

Tamiflu update on H5N1

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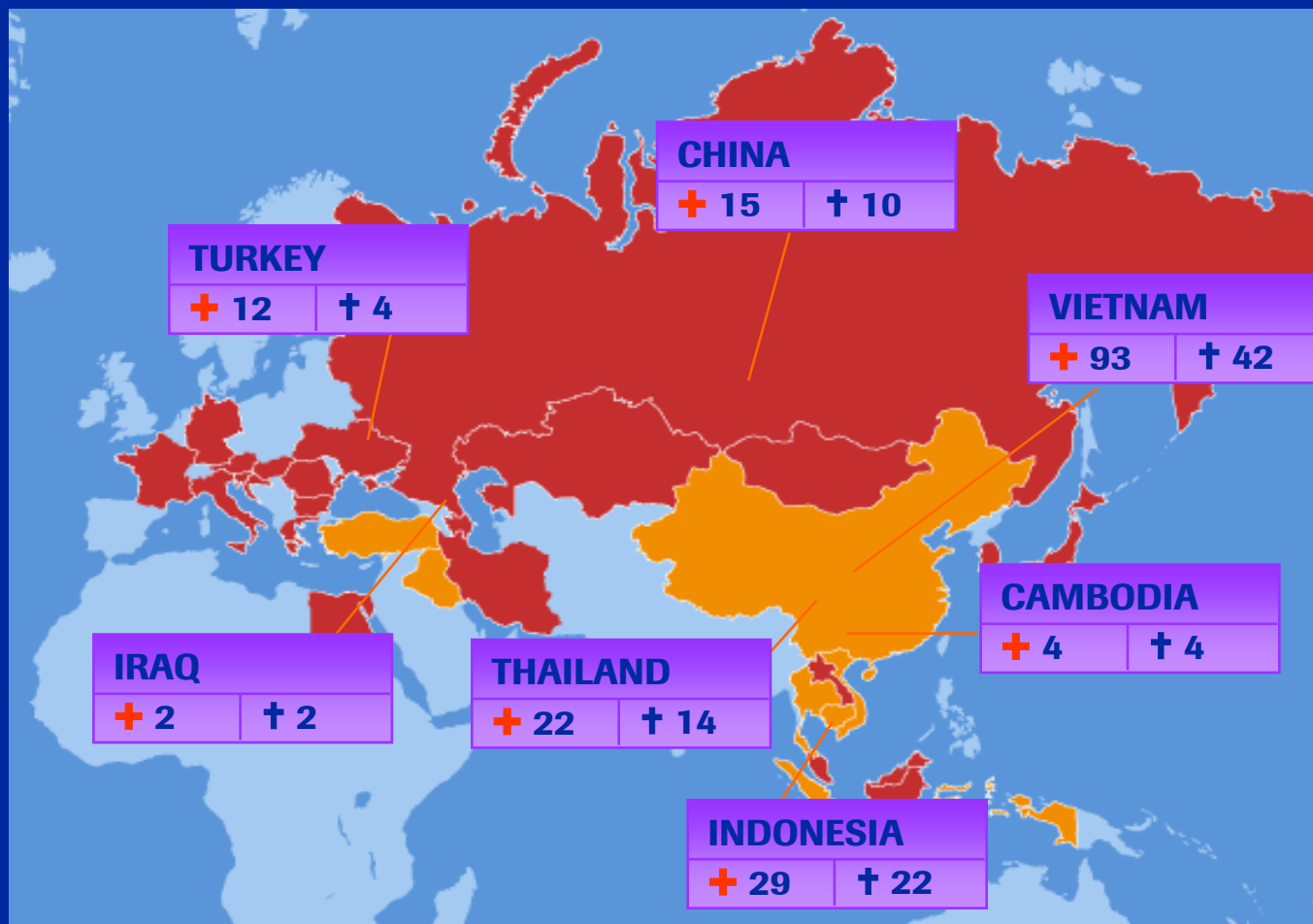


Objectives

- Update on H5N1 and Tamiflu
- Future research directions in H5N1

Countries with H5N1 Infections in Birds & Humans

December 2003 – March 13 2006



- 7 countries with H5N1 infection in humans
- 177 lab confirmed cases – 98 deaths

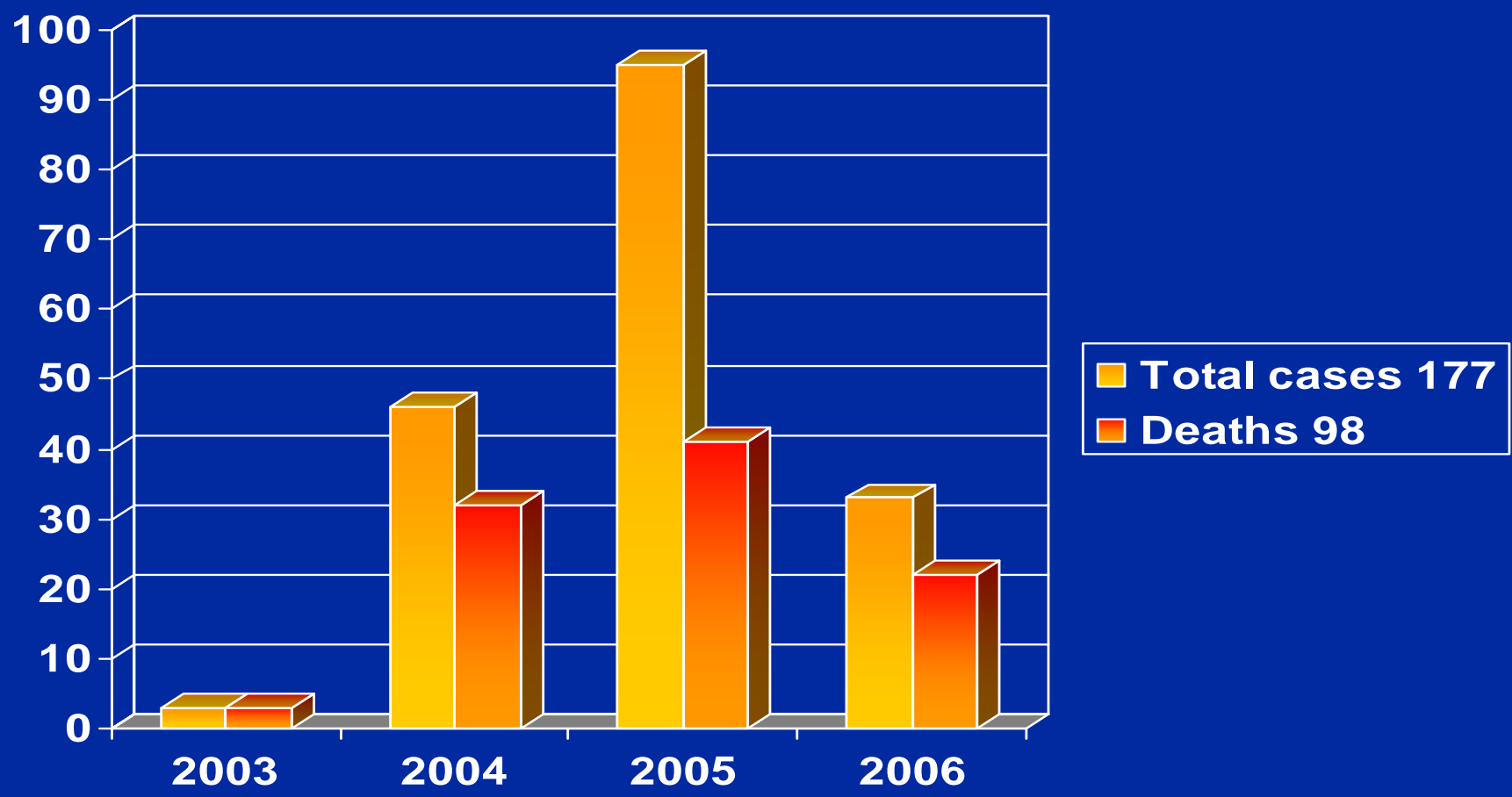
■ H5N1 in Birds
■ H5N1 in Humans

Clinical course of H5N1 influenza is different to seasonal influenza

- **Ill-defined and varied symptomatology**
- **Initial Symptoms:**
 - High Fever $>38^{\circ}\text{C}$
 - Influenza-like illness
 - Diarrhoea, vomiting, abdominal pain
 - Pleuritic pain
 - Bleeding from nose or gums
- **Clinical course**
 - Lower respiratory tract infection
 - Respiratory distress
 - Viral pneumonia
 - Respiratory failure and acute respiratory distress syndrome
 - Multiorgan failure (kidney, heart etc)
 - Death

Confirmed Human Cases of H5N1 Reported to WHO

Cumulative Number (as of Mar 13, 2006)



*Total number of cases includes number of deaths.
WHO reports only laboratory-confirmed cases.*

H5N1 is a collection of different viruses

- H5N1 is an influenza subtype (immunological) classification NOT a single virus entity.
- H5N1 HK 1997 is not the same as H5N1 Vietnam 2004 which is not the same as H5N1 Turkey 2005/6
- For H5N1 to be the next pandemic strain then it must change again, perhaps be a different sub-type - we do not know what it will look like

H5N1 presents a difficult target for clinical investigation

- Moving/evolving target
 - Differences in behaviour of H5N1 virus
 - How can the relevance of today's results be maximised to counter a pandemic strain?
- Logistics
 - Clinical nature of disease (rare and geographically dispersed)
 - Infection control and biosafety considerations (BSL3 environments)
 - Reliance on external contributors for access to H5N1 samples/data
 - Signs of competitive versus collaborative research environment

Tamiflu in influenza

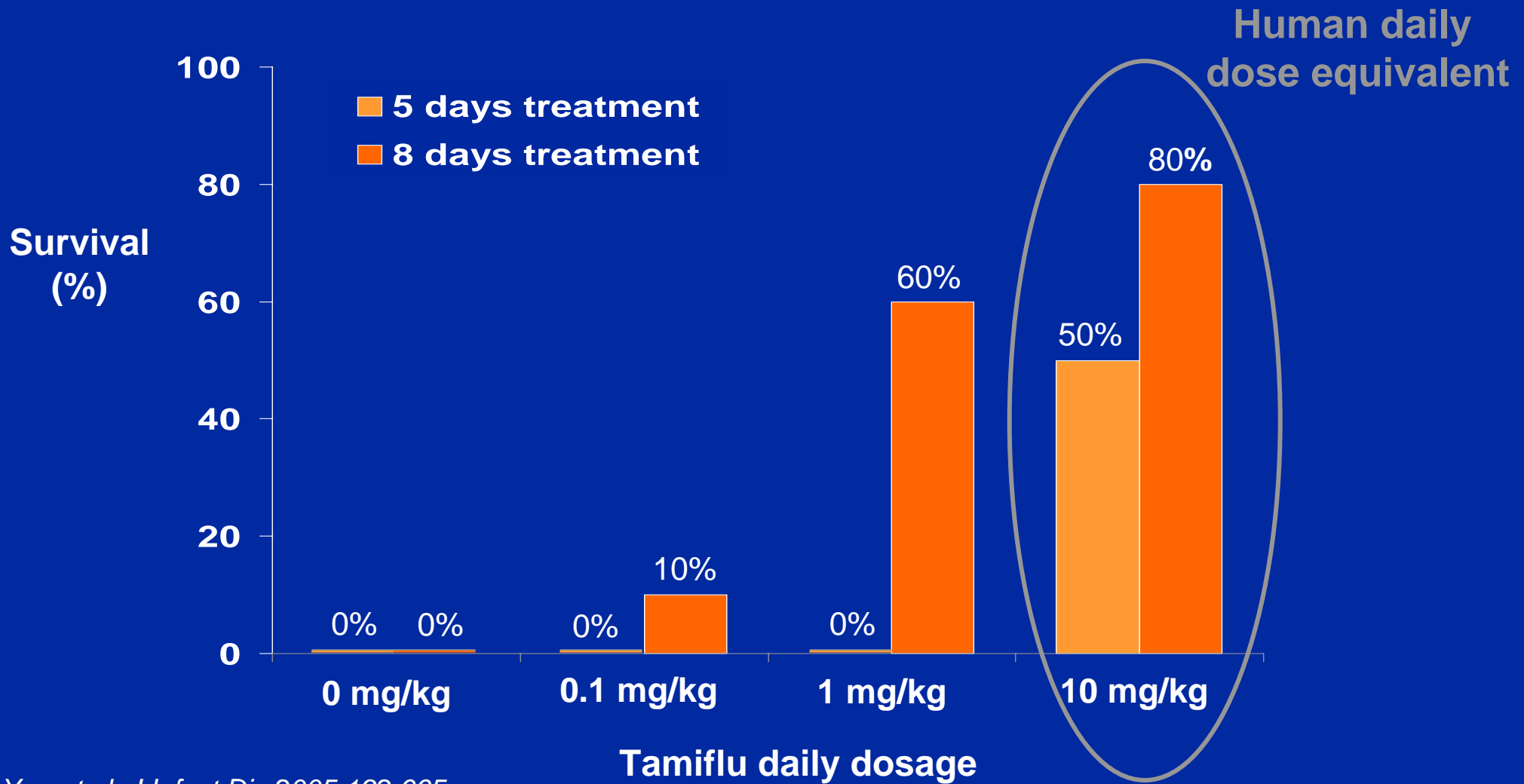
- Seasonal influenza – database 11'000 individuals studied
 - one capsule twice daily for five days
 - earlier the better
- H5N1 – all anecdotal evidence
 - reliant on case histories
 - earlier the better

Recommendations for the use of Tamiflu in H5N1 will be heavily reliant on laboratory data



- Increases reliance on pre-clinical influenza models
 - Mouse model for rapid screening of many H5N1 viral strains
 - Ferret model for replicating the pathogenicity of H5N1 in human subjects

Data from the mouse model infected with highly pathogenic Vietnamese H5N1 strain



Data from other species infected with highly pathogenic Vietnamese H5N1 strain

- All control animals infected with the Vietnamese human isolate died
 - Virus found in multiple organs
- Tamiflu at equivalent to human dose for 5 days starting 4h post-inoculation
 - 3/3 animals survived
 - Virus eliminated in all organs examined except brain

Data presented by Dr.Govorkova in London January 2006

So what do we know so far?



- Tamiflu highly effective in seasonal influenza
- Tamiflu is active against H5N1 *in vitro*
- Both mouse and ferret data confirm high virulence of the Vietnamese H5N1 strain
- Tamiflu is active in H5N1 in both animal models if given early
- Limited case histories support clinical efficacy of Tamiflu in H5N1 infected people when given early

BUT....

Where next?

- The current avian H5N1 strain IS NOT a human pandemic strain
- H5N1 must change again to become a human pandemic strain
- Tamiflu needs to be studied against the virus as it evolves

Research Underway

- Modeling and simulation work
 - gain additional insights into the virulence of H5N1 as it evolves
 - use these systems to allow rapid predictions on optimal use of Tamiflu against evolving strains
 - this knowledge and methodology will help when a human pandemic strain arises
- Collaborations underway with researchers and clinicians

“Call to action” for further collaboration



- Roche is interested in further collaboration with research groups currently working on H5N1 viruses
- Roche would like to extend the collaboration with external clinicians to collect new clinical data on treatment of clinical cases of H5N1
- Interested parties should e-mail their interest to research.tamiflu@roche.com

H5N1 is a wake up call

We need a broad based
collaboration between all
parties involved to address this
strain and prepare for the
pandemic virus