BRINGING

CHILDHOOD FLU VACCINATION
TO THE NEXT LEVEL

Report and roadmap to actions

European Scientific Working group on Influenza
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Introduction

In the US, the Centers for Disease Control and Prevention (CDC) and the American Academy of Paediatrics (AAP) recommend a seasonal flu vaccine for every child aged 6 months and older. But in Europe the situation is quite different, with different policies in different countries.

This diversity 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.

On 28 September 2018, ESWI brought together some 60 influenza stakeholders for a day of presentations and debates on paediatric influenza vaccination. The aim of the meeting was to bring childhood influenza vaccination to the next level and to that end ESWI organized a stakeholders table for partner organizations, combined with a number of scientific contributions, Q&A and debate. The event was available via live stream video, reaching 590 viewers worldwide, many of whom weighed in on the discussions via Twitter and e-mail.

This magazine provides a report of the lectures and the discussions held at the Summit and, of course, provides an account of how the discussions can be converted into a concrete action plan.

All texts can be copied and distributed freely.
THE PEDIATRIC FLU COMMUNITY: getting acquainted

EUROPEAN SCIENTIFIC WORKING GROUP ON INFLUENZA (ESWI)

Ted van Essen, Secretary

ESWI is a partnership of scientific experts and organizations of public health officials, healthcare professionals, at-risk patients and the elderly. The aim of the group is to reduce the number of influenza victims in Europe and to that end, it focuses on stakeholder communication to raise awareness and cooperation in the fight against influenza.

To realize its objective, ESWI has established long-term structural partnerships with influenza stakeholder organizations:
The question whether or not to vaccinate healthy children and adolescents against influenza had long divided the scientific community. To help answer the question and reach a scientific consensus, ESWI joined forces with the European Society for Paediatric Infectious Diseases (ESPID) to organize a multitude of symposia and meetings as well as reports, articles and videotaped lectures on this topic:

**INFLUENZA VACCINATION OF CHILDREN: SENSE OR NONSENSE?**
JOINT ESWI/ESPID SYMPOSIUM AT THE 5TH ESWI INFLUENZA CONFERENCE
(15 SEPT 2014 IN RIGA)

**INFLUENZA VACCINATION OF CHILDREN: A CRITICAL APPRAISAL**
JOINT ESWI/ESPID SYMPOSIUM AT THE 34TH ESPID ANNUAL MEETING
(14 MAY 2015 IN LEIPZIG)

The meeting report has been published as a scientific paper

**INFLUENZA PREVENTING POLICIES FOR CHILDREN**
SCIENTIFIC SYMPOSIUM
(14 JUNE 2017 IN LEUVEN)

The easy-to-grasp report of this scientific symposium is available on the ESWI portal website:

Symposium lectures have been videorecorded. All recordings are available on ESWI TV at
http://eswi.org/eswi-tv/

**SHOULD CHILDREN BE VACCINATED AGAINST INFLUENZA?**
JOINT ESWI/ESPID SYMPOSIUM AT THE 6TH ESWI INFLUENZA CONFERENCE
(10 SEPT 2017 IN RIGA)

Symposium lectures have been videorecorded. All recordings are available on ESWI TV at
http://eswi.org/eswi-tv/

**CHILDHOOD IMMUNISATION AGAINST INFLUENZA - WHAT ARE THE OPTIONS?**
JOINT ESWI/ESPID SYMPOSIUM AT THE 36TH ESPID ANNUAL MEETING
(30 MAY 2018 IN MALMO)

The lectures of the Childhood Influenza Vaccination Summit on 28 September 2018 are available on ESWI TV too:
http://eswi.org/eswi-tv/category/eswisummit18/

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**EUROPEAN PUBLIC HEALTH ALLIANCE (EPHA)**

Sascha Marschang,
Interim Secretary General

The European Public Health Alliance is the largest European organization representing the public health community with over 90 member organizations, including disease specific organizations as well as health professionals and organizations of the elderly and patients. ESWI has been a member of EPHA since 2011.

EPHA takes a public health angle to vaccination as it works to obtain universal access to health care for all and to reduce inequalities. To achieve this, it advocates for more citizen involvement and transparency in political public health decision-making at the EU level.

Current influenza vaccination issues, according to EPHA:
- Underestimation of the burden of seasonal flu
- Risk group targets are not reached in vast majority of EU member states
- Access to vaccination is often only via GP/treating physician
- Low health literacy
- Lack of alignment at national, European and international level
- No life-course approach to vaccination
- Lacking data, fragmented research
- Different definitions of risk groups and different priorities

EPHA is willing to help improve awareness of the influenza burden of disease data in the public health community. The group will call upon the influenza experts of ESWI to address these issues in their communication with relevant member organizations.
The European Confederation of Primary Care Paediatricians (EPCP) is a group of over 25,000 primary care paediatricians from 17 European countries, organized in 20 national societies. Primary care paediatricians are the initial contact persons for all undifferentiated unselected concerns of children, adolescents and their families, and to support their work the EPCP publishes position statements, research papers and curricula, including the recent statement on how to deal with vaccination hesitancy in primary care, a 10 points tool for primary care paediatricians:

- Paediatricians and their associations should support laws and regulations for more mandatory vaccinations
- Be responsible. Some providers convey doubts and increase patients’ uncertainties, despite scientific evidence
- Participate in campaigns and local health fairs in the community
- Use every contact to check immunization status. Be aware that missed opportunities contribute to low vaccination coverage rates.
- Take your time to listen carefully to concerns and fears of parents and adolescents
- Clarify the role of false contra-indications for vaccinations
- Do not discontinue patient care in case of vaccine refusal
- Put the role of media and the internet (anti-vaxxers) in the correct perspective
- Provide reliable sources of information
- Use vaccine coverage rates to analyze the success of campaigns and other efforts to increase the coverage.

The European Academy of Paediatrics (EAP) is part of the European Union of Medical Specialists (EUMS) and advocates the interests of children in the EU institutions in Brussels, as well as improving standards in training, service and research of paediatricians. To strengthen its voice, EAP aims to merge the paediatric forces of EAP with the European Paediatrics Association (EPA) and EPCP.

The EAP Vaccination Working Group closely collaborates with the early career paediatricians assembled in Young EAP to educate and inform paediatricians about vaccines and vaccination through weblogs, position statements and scientific publications.

Via paediatric practices, EAP conducted a survey on vaccine confidence with parents. With more than 6,000 respondents from 18 countries, the results of the survey are currently being evaluated. It is clear, however, that influenza issues should be included in future surveys.

Young EAP successfully uses social media to disseminate science-based information about vaccines as well as to counter hoaxes and anti-vaccination statements.

The EAP Vaccination Working Group strongly believes in collaborative efforts with other interest groups to achieve its objectives. Some examples:

- Methods for assessment of Vaccination Coverage (WHO, ECDC, Ministries of Health)
- Influenza Vaccination Coverage in Children (ESWI, ECDC)
- Vaccination of Migrant Children in Europe (ADVAC, ECDC, ESPID, WHO)
- Vaccine shortages (Vaccines Europe...)
- ADVANCE Project (Erasmus University, IMI/EU, ECDC)
- Vaccination Hesitancy (EAPRASnet – Parent Survey / LSHTM, AAP)
- Electronic Vaccination Record (ECDC...
PHARMACEUTICAL GROUP OF THE EUROPEAN UNION (PGEU)

Jan De Belie, Professional Affairs Advisor

The Pharmaceutical Group of the European Union represents community pharmacists at the European level, grouping the national professional bodies and pharmacists’ associations of 32 countries.

Community pharmacists play an important role in vaccination as they can help to raise awareness, via campaigns and personal contacts, and lower the threshold for getting vaccinated. Pharmacists offer easy accessibility and have plenty of opportunities to provide evidence-based, unbiased and balanced information, complementing the information patients may already have received from their GP or paediatrician. The pharmacy also offers an access point in rural areas where there might be not a lot of other facilities. There is also an increasing trend of pharmacists providing vaccines and immunization as in a number of countries, pharmacists indeed already provide flu vaccination services, complementing the role of GPs, reaching people that have never been vaccinated before.

EUROPEAN SOCIETY FOR PEDIATRIC INFECTIOUS DISEASES (ESPID)

Hanna Nohynek, ESPID Board Member

The European Society for Paediatric Infectious Diseases unites individual paediatricians from all European countries to promote science and research, education and public health in the field of paediatric infectious diseases.

Influenza is high on the agenda of the ESPID annual congresses, with several talks dedicated to the disease, and symposia jointly organized by ESPID and ESWI. Since these joint symposia reach out to the professional community of paediatricians, the meetings complement the ESWI Summits which are targeting all stakeholder organizations involved in childhood immunization.

ESPID experts are involved in the Advanced Vaccinology Course (ADVAC) as lecturers, while ESPID also provides scholarships to young paediatricians to learn more about immunology and vaccines.

ESPID recently has launched its brand new Vaccine Handbook App, a practical guide for clinicians, drawing together the latest vaccine science and guidance into a concise, user-friendly, electronic resource.
Setting the scene

- Why is flu an important disease in children? An introduction
  TERHO HEIKKINEN, University of Turku, Finland

- The burden of paediatric influenza in the US: mortality, hospitalizations, outpatients visits and other outcome
  PATSY STINCHFIELD, Advisory Committee on Immunization Practices

- Efficacy of vaccination in children: overview of available vaccines, recommendations and impact of vaccination
  AB OSTERHAUS, ESWI chair
Why is flu an important disease in children?  
An introduction

Annually, 5-10% of adults and 20-30% of children develop symptomatic influenza, with severe disease in 3-5 million individuals and up to 500,000 deaths. Globally, up to more than 100,000 children under five die of influenza. Influenza attack rates vary per age group and are consistently higher in children, with a four- to five-fold difference between children and adults. Influenza in children often leads to complications, with otitis media by far the most frequently observed. About 40% of children under three develop otitis media following influenza, often requiring antibiotics treatment. The incidence of influenza-related hospitalization is highest among the youngest children, especially under 6 months (Fig.).

It is important to note that the vast majority of the burden of influenza in children is in the out-patient setting where viral diagnosis is usually not performed. Shedding of influenza virus is longer and reach higher titers in the younger age groups than in adults.

“There is a consensus that children are the main disseminators of influenza in the community.”

WHO recommends seasonal influenza vaccination in children of 6 months to 5 years of age, yet in Europe, the decision is left to each Member State. Only a handful of EU countries currently includes influenza vaccination in the official childhood vaccination program and even fewer have actually implemented it. Influenza vaccination provides two types of benefits: not only vaccination benefits to children against complications and severe illness but also offers protection against influenza in other age-groups, in particular vulnerable age groups, due to reduced transmission from children.

“There is ample evidence on the large burden seasonal influenza imposes on young children and on the benefits of vaccination for children and other age groups. Every country needs to evaluate influenza vaccination in children based on such evidence, as well as on local cost-effectiveness analyses.

Terho Heikkinen  
Turku University, Finland
The burden of paediatric influenza in the US: mortality, hospitalizations, outpatient visits and other outcomes

In the US, flu vaccine policy was initiated in the 1960s, when the US Surgeon General recommended flu vaccination for individuals aged 65 and over, individuals with chronic illness and pregnant women. It was not until in the 2000’s that ACIP added other risk groups for recommended influenza vaccination, including infants 6-23 months, healthcare professionals and older children. Since 2010, ACIP recommends universal flu vaccination for everyone 6 months of age and over, to avoid limiting vaccination to risk groups and age groups.

Evidence that flu vaccine reduces risk of severe illness, ICU admission and death in children and adults has lately much increased.* One of the major limiting factors to influenza vaccine effectiveness currently remains low vaccination coverage, even in children, which has never broken 70% in the US. In one large Midwest US children’s hospital 3 season retrospective study, severe influenza was typically observed in children who were home sick longer before seeking medical care, in children with underlying chronic conditions, and importantly, in children who had more than one missed opportunity to get vaccinated when in health care settings.+

Monitoring laboratory-confirmed pathogens can help make burden predictions for hospital admissions. Evaluating the situation in Australia can also be relatively predictive of the upcoming influenza season in the US and Europe. Yet, flu seasons are never alike in terms of epidemiology, severity and timing.

“If you have seen one flu season, you have seen one flu season.”

Because of the range of severity of influenza illness, many people think of it as ‘just the flu’. However, there are many families who have lost children to influenza, and for them it’s not “just the flu”.

*Pediatric patients who were fully vaccinated were 74% less likely to be admitted to an intensive care unit for influenza-related illness. Ferdinand, Jill, Belongia, Ed, Pediatrics 2013

*Flu Vaccine reduced risk of flu-associated deaths by 51% in children with chronic conditions and by 65% in healthy kids. 2017 CDC study

*In adults, flu vaccine reduced severity, hospitalizations, ICU admission August, 2018 CDC study

Efficacy and safety of seasonal influenza vaccines in children

Currently, individual countries define their own recommendations and risk groups for influenza vaccination. Available vaccines include tri- and quadrivalent inactivated vaccines and live attenuated vaccines. Of note, the latter are contraindicated for children with immune compromising conditions.

By 6 years of age, all children have had influenza at least once. Before that, children may be immunologically naïve to influenza. Influenza-related complications and hospitalization are major issues in children, especially in the youngest age groups. Influenza-related mortality may further be underdiagnosed.

Influenza vaccination offers the best defence against these.

Challenges faced by influenza vaccination include influenza A antigenic drift, requiring vaccine strain adaptation twice a year, and the circulation of two influenza B lineages. Before quadrivalent vaccines, the choice of the vaccine B lineage was made haphazardly, often resulting in no or limiting match with the circulating B virus. Pre-existing antibody titers against influenza B strains determines cross-protection upon mismatch. Because of limited pre-existing immunity in children, the youngest age groups can particularly benefit from quadrivalent vaccines.

“The inactivated influenza vaccines are amongst the safest vaccines that we know.”

Recent randomized controlled clinical trials on quadrivalent influenza inactivated vaccines in large number of young children aged 6-35 months across several influenza seasons and countries demonstrate their high safety and efficacy profiles. These landmark studies performed by GSK and Sanofi-Pasteur showed no difference in local and general adverse reactions between the comparator or placebo and the vaccines. In both studies, vaccine efficacy in reducing laboratory-confirmed influenza reached between 50 and 75%, with higher level of protection in case of matching strain and severe influenza. Additional exploratory endpoints further demonstrated significant reduction in antibiotics usage, GP visits, ER visits and hospitalization.

Fig. QIV vaccine efficacy against moderate-to-severe and any influenza (Claeys et al. The Lancet Child & Adolescent Health 2018)
From theory to practice

- **FINLAND**: Cost-effectiveness of influenza vaccination in healthy children
  HANNA NOHYNEk, National Institute for Health and Welfare, Finland

- **UK**: Latest developments in the roll-out of the childhood flu program in the UK
  RICHARD PEBODY, Public Health England
Influenza vaccine cost effectiveness in children in Finland

Finland performs cost effectiveness studies since 2000 in order to base the national vaccination program on evidence of sufficient reduction of a significant public health disease burden, of vaccine safety and of acceptable balance between health benefits and economic costs.

Cost-effectiveness analyses of Finnish cohort and register data suggest that the influenza vaccine would not only be cost-effective but even cost-saving in individuals under 13 years of age (Fig.). These results are based on a static model assessing annual savings per vaccinated child and total annual savings from a health-care and societal perspectives. Sensitivity analyses demonstrated the robustness of the model. Note that the indirect impact of influenza vaccination of children on other age groups (through reduced transmission) was not included in this model.

“Cost effectiveness analysis is a useful tool to justify health interventions on a population level.”

Influenza vaccine coverage in children in Finland was around 40% pre-pandemic and dropped below 20% post-pandemic because of the issue of narcolepsy associated with the pandemic vaccine. The introduction of a live attenuated vaccine brought coverage back to close to 40% in recent years. In 2018, cost effectiveness informed the program, which has been extended to children below 7 years of age. Based on the national register data of hospitalization discharge, laboratory data and laboratory-confirmed out-patient data, vaccine effectiveness ranged from 40 to 50%.

Given differences observed in vaccine effectiveness, brand-specific vaccine effectiveness needs to be assessed, which is being addressed by the IMI DRIVE consortium. Vaccine effectiveness estimation can be assessed in real-time based on health records and registers, and needs to be refined in light of propensity, health status, previous vaccination history, and circulating strains. A hospital-based vaccine effectiveness surveillance in children has been established, also aiming at improving our understanding of the reasons to accept or refuse vaccination.

“Register data can be used both for programme monitoring and development, as well as guiding decision making, and informing society at large.”

Fig. Annual savings per vaccinated child and total annual savings from the health care provider and the societal perspective in cumulative cohorts of children in the vaccination program (Salo et al. Vaccine 2006)
Latest developments in the roll-out of the childhood flu program in the UK

The projected direct and indirect impact of the introduction of paediatric influenza vaccination showed high cost effectiveness in the UK, leading to the UK childhood flu program. The roll-out of flu vaccination for healthy children 2 to 16 years of age with the newly licensed intranasally administered live attenuated influenza vaccine (LAIV) was started in the 2013-2014 season. It was initially targeted at children of 2-3 years of age and later extended to older age groups. In parallel healthy school age children in geographically-discrete pilot areas were offered LAIV to assess the optimal mechanisms of delivery of the vaccine program for this group.

“The UK has had a longstanding influenza vaccine program, targeted traditionally at individuals at high risk of developing severe disease. Despite these programs, there remains evidence of significant residual disease burden in these populations.”

The program lately achieved uptake levels above 40% in pre-school age children and approximately 60% in primary school age children. It identified schools as the optimal delivery route for school age children. Although the USA reported poor LAIV effectiveness during the 2015-2016 season, LAIV effectiveness in the UK was reportedly good, reaching close to 60% against all strains, approximately 40% against influenza A H1N1pdm09 and 80% against influenza B. Likewise, LAIV effectiveness was almost 60 and 80% against influenza A H3N2 and B, respectively, during the 2016-2017 season in the UK. A change of the influenza A H1N1pdm09 strain in the 2017-2018 vaccine appears to have improved LAIV effectiveness against H1N1pdm09.

The population impact of the program was assessed during the 2014-2015 and 2015-2016 seasons. Consistent decreases in disease incidence and influenza positivity in primary and secondary care were observed in school age pilot areas in both targeted and non-targeted age groups compared to control areas (Fig.). The introduction of the childhood LAIV program has proved highly successful and will continue to be rolled-out in the coming seasons.

“It is important to have strong on-going surveillance of paediatric programs to evaluate their performance.”

Richard Pebody
Public Health England, UK
Bringing childhood vaccination to the next level
NEED
Provide convenient and low-threshold access to influenza vaccines

POSSIBLE SOLUTIONS AND ACTIONS
Pharmacists can offer additional access to vaccination. Data show that when pharmacies are involved in vaccination, general vaccination rates go up as pharmacies complement the work of GPs. After all, many people who do not regularly visit the hospital or a GP, can be reached via community pharmacists. Pharmacies can even play a role in paediatric vaccination proper, if they are given access to shared electronic health records.

All physicians should be allowed to vaccinate. In many countries, including Austria, paediatricians are not allowed to vaccinate adults. It is hence impossible to vaccinate parent and child during the same consultation.

NEED
Increase vaccine confidence and counter parental doubts on the safety and effectiveness of influenza vaccines

POSSIBLE SOLUTIONS AND ACTIONS
Provide a consistent flow of information through all levels of healthcare, both primary and secondary care. National and international organizations of professionals and patients need to inform their members with the latest statistics and evidence before the start of the influenza season. This evidence needs to be compiled in a collaborative, multidisciplinary approach to create consistent information. At the same time, communication must be transparent and also mention the unknowns, as was demonstrated from the narcolepsy tragedy in Finland. (Although influenza vaccines are among the safest of vaccines, in the aftermath of the 2009 pandemic, health experts were 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. It is still not clear whether the disease was caused by the vaccine or the influenza virus.)

Involve “behavioural economics”, a new emerging field that studies the economical impact of patients’ behaviour. The Finnish Institute for Health and Welfare (THL) has engaged an anthropologist to truly understand the nature of hesitancy in a cross-professional approach.

NEED
Strengthen the role of healthcare workers in influenza vaccination

POSSIBLE SOLUTIONS AND ACTIONS
Provide health care workers (and especially GPs) with incentives to vaccinate the at-risk groups against influenza.

Improve basic education and training of paediatricians and other health care workers in terms of vaccinology, microbiology and immunology. Still, not all paediatricians are aware of the benefits of flu vaccination, and recent developments (LAI, H3N2 egg adaptation, wrong B in TIV, adjuvanted vaccines) add to the confusion. The influenza community hence must continue to join forces and provide science-based evidence and information to paediatricians in symposia and via publications. After all, studies show that if healthcare workers recommend the influenza vaccine to their patients, patients are twice as likely to have the vaccine. In addition, nearly 50% of the vaccination coverage can be attributed to the personal recommendation by a healthcare professional.
Foster the debate on “mandatory vaccination” of paediatricians and health care workers. Summit participants strongly agree that vaccination of healthcare workers is key to protect patients against influenza and unvaccinated caregivers should not be allowed to care for frail patients. Now is the time to assess the pros & cons of compulsory vaccination versus negotiated vaccination and to issue a joint standpoint, supported by all stakeholder organizations.

**NEED**
Assess and highlight the indirect impact of influenza in children

**POSSIBLE SOLUTIONS AND ACTIONS**
Adopt a more “holistic view” and make better use of the secondary data (health records) to better understand the role of children as transmitters of influenza and their impact on the health status of other parts of the population, notably on the older adults.

Introduce life-long vaccination, i.e. vaccination schemes for different phases of life, from young infants to the very old adults.

**NEED**
Convince national governments to install influenza immunization programmes for children

**POSSIBLE SOLUTIONS AND ACTIONS**
Patient organizations need to play an active role and help determine national health policy. Since organizations of influenza patients are non-existent, other interest groups need to step in, as demonstrated by an example from the Netherlands, where the national union of the elderly was alarmed by the fact that it had lost 10,000 members to the flu.

Cost-effectiveness studies in Finland and the UK have demonstrated that influenza immunisation of children in these countries provides both health benefits and economic benefits. Obviously, cost-effectiveness is dependent on how national health care systems are organized, studies must hence be set up in individual countries to assess the potential benefits. In this context, ECDC is developing a system and tool box to assist national governments in performing cost-effectiveness studies.
JOINT ESWI/ESPID SYMPOSIUM AT THE 37TH ESPID ANNUAL MEETING
6-11 MAY 2019, LJUBLJANA
ESWI and ESPID will translate science towards paediatricians, focusing on current issues and explaining some of the most recent confusing developments.

TOWARDS INFLUENZA VACCINATION PROGRAMMES FOR HEALTH CARE PROFESSIONALS
13 SEPTEMBER 2019, BRUSSELS
ESWI Science Policy Flu Summit,