REPORT

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INFLUENZA PREVENTING POLICIES FOR CHILDREN

This report is based on lectures and discussions of the Scientific Symposium ‘Influenza Preventing Policies for Children’, held on 14 June 2017 at the Faculty Club of the University of Leuven, Belgium.

Participants from over 25 countries across the world, including scientists, virologists, paediatricians, family doctors, public health officials and policy makers and the private sector, came together to share the latest scientific findings on child vaccination and vaccine efficacy in children and discuss approaches and best practices.

The aim of this report is to provide stakeholders with relevant information to make more informed and homogenous decisions. Many stakeholders are involved. The key question is: should we vaccinate children and with what vaccines? ESWI’s goal is to create a common view on how to approach the issue.

This report is being disseminated within the scientific community and amongst European policy makers and ESWI partner organizations.

THE DIVERSITY
Raising the topic of influenza vaccination of children is like opening the door to a highly sensitive area. And the reasons for this are quite simple. Not only is the vaccination debate an ongoing process in itself, regularly fuelled by new research, findings and statements, but it is also hard to imagine a more sensitive topic overall than children’s health.

In the US, the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP) recommend a seasonal flu vaccine for every child aged 6 months and older. In Canada, the Canadian Paediatric Society encourages an annual influenza vaccination for all children over 6 months.

But in Europe the situation is quite different, with different policies in different countries. Firstly, on a trans-European scale, vaccine
recommendations in children take many different forms, from being all-encompassing to being virtually- or non-existent. Secondly, when in place, they differ both in terms of priority groups and of vaccine types. And thirdly, European countries show a wide diversity in vaccination uptake. When asked, paediatricians in different European countries will also respond differently to the question of whether children should be vaccinated.

Good prevention policies are served by clear communication and international coherence. Maintaining different guidelines across borders does just the opposite and adds to information disorder and confusion in the public domain.

**THE BURDEN**

The diversity in policies stands in contrast with the overall uniform burden from influenza in children. All children are vulnerable to influenza and its complications. An estimated 20 to 30% of children get influenza every year. And many of them end up in the doctor’s surgery or the hospital.

Firstly, the younger the child, the more severe the clinical presentations and the higher the possible risk of hospitalization. In children aged six months to four years, influenza hospitalisations are comparable to those for the groups for whom vaccination is recommended in Europe, like elderly people or adults with underlying conditions. Half of the children hospitalized have no known underlying health condition.

Secondly, we must learn to approach the flu burden in children as a whole. Influenza in children also causes substantial side effects. Children play a significant role in transmitting influenza, from outpatient children and caregivers, to parents and families and thus the community at large. Children also shed the virus earlier and for a longer time. A more universal immunization of children therefore also has large beneficial effects on the population at large, by dampening the overall transmission of influenza.

Thirdly, there is an important synergy at play that also aggravates the overall burden. And this synergy is underestimated, both in numbers and in severity. Viral infections increase the risk of developing overwhelming secondary bacterial disease. This viral-bacterial synergy is an important mortality factor. We also know that flu-related secondary bacterial infections and severe complications in children occur without any known underlying risk factors.

The arguments at play are both emotional and rational/economic. By preventing flu in all children, we can reduce the number of health visits and influenza-related hospitalizations and deaths, not only in children but also in the community at large.

**WHERE DO WE GO?**

The main objectives of this symposium were to pave the way towards well-balanced influenza preventing policies for children in Europe and to create awareness and attention for childhood flu vaccination as a priority topic on the public health policy agenda. Creating a common approach takes time and the symposium should hence be seen as the starting point of a trajectory that will continue to fuel the scientific/policy debate. In the next months, this trajectory will lead to Riga, where the symposium outcome will feed into the programme of the Sixth ESWI Influenza Conference, and to Malmö, where ESPID and ESWI will hold a joint symposium on flu vaccination of children at the 36th annual ESPID Congress.
Influenza Vaccination Recommendations and Coverage Rates in Europe

THE AGE FACTOR
Jolita Mereckiene presented an overview of seasonal vaccination recommendations and coverage rates in the European zone, based on ECDC’s VENICE Study data. The European recommendation map on influenza vaccination for children proves to be highly fragmented and variable.

In 2012, WHO updated its vaccination recommendations, including pregnant women and children younger than 5 years. But based on data for the 2014-2015 flu season, “only 9 out of 30 countries involved in the VENICE study have put recommendations for healthy children in place”, Jolita Mereckiene said.

“The majority of the countries did not have a recommendation for children in the season 2014-2015. Since then, we have had two more influenza seasons, and some countries might have introduced recommendations, however, I have not seen any confirming information,” Jolita Mereckiene said.

The recommendations already in place are also very different. In the UK, for example, seasonal influenza vaccination is recommended for various age groups between 2 and 11 years. In Latvia and Slovenia vaccination is recommended for children between 6 months and 2 years of age. Finland goes up to the age of 3 years, Malta to children less than 5 years old, Slovakia to 12 years, while Estonia, Poland and Austria recommend vaccination for children and teenagers up to 18 years old.

THE UNDERLYING HEALTH FACTOR
Children and adolescents aged ≥6 months and older are included in a vaccination program, however, not because of their age, but because of an underlying health condition (in 2009 the EU Council recommended achieving a 75% vaccination coverage rate by 2014-2015 in older age groups and those with chronic medical conditions). According to the latest data, all (or almost all) countries in the Venice study recommend vaccination for those with respiratory diseases, cardiovascular diseases, renal diseases or metabolic disorders.

Asked why neurological diseases, being one of the most important risk factors for children, were not included in the overview, Mereckiene responded that this data...
was not yet readily available. She indicated, however, that ECDC has recently published its findings on the various vaccination approaches for the neurologically diseased.

In terms of household contacts for those possibly at risk, in this context household members in contact with children less than six months of age, vaccination is only recommended in one third of the 'VENICE Study' countries.

THE IMPLEMENTATION GAP

Jolita Mereckiene also presented vaccination coverage data which reflect the real implementation of the various vaccination recommendations for children when such recommendations are put in place. These data indicate a gap between recommendations and actual vaccination practice. Vaccination coverage for children in recommending countries is low, hardly reaching a few per cent. In Finland, where vaccination is recommended for every child from the age of 6 months to 3 years, vaccination coverage within the age group remains below 40 per cent. Only in the UK vaccination coverage reaches the 50 to 70 per cent mark.

"Only the UK stands out with coverage rates hovering around 50-70%"

ON HARMONIZATION

Might we expect a more harmonized trans-European approach to immunization recommendations for children? It is possible, but it will also take time. Jolita Mereckiene referred to the harmonization trend in pregnancy-related influenza recommendations. “In 2007-08 only 10 out of 30 countries recommended vaccination of pregnant women. By 2014-2015 already 27 recommended vaccination. 25 countries recommended vaccination of all pregnant women and two countries included pregnant women with clinical risk in their list”, Jolita Mereckiene said. Immunising pregnant women protects the smallest and most vulnerable children - those aged under 6 months. But with actual uptakes ranging from extremely low to moderate, from less than 1 per cent to 58 per cent, also in pregnant women, much work remains to be done. And the question remains as to whether practical evidence shows divergent professional attitudes towards vaccination in different subgroups, for example towards vaccination of pregnant women vs vaccination of children.

Improving vaccination coverage is only possible by going into the behavioural details for each of the specific subgroups. Recommending vaccination in children will not suffice. In the end, it is all about compliance. The Venice Study demonstrates the vaccination coverage gap, regardless of the targeted population group (medical workers, elderly, chronically diseased and pregnant women…). “Some countries still do not monitor vaccination coverage amongst older population groups and as a result have no data about the success of prevention campaigns”, Jolita Mereckiene said. She urged all countries to strengthen their monitoring systems. She also said more research is needed to see how recommendations can be effectively translated into higher vaccination coverage, in order to clarify the reasons for non-vaccination and pinpoint the positive drivers in countries that already achieve targets of 75%.

1 VENICE stands for Vaccine European New Integrated Collaboration Effort. The objective of the Venice project is to promote and share knowledge and best practices in vaccination. The project started in 2006. And the surveys involve all EU-member states together with Iceland, Liechtenstein and Norway. Until now, VENICE conducted seven of these international seasonal influenza surveys, next to the 2009-10 pandemic survey, all based on the same methodology.


TAKE HOME MESSAGES

- The European recommendation map of influenza vaccination for children proves to be highly fragmented and variable.
- Most European countries do not recommend vaccination for healthy children at all.
- Even when recommended, compliance remains extremely low.
- Only the UK stands out with coverage rates hovering around 50-70%.
- More research is needed to see how recommendations can be effectively translated into higher vaccination coverage.
Epidemiology and burden of the flu in children

THE BURDEN
Prof. Susanna Esposito has a long-standing track record in epidemiology. She recently moved from the University of Milan to the University of Perugia where she became a full professor of pediatrics, still continuing her research. Prof. Susanna Esposito’s presentation was aimed at summarizing the influenza burden in children, in terms of health outcomes and socio-economic side effects.

Many effects contribute to the overall influenza burden. The most evident is healthcare consultation. Susanna Esposito referred to data on Emergency Room (ER) visits collected during the 2003-2004 season in Milan: “30 per cent of ER visits were related to influenza viruses. This means that the burden for pediatricians and families is really, really relevant.”

When excess treatment events are taken into account, influenza is again a major influence. Data from the US over the course of 19 consecutive seasons show peaks in outbound patient visits and antibiotics courses, especially in the first years of life between 1 and 3 years. “We know that in influenza season, when pediatricians visit a young child with fever without specific symptoms, there is a tendency to overprescribe antibiotics”, Susanna Esposito said. “We try to do our best to reduce the unnecessary use of antibiotics, but this is what happens in clinical practice.”

“Influenza in the paediatric population is one of the main reasons for going to the Emergency Room.”

“Children have high rates of seasonal influenza infection and illness. An estimated 20-30% of children are attacked by influenza each year. And the rate of hospitalization for influenza in children under 3 years is extremely high, with the age group up to five months being extremely relevant for hospitalization. Usually infants develop high fever, being an indication to hospitalize the child. “When we consider the healthy population in the first 3 years of life, the risk of hospitalization due to influenza is even higher than in adults with chronic diseases and the elderly, thus for groups for whom influenza vaccination is recommended”, Susanna Esposito said.

Looking at the mortality burden, data from the US indicate that the risk of mortality is primarily present in the first 6 months of life up to the age of 2 years. “Of course, it is not as high as in the elderly, but it is higher than observed in adults”, Susanna Esposito said.

WHAT IS THE CLINICAL AND SOCIO-ECONOMIC IMPACT OF THE BURDEN OF INFLUENZA ON CHILDREN? WHAT IS THE IMPACT OF CHILD INFLUENZA ON THE COMMUNITY? AND HOW TO COPE WITH EMERGING INFLUENZA VIRUS AND RELATED PROBLEMS IN THE PAEDIATRIC POPULATION?
During the 2003-2004 influenza season in the US, the median age of children who died was 3 years of age. 63% were younger than 5 years old. 31% died outside of a hospital setting. 29% died within 3 days of the onset of the illness. And almost half (47%) of the children who died had previously been healthy.

**TRANSMISSION EFFECTS**

Compared to adults, children shed the influenza virus earlier, and also for a longer period. “Drilling down into the data, we notice that adolescents present a very high risk of transmitting influenza to their friends, especially during weekdays when they attend school”, Susanna Esposito said. “Even in conditions ahead of the onset of an influenza epidemic and school closures, the risk of influenza transmission is extremely high. And this risk remains high even after school closure. What happens is that parents send their children back to school as soon as fever signs disappear. Therefore, we should consider the problem of virus shedding.”

Children also represent a major pathway of influenza transmission to other family members, like parents, brothers and sisters, and into the community. “The impact on households is similar to that of hMPV’s (metapneumovirus) and is even higher than the one observed in RSV (Respiratory Syncytial Virus). The contacts’ days lost from work range from 1 to 10, with 4 days as median. The contacts’ days lost from school range from 1 to 15, with 5 days as median.”

“Immunizing children, when done universally, can have a significant impact not only on the pediatric population, but also on the population at large”, Susanna Esposito said. She referred to a Canadian study conducted in the Hutterite community some years ago on children between 3 and 15 years (n=947). This study reveals that in closed communities, when adopting a universal vaccination strategy in the pediatric population, a protective effectiveness of around 60% in the overall population of non-vaccinated individuals (n=2,326) is attainable.

“Immunizing children, when done universally, can have a significant impact not only on the pediatric population, but also on the population at large.”
THE PROBLEM OF EMERGING STRAINS

Given the clinical burden of influenza in children and also the high transitory effects to other age groups, excessive use of antibiotics, school and work absenteeism and the resulting socio-economic costs and disturbances, Susanna Esposito urged that close attention be given to the problem related to the emerging virus strains. “The data regarding the different strains present some remarkable differences in outcome (i.e., risk of hospitalization, days of school absenteeism and antibiotic use). The clinical presentation of influenza A/H1N1 and influenza B appears similar, but influenza B causes a much higher hospitalization rate. On the other hand, influenza A/H3N2 appeared the most severe in outcome.” Susanna Esposito observed that influenza B viruses are extremely common in children between 5 to 10 years. And data coming from the US, looking at the results in terms of the mortality rate, indicate that in some seasons influenza B was associated with a higher rate of mortality.

In order to limit the overall burden of influenza in children, vaccine mismatches should be prevented wherever possible. But in five out of ten influenza seasons between 2001 and 2011, the predominant circulating influenza B lineage was different from that chosen for the vaccine. As a result, past influenza vaccination campaigns had limited effectiveness against influenza B epidemics where the disease was caused by opposite-lineage influenza B strains.

This reduced effectiveness in such seasons could be avoided if seasonal influenza vaccines included four strains, one strain from each B lineage in addition to A/H1N1 and A/H3N2 strains. “Considering the evolution of the different influenza lineages, the opportunity of having a second B strain in the vaccine is extremely important for the pediatric population”, Susanna Esposito said. “With universal vaccination, we can even protect those at risk who don’t respond well to vaccination, and need to be protected by reducing the circulation of the pathogen in the community.”

ON UPTAKE PROMOTION

When asked how vaccination uptake could be promoted, Susanna Esposito answered that those benefiting most might play an advocacy role. “Parents of children with a history of recurrent respiratory infections, that means not only those with chronic disease, but those children who are always ill when starting day care, are in the end very happy with influenza vaccination, because they have the perception of reduction in the burden of infection in their children... it’s not only about protecting the child, it’s also about protecting others and yourself. It’s all about indicating the personal, group and even system advantages. You perform a sort of population strategy and not only a strategy aimed at the vaccination of your patients.”

TAKE HOME MESSAGES

- The burden of influenza in children is high both in terms of frequency and severity.
- Influenza in children also has a high negative socio-economic impact.
- Influenza is very common in the pediatric age group during epidemics and can cause serious disease.
- Children represent the major pathway of influenza transmission in the community and households.
- Influenza vaccination represents the best strategy to reduce the burden of influenza in children and the community.
Bacterial super-infections are underestimated

**COMPLICATIONS OF INFLUENZA**

**FLU IS KNOWN TO PLAY A RISK-AGGRAVATING ROLE IN BACTERIAL SUPER-INFECTIONS. “THE IMPORTANCE OF VIRAL-BACTERIAL SYNERGY IN INFECTIONS BY INFLUENZA IS PROBABLY UNDERESTIMATED. VACCINATION AGAINST INFLUENZA MAY OFFER AN ATTRACTIVE STRATEGY TO LIMIT THE DEVELOPMENT OF SECONDARY BACTERIAL DISEASE”, SAYS PROF. RONALD DE GROOT.**

**VIRAL-BACTERIAL SYNERGY**

In his talk, Prof. Ronald de Groot challenged the view on the overall flu burden, giving an insight into how viruses and bacteria team up to cause more severe illness in the patient, like e.g. pneumonia. The importance of viral-bacterial synergy causing a bacterial super-infection in addition to the already present infection by influenza is probably underestimated, Ronald de Groot said.

“Especially in young children, diagnosing bacterial lower respiratory tract infections is a difficult clinical challenge. It is not easy to get a grip on the situation when influenza is complicated by a bacterial super-infection. But viral infections have been well known for increasing the risk of severe secondary bacterial infection. Viral-bacterial synergy is certainly an important mortality factor.

“Viral infection is well known for increasing the risk of severe secondary bacterial infection.”

Viral-bacterial synergy has been observed for many viruses and bacteria (e.g. the respiratory syncytial virus and Staphylococcus aureus). “Viral-bacterial synergy can manifest itself in two ways”, Ronald de Groot said. “The first one, excellently reviewed in the Lancet in 2014, is a very rapid presentation where mortality kicks in, sometimes within 24 hours of the first symptoms. This presentation is due to ARDS (10-15%) and not caused by bacterial super-infection. The second presentation which is much more usual (85-95%) and needs more time to develop is due to bronchopneumonia and is mostly caused by bacterial super-infection. Both presentations are present in local epidemics and global pandemics.”

To answer the question ‘Is flu in children related to high mortality rates?’, Ronald de Groot referred to two studies. The first is a study by Finelly et al. published in Pediatrics (2008), investigating 166 recorded deaths in the US in the 2004-2007 timeframe in a population of 313,7 million. “This mortality rate corresponds with the findings in the Netherlands, where in a population of 17 million approximately 1 flu-related child deaths are recorded each year”, Ronald de Groot said. The second study from Bhat et al., published in the New England Journal of Medicine (2005), investigated deaths during the 2003-2004 outbreak, “where in 50% of the cases underlying conditions were present. In the study of Finelly et al. only 6% percent of the risk groups were fully vaccinated. The Finelly study observed during three study seasons bacterial infection in 6, 15 and 34% of cases. This increase may have been due to more awareness.” Ronald de Groot concluded that “mortality due to flu is rare, but bacterial super-infection plays an important role therein”. “The mortality rate is highest in infants below 6 months of age who can’t be covered by vaccines against influenza. Hospitalization rates for acute respiratory disease attributable to influenza virus among children without
high-risk conditions are by far the highest in the 0 to 1 year population. But this risk decreases fast with age.”

The best data on viral-bacterial synergy is harvested during major influenza pandemics resulting in excess deaths, such as the 1918 Spanish Flu, 1957 Asian influenza, 1968 Hong Kong Influenza and the 2009 Swine Flu pandemic. “The best-known autopsy study of Morens et al. in the Journal of Infectious Diseases (2008) reported on autopsy cases from the 1918 pandemic. The causative agents in children and adults who died were first and foremost Streptococcus pneumoniae, which was an important agent during the 1918 outbreak. But Staphylococcus aureus was also a major pathogen as observed during the 2009-2010 season. Streptococcus pyogenes and Haemophilus influenzae are also found, but less common. There is a difference in the type of bacteria prevailing during the various outbreaks. And there are also differences in the affected age range and in mortality rates.”

MECHANISM OF DISEASE
“It takes a couple of days for a child with flu to develop pneumonia and subsequently coming to a hospital”, Ronald de Groot said, explaining the underlying mechanism. “Initially there is a depletion of alveolar macrophages and there will be an impairment of innate immunity that will enable bacterial overgrowth. At some stage the impairment of the innate immunity leads to a situation where bacteria can’t be cleared, resulting in an overwhelming infection. In detail, you get a dysfunction of lung physiology, epithelial cell barrier damage, endothelial cell activation, neutrophil induced damage and the destruction of alveolar macrophages. There will be virus effects on immunity against bacteria, increased inflammation and in the end also bacterial interference with anti-viral immunity. On top of that, there are strain-specific differences in the overall pathology.”

“Mortality due to flu is rare, but bacterial super-infection plays an important role therein.”

Ronald de Groot also unveiled some results of a forthcoming study (not yet published) on H1N1 infections in the Netherlands in hospitalized children (n=940). “It is the first time ever that all hospitals (except 5 small ones) were involved and all pediatricians were asked if they had a child with PCR-confirmed infection by influenza. The results show an outbreak of seven to eight weeks. 50% of the children had underlying disease. The study also delineated risk groups: young age, pre-existing heart and lung disease, prematurity, hematological disorders, and neuromuscular and psychomotor disorders. A higher risk related to Down syndrome, diabetes, cystic fibrosis and metabolic disorders could not be confirmed, because of the limitation in the numbers involved in the study. This also shows that in order to acquire adequate data about risk groups, we really need larger numbers,” Ronald de Groot concluded.

TAKE HOME MESSAGES

- Bacterial-viral co-infection is common during severe acute lower respiratory infection by influenza.
- Infections by influenza modulate the antibacterial response in multiple ways and lead to increased pneumococcal replication in the upper respiratory tract.
- Increases in upper respiratory tract pneumococcal load are associated with increased severity of pneumococcal disease and with inter-individual spread.
- Vaccination against influenza virus may offer an attractive strategy to limit the development of secondary bacterial disease.
THE EFFECTIVENESS OF INFLUENZA VACCINES IN CHILDREN

Quadrivalent Vaccines are a Good Match for Children

For years influenza vaccines were designed to protect against three different flu strains, two A strains and one B strain. The more recent quadrivalent vaccines broaden this protection by covering two A strains and both B strains. By broadening the target design, the vaccine limits the chance of a mismatch between the influenza B vaccine component and the circulating B strains. Especially for children, adding both B strains to the vaccine is beneficial because they have less been exposed to viruses of both influenza B lineages than older people and therefore do not profit from pre-existing immunity against these viruses.

“Any vaccine composition mismatch has more severe implications in children.”

A new meta-regression study on immunogenicity trials and controlled field trials conducted by Beyer, Palache, Boulfich and Osterhaus, which was recently published in Vaccine, measures the impact of influenza B lineage and specific pre-seasoned immunity on the effectiveness of influenza vaccines. “This literature review looked at both the available clinical data on quadrivalent vaccines and the serological data”, Ab Osterhaus said. “The study shows that the difference in effectiveness between quadrivalent vaccines (QIV) and trivalent influenza vaccines (TIV) is higher in children than in older age groups, in favour of QIV. The pre-existing protection rate in the older population is also higher, implying that any vaccine composition mismatch has more severe implications in children. So especially in children, QIV offers extra protection”, said Ab Osterhaus.

“Amongst the vaccine types available, quadrivalent vaccines (QIV) often come up as the number one choice for children.”

Osterhaus also referred to industry studies. GSK for example conducted a phase III trial pediatric study on the effectiveness and safety of its Fluarix Tetra QIV in children 6 to 35 months of age. This observer-blind, randomized, non-influenza comparator controlled study was conducted in 13 countries (n=12,018) on five independent cohorts over five influenza seasons (2011-2014). “The study showed that there is no issue of vaccine safety and reactogenicity”, Ab Osterhaus said. “There are local symptoms. And the same was true for the more general symptoms”, Osterhaus said. “You always have to show these data. They become interesting when things go wrong. But the results clearly show that there is no issue with safety, as is also true for other influenza vaccines.”

The primary objective of the GSK study was to confirm efficacy of the vaccine in the prevention of RT-PCR confirmed moderate to severe influenza due to any strain versus RT-PCR confirmed influenza of any severity due to any strain. The efficacy against moderate-to-severe influenza was 63.2%. In any influenza, efficacy reached 49.8%. “Of course, you can always do better, but almost 63 and 50 are significant percentages”, Osterhaus said.

The quoted GSK study also showed high protective rates in influenza-associated lower respiratory illness, acute otitis media and influenza A and/or B disease due to matching strains or any seasonal influenza strain, showing protective rates ranging from 50 up to 70 plus %.

“We are not talking about mortality, but about the disease burden and its impact on the healthcare system”, Osterhaus said. “Among children with confirmed influenza of any severity, and compared with the control group, the vaccine...
led to a reduction in the use of antibiotics by 50%. The number of GP visits dropped by 46%. And ER visits went down by 79%. In moderate- and-severe influenza the benefits were even higher, with a reduction of 69% in the use of antibiotics, 65% in GP visits and 80% in ER visits. These are interesting and encouraging numbers.”

Sanofi Pasteur conducted a study with a similar set-up on the efficacy and safety of its QIV Vaxigrip Tetra in about 5,000 children from 6 to 35 months of age. The trial assessed the vaccine’s efficacy in four continents (including 34 centers in Europe), during four distinct influenza seasons between March 2014 and September 2016, periods in which influenza circulation was confirmed. Again the safety profile of QIV was similar to that of the placebo group and to that of TIV. And again efficacy was confirmed, with an efficacy rate of about 50%. Ab Osterhaus: “The interesting thing in this study is the mismatch between vaccine strain and circulating virus is an important confounding factor for vaccine effectiveness in the field. Although true mismatches occur relatively seldom, when they occur they may reduce vaccine effectiveness considerably, as we experienced two seasons ago. Such mismatches are damaging for perceptions of how well vaccines work and perform. As a result, when mismatches are reduced, the vaccine debate will also gain clarity. Therefore reduction of mismatches will not only increase overall vaccine effectiveness, but also the public perception about influenza vaccination.”

“The overall protection range of quadrivalent vaccines in children ranges from 50 to 70% plus.”

**MISMATCHES: INFREQUENT BUT IMPORTANT**

The mismatch between vaccine strain and circulating virus is an important confounding factor for vaccine effectiveness in the field. Although true mismatches occur relatively seldom, when they occur they may reduce vaccine effectiveness considerably, as we experienced two seasons ago. Such mismatches are damaging for perceptions of how well vaccines work and perform. As a result, when mismatches are reduced, the vaccine debate will also gain clarity. Therefore reduction of mismatches will not only increase overall vaccine effectiveness, but also the public perception about influenza vaccination.

“The epidemiology of influenza is such that viruses, at least the new influenza A virus strains, appear to emerge in south-East Asia, basically, and are being seeded into the Northern hemisphere and subsequently into the Southern hemisphere. They don’t seem to flip back and forth, as we have thought in the past. Knowing the hotspots of newly emerging seasonal influenza viruses is important for strain selection purposes, as we can put more emphasis on viruses found in these areas. And when we see new strains coming up, we should also realize that this is just one side of the coin. The flipside is probably equally important: how well protected are the population at large and the risk groups, against the emerging viruses, by previous exposure and resulting antibody landscapes? In the strain selection procedure, antibody landscapes will therefore be introduced as an important adjunct to existing procedures focusing on viruses alone. Finally, the time between strain selection on the one hand and first vaccine in man on the other, may in the future be reduced considerably by using novel vaccine production technologies. This will reduce the time during which the virus may change after strain selection. Therefore I dare say that all these new developments combined, will eventually lead to a significant reduction of the risk of influenza vaccine strain mismatch and therefore improve vaccine effectiveness,” Ab Osterhaus concluded.

**TAKE HOME MESSAGES**

- Influenza B lineage mismatch for vaccine efficacy is most relevant for children.
- Safety profiles for QIVs are similar to those previously observed for TIVs.
- Efficacy from QIVs in reducing laboratory-confirmed influenza in children ranges from 50 to 70 plus %.
- Protection level depends on the matching of vaccine strain versus circulating strains.
- The potential gains in reduction of antibiotic usage, GP visits and ER hospitalization are significant.
Lessons learned from the United Kingdom

In the 2016-2017 season, the UK completed its fourth season of roll-out of its paediatric live attenuated influenza vaccine programme.

Tradition

The UK like other countries has a long history of an annual vaccine programme targeted at individuals at higher risk of severe disease, traditionally employing a trivalent inactivated vaccine (TIV). The aim of this programme is to provide direct protection to those target groups, the over 65’s and higher risk groups under 65 years, including pregnant women.

Richard Pebody shared past experiences and commented on uptake levels. “We’ve done reasonably well to date”, he said. “For the over 65s, we’ve been approaching the WHO and the EU-council target of 75% for a number of seasons since the early 2000s. And for the under 65s at risk, we’ve hovered around 50% for a long time. And this percentage covers a heterogeneous uptake by different risk groups.

For some of the groups at high risk of severe disease, the uptake is well below 50%, and despite a lot of effort, we’ve not been really able to take uptake any higher than that 50%.”

“Despite the selective programme, the UK still sees a lot of flu, with significant burden of disease due to flu both in terms of deaths, mainly in the elderly, and hospital admissions”, Richard Pebody said. “The highest hospitalization rates are in the infants, particularly those under 6 months of age and those between 6 months and 4 years of age. We also know that the effectiveness of the inactivated vaccine in some of those key groups can be moderate at best, particularly in the older age groups and the very young. And those are clearly perhaps the most vulnerable groups.”

Building an extended approach

In an effort to further reduce the burden of disease and dampen flu transmission the UK decided on a new strategy. “We know children are very important drivers of flu transmission in the population”, Richard Pebody said. “We also saw the arrival of intra-nasally administered cold adapted live attenuated influenza vaccine (LAIV), which has been licensed in Europe since 2011. So we asked ourselves if we should be targeting healthy children with flu vaccine to try to further reduce the burden of disease, both by directly protecting the children and potentially others in the population. The data from studies prior to the 2009 pandemic demonstrate that the LAIV worked very well in kids. The pooled vaccine effectiveness estimate was encouraging, in particular when compared to the performance of the inactivated vaccine in healthy adults.”

The UK undertook a modelling exercise to try and predict what the impact would be of a range of extensions to the existing programme”, Richard Pebody said. “This was done by building a transmission model to estimate the impact of the current selective programme, to predict the direct and indirect effects of various programme extensions, and to look at what the costs of those extensions and the savings would be, in particular looking at QALYs (Quality of Life Year).”

The modelled extensions ranged in ambition from an extension to offer vaccine to all children 6 months to under five years of age to offering vaccine to all 6 months to 64 year low-risk individuals. Results from the exercise were published in BMC Medicine in 2015.
COST-EFFECTIVENESS OF A PAEDIATRIC PROGRAMME
“Taking into account only the health care costs, the results from the economic modelling predicted that any programme extension involving the vaccination of kids was on average cost-effective even at 30% uptake, whereas extensions involving the addition of older adults (50-64 years of age) were unlikely to be cost-effective.”

AMBITIOUS PROGRAMME
Based on the predicted direct and indirect impact of a programme extension involving children, the UK Joint Committee on Vaccination and Immunisation (JCVI) in 2012 made the recommendation to roll out a universal programme over a number of seasons, ultimately to be targeted at all healthy children aged from 2 to 16 years, employing the newly licensed live attenuated influenza vaccine (LAIV). Richard Pebody: “The recommendations involved a single dose of LAIV for healthy children, and two doses for children at risk under nine years of age being vaccinated for the first time. Children who were contraindicated LAIV, because of severe underlying risk factors such as immunosuppression or severe asthma, were offered the alternative inactivated vaccine (IIV). The programme was initially introduced with a trivalent vaccine and switched to the quadrivalent vaccine as soon as this became available.”

The 2016-2017 season was the fourth season of the roll-out of the extended children programme across the UK. It has been a natural step-by-step experiment. “Initially, in 2013-2014, vaccination was just offered to all healthy 2 to 3 year olds, delivered through primary care”, Richard Pebody said. “The following year 4 year olds were included. In 2015-2016 the programme was extended to the first two years in all primary schools across the UK, what we call years one and two. And then last year it went out to all children in year 3 in primary schools.”

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There was also variation in the way the programme was rolled out, both in England and across other parts of the UK. Richard Pebody: “In England pilot programmes were run in geographically discrete areas that varied by season. There were also some differences in the roll-out within Scotland, Northern Ireland and Wales. The aim of the pilots in England was to determine the optimal delivery strategy to vaccinate children of school age in terms of uptake and cost, in particular comparing vaccination in school vs vaccinating in pharmacy.”

For the programme through primary care, in pre-school kids, uptake has hovered at around 40% in England. The school age pilots in England showed overall uptake levels in excess of 50%, but with strong variations in uptake by delivery mechanisms. “The highest uptake for school age children clearly was being obtained in a school setting rather than through a pharmacy or GP setting. Most parts of the country are now moving towards a school based delivery programme for children of school age.”
We also did a pooled vaccine effectiveness estimate in 2-17 year olds for the three seasons from 2013 to 2016 we had the data for. The quadrivalent intranasal vaccine showed an overall effectiveness of 53.1%, with 35.6% against H1N1pdm09, 46.7% in H3N2 and 86.9% in B, compared to a 31.5% overall effectiveness for the injectable vaccine, with 100% in H1N1pdm09, around 22% in H3N2 and 24.8% in B, although again numbers were smaller for the injectable vaccine estimates.

**IMPACT**
What has the impact of the extended flu programme been so far? The introduction of the programme in pilot areas presented a natural experiment for seeing whether the epidemiology of flu in the pilot areas was different from the epidemiology in the rest of the country. And consistent decreases were found both in disease incidence in targeted and non-targeted age-groups in primary school age pilot areas vs areas where children of primary school age were not offered vaccine.

“What we have been doing is enhancing our surveillance in the pilot and non-pilot areas and we have compared the epidemiology of flu against the range of different endpoints”, Richard Pebody said.

“For the quiet H1N1pdm09 2013-2014 season, across all ages the overall cumulative incidence was lower in pilot compared to non-pilot areas, with for example a 50% reduction across all ages in the cumulative incidence of ILI in primary care in these pilot areas. In the busier 2014-2015 season we noticed a reduction in cumulative incidence of influenza-like illness consultations in primary care in the targeted primary school age group in pilot versus non-pilot areas. But the same also applies when looking at the indirect effects in the under 5 year olds and in the adults as well when comparing pilot with non-pilot areas.”

“Going to the secondary care indicators, laboratory confirmed hospitalizations and ICU admissions, the lab confirmed hospitalization rate in pilot areas was lower, in both under 5 year olds and adults and also for ICU admissions, although the size of the impact is less when looking at the more severe endpoints.” When looking at the most severe endpoint, the difference was close to none when excess all cause mortality was considered. But when looking at respiratory excess mortality, the UK did see significantly less excess mortality in pilot areas compared to non-pilot areas in the 2014-15 season.

**TAKE HOME MESSAGES**
- The UK has completed its fourth season of rollout of its paediatric live attenuated influenza vaccine programme.
- The programme was based on modelling and economic evaluation of projected programme impact.
- The programme to date has shown clear evidence of LAIV’s effectiveness. Unlike in the US, overall LAIV vaccination effectiveness was good, particularly against flu B, though lower against H1N1pdm09.
- The same evidence goes for the population impact of primary-school age vaccination at -50% uptake. Vaccination clearly prevents influenza in the paediatric age group and as a result has a positive impact on primary care indicators, and suggestion of reduction in hospitalizations and ICU admissions in areas offering influenza vaccine to children of primary school age.
- JCVI has reviewed the UK programme in the light of the US observations, and continues to recommend the on-going introduction of the childhood LAIV programme, but has highlighted the importance of on-going enhanced surveillance and further studies as the programme is rolled out to additional age-cohorts.
The LAIV efficacy debate

THE LAIV WITHDRAWAL FROM THE US MARKET RAISED MANY EYEBROWS IN EUROPE AND THE UK. NECESSARY TO SAY THE ACIP STORY ON NASAL SPRAY VACCINE EFFECTIVENESS CAST ITS SHADOW ON OUR SYMPOSIUM DEBATE.

In June 2016 the US Advisory Committee on Immunization Practices (ACIP) voted that the Live Attenuated Influenza Vaccine (LAIV) should not be used during the 2016-2017 flu season. ACIP is a panel of immunization experts that advises the Centers for Disease Control and Prevention (CDC). The ACIP vote was based on data showing poor or relatively lower effectiveness of LAIV in children and adolescents from 2013 through 2016. In his talk, Richard Pebody (UK) confirmed that the UK results counter-indicate the US experience. “We have been looking very, very closely at our own data to try to see what’s going on in the UK setting and whether we are seeing similar observations as in the US,” Pebody said. But for the three seasons 2013 through 2016, the quadrivalent intranasal vaccine showed an overall effectiveness of 53.1% in 2-17 year olds compared to 31.5% overall effectiveness for the injectable vaccine. “The LAIV vaccine proved to be significantly effective, quite different from the results presented in the US,” Pebody said.

In the margins of her talk, Prof. Kristina Angel Bryant (US) commented on the ACIP’s disapproval of the LAIV nasal spray vaccine. “The ACIP is a thoughtful group of people”, she said. “History suggests that they are willing to reconsider, to change their minds. The decision generated a lot of discussion in the US. Remember just a few years ago (2014-2015 - Ed.) CDC and ACIP had a preference for LAIV. I think that based on that, the ACIP will continue to consider data from multiple sources. And I do think that the ACIP as a body has a history of continuously re-evaluating.”

During the closing debate, Prof. Bryant was reminded of the revision question. “We have the vaccine effectiveness database; it’s a rich source of data and it’s hard to ignore your own data”, she said. “If you have data that says ‘Oh, this doesn’t work’, then it is very challenging for policymakers to ignore that. But that’s not to say that it can’t be revisited.”

Kristina Bryant also said she did not have an inside track on the ACIP story. “When I talked with colleagues at CDC they said ‘We don’t really have updates for you to give’... A timetable for when it will be revisited? ... difficult to say. We will just have to wait and see.”

But with no future use of LAIVs in the US, no new data will be generated potentially counter-indicating the earlier negative tests, an audience member replied. Dr. Hanna Nohynek (Finland) endorsed this viewpoint: “What I understand is that revisiting is not on the next ACIP agenda”, she said. “According to my understanding, there is not sufficient new LAIV effectiveness data there in the US. So it will not be revisited this season. That’s one of the major concerns, because when the product is off the market for too long, it will disappear, and we will not have a product anymore. I would really want to put all the data we have from the different countries on the table. Finland will continue recommending LAIV to all those 2 years of age and will share data for those who need to know.”

“From the UK perspective, we will continue to evaluate our programme extremely closely”, Richard Pebody concluded. “We will continue the roll-out and share our results with our colleagues in the US and within ACIP, whatever those results might bring up. And hopefully that might help informed decision making.”
The Belgian perspective on child flu

BELGIUM HAS NO REAL INFLUENZA VACCINATION POLICY FOR CHILDREN. BUT WILL IT EVENTUALLY CHANGE ITS ‘WAIT AND SEE’ ATTITUDE? “THE ANSWER IS YES, OF COURSE WE WILL, AT SOME MOMENT IN TIME”, SAID PROF. MARC VAN RANST. IT ALL COMES DOWN TO BUILDING UP MOMENTUM AND SECURING COST-EFFECTIVENESS.

WHAT IS KNOWN
Children, adorable as they may be, live in a cloud of particles when they have a respiratory infection, whether a cold or an influenza infection. “If you want to look for a population that spreads the disease, children are the ones to look for”, Prof. Marc Van Ranst said. “We know that vaccination helps prevent transmitting influenza. We also know that children are the big amplifiers of epidemics. And we know that children aged 6 to 59 months figure prominently in the WHO recommendations. However in our own High Health Council recommendations, with regard to children, we only go so far when they suffer from a chronic medical condition.” Whilst the pandemic changed the attitude of pediatricians towards immunizing children, making pediatricians quite open to influenza vaccination, that momentum now seems to have faded away.

VACCINATION RATE
All things considered, Belgium is doing fairly well in terms of vaccination, Van Ranst said, showing figures for Flanders, the northern region of the country. “But vaccination willingness in Belgium has declined since 2004, most prominently in the southern part of the country. In Wallonia and Brussels, a sort of vaccine fatigue has set in. In contrast vaccination uptake in Flanders has remained quite stable, even after the 2008-2009 pandemic”, Van Ranst said.

Uptake data for the youngest age groups are scarce to unavailable. In the 15-24 olds the uptake rate is 32% for women and 23% for men. In the age group from 0 to 10 years, collected data indicate that only 0.3% are vaccinated. “That rate has probably gone up a little in recent years, but not all that much. We are also definitely not vaccinating all the at-risk children”, Van Ranst concluded.

MODELLED IMPACT
Van Ranst also commented on an article published by Quintiles, assessing the public health impact of a pediatric vaccination programme in Belgium, using an intranasal tetravalent LAIV. The data show that vaccinating half of the pediatric population would already change the epidemiology of the influenza epidemic. “Most of the models are going to show that vaccination is going to have a real impact”, Van Ranst said.

In 2012 the Belgian Government prompted researchers at KCE, the Belgian Federal Health Knowledge Center, to think about prioritizing children for vaccination. Consequently researchers from the University of Antwerp were asked to rate the cost-effectiveness. “Calculations indicated an incremental cost ranging from €42,000 up to €44,000 per QALY (Quality of Life Year) gained, depending on the age group concerned and the various vaccination options”, Van Ranst said. “In Belgium, such cost levels are considered to be non cost-
Cost-effectiveness of various vaccination options, each compared to the current Belgian situation, at 50% coverage.

effective. But a reduction of 25% in vaccination costs would lead to median incremental costs per QALY of around €30,000 to €32,000, and these levels would be more acceptable.”

The exercise’s conclusion was that an influenza vaccination programme for children would be as cost effective as other already reimbursed vaccine programmes in Belgium, but only when costs are reduced by 25%. It was also said that childhood vaccination should not replace the vaccination of adults at risk. The models used showed a preference for LAIVs over TIVs, at least at comparable prices. The quadrivalent LAIVs performed better in the used models, but not all that much.

**WHAT’S NEXT?**

Will Belgium eventually vaccinate its children? “The answer is yes, of course we will, at some moment in time”, Van Ranst said. “It’s quite remarkable that for some vaccines, Belgium was an early adopter. And for some we are more hesitant than others. We will have to rebuild the lost momentum. But we can also be shamed into a vaccination programme, when such programmes prove to work in other countries. But then again, it’s not something you can do overnight. You have to think things through; roll out the programme in a proper way. But, at the same time, the mountain is not insurmountable.”

**TAKE HOME MESSAGES**

- Belgium does not recommend vaccination of healthy children in a regular winter season.
- In 2009 the Belgian paediatricians became quite open to influenza vaccination. But since then the momentum has faded away.
- In Belgium, an influenza vaccination programme for children would be considered cost effective only when vaccination costs can be reduced by 25%.
UNIVERSAL VACCINATION OF CHILDREN

The Finnish approach

DR. HANNA NOHYNEK EXPLAINED HER COUNTRY’S APPROACH TO A UNIVERSAL VACCINATION PROGRAMME FOR CHILDREN. IN FINLAND IMMUNIZING CHILDREN REVEALED TO BE COST SAVING UNTIL THE AGE OF THIRTEEN YEARS. BUT THEN CAME THE PANDEMIC.

FOUR STEPS
Before explaining the workings of the decision-making mechanism through which new vaccines are added to the Finnish national universal vaccine programme, Dr. Hanna Nohynek first set out the context in which the programme is rolled out.

Since 1992 Finland has had a national infectious disease register in place. And since the pandemic of 2009 a national vaccine register has also been up and running. Every decision to add new vaccination extensions to the universal programme follows a four-step process. “The main question is whether universal vaccination provides a sufficient reduction of a significant public health disease burden. Therefore, both the epidemiology and severity of the disease, and the effectiveness of the vaccine, are taken into consideration. If there is sufficient disease burden, we move to step two and check if the vaccine is safe enough to those who will be vaccinated. We’ll also ask whether the vaccine is safe enough on a population level, e.g. if by reducing the disease in children we are not transferring the disease to other age groups.” As a last step, the balance between the related health benefits and economic costs is examined. “Unlike other countries, we don’t have an official QALY threshold”, Hanna Nohynek said. “It has varied from vaccine to vaccine. But the balance is extremely important if we want to justify the use of taxpayers’ money. There has to be sufficient health return value for money.”

“If we want to justify the use of taxpayers’ money, there has to be sufficient health return value for money.”

ON THE CHILDREN’S PROGRAMME
Any vaccine introduction since 2003 has gone through the formal four-step evaluation process. “This does take time. People have been upset that we don’t get a new vaccine into the programme within two years, but that’s just how it is now,” Hanna Nohynek said.

“When the cost-effectiveness of influenza vaccination in healthy children was taken into consideration, the conclusion in Finland was that influenza vaccination in healthy children is cost-saving until the age of thirteen years. Based on this, in 2007 a recommendation for influenza vaccination of children from 6 to 35 months of age was put into the programme.”

“The actual conclusion in Finland was that influenza vaccination in healthy children is cost-saving until the age of thirteen years.”

COVERAGE IN CHILDREN
In the early years, influenza vaccination coverage in Finnish children hovered around the 40% mark, that’s to say until the pandemic’s narcolepsy incident made numbers drop considerably.

“The coverage, especially in the young, went down from 40% to 13%”, Hanna Nohynek said. “And it’s been dragging along there for quite a while. We were thinking that if we introduced a LAIV it would be easier for parents small steps and to gradually expand, but then came the pandemic, and that messed up a lot of things. In 2012, we included the close contacts of medical risk groups, including children, who would then be eligible in order to increase the uptake.”

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to accept the vaccine, which was also considered more efficacious. The LAIV was then introduced in 2015-2016. And whether due to that or a kind of forgetting about the narcolepsy shadow, uptake has now gradually increased amongst the young.”

Figures for the 2015-16 season demonstrate that the vaccine uptake amongst 2-year olds (24-35 months) almost doubled with the LAIV compared to the TIV, going up from 7.5% to 14%. For the younger age groups, the uptake (TIV) was about 25-30%. For the 3 to 6 year olds, uptake (TIV) was around 12%.

**EFFECTIVENESS**

For the 2016-2017 season, dominated by influenza A(H3N2), coverage amongst 6 to 35 month olds was 32%. Vaccine efficacy in total was 41% (with a 95% confidence interval of 28-51%). “If we said that we had a very good vaccine, of course that would not be true”, Hanna Nohynek said. “I don’t like to sell the issue of child immunization with vaccine effectiveness data, I’d prefer to sell it with disease burden data and how much we avert of it with the vaccine. We need to be getting better at that, on how we measure influenza burden.”

With regard to which vaccine is more efficacious than the other, Dr. Hanna Nohynek presented the 2016-17 season results on the LAIV trivalent or TIV in the 2 year olds. “Crude analysis shows they are both performing just as well. Effectiveness of LAIV in laboratory confirmed disease was 35.7 % and of TIV it was 36.8%. And when adjusted with propensity scores and the data from the various registers, the TIV shows an efficacy of 54.6% and the LAIV of 37.7%. Confidence intervals overlap widely. So I couldn’t say from this data that one is better than the other. They look similar to me.”

**PARENTS’ ATTITUDES**

In preparation for the LAIV introduction campaign, the parents’ attitudes towards influenza were examined (N= 697). Around one third were negative or extremely negative about the vaccine. A little less than half of the mothers and fathers questioned were quite positive to extremely positive. Why then did these positively oriented parents not all have their children vaccinated? “When asked, positive parents mostly referred to practical logistical reasons like clinic opening times and ‘having no time’ (20%)”, Hanna Nohynek said. “But there were also those who said that influenza was not a severe enough disease for their child (16%), that their child was healthy and therefore didn’t need the vaccine.”

**BEAUTY OF THE SYSTEM**

Using the coverage data from the Finnish National Influenza Register, THL is now measuring influenza vaccine effectiveness by population-based register linkage. “The beauty of the system is not only the linkage of vaccination and infectious disease register data, but also of other personal healthcare registered data, through the accompanying personal identification. We have access for example to national birth register data, hospital discharge registers and other care registers. As a result, we can assess differences between the vaccinated and the non-vaccinated and we can build propensity scores in order to better understand our cohort study analysis.”

The register system allows data-miners to drill down deep. “We will continue to refine vaccine effectiveness estimations in the light of propensity, health status, previous vaccination history and circulating strains”, Hanna Nohynek announced. “With the registered data we now have at hand, we will be able to follow the vaccinated and non-vaccinated over time. We are also in the process of establishing hospital-based effectiveness surveillance for children, because with the laboratory data, we don’t have a good handle on why the sample was taken and what kind of influenza or disease was prevented. We only know that the influenza test was positive, and that is not sufficient if you want to fully understand the disease burden. You need to know the seriousness of what has been prevented.”

“I don’t like to sell the issue of children immunization with vaccine effectiveness data, I’d prefer to sell it with disease burden data.”

**TAKE HOME MESSAGES**

- In Finland immunizing children revealed to be cost-saving until the age of thirteen years.
- Finland still experiences post pandemic effects, when uptake dropped on average to 13%. The narcolepsy incident still casts its shadow.
- Since 2015-2016 uptake is gradually increasing. The introduction of the LAIV might play a role for the young.
- In order to win popular acclaim, we need to be getting better at how we measure and communicate the influenza burden in children.
- Influenza is still thought of as a not sufficiently severe disease to be in need of a vaccine.
IN FINLAND, THE PANDEMIC VACCINES LINK TO NARCOLEPSY STILL INFLUENCES FLU VACCINE UPTAKE BY CHILDREN AS WELL AS THE UPTAKE OF OTHER NEWLY INTRODUCED VACCINES. “MANY QUESTIONS REMAIN”, DR. HANNA NOHYNEK (FINLAND) SAID.

During the 2009 pandemic, flu experts were unexpectedly confronted with a very important safety concern that had never been associated with any vaccine before: an increasing number of narcolepsy cases in Swedish and Finnish children. The vaccine used was Pandemrix.

**SHEDDING LIGHT**

This narcolepsy tragedy still casts a long shadow. Dr. Hanna Nohynek shed light on the current situation and the state of the public opinion. “People are reminded constantly of the narcolepsy incident”, Hanna Nohynek said. “The press are very good at showing individual stories of children and young adults, who are severely affected. There are over 200 of those in Finland. And many of them, around 10%, are very seriously affected. Their personalities have changed. They have had difficulties in getting sufficient help from the medical community and society, they are perfect prey for media attention.”

**MANY QUESTIONS REMAIN**

Hanna Nohynek also referred to the Verstraeten et al. (2015) critical appraisal of observational studies on the narcolepsy issue. “The authors acknowledge that currently available data suggest an increased risk of narcolepsy following vaccination with Pandemrix, however from an epidemiologist’s perspective, significant methodological limitations of the studies have not been fully addressed and this raises questions about the reported risk estimates. What is the biological mechanism? Is there causality? Did the vaccine contribute to what we have seen, or was it some other underlying cause or environmental factor? To what extent did the natural A(H1N1) infection play a part and to what extent did the vaccine then further contribute to this onset? So there are a whole lot of question marks. Many questions remain.”

**TRANSPARENT COMMUNICATION**

Until answers to these questions are found, the policy is to remain very transparent on what is known and what is not known, said Dr. Hanna Nohynek. “I don’t go arguing with the families who have narcoleptic children. I can convey my compassion to them; it is a tragedy to have one’s child seriously and chronically ill after good intentions. Whenever vaccines are involved, the number one concern is safety. But at the same time, I will tell them that there are many things that we simply don’t know yet. And another important message is that we could not have foreseen this beforehand.”

“We calculated that with a baseline incidence of 1 per 100,000 we would have had to have 300,000 study subjects to see the narcolepsy signal during a clinical trial. So it is clearly impossible to capture very rare events in the pre-license phase. And we don’t know the biological mechanism behind what happened yet. But the scientific community is working on it. We in Finland are still monitoring the trends. We perform annual population register based surveillance and validation on how many new narcolepsy cases have emerged. It should also be remembered that previously, for this kind of disease, the mean time period from first symptoms to diagnosis was more than five years. This has now been reduced to less than two years. And the narcolepsy has gained far more visibility and receives a lot more public awareness and sympathy. We will never go back to what it used to be.”
Lessons learned from the US

SINCE 2010, THE US GOAL HAS BEEN TO IMMUNIZE EVERYONE WHO IS AT LEAST 6 MONTHS OF AGE. WHY VACCINATE CHILDREN? “BECAUSE FLU KILLS KIDS, AND IT KILLS HEALTHY KIDS. WE HAVE A VACCINE THAT IS SAFE AND EFFECTIVE. THIS VACCINE REDUCES HOSPITALIZATION AND MORTALITY”, PROF. KRISTINA BRYANT SAYS.

UNIVERSAL VACCINATION STRATEGY

The burden of influenza on children is substantial, and the US is no exception. Influenza results in millions of healthcare outpatient visits for influenza and an associated healthcare cost that is in the billions. Prof. Kristina Bryant presented the US experience.

How did the US manage to immunize all children? “The influenza vaccine has been part of the US health platform since the 1960’s”, Kristina Bryant said. “The immunization of children is relevantly recent. Historically the programme focused on people at risk and older citizens. In 2002 providers were encouraged to consider vaccinating children from 6 to 23 months old and their household contacts. In 2006 that recommendation was expanded to children 6 to 59 months old and their household contacts, to further expand in 2008 to all children and adolescents from 6 months up to 18 years old. Since 2010 the goal has been to immunize everyone who is at least 6 months old.”

The fact that children easily develop complications from influenza, even without known underlying risk factors, is a major reason for addressing the influenza burden by means of universal vaccination. Prof. Kristina Bryant: “If you just focus on risk factors and think that your approach is going to keep kids out of hospital and protect them from dying, you are going to miss children who will have morbidity if not mortality. Risk-based strategies can be challenging to operationalize and will fail to prevent considerable morbidity.”

“Risk-based strategies can be challenging to operationalize and will fail to prevent considerable morbidity.”

THERE’S A LOT TO BE SAVED

Why vaccinate children? “Because flu sends healthy kids to hospital. Half of the children hospitalized have no known underlying health condition. Flu kills kids, and it kills healthy kids. In recent years the death toll in the US is around one hundred. And we have a safe and effective vaccine. This vaccine reduces hospitalization and mortality. Admittedly the effectiveness is lower in the under 2 year olds; so we still need better vaccines. But that is not to say we should not use the vaccines we have right now. Another reason is to offer indirect protection towards those in the community who are not immunized.”

Kristina Bryant for her part stressed the protective capability of vaccination against severe flu consequences. She referred to a study by critical care doctors in paediatric intensive care units across the US (2010-2012). Immunization effectiveness against severe influenza proved to be around 70% to 80% plus. “The cases were children who were admitted to the ICU with severe respiratory illness and confirmed influenza. There were 44 confirmed cases. The overall immunization rate was low, with 18% of cases and 31% of controls that had been immunized. The average age in cases and controls was in the 3 to 4 range.” Vaccination further prevents flu-associated deaths. Prof. Bryant referred to the 2017 published

PROF. KRISTINA ANGEL BRYANT, University of Louisville School of Medicine, USA
cohort study by Flannery et al. over four seasons (2010-2014). “The bottom line is that vaccine effectiveness against paediatric death from flu was 65% (51% in high risk conditions and 65% with no high-risk conditions). So, getting vaccinated is protective against dying from the flu.”

“We still need better vaccines. But that is not to say we should not use the vaccines we have right now.”

**CHALLENGES**

Vaccination rates in the US have been steadily climbing, season after season. For the 2014-2015 season vaccination coverage just missed the 60% mark. Kristina Bryant: “Our immunization rates are still below target. At the beginning of the season, we are at about 40%, and it takes most of the season to reach 60%. Obviously, we want to immunize all children before the season starts, but we are not there yet. Coverage decreases as age increases. Young children tend to go to the doctor more often than older children do. We know that it can be difficult to get teenagers in. We have no approved vaccines for children younger than six months, and we know they are at the highest risk for complications of influenza. So what we try to do is immunize mothers, and we routinely immunize pregnant women and close contacts through the cocooning strategy.”

The ambiguity around vaccine effectiveness remains baffling. “We’ve heard about effectiveness from 50% up to 80%”, Kristina Bryant said. “But how do you communicate that in the media and in the surgeries? Parents come in and say: ‘We all got the flu vaccine but got flu anyway’. Well, in some years, that’s going to happen. We know from emerging data that the flu vaccine is very effective against severe outcomes, so we need to think how to communicate this in the examination room.”

In order to increase coverage, we also need to work harder at implementing evidence-based strategies for delivering flu vaccine, Kristina Bryant said. By this she means a combination of strong recommendations from the provider, immunization information systems, immunization in multiple settings without the need for an appointment, the use of standard orders, provider reminders and provider assessment and feedback. In the US, the majority of children get their vaccine in the doctor’s surgery.

“The challenge of immunizing so many kids over a short period of time is to immunize them when you see them.”

**EVERY CONTACT POINT IS AN OPPORTUNITY**

“I think in general we are working harder to deliver vaccines at other places. In the hospital where I work, we immunize in-patients before they go home. The challenge of immunizing so many kids over a short period of time is to immunize them when you see them. And my hospital has decided to provide the vaccine free of charge. If you come to the ER with an ear infection or a broken arm, we offer you a flu vaccine. In fact, we also immunize parents at the hospital and will immunize siblings of admitted inpatients. But at the same time, we also need an increasing number of vaccine options and capacity. Adjuvanted vaccines may play an increasing role in the future [the US did not have to deal with the narcolepsy challenge - Ed.].”

**TAKE HOME MESSAGES**

- A recommendation to provide influenza immunization to all children can be implemented.
- Influenza immunization prevents severe complications from flu.
- Influenza immunization prevents death from flu.
- Risk-based strategies can be challenging to operationalize and will fail to prevent considerable morbidity.
- Sharing of data and best strategy practices is crucial.
Influenza in children: burning topics

IF INDEED CHILDREN SHOULD BE ROUTINELY VACCINATED AGAINST INFLUENZA HOW THEN CAN WE TACKLE THE OBSTACLES TO THE IMPLEMENTATION OF VACCINATION RECOMMENDATIONS? THE AUDIENCE DEBATE TOOK THINGS FURTHER AND COLLECTED SUPPLEMENTARY QUESTIONS, ANSWERS AND REMARKS.

In Europe, few countries recommend universal influenza vaccination for children, for various reasons. How do we resolve the grey areas on the European map? What are the starting points for moving forward? Would a European scaled vaccination effectiveness study among children be of any help?

“That would be a nice idea, in particular bearing in mind that there is an established mechanism of conducting such studies in Europe”, Dr. Jolita Mereckiene (Ireland) said. “However only few countries recommend the vaccine for healthy children and with the small proportion of children being vaccinated, it would be not easy to collect data and to achieve a big enough sample size in order to get reliable vaccine effectiveness results.”

“I wonder why we can’t initiate European scaled studies focusing on very frequent diseases”, added Dr. Catherine Weil Olivier, Honorary professor of Paediatrics (France) to the debate. “In Europe, we have an annual birth cohort of 5 million kids. Among them 10% will be at risk. This includes in large part respiratory disease, mainly asthma. Why not try to have a cohort of children with an underlying condition versus a control group of healthy children, and try to understand the effectiveness of the vaccine, preventing e.g. recurring asthma? I’m quite sure it is feasible.”

“Indeed, the way to move forward is to focus on specific risk groups where a recommendation is already in place”, Prof. Ronald de Groot said. “And we can surely find support from patient organizations to start vaccinating. We can use that as a starting point to move forward.” Ronald de Groot also remarked that local health care culture and quality will influence data, making it difficult to compare numbers and studies. “In the Netherlands”, he said, “GPs don’t want to see influenza related cases. They basically tell them to stay at home, take an aspirin and sit it out. And only when things go really wrong will they visit the patient. So Dutch data on GP visits underestimates the real burden.”

“After the pandemic, all institutions received a recommendation to declare hospitalizations due to influenza”, said Dr. Raúl Ortiz de Lejarazu, Director of the Spanish National Influenza Center. “It would be very interesting to see how many of the hospitalized infants are vaccinated. It’s a primitive approach, but it’s at least an approach. I would like to see this data.”

Dr. Richard Pebody (United Kingdom) suggested the I-Move network, a
Parents still need to be convinced of the benefits of vaccination for their child. How do we get parents to comply with any vaccination recommendation? Can patient organizations play a decisive role?

Elena Moya represented COMO, the Confederation of Meningitis Organizations, a global pro-vaccination patient group, fighting against meningitis but also against any viral or bacteriological disease. "When wanting to reach out to patients, patient groups are the number one ally", she said. "In the UK, patient organizations have been a tool to reach patients. We sail on the same boat, experts, health authorities and patient voices alike. We all want to reach the same shore, which is better health and healthy kids. We all want to prevent terrible diseases." Elena Moya also made an appeal for an alliance to fight anti-vaccine groups. "They are powerful and the media love them, I don't know why", she said. "Anti-vaccine activists proclaim things like 'vaccination is related to autism'. In 2017! We need to be united to fight against this anti-vaccine populism, because it causes a lot of damage."

"What I've learned from the meningitis foundation in the UK is that you have done a fantastic job", Prof. Ronald de Groot answered. "One to support the professionals with their research and two by pushing the agenda on vaccination. There should be an independent forum of parents of children who were affected by severe influenza related illness or mortality. Such a forum would represent a powerful voice towards politicians and the public. We could work together, professionals and affected parents alike on a multi-disciplinary level, to move awareness forward. We as paediatricians would like to start such a patient forum, because we feel it would make things easier."

Studies on immunogenicity in children under 9 years of age say two doses are preferable in terms of immunogenicity. The US goes for two doses. The UK opts for one dose. Should we go for effectiveness or for the bigger perspective of the public health benefit?

"In the US, the rationale is immunogenicity among young children", Prof. Kristina Angel Bryant (US) said. "We have reasonable data to say that the vaccine is not so immunogenic in young children. Vaccine effectiveness is somewhere around the order of 50 to 80%. So we want to maximize what we can do to make it effective."

"In the UK, kids with underlying at-risk conditions under nine years and being vaccinated for the first time, are still offered two doses of vaccine, on the premise that we want to maximize individual benefit", Dr. Richard Pebody said. "For the healthy children, we go with a single dose of vaccine, on the premise that a single dose does still provide pretty reasonable protection. The vaccine will go further allowing more children to be vaccinated and obtain the direct benefits of vaccination. There are also the indirect population benefits that we consequently achieve by improving coverage in children." Pebody also highlighted the practical difficulties in delivering two doses of vaccine. "We know that we have to vaccinate a very large number of children in a short space of time. We have about 16,000 primary schools in England. We have to go to all of them in a space of 2 to 3 months. It's a huge logistical challenge."

"I understand that the US is sticking with effectiveness, while the UK goes for public health impact", Dr. Catherine Weil Olivier concluded. "I think that in modern vaccinology, we have to go more and more for the public health impact."

Ab Osterhaus stated that in principle the question arises what the effect would be of giving one vaccination and increasing the number of people you reach compared to giving two vaccinations where the compliance would remain relatively low. It might be better to try to increase the coverage of one vaccination than to go for two vaccinations. On a completely different issue he wondered whether from a public health perspective, you may vaccinate children to (also) protect the elderly. "For me, it’s a non-discussion", he said, "but the question that arises is an ethical one, that also deserves our attention."

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How are US parents persuaded to pay a return visit for their child’s second dose?

“Fortunately, during the first few years of life there are lots of visits to the paediatrician scheduled for health maintenance. You increase uptake by taking opportunities to immunize that are not immunization visits and by immunizing in out of office visits. It’s still a challenge”, Prof. Kristina Angel Bryant answered.

“In Europe, we developed a multivalent vaccine to specifically prevent the need for multiple vaccination in a single session, while in the US it is apparently accepted to administer even three to four shots in a single session”, Prof. Ronald de Groot said. “This again brings major cultural differences to our attention. I fear that a move to multiple shots per session would decrease the overall uptake percentage. The risk to cannibalize on uptake is even present in the two shots option.”

With what message could we reach those that need to be convinced?

Dr. Renata Menezes brought the Brazilian experience to the table. “Brazil’s vaccination policy is very effective”, she said. “Brazil opts for the two doses. Since 2014 the goal has been to reach an 80% plus uptake for the two dose vaccination, and we have achieved this goal. Our government is closely involved in the vaccination programme. And also the media go strong on the subject. I remember the friendly vaccination campaign from my own childhood, using the image of a little drop with a happy face. On every corner, in every street, in every park, in every school, brochures were distributed. And in the media, the little happy droplet was omnipresent. This happy face managed to raise uptake a lot in Brazil. Part of the current Brazilian campaign is about how the disease can affect children, the elderly and how the vaccine can shield against complications. When people are well aware of the symptoms and the risks involved, it can really make a difference.”

“Many European countries have tried friendly campaigns”, Prof. Ab Osterhaus said. “But public opinion at large still has a wrong idea about what influenza could cause in children. In the media influenza is often portrayed as a very mild disease.” In the US, it is more common to build on particular stories, for example the death of a child with a name, a face and a family. “This personalization of the flu burden, this kind of storytelling, is something we in Europe usually don’t practice”, Ab Osterhaus said. “We never show a picture of a child flu victim. We never show a child that died from the disease. We would be maligned. We need to be aware of the social cultural context playing in the background.”

Healthcare workers also need to be persuaded to advocate influenza vaccination of children. How can GPs be convinced?

According to Dr. Ted van Essen, GP (Netherlands) there are two problems. “The first is a leadership problem”, he said. “Vaccinating children against influenza should be on the main European agenda. It is also about the leadership within our countries and professional organizations. A European standpoint on vaccination would really help epidemiologists, paediatricians, general practitioners and all those further involved, as a starting point to build upon. And that is where we have to aspire to.” The other is a communication problem. “The talk about vaccine effectiveness is a very tough one. So we have to focus on the burden of disease. We should also explain that with such a high burden of disease, even lower vaccine effectiveness is not that bad. In the old days, we just could tell the patient to get vaccinated. But nowadays, the patient expects to be informed and wants to be convinced.”
Summary

Despite WHO’s recommendations to routinely vaccinate young children against influenza, only very few EU Member States have actually included this target group in their influenza vaccination programmes. Yet, data clearly demonstrate that influenza, especially in young children, is not an innocent disease.

There is not a single answer for Europe, but a first step to better protect children against influenza would be to inspire more European countries to implement a recommendation for childhood flu vaccination, knowing that a recommendation in itself will not suffice. We also have to work on awareness, bottom-up, from patient organizations, parent organisations, to nurses, GP’s and paediatricians. To do so, national stakeholders must identify and select the most apt approach for each individual country. Bottom-up strategies are indeed called for here, because only in that way we can incorporate local sensibilities and understand all stakeholders’ preoccupations. Hence, there is an urgent need to develop the evidence base for all individual countries, in order to assess the burden, highlight the importance of childhood influenza policies and make more informed decisions possible.

The protection from an influenza vaccination programme aimed at children goes far beyond the individual child. Vaccination prevents influenza in the pediatric age group and can significantly reduce the transmission to the population at large. To achieve enhanced protection against influenza, there is a diversity of vaccines available, either trivalent or quadrivalent. Their safety is not an issue. Efficacy and eventually effectiveness could be better, but the level achieved is acceptable. The overall data on effectiveness and efficacy are quite good.