



Tamiflu Media Briefing

7 September 2009



Agenda



Programme (CET)

Welcome and introduction

William M. Burns
CEO Division Roche Pharma

Roche's role in pandemic

Catherine Steele
Deputy Pandemic Taskforce Leader

Physician perspective

Anand Kumar
Health Sciences Centre, Winnipeg, Canada

Roche scientific update

David Reddy
Pandemic Taskforce Leader

Summary

William M. Burns
CEO Division Roche Pharma

Q&A

All

Buffet lunch and Interviews



Welcome

William M. Burns, CEO Division Roche Pharma

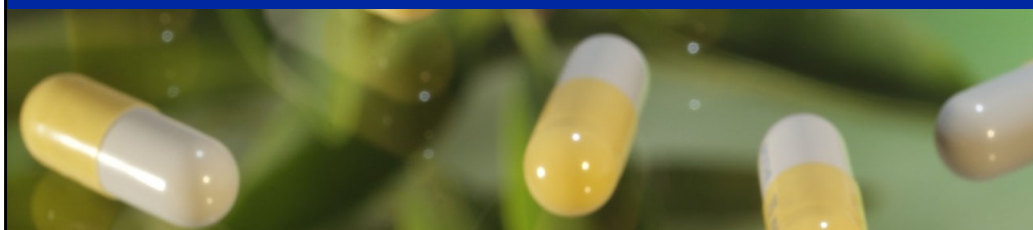


Why we are here today?

- Threat of avian flu was a call to action; the emergence of pandemic (H1N1) 2009 was a second call to action
- Roche has assisted governments and WHO with preparation for an influenza pandemic since 2001
- Roche's corporate and social responsibility involved and continues to involve:
 - Manufacturing, developing world and government initiatives
 - Working with WHO, governments and health authorities
- Roche's role now is to provide Tamiflu to patients in need and meet supply demand across the world
- Roche continues to address medical and regulatory needs

Roche's Role in Pandemic

Catherine Steele, Deputy Pandemic Taskforce Leader



Roche's role and responsibility in pandemic

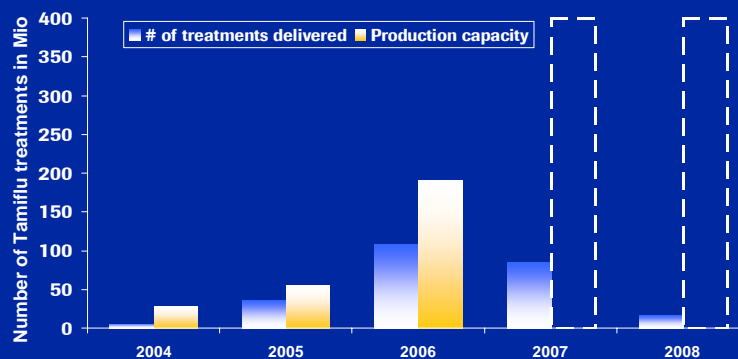
- Working with governments since 2001 to establish pandemic preparedness
- Establish roles and responsibilities of Roche and stakeholders before and during a pandemic
- Phase 4: containment measures
 - Deliver WHO rapid response stockpile
 - Fulfill existing orders from governments
 - Increase rapid response effort for containment
- Phase 5-6: containment measures have failed
 - Seek input from WHO/international agencies/experts on allocation of Tamiflu
 - 'First come, first-served' principle where priorities cannot be defined

Access to Tamiflu in the developing world



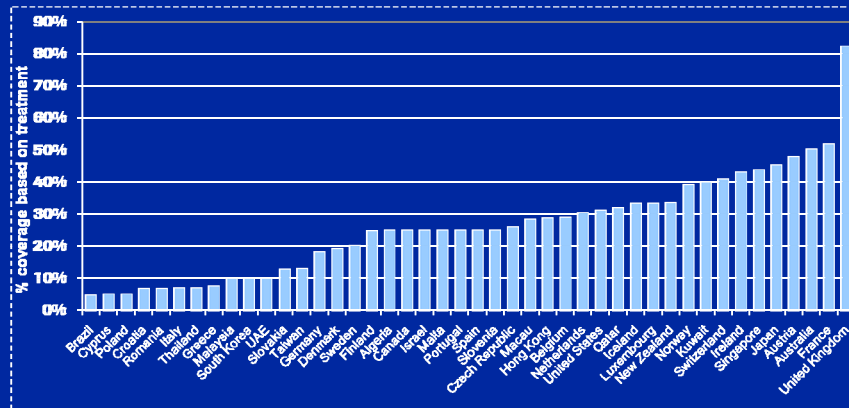
- **No patents** in the world's Least Developed Countries
- **Tiered pricing since 2004** distinguishing between developed and developing countries
- **Sub-licences** to three manufacturers in China and India
- **Knowledge transfer** to a manufacturer in South Africa
- **Almost 11 million packs donated** to WHO
 - Half deployed May 2009
 - Replenished stockpile including packs for children
- **Tamiflu Reserves Programme** initiated
 - Pandemic insurance policy for world's least resourced nations

Manufacturing capacity for Tamiflu



- By 2007 Roche had established a Tamiflu production network capable of producing 400 million courses of treatment (4 billion capsules) / year if required
- Network of 19 partners in 10 countries on three continents
- Today, 96 governments have received a total of 270 million courses of treatment

Published antiviral stockpiles > 5% - in % of total population based on treatment



Sources: Media / National pandemic plans (last updated 3 September 2009) and population figures from GeoHive.com (as of Aug 2007)

These figures:

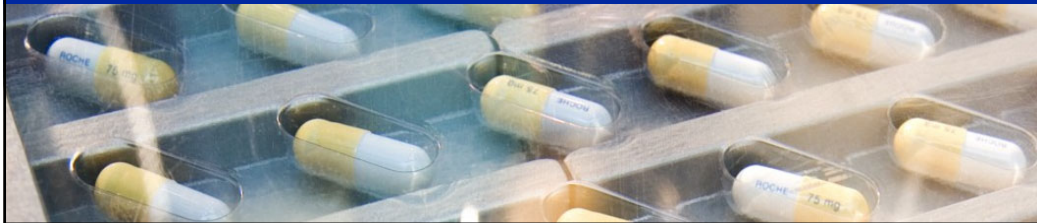
- Illustrate the number of antiviral treatments that governments *have stockpiled or intend* to stockpile, as a percentage of the total country population
- Are *publicly available* figures - that have been made public either via national pandemic plans, media releases or personal communication
- May not be a true reflection of actual stockpiles i.e. some governments may have stockpiled more but have not publicly communicated updated figures
- Report antiviral stockpiles - in some cases the coverage includes Tamiflu and Relenza, in others only Tamiflu

Steps taken to assist governments and patients

- **Smaller capsules, 30 mg and 45mg**, developed for children
- **Preparing an oral solution from** capsules for children and adults who have difficulty swallowing
- **Shelf-life extended for government stockpiles** from five to seven years in a number of markets including US and Europe
- Method developed to extract active ingredient from expiring capsule stockpiles for **reprocessing** into new capsules
- **Stability data** provided to governments to help them make informed decisions about extending stockpile shelf-life

Scientific Update

David Reddy, Pandemic Taskforce Leader



Discussion topics

- Efficacy of Tamiflu
- Safety of Tamiflu
- Antiviral resistance
- Use of Tamiflu for pandemic H1N1 (2009) virus
- Pandemic research activities



Tamiflu efficacy summary

Prevention and treatment of seasonal influenza

- **Prevention**
 - 84-92% reduction in laboratory confirmed influenza^{1,2}
- **Treatment**
 - 30% reduction in illness duration³ – greater if used earlier⁴
 - 40% reduction in severity of illness³
 - 55% reduction in lower respiratory tract infections requiring antibiotics⁵
 - 40% reduction in otitis media⁶
 - 61% reduction in hospitalizations⁵

1. Welliver et al. JAMA 2001; 285: 748-754.
2. Peters PH Jr, et al. J. Am. Geriatr. Soc. 2001; 49: 1025-1031.
3. Tinslor JJ, et al. JAMA. 2000; 283: 1016-1024
4. Aoki F, et al. Journal of Antimicrobial Chemotherapy, 2003; 51: 123-129.
5. Kaiser L, et al. Arch Intern Med. 2003; 163: 1667-1672.
6. Whitley et al. Pediatr Infect Dis J 2001;20:127-33



Tamiflu efficacy in avian influenza

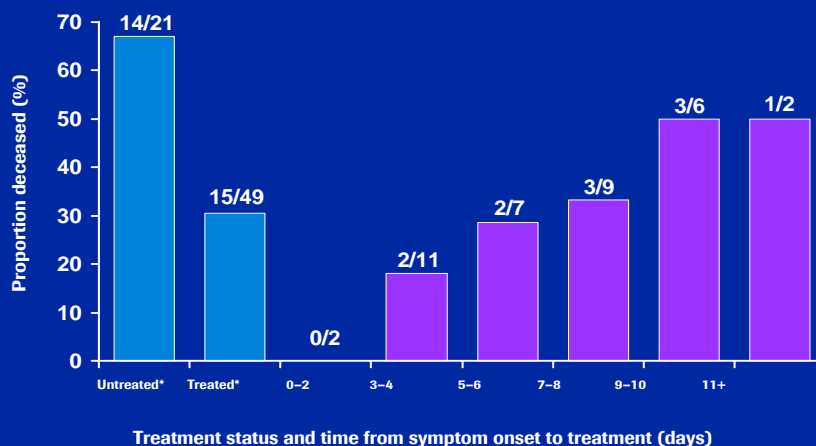
Avian Influenza Registry

- H5N1 remains a threat
- Need for international clinical management database, systematically compiled and analysed
- Data
 - collected in-country from laboratory-confirmed cases, or
 - from published case series where adequate data are available
 - anonymous, validated and entered into secure database



Earlier treatment associated with greater survival

Case fatality for first 72 cases in Avian Influenza Registry
Time from symptom onset to treatment with oseltamivir



*2 patients have unknown survival and are excluded; **Of 50 patients who received oseltamivir as treatment, 7 are excluded due to missing treatment start dates, and 6 are missing due to symptom onset dates
Data as of 17 March 2009 in 72 patients
Toovey et al. The Lancet Conferences: Influenza in the Asia Pacific, August 22-23, 2009, Beijing.



Tamiflu safety profile

Tamiflu is generally well tolerated

- Tamiflu used by around 60 million patients worldwide¹
- In clinical trials, Tamiflu demonstrated to be generally well tolerated
- Majority of adverse drug reactions resolved within 1-2 days²
- Main adverse events in clinical studies were nausea and vomiting²
- Roche continues to closely monitor for adverse events

1. Roche data on file
2. EU Tamiflu Summary of Product Characteristics



Safety of Tamiflu in children¹ *Adverse events with frequency > 5%*

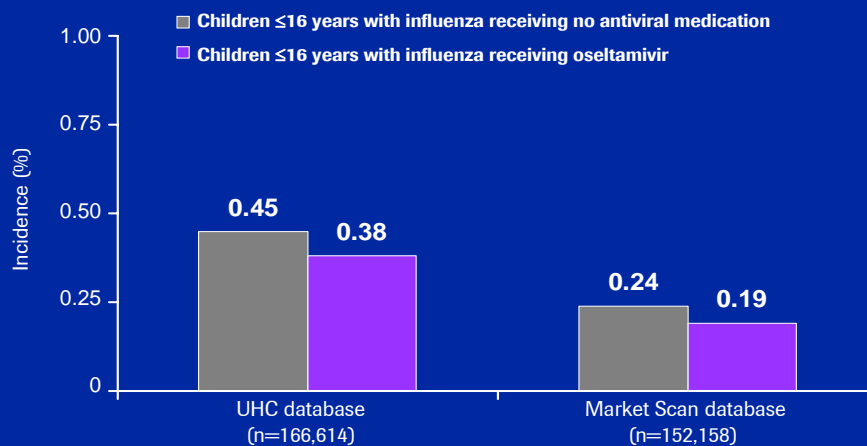
	Placebo (n=353), n (%)	Oseltamivir (n=342), n (%)
All body systems	185 (52.4)	168 (49.1)
Vomiting	30 (8.5)	49 (14.3)
Diarrhoea	37 (10.5)	30 (8.8)
All serious adverse events	2 (<1)	3 (<1)

~1% of participants discontinued due to vomiting
no adverse effect on pulmonary function seen in asthmatic children²

1. Whitley et al. *Pediatr Infect Dis J* 2001;20:127-33
2. Johnston et al. *Pediatr Infect Dis J* 2005;24:225-32



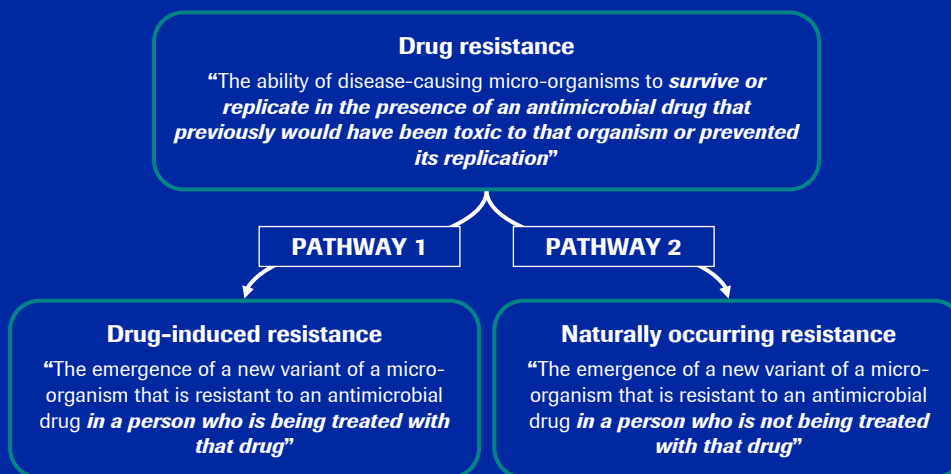
No increased risk of neuropsychiatric events seen in children with influenza taking Tamiflu versus not taking Tamiflu



UHC Database = United Healthcare Database
MarketScan Database = Medstat MarketScan Commercial Claims and Encounters Database

Toovey et al. *ISRV* 2008

Resistance may emerge in the presence or absence of drug therapy



Tamiflu-resistant seasonal influenza A/H1N1 (H275Y) viruses emerged in the 2007–08 season

- Tamiflu-resistant seasonal influenza A/H1N1 virus unexpectedly emerged in Europe during the 2007–08 season^{1,2}
- Clinical symptoms similar to those observed with Tamiflu-sensitive viruses^{4,5,6,7}
- Emergence of this strain unlikely to be drug-related
 - Patients from whom resistant isolates were obtained had not taken Tamiflu³
 - Tamiflu used infrequently in countries where resistant virus first isolated^{1,8}
 - Pandemic (H1N1) 2009 genetically very distinct from Tamiflu-resistant seasonal influenza A (H1N1) H275Y^{10,11,12}
 - Pandemic (H1N1) 2009 virus fully sensitive to Tamiflu
 - Pandemic (H1N1) 2009 now overwhelmingly the dominant H1N1 virus

1. Meijer et al. Emerg Infect Dis 2009;15:552–60; 2. Dharan et al. JAMA 2009;301:1034–41; 3. Hauge et al. Emerg Infect Dis 2009;15:155–62; 4. Gooskens et al. JAMA 2009;301:1042–6; 5. van der Vries et al. N Engl J Med 2008;359:1074–6; 6. Bhat et al. N Engl J Med 2005;353:2559–67; 7. Thompson et al. JAMA 2003;289:179–86; 8. Kramarz et al. Euro Surveill 2009;14. pii. 19112; 9. Rameix-Welti et al. Antimicrob Agents Chemother 2008;50:3809–15; 10. WHO. Wkly Epidemiol Rec 2009;84:173–9; 11. CDC. Available at: <http://www.cdc.gov/h1n1flu/recommendations.htm>; 12. ECDC. Euro Surveill 2009;14:19238



Pandemic (H1N1) 2009: resistance update

Low levels of resistance observed

- Pandemic (H1N1) 2009 is susceptible to Tamiflu
- Isolated cases (13) of resistance have been reported
- A low percentage of resistance was seen in clinical trials (0.32% – 4%)^{1,2}
- Isolated cases of Tamiflu resistant pandemic (H1N1) 2009 is expected in line with observations from the low frequency seen in clinical studies
- No evidence of onward transmission of the virus
- Illness mild and self limiting and all patients recovered

1. Aoki et al Antiviral Therapy 12:603-616
2. EU Tamiflu Summary of Product Characteristics



Studies to address resistance

- International resistance surveillance and clinical outcome study (NV20237)
- PK study of oseltamivir with amantadine (Roche/Novartis, published)
- PK study of oseltamivir with rimantadine
- Two investigator-led clinical studies investigating Tamiflu in combination with Relenza and with amantadine

WHO Guidelines for Pharmacological Management of Pandemic (H1N1) 2009 Influenza. August 2009



Mild to moderate uncomplicated clinical presentation	
At risk population	Oseltamivir or zanamivir
Otherwise healthy	"Need not treat"
Severe or progressive clinical presentation	
At risk population	Oseltamivir (zanamivir should be used where virus is known to be resistant to oseltamivir, or if oseltamivir unavailable)
Otherwise healthy	

At risk populations: Infants and children aged less than 5, the elderly (>65 years), nursing home residents, pregnant women, patients with chronic co-morbid conditions such as cardiovascular, respiratory or liver disease, diabetes, and those with immunosuppression related to malignancy, HIV infection or other diseases.

Ongoing and planned research activities to support safe and effective use of Tamiflu in the current pandemic



- Vulnerable populations
 - Children < 1 year of age
 - Pregnancy and lactation
 - Obese patients
 - Immunocompromised patients
 - Severely ill patients
- Assessing dose and duration of treatment in the current pandemic
- Pandemic pharmacovigilance activities

Tamiflu in infants <1 year



- European Medicines Agency positive opinion for children 6–12 months
 - Data from 2,400 infants <1 year of age collected in observational studies shows safety profile consistent with established profile in older children
 - Study CASG114: 3mg/kg twice daily provides drug levels in children aged 6 – 12 months similar to those shown to be safe and effective in adults and older children
- Ongoing activities in infants <1 year
 - CASG 114 (US)
 - Roche – PK, PD and safety of oseltamivir in infected infants <1 year
 - Safety monitoring – observational safety study in children <2 years

Tamiflu in pregnancy



- WHO, ECDC and US CDC guidance support the use of Tamiflu in pregnant women and in current pandemic
- Limited post-marketing and retrospective observational surveillance data in conjunction with animal studies do not indicate harmful effects on pregnancy, embryonal/foetal or postnatal development
- Pregnancy registries being developed to collect safety data during the pandemic

Studies of Tamiflu in other vulnerable patient groups



- Obese patients
 - PK study in obese patients
- Immunocompromised patients
 - Immunocompromised prophylaxis study (NV20235) completed
 - Immunocompromised treatment study (NV20234) ongoing
- Severely ill patients
 - Three PK studies in ICU patients investigating Tamiflu drug levels following nasogastric administration (Canada)
 - I.V. development program

Studies investigating dose, duration and resistance



- Clinical/virological outcomes in otherwise healthy individuals
 - Six studies investigating efficacy and safety of different doses and durations of oseltamivir treatment in patients infected with pandemic (H1N1) 2009
 - Endpoints: viral shedding, resistance and clinical symptoms
- Post exposure prophylaxis versus early treatment?

Summary



- Tamiflu efficacious in treatment of influenza in adults and children
- First data from avian influenza registry supports WHO observation that Tamiflu may reduce mortality in patients with H5N1 infection when used early
- Established good safety and tolerability profile in children including asthmatics
- No increase in neuropsychiatric symptoms of influenza seen with Tamiflu
- Ongoing research in vulnerable populations
- Guidelines recommend Tamiflu for treatment of pandemic (H1N1) 2009 infection in at-risk groups and for all patients with severe or progressive illness

Summary



William M. Burns, CEO Division Roche Pharma



Summary



- Since 2001, Roche has been working with, and continues to work closely with, governments and WHO on the role of Tamiflu in pandemic preparedness and its availability
- The well-being of patients and effective use of our medications is a priority
- Roche is committed to its role in supporting WHO and governments in their first line of defence activities against a pandemic



We Innovate Healthcare