

# **TAMIFLU<sup>®</sup> MedKit for Pandemic Influenza**

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Hoffmann-La Roche Inc.

October 29, 2008

# Presentation Outline

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- Introduction/Overview
- TAMIFLU MedKit
  - Stakeholder Feedback
- Pandemic Planning
  - Resistance
  - Collection and Reporting of Safety Information
  - Communication Plan
- Proposed Studies
- Conclusions

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## Roche Delegation

William Blumentals, PhD	<i>Medical Data Analytics</i>
Ellen Carey, PharmD	<i>Global Regulatory Leader</i>
Brian Davies, PhD	<i>Clinical Pharmacologist</i>
Barbara Donner, MD	<i>Safety Director</i>
Regina Dutkowski, PhD	<i>Clinical Science Leader</i>
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David Reddy, PhD	<i>Life Cycle Leader, TAMIFLU</i>
Susan Sacks, PhD	<i>Director, Epidemiology</i>
Miklos Salgo, MD, PhD	<i>Clinical Science Leader, HIV</i>
James Smith, PhD	<i>International Medical Leader</i>
Duane Voss, BA	<i>Program Director, Regulatory CMC</i>

## Experts Available

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David Bradford, PhD

*Sr. Vice President for OTC Switches  
PEGUS Research*

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Donald Low, MD

*Chief of Microbiology  
Mt. Sinai Hospital and  
Toronto Medical Laboratories*

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# TAMIFLU

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## *Indication and Usage*

- Indicated for the treatment and prophylaxis of influenza in patients 1 year and older

## *Dosage and Administration*

		<b>Treatment BID x 5d</b>	<b>Prophylaxis QD x 10 d</b>
<b>Adults and Adolescents (≥ 13 years)</b>		75 mg	75 mg
<b>Children (1-12 years)</b>	<b>&lt; 33 lbs</b>	30 mg	30 mg
	<b>34-51 lbs</b>	45 mg	45 mg
	<b>52-88 lbs</b>	60 mg	60 mg
	<b>&gt; 88 lbs</b>	75 mg	75 mg

# TAMIFLU

## *Most Frequent Adverse Events*

<b>Adverse Event</b>	<b>Treatment</b>		<b>Prophylaxis</b>	
	<b>PBO (N=716)</b>	<b>TAMIFLU (N=724)</b>	<b>PBO (N=1688)</b>	<b>TAMIFLU (N=1790)</b>
<b>Nausea</b>	40 (6%)	72 (10%)	56 (3%)	129 (7%)
<b>Vomiting</b>	21 (3%)	68 (9%)	16 (1%)	39 (2%)
<b>Diarrhea</b>	70 (10%)	48 (7%)	40 (2%)	50 (3%)

## *Postmarketing Serious Adverse Events*

- Rare reports of skin/hypersensitivity reactions
- Neuropsychiatric adverse events, sometimes leading to injury
  - Reported in influenza patients with or without TAMIFLU use
  - Contribution of TAMIFLU has not been established

# TAMIFLU

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## *Clinical Studies*

### Treatment of Influenza

- 849 influenza-infected adults and 452 influenza-infected pediatrics
- Primary endpoint
  - Adults: Time to improvement of all influenza-associated symptoms
    - 1.3 day reduction in median time to improvement compared to placebo
  - Pediatrics: Time to freedom from illness
    - 1.5 day reduction in total composite time to freedom from illness compared to placebo

### Prophylaxis of Influenza

- 1992 adults and 201 pediatrics enrolled in seasonal or post-exposure prophylaxis studies
- Primary endpoint: incidence of laboratory-confirmed clinical influenza
  - Seasonal in adults: 76%-92% protective efficacy
  - PEP in adults: 68%-89% and in pediatrics: 80% protective efficacy

## Rationale for MedKit

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- While government pandemic preparations are ongoing, individual action and responsibility are necessary
- Pandemic preparations have been ongoing:
  - Federal/State government antiviral stockpile at 81 million treatments
  - Corporate guidelines issued by HHS/CDC in 2007 to protect employees and maintain business continuity
- Pandemic MedKit allows households to prepare
  - Immediate access to antivirals when first symptoms appear
  - Reduce barriers to obtain and utilize antivirals

# WHO Guidance on the Role of Antivirals in the Management of Avian and Pandemic Influenza Infection

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## Human Infection with H5N1 Avian Influenza<sup>1</sup>

- “Oseltamivir ... remains the primary antiviral agent of choice for the treatment of A(H5N1) virus infections.”
- “Limited observational evidence suggests that early oseltamivir administration may be associated with reduced mortality in patients”

## Pandemic Influenza<sup>2</sup>

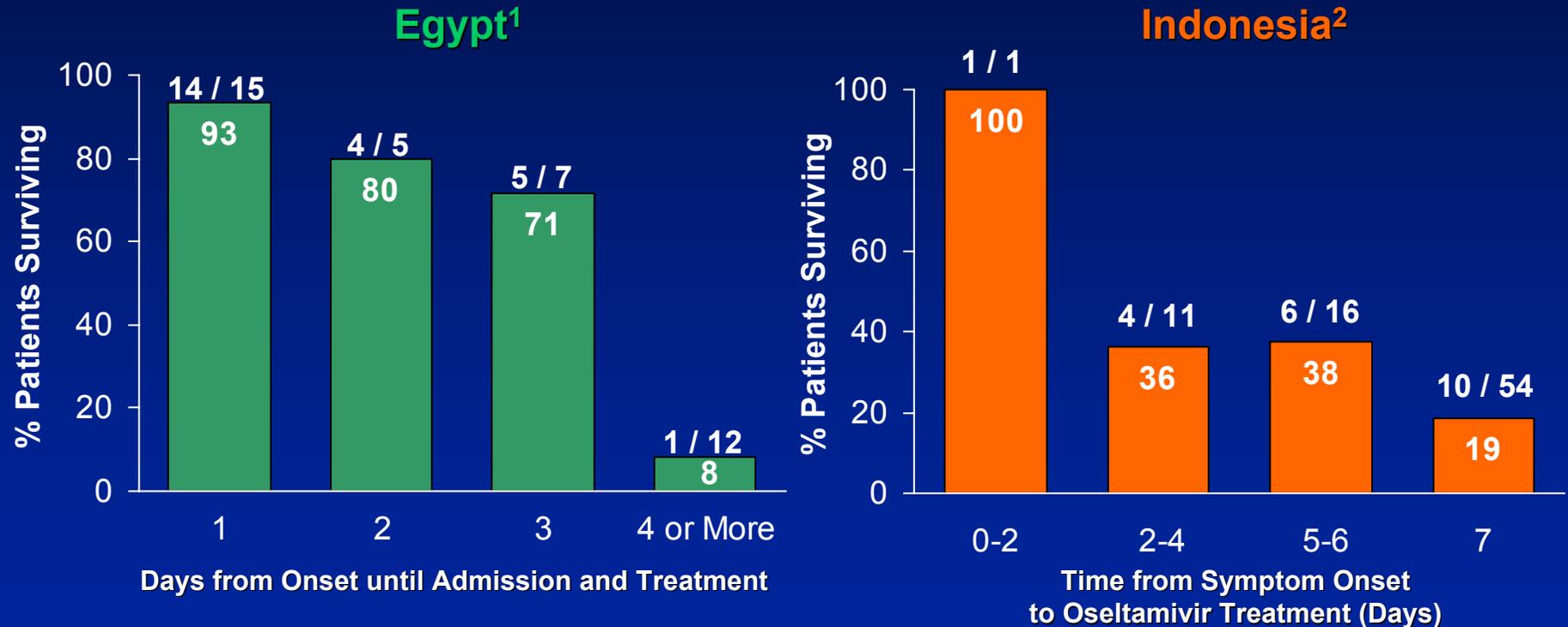
- “Pending the availability of vaccines, antiviral drugs will be the principal medical intervention for reducing morbidity and mortality”
- Stockpiling ensures sufficient supplies of antivirals

1. Clinical management of human infection with avian influenza A(H5N1) virus. World Health Organization 15 August 2007. [http://www.who.int/csr/disease/avian\\_influenza/guidelines/ClinicalManagement07.pdf](http://www.who.int/csr/disease/avian_influenza/guidelines/ClinicalManagement07.pdf)

2. Avian influenza: assessing the pandemic threat. WHO, January 2005

# Survival in H5N1 Case Studies

## Case Series from Egypt and Indonesia



1. Adapted from Abdel-Ghafar. *Working On the Front Line with H5N1*. Perspectives in Interpandemic Influenza, Madrid, Spain 2007

2. Adapted from Nyoman Kandun et al. Factors associated with case fatality of human H5N1 virus infections in Indonesia: a case series. *The Lancet*. Published online August 14, 2008

## Regulatory Framework for TAMIFLU MedKit

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- Current pathways for drug approval:
  - Prescription
  - Over-the-Counter (OTC)
- OTC pathway requires differentiation of MedKit from seasonal TAMIFLU
  - By indication, dose or patient population
- Roche constrained to prescription pathway
  - No differentiation between the MedKit and seasonal TAMIFLU identified
- OTC-like mechanism would likely maximize access to the MedKit
  - For individuals who would not or could not see a healthcare provider
- Creation of alternative regulatory approval mechanism may be appropriate for MedKit

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# TAMIFLU MedKit Contents

*Designed to Maximize the Likelihood of Compliance  
and Proper Use of TAMIFLU*



## Dosage Strength for TAMIFLU MedKit

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- One dosage strength (75 mg capsules) included in TAMIFLU MedKit
  - Ability to adjust dose for growing children
  - Less confusion for households with children (e.g., selection of wrong dosage strength)
  - Simplifies dispensing of kits for household members of different ages
- Mixing studies have been conducted to support the mixing of capsule content in different foods
  - Stability
  - Palatability
  - Preservative efficacy

# CDC Pandemic Influenza Diagnostic Algorithm

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- CDC algorithm designed for appropriate use of antivirals in a pandemic
  - Included in TAMIFLU MedKit Educational Booklet
- Developed by CDC for diagnosis of influenza outside of healthcare setting during a pandemic
  - Refers patients with underlying medical conditions to their healthcare professional
- To be applied only:
  - After a health department declaration of pandemic
  - For individuals with new onset of flu symptoms and their household members

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## Stakeholder Feedback on TAMIFLU MedKit

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- HHS Meeting with medical and pharmacy societies identified challenges
  - Need to address burden on HCP
  - Inappropriate use
  - Timing of use
  - Resistance
  - Adverse events
- Roche planning Scientific Advisory Board
  - Will invite representatives from: AAP, AMA, APhA, AAFP, IDSA, NACDS, PBMs

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# **Ongoing Pre-Pandemic Preparedness Activities**

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## **Avian Flu Registry**

- Global, multi-center, observational registry of patients with H5N1 infection
- To collect information on:
  - Clinical course and outcome of H5N1 infection
  - Treatments and dosing regimen used

## **Dose Prediction Model**

- Model will predict TAMIFLU dosage required to suppress viral replication
- Model combines nonclinical and seasonal clinical data
  - H5N1 data to be incorporated

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## Drug-Induced Resistance

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- Low incidence of resistance during treatment with TAMIFLU<sup>1</sup> in large clinical studies
  - Adults 0.32%
  - Children 4.1%
- No resistance observed in any of the prophylaxis clinical studies
- Low fitness and transmissibility
- High barrier to resistance

## Incidence of Resistance to Oseltamivir from Community Surveillance Samples<sup>1,2</sup>

	2003-04	2004-05	2005-06	2006-07
US	N/A	0/370 (0%)	0/647 (0%)	5/584 (0.9%)
Japan	3/1180 (0.3%)	0/618 (0%)	4/429 (1%)	N/A

### Low incidence of resistance in countries with high use of TAMIFLU

- Prescriptions for corresponding period:
  - Over 8 million in US
  - Over 29 million in Japan

1. Sheu et al AAC 52:3284-3292 (2008)

2. NISN: *Weekly Epidemiol. Record*; 17;149-150(2007)

# Naturally Occurring Resistance

- Naturally occurring resistance to any drug may arise and disappear spontaneously
  - Appears to be driven by antigenic drift and not by antiviral use
- Increased incidence of resistance to oseltamivir observed in 2007/08 season in H1N1 seasonal viruses
  - Associated with H274Y\* and additional mutations<sup>1</sup>
  - No apparent relationship to oseltamivir use or exposure

## Prevalence of H1N1 Resistance<sup>2</sup>

Global Prevalence	15%
Europe	25%, Range 0-67%
US	11%
Japan	3%

**On-going Surveillance is Crucial**

\*Some scientists use N1 numbering (275Y) and some use N2 numbering (274Y) for same mutation in N1

1. Rameix-Welti M et al *PLoS Pathog* 4:e1000103

2. [www.who.int/csr/disease/influenza/oseltamivir\\_summary/en/index.html](http://www.who.int/csr/disease/influenza/oseltamivir_summary/en/index.html) (Q4 2007-Q1 2008)

# Roche Plan for Resistance Monitoring

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## Seasonal Influenza:

- Roche convened expert panel for guidance on resistance data generation, analysis and communication
- Roche initiating large, global Influenza study (IRIS)
  - 1,200 patients per influenza season (2008-2011)
  - To evaluate clinical course and monitor naturally occurring and treatment-induced resistance to all anti-influenza drugs

## Pandemic Influenza :

- WHO/CDC currently have extensive surveillance system, expected to continue during a pandemic
- Roche open to discuss opportunities to augment WHO/CDC activities, such as a variant of the IRIS study currently ongoing

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## Pharmacovigilance Plan for Pandemic

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- Roche anticipates increased Adverse Event Reports for TAMIFLU
- Roche will request HCP and consumer AE reporting via:
  - TAMIFLU MedKit educational booklet
  - Roche website
  - Radio, newspaper, and TV
- Enhanced HCP and consumer adverse event reporting mechanisms:
  - Telephone
  - Electronic (web page, e-mail)
  - Paper (mail, fax)
  - Consumer AE reporting form included in TAMIFLU MedKit

# Pharmacovigilance Communications

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## Process Defined and Established for:

- **Continual** reporting to Health Authorities
  - Biweekly TAMIFLU reports once WHO declares pandemic, Phase V
  - Analysis of aggregate data with emphasis on populations of special interest (pregnant and lactating women)
  - Identification of new safety information possibly impacting public health
- **Urgent** communication of safety information impacting patient or public health
  - To patients, public, HCPs and other stakeholders
  - In collaboration with FDA, WHO, CDC
  - Process for rapid distribution of safety information established

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## Roche Pandemic Communication Plan

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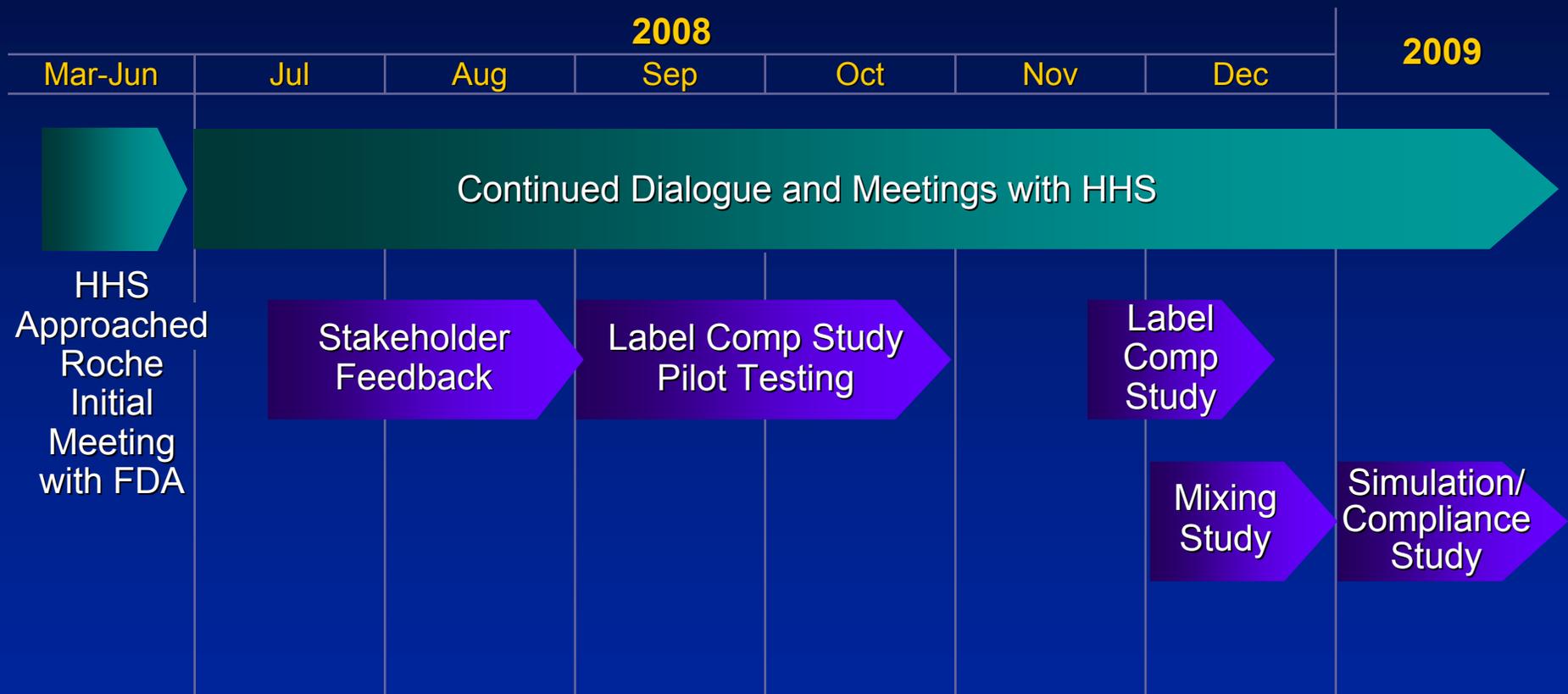
- Roche will collaborate with CDC, FDA, HHS, and WHO to disseminate consistent information
- Communications may address:
  - Resistance
  - Safety
  - Dosing
- Various media channels will be used
  - TV – Public Service Announcement (PSA)
  - Web-based
  - Print
- Communications will also be coordinated through medical/pharmacy societies

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# TAMIFLU MedKit Development Plan



## Label Comprehension Study Design

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- Standard mall-intercept screening and recruitment
- 667 Respondents: 400 > 8<sup>th</sup> grade reading level and 267 ≤ 8<sup>th</sup> grade reading level
- Structured and scenario questions evaluating:
  - Drug Facts-like label
  - TAMIFLU MedKit booklet
- Screening and demographic questions

# Simulation/Compliance Study

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- Study in approximately 2,000 households
- Key objectives:
  - To evaluate the subject's intended actions based on responses to pandemic scenarios
  - To assess the number of intact TAMIFLU MedKits returned relative to the total number returned
- Methods
  - Questionnaire with various scenarios that might be encountered in the event of a pandemic
  - TAMIFLU MedKits will be placed in homes for a 6-month period covering one influenza season
  - Return of TAMIFLU MedKit at end of influenza season with follow-up questionnaire
  - “Non-compliance” defined as missing capsules at the end of the study

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# Potential Risks and Mitigation Strategies with TAMIFLU MedKit for Home Stockpiling

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## Adverse Events

- Safety profile well established with > 55 million prescriptions filled since 1999
- Comprehensive strategy for collecting adverse event reports during a pandemic

## Viral Resistance

- Resistance patterns to antivirals monitored as part of worldwide surveillance

## Dose

- Roche Dose Prediction Model will include data on emerging pandemic strains

## Incorrect Diagnosis or Concomitant Secondary Bacterial Infections

- Complications of influenza decreased with treatment
- CDC Algorithm identifies patients requiring medical evaluation or not improving on treatment

## Benefits of TAMIFLU MedKit for Home Stockpiling

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- Increased availability for more widespread early treatment and household prophylaxis
  - Decreased burden on health care system and providers
  - Access prior to pandemic facilitates social distancing
  - Empowers individual and households to prepare for pandemic as part of individual protective measures
- Individual protection pending availability of a vaccine

## Benefits of TAMIFLU MedKit for Home Stockpiling

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- HHS Modeling for government and household stockpiling
- Suggests significant improvements in mortality and morbidity with treatment and prophylaxis\*
  - Number of antiviral regimens 167.1 mil.
  - Deaths prevented 288,000
  - Hospitalizations prevented 2.427 mil.

\* Proposed guidance on antiviral drug use during an influenza pandemic.  
Department of Health and Human Services. May 28, 2008.  
<http://aspe.hhs.gov/panflu/antiviraluse.html>, accessed October 15, 2008, p. 21

## H5N1 Mortality Outcome with and without TAMIFLU

Country	Clade	Survivors/ Treated (%)	Survivors/ Untreated (%)
Vietnam	1	42/72 (58)	4/13 (31)
Thailand	1	3/10 (30)	2/7 (29)
Cambodia	1	–	0/6 (0)
Turkey	2.2	4/7 (57)	0/1 (0)
Egypt	2.2	20/34 (59)	–
Indonesia	2.1	19/65 (29)	1/29 (3)
<b>TOTAL</b>	<b>–</b>	<b>88/188 (47)</b>	<b>7/56 (12)</b>

p<0.001

**“Observational Data on Treatment with Oseltamivir in the Early Stages of the Disease Suggest Its Usefulness in Reducing A(H5N1) Virus Infection-associated Mortality”**

*~ World Health Organization 2007<sup>1</sup>*

1. Clinical management of human infection with avian influenza A (H5N1) virus. WHO 2007  
Table: Writing Committee of the WHO. *N Engl J Med* 2008;358:261–73

## Conclusions

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- TAMIFLU MedKit addresses currently unmet public health needs
- Roche supports identification of optimal regulatory mechanism to maximize access to TAMIFLU MedKit
- Collaboration with HHS, CDC and FDA to implement the appropriate development program
- Pandemic Planning
  - IRIS: study to evaluate clinical course and monitor resistance
  - Plans for enhanced AE collection and communication with Health Authorities and the public
  - Collaboration with CDC, FDA, HHS, and WHO to disseminate consistent information

# **TAMIFLU<sup>®</sup> MedKit for Pandemic Influenza**

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