Moving Europe towards further action
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ESWI FLU SUMMIT 2015
FOREWORD

The emergence of new avian influenza viruses in humans like the H7N9 and H10N8 flu viruses, and the continued threat of H5N1 clearly emphasize the unpredictable and global character of this infectious disease. To cope with a future pandemic outbreak of influenza, heightened readiness is needed as well as improved outbreak prevention of seasonal influenza in various risk groups. To address these urgent public health issues, ESWI has brought together the European influenza community in the fourth edition of the Science Policy Flu Summit. On 30 September 2015, 94 public health officials and decision makers gathered at the International Press Centre in the heart of the European Quarter in Brussels for a day of tailored lectures, Q&A sessions and networking.

Although the Summit had been designed to give an overview of the scientific advances in the influenza field and to provide a platform for the exchange of information and ideas, the main goal of the event was to develop an influenza action plan for Europe. Indeed, the lively debates have yielded a clear and practical roadmap, listing the most urgent actions that need to be taken in order to reduce the impact of influenza in Europe. This magazine provides a report of the lectures and the discussions held at the Summit and, of course, provides an account of how the roadmap can be converted into a concrete action plan, to be implemented in the next few years.

All texts can be copied and distributed freely. Additional questions to the Summit’s faculty can be asked via ESWI’s management.

contact details see next page
The following partners have provided unrestricted grants to support the Science Policy Flu Summit. Unrestricted grants imply that the partners financially supported the Summit, but have not been involved in the preparation of the Summit in any way.

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.

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.
WHY IS A SCIENCE POLICY FLU SUMMIT NECESSARY?

EXPECTED VIRUS THREATS CONTINUE TO Emerge IN HUMANS, AND THEY OFTEN ORIGINATE FROM THE ANIMAL WORLD. "SOME OF THE MOST DEVASTATING NEW HUMAN INFECTIONS, LIKE EBOLA, MERS COV, HIV AND OF COURSE THE H1N1 PANDEMIC INFLUENZA VIRUS, HAVE NATURALLY TRANSMITTED FROM ANIMALS TO HUMANS", SAID AB OSTERHAUS. "SCIENTISTS AND PUBLIC HEALTH OFFICIALS THEREFORE NEED TO WORK TOGETHER TO ATTAIN OPTIMAL HEALTH."

NO TIME FOR COMPLACENCY
"If we look at what we have achieved through vaccination, the results are fantastic. Smallpox has been eradicated, we have brought most of the childhood diseases under control in the industrialized world. But there is no time for complacency, as is painfully demonstrated by the increasing number of human MERS coronavirus (MERS-CoV) infections, partly due to increase in nosocomial transmission, but also because of ongoing transmission from dromedary camels to humans. The most prominent mode of camel-to-human transmission is probably through human contacts with respiratory excreta although transmission via milk or urine cannot be ruled out. To date, we have seen 1,369 confirmed cases of MERS-CoV infection, 520 of which have succumbed to the virus. This goes to show how viruses continue to (re-) emerge and that they know no borders in our globalizing world," warns Ab Osterhaus. A recent and very devastating pandemic infectious disease outbreak fuelled by a complex mix of predisposing factors in our modern society was caused by the emergence of HIV/AIDS in Africa some 30 years ago. Today, the virus claims more than one million lives each year, with more than 20 million deadly victims in total since its emergence.

AVIAN INFLUENZA THREAT
In the past century, more than 50 million people died in four pandemic outbreaks of influenza. "The most recent one, the 2009 H1N1 Mexican flu pandemic, caused 0.3 to 0.5 million deaths, which is more than a normal seasonal influenza, and the impact was highest among young people," Ab Osterhaus explained. "Migratory birds are a reservoir for all types of flu viruses. Typically, these avian viruses cause little or no illness in wild birds. But when they are transmitted to domestic poultry, they may acquire mutations and change into so-called highly pathogenic avian influenza (HPAI) viruses. These HPAI viruses do not easily transmit to humans, unless they evolve and acquire new mutations. Pigs are ideal mixing vessels as they can be infected by both avian and human influenza A viruses. Hence, we face the constant threat of a new pandemic outbreak of influenza."

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 is quite efficient in infecting humans", Osterhaus said. "In three seasons, 593 people have been infected, of whom 105 have died, and the virus continues its spread."

Both H5N1 and H7N9 are possible origins of a new pandemic."
spread. In contrast to the H5N1 virus, however, H7N9 is a low pathogenic virus. An H7N9 infected chicken doesn’t just drop dead. The low pathogenic character may sound like good news, but it makes it more difficult to trace the virus and monitor its spread in the chicken population. We now know, however, that the virus can spread from human to human, although not very efficiently. But it is impossible to say whether it is going to take off."

**THE NEED FOR A SCIENCE POLICY SUMMIT ON INFLUENZA**

"A major rational for organizing the Science Policy Flu Summit stems from the recently held Fifth ESWI Influenza Conference," Ab Osterhaus continues. "Where about 150 key opinion leaders in public health attended the Science Policy Interface, a separate programme designed to bridge the gap between science and health policy. From the participants’ comments, ESWI had learnt that public health officials have a huge interest in policy-related scientific information and ESWI’s annual summits are an attractive platform to answer these needs. ESWI strongly believes scientists need to reach out and work with public health officials, healthcare professionals, at-risk patients and the elderly. That is precisely why ESWI has established constructive working relations with a multitude of stakeholder organizations. The European Public Health Alliance is one of these partner organizations and we thank EPHA for their contribution to this Science Policy Flu Summit."

"If we look at what we have achieved through vaccination, the results are fantastic. But there is no time for complacency."

**LESSONS LEARNED**

1. It is impossible to tell where and when the next influenza pandemic will spark off.
2. We are still unprepared to cope with a major outbreak of pandemic influenza.
3. Scientists have the moral obligation to reach out and work with the many groups of people who need scientific evidence in their daily practice.
IS INFLUENZA ON THE AGENDA OF EUROPEAN PARLIAMENT?


THE CRUCIAL ROLE OF ENVI
"The influenza debate on a European level is highly needed," according to Bart Staes at the opening of his lecture. "After all, we now see that pandemic preparedness is no longer on top of the political agenda. In addition, there is a lack of equitable access to medical countermeasures in Europe, and, what is worse, there is a lack of solidarity between EU Member States, as seen during the 2009 pandemic." There is hence a crucial role to play for the EP Committee on the Environment, Public Health and Food Safety (ENVI). Bart Staes explains: "Surely, our work in the ENVI committee is of high social relevance, as one of our major topics is improving public health protection against virus threats such as influenza. To that end, we closely monitor the EC's influenza policy."

THE PARLIAMENTARY FRAMEWORK FOR INFLUENZA
"During the 2009-2014 term, we have had three major parliamentary debates on the influenza topic. First of all, there was the lively debate on the Third Health Programme (2014-2020). Secondly, there was the decision taken by the EP and the Council of Ministers on serious cross-border threats. And thirdly, we issued a non-legislative resolution on the evaluation of how the 2009 H1N1 influenza pandemic had been managed in the EU", Bart Staes said.

1. Third Health Programme (2014-2020)
   - Adopted on 26 February 2014
   - Aims to contribute to the creation and maintenance of robust mechanisms and tools to detect, assess and manage major cross-border health threats
   - Aims to support coordinated public health measures at Union level to address different aspects of cross-border health threats
   - Seeks to benefit from complementarity with the work programme of the European Centre for Disease Prevention and Control (ECDC)

2. Decision by the EP and the Council of Ministers on serious cross-border threats
   - Gives the EC the right and the duty to recognise a situation of public health emergency. In other words, this decision is a tool for the EC to act as soon as an epidemic of human influenza with pandemic potential has been detected.

"The outcomes of the Science Policy Flu Summit will be of high interest to the members of the ENVI Committee."
WHO IS BART STAES?

- Member of European Parliament since 1999 (Greens)
- Member of the EP Committee on the Environment, Public Health and Food Safety (ENVI) since 1999
- Main topics of interest hence include:
  - Climate and energy
  - Democracy and human rights
  - Food safety and agriculture
  - Finance and trade
  - Anti-fraud/Transparency
  - Public health
- Aims to achieve a social, solidary and sustainable European Union

3. European Parliament resolution on the evaluation of the management of H1N1 influenza in 2009-2010 in the EU

- Calls for the revision of influenza pandemic prevention plans established in the EU and its Member States
- Urges the European Union to allocate more resources to research and development regarding preventive measures in the field of public health care
- Invites the ECDC to contribute to reviewing best practices on national influenza preparedness plans
- Calls for an assessment of the influenza vaccination strategies recommended in the EU and applied in the EU Member States

Joining forces to reduce the impact of flu in Europe

“In the current parliamentary term, MEPs continue to tackle the influenza issue, although it is only fair to say that the number of influenza-related parliamentary questions has dropped dramatically since 2014,” Bart Staes admits. “Still, we have raised issues such as the barriers to seasonal influenza vaccination coverage, influenza vaccination of healthy children and the implementation of the 2009 Council Recommendation on seasonal influenza vaccination. This leads me to believe that Members of European Parliament - and the ENVI Committee members in particular - share many of the concerns with the audience of the Science Policy Flu Summit. I therefore call upon all members of the influenza community to join forces in order to reduce the impact of influenza in Europe.”

“I call upon all members of the influenza community to join forces in order to reduce the impact of influenza in Europe.”
“THE INFLUENZA VACCINATION ISSUE IS A MULTIFACETED ONE,” SAID MICHAEL SULZNER, “AND SINCE VACCINATION IS A COMPETENCE OF THE MEMBER STATES, THE COMMISSION HAS A SUPPORTIVE ROLE TO PLAY. TO GET A CLEAR VIEW ON THE NEEDS AND CHALLENGES WITH REGARD TO THE STATE OF PLAY ON THE IMPLEMENTATION OF THE COUNCIL RECOMMENDATION ON SEASONAL INFLUENZA VACCINATION, DG SANTE ORGANIZED A HIGH LEVEL STAKEHOLDER MEETING IN LUXEMBOURG IN APRIL 2015.”

EU COUNCIL RECOMMENDATION ON SEASONAL INFLUENZA VACCINATION
The competence for vaccination policies and programmes is with the EU Member States. The role of the Commission is limited to support national vaccination policies and efforts to maintain or increase vaccination against vaccine-preventable diseases. Against this background, the 2009 Council Recommendation on seasonal influenza vaccination aims to concert actions at the EU level to encourage vaccination among risk groups and health care workers in order to mitigate the impact of seasonal influenza,” Michael Sulzner elaborated. “It encourages Member States to adopt action plans and policies to improve seasonal influenza vaccination coverage. After all, the target was to reach a 75% vaccination coverage rate of the elderly by the 2014/15 winter season. We now know that few countries have even come close to reaching that target. To address this issue, the Commission developed a report - based on a technical review by ECDC - which revealed a number of challenges and shortcomings as regards the implementation of the Council Recommendation. The report also included quite a few proposals to improve the current situation. Hence the organization of the high level stakeholder event in Luxembourg.”

AIMS OF THE HIGH LEVEL HEARING ON SEASONAL INFLUENZA

- To contribute to comprehensive understanding of the impact and the benefits of vaccination
- To share best practices in implementing seasonal influenza vaccination programmes
- To identify measures to increase seasonal influenza vaccination coverage rates

MAIN FINDINGS
The workshop yielded several interesting insights. Michael Sulzner explained: “First of all, it is crucial to have political leadership and policy ownership in order to make sure that vaccination programmes contribute to sustainable health systems. It is also crucial to have good programme coordination and national delivery frameworks in place, i.e. to define roles and responsibilities and mode of actions. The meeting also underlined the importance of programme-integrated communication strategies, targeting healthcare workers and the general public, but also public health decision-makers. The economic benefits of influenza vaccination, for instance, was regarded as a powerful tool to convince policy makers of the need to increase influenza vaccine uptake rates. It is also important to note that the stakeholders recognized the role of industry in influenza strategies and the need to include the industry perspective in the discussions.”

“There are indications of only limited influenza action plans in a number of EU member states.”

DR. MICHAEL SULZNER, Public Health Directorate, DG Health & Food Safety
Interestingly, the stakeholders also discussed the basic elements of a successful annual influenza plan. They found that there should be information with regards to policy decisions, there should be an oversight of supply of antiviral medicines as well as information about the procurement and distribution of influenza vaccine. Obviously, this goes to show that influenza plans need to build on a variety of components. Vaccine management (purchase, stockpiling and delivery processes) is but one of the many elements.

THE WAY FORWARD

“The Council of the European Union adopted conclusions on vaccinations as an effective tool in public health on 1 December 2014 and we consider these conclusions as an important tool to put the influenza issue back on the public health agenda in the EU. The document calls for closer cooperation between the Member States, but also between the Member States and the European Commission. One quite interesting invitation to Member States and industry is to find best ways to allow stakeholders, including industry and civil society, to express their views on the flu vaccination issue. Another important invitation looks at developing joint action programmes to share best practices on national vaccination policies. And finally, the Council conclusions invite Member States to invest more in vaccination research and development, but also in the exchange of information related to the monitoring of vaccination impact."

"We need to find the best ways to involve all stakeholders, including industry, in a joint process to improve vaccination programmes."
INFLUENZA IS AMONG THE LEADING CAUSES OF INFECTIOUS DISEASE MORBIDITY AND MORTALITY IN EUROPE. "SO WE NEED TO TAKE THE POLICY DISCUSSION ABOUT INFLUENZA FORWARD, AND PUT THE ISSUE BACK ON THE AGENDA OF EUROPEAN AND NATIONAL POLICY MAKERS," SAID PASI PENTTINEN, ACTING HEAD OF THE DISEASE PROGRAMME FOR INFLUENZA AND OTHER RESPIRATORY VIRUSES AT ECDC.

EXCESS DEATHS AND VACCINE EFFECTIVENESS

“According to preliminary data of the European monitoring of excess mortality for public health action, there have been more than 90,000 excess all-cause deaths among the elderly during the winter 2014-2015,” Pasi Penttinen reported. “It is reasonable to assume that the large majority of these deaths have been caused by influenza infection. 90,000 excess deaths in only 17 EU countries... It really surprised me to see that this news did not make the headlines. Now, we know that the circulating A(H3N2) subtype has been drifting away from the vaccine strain, which has resulted in low vaccine effectiveness this season. Data gathered by the ECDC funded I-Move project indeed confirm that effectiveness was low not only against H3N2, but also against H1N1 and only slightly better against B-viruses. The only really positive signal was the good effectiveness against H1N1 among children.”

“One could argue that the severe impact of influenza during the past season is due to suboptimal vaccine effectiveness. However, such an effect is to be expected only if the vaccines are used routinely.”

This picture shows the weekly pooled mortality in blue from 17 European countries for over 65 years olds on the top graph and for all ages on the lower graph. The excess mortality is calculated from the upper dashed line representing deviations from the weekly mean. According to these calculations over 90,000 excess winter deaths were recorded in 17 European countries.
INFLUENZA VACCINE UPTAKE

“One could argue that the severe impact of influenza during the past season is due to suboptimal vaccine effectiveness,” Pasi Penttinen continued. “However, such an effect is to be expected only if the vaccines are widely used. So we need to take a look at the vaccination rates first. According to the Council Recommendation on seasonal influenza vaccination, adopted in 2009, influenza vaccination is recommended for older age groups, people with chronic medical conditions and healthcare workers. In 2012, the World Health Organization recommended the vaccination for two additional groups: pregnant women and children under 5 years of age.”

“ECDC monitors the influenza vaccination coverage through surveys conducted by the VENICE group since 2008. According to those surveys, all countries recommend vaccination of the older age groups. The age specified differs between countries, the majority of member states (22) recommend seasonal influenza vaccination for individuals 65 years and older. Sadly enough, vaccination coverage rates for the older population are suboptimal in most of the countries (except in the Netherlands and the United Kingdom), did not increase in five influenza seasons since 2008 and do not meet the target of the Council Recommendation.”

“Large discrepancies between recommendations and vaccination coverage monitoring exist for clinical risk groups and HCWs.”

LESSONS LEARNED

1. Recommendations for influenza vaccination exist in most of the countries for the main clinical and occupational risk groups in addition to the elderly
2. Additional efforts are needed to increase vaccination coverage rates in the elderly as vaccine uptake has decreased since the 2009 H1N1 pandemic
3. All countries should strive to monitor vaccine coverage for the elderly as well as people with chronic medical conditions, health care workers and pregnant women
4. Social behavioural interventions are the first line of defence against a newly emerging disease, including the next influenza pandemic

ROADMAP ACTION #3
Facilitate studies on vaccine acceptance and risk perception, involving social scientists.
HEALTH EQUALITY
AND SUSTAINABLE
ACCESS TO
VACCINES /
JOINT PROCUREMENT

VACCINATION IS A VERY EFFECTIVE, PREVENTIVE PUBLIC
HEALTH TOOL. "BUT STRONG POLITICAL LEADERSHIP AND
STRUCTURAL COLLABORATION WITH ALL STAKEHOLDERS
IS NEEDED TO MOVE THE INFLUENZA PREVENTION
ISSUE FORWARD," SAID PEGGY MAGUIRE, EPHA BOARD
MEMBER AND DIRECTOR GENERAL OF THE EUROPEAN
INSTITUTE OF WOMEN’S HEALTH.

VACCINATION CHALLENGES
"To increase the uptake of influenza vaccines in the most
vulnerable target groups, we see some challenges
lying ahead," Peggy Maguire warned the Summit audience.
"There are, for instance, the ethical considerations.
How do we balance the freedom of choice and the
obligation for healthcare workers to take good care of
their patients? How do we prevent vaccination policies
from being exclusive? Other challenges that we need
to tackle are the barriers in accessibility: vaccines are not
affordable for all, some groups - like undocumented migrants
- experience a high threshold to vaccination and low health
literacy correlates with sub-optimal vaccination rates and
reduced use of preventive services."

"Vaccination remains the most powerful and effective public
health measure available."

INCREASE CONFIDENCE
To address the challenges, we need to know the reasons
why vaccines aren’t taken up. "People choose not to
be vaccinated for four main reasons: fear of the unknown,
lack of understanding, lack of time and taboos around
vaccination. The issue here is hence to increase or restore
the public’s confidence in vaccination. To that end, we need to improve
communication strategies providing access to reliable,
evidence-based and tailored information. Special attention
should go to informing women about the benefits of
vaccination as they often take care of little children and the
elderly. The ECDC’s technical report clearly showed that
the level of health literacy of pregnant women correlates
with the level of vaccine uptake of their children. We
also definitely need more research to make sure we
use the right interventions that influence behaviour change. We need to integrate
communication with health promotion, which, I think,
is a competency of the EU Commission. And finally, we

PEGGY MAGUIRE, EPHA Board Member
WE NEED TO

- Develop stronger political leadership and willingness to cope with coordination of public health systems
- Promote societal commitment, citizen involvement and guidance to make vaccination programmes work
- Build trust and understanding, e.g. by recognising the role of women
- Advocate for making vaccination the norm for society, in particular with regard to childhood immunisation and across the lifespan
- Develop an integrated communication strategy to proactively communicate evidence

“EPHA is looking forward to strengthening the collaboration with the EC, ECDC and all stakeholders to move the vaccination and prevention issues forward.”

JOINT PROCUREMENT
“EPHA finds the EC’s joint procurement initiative a very positive one. Although some questions still need to be addressed regarding the decision-making processes and the ability to take initiatives. Can industry misuse this exercise by forming clusters? Can stronger countries work together to further weaken the poorer countries in the EU? And where is the voice of patients and civil society? However, we are convinced that the initiative will lead to better access and more affordable vaccines.”

About the European Public Health Alliance
EPHA is Europe’s largest network representing the public health community with over 100 member organizations. Members include disease specific organizations as well as health professionals and organizations of the elderly and patients. EPHA advocates for more citizen involvement and transparency in political public health decision-making at the EU level. We work together to obtain universal access to health care for all and to reduce inequalities.

ASSET Project: tackling information gaps on pandemics and epidemics
http://www.asset-scienceinsociety.eu/

ROADMAP ACTION #4
Facilitate the generation of more scientific evidence on the role of healthcare workers in nosocomial spread of influenza.
“SINCE INFLUENZA VIRUSES ARE IMPOSSIBLE TO PREDICT, WE MUST WARN EUROPEAN PUBLIC HEALTH OFFICIALS FOR COMPLACENCY WHEN IT COMES TO PREPARING OUR HEALTHCARE SYSTEMS FOR THE NEXT INFLUENZA PANDEMIC,” TED VAN ESSEN TOLD HIS SUMMIT AUDIENCE. “IT IS ESSENTIAL FOR NATIONAL GOVERNMENTS TO STRENGTHEN THEIR RESPONSE PLANNING, BUILDING ON THE LESSONS LEARNED FROM THE 2009 H1N1 PANDEMIC. BUT HAVE THEY DONE SO?”

**BENCHMARK: THE ESWI FLUQUEST SURVEY**

“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 Van Essen. “The pandemic itself had been handled quite well in Europe. But since then few national authorities have evaluated their response plans. To get a clear picture of the situation, ESWI had carried out 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 a point of reference. The FluQuest survey revealed some remarkable and worrisome trends and differences in influenza pandemic response planning in Europe. Today, it would be highly interesting to discuss whether pandemic preparedness in Europe has improved since the publication of the FluQuest findings.”

**PREPAREDNESS PLAN UPDATES ARE OFTEN POSTPONED**

“Few countries have their act together”, concluded Van Essen. “Even today, only a minority of 8 out of 28 EU countries has updated its pre-pandemic preparedness plan. Obviously, several other countries lack the sense of urgency to revise their plans, for a variety of reasons: lack of political interest, lack of scientific consensus over the pandemic evaluation or because they are waiting for a coordinated response by WHO and ECDC. The latter is known to move into a ‘all hazards’ approach instead of a disease specific approach.”

**FOCUS ON FLEXIBILITY**

“Whereas many pre-pandemic preparedness plans chose to strictly abide to WHO’s pandemic preparedness phases, most countries which have already revised their PPPs, have built in some flexibility or even developed their own set of phases. It is important to note that this does not contradict with the new WHO Pandemic Influenza Risk Management Guidance document that has been issued in 2013. In fact, countries are indeed advised to develop their own national risk assessments based on local circumstances.”

**ANTIVIRAL STOCKPILING**

“The most widely used antiviral drugs against influenza are the neuraminidase inhibitors oseltamivir and zanamivir. While the new antiviral peramivir was licensed for use during the pandemic in US and Japan, the same holds true for another new drug, laninamivir, which was licensed for use in Japan. We’ve witnessed large-scale antiviral stockpiling since 2005 due to the intense fears of an imminent H5N1 avian influenza pandemic. Since then, however, controversy has arisen due to the allegedly ‘mild’ course of the 2009 H1N1 pandemic as well as to scientific debate about effectiveness of oseltamivir. As a consequence, it is now unclear whether individual countries are maintaining stockpile level to ensure continued preparedness.”

**PANDEMIC VACCINES**

“Although, in the post-pandemic era, governments are hesitant to openly communicate about their agreements with vaccine producing companies, it is clear that some countries...
currently have Advanced Purchase Agreements in place, which are less binding than the traditional pandemic vaccine contracts. A possible solution, of course, is the Joint Procurement Agreement, approved by the Commission in April 2014, which will enable all EU countries to procure pandemic vaccines and other medical countermeasures as a group, rather than individually. On 22 September 2015, France became the 22nd EU country to sign the agreement."

"HEALTHCARE CAPACITY HAD BEEN PUSHED TO THE LIMIT
"Although primary care and hospital care systems were able to cope with all patients, it is estimated that many countries were close to 100% occupation of hospital capacities. Consequently, general and specialized hospital capacity would have been overstretched if the pandemic would have been worse, and then the question of who to treat and who not to treat is an important one to be addressed. But surprisingly, the lack of hospital capacity and the question of triage is not calculated in pandemic preparedness plans."

COMMUNICATION IN TIMES OF AN INFLUENZA PANDEMIC
"In virtually all the countries, we have experienced a communication flaw. In part this was due to the fragmentation of responsibilities in several European countries and the lack of concerted communication on an international level. This trial and error communication, however, left room for confusing messages on the social media, as we have seen. Still, many governments choose not to install a single flu spokesperson to inform the public at large. The Belgian example, however, showed the obvious benefits of channelling the media attention to one single person."

LESSONS LEARNED
1. Flu viruses are unpredictable and are constantly changing
2. European policy makers are, in general, complacent to develop decisive pandemic response plans, based on lessons learned during the 2009 pandemic
3. Revised pandemic preparedness plans are often extremely flexible
4. EU countries await actions by WHO, ECDC and DG SANTE
5. Challenges lie ahead in terms of vaccine/antiviral stockpiles, vaccine procurement and healthcare capacity

On the role of WHO

The WHO Pandemic Influenza Risk Management Guidance, issued in 2013, was developed after a thorough evaluation of pandemic management by WHO and its Member States. In 2011 already, WHO has established the Pandemic Influenza Preparedness (PIP) Framework. It is a unique framework that involves WHO, its member states, industry and the civil society. It has established a separate fund to help improve pandemic preparedness in as many countries as possible. Obviously, WHO’s Global Influenza Surveillance and Response System (GISRS) plays a key role in the PIP Framework.
On 22 December 2009, the Council of the European Union adopted a recommendation encouraging member states to implement action plans to improve seasonal influenza vaccination coverage. The main objective was to reach the WHO target of 75% vaccination coverage of the elderly and ideally of all other target groups by the 2014/15 winter season. "There are, however, huge discrepancies in seasonal influenza vaccine uptake throughout Europe, with only the UK and The Netherlands achieving the European Council Recommendation. Now, general practitioners have an extremely important role to play in flu vaccine uptake, as also stated in the conclusions of the high-level hearing on the implementation of the Council Recommendation on seasonal influenza vaccination, held on 30 April 2015 in Luxembourg."

"We need a common approach for the implementation of routine seasonal influenza vaccination in Europe."

CORE GUIDELINES
The UK and the Netherlands both have well-developed influenza vaccination guidelines for General Practitioners, while in many other European countries guidelines either do not exist or are less clear or less official. "So we really need to create a common ground, a common approach for the implementation of routine seasonal influenza vaccination in Europe. As a matter of fact, to provide clearer information and to improve coverage, we have established a European expert group, consisting of 21 General Practitioners and immunization specialists. This expert group has developed core guidelines for GPs, actually a synthesis of the national guidelines and best practices of the UK and The Netherlands. In this work, we address important topics such as the epidemiology and burden of disease, diagnosis, vaccination recommendations, types of influenza vaccines and vaccine effectiveness and safety. And of course, we pay specific attention to the role of GPs in influenza vaccination: the importance of General Practitioner endorsement, selecting and notifying individuals eligible for influenza vaccination, organisation of vaccination, patient records, storage of influenza vaccines and communication with patients."

"Countries with high influenza vaccination coverage rates all involve their GPs very well."

"WE ARE DEALING WITH A VERY UNPREDICTABLE VIRUS THAT CAUSES IMMENSE SUFFERING IN OUR PATIENTS AND COMMUNITIES, IT PARALYZES HOSPITALS, PUBLIC TRANSPORT... SO WE NEED TO FIND BETTER WAYS TO PREVENT FLU VIRUS OUTBREAKS," SAID GEORGE KASSIANOS, PRESIDENT OF THE BRITISH GLOBAL AND TRAVEL HEALTH ASSOCIATION AND IMMUNISATION LEAD OF THE ROYAL COLLEGE OF GENERAL PRACTITIONERS.
Together, the expert group members form a committee called RAISE (Raise Awareness of Influenza Strategies in Europe)

**NEXT STEPS**

“We strongly believe our core guidelines can be a powerful tool to help raise influenza vaccine uptake in at-risk groups, especially in Eastern European countries. But to get there, more work needs to be done. First of all, we will open up our paper for comments by submitting it for publication in a peer-reviewed journal. In the coming months, the Expert Group members will also work with European bodies to have the guidelines endorsed at a European level. At the same time, we will work with national bodies to get their endorsement and to have the document translated in local languages if needed. And finally, we look forward to developing an interactive electronic tool to make the content of the guidelines available in a user-friendly way.”

“*When meditating over a disease, I never think of finding a remedy for it, but instead a means of preventing it.*” - Louis Pasteur (1822-1895)

**ROADMAP ACTION #5**

Endorse and disseminate European vaccination and treatment guidelines for General Practitioners
THE SOCIO-ECONOMIC IMPACT OF INFLUENZA: WEIGHING THE BENEFITS AND THE COSTS OF INFLUENZA VACCINATION

THE POTENTIAL BENEFITS OF FLU VACCINATION BUT ALSO ITS COSTS – WHETHER DIRECT, INDIRECT OR “AVOIED” TO SOCIETY – AREN’T EASY TO CALCULATE. HOW CAN WE USE COST-EFFECTIVENESS STUDIES TO SUPPORT AND SHAPE EVIDENCE-BASED VACCINATION INTERVENTION STRATEGIES?

Mark Jit and his colleagues within the Modelling and Economics Unit at Public Health England use economic models that weigh the direct and indirect costs in a situation with vaccination versus those associated with no vaccination, to yield an estimate of the burden that vaccination can prevent. “If you vaccinate certain groups, you reduce the burden to a certain level, but you always have to pay something if you want to do interventions,” he said, adding that the more important question regarding the value of an intervention relates to the averted health burden. The reduction in health burden can be measured in quantities like episodes of disease prevented or life years gained. The question to ask then is: does the reduction of flu’s burden to society as a result of vaccination justify the cost of the intervention?”

In more technical terms, the cost-effectiveness of a vaccination programme is the ratio of the cost of the intervention (economic burden plus vaccination costs) to a relevant measure of its effect. It can be used in a decision rule in resource allocation as it helps to determine if new treatments, therapies or preventive interventions provide better value relative to the current situation.

BENEFITS OF VACCINATING YOUNG CHILDREN

The UK decided to roll out an influenza vaccination paediatric programme as of September 2013. “This is a massive influenza vaccination programme,” said Mark Jit. “In terms of number of doses, it’s the largest expansion of the UK influenza immunization programme ever. This decision was taken on the basis of a number of criteria, including an assessment demonstrating cost-effectiveness. If we look at the results of the analysis that fuelled the decision to introduce paediatric flu vaccination in the UK, we see a much higher number of prevented infections in high risk groups and a considerable increase in the number of deaths prevented as compared to the situation where we did not immunize the 5 to 16 year olds.” (see figure 1)

“The purpose of healthcare is not primarily to save money, its purpose is to improve people’s health.”
THE INFLUENZA BURDEN ICEBERG
The number of hospital admissions, primary care attendances and deaths only represents the top of the influenza burden “iceberg”. From an economic perspective, many other socioeconomic effects are important. For example, flu leads to lost productivity and a reduced work force capacity. There are the out-of-pocket costs that households pay for doctor visits and the money spent on over-the-counter and prescription medications. And what is the cost of human suffering? Besides microeconomic costs, influenza also generates costs on a macroeconomic level. For example, in a pandemic, when people are less likely to work, travel and shop, the labour supply and consumer spending drops. Furthermore, some businesses will have to close temporarily or might even get into more serious trouble because of disrupted supply chains. So vaccination might help to minimise the shock to the national economy caused by a pandemic. The role of health economics is to weigh the benefits and the costs as an evidence base for making health care investment decisions.

Commenting on the results of a review of cost-effectiveness review studies on flu vaccination he was involved in, Mark Jit explains: “There is already strong evidence that vaccination of children, the elderly and risk groups is cost-effective. And most EU countries have good recommendations in place, but funding policies do not always correspond with these recommendations. Obviously, this is a complicated matter that has to do with finances and political decision-making. We have to bear in mind that while cost-effectiveness is useful in terms of informing public health interventions, economic findings need to be translated into terms that are meaningful to the general public, finance ministers and health insurance agencies.”

LESSONS LEARNED
1. Chronically-ill patients risk missing out on 1.
   There is strong evidence that vaccination of children, the elderly and risk groups is cost-effective.
2. There is a gap between epidemiological and economic evidence for seasonal influenza vaccination, and actual vaccination uptake in the EU.
3. The number of hospital admissions, primary care attendances and deaths only represent the top of the influenza burden “iceberg”.
4. The UK decided to roll out a paediatric influenza vaccination programme, based on a detailed assessment of the cost-effectiveness of this intervention.

“If a public health intervention is cost-effective, it basically means that it is good value for money and hence worth the investment.”

Reimbursement of costs is a strong driver to enhance flu vaccine uptake. Yet payment mechanisms vary widely across Europe.

**Status of influenza vaccine recommendations**

![Graph showing status of influenza vaccine recommendations](image)


**ROADMAP ACTION #6**
Bring financial and health government officials together with health economists to discuss cost-effectiveness data and their significance for the economic and the public health domains.
FINLAND HAS A LONG-STANDING HISTORY OF VACCINATING CHILDREN AGAINST INFLUENZA. TERHO HEIKKINEN PROVIDES A CLEAR PICTURE OF THE SCIENTIFIC BASE FOR THE FINNISH DECISION TO ROUTINELY IMMUNIZE YOUNG CHILDREN.

FINLAND HAS A LONG-STANDING HISTORY OF VACCINATING CHILDREN AGAINST INFLUENZA. TERHO HEIKKINEN PROVIDES A CLEAR PICTURE OF THE SCIENTIFIC BASE FOR THE FINNISH DECISION TO ROUTINELY IMMUNIZE YOUNG CHILDREN.

SHOULD CHILDREN BE VACCINATED AGAINST INFLUENZA?

"Each year up to 100,000 children under the age of 5 die of influenza worldwide," Terho Heikkinen said at the opening of his Summit talk. "99% of these cases occur in the developing world. But even in the United States, each season about 100 children die of influenza, 43% of whom were previously healthy children who succumbed to a disease for which we have a vaccine readily available." Terho Heikkinen, however, argues that mortality is not the main reason why we should vaccinate children. "Looking at the attack rates of influenza, we see a totally different picture. In every flu season, regardless of the circulating strain, attack rates are highest in children.

Studies conducted in Finland show that every season every sixth of all children fell ill with influenza. Although most cases are not life threatening, we often see complications that go beyond the usual symptoms. In fact, studies demonstrated that 40% of the under 3 year old with influenza develop acute otitis media, which in most countries results in antibiotic treatment."

Severe disease may even contribute to hospitalization. Terho Heikkinen presented data from a study that covered 16 consecutive influenza seasons, confirming that the youngest children are at highest risk of being admitted to hospital. (see figure 1)

VACCINATION OR NO VACCINATION?

"Children are the main disseminators of influenza viruses in the households and in the community," argued Terho Heikkinen. "Children are the engines that transmit influenza to other age groups in society, especially to the elderly and the vulnerable. So, should we vaccinate all children against influenza, not only those with an underlying condition? The question was raised for the first time in the New England Journal of Medicine some 15 years ago. Since then, vaccination recommendations have changed rapidly, especially in the US, where they now have a recommendation to vaccinate everyone, including the healthy adults."

Figure 1: Age-specific incidence data for hospitalizations with confirmed influenza
"Is influenza a more severe illness in the US than in Europe?"

The situation in Europe is slightly different. "Is influenza a more severe illness in the US," Heikkinen asked. "Prior to the UK's decision to routinely vaccinate young children, only four countries recommended vaccination of healthy children: Austria, Finland, Malta and Slovenia. Of these countries, Finland was the only country to really implement the recommendation by including the flu vaccine in the routine vaccination programme. So it is high time to consider the possible hurdles for childhood vaccination. Certainly, influenza is a severely underestimated illness, as many people mistakenly think it is not much worse than a common cold. A second hurdle is the lack of data on the cost-effectiveness of vaccination. But the most important obstacle to expanding vaccination programmes are the Cochrane reviews that doubt vaccine efficacy in young children. Even their latest review bluntly concludes that 'in children under the age of two, the efficacy of inactivated vaccine was similar to placebo'. This conclusion, however, is flawed because many valid studies were not included in the review. For instance, an observational cohort study with virologically confirmed endpoints showed that the flu vaccine was 79% effective for influenza A in children under 2 years of age, with an overall efficacy of 66% against any influenza. So in spite of the Cochrane reviews, we must conclude that there is no particular efficacy issue of flu vaccines in young children."

Importantly, Heikkinen reported that, in Finland, economical studies not only showed that vaccinating children is cost-effective, but even cost-saving for children up to the age of 14 years. "Even if we do not take into account the savings from reduced parental absenteeism from work, Finland could save over €4 million annually if we were to routinely vaccinate all children under the age of 15 against influenza. Our vaccination programme yields health benefits while saving costs at the same time. It is a real win-win situation."

"Current influenza vaccination policies in the EU are often based on severely outdated data."

**LESSONS LEARNED**

1. Each year every sixth of all children in Finland falls ill with influenza.
2. 40% of the under 3 year olds with influenza develop acute otitis media.
3. Children are the main transmitters of influenza to others, especially to the elderly and the vulnerable.
4. The Cochrane review comes to a wrong conclusion about vaccine effectiveness in children, due to the limited number of studies considered.
5. We need to educate health-care professionals and parents about recent advances in the prevention of influenza.

**NEXT STEPS**

"Based on what we now know, every EU country should re-evaluate its influenza vaccine recommendations. Current policies are often based on severely outdated data, so we need to bring the new study results to our decision-makers. Secondly, local cost-effectiveness analyses should be carried out in the different countries, because obviously, the Finnish results do not automatically apply to all systems. And finally, we need to educate health-care professionals and parents about recent advances in the prevention of influenza."

**ROADMAP ACTION #7**

EU pediatricians to re-evaluate the existing cost-effectiveness data in order to reach a balanced view on childhood vaccination and antiviral recommendations as a guideline for all EU countries.

Although conducted in a season with an influenza B mismatch, the study shows an overall vaccine efficacy of 66% in all children as well as in those under 2 years of age.
DO INFLUENZA VACCINES ACTUALLY WORK IN THE ELDERLY?

"It’s a confusing world in terms of the literature," said Jonathan Van-Tam, "when authoritative journals such as Lancet Infectious Diseases publish an article that says 'Influenza vaccines can provide moderate protection against virologically confirmed influenza. Evidence for protection in adults aged 65 years or older is lacking.' Journalists tend to rephrase this type of articles and before you know it the message in the media and the social media is that vaccines are not effective at all in the elderly."

"If the lack of evidence for effectiveness in the elderly is so obvious, why do major independent advisory committees continue to recommend vaccination for the elderly?"

Another review that questioned the benefits of influenza vaccination was published by the Cochrane Collaboration. Van-Tam: "With its review of 75 eligible studies, comprising 100 datasets, 14 different outcomes and 4 sub-groups, Cochrane adopted a highly stratified approach. Some minor errors were made in the assignment of studies to virus circulation or non-circulation periods. The mosaic of results led the authors to believe they were unable to reach clear conclusions about the effects of vaccines in the elderly. But if the lack of evidence for effectiveness in the elderly is so convincing, why do major EU based independent advisory committees (like ACIP, JCVI, STIKO) continue to recommend vaccination for the elderly? An alternative answer was offered by a new collaborative study that we conducted based on exactly the same data used by Cochrane, applying an alternative and simpler framework of analysis."

"The Cochrane statisticians sometimes failed to successfully distinguish between seasons with high, mild or no circulation of an influenza virus. But of course, when virus is not circulating, the vaccine cannot protect against a non-existent entity, and you get a low or even a zero vaccine effectiveness estimate. Also, vaccine effectiveness estimates will vary according to outcome. We now know that if laboratory confirmed influenza infection is the outcome then the answer will be as accurate as it can be; but outcome measures such as influenza-like illness (ILI) do include..."
illnesses due to other non-influenza respiratory virus, when of course influenza vaccine can’t be expected to work. And of course there is the problem that in some seasons we have a vaccine mismatch to a greater or lesser extent. In our study, we took the same 75 eligible studies and first corrected the small number of assignment errors of studies to circulation periods. The outcomes were then re-plotted on the basis of simple, policy-relevant scenarios: laboratory-confirmed influenza, syndromic influenza-like illness (ILI), complications and periods of no virus circulation. With an efficacy against laboratory-confirmed influenza of just under 50%, the revised Cochrane study provided ample evidence of the efficacy of influenza vaccines in the elderly. Our study also revealed vaccine effectiveness against influenza-like-illness without virus confirmation of above 30%; and against influenza-related complications of around 25%. So, if you apply a simpler and more logical analysis framework, you get a different picture from exactly the same data.”

**LESSONS LEARNED**

1. Influenza vaccines are not a perfect tool in the elderly, as they do not achieve the same high effectiveness levels we associate with childhood vaccines
2. Nevertheless, taken year on year, there is strong evidence for the ability of influenza vaccines to reduce the risk of influenza infection, influenza-like illness and influenza-related complications in the elderly
3. Every year flu vaccination yields a meaningful individual patient benefit, unless there is substantial mismatch.
4. There are also meaningful public health benefits when applied at the elderly population level
5. The ‘Cochrane re-arranged study’ provides ample evidence of the ability of influenza vaccines to reduce the risk of influenza infection and death in the elderly

**ROADMAP ACTION #8**

Extend invitation to the Board of the Cochrane Collaboration to meet and to discuss influenza vaccine and antiviral effectiveness

**ROADMAP ACTION #9**

More studies are needed on the effectiveness of flu vaccination in different age groups and the public at large
HOW EFFECTIVE ARE ANTIVIRAL DRUGS AGAINST INFLUENZA?

ANTIVIRALS USED IN INFLUENZA
The most popular class of antivirals, the neuraminidase inhibitors, include oseltamivir and zanamivir. New antivirals, like peramivir and laninamivir, are not licensed for use in Europe. “Other influenza antiviral agents are currently being evaluated, including Favipiravir and Fludase, which are not influenza-specific. Therefore, this talk will only focus on oseltamivir and zanamivir,” said Puja Myles. “And to assess their effectiveness, I have brought together the evidence from three recent studies on the subject.”

ALTHOUGH VACCINES ARE CORNERSTONES OF PUBLIC HEALTH’S ARSENAL FOR THE PREVENTION AND CONTROL OF INFLUENZA, ANTIVIRAL DRUGS PLAY AN ESSENTIAL ROLE IN PREVENTION AND TREATMENT OF THE DISEASE. BUT HOW WELL DO THEY WORK?

Summary of key evidence on antiviral effectiveness

   - This review assessed 20 Roche sponsored randomized placebo controlled trials in previously healthy adults and children.
   - The authors found faster symptom relief by about a day. They also found that if self-reported pneumonia from the participants was considered, influenza-related pneumonia was prevented in one person for every 100 adults treated with oseltamivir.
   - This review, however, had some limitations: it did not take into account the individual level data, and it tried to pool study-level effect estimates from trials that used different data measures.

2. Dobson et al. (2015): Independent re-analysis of Roche trials data
   - This meta-analysis was commissioned by the Multiparty Group for Advice on Science (MUGAS) foundation to address the limitations of the Cochrane review. A total of nine randomised trials comparing the licensed 75mg twice daily dose of oseltamivir to placebo in 4328 adults were included. The data were standardized and pooled at the individual participant level.
   - Analysis of the clinical data clearly showed significant reductions in the duration of influenza virus infection. In patients with proven influenza infection, time to alleviation of all symptoms was shortened by an average of 25.2 hrs and lower respiratory tract complications requiring antibiotics more than 48 hours after study entry were reduced by an estimated 44% compared with placebo. Concomitantly, the timely use of oseltamivir reduced the number of hospital admissions for any cause by an estimated 63% in adults with laboratory confirmed-influenza.

3. Muthuri et al. (2014): Observational data on hospitalised pandemic influenza patients
   - The total sample size in this review was nearly 170,000 patients, including almost 30,000 patients (across all age ranges) admitted to hospital between 2 January 2009 and 14 March 2011. The study findings indicated that patients hospitalised with H1N1 influenza during the 2009-2010 pandemic were 18% less likely to die if they were given neuraminidase inhibitors. The risk of death was halved when treatment was started within 2 days of the onset of the illness, when compared with people who received later antiviral treatment or no antiviral treatment at all. The data also suggest that even when the 48-hour mark following symptom onset has passed, treatment might nonetheless confer mortality benefits to critically ill patients.
WHAT DOES THE COMBINED EVIDENCE TELL US ABOUT ANTIVIRAL EFFECTIVENESS?

"In previously healthy patients with mild or moderate influenza, you could expect to see a reduction in time to symptom alleviation, and fewer influenza-related complications requiring antibiotics and hospital admissions. In more severe influenza cases, we saw a reduction in mortality. Optimal benefit is achieved if treatment is started within two days of illness onset and there are indications that treatment administered even beyond two days onset may be of benefit in critically ill adult patients. Importantly, oseltamivir has a good safety profile."

POLICY IMPLICATIONS: CLINICAL GUIDELINES

"When developing clinical guidelines, a pragmatic approach is called for, not only taking into account the scientific evidence but also resource considerations. As a rule, a previously healthy patient with mild influenza can be treated in primary care without the need for viral diagnostics or antivirals. However, in high-risk patients and those who are markedly unwell or deteriorating, it would be prudent to administer antivirals as soon as possible. It is also advisable to use rapid influenza diagnostic tests (RIDTs) if available and if resources allow it, to support clinical diagnosis."

"In hospitals, where patients admitted with influenza, by definition, have severe infection and may already be several days into the illness, antiviral treatment should be presumptive based on clinical suspicion or diagnostic test results. The emphasis should be on immediate treatment and this might occur alongside antibiotic treatment if a bacterial aetiology cannot be excluded. If adequately taken respiratory specimens later fail to confirm influenza, the antiviral treatment may be stopped. With respect to children, the efficacy debate is still ongoing. Healthcare workers are hence advised to use their clinical judgment until the scientific issue is adequately resolved."

POLICY IMPLICATIONS: ANTIVIRAL STOCKPILES

"Was the previous decision to stockpile the right one," Puja Myles asks the Summit audience. "The Muthuri et al. study clearly endorses the policy decision to stockpile and use antivirals in treating hospitalised patients during the 2009-2010 pandemic, based on the estimated mortality reduction alone. As to whether we should continue stockpiling in the future, we all know that stockpiling decisions are multifaceted and cannot be taken on effectiveness evidence alone. It very much depends on the actual context. And which antivirals should we stockpile? I think it would be sensible to have a mixed stockpile. For future decisions, we need to consider all available treatment options, antimicrobial resistance, ease of administration, safety profile, storage, and economics."

LESSONS LEARNED

1. In a high-risk patient it would be recommendable to administer antivirals as soon as possible.
2. Optimal benefit is achieved if treatment is started within two days of illness onset.
3. The decision to stockpile and use antivirals in treating hospitalised patients during the 2009-2010 pandemic was justified given the empirical evidence.
4. With respect to children, the antiviral efficacy debate is still ongoing.
On average, every person contracts the flu once every 10 years because his immunity to previous brushes with the disease declines over time, allowing the virus to evolve and thus escape the accumulated immunity. Key to this vulnerability is the phenomenon of antigenic “drift” or slight mutations in the composition of a virus’ antigens. The latter are antigens on the surfaces of virus particles which, when recognised as foreign by the host organism, prompt the latter to produce matching antibodies to kill the invader.

Viral antigens constantly evolve, however, and are classified by researchers in clusters according to how closely they resemble one another. The farther an antigen moves away from a given cluster, the more “novel” it becomes and the more easily it can escape the host organism’s inventory of antibodies designed to recognise and kill it.

“This is precisely why the WHO Global Influenza Surveillance and Response System was set up over 50 years ago now,” said Derek Smith, who models the genetic evolution and spread of influenza viruses. “They track the evolution of the virus in three main areas: there is the epidemiological tracking of how much flu there is in different places, and the virological surveillance looking at the virus genetically and antigenically. The key piece of information for vaccine strain selection is the antigenic data, this is the aspect of the phenotype that tells us whether or not the virus has evolved to evade our immunity.”

"Antigenic mapping really exemplifies the synergy between science and public health in the influenza world."

Each of the coloured dots represents a different strain of flu virus and the distance between the dots indicates how similar they are to each other antigenically. This map shows the evolution of the H3N2 flu viruses from their most recent introduction in 1968 to 2002. Each time the virus jumps from one cluster to another, then the world’s influenza vaccines need to be updated.

If someone is vaccinated against antigens based on a previous cluster, they are unlikely to have much protection from the subsequent clusters over time. "The fundamental question when choosing the vaccine strain is hence: what is the virus going to do next,” said Derek Smith. "Antigenic cartography provides a good picture of the virus evolution and enables us to predict the virus’s next step. This is evolution in front of our eyes. It really exemplifies the synergy between science and public health in the influenza world."
The WHO Global Influenza Surveillance and Response System comprises of 130 national influenza centres who collect influenza viruses locally and send them to one of the five WHO collaborating centres where the strains are analysed genetically and antigenically. These data are then processed by Prof. Smith’s laboratory in Cambridge to produce the antigenic maps.

VACCINE MISMATCH
In February each year, the WHO vaccine strain selection committee meets to decide which strains should go into the vaccine in order to provide protection during the next flu season. The strains need to be selected that early in order to allow the production of 350 million doses of vaccine by the start of the next seasonal flu outbreak. Figure 3 shows the strain selection for 2005, in the perfect middle of the cluster. By December 2005, however, the virus had drifted to another cluster (figure 4). Consequently, the 2005 flu vaccine did not offer good protection against the virulent strain. This is a classical example of a mismatch, like it also happened in the 2014/15 winter season.

“What can we do about that,” asks Derek Smith. “In fact, there is experimental data coming up that shows that evolution appears to be much more constrained than we thought. There are also computational techniques to address the question of predicting the evolution. Obviously, being able to predict the evolution of the virus would be a big step forward for future vaccines. We really need to further invest in these experimental modelling techniques, while also investing in new approaches to develop better influenza vaccines.”

LESSONS LEARNED
1. Influenza viruses are constantly changing, including during the time between vaccine virus selection and the influenza season.
2. The WHO Global Influenza Surveillance and Response System is the best surveillance system for any pathogen in the world.
3. Antigenic cartography visualizes virus evolution through maps of clusters that show the antigenic relationships among the viruses.
4. Better techniques to predict the evolution of the virus are on the horizon.
The influenza virus was discovered as a pathogen in 1933. Testing of potential influenza vaccines started soon after that. With live vaccines first, tested on inmates in the US. Soon after that, other vaccine approaches were tested: whole virus inactivated vaccines, split vaccines, subunit vaccines, live attenuated vaccines and the use of adjuvants, i.e. the whole range of vaccine approaches that are still being used today. “Vaccine technology hasn’t changed that much over the last four decades,” said Gerd Sutter. “In Germany today, most vaccines are still egg-based, trivalent, inactivated vaccines that are used without an adjuvant. These vaccines are very safe, but they have some major shortcomings: they are immunogenically weak, they mostly induce antibody responses to surface antigens of the virus and provide only little long lasting immunity. This obviously reduces their efficacy against seasonal drift variants and in immunocompromised patients. And they offer little or no protection against new influenza viruses that enter the human population, like the avian H7N9 virus.”

NEW WAYS TOWARDS BETTER VACCINES
Clearly, there is room for improvement in vaccine development and design. Gerd Sutter explains: “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. To reach that objective, different strategies can be followed. First of all, we can target better and other antigens than the haemagglutinin and neuraminidase surface proteins. Ample possible target candidates exist and an interesting route is to target portions of viral elements that are genetically conserved, thus against virus elements that are common in all influenza viruses. Secondly, new vaccines need to produce a higher antibody count, or more specific antibodies, but also T-cells. Thirdly, vaccine delivery can be optimized to relocalize or modify these antigens for better presentation to the immune system. And, finally, an important tool is the proper triggering of our immune system, based on our advanced knowledge of the danger signals that elicit the immune response to an invading agent. In fact, basically all new approaches in influenza vaccine development are mimicking - at least in part - some of these danger signals. Here, the most powerful vehicles are probably the recombinant viruses, as they have the ability to express proteins from foreign pathogens and induce specific immunological responses against these antigens in vivo.”

MODIFIED VACCINIA VIRUS ANKARA
“In FLUNIVAC, the European Influenza virus universal vaccine development programme, we chose the Modified Vaccinia virus Ankara (MVA) as a vehicle to test various approaches of influenza vaccine development,” Gerd Sutter continued. MVA was developed at Sutter’s institute in Munich during the 60s and is characterised by a replication deficiency in vivo and in vitro. “This means that the virus is not able to form new infectious particles. In 2013, MVA was licensed in Europe and Canada to replace the old smallpox vaccine stocks.”

“Better vaccines are technically feasible already. The question is: “How do we introduce them?”
All of that allowed the development of MVA as a vector system. "The background virus has an excellent safety database," said Sutter. "By now, various candidate vaccines are in clinical trials, and the virus is fit for large-scale production. In fact, in a collaborative effort with the Erasmus MC Rotterdam, we have been investigating recombinant MVA as a candidate vaccine against avian influenza, more specifically against the highly pathogenic avian influenza H5N1. Many animal models, from mice to macaques, have yielded excellent data with regard to protective efficacy and immunogenicity, which allowed us to push for the clinical evaluation of MVA-H5 vaccine."

**MVA-H5 vaccine induces immunity to influenza H5N1**

A double-blinded randomized study involving 80 young, healthy adults demonstrated that the MVA-H5 vaccine elicits rapid protective immunity when using a standard dosage. A booster vaccine given one year after primary vaccination dramatically raised the level of H5 specific antibodies.

**H5N8 AVIAN INFLUENZA**

In 2014, around the time the MVA-H5 vaccine study was completed, a new highly pathogenic avian influenza virus variant emerged in Asia. "This H5N8 avian flu virus quickly spread to Europe and North America, which offered an opportunity to test the level of cross immunity induced by our MVA-H5 vaccines. Tests at the Erasmus MC clearly showed that MVA-H5 had indeed elicited substantial levels of cross reactive antibodies against a virus that was clearly distinct from its ten year older ancestor."

"Looking at the different approaches to design new influenza vaccines," Gerd Sutter concludes, "it is obvious that we are technically ready to develop better vaccines. But clearly, regulatory issues and lack of economical interest are the main hurdles to their actual introduction."

**LESSONS LEARNED**

1. The vast majority of our current influenza vaccines are still egg-based, trivalent, inactivated, unadjuvanted vaccines.
2. We have to address the perception with policy makers and the general public that genetically modified viruses aren't safe.
3. Recombinant viruses are probably the most powerful and promising vehicles for improved vaccine development.
4. Funding is needed to conduct large efficacy studies in humans in order to validate the promising pre-clinical results.
5. Regulatory issues are an important hurdle to the introduction of vaccines that target different antigens.
ROADMAP TO MOVE EUROPE TOWARDS FURTHER ACTION

THE FRUITFUL DEBATES DURING THE SCIENCE POLICY FLU SUMMIT YIELDED A CLEAR PICTURE OF THE MOST URGENT ACTIONS THAT NEED TO BE TAKEN IN ORDER TO REDUCE THE IMPACT OF INFLUENZA IN EUROPE. IN A CONCERTED EFFORT, THE MEMBERS OF THE EUROPEAN INFLUENZA COMMUNITY GATHERED AT THE EVENT, INCLUDING POLICY-MAKERS, ACADEMICS, PUBLIC HEALTH ORGANIZATIONS, PATIENT ORGANIZATIONS AND THE INDUSTRY, DISCUSSED AND APPROVED A HIGHLY NEEDED INFLUENZA ACTION PLAN FOR EUROPE:
**ACTION #1**
Develop strategies to mend the communication gap between national governmental and international public health organizations (joint procurement, pandemic preparedness)

**ACTION #2**
Develop strategies and mechanisms to improve collaboration (on a national and an international level) to stimulate epidemic and pandemic preparedness

**ACTION #3**
Facilitate studies on vaccine acceptance and risk perception, involving social scientists.

**ACTION #4**
Facilitate the generation of more scientific evidence on the role of healthcare workers in nosocomial spread of influenza

**ACTION #5**
Endorse and disseminate European vaccination and treatment guidelines for General Practitioners

**ACTION #6**
Bring financial and health government officials together with health economists to discuss cost-effectiveness data and their significance for the economic and the public health domains

**ACTION #7**
EU pediatricians to re-evaluate the existing cost-effectiveness data in order to reach a balanced view on childhood vaccination and antiviral recommendations as a guideline for all EU countries

**ACTION #8**
Extend invitation to the Board of the Cochrane Collaboration to meet and to discuss influenza vaccine and antiviral effectiveness

**ACTION #9**
More studies are needed on the effectiveness of flu vaccination in different age groups and the public at large

**ACTION #10**
Organization of a vaccines-for-the-future workshop on strain selection and new manufacturing technologies

ESWI is dedicated to take further action, and calls upon all parties involved in influenza monitoring, prevention and treatment to address these influenza needs in Europe. In close collaboration with its partner organizations, ESWI is ready to facilitate the implementation of the action plan and it invites all stakeholders to put themselves forward to initiate or collaborate in the execution of the influenza roadmap. Together, we can get into action and reduce the burden of both epidemic and pandemic influenza in Europe!