The Third European Influenza Summit
Brussels, May 2nd 2013

Organised by
European Scientific Working group on Influenza
## Programme

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FOREWORD

With the emergence of the H7N9 bird flu virus in South Eastern China emphasizing the potentially devastating impact of influenza on society, ESWI brought together more than 90 representatives of organizations of healthcare providers, senior citizens, at-risk patients and public health authorities at the third edition of its annual influenza summit. To keep track of the many evolutions in the field of influenza, new developments and future challenges laid at the heart of the event.

On 2 May 2013, the influenza community gathered at the Institute of European Studies at the Free University of Brussels for a day of tailored lectures, Q&A sessions and networking. Since recent studies, surveys and reviews have shed new light on some of the most intriguing influenza issues, the Summit faculty translated the newest scientific data into practice, covering questions like: Will there ever be a universal influenza vaccine? Is H5N1 bird flu still a public health threat? Is the influenza vaccine safe for pregnant women? Is it effective in the elderly? What is the future of antiviral flu drugs? And is Europe sufficiently prepared to cope with a severe outbreak of pandemic influenza? In light of the H7N9 bird flu crisis, Prof. Ab Osterhaus, chair of ESWI, opened the Summit with an overview of the latest scientific information concerning this newly emerging bird flu virus and its possible threat to humankind.

This magazine provides a report of the lectures and the discussions held at the Summit. The text can be copied and distributed freely. Additional questions to the Summit’s faculty can be asked via ESWI’s management (contact details see below).

The Fourth European Influenza Summit will be organized in May 2014.

ABOUT ESWI

The European Scientific Working group on Influenza (ESWI) is a partnership organization of stakeholders with a clear mission: to reduce the number of influenza victims in Europe.

Partnership organizations like ESWI are established to meet specific objectives and to undertake projects to address problems that neither partner could tackle adequately on his own. A successful long-term partnership is built on common grounds. In the case of ESWI, this common ground is a social concern to improve public health in Europe.

If you need further information please check the ESWI website at www.eswi.org or contact the ESWI manager, Mr. David De Pooter, at david.depooter@eswi.org or +32 479 45 74 46.

Also visit:
www.flucommunity.org
www.flucentre.org
www.eswiconference.org

bioCSL, formerly known as CSL Biotherapies, has provided an unrestricted grant to support the ESWI Influenza Summit. An unrestricted grant implies that bioCSL financially supported the Summit, but has not been involved in the preparation of the Summit in any way.
BRIEF

On Influenza Viruses
A, B and C: these are the three types of human influenza viruses.

The A and B viruses are responsible for seasonal flu epidemics each year. Influenza C type infections cause a mild respiratory illness and are not thought to cause epidemics.

Influenza A viruses are divided into subtypes depending on the genes that make up the surface proteins: the haemagglutinin (H) and the neuraminidase (N). There are currently seventeen haemagglutinin subtypes and nine different neuraminidase subtypes.

Influenza A viruses can be further broken down into different strains. The haemagglutinin and neuraminidase antigen is described in parentheses. Current subtypes of seasonal influenza A viruses found in people are influenza A (H1N1) and influenza A (H3N2) viruses.

Birds are a reservoir for all subtypes of A viruses. Typically, these avian viruses cause little or no illness in wild birds. Therefore they are called low pathogenic avian influenza (LPAI) viruses.

When LPAI viruses of the H5 or H7 subtypes are transmitted to domestic poultry and go to reproductive cycles, they may acquire mutations in the haemagglutinin and change into so-called highly pathogenic avian influenza (HPAI) viruses. These HPAI viruses can cause very severe disease outbreaks in domestic poultry, resulting in up to 100% mortality.

These HPAI viruses do not easily transmit to humans, unless they evolve and acquire new mutations. Pigs are ideal mixing vessels. They can be infected by both avian and human influenza A viruses as well as by true porcine influenza viruses. The intermediary role of pigs readily seems to allow for an exchange of genome segments between both avian and human/mammalian influenza A viruses.

This transformation process may result in a completely new virus with pandemic potential. Pandemic influenza refers to the emergence of a major new subtype of influenza A virus against which the entire human population has little or no immunity. Pandemic viruses reappear as seasonal influenza viruses in the post-pandemic era.

The influenza A (H1N1) virus that emerged in the spring of 2009 and caused the first flu pandemic in more than forty years is a reassortment between different swine viruses, which eventually are all of avian origin. The virus has now replaced the old H1N1 virus that was previously circulating among humans.

The H7N9 virus emerging in Asia in early spring 2013 could become a pandemic virus when it acquires the ability to transmit from human to human. At present, we do not know if the virus will gain that ability. But we have to be prepared. A pandemic could happen, this year, next year, in ten years or later. And it could originate from the H7N9 virus, or from the good old H5N1, only needing a handful of mutations to become a global human threat. At the end of the day, pandemics are just as unpredictable as the viruses themselves.

There are three representations of flu in humans: seasonal influenza, avian influenza and pandemic influenza.

Seasonal influenza or ‘winter flu’ outbreaks occur annually in humans in the moderate climate zones. They are currently caused by one of the two subtypes of influenza A viruses, H1N1 or H3N2, or by an influenza B virus.

Avian influenza or ‘bird flu’ is a disease caused by an avian influenza A virus that normally infects only birds.

Avian influenza virus infections in humans may be severe and even lethal, but they do not spread easily in the human population. However, should an avian influenza virus acquire the capability to transmit efficiently from human to human, an influenza pandemic could break out.
Will H7N9 Spark the Next Pandemic?

Could the H7N9 bird flu that appeared in China in early 2013 spark a new pandemic? Well, it’s just impossible to say. For that matter, the H5N1 virus could also cause a pandemic. Viruses are simply unpredictable. “I’d rather predict that a pandemic will happen, because then there is a high chance it will not”, said Ab Osterhaus. “We need to prepare for the worst and hope for the best.”
CROSSING THE GAP

Influenza is playing hard to get. The virus itself is a master in the art of metamorphosis. It is changing its character and moving year after year.

Flu appears in three formats, seasonal, avian and pandemic. Avian flu doesn’t transmit from human to human efficiently. But influenza viruses are unpredictable and “smart”. Pandemics are all caused by an avian flu that acquired the ability, by mutation or reassortment of their genetic material, to cross the gap from human to human.

Influenza A viruses are divided into subtypes depending on the genes that make up the surface proteins. At present, seventeen haemagglutinins and nine neuraminidases have been identified. With the exception of H17 all of these have been found in birds, all over the world. In Europe, 20% of birds would test positive for some kind of influenza. We know this from examining bird faeces. These birds don’t get sick, but they may spread the virus to poultry and pigs. The bird viruses are also transmitted to humans, through direct contact, for example, with infected poultry.

LOW PATHOGENIC H7N9

The H7N9 bird flu virus emerged in early 2013. Its hotspot is located around Shanghai, and the virus has been detected in chickens, ducks, one or two pigeons and in the environment as well. “The virus seems very efficient in infecting humans”, Osterhaus said. “To date (May 2nd, 2013) 126 people have been hospitalised, of whom 24 have died, and it continues its spread. But all cases seem sporadic from bird-to-human. We think bramblings have played a role in the viral transmission chain. There is no evidence yet of ongoing human-to-human transmission. And in contrast to the H5N1 virus, H7N9 is a low pathogenic virus to poultry. An H7N9 infected chicken doesn’t just drop dead. The low pathogenic character is good news; however it makes it more difficult to trace the virus back to its main host source. Preferably, as a preventive measure, you should kill all birds that are possibly infected by the virus. But to this day, we just don’t know if and which poultry are the main host. We also don’t know if there is an intermediate host.”

Handful of mutations

At present, special attention is being paid to the H5 and H7 bird flu types. “If we want to answer the question of whether H7N9 will cause a pandemic,” Osterhaus said, “we might as well ask ourselves why H5N1 hasn’t caused a pandemic yet. It is a highly pathogenic virus, leading to a fatality rate of more than 50% in the people hospitalised. H5N1 started off in Asia, and has moved to the Middle East, Africa – especially Egypt – and European countries, where migrating birds have been spreading the virus.” If H5N1 becomes transmissible between humans, for example through sneezing, it can quickly spread. The key to acquiring such pandemic potential lies in its ability to gain the capability to efficiently replicate in the upper respiratory tract, just like a seasonal influenza virus does. Ab Osterhaus and his Viroscience team at Erasmus MC built a ferret-to-ferret model to examine what the virus would need to efficiently replicate in the upper respiratory tract of a ferret. “We found out that the virus only needs five mutations”, Osterhaus said, “to become transmissible. All these mutations are present in the real world, but have just not come together yet. Five mutations are very few, a mere handful.”

“The key to acquiring pandemic potential lies in the ability of the virus to efficiently replicate in the upper respiratory tract.”

Human-to-human transmissible H7N9 could spread from Asia to the rest of world within days, following major air traffic routes

<table>
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<tr>
<th>Residents within 2 hours of airport (million)</th>
<th>Passengers per month</th>
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<tr>
<td>&lt;1</td>
<td>&lt;1,000</td>
</tr>
<tr>
<td>1-5</td>
<td>1,000-2,500</td>
</tr>
<tr>
<td>5-10</td>
<td>2,500-5,000</td>
</tr>
<tr>
<td>&gt;20</td>
<td>5,000-10,000</td>
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<tr>
<td>&gt;15,000</td>
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“What we do know is that given the hotspot and once the virus gains the ability to spread from human to human, we will develop cases in Europe in one or two days”, Osterhaus explained. “The spread really follows the path of major air traffic. So we need to set up surveillance, and for humans, seasonal surveillance is the basis for pandemic surveillance. Also, the migratory routes of birds play an important role. So we need to set up early warning and rapid response systems. As a matter of fact, we are already collaborating with ornithologists to map the migrating routes of birds.”

Last century, more than 50 million people died from pandemic flu. Low pathogenic viruses for poultry were at the basis of all four previous pandemics. “The argument that a low pandemic virus can’t cause a pandemic is simply not valid”, said Osterhaus. “Both H5N1 and H7N9 are possible origins of a new pandemic. The 2009 H1N1 Mexican flu pandemic came with a fatality rate of a few per cent. It caused 0.3 to 0.5 million deaths. But H7N9 and H5N1 respectively caused a fatality rate of 20% and 60% among the hospitalized.”

**Recent Zoonotic transmissions of influenza A virus**

<table>
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<tr>
<th>SUBTYPE</th>
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<th># CASES</th>
<th># DEATHS</th>
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<td>UK</td>
<td>1996</td>
<td>1</td>
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<td>Hong Kong</td>
<td>1997</td>
<td>18</td>
<td>6</td>
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<td>SE-Asia</td>
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<td>2?</td>
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<td>Hong Kong</td>
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<td>2?</td>
<td>1</td>
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<tr>
<td>H7N7</td>
<td>Netherlands</td>
<td>2003</td>
<td>89</td>
<td>1</td>
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<td>H7N2</td>
<td>USA</td>
<td>2003</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>H7N3</td>
<td>Canada</td>
<td>2004</td>
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<td>0</td>
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<td>H5N1</td>
<td>SE-Asia/M-East/Europe/W-Africa</td>
<td>2003-13*</td>
<td>&gt;630</td>
<td>&gt;350*</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>H7N9</td>
<td>PR China</td>
<td>2013</td>
<td>126</td>
<td>24</td>
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*CFR ~ 60%*  

**Lessons Learned**

1. A pandemic could happen this year, next year, in ten years or later. We just don’t know.  
2. H5N1 needs only a handful of mutations to become easily transmissible from human-to-human.  
3. Both H5N1 and H7N9 have pandemic potential and would start spreading among people within days.  
4. The main source of H7N9 remains unknown, but since humans become infected, there should be infected animals, probably birds.  
5. H7N9 has a fatality rate of 20%. H5N1 even comes with a fatality rate of up to 60% in hospitalized patients.
WHO INFLUENZA VACCINATION RECOMMENDATIONS

Pregnant Women are an Important Target Group

The World Health Organization (WHO) emphasises the importance of pregnant women as a key target group when it comes to flu vaccination. Ms. Michala Hegermann-Lindencrone reminds us of the fact that European countries hold widely divergent policies regarding vaccination of pregnant women, and that vaccination uptake varies substantially.
TARGET GROUPS
WHO provides recommendations for its member states regarding target groups for national influenza vaccination programmes, but it cannot oblige member states to enforce these. The national identification of risk groups is generally based on burden of disease, cost-effectiveness and feasibility of vaccinating and other operational considerations.

In its 2012 recommendations, WHO emphasizes pregnant women as an important target group for annual influenza vaccination. While pregnant women are not a new target group, WHO recommends that in countries establishing or considering expanding influenza vaccination, pregnant women should be given highest priority. In addition, WHO continues to recommend vaccination of health care workers, children between 6 and 59 months, the elderly and those with high-risk conditions.

VULNERABILITY OF PREGNANT WOMEN
Pregnant women are vulnerable to influenza infection. They are at a higher risk of severe disease and death compared to non-pregnant women, especially if they also have an underlying condition such as asthma, diabetes or obesity. A flu infection during pregnancy also increases the risk of preterm birth, low birth weight, stillbirth and emergency caesarean. Furthermore, and as a positive side effect, vaccination of the mother can reduce infection of the infants up to the age of six months. “Given the fact that vaccines are safe and effective in pregnant women, and the overall increase in acceptance of flu vaccination among pregnant women during the 2009 pandemic, we should now put our effort into improving awareness of the importance of seasonal influenza vaccination”, said Ms. Michala Hegermann-Lindencrone.

Pregnant women may be vaccinated at any stage of their pregnancy. Therefore, WHO recommends countries that are considering initiating or expanding existing vaccination programmes for influenza, to aim firstly at pregnant women.

VARIETY OF APPROACHES
The 2011 ECDC/WHO VENICE survey identified diverse vaccine recommendations in the 2009-2010 season and also looked into the monitoring of the vaccination uptake across 53 countries. As for children, the majority of European countries didn’t recommend vaccination, except for some specific medical risk groups of children. And while the overall majority of European states recommend vaccination in the elderly and recognises the same need for health care workers and clinical risk groups, the survey shows a wide variety of approaches regarding pregnant women.

Some countries recommend vaccination for all pregnant women, some recommend it for some, some make no recommendation at all. Moreover, monitoring systems and, as a result, data on vaccine uptake in pregnant women only exists in a few countries, which makes it difficult to monitor progress and impact.

OTHER RISK GROUPS
Next to pregnant women, the other risk groups remain important targets. Elderly people are a well-known risk group, but data on their vaccine uptake show high disparities from one country to another and, with the exception of the Netherlands, no country reaches the WHO 2010 target of 75% coverage. Young children are another target group because “they play a central role in transmitting the virus in a community and have a higher risk of developing seasonal influenza.”

Seasonal influenza vaccine recommendation for pregnant women

Source: WHO-Europe, Venice survey 2009/2010 season
severe disease.” People with chronic diseases represent an obvious target group, but "they are more difficult to identify individually because of the wide range of possible underlying conditions.” Also health care workers are an important group, because nosocomial cases and outbreaks of influenza associated with infected healthcare workers can have severe consequences for especially vulnerable patients.”

However, uptake in these target groups remains low, despite the safety of the vaccine. The low vaccine uptake in key target groups in some countries, despite strong evidence of burden and severity, is mainly due to a lack of awareness amongst risk groups, a lack of recommendations from medical providers, or the absence of easy access to vaccination.

Current WHO recommendations

2012
1st priority: pregnant women
other groups:
• health care workers
• children 6 to 59 months
• elderly
• high-risk conditions
(no order of priority)

Lessons Learned

1. In its last position paper, WHO states that pregnant women must be prioritized in newly established vaccination programmes or in countries expanding target groups for influenza vaccination.
2. Pregnant women may be vaccinated against influenza at any stage of their pregnancy.
3. Vaccination for health care workers, children between 6 and 59 months old, the elderly and people with high-risk conditions is highly recommended.
4. In the case of a pregnant woman, the vaccination’s de-risking effect combined with the positive side effects for the young infant clearly outweigh and outnumber any possible negatives.
5. Data on vaccination uptake in pregnant women are limited, making it difficult to assess the progress made.
Dr. Lill Trogstad
Norwegian Institute of Public Health

NORWEGIAN FOLLOW-UP AFTER LAST PANDEMIC

Influenza Vaccination of Pregnant Women

Dr. Lill Trogstad explains how the Norwegian Institute of Health set up its survey to examine the pandemic’s impact on pregnant women and newborn babies.
“In order to examine the pandemic’s consequences, we set up a three-stage survey pyramid.”

MOTHER AND CHILD
There is a clear reason for WHO recommending that pregnant women be given the highest priority when it comes to vaccination: pregnant women are more likely to develop severe illness and die from influenza as compared to the general population, and this fact remains underexposed in today’s prevention policies. During the 2009 pandemic, 5% of deaths in the US were reported in pregnant women, while this group accounts for only 1% of the population. Pregnant women are also more likely to be hospitalised.

Influenza during pregnancy also inflicts negative effects on the child, and although the effects may not have been thoroughly studied, they should best be avoided. Only a few studies are dealing with the issue. But transplacental transmission of the virus, for example, has been reported. “Cases seem to be rare, but have been described”, said Trogstad. “So viremia is probably not the only way influenza infection influences the child. Furthermore, the adverse effects that have been reported, like birth defects, congenital defects of the central nervous system, pregnancy loss, preterm delivery and death, and the long-term consequences, like development delay and neuropsychiatric disorder, may also be caused by hyperthermia or the maternal inflammatory response itself.”

Setting aside the risks of non-vaccination, research shows vaccination has more positive effects than we think, including for the newborn child. “As for influenza vaccination in pregnancy, there are several reports stating that vaccination reduces maternal illness, and seroprotection at similar rates as non-pregnant women have been reported, with antibody levels similar to non-pregnant women. Regarding the foetal effects, there is clear evidence vaccination has a protective effect against influenza, up to six months after birth. There are also studies reporting that vaccination during pregnancy increases birth weight and reduces the risk of SGA infants, preterm delivery and foetal death.”

SURVEY-PYRAMID
Norway has a large number of national registries, all based on the personal ID number. The unique ID permits linkage of all these registries. “When the pandemic hit in 2009, we, the Norwegian Institute of Health, decided to take advantage of the data that was already available and that we knew would be generated. In order to examine the pandemic’s consequences, we set up a three-stage survey pyramid”, Trogstad said.

“Firstly, we used the population registry of Norway, from which we extracted all women between the ages of 15 and 49. To this dataset we linked primary-care data, immunisation data from the Immunisation Registry, data from the Surveillance System of Infectious Diseases which reported all laboratory H1N1 results, and data from the Medical Birth Registry of Norway.”

“The aim of the linkage was to assess the risk of foetal death after pandemic influenza virus infection or after vaccination. A few other studies have also done similar register linkages, but none have, to our knowledge, had the opportunity to look into influenza infection in addition to vaccination status, which is quite important”, Trogstad said.

“The pandemic started in October 2009 and peaked in mid-November. Pandemic vaccines became available in Norway on October 19th – we used Pandemrix – and vaccinations were reported on an individual day-by-day basis (see graph). Curves of the pandemic and of vaccinations are completely overlapping. Vaccination in a flu environment creates huge problems when you try to analyse and disentangle the effects of influenza and vaccination. To overcome that problem we used cox regression models and time dependent variables.”

Reduced Risk of Influenza
In Norway, vaccination was recommended in the second and third trimester of pregnancy. Earlier vaccinations were not an issue due to additional risk factors or because the woman didn’t know she was pregnant. “More than 100,000 births were studied during the period”, Trogstad said. Among them 492 stillbirths occurred. The vaccination coverage for the entire population was 45%, and 38% for women in the age group 15 to 49, while pregnant women in the same age category had vaccination coverage of 55%. We also found out that vaccination during pregnancy was not associated with an increase in foetal death; and that vaccinated women had 70% less risk of catching influenza; a ratio of 0.3. “Overall, all women who were pregnant during the pandemic wave, starting in October and ending on December 1st, had an increased risk of foetal death; our study shows a ratio of 1.26.

Confirmed H1N1 cases and vaccination uptake during pregnancy in Norway during the 2009 pandemic
“Vaccination during pregnancy was not associated with an increase in foetal death, and vaccinated women had 70% less risk of influenza infection.”

Importantly, women who had received the diagnosis of influenza from their GP, showed almost a double risk of foetal death with a ratio of 1.9.”

NORFLU COHORT
“As a second survey stage, we had a large pregnancy cohort running in Norway, the ‘Norwegian mother and child cohort study’ (MoBa),” Trogstad said, “which had already recruited more than 100,000 mothers and their children. Unfortunately, when the pandemic hit, recruitment for that study had already stopped for a year. Nevertheless, we could take advantage of the knowledge already gathered and we decided to set up a new pandemic cohort study, the NorFlu Cohort, and recruited 4,000 women who were pregnant during the pandemic. The NorFlu Cohort is our third survey stage.”

The aim of NorFlu is twofold: firstly, to investigate perinatal outcomes and children’s cognitive development, according to maternal exposure; and secondly, to study the relative importance of antibody mediated immunity as compared to cell mediated immunity in the protection against influenza. “We decided to invite all women with their last menstrual period between June 1st and December 1st. In total, approximately 4,200 women were recruited in hospitals in Oslo and Bergen, starting March 15th. We recruited women at the time of their ultrasound appointment, around week 17, 18 and 19. All babies in the Cohort were born by September 25th, 2010. And we also recruited 330 control women.”

All women received two questionnaires, one with general health and pregnancy questions, and one with questions specifically related to influenza, the use of a vaccine and antivirals, etc. “The follow-up was done after six and eighteen months. Currently, we are collecting data from the children at age three. We are also setting up a clinic to perform psychological testing on a subsample of these children. This will take place during autumn 2013.”

A lot of data collection has been going on. Trogstad presented preliminary results: “15% of the women reported that they were infected during pregnancy. 74% of them reported they were ‘quite ill’ or ‘very ill’. 85% had to stay in bed for more than three days, and up to eleven days. From the 400 women, six were admitted to hospital with influenza. There were no maternal deaths. 57% were vaccinated, while only 2% used antivirals whilst being pregnant.” Also, 2,600 maternal blood samples were analysed. “40% had protective antibody levels against influenza A H1N1. But it remains unclear and an issue for further immunological studies whether this represents influenza infection or the effect of vaccination. We also didn’t find any difference in gestational length or birth weight according to the vaccination status, as has previously been reported by others.”

Lessons Learned

1. Vaccination during pregnancy is safe and reduces maternal illness.
2. During the H1N1 pandemic in Norway, vaccinated pregnant women’s risk of influenza was reduced by 70%.
3. Influenza infection in pregnancy was associated with almost a double risk of foetal death.
4. Continued efforts should be made to study the impact of influenza and vaccination on pregnancy and on the long-term health effects among children.
5. Immunological mechanisms in pregnant women need to be explored in future studies.
6. Prospective epidemiological studies may provide new insights.
A flu infection can seriously affect an elder person’s capabilities, making this person less independent and leading to a lower quality of life. This effect leads to an increased demand in health and social care for older people. Vaccination helps to add quality to life and to attenuate the rising costs associated with a higher demand for care and support, says Dr. Janet E. McElhaney.
“Vaccination can add quality to lives.”

AGEING POPULATION GETTING OLDER
There are now more people over the age of 65 than there have ever been in the history of mankind. And at the same time, life expectancy continues to rise, which means the population will also grow older and older. The impact of this is not just on mortality; it is even bigger in terms of disabilities among older people.

“We are well aware of the high mortality rates among older people who are infected with influenza; 90% of influenza deaths occur in older people”, McElhaney said. “But something more important is the impact of influenza illness in terms of independence and care needs in older people. For every influenza death, there are three to four influenza hospitalisations, and most are for people above the age of 65.”

TURNING FRAILTY INTO VITALITY
With ageing, our health becomes more vulnerable. Older people are more fragile and face a long recovery from influenza infection. Flu simply adds to the already frailty, and might lead to all kinds of complications, quickly turning older people’s lives upside down, making them care-dependent, in some cases even for many years.

Consequently, the ageing population and its increased frailty will lead to a significant rise in social welfare expenditure. “The mismanagement of seniors’ health and antibiotic resistant bacteria are among the biggest risks to the world economy”, said McElhaney, quoting Globe and Mail. “Therefore we have to keep this in mind when we are looking at things like vaccine effectiveness in terms of preventive strategies to reduce costs.”

COCHRANE RE-ARRANGED
Recent reports have once again questioned the benefit of influenza vaccination in the elderly. McElhaney referred to the controversy raised by the Cochrane review. “Cochrane statisticians used 75 articles from a database of 4,000 publications, using mainly observational studies. They performed 100 single meta-analyses, according to various vaccine types, study designs, populations and outcome case definitions.”

“The problem with the Cochrane data analysis is its mathematical approach; it is guided mainly by formal and not by biological criteria,” said McElhaney, “which wrongly resulted in the assumption that the data are inconclusive and cannot be interpreted.” In addition, Cochrane’s analysis is statistically flawed. “It does not distinguish between seasons with high, mild or no circulation at all of an influenza virus. Nor does Cochrane distinguish between vaccines with a good or a poor match for circulating flu strains.”

“The conclusion from the formal statistical approach of the Cochrane analysis is that influenza vaccine is more effective in frail older people who live in assisted living or nursing homes than in community-dwelling elderly people – from a biological perspective, this makes no sense. In the press, this message was further simplified to ‘there is no benefit from influenza vaccination in community-dwelling elderly people’.”

Janet McElhaney unveiled the forthcoming publication of a new collaborative study conducted by herself, Walter E.P. Beyer (Department of Viroscience, Erasmus MC, Rotterdam, The Netherlands), Derek Smith (Department of Zoology, University of Cambridge, UK), Arnold Monto (School of Public Health, University of Michigan, US), Jonathan S. Nguyen Van-Tam (University of Nottingham, UK) and AB Osterhaus (Head of Department of Viroscience, Erasmus MC, Rotterdam, The Netherlands) on the same data the Cochrane statisticians used. The big difference however is that these data are now re-arranged and analysed from a decipher viewpoint that also makes biological sense. “The findings of this Cochrane re-arranged study provide ample evidence of the ability of influenza vaccines to reduce the risk of influenza infection, and influenza-related disease and death in the elderly. If we think about the logic behind the data and look at them from a biological viewpoint, instead of a purely statistical viewpoint, it becomes very clear that vaccination makes sense.”

The aim of the re-arranged study is to counter the old myths and misconceptions about vaccination nurtured by Cochrane’s reviews and their coverage in the general media. The detailed results of this Cochrane re-arranged study will be published later this year.

START MAKING SENSE
“Vaccines are safe and vaccination makes sense”, McElhaney said. “And although the effectiveness of the current influenza vaccine in preventing respiratory illness in older people is declining and is only 27 to 40%, it is cost-saving because we are preventing hospitalisation. Also, vaccination prevents the risk of missing flu diagnoses; something which regularly happens in the case of older people admitted to hospitals. Moreover, influenza in the elderly is no longer a cause of the ‘common cold’. Strokes, heart failure, pneumonia, ischemic heart disease, cancer and even hip fracture; every single leading cause of catastrophic disability has been linked to influenza. And the reason is that these older folks may do quite well in their community, but when you put them in a hospital bed, they will lose up to 5% of their functional muscle strength each day in bed, and they go home dependent on others in their daily activities. Vaccination that prevents flu will add to the vitality of the elderly and also prevent catastrophic disability.”

“It is clear that we can protect older people and add quality to their life in many ways. Not only by vaccinating them, but also by vaccinating children..."
and health care workers. Populations are getting older, and flu constitutes a major threat for this risk group. Older people are also living longer with chronic diseases. Influenza has a major impact on their quality of life. Policy decisions based on the reports questioning influenza vaccination likely lead to devastating personal consequences for the older population at a cost that our health care system cannot afford. The question we should ask ourselves is: ‘Are we prepared to face the consequences of not vaccinating risk groups like the elderly?’

**Lessons Learned**

1. The mismanagement of seniors’ health is among the biggest risks to the world economy.
2. Risks related to flu increase with age, adding to the imminent frailty of the elderly person.
3. The Cochrane analysis, questioning vaccination effectiveness in the elderly, is guided mainly by formal and not by biological criteria and is statistically flawed.
4. From a biological perspective, the conclusion from the Cochrane analysis makes no sense.
5. Vaccination in elderly people can turn frailty into vitality and will also prevent catastrophic disability.
DIFFERENCES IN PANDEMIC PREPAREDNESS IN EUROPE

ESWI

Flu Quest Results

“We must warn European public health officials for complacency when it comes to preparing our healthcare systems for the next influenza pandemic,” Ab Osterhaus told the Summit audience. “It is important to evaluate pandemic response processes after the 2009 pandemic outbreak of H1N1 influenza, yet few countries have done that. To get a clear view on the issue, ESWI has set up an evidence-based comparison of responses and preparedness plans in Europe.”
Prof. Osterhaus leaves no doubt about it: he will not reveal any FluQuest study results during this Summit session, as an entire workshop will be dedicated to the study outcomes on 3 May 2013. Yet the ESWI chair emphasizes that the FluQuest survey indeed revealed some remarkable and worrisome trends and differences in influenza pandemic response planning in Europe.

“The pandemic outbreak of H1N1 influenza in 2009 provided an important test of Europe's preparedness activities and ability to respond to a large-scale public health emergency,” said Osterhaus. “The pandemic itself had overall been handled well in Europe, the US and Japan. But in the aftermath of the pandemic, few national authorities have evaluated their response plans.” To get a clear picture of the situation, ESWI has set up a comparative analysis of pre and post pandemic plans in nine European countries: Austria, Belgium, the Czech Republic, Finland, France, Germany, the Netherlands, the UK and Turkey, with the US and Japan serving as points of reference. The selection criteria for these countries were mainly of geographical nature: regional clustering allowed identification of differences in countries that otherwise have fairly similar healthcare systems.

Respondents in the various participating countries had been asked to fill out an extensive survey with questions organized according to six areas of focus:

- Seasonal Influenza Surveillance, vaccination and communication
- Pandemic Influenza Planning and Coordination
- Pandemic Influenza Situation Monitoring
- Pandemic Influenza Prevention, Mitigation and Treatment
- Pandemic Influenza Healthcare Capacity
- Pandemic Influenza Communication

Ab Osterhaus emphasizes that ESWI has set up the survey with a number of clear objectives: to learn about Europe's level of pandemic preparedness, to gain a clear view on the rationales for changes in pandemic response policies, and—ultimately—to enhance European preparedness for the next influenza pandemic. “This also implies that ESWI explicitly did NOT aim to facilitate the establishment of new preparedness plans nor did we want to facilitate the revision with clear guidelines. ESWI recognizes the importance of evaluation efforts currently being carried out by WHO and ECDC and does not want to duplicate their work in any way.”

In conclusion, Prof. Osterhaus informs his audience about two upcoming publications which will highlight the survey results: a scientific article is in preparation already and will be co-authored by all respondents, while the lectures and discussions of the 3 May 2013 FluQuest Workshop will be brought together in a separate report.

Questions answered by the FluQuest survey:
1. How has the 2009 pandemic affected current influenza surveillance, antiviral stockpile and flu vaccine uptake?
2. Why and how were preparedness plans updated after the 2009 pandemic?
3. Is a revision of WHO pandemic phasing needed?
4. What are the current pandemic vaccine and antiviral procurement strategies?
5. Are European healthcare facilities ready to cope with a severe outbreak of pandemic influenza?
The number of effective antiviral agents available is quite limited at the present time, and resistance of influenza viruses to one class of current antivirals is widespread. But luckily enough, a fair number of new products have also advanced in clinical development. Prof. Frederick Hayden discussed the progress made in the development of novel antiviral agents and treatments.
**THE OVERALL GOAL**
Prof. Frederick Hayden, a recognized expert on influenza antivirals, opened his remarks by stating “We have good antivirals, and there are compelling data that indicate, with proper use, they can reduce mortality and complications. But there is still the need to expand the armamentarium. We need new agents and we need to study additional approaches like combinations for more effective therapy.”

“What we have to accomplish with the use of antivirals is controlling virus replication until the host immune response clears the infection. Current drugs don’t kill the virus, they are not virucides, but they rather inhibit replication on a cellular level, preventing spread within the respiratory tract, and protect uninfected cells until the host immune response can kick in. That’s why we see particular problems in immunocompromised hosts.”

**TWO CURRENT CLASSES**
There are currently two classes of approved antivirals, Hayden explained: “The adamantanes, which have this early effect of inhibiting uncoating of the viral genome, and the neuraminidase inhibitors, which have a late effect preventing the release of a virus from infected cells and their spread within the respiratory tract. But there are multiple other potential targets. We do have agents which are active at different steps in the intracellular replication, but also in some cases, like antibodies, which act directly on the virus itself.”

With regard to the currently approved agents, most countries have at least one adamantane - amantadine and/or rimantadine - and one or more licensed neuraminidase inhibitors – oseltamivir, zanamivir, peramivir, and laninamivir.

**PROBLEMS**
“One of the problems with the adamantanes is that their spectrum is limited to influenza A only, because they target the M2-protein which is only present in A-viruses. Another problem is that antiviral resistance is currently widespread. We see this in the circulating H3N2, pandemic H1N1 2009, most avian H5N1 and now also in the avian H7N9 viruses. So there really remain very few indications for use of these agents,” Hayden said.

“With regard to the neuraminidase inhibitors, oseltamivir has the advantage of easy administration compared to the inhaled zanamivir. This is also associated with the limitations in the age of use, because the patient has to utilise the proprietary Diskhaler inhalation device. With oseltamivir, we now have data from work done during the pandemic, telling us it can be used safely in neonates and young infants.; two weeks of age is the approved age now in the US.”

**PUBLIC HEALTH PERSPECTIVE**
From a public health perspective though, one needs to consider more serious outcomes and severe influenza, Hayden said. “In addition to reduction of complications, we want to see reductions in pneumonias and hospitalisations, in particular in their frequency as well as duration. And the key is to see whether severe outcomes can be mitigated and deaths reduced, as was observed with timely oseltamivir treatment during the 2009 pandemic.” A parallel public health goal is to avoid transmissible resistant viruses, Hayden said. “This is what we experienced in the 2008-2009 season, when global circulation of a seasonal H1N1 virus highly resistant to oseltamivir occurred. This should be considered as a warning. Continued vigilance is certainly required.”

**NEW THERAPEUTICS**
There are a fair number of promising new products that have advanced in clinical development. Hayden presented an April 2013 update of the list. “Three of these new drugs are neuraminidase inhibitors – intravenous zanamivir, intravenous peramivir and inhaled laninamivir – and they are all in phase 3 trials. The list contains another four agents – favipiravir or T-705, DAS181, nitazoxanide and VX-787 – that have different mechanisms of antiviral action and hence are active against both adamantane and neuraminidase inhibitor resistant variants.”
In order to control infections as rapidly as possible, the combined use of antivirals is key. Hayden said. "There have been a limited number of studies that have been testing or evaluating the use of antiviral combinations in humans. The combination of oseltamivir and inhaled zanamivir actually did worse than oral oseltamivir in a carefully conducted study in France. We also know that the triple combination of amantadine, ribavirin and oseltamivir looked promising not only in animal models but also in an observational study in Korea, where it was used in critically ill pandemic H1N1 patients. Other studies in Hong Kong focused on the use of convalescent plasma or hyperimmune globulin containing high titers of neutralizing antibody or a conventional immunoglobulin treatment. They found evidence of more rapid viral clearance and also, notably in those who were treated early (within five days), decreased mortality. This combination approach should be taken forward, perhaps in the context of avian H7N9 in the future", Hayden said.

**WHO Guidelines on Influenza Virals**

WHO is in the process of updating its influenza antivirals guidelines. The 2010 WHO guidelines and more recent CDC ones recommend that any patients with serious, progressive, or hospitalizing influenza indicate receive oseltamivir therapy. The key message is not to wait for laboratory confirmation, but to start treatment as soon as possible. Also uncomplicated influenza in higher risk groups should be treated with the neuraminidase inhibitor oseltamivir or zanamivir as soon as possible. Viruses known or suspected to be oseltamivir resistant should be treated with zanamivir as soon as possible.

### Population

<table>
<thead>
<tr>
<th>Pandemic Influenza A (H1N1) 2009 and other seasonal influenza viruses</th>
<th>Influenza viruses known or suspected to be oseltamivir resistant</th>
</tr>
</thead>
</table>

### Uncomplicated clinical presentation

<table>
<thead>
<tr>
<th>Patients in higher risk groups</th>
<th>Treat with oseltamivir or zanamivir as soon as possible</th>
<th>Treat with zanamivir as soon as possible</th>
</tr>
</thead>
</table>

### Severe or progressive clinical presentation

<table>
<thead>
<tr>
<th>All patients (including children and adolescents)</th>
<th>Treat with oseltamivir as soon as possible (zanamivir should be used if oseltamivir unavailable)</th>
<th>Treat with zanamivir as soon as possible</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Patients with severe immunosuppression</th>
<th>Treat with oseltamivir as soon as possible. Consider higher doses and longer duration of treatment</th>
<th>Treat with zanamivir as soon as possible</th>
</tr>
</thead>
</table>

### Selected Influenza Virals in Clinical Development – April 2013

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Spectrum</th>
<th>Route</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zanamivir</td>
<td>NA</td>
<td>A + B</td>
<td>IV</td>
<td>3</td>
</tr>
<tr>
<td>Peramivir</td>
<td>NA</td>
<td>A + B</td>
<td>IV</td>
<td>3</td>
</tr>
<tr>
<td>Laninamivir</td>
<td>NA</td>
<td>A + B</td>
<td>Inhaled</td>
<td>3</td>
</tr>
<tr>
<td>Favipiravir</td>
<td>Polymerase</td>
<td>A, B, C</td>
<td>Oral</td>
<td>3</td>
</tr>
<tr>
<td>DAS181</td>
<td>HA receptor</td>
<td>A + B, ‘PIV</td>
<td>Inhaled</td>
<td>2</td>
</tr>
<tr>
<td>Nitazoxanide</td>
<td>HA, IFN inducer</td>
<td>A + B</td>
<td>Oral</td>
<td>2→3</td>
</tr>
<tr>
<td>VX-787</td>
<td>Novel</td>
<td>A</td>
<td>Oral</td>
<td>2</td>
</tr>
</tbody>
</table>

1. Licensed in Japan,  
2. Licensed in South Korea + China  
3. Spectrum includes some non-influenza viruses

### Lessons Learned

1. Medical needs for a more effective therapy for severe influenza certainly exist, notably in at-risk patients and especially in immunocompromised hosts.
2. Our number of antivirals of proven effectiveness is quite limited at the present time.
3. The resistance of viruses to adamantanes is widespread and should be considered as a public health warning.
4. Do not wait for laboratory confirmation, start treatment as soon as possible.
5. Progress is being made in the development of intravenous neuraminidase inhibitors and other novel antivirals, therapeutic antibodies and combinations.
The Safety Issue

If you shake an apple tree, even the unripe apples will fall faster. Prof. Miriam Sturkenboom used this metaphor to indicate potential biases in vaccination side effect studies. Increased awareness of side effects can potentially increase the number of cases reported. We should also not forget that flu itself triggers a lot of side effects now frequently associated with vaccination.
**PANDEMIC VACCINE SAFETY**
Seasonal trivalent influenza vaccines (TIVs) are usually supplied as live attenuated or non-adjuvant vaccines. Their licence is mostly based on experience. Very few trials have been done with these vaccines. But safety data are abundant, typically from spontaneous reports and active surveillance post-marketing programmes. A good resource there is the vaccine safety data link in the US, and also CDC that has accumulated a lot of information.

TIVs are administered as an injection and therefore may cause reactions at the injection site, such as pain, redness and swelling. “These reactions occur with 60%+ of people, but are often mild and disappear after two days. So this is nothing serious”, Prof. Miriam Sturkenboom said.

“There are some systemic events that might occur after TIV vaccination, but they also are often mild and limited. In people who have never been vaccinated before, you may see more reactions, like fever, malaise, myalgia, and ocular or respiratory symptoms, like red eyes, hoarse voice or a cough.” One of probably the rarest serious adverse events would be Guillain-Barré Syndrome (GBS), which was a concern with the swine flu vaccine in the US in 1976. “GBS was quite important when we started looking at the safety of the pandemic influenza vaccine in 2009”, Sturkenboom said.

Compared to TIVs, pandemic influenza vaccines are quite another story. “They were licensed through a fast track procedure, with limited safety data. Many countries in Europe and Canada used oil-in-water adjuvanted vaccines, like AS03 and MF59, and especially around AS03, there was very little evidence. In the US, mostly non-adjuvanted vaccines were being utilised”, Sturkenboom said.

The urgency involved in getting the vaccines ready for deployment also meant that the time to conduct safety studies before licensing was very limited. But on the other hand, extensive post-marketing surveillance programmes were set up. This led to a steep rise in the number of safety studies published from 2010 onwards.

**ADVERSE EVENTS**
Prof Sturkenboom focused on the pandemic influenza vaccine. “Once the pandemic vaccines were licensed, the EMA and FDA put a strong risk management programme in place, in close collaboration with the WHO. The first goal of this programme was the calculation of background rates of events of interest, like anaphylactic reactions, convulsions, demyelination, encephalitis, etc. There were priority concerns, especially about GBS, because of the past experience with the swine flu in 1976. At that time, 51 cases of paralysis, of which four were fatal, were recorded out of a total of 34.9 million Americans immunised, representing an eight-fold increase. Therefore, a key item of the pandemic safety programme was to predict the number of expected GBS cases. The expected calculation should be possible, because all of the spontaneous reports would come in before any of the active surveillance programmes deliver results. Other goals were the continuous monitoring of adverse events and the setting up of the active surveillance programmes, both publicly funded as well as privately coordinated.”

**GUILLAIN-BARRÉ**
For most of the social interest events that were predefined, there was no issue at all. “There was an issue surrounding anaphylactic reactions, but it is very difficult to report, because it can actually go from an allergic reaction to any type of an anaphylactic shock, and when this was looked into, there was no real concern.”

As far as the active surveillance of Guillain-Barré is concerned, several studies were conducted, a global one and one in the US and in Europe. “Most of the studies show a significantly increased risk. In the US, which was using a non-adjuvanted pandemic vaccine, the incidence rate shows a figure of 2.35, which is significantly high”, Sturkenboom said. “But it was very difficult to adjust for the fact that influenza itself is a strong risk factor for Guillain-Barré. As a result, doubts can remain, because the wild type virus, and not the vaccine, causes Guillain-Barré.”

In Europe, ECDC funded two studies: a case controlled study in four countries; and a self-controlled study in seven other countries. “The case controlled study took place in Denmark, Sweden, the Netherlands and the UK. Adjustments could not be made in all these countries. For example, the Danish could not adjust for wild type virus infections. Denmark reported a 9.5-fold increase in the risk of contracting Guillain-Barré following the pandemic vaccine. On the other hand, the other countries showed an initial increased risk, and, after adjustment, the estimate went down. In the Netherlands, the risk went from a 2.5 unadjusted rate to 0.6 when it was adjusted. The UK showed a similar pattern. The self-controlled case in seven other countries also showed similar results.”

A global study yielded a total of 535 Guillain-Barré cases. “Overall, with all of the data put together, there is a risk of 2.86”, Sturkenboom said. “However, if you stratify between adjuvanted and non-adjuvanted vaccines, the risk is highest for the non-adjuvanted vaccines. In Europe where they used the adjuvanted vaccines, there was no increased risk. In the US, where the non-adjuvanted vaccine was used, the risk increased. The question is whether the augmented risk is due to the non-adjuvanted vaccine itself or its lower effectiveness compared to the adjuvanted vaccine. And besides this, the wild type virus still has an effect which can cause the Guillain-Barré syndrome.”
“We don’t know if the narcolepsy issue is due to the vaccine or something else.”

**SURPRISE NARCOLEPSY**

Sometimes, the unexpected happens. During the pandemic, flu experts were suddenly confronted with a safety issue that had never been associated with any vaccine before: an increasing number of cases of narcolepsy in Swedish and Finnish children. The pandemic influenza vaccine used in Finland and Sweden was Pandemrix.

"Narcolepsy is a rare sleep disorder that has to do with excessive daytime sleepiness", Sturkenboom explained. "The most serious symptom is cataplexy, a temporary muscle weakness in response to emotions such as laughter and anger, that looks like a convulsion; people fall down and will lie there, fully conscious, for a few seconds to several minutes. Usually, narcolepsy is a highly underdiagnosed disease. The interval between symptom onset and diagnosis remains quite long, typically around ten years. This makes it very difficult to study if you have a safety issue occurring within one year of the start of a vaccination campaign, because not enough time has passed for the disease to occur naturally.”

The first suggestion that vaccination might be associated with narcolepsy was made in February 2010 in Finland. And from August 2010 onwards, the narcolepsy issue received a lot of media attention in Sweden and Finland. The number of reported cases peaked. Suddenly more and more people were diagnosed.

“Clearly, the media attention raised public awareness about the potential association”, Sturkenboom said. "The question is whether the number of cases is biased by the fact that the subject got more attention and suddenly more people made an association with a disease that otherwise takes a long time to get diagnosed. Do we see a signal because there is increased awareness, or because there is a true association? If you have a disease with a long time between onset and diagnosis, raised awareness of a vaccine associated with the disease will lead to early diagnosis of those who have been vaccinated. That bias can create a problem when you do an observational study.”

In response to the signal, various studies were done. "Finland", Sturkenboom said, “conducted a cohort study in children, which showed a very high risk of 12.7. Sweden used several designs with estimates ranging from 6.6 to 1.6. Ireland did a cohort study similar to the Finnish design and also reported a risk of 13, also in children. A recent UK study likewise showed an association in children. All of those designs indicate a risk, but the problem with these studies is that, just to have enough cases, they include the time after the media attention. And it is very difficult to get rid of that bias. Nevertheless, it remains very clear that most of the cases were referred to a specialist after the media attention, and very few cases were diagnosed prior to the media attention.”

**THE VAESCO-STUDY**

Sturkenboom also referred to the VAESCO-study, funded by ECDC. The VAESCO-study included eight countries, and its purpose was to figure out whether the association was due to the media attention or not. Therefore, it reviewed the available data from the signalling countries Finland and Sweden firstly prior to the media attention and secondly with the period of media attention included. "The relative risk before attention was 14.2, and when the entire period was taken under consideration, the risk rose to 36.3”, said Sturkenboom, indicating media attention clearly had its effect. "In the non-signalling countries France, the Netherlands, Italy, the UK and Denmark, the analysis of reported cases prior to attention led to an insignificant risk in children and a slightly higher insignificant risk in adults. If the entire period is taken under consideration, the estimate also goes up here.”

In all, results seem a bit awkward, adding to the confusion. "There seems to be an association in children, which is confirmed in signalling countries, but not confirmed in non-signalling countries. There seems no association in adults in signalling countries, but there is in non-signalling countries. We just can’t say there is a conclusive answer”, Sturkenboom said. "We don’t know if the narcolepsy issue is due to the vaccine or something else, like a vaccine production method. And at the same time, it is very important to know the root cause, not because of a vaccine that isn’t there anymore, but because of the adjuvant.”

In mid-2011, the European Medicines Agency published a recommendation restricting the use of Pandemrix in people under the age of 20, stating that Pandemrix should only be used in the absence of seasonal trivalent influenza vaccines. "But if the adjuvant is causing the association, it is quite odd that the association doesn’t happen with other vaccines that use the same adjuvant. Therefore we need to know the root cause of this narcolepsy issue. If we can’t use adjuvanted vaccines in children anymore, we have a problem”, Sturkenboom concluded.
Adverse events: expected/observed cases of special interest

<table>
<thead>
<tr>
<th>ADVERSE EVENT OF SPECIAL INTEREST</th>
<th>CELVAPAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>RATE</td>
<td>EXP CASES</td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>6.6</td>
</tr>
<tr>
<td>Convulsions</td>
<td>156.7</td>
</tr>
<tr>
<td>Demyelination</td>
<td>15.9</td>
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<tr>
<td>Encephalitis</td>
<td>2.8</td>
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<tr>
<td>Facial palsy</td>
<td>25.6</td>
</tr>
<tr>
<td>Guillain Barre syndrome</td>
<td>2.2</td>
</tr>
<tr>
<td>Neuritis</td>
<td>2</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>19.3</td>
</tr>
</tbody>
</table>

From: Kurz Vaccine Volume 29, Issue 26 2011 4378 - 4387

Sudden increase in spontaneous reports of Pandemrix-narcolepsy in EUDRAVIGILANCE database after August 2010

Spontaneous reports of H1N1/Narcolepsy

This demonstrates awareness of the association

Lessons learned

1. The adjuvanted pandemic vaccine generated no increased risk of Guillain-Barré. When a non-adjuvanted vaccine was used, the risk increased.
2. We should not forget flu itself triggers a lot of the possible side effects now frequently associated with vaccination.
3. It is always possible that you measure the effect of the pandemic and not of the vaccination.
4. We don’t know if the narcolepsy issue is due to the vaccine or something else.
5. Media attention on the possible association between a vaccine and a side effect in itself can possibly bias the association.
NEW VACCINE DESIGN LEADS TO NEW POSSIBILITIES

Types and Modes of Administration

Better vaccines are on the horizon. Prof. Gerd Sutter documented the progress made in vaccine development and presented his and others’ ideas on future strategies in vaccine research, development and design.
“Today, we’re addressing yesterday’s hopes. We’re making continuous progress. But this doesn’t mean there is no more room for further improvement.”

CONTINUED PROGRESS
The 1918 pandemic was particularly puzzling to doctors. Researchers didn’t even discover the influenza virus until 1933. Clinical testing of potential influenza vaccines started soon after that. The first clinical trials were performed in the US, in the mid-1930s, using crude virus preparations. Soon after that, more conventional vaccine approaches were tested, with virus inactivated vaccines, and also using adjuvants, like mineral oil and even peanut oil, with data from the 1950s clearly demonstrating that these crude adjuvants unmistakably enhanced the antibody response and also the longevity of antibody response.

Our current vaccines, which are mostly inactivated vaccines, are used without an adjuvant and administered through intramuscular injection. They exist in different formulations and the vast majority of them are egg produced. But things are changing. In Europe, the first licensed live attenuated vaccine, which contains a weakened form of the virus, is ready available. It offers the advantage of needle-free delivery, through the intranasal route, and makes vaccination a much less unpleasant experience for children. When children dislike vaccination, it’s generally because of the needle that’s involved. And in the US, the first cell-based vaccines produced with the involvement of tissue culture are already licensed.

"Today, we’re addressing yesterday’s hopes. We’re making continuous progress. But this doesn’t mean there is no more room for improvement", Prof. Gerd Sutter said. "Ample challenges exist. Think about increased efficacy in the elderly. Think about faster production cycles, increased manufacturing capacity and the abilities to efficiently prepare immunizations against a suddenly emerging potential pandemic virus. The overall goal would be of course to generate a solid protective vaccine against drift variants of an influenza A virus subtype, or even a universal vaccine, against all influenza A viruses and potentially across subtypes.”

THE MAIN TARGETS FOR NEW DEVELOPMENTS
For Sutter, the main objective is very clear. "We need to work on providing even more solid protective immunity. And this means certainly getting a higher antibody count, or more specific antibodies, or cross-neutralizing antibodies. But I am also a strong believer in inducing T-cell immunity. And despite the fact that it is difficult to measure the impact of T-cell immunity induced by vaccination, especially in human clinical trials, we know from mouse-models that it’s a promising route. We need to explore this route in our vaccine development to get better vaccines in the future.”

“We will certainly also target additional antigens, besides haemagglutinin and neuraminidase surface proteins”, Sutter said. "Ample possible target candidates exist. We will also optimise the immunostimulation upon vaccination and test additional antigens for immunisation. Additionally, the modern adjuvants – oil-in-water emulsions, TLR-ligands – promise, compared to mineral oil, minor adverse effects in clinical trials. We have become able to prepare our antigens in different ways – cell derived, recombinant proteins – and work on new delivery systems; live influenza viruses that have been modified, and gene or vector vaccines that deliver influenza antigens.”

BOOSTING IMMUNE RESPONSES
Modern molecular biology tools make it possible to produce antigens in a more efficient way. "There’s a wealth of information on immunity stimulation”, Sutter said. "Our immune system very efficiently recognises the viruses at multiple steps of their infectious life cycle. The immune system is key when it comes to boosting adaptive immune responses and driving the antibody or T-cell reactions. Basic research results prove that many of our empirical developed vaccine approaches are nothing less than mimics of live virus infections and live viruses, and basically provide the danger signals that trigger the immune system response. Over the next few years, we will have to sort out the most suitable danger signals to be used.”

“A quite obvious approach is to use genetic vaccines that have different means of providing these immune stimulating activities, like naked nucleic acids’ DNA and RNA, where we now understand they can be recognised by cytoplasmic and endosomal receptors of the immune system, triggering important interfering responses, or by the use of vector viruses, which need no adjuvants, because they are viruses themselves and naturally deliver the danger signal that is needed to stimulate the immune system.”

MODIFIED VACCinia VIRUS ANKARA
Sutter presented a research example: the Modified Vaccinia Ankara (MVA). MVA was developed at Sutter’s institute in Munich during the 60s, in an attempt to generate a safer smallpox vaccine, and has been administered safely to more than 100,000 people. “MVA is characterised by a replication deficiency in vivo and in vitro”, Sutter explained. “The virus is not able to form new infectious proteins. It can only form non-infectious particles. And despite that, it can express all classes of pox viral genes; early, intermediate and late.”

All of that allowed the development of MVA as a vector system. “By now, various candidate vaccines are in clinical trials,” said Sutter, “and the virus is fit for large-scale production. It is important that recombinant viruses can be generated and used, under biosafety level 1. The viruses have been used in a small clinical trial, a few thousand patients, and we have
experienced an acceptable safety profile so far. They also have clear immunostimulatory capacity and induce a balanced cellular and humoral immune response. And when we tested the MVA vaccine in an animal model, where protection by immunisation relies strictly on T-cell responses, we discovered MVA had a solid protective capacity as a T-cell vaccine.”

“The first recombinant MVA virus vaccine targeting influenza demonstrated that it is able to induce a high level of protective antibody responses, delivering HA-NP proteins from the H1N1-virus. So, when the new influenza viruses H5N1 and pandemic H1N1 surfaced, it was an obvious choice to start tests on the capacity of MVA as an influenza vaccine candidate, in a collaborative effort with Ab Osterhaus, Guus Rimmelzwaan and Joost Kreijtz.”

“What we have tested over the past few years is a simple vaccine, delivering H5N1-haemagglutinine inserted in MVA, and under the control of a strong synthetic pox virus specific promoter. The immunisation with this H5N1 vaccine in different animal models induced solid protection correlated with homologous antibody titres (A/Vietnam/1194/04) and protection even in the absence of detectable antibodies (A/Indonesia/5/05), at least giving a hint that HA specific T-cell immunity might also play a role. Based on these results, clinical evaluation of the MVA-H5 vaccine is warranted”, Sutter concluded.

During question time, following Sutter’s presentation, Ab Osterhaus inserted another important message on MVA: “If you want to go for a pandemic vaccine”, Osterhaus said, “you want to distribute it worldwide. One issue is that it should be easy to produce. Another issue is stability. Current vaccines need a cold chain, causing logistical pains, whereas an MVA-based vaccine can be sent into Africa without the need for any cold chain whatsoever for quite some time.”

Lessons Learned

1. We need to work on providing even more solid protective immunity.
2. The vast majority of our current modern vaccines are still egg produced, but things are changing.
3. Better vaccines are on the horizon, inducing T-cell immunity, targeting additional antigens and using new delivery systems.
4. We must learn from fundamental research on innate immunity and adaptive responses.
5. Vector technology and vaccine technology are ready to react to new upcoming threats.

“The overall goal would be of course to generate a solid protective vaccine against drift variants of an influenza A virus subtype, or even a universal vaccine, against all influenza A viruses and potentially across subtypes.”
An ideal influenza vaccine essentially does one thing: it prevents the virus from binding to the receptors of the respiratory cells. Since influenza viruses are shape shifters, a universal vaccine, capable of targeting a range of virus types or even subtypes, and armed with extended longevity, would certainly increase overall human protection. Prof. Xavier Saelens explained the challenges developers of universal vaccines face, and commented on the progress made.
IT ALL STARTS WITH A KISS
The influenza virus likes to replicate in our respiratory epithelial cells. The virus finds its receptors on these cells, enters its hosts, multiplies tremendously and starts to make us ill.

Haemagglutinin (HA) plays a vital role in viral cell entry. The process of finding the cell surface and the processes by which the virus is absorbed by the cell and fuses with it are all controlled by the HA proteins on the surface of the virus.

What currently used influenza vaccines or HA-specific antibodies try to do is to bind to the HA proteins on the virus’ surface and block viral attachment to the sialic-acid receptor present on the respiratory epithelial cell. That way, they also block the virus’ propagation cycle.

Current flu vaccines work and are safe, but have to be administered annually. That is because human influenza viruses have learned to deal with HA-specific antibodies, for example induced by these vaccines, and transforms itself almost every year, by changing the shape of the HA. Therefore, we need new vaccine compositions almost every year to try matching the HA in the viruses that will dominate the next influenza season.

OVERCOMING LIMITATIONS
Such an annual vaccine covers only a select few strains of the virus. This selection is based on the World Health Organization’s best bet as to which strains around the world will be most prevalent in the coming flu season. Since it takes months to develop and produce a seasonal flu vaccine in large enough quantities, and since reality doesn’t always meet predictions, the annual flu vaccines may not provide full-proof protection.

Vaccines that could protect against many strains and subtypes of influenza could help and would also enhance our preparedness for a future pandemic, Xavier Saelens said. But even with a universal vaccine, you would need a well-chosen target of the virus. “We can dream about eradicating the flu with a universal vaccine, like we did with smallpox. But that’s quite impossible because of the huge animal reservoir in which influenza A viruses thrive. Perhaps it is more realistic to think about protection against all human influenza A types (H1N1, H2N2, H3N2) without forgetting about influenza B viruses.”

Also the question of longevity remains. “The customer probably prefers lifelong protection with one or just a few vaccinations, or for ten or five years”, Saelens said. “So, universality translates itself in many characters, which are all somewhat universal in their combination.”

M2E
One way a vaccine would become more universal is if it were to entice the immune system to make antibodies against portions of viral elements that are genetically conserved, thus against epitopes on the virus that are common in all influenza viruses. Xavier Saelens’ research group is working on a universal influenza A vaccine based on the extracellular domain of the Matrix protein 2 (M2) protein, a proton-selective ion channel protein, integral in the viral envelope of the influenza A virus. That work has been going on for more than ten years now. “In 1999, our group, at the time headed by Walter Fiers, was the first to bring universal vaccines into the literature, with a research paper describing the protective potential of a vaccine based on M2”, Saelens said. “Why did we choose M2e? The main reason is that it is conserved. Genetically, the coding information for M2e leaves very little room for mutations. There are only a few positions that differ among different influenza A viruses, but it is not comparable to HA’s drifting speed. A combination of just a few M2e-variants blended in one vaccine would simply cover this limited natural diversity in M2e. In animal models such as laboratory mice, the M2e vaccine protects very well against influenza A virus infection. Our own data prove that M2e-immune mice are protected against different subtypes of influenza.”

Before transferring the M2e vaccine from the lab to the clinic, certain issues had to be addressed first, said Saelens. “What is nice about M2e is that protection largely, if not exclusively, depends on antibodies, and these are fairly easy to sample and to analyse. We can also make a fair guess
from our experience with mice about how many M2e-specific antibodies are required for protection. In collaboration with Acambis Inc (now part of Sanofi Pasteur) a Phase I clinical study was performed with the M2e-vaccine in healthy volunteers. That study learned that the vaccine is safe and induces anti-M2e antibodies in humans. However, to this date we don’t know yet whether these antibody levels would protect against human influenza. The longevity of M2e-specific antibodies could still be improved. A potential hurdle for further clinical development of the M2e vaccine is that the patent protection is fading, which could be a set back for our institute. However, this may also stimulate initiatives from other researchers as well as the industry to invest in this technology. In any case, demonstrating protection in humans with an M2e-based vaccine would require a costly and large field study. Having an M2e-based vaccine ready in case of a pandemic outbreak should certainly be considered as part of a pandemic preparedness plan.”

**HA ANTIBODIES**

Haemagglutinin (HA) is a very variable target. Saelens explained: “The virus has ways to fool our immune system almost every year. Still this fascinating viral glycoprotein has its limits. In 1993, the Japanese scientist Dr. Okuno isolated an unusual monoclonal antibody, designated C179, which could neutralise different H1 and H2 viruses but not H3 viruses.”

Dr. Okuno’s data indicated that C179 targeted the stem region of HA, thereby inhibiting the membrane fusion activity of HA. Since such fusion is essential for the virus to infect its host cell, C179 could neutralize influenza A viruses with H3 or H2 HA, a unique and surprising finding. His report was the first to describe the presence of conserved antigenic sites on HA not only in a specific subtype but also in two subtypes of the influenza A virus.

“In the past five years or so, other groups have discovered other antibodies that bind to conserved parts of HA (e.g. the stem), and remarkably such antibodies also appear to be present in humans (examples include monoclonal antibodies CH65, F16, F10, C05 and CR8020). Some of these antibodies even recognise the receptor-binding site and bind to multiple influenza A virus subtypes. The F16 antibody can bind and inhibit in vitro the infection of almost all influenza A subtypes, from H1 up to H16. However, one has to look very hard, to find these broadly reactive HA-specific antibodies in humans. We know they are there, possibly in most people that have been infected with influenza viruses, but in limited quantity compared to antibodies that bind the highly variable parts of HA. The challenge is now to design antigens that can induce such broadly binding antibodies. It is also not clear how much of these antibodies would be required to protect against human influenza although clinical studies are on their way to try to address this question. Researchers have found that these antibodies pop up more easily in people who have been vaccinated with the pandemic H1N1 2009 vaccine, but despite that they tend to wane over time. Identifying and quantifying such antibodies in clinical samples requires fairly complex laboratory assays, making it more challenging to determine correlates of protection as compared with licensed flu vaccines.”

**T-CELL BASED IMMUNITY**

The internal antigens, which are residing within the virus and are produced abundantly in infected cells, are also potential targets for a universal vaccine because they are very well conserved across subtypes. Immunity directed against these internal antigens relies mainly on what is called ‘cellular immunity’ or ‘T cell immunity’. While such immunity can be very potent, it is in general more difficult to induce cellular immunity with a vaccine. Some efforts, for example from a group at the Jenner Institute in Oxford, have focused on the use of Vaccinia virus (that is the vaccine that was essential to eradicate Smallpox from nature), or rather a more safer variant of Vaccinia virus, called MVA, to elicit immunity against the conserved Matrix 1 and Nucleoprotein of influenza A. In a group of volunteers, the research team headed by Sarah Gilbert noticed that this vector was able to induce T-cell responses against the target
antigen and they also collected some evidence of protection. A surprising and interesting finding was that apart from so-called CD8 T cells also CD4 T cells directed against influenza antigens are involved in (broad) protection against human influenza. In the future, we can expect interesting developments in this field of T-cell immunity. “Nevertheless the safety and the robustness of the vectors remain an issue”, Saelens said. “The question is also how many T-cells and of which specificity we need; most of us have T-cells against influenza antigens, yet still we get the flu from time to time.”

CHANCES OF SUCCESS
“Talking about challenges”, Saelens said, “a universal vaccine should clearly induce a much broader protection than currently licensed influenza vaccines do. However, such a vaccine cannot be inferior to anything that is on the market already and demonstrating better protection with a broadly protective influenza vaccine than a conventional influenza vaccine that matches well with the circulating influenza viruses, is challenging. In terms of pandemic preparedness, universal vaccines would clearly be a breakthrough but somebody would have to stockpile these vaccines. That of course comes with a cost, and somebody would have to pay for that. At this stage, it is not very clear if a commercial market for universal vaccines exists. Pandemic outbreaks occur infrequently, and are unpredictable. And when the shelf life of a stockpiled universal vaccine has expired, who will invest in the new stock? Furthermore, in order to measure the effectiveness of new influenza vaccines in humans, you need large clinical trials. In the end we will probably need a universal vaccine that induces, in a very safe way, both B and T cells that are cross-reactive. Such a vaccine will require robust expression platforms. After all, that production platform will have to compete with the chicken egg system that is cheap and gives high yields.”

“I expect that within the next five years, we will be able to demonstrate that HA stem-specific antibodies are protective in humans”, Saelens said. “We will likely also have a potent HA-derived immunogen that elicits stem-specific antibodies. Regarding T-cells, we will hopefully see safe vectors for T-cell-based vaccines that have moved further into clinical trials. I think that in the end, it would be nice to combine conventional vaccines with M2e and HA stem antigen vaccines. And neuraminidase has been largely overlooked, although it is also a very interesting antigen. Finally, there remains a lot to be learned from a better understanding of humans’ innate immunity against influenza”, concluded Saelens.

Lessons Learned
1. A universal vaccine is possible but should not be inferior to anything on the market.
2. At this moment, it is not very clear if a commercial market for universal vaccines exists.
3. Different pathways are open: M2e and HA stem antigen vaccines and T-cell based vaccines.
4. In order to measure the effectiveness in humans, large clinical trials will be needed.
5. A universal vaccine will need an expression platform as robust as the proven chicken egg platform.
The Threat of an H5N1 Pandemic

The H5N1 strain has been circulating across the vast expanse of the Earth for more than a decade, occasionally causing human fatalities. Does this mean the virus is unable to cause a pandemic? Or might we just have been very lucky? Dr. Colin Russell sheds some light on the factors that influence the strain’s pandemic capabilities.
“It only takes H5N1 three to five mutations to become aerosol transmissible from mammal to mammal.”
“People just get tired of hearing over and over again that there might be a flu problem.”

H5N1 and the amount of mutations needed to become aerosol transmissible

Hypothesis 1 - It’s not possible for H5N1 to become human-to-human transmissible

Hypothesis 2 - It is possible but requires too many mutations to happen naturally

5 mutations


Lessons Learned

1. An outbreak of H7N9 does nothing to diminish the threat of an H5N1 pandemic.
2. H5N1 viruses might only need a handful of mutations to become aerosol transmissible and cause accelerating damage to humans.
3. The probability of H5N1 gaining aerosol capabilities is influenced by a complex interaction of factors.
4. At this point, we simply don’t have enough information to make any pandemic prediction.
5. There is a lot of science to be done.
H5N1 and the amount of mutations needed to become aerosol transmissible
Partner Organisations

The European Scientific Working group on Influenza is a network of partner organizations that share the same goal: to reduce the burden of influenza in Europe.

To realize its objectives, ESWI works with the following organizations:

ESWI website: eswi.org

Knowledge Centre for Healthcare Providers: flucentre.org

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