

## **Pandemic Influenza Update**

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Transplantation*

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# Summary of presentation

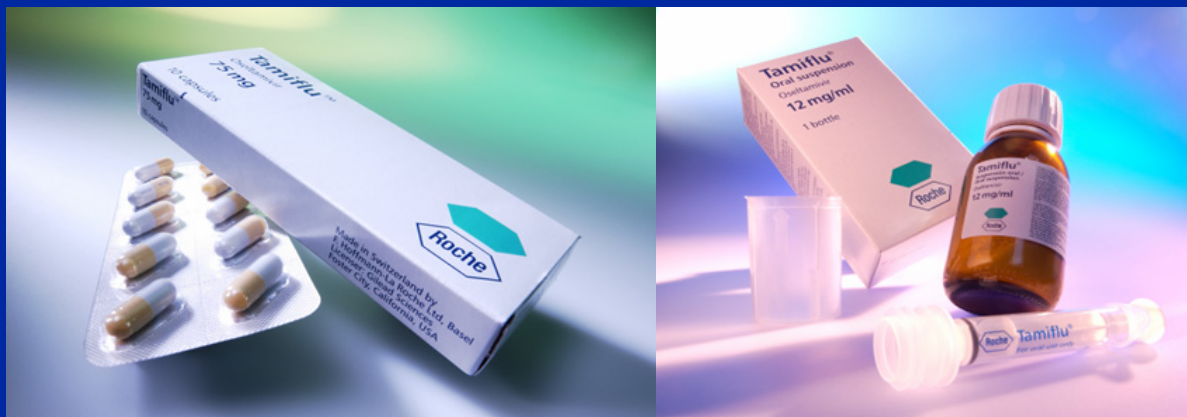
- Role of antivirals in a pandemic
- Update of pandemic stockpiling by governments and corporations
- Modelling in a pandemic
- Update on research initiatives and other areas
  - Resistance
  - Neuropsychiatric events
  - H5N1 research

# Tamiflu for the treatment and prevention of influenza

- Orally-administered influenza neuraminidase inhibitor
- Active against all strains of influenza (A and B) tested to date
- Approved in over 80 countries
- Treatment of influenza in patients aged  $\geq 1$  year
  - Shortens duration of influenza illness
  - Shortens severity of symptoms
  - Avoids complications and unnecessary antibiotic use
  - Stops virus spreading to other people
  - Reduces individual and societal burden
- Prevention of influenza in patients aged  $\geq 1$  year
  - Reduces risk of illness (individual and societal burden)

# Role of antivirals in a pandemic

- “Once a pandemic has been declared...the role of antiviral drugs is unquestionable”
- Advance stockpiles are the only way to meet the needs of the first wave of a pandemic
- “Pending the availability of vaccines, antiviral drugs will be the principle medical intervention for reducing morbidity and mortality”



## WHO recommendations

### *Where neuraminidase inhibitors are available*

- In April 2007, the WHO reconfirmed recommendations for the treatment of patients with confirmed or strongly suspected human infection with the H5N1 virus in the current pre-pandemic situation<sup>1</sup>

## Treatment

- Tamiflu treatment (strong recommendation)
- Zanamivir as an alternative (weak recommendation)
- Applies to adults (including pregnant women) and children
- Dosage regimen same as for seasonal influenza

1. World Health Organization. WHO Rapid Advice Guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus. Available at: [http://www.who.int/entity/medicines/publications/WHO\\_PSM\\_PAR\\_2006.6.pdf](http://www.who.int/entity/medicines/publications/WHO_PSM_PAR_2006.6.pdf). Accessed November 21, 2006.

# WHO recommendations

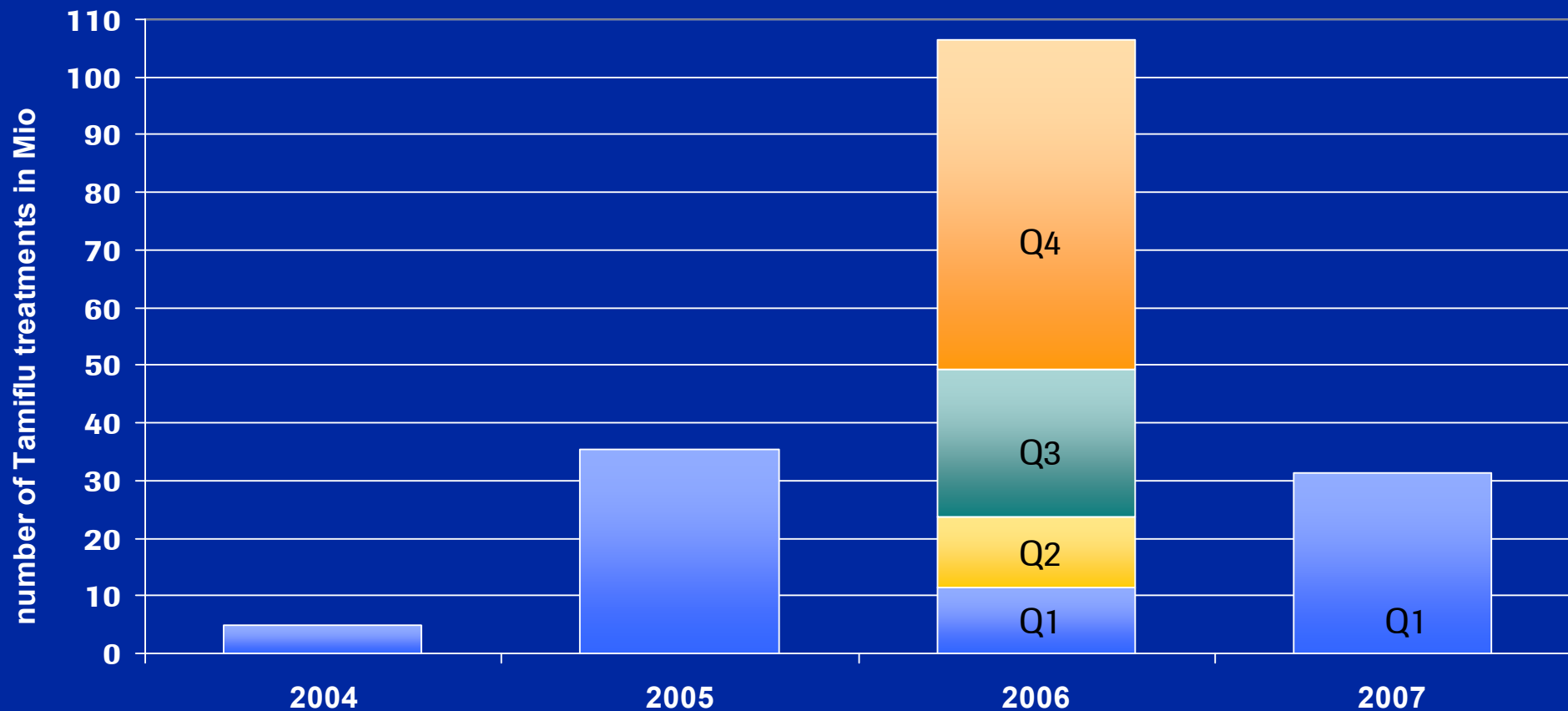
## *Where neuraminidase inhibitors are available*

### Prevention

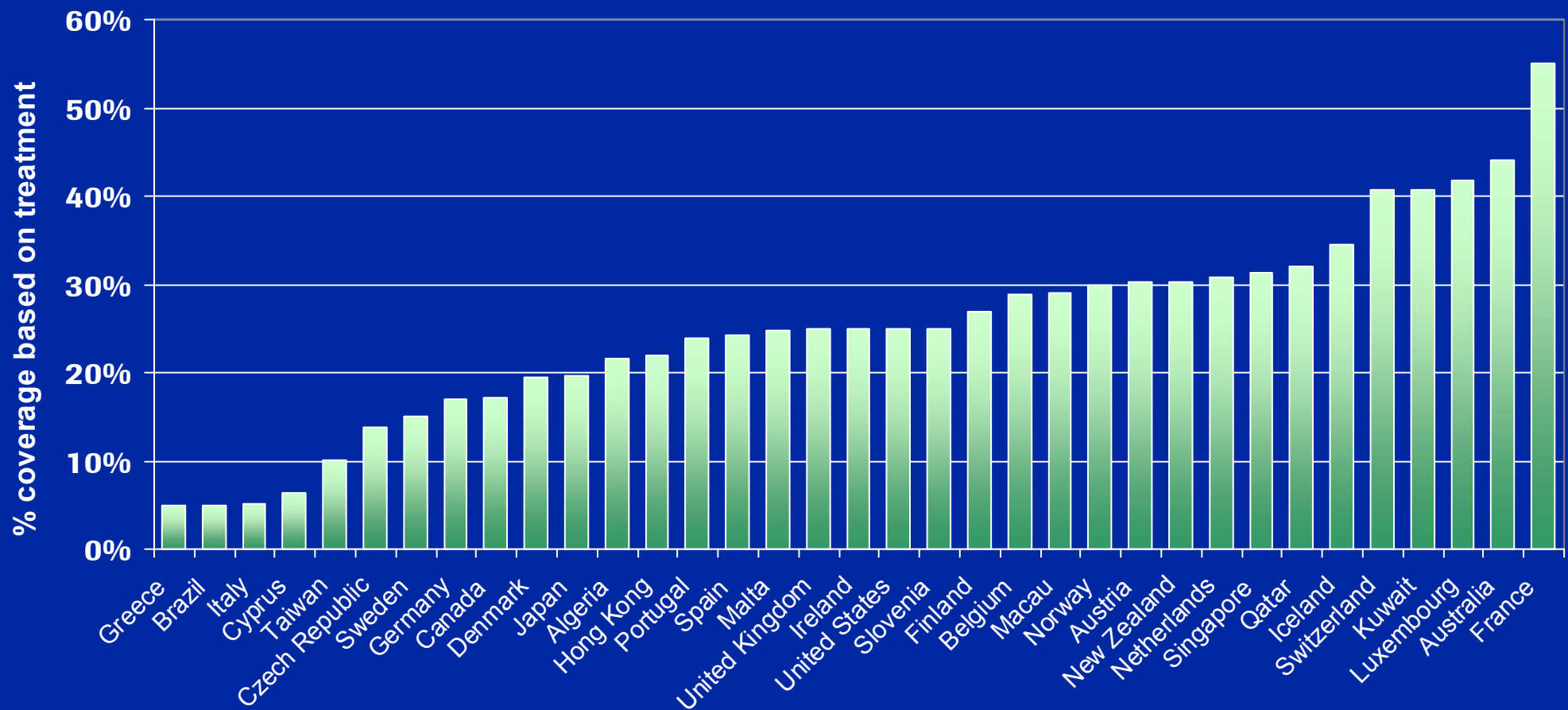
- In high risk exposure groups Tamiflu / zanamivir (alternative) should be administered (strong recommendation)
- In moderate risk exposure groups Tamiflu / zanamivir might be administered (weak recommendation)
- Continuing for 7-10 days after the last known exposure
- Regimen for H5N1 is as recommended for seasonal influenza

# Update of government pandemic stockpiling

- Roche has
  - Received orders or letters of intent from the governments of more than **80 countries**,
  - Accounting for firm orders of **~215 million treatment courses**



# Published targeted levels of stockpiles > 5% in % of total population based on treatment




Sources: Media / National pandemic plans (as of April 1, 2007)

# Strategies for mitigating a flu pandemic

*Analysis based on modeling by Ferguson et al. and Gani et al.*

	No intervention	Treatment*
Antiviral stockpile required (% of total population)	<b>0</b>	<b>29%</b>
Clinical attack rate (cumulative)	<b>34%</b> <b>US: 102m ill</b> <b>EU: 204m ill</b>	<b>32%</b> <b>96m</b> <b>192m</b>
Death rate (per 1'000)	<b>6.8</b>	<b>3.2</b>

\* within one day after onset of symptoms



**Focus on  
reduction of  
morbidity &  
mortality**

Data from:

1 Ferguson N, Nature 2006 442:448-452

2 Gani R EID 2005 11: 1355-1362

# Strategies for mitigating a flu pandemic

*Analysis based on modeling by Ferguson et al. and Gani et al.*

	No intervention	Treatment*	Treatment* + PEP of household contacts
Antiviral stockpile required (% of total population)	<b>0</b>	<b>29%</b>	<b>57%</b>
Clinical attack rate (cumulative)	<b>34%</b> <b>US: 102m ill</b> <b>EU: 204m ill</b>	<b>32%</b> <b>96m</b> <b>192m</b>	<b>22%</b> <b>66m</b> <b>132m</b>
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**Focus on reduction of morbidity & mortality**

**Focus on reduction of clinical attack rates, in addition to morbidity & mortality**

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# Strategies for mitigating a flu pandemic

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	No intervention	Treatment*	Treatment* + PEP of household contacts	Treatment* + PEP of ALL contacts
Antiviral stockpile required (% of total population)	<b>0</b>	<b>29%</b>	<b>57%</b>	<b>102%</b>
Clinical attack rate (cumulative)	<b>34%</b> <b>US: 102m ill</b> <b>EU: 204m ill</b>	<b>32%</b> <b>96m</b> <b>192m</b>	<b>22%</b> <b>66m</b> <b>132m</b>	<b>13%</b> <b>39m</b> <b>78m</b>
Death rate (per 1'000)	<b>6.8</b>	<b>3.2</b>	<b>2.2</b>	<b>1.3</b>

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**Focus on  
reduction of  
morbidity &  
mortality**

**Focus on reduction  
of clinical attack  
rates, in addition to  
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**Maximal reduction  
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Death rate (per 1'000)	<b>6.8</b>	<b>3.2</b>	<b>2.2</b>	<b>1.3</b>
Predicted deaths US	<b>693'600</b>	<b>307'200</b>	<b>145'200</b>	<b>50'700</b>
EU	<b>1.38m</b>	<b>614'400</b>	<b>290'400</b>	<b>101'400</b>

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\* within one day after onset of symptoms

**Significant reduction of illness & death (>80%)**



# Limitations of national preparedness

## *Current status*

- Many governments have made pandemic plans which include stockpiles of antivirals, however....
  - Government anti-viral stockpiles are limited (20-25% is likely not to be enough to mitigate impact)
  - Most plans do not identify priority groups
  - Detailed logistical plans are often lacking
  - Most plans do not clearly address treatment vs prevention
- Some governments have encouraged businesses to prepare their own pandemic plans
  - Estimated global economic losses could be \$ 2- 4.4 trillion<sup>1</sup>

# Why should companies stockpile antivirals?

- Employee
  - Reduces morbidity and mortality
  - Pandemic flu vaccination will not initially be available when the pandemic hits
- Business Continuity
  - Ensure continuity of critical operations by providing antiviral treatment to essential/all employees (+ family members)
- Organisation/Society
  - Companies that provide critical infrastructure services have a responsibility to plan for continued operation in a crisis and should plan accordingly.
  - Supplementing product stockpiled by governments would
    - help to ensure broader and faster accessibility in the event of a pandemic
    - could contribute to a reduction in pandemic flu transmission / clinical attack rates

# Update of corporate pandemic stockpiling

- Roche has
  - received orders from **> 250 corporations**
  - accounting for **~5 million treatment courses**

**Resistance**  
**Neuropsychiatric events**  
**H5N1 research**

*David Reddy, Roche Pandemic Taskforce  
Leader*

# Responsible use of antivirals will minimise resistance

- Resistance cannot emerge in the absence of the influenza virus
- For seasonal influenza overall incidence of resistant virus is 0.32% in adults and 4.1% in children aged one to 12

For avian influenza (H5N1), very few cases of resistance have been reported

- 3 cases in 2005<sup>1,2,3</sup>
- Issues include under-dosing and late intervention
- 2 additional cases in Egypt are currently being investigated

## Responsible use of antivirals will minimise any resistance

1. De Jong *et al.* Oseltamivir Resistance during Treatment of Influenza A (H5N1) Infection. *NEJM*. 2005; 253; 2667-72
2. Mai Le Q, *et al.* Isolation of drug resistant H5N1 virus. *Nature* 2005; 437 1108
3. De Jong MD, *et al.* Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. *Nature Med* 2006

## Neuropsychiatric events

*NO established causality between Tamiflu and such events*

- Influenza itself causes neuropsychiatric events
  - Neuropsychiatric events were reported in Japan prior to the availability of Tamiflu
  - Data has shown similar rates of neurologic and psychiatric events in patients not treated and treated with Tamiflu
- Reports of abnormal behavior / death in adolescent patients with influenza taking Tamiflu emerged in Japan
  - Most reports were recorded after first dosing when symptoms of influenza are most severe
  - Events very rare - 8 deaths related to neuropsychiatric abnormalities out of 45 million patients treated world-wide
- US and European health authorities concluded that no causal link could be established between Tamiflu and these events. However, label updated to advise physicians and patients to monitor for abnormal behaviour in all influenza patients.
- More information being gathered

# Current data supports the use of Tamiflu in human H5N1 infection

- Limited number of confirmed cases; geographically dispersed
- Oseltamivir generally administered too late<sup>1,2,3</sup>
- Benefit appears greatest when given early<sup>4,5</sup>
  - Thailand<sup>4</sup>: “patients who survived tended to have been treated with oseltamivir earlier.”
  - Turkey<sup>5</sup>: “the interval between onset of illness and time to treatment with oseltamivir tended to be shorter among the patients who survived.”
  - Egypt: Anecdotal evidence from the recent cases in Egypt
    - “The faster a patient can be treated with antiviral, the better their chance of recovery”.

1. Hien TT, *et al.* Avian influenza A (H5N1) in 10 patients in Vietnam. *N Engl J Med* 2004;350:1179-88.
2. De Jong *et al.* Oseltamivir Resistance during Treatment of Influenza A (H5N1) Infection. *NEJM*. 2005; 253; 2667-72
3. De Jong MD, *et al.* Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. *Nature Med* 2006
4. Chotpitayasunondh T, *et al.* Human disease from influenza A (H5N1), Thailand, 2004. *Emerg Infect Dis* 2005;11:201-9.
5. Oner AFO, *et al.* Avian influenza A (H5N1) infection in eastern Turkey in 2006. *NEJM* 2006; 355:1-7

# WHO revised guidance on use of Tamiflu in a pandemic

*Updated April 2007*

- Experience with early oseltamivir treatment suggest its usefulness in reducing H5N1-associated mortality
- Modified regimens of oseltamivir treatment, including double the dose, longer duration and possibly combination therapy with amantadine may be considered on a case by case basis
- Corticosteroids should not be used routinely, except for persistent septic shock with suspected adrenal insufficiency
- Antibiotic prophylaxis should not be used

# Key Issues & Questions Regarding Tamiflu for the Treatment of Pandemic Influenza

- 1. If H5N1 is to become the next pandemic strain it must change further and acquire characteristics required for efficient human-to-human transmission**
  - What measures can we put in place to rapidly determine any Tamiflu dose adjustments required for a new strain when it arises?
  - Will it be necessary to increase dose/duration for patients who present late in the course of infection?
- 2. Human infections with H5N1 are rare & geographically dispersed**
  - How can we best learn from limited clinical experiences?
- 3. Health care professionals may need to take Tamiflu prophylaxis for longer than supported by current label / safety data**
  - Is it feasible to undertake a longer prevention study?
- 4. Clinical development activities to address high unmet need in children**

## Research initiatives to learn more about the H5N1 virus

- **Pre-clinical virology studies looking at different H5N1 strains to optimise the dose of Tamiflu**
  - H5N1 strains differ in virulence and pathogenicity
  - Oseltamivir is active against all strains tested
  - Data is being published / presented on an ongoing basis

# Research initiatives to learn more about the H5N1 virus

- **Avian/Pandemic Influenza Registry**

- Registry developed
- Discussions with WHO on open data sharing with all interested parties

## **Prospective / randomized clinical trial exploring high vs standard dose oseltamivir**

- Collaboration between Roche, US NIH and the SE Asia Influenza Clinical Trials Network
- Study population will include hospitalized adults and children with severe influenza (n=300) or suspected avian influenza (n=100) infection
- Tamiflu 75mg twice a day vs 150mg twice a day

# Research initiatives to learn more about the H5N1 virus

- **Long-term prevention in healthcare workers**
  - 6 weeks prevention already studied and approved
  - 20 weeks prevention at standard dose to be conducted by South-East Asian Influenza Clinical Trials Network
- **Intravenous programme**
  - Investigation of an intravenous treatment formulation

# Addressing therapeutic needs of children in a pandemic

- **Dosing**
  - Small capsules
  - Extemporaneous preparation
  - Taste masking
- **Development programme in children less than 1 year old**
  - Prospective data from approx 1500 children less than 1 year old taking Tamiflu
  - Pre-clinical studies
  - NIH collaborative study

## Summary

- WHO provides a strong recommendation of Tamiflu as the first line treatment and prevention against avian influenza
  - Roche is undertaking several new research initiatives to study the optimal use of Tamiflu against the evolving H5N1 avian influenza virus
- WHO advocates stockpiling by governments for pandemic preparedness but amounts vary
  - Current government emphasis is on treatment – prevention could reduce mortality further
  - Corporate stockpiling will supplement government reserves and provide social and economic benefits