

Travellers need immediate access to Tamiflu when entering areas at risk from avian or seasonal influenza

JR Smith, SC Wood

F. Hoffmann-La Roche Ltd, Basel, Switzerland

Introduction

The protection of global travelers against influenza is an increasing concern in travel medicine.

Seasonal influenza is responsible for significant morbidity and loss of productivity in corporate employees and travelers each year. While vaccines are normally the mainstay of preventing influenza infection, movement between the northern and southern hemispheres will not only take travelers into an influenza season and potential epidemic situation, but also expose them to virus strains not circulating in their countries, and potentially not covered in their local vaccines.

Since January 2006, the range of H5N1 viruses has greatly extended from being mostly confined to East and South East Asia to outbreaks spreading into Europe, the Middle East and Africa meaning that travelers will be increasingly likely to enter into an affected region. Travelers need reassurance that they can be protected from developing this life-threatening disease if exposed.

Burden of influenza in travelers

Travelers are exposed to particular conditions putting them at greater risk of being infected with seasonal influenza. They will be in contact with large numbers of individuals, often in confined locations, many of whom may be carrying an infectious agent. Attack rates as high as 72% have been reported in aircraft.¹ Cruise ships, with their closed environment and large number of passengers from different countries are particularly prone to influenza outbreaks, with attack rates of influenza-like illness of 17–37% reported^{2,3,4}. A review of respiratory tract infections in travelers from the GeoSentinel Surveillance System (1997–2002) showed that respiratory illness was second only to gastrointestinal infection as a cause of illness in travelers⁵. Vaccination to protect against seasonal influenza has been recommended by the US Advisory Committee on Immunisation Practices for all tropical travelers, all travelers going to the southern hemisphere between April and September, and all travelers with organised tour groups at any time of the year. Because of the difficulties in obtaining vaccine containing the most likely circulating strain at destination, especially if traveling to the opposite hemisphere, antiviral drugs as prophylaxis during the travel or treatment or post-exposure prophylaxis after exposure to virus should be considered.

The current avian and human H5N1 influenza epidemic has been in resurgence since 2004, spreading out of the South East Asian countries into Europe, the Middle East and Africa.⁶ Avian H5N1 influenza is widespread across the globe (Figure 1). In many parts of Asia, avian influenza has already become or is becoming endemic, firmly

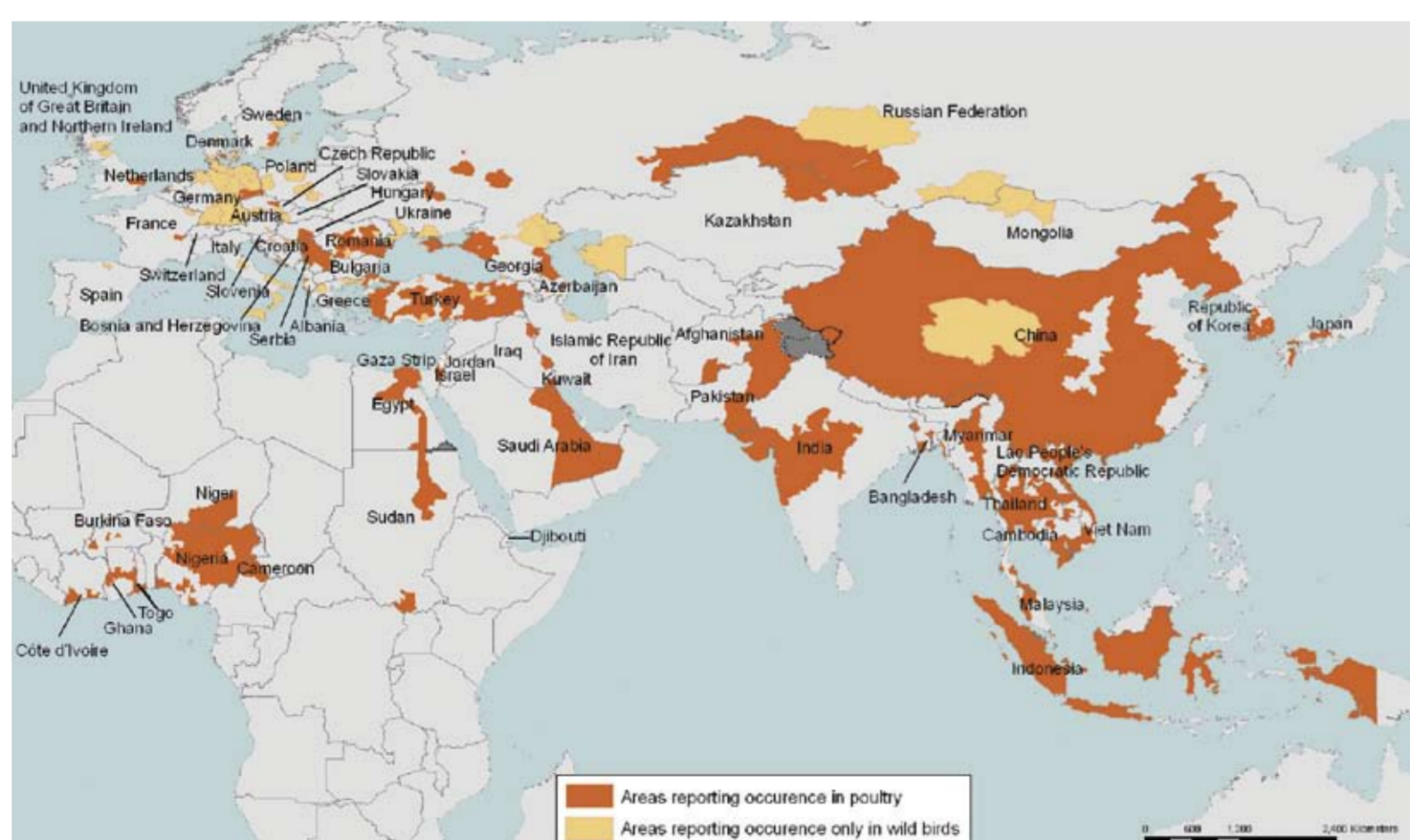


Figure 1. Countries reporting localised outbreaks of H5N1 in birds since 2003 (World Health Organization).

entrenching itself in the poultry populations. One implication of this is that outbreaks in poultry can become more prevalent and pose more opportunities for travelers to come into contact with ill birds, thus providing more opportunities for human infection. As of August 2007, a total of 319 human infections have been reported, with a total of 192 deaths (Figure 2). Almost all of these have been associated with close contact with infected poultry.

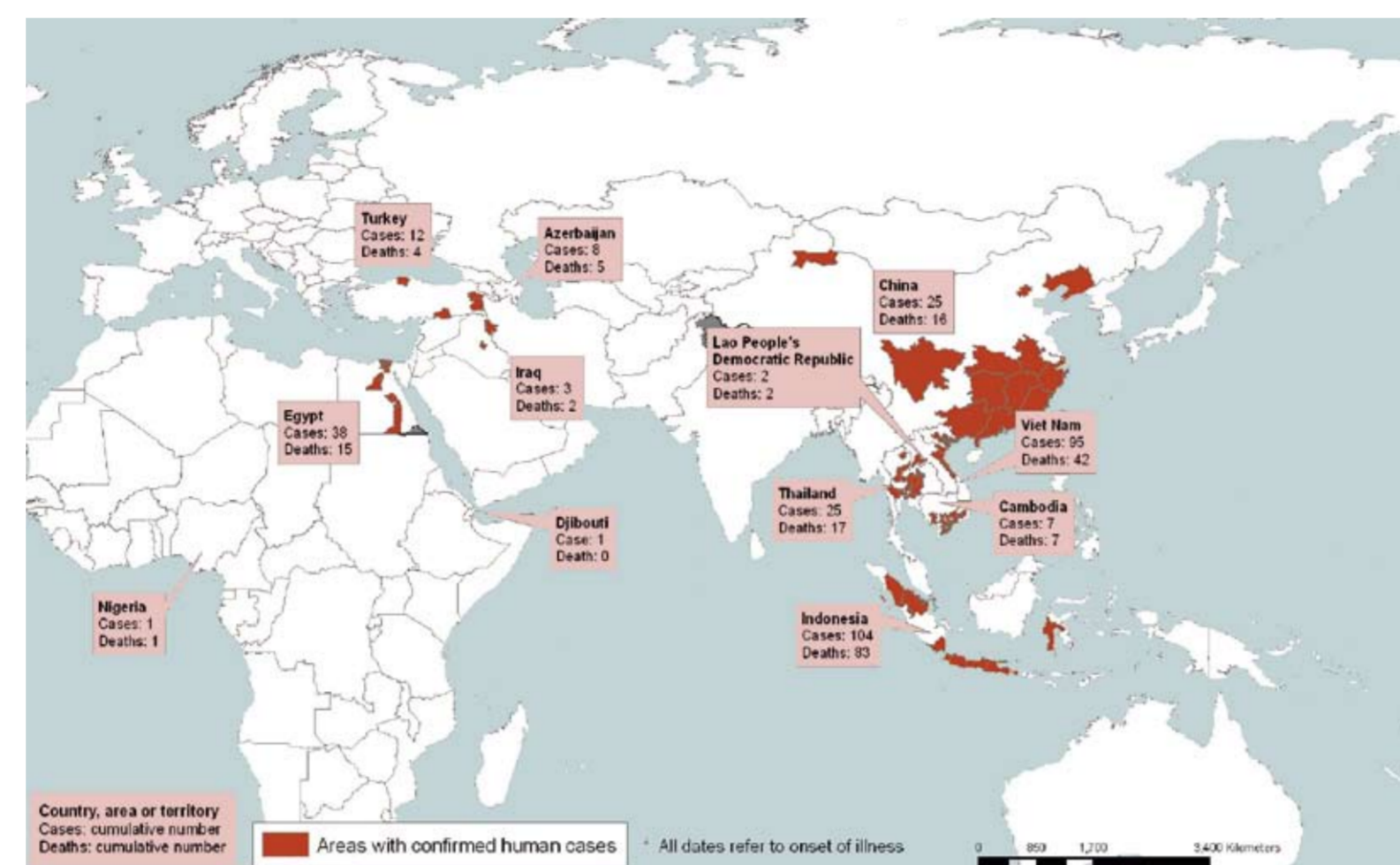


Figure 2. Countries with confirmed cases of human H5N1 avian influenza since 2003 (World Health Organization).

Tamiflu® (oseltamivir phosphate)

- Tamiflu® is an antiviral agent that is effective against all strains of influenza (A and B) that can affect humans⁷, and it can be given either as treatment for influenza (75 mg twice daily for 5 days), or prophylaxis (75 mg once daily for 10–42 days).^{8,9}
- Tamiflu® can be administered as an oral capsule, or as an oral suspension or small low dose capsules for children.

Treatment of influenza

- Treatment with Tamiflu® results in patients recovering more quickly from the symptoms of influenza, and in a faster return to normal health and activity compared with patients receiving symptom relief medication (e.g. paracetamol).^{10,11}
- Furthermore, the benefits of Tamiflu® can be improved by administering the drug as soon as possible, and no later than 48 hours, after symptom onset (Figure 3).¹² In an open label study, earlier intervention with oseltamivir was associated with a statistically significantly shorter illness duration (p < 0.0001). The total duration of illness was almost halved if patients were treated early (<12 hours) compared with those who received oseltamivir at 48 hours (median duration reduced by 74.6 hours, 41%).

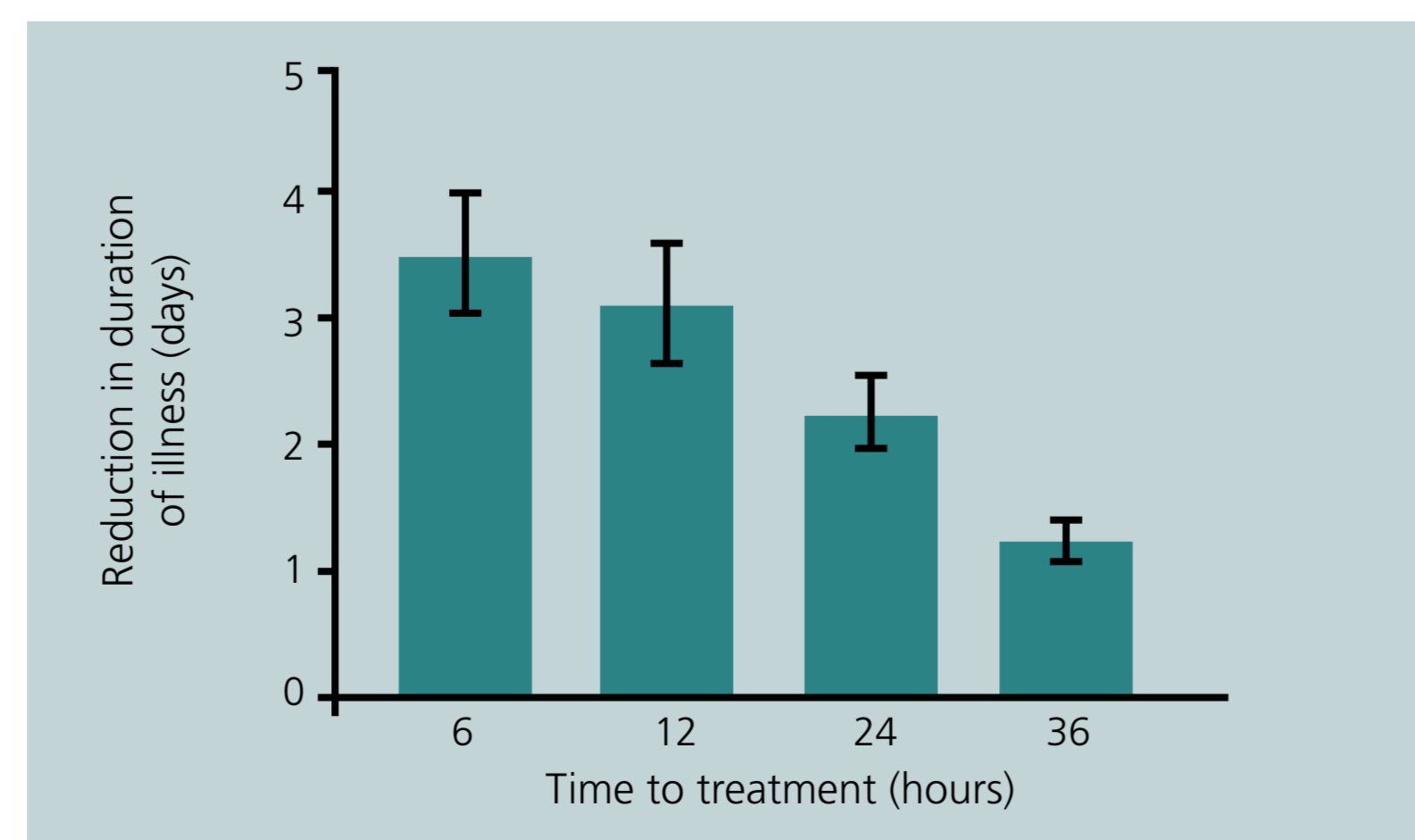


Figure 3. Beneficial effect of taking Tamiflu® early after symptom onset on duration of illness.

Animal studies show Tamiflu is effective in the treatment of H5N1 influenza

- Administration of Tamiflu® provided a decrease in mortality in mice infected with H5N1 (Table 1), and chickens infected with H5N2 or H7N7, at doses equivalent to the currently approved dose in humans.^{13,14,15,16}

Table 1. Effect of duration and dosage of Tamiflu® on survival of mice infected with H5N116

Treatment duration	Tamiflu dosage mg/kg/day	% survival	p value
5	0	0	NS
	0.1	0	NS
	1	0	NS
	10	50	p<0.01
7	0	0	NS
	0.1	10	NS
	1	60	p<0.01
	10	80	p<0.01

Abbreviation: NS = not significant.

- In treatment of H5N1-infected mice with a neuraminidase inhibitor increases survival, and survival increases with earlier treatment (Figure 4)

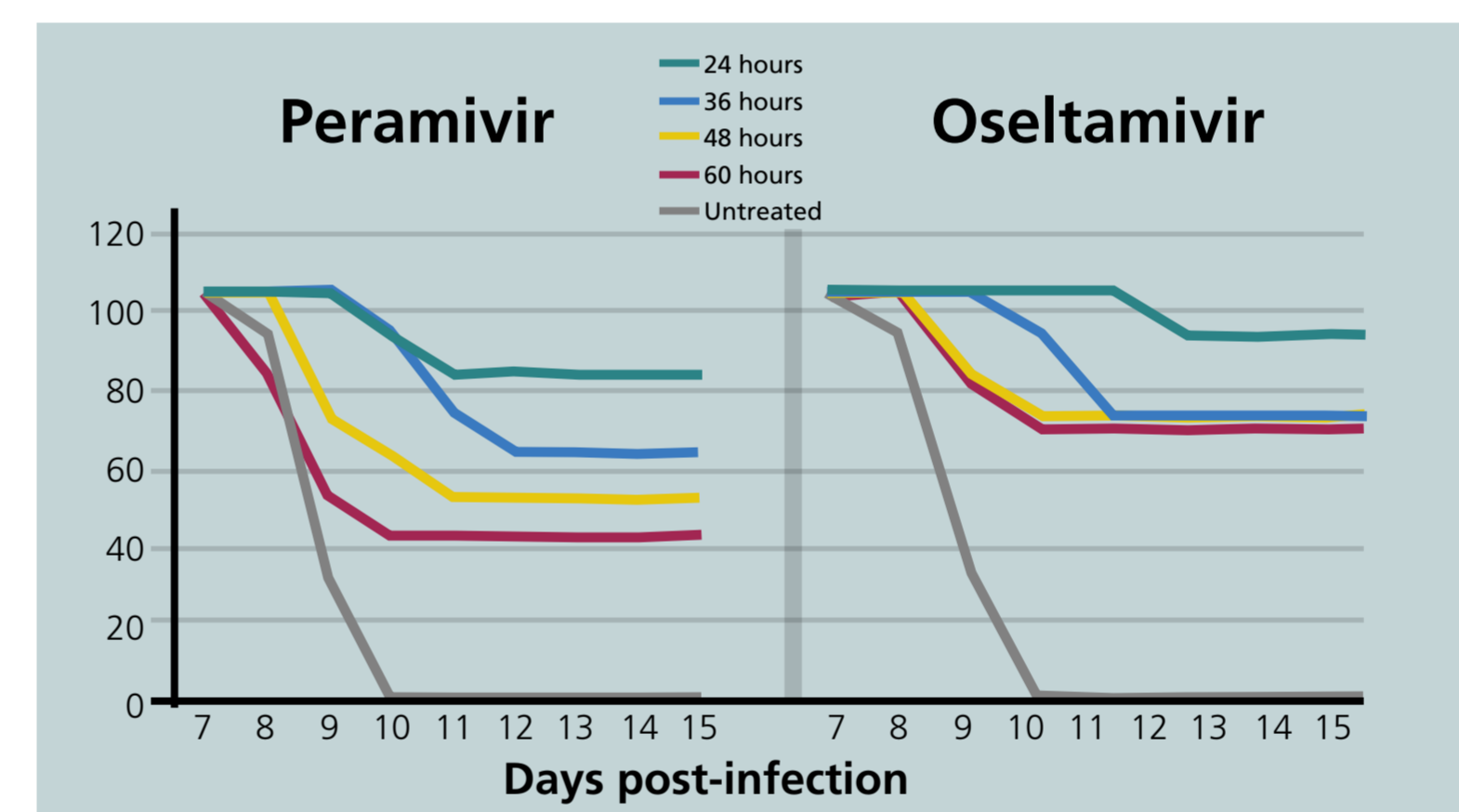


Figure 4. Beneficial effect of administration of Tamiflu early after H5N1 infection in mice

This proof of principle translates into what has been observed clinically in humans infected with H5N1.

- Anecdotal evidence from the recent flurry of cases in Egypt to suggest that **the faster a patient can be treated with antiviral, the better their chance of recovery** (Dr Hassan E. El Bushra, Regional Advisor, Emerging Diseases, WHO, personal communication).
- In a recent case of a 2-year old child in Egypt infected with H5N1, the good clinical outcome was attributed to the rapid administration of Tamiflu. **“He’s in good condition now because Tamiflu was given within 24 hours after the onset of symptoms,”** John Jabbour, a World Health Organisation official in Cairo, told Reuters.
- In a published series of patients in Turkey who were hospitalized with H5N1 infection, **“the interval between onset of illness and hospitalization – and thus the time to treatment with oseltamivir – tended to be**

shorter among the patients who survived than among those that died.”¹⁸

Prevention of influenza

- In addition to effectively treating influenza infection, Tamiflu® can be given to patients who have been in contact with an infected person to minimise their risk of infection.
- In a study of households from North America and Europe, Tamiflu® protected 80% of patients (adults and children) against infection following contact with an influenza-infected individual.⁹
- In South Korea, prophylaxis with oseltamivir protected workers involved in culling infected birds H5N1 from developing disease, despite being infected with H5N1. Tests on 9 workers in South Korea who had been involved in slaughtering birds infected with H5N1 had been infected with the virus. They had made antibodies to the virus, but had not developed any symptoms. All the workers had been receiving oseltamivir as prophylaxis during their work. This shows that oseltamivir protects against developing clinical illness, but also that at the same time people can develop an immune response to the influenza virus.

Speed of access to Tamiflu® is critical to clinical success

- The scientific rationale and observed clinical results imply that Tamiflu® should be taken as soon as possible after (or even before) the initiation of influenza viral replication for maximum impact on viral load and therefore symptom severity and infectivity.
- For seasonal influenza, Tamiflu® should be prescribed and taken as soon as possible after symptoms appear for optimal clinical benefit.
- For pandemic influenza, it is clear that any delay in access to Tamiflu® could be a question of life or death. Infected people and groups to be protected need access to neuraminidase inhibitors immediately both to reduce the severity of the symptoms and limit the infectivity and disease spread.

Conclusions

- Tamiflu® is effective in treating seasonal influenza, reducing the severity and duration of illness, the incidence of complications and preventing death. Tamiflu® is also effective when used prophylactically to prevent influenza infection.
- This excellent efficacy also applies to pandemic influenza, including the currently circulating H5N1 strain.
- Travellers need immediate access to Tamiflu® to ensure that they can take the medication within hours of being exposed to avian or seasonal influenza. Tamiflu® should be part of travel medicine recommendations for people travelling to regions where seasonal influenza is epidemic or where avian influenza is circulating.

References

- Moser MR et al. An outbreak of influenza aboard a commercial airliner. *N Engl J Med* 1979; 100: 1-6
- Brotherton JM et al. A large outbreak of influenza A and B on a cruise ship causing widespread morbidity. *Epidemiol Infect* 2005; 130: 263-271
- Miller J et al. Influenza A outbreak on a cruise ship. *Can Commun Dis Rep* 1998; 24: 9-11
- Miller JM et al. Cruise ships: high risk passengers and the global spread of new influenza viruses. *Clin Infect Dis* 2000; 31: 423-428
- Leder K et al. Respiratory infections in travelers: a review of controlled trial. *Lancet* 2000; 355: 1845-50
- WHO as of 16/08/07; <http://gamapserver.who.int/mapLibrary/>
- Roberts RA, Wiltshire HR, Mendel DB, et al. Oseltamivir carboxylate is effective against all subtypes of influenza neuraminidase. *ASM Biodefense Research Meeting* 2003, Baltimore, Maryland, USA
- Nicholson K, Wood JM, Zambon M. *Influenza*. *Lancet* 2003; 362: 1733-45
- Hayden F, Belshé GR, Villanueva C, et al. Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without post-exposure prophylaxis. *J Infect Dis* 2004; 189: 460-9
- Miller JM et al. Efficacy and safety of oseltamivir in the treatment of acute influenza: a randomised controlled trial. *Lancet* 2000; 355: 1845-50
- Meijer A, van der Goot JA, Koch G, et al. Oseltamivir reduces transmission, morbidity and mortality of highly pathogenic avian influenza in chickens. *International Congress Series* 2004; 1263: 1016-24
- Aoki FY, MacLeod MD, Paggiaro P, et al. Early administration of oral oseltamivir increases the benefits of influenza treatment. *J Antimicrob Chemother* 2003; 51: 123-9
- Roberts RA, Wiltshire HR, Mendel DB, et al. Oseltamivir carboxylate is effective against all subtypes of influenza neuraminidase. *ASM Biodefense Research Meeting* 2003, Baltimore, Maryland, USA
- Leneva I, Roberts AN, Govorkova EA, et al. The neuraminidase inhibitor GS4074 (oseltamivir phosphate) is efficacious against influenza viruses Antimicrob Agents Chemother 2001; 45: 2723-2732
- Over AJO, et al. Avian influenza A (H5N1) infection in Eastern Turkey in 2006. *N Eng J Med* 2006; 355: 1-7
- Yen HL, Muenst AS, Webster RG, et al. Virulence may determine the necessary duration and dosage of oseltamivir treatment for highly pathogenic avian influenza virus in mice. *J Infect Dis* 2005; 192: 665-72
- Govorkova EA et al. Comparison of efficacies of RW-270201, zanamivir and oseltamivir against H5N1, H9N2 and other avian influenza viruses. *Antimicrob Agents Chemother* 2001; 45: 2723-2732
- Over AJO, et al. Avian influenza A (H5N1) infection in Eastern Turkey in 2006. *N Eng J Med* 2006; 355: 1-7