Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Scoping Report

Universal influenza vaccination in children

30 June 2020

Safer Better Care

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Key points

The purpose of this scoping report is to provide a preliminary assessment of the currently available evidence for universal influenza vaccination of children in order to inform consideration by the Minister for Health of its inclusion in the national immunisation schedule.

The Health Information and Quality Authority (HIQA) agreed to undertake this scoping report following a formal request from the Head of the Health Protection Unit in the Department of Health.

The key findings of this scoping report are:

- Seasonal influenza is associated with a significant burden of illness, antibiotic consumption and health resource use in children. Vaccination is the most effective strategy to reduce influenza-associated morbidity, mortality and virus spread.
- A range of seasonal influenza vaccines are licensed and available for use in the European Union (EU). These include inactivated influenza vaccines (IIV), some of which are approved for children from the age of six months, and the live attenuated influenza vaccine (LAIV) which is recommended for children from 24 months of age.
- Universal vaccination of children for seasonal influenza has not to date been listed on the Irish primary childhood immunisation schedule or as part of the school vaccination programme. The national immunisation guidelines for influenza (updated October 2019), strongly recommend annual vaccination with the quadrivalent inactivated influenza vaccine (IIV4) of children aged six months and older in specific clinical risk groups who may be at increased risk of influenza-related complications. Vaccination is also recommended for household contacts of individuals at high risk of influenza complications.
- Universal paediatric influenza vaccination programmes are currently offered in Finland and the United Kingdom.
- A 2018 systematic review found that in children years, LAIV and IIV reduce the proportion of children who have influenza and influenza-like illness (ILI) compared with no vaccination or placebo.
- Influenza vaccines have been shown to be safe and are well-tolerated in children, including those with moderate to severe asthma. However, vaccination can be associated with rare serious adverse events.
- Most of the clinical and economic burden prevented by universal childhood influenza vaccination is not limited to the vaccinated population. Vaccination of

children affords indirect protection to others including household members and older populations against influenza-related morbidity and mortality.

- Cost-effectiveness analyses from the UK and The Netherlands indicate that paediatric influenza vaccination is likely to be cost-effective. Indirect protection, arising from herd immunity, may make a significant contribution to the cost-effectiveness of vaccination. Cost-effectiveness is also highly dependent on vaccine uptake.
- The potential budget impact associated with the introduction of the programme is likely to be substantial.
- In the context of COVID-19, international public health agencies have advised that expanding coverage of the seasonal influenza vaccine is one of the most effective strategies to reduce pressure on the health and social care system in the 2020 to 2021 influenza season. Specifically, influenza vaccination will minimise the risk of co-infection with influenza viruses and SARS-CoV-2.
- Current indications for SARS-CoV-2 testing include onset of a number of symptoms common to both COVID-19 and influenza, thus individuals with influenza are likely to present for SARS-CoV-2 testing. A reduction in incidence of influenza would likely reduce the demand for SARS-CoV-2 testing and the associated requirement for restricted movement pending test results.
- On 18 May 2020, the Minister for Health announced that influenza vaccination would be provided for all children aged between 2 and 12 years from the 2020 to 2021 influenza season onwards.

List of abbreviations used in this report

aVE	Adjusted vaccine effectiveness
CDC	Centres for Disease control and Prevention
COVID-19	Coronavirus disease 2019
DDD	Defined daily dose
ECDC	European Centre for Disease Prevention and Control
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IIV	Inactivated influenza vaccine
IIV3	Trivalent inactivated influenza vaccine
IIV4	Quadrivalent inactivated influenza vaccine
ILI	Influenza-like illness
LAIV	Live attenuated influenza vaccine
LRTI	Lower respiratory tract infection
PCR	Polymerase chain reaction
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RTI	Respiratory tract infection
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
WHO	World Health Organization

Purpose

The purpose of this report is to provide a preliminary assessment of the currently available evidence (including ongoing research) for universal influenza vaccination of children in order to inform consideration by the Minister for Health of its inclusion in the national immunisation schedule.

1. Introduction

A request in relation to a potential health technology assessment (HTA) of a universal influenza vaccination programme for children in Ireland was received from the Head of the Health Protection Unit in the Department of Health.

This scoping report represents an extensive (but not exhaustive) assessment of the available evidence in relation to universal influenza vaccination in children. An expert review of the draft report was provided by the Chair of the National Immunisation Advisory Committee prior to finalisation.

1.1. Description

Seasonal influenza A and B viruses circulate and cause disease in humans every year and, in temperate climates, winter epidemics occur yearly. While influenza affects people of all age groups, the illness is more severe in the elderly, in children less than four years of age and those with chronic disease or immunosuppressive conditions.[1] It is estimated that 20-30% of children are infected with influenza A or B viruses each year.[2] This translates into significant illness and healthcare resource use. Laboratory-confirmed influenza accounts for a considerable proportion of hospitalisations (0.3%-20%), medical visits (1.7-2.8 visits per case) and antibiotic prescriptions (7%-55%) in children. Young children are reported to have the highest rates of healthcare utilisation.[3]

Influenza immunisation is the best available strategy to reduce influenza-associated morbidity, mortality and virus spread. To facilitate strain-specific vaccination, the World Health Organization (WHO) issues recommendations to vaccine manufacturers regarding vaccine strain inclusion.[4] These are based on predictions of the likely circulating strains which have been informed by analysis and interpretation of global surveillance data.[4, 5] Recommendations are issued for the composition of both trivalent (two A strains and one B strain) and quadrivalent (two A strains and two B strains) vaccines and include specific viral subtyping for influenza A.[5]

A range of seasonal influenza vaccines including inactivated influenza vaccines and live attenuated influenza vaccines (LAIVs) are licensed and available for use in the

EU.[6] Licensed vaccines available in Ireland for the immunisation of children include the quadrivalent (IIV4) and trivalent (IIV3) inactivated influenza vaccines (approved for children from six months of age) and live attenuated influenza vaccines (LAIVs) (approved for children and adolescents from 24 months to less than 18 years of age).[1] All currently available LAIVs are quadrivalent vaccines containing two influenza A strains (H1N1 and H3N2 subtypes) and two influenza B strains (Victoria and Yamagata lineages) in line with WHO recommendations.[6]

The WHO recommends vaccinating children aged 6-59 months against influenza.[7] Universal influenza vaccination of children is available in a number of European countries, specifically Finland (six months to six years) and the UK.[8, 9] A phased universal childhood programme commenced in the UK programme in 2013/2014 for children aged two to three years. For the 2020/2021 season, vaccination will be available for children age two to 10 years, with roll-out ultimately to all children aged two to 16 years. The programme is school-based for older children; vaccination for those aged two to four years is delivered through primary care. LAIV is used in the UK programme for a number of reasons as summarised from the Joint Committee on Vaccination and Immunisation report in 2012 that led to its incorporation in the UK programme:[10]

- LAIV is more effective than IIV in children aged 6-17 years as well as in younger children and may offer protection against drifted strains.
- LAIV has a good safety profile in children aged >2 years and has an established history of use in the US.
- LAIV is comprised of whole virus, so it may offer important longer-term immunological advantages to children by replicating natural exposure/infection to induce potentially better immune memory to influenza that may not arise from the annual use of inactivated vaccines.
- Attitudinal research suggested that as LAIV is administered by nasal spray, it may be more widely accepted by parents of school-aged children and school-aged children themselves compared with injected influenza vaccine.

The IIV continues to be used for children in high-risk groups for whom the LAIV is contraindicated.

Universal vaccination for seasonal influenza is not currently included in the Irish primary childhood immunisation schedule or as part of the school vaccination programme.[11, 12] The Irish national immunisation guidelines for influenza (updated October 2019) strongly recommend annual influenza vaccination with the IIV for children belonging to specific clinical risk groups who may be at increased risk of influenza-related complications. Vaccination is also recommended to reduce the risk

of transmission for household contacts of adults at high-risk of influenza-related complications.[1]

Influenza vaccination uptake in many European countries remains suboptimal. The increased use of childhood vaccination represents an opportunity to not only reduce the substantial burden of disease in this population, but also to provide indirect protection for those most at risk of serious complications due to the role children play in transmission of the virus.[13] A further suggested benefit of universal influenza vaccination in children is the potential to reduce antibiotic consumption and adverse effects associated with antibiotic resistance. Antibiotic overuse in viral infections is well documented,[14, 15] with evidence also that young children receive by far the most antibiotics for respiratory tract infections (RTIs) at a population-level.[16] As noted, England and Wales began to roll out universal vaccination with LAIV for children aged 2 to 16 years of age in 2013. A modelling study using UK data projected a 5.3% reduction in antibiotic presciptions per 1,000 person years (or 0.8% of the total antibiotic dispensing rate for primary care). Given an ongoing secular trend toward reduced consumption (fall of 2.5% each year in England during the period 2012-2018), the authors suggested that this would not represent a substantial reduction in antibiotic consumption or adverse health outcomes associated with antibiotic resistance. However, they noted that it may improve cost-effectiveness of paediatric LAIV.[17] Assuming a similar percentage reduction could be achieved in Ireland, the absolute reduction is likely to be larger, given higher rates of antibiotic dispensing in primary care (2018: 20.9 daily defined doses (DDD)/1000 inhabitants and per day in Ireland versus 16.3 DDD/1000 inhabitants and per day in the UK).[18]

2. Scope

2.1. Research Question

Table 2.1. Research question outlined in the PICO format

Criteria	Definition
Population	Children <18 years of age with or without underlying medical conditions. Potential subgroups of interest: ▪ Infants (6 months–2 years) ▪ Pre-school children (2–5 years) ▪ Primary school children (5–13 years) ▪ All children (six months–18 years)
Intervention	▪ Live attenuated inactivated influenza vaccines (LAIV) ▪ Inactivated trivalent influenza vaccines (IIV3) ▪ Inactivated quadrivalent influenza vaccines (IIV4) Studies assessing monovalent or bivalent vaccines will be excluded.
Comparator	▪ Eligible comparators are any seasonal influenza vaccine (head-to-head comparisons): – LAIV – IIV3 – IIV4 ▪ Placebo ▪ No vaccination ▪ Other type of vaccine (e.g. rubella, polio, hepatitis b)
Outcomes	**Clinical effectiveness** **Primary outcome** ▪ Laboratory-confirmed influenza (symptoms of influenza with a positive laboratory diagnosis by PCR, virus culture or antigen detection) **Secondary outcomes** ▪ Influenza-associated hospitalisation or pneumonia ▪ Influenza-associated mortality

	▪ Influenza-like illness (ILI) defined using internationally accepted case definitions (e.g. WHO, US CDC, EU)* **Safety – Main outcomes** ▪ Serious adverse events ▪ Systemic adverse events ▪ Local adverse events **Cost-effectiveness** ▪ Any relevant measure of cost or benefit
Study design	Eligible studies will be assessed for suitability with reference to the hierarchy of evidence.

3. Literature search

A search of the literature was conducted on 24 March 2020 in the *PubMed Clinical Queries Tool* in line with HIQA's standard operating procedure for the conduct of scoping reports. The following search terms were used: (Influenza vaccination OR influenza immunisation) AND (children OR paediatric). Results were limited to English-language studies conducted in humans and published since 2010.

The search was supplemented by ad hoc Internet searches, in addition to targeted searches of the websites of HTA agencies and public health bodies.

PROSPERO was also searched to identify any ongoing systematic reviews. Two systematic reviews assessing the clinical effectiveness of seasonal influenza vaccination in children relevant to the research question outlined in Table 2.1 were identified.[19, 20]

4. Potential clinical impact

- In 2018, among children aged less than five years, globally there were an estimated 110 million influenza virus episodes, 10 million influenza-associated acute lower respiratory tract infections (LRTI) cases, 870,000 influenza-associated acute LRTI hospitalisations and up to 34,800 overall influenza-associated acute LRTI deaths.[21]

* WHO definition: An acute respiratory infection with: measured fever of ≥38°C and cough with onset within the last 10 days. US CDC definition: Fever (temperature of 37.8°C or greater) and a cough and, or a sore throat in the absence of a known cause other than influenza. EU definition: Sudden onset of at least one among: fever, feverishness, headache, malaise, myalgia, and at least one among: cough, sore throat, shortness of breath.

- A 2018 systematic literature review and meta-analysis of case-control and cohort studies found that children sustain the highest burden of disease during each seasonal influenza outbreak.[22]

- A 2018 Cochrane review by Jefferson et al. included 41 randomised controlled trials (RCTs) in healthy children (<16 years). LAIV was found to probably reduce the risk of influenza infection in children from 18% to 4% based on moderate certainty evidence, and may reduce ILI by a smaller degree (17% to 12%, based on low-certainty evidence) compared with no vaccination or placebo. Inactivated vaccines were reported to reduce the risk of influenza in children from 30% to 11% (high-certainty evidence), and probably reduce ILI from 28% to 20% (moderate-certainty evidence). Very few RCTs in children less than two years of age were found.[23]

- Based on the findings of a systematic review published in 2012, LAIVs consistently show highest efficacy in young children (aged 6 months to 7 years).[24]

- There is some evidence to suggest that influenza vaccination of children confers indirect protection in some, but not all settings.[25]

- In Finland, IIV3 and LAIV were used in parallel in two year old children for three consecutive influenza seasons: 2015-2016, 2016-2017 and 2018-2019. The register-based cohort studies included >60,000 children for each influenza season. The effectiveness of the vaccines varied across the influenza seasons. LAIV and IIV4 were recommended to replace IIV3 in this population in Finland, due to their greater effectiveness against influenza type B, although neither vaccine demonstrated strong beneficial effects.[26]

- Since 2013, influenza vaccination is recommended for all children from six months of age in Austria; however, it is not linked to government funding or reimbursed by general health insurance. This may have impacted vaccination coverage in Austrian children which is noted to be very low (<5%). Two Austrian databases were queried for influenza-associated hospitalisations during 2002–2016. Reported influenza-associated hospitalisation and mortality demonstrate a high burden of influenza in the Austrian paediatric population corresponding with a low vaccine uptake rate.[27]

- End-of-season 2018 to 2019 UK data for children 2 to 17 years of age provides evidence of overall significant adjusted-vaccine effectiveness (aVE) for LAIV against any laboratory-confirmed influenza infection in primary care (aVE =48.6% (95% CI: −4.4, 74.7).[28] Data from England also provides evidence of overall significant adjusted vaccine effectiveness (aVE) for LAIV and IIV4 against

influenza-associated hospitalisation in children 2-17 years of age in 2018 to 2019 (aVE =63.5% (95% CI: 34.4-79.7) and 2015/2016 (aVE =33.4% (95% CI: 2.3-54.6).[29, 30]

- A 2018 report by Gallagher et al. estimated the impact of introduction of a LAIV vaccination programme on the burden of influenza in primary care in Northern Ireland across seven influenza seasons. Analysis was conducted overall and stratified by age; rates in children under 14 years of age were used to measure direct impact and rates in individuals aged 14 years and over to measure indirect impact. High uptake of vaccination was observed from the programme introduction, with consistent uptake of over 50% in pre-school age groups and over 75% in primary school age groups. Statistically significant reductions were found in GP in-hours consultations and in out-of-hour calls both overall and in the under 14 years group.[31]

- According to the Centre for Disease Control and Prevention (CDC), currently available IIVs are generally well-tolerated by children.[32]

- The 2018 Cochrane review of RCTs by Jefferson et al. noted that adverse events were not well described in available studies. For the LAIV, fever, assessed as a reported increase in temperature was presented as an outcome in most of the RCTs, with large differences among trials. The authors highlighted the requirement for standardised approaches to the definition, ascertainment and reporting of adverse events.[23]

- A 2015 review of the published English-language literature concluded that LAIVs are well tolerated in children. Transient symptoms of rhinorrhea and congestion were noted to be the the most common adverse events with an increased risk of fever noted in younger children (less than 3 years of age). No increased risk of febrile seizures were noted with LAIV. Data for LAIV in children less than two years of age and in those with underlying health conditions were noted to be limited. Local injection site reactions (that is, pain, tenderness, swelling) are very common with IIV; however most are noted to be mild and transient in severity. The review concluded that several influenza vaccines have been shown to be very safe in children; however, it was also noted that influenza vaccines can be associated with rare serious adverse events.[33]

- It has been observed that by the beginning of the 2013 to 2014 influenza season, more than 80 million doses of LAIV had been distributed, mostly in the US, including over 50,000 doses as part of its clinical development programme; the vaccine was generally well-tolerated. While LAIV has not been associated with an increase in hospitalisations, nor higher rates of anaphylaxis, Guillain-

Barré syndrome or encephalitis, it is noted that studies are typically not powered to detect extremely small increases in rare events.[34]

- Post-authorisation safety studies have been undertaken to describe the safety of LAIV in children and adolescents with high-risk underlying conditions, including asthma for which safety data were limited.
    - A population-based prospective cohort study conducted in England investigated safety events in 11,463 children and adolescents (aged 2-17 years) with asthma or other high-risk medical conditions who received LAIV, either as a trivalent or quadrivalent formulation in the 2013–2014 or 2014–2015 influenza seasons, respectively. The risk of hospitalisation after LAIV administration did not vary significantly compared with matched unvaccinated controls in both seasons (that is, with LAIV3 in 2013–2014 and LAIV4 in 2014–2015) and was consistently lower than after IIV administration, within 42 days or in the first six months post vaccination. None of the specific medically attended events of interest (that is, hypersensitivity, seizures and convulsions, vasculitis) that were examined occurred at an increased rate among LAIV recipients.[34]
    - A prospective, multicenter, open-label, phase IV intervention study conducted during the 2016 to 2017 influenza season included children (n=478) with moderate to severe asthma, and preschool children with recurrent wheeze who received LAIV.[35] LAIV was found to be well tolerated in the vast majority of children with asthma or recurrent wheeze. Two serious adverse events occurred during the study which were considered to be potentially attributable to LAIV.[35] The study provided evidence to support the revised UK guidance for the 2019 to 2020 season that 'children with asthma on inhaled corticosteroids may safely be given LAIV, irrespective of the dose prescribed'.[36]
- Electronic surveillance of the occurrence of adverse events following influenza vaccination collected by the Canadian National Vaccine Safety (CANVAS) network for 4,387 children vaccinated with LAIV, IIV4 (the most frequently administered vaccine) or IIV3 in 2017 to 2018 and 3,677 in 2018 to 2019 reported that health event rates were not significantly different between vaccinated and control children groups.[37]
- A systematic review of the effectiveness and safety of LAIV compared with IIVs in children is currently underway by the European Centre for Disease Prevention and Control (ECDC) and was scheduled to complete in the second quarter of 2020.

5. Potential economic impact

- A systematic review of cost-effectiveness of population level or sub-group specific influenza immunisation programmes retrieved 10 studies exclusively in children. From a health services perspective, influenza vaccination was found to be most cost-effective in younger children.[38]
- A systematic review of vaccines for the prevention of seasonal influenza across different age groups identified 11 studies. All of the studies included children. Based on the evidence summarised in this review, the authors concluded that seasonal influenza vaccination programmes in school-age children can be cost-effective from the perspective of the national health system, and can be cost-saving from a societal perspective in European countries.[39]
- Pitman et al. compared vaccinating all children to vaccinating only high-risk children in England and Wales using a dynamic transmission model. Vaccinating all 2-18 year olds with LAIV was estimated to be the most cost-effective policy in an incremental cost-effectiveness analysis, at an assumed annual vaccine uptake rate of 50%. The mean incremental cost-effectiveness ratio (ICER) for this policy was estimated at £251 per quality adjusted life year (QALY) relative to current practice (vaccinating at-risk groups and those ≥65 years), that is, highly cost-effective. The analysis also suggests that indirect protection, arising from herd immunity, may make a significant contribution to the cost-effectiveness of paediatric influenza vaccination.[40]
- Thorrington et al. aimed to determine whether targeted vaccination in either primary or secondary schools would be more cost-effective than a programme stretching across both school groups. Overall, vaccination of healthy school children in the UK was found to be cost-effective with an ICER of £16,152 per QALY saved based on heterogeneous vaccination coverage across primary and secondary schools. The model suggested that influenza transmission can be eliminated for a particular season by vaccinating both primary and secondary school children, but not by vaccinating only one group.[41]
- In England, given the projected reduction in the population-wide burden of influenza B, it has been reported that the introduction of quadrivalent LAIV to low-risk healthy children is likely to be cost-effective compared with trivalent LAIV based on modelling exercises.[42]
- Vaccinating children indirectly protects other age groups. In this way, universal influenza vaccination programmes reduce the potential impact of any vaccination programme in the remaining population, thereby decreasing the amount that should be spent on those vaccination programmes after a successfully

implemented paediatric programme.[42] Hodgson reported that paediatric vaccination would reduce the number of low-risk elderly influenza cases to a greater extent than would vaccination of the low-risk elderly themselves.[43]

- Vaccination of children aged 2-16 years at 50% coverage was found to be cost-effective in The Netherlands when assessed from the healthcare payer's and societal perspective. However, childhood influenza vaccination was not cost-effective when only outcomes for the children themselves were considered.[44]

- Management and treatment of drug-resistant infections increases healthcare costs. A suggested additional benefit of influenza vaccination is a reduction in antibiotic consumption and or adverse health outcomes associated with antibiotic resistance, leading to improved cost-effectiveness. Such potential benefits were not considered in any of the cost-effectiveness analyses identified in this scoping review.

6. Decision-making and policy considerations

- The national immunisation guidelines until now strongly recommended annual seasonal influenza vaccination for children aged six months and older who are at increased risk of influenza-related complications due to identified comorbid conditions. Vaccination was also recommended for children who are household contacts of an at-risk person to reduce the risk of transmission to those at high risk of influenza complications. The seasonal influenza programme was based on IIV3 from 1998 to 2018; IIV4 was introduced in 2019.

- Influenza vaccines have been shown to be safe and well-tolerated in children. However, influenza vaccines can be associated with rare serious adverse events, with the majority of studies not powered to detect extremely small increases in rare events.

- A number of countries include universal influenza vaccination of children in their immunisation programmes.

- Most of the clinical and economic burden prevented by universal childhood vaccination is not among the vaccinated population, but among older adults through indirect protection. The impact of the introduction of universal childhood vaccination should be considered in the context of the entire population, not just the target-group alone.

- Based on clinical and cost-effectiveness data, it has been suggested that children should be considered a priority for seasonal influenza vaccination, due to their role in transmission of the virus and high healthcare resource use for influenza-associated episodes in this group.[45, 46]

- The seasonal influenza vaccine is currently administered to eligible populations by general practitioners and pharmacists at a fee of €15 under fee-per-item agreement between the HSE and healthcare providers.[47]

- For currently existing school-based immunisation programmes in Ireland, recent uptake rates are in excess of 80%.[48] Uptake of seasonal influenza vaccination is highly variable across Europe. Overall uptake of the universal paediatric influenza vaccination programme in the United Kingdom exceeds 50%.[31, 49, 50] In Finland, vaccine coverage is steadily increasing, but remains low among two years olds (that is, 7-20% depending on the type of vaccine and influenza season).[26]

- School-based vaccination is likely to achieve higher coverage than delivery via primary care providers.[49, 50] While achieving greater equity of care, school-based influenza vaccination programmes are highly resource intensive. However, the clinical and cost-effectiveness of a universal paediatric vaccination programme is highly dependent on the uptake rate. The likelihood of attaining high coverage is an important component of decision-making regarding introduction of influenza vaccination programmes.

- National immunisation guidelines published by the HSE highlight that the ideal time for vaccination is from September to October, although the vaccine may be given until the end of April. Furthermore, for the LAIV vaccine which is administered intranasally, children under the age of nine years require two doses of the vaccine administered four weeks apart if they are receiving the vaccine for the first time. Given these requirements and the potential requirement to vaccinate a large cohort of children on an annual basis, it is likely that inclusion of universal influenza vaccination for all children, or even all younger children (up to and including primary school) would give rise to substantial logistical challenges for the national programme. For example, total enrolment in mainstream primary schools (n=3,106 schools) was approximately 560,000 in September 2019.[51] Such challenges could be partly mitigated by phased implementation, and consideration of alternative vaccination settings including extension of the pharmacy-based influenza programme which is currently limited to those aged 18 years and older.[1]

- While international evidence suggests that universal influenza vaccination of children is likely cost-effective, that is, that it may represent an efficient use of resources, consideration must also be given to the potential budget impact, as this addresses the question of affordability. Given the requirement for multi-annual vaccination, and the cohort size (approximately 60,000 children for each birth year), the combined cost of the vaccine plus its administration will be substantial. While cost offsets in terms of reduced hospitalisations and other

healthcare utilisation may be anticipated, decision-making will need to take consideration of competing priorities in the context of a finite healthcare budget.

- It has been acknowledged that the health system and wider society should prepare for the potential for co-epidemics of COVID-19 and seasonal influenza in 2020 to 2021.[52] It has been suggested that strategies to mitigate the morbidity and mortality associated with co-circulation of SARS-CoV-2 and seasonal influenza viruses should include attainment of optimal influenza vaccination coverage, including near-universal coverage among healthcare personnel and other groups at high risk of complications from influenza and COVID-19.[52]

- A single-centred study of COVID-19 patients has indicated that during the early stages of the COVID-19 outbreak in Wuhan (12 January – 21 February, 2020) co-infection of SARS-CoV-2 and influenza viruses was highly prevalent (Influenza A: 49.8% and Influenza B: 7.5%).[53] Early evidence from a systematic review of studies published up to 17 April 2020 suggests that COVID-19 patients with co-infections (bacterial, fungal or viral) may be at increased risk of poor outcomes. While an increased risk of mortality was also reported in COVID-19 patients with a co-infection compared with those with no co-infection, the data were limited to hospitalised patients and included co-infection with bacterial and fungal pathogens.[54]

- Updated guidance on influenza vaccination from the Queensland Department of Health and Public Health England advises that influenza vaccination will be one of the most effective available interventions to reduce pressure on the health and social care system in the 2020 to 2021 influenza season.[36, 55] Influenza vaccination will reduce the severity and transmission of influenza, and may reduce susceptibility to other respiratory viruses, such as coronaviruses.[55]

- The current data suggest that the burden of COVID-19 in children is low[56] and, based on limited evidence, that they do not substantially contribute to the transmission of SARS-CoV-2.[57] However, reductions in the incidence of influenza in this cohort, would reduce the overall burden of influenza in the population. Current indications for SARS-CoV-2 testing include onset of a number of symptoms of acute respiratory infection. Given the overlap between influenza and COVID-19 symptoms, individuals with influenza are likely to present for SARS-CoV-2 testing. Therefore, in the context of the current pandemic, a reduction in incidence of influenza would likely reduce the resource requirements for SARS-CoV-2 testing, as well as reducing the organisational and economic challenges arising from a requirement for self-isolation or restriction of movement pending test results.

- On 18 May 2020, the Minister for Health announced that influenza vaccination would be provided for all children aged between 2 and 12 years from the 2020/2021 influenza season onwards.[58]

7. Conclusion

Data from the Global Burden of Disease Study 2017 indicate that the greatest number of influenza lower respiratory tract (LRTI) episodes, deaths, and hospitalisations occur in young children and elderly adults. Targeting specific age and risk groups with the highest disease burden for influenza vaccination could substantially reduce the burden of influenza LRTIs.[59] Influenza vaccines have been shown to be safe and well-tolerated in children, although they can be associated with rare serious adverse events. Based on the evidence summarised in this preliminary scoping review, a universal influenza vaccination programme for children is likely to be clinically and cost-effective if high uptake rates can be achieved. It is suggested that indirect protection, arising from herd immunity, may make a significant contribution to the cost-effectiveness of a paediatric influenza vaccination programme. Careful consideration of competing priorities on the healthcare budget and how best to implement such a programme will, however, be required to mitigate challenges arising from the cost and logistical challenges of having to vaccinate a large cohort within a short time frame on an annual basis.

In the context of the current COVID-19 pandemic, strategies to mitigate the morbidity and mortality associated with co-circulation of SARS-CoV-2 and seasonal influenza viruses include attainment of high influenza vaccination coverage. A reduction in the incidence of influenza would likely also reduce the resource requirements for SARS-CoV-2 testing, as well as reducing the organisational and economic challenges arising from a requirement for self-isolation or restriction of movement pending test results.

On 18 May 2020, the Minister for Health announced that influenza vaccination would be provided for all children aged between 2 and 12 years from the 2020/2021 influenza season onwards.[58]

References

1. Health Service Executive (HSE). Chapter 11 - Influenza (updated October 2019). Available from: https://www.hse.ie/eng/health/immunisation/hcpinfo/guidelines/ [Accessed 23/04/2020].
2. World Health Organization (WHO). Seasonal influenza [online]. Available from: https://www.who.int/ith/diseases/influenza_seasonal/en/ [Accessed 24/03/2020].
3. Antonova EN, Rycroft CE, Ambrose CS, Heikkinen T, Principi N. Burden of paediatric influenza in Western Europe: a systematic review. BMC Public Health. 2012;12:968-.
4. World Health Organization (WHO). Seasonal Influenza 2018. Available from: https://www.who.int/en/news-room/fact-sheets/detail/influenza-(seasonal) [Accessed 24/03/2020].
5. Paules CI, Sullivan SG, Subbarao K, Fauci AS. Chasing Seasonal Influenza - The Need for a Universal Influenza Vaccine. The New England journal of medicine. 2018;378(1):7-9.
6. European Centre for Disease Prevention and Control (ECDC). Types of seasonal influenza vaccine [online]. Available from: https://www.ecdc.europa.eu/en/seasonal-influenza/prevention-and-control/vaccines/types-of-seasonal-influenza-vaccine [Accessed 24/03/2020].
7. World Health Organization (WHO). Vaccination [online]. Available from: http://www.euro.who.int/en/health-topics/communicable-diseases/influenza/vaccination [Accessed 24/03/2020].
8. Finnish Institute for health and welfare. Vaccination programme for children and adolescents [online]. Available from: https://thl.fi/en/web/vaccination/national-vaccination-programme/vaccination-programme-for-children-and-adolescents [Accessed 23/04/2020].
9. Public Health England. The National Childhood Flu Immunisation Programme 2019/20 Information for healthcare practitioners. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/815744/Childhood_flu_programme_information_for_healthcare_practitioners_2019_2020.pdf [Accessed 24/03/2020].
10. JCVI statement on the annual influenza vaccination programme – extension of the programme to children 25 July 2012. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/224775/JCVI-statement-on-the-annual-influenza-vaccination-programme-25-July-2012.pdf.
11. Health Service Executive. Immunisation Schedule (updated 24.04.2020). Available from: https://www.hse.ie/eng/health/immunisation/pubinfo/pcischedule/immschedule/.
12. Health Service Executive. School Programme (updated 15.06.2020). Available from: https://www.hse.ie/eng/health/immunisation/pubinfo/schoolprog/.
13. McGuire A, Drummond M, Keeping S, (2015). Childhood & Adolescent Influenza Vaccination in Europe. LSE Enterprise. Available from:

http://www.lse.ac.uk/business-and-consultancy/consulting/assets/documents/childhood-adolescent-influenza-vaccination-in-europe.pdf [Accessed 24/03/2020].
14. Brennan-Krohn T, Ozonoff A, Sandora TJ. Adherence to guidelines for testing and treatment of children with pharyngitis: a retrospective study. BMC pediatrics. 2018;18(1):43.
15. van Houten CB, Cohen A, Engelhard D, Hays JP, Karlsson R, Moore E, et al. Antibiotic misuse in respiratory tract infections in children and adults-a prospective, multicentre study (TAILORED Treatment). Eur J Clin Microbiol Infect Dis. 2019;38(3):505-14.
16. Akkerman AE, van der Wouden JC, Kuyvenhoven MM, Dieleman JP, Verheij TJM. Antibiotic prescribing for respiratory tract infections in Dutch primary care in relation to patient age and clinical entities. Journal of Antimicrobial Chemotherapy. 2004;54(6):1116-21.
17. Chae C, Davies NG, Jit M, Atkins KE. Effect of Pediatric Influenza Vaccination on Antibiotic Resistance, England and Wales. Emerg Infect Dis. 2020;26(1):138-42.
18. European Centre for Disease Prevention and Control. Rates by country. Available from: https://www.ecdc.europa.eu/en/antimicrobial-consumption/database/rates-country [Accessed 25/06/2020}.
19. Nicki Boddington, Richard Pebody, Isabelle Pearson, Punam Mangtani, Heather Whitaker. Effectiveness of seasonal influenza vaccination in preventing severe influenza in children: a systematic review. PROSPERO 2019 CRD42019149315 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019149315. [Accessed 24/03/2020].
20. Haifa Aldhamy, Louise Tanner, Majid Althaqafy, Blaise Onyekwere, Mark Pearce. The effectiveness and efficacy of influenza vaccines among children: a systematic review of RCTs. PROSPERO 2019 CRD42019141678 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019141678 [Accessed 24/03/2020].
21. Wang X, Li Y, O'Brien KL, Madhi SA, Widdowson MA, Byass P, et al. Global burden of respiratory infections associated with seasonal influenza in children under 5 years in 2018: a systematic review and modelling study. The Lancet Global health. 2020;8(4):e497-e510.
22. Restivo V, Costantino C, Bono S, Maniglia M, Marchese V, Ventura G, et al. Influenza vaccine effectiveness among high-risk groups: A systematic literature review and meta-analysis of case-control and cohort studies. Human Vaccines & Immunotherapeutics. 2018;14(3):724-35.
23. Jefferson T, Rivetti A, Di Pietrantonj C, Demicheli V. Vaccines for preventing influenza in healthy children. The Cochrane database of systematic reviews. 2018;2(2):Cd004879.
24. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. The Lancet Infectious diseases. 2012;12(1):36-44.

25. Yin JK, Heywood AE, Georgousakis M, King C, Chiu C, Isaacs D, et al. Systematic Review and Meta-analysis of Indirect Protection Afforded by Vaccinating Children Against Seasonal Influenza: Implications for Policy. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2017;65(5):719-28.
26. Baum U, Kulathinal S, Auranen K, Nohynek H. Effectiveness of 2 Influenza Vaccines in Nationwide Cohorts of Finnish 2-Year-Old Children in the Seasons 2015–2016 Through 2017–2018. Clinical Infectious Diseases. 2020.
27. Kohlmaier B, Svendova V, Walcher T, Pilch H, Krenn L, Kurz H, et al. A severe influenza season in Austria and its impact on the paediatric population: mortality and hospital admission rates, november 2017 - march 2018. BMC Public Health. 2020;20(1):178.
28. Pebody RG, Whitaker H, Ellis J, Andrews N, Marques DFP, Cottrell S, et al. End of season influenza vaccine effectiveness in primary care in adults and children in the United Kingdom in 2018/19. Vaccine. 2020;38(3):489-97.
29. Pebody RG, Zhao H, Whitaker HJ, Ellis J, Donati M, Zambon M, et al. Effectiveness of influenza vaccine in children in preventing influenza associated hospitalisation, 2018/19, England. Vaccine. 2020;38(2):158-64.
30. Boddington NL, Warburton F, Zhao H, Andrews N, Ellis J, Donati M, et al. Influenza vaccine effectiveness against hospitalisation due to laboratory-confirmed influenza in children in England in the 2015-2016 influenza season - a test-negative case-control study. Epidemiology and infection. 2019;147:e201.
31. Gallagher N, Jessop L, Sartaj M, Johnston J. Impact of live attenuated influenza vaccination programme for healthy children in Northern Ireland: A comparison of seven influenza seasons, 2010/11-2016/17. Vaccine. 2018;36(4):521-6.
32. Centers for Disease Control and Prevention (CDC). 2019. Safety of influenza vaccines [online]. Available from: https://www.cdc.gov/flu/professionals/acip/safety-vaccines.htm.
33. Halsey NA, Talaat KR, Greenbaum A, Mensah E, Dudley MZ, Proveaux T, et al. The safety of influenza vaccines in children: An Institute for Vaccine Safety white paper. Vaccine. 2015;33:F1-F67.
34. Caspard H, Steffey A, Mallory RM, Ambrose CS. Evaluation of the safety of live attenuated influenza vaccine (LAIV) in children and adolescents with asthma and high-risk conditions: a population-based prospective cohort study conducted in England with the Clinical Practice Research Datalink. BMJ Open. 2018;8(12):e023118-e.
35. Turner PJ, Fleming L, Saglani S, Southern J, Andrews NJ, Miller E. Safety of live attenuated influenza vaccine (LAIV) in children with moderate to severe asthma. The Journal of allergy and clinical immunology. 2020;145(4):1157-64.e6.
36. Public Health England. Chapter 19: Influenza. In: Immunization against infectious disease. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/796886/GreenBook_Chapter_19_Influenza_April_2019.pdf Date accessed: 24 June 2020.

37. Bettinger Julie A , De Serres Gaston , Valiquette Louis , Vanderkooi Otto G , Kellner James D , Coleman Brenda L , Top Karina A , Isenor Jennifer E , McCarthy Anne E , on behalf of the Canadian Immunization Research Network . 2017/18 and 2018/19 seasonal influenza vaccine safety surveillance, Canadian National Vaccine Safety (CANVAS) Network. Euro Surveill. 2020;25(22).
38. Ting EEK, Sander B, Ungar WJ. Systematic review of the cost-effectiveness of influenza immunization programs. Vaccine. 2017;35(15):1828-43.
39. Valcárcel Nazco C, García Lorenzo B, del Pino Sedeño T, García Pérez L, Brito García N, Linertová R, Ferrer Rodríguez J, Imaz Iglesia I, Serrano Aguilar P. Coste-efectividad de la vacunación contra la gripe estacional para diferentes grupos de edad: Una revisión sistemática. Rev Esp Salud Pública.2018;92: 17 de octubre e201810075.
40. Pitman RJ, Nagy LD, Sculpher MJ. Cost-effectiveness of childhood influenza vaccination in England and Wales: Results from a dynamic transmission model. Vaccine. 2013;31(6):927-42.
41. Thorrington D, Jit M, Eames K. Targeted vaccination in healthy school children - Can primary school vaccination alone control influenza? Vaccine. 2015;33(41):5415-24.
42. Thorrington D, van Leeuwen E, Ramsay M, Pebody R, Baguelin M. Cost-effectiveness analysis of quadrivalent seasonal influenza vaccines in England. BMC Med. 2017;15(1):166.
43. Hodgson D, Baguelin M, van Leeuwen E, Panovska-Griffiths J, Ramsay M, Pebody R, et al. Effect of mass paediatric influenza vaccination on existing influenza vaccination programmes in England and Wales: a modelling and cost-effectiveness analysis. The Lancet Public health. 2017;2(2):e74-e81.
44. de Boer PT, Backer JA, van Hoek AJ, Wallinga J. Vaccinating children against influenza: overall cost-effective with potential for undesirable outcomes. BMC Medicine. 2020;18(1):11.
45. Antonova EN, Rycroft CE, Ambrose CS, Heikkinen T, Principi N. Burden of paediatric influenza in Western Europe: a systematic review. BMC Public Health. 2012;12(1):968.
46. Willis GA, Preen DB, Richmond PC, Jacoby P, Effler PV, Smith DW, et al. The impact of influenza infection on young children, their family and the health care system. Influenza Other Respir Viruses. 2019;13(1):18-27.
47. Primary Care Reimbursement Service (PCRS). Primary Care Reimbursement Service Statistical Analysis of Claims and Payments 2018. Available from: https://www.hse.ie/eng/staff/pcrs/pcrs-publications/annual-report-2018.pdf [Accessed 24/03/2020].
48. HSE Health Protection Surveillance Centre (HPSC). DTaP-IPV & MMR vaccine uptake in Junior Infants, in Ireland, 2017/2018. Dublin: HSE HPSC; 2020 Available from: https://www.hpsc.ie/a-z/vaccinepreventable/vaccination/immunisationuptakestatistics/immunisationuptakestatisticsforjuniorinfants/DTaP-IPV%20and%20MMR%20vaccine%20uptake%202017-2018%20v2.0.pdf [Accessed 24/03/2020].

49. Pebody RG, Green HK, Andrews N, Boddington NL, Zhao H, Yonova I, Ellis J, Steinberger S, Donati M, Elliot AJ, Hughes HE, Pathirannehelage S, Mullett D, Smith GE, de Lusignan S, Zambon M. Uptake and impact of vaccinating school age children against influenza during a season with circulation of drifted influenza A and B strains, England, 2014/15. Euro Surveill. 2015;20(39):pii=30029. Available at: https://www.eurosurveillance.org/images/dynamic/EE/V20N39/art21256.pdf.
50. Pebody RG, Green HK, Andrews N, Zhao H, Boddington N, Bawa Z, Durnall H, Singh N, Sunderland A, Letley L, Ellis J, Elliot AJ, Donati M, Smith GE, de Lusignan S, Zambon M. Uptake and impact of a new live attenuated influenza vaccine programme in England: early results of a pilot in primary school-age children, 2013/14 influenza season. Euro Surveill. 2014;19(22):pii=20823. Available at: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20823.
51. Department of Education and Skills. Statistical Bulletin. Enrolments September 2019- Preliminary Results. Available from: https://www.education.ie/en/Publications/Statistics/Data-on-Individual-Schools/enrolments/statistical-bulletin-enrolments-september-2019-preliminary-results.pdf.
52. Gostin LO, Salmon DA. The Dual Epidemics of COVID-19 and Influenza: Vaccine Acceptance, Coverage, and Mandates. JAMA. 2020.
53. Yue H, Zhang M, Xing L, Wang K, Rao X, Liu H, et al. The epidemiology and clinical characteristics of co-infection of SARS-CoV-2 and influenza viruses in patients during COVID-19 outbreak. Journal of medical virology. 2020.
54. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. The Journal of infection. 2020.
55. Queensland Department of Health. 2020 influenza vaccination guidelines (updated 5 May 2020). Available from: https://www.health.qld.gov.au/clinical-practice/guidelines-procedures/diseases-infection/immunisation/service-providers/influenza.
56. European Centre for Disease Prevention and Control. Q & A on COVID-19 (updated 24 April 2020). Available from: https://www.ecdc.europa.eu/en/covid-19/questions-answers.
57. Health Information and Quality Authority. Evidence summary for spread of COVID-19 by children (published 3 June 2020). Available from: https://www.hiqa.ie/reports-and-publications/health-technology-assessment/evidence-summary-spread-covid-19-children.
58. Department of Health. Minister for Health announces influenza vaccines to be made available without charge to all children aged 2-12 and all risk groups (published 18.05.2020). Available from: https://www.gov.ie/en/press-release/b9bfa1-minister-for-health-announces-influenza-vaccines-to-be-made-availabl/.
59. Troeger CE, Blacker BF, Khalil IA, Zimsen SRM, Albertson SB, Abate D, et al. Mortality, morbidity, and hospitalisations due to influenza lower respiratory tract infections, 2017: an analysis for the Global Burden of Disease Study 2017. The Lancet Respiratory Medicine. 2019;7(1):69-89.

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