseltamivir and RWJ-270201:
  - were active against influenza A/HK/156/97 (H5N1)
  - significantly reduced virus titers in mouse lungs and prevented the spread of virus to the brain
  - protected mice from lethal infection with H5N1 virus
    - oseltamivir
      - 24 h after virus inoculation - 90% of animals survived
      - 60 h after virus inoculation - 65% of animals survived
    - RWJ-270201
      - 24 h after virus inoculation - 80% of animals survived
      - 48 h after virus inoculation - 50% of animals survived

Govorkova, E. *et al*. 2001. Comparison of efficacies of RWJ-270201, zanamivir, and oseltamivir against H5N1, H9N2, and other avian influenza viruses. Antimicrobial Agents and Chemotherapy, Oct. 2001, p. 2723–2732

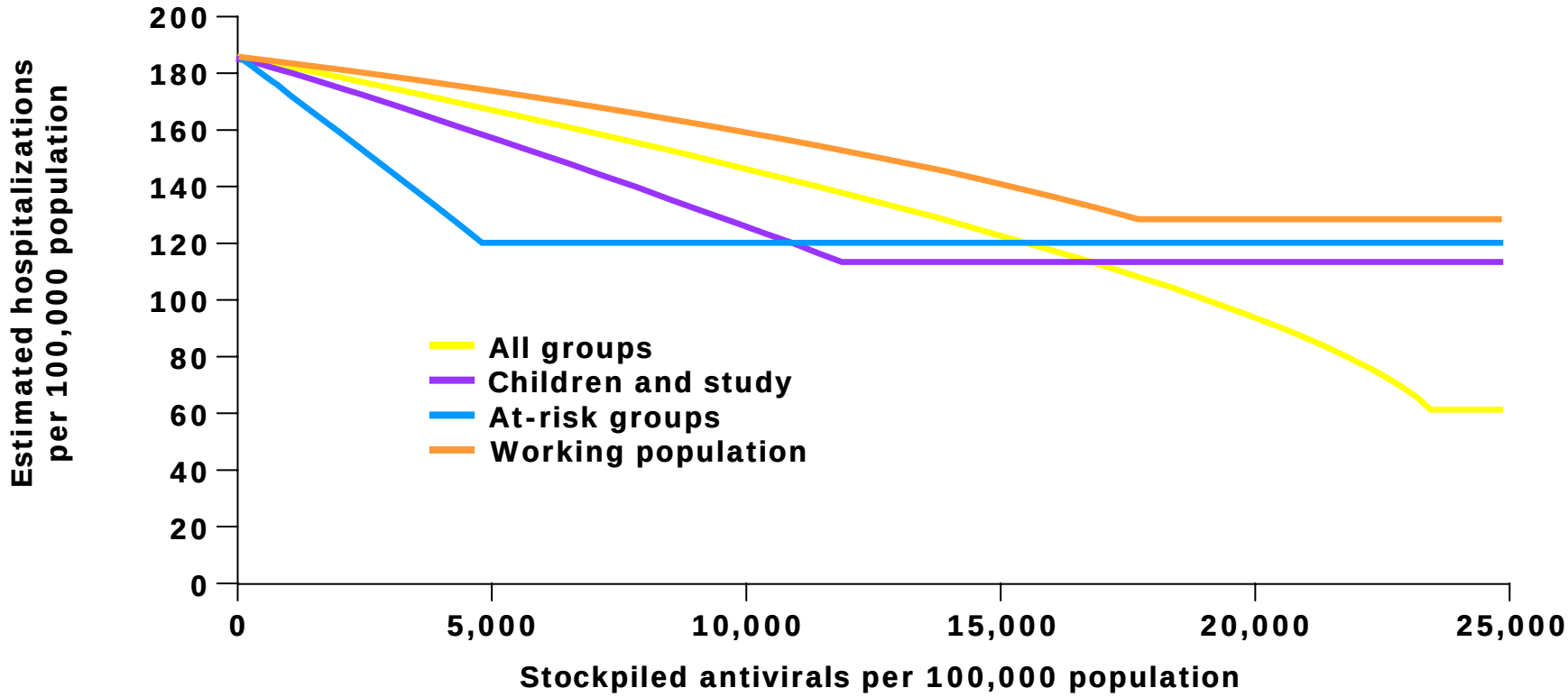
Clinical experience with oseltamivir in the treatment of people infected with H5N1

- Limited number of cases; geographically dispersed
- Vast majority of confirmed cases received oseltamivir late
- Benefit appears greatest when oseltamivir is given early
- Survival may correlate with rapid reduction in virus titre
- Resistance reported during therapy in 3 cases
  - timeframe and mutation pattern consistent with seasonal influenza
  - issues include under-dosing and late intervention
  - retained sensitivity to zanamavir

Anti-viral pandemic response models

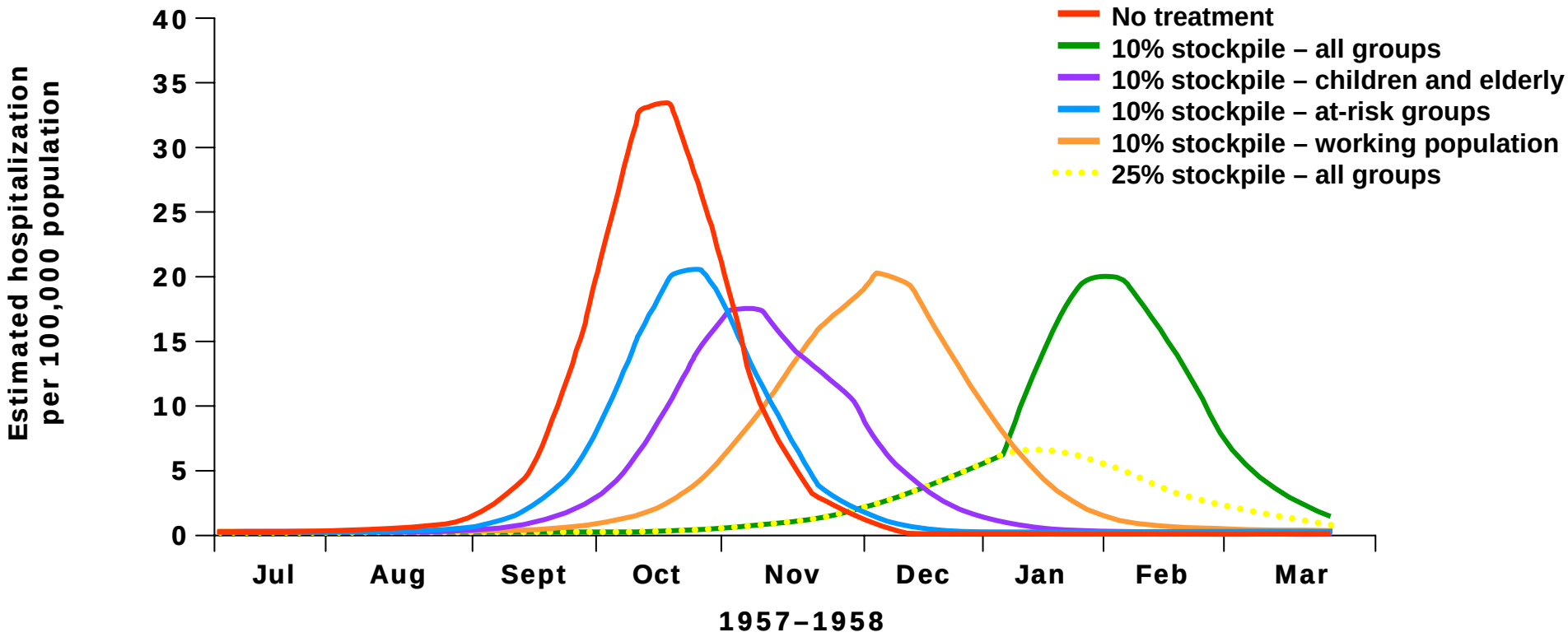
Global Stockpile	Regional Stockpile	National Stockpile
Purpose: To support containment, either directly or by replenishing other stockpiles that were used to support containment, anywhere in the world **Timing:** Time/site of outbreak of a human pandemic. **Application:** WHO administered. Treatment of infected individuals and geographically targeted prophylaxis.	**Purpose:** To support any of the countries within a defined region in the management of avian or pandemic influenza outbreaks. **Timing:** Pandemic phase III and later. **Application:** Regionally-located stockpile administered by the WHO. Treatment of individuals with confirmed or suspected avian or pandemic influenza virus infection and high risk exposure groups.	**Purpose:** Response to outbreaks within the country or the treatment and prophylaxis of citizens during a pandemic. **Timing:** Pandemic phase III and later. **Application:** Stockpile under the control of a specific nation and positioned within its borders. Treatment of individuals with confirmed or suspected avian or pandemic influenza virus infection and high risk exposure groups.

A stockpile of 20%–25% could provide a 67% reduction in hospitalizations



Adapted from Gani et al. 2005
Based on 1957 pandemic
Estimated hospitalizations per 100,000 population when different antiviral treatment strategies are applied

25% stockpile and targeting all groups significantly reduces and delays hospitalizations



Scenarios:
- 1957 pandemic
- stockpile fixed at 10% of the population
- stockpile fixed at 25% of the population
- all clinical cases are treated
- when no treatment is administered

Adapted from Gani et al. 2005

Pharmacological management of avian influenza
WHO recommendations; where neuraminidase inhibitors are available

Treatment in patients with confirmed or strongly suspected H5N1 infection:

- Tamiflu (oseltamivir) treatment (strong recommendation)
- Relenza (zanamivir) as an alternative (weak recommendation)

Applies to adults (including pregnant women) and children
Regimen for H5N1 is as recommended for seasonal influenza

World Health Organization. WHO Rapid Advice Guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus. 2006.

Pharmacological management of avian influenza
WHO recommendations;
where neuraminidase inhibitors are available

Chemoprophylaxis:

- In high risk exposure groups oseltamivir / zanamir (alternative) should be administered (strong recommendation)
- In moderate risk exposure groups oseltamivir / zanamavir might be administered (weak recommendation)

Continuing for 7-10 days after the last known exposure

Regimen for H5N1 is as recommended for seasonal influenza

World Health Organization. WHO Rapid Advice Guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus. 2006.

Anti-viral stockpiles
Levels of coverage

- Overall clinical attack rates during pandemics have reached 30–35% [1]
- Coverage required depends upon the virulence of the virus once a pandemic starts
- Stocks required for treatment and for prophylaxis
  - Post exposure prophylaxis
  - Prophylaxis for essential services workers
- The Infectious Disease Society of America recommends stockpiling for 50% of the population [2]
- Stockpiles equivalent to 50% of the population, allowing post-exposure prophylaxis in households could reduce clinical attack rates by 40–50% [3,4]

1. Glezen WP. *Epidemiol Rev* 1996; **18**: 64–76.
2. US Department of Health and Human Services. HHS pandemic influenza plan. 8 November 2005.
3. Ferguson NM, *et al. Nature* 2006, 442(7101):448-452.
4. Wu JT *et al.* PLoS Med 3(9): e361.

Surge production of anti-viral agents is not an option for pandemic response

- Manufacturing of antiviral agents generally geared towards significantly lower
  seasonal demand for these products
- Responding to a pandemic with surge production is not an option due to
  - long timelines for scale up,
  - sourcing of raw materials and
  - manufacturing cycle-times
- Contingency planning needs to be in place to cope with the demands of a pandemic
- The WHO has advised that “Stockpiling drugs in advance is presently the only way to ensure that sufficient supplies are available at the time of a pandemic” [1]

Avian influenza: assessing the pandemic threat” WHO January 2005

Increasing availability of neuraminidase inhibitors for pandemic use

Actions to date:

- Significant “at risk” increase in production capacity by “originator” companies
  - Global manufacturing capacity has been increased by around 10-fold over the last 2 years
  - Roche production capacity approaching 400 million courses of therapy / year
- Price reductions for medicine purchased by governments for pandemic use
- Sublicenses offered to generic manufacturers
  - Oseltamivir: sublicenses to 2 companies in China, 1 company in India, technical knowledge transfer to African company
  - Zanamavir: Sublicense in China
- 3 million courses of oseltamivir therapy “rapid response stockpile” placed at disposal of WHO
- 2 million courses of oseltamivir therapy donated to WHO as a regional stockpile

Summary

1. *In vivo* animal data supports activity of neuraminidase inhibitors against human clinical isolates of H5N1
2. Approved for treatment / prevention of influenza; extensive experience and safety data
3. Manufacturing generally geared towards significantly lower seasonal demand for these products - Manufacturers of neuraminidase inhibitors have scaled-up production to support government stockpiling efforts
4. “Stockpiling drugs in advance is presently the only way to ensure that sufficient supplies are available at the time of a pandemic.”