



# Influenza

INFORMATION AND NEWS ON INFLUENZA

## EDITORIAL

The threat of an influenza pandemic in Hong Kong in 1997 has increased interest in emerging influenza viruses. In collaboration with the World Health Organization (WHO), ESWI has prepared a plan to assist countries to respond adequately to future threats of a potential pandemic. This document will be published before the end of the year. Various other new publications are shedding light on the epidemiology and, in particular, the molecular biology of emerging influenza strains. Exciting studies in this field as well as reports on other aspects of influenza were presented at the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) meeting held recently in San Diego, USA. A review of some of the presentations given at the conference appears in this issue of *Influenza*.

### Socioeconomics

On 5 and 6 October 1998, a meeting initiated by ESWI and entitled, *The Socioeconomics of Influenza and Its Control Measures*, was held at the headquarters of the WHO in Geneva, Switzerland. This meeting coincided with the 50th anniversary of the WHO's programme on influenza surveillance. (A WHO global conference to mark this event will be held in February 1999.)

The meeting was a continuation of the meeting held in Brussels in 1995 which was devoted to an economic evaluation

of the consequences of influenza in Europe. At the end of the Brussels meeting, Professor Thomas Szucs (Munich, Germany) summarised the discussions in a session appropriately titled, *What do we not know? What work is required?*

Seventy health care decision makers from 25 European countries attended the recent Geneva meeting, chaired by Professor Szucs. This symposium aimed to update our knowledge on the socioeconomics of influenza and to provide attendees with support for assessing the societal impact of the disease, its prevention and treatment. Turn to page 9 of this bulletin for the report.

### Policy change

It is expected that discussions between policy makers and scientists will further contribute to improving our control of influenza and reducing its considerable annual burden. Better influenza control can only be achieved if immunisation policies evolve. An example of evolving policy occurred recently in the UK where the Department of Health decided to recommend influenza vaccination for all those aged 75 years and over, regardless of their medical status. This decision was based on both scientific and socioeconomic data.

### Options meeting

In May 1996, more than 400 scientists gathered for the third international

meeting on *Options for the Control of Influenza* in Cairns, Australia. This meeting was particularly successful and provided an outstanding opportunity to assess advances in our knowledge of all areas of the disease. On behalf of the International Scientific Committee for the *Options* meetings, ESWI has been asked to organise the next meeting. We are therefore pleased to announce that *Options for the Control of Influenza IV* will probably be held from 23–28 September 2000 in Heraklion, Crete.

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Chair, ESWI

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## EU REGULATORY PROCEDURES FOR INFLUENZA VACCINES

Influenza vaccines, like all medications, are subject to manufacturing and marketing authorisation (licensing) procedures. In most European Union (EU) member states, influenza vaccines are also subject to batch release procedures operated by Official Medicines Control Laboratories (OMCL).

### Changes to the authorisation procedure

One of the most significant changes during the past decade has been the gradual 'Europeanisation' of regulatory procedures. This Europeanisation has been particularly rapid and effective for the influenza vaccine.

The procedure for obtaining authorisation to market an influenza vaccine used to be operated at the Member State level. In 1997, the Committee for Proprietary Medicinal Products (CPMP), which provides scientific advice on EU licensing procedures, developed a model for a 'Core Dossier' setting out the format and content of a common EU Marketing Authorisation Application (MMA) for influenza vaccines. Through mutual recognition of the original Member State's approval, simultaneous vaccine approval is possible across the EU. Once the core part of the vaccine receives uniform approval, the procedure for future vaccine variations is simplified considerably.

### Exceptional circumstances

Among the various vaccines produced, the influenza vaccine is an exceptional case. The composition of the vaccine virus strain has to be modified almost every influenza season so that the antigenic composition closely matches the circulating influenza virus strains. In addition, rapid regulatory approval must be obtained for the strain modifications recommended by the WHO as the time between identification of a new circulating virus strain and the time that the adapted vaccine has to be available

is short. The CPMP has set up a system for the yearly strain change which is similar to the MAA, with mutual recognition available.

A very important role is also played by the WHO influenza reference laboratory at the National Institute for Biological Standardisation and Control (NIBSC) in the UK. Each year and under severe time pressure, the laboratory produces the high-yield reassortants required for production. The NIBSC also produces the reference antigens and antisera needed for in-process and final product testing by manufacturers and OMCLs.

In the early 1990s, the *ad hoc* Influenza Group developed the first Batch Release Guideline on influenza vaccine. Several institutions are involved in batch release:

- *The OMCL vaccine batch release network* is responsible for developing new batch release guidelines and adapting existing ones. The network (co-ordinated by the European Department for the Quality of Medicines in Strasbourg) also facilitates standardisation by organising collaborative proficiency studies in influenza vaccine testing.
- *The WHO influenza centre at the NIBSC* initially developed the Single Radial ImmunoDiffusion (SRID) method which has become the standard method for assaying influenza vaccines. The centre provides updated antigen and antiserum reference preparations which are used world wide.
- *The European Pharmacopoeia* has published the legally binding monographs that describe production and control procedures for all current types of influenza vaccine as well as more general monographs on vaccines and production substrates.

### Future developments

Regulatory authorities and the pharmaceutical industry are working to produce safer, more effective vaccines. Research is being undertaken in the following areas:

*Mammalian cell vaccines:* Traditionally, influenza virus vaccine strains have been produced and propagated in embryonated eggs. Producing vaccine using large scale mammalian cell fermentation may offer a more efficient means of reacting to newly emerging strains. The scientific and regulatory implications of this approach are being discussed.

*DNA vaccines:* Conventional vaccination is based on administration of antigens to the host. DNA plasmids have been used to convey the genetic message needed for *in situ* production of vaccine antigens in the host, thus providing a system of antigen presentation that closely mimics a viral infection. Rapid progress is being made, particularly for influenza vaccines.

*New adjuvants:* Different ways of presenting the vaccine antigen to selected branches of the immune system through the use of newly developed adjuvants may yield influenza vaccines that are more efficacious in difficult target populations such as the elderly.

*Paediatric formulations:* The quantity of antigen needed to protect infants against influenza is being assessed.

The European system has been effective in communicating important information (e.g. the threat of avian influenza H5N1) to all interested parties. Continued EU co-ordination is vital to provide effective vaccines against newly emerging and potentially pandemic strains, should this prove necessary.

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## REPORT OF KEY INFLUENZA PRESENTATIONS FROM ICAAC, SAN DIEGO, USA, 25–28 SEPTEMBER, 1998

The millennium will probably begin with several major new approaches to influenza control, and new international co-operations for responding in the event of a pandemic threat or actual pandemic. This appeared to be the message from reports at ICAAC presented during a special symposium on influenza. Concern about the health care burden influenza imposes and the outcomes of genetic and biological developments may result in new approaches for tackling influenza.

### 1918 pandemic – new data

Dr JK Taubenberger (Washington, DC), the US pathologist who published studies on the molecular composition of the 1918 virus, reported that an additional sample suitable for molecular analysis had been obtained from the body of an Inuit village resident in Alaska (about 80% of the residents had died in the 1918 pandemic). Until this recent discovery, only two usable samples from military personnel who died in 1918 had existed. Sequencing of the HA gene has been completed for the three specimens to the extent that it can be said they are virtually identical, with each of the two new samples differing by only a single base from the previously reported specimen. Work is almost complete on the neuraminidase, and by the end of 1999 is expected also to include data for M, NP and NS genes. Polymerase sequences will be slower, as RNA fragments identified are only about 100 bases long. From the additional data it can be concluded that there was no direct transfer of an avian influenza gene to mammalian hosts in 1918 but that it had existed in a mammalian reservoir for about 10–20 years before the pandemic.

Dr NJ Cox's (Atlanta, GA) presentation on avian influenza in Hong Kong provided the clearest data yet on the ability

of avian influenza to cross the species barrier into man. Work continues to develop different experimental vaccines. These may be used to evaluate the human immune response to a novel H5 antigen. Under development are an inactivated vaccine made from influenza H5 virus, a vaccine produced by insertion of the HA gene into a baculovirus, and a cold-adapted live attenuated vaccine.

### Immune system studies

Two new approaches in the form of 'knock-out' mice and recombinant DNA expressed proteins are now available to improve our knowledge of the role of different components of the immune system, reported Dr T Braciale (Charlottesville, VA). In the former case, lines of mice in which different immune capabilities have been selectively eliminated allow more reliable interpretation than earlier methods. For example, different CD4+ cell types can be studied that are responsible for antibody production or cytokine response, with one beneficial and the other detrimental to the host.

The second new approach uses recombinant DNA expressed major histocompatibility antigen proteins, combined with beta-2 macroglobulin proteins, and synthetic peptides representing MHC-dependent antigens. Provided they are then aggregated to tetrameric forms, these complexes (after labelling with a marker such as fluorescein) allow quantitation of specific antigen binding subsets of CD8+ T cells. Such an approach in a demonstration study in mice shows that 7 days are needed to see such cells appear after primary infection, vs 5 days after secondary infection. These types of models should help elucidate the protective role of CD8+ cells in infections other than primary ones, and ultimately may enable immunoprophylactic approaches to be

used against influenza viruses regardless of their HA. (*Author's comment: While not proven, it may be possible that live intranasal vaccine could ameliorate the virulence of a pandemic influenza by advancing the cytotoxic T cell response to infection.*)

### The promise of live vaccines

The role of non-humoral immunity is certainly evidenced by results with live intranasal vaccines. Dr RB Belshe (St Louis, MO) added new information about US efforts intended to lead to licensing and use of cold-adapted vaccines. Efficacy and safety in young children average age 3½ years was documented in trials during the 1997/98 winter (further supporting 1996/97 results). For most subjects, this trial had initially involved vaccination by spray-syringe with two doses of cold-adapted virus, based on the master strains developed in Ann Arbor, and containing the same trivalent antigenic composition as recommended for inactivated vaccines. In the winter of 1996/97, the vaccine A (H3N2) and B strains closely matched the epidemic strains. In the autumn of 1997, about 85% of children were re-vaccinated with a trivalent vaccine in which only the H1N1 strain was changed. However, during 1997 the A/Sydney (H3N2) strain became dominant and inactivated vaccines have not been shown to be effective against this variant except to a possible low level.

But the live vaccine had an 87% overall efficacy rate against laboratory confirmed influenza (CI: 75–92%) in re-vaccinated children compared with children given placebo in both years. The situation is more complex than first viewing indicates: children given placebo in year 1 but who were infected in year 1 were also highly protected against the A/Sydney strain. Nevertheless, the overall finding is clear: in well-vaccinated children efficacy was high. ▶

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Protection was equivalent across all age groups of children, although serum antibody responses to vaccination and serum titres were higher in the younger children. This occurs because live vaccine has a low 'take' in children with pre-existing antibody, when measured by serum HI response. The efficacy data suggest that resistance to infection after live vaccination occurs for other reasons, such as probably local immunity. (Author's comment: In view of data on the role of neuraminidase inhibitors, one might also suggest that live vaccines could have improved performance over inactivated vaccines when the HA drifts on account of inducing immunity to this viral component, as well as HA.)

Currently, two doses of trivalent vaccine are needed initially in unprimed children to obtain demonstrable immunity (serum HI) to all virus haemagglutinins included, due to perceived interference in some cases between infection by different strains. (Author's comment: The high protection seen even when antigenic drift occurred raises the question whether two doses are needed to obtain adequate immunity. This is important for economic and compliance issues in medical or public health practice. Data for the subset of children given only a single dose in the first year and re-vaccinated in the second year were not individually reported.)

## Neuraminidase inhibitors

Several different studies on neuraminidase (NA) inhibitors were reviewed by Dr FG Hayden (Charlottesville, VA)

for the two currently studied compounds that were designed to target the substrate binding site in influenza NA. The first, zanamivir, is not absorbed well through biological membranes and must be applied topically (although i.v. use was also described in the conference). Latest data show that an intranasal inhaler may be used for delivery. Taken for 4 weeks after community surveillance showed influenza to be spreading, healthy, non-vaccinated adults aged 17–64 years were protected to 84% (CI: 55–94%) from laboratory confirmed febrile influenza.

In a treatment study in the Southern Hemisphere (mainly Australia), reduction in shedding of virus and earlier decrease in symptoms were observed. Only patients with onset <36 h were enrolled. Rates of hospitalisation and antibiotic use in high-risk patients decreased significantly, from 46% to 14% and 41% to 16%, respectively.

(Author's comment: The epidemic involved both type A and B viruses in approximately a 2:1 ratio, and represents perhaps the clearest demonstration to date of the value of the NA inhibitor over amantadine/rimantadine, which regrettably were not compared in these studies. Co-circulation of type A and B viruses in high-risk adults is an infrequent event, however.)

Similar trials of oral administration of the second NA inhibitor, GS 4104, were performed in the USA in 1997/98. Combined results from one multicentre prevention study showed an overall reduction in 'confirmed clinical flu' from 4.8% in the placebo group to about

1.2% in the groups receiving 75 mg either twice or once per day (protection 74%).

Oral therapy was also studied at 60 sites for 18–64-year-old adults without risk factors for influenza complications, presenting with fever 100°F within 36 hours of illness onset. Fever lasted a mean 103h for the placebo group vs 70–72h for treatment groups (75mg or 150mg, twice daily). Although rates of complications such as sinusitis and bronchitis in the placebo group were low, they were reduced about 50% with treatment.

As with any anti-infective, a key question is the issue of antiviral resistance. With influenza NA inhibitors this can occur through three mechanisms described: mutation in the HA which reduces its affinity for neuraminic acid receptors; mutation in the NA which reduces affinity for inhibitor; and mutation in NA which reduces enzyme activity. Recent information was communicated that an immunocompromised 18-month-old child treated with one of the compounds had continued to shed virus, and that on day 8 this virus was resistant to drug through an HA affinity mutation, and on day 12 through an NA activity mutation. Provisional results suggest that the mutations seen affecting the resistant viruses often may decrease overall stability or replication of the mutants, putting them at a competitive disadvantage with wild type virus.

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## INFLUENZA MESSAGE TO EUROPEAN RESPIRATORY PHYSICIANS

Treat influenza seriously – this was the message to delegates at the European Respiratory Society (ERS) Annual Congress who attended the symposium, *Meeting the Challenge of Influenza*, sponsored by F. Hoffmann-La Roche.

Experts in the field discussed topics ranging from epidemiology and the clinical/economic consequences of influenza

to current and future options for control, including the new neuraminidase inhibitor class of drugs. The symposium ended with the conclusion that these new drugs take a significant step towards the management of influenza.

A full report of the symposium will appear in the next bulletin. The ERS Annual Congress was held in Geneva, Switzerland, from 19–23 September 1998.

## THE EUROPEAN INFLUENZA SURVEILLANCE SCHEME

The World Health Organization (WHO) initiated the CARE Telematics project, which was initially funded by the European Union, in 1992. The project aimed to improve the surveillance of influenza in Europe through collecting clinical and virological data on the disease from national networks and disseminating the data to the appropriate authorities. In 1995, the CARE working group decided to extend its activities and created the European Influenza Surveillance Scheme (EISS) under the leadership of The Netherlands Institute for Primary Care (NIVEL). The main objectives of EISS are to detect outbreaks of influenza at an early stage, identify the causative viral strains and rapidly assess related morbidity. Additionally, EISS aims to detect new strains and the potential for an emerging pandemic virus. Comparing EISS data with data from other national surveillance networks is essential and is facilitated by the classification of influenza activity into five stages [1].

### Operation of the scheme

EISS comprises 17 institutions (see box), mainly WHO Collaborating Centres or National Influenza Centres (NIC). The EISS system is based on a password-protected Internet application, tailored to EISS group specifications (designed by Quad Logic, France), with its own World Wide Web server [2].

Each week during the influenza season, clinical and virological data are collected from appointed sources. Data are gathered from general practitioners and, in some cases, paediatricians, who form a sentinel network connected to their respective virology laboratories. Virological and serological data are also collected weekly from other sources such as hospitals. When data arrive from the Web, the EISS application converts the data into standard field values and specific standard query language

(SQL) commands instruct the database software to enter or update the data.

### Graphical representations

Three graphs are then generated for the EISS regions. The first shows the number of isolates/detections of influenza viruses split by type and sub-type for that week. A second graph details the total weekly number of influenza viruses and respiratory syncytial virus isolated or detected. The third graph displays the number of influenza-like illnesses (ILI) or acute respiratory infections (ARI) reported for the various EISS regions.

A global map for each area depicts the intensity of the epidemic using five colour-coded classification levels and the dominant type or sub-type of influenza virus. This graph is generated by compiling data from the clinical and virological elements. The database can be downloaded on a real-time basis, either as a whole or in parts, by week, area or both.

EISS currently acts as an early warning system in a region comprising

approximately 281 million inhabitants. The sentinel networks also allow for a distinction between strains from community-based populations and hospitalised patients [1]. Epidemiological and technological developments have enabled the CARE Telematics project to evolve into the present-day EISS. These developments have resulted in the guarantee of validated data and the technological capability to adapt hardware and software to the specific needs of the project.

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### EISS Institutions

Belgium	Scientific Institute for Public Health – Louis Pasteur
Czech Republic	NIC, Prague
England and Wales	Royal College of General Practitioners; Public Health Laboratory Service and Communicable Disease Surveillance Centre
France	OPEN ROME, Institut Pasteur and Centre Hospitalo-Universitaire Lyon I forming the Groupes Régionaux d'Observation de la Grippe (GROG)
Germany	Arbeitsgemeinschaft Influenza (AGI); NIC, Berlin
The Netherlands	Netherlands Institute for Primary Care (NIVEL); National Institute for Health and Environmental Hygiene (RIVM)
Portugal	Instituto Nacional de Saude
Scotland	GP Spotter Scheme
Spain	Medicos Sentinela of the Instituto de Salud Carlos III
Switzerland	Swiss Federal Office of Public Health; NIC, Geneva; and the GP network, Sentinella

## THE IMPORTANCE OF ANIMAL INFLUENZA SURVEILLANCE

Although descriptions of influenza can be found in ancient history, reports on the outbreaks of influenza in 1510 suggest this to be the first documented influenza pandemic. Since then, influenza pandemics have been described many times [1]. It was not until the end of the 19th century that the subtype of influenza viruses involved in these pandemics was identified when serological studies revealed the presence of influenza A viruses with H2 and subsequently H3 haemagglutinin. Following isolation of the first human influenza virus in 1933 [2], more detailed information about the viruses that have caused pandemics in the 20th century has been obtained. An influenza A virus of the H1N1 subtype caused the devastating Spanish flu pandemic of 1918. Analysis of gene fragments of this virus revealed it was closely related to swine viruses from that period and therefore could be transmitted to humans from pigs [3].

In 1957, an influenza A (H2N2) virus emerged causing the Asian flu pandemic. From the viral genome of eight RNA segments, five were derived from human viruses and three gene segments were related to avian influenza viruses. As such, this virus must have been the result of a reassortment event following double infection of viruses of human and avian origin. A similar event preceded the emergence of the 1968 pandemic influenza A (H3N2) virus. In this case, only two new gene segments were introduced into the virus, but among these was the gene coding for the immunodominant haemagglutinin. These gene segments were also of avian origin. Sequence analysis of influenza virus gene segments of the 1957 and 1968 pandemic influenza viruses showed that the emerging viruses contained avian-like genes coding for surface glycoproteins in a background of genes of human phylogeny [4]. The presence of genes and thus proteins of

avian origin in a human-avian reassortant seems to be a prerequisite for an influenza virus to obtain pandemic potential.

Therefore, monitoring influenza viruses in animal species is the first step in being prepared for influenza virus subtypes that may eventually emerge in humans. To date, all known influenza virus subtypes have been found in migrating birds and waterfowl. These birds are asymptotically infected in the gastrointestinal tract and can be considered the reservoir of influenza A virus subtypes (Figure 1). From this reservoir, viruses can be transmitted to a variety of species. Influenza viruses have established themselves and cause disease in, for example, horses, pigs and poultry [4].

Avian influenza viruses from the reservoir do not seem to replicate efficiently in humans upon direct transmission [5] which implies that an intermediate host is involved in generating avian-human reassortant viruses. Previously, pigs have been postulated as the potential intermediate host or 'mixing vessel' [6]. This role has been supported by the fact that these animals contain the

appropriate receptors for effective replication of both avian and human influenza viruses [7]. In addition, human-avian reassortant viruses were actually isolated from pigs [8] and these viruses also managed to infect humans [9].

In 1997, several cases of direct transmission of avian viruses to humans occurred in Hong Kong [10], but these viruses did not originate directly from the avian reservoir. The viruses originated from infected poultry and appeared to be of the highly pathogenic influenza A (H5N1) subtype. Although concerns were raised as to whether this was the start of the next influenza pandemic, the viruses did not manage to spread efficiently amongst the human population. After culling all chickens in the area, no further infections were reported. Phylogenetic analysis of the H5N1 viruses revealed that all gene segments were of avian origin [11]. The fact that this virus did not contain any genes of human origin probably limited its pandemic potential. However, one important conclusion that can be drawn from these events is that man himself may act as an intermediate host for a reassortment event.

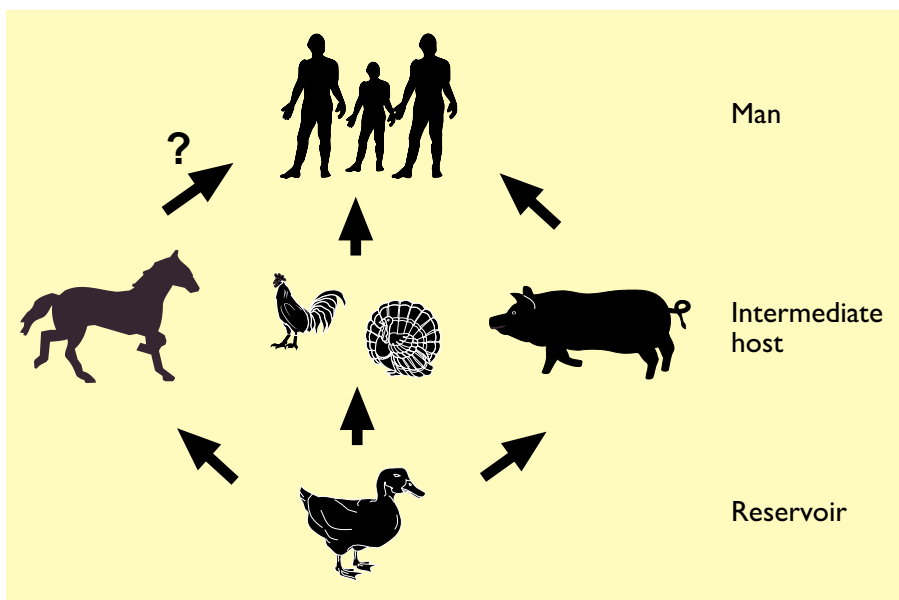


Figure 1. Transmission of influenza virus through the species.

## INFLUENZA VACCINATION POLICY IN POLAND

In Poland, the incidence of influenza ranges on average from 200–6,500 per 100,000 (data for seasons from 1979/80 to 1997/98), while the annual death rate ranges from 30–212. As in many other countries, influenza continues to be a major public health problem [1]. National vaccination recommendations for particular patient groups are in line with recommendations by other institutions such as the World Health Organization (WHO).

### Strain research

Inactivated, but not live virus vaccines are available in Poland. Research carried out during the 1980s at the WHO National Influenza Centre (NIC), Department of Virology, National Institute of Hygiene, Warsaw, on the replication of influenza virus strains at low temperatures resulted in two potential cold-adapted mutant strains

(A/Pol/L/71 [H3N2] and A/Pol/79/85); these may be suitable gene donor strains for recombinant live virus vaccines. In 1983–84, vaccines of improved quality and efficacy were produced on a laboratory scale by the Laboratory of Respiratory Infections at the National Institute of Hygiene, in co-operation with the Warsaw Military Institute of Hygiene and Epidemiology. Until 1989, inactivated influenza vaccines were produced by the Laboratory of Sera and Vaccines in Cracow [2], but since 1992 only foreign brands of inactivated vaccines have been available.

### Publicity drive

In the past, it has not been very common for Poles to obtain vaccination against influenza. However, in recent years the NIC has taken a number of initiatives to increase the general population's knowledge and awareness of

influenza. A national media campaign to provide specific information on the vaccines available and their optimal use to prevent influenza and its complications takes place each year. Poles for whom immunisation is recommended are encouraged to be vaccinated annually against influenza. A similar campaign is directed at physicians and scientific societies by the NIC, which gives lectures to these groups on the epidemiology, virology, diagnostics and prophylaxis of influenza. Since 1993, the NIC, together with the Medical Schools in Warsaw and Lodz and the Psychosomatic Institute in Warsaw, has performed studies to evaluate the humoral response to influenza vaccines in selected high-risk groups.

As a result of this pro-active approach to influenza prevention, a steady

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Another human influenza pandemic is inevitable. Although no predictions can be made, the virus that will cause this pandemic will most likely contain gene segments from current animal influenza viruses. In addition, animals may play a role in preparing the virus by adapting an avian influenza virus to a mammalian host or by hosting a reassortment event.

Therefore, influenza surveillance should not be restricted to human influenza viruses but should also be extended more systematically into the animal world. Although earlier observations indicate that pigs and poultry are important candidates for surveillance, we should keep an eye open for other animals that host influenza replication.

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increase in vaccine use has been realised in Poland. In the 1992/93 season, 0.52 doses were used per 1,000 inhabitants; the average for the period between the 1993/94 and 1995/96 seasons was 1.9 and this increased significantly to 7.9 in 1996/97 and to 22.1 in 1997/98.

## Changing attitudes

We expect that as a result of our campaigns, more and more people will be convinced that 'prevention is better than cure'. We are pleased that interest in vaccination against influenza is increasing, not only among individuals at risk but also among employers, with many companies and institutions now guaranteeing immunisation for their employees.

Studies related to the economics of influenza and its prevention have been undertaken in several countries [3] and some type of reimbursement often exists for influenza vaccination. This is not the case in Poland at present, but we hope that the costs of vaccination against influenza will be reimbursable in the near future, at least for high-risk groups.

L.B. Brydak

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## CALENDAR OF EVENTS – 1999

DATE	VENUE	TITLE	ORGANISER
17-19 March 1999	Brighton, UK	4th European Conference on Vaccinology	EFPIA/EVM 250 Avenue Louise (bte 091) 1050 Brussels Belgium Tel: +32 2 626 25 55 Fax: +32 2 626 25 66
21-26 March 1999	Jerusalem, Israel	12th International Conference on Antiviral Research	Ehud Katz Department of Virology Hebrew University Hadassah Medical School PO Box 12272 Jerusalem, 91120 Israel Tel: +972 2 675 8557 Fax: +972 2 678 4010
4-7 July 1999	Birmingham, UK	21st International Congress of Chemotherapy	Gardiner-Caldwell Communications Ltd Victoria Mill Windmill Street Macclesfield Cheshire, SK11 7HQ UK Tel: +44 1625 664000 Fax: +44 1625 610260
10-14 July 1999	Amherst, MA, USA	18th Annual Meeting of the American Society for Virology	American Society for Virology 8701 Watertown Plank Road Milwaukee, WI 53226-0509 USA Tel: +1 414 456 8104 Fax: +1 414 456 6566
3-5 August 1999	Melbourne, Australia	Macfarlane Burnet Centenary Conference on Virology	Melbourne Convention Centre 114 Flinders Street Melbourne, VIC 3000 Australia Tel: +61 3 9654 2288 Fax: +61 3 9654 8195
9-13 August 1999	Sydney, Australia	11th International Congress of Virology	IUMS Congress Secretariat GPO Box 128 Sydney, NSW 2001 Australia Tel: +61 3 961 0043
2-5 September 1999	Budapest, Hungary	3rd Congress of the European Society for Clinical Virology	Dr Sytske Welling European Society for Clinical Virology, Laboratorium voor Medische Microbiologie Hanzeplein 1 Groningen, NL-9713 GZ The Netherlands Tel: +31 50 363 3514 Fax: +31 50 363 3528
9-13 October 1999	Madrid, Spain	9th Annual Congress of the European Respiratory Society	Mrs Rosine Fieve European Respiratory Society Boulevard de Grancy 1 1006 Lausanne Switzerland Tel: +41 21 613 0202 Fax: +41 21 617 2865

## THE SOCIOECONOMICS OF INFLUENZA MEETING

Researchers and policy makers from a wide range of countries met at the headquarters of the World Health Organization (WHO) in Geneva, Switzerland, on 5 and 6 October 1998, to discuss the socioeconomic issues surrounding influenza and options for control measures. Fifty years ago, the WHO established a worldwide influenza sentinel network to promote influenza surveillance and control of the disease. Much progress has been made during the past 50 years and the October meeting was an opportunity to review and celebrate the WHO's initiative.

The meeting also fulfilled ESWI's desire to continue the debate on the socioeconomic aspects of influenza. As noted in the Editorial, this meeting followed on from that held in Brussels two years ago, at which researchers and policy makers discussed the need for socioeconomic studies that would evaluate the consequences of influenza and the costs associated with immunisation programmes.

Socioeconomic research on influenza has become extremely important. Over the past few years, a large body of economic and epidemiological data has been compiled and used as a basis for steering policies. This type of research has not only become an integral part of WHO studies, but has also received strong support from ESWI.

In response to demands from decision makers for evidence of the consequences of technological change in health care, economic assessments have evolved. Decisions about health care technologies used to be based almost entirely on the clinical safety, efficacy and quality of the approaches used. But policy makers are increasingly insisting on hard data and are no longer content simply to take the benefits and costs of health care interventions on faith.

In the light of these changes, public health policy on influenza and influenza vaccination will greatly depend on the economic impact of the disease, and appropriate research activities will be required. This is particularly so for influenza prevention, as currently there are insufficient economic data to support the formulation of health policy. Although studies in some countries have been performed to evaluate the burden of influenza (e.g. in France, Germany, Austria and Italy), little data are available for other countries.

One important aspect of evaluating the economic impact of influenza is to consider it from an individual perspective. This would mean addressing the specific needs and views of the individual to whom the results of the economic study are addressed. Until now most economic evaluations have been undertaken from a societal and provider perspective but increasingly, individual patient and employer perspectives are being sought. This is particularly important because many studies have shown a workplace benefit to preventing influenza in healthy adults. Most European health care systems are financed directly or indirectly on the basis of income from paid labour so the positive effects of influenza prevention on productivity will also be important on a societal level.

Additionally, the burden on the individual has to be taken into account – not only because many patients already pay for a large proportion of medicines, but also because tight constraints in the overall employment situation means that employees cannot afford to remain away from their workplace.

The overall objectives of the meeting were to:

- summarise and appraise the available evidence on the socioeconomic impact of influenza

- identify the needs of policy makers with respect to economic data
- develop recommendations supporting the expanded control of disease on the basis of socioeconomic evidence and
- stimulate discussions and promote the exchange of ideas among researchers and policy makers.

The meeting consisted of several scientific sessions devoted to the following topics:

- assessing the impact of influenza
- the economic significance of influenza
- prevention and control of influenza
- the socioeconomic impact of the prevention and control of influenza.

Additionally, specific issues were discussed in syndicated working groups with the results then summarised and discussed in the plenary sessions by the respective moderators.

The full proceedings from the meeting will be published as a supplement to *Pharmacoeconomics* and will be available to all interested parties.

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## EUROPEAN VIROLOGY 2000

### Glasgow, Scotland, UK 17–21 September, 2000

A joint conference of the European Society for Clinical Virology (ESCV), the Society for General Microbiology (SGM), UK, the Gesellschaft für Virologie (GSV; the German-speaking society for virology), as well as many other national virology societies in Europe, will take place from the evening of Sunday 17 September to Thursday 21 September, 2000, in Glasgow, Scotland, UK. This conference replaces separate meetings that the societies had planned and is the first of its kind.

European Virology 2000 aims to bring together clinical and basic virologists in a single forum. Morning plenary sessions will focus on the interface between clinical and basic virology. The most important criterion for inviting speakers will be that they are good teachers who can get a message across to both clinical and basic scientists. In the afternoon, short parallel sessions

will focus separately on the clinical or basic aspects so that both sets of participants can hear of the latest developments in their specialist subjects.

Submitted abstracts will be reviewed anonymously and those receiving the top scores will be allocated to oral presentation. The next 20–30 highest scoring abstracts will be presented during a special poster session at an evening function. All other accepted abstracts can be viewed at a dedicated poster session, at which authors will be expected to be available to discuss their posters.

There will also be two sessions at which a noted virologist will present the salient features from selected posters to delegates. At other meetings these sessions are very well attended and it is hoped that they will prove equally popular at European Virology 2000. A commercial exhibition, social events, opportunities for company sponsorship and industry satellite symposia are also planned.

A local Organising Committee and a Scientific Committee comprising members from each of the participating organisations have been set up.

It is hoped that more than 1,000 virologists will participate. To encourage young scientists and PhD students to attend, discounted registration will be offered to these individuals. European Virology 2000 should not be seen as the first in a series of meetings, rather as a one-off venture. But if this meeting is successful, the Spanish society has offered to host a similar meeting in 2003.

For further information about the meeting, please either e-mail me at [w.carman@vir.gla.ac.uk](mailto:w.carman@vir.gla.ac.uk) or fax me on +44 (0)141 337 2236.

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## BOOK REVIEW

### The Textbook of Influenza

Editors: KG Nicholson, RG Webster, AJ Hay

Publisher: Blackwell Science Ltd, Oxford, UK; Price: £69.50

The review of such a comprehensive manuscript on all aspects of influenza presents some difficulties. It contains contributions from an international team of 55 acknowledged experts and is equally a textbook in both the clinical and virological areas of influenza.

From my perspective as a practising physician with a particular interest in influenza surveillance, I posed three questions:

- *Does it help me in preventing and managing influenza?* Issues such as the complications of influenza, the safety of vaccination and the spread of infection were all clearly presented.
- *Is it up to date?* The descriptive data about new drugs for the treatment of influenza, current vaccines and future

perspectives were all highly relevant to the current situation. Indeed, the editors and publisher should be commended in this particular achievement involving so many contributors.

- *Is it readable?* Presentations on the history of influenza, the complexities of vaccine manufacture and the recent Hong Kong experience were particularly interesting even though not immediately relevant to my requirements. Some of the technical sections were difficult to read because of the convention of referencing authors by name in parentheses. Since there were so many, numerical indexing might have been preferable.

An enormous amount of work has produced an extremely valuable reference document for anyone interested in influenza.

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## THE UK EXTENDS ITS INFLUENZA IMMUNISATION POLICY

This year the UK has extended its recommendations for annual influenza immunisation to include all people aged 75 years and over. Previously the recommendations were limited to those with underlying diseases which rendered them at increased risk of serious illness or exacerbation of the underlying disease should they develop influenza. This included adults and children with chronic respiratory, heart or renal disease, diabetes or immunosuppression due to disease or treatment. Those in long-stay residential care accommodation where influenza, once introduced, may spread rapidly [1] were also recommended to be immunised.

Although several countries have introduced an age-based policy, the costs and benefits of extending the UK policy to include all those above a certain age had not been clear. Many studies of the effectiveness of influenza vaccine, both in medical and cost-benefit terms, had been among institutionalised patients who were already recommended for vaccine in the UK. Other studies had been performed in the USA where the cost of vaccine and the cost and pattern of medical care are different. Few studies differentiated between 'high' and 'lower' risk elderly, allowing an estimate of the incremental benefit of an age-related policy over and above the current policy of immunising those with most to gain, and most studies did not stratify for different age bands.

More UK data have become available in recent years which confirm that the elderly without high-risk conditions do have an increased morbidity due to influenza, although of a lesser order than those with underlying medical conditions [2–5]. These data have now been used in cost-benefit analyses which show the value of immunising all those aged 75 years and over. The benefits for younger age groups are less clear and will be subject to further investigation and analysis.

Doctors and senior nurses were informed of the change in policy in August 1998 in a letter from the Chief Medical and Nursing Officers [6]. The recommendation followed the Government's acceptance of advice from the Joint Committee on Vaccination and Immunisation, the independent scientific advisory committee which advises on immunisation policy. The letter emphasised that the major morbidity and mortality from influenza is still within the former 'risk' groups who should continue to receive high priority for vaccine.

Most influenza vaccine in the UK is administered in primary care. Although total use of vaccine has risen year by year, as it has in most other European countries, how far this was in line with the recommended national policy was not known, other than from a few local studies.

A new study using routinely collected data recorded from general practices contributing to the General Practice Research Database (GPRD) in England and Wales has looked at vaccine uptake and changes over time between July 1989 and June 1997 (before the change in policy) [7]. This now gives a clearer picture of the implementation of influenza immunisation policy in England and Wales.

Overall uptake is poor, particularly in the younger age groups. Taking all age groups, uptake increased in the designated risk groups from 19% in 1989–90 to 23% in 1996–97. Uptake in high-risk groups over the age of 65 years increased from 33% in 1989–90 to 44% in 1996–97; in those under 65 only a modest increase was achieved, from 10% in 1989–90 to 12.4% in 1996–97. About 45% of those over 75 years of age with another indication for influenza immunisation and one-third of those without such an indication were

being immunised before the recent change in policy.

The letter to doctors suggested ways in which uptake might be improved. Better organisation of influenza immunisation programmes in primary care, and opportunistic immunisation during hospital admissions, before discharge from hospital and in outpatient clinics were proposed.

J. Leese

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## CAPE TOWN CONFERENCE

An international conference, 'Reflections on the Influenza Pandemic of 1918 After 80 Years', was held at the University of Cape Town, South Africa, in September 1998. Participants, while mainly from the social sciences, also included several influenza, medical science and public health experts.

Several examples of the pandemic's severity were covered that are little reported elsewhere. This included the considerable mortality in India where analyses of colonial records suggest that about 8% of the 250 million population died – a much higher percentage than in developed countries. Mortality was also higher in rural areas and in provinces affected by drought. Although overcrowding was undoubtedly a significant risk factor, the related factors of famine and low socio-economic level also played an important role. Other presentations described the horrendous impact on East African native populations who were involved in the war there, and on isolated populations such as fur trappers in Canada.

Several presenters reported on investigations into the spread of disease by troop ships returning from Europe along the African coast and on to Australia and New Zealand, examining the reasons why quarantine could not, realistically, prevent the epidemic spreading.

Many descriptions of the pandemic demonstrated how important basic nursing and care support were in

helping people to survive. Community-based efforts may often have made a considerable difference as governments were either unprepared or the war (and other factors) meant that there was a drastic shortage of trained nurses and doctors. While the short-term impact of the unusually high morbidity and mortality in normal healthy working-age adults is well known, a new analysis of life expectancy suggested that there was a significant long-term demographic effect on the male population in the US compared with the female.

Two ESWI members gave presentations in the last session at the meeting. One explored how lessons learned from the 1918 disaster could help in preparing for the next pandemic, and the second described the unusual severity of the epidemic on pregnant women in low socioeconomic groups. This led to the question of whether, in non-industrialised countries, there was a rationale for making a low-cost live influenza vaccine available for pregnant women after the first trimester. Considerable discussion followed these presentations, and thus the meeting ended with many unresolved questions that reminded us of the public health responsibility to consider the needs of non-industrialised countries when planning our response to a future pandemic.

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