



# Influenza

INFORMATION AND NEWS ON INFLUENZA

## EDITORIAL

The recent outbreaks of avian influenza virus in The Netherlands (H7N7 outbreak) and Asia (H5N1 outbreak) posed serious risks for the emergence of a human pandemic influenza virus, since sometimes fatal bird-to-human transmissions occurred, at a time when human influenza A virus (H3N2) was also circulating.

For the time being, human-to-human transmission of the avian virus in Asia remains to be proven, but this had been the case in The Netherlands, where three such events were demonstrated. A coordinated international effort is now needed. All available means must be used to control the avian influenza in Asia to reduce the risk of a new pandemic influenza strain emerging to an absolute minimum. The involvement of international organisations such as the World Health Organization (WHO), the Food and Agriculture Organization (FAO) and the Office International des Epizooties (OIE) as well as the cooperation of national authorities is of the utmost importance. Of course, ESWI also has a major role to play in the battle against influenza. This bulletin aims to inform the scientific and medical community of recent developments in the fight against influenza and thus contribute to ESWI's mission statement: 'To reduce the impact of epidemic and pandemic influenza in Europe by optimising the ways to combat this disease'.

The bulletin is not the only line of communication open to ESWI. In October 2002, more than 500 scientific stakeholders attended the first European Influenza Conference in Malta, which proved to be an overwhelming success.

Ideas were conveyed, contacts were made, profound debates were held. Given the precious scientific content and the positive outcome of this conference, ESWI is proud to announce the Second European Influenza Conference. Not only are we aiming at a larger audience, we will also reshape the conference structure according to ESWI's strategic approach. We will work with very specific target audiences, allowing more interaction. The conference will take place on 11–14 September, 2005 and will again be held in St Julians, Malta.

ESWI's collaboration with national influenza networks is another pillar of the ESWI strategy. In Germany, Poland and Sweden, ESWI recently brought together influenza stakeholders who have been discussing and analysing the current situation in their countries. Based on this analysis, some important decisions have been made and are now being carried out. By doing this, the bonds between these influenza networks have been tightened, allowing a closer cooperation.

You will notice that a questionnaire is included in this bulletin. With a number of short questions, ESWI aims to assess your appreciation of the bulletin. Your input can help us to improve it, and therefore I kindly invite you to fill out the questionnaire and to return it to our management's offices in Antwerp, Belgium. The questionnaire can also be found on the ESWI website at [www.eswi.org](http://www.eswi.org). In the end, the battle against influenza can only be won with your help.

A.D.M.E. Osterhaus  
Chair, ESWI

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## INFLUENZA PANDEMIC PREPAREDNESS: THE EUROPEAN VACCINE MANUFACTURERS' PERSPECTIVE

Vaccination will be the most effective way of controlling influenza in the event of a pandemic, when a specific vaccine will have to be rapidly developed and produced in large quantities. If an influenza pandemic occurs before adequate preparation has been made, there is a substantial risk of delayed supply, including possible measures by countries with production facilities to limit or prevent export to countries without such facilities. To optimise response to this potential threat, the European Union (EU) and several member states (MS) have developed pandemic preparedness plans. The World Health Organization (WHO) has provided detailed guidance on the content of these plans, including the need to ensure adequate supplies of pandemic vaccines. The European Vaccine Manufacturers (EVM<sup>®</sup>) are committed to addressing the challenges posed by the threat of an influenza pandemic.

*The European Vaccine Manufacturers are committed to addressing the challenges posed by the threat of an influenza pandemic.*

### Vaccine availability

The availability of influenza pandemic vaccines relies on several factors, the most important being to adapt production capacities to prevent inadequate and delayed supply. Influenza vaccine manufacturers located in the EU (France, UK, The Netherlands, Germany and Italy) currently produce 70% of the global supply (260 million doses in 2003), of which >50% are distributed outside the EU. During a potential influenza pandemic, a total of 450 million European citizens could be protected. Several factors first need addressing:

- The vaccine industry lacks information about the amount of vaccines that would be required in a pandemic. The available facilities would be the same as for inter-pandemic vaccine production. Therefore, it is essential to establish production forecasts, given that it takes 3–5 years to develop, build and validate a new production facility.
- Pandemic vaccine production capacities will be influenced by the fact that the vaccine will be monovalent. This could increase the amount of vaccine by

1.5–3 times, assuming that a one or two-dose schedule with the same antigen content is necessary.

- The production processes (whole versus split virion or subunit vaccines), use of adjuvants or multidose presentations and the availability of cell-culture processes for industrial production also represent key technological challenges.
- Development and production are exposed to constraints such as intellectual property rights. For example, the use of reverse genetics to prepare pandemic vaccine strains; genetically modified organisms (GMO) regulations in the EU; the risk of producing vaccines that would not be used (false alarm); competition with ongoing production of regular inter-pandemic influenza vaccines and other new human vaccines, leading to potential disruption; liability issues relating to a vaccine developed in an emergency and used in mass vaccination campaigns.

To protect 50–100% of the 450 million EU inhabitants in the case of a pandemic, 150 million doses of vaccine need to be distributed during inter-pandemic periods. An increase in vaccine coverage from the current 20% to 33% of the population would be an appropriate way to get production capacity to acceptable levels.

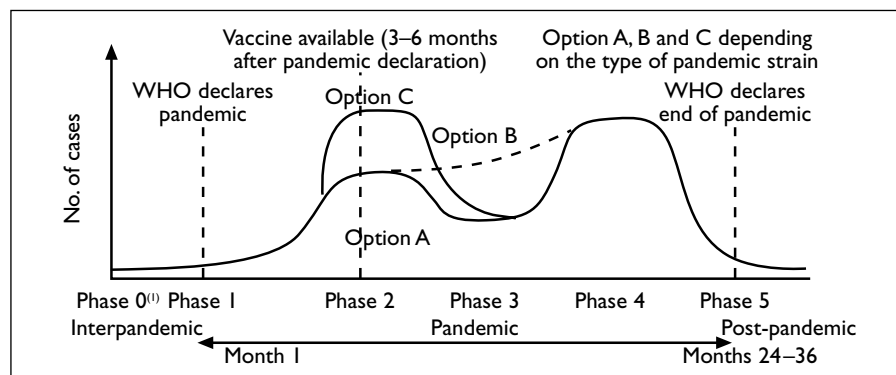
*To protect 50–100% of the 450 million EU inhabitants ... 150 million doses of vaccine need to be distributed ...*

### Pandemic preparedness plans and influenza vaccine development, production and supply

Influenza pandemic preparedness plans consist of identifying levels of alerts and different phases for which specific actions have to be conducted. This also applies to vaccine manufacturers who have to conduct specific actions during these different phases to ensure the development, production and supply of vaccines (Figure 1).

- **Phase 0:** the inter-pandemic period when manufacturers should develop and license pandemic-like vaccines and the pandemic vaccine itself and adapt production facilities.
- **Phase 1:** confirmation of pandemic onset when production will start and implementation and supply strategies will be established. The vaccine should be available 3–6 months after pandemic declaration.
- **Phase 2:** global spread. Maximum production effort, during which manufacturers should ensure the quality of vaccine distribution and active monitoring of vaccine safety and effectiveness.
- **Phase 3:** end of the first wave. Production planning is now a major challenge; there is the possibility of a second wave or a return to an inter-pandemic period.
- **Phase 4:** 3–9 months from the end of the first wave, with a second wave of regional outbreaks. Industry faces difficulties in estimating remaining needs for pandemic vaccines while switching back to inter-pandemic vaccines.

**Figure 1. EVM modelling of the pandemic phases (adapted from WHO influenza pandemic preparedness plan). Options A, B and C are possible different pandemic waves to be faced.**



- **Phase 5:** end of the pandemic. Indices of influenza activities return to interpandemic levels.

### EVM proposal for action

In order to adequately address the challenges posed by a possible influenza pandemic, the EVM have proposed to the MS, with EU support, long-term commitments concerning the following topics.

#### 1. Research and development activity and fast-track regulatory approval

The EVM are committed to developing, and getting marketing authorisation for, pandemic vaccines. The EU and MS should support research and development and rapid registration of pandemic-like vaccines.

#### 2. Supply capacity

Supply needs for influenza pandemic vaccines should be anticipated between MS and EVM members. MS should determine their needs for a pandemic and adapt their interpandemic use accordingly. Therefore, to potentially protect 50–100% of the EU population in case of a

pandemic, vaccination coverage rates in the interpandemic period should increase from 20% to 33% (by extending national recommendations to younger age groups; 'over 50 years and children'). This should answer a public health need by reducing influenza morbidity and outbreaks as recommended by the WHO. To meet vaccine demand in the case of a pandemic, the EVM are committed to increase their production capacities in line with the commitment of MS.

#### 3. Equitable distribution

In the event of a pandemic, ensuring equitable distribution between countries is a critical aspect of disease control. Collaboration is needed to ensure vaccine distribution in accordance with public health needs inside and outside the EU. The pricing of influenza pandemic vaccine in European MS could represent a potential issue if it is not properly addressed and anticipated. Establishing a pricing policy would contribute to optimal access for European citizens regardless of national status.

#### 4. Liability

Vaccine manufacturers are committed to complying with requirements related to the quality of vaccines. Exposure to liability will differ from normal marketed vaccines, and will relate to a vaccine developed in an emergency and used in mass vaccination campaigns.

The above commitments are closely related and should be considered as a global approach to cover all issues that may impact the relevant and timely availability of influenza vaccines in a pandemic. This approach stresses the definite need for a partnership between EVM members and MS, with the support of the EU, to ensure risk sharing in this complex and unpredictable situation that needs to be anticipated and that will require exceptional measures.

\*Aventis Pasteur, Aventis Pasteur MSD, Baxter, Berna Biotech, Chiron Vaccines, GlaxoSmithKline Biologicals, Solvay Pharmaceuticals, Wyeth.

**D. Hoch**

*President of the European Vaccine Manufacturers*

## WHO RECOMMENDATIONS FOR INFLUENZA VACCINE COMPOSITION

It is recommended that vaccines for the 2004–2005 northern hemisphere influenza season contain:

- an A/New Caledonia/20/99(H1N1)-like virus
- an A/Fujian/411/2002(H3N2)-like virus\*
- a B/Shanghai/361/2002-like virus.\*\*

Recently, in Europe, the B/Jiangsu/10/2003 has been recommended as the vaccines' B/Shanghai/361/2002-like strain, the strain recommended by the WHO (<http://www.emea.eu.int/pdfs/human/bwp/110404en.pdf>). This is also an acceptable strain for the USA (The Vaccine and Related Biological Products Advisory Committee, 17 March 2004).

For more detailed information please see:

Recommended composition of influenza virus vaccines for use in the 2004–2005 influenza season. *Wkly Epidemiol Rec* 2004; 79: 88–92.

Source: WHO Global Influenza Surveillance Network

\*The currently used vaccine virus is A/Wyoming/3/2003. A/Kumamoto/102/2002 is also available as a vaccine virus.

\*\*Candidate vaccine viruses include B/Shanghai/361/2002 and B/Jilin/20/2003 which is a B/Shanghai/361/2002-like virus.

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**www.eswi.org**

## IS THERE A NEED FOR MONITORING THE SEVERITY OF INFLUENZA?

The 2003–2004 influenza season in the northern hemisphere started abruptly with reports from Ireland of severe influenza at a boarding school and from the UK of six influenza deaths in children. The reports created alarm and requests were sent to member countries of the European Union from various organisations, asking for information on unusual events. In the USA, 129 deaths among children have been reported (10 February, 2002). It has not been possible to estimate whether this indicated a more pathogenic infection than normal since there were no comparative data. These events clearly point to the need for monitoring not only seasonal incidence, but also severity of influenza. The A/Fujian/411/2002-like viruses dominating this year seem to have affected mainly children. It could be that the proportion of children getting severe infections is no higher than normal, but it could also be that the virus *per se* is more pathogenic than its predecessors. Within existing influenza monitoring systems this cannot be firmly evaluated.

Individual influenza virus lineages have differing virulence, depending on the phenotype [1,2]. At the extreme end are the highly pathogenic avian influenza viruses (HPAI) that harbour influenza A/haemagglutinin 5 (H5) or H7. One mechanism by which these viruses become more pathogenic is well documented. Basic amino acids are accumulated at the cleavage site of the haemagglutinin (HA), which allows for intracellular cleavage of the HA and renders the HA virus independent of extracellular proteases. Through this method viruses acquire the potential for systemic spread. Recent data also indicate that these viruses are more efficient at inducing pro-inflammatory cytokines, particularly tumour necrosis factor- $\alpha$  and interferon- $\beta$ , than circulating H1 and H3 viruses. An intense cytokine response may aggravate the symptoms of influenza upon infection in humans [3], but inhibition of parts of the response may also be deleterious. The Spanish influenza was the most pathogenic influenza infection adapted to man during the 20th century. Sequencing old material and using reverse genetics have led to the discovery of mutations in this virus, indicating independence of HA cleavage from exogenous proteases. Escape from the effect of interferon mediated by the non-structural NS1 protein is another molecular basis for the pathogenicity of the Spanish influenza virus [4].

The Asian influenza of 1957, caused by A/H2, resulted in more deaths among

children and pregnant women than its successor, the Hong Kong A/H3 virus of 1968. The controversial reports on increased incidence of schizophrenia after influenza during pregnancy could also be related to a particular virus phenotype. Pathogenicity factors for the A/H2 virus have not been reported, but reverse genetics could provide a means for their identification. Also, H3 is regarded as being more pathogenic than the influenza B and H1 viruses circulating today. Upon co-circulation of influenza H3 viruses with H1 and/or B viruses, a higher proportion of A/H3 infections are observed in hospitalised patients compared with patients in the community. The reasons for this are not known but could be explored using modern technology.

A severe clinical outcome from influenza may be the result of the virus' pathogenicity, but may also result from subsequent complications such as bacterial super-infections. Attention should therefore also be given to viral mechanisms that may aid the occurrence of bacterial super-infections. More research is needed in this area to identify specific viral determinants involved.

Today, influenza vaccines and efficient antiviral agents are available. Their use is widely recommended in patients at risk of severe influenza. Children from 6–23 months are included in this risk group in the USA, but not in Europe. These recommendations are not generally agreed with in Europe, but if we could have predicted the effect of the A/Fujian influenza outbreak, in terms of the number of sick children and the number with a severe outcome, simultaneously with the selection of the vaccine strain, we might have encouraged more extensive vaccination and the production of more vaccine for the season. A more liberal use of antivirals may also be indicated if we know that a predicted epidemic strain is likely to be highly pathogenic. With early warning, production can be adapted.

It will be a major research effort to identify pathogenicity markers with certainty, especially since the effects in mice and men are not identical. Improved understanding of the protective immunity in the population, considering both the humoral and cellular immune responses, should provide better predictions of influenza impact. Mathematical modelling taking into account antigenic distance between influenza variants, as well as previous impact related to age groups and time frame of influenza virus type and subtype circulation, may provide additional clues.

The first thing we need to do is to improve our knowledge of the clinical outcome of circulating strains. Reporting respiratory deaths in children could be considered, and wider use of molecular techniques for the determination of pathogens could be performed on post-mortem material. Adding 'sentinel hospitals' to existing surveillance systems would also be useful. Calculating the ratio between the number of hospitalised patients with suspected influenza and the number of outpatients, related to age groups, could be another tool to provide information about the virulence of circulating strains. A systematic follow-up of the clinical outcome of virologically confirmed cases from the community would be yet another possibility. Data could then be related to genotype and phenotype of the seasonal virus. In some years there would probably be enough data to predict, not only antigenicity, but also pathogenicity of the expected strains. Such knowledge would aid in the planning of a variety of healthcare resources related to influenza activity.

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## ESWI'S COLLABORATION WITH NATIONAL NETWORKS

As mentioned in the previous bulletin, ESWI has a new initiative to liaise with major stakeholders and policy makers at a national level, to improve influenza awareness and current influenza prevention programmes. Following initial workshops to formulate national action plans for an improved influenza control programme; tailor-made projects have been prepared and are in progress.

During the preparations for the initial workshops and during the meetings, we consistently observed that many of the key stakeholders involved in implementing effective programmes were not accustomed to meeting and communicating effectively. For example, we noticed a remarkable, although unintended, barrier of communication between representatives of public health organisations and general practitioners. However, both of these key stakeholders,

who have different roles in national programmes for the control of influenza, showed great interest in improving influenza control programmes. Despite our efforts, we observed that neither group are currently used effectively, due to an obvious lack of synergy between the different parties activities. Following the ESWI-initiated workshops, the stakeholders in the different countries are now working together to initiate projects and realise their jointly formulated national action plans for an improved control of influenza. Wherever possible, ESWI will provide help and play an active facilitating role in the national networks. By collaborating with these networks, ESWI strives to obtain maximal effects of its efforts.

Following our observation of unintended, but nevertheless existing, communication barriers between different stakeholders, we strongly recommend that all those involved

in national influenza prevention programmes evaluate their communication lines with other stakeholders and, if necessary, take steps to improve them. We strongly believe that effective communication and collaboration is an essential prerequisite for effective influenza prevention programmes to succeed at a national level.

The current avian influenza episode once again warns us that we should not underestimate the threat of an emerging influenza pandemic. The first step to prepare for the control of a future pandemic is the routine control of annual recurring influenza epidemics. Therefore, the implementation of effective annual national influenza prevention programmes should not be delayed any longer.

**B. Palache**  
ESWI adviser

## FLUMIST™: HISTORY AND FUTURE

In June 2003, a trivalent live attenuated influenza vaccine (LAIV), Flumist™, was approved for use in the USA in healthy children and adults aged 5–49 years, not at high risk for complications of influenza. This intranasally administered vaccine contains cold-adapted, live, attenuated influenza viruses expressing the same haemagglutinin (HA) and neuraminidase (NA) antigens as the strains in the currently available trivalent inactivated vaccine. LAIV was a welcome alternative to inactivated split virus vaccines that require intramuscular injection. LAIV is indicated for healthy individuals who want to avoid contracting influenza or transmitting it to high-risk contacts. Concerns have been raised about potential transmission of the live, albeit attenuated, viruses contained in LAIV. These concerns have led to variable restrictions of its use in high-risk settings. The vaccine must be stored below  $-15^{\circ}\text{C}$  to maintain LAIV viability. This temperature is below that of a standard refrigerator, so special packaging is required to maintain the cold chain to preserve viability. These factors contributed to a slow uptake of LAIV until the early onset of influenza in October 2003 increased the demand for, and diminished the supply of, split-virus vaccine. The use of LAIV was then promoted in the indicated population.

LAIV is produced from cold-adapted strains of influenza A and B into which the genes encoding the HA and NA antigens for the

current vaccine strains have been inserted. The surface glycoprotein components are identical to those contained in the split-virus vaccine for a given year. The mechanism of protection conferred by LAIV appears to be mediated by serological and mucosal antibodies, although a sole measure of protection has not been defined. There is also a theoretical benefit of more effective stimulation of the cell-mediated immune response with live viruses compared with killed viruses in standard vaccines. However, this was not demonstrated in older adults when LAIV was administered in addition to the standard parenteral killed vaccine.

LAIV is well tolerated. The attenuated live viruses produce mild flu-like symptoms related to influenza virus infection of the nasal epithelium in 19–44% of recipients compared with 14–27% of placebo recipients. This may in part be due to the cold adaptation of these viruses, which limits viral replication to areas with cooler temperatures such as the upper airways. The cold-adapted strains replicate efficiently at  $25^{\circ}\text{C}$ , whereas replication of the wild-type virus is restricted at this temperature. The introduction of this vaccine has raised concerns relating to the potential for viral shedding from the nasal passages of vaccinated individuals, causing transmission to high-risk contacts. Clinical trials of LAIV in immunocompromised hosts, such as those who are HIV-positive, have not demonstrated any increase in adverse effects

of vaccination, prolonged viral shedding, or evidence of reversion to the wild-type virus compared with healthy controls. Further studies are needed to confirm that the risk of viral transmission causing illness in high-risk contacts remains acceptably low.

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## EU WORKSHOP ON INFLUENZA

On 6 November 2003, a European Workshop on Human Pandemic Influenza Vaccines took place in Brussels, Belgium. More than 70 people from all over Europe attended the meeting, including European Union (EU) and World Health Organization officials, influenza experts, academics and representatives from industry. The main meeting objective was to discuss pandemic preparedness and minimise the risks from a European perspective. The meeting focused on the need for a coordinated community response in case of a pandemic by:

- Identification of the key components of a response.
- Identification of EU Commission and European Agency for the Evaluation of Medicinal Products (EMA) activities facilitating and coordinating member states activities.
- Setting EU response into a wider international context.

Since vaccines are to play a key role in containing the effects of a future pandemic, issues related to pandemic vaccines were

discussed extensively (also see the report below by L.C. Lambert and S. Kim on the NIAID meeting in the USA). The need for registration requirements in relation to the many 'unknowns' for a future pandemic vaccine was particularly addressed. The concept of a 'mock-up core-dossier' to be submitted for approval in advance of a real pandemic was introduced. The core-dossier for a pandemic vaccine needs to contain the routine information for any influenza vaccine including serological data from clinical studies with a 'mock-up' pandemic virus strain. The mock-up dossier would need to contain dose response data and data from adjuvanted and non-adjuvanted vaccine formulations, if an adjuvant is to be used in the pandemic vaccine formulation. The meeting recognised that the current Committee for Proprietary Medicinal Products (CPMP) serological criteria for the licensing of annual influenza vaccines are not validated for the pandemic situation. However, due to lack of other validated predictive outcome measures, no other requirements were considered practical, except for the

measurement of neutralising antibodies. A clinical trial will also be needed to ascertain the safety of the mock-up pandemic vaccine.

Once a mock-up dossier has been approved, a licence for the real pandemic vaccine for the member states of the EU will be granted. Manufacturers will provide the necessary variation file to reflect the real pandemic vaccine strain. The licence for the real pandemic vaccine will be granted before clinical data are collected and reported to the regulatory authorities. This regulatory mechanism provides an appropriate balance between making pandemic vaccines available as soon as possible in case of a global emergent situation, and having sufficient confidence in the safety and efficacy of a new vaccine to be distributed on a global scale.

A note for guidance for the registration of pandemic influenza vaccines in the member states of the EU, along these lines, will be issued by the EMA shortly.

B. Palache  
ESWI adviser

## PANDEMIC PREPAREDNESS: DEVELOPING A CLINICAL TRIAL RESEARCH PLAN

On 22–23 September 2003, the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health in Bethesda, Maryland, USA, held a workshop to develop a clinical trial plan for pandemic influenza vaccines. Forty-eight people took part, including representatives from US and international agencies, academic research institutions and vaccine manufacturers.

The workshop objectives were to:

- Review clinical studies that have been previously conducted with vaccines containing novel haemagglutinins (HAs) and neuraminidases (NAs).
- Discuss manufacturing and regulatory issues related to the production and clinical evaluation of pandemic influenza vaccines.
- Identify pandemic reference strains, reagents and needed vaccines.
- Determine the types of vaccine studies that need to be conducted during inter-pandemic periods to build a scientific base of knowledge and to improve preparedness for responding to future pandemics.

- Identify key points for the design of a clinical trial protocol to evaluate a pandemic vaccine.

Key lessons learned from past clinical trials of pandemic influenza vaccines included understanding that increasing purity of a vaccine is likely to reduce its reactogenicity and increasing the vaccine dose, giving two doses or using an adjuvant has been shown to increase the antibody response. Priming is considered a major factor for determining response to one dose of vaccine, but it is recognised that vaccine efficacy is likely to be variable and may not relate well to serum HA antibody titres. Results from several recent clinical trials using novel HAs noted relatively poor immune responses in healthy adults and, as a result, more studies are needed to determine if the HAs are truly less immunogenic in some unique way, or whether these results reflect what would be expected from any vaccine used in a group that was totally unprimed.

The decision on which animal influenza virus strains are of the highest priority for use in the production of vaccines for clinical trials is part of ongoing discussions by the World Health Organization (WHO). Priority is based on whether or not a particular strain

has caused disease in humans or has recently spread in mammals, and how widespread the strains are in avian species, particularly domestic birds in close contact with humans. At the NIAID meeting, participants agreed that the highest priority for future vaccine studies should be animal influenza viruses that have recently infected humans, particularly H5 influenza. Strains of H5 influenza are known to have caused infections and deaths in 1997 and 2003 so much more clinical information on H5-based influenza vaccines is urgently needed. It was also noted that the continual appearance of antigenically distinct H5 strains might hinder efforts to develop a library of vaccine reference strains against all subtypes with pandemic potential.

*Strains of H5 influenza are known to have caused infections and deaths . . . more clinical information on H5-based influenza vaccines is urgently needed.*

Biosafety issues in the context of the production of influenza vaccines derived from

reassortant avian influenza strains were also discussed at the meeting. Safety and risk must be assessed from the standpoint of both humans and the environment. The removal of HA multibasic amino acids is a good safety procedure as evidence indicates that it reduces pathogenicity for birds and mammals. Pathogenicity should then be tested in chickens, ferrets and mice if appropriate.

A description of how influenza vaccines are currently licensed in Europe was presented, including a 73-day fast-track procedure for the annual update of European influenza vaccine licences and the review of data from small clinical studies. Currently an Expert European Panel is considering a plan that would institute a new 'rolling review' process to permit the ongoing review of pre-clinical and clinical pandemic vaccine data as they become available. A representative from the US Food and Drug Administration (FDA) reviewed the routine licensing actions for influenza vaccines in the USA, noting that a manufacturing supplement to an existing licence for annual strain changes does not require clinical data for FDA approval. During an influenza pandemic, the new pandemic strain used in a US-licensed manufacturing process would be reviewed as a manufacturing supplement for a strain change, and either a wild-type or a genetically engineered reference strain acceptable to the WHO could be used to produce the vaccine. Additional pandemic preparedness activities that should be done now include manufacturing investigational influenza vaccines using subtypes with pandemic potential according to current licensed processes where feasible. Evaluating products for safety and efficacy is crucial to maintaining confidence in the vaccines after the pandemic is over. The FDA has mechanisms for dealing with novel vaccines in a pandemic

situation, such as informed consent under an investigational new drug application.

An inventory of the currently available reference strains from around the world was generated for the meeting. The list included a 2003 H7N7 reference strain from The Netherlands, two 2003 H5N1 strains from a clinical isolate in Hong Kong, all produced using reverse genetics, and a G9-like H9N2 candidate produced by classical reassortment. The production of other reference strains were reported to be 'in progress', including H7N1 from a highly pathogenic Italian virus, a H7N7 using the apathogenic H7 and H10N7 from The Netherlands and a North American H7N3.

Vaccine manufacturers noted that they are likely to be limited in their choice of strains by local regulatory and quarantine authorities. Other issues discussed regarding genetically engineered reference strains included their inclusion as genetically modified organisms by European regulatory authorities, intellectual property issues and the US Select Agent Rule that covers highly pathogenic H7 and H5 subtypes of influenza A. Research reagents for numerous influenza A subtypes are available globally through the NIAID-influenza repository. It was recommended that manufacturers who produce investigational lots of vaccines for clinical trials make small amounts of purified HA available for production of standardised reference reagents to assess vaccine potency.

During the next pandemic, vaccine manufacturers will need to be told how to formulate a vaccine that has the greatest likelihood of providing protection against the virus. To produce this information additional clinical trials must be conducted during interpandemic periods. Key points for the design of these clinical trials were

discussed at the workshop and included developing clinical trial protocols to look at the optimal use of antigens and conducting simple, large trials to find statistically significant differences for dose range and dosing intervals among different populations. To date, clinical studies in humans using avian influenza viruses have shown that a single measure of antibody response (i.e. HA inhibition assay) is not enough. Assessing the neutralising antibody response is potentially useful but may require additional optimisation. Other immunological measurements that could be used in trials include single radial haemolysis, NA antibody, secretion antibodies and cell-mediated immunity. If feasible, immunogenicity assessments should be conducted at a single laboratory to make the data more meaningful.

There was an overall consensus that when a novel HA strain is being evaluated, safety and immunogenicity studies in adults should be conducted first, as they may provide much of the needed information. However, studies in children must be done to generate safety and reactogenicity data. As the size of the elderly population is growing globally, they too should be included in the planning of pandemic vaccine trials.

This article is based on formal presentations by the following and subsequent discussions with meeting participants: **R. Couch**, Baylor College of Medicine, USA; **N. Cox**, CDC, USA; **L. Lambert**, NIAID/NIH, USA; **K. Midthun**, US FDA; **K. Nicholson**, Leicester Royal Infirmary, UK; **J. Treanor**, University of Rochester, USA; **K. Stohr**, WHO, Switzerland; **R. Webster**, St. Jude Children's Research Hospital, USA; **J. Wood**, NIBSC, UK.

L.C. Lambert, S. Kim  
NIAID, USA



## CALENDAR OF EVENTS

DATE/VENUE	TITLE	ORGANISER/SECRETARIAT
1-4 May 2004 Prague, Czech Republic	14th European Congress of Clinical Microbiology and Infectious Diseases	14th ECCMID c/o AKM Congress Service PO Box CH-4005 Basel Switzerland Phone: +41 61 686 77 11 Fax: +41 61 686 77 88 E-mail: info@akm.ch
2-6 May 2004 Tucson, USA	17th International Conference on Antiviral Research	17th ICAR Courtesy Associates 2025 M Street, NW, Suite 800 Washington, DC 20036 USA Phone: +1 202 973 8690 Fax: +1 202 331 0111 E-mail: isar@courtesyassoc.com
23-27 May 2004 New Orleans, USA	104th General Meeting of the American Society for Microbiology	American Society for Microbiology 1752 N Street, NW Washington, DC 20036-2904 USA Phone: +1 202 942 9356 Fax: +1 202 942 9340 E-mail: meetings@asmusa.org
24-26 May 2004 Lisbon, Portugal	1st International Conference on Influenza Vaccines for the World (IVW)	Caroline Sumner IVW 2004 Conference Manager Meetings Management The Barn, Rake Meadow, Station Lane, Milford Surrey GU8 5AD UK Phone: +44 (0) 1483 427770 Fax: +44 (0) 1483 428516 E-mail: csumner@meetingsmgmt.u-net.com
24-26 May 2004 Arlington, USA	Seventh Annual Conference on Vaccine Research	Sharon Cooper-Kerr/Sheena Majette Seventh Annual Conference on Vaccine Research National Foundation for Infectious Diseases 4733 Bethesda Avenue, Suite 750 Bethesda, Maryland 20814-5278 USA Phone: +1 301 656 0003 x19 Fax: +1 301 907 0878 E-mail: vaccine@nfid.org
1-4 June 2004 Amsterdam The Netherlands	Conference of the European Society of General Practice/ Family Medicine – WONCA	c/o WONCA Europe 2004, Secretariat Dutch College of General Practitioners PO Box 3231 3502 GE Utrecht The Netherlands Phone: +31 30 288 1700 Fax: +31 30 287 0668 E-mail: evenementen@nhg-nl.org
5-9 September 2004 Madrid, Spain	7th Annual Meeting of the European Society for Clinical Virology: EuroVirology 2004	Grupo 7 Viajes C/ General Moscardó 32, 1º A 28020 Madrid Spain Phone: +34 91 534 05 40 Fax: +34 91 535 26 01 E-mail: secretariat@madridvirology2004.com

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