



# Influenza

INFORMATION AND NEWS ON INFLUENZA

## EDITORIAL

The main goal of the European Scientific Working group on Influenza (ESWI), as asserted in its mission statement, is 'to reduce the impact of influenza in Europe'. As one way to achieve this, ESWI tries to stimulate the fulfilment of recommendations for the prevention and treatment of influenza issued by many national health authorities.

In 1995, ESWI published a paper describing similarities and discrepancies in recommendations for the control of influenza in 24 European countries [1]. At the same time, a paper which reported on the total influenza vaccine usage in 18 developed countries from 1980 to 1992 was published in the same journal [2]. This project to monitor the vaccine usage in developed countries continued and in 1997 an update including data up to 1995 was published, this time providing similar information on 22 developed countries [3]. In 1996, the author of these papers, Professor Fedson, asked ESWI to continue this project. The resulting paper, distributed together with this issue of *Influenza*, reported on the total vaccine use in 29 countries up to 1997 [4].

The three papers clearly show that the uptake of influenza vaccines has considerably increased during the nineties, but they also conclude that the full benefits of influenza vaccination have yet to be achieved in any country. Moreover, they show a clear relationship between vaccine uptake and reimbursement policies. Because influenza vaccines do not prevent influenza in all

circumstances, the recent development of neuraminidase inhibitor drugs (see page 4) has provided a timely expansion in methods for effectively treating influenza infections.

With the increased use of vaccine in recent years and the availability of new types of vaccines and new, effective drugs for the treatment of influenza infections, we might assume that progress is being made in the control of influenza. We must be prudent, however, because there is little information about the vaccination rates in the various at-risk populations in different countries. In addition, there are no data available on the use of neuraminidase inhibitors in actual clinical practice.

Although ESWI believes that current trends in influenza control are positive, we also feel that there is a strong need for further research to measure and quantify results of intervention programmes in future years. ESWI has therefore decided to encourage and provide grants for focussed research projects in three areas in the next 3 years.

- I. Guidelines for the control of influenza, including the role of antivirals in overall management of annual influenza outbreaks.
- II. Vaccine coverage (including at-risk groups), related to vaccine effectiveness at a population level.
- III. Burden of influenza disease in specific groups.

Collaboration with different institutions and organisations will be sought by ESWI for these projects. Hopefully, this research programme will ultimately help to provide evidence of a reduced impact of influenza, which is the ultimate objective of ESWI.

R. Snacken  
Chair, ESWI

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### Virus similarities

A major mystery of influenza epidemiology is that viruses of very similar structure and properties occur in man and several other animal species. These viruses cause both epidemic and pandemic human infections, and major diseases of birds, horses, pigs, seals, minks and other species. Since the Hong Kong pandemic in 1968, the idea that human pandemic strains emerge through reassortment of animal strains, probably in pigs, has been proven correct. Comparing different points of view on animal influenza is therefore of great interest for both human and animal virologists. A symposium on animal influenza and its relationship with human disease, organised by the European Society for Veterinary Virology and the University of Ghent, was held from 16–18 May, 1999 in Ghent. Some of the major results presented will be reviewed briefly here.

The main sessions were devoted to the following subjects:

1. Interspecies transmission
2. Pathogenesis, virulence and immunity
3. Evolution and prevalence of influenza viruses in animal species
4. Vaccination and antivirals.

### Host specificity conferred by haemagglutinin

Host specificity is a key property of influenza viruses, and involves recognition by virus haemagglutinin molecules of specific receptors on susceptible cells. Human and avian cells differ in the linkage of these receptors to galactose – human receptors are 2,6-linked, avian receptors are 2,3-linked. This explains why avian viruses cannot easily infect human cells. However, the episode of avian flu in Hong Kong in 1997 has shown that exceptions do occur, although generally the efficacy of infection is

considerably reduced. Aquatic birds probably act as reservoirs for genetic variants of the virus, as they have been found to contain all known serotypes of haemagglutinin and neuraminidase. The viruses can persist for a few weeks in a single bird and can remain active without causing disease.

Other steps are also involved in the virus life cycle. For example, some proteins are needed by the virus for replication. PB2 protein, an integral part of the viral polymerase complex, is one of the critical sites; results were presented showing that a single amino acid substitution could modify the efficiency of replication in human cells.

### Structures involved in virulence

The structure of a virus has many components that contribute to its virulence. It appears that proteolytic cleavage sites are as important as glycosylation sites. Proteolysis, an essential step of virus maturation, is easier when basic amino acids are present near the cleavage site; however, some non-pathogenic strains also have these amino acids at the correct site. Studies have shown that interactions between the receptor binding site and adjacent oligosaccharides of haemagglutinin are crucial for the potential of viruses to grow efficiently in host cells. It is also interesting that in mice, as in chick embryos, infection is not always limited to the lungs – some strains of virus are also found in other tissues. Replication of influenza virus has a complex effect on the cytokine system. Some agents such as IL-1 $\beta$ , IL-1 $\alpha$  and IFN- $\gamma$  play a role in virus pathogenesis in mice, but this has not been found in ferrets.

### Pigs as 'mixing vessels'

Pigs serve as reservoirs of H1N1 and H3N2 influenza viruses and are thought to be involved in interspecies

transmission. Several examples of reassortants have been found in Europe and in the USA, causing epidemics in pigs.

These viruses were thought capable of infecting man, reinforcing the hypothesis that pigs act as 'mixing vessels' for influenza viruses. In addition, it has been found that viruses of the same pig subtype are not always identical, and antigenic drift can be observed. This is also true for equine viruses which continue to evolve, and H3N8 viruses, of which there are two distinct subtypes from European and American lineages.

### Animal vaccine strains

It is surprising for those familiar with the strategy of human vaccinations, which involves annual adaptation of vaccine strains to the actual epidemiological situation, to see that this principle is not applied to animal vaccines, even though similar genetic drifts have the same effects on specific immunity. However, the new approach to DNA vaccines in humans has also been applied to horses and pigs. Initially, the vaccines provided partial protection from challenge, though not complete immunity, but once virus-challenged, pigs developed a very strong HI antibody response through a priming effect of the DNA vaccine. Other vaccines include an oil-emulsion vaccine for H5 viruses, used in avian influenza, and the ISCOM vaccine, used successfully in horses. The oil-emulsion vaccine provides a decrease in virus shedding as long as the vaccine and wild strain virus carry haemagglutinin molecules with 90% homology to each other.

Antivirals are also effective against animal influenza. Results of studies with the established agent rimantadine, and the newer zanamivir, have shown an efficacy in animals that is equivalent to that obtained in human studies.

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### Recommendations for vaccination

The Swiss Federal Office for Public Health publishes annual recommendations on vaccination against influenza. As in many other countries, the 1998/99 report recommended influenza vaccination for individuals older than 65 years, for adults and children with cardiac or pulmonary illness, for residents of rest homes and health institutions, and for patients with chronic diseases [1]. For these groups, medical insurance companies guarantee reimbursement of vaccination costs. Also recommended for vaccination were the medical staff and other personnel of health care institutions, as well as the family and contacts of those individuals at risk, but in these cases no reimbursement is available.

In Switzerland, the health authorities of the 23 cantons are free to organise and promote vaccination programmes on a local basis. This leads to inconsistent rates of vaccination coverage within the country.

### Low coverage rates

Switzerland (together with Austria) holds one of the lowest vaccination coverage rates in Europe, with an estimated 61 individuals per 1,000 vaccinated in 1996, 75 per 1,000 in 1997, and 100 per 1,000 in 1998. These figures are based on the quantity of vaccine sold, and so do not give any information about how many people actually receive the drug, and do not take account of the amount of unused vaccine.

Every 5 years, the Federal Office for Statistics conducts a health survey amongst the Swiss population. In 1997, a question regarding influenza vaccination was introduced for the first time. It asked: 'Have you ever been vaccinated against influenza?', with possible answers: 'yes, within the last 2 years'; 'yes, more than 2 years ago'; or 'no, never'.

Of the 10,614 persons who provided information about their vaccination status, 80.6% had never been vaccinated for influenza. Only 11.7% had been vaccinated within the last 2 years, and 7.5% last received the vaccine more than 2 years ago. The details are listed by sex and age group in Table 1.

### Different vaccination rates by region

Dividing the country into three regions depending on the first language spoken reveals differences in the levels of vaccination coverage in the different language areas (Table 2). The higher rates for the French-speaking region can be explained by the 'Tous unis contre la grippe' (Everyone united against flu) campaign, which has been used to promote influenza vaccination in this region for a number of years. It may

also be because of the influence of the French campaign, broadcast on French TV and radio channels, and other media which are easily accessible in that part of Switzerland. These differences in the uptake of vaccination amongst the linguistic regions are consistent with the results of other studies [2,3].

These data confirm that the vaccination coverage for influenza in Switzerland is poor and well below that of its neighbouring countries. It raises the question of whether promotion of influenza vaccination programmes should be coordinated at the national level while taking into consideration the cultural regional differences, or be left to the cantons but with more active support from the national health authority.

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Table 1. Percentage of individuals (n=10,614) vaccinated against influenza during the 2 years preceding the survey (Switzerland, 1997).

Age group	Male (%)	Female (%)	Total (%)
15–24	3.6	4.9	4.3
25–34	3.7	4.4	4.1
35–44	6.0	6.0	6.0
45–54	8.2	8.0	8.1
55–64	10.8	14.5	12.6
65–74	29.8	34.9	32.7
75+	43.9	46.6	45.6
All	10.2	13.1	11.7

Source: Swiss Health Survey, Federal Office for Statistics, 1999.

Table 2. Vaccination coverage rate per linguistic region in Switzerland, 1997 (n=10,614).

Language spoken	Vaccinated in the last 2 years (%)	Last vaccinated more than 2 years ago (%)	Never vaccinated (%)
German	9.7	8.2	82.0
French	17.8	5.9	76.1
Italian	11.2	6.7	81.9

Source: Swiss Health Survey, Federal Office for Statistics, 1999.

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## CONTROLLING INFLUENZA BY INHIBITING THE VIRUS'S NEURAMINIDASE

### Discovery of new drugs

Throughout recorded history influenza has remained a widespread, unpredictable disease with high morbidity and mortality, particularly among the elderly. Despite intensive screening of many thousands of substances for anti-influenza activity, only two drugs, amantadine and rimantidine, were originally found effective in influenza treatment. However, these compounds are only active against influenza Type A, and they cause undesirable side effects and rapid selection for any resistant mutant viruses.

Currently, there are several drugs which seem to be effective in treating all strains of Type A and B virus. They stop influenza virus replication by inhibiting the virus's neuraminidase enzyme. This article will briefly summarise the current status of these drugs.

### Function of neuraminidase

The neuraminidase enzyme cleaves terminal sialic acid groups from carbohydrate side chains on host cell surface proteins and on the haemagglutinin and neuraminidase of newly synthesised influenza virus particles. This destroys receptors for the virus both on the host cell and on the newly formed virus particles themselves and allows the virus to spread through the body. If the virus neuraminidase is inhibited, or absent (e.g. in temperature-sensitive mutants at the restrictive temperature), the newly formed virus particles form large aggregates on the surface of the infected cell and the infection is effectively terminated.

Sialic acid, the product of neuraminidase action, is itself a mild inhibitor of the enzyme. Dehydrated sialic acid (DANA; a transition state analogue) is a much stronger inhibitor. DANA inhibits viral, bacterial and mammalian neuraminidases and although it was shown to inhibit influenza viruses in cultured cells, no *in-vivo* activity was ever found.

Determination of the 3-D structure of influenza virus neuraminidase in 1983 revealed an active site cavity conserved among all Type A and Type B influenza viruses despite wide variation in other regions of the enzyme. This suggested that a 'plug-drug' developed against one strain would be effective against all strains, even those which have not yet appeared in man.

Three such plug-drugs have so far been developed. One (GGI67, zanamivir or Relenza™), has been approved for general use in Australia, most of Europe and the USA; a second (GS4104, Tamiflu™) has been approved in Switzerland and the USA; and the third (RWJ-270201) has performed well in Phase II clinical trials and will be in Phase III trials soon.

### The development of the novel 'plug-drugs'

#### 1. Relenza

Relenza (GGI67, zanamivir) was the first inhibitor to be developed from a knowledge of the crystal structure of influenza neuraminidase. Developed with the assistance of Biota Holdings and Glaxo Wellcome, it is based on the structure of DANA. Studies of this structure when bound in the active site of influenza neuraminidase showed that opposite the 4-hydroxyl group of DANA was a pocket containing two conserved glutamic acid residues, E119 and E227. These did not themselves interact with the substrate, but replacement of this 4-hydroxyl group by a guanidino group resulted in a new compound (GGI67). This inhibited influenza neuraminidase 1,000-fold more than DANA but had little activity against bacterial, mammalian or other viral neuraminidases. The stronger binding of GGI67 was due to ionic interactions of the guanidino group with Glu 119 and Glu 227. However, this added group also conferred such poor bioavailability on GGI67 that it could

only be administered to animals as a nasal powder or spray in order to be effective in stopping influenza virus replication in the respiratory tract.

#### 2. GS4104 (Tamiflu)

Following Biota's success with GGI67, Gilead Sciences in California sought to develop an equally effective, and orally bioavailable, influenza neuraminidase inhibitor which could be taken as a pill.

Crystallographic studies of sialic acid and DANA bound to influenza neuraminidase showed that the C7 hydroxyl of the glycerol side chain did not interact with any active site residue and could be replaced without affecting binding. The X-ray studies also showed the existence of a large hydrophobic pocket in the neuraminidase which acted as a subsite for the glycerol group. Consequently, a carbocyclic sialic acid analogue was synthesised in which the CHOH group at C7 was replaced by O, the rest of the glycerol side chain was replaced by a 3-pentyl group and the OH at C4 was replaced by NH<sub>2</sub>.

The resulting compound, GS4071, was almost as good an inhibitor of influenza neuraminidase as GGI67, but unfortunately also showed similarly poor bioavailability. However, the ethyl ester of GS4071 (GS4104) showed good oral bioavailability and was taken over by Hoffmann-La Roche for clinical testing; it will be marketed under the name Tamiflu.

#### 3. RWJ-270201

This cyclopentane (five-membered ring) derivative was synthesised by BioCryst Pharmaceuticals from a knowledge of the crystal structure of influenza neuraminidase and is a potent and selective inhibitor of the enzyme. This inhibitor is being developed further by Johnson and Johnson, but little information has so far been made available. It appears to be at least as good an inhibitor of influenza neuraminidase as GGI67 and

## OPTIONS FOR THE CONTROL OF INFLUENZA IV: ADVANCE INFORMATION

ESWI is currently organising the next world congress on influenza: 'Options for the control of influenza IV', to be held in Hersonissos in Crete, Greece, 23–28 September, 2000. Like the three previous Options meetings, Options IV is expected to bring together scientists involved in all aspects of influenza research.

The scientific programme will be organised in the form of morning plenary sessions presented by invited experts, followed in the afternoon by parallel workshops and round-table sessions involving a mixture of invited speakers and submitted papers. Disease-related topics will have a prominent place in the programme and will largely focus on the pathogenesis of influenza and the involvement of the immune response in protection and disease development. The role of new generations of vaccines and antivirals – either alone or in combination – to combat influenza at the patient and community level, and topics related to the epidemiology and impact of the disease, will be important



Hersonissos, Crete; venue for the Options IV meeting.

subjects. Also, new insights into the molecular biology and structure-function relationship of the influenza virus will be presented, along with their practical implications for fighting the illness. Finally, our understanding of the ecology of the virus will be addressed.

For practical reasons and to allow for an optimal exchange of information, it has been decided to limit the total number of participants to 800. In the light of the

increased interest in influenza control, stimulated largely by recent developments in several of the areas that will be covered, it is envisaged that a strict policy of acceptance of participants will be adopted. Further details will be provided in the second announcement to be distributed this month.

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GS4071 and, like GS4104, is orally bioavailable.

Preliminary results from a Phase II study showed that healthy volunteers infected with a susceptible strain of influenza A had statistically significant reductions in viral titres after treatment with RWJ-270201. The study also showed that the drug was tolerated at all dose levels.

### Mutant viruses show resistance

Mutant viruses resistant to GGI67 and GS4071 have been found. Some of these resistant mutants show changes only in haemagglutinin and not neuraminidase. These HA mutants seem to replicate well *in vitro* in the presence of

the drugs, but do not appear to be resistant *in vivo*.

Resistant viruses with mutations in the neuraminidase enzyme have also been found. The mutations occur at Glu 119 which changes to Gly, Ala or Asp and at Arg 292 which changes to Lys. However, neuraminidase in these mutants seems compromised in some way; mutant viruses may therefore replicate less well than wild-type in animals. Also, mutant viruses resistant to one of the drugs may not be resistant to the other two.

### Future prospects

Relenza and Tamiflu have proved successful in reducing the severity of influenza infections in clinical trials. Relenza has been approved for use in Australia, most of Europe and the USA, and

Tamiflu has been approved in Switzerland and the USA.

Problems will be encountered, however, with the use of these drugs in the general population. They need to be given very early after infection in order to be effective and need to reach the site of infection at a high enough concentration. Most importantly, they will only be effective against influenza virus, and not against other agents that cause symptoms commonly thought of as 'a dose of the flu'. If these conditions are not met, the drugs might gain an undeserved bad reputation. This would be unfortunate as they do indeed seem to offer an effective and safe way of treating influenza infections caused by all strains of influenza, whether Type A or Type B.

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## INFLUENZA VACCINE UPTAKE AND DISTRIBUTION IN ENGLAND AND WALES

Annual immunisation against influenza is currently recommended in England and Wales for patients at high risk of complications of infection and, more recently, for those aged 75 years and over. Although figures have been available for the total number of influenza vaccine doses supplied in England and Wales, no information has been provided about uptake and distribution of vaccine within population subgroups. A study carried out by the Public Health Laboratory Service (PHLS) Communicable Disease Surveillance Centre to examine this issue [1] aimed to determine overall vaccine uptake and changes over time with specific reference to those at high risk and to those aged 65 years and over.

### Survey of vaccine uptake

The study used records from the General Practice Research Database in England and Wales (maintained by the Office for National Statistics) for the period July 1989–June 1997. This database includes information from consultations with all those patients registered to participating practices. The number of patients covered by this scheme ranged from 362,000 to 2,878,000 in the years studied. Patient demographics were recorded, and in addition, information about influenza vaccine administration and underlying medical conditions was obtained.

### Increase in vaccination uptake

The proportion of patients defined as being at high risk of the complications of influenza increased yearly from 12.3% of all registered patients in 1989–90 to 18.4% in 1996–97. Overall vaccine uptake increased from 6.4% in 1989–90 to 8.6% in 1996–97. In those at high risk, uptake increased from 19.2% in 1989–90 to 23% in 1996–97. Uptake in those with no high-risk medical condition increased very little over this period, from 4.5% to 5.4%.

As expected, vaccine uptake increased with age in both those with high-risk conditions and those with no such condition. In the 65–74 year age group with no high-risk condition, uptake increased from 16.8% in 1989–90 to 22.9% in 1996–97. Among the same age group with high-risk conditions, uptake increased from 32.4% to 43.5%. However, during the 1995–96 study year one-third of high-risk patients who eventually received vaccine were still unvaccinated at the beginning of November.

### Changes in the immunisation policy

Despite improvement, vaccine uptake in high-risk patients remains inadequate; this is particularly so in younger groups.

In addition, high-risk patients remaining unvaccinated after the onset of the influenza season should receive early immunisation. This study was carried out before the introduction of a revised policy in the UK which recommended

*... vaccine uptake in high-risk patients remains inadequate; this is particularly so in younger groups.*

immunisation for all those aged 75 years and over. To examine the effect of the change in policy, the PHLS Communicable Disease Surveillance Centre plans to carry out further analyses using data for more recent years as soon as these are available.

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## INFLUENZA VACCINATION OF HEALTH CARE WORKERS

The elderly and other people with high-risk medical conditions disproportionately bear the burden of serious complications of influenza, such as hospitalisation and death. Health care workers have been found to be important sources or vectors for transmission of influenza to high-risk patients in various health care settings, including hospitals and long-term care facilities. Accordingly, health care workers are

also included among target vaccination groups [1].

### Tangible benefits in controlled trials

Recent placebo-controlled trials have confirmed that vaccination with trivalent, inactivated influenza virus vaccines is highly effective among healthy working adults in general [2] and among health care workers in particular [3].

The benefits of vaccination for the individual include fewer episodes of illness, reduced absence from work, and lower rates of health care use (Table 1). Limited data exist regarding the effect of health care worker immunity on illness rates among patients. One study conducted among 12 nursing homes in Glasgow, however, confirmed that high employee vaccination rates were associated with lower rates of illness and

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death among the residents of these facilities [4].

### Safety of vaccination

Vaccination is also very safe; it is not associated with increased rates of systemic symptoms compared with placebo either in elderly [5] or healthy adult populations [6] (Table 2). Local reactions at the injection site are, however, more common among vaccine recipients, but are generally mild and usually do not interfere with the ability to perform daily activities.

### Disappointing take-up rates

Despite compelling reasons for vaccination, many health care workers are not immunised. One study of physicians and nurses at a medical centre in

Minneapolis found that only 61% of the workers had been immunised [7]. Concerns about vaccine side effects and failure to understand that they were in a target group were the factors most frequently cited for not being immunised. Factors associated with receipt of vaccine, on the other hand, included personal desire to avoid illness, recognition of the importance of protecting patients, and convenient access to inexpensive or free vaccine. Another study of health care workers at the University Hospitals of Geneva found that at baseline 90% of health care workers had not been immunised [8]. The major reasons for rejection of vaccination in this group were confidence in their ability to avoid illness, perceived low risk of illness, and doubts regarding vaccine efficacy. Immunisation rates increased significantly the following season with the implementation of a

multi-faceted programme that included educational elements addressing the specific concerns raised by health care workers. The programme also included on-site availability of free vaccine.

It is thought that interventions to enhance influenza vaccination rates among health care workers should clarify the rationale for vaccination, address issues of vaccine safety and effectiveness, and promote convenient access to inexpensive or free vaccine.

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Table 1. Effectiveness of influenza vaccination in health care-working healthy adults (n=849) [2].

Outcome	Vaccine effectiveness (%) (95% confidence interval, %)	p value
Number of URIs	25 (12–38)	<0.001
Days of URI	20 (2–38)	0.03
Days of absenteeism due to URI	43 (17–69)	0.001
Health care visits for URIs	44 (14–73)	0.004

URI=Upper respiratory tract illness.

Effectiveness of influenza vaccination in health care professionals (n=264) [3].

Outcome	Vaccine efficacy/effectiveness (%) (95% confidence interval, %)	p value
Serologic influenza A	88 (47–97)	0.001
Serologic influenza B	89 (14–99)	0.03
Days of febrile URI	29 (–22–59)	NS
Days of work absenteeism	53 (–56–86)	NS

NS=not significant.

Table 2. Proportion of healthy working adults reporting side effects during the 7 days following vaccination [Adapted from 7].

Symptom	Vaccine group	Placebo group	p value
Fever	6.2	6.1	0.96
Tiredness	18.9	19.4	0.93
Feeling under the weather	16.0	17.5	0.63
Muscle aches	6.2	5.7	0.84
Headache	10.8	14.4	0.14
Arm soreness*	63.8	24.1	<0.001

\*Arm soreness was mild to moderate in >90% of people experiencing local symptoms.

Approximately 90% of people showing these symptoms did not experience decreased use of the arm.

## CALENDAR OF EVENTS – 1999–2000

DATE/VENUE	TITLE	ORGANISER/ SECRETARIAT
10–12 December 1999 Georgetown Cayman Islands	2nd International Symposium on Influenza and other Respiratory Viruses	The Macrae Group Suite 8E 230 East 79th Street New York, NY 10021 USA Tel: +1 212 988 7732 Fax: +1 212 717 1222
3–5 February 2000 Stockholm, Sweden	Winter Meeting of the European Society for Clinical Virology	Professor Anders Vahlne Department of Virology Huddinge University Hospital SE-141 86 Huddinge Stockholm Sweden Tel: +46 8 585 813 13 Fax: +46 8 585 879 33
12–15 March 2000 Munich, Germany	8th Biennial Conference on Anti-infective Agents and Chemotherapy	Futuramed Congress Org. PO 830358 D-81703 Munich Germany Tel: +49 89 671 088 Fax: +49 89 670 01434
16–21 April 2000 Baltimore, USA	13th International Conference on Antiviral Research	Courtesy Associates Suite 710 2000 L Street NW Washington, DC 20036 USA Tel: +1 202 973 8690 Fax: +1 202 331 0111
8–12 July 2000 Fort Collins, 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 6566
23–28 September 2000 Hernissos, Crete Greece	Options for the Control of Influenza IV	Biomedica 101 Rue Mademoiselle Paris 75015 France Tel: +33 140 650 031

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Gardiner-Caldwell Communications Ltd  
Victoria Mill, Windmill Street, Macclesfield, Cheshire SK11 7HQ, UK  
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