



## EDITORIAL

### H5N1 influenza in birds: a pandemic threat

The current threat posed by the unprecedented spread of the highly pathogenic avian influenza virus, H5N1, in Asia, the Middle East (Egypt, Turkey, Sudan), Europe (Hungary and UK) and Africa (Nigeria), associated with extensive mortality among poultry, wild birds and mammals, has highlighted the urgent need for influenza pandemic preparedness. Human contact with infected birds has resulted in more than 260 reported severe human cases of H5N1 influenza, of which more than 160 were fatal. The H5N1 avian influenza strain isolated from the outbreak notified by Hungary is 99.4% similar to the strain that infected some countries of Europe last year. So far only a few cases of human to human transmission of this infection have been observed worldwide. However, the virus may acquire the ability to spread efficiently from human to human by mutation or mixing its genetic material with a human influenza virus. This may then result in an influenza pandemic. Therefore, according to World Health Organization (WHO) recommendations, European member states should develop influenza pandemic preparedness plans (PPPs). Key elements of PPPs are the establishment of influenza surveillance, stockpiling of antivirals, establishment of contingency plans and the possibility to vaccinate their populations with a pandemic vaccine. International collaborations between all the stakeholders in the respective countries to achieve these goals is of crucial importance. Although considerable progress in most of these

areas is being made in most EU member states, the timely availability of a safe and effective pandemic influenza vaccine is a matter of serious concern.

After the identification of a future pandemic influenza virus, a vaccine should be made as soon as possible. However, it has been shown that the current formulations used for seasonal influenza will not be sufficiently potent against a newly emerging pandemic influenza virus: new generations of more potent influenza vaccines should be used. Several candidate prototype H5N1 vaccines have been tested in animal models and promising vaccine candidates have been identified by the pharmaceutical industry in close collaboration with academic groups in Europe. Some of these are now being tested in clinical trials in humans. Funding of these trials with prototype vaccines in humans cannot be the sole responsibility of the vaccine manufacturing companies, which may not be expected to receive return on their investment. Since >60% of influenza vaccines are currently produced by European vaccine manufacturers, *public private partnerships* between the EU or its member states and the influenza vaccine manufacturers should now be created to speed up the process of developing candidate pandemic influenza vaccines. This will not only contribute to the urgently needed European, but also to global influenza pandemic preparedness.

In 2007, ESWI has important plans to contribute to influenza preparedness. In June, ESWI will organise a laboratory training course in the Erasmus MC in Rotterdam, The Netherlands. As in 2005, the target group are young scientists with an interest in

influenza epidemiology and virology. More information is to be found on our recently restyled website [www.eswi.org](http://www.eswi.org). Also ESWI is currently organising its Third European Influenza Conference, which will take place in September 2008 in Vilamoura, Portugal. More information is to be found in this edition of ESWI's *Influenza* bulletin.

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*Chair, ESWI*

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## THE THIRD EUROPEAN INFLUENZA CONFERENCE

ESWI was founded at the first Options for the Control of Influenza Conference in 1992. In 2002, ESWI organised the First European Influenza Conference in Malta. While the Options conferences have a worldwide perspective, ESWI's influenza conferences are specifically focused on Europe in the context of global influenza issues. Following the success of the previous editions and in response to the high level of interest shown, ESWI is looking forward to travelling to Vilamoura, Portugal, for the

Third European Influenza Conference. By holding these two conferences alternately, all parties involved are in a position where they can be kept on top of developments in the rapidly evolving field of influenza, and thereby be ready to combat the impact of epidemic and pandemic influenza.

### Science

The Third European Influenza Conference, 14–17 September 2008, will have a major focus on

science and an emphasis on new work. Once more it will offer scientists a full programme of oral presentations, posters and satellite symposia.

### Government representatives and opinion leaders in healthcare

Beyond science is the public health burden of epidemic influenza, and the potentially devastating impact of pandemic influenza. Scientific

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information and communication among scientists, policy makers, and healthcare professionals already helps to reduce significantly the burden of influenza and steps have been taken in pandemic planning, but more needs to be done. Thus, in addition to the traditional scientific content, the

conference will again have sessions for government representatives and thought leaders in healthcare work. Sessions in these issues are to cover a broad area, from an introduction to influenza and the danger of the virus, to pandemic preparedness and the economic impact of

influenza on society. The aim is to inform, educate and raise awareness within new target groups.

D. DE POOTER  
ESWI



VILAMOURA | PORTUGAL | 14-17 SEPTEMBER 2008



## TOWARDS A GLOBAL INFLUENZA TASK FORCE?

As announced in a previous edition of the *Influenza* Bulletin, ESWI has been facilitating the formation of a European Influenza Task Force by helping to identify the respective participants and representatives, stimulating communication among them, and helping to create the political will and the required funding possibilities for this initiative.

Through these efforts, ESWI has clearly played a catalytic role, seeing that through the course of 2006 remarkable initiatives have been launched that closely fit ESWI's Task Force objectives. August 2006 saw the start of the Global Initiative on Sharing Avian Influenza Data (GISAID). Its initiators recognise that H5N1 represents an

unprecedented model of how influenza infections may become widespread, while the current level of collection and sharing of data is inadequate given the magnitude of the threat. Scientists participating in the GISAID consortium would therefore agree to share their sequence data, to analyse the findings jointly, and to publish the results collaboratively. Secondly, the WHO plans to establish a Pandemic Influenza Task Force hold exceptional opportunities for a high level of global cooperation. Not only would such cooperation be an excellent answer to the WHO Call for Regional Preparedness, the creation of a Global Influenza Task Force would also imply the accomplishment of an important objective of the international influenza community.

This Pandemic Influenza Task Force will advise WHO on potential public health issues of international concern related to avian and pandemic influenza, including issues such as the appropriate phase of pandemic alert, the declaration of an influenza pandemic, and appropriate international response measures.

Seeing that the fight against influenza can only be won if all parties involved are ready to collaborate, ESWI is an active supporter of GISAID and the WHO Pandemic Influenza Task Force.

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## INFLUENZA IN TRAVEL MEDICINE

### Incidence of influenza in travellers

Travel presents unique opportunities for close contact with large numbers of other individuals, many of whom may harbour influenza and other respiratory pathogens. For example, an airplane carrying 54 passengers, one of whom had influenza, was grounded for 3 hours with ventilation failure, clinical influenza developed in 72% of the passengers [1]. Another example is cruise ships, their closed environments and large numbers of passengers have shown to present unusually high-risk situations for influenza transmission. Attack rates for influenza-like illness have ranged from 17–37% in reported outbreaks, which can involve hundreds of cases [2–5]. Based on almost 19,000 patient records in the GeoSentinel Surveillance System pre-SARS, 12.8% of ill travellers returning from East Asia and 7.8%

from all destinations had respiratory illness, making it second to gastrointestinal infection [6].

Laboratory confirmation of influenza is performed infrequently, but probably accounts for at least 5–6% of respiratory illness reported in travellers. Limited prospective data support a widely held suspicion that influenza may be the most common vaccine-preventable disease in travellers [7].

### Indications for vaccinating travellers

Initial national strategies for routine vaccination involved targeting those at greatest risk for morbidity and mortality. While this is still a valid strategy, increasingly, national guidelines include strong statements that vaccination is indicated in otherwise-healthy individuals.

In addition to the benefits of the protection of the

individual, vaccination of travellers potentially serves to prevent outbreaks and the spread of new antigenic drift variants. At the time of a pretravel consultation, the provider should make two determinations (Table 1). First, does the itinerary include destinations where influenza is known to be circulating? Second, is the traveller in a risk group in which annual influenza vaccination is indicated according to normal national guidelines, and, if so, has the traveller already had the most currently available domestic vaccine?

### Cross-hemisphere summer to winter travel

A traveller going from summer in one hemisphere to winter in the other has two choices. Firstly, they could seek vaccination upon arrival, but this is often logistically difficult, and the influenza vaccine requires a minimum of 1 week

to offer protection. Alternatively, the traveller could be vaccinated with his or her own hemisphere vaccine and hope there is sufficient cross-protection. The utility of this approach varies from year to year depending on how closely northern and southern circulating strains are matched. In general, it is always preferable to vaccinate with the vaccine at hand than travel with no vaccine protection.

Most evidence indicates that there is no benefit to vaccinating patients more than once a year [8]. For travellers, this means that if they received routine influenza vaccine in their home hemisphere, another dose is not needed for travel. The exception to this would be long-stay or frequent travellers who, during their travel, have access to an opposite-hemisphere vaccination that contains different and more recently recommended influenza strains. Also, routine vaccination should be offered to those who have relevant indications despite previous vaccination for travel (even if only a short time has elapsed).

### Tropical travel any time of year

Even though influenza is a year-round risk in tropical zones, the strain guidelines are less defined. Adequate surveillance is carried out in a few tropical countries, so blanket recommendations at any time of year are not made by the WHO. In the absence of specific information, tropical travellers should be vaccinated with the most recent vaccine that is available. In many tropical countries and particularly in Asia, both northern and southern hemisphere vaccines are distributed in sequence each year, so a new vaccine formulation is available every 6 months.

With the above complexities in mind, there arises a number of situations in which it is impossible to adequately vaccinate travellers, such as departing in <1 week, exposure to avian influenza, pandemic influenza at the destination or lack of vaccination supplies. After a discussion of the pros and cons, these travellers should consider the use of standby antiviral drugs.

### Use of antiviral agents

Antiviral drugs are an adjunct to influenza vaccine but should never be used as a sole substitute for indicated influenza vaccination. For self-treatment or prophylaxis in the traveller, oseltamivir is the only practical choice. M2 inhibitors have

**Table 1. Influenza vaccine indications for travellers.**

#### In traditional risk groups

- Vaccinate all travellers\* aged  $\geq 65$  years, those between 6 and 23 months, and all travellers of any age with any chronic or immunocompromising conditions who are planning to do any of the following
  - go to the tropics
  - go on cruises
  - travel with organised tour groups
  - travel to or within temperate climates during the influenza season at the destination†

#### Other risk groups

- Consider influenza vaccination for any tropical, cruise ship, tour group, or influenza-season temperate traveller wishing to decrease the risk of influenza illness or the risk of having respiratory symptoms mistaken for SARS
- Use Flunet or available surveillance websites ([www.rhone.b3e.jussieu.fr/flunet](http://www.rhone.b3e.jussieu.fr/flunet), [www.eiss.org/index.cgi](http://www.eiss.org/index.cgi), [www.cdc.gov/ncidod/diseases/flu/weekly.htm](http://www.cdc.gov/ncidod/diseases/flu/weekly.htm), [www.who.int/csr/disease/influenza/vaccinerecommendations/en/](http://www.who.int/csr/disease/influenza/vaccinerecommendations/en/)) to prioritise for travel to countries with current widespread or epidemic influenza activity or countries with current high intensity of influenza activity

\*Unless vaccinated the previous winter in the home hemisphere.

†The flu season in temperate areas of the northern hemisphere is November–April; the flu season in temperate areas of the southern hemisphere is April–October

significant adverse effects in many people, and zanamivir requires use of a non-intuitive inhaler device.

### Self-treatment with oseltamivir

When used for treatment, oseltamivir administered within 48 hours of symptom onset can shorten illness by up to 1.5 days [9,10]. Possible scenarios for suggesting that an inadequately vaccinated adult traveller (includes children aged >12 years) should carry a self-treatment course of 75mg orally twice daily for 5 days include going to the tropics, on cruises or to temperate climates during the influenza season. Travellers who carry oseltamivir should be advised to make every effort to administer therapy only under medical advice.

Many travellers are aware that even under optimal circumstances of appropriate administration, the influenza vaccine is only 70–90% effective. These travellers may request a prescription of a self-treatment course of oseltamivir as a precaution. This must be handled on a case-by-case basis but should be encouraged only when the traveller will actually be at risk. Possible scenarios for suggesting that an inadequately vaccinated traveller consider ongoing chemoprophylaxis with oseltamivir 75mg orally once daily, include short-term, critical missions to areas where surveillance reports clearly document widespread or epidemic-level influenza activity, anticipation of occupational exposure to avian influenza or anticipation of exposure to a pandemic strain of influenza. Prophylaxis may begin on arrival at the destination

or only after a suspected exposure. This can be decided after a discussion of the travel circumstances with the traveller. The duration of protection lasts as long as dosing continues, but a minimum course of 7 days is recommended. Safety and efficacy have been demonstrated for up to 6 weeks.

### Summary

Most healthcare providers focus on classical preventable diseases when counselling travellers. However, influenza poses a significant risk in selected populations and destinations. Healthcare providers and policy makers should increasingly focus on the impact of influenza on travellers and its consequences given the worldwide increase and importance of travel.

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## WHY SHOULD HEALTHCARE WORKERS BE VACCINATED AGAINST INFLUENZA?

Healthcare workers (HCWs) with close patient contacts have an increased risk of exposure to, and transmission of, influenza viruses [1,2]. Very high influenza attack rates in HCWs (up to 59%)

have been reported [3]. In addition, occasional reports are published where HCWs were identified as the suspected vector of influenza infections in a neonatal intensive care unit [4] as well as in an

organ transplant unit [5].

The safety and efficacy of influenza vaccines in healthy adults is well documented [6,7]. HCWs

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constitute a subgroup of healthy adults. Provided there is a good antigenic match, vaccination reduces influenza morbidity in healthy adults by 70–90% [8]. In addition to their own benefits, it has been shown that vaccinating HCWs will reduce crude patient mortality in long-term care geriatric hospitals [9]. A recent systematic literature review also demonstrated that vaccination of HCWs in health institutions is not only protective for them, but also indirectly reduces the morbidity of their patients [10]. In line with these results, Hayward et al. [11] concluded from a pair-matched cluster, randomised controlled trial in large private-chain care homes in the UK, that vaccinating care home staff against influenza can prevent deaths, health service use and influenza-like illness in residents during periods of moderate influenza activity. HCWs should be able to provide care for their patients at all times, particularly at the time of the so-called 'winter burden', where many respiratory infections, including influenza, cause considerable morbidity in the population and when the health systems may be overstretched and medical staff are needed most. In a placebo-controlled study in two paediatric hospitals in Finland, a considerable reduction of sick leave days between vaccinated and placebo-treated HCWs was observed [12].

In conclusion, available evidence suggests that vaccination will be beneficial for both HCWs who are in contact with patients and often also for the patients they are taking care of. Based on these considerations, in 2004 the WHO recommended that HCWs who are in contact with patients should be included in national recommendations for annual influenza immunisation [13]. In 2004, most of the Western European countries, but not all, followed this recommendation [14]. In the USA, a CDC national health objective has been formulated to achieve HCW vaccination rates of 60% by 2010 [15].

Poland et al. [16] even suggested that annual influenza immunisation should be a requirement for every HCW with direct patient contact, unless a medical contraindication exists or an informed declination is signed by the HCW. The latter part of their recommendation does not fit the health culture in Europe. Nevertheless, the scientific evidence and considerations leading to the suggestion by Poland et al. do also apply for Europe. A better compliance by HCWs in Europe and elsewhere with the WHO's recommendations [13] for annual immunisation against influenza is warranted and should be seriously considered for their own interest as well as in the interest of their patients.

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## SOME CHALLENGES AND PITFALLS IN THE INTERPRETATION OF SYSTEMATIC REVIEWS OF INFLUENZA VACCINE EFFICACY AND EFFECTIVENESS

### Introduction

Meta-analyses are systematic reviews of the medical literature designed to facilitate interpretation of published data in which statistical methods are used to summarise and combine the results from multiple primary studies. In the case of influenza vaccination, several meta-analyses have been published looking at the efficacy and effectiveness of influenza vaccinations among people in different age groups. Some challenges and pitfalls in interpreting these meta-analyses include ensuring the appropriate interpretation of the numbers, assessing the appropriateness of the data pooling, and evaluating whether some conclusions presented are supported by the data presented.

### Magnitude of benefit: differentiating between relative risk reduction (RRR) versus absolute risk reduction (ARR) [1]

For influenza vaccinations in healthy adults, some have suggested the following. As the RRR of vaccination against serologically defined influenza is 69% while it is 22% against clinically defined illness without laboratory confirmation, influenza

vaccine is 'much less' effective against clinical illness. The error in this logic is that the RRR does not provide information about the actual number of cases prevented. We need to know the ARR in order to make a sound conclusion about how the RRR of 69% relates to the RRR of 22%.

Studies looking at influenza vaccination and serologically confirmed influenza-like illness found the following: 8.4 cases per 100 in unvaccinated and 2.3 cases per 100 in vaccinated patients for an RRR of  $(8.4-2.3)/8.4$  or 69% and an ARR of  $8.4-2.3$  or 6.1 cases per 100 patients.

Studies looking at influenza vaccination and clinical illness found that 44.1 cases per 100 unvaccinated and 30.6 cases per 100 vaccinated patients for an RRR of  $(44.1-30.6)/44.1$  or 22% and an ARR of  $44.1-30.6$  or 13.5 cases per 100 patients.

A more appropriate way of talking about the RRRs in these studies would be to indicate that the 69% reduction in laboratory confirmed illness translates into a 22% reduction in all clinical illnesses (many of which are caused by other viruses as well). In either case, the actual number of cases prevented is around 6–14 per 100 people.

### Negative studies: differentiating between lack of power and actual exclusion of benefit [2]

In the case of influenza vaccination of the elderly, it has been observed that the RRR for preventing laboratory-confirmed influenza illness is 81% with a 95% confidence interval (CI) that includes 0 (–101–98%). Based on this, some have concluded that vaccination is 'apparently ineffective' with regard to this outcome. The error in this logic is equating lack of statistical significance with an exclusion of benefit.

Not all negative studies exclude benefit. In this example, the point estimate of 81% actually suggests substantial benefit while the CI is very wide suggesting that the study lacks statistical power. In fact, the upper limit of the CI goes to 98%, suggesting that the findings are indeed compatible with a high degree of effectiveness. The more appropriate interpretation of these findings all else being equal, would be: influenza vaccination may be effective against laboratory confirmed illness in the elderly, but these findings are not definitive.

### Assessing the appropriateness of pooling the data: determining if the primary studies are similar enough with regard to subjects, interventions, outcomes, and study methods to warrant a meta-analysis [3]

An important consideration in evaluating meta-analyses is whether there is substantial heterogeneity in the design of the studies and whether there is substantial heterogeneity in the results of the studies. The former can be caused by differences with regard to subjects, intervention, outcomes, and/or study methods.

In the case of influenza vaccination and healthy adults, many studies have used quite different case definitions for clinical illness such as febrile upper respiratory illness versus all upper respiratory illness. These case definitions can differ substantially in their sensitivity and specificity for true influenza, and thus the RRRs associated with vaccination in these studies will also differ depending on the case definition used. In a meta-analysis designed to explore the implications of this heterogeneity of case definitions,

for the more specific case definitions, the combined RRR was 54% vs 11% for less specific but more sensitive case definitions. This variability in case definitions is important and represents a critical study design issue that raises questions about the appropriateness of pooling data from some of these studies.

### Agreeing or disagreeing with the conclusions: confirming that the conclusions are supported by the data [1,4]

Influenza vaccination of healthy working adults has been found to reduce illness by 6.1 cases of serologically confirmed illness per 100 and work loss by 16 days per 100. From these findings some have concluded that universal immunisation of healthy adults is not supported. However, formal health economic studies using values consistent with the results of the meta-analyses have actually found that vaccination in this group may not only be cost effective but even cost saving.

### Conclusion

Appropriate interpretation of the medical literature, including meta-analyses, is fraught with

challenges and pitfalls. In the case of influenza vaccination, several misinterpretations and mistakes have been made. With a clear understanding of what the numbers mean, whether studies included in the analysis are heterogeneous in important ways, and if the proposed conclusions are supported by the findings, we will be in a better position to understand what the benefits of influenza vaccination really are – an understanding essential to informed policy and practice.

This is a summary of a talk given at the Influenza Vaccines for the World Conference, Vienna, Austria in October 2006.

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## APACI: PROGRESS WITH INFLUENZA AWARENESS IN THE ASIA-PACIFIC

Promotion of the use of seasonal influenza vaccines has always been an integral part of pandemic preparation. The current level of global concern over the spread of the H5N1 virus, the ongoing occurrence of human infections in an ever-increasing number of countries and the threat of another human pandemic, is engendering a renewed focus by many countries on the promotion of seasonal influenza vaccination and on the establishment of programmes by others.

Against the background of the successful Australian and New Zealand coordinated

approach to the promotion of influenza awareness, the Asia-Pacific Advisory Committee on Influenza (APACI) was established early in 2002. This involved partnerships between the public sector and the pharmaceutical industry and recognised that few other countries in the Asia-Pacific region had influenza control guidelines or policies, or were routinely using influenza vaccine. APACI's objectives were to address issues relating to influenza awareness education and the poorly understood epidemiology and impact of the disease in Asia (see Mission Statement and Organisational Structure below).

### Recent activities

Highlights of APACI's activities include the formation of 'The Influenza Foundation/Thailand' in August 2004 and 'Influenza Foundation/India' in October 2005. Each are lead by APACI board members, and both have objectives of increasing influenza awareness, establishing coordinated education in these countries and endorsing APACI's leadership role in the region.

APACI's communication strategy is to provide influenza-related information for the general public, the media, primary healthcare physicians and

### Mission Statement

To promote influenza awareness in the Asia-Pacific region, with the intent to improve the prevention and control of influenza.

### Objectives

1. To identify and develop activities that complement the WHO's Global Agenda on Influenza Surveillance and Control.
2. To assist the development of country-specific public awareness programmes.
3. To promote influenza awareness among healthcare professionals in the region.

4. To provide educational resources to support influenza awareness activities.
5. To assist the process of establishing or reviewing country-specific recommendations for influenza prevention and control.
6. To facilitate the timely access to, and supply of, influenza vaccines and antivirals.

### Organisational structure

APACI is structured to include members, associate members, sponsors and advisers. Members and associate members are influenza researchers,

public health officials and infectious disease experts from countries in the Asia-Pacific region. Member countries include Hong Kong SAR, New Zealand, Australia, China, South Korea, Malaysia, Taiwan, Singapore, Thailand, The Philippines, India, Indonesia and Vietnam. The committee is a joint initiative, supported by five pharmaceutical companies: Sanofi Pasteur, Chiron Vaccines, GlaxoSmithKline, Solvay Pharmaceuticals and Roche and is coordinated by a professional secretariat.

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infectious disease specialists in the Asia-Pacific region. Communication within the region is facilitated by a newsletter entitled *Influenza: Asian Focus*, which is published twice a year. *Influenza: Asian Focus* carries articles by APACI members and advisers with the objective of providing timely information on influenza-related activities in Asia. *Influenza: Asian Focus* is now available online on the APACI website [www.apaci-flu.com](http://www.apaci-flu.com).

Other resources available on the website include

PowerPoint lecture slides. The website has 'shopping basket' facilities which allow the creation of individual slide sets for influenza awareness presentations. Other educational resources to support influenza awareness activities will be progressively accessible on the site.

Following APACI board meetings held twice a year in different countries, press conferences are held in an ongoing attempt to improve accessibility to the media by our members and the promotion of

educational activities by APACI members regarding influenza in each country and in the region.

All of APACI's activities over the past 5 years have been supportive and complementary to those of the WHO's Global Agenda on Influenza.

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## PANDEMIC INFLUENZA: VACCINES AND NEW GENERATION ANTIVIRALS

The continuing spread of the H5N1 subtype of highly pathogenic avian influenza virus (HPAI) in wild birds and domestic poultry, represents the most serious risk of a human influenza pandemic in decades. The WHO has declared that the HPAI H5N1 virus strain meets two of the three key criteria needed for a pandemic. The final WHO criterion of efficient human-to-human transmission has not been observed to date. However, most experts believe that a future influenza pandemic is inevitable.

Different studies suggest that global economic losses during a pandemic could be up to US \$4.4 trillion [1] due to the enormous morbidity typically associated with influenza, leading to absenteeism, schools closing, disruption in supply chains, declining productivity and crowded hospitals.

### The role of vaccines in a pandemic

Pandemic influenza vaccines are different from those currently in existence. To develop safe and effective pandemic vaccines, a number of different concepts have to be investigated. Most research is focused on inactivated vaccines, but the live virus vaccine approach is also being explored [2]. Most pandemic vaccine research is focused on the concept of 'antigen-sparing' and broadening of the immune response which means that preferably a single, but more likely two, lower-than-usual vaccine doses are needed to induce an adequate immune response. Different adjuvant systems are being tested and encouraging results from clinical trials have been reported [3,4].

New approaches for production of pandemic vaccines are being developed as viruses for influenza vaccines are usually produced in embryonated chicken eggs. However, in case of a widespread outbreak of an avian influenza virus that affects poultry on a large scale the availability of eggs may decline. Alternative cell culture technologies are currently being developed for seasonal and pandemic vaccines [5-8]. Also, the modern

technology of reverse genetics has been introduced to rapidly produce attenuated vaccine seed-viruses from highly pathogenic wild type viruses [9]. Overviews of prototype pandemic vaccines that are currently in development are reported elsewhere [4].

Assuming that safe and efficacious pandemic vaccines can be produced, the total volume of vaccine produced in a certain amount of time will be determined by: 1) the protective dose needed for each immunisation; 2) the total global vaccine production capacity; and 3) the availability of adequate numbers of fertilised hens' eggs or cell culture fermentation plants. Also, capacity for filling vials and needles, as well as the infrastructure for its distribution will be critical for the actual administration of the vaccine to the population.

Production of an influenza vaccine that matches the pandemic influenza strain causing human-to-human transmission cannot begin until after the pandemic virus has emerged. Due to the rapidity of infection, the world may have little time to prepare a vaccine before the first pandemic wave. Therefore, it is likely that a vaccine will not arrive in time, making a need for a pre-pandemic vaccine.

The development and stockpiling of a pre-pandemic vaccine that confers cross-protection against potential drift strains is of obvious benefit for a pandemic. The use of a pre-pandemic vaccine is therefore considered to be one of the most effective strategies for reducing infection rate and consequently morbidity and mortality. Clinical and preclinical trials have shown that some adjuvanted pre-pandemic vaccines induce a marked cross-immunity against a drifted strain which belong to a different clade from the virus used in the vaccine. These data support the hypothesis that utilising an adjuvanted pre-pandemic vaccine to prime an individual's immune system will allow better immune responsiveness upon subsequent infection with a pandemic virus strain. As a result the morbidity and mortality from a pandemic influenza virus may be dramatically reduced.

### The role of antivirals in a pandemic

Due to the challenges of the timely production and delivery of matched vaccines in response to a pandemic, antiviral drugs must be considered as a key medical intervention for providing both protection against disease and therapeutic benefit in infected persons during the initial stages of a pandemic. As a result, the WHO has recommended that national governments should consider stockpiling antiviral agents in advance of a pandemic, as a component of their pandemic preparedness plans [10].

The neuraminidase inhibitors, a novel generation of influenza antiviral compounds, act by specifically inhibiting the neuraminidase enzymes that are present in all influenza subtypes, thereby inhibiting further replication of the virus. Oseltamivir (Tamiflu®) and zanamivir (Relenza®) are neuraminidase inhibitors which were initially developed for the management of seasonal influenza. Oseltamivir administered orally and zanamivir given via inhaler, are both indicated for the treatment and prophylaxis of influenza in children (1 year and above for oseltamivir and 5 years and above for zanamivir) and adults. The WHO currently recommends treatment with oseltamivir, or alternatively zanamivir, in patients with confirmed or strongly suspected H5N1 infection, and for post-exposure prophylaxis of high risk exposure groups (Table 1) [10].

### Neuraminidase inhibitors and pandemic influenza

Zanamivir and oseltamivir are able to effectively inhibit the human isolates of H5N1 *in vitro* and are effective against H5N1 infections in animal models [11,12].

Zanamivir administered intranasally has been shown to be effective in preventing death in H5N1-infected mice [12]. Similarly, early intervention with oseltamivir has been shown to prevent mortality in H5N1-infected ferrets. In addition, pre-exposure prophylaxis with oseltamivir in ferrets

(when administered 24 hours and 4 hours before virus inoculation) prevented death and inhibited viral replication (with only minor clinical symptoms) without preventing the development of an immune response (13).

Although clinical experience with H5N1 is limited, the available clinical information supports the use of oseltamivir, to both treat and prevent human infection with H5N1. Recent reports from Thailand, Turkey and Vietnam indicate that when administered earlier rather than later, oseltamivir provided greater benefit.

As with all antiviral agents, the potential exists for an influenza virus to emerge with decreased sensitivity to antiviral treatment. There is growing evidence of the development of an oseltamivir-resistant influenza virus in seasonal influenza (H1N1 or H3N2) [14–16] and also in H5N1 human infection [17]. The oseltamivir resistance mutations, H274Y and E119V, do not affect the binding of zanamivir to neuraminidase and these mutated viruses retain zanamivir sensitivity. This is consistent with the hypothesis that resistance may develop more readily to oseltamivir than to zanamivir [18,19] because a conformational change in the viral neuraminidase is required for oseltamivir binding but not for zanamivir binding. Whilst the emergence of resistance to zanamivir in the future cannot be excluded, the emerging evidence of differences in the resistance profiles of oseltamivir and zanamivir is an important factor to consider in the stockpiling of relevant antivirals for a potential influenza pandemic.

The vast majority of data collected from thousands of patients worldwide who were treated with oseltamivir for seasonal influenza, indicates that incidence of resistant viruses are rare: 0.4% in adults and 4% in children [20]. Resistant viruses have been found to be both less fit and less transmissible than the wild type virus in animal models and did not alter the clinical course of the illness. A position statement on antiviral resistance in H5N1 viruses has been issued by the NISN concluding that ‘the available data do not indicate that potential oseltamivir resistance should be a deterrent to its stockpiling for pandemic response, but that both inhaled zanamivir, as well as oseltamivir, would be an appropriate choice for pandemic response stockpiles’.

Oseltamivir has been purchased by more than 80 governments around the world for stockpiling. Zanamivir has also been purchased by a number of governments as part of their pandemic planning strategies. Influenza viruses that have become resistant towards oseltamivir, may still be susceptible to zanamivir. As zanamivir is administered by inhalation its absorption outside the lungs is limited. Although H5N1 is primarily a respiratory infection it has also been reported to possibly involve organ systems outside the respiratory tract, therefore, the limited systemic absorption of zanamivir may have implications for its role in the

**Table 1. WHO guidelines for treatment and prophylaxis of patients with confirmed or strongly suspected H5N1 infection [10].**

**In traditional risk groups**

- Oseltamivir treatment (strong recommendation)
- Zanamivir as an alternative (weak recommendation). Applies to adults (including pregnant women) and children. Treatment dosage and duration as for seasonal influenza

**Prophylaxis**

- In high-risk exposure groups oseltamivir/zanamivir (alternative) should be administered (strong recommendation)
- In moderate-risk exposure groups oseltamivir/zanamivir (alternative) might be administered (weak recommendation) Continuing for 7–10 days after last exposure. Treatment dosage and duration as for seasonal influenza

treatment of infected individuals. However, currently, there is no reported clinical experience in using zanamivir against H5N1.

There have recently been reports from Japan about patients with influenza who were taking oseltamivir experiencing abnormal behaviour including, in a small number of instances, death. Similar abnormal behaviour has recently been reported in patients taking amantadine and zanamivir. There have also been reports of such events including death in patients with influenza who are not taking antivirals.

No causal link between such events and oseltamivir has been established. In view of the fact that such reports have been received, Roche has updated its product information to advise physicians that such events have been reported and to advise patients and their care-givers to watch for signs of abnormal behaviour in all patients with influenza.

Both the Japanese government and the WHO have issued statements that reports of abnormal behaviour do not alter advice regarding the stockpiling and use of oseltamivir for pandemic preparedness.

**Stockpiling of antivirals**

The manufacturing of influenza antivirals has historically been geared towards the seasonal demand for the medications. Timelines associated with the surge in production of antivirals during a pandemic outbreak would not meet the requirements for a ‘rapid response’ and therefore, the WHO has advised that ‘stockpiling drugs in advance is presently the only way to ensure that sufficient supplies are available at the time of a pandemic’.

The WHO has developed three models for the stockpiling of antivirals.

1. **Global antiviral stockpile.** A stockpile created to support containment, either directly or by replenishing other stockpiles that were used to support containment, anywhere in the world.
2. **Regional antiviral stockpile.** A stockpile developed to support any of the countries within a defined region.

3. **National antiviral stockpile.** The annual production capacity for oseltamivir is 400 million treatment courses per year, and manufacturers of both oseltamivir and zanamivir will have 2007 production capacity which exceeds the current demand for government pandemic stockpiling and demand for seasonal use of the product.

The stockpiling of antivirals in advance of a potential influenza pandemic could help contain the disease or slow the spread of the virus and reduce its impact.

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### CALENDAR OF EVENTS

Date/Venue	Title	Organiser/Secretariat
17–23 June 2007	Options for the Control of Influenza VI Conference	MediTech Media Conferencing, Inc. Six Concourse Parkway, Suite 3000 Atlanta, GA 30028 USA Tel: +1 404 233 6446 Fax: +1 404 233 2827 E-mail: optionsviregistrations@meditechmedia.com
1–5 September 2007 Nürnberg, Germany	3rd European Congress of Virology	MCN Medizinische Congressorganisation Nürnberg AG Neuwieder Str. 9 90411 Nürnberg Germany Tel: +49 (0) 911 393 1610 Fax: +49 (0) 911 393 1655 E-mail: eurovirology@mcnag.info
17–20 September 2007 Chicago, USA	47th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)	American Society for Microbiology Department of Meetings and Industry Relations 1752 N Street, NW Washington, DC 20036-2904 USA Tel: +1 202 942 9248 Fax: +1 202 942 9340 E-mail: icaac@asmusa.org
12–14 October 2007 Madrid, Spain	Perspectives in Interpandemic Influenza	Imedex 4325 Alexander Drive Alpharetta GA 30022 USA Tel: +1 770 751 7332 Fax: +1 770 751 7334 E-mail: meetings@imedex.com
17–20 October 2007 Paris, France	13th Annual Regional Conference of the European Society of General Family Practice/Family Medicine (WONCA)	GEMBA Lifesciences Cécile Menu 130-132, rue de Normandie 92400 Courbevoie France Tel: +33 (0) 1 49 97 02 02 Fax: +33 (0) 1 49 97 02 11 E-mail: congress@gembalifesciences.com
15–18 November 2007 Bangkok, Thailand	World Society for Pediatric Infectious Diseases (WSPID)	Kenes International/WSPID 17 Rue de Cendrier, PO Box 1726 CH-1211 Geneva 1 Switzerland Tel: +41 22 908 0488 Fax: +41 22 732 2850 E-mail: wspid@kenes.com
13–17 April 2008 Montréal, Canada	Annual International Conference on Antiviral Research	Courtesy Associates 2025 M Street, NW Suite 800 Washington, DC 20036 USA Tel: +1 202 973 8690 Fax: +1 202 331 0111 E-mail: ISAR@courtesyassoc.com
19–22 April 2008 Barcelona, Spain	18th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)	18th ECCMID c/o ESCMID Executive Office PO Box 4005 Basel Switzerland Tel: +41 61 686 77 99 Fax: +41 61 686 77 98 E-mail: info@eccmid-icc.org

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