



EDITORIAL

The 24th edition of ESWI's *Influenza* bulletin is being published on the eve of the Third European Influenza Conference to be held in Vilamoura, Portugal, 14–17 September. The conference is being organised as part of our group's 15th anniversary celebrations. The comprehensive programme, contributions from renowned chairpersons and speakers, and truly innovative concept, will all combine to ensure a successful and highly valuable ESWI gathering.

It is also important to remember that the ESWI conference serves as a reflection of our overall strategy as laid down in our policy and action plans. The responsibility for reducing the impact of epidemic and pandemic influenza on society is one that is shared by many different parties. ESWI aims to support this effort by identifying and communicating with the stakeholders and providing them with opportunities for interaction. In its work so far, ESWI has contributed to setting up Country Influenza Stakeholder Networks in different European Union countries. By implementing their jointly developed action plans, i.e. carrying out the various influenza activities agreed upon, national stakeholders are able to make considerable progress in the fight against influenza. In all countries, the active support of policymakers and healthcare professionals has proven key to the success of the network.

ESWI's strategy pays particular attention to healthcare workers (HCWs), given the crucial role they play in increasing influenza

vaccination coverage rates worldwide. Evidence shows that the proactive behaviour of general practitioners is the main driving force behind many at-risk patients deciding to have their influenza vaccination. Unfortunately, for a variety of reasons many HCWs underestimate the importance of their role.

To address this, the conference will see ESWI launch its 'Online influenza knowledge centre for healthcare workers'. This attractive and user-friendly web application aims to inform HCWs on the ins and outs of seasonal, pandemic and avian influenza, and to encourage them to vaccinate their at-risk patients and also to be vaccinated themselves. Scientists and policymakers are encouraged to actively promote and share this valuable tool among the leading healthcare professionals they deal with in their work. ESWI's online flu centre can be used free of charge at www.flucentre.org.

Another cornerstone of ESWI's policy is the support provided to young scientists. Through the Young Scientist Fund, named after ESWI's founding chairman Professor Claude Hannoun, ESWI has provided grants to some 50 promising scientists. Successful grant applicants will play an active role in the Third European Influenza Conference, each presenting their research either orally or in poster format. In addition, 12 young scientists will act as co-chairs during all scientific sessions at the conference. The organising committee based this innovative

decision on the evaluation of the Second European Influenza Conference, where the young scientists' contributions received high praise. This move also fits in with ESWI's ongoing commitment to the future of the influenza field.

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CONTENTS

- PAGE 1** – Editorial
- PAGE 2** – How to evaluate vaccine effectiveness
- PAGE 2** – The ethics of mandatory vaccination against influenza for healthcare workers
- PAGE 3** – The fourth orthomyxovirus research conference: a report by the young scientist award winner
- PAGE 4** – ESWI's general strategy towards young scientists
- PAGE 4** – Report on DG SANCO's vaccination strategy workshop 13–14 February 2008
- PAGE 5** – Oseltamivir resistance: current insights
- PAGE 6** – 15 years of ESWI
- PAGE 8** – Calendar of events



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HOW TO EVALUATE VACCINE EFFECTIVENESS

Inactivated influenza vaccines were developed more than 60 years ago in the setting of World War II to protect young adults in the military from influenza-related morbidity. Repeated placebo-controlled trials, using mainly serologic endpoints, showed that the vaccine was 70–90% efficacious in preventing influenza infection. However, severe influenza morbidity and mortality has long been recognised to occur mainly in older individuals plus those with defined chronic medical conditions. Controlled trials have only rarely been carried out in these populations. Such trials became more problematic ethically as more and more countries recommended the use of vaccine in these high-risk populations, even though efficacy has been repeatedly demonstrated only in younger people.

In the USA in the early 1990's, a priority was placed on demonstrating influenza vaccine effectiveness in those aged 65 years and older for the prevention of hospitalisation. The first three studies, all observational in design, were carried out with somewhat different methods. However, they came up with similar results, that standard influenza vaccine prevents at least 30% of all hospitalisations for cardiorespiratory outcomes during the influenza season [1–3]. As many of these hospitalisations, during broadly defined influenza periods, are not influenza related; these results were considered a very positive demonstration of the value of vaccination. In these and subsequent vaccine effectiveness studies for serious outcomes, there was no attempt to identify the causative organism; influenza seasons were defined using viral surveillance data and not laboratory results from study participants. Studies using all-cause mortality as the outcome have suggested that up to 50% of winter deaths might be prevented by influenza vaccination [4].

All of these studies were observational in design (i.e. not randomised trials), and each made adjustments in analyses because of differences

found between vaccinated and unvaccinated individuals. For example, these studies consistently demonstrated that vaccinated individuals tended to have more underlying medical conditions; that is, they were thought to be less healthy than those not vaccinated. Those vaccinated, being less healthy, would be more likely to have severe outcomes, and adjustment for these differences resulted in an increase in estimates of effect. Thus, the issue of how adjustment was carried out was always of concern. It was noted in some studies that there was no vaccine effectiveness during the summer, when influenza was not present; indicating that the adjustment had been properly handled.

Recently, it has been pointed out that this type of analysis could be overestimating vaccine effectiveness in older populations, particularly with regard to mortality effects [5]. In the USA and some other countries that have increased annual vaccine coverage among the elderly, there should have been a fall in mortality in the winter season. Such a drop has not been observed. Also, when looking at observational studies themselves, it has been found that the vaccinated, instead of being less healthy than the unvaccinated, may actually be healthier when health status includes assessments of functional status, such as ability to eat or bathe without assistance [6]. Those not vaccinated have been found in several recent studies to have decreased functional status, and these disabilities have not, in general, been recognised using information available in administrative databases.

This controversy concerning possible confusion in assessments of influenza vaccine effectiveness in the elderly, and the kind of studies necessary to resolve it, will be discussed at the ESWI meeting in Vilamoura. The Cochrane collaboration report will serve as background [7]. This meta-analysis synthesises a number of studies, almost all of which were observational in nature. Thus, studies of different methodologies were included. Differentiation was made between influenza that

was laboratory confirmed and influenza-like illness that was not. However, in the later category, there was a great deal of heterogeneity in case definitions used. Controlling for confounding again was an issue in these studies. Overall, it was concluded that among both those in nursing homes and those independently living, no efficacy could be demonstrated against laboratory confirmed disease, largely because of small numbers. However, there was effectiveness in nursing home residents against influenza-like illnesses and more severe outcomes such as hospitalisations. In the independently living elderly, the vaccine did not appear effective in preventing influenza-like illness, perhaps because of definitions used. It was found to be effective in preventing hospitalisations for diagnoses such as influenza, pneumonia and other cardiorespiratory outcomes.

Unlike the meta-analytic approach of the Cochrane collaboration, at Vilamoura we will be focusing on individual studies and their methods in an effort to understand the current evidence base for vaccine effectiveness among the elderly. We will also be discussing new approaches that may be used to resolve unsettled issues.

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THE ETHICS OF MANDATORY VACCINATION AGAINST INFLUENZA FOR HEALTHCARE WORKERS

Introduction

The risk of influenza-related complications among patients, who are often both frail and elderly, is particularly high and the possibilities for individual patients to protect themselves are limited, since

even vaccination results in a protection of 50–70% of the population at best. Vaccination of healthcare workers (HCWs) in long-term care facilities results in indirect protection of patients who are at high risk of influenza [1,2]. Furthermore, influenza can

have a disrupting effect on the continuity of care. On these grounds some organisations have issued guidelines in which influenza vaccination of HCWs is recommended. In spite of these recommendations, the uptake of influenza vaccination among HCWs in

response to voluntary vaccination programmes is generally incomplete. One may ask, therefore, whether it is necessary and morally justifiable to impose a mandatory vaccination programme. The aim of this article is to evaluate whether mandatory vaccination is justifiable. We focus our discussion on the vaccination of HCWs in long-term care facilities.

Voluntary vaccination programmes

Several studies imply that vaccine uptake can be significantly raised by combining several interventions in a vaccination campaign [3]. It is also important to realise that even a relatively modest increase in vaccine uptake may have a significant impact on the health of nursing home residents. A 50% uptake might serve as a reasonable and defensible threshold at the moment. Given the evidence stated we think healthcare institution boards have a moral obligation to reduce avoidable risks for persons within the institution. Therefore, they ought to implement voluntary vaccination campaigns directed at HCWs who, during their work, are in close contact with residents. It remains possible though that even a state-of-the-art voluntary campaign does not result in a vaccine uptake of more than 50%. Would it be justifiable ethically to introduce mandatory vaccination?

Some arguments in favour of mandatory vaccination

When we speak of a mandatory programme we mean a conditional one in which yearly vaccination is considered to be a requirement for the job. Generally speaking people have a moral obligation not to harm each other. When infecting someone else could have been prevented, but is not, this can be regarded as harming that person. This is relevant not only in cases where one knows oneself to be infected but also when one is not aware of being infected and transmission may be prevented by taking general preventive measures. Some possible limits to what can be reasonably expected from someone would be where the burden of taking the preventive measure

outweighed the benefits for others, or if a measure involved significant risks for the vaccinated person. On balance we consider that the duty not to infect others holds in the case of influenza, as the considerable benefits for the nursing home residents outweigh the rather small burden and risks on behalf of the HCWs. If the duty not to infect others is a duty for all individuals, then this will certainly be an important one in healthcare, since health is a primary value.

One could argue that it is one thing to expect HCWs to provide benefits for patients and to expect them not to directly harm them, but it is quite something else to expect HCWs to harm themselves in order to benefit their patients. This would seem to be a reasonable position if indeed harm would be involved. However, to describe the influenza vaccination as harmful seems implausible. Yet, some will see vaccination as harmful indeed: the conscientious objector. To him we will turn shortly.

Some arguments against mandatory vaccination

Mandatory vaccination programmes involve constraints to personal autonomy and freedom of choice. The least one can say is that a strong justification is needed for such constraints. Such a justification would seem to follow from the serious effects an influenza infection may have on the frail elderly. The argument of harm to others would seem to justify some limitation of autonomy for those caring for the frail elderly. Obviously, it would be morally superior if sufficient vaccination rates could be reached with voluntary influenza vaccination programmes.

Institutions mandating immunisation of HCWs may find resources consumed with tracking persons who do not comply with the programme. These opportunity costs may limit the resources available for education and free access to vaccinations. However, the same argument could also be used as an argument for mandatory vaccination. Performing time-consuming educational programmes to increase voluntary vaccination uptake may diminish opportunities in terms of time available for normal care.

What place for conscientious objectors?

Arguments from conscience or philosophical objection have a long tradition in the debate about mandatory vaccination. We think any mandatory programme should grant conscientious objectors the possibility of refusing vaccination without any consequences. While we consider it justified to require the objectors to state the reasons for their objections, it doesn't seem possible to distinguish between legitimate and illegitimate reasons. Therefore, we use the term 'conscientious objectors' in a rather broad sense, covering all individuals who have – subjectively – strong reasons to object to the vaccination. This policy will at least have the benefit of requiring HCWs to consider the consequences of their omission in relation to vaccination.

Conclusion

In conclusion we think that long-term care institutions caring for the frail elderly have the moral responsibility to implement voluntary programmes for vaccination of HCWs against influenza who are in direct contact with these residents. When the vaccination uptake remains below a certain level a mandatory programme may be justified. The main justification stems from the duty of HCWs not to harm a patient when one knows there is a significant risk of harm through infection and the intervention to reduce this chance has a favourable balance of benefit (effect) over burdens and risks. Whilst we see a place for conscientious objection, this should not be confused with ignorance or indifference towards the benefits of greater uptake of influenza vaccine among persons working in nursing homes.

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THE FOURTH ORTHOMYXOVIRUS RESEARCH CONFERENCE: A REPORT BY THE YOUNG SCIENTIST AWARD WINNER

An award is almost always a good thing, especially when that award is associated with some amount of prestige. Better awards tend to come with prestige, and the added bonus of money or some other highly desirable commodity, like an iPod. However, some awards come with penalties but the

penalties of the really good prizes can be worth more than the award itself.

The ESWI awards for the best oral and poster presentations at the 2007 Orthomyxovirus Meeting in Woods Hole, Massachusetts, USA were iPods and I

felt honoured to receive an award. I had just spent 2 days with approximately 75 of the best young scientists involved in influenza research. The talks started first thing in the morning and ran until late in the evening, with short breaks for meals in between. After dinner we would all pour into the

(Continued on page 4)

bar where the liquor flowed and informal conversations continued until the small hours of the morning. Every person at the meeting had either given a talk or presented a poster and so no-one escaped without presenting at least a little bit of science. By the time the meeting was over I was exhausted, I hadn't slept much and I'd been talking science for almost 3 days straight but then the meeting wasn't meant to be a holiday, it was an opportunity to meet and learn from other young scientists. When the ESWI awards were announced I was pleased to get a shiny new iPod.

It wasn't until after leaving Woods Hole that I found out what I had really won. The iPod turned out to be a little teaser award, a little bit of padding before the real award hits. When you win an ESWI award you become involved with ESWI – the penalty that is its own sort of award. My involvement with ESWI

initially assumed the form of coordinating the Young Scientist Grants for the Third European Influenza Conference to be held in Vilamoura, Portugal in September. This involved advertising the grants, reviewing the applications, and coordinating the involvement of the other Orthomyxovirus Meeting ESWI prize winners. The ESWI award winners, along with a few others, have selected the Young Scientist Grant winners and organised the Young Scientist Plenary Session for the Vilamoura meeting. Along with Claude Hannoun, I have been given the pleasure of chairing the session.

I learned a lot about organising a conference from working on the Young Scientist Grants and Plenary Session but once those organisational tasks were mostly settled my now not-so-shiny-new iPod bought me some quality time with the abstracts for

the rest of the Vilamoura meeting. As other members of the organising committee before me, I read every single one of the approximately 300 abstracts submitted for the conference to help shape the poster session of the meeting. At first a little daunting, it turned out to be an amazing opportunity to get a very broad view of the current state of influenza research and get involved in the meeting at a much deeper level.

Looking back to the Orthomyxovirus Meeting in Woods Hole, if there had been a choice between an iPod and the 'opportunity' to read 300 abstracts for a meeting in Portugal I would have naïvely chosen the iPod. However, knowing what I know now, give me the 300 abstracts . . . and the iPod.

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ESWI'S GENERAL STRATEGY TOWARDS YOUNG SCIENTISTS

ESWI has been actively encouraging the careers of young scientists for many years, young scientists are the lifeblood of our field. Some of the best and most innovative ideas come from young scientists, they do much of the heavy lifting on many projects, they are often fun, and most importantly, they are the future. It benefits us all if the best stay in our field.

In 2001, Ron Fouchier came to us with the idea for the Orthomyxovirus Meeting. A meeting he said which would be wall-to-wall science from early to late, with short meal breaks, then to the bar afterwards for more science. Most importantly a meeting where 'the people actually doing the work presented, and the grey-hairs were in the audience'.

ESWI sponsored the meeting without a moment's hesitation, and have done so for each subsequent meeting.

The ESWI prizes for best presentations and posters at the last two orthomyxovirus meetings have included a full scholarship and a talk in the Young Scientist Plenary Session at the European Influenza

Conference. At the Second European Influenza Conference in Malta, we were told by a number of people that the Young Scientist Plenary was the best session of the meeting. We much look forward to the Young Scientist plenary at the Third European Influenza Conference in Vilamoura.

ESWI also gives young scientist scholarships to other young scientists to attend the European Influenza Conference based on an open competition. The ESWI Young Scientist Fund is named after Claude Hannoun, the first ESWI chair, and promoter of young scientists for many years. There were 20 available at the last two conferences and for the next conference more than 50 have been awarded, 28 from Europe, and 26 from the rest of the world.

At this year's conference, the co-chair for almost every scientific session will be a young scientist. We will also add a young scientist as a full voting member of ESWI. We will pay special attention so that the member will have as little as possible time taken away from science, but we want their representation, and we want them to have an opportunity to contribute in a policy setting.

In Vilamoura we will announce the winner of a new initiative, a prize for a body of work by a young scientist. The competition is open to all young scientists throughout the world, and will be judged by an international committee spanning all of influenza.

Finally, there are the hands-on laboratory training courses. These courses last a week and teach basic influenza laboratory work. These have been run three times, at the Institute Pasteur in Paris, France once and at Erasmus MC in Rotterdam, The Netherlands twice, each time with about 20 participants.

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REPORT ON DG SANCO'S VACCINATION STRATEGY WORKSHOP 13-14 FEBRUARY 2008

Introduction

From 13-14 February 2008, a workshop on vaccination strategy was held in Luxembourg. The aim of the workshop was to merge specialists from

academia, government and industry to share their expertise and knowledge in the field of vaccination strategies. Although the benefit of vaccines is clearly indicated, vaccination coverage rates in at-risk

populations are quite low on average. However, the European Commission developed several initiatives with the intention to combat the burden of infectious diseases at European Union (EU) level.

One example is the Council Recommendation for Member States (MS) to achieve a 75% seasonal influenza vaccination coverage rate in at-risk groups. Additionally, a proposal is in progress to amend and sustain high vaccination coverage against particular childhood diseases.

For achieving this goal, scientific advice, surveillance and international collaboration while respecting the national autonomy in the area of immunisation should lead to common policies in the future.

Results from the workshop

During the first day, the spotlight was on disease elimination through vaccination, especially on the role of the EU in supporting MS to reach the target of the World Health Organization (WHO) strategic plan on measles and rubella. However, this report will focus on the second day, which was dedicated to the seasonal influenza vaccine. Vincent Houdry (DG SANCO C3) underlined in his presentation that influenza continues to be a considerable health problem in Europe, especially in at-risk people. The European Parliament supports the significance of improving the seasonal vaccination coverage rates in the population by the resolution on the strategy against an influenza pandemic, which determines the coverage rate of the elderly to 75% by 2010/11 [1]. Nevertheless, the current vaccination coverage survey data have shown that most MS are far from reaching this target. A survey in 11 European countries conducted by the University of Zurich, Switzerland, showed vaccination levels in the elderly ranging from 23% in Poland to 70% in Spain (average across all countries: 51%). Even lower was the coverage among chronic illness sufferers under the age-defined limit (ranging from 14% in Poland to 59% in the UK). Advice from the family doctor or nurse and receiving further information about the vaccine regarding tolerance and efficacy, as well as knowing more about the disease itself, would have encouraged more people to get vaccinated.

In order to improve the overview on current vaccination programmes and how they are realised and

monitored, the VENICE (Vaccine European New Integrated Collaboration Effort) survey was implemented by the European Centre for Disease Prevention and Control (ECDC). There is an almost complete convergence of European policies on seasonal influenza vaccination, which underline the elderly group and those with chronic diseases as at-risk groups who deserve influenza immunisation. The data indicated the similarities and discrepancies between countries, with special focus on the vaccination uptake in the elderly. However, the results from the study emphasised the fact that vaccines are underused in many countries and are far from reaching the WHO targets.

Immunisation policies in The Netherlands and Czech Republic were presented focusing on measles and rubella elimination, human papillomaviruses and seasonal influenza vaccination. The Dutch government has a National Immunisation Programme, which makes vaccines free of charge but not obligatory. Hence, the coverage in primary care centres and nursing homes is considerably high. On the other hand, the Czech system showed outstanding coverage rates in obligatory vaccinations, but a very low level in the recommended vaccinations like influenza, as the recommended vaccinations are not perceived as essential by the Czech population.

In working groups, approaches to improve vaccine uptake were determined. A principal postulation was a clearer definition of target groups that should benefit from seasonal influenza vaccination. Healthcare workers (HCWs) seem to play an important role in recommending the vaccine to their at-risk population. Nevertheless, healthcare professionals indicate extremely low vaccination coverage and are often disinclined to promote vaccination. Reasons for their reservation towards vaccination are still not fully established and need further investigation. Furthermore, to enhance vaccination coverage rates, key drivers have to be activated and barriers remedied. The realisation of the following actions were deemed to be promising: information campaigns on seasonal influenza immunisation among at-risk groups and HCWs,

the opportunity of an explicit incentive for HCWs who carry out vaccinations, and ameliorate access to vaccine on a practical and a financial level. Finally, the monitoring and surveillance of the development of influenza vaccination coverage rates have to be invariably put into practice.

Conclusion

The vaccine uptake of MS differs widely and is in most states far from the 75% vaccination coverage target. For reaching the objective in the elderly group by 2010/11 strong efforts must be undertaken from each MS. However, reasonable endeavours have to be used at national and international levels to enhance coverage rates in all target groups. A more precise definition of the at-risk groups, a scientific focus on the impact of vaccination, the need for studies on principal driving forces and barriers in all MS, the information and education campaigns towards at-risk groups and also the involvement of HCWs in vaccination campaigns could lead to a positive development of the seasonal influenza vaccination coverage rates. A high vaccination level would not only decrease the mortality and overall disease burden of influenza, but also enhance the manufacturing capacity for producing life-saving influenza vaccines in case of a pandemic.

In conclusion, the participants of the workshop in Luxembourg have designated the important role of the EU, the ECDC, Health Programme 2008–2013, Seventh Research Framework Programme (FP7) and MS to fill the determined gaps.

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OSELTAMIVIR RESISTANCE: CURRENT INSIGHTS

Its broad antiviral activity against influenza A and B viruses and the ease of its oral administration have rendered the neuraminidase (NA) inhibitor, oseltamivir, an attractive agent for treatment and prophylaxis of influenza and, in many countries, the

drug of choice to stockpile as preparation for a possible pandemic caused by influenza A (H5N1). However, reports of oseltamivir resistance in human H5N1 infections and the recent sudden emergence of oseltamivir resistant seasonal influenza A (H1N1)

viruses have led to some concern regarding its future use for prevention and treatment of seasonal and pandemic influenza. This review briefly summarises current insights into the emergence of oseltamivir resistance in influenza viruses.



Mechanism of oseltamivir resistance

Clinically relevant resistance to oseltamivir is mainly caused by mutations in its target enzyme, the viral NA. Most resistance-conferring NA mutations (i.e. H274Y, R292K, N294S) that are observed in clinical virus isolates interfere with oseltamivir binding by preventing a conformational change in NA that is needed to accommodate the bulky oseltamivir carboxylate molecule. Since the binding of the NA inhibitor, another influenza drug, zanamivir, does not require such conformational changes, therefore, viruses harbouring such mutations remain susceptible to zanamivir. Another resistance mutation found in clinical isolates, E119V, is thought to affect binding efficiency of oseltamivir by allowing binding of an additional water molecule.

In view of their location at or close to the catalytic site of NA and the critical function of NA in the viral life cycle, resistance-conferring NA mutations can be expected to affect enzymatic activity of NA and to reduce viral fitness. Indeed, these effects were confirmed in *in vitro* and animal studies, which resulted in initial optimistic expectations of a low propensity of the drug to select for viable resistant mutants, and if such variants should emerge, expectations of limited spread between humans and low clinical relevance.

Oseltamivir resistance in community isolates

In accordance with the above expectations, the occurrence of oseltamivir resistance in the absence of drug pressure was rare until recently. No reductions in susceptibility were observed in viruses isolated prior to the registration of oseltamivir in 1991, and since then until late last year, resistance rates in (untreated) community isolates have remained below 1% worldwide. In Japan, these low resistance rates were observed despite substantial use of oseltamivir (5–9 million courses prescribed annually since 2002).

However, since late 2007, community surveillance studies revealed dramatic worldwide increases in the prevalence of oseltamivir resistance in H1N1 strains, conferred by the H274Y NA mutation. Reported overall resistance rates currently vary

from 5% in Asia, to 16% in the Americas and to 26% in Europe [1]. This sudden emergence of resistant H1N1 variants was not associated with increased exposure to the drug: the use of oseltamivir is uncommon in most countries and regions where high resistance rates were observed, and no link between oseltamivir use and resistance was noted at the individual level. Furthermore, in Japan, with its relatively high consumption of the drug amongst its population, the prevalence of resistant H1N1 strains is still relatively low (3%). Preliminary data do not suggest the existence of a single origin of the resistant strains but further genotypic analyses are ongoing. The striking and concerning fact that these resistant H1N1 variants emerged in the apparent absence of drug pressure despite expected reductions in NA activity conferred by the H274Y NA mutation, suggest mechanisms or mutations that compensate for a viral fitness reduction caused by the resistance mutation in these viruses. In this respect, a recent interesting paper showed evidence of increased NA activity in recent H1N1 strains, potentially resulting in an imbalance in the close functional relationship between NA and HA [2]. The authors hypothesise that this imbalance may be restored by the reduction in NA activity conferred by the H274Y mutation, hence increasing its relative fitness and explaining its maintenance and spread in the absence of drug pressure.

Oseltamivir resistance development during treatment

Initially reported rates of oseltamivir resistance in isolates obtained during or after treatment varied from approximately 0.4% in adults to 4% in children. The higher resistance rates in children could in part be explained by the occurrence of primary infections in young children, which is associated with more prolonged and higher levels of viral replication owing to a lack of previous immunity. Particularly high and worrying rates of resistance of up to 18% have been reported in Japanese children treated with oseltamivir. These high resistance rates may have been related to suboptimal dosing, which, together with the possibility of high replication rates during primary infection, provide excellent conditions for the emergence and selection of resistant viral mutants. A similar scenario may apply to the treatment of human infections with highly pathogenic H5N1 viruses that are all

primary infections, associated with high replication rates whereas the dosing or oral drug delivery in these (often intubated) patients may well be inadequate. Therefore, it should perhaps not be surprising that resistance development during prophylaxis or treatment of H5N1 infection has already been reported in several cases despite the relatively low numbers of documented and treated patients worldwide.

In uncomplicated seasonal influenza, the emergence of resistant viruses during treatment does not seem to adversely affect the clinical or virological outcome, which may reflect the usually benign and self-limiting natural course of influenza. However, in immunocompromised patients, who are at risk for complications of seasonal influenza, resistance development during treatment may be associated with prolonged viral shedding and poor outcome. Likewise, a clear association between resistance development and disease progression during treatment has been observed in H5N1-infected patients [3]. Prevention of resistance development or the institution of alternative treatment when resistance develops seems essential in these settings.

Conclusions

The recent emergence of oseltamivir-resistant H1N1 viruses is concerning. Rapid monitoring of resistance and expanding the arsenal of available antivirals become essential, especially for patients at high risk of complications. In human H5N1 infections and in high-risk patients with seasonal influenza, minimising the risk of resistance development during treatment, e.g. by combinations of antivirals, is warranted.

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15 YEARS OF ESWI

In a way, the conception and creation of ESWI was triggered by the organisation of the second 'Options for the Control of Influenza' meeting in 1992. During a private conversation between Alan Kendal and myself in Geneva in 1990, I mentioned

that the proceedings of a conference held in Keystone, Colorado, USA in April 1985 was my favourite source of reference. Alan had actively participated, at the Centers for Disease Control and Prevention (CDC), in the organisation of this

conference where data and results of research on all aspects of influenza had been presented in a comprehensive fashion. The proceedings were the basis of recommendations for the optimal use of available control.

However, several years had passed and considerable new information had, in the meantime, been obtained in these fields. Developments of surveillance networks occurred and large studies had been published on the application of available inactivated vaccines. The decision to have another meeting was then promptly taken and implemented with the help of the Société Française de Microbiologie – I was its Vice-President at that time. The Society became the working force for the practical organisation, especially thanks to its Treasurer, Louis Bobichon. The idea of a ‘closed’ meeting in a secluded mountain site, like Keystone, was kept, in order to ensure better opportunities for socialising and networking between the participants. Alan and myself paid a site visit to two famous ski resorts that were not active in September: Les Diablerets in Switzerland and Courchevel, in Savoie, France. This latter site was finally selected for the international conference ‘Options for the Control of Influenza II’.

In order to establish the budget, we met with contacts from pharmaceutical companies and explained our projects. They were quite interested since they knew that influenza-related products such as vaccines or antivirals were not well known by the public or even by the medical profession. More generally, influenza was not recognised as a subject of great concern by public health officials. The companies agreed to support the project of a conference with enthusiasm. The conference attracted 350 participants and was unanimously considered as very useful and successful.

In addition, it was clear that a single scientific meeting would not be enough to increase the awareness of the dangers of influenza and its medical, social and economic consequences at European level. As Bram Palache had noted in 1991, there was an influenza ‘paradox’ since there was, in many countries, clear recommendations for individual vaccination of high-risk patients but . . . very low rates of vaccine uptake. The idea emerged slowly, during the preparation of the meeting, that a specific structure, a working group of scientists of different orientations could be useful in Europe to gather information, to serve as a reference and expertise in the matter and to redistribute validated messages for public health interventions. A similar group (GEIG) had been useful in France in a national context.

It was interesting to use the Courchevel Conference to have this project discussed, evaluated and initiated. A small group (Alan Kendal, Bram Palache and myself) convened a limited meeting with 12 colleagues from different countries in Europe in order to appoint a constitutive committee that would define the type of structure able to fulfil the expected functions. One of the main principles was to maintain a strict independence of the scientific group in relation to the financing by industry. It was originally created as

a French association named European Scientific Working group on Influenza (ESWI), under the law (1901), which describes the regulations applicable to this type of structure to guarantee its independence, with an Executive Board elected by the assembly of members. The Scientific Board comprised 12 voting members from different European countries, an Adviser from the US (Alan Kendal) and a Liaison Officer with vaccine manufacturers (Bram Palache). A few years later, an Adviser from the World Health Organization (WHO; Daniel Lavanchy) joined the group.

Objectives and subobjectives were formulated in a strategic plan elaborated for a 2-year period. A mission statement was formulated as:

ESWI to reduce the impact of influenza in Europe

For several years, ESWI activities were oriented towards promoting European collaboration on influenza, improving the flow of information on surveillance networks that were developing in Europe, harmonising policies on vaccination and antiviral concepts and strategies, and contributing to training and education. Several ad hoc scientific meetings were initiated (socio-economics of influenza [1], pandemic preparedness) in collaboration with the WHO and other authorities. Information material was edited such as periodic Bulletins (this is the 24th) or letters to specific targets. Practical laboratory courses were organised.

After my retirement, in 1996, René Snacken became the second Chairman of ESWI. In 1998, ESWI became an international association governed by the Belgian law (of October 25, 1919) with a new chart. The purpose of the new association was redefined more precisely as, ‘to contribute to the attempts to reduce the clinical and economic impact of influenza in Europe’ by

- i) Promoting European collaboration on influenza.
- ii) Stimulating and coordinating research projects on influenza.
- iii) Contributing to training and educational programmes in the field.
- iv) Providing high-quality information on influenza and promoting appropriate distribution.
- v) Improving existing influenza surveillance networks and implementing rapid systems of international communication.
- vi) Elaborating proposals to harmonise policies on influenza among European countries and assisting governments in developing pandemic plans.

Twelve voting members, senior members, advisers and benefactor members were appointed to the Board. It became necessary to redirect ESWI objectives from a purely ‘science-oriented’ to a more ‘communication-oriented’ function.

Link.inc was therefore appointed in that respect and Ab Osterhaus became the new Chairman of the Executive Board.

The conference ‘Options for the Control of Influenza III’, organised by Australian colleagues, was held in Cairns, Australia in 1996, where it was decided that Options IV would go back to Europe and be held in 2000 in Crete. ESWI volunteered to take charge of organising the event. The meeting was a full success and with the experience gained, it became clear that there was a demand for similar meetings at the European level that would alternate with the international gatherings.

The ‘First European Influenza Conference’ was therefore organised by ESWI in Malta on 29–23 October 2002 with 350 participants [2] and the second again in Malta on 11–14 September 2005 with 795 participants [3]. A new conference concept was experimented with in addition to the usual scientific sessions with a specific track for policy-makers and healthcare providing professionals. The third is arranged for Villamoura, Portugal this September.

Looking back to the initiative taken 15 years ago to launch ESWI, one can easily perceive that the goals of bringing together scientific experts and stakeholders such as opinion leaders in public health, government representatives and policy makers have been attained and that this innovative concept has been useful in the roadmap towards ‘reducing the impact of epidemic and pandemic influenza in Europe’.

C. HANNOUN

Founding father of ESWI, Paris, France

References

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2. Proceedings of the First European Influenza Conference. Malta, 20–23 October 2002. Virus Res 2004;103:1–211.
3. Proceedings of the 2nd European Influenza Conference, Malta, 11–14 September 2005. Vaccine 2006;24:6575–806.

CALENDAR OF EVENTS

Date/Venue	Title	Organiser/Secretariat
14–17 September 2008 Vilamoura, Portugal	Third European Influenza Conference	Global Conference Organisers Parabol 160 3364 DM Sliedrecht The Netherlands Tel: +31 184 496 999 Fax: +31 184 421 065 E-mail: ESWI2008@GCOeurope.com
25–28 October 2008 Washington DC, USA	Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)	American Society for Microbiology 1752 N Street, NW Washington, DC 20036 USA Tel: +1 202 737 3600 Fax: + E-mail: icaac@asmusa.org
4–5 December 2008 Paris, France	International Conference on Avian Influenza in Humans (ICAIH)	ICAIH 2008 International Society of Antioxidants in Nutrition & Health 15 Rue de la Paix Paris France Tel: +33 01 55 04 77 55 Fax: +33 01 55 04 77 57 E-mail: isanh@isanh.com
23–24 January 2009 Sacramento, USA	27th Annual Infectious Diseases Conference	Sherrri Dragonetti Office of Continuing Medical Education 3560 Business Drive, Suite 130 Sacramento, CA 95820 Tel: +1 916 734 5390 Fax: +1 916 734 0742 E-mail: Sherrri.Dragonetti@ucdmc.ucdavis.edu
25–29 February 2009 Hong Kong, China	8th Asia Pacific Congress of Medical Virology	Clemson Lo Congress Secretariat, APCMV 2009 MV Destination Management Hong Kong, China Tel: +852 2735 8118 Fax: +852 2735 8282 E-mail: apcmv09@mvdmc.com
25–27 March 2009 Seville, Spain	International Symposium on Viral Respiratory Disease Surveillance (ISIRV)	Amy Kline-Carbonara Tel: +1 404 443 1513 E-mail: amy.carbonara@intmedpress.com
27–30 April 2009 Cannes, France	International Conference on Influenza Vaccines for the World (IWV)	IWV 2009 John Herriot Meetings Management The Barn, Rake Meadow Station Lane Milford, Surrey UK, GU8 5AD Tel: +44 (0)1483 427770 Fax: +44 (0)1483 428516 E-mail: jherriot@meetingsmgmt.u-net.com
3–7 May 2009 Montreal, Canada	Annual International Conference on Antiviral Research (ICAR)	Courtesy Associates 2025 M Street, NW Suite 800 Washington, DC 20036 USA Tel: +1 202 973 8690 Fax: +1 202 331 0111 E-mail: ISAR@courtestassoc.com
16–19 May 2009 Helsinki, Finland	19th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)	19th ECCMID c/o ESCMID Executive Office PO Box 4005 Basel Switzerland Tel: +41 61 686 7799 Fax: +41 61 686 7798 E-mail: info@eccmid-icc.org

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