



Influenza

INFORMATION AND NEWS ON INFLUENZA

INFLUENZA A (H5N1) IN HONG KONG: A PANDEMIC THREAT?

In May 1997, a three-year-old boy died in Hong Kong after developing a flu-like syndrome. A virus isolated from a tracheal aspirate was characterised as influenza A, but could not be typed further with the panel of antisera used for the characterisation of influenza A viruses in humans and pigs. However, using a panel of antisera directed against all known haemagglutinins and neuraminidases of influenza A viruses, the virus was tentatively classified as H5N1 or H5N4. Sequence analysis confirmed that the virus belonged to the H5N1 subtype [1].

Subsequent sequence analysis of all the gene segments demonstrated that it was related to an avian influenza virus which, in March 1997, had caused the deaths of 7,000 chickens in Hong Kong.

It was concluded that the virus probably did not result from a reassortment event in another mammalian species. Additionally, the virus was highly pathogenic for chickens on experimental infection [2]. By year end, 17 additional cases of H5N1 influenza had been detected in humans; five proved fatal. An avian reservoir was considered the most likely explanation [3] as contact with infected birds at local live poultry markets was established in many cases. On 28 December 1997 this prompted the Hong Kong authorities to order the slaughter of all 1.6 million fowl. Since this action, no new human cases have been reported.

What can we learn from the Hong Kong episode? There was the potential for an influenza pandemic, but the virus's inability to spread through human-to-human transmission limited this. The incident highlighted the importance of being prepared and allowed National Influenza Centre systems and procedures to be tested – the WHO successfully co-ordinated the virological and epidemiological studies required. But research into alternative drugs and studies on the unusually high pathogenicity of the H5 virus are needed.

Following the incident, work preparing a seed virus was initiated, but embryonated chick eggs were not a suitable vaccine substrate since the virus is lethal to chickens. Different strategies,

such as preparing surrogate non-lethal vaccine strains, genetically engineering the original Hong Kong strains to become non-hazardous and preparing recombinant DNA derived haemagglutinin antigens from baculovirus-infected insect cells, are being pursued. We have demonstrated that a vaccine based on adequately adjuvanted glycoproteins of the H5N1 virus is fully protective in the chicken model [4]. Whether the H5N1 virus may acquire pandemic potential on mutation or reassortment cannot be predicted but national and international authorities must do as much as possible to prepare for a pandemic threat.

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INFLUENZA VACCINE STRAINS FOR THE 1998–99 SEASON

Introduction

It is important to make sure that the vaccine virus strains are regularly updated to match those strains causing influenza infections in the community. In February 1998, the World Health Organization (WHO) met in Geneva to recommend influenza vaccine strains for next winter [1]. The following report is a summary of the data reviewed by the WHO.

Influenza activity (October 1997–February 1998)

Although influenza outbreaks due to influenza A (H3N2) have occurred in parts of Asia, the USA and some countries in the southern hemisphere, there has been little activity throughout Europe. However, at the beginning of February, influenza A (H3N2) was reported in several European countries and activity is gradually increasing. In general, the incidence of influenza A (H1N1) and B activity has been sporadic, although outbreaks associated with influenza B have occurred in China.

Antigen characteristics of recent isolates

Influenza A (H3N2) isolates were related antigenically to either A/Wuhan/359/95 (antigenically equivalent to the 1997–98 vaccine strain A/Nanchang/933/95) or to A/Sydney/5/97. Gradually the proportion of A/Sydney/5/97-like isolates has increased throughout the current season.

The majority of influenza A (H1N1) viruses were antigenically related to A/Bayern/7/95 virus (equivalent to the 1997–98 vaccine strain A/Johannesburg/82/96). However, a significant number of isolates from Asia and several isolates from Africa, Europe and North America resembled a variant, A/Beijing/262/95.

Recent influenza B viruses resembled B/Beijing/184/93 and the 1997–98 vaccine virus B/Harbin/7/94. Viruses resembling an earlier reference strain B/Victoria/2/87 persisted only in China and Japan.

Vaccine studies

Current vaccines containing A/Nanchang/933/95 (H3N2), A/Johannesburg/82/96 (H1N1) and B/Harbin/7/94 strains, have been clinically evaluated in adults and the elderly and their post-immunisation antibodies have been tested against a variety of recent viruses.

For the A (H3N2) vaccine component, there were satisfactory antibody responses in approximately 81% of adults and 68% of the elderly, but when antibody was tested against A/Sydney/5/97-like strains, the responses were lower in titre (approximately 50%) and frequency than those to the vaccine strain.

For the A (H1N1) vaccine component, satisfactory antibody responses were detected to the majority of recent isolates in approximately 100% of adults and 96% of the elderly. However, post-immunisation antibody responses to A/Beijing/262/95 were much lower in titre (approximately 80%) and in frequency.

A trial vaccine containing A/Beijing/262/95 virus stimulated equivalent antibody responses to both A/Beijing/262/95-like and A/Johannesburg/82/96-like viruses.

For the influenza B vaccine component, satisfactory antibody responses to the majority of recent B isolates were detected in approximately 96% of adults and 81% of the elderly.

Recommendations for the vaccine composition

The WHO recommended that the following strains are included in vaccines for use in 1998–99:

- an A/Sydney/5/97 (H3N2)-like virus
- an A/Beijing/262/95 (H1N1)-like virus
- a B/Beijing/184/93-like virus.

Influenza A (H5N1)

The situation in Hong Kong is reviewed on the front page by Professor A. Osterhaus. In the absence of continuing human infection with influenza A (H5N1) virus or any evidence of spread beyond Hong Kong, the production of influenza A (H5N1) vaccine for general use was not recommended by the WHO.

Influenza vaccine strains for the European Union

The reference strains nominated by the WHO were accepted for vaccine production by the EU Committee for Proprietary Medicinal Products (CPMP). In addition, the high-yielding reassortants X-127 (antigenically equivalent to A/Beijing/262/95) and IVR-108 (antigenically equivalent to A/Sydney/5/97) were accepted for use in EU vaccines.

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Reference

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THE CASE FOR ROUTINE INFLUENZA IMMUNISATION FOR CHILDREN

Introduction

Despite delivery of record amounts of inactivated influenza vaccine (TIV), excess pneumonia and influenza deaths continue to occur unabated in the USA. High levels of excess mortality reported from 121 US cities for 1997–98 makes this the first season since 1975–76 that high excess mortality has occurred on two successive seasons caused by the same influenza subtype. Although TIV has proven to be effective in significantly reducing influenza-related mortality and hospitalisations, it is not perfect. Chronically ill patients may not have optimal responses to vaccine and may not be accessible for vaccination. Vaccination rates have improved for elderly subjects (about 60%) but remain very low for high-risk patients <65 years of age. It is obvious that a new approach to prophylaxis is needed to control epidemic influenza.

Influenza in schoolchildren

Schoolchildren invariably have the highest attack rates during influenza epidemics. Epidemiological observations document that children are important for the spread of influenza in the community. In the pandemics of 1918 and 1957, even though both viruses were active in the summer, the first wave did not peak until about six weeks after schools were in session. For inter-pandemic periods, schoolchildren predominate among persons presenting to clinics during the early stage of influenza epidemics. The age distribution of culture-positive persons changes during the course of the epidemic, with a shift to preschool children and adults as the epidemic progresses.

Hospitalisations of persons aged ≥65 years of age tend to occur during the last half of the epidemic. These observations support the thesis that schoolchildren are important disseminators of

influenza in the community. In addition, a series of family studies have demonstrated that children are the main introducers of influenza into the household. Furthermore, statistical modelling based on longitudinal community and family studies have confirmed the role of children for introducing influenza into the household and have found that immunisation of schoolchildren would be effective for epidemic control.

Links to other conditions

The high morbidity of children is not without sequelae. About 20% of children <10 years of age have medically attended illnesses during influenza epidemics. Otitis media is a frequent complication of influenza virus infection and immunisation can reduce the overall incidence of acute otitis media by 30%. Virus infections, particularly influenza, trigger asthma attacks that lead to hospitalisation of school-aged children. Children <5 years of age have high hospitalisation rates for pneumonia and other acute respiratory conditions during influenza epidemics; rates average 42/10,000 and sometimes approach the rates for persons ≥65 years of age.

In contrast to the elderly, very few (<15%) of the hospitalised preschool children have chronic conditions that would put them in the priority groups for influenza vaccine indicated by the current recommendations. These hospital rates do not include children with proven influenza virus infections that have major involvement of other organ systems. Febrile convulsions and encephalopathy, myocarditis and pericarditis are common diagnoses. Febrile infants <2 months of age often are admitted for workup to rule out bacterial sepsis. Severe myositis may accompany influenza virus infections – particularly influenza B. Therefore, children have serious morbidity which justifies the prevention that can be afforded by influenza immunisation.

Challenges

The use of licensed TIV is increasing, but even if all high-risk persons among the groups given priority received vaccine each year, influenza epidemics would continue to occur. Healthy schoolchildren, preschool children in daycare, college students and working adults would continue to have high morbidity and would continue to spread the virus in the community. Vulnerable high-risk patients would be at risk because of repeated exposure by contact with infected persons. This is a daunting challenge even for vaccinated high-risk patients.

Pandemics may present another challenge to control efforts because the interval between the recognition of the pandemic virus and the beginning of the pandemic may be brief. The lead time necessary for production of a monovalent vaccine is at least three months. It is unlikely that sufficient vaccine can be produced and distributed in the short time available. Elderly and high-risk patients cannot be mobilised rapidly for vaccination. Schoolchildren represent an accessible population for the rapid delivery of vaccine, which could dampen the spread of the virus in the community and allow more time for delivery to the high-risk groups.

Cold-adapted vaccine

Priorities for the use of vaccine have been discussed and cogent arguments can be made for giving priority for vaccination to several different segments of the population. The resulting tension can be relieved by inserting use of a vaccine other than the currently licensed inactivated vaccine. The live, attenuated cold-adapted influenza vaccine of Maassab that is administered by nasal spray could prove to be an effective tool for epidemic control. The cold-adapted attenuated vaccine has been studied extensively for over

20 years but is not yet licensed. Investigations have shown this vaccine to be superior to inactivated vaccine for children 3–9 years of age and equivalent to inactivated vaccine for older children and young adults. The cold-adapted vaccine has not been tested sufficiently in high-risk patients to allow its use in such patients, thereby reducing competition for use in older subjects. The cold-adapted vaccine would complement the use of inactivated vaccine; if licensed today it would not change the priorities for the use of the inactivated vaccine.

Advantages

The cold-adapted vaccine has several advantages for use in epidemic control. Not only does it provide better protection for children aged 3–9 years who usually have the highest attack rates, but studies also have suggested that the cold-adapted vaccine provides broader and longer-lasting immunity against variants of influenza A. The cold-adapted

vaccine is certainly easier to administer and more acceptable to young children. The important putative advantage of cold-adapted vaccine has yet to be demonstrated – the use for epidemic control. The concept of immunisation of schoolchildren to reduce community morbidity is not new. Monto *et al.* immunised schoolchildren in Tecumseh, Michigan, with inactivated influenza vaccine in 1968 and found lower total morbidity than that experienced by a matching community during the first wave of the influenza A (H3N2) pandemic. Monto suggested at that time that the use of an intranasal vaccine (cold-adapted) might effect epidemic control more readily and at a lower cost.

Several resources now available should facilitate the evaluation of the cold-adapted vaccine for epidemic control. The advantages of the vaccine are listed above. The ready availability of morbidity data from computerised sources will allow assessment of the vaccine's effect. The epidemic can be defined for the community by virological surveillance

which can simultaneously provide validation of the programme. Rates of visits for medical care and of hospitalisations for acute respiratory conditions can be measured for the intervention site as well as the comparison site. The difference in morbidity rates could provide evidence of herd immunity provided by immunisation coverage of school-aged children. Thus, it is evident that routine immunisation of children will not only reduce serious morbidity for the vaccinated children but also has the potential to interrupt the spread of influenza virus to the community.

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Further reading

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ESWI ACTIVITIES

Educational project

One of ESWI's objectives is to provide scientifically based information about influenza and its prevention to the medical profession. In 1997, ESWI distributed a questionnaire to members of the European medical community to ascertain whether there was a need for new training or educational tools. Responses clearly indicated that General Practitioners (GPs) in many countries would welcome a 2–3 page influenza leaflet as an additional aid to existing information. Responders also showed interest in a video tape.

It has therefore been agreed that ESWI will prepare a leaflet on influenza for GPs which, it is hoped, will cut across

the various specific educational needs and national health systems in Europe.

Surveillance and diagnosis

The availability of up-to-date epidemiological data on influenza is dependent on the laboratory techniques used to isolate and identify viruses from clinical specimens. Currently, different techniques are used by different European laboratories. These variations in methodology can lead to complications when comparing data from diverse sources.

To try and address this problem, ESWI has put together an inventory of methods currently used in the laboratories of National Influenza Centres in 28 European countries. A paper based

on this initiative has been submitted for publication and an ESWI-sponsored training programme is now being considered for key personnel in these laboratories who would like training in the most commonly used techniques.

Pandemic plan

The World Health Organization (WHO) and ESWI are working together to develop a pandemic plan that describes different phases of pre-pandemic and pandemic periods. The objective is to provide a generic skeleton plan which national health authorities subsequently can adapt to their own health systems. In some countries, tailor-made pandemic contingency plans already exist, but many countries do not have such plans in place yet. ▶

NEW DEVELOPMENTS IN INFLUENZA VACCINES

Current inactivated influenza vaccines need to be adapted annually to accommodate continuous antigenic changes of the surface glycoproteins of the virus. Each year it is a race against time to produce sufficient quantities of vaccine that will be efficacious against the strains most likely to cause epidemics during the next influenza season.

Although the benefits of the current inactivated vaccine have been shown in numerous studies, especially in reducing complications in the elderly, efficacy concerns may give rise to doubts about its usefulness and contribute to conservative vaccination practices by some physicians. The recent episode in Hong Kong has also highlighted the difficulty of producing a vaccine from an unmodified human H5NI isolate because of its high pathogenicity for chick embryos as well as for humans.

The production of a high growth reassortant has been proposed to bypass this problem. But it is clear that the unusually large number of vaccine doses that will be required in case of the emergence of an influenza pandemic strain necessitates a more rapid production of vaccine.

Alternative approaches for obtaining large quantities of vaccine quickly are currently in development, for instance, vaccines prepared by cell-culture techniques which may potentially yield vaccines that are antigenically more closely related to circulating strains and therefore have improved immunogenicity. Other approaches to increase the effectiveness of inactivated influenza vaccines are also being developed: adjuvants, purified neuraminidase, liposomes, virosomes, immune-stimulating complex, CTB-conjugated vaccines, synthetic peptides, recombinant vaccines and DNA vaccines. Some of these new vaccines were marketed during the last influenza season: a virosomal vaccine was available in Switzerland and an adjuvanted influenza vaccine in Italy.

All of these new technologies are promising, but it must be kept in mind that any new vaccine (assuming it has a similar safety and tolerability profile to the existing vaccine) should offer one or more advantages over the current vaccine, such as mucosal and cellular immunity, decreased production time, lower production and administration costs, improved compliance, more convenient routes of administration, etc.

Cold-adapted live attenuated vaccine, developed in Russia 30 years ago and now widely tested in the USA, seems to be a promising vaccine for children. It has been shown to be safe and highly immunogenic in this population so take-up should be high. The concept of a *master strain*, which is able to transfer the attenuation properties to new variants among recent circulating strains has raised the possibility of single administration to children while adults and the elderly will continue to receive the inactivated vaccine annually.

Despite the shortcomings of inactivated influenza vaccines and the prospect of more efficacious vaccines in future, increased use of current vaccines in accordance with national immunisation policies is the only way to reduce the recurrent burden of influenza epidemics. The use of existing antiviral drugs as well as the development of new antiviral drugs should enable countries to meet this important public health objective.

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ESWI activities (cont'd)

In light of the recent emergence of the H5NI avian influenza virus, the pandemic plan has been revised to take account of situations that had not been considered when the original draft was prepared. The final version of the plan will be published after appropriate internal peer review procedures have been completed.

Socioeconomics of influenza

In 1995, ESWI organised an international symposium to evaluate the socio-economic aspects of influenza epidemics and control measures for the

disease. The proceedings of the meeting were published in *PharmacoEconomics* (1996; 9 suppl 3: 1–81). A review of the available literature showed that different methodologies were used to assess the economic benefits of vaccination programmes. Although the literature demonstrated the economic benefits of vaccination programmes, the data were considered insufficient to generalise the results. Since 1995, a number of new economic evaluations have been performed and the results of some have been published. In light of this new information, a follow-up meeting will be held in October 1998 in Geneva, Switzerland, as part of a larger meeting

to be organised by the WHO to celebrate the 50th anniversary of its influenza surveillance programme.

Options for the Control of Influenza IV meeting

ESWI has been asked to organise the Fourth International Conference on Options for the Control of Influenza which will take place in Europe in the year 2000. More information will be provided about the location, date and Organising Committee in the next issue of this bulletin.

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JUSTIFYING THE COST OF IMMUNISATION

In the October 1997 issue of *Influenza* (No. 7), Dr Fleming's article appeared to attempt to justify the NHS 'costings' (or lack of same) for routine influenza immunisation. It caught my attention because it did not have a conclusion (e.g. is the current policy effective?), but appeared to emphasise the cost of vaccine rather than lives or healthcare expenditures saved by the vaccine. In fact, when one does look at the cost of caring for persons ill with influenza (direct cost), and particularly when one looks at lost productivity (indirect cost), it becomes apparent that influenza vaccine is extremely cost-effective. It has been said to be more cost-effective than mammography and screening for cervical cancer via pap smear. I personally have never understood why the Chief Medical Officer (CMO) in the UK does not support the use of influenza vaccine more enthusiastically, particularly since the cost of healthcare is supported by the Department of Health. I have always been reminded by my UK colleagues that it is too expensive to lower the age or recognise additional risk factors as justification for providing vaccine to more of the 'at-risk' population. However, the real cost of providing healthcare to ill patients is far more expensive than preventing a disease such as influenza even though vaccine is more expensive in the UK (about twice as expensive as the USA).

In general, the medically at-risk group of a developed country is about 20% of

the population and as we improve the health of those citizens with the risk conditions, the percentage will increase to a higher absolute number. Influenza has many outcomes when it strikes. Usually, about 10% of the population will develop clinical symptoms in any given outbreak. Untreated, those adults or students will not be able to attend work or school for about three days, and they will spread the disease to many other susceptible persons if they do. (Treatment of infected patients with amantadine or flumadine will decrease the risk of spread and decrease the days of lost work or school.) Many thousands of people will develop minor but costly respiratory infection complications such as bronchitis, sinusitis, otitis media, or more seriously, pneumonia. Acute myocardial infarction and stroke also rise during an influenza outbreak. In the USA, about 10,000–40,000 people will die of these three serious complications of influenza. Vaccine has been shown to reduce morbidity in every age group ever studied and reduce mortality (about 60–95% effective depending on age) in the high-risk and elderly patient.

I believe that Dr Fleming should emphasise that preventive care policies should be based not on the cost of the policy, but on the savings or cost/benefit aspects of any given preventive medicine policy [1, 2]. Though Dr Fleming did not put forth a conclusion in this paper, he did emphasise the cost of expanding

the use of influenza vaccine. I would encourage Dr Fleming and the CMO to rapidly and broadly expand the use of influenza vaccine [3, 4]. I also recommend that resources be allocated to determine what the true direct and indirect costs of influenza are to the UK health system. I think they will discover that aggressive use of vaccine would save the UK taxpayer millions of pounds of healthcare expenditures.

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review and changed only on the basis of sound evidence. Initiatives have been taken in the UK to evaluate the costs of influenza and benefits of vaccination in the low-risk population aged 65 years and over.

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Dr Fleming replies

The report estimates the size of the population at risk given present policy for influenza immunisation in England and Wales and goes on to estimate the impact of variations from that policy. Dr Mostow states that about 20% of the population of a developed country is at risk. The figure depends on the definition of risk and how carefully it is measured. I estimated 11.8% of the population and this figure was derived

from a large population (500,000) monitored for a year. This figure is very similar to the 11.6% estimated by Govaert in The Netherlands [1].

I agree with Dr Mostow that preventive care policies need to be established on the basis of cost/benefit analysis. Whilst studies of clinical effectiveness may be transferable between countries and healthcare systems, studies of cost-effectiveness are not. Preventive care policies should be kept under constant

ANTIVIRALS FOR INFLUENZA

Each year about 5–20% of the population is infected by influenza. Since routine vaccination is generally recommended only for elderly people and those with chronic medical conditions, the social and economic burden of influenza remains enormous. Antivirals are required that: are effective against both influenza A and B, are inexpensive and easy to administer; can be given intravenously in life-threatening situations and have negligible adverse effects; are safe during pregnancy, effective prophylactically and therapeutically, and do not lead to drug resistance. How close are amantadine and rimantadine and the new neuraminidase inhibitors to the ideal drug?

Amantadine and rimantadine

Amantadine and rimantadine inhibit H1N1, H2N2 and H3N2 strains of influenza A but are inactive against influenza B. They inhibit equine and avian influenza A, including the H5N1 virus, and future pandemic strains should be susceptible. Early expectations were diminished by observations that resistance of influenza A viruses could be readily obtained in the laboratory. Resistance emerges frequently and rapidly during treatment, and resistant strains are genetically stable, transmissible, and cause treatment-resistant disease.

Both drugs cause similar dose-related adverse effects, mostly mild central nervous system effects and gastrointestinal symptoms. However, due to differences in their pharmacology, these occur more frequently with amantadine, especially in the elderly in whom hallucinations, anxiety, weakness, ataxia, falls, dizziness, increased confusion, psychoses and insomnia are reported.

Prophylaxis with amantadine or rimantadine during outbreaks reduces illness rates by 70–90% and infection by

40–80%. Post-exposure prophylaxis in the family setting is highly effective when either drug is given to contacts only. The emergence of drug resistance renders post-exposure prophylaxis ineffective when the agents are given to contacts and index cases simultaneously. Uncontrolled studies suggest that mass administration to elderly residents of nursing homes interrupts transmission of influenza A. This approach involves simultaneous treatment of cases and contacts and has led to the emergence and possible transmission of drug-resistant virus among residents.

Both drugs are effective as treatment for naturally occurring influenza A when given within 48 hours of onset. They ameliorate influenzal illness and fever and reduce the duration of illness by about 24 hours. Peripheral airways abnormalities also improve more rapidly.

Neuraminidase inhibitors

During the early to mid-1970s, analogues of sialic acid were found to inhibit influenza replication in cell culture but were inactive in vivo. The prototype inhibitor (Neu5Ac2en) was subsequently modified and 4-Guanidino-Neu5Ac2en (GGI67 or zanamivir) was found to be a potent and highly selective inhibitor of a wide range of influenza A and B viruses in vitro. In animal models, zanamivir was effective when given by both intranasal and aerosol administration and when started before infection or shortly afterwards. It has poor oral availability and failed to protect chickens (in whom some avian strains spread beyond the respiratory tract) when drug and virus were given by the intra-tracheal route. However, influenza infection in man is largely confined to the respiratory tract.

A third generation of neuraminidase inhibitors was developed to be effective

orally. GS4104, an Neu5Ac2en analogue, is an ethyl ester pro-drug with in vitro activity against influenza A and B comparable to zanamivir. It is effective orally in animal models of influenza infection, was well tolerated in phase I studies and its efficacy is currently being evaluated in man.

Mutants with decreased sensitivity to the neuraminidase specific inhibitors have been isolated in vitro, but they do not arise readily, and their relevance to man remains to be established.

In an experimental model of human influenza, twice daily intranasal zanamivir was well tolerated. Prophylaxis was 82% effective in preventing laboratory evidence of infection and 95% effective in preventing febrile illness. Early treatment reduced the median duration of viral shedding by three days and the frequency of febrile illness by 85%. Prophylaxis or early treatment also reduced the incidence of middle ear pressure abnormalities in experimental influenza A and B.

In a randomised, double-blind, placebo-controlled study, the median length of time to alleviation of major influenzal symptoms was one day shorter (4 vs 5 days) in patients given inhaled and intranasal zanamivir and in those given inhaled zanamivir alone than in those given placebo. A reduction in the time to alleviation of symptoms was seen only in patients with fever of $\geq 37.8^{\circ}\text{C}$ at enrolment (58% of subjects), and in those in whom treatment was initiated within 30 hours of onset (50% of subjects).

Summary

The use of amantadine and rimantadine should be guided by a careful assessment of potential risks and benefits and by diagnostic considerations. Both are effective prophylactically during community outbreaks but their potential adverse effects restrict their use to

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those with high-risk conditions. Great benefit could be gained from wide-spread prophylaxis during a pandemic, but it is unlikely that more than a minute fraction of the global population could be treated given current supplies.

Post-exposure prophylaxis is effective but requires confirmatory diagnostic testing of the index case for optimal use. Drug administration during institutional outbreaks involves both treatment and prophylaxis which is ineffective in the family setting. Residents are monitored closely for influenza illness and therapy is initiated immediately if influenza is in the community. However, without diagnostic testing of index cases, drug administration could be inappropriate since illnesses caused by other respiratory viruses are clinically indistinguishable. This approach requires a considerable amount of organisation, not least to ensure that patients do not have renal impairment. Moreover, unless the

outbreak is recognised and dealt with quickly, there is a danger that any benefits from treatment are outweighed by the risks.

Treatment studies reveal modest benefits from both amantadine and rimantadine in the treatment of established influenza. Few practitioners follow this strategy, however, either because patients present too late, or because of difficulties in diagnosis, or lack of awareness.

The new neuraminidase inhibitors offer hope for the future, primarily because they are active against influenza B, seem to be well tolerated, and resistance is evidently more difficult to generate in vitro than with amantadine and rimantadine. Whether they are used or not may depend upon the availability of an inexpensive, rapid, near-patient diagnostic test.

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IN MEMORIAM

It is with great sadness that we report the death of Karin Esteves. Karin, who worked with Daniel Lavanchy at the World Health Organization, died suddenly on 29 April 1998. We extend our deepest sympathy to her family and colleagues.

NEW MEMBERS

ESWI is pleased to welcome Dr Isabella Donatelli and Professor Albert Osterhaus as members of the group. Dr Donatelli, a virologist, is Director of the National Influenza Centre, Instituto Superior de Sanita, Rome, Italy. Professor Osterhaus works in the Department of Virology at Erasmus University, Rotterdam, The Netherlands.

INFLUENZA BULLETIN

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