



INFORMATION AND NEWS ON INFLUENZA

**EDITORIAL**

As a consequence of the avian H5N1 influenza outbreak in Hong Kong in 1997/98 [1], the World Health Organization, in collaboration with the European Scientific Working group on Influenza (ESWI), has developed and published its first 'pandemic preparedness plan' [2]. The objective is to help national public health authorities to develop local contingency plans in case of a pandemic threat. The Hong Kong episode and subsequent isolations of avian influenza viruses in the human population should be considered as a warning that a pandemic may indeed occur in the future, and should not be considered as a remote theoretical possibility.

In a further attempt to reduce the impact of influenza on a global scale, the WHO, again in collaboration with ESWI and other public health authorities, has undertaken a project to draft recommendations for annual influenza prevention activities. As with the 'pandemic preparedness plan', the objective of these recommendations is to help national health authorities, both in developed and developing countries, to formulate or modify their own influenza recommendations.

In this issue, Dr Kendal explains the process that will lead to the first WHO-directed recommendations for the prevention and control of influenza. ESWI is pleased that these recommendations will be presented and discussed during the 'Options for the Control of Influenza IV' meeting in September in

Crete, Greece. We hope that they will be instrumental in encouraging international health authorities to endorse and stimulate effective influenza control programmes, possibly leading to a reduced impact of the disease on a global scale.

For the first time, ESWI is organising a course on basic laboratory techniques, to be held at the Pasteur Institute in Paris, from 17–21 July (course director: Professor van der Werf). The aim is to teach the latest techniques to less experienced laboratory technicians and researchers from influenza research institutes, surveillance centres and laboratories. The course – 'Basic laboratory techniques in influenza diagnostics' – was first announced in *Influenza* bulletin number 11 and on ESWI's website ([www.eswi.org](http://www.eswi.org)). Late applications for the few remaining places on the course can be made via ESWI's website.

Preparations for the 'Options for the Control of Influenza IV' meeting in September are progressing well. ESWI is honoured to organise this prestigious international meeting, in which there is a tremendous interest. We would like to acknowledge the efforts of many people in the organisation of the meeting. The professional support from Biomedica and the active help of coordinators, organising and scientific committee members, advisors, chairpersons, invited speakers, and all those who have submitted abstracts, are ensuring that the 4th meeting in the series will again be a successful event.

ESWI also wishes to express its gratitude to the sponsors who are contributing so generously toward the meeting.

A.M. Palache

ESWI Editorial Board

**References**

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2. WHO, Geneva 1999. Influenza pandemic preparedness plan. Responding to an influenza pandemic or its threat: The role of WHO and guidelines for national or regional planning.

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## SYMPOSIUM ON INFLUENZA AND OTHER RESPIRATORY VIRUSES

The first day of the International Symposium held in Grand Cayman, British West Indies, in December 1999, focused on the impact of respiratory viruses on immunocompromised individuals. Dr Per Ljungman of Huddinge Hospital, Sweden, described results of a European study involving approximately 2,000 bone marrow transplant patients. Those with respiratory syncytial virus (RSV) and upper respiratory tract infection symptoms had a survival rate of 90%, compared with 50% for those with pneumonia. An improved survival rate (40–55%) was seen in patients with lower respiratory tract infections who received ribavirin with or without immunoglobulin compared with untreated patients (28%).

Another study, described by Dr Marie Griffin from Vanderbilt University, Nashville, USA, found that in HIV-infected women, influenza increased the risk of hospitalisation for acute cardiopulmonary conditions. Despite the limited risks of increasing transient HIV viraemia, Dr Griffin added that significantly less respiratory illness is seen in influenza vaccine recipients compared with non-vaccinated individuals.

### Pandemic influenza: are we prepared?

Increased communication and co-ordination between the WHO and national centres are crucial for a rapid response to an emerging pandemic – according to an expert panel who gathered to discuss public health issues involved with influenza pandemics. A major obstacle is the time taken to create a new vaccine – at present estimated at a minimum of 12 weeks. Production and appropriate distribution of drugs is also a major concern and panellists were divided in their opinion over the use of antiviral drugs in a pandemic.

The source of human influenza and the next pandemic was discussed by Dr Robert Webster of St Jude Children's

Research Hospital, Memphis, USA. Wild aquatic birds – the main reservoir for influenza – transmit viruses to other birds and animals. Pigs commonly act as a link between birds and humans, but in the 1998 Hong Kong influenza outbreak, direct transmission to humans occurred. According to epidemiological evidence, interspecies activity may be important in disease transmission. Increased opportunities for transmission between pigs, chickens and humans could result in the next influenza pandemic.

### Diagnostic dilemmas in influenza

The second day of the Symposium focused on the diagnosis of influenza. Dr Jeffery Taubenberger from the Armed Forces Institute of Pathology, Washington, USA, discussed results of haemagglutinin gene sequencing of samples conserved from victims of the 1918 influenza pandemic. Although many avian characteristics are present, the 1918 human strain was closely related to swine viruses and probably acquired its virulent characteristics in mammals.

Despite advances in the diagnosis of influenza, Dr Annika Linde of the Swedish Institute for Infections and Disease Control, Stockholm, Sweden,

*Increased opportunities for transmission between pigs, chickens and humans could result in the next influenza pandemic.*

stressed the importance of assessing commercially available tests in standardised clinical studies. Dr Linde's studies showed that antigen-based detection tests are 60–90% specific, suggesting that the specificity should be improved. Newer tests based on genome amplification are of a similar sensitivity to direct immunofluorescence performed in specialised laboratories, but the choice of

primers used is controversial. Dr Linde stressed that culture should also be used for surveillance of circulating strains of influenza.

A real-time quantitative PCR amplification assay, the *TaqMan* PCR detection system, was assessed for the detection of influenza A by Dr Leontine van Elden from the University Medical Centre, Utrecht, The Netherlands. Dr van Elden explained that diluted samples provided very low detection rates, but the method was extremely specific for a variety of influenza A viruses, without cross-reacting with other respiratory viruses. Compared to serology, the real-time PCR method was 82% sensitive, compared with 38% for culture, 63% for immunofluorescence and 94% for an in-house nested PCR method.

### The role of neuraminidase inhibitors in influenza

Information from analysis of the structure and chemical composition of the catalytic site of neuraminidase has led to the development of new inhibitors such as zanamivir and oseltamivir. The final day of the Symposium included discussions on the future prospects for neuraminidase inhibitors. Dr Noel Roberts from Roche Products, Welwyn Garden City, UK, presented results in which resistance to oseltamivir was detected in only 1% of approximately 600 patients tested. New neuraminidase inhibitors are in development and, according to Dr Diane Young from the Pharmaceutical Research Institute, New Jersey, USA, a new oral compound, RWJ-270201, showed favourable in-vitro activity against influenza A and B compared to zanamivir and oseltamivir. Further analysis of the neuraminidase molecule will no doubt give rise to additional compounds active against influenza viruses.

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## INFLUENZA VACCINE STRAINS FOR THE 2000–2001 SEASON

The World Health Organization (WHO) recently made recommendations for the composition of influenza virus vaccines for use in the Northern Hemisphere 2000–2001 season [1]. Virus activity between October 1999 and February 2000 was largely due to influenza A (H3N2) viruses, with moderate to severe outbreaks in the Americas, Asia and Europe. In contrast to the previous season, influenza A (H1N1) activity was widespread, with outbreaks in Spain and parts of Asia. Influenza B viruses circulated at low levels throughout the world.

### Virus characterisation

The majority of influenza A (H3N2) viruses were antigenically closely related to A/Moscow/10/99 and A/Panama/2007/99, and often there was also similarity to the vaccine strain, A/Sydney/5/97. Most of the influenza A (H1N1) viruses were antigenically related to A/New Caledonia/20/99, but could be distinguished from the vaccine

strain A/Beijing/262/95. All the influenza B viruses examined resembled B/Beijing/184/93 and the widely used vaccine strain B/Yamanashi/166/98. B/Shangdong/7/97-like viruses were not isolated.

### Vaccine recommendations

Current vaccines containing A/Sydney/5/97 (H3N2), A/Beijing/262/95 (H1N1) and B/Yamanashi/166/98 were clinically evaluated in adults and the elderly, and their post-immunisation antibodies tested against the vaccine viruses and recent influenza strains (Table 1).

The WHO recommends the following strains be included in vaccines for the 2000–2001 season in the Northern Hemisphere:

- an A/Moscow/10/99 (H3N2)-like virus

- an A/New Caledonia/20/99 (H1N1)-like virus
- a B/Beijing/184/93-like virus.

The WHO also advises that the A/Panama/2007/99 is very similar to the A/Moscow/10/99 strain, and that the most widely used B/Beijing/184/93-like vaccine strain is B/Yamanashi/166/98.

At the European Union Committee for Proprietary Medicinal Products, the WHO vaccine recommendations were accepted. The inclusion of the high-yielding reassortants RESVIR-17 (antigenically similar to A/Panama/2007/99 and A/Moscow/10/99) and IVR-116 (antigenically equivalent to A/New Caledonia/20/99) were accepted for use in EU vaccines.

J.M. Wood

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**Table 1. Responses in adults and the elderly immunised with influenza vaccines.**

Vaccine strain	Percentage satisfactory response to vaccine virus (range) <sup>a</sup>	
	Adults	Elderly
A/Sydney/5/97 (H3N2)	86 (67–100) <sup>b</sup>	77 (30–100) <sup>b</sup>
A/Beijing/262/95 (H1N1)	84 (63–100) <sup>c</sup>	57 (33–100) <sup>c</sup>
B/Yamanashi/166/98	94 (70–100)	75 (50–100)

<sup>a</sup>Satisfactory response is a haemagglutination inhibition titre of  $\geq 40$

<sup>b</sup>Frequency and titre of antibody were reduced against recent isolates

<sup>c</sup>Frequency and titre of antibody were reduced against A/Caledonia/20/99-like viruses

Source: WHO recommendations for vaccine development in the Northern Hemisphere, 2000–2001.

## RECOMMENDATIONS FOR ANNUAL PREVENTION OF INFLUENZA

ESWI, who previously assisted the WHO to develop pandemic planning guidelines, is now supporting the WHO to develop updated recommendations for Annual Prevention of Influenza. A group of experts from Australia, Europe, Japan and the USA have discussed the type of document that would assist public health authorities in countries having different levels of knowledge on influenza and its control. A draft document was prepared in early 2000, and the latest

recommendations will be reviewed by a larger group of experts at a WHO consultation this summer. ESWI, whose members have been involved throughout the process, has provided time at the end of the 'Options for the Control of Influenza' meeting in September, for results to be presented by the WHO. The recommendations are expected to indicate important omissions in the knowledge and control of influenza and should stimulate efforts to obtain information for inclusion in future revisions.

Recurrent epidemics of influenza have a large cumulative effect on morbidity and mortality in many countries.

Implementation of the recommendations will be an important public health measure in its own right. Furthermore, the ability to respond to any future threat of, or actual, pandemic will be improved by a global public health infrastructure for influenza prevention.

A.P. Kendal

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## SEQUENCING INFLUENZA A VIRUS FROM THE 1918 PANDEMIC

In 1918–1919, an influenza pandemic of unprecedented virulence swept the globe, killing 40 million people. Although not isolated at the time, it is now possible to study the genetic features of the 1918 virus using fixed and frozen tissue specimens. An understanding of the genetic make-up of the most virulent influenza strain in history may facilitate prediction and prevention of future pandemics.

The 1918 pandemic was exceptional in both breadth and depth. The main wave of the pandemic occurred between September and November of 1918. Up to 30% of the US population may have been infected. The disease was exceptionally severe, with mortality rates of over 2.5% among the infected, compared to less than 0.1% during other influenza epidemics. Incredibly, some isolated populations had mortality rates of over 70%.

Furthermore, in the 1918 pandemic, most deaths occurred among young adults – a group normally having a very low death rate from influenza. The death rate as a result of influenza and pneumonia in 15 to 34 year-olds was more than 20 times higher in 1918 than in previous years, with 99% of excess deaths among people under 65 years of age. In total, an estimated 675,000 American citizens died, and the impact was so profound as to depress the average life expectancy in the US by more than 10 years.

### Sequencing influenza A from the 1918 pandemic

The broad goal of this project was two-fold:

- 1) To find the origin of the 1918 influenza virus
- 2) To determine whether any genetic features of the sequence could give an insight into the virulence of this strain.

Three cases positive for 1918 influenza RNA were identified from New York,

South Carolina and Alaska. Using this material, full-length RNA segment sequences were generated, including haemagglutinin (HA), neuraminidase (NA) and non-structural (NS) segments.

While serological data suggest that the 1918 HA resembles the HI antigen subtype of swine influenza isolated in 1930, the avian origin of the 1957 and 1968 HAs gave rise to the possibility that the 1918 HI may be more similar to an avian HI. The complete coding sequence of the HI gene generated from all three cases closely resembled each other. Of the 981 bases of the HAI domain of this gene, only two nucleotide differences were noted among the three cases. One of these

*... in the 1918 pandemic, most deaths occurred among young adults ...*

differences – found in the New York case – caused an amino acid change not found in the South Carolina and Alaska cases. Interestingly, this change occurred in a critical amino acid involved in receptor binding. The overall receptor-binding pattern for the 1918 HA is most similar to that found in classic swine influenza strains. It is possible that the New York influenza binds specifically to both avian- and mammalian-type receptors – a property shared with classic swine influenza viruses.

Full-length sequences of the 1918 HA and NA show that they are most closely related to the human and swine influenza strains of the 1930s. Although more closely related to avian strains than any subsequent mammalian H1N1, the 1918 strains are phylogenetically distinct from current avian H1N1s. It is probable that the HA involved in the pandemic did not pass directly from an

avian source to its pandemic form, but rather spent an unknown length of time adapting in a mammalian host. Whether this host was human or swine remains unclear. Phylogenetic analyses of the full-length 1918 HA and NA sequences consistently place them near the root of the mammalian clade. It is likely that the 1918 virus is closely related to the common ancestor of all subsequent human and swine H1N1 strains.

An alternative hypothesis is that the 1918 virus may have acquired its HA and NA by shift from an avian virus immediately prior to the pandemic. If avian influenza genes are in evolutionary stasis, as has been suggested previously, the 1918 virus would not resemble current avian strains in phylogenetic terms. For the 1918 strain to be the result of a direct introduction of avian HA and NA, it would have been necessary to have drift within the avian clade over the previous 80 years. Since there are no known avian virus isolates from 1918, this hypothesis cannot be tested.

### Hypotheses speculating on the origin of the 1918 virus

Different mortality patterns among influenza pandemics suggest that the viruses emerge in different ways. The pandemic of 1890 demonstrated a mortality pattern that differed from those of 1957 and 1968. While morbidity was high in each year from 1890 to 1892, mortality was low in 1890, rose in 1891 and peaked in 1892. In 1957 and 1968, mortality was highest in the first year of the pandemic. In light of the 1890 pattern, it is intriguing to note that prior to the 1918 pandemic, the mortality rate from influenza and pneumonia began to rise in 1915 and 1916. The rate then dipped slightly in 1917 and rose sharply with a classic 'herald' wave in the spring of 1918, finally skyrocketing with the most virulent form in the autumn and winter of 1918/19. It is possible that a poorly adapted H1N1

was beginning to spread in 1915, causing some serious illness but was not yet fully adapted. However, if a strain with novel surface proteins caused enough illness to affect national death rates, it should have caused a pandemic earlier, and significant numbers of people would have been immune in 1918. Currently it is impossible to distinguish fluctuations in mortality caused by drift in the previous strain (possibly H2N2) from early waves of a newly emerging virus. Both the 1957 and 1968 pandemics were preceded by mild waves early in the same year, and there is evidence that the 1968 pandemic virus had begun to circulate several years earlier. Because the reassorted viruses of 1957 and 1968 had human-adapted internal genes – perhaps after a surface protein shift – neither virus required long adaptation periods before causing pandemics.

*A number of scenarios for the origin of the 1918 flu are possible:*

1. It could have been an entirely avian virus that entered the human population in 1918, already capable not only of infecting people – as was the 1997 Hong Kong 'chicken flu' – but also of spreading with extreme efficiency from human to human.
2. A wholly avian virus could have entered the human population some

years before 1918, gradually establishing itself and adapting toward efficient replication and transmission in humans.

3. It could have been a reassortant virus with some genes of avian and others of human origin, as were viruses responsible for the pandemics of 1957 and 1968.
4. The 1918 virus pandemic may have arisen from a previously circulating human virus that had mutated to such an extent that, antigenically, it was completely unrecognisable.

The extent of the pandemic and the fact that it arose in a mild wave followed by more severe waves make the latter possibility the least likely. The supreme efficiency with which the 1918 influenza spread, and the evidence that many different genes contribute to host specificity, argue against an immediate avian origin. Distinguishing between a wholly avian virus adapted in humans for some years, and a reassortant virus with some genes from immediate avian origin, and others from a previously circulating human strain will be difficult given the lack of contemporary avian or pre-1918 human strains for comparison.

### Hypotheses for virulence of the 1918 virus

Little is known of how genetic features of influenza viruses affect virulence.

Virulence of a particular influenza strain is complex and dictated by host adaptation, transmissibility, tissue tropism, and replication efficiency. The genetic basis for each of these features is not yet fully characterised, but is likely to be polygenic in nature. However several identified mutations are known to radically change the behaviour of a given flu strain. In the case of the 1918 virus, neither the HA cleavage site mutation nor the NA  $\Delta 146$  mutation of WSN/33 were present. Both of these changes have been shown to affect tissue tropism of the viral strain. These genetic features and the clinical and pathological spectrum of disease in 1918 all suggest that the 1918 virus was not pantropic.

Full-length sequences will allow complete phylogenetic analysis of each segment, helping to elucidate the origin of the 1918 virus. Whether any particular genetic feature of the virus can be directly related to its exceptional virulence is unclear. It is hoped that knowledge gained from studying this very successful human pathogen can be applied to prevent or at least predict the emergence of new influenza viruses with pandemic potential.

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## OPTIONS FOR THE CONTROL OF INFLUENZA IV: UPDATE

Preparations for the 4th meeting in the 'Options for the Control of Influenza' series, to be held in Hersonissos, Crete, Greece, 23–28 September, 2000, are in full progress.

The number of satellite symposia and expected participants reflect the increased global interest in influenza. Between 350–450 participants attended previous 'Options' meetings, but more than 800 people have now registered for the 'Options IV' meeting. Approximately 370 abstracts have been

submitted for oral or poster presentations. Abstracts received by the organising committee were distributed to the chairpersons of the scientific sessions. Each chairperson was asked to submit the proposed content of his or her session to the scientific committee for formal approval. In addition to inviting speakers to contribute to scientific sessions, chairpersons were also asked to review abstracts and select some for oral presentation. Reviewed abstracts not selected for oral presentations will be presented in poster format.

ESWI is pleased to provide financial support for 25 young scientists to attend the meeting.

The scientific programme has now been finalised and can be found on ESWI's website at [www.eswi.org](http://www.eswi.org). An abstract book will be available at the congress and Elsevier Science will publish proceedings of the meeting in March 2001.

A.M. Palache

Member of the  
Organising Committee

## REVERSE GENETICS FOR THE CONTROL OF INFLUENZA

For the first time, systems are available for the highly efficient generation of influenza viruses without technical limitations [1, 2]. These systems require only DNA cloning and transfection techniques, and are therefore easily adaptable by laboratories working in the fields of molecular biology and virology. One of the most intriguing applications of these systems may be the generation of live attenuated influenza virus vaccines.

The new systems allow generation of viruses entirely from cloned cDNAs. In one system [1], human embryonic kidney cells were transfected with eight plasmids, each encoding a viral RNA of A/WSN/33 (H1N1) virus, flanked by human RNA polymerase I promoter and mouse RNA polymerase I terminator sequences (Fig. 1). Transcription of these viral genes by cellular RNA polymerase I yielded all eight influenza viral RNAs. Cotransfection with protein expression plasmids for the nucleoprotein and polymerase proteins resulted in the generation of infectious viruses.

Inactivated virus vaccines are currently used in humans and animals, but have poor efficacy, partly due to inadequate cell-mediated and local IgA responses. Attenuated virus strains can be generated by multiple passages of viruses

in heterologous hosts and/or at non-permissive temperatures, or by previous reverse genetics methods that rely on helper-virus. However, these procedures are time consuming, cumbersome and – with regard to the former method – unpredictable. Although cold-adapted live vaccines are phenotypically stable and as efficacious as inactivated vaccines [3], there is room for improving their efficacy.

Using this new system for influenza virus generation, a 'master strain' can be designed with multiple attenuating mutations in the genes that encode internal proteins, while maintaining the immunogenicity of the strain. The introduction of multiple attenuating mutations in the viral genome should make a reversion to the wild-type sequence remote, thus ensuring the genetic stability of the master strain. In cases of influenza virus outbreaks involving new haemagglutinin and/or neuraminidase subtypes, the genes encoding these viral glycoproteins could then be combined with the remaining genes of the master strain for rapid vaccine production.

In addition, this new system for the generation of influenza virus may also prove useful for gene delivery purposes. Virus-like particles could be generated that

contain the genes encoding the proteins required for influenza virus replication and transcription, i.e., the nucleoprotein and polymerase proteins, together with the protein of interest [4, 5]. These infectious particles would deliver the protein of interest into the target cells. Unless these particles contain the genes encoding structural proteins, no infectious progeny viruses can be produced.

In conclusion, the system for the generation of influenza virus from cloned cDNA provides us with the means to specifically engineer safe and protective live attenuated virus vaccines, as well as to generate virus-like particles for the delivery of viral or non-viral genes.

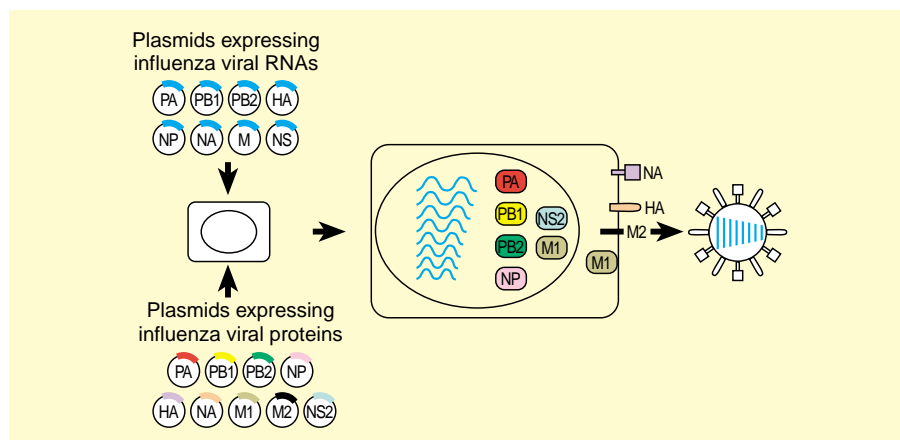
G. Neumann<sup>1</sup> and Y. Kawaoka<sup>1,2</sup>

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**Fig. 1.** Kidney cell transfected with eight plasmids encoding viral RNAs of A/WSN/33 (H1N1) virus, flanked by human RNA polymerase I promoter and mouse RNA polymerase I terminator sequences. The kidney cells were cotransfected with protein expression plasmids for nucleoprotein and polymerase proteins. HA, haemagglutinin; PB1, PB2, PA, RNA transcriptase components; NP, nucleoprotein; M1, M2, matrix proteins; NA, neuraminidase; NS, NS2, non-structural proteins.

## CONTROL OF INFLUENZA IN THE IMMUNOCOMPROMISED

Influenza viruses are the cause of recurring respiratory illness in the general population, resulting in significant annual mortality in certain high-risk groups. This usually results from serious complications such as pneumonitis, secondary bacterial infections and heart failure. Annual vaccination against influenza is therefore recommended for high-risk groups. These include patients with cardiac, pulmonary or renal disease, those with diabetes mellitus, the elderly and immunocompromised patients. The latter form a heterogeneous group of patients who, as a result of disease or medical treatment, have reduced immunity to infectious agents.

Immunocompromised individuals include those infected with HIV, solid-organ recipients who receive immunosuppressive drugs, and patients receiving cytostatic drugs or undergoing radiotherapy for the treatment of neoplasms. These patients may suffer more

reduced in such patients [3]. In these studies, a significant proportion of the vaccinees responded to vaccination and developed protective antibody titres. Moreover, their antibody responses were further enhanced using two- or three-dose vaccination regimens [3, 4].

On the whole, published data indicate that solid-organ recipients can be vaccinated effectively against influenza despite immunosuppressive therapy. Also, in HIV-infected individuals the response to influenza vaccination may be severely impaired. This impairment is associated with a decrease in the number and functionality of CD4+ T lymphocytes, but a varying response to vaccination is seen in those with CD4 counts of >100/mm<sup>3</sup> [5]. With the advent of highly active anti-retroviral therapy (HAART), HIV replication can be suppressed, resulting in an increase in the number of CD4+ lymphocytes. Indeed, the antibody response following influenza vaccination is restored in HIV-infected individuals successfully treated with HAART [6].

*... vaccination of HIV-infected individuals can prevent symptomatic influenza infection.*

severely from influenza-related symptoms, with a prolonged duration of illness and viral shedding.

Paradoxically, vaccination against infectious diseases in these patients may be less efficacious or not efficacious at all due to their poorly functioning immune systems. For example, in immunocompromised solid-organ recipients, the response to influenza vaccination is severely impaired [1]. However, the efficacy of standard, one-dose influenza vaccination is controversial, since in some studies the responses of solid-organ recipients were not significantly different from those in healthy control subjects [2]. More recent studies in liver and heart transplant recipients indicate that the antibody response is

It has been speculated that influenza vaccination of HIV-infected individuals may lead to the activation and proliferation of CD4+ lymphocytes, supporting replication of HIV and resulting in higher HIV loads [7]. These findings are controversial since other investigators have either failed to demonstrate vaccination-induced enhancement of HIV loads, or have shown that transient elevations of viral loads are rare [8]. On the other hand, it should be realised that vaccination of HIV-infected individuals can prevent symptomatic influenza infection [8], mass immune activation and subsequent complications. Influenza vaccination may, therefore, indirectly contribute to the control rather than the promotion of HIV replication.

G.F. Rimmelzwaan and A.D.M.E. Osterhaus

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## CALENDAR OF EVENTS – 2000

DATE/VENUE	TITLE	ORGANISER
8–12 July 2000 Fort Collins, Colorado, USA	19th Annual Meeting of the American Society for Virology	Department of Microbiology and Molecular Genetics Medical College of Wisconsin 8701 Watertown Plank Road Milwaukee, WI 53226–0509 Tel: +1 414 456 8104 Fax: +1 414 456 6535
30 August – 3 September 2000 Florence, Italy	World Congress on Lung Health and 10th European Respiratory Society Annual Congress	ERS, Congress Secretariat 1 Boulevard de Grancy 1006 Lausanne Switzerland Tel: + 41 21 613 0202 Fax: + 41 21 617 2865
17–21 September 2000 Glasgow, UK	European Virology 2000	Dr Bill Carman Institute of Virology University of Glasgow Church Street Glasgow G11 5JR UK Tel: + 44 141 330 4017 (ext. 6254) Fax: + 44 141 337 2236
23–28 September 2000 Hersonissos Crete, Greece	Options for the Control of Influenza IV	Biomedia 101 rue Mademoiselle Paris 7501 France Tel: + 33 142 190 024 Fax: + 33 140 650 031

### LATE-BREAKER ABSTRACTS

The 'Options IV' Programme Committee recognises that major scientific discoveries and important disease outbreaks may occur at any time. Late-breaker presentations will highlight new and significant research developments or outbreaks that have occurred since the original 'Options IV' abstract deadline of 31 March, 2000.

*The deadline for late-breaker abstract submission is 30 June, 2000.*

Accepted submissions will be presented during late-breaker sessions on 25 and 27 September, 2000. Abstracts for late-breaker sessions will not be included in the abstract book, but will be distributed in the conference bag.

### INFLUENZA BULLETIN

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