Forging an influenza coalition in Europe
# Table of content

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Programme</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Foreword</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>The 2015 Influenza Roadmap now part of ESWI’s 2016/17 action plan</td>
<td>AB OSTERHAUS, ESWI CHAIR</td>
</tr>
<tr>
<td>8</td>
<td>Newly emerging H5-H7-H9 influenza viruses: real threats?</td>
<td>AB OSTERHAUS, ESWI CHAIR</td>
</tr>
<tr>
<td>10</td>
<td>Present and future of influenza antivirals: an overview</td>
<td>ERHARD VAN DER VRIES, RIZ HANNOVER, GERMANY</td>
</tr>
<tr>
<td>12</td>
<td>How to improve influenza vaccine effectiveness?</td>
<td>FLORIAN KRAMMER, MOUNT SINAI SCHOOL OF MEDICINE, US</td>
</tr>
<tr>
<td>14</td>
<td>The changing landscape of childhood influenza vaccination</td>
<td>ADAM FINN, CHAIR EUROPEAN SOCIETY FOR PAEDIATRIC INFECTIOUS DISEASES (ESPID)</td>
</tr>
<tr>
<td>16</td>
<td>Objectives and results of WHO’s annual Flu Awareness Campaign &amp; Targeting pregnant women through the TIP FLU approach</td>
<td>CAROLINE S. BROWN, WHO REGIONAL OFFICE FOR EUROPE</td>
</tr>
<tr>
<td>18</td>
<td>The role of primary care physicians in enhancing epidemic and pandemic preparedness</td>
<td>GEORGE KASSIANOS, IMMUNISATION LEAD FOR THE ROYAL COLLEGE OF GENERAL PRACTITIONERS, UK</td>
</tr>
<tr>
<td>20</td>
<td>Influenza vaccination of travellers: an expert opinion</td>
<td>MARCO GOEIJENBIER, INSTITUTE FOR TROPICAL INFECTIONS, HAVENZIEKENHUIS ROTTERDAM</td>
</tr>
<tr>
<td>22</td>
<td>The burden of flu on asthma patients</td>
<td>TED VAN ESSEN, UNIVERSITY MEDICAL CENTER UTRECHT, THE NETHERLANDS</td>
</tr>
<tr>
<td>24</td>
<td>The benefits of flu vaccination for diabetes patients</td>
<td>MARCO GOEIJENBIER, INSTITUTE FOR TROPICAL INFECTIONS, HAVENZIEKENHUIS ROTTERDAM</td>
</tr>
<tr>
<td>26</td>
<td>The role of respiratory physicians during flu outbreaks</td>
<td>GERNOT ROHDE, ASSOCIATE PROFESSOR OF RESPIRATORY MEDICINE AND ERS MEMBER</td>
</tr>
</tbody>
</table>
09:00-09:15 Coffee / welcome

09:15-09:30 Introducing Influenza: a moving target and a secret killer
AB OSTERHAUS, ESWI CHAIR

09:30-09:45 Newly emerging H5-H7-H9 influenza viruses: potential threats?
AB OSTERHAUS, ESWI CHAIR

09:45-09:55 AUDIENCE DEBATE

09:55-10:10 Present and future of influenza antivirals: an overview
ERHARD VAN DER VRIES, RIZ HANNOVER, GERMANY

10:10-10:20 AUDIENCE DEBATE

10:20-10:35 How to improve influenza vaccine effectiveness?
FLORIAN KRAMMER, MOUNT SINAI SCHOOL OF MEDICINE, US

10:35-10:45 AUDIENCE DEBATE

10:45-11:00 The changing landscape of childhood influenza vaccination
ADAM FINN, CHAIR EUROPEAN SOCIETY FOR PAEDIATRIC INFECTIOUS DISEASES (ESPID)

11:00-11:10 AUDIENCE DEBATE

11:10-11:30 Objectives and results of WHO’s annual Flu Awareness Campaign & Targeting pregnant women through the TIP FLU approach
CAROLINE S. BROWN, WHO REGIONAL OFFICE FOR EUROPE

11:30-12:00 AUDIENCE DEBATE AND SUMMARY OF THE DISCUSSIONS

12:00-13:00 Lunch

13:00-13:15 The role of primary care physicians in enhancing epidemic and pandemic preparedness
GEORGE KASSIANOS, IMMUNISATION LEAD FOR THE ROYAL COLLEGE OF GENERAL PRACTITIONERS, UK

13:15-13:25 AUDIENCE DEBATE

13:25-13:40 Influenza vaccination of travellers: an expert opinion
MARCO GOEIJENBIER, INSTITUTE FOR TROPICAL INFECTIONS, HAVENZIEKENHUIS ROTTERDAM

13:40-13:50 AUDIENCE DEBATE

13:50-14:05 The burden of flu on asthma patients
SUSANNE KRAUSS-ETSCHMANN, CHAIR EXPERIMENTAL ASTHMA RESEARCH AT THE RESEARCH CENTER BORSTEL

14:05-14:15 AUDIENCE DEBATE

14:15-14:30 The benefits of flu vaccination for diabetes patients
MARCO GOEIJENBIER, HAVENZIEKENHUIS ROTTERDAM
AB OSTERHAUS, ESWI CHAIR

14:30-14:40 AUDIENCE DEBATE

14:40-14:55 The role of respiratory physicians during flu outbreaks
GERNOT ROHDE, ASSOCIATE PROFESSOR OF RESPIRATORY MEDICINE AND ERS MEMBER

14:55-15:05 AUDIENCE DEBATE

15:05-15:30 Conclusions of the Summit
AB OSTERHAUS, ESWI CHAIR
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.

European Scientific Working group on Influenza

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.

PARTNER ORGANIZATIONS

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.
Foreword

The European Scientific Working group on Influenza (ESWI) organizes its Science Policy Flu Summits on an annual basis. The main aim of these one-day meetings is to establish an interface between science and policy, to provide public health officials and other influenza stakeholders with a platform to exchange information and ideas, and to keep track of the latest scientific data with respect to influenza. The fifth edition of the Science Policy Flu Summit was held on 28 September 2016 at the International Press Centre in the heart of European Quarter in Brussels. About 100 healthcare workers, policy makers, organizations of at-risk patients and senior citizens, and scientific researchers gathered for a day of tailored lectures, Q&A sessions and networking. Building on its rich history of working with partner organizations, the ESWI Summit showcased successful collaborations in different fields such as travel medicine, the protection of diabetes patients and asthma patients, and the role of healthcare professionals in flu prevention. Different parties approached the influenza issue from their specific perspectives and public health authorities reported on the influenza challenges that lie ahead. At the same time, the Summit provided an excellent opportunity to review the influenza roadmap that had been established at the 2015 edition of the Summit.
The 2015 Influenza Roadmap now part of ESWI’s 2016/17 action plan

**Symposium on new influenza vaccine production technologies**

Classical influenza vaccine production platforms, largely based on the use of embryonated chicken eggs, are slow, and the relatively long production time may cause major problems, especially when new seasonal influenza virus strains and pandemic viruses emerge. The implementation of novel and faster production platforms, based on state of the art technologies is urgently needed. ESWI will therefore organize a scientific symposium during the 6th ESWI Influenza Conference in Riga (September 2017) to provide an overview of state of art influenza vaccine research and identify major research gaps and needs to come to more effective seasonal influenza vaccines.

**Closed ESWI/Cochrane Collaboration meeting**

In light of the urgent need for clear guidance on influenza vaccine and antiviral effectiveness, ESWI contacted the Cochrane Collaboration, as suggested by the 2015 Summit, to meet in order to align our output on this important issue.

**Validate guidelines on influenza vaccination for healthcare workers**

A European expert group, consisting of 21 General Practitioners and immunization specialists, has developed core guidelines for GPs, that can help them prepare and implement their vaccination campaigns. Through its Board Member Ted van Essen, ESWI will work with European bodies to have the guidelines endorsed at a European level. We will also work with national bodies to get their endorsement and have the guidelines translated and adapted to the local circumstances and needs.
Review the scientific evidence underpinning flu vaccination recommendations for priority groups

PEOPLE WITH DIABETES
Many national and international guidelines advise people with diabetes to be annually vaccinated against influenza. But the evidence that underpins these recommendations is fragmented and underexposed. ESWI will therefore review, publish and disseminate the scientific base for recommending routine vaccination of diabetes patients.

TRAVELERS
Seasonal influenza lays a heavy burden on travelers, including those who participate in major sporting events, pilgrimages or music festivals. Yet, recommendations regarding influenza in travel medicine are scarce. It is therefore high time to harmonize international and national travel medicine guidelines for influenza prevention and treatment. To that end, ESWI and ISTM (International Society for Travel Medicine) have joined forces to review existing flu recommendations for travelers. The result of their work is now online: www.ncbi.nlm.nih.gov/pmc/articles/PMC5505480/

THE ELDERLY
Older adults are among the highest risk groups for serious complications of influenza, and are thus included among the high priority groups for annual influenza vaccination in many countries. However, observational studies to estimate influenza vaccine effectiveness have several limitations. The test-negative case-control design has recently emerged as a method to estimate influenza vaccine effectiveness by comparing vaccination rates in those with laboratory-confirmed influenza to those with other acute viral respiratory illnesses. ESWI will prepare and publish a review that provides a perspective on how test-negative case-control study designs and new insights into mechanisms of protection have considerably strengthened influenza vaccination policy decisions for older adults that have historically been undermined by the conclusions of observational studies.

Stimulate collaboration between national and international influenza stakeholders
ESWI intends to expand its Country Influenza Stakeholder Networks (CISN) project to include additional European countries. CISN are national networks of trustful and supporting stakeholders with an interest in reducing the burden of flu. Over the past years, the CISN have proven an effective methodology to tackle influenza nationwide and, ultimately, to enhance public health. The key success factor is surely the collective approach, which incites national stakeholders to cooperate and to take personal initiatives. It is the fit way to draw up action plans that get the entire network’s approval and support. The experience from building networks in different countries, including Turkey, Finland, Sweden and Austria, reveals that every country requires a tailor-made approach.
Newly emerging H5-H7-H9 influenza viruses: real threats?

Some 30 years ago, we thought we had it all under control," said Ab Osterhaus, Research Center for Emerging Infections and Zoonoses, Hannover, and ESWI chair. "The results of what we have achieved through vaccination are remarkable indeed, with the eradication of smallpox and rinderpest. But there is no time for complacency, as is painfully demonstrated by the frequent emergence of new infectious diseases, like Ebola, SARS, MERS CoV, Zika and of course influenza."

"Migratory birds, mainly aquatic birds, are the reservoir of all subtypes of influenza viruses. They spread the virus via their faeces, infecting all sorts of bird and mammal species, including poultry and pigs, but also humans. It has long been thought that human infection with avian influenza viruses had to come from pigs infected by birds, but we now know that humans can become infected from poultry directly. We demonstrated this mechanism in 1997, when we saw the first case of a for poultry highly pathogenic H5N1 (HPAI H5N1) influenza virus infection in a young boy in Hongkong. In a short time, 18 people became infected, six of whom died. Cleaning out live bird markets marked the end of the HPAI H5N1 threat at that time. But HPAI H5N1 remains a major cause for concern. "Between 2003 and 2016, HPAI H5N1 viruses have caused about 900 severe human cases, with a mortality rate of over 50%," said Osterhaus. "HPAI H5N1 virus spread from Southeast Asia to Central Asia, Africa and Europe, with some children even dying from the infection at the doorstep of Europe, in Turkey. Related HPAI H5 viruses also crossed over from the northern part of Eurasia into western north America, from where the virus was spreading eastward. This made it necessary to take draconic measures to control the virus and protect poultry. No human cases were associated with this virus so far."
ONLY A HANDBULK OF MUTATIONS
The fundamental question is what these avian flu viruses need to become transmissible from human to human and thus acquire pandemic potential. “The seasonal H3N2 virus replicates very well in the upper respiratory tract, which makes it easily transmissible because it can spread through a simple sneeze, whereas HPAI H5N1 virus replicates abundantly in the lungs, but not in the upper respiratory tract.” Why hasn’t HPAI H5N1 virus acquired the capacity to efficiently spread from humans to humans yet, although it has been circulating for almost two decades now? “A few years ago, two papers caused major scientific controversy, one was published by Yoshihiro Kawaoka’s group of the University of Tokyo, and the other by Ron Fouchier’s group of Erasmus MC Rotterdam. Their teams had demonstrated that it was possible to make HPAI H5N1 virus transmit efficiently between ferrets via the air. They also found out it only takes a handful of mutations, for this virus to become transmissible between ferrets, and probably between humans. What is quite alarming is that viruses collected from poultry in Southeast Asia have been found to already have some of these mutations and combinations thereof. Today, we suspect that if the HPAI H5N1 virus ever acquires the mutations to transmit efficiently from humans to humans, it will probably happen in immunocompromised patients.”

THE LOOMING H7N9 THREAT
HPAI H5N1 influenza virus perfectly illustrates the difficulties in predicting influenza outbreaks. “Influenza really is a moving target. Whilst we were all expecting an H5N1 pandemic originating from the live bird markets in Asia, we got a pandemic outbreak of H1N1 influenza virus that came from pigs in Mexico. And we should not forget that other influenza viruses with pandemic potential are circulating. The H7N9 bird influenza virus emerged in humans in China early 2013. In the mean time more than 1500 people have become infected, with a case fatality rate of around 40% in hospitalized patients. In contrast to the HPAI H5N1 virus, H7N9 virus is a low pathogenic virus for poultry. The low pathogenic character may sound like good news, but it makes it more difficult to trace the virus and monitor its spread. To date, the virus has not been found outside Chinese borders, with the exception of people who travelled from China, and we don’t know whether it will ever acquire the ability to efficiently spread from human to human. We have seen small clusters of human to human transmission already and experiments in ferret models have indicated that H7N9 virus is capable to naturally transmit, albeit not very efficiently. Whether H7N9 influenza virus will be at the basis of the next pandemic is impossible to say, but, in contrast to H5N1, it does replicate well in the upper respiratory tract of humans.”

H10N7 IN SEALS
In 2014, an outbreak of influenza occurred among harbour seals in Swedish, Danish, German and Dutch waters. In the coastal waters of Schleswig-Holstein in Germany alone, almost 12% of the local seal population had died. “H10N7 influenza virus was isolated from the lungs and throat of animals found dead along the shore. Of course we wondered where the virus came from. Sequence analysis of viral gene segments revealed that the virus came from mallards. This outbreak provided a unique opportunity to study cross-species transmission and to advance our understanding of how avian influenza viruses may adapt to a mammalian host. At the same time, it is a perfect illustration of the threat posed by all avian influenza viruses infecting mammals.”

LE SSONS LEARNED
1. HPAI H5N1 virus needs only a handful of mutations to become easily transmissible from human-to-human.
2. In our globalized world, infectious diseases could spread all over the world in just a few weeks.
3. Severe infection with H7N9 influenza virus may cause a case fatality rate of 40% and the virus probably naturally transmits between humans, albeit limitedly.
4. International collaboration is key to early detect and monitor newly emerging viruses, using the best technologies available.

“There is no time for complacency, as is painfully demonstrated by the frequent emergence of new infectious diseases.”
Present and future of influenza antivirals: an overview

“ANTIVIRALS REALLY STARTED OFF IN 1999, WHEN NEURAMINIDASE INHIBITORS ZANAMIVIR AND OSELTAMIVIR WERE APPROVED FOR THE TREATMENT AND PROPHYLAXIS OF INFLUENZA,” STATED ERHARD VAN DER VRIES OF THE RESEARCH CENTER FOR EMERGING INFECTIONS AND ZOONOSES IN HANNOVER, GERMANY.”

Actually, another class of antiviral drugs against influenza, the M2-channel inhibitors, amantadine and rimantadine, have been around since the 1960s. Since influenza viruses become easily resistant to the drugs, however, they are no longer in use today.

“This means that the neuraminidase inhibitors are the only effective antiviral drugs against influenza currently available. In this context, it is good to note that new Ni have been developed, with peramivir licensed for sale in the US since 2014 and laninamivir currently licensed in Japan.”

However, the ongoing outbreaks of avian influenza in humans highlight the need for highly effective antiviral drugs. “A recent key event in our efforts to develop such drugs was solving the polymerase complex. Because, like for the neuraminidase inhibitors, this will be the beginning of a new era of antiviral development. Indeed, the most promising antivirals intervene during the first stage of infection, when the virus binds to the receptor, or later on during transcription of the virus genomic material.

New classes of antivirals are on the horizon, most notably the polymerase inhibitors and the monoclonal antibodies. Nitazoxanide is a fifth type of inhibitors, currently approved in the US as an antiparasitic drug, which inhibits the maturation of the viral proteins.”
“The worldwide spread of the H5N1 bird flu virus as of 2003 encouraged governments all over the world to stockpile these drugs. Today, brand new antivirals are at the horizon.”

**JNJ-63623872 (VX-787) - Janssen**
- Targets the PB2 subunit of the polymerase complex
- Effective against a broad range of influenza A strains
- Highly effective against H5N1 in a lethal mouse model even when treatment is delayed by 120 hours
- Human challenge study demonstrated significant reduction of viral shedding as compared to placebo. Also demonstrated reduction of clinical symptoms and duration of clinical symptoms
- Phase II studies ongoing

**AL-794 (AL-719) - Alios**
- First polymerase acidic protein (PA) inhibitor
- Human challenge study (n=60) with A/H3N2 virus (A/Perth/16/2009)
- was generally safe and well tolerated
- The 150mg treated group showed a significant reduction of viral load, time for the virus to become undetectable and time to resolution of symptoms.

**RG6152 (Roche)**
- PA inhibitor
- Broad and potent antiviral activity against influenza A and B viruses
- Phase II trial showed significant reduction of viral load and time to alleviation of seven flu symptoms.

**VIS410**
- inhibits hemagglutinin (HA) mediated membrane fusion
- effective in mice
- challenge study in healthy volunteers demonstrated reduction of viral load by up to 76% and a reduction of resolution of upper-respiratory symptoms at day 2.

**RG7745**
- Human challenge study demonstrated a decrease of influenza viral load of up to 98% compared with placebo
- Phase II studies are currently ongoing as a monotherapy for acute uncomplicated seasonal influenza A in otherwise healthy adults, and in combination with oseltamivir versus oseltamivir in patients with severe influenza A infection

**MEDI-8852**
- Binds to HA stem region (as opposed to binding to the receptor binding site) which is more conserved among different influenza A subtypes
- Currently a phase Ila/IIb is ongoing
- Highly effective in mice
- Considerable clinical response in ferrets
INFLUENZA VACCINES ARE SAFE AND EFFECTIVE. BUT THERE IS STILL AMPLE ROOM FOR IMPROVEMENT. “WE REALLY NEED INFLUENZA VIRUS VACCINES THAT OFFER BROADER, BETTER AND LONGER LASTING PROTECTION,” STATED FLORIAN KRAMMER. “RESEARCHERS ARE EXPLORING DIFFERENT PATHWAYS TO REACH THIS OBJECTIVE AND SOME PROMISING NEW VACCINE CANDIDATES ARE ON THE HORIZON.”

“Changing colours illustrate antigenic drift of influenza viruses.”

The influenza virus RNA genome has eight segments, and the nature of an RNA genome is that it mutates constantly, possibly leading to reassortments,” said Florian Krammer. “If we take a closer look at the dynamics of influenza virus in humans, we see that the H1N1 virus jumped into the human population in 1918, causing a huge pandemic. Humans then developed herd immunity (community protection) and the virus had to change its antigens in order to escape our antibody response. This process is called the antigenic drift and it is one of the reasons why it is very hard to make effective vaccines. In 1957, the H1N1 virus was replaced by an H2N2 influenza virus, a completely different subtype. The same happened in 1968, when the H3N2 virus emerged and the H2N2 virus died out. This kind of change is called an antigenic shift and marks the start of an influenza pandemic.” Today, three types of influenza are circulating: H1N1, which goes back to the 2009 pandemic, H3N2 and influenza B. “In fact, there are two separate lineages of influenza B. This is yet another challenge for vaccine development.”

**A brief introduction to influenza viruses**

There are four flavours of influenza viruses: A, B, C and D. The A and B viruses are responsible for the annual seasonal influenza epidemics. Influenza type C infections cause a mild respiratory illness and are not thought to cause epidemics, whereas influenza D viruses primarily affect cattle and are not known to infect or cause illness in people.

Influenza A viruses are divided into subtypes depending on the genes that make up the surface proteins: the haemagglutinin (HA) and the neuraminidase (NA). There are eighteen different haemagglutinin subtypes and nine to eleven different neuraminidase subtypes. HA and NA are the targets to which antibodies are induced by the currently available vaccines.

Influenza A viruses can be subdivided into different strains. Current subtypes of influenza A viruses found in humans are influenza A (H1N1) and influenza A (H3N2).
SURVEILLANCE AND STRAIN SELECTION
To keep up with the ever-changing viruses, the World Health Organization performs worldwide surveillance. “Based on this surveillance, WHO makes predictions as to which viruses will be circulating the next year so that vaccine manufacturers can update their vaccines to match the circulating strains. Vaccine production for the Northern hemisphere usually starts in February and vaccines are delivered by October/November. This means that there is no way back in case of a mismatch. In fact, if we take all these hurdles into account, we should conclude that influenza vaccines work pretty well.”

TOWARDS BETTER INFLUENZA VACCINES
To increase their levels of protection, influenza virus vaccines should induce stronger and broader immune responses. “Some parts of the virus change very little. If a vaccine were to entice immune responses targeting those conserved regions, it should automatically become more universal. Major efforts are ongoing to develop such broadly protective influenza virus vaccines and the first option is to target internal proteins with T-cell based vaccines. The second option is to induce antibodies against the extracellular domain of M2 protein (M2e), a proton-selective ion channel protein integral in the viral envelope of the influenza virus. There is also growing interest in the neuraminidase as it appears to shift less than the haemagglutinin. And the haemagglutinin itself has a part, the stalk, which is relatively conserved. In fact, the membrane distal head of HA is extremely variable, but the stalk closest to the membrane is conserved in all influenza viruses making it a very good target for universal influenza virus vaccines. Currently, a considerable number of vaccine candidates are in the early clinical or pre-clinical stages. But it will take at least another 15 years for them to appear on the market. In the meantime, my advice is to get your ‘flu shot’ every year.”
The changing landscape of childhood influenza vaccination

“VACCINES ARE TRADITIONALLY USED TO PROTECT THE RECEIVER OF THE VACCINE AGAINST ILLNESS. TO ASSESS A VACCINE’S EFFICACY, WE LOOK AT THE DIRECT PROTECTION IT OFFERS, MUCH LIKE EDWARD JENNER DID MORE THAN 200 YEARS AGO. OF COURSE, HE HAD NO CONCEPT OF INDIRECT PROTECTION,” SAID ADAM FINN, PROFESSOR OF PAEDIATRICS AT THE UNIVERSITY OF BRISTOL AND PRESIDENT OF ESPID. “AND INDIRECT PROTECTION IS CERTAINLY AN IMPORTANT ASPECT OF FLU PREVENTION.”

Universal flu vaccination of children is recommended in only 8 European countries, and of those only 4 countries actually fund their programmes to vaccinate children. “The UK decided to roll out an influenza vaccination paediatric programme as of September 2013. And I am going to demonstrate how this has been a success, notwithstanding some of the concerns around the live attenuated intranasal vaccine (LAIV) which we are now using in the UK. The idea is to immunize all children, not only to stop them from getting the flu, but also to prevent them from transmitting flu to the children around them and to their parents and grandparents.”

Concept slide: children excrete virus much longer and in much higher quantities than adults do.
“It is not unreasonable to characterize seasonal influenza for young children as a pandemic outbreak every year. Many of these individuals have never had flu before and have no previous immunity. That is why young children with influenza come into hospital and go to GP surgeries in high numbers during the season.”

“Japan was immunizing its school children against influenza until the 1980s, when the programme was discontinued. We can see how excess mortality, mainly older people dying from flu, went down while school children were being vaccinated and there is clear evidence of the mortality going back up after the programme was abandoned. In the US, increasing vaccine uptake rates are not associated with lower excess mortality rates and that may be explained by the fact that, historically, influenza vaccines in the US mainly went to the elderly and other risk groups, not so much to children.” A 2010 cluster randomized study in isolated communities in Canada revealed that 3.1% of immunized adults in communities in which children were immunized got influenza vs 7.6% in unimmunized communities, pointing at a 61% effectiveness rate against flu in adults by immunizing children. “This is very good evidence of indirect protection using inactivated flu vaccine.”

The UK uses the live attenuated intranasal vaccine to immunize 2 to 7 (now 9) year old children with a single dose. “The LAIV has been licensed in Europe for several years from the age of 2. There are some theoretical concerns about its safety under that age, although we know there is also efficacy in the under two years old. Since the introduction of the universal vaccination programme, we also started vaccinating primary and secondary school children in pilot programmes in different parts of the country and then more generally. We achieved fairly high coverage of around 60% in these pilot school-based projects, which actually is much higher than in areas where they attempted to administer the vaccine through pharmacies or primary care. Hence my clear message: if you want to give school aged children a vaccine, go and give it in the school.”

“We vaccinate children against influenza, not only to protect these children against influenza, but to protect everybody else as well.”
Objectives and results of WHO’s annual Flu Awareness Campaign & Targeting pregnant women through the TIP FLU approach

A YEARLY SEASONAL FLU VACCINE IS THE BEST AVAILABLE PREVENTION AGAINST INFLUENZA. WHO THEREFORE PROVIDES RECOMMENDATIONS REGARDING PRIORITY GROUPS FOR INFLUENZA VACCINATION AND WHO’S EUROPEAN OFFICE ACTIVELY ENCOURAGES ITS 53 MEMBER STATES TO INCREASE UPTAKE OF SEASONAL INFLUENZA VACCINES.

“Before developing interventions, you need to know what the issues are”, said Caroline Brown, head of the Influenza and Other Respiratory Pathogens Programme of the WHO Regional Office for Europe. “That’s why in 2011 we started collecting data on influenza vaccination programmes in the region. The objectives were to describe seasonal national influenza immunization policies, assess vaccination coverage, and identify gaps in provision. And secondly, to identify progress toward the 2010 WHO goal to attain 75% coverage in elderly.”

“A major outcome of the survey was that few countries have systems to monitor the uptake of flu vaccines in the different at-risk groups. Most countries monitor uptake in the elderly and in children, but not in other risk groups and very few monitor uptake in pregnant women. So you could say we are working blindfolded. That is why we issued a manual on influenza vaccination coverage methods, basically to help countries develop monitoring systems.”

WHO/EUROPE FLU AWARENESS CAMPAIGN
WHO/Europe launched the Flu Awareness Campaign initiative in 2013 with the aim to increase uptake of seasonal influenza vaccination in risk groups. The 2013/14 campaign was targeted at healthcare workers and was a regionwide campaign. As of the next season, however,
Influenza vaccine uptake in pregnant women rose from less than 1% to almost 15% in the first season of TIP FLU’s pilot implementation in Lithuania.

Summary of general challenges in influenza vaccination

- There is a low perceived demand in most risk groups (except in a few countries)
- Lack of monitoring of vaccination uptake
- Limited or no access to vaccine in low resource countries
- Lack of data on clinical and economic burden of disease
- Moderate vaccine effectiveness – difficult to communicate. Limited evidence to support the hypothesis that vaccination mitigates influenza illness severity
The role of primary care physicians in enhancing epidemic and pandemic preparedness

"GENERAL PRACTITIONERS PLAY A CRUCIAL ROLE IN INFLUENZA VACCINATION PROGRAMMES. PROVIDING THEM WITH CLEAR GUIDELINES WILL HELP RAISING FLU VACCINATION COVERAGE RATES IN EUROPE," SAID GEORGE KASSIANOS, IMMUNISATION LEAD OF THE ROYAL COLLEGE OF GENERAL PRACTITIONERS.

In December 2009, the Council of the European Union adopted a recommendation encouraging member states to improve seasonal influenza vaccination coverage. The main objective was to reach the WHO target of 75% vaccination coverage of the elderly (>65y) and all other risk groups. "There are, however, huge discrepancies in seasonal influenza vaccine uptake throughout Europe, with only some parts of the UK achieving the European Council Recommendation. In contrast, countries like Romania, Estonia and Latvia achieve very low immunization rates of close to 10% or less. I believe that one of the reasons for this underachievement is the absence of information for general practitioners that engages and empowers them to vaccinate."

THE EXAMPLE FROM THE NETHERLANDS AND THE UK
The Netherlands and the UK both have well-developed influenza vaccination guidelines for General Practitioners. In addition, both countries have well-established primary care systems. "In the UK, for instance, over 90% of patient care is delivered by primary care. NHS constantly updates its Green Book and every winter it issues a flu plan, while all GPs also receive an explanatory letter from our Chief Medical Offer. In the Netherlands, the Dutch College of General Practitioners issues excellent guidelines for GPs as well, while in many other European countries guidelines either do not exist or are less clear or less official. So we really needed to create a common ground, a common approach for the implementation of routine seasonal influenza vaccination in Europe."

"If we, the GPs, do not recommend it, many of our patients will not get the influenza vaccine."
Seasonal influenza vaccine uptake rates vary greatly across Europe.

“In many EU countries, influenza guidelines for GPs either do not exist or are unclear.”

HARMONIZING THE DIAGNOSIS AND MANAGEMENT OF INFLUENZA BY GPS

A European expert group, consisting of 21 General Practitioners and immunization specialists, has therefore developed core guidelines for GPs, that can help them prepare and implement their vaccination campaigns. “Our paper actually includes a synthesis of the national guidelines and best practices of the UK and the Netherlands. The aim of our work was to harmonize the diagnosis and management of influenza by GPs and thus to move towards reaching the 75% target throughout Europe. To that end, we have published the guidelines, a Flu Plan for Primary Care, in Drugs in Context under a Creative Commons license that allows the readers to download the document as a Word file and to modify it according to their local situation.”

“In our work, we address different topics such as the epidemiology and burden of disease, diagnosis, vaccination recommendations, types of influenza vaccines, special target groups for vaccination and vaccine effectiveness and safety. And of course, we pay specific attention to the role of GPs in influenza vaccination: the importance of GP endorsement, selecting and notifying individuals eligible for influenza vaccination, organisation of vaccination, patient records, storage of influenza vaccines and communication with patients. The last paragraphs are about misconceptions and FAQ, so as to arm the GPs with answers to possible questions.”

NEXT STEPS

“We will 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 of course, we will also engage with national bodies to get their input and support for dissemination.”
Influenza vaccination of travellers: an expert opinion

SEASONAL INFLUENZA IS THE MOST FREQUENT VACCINE-PREVENTABLE INFECTIOUS DISEASE IN TRAVELLERS. YET, SURPRISINGLY, RECOMMENDATIONS REGARDING INFLUENZA IN TRAVEL MEDICINE ARE SCARCE. IT IS THEREFORE HIGH TIME TO HARMONIZE INTERNATIONAL AND NATIONAL TRAVEL MEDICINE GUIDELINES FOR INFLUENZA PREVENTION AND TREATMENT. TO THAT END, ESWI AND ISTM (INTERNATIONAL SOCIETY FOR TRAVEL MEDICINE) HAVE JOINED FORCES TO REVIEW EXISTING FLU RECOMMENDATIONS FOR TRAVELERS. EXPERTS FROM BOTH ORGANIZATIONS HAVE ALSO LISTED SOME INTERESTING SUGGESTIONS FOR IMPROVEMENT. THEIR FINDINGS HAVE BEEN PUBLISHED IN THE JOURNAL FOR TRAVEL MEDICINE.¹

“In our globalizing world, air travel becomes more important almost every day, with an estimated number of passengers of 6.4 billion by 2030“, said Marco Goeijenbier, member of the ESWI/ISTM expert group. “We see an increase in travel to exotic destinations and mass gatherings, also by older travellers and people with co-morbidities, for instance persons with severe disease for which we now have very efficient immunosuppressant drugs. These are all important evolutions with respect to acquiring and spreading infectious diseases like influenza.”

Travellers routinely check whether they have been fully vaccinated against measles, rubella, mumps, diphtheria, tetanus and pertussis before starting their travel. And obviously, other vaccines (like the rabies or yellow fever vaccine) are highly recommended for those who travel to areas where disease is endemic. Yet, the flu shot rarely appears on the list of recommended vaccinations for travellers. “This is nicely shown in a recent paper by ISTM member Robert Steffen, who listed the most common traveller’s diseases in order of prevalence. Traveller’s diarrhoea is at number one, but the first vaccine-preventable disease on the list is influenza. However, according to the medical guidelines for travellers, a young healthy man travelling to Indonesia for three weeks should be recommended vaccinations against typhoid, hepatitis A and poliomyelitis. Not against influenza.

And yet, the incidence of influenza in travellers is fairly high. Mutsch et al. report a seroconversion of more than 1% of which a highly significant number of travellers had sought medical attention. Another study showed that persons who travel to East and Southeast Asia have a sevenfold higher risk of acquiring influenza compared to those who stay at home.”

WHY WOULD YOU CONSIDER VACCINATING YOUNG, HEALTHY TRAVELLERS AGAINST INFLUENZA?

- To avoid local doctor’s visits. Such visits enhance the risk of infection with multiresistant microorganisms.

CROSSING THE HEMISPHERES

“Although travellers going to the opposite hemisphere are advised to be vaccinated with a vaccine containing strains circulating at their destination, this advice is difficult to implement,” Marco Goeijenbier explained. “Even in years when the northern and southern hemisphere vaccines contain identical strains, the shelf life of the local winter influenza vaccine has typically expired when travel is considered and neither the following winter season vaccine nor the opposite hemisphere vaccine are available.”
BEYOND VACCINATION
“Travellers seeking pre-travel advice should be recommended to get an influenza vaccination. But some non-pharmaceutical measures should be taken into account as well, such as the use of face-masks, regular hand washing and avoidance of places with questionable sanitation. And finally, antiviral drugs against influenza should be part of our pre-travel advice too, as they can be used for pre- and post-exposure prophylaxis, especially when no vaccine is available. They can also offer an extra treatment option in specific situations like cruise ship travel or mass gatherings.”

MASS GATHERINGS AND CRUISE SHIPS
It is easy to imagine how large gatherings like the Hajj and Umrah, or international sporting events and festivals could play a role in the global spread of influenza. “Saudi Arabia has imposed mandatory influenza vaccination for Hajj pilgrims, and coverage rates are therefore very high. Other mass gatherings, like the Olympics or music festivals are not in the guidelines.”

Popular means of mass travel, like cruise ships, require special attention from a public health perspective. “Modern cruise ships carry over 5,000 passengers served by more than 2,000 crew members, who can function as reservoirs for influenza viruses between trips. Routine vaccination of crew members against the flu would hence be a logical thing to do. In this context, it is good to note that larger cruise companies have guidelines for crew members about isolation of passengers with a possible flu infection and the use of antivirals.”

AVIAN INFLUENZA
Avian influenza (or the bird flu) poses another threat to travellers, especially those travelling to South-East Asia where bird flu viruses like H5N1 and H7N9 continue to circulate. Although bird flu only sporadically occurs in humans, preventive measures do play a role in dealing with traveller’s risk. After all, there are no bird flu vaccines available, so guidelines should concentrate on raising awareness of travel medicine professionals and adjusting traveller’s behaviour through pre-travel advice.

CONCLUSIONS
- There is high incidence of flu in travellers
- Vaccine coverage among travellers can be greatly improved
- There are no universal guidelines
- Vaccines need to be improved, mainly in terms of efficacy, shelf life and availability
- Specific antivirals for the early treatment or prevention of seasonal and avian influenza in travellers deserve more attention

1 “Travellers and influenza: risks and prevention” by M. Goesenbier et al. is available in open access via this link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5505480/
The burden of flu on asthma patients

SINCE THE LATE 50’S OF THE LAST CENTURY, DOCTORS HAVE BEEN ADVISED TO VACCINATE ASTHMA PATIENTS AGAINST INFLUENZA. THE MAIN OBJECTIVE OF ROUTINE VACCINATION WAS TO PREVENT COMPLICATIONS FROM INFLUENZA INFECTION LIKE SEVERE ASTHMA ATTACKS AND PNEUMONIA. “EVIDENCE TO UNDERPIN THIS RECOMMENDATION, HOWEVER, IS FRAGMENTED AND DESERVES OUR FULL ATTENTION,” STATED DR. TED VAN ESSEN.

Enhancing awareness of the scientific base for influenza vaccination may help revert a devastating trend. Ted van Essen: “The current vaccination rate in The Netherlands for all risk groups (including asthma patients) is now back at the same level where it was 20 years ago: 50%. We had seen a remarkable increase in uptake rates as of 1997 until 2009, the year of the H1N1 pandemic influenza outbreak. When we single out the under 65 years of age with a medical condition, we see that the influenza vaccine uptake rate has even dropped to a dramatic 27% in the 2014/15 season.”

Children are particularly at risk when infected with an influenza virus. Van Essen: “Up to 40% of the under 3 years old develop acute otitis media after an influenza infection and 3-4% get ill with pneumonia.” But what about the impact of influenza on asthma patients? Van Essen: “We now know that asthma exacerbations are

“Asthmatic children under 3 years old have a six times higher chance of hospitalization with an influenza infection than non-asthmatic children.”
triggered by dust mites, pollen and respiratory infections. Indeed, infection with a virus or bacteria can lead to a transient wheeze, but could also trigger a persistent wheeze leading to an asthma attack. Interestingly, when we examine the most common infections in hospitalized asthma patients, we see that more than half of all infections is caused by an influenza A virus. This evidence shows that exacerbations are often caused by influenza and hence provides a very good reason to routinely vaccinate asthma patients against the flu. More compelling evidence comes from comparing the average influenza-attributable hospitalization rates of asthmatic children and healthy children. We then see that asthmatic children under 3 years old have a six times higher chance of hospitalization with an influenza infection than non-asthmatic children.”

The ultimate epidemiological evidence to support flu vaccination of people with asthma can only come from a robust randomized controlled trial. “Such trial, however, has never and will never be conducted. It would indeed be highly unethical to give asthma patients placebo instead of a flu vaccine. This leads to the paradoxical situation where an apparent lack of convincing evidence leaves room to all kinds of anti-vaccination activists to promote vaccine resistance. Scientific consensus over the benefits of influenza vaccination of asthma patients is hence dearly needed and the available evidence must be used to inform and convince both healthcare workers and patients.”

More than half of all infections in hospitalized asthma patients is caused by influenza A virus.
The benefits of flu vaccination for diabetes patients

Many national and international guidelines advise diabetes patients to be annually vaccinated against influenza. But the evidence that underpins these recommendations has long been fragmented and underexposed. ESWI has reviewed the scientific base for recommending routine vaccination of diabetes patients and conclude that with the data available vaccination should be encouraged.

Diabetes facts

- Type 1 diabetes is caused by the body’s immune system attacking the insulin producing cells in the pancreas. The body no longer produces insulin and glucose levels rise. Treatment with insulin injections is always required for survival.
- In Type 2 diabetes, the pancreas still often produces some insulin but either not enough or it is not used properly by the various organs in the body.
- Diabetes patients are a particularly heterogeneous patient group.
- Diabetes is influenced by genetic, epigenetic, behavioral and environmental factors.
- The same long-term complications can arise in both types of diabetes. The complications affect the eyes, the heart and vascular system, the kidneys and the nerves.
- Worldwide, about 387 million individuals suffer from diabetes, with type 2 diabetes accounting for up to 95% of all cases.
- 46.3% of people with diabetes are undiagnosed.
- New predictions anticipate that the number of patients with diabetes will reach almost 600 million by 2035.
- 11% of total healthcare expenditure in the world is attributed to diabetes-related costs.

“Since conventional vaccination programs appear to be inadequate to reach diabetes patients, other strategies should be considered.”
**DIABETES AND INFLUENZA**

Every diabetes patient is advised to get the annual influenza vaccine. “But we see that influenza vaccination uptake rates in at-risk groups like diabetes patients are decreasing. In fact, estimations from recent years indicate vaccination rates of only 10% in diabetes patients in Poland, 40% in Germany and 70% in the Netherlands in 2004-2006,” explained Marco Goeijenbier of the Rotterdam Harbour Hospital.

“Generally speaking, people with diabetes (especially those with severe diabetes) are more susceptible to infection than healthy people and have greater chance of developing pneumonia when infected with influenza. Another interesting example comes from the tuberculosis field. Tuberculosis tends to be more severe in patients with diabetes, and especially in patients with poorly controlled diabetes. It is hence even feared that diabetes will threaten the control of tuberculosis globally.

And even more compelling evidence comes from Canada, where surveillance data showed that diabetes triples the risk of hospitalization and quadruples the risk of intensive care unit admission once hospitalized for H1N1 influenza. A potential explanation could be that diabetes reduces the overall immune responsiveness.”

Evidence suggests that influenza vaccination among adult and elderly diabetes patients is efficacious and safe, and that is why WHO recommends the influenza vaccine for all patients with all types of diabetes. And yet, flu vaccine uptake rates are decreasing. A worldwide survey among diabetes patients revealed that fear of adverse reaction to the vaccine or not believing to belong to a risk group are amongst the main reasons for refusal of vaccination.

“Diabetes patients do benefit from their yearly influenza vaccination and therefore efforts should be made to increase vaccination coverage. Conventional vaccination programs appear to be inadequate to reach this risk group and hence other strategies should be considered.”

“Persons with diabetes tend to have a higher chance of a complicated influenza infection, for instance by developing a (severe) pneumonia.”
GERNOT ROHDE, ASSOCIATE PROFESSOR OF RESPIRATORY MEDICINE AND ERS MEMBER

The role of respiratory physicians during flu outbreaks

THE EUROPEAN RESPIRATORY SOCIETY (ERS) AND ESWI HAVE BEEN WORKING TOGETHER FOR SEVERAL YEARS NOW TO PUT INFLUENZA ON THE AGENDA OF PULMONOLOGISTS. “THIS COOPERATION IS BEARING FRUIT NOW,” SAID GERNOT ROHDE, ERS EDUCATION COUNCIL CHAIR. “THE JOINT ERS/ESWI SYMPOSIUM ON INFLUENZA, HELD AT THE RECENT ANNUAL ERS CONGRESS IN LONDON, IS AN EXCELLENT EXAMPLE OF THIS FRUITFUL COLLABORATION.”

ERS and ESWI have jointly organized the “Influenza and Respiratory Physicians” symposium at the annual ERS Congress in London on 5 September 2016. This initiative stemmed from the need to provide respiratory physicians with the latest scientific advances in the influenza field. In four lectures, the symposium faculty addressed the disease in many different aspects, including the epidemiology of flu, management of patients with severe influenza and strategies to identify high-risk patients.

“One of the major issues that came out of the discussions during the symposium is to not forget to include pulmonologists in the efforts to enhance influenza vaccination coverage rates in the at-risk groups,” explained Gernot Rohde. “We also touched upon the role of pulmonologists during pandemics, and in this context, one very important fact often remains underexposed in the discussions about pandemic preparedness: during the 2009 H1N1 pandemic, many European countries were close to 100% occupation of their hospital capacities.”

“During the 2009 H1N1 pandemic, many European countries were close to 100% occupation of their hospital capacities.”

The five most common comorbidities associated with H1N1/09 influenza hospitalized patients in the UK.
“Another important topic on the symposium agenda was an overview of the mechanisms for transmission and spread of influenza. Pulmonologists need to be aware of these mechanisms and ERS is actively educating its members on this issue. After all, we are involved in the educational work package of the PREPARE FP7 project, a project dedicated to enhancing preparedness for pandemic outbreaks. The main eye opener for me, however, was the fact that only a very small percentage of patients in the emergency rooms during the pandemic received antivirals in a timely fashion, while many patients received an antibiotic treatment instead. So there is a lot to improve when it comes to the management of the severely ill.”

About the European Respiratory Society

The European Respiratory Society is a worldwide organization, covering 159 countries and more than 36,000 members. It has three main pillars:

- ERS focuses on science through its European Respiratory Journal, its annual congresses (attracting up to 23,000 participants), clinical research collaborations (the impact of influenza on asthma patients may well be an interesting research topic) and the ERS Research Agency, which helps groups to obtain research funding in a collaborative approach.

- Education is ERS’s second pillar. In the past years, ERS has developed the HERMES curriculum on respiratory infections, in the aim to provide a comprehensive track on this type of infections in order to raise the knowledge base of pulmonologists on this matter. ERS also organizes high level (online) courses and skill based trainings.

- ERS’s Advocacy Council is based in Brussels. The Council mainly links ERS with other organizations to promote awareness for respiratory disorders at national, EU and global level. One of the main organizations it works with is the European Lung Foundation, a patient organization directly associated with ERS.

Take home messages for pulmonologists:

1. Seasonal influenza is a vaccine preventable disease but vaccine uptake is insufficient
2. Influenza pandemics have demonstrated the vulnerability of health-care systems
3. Knowledge about reservoirs, intermediate hosts and spread is mandatory in order to identify patients at risk
4. Early treatment with anti-influenza drugs saves lives
5. Respiratory diseases are important co-comorbidities and risk factors in influenza

“There is a lot to improve when it comes to the management of severely ill influenza patients.”

ERS educational activities