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Childhood and adolescent influenza vaccination in Europe:

A review of current policies and recommendations for the

future

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Summary

Children and adolescents experience some of the highest rates of influenza infection and the subsequent burden on both infected children and their parents/carers is substantial. Vaccinating children and adolescents against seasonal influenza has the potential to reduce the burden of disease in both vaccinated and unvaccinated individuals due to the pivotal role that younger age groups play in the transmission of infection. While countries such as the USA, Canada and the UK have consequently recommended the universal vaccination of children, the vast majority of European countries have not yet extended their vaccination policies to this age group. This review examines the rationale for childhood and adolescent vaccination against seasonal influenza and reviews current vaccination policies in Europe. We discuss key policy considerations for European countries that must be considered when extending vaccination programmes to younger age groups alongside recommendations for European policy makers based on our findings.

Keywords: Influenza, vaccine, childhood, adolescent, policy, Europe

Introduction

Influenza is a highly infectious virus that affects the respiratory tract. Influenza viruses are categorized as either type A, B or C, with the majority of clinical illness caused by types A and B [1].

Although otherwise healthy individuals who contract the virus can usually expect to make a full recovery, the virus may have serious consequences for some groups, such as the very young, the elderly and those with chronic illnesses [2]. Its impact on morbidity and mortality amongst these groups is significant; The European Centre for Disease Prevention and Control (ECDC) estimates that each year the average number of people in Europe who die prematurely due to influenza infection is 40,000 [3]. The virus also places significant strain on health systems when its circulation is at its peak [4].

Countries that have employed mass influenza vaccination have historically targeted those most at risk of serious complications. However, in the last 10 years some health authorities have also opted to vaccinate healthy children. Children experience some of the highest attack rates during influenza outbreaks [5] and also play a key role in the spread of the virus [6], although they do not experience the same rates of complications or death as at risk-groups [7]. Vaccinating children has therefore been seen by some as an effective way to deliver health gains through the direct protection of children themselves and also indirect protection of others, such as relatives and family members, who may have otherwise come into contact with the virus. However, the inclusion of healthy children and adolescents within seasonal influenza vaccination programmes remains far less widespread than for the elderly or people with predisposing conditions.

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This review examines the rationale for childhood and adolescent vaccination against seasonal influenza and reviews current vaccination policies in European countries. We discuss key policy considerations for European countries that need to be considered when extending vaccination programmes to younger age groups and provide recommendations for European policy makers based on our findings.

Rationale for the seasonal vaccination of children and adolescents against influenza

For those countries with current influenza vaccination programmes for children and adolescents, the detailed reasons underpinning vaccination policy differ between them but can nonetheless be grouped into two broad categories: (1) reducing the burden of disease in younger age groups through direct protection, and (2) indirectly protecting high-risk groups from disease by disrupting community transmission (also known as "herd protection").

Direct protection

The burden of influenza amongst children is substantial, with attack rates reaching 20–30% of the population on average in each influenza season [8] There is the potential for more serious complications in children such as acute otitis media [9], bacterial co-infections such as pneumonia [8] or methicillin-resistant *Staphylococcus aureus* [10], and febrile seizures [11]. Vaccination against influenza has been shown to reduce the incidence of acute otitis media by over 35% [12,13] and reduce the chance of contracting more serious complications such as pneumonia [14]. There have been isolated reports that uncomplicated and complicated influenza or influenza-like illness (ILI) in children and adolescents has a significant impact on health-related quality of life [15]. Influenza cases among children and adolescents also place a substantial burden on healthcare systems in terms of resource utilisation. Data from the USA during the 2002–2003 and 2003–2004 influenza seasons, for example, showed that medical clinic and emergency department visits due to laboratory-confirmed influenza in children <5 years were estimated to be in the range of 50–95 and 6–27 per 1000 children, respectively [16]. The risk of

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hospitalization for healthy children generally decreases with age, with children aged ≤4 years experiencing rates similar to other groups, who have traditionally been targeted for vaccination [7].

A number of estimates are available for the indirect costs of influenza in adults due to both absence from work and reduced productivity while at work (known as presenteeism) [17,18]. The specific impact that childhood influenza has on the wider economy due to parents and responsible individuals taking time off work to care for those who become sick has also been investigated. A prospective cohort study carried out in three large US companies found that employees with at least one child in their household with self-reported acute respiratory tract infection (ARI) reported significantly higher levels of absenteeism due to household illness or injury (mean 0.8 vs 0.3 days per month) than those with no children reporting ARI [19]. Those with children who had ARI that met the criteria for ILI also had greater lengths of absence due to household illness or injury than others (0.9 vs 0.5 days per month). Although these results should be treated with caution as they rely on self-reported illness, they do give some indication of the extent to which influenza in children impacts those around them.

The above evidence on the negative impact of influenza in children, along with the availability of safe and effective vaccines and a desire to increase uptake in children at risk of complications, provided the rationale for the USA's Advisory Committee on Immunization's (ACIP) decision to recommend all children aged 6 months and over to be vaccinated against influenza on an annual basis [20]. A similar argument was put forward by the Canadian National Advisory Committee on Immunisation (NACI) in recommending the vaccination of children aged 6 months to

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<2 years in the 2011–2012 influenza season [21], with the upper age limit extended to <5 years in the following season [22].

Two recent systematic reviews on the burden of childhood and adolescent influenza in Europe reveal a similar picture to the one seen in North America, with high rates of infection and healthcare utilisation [23,24]. For example, data drawn from England [7] over the course of eight consecutive seasons (2000–2001 to 2007–2008) show similar rates of general practitioner consultations (61 per 1000) and hospitalizations (two per 1000) for children aged 6 months to 4 years to those seen in the USA. Estimates of the proportion of parents having to take time off work to care for a child with laboratory-confirmed influenza range between 11.2 and 61% for Western Europe [23]. The average number of days absent ranged from 1.3 to 6.3 (median range 2–4) per influenza case [23]. A study in Sweden found clear co-variation of seasonal ILI visits and temporary parental absence from work due to caring for ill children [25]. Parental absenteeism due to childhood influenza is expected to increase as female labour market participation for those aged between 20 and 64 years moves towards the 75% target set by the European Commission in 2010 [26].

Indirect protection

The rate at which infections emerge within a population depends largely on the frequency and type of contact which occurs between individuals, the residual level of immunity within the population (i.e., the size of the susceptible population), the effectiveness of available vaccines [27] and the basic reproductive number, R_0. R_0 is defined as the average number of secondary infections due to a single case when placed in an entirely susceptible population [28]; $R_0 \geq 1$ is required for a virus to

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remain in circulation. The R_0 for influenza has historically ranged anywhere from 1.1 to 3.7 [28]. The reproduction number can be used to determine the threshold for the proportion of protected individuals above which transmission will be disrupted (1−[1/R_0]), with higher reproduction values requiring greater levels of protection.

Reaching this threshold for influenza is challenging for a number of reasons. Firstly, the continually evolving nature of influenza viruses means that the degree of susceptibility within populations remains high from year to year, particularly for type A viruses [29]. In addition, older children and young adults are particularly susceptible to influenza B [30], the incidence of which can vary dramatically between seasons [31]. Some mutations can also make the virus more infectious, which can in turn increase the value of R_0 [29]. Secondly, available vaccines are not 100% effective, for example in seasons where there is a poor match between the vaccine strains and the circulating virus and for populations whose immune systems are weaker, such as the elderly [19]. As the critical threshold for protection is proportional to the effectiveness of vaccination, low vaccine effectiveness can mean prohibitively high values for the critical threshold for protection [28].

The increased frequency of contact amongst children as well as between them and adults, relative to other age groups [6], gives rise to the possibility of targeting children and adolescents for influenza vaccination to provide indirect protection to other members of the population through reduced transmission [32], as well as direct protection to the children. The generally higher vaccine efficacy of newer influenza vaccines (e.g., live attenuated, already licensed and available, [33] and adjuvanted influenza vaccines, yet to be licensed in most countries for children [34], means the level of coverage in this population required to reduce incidence

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among other age groups may be lower than for groups more commonly targeted for vaccination, such as the elderly. The low effectiveness of live attenuated influenza vaccine (LAIV) noted in the 2013–2014 season in the USA is believed to be a result of heat exposure during shipping and the poor thermal stability of A/California H1N1 LAIV strain from a pre-existing mutation in the stalk region in the master virus seed [35]. A more stable strain was selected for the 2015–2016 season [35].

Data derived from a nu

mber of observational studies demonstrate the impact that vaccinating younger age groups can have on influenza transmission [36-38]. Japan was the first country to implement routine vaccination of healthy schoolchildren after experts identified them as key spreaders of infection during a series of major epidemics during the 1950s [39]. Between 1962 and 1987 when the routine programme was in operation, mortality attributable to influenza and pneumonia fell by 10,000–12,000 deaths per year, while all cause-mortality declined by 37,000–49,000 deaths per year. Importantly, no comparable decline was observed in the USA over the same period (where no childhood influenza vaccination programme was in place) and deaths in Japan promptly rose after the programme was discontinued, which when taken together appear to suggest that the decline in mortality was strongly associated with the childhood influenza vaccination. However, it should be noted that the prevalence of multi-generational homes in Japan at the time may have contributed to the herd protective effect, as family members were more likely to be exposed to influenza infection from close relatives (particularly children).

As many observational studies of the effect of influenza vaccines lack laboratory-confirmed viral endpoints [40], there has been a desire for randomized

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clinical trials (RCTs) to confirm the presence of indirect protection. One classic example is a cluster randomized trial of trivalent inactivated influenza vaccine (TIV) delivered to children aged between 36 months and 15 years in Hutterite communities in western Canada. The study showed that the vaccine was 61% effective at preventing influenza among unvaccinated persons in communities randomized to receive the vaccine [41]. A similar interventional study of the effectiveness of school-based influenza vaccination found that most outcomes related to ILI were significantly lower in households where the child had received vaccination compared to control households where the child had not [42]. The results of studies such as these, which demonstrate indirect protection from childhood and adolescent vaccination against influenza, have constituted the evidence base used to recommend universal influenza vaccination for those aged ≥6 months in the USA [43].

Overview of existing programmes

For the purposes of reviewing current vaccination policy towards influenza among all countries in the European Union, we have placed them into six regions based on geographical proximity. The groups and their constituent countries can be found in TABLE 1.

Only eight countries currently have a general recommendation for the vaccination of children and/or adolescents against influenza: Austria, Finland, Latvia, Malta, Poland, Slovakia, Slovenia and the UK (FIGURE 1). Of these, only Finland, Latvia and the UK provide the vaccine free of charge. FIGURE 2 shows how these countries are distributed among the different regions and indicates that no single region favours the strategy of vaccinating children and adolescents over another. A brief overview of the existing recommendations in each region and their levels of vaccine coverage is provided below, with data drawn from the ECDC [44] and the Vaccine European New Integrated Collaborative Effort (VENICE) survey of countries for the 2011–12 influenza season [45].

Baltic countries

Latvia is the only Baltic country with a positive vaccination recommendation for the young. Health authorities provide TIV free of charge to all children aged ≥6 months and <3 years, as well as to those aged ≥65 years. This is in keeping with its general approach to vaccination policy, which is amongst the most aggressive in Europe [46]. For example, vaccination is mandatory for all state employees and Latvian health care providers, with the latter required to obtain a signature from any person who refuses to be vaccinated as evidence that all relevant information on the risk of disease has been provided. Despite these measures vaccination coverage remains

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very low according to the most recent VENICE group survey (0.1% for those aged 6–23 months) [45].

Central European countries

Both Poland and Austria recommend the vaccination of children and adolescents using TIV, the latter opting to vaccinate from ≥7 months to <16 years and the former from ≥13 months to <18 years. The recommendations in both countries were originally made in 2010 [47] although Austria subsequently reduced the upper limit from <18 to <16 years [48]. Neither country provides public funding for these programmes nor has a high vaccination coverage rate (2.4% for those aged 5–14 years). Germany and Liechtenstein both provide influenza vaccine free of charge for persons aged ≥60 and ≥65 years, respectively, with the German state of Saxony including those aged ≥6 months within their recommendations [49].

Eastern European countries

In Eastern Europe, Slovenia and Slovakia recommend seasonal vaccination of children, the latter for ages ≥6 months to <13 years and the former for ages ≥6 months to <3 years, with no reimbursement of vaccine costs. Vaccination rates are below 3% in both countries [45]. Slovenian vaccination policy differs from most other European countries in that childhood vaccination across nine disease areas is mandatory (not including influenza), with no exceptions based on religious belief and fines for those who fail to comply [46]. The remaining countries do not have childhood or adolescent vaccination policies, but have policies for adults [44].

Nordic countries

Finland has had a publicly funded vaccination programme for all healthy children aged 6–35 months since 2007–2008 [50]. Importantly, this is part of their routine

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schedule and as a result they have achieved higher levels of uptake than other countries with a childhood recommendation (36.2% in 2007–2008) [51]. Iceland also provides reimbursement for vaccine but only for those aged ≥60 years.

Southern European countries

Among Southern European countries only Malta has a positive recommendation for childhood influenza vaccination (≥6 months to <3 years) but this is not part of the routine schedule.

Western European countries

The UK government's advisory body on vaccine policy, the Joint Committee on Vaccination and Immunisation (JCVI), issued a recommendation that all healthy children and adolescents aged ≥2 to <17 years be vaccinated using LAIV [52]. The intention is for the programme to be phased in over a number of years, starting in the 2013–2014 season. The pilot programmes introduced in the 2013–2014 and 2014–2015 seasons were mainly delivered through schools and achieved promising results, with an average uptake of 52.5% in 2013–2014 and 56.8% in 2014–2015 in primary schools in England [53,54]. Furthermore, results from the 2014–2015 season revealed that vaccinating primary school age children in pilot areas resulted in significant and non-significant reductions in a range of surveillance indicators for both the targeted age groups and wider society (due to herd protection) [54]. No other Western European countries currently have recommendations for childhood or adolescent vaccination.

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Key policy considerations for the introduction of childhood and adolescent vaccination programmes in Europe

Our review reveals that fewer than half of European countries currently have recommendations for healthy childhood and adolescent vaccination (FIGURE 2), despite evidence to support the vaccination of this age group as a strategy to reduce the burden of influenza. The limited roll out of influenza vaccination for healthy children, along with the variation in recommendations among countries who have them, is confirmation that a European consensus has yet to be reached over the policy.

Where data are available, they indicate that vaccination rates in age groups with a national recommendation are very low. In addition, only three countries, Latvia, Finland and the UK, have public funding for childhood and adolescent vaccination programmes. Even with public funding, however, vaccination rates are extremely low in Latvia, especially when compared with the good uptake achieved in the first year of the UK's childhood vaccination programme [45,53]. This suggests that a complex set of factors contribute to the success of childhood and adolescent vaccination programmes and need be considered by policy makers. Below, we consider key policy considerations for European countries considering the implementation of childhood and adolescent influenza vaccination programmes and summarise our recommendations.

Evidence of vaccine efficacy and safety

The starting point for policy makers when evaluating whether a new vaccine should be recommended and introduced into the schedule is evidence of efficacy and safety. While evidence is usually provided through a RCT, the need for the rapid

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evaluation of influenza vaccines due to changing compositions from season to season and infeasibility of carrying out annual RCTs has led the European Medicines Agency to develop a unique set of processes for their authorization for human use, which in some circumstances permits the use of data from comparative studies on immunogenicity instead of that which would normally come from an RCT [55].

Nevertheless, a number of different meta-analyses of RCTs have examined the efficacy of inactivated and LAIVs administered to healthy children. These studies have demonstrated good efficacy for LAIV in children aged >2 years [56,57] and superior efficacy compared with TIV [56]. In contrast, there is limited evidence for the efficacy of influenza vaccines in children aged <2 years, the group most at risk of complications and death due to the virus. As for adjuvanted vaccines, a phase III trial carried out in 2011 found it to provide 83% immunological efficacy (95% CI 74–93%) in children aged from 6 months to <6 years, compared to just 43% (95% CI 15–61%) for standard TIV [58] However, this vaccine is currently unlicensed in Europe [59]. Countries will have to consider the varying efficacy between age groups when selecting target populations for new vaccination programmes and any safety signals, such as the recent signal for narcolepsy seen with the pandemic influenza vaccine [60].

A number of observational studies have been carried out in European children to determine the effectiveness of influenza vaccines in real world conditions. An observational cohort study carried out in Finland showed TIV to be 83% (95% CI 58–93%) effective at preventing influenza in children aged 7–50 months [12] Another similar Finnish study of TIV showed effectiveness against influenza A to be 84%

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(95% CI 40–96%) and 45% (95% CI –34 to 78%) for influenza B [61]. A multi-centre case-control study of inactivated influenza vaccine effectiveness during the 2012–2013 season found that, after adjusting for the impact of comorbidities, the pooled vaccine effectiveness across inactivated influenza vaccine types in those aged 0–14 years was 22% (95% CI –37 to 56%), 37% (95% CI –44 to 72%) and 36% (95% CI –41 to 71%) against influenza B, influenza A (H1N1) and influenza A (H3N2), respectively [62].

There are currently limited effectiveness data for live attenuated and adjuvanted vaccines in European populations due to their limited usage in routine practice. Results from the 2014–2015 season in the UK, which was characterised by the circulation of drifted influenza A and B viruses, found that LAIV provided non-significant positive protection against influenza A and significant protection against B [63]. These results support literature that indicates that LAIV can provide cross-protection against drifted strains [63].

The apparent lack of data on effectiveness of both TIV and LAIV in healthy children has been cited as a significant barrier to the wider implementation of childhood influenza vaccination [24,64]. However, this is largely due to the vaccines being used sparingly in this age group across Europe. The UK programme is likely to fill this gap for LAIV in years to come, yet the willingness of health authorities in the UK to introduce the vaccine based on current evidence and modelling suggests that in the meantime other countries may choose to implement their own programmes rather than wait for this information to become available.

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Local evidence to support the impact of vaccination

While further RCTs such as the one carried out Loeb *et al* [41] would be of great assistance to other countries considering whether or not to introduce the routine vaccination of children and adolescents against influenza, the scope to conduct such trials in the future is heavily constrained on the grounds of practicality (randomizing entire communities is unfeasible),cost, and whether such studies are ethical [40]. In the absence of RCT evidence, observation studies with virologically confirmed endpoints are widely regarded as the next best option for clinical studies of influenza vaccination, but also require resources which may not be readily available in all countries [40]. A solution to this problem is to utilize mathematical modelling to produce estimates for the likely direct and indirect impact of vaccination programmes on seasonal influenza epidemics in terms of health and economic outcomes [27]. This approach is appealing as models are relatively cheap to produce compared to large trials, although the data requirements, such as virological surveillance and contact pattern data, can be burdensome to collect if not already available [65]. Another limitation of such models is that they require various assumptions to be made, such as levels of pre-existing immunity within the population, which makes their predictions uncertain. This can be mitigated by carrying out sensitivity analyses to test the robustness of model findings.

The UK's JCVI has a long history of using mathematical models to inform its policy recommendations. For example, the UK was the first country to implement mass vaccination against meningitis C, with the decision largely based on the predictions of a dynamic transmission model [66]. Modelling work done by the Health Protection Agency, now Public Health England, who support the work of the JCVI, showed that the impact of extending the seasonal vaccination programme in the UK

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to include those aged from 2 to 18 years (using LAIV) was likely to be highly cost-effective based on the UK threshold [52]. A similar analysis published around the same time noted that vaccinating this age group was estimated to result in net cost savings among unvaccinated members of the population, with the greatest impact seen among the elderly even though they themselves had high pre-existing vaccination coverage (75%) [67]. In 2012, the JCVI considered the evidence and recommended a staggered roll out of an extended vaccination programme for those aged 2–16 years. The rationale for the phased introductions was that it would allow for additional capacity to deliver the vaccines in schools to be created, while at the same time limiting the disruption to existing services. Subsequent modelling work has gone even further and suggested that targeting infants and adolescents rather than at risk groups at the time when the programme was first implemented may have been a more efficient strategy for reducing the burden of influenza [68]. The phased roll out of the UK's programme has allowed for early assessment of its effects, with early evidence suggesting indirect protection may be occurring [53]. Such an approach may be appealing to other countries as it avoids inertia from the continuing absence of direct evidence while mitigating the risk of required capital investments. A similar cost-effectiveness analysis from Finland concluded that influenza vaccination would be cost saving in all children ≤13 years [69].

Healthcare system factors

The structure of a country's healthcare system places a number of constraints on decision makers when determining optimal vaccine policy [70]. Important considerations include whether policies are made at the national or local level [70], the availability of funding and reimbursement for vaccines and existing capacity to deliver vaccination programmes [71], for example through schools. There are also

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interdependencies between these areas which influence the feasibility of

implementing childhood influenza vaccination. Many countries have created National

Immunisation Technical Advisory Groups (NITAGs), which sit either within

government or independent of it, to produce guidance on changes to the existing

schedule of vaccinations as well as the introduction of new vaccines [72]. However,

there is heterogeneity across NITAGs in both their capabilities and the extent to

which their recommendations impose a legal requirement on governments to ensure

their implementation [73].

In England, the Health Protection (Vaccination) Regulations 2009 requires "so

far as is reasonably practicable, that the recommendations of JCVI are

implemented", so long as their assessments demonstrate cost-effectiveness [74].

The JCVI is also supported by staff from Public Health England, the national agency

responsible for health protection and promotion, which has access to high quality

virologic surveillance data along with extensive information on resource use [68].

This is made possible by the highly centralized nature of the National Health Service

in England, along with the long-term investment that has been made in the

infrastructure to allow both epidemiological data collection and analysis [75].

Centralized systems can also take advantage of their monopsony powers to

negotiate lower vaccine prices [76]. This has been the case in England as well as the

other UK territories, where a centralized system has also helped foster a system of

school nurses who are able to facilitate mass vaccination of children in schools [77].

The pre-existing capacity to deliver vaccination through schools is important for a

number of reasons. Firstly, a minimum level of coverage must be achieved among

children and adolescents in order for community transmission to be disrupted, and

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consequently for the benefits from protection to be realised [28]. Although some

progress has been made in increasing uptake in countries which already have these

programmes such as Finland and the USA, uptake remains suboptimal [78]. School-

based mass vaccination programmes can potentially deliver higher levels of uptake

and they been used successfully in the USA for a number of years [42], although

robust data of their actual effect is limited [79]. The first year of the UK's extended

influenza vaccination programme for children carried out a number of school-based

pilots, which suggested that a variety of school settings are feasible and can achieve

a good level of coverage [80]. School-based programmes have the added benefit

that the vaccine can be delivered prior to onset of the influenza season and can also

serve to reduce the administration costs of delivering influenza vaccines, which have

been recently shown to be slightly higher for LAIV than TIV [81]. However, there are

barriers to implementing school-based systems: creating or enhancing the

healthcare infrastructure along with educational provider arrangements can be

challenging and costly.

Nevertheless, previous experience has demonstrated that childhood

vaccination programmes can be delivered through private (e.g., USA) [82] or public

systems (e.g., UK) [53] with good uptake and through a number of different services

such as primary healthcare providers, nurses, healthcare support workers and

school nurses [80]. Countries looking to implement such programmes will likely have

to adapt programmes to their existing infrastructure or alternatively invest in

developing healthcare infrastructure.

Economic considerations

Providing vaccines free of charge has also been shown to have an important effect on uptake [83,84]. In countries where the assessment process for vaccines contains a health economic component, the cost-effectiveness of new programmes, such as influenza vaccination for healthy children, is likely to be highly sensitive to both the costs of the vaccine and its administration. In these circumstances, the ability of those responsible for procuring the vaccine to negotiate a favourable price, either through volume discounts or tender processes, becomes a key determinant of whether new vaccines can be introduced. In contrast, systems with no central funding may be more able to deliver recommendations which are broader in scope due to the absence of a budget constraint. A counterbalance to this is that if the vaccine is to be funded via insurance programmes or out of pocket expenditures, the absence of national risk pooling reduces the value of vaccination to the individual. This is because the indirect benefits from herd protection are less important in individual consumption decisions, possible leading to lower coverage. In this case, policy makers might focus their own limited resources on exploring the viability of programmes which are viewed as having a greater likelihood of success.

Reimbursement of vaccine alone may not be able to guarantee sufficient levels of coverage to justify vaccinating children against influenza, however. Another major driver of vaccine coverage is physician engagement with the programme and the perceived benefit, both to themselves and their patients [85]. While centrally or regionally procured, vaccinations can improve the cost-effectiveness profile of vaccination programmes at the population level, they provide weak financial incentives to private physicians as time spent administering the vaccine could be substituted for more lucrative activities. This is an important issue in the context of an

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intervention that has low perceived health benefit, such as influenza prevention in the pediatric population. As a result of this, many countries offer financial incentives to physicians to ensure sufficient levels of coverage can be reached [84]. While research on the effectiveness of such incentives is generally of a low quality, it does support the use of such incentives [86]. These create an additional cost for vaccination programmes which become part of the implementation decision.

TABLE 2 gives an overview of health system and vaccination policy features for a sample of European countries [72]. Countries like the UK, Ireland and Sweden who have tax funded healthcare systems with national risk pooling, tender procurement processes and the infrastructure for delivering vaccinations through both primary care and schools appear to be those most suited to implementing seasonal influenza vaccines. At the other end of the spectrum are countries like Germany, France and Belgium where vaccinations are primarily paid for by social health insurance schemes, funded through employee and employer payroll contributions, and largely administered by private physicians. It is therefore perhaps understandable that these countries have yet to move to a more comprehensive influenza vaccination programme for healthy children and adolescents.

Demographic factors

Decisions regarding the best way to combat the threat posed by seasonal influenza epidemics are heavily influenced by the characteristics of the populations which are at risk, as these are key drivers of disease epidemiology. Clearly the size of the school-aged population is an important determinant of the impact that influenza cases have on both child and parental wellbeing as well the wider health system and economy. FIGURE 3 shows the proportion of the population aged 0–14 years for

selected European countries. Of the countries with a recommendation for childhood vaccination (those highlighted in red), only the UK and Finland have proportions of school-aged children above the median of 15.4%. However, a relatively large young population does not guarantee that the burden of influenza among them will be significant, with variables that influence this also having important implications for whether vaccinating children can provide indirect protection to at risk groups. A distinction should be drawn between high-risk groups (e.g., the elderly, infants and those with predisposing health conditions) and high transmission groups (e.g., school-aged children) [87]. In some circumstance both groups may overlap but usually the amount of transmission from child-to-child and from children to other age groups are key determinants of overall burden, and to a large degree depend on demographic variables such as household size, levels of urbanization and social contact patterns [6].

The profile of national workforces is another important factor when considering the potential benefit of vaccinating children against influenza. Female labour market participation has been steadily increasing since the early 1990s [88] and is expected to increase in the coming years. Therefore, the proportion of children for whom both parents are in paid employment is also likely to rise. This limited excess capacity in labour markets makes protecting children against influenza much more appealing than in circumstances where staff off sick can easily be replaced. Furthermore, if older relatives are expected to act as informal care providers under these circumstances, this could increase transmission between children and those most at risk of complications, which further strengthens the case for vaccinating children in the first place.

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Cultural factors

The ethical and practical justification for exposing otherwise healthy young people to the risks associated with the vaccine, no matter how small, to protect primarily themselves, but also others, depends largely on the prevailing cultural trends in the countries in question and has to be taken in to account when discussing vaccination policy. It could be argued that countries with existing vaccine schedules that achieve high coverage already demonstrate that the social value of vaccination is well understood by the public, as the individual risk trade-off in the case of diseases with extremely low incidence such as diphtheria and polio may not be sufficient alone to justify their continuing acceptability among parents. However, the inclusion of these diseases within combination vaccinations, which distributes the disutility of adverse events across diseases, may partly explain why uptake has not fallen.

From an ethical standpoint, the acceptability of the vaccine in question by different faith groups also has to be considered. In the UK, the use of porcine gelatine in the LAIV used in the childhood immunization programme drew attention in the media. However, many multi-faith groups have deemed the vaccines acceptable and Public Health England has published advice from representatives of faith communities [89].

An important practical consideration is the acceptance of the vaccine from the general public and the sensitivity of public opinion regarding external messaging on the safety and efficacy of the vaccine [90], particularly in light of recent anti-vaccination movements. Latvia had the highest proportion of respondents (82%) who had no intention to take the seasonal influenza vaccine in a recent Eurobarometer survey, suggesting that strong scepticism among the population about the need for

vaccination could be driving the low influenza vaccination rates despite a publicly-funded programme.

The agency model of medicine in which patients handover responsibility for care decisions can become problematic when the views of perceived sources of expertise, such as media outlets, are not supported by empirical evidence (for example, as happened with the measles, mumps and rubella vaccine controversy in the UK [91]). As the downstream effects of falls in coverage can be highly detrimental for public health [92], providing accurate, clear, information regarding the safety and/or effectiveness of vaccination is essential to gain public confidence. For example, the JCVI have explicitly stated that in rolling out the expanded influenza vaccination programme in the UK, extra care must be taken to "inform and educate parents, children, healthcare professionals and others about influenza, the live attenuated intranasal vaccine and the benefits of the extending the programme to children and to the wider population…" [52]. Attitudinal research in England and Scotland revealed that, in general, the introduction of the expanded vaccination programme with LAIV was well-accepted by children and their parents [80]. While the UK has had success in expanding its schedule while maintaining high levels of uptake, it remains to be seen whether this will continue with the roll out to older age groups and, if so, whether other European countries attempt to replicate the approach.

Overall, it is clear that childhood and adolescent vaccination against influenza can offer substantial benefits, although these will differ in scale between different countries. Here, we identified a number of issues that need to be considered by

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countries looking to implement a new childhood and adolescent influenza

vaccination programme. We provide a summary of our recommendations below.

Recommendations

- Ensure robust efficacy and safety data exist for the vaccine in question.

- Utilize modelling to provide country- or region-specific data on the health or

  economic impact of vaccination to support policy and payer decision making.

- Consider existing healthcare infrastructure that can be utilized for a mass

  vaccination programme and the logistics and expense of developing new

  infrastructure.

- Utilize experiences from other countries to guide the implementation of local

  programmes.

- Consider local demographics that may affect the potential impact of the vaccine.

- Develop country-specific solutions to enable to sufficient uptake of the vaccine for

  the levels of indirect and direct protection desired, e.g., reimbursement for all or

  some of the target population and physician engagement.

- Develop clear and consistent messaging for the public surrounding the efficacy

  and safety of the vaccine.

- Anticipate local cultural issues that may affect the reception of the vaccine and

  determine strategies to manage any issues.

Conclusions

The unpredictability of the influenza virus continues to present a major challenge to healthcare professionals and policy makers alike. Vaccination nonetheless remains the most effective means of reducing the incidence and severity of influenza, yet uptake of the vaccine in many European countries remains suboptimal. The increased use of childhood vaccination is an opportunity to not only reduce the substantial burden of disease in this age group, it can potentially also help to close gaps in protection for those most at risk of serious complications due to the pivotal role they play in the spread of the virus.

Major barriers to the addition of influenza vaccination to routine childhood schedules include questions over vaccine effectiveness, especially in those aged <2 years, its impact on transmission, acceptability among parents and guardians, and the costs of implementation. While many countries will be closely watching the roll out of the UK programme for answers to these questions, and ultimately to the question of whether they should implement their own, choosing to set up their own limited pilot programmes, guided by existing data, may lead to better outcomes in the long run as these can be properly tailored to local circumstances. Countries with younger populations, a high disease burden and population density along with low levels of coverage and the possibility of delivering the vaccine within their existing architecture should be prime candidates.

Expert commentary

It is becoming increasingly apparent that children bear a high burden of influenza, which has historically been underestimated [23]. A growing body of evidence indicates that the vaccination of children can reduce the burden of influenza in children themselves, and also provide indirect "herd protection" benefits to the wider community [41,42]. The implementation of childhood and adolescent vaccination programmes is therefore a strategic approach to control influenza infections and reduce the burden of disease in the population. The UK's Joint Committee on Vaccination and Immunisation [52] agreed with this view, and in 2012 issued a recommendation that the UK implement a childhood immunization programme, starting in the 2013–2014 influenza season. Preliminary results from the UK's childhood vaccination programme against influenza indicate that a national programme delivered to children either through general practitioners or school-based programmes can achieve a good uptake and may provide indirect benefits to the wider population [53,80]. However, other European countries have seemed reluctant to include healthy children and adolescents within seasonal influenza vaccination programmes, with only a minority currently having such programmes. The current situation highlights a European consensus has yet to be reached over the policy. Countries may be waiting for further external data on the impact of childhood and adolescent vaccination programmes, but we believe that there is sufficient evidence for European countries to introduce pilot programmes for the vaccination of healthy children against influenza. Local pilot programmes will enable countries to gather data to tailor their programmes to local circumstances and support future national programmes. We hope that the policy considerations discussed in this article will

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provide countries with guidance to implement national childhood and adolescent

vaccination programmes for influenza.

Five-year view

Childhood and adolescent influenza vaccination programmes are likely to become increasingly common across Europe in the future, despite some initial hesitance to their adoption. Countries with existing childhood and adolescent vaccination programmes – and public funding for vaccines – are ideal candidates for the introduction of a childhood and adolescent influenza vaccination programme and are likely to be the first to introduce such programmes. Countries considering the implementation of childhood and adolescent vaccination programmes are likely to look to the UK in the coming years as the UK extends its national childhood vaccination programme to older age groups. By 2018–2019, the UK is expected to have rolled out the programme to children aged 2–16 years [52,93]. Data from successive seasons of the UK's programme will be eagerly awaited by countries looking to assess the impact of childhood and adolescent vaccination programmes in Europe. However, countries will also have to consider local and regional factors that may affect the implementation of such programmes.

Key issues

- Children and adolescents experience some of the highest rates of influenza infection during seasonal epidemics. The negative effects of influenza on both infected children and their parents/carers is substantial.

- Vaccinating children against seasonal influenza has the potential to reduce the burden of disease in both vaccinated and unvaccinated individuals due to the pivotal role that younger age groups play in the transmission of infection.

- Vaccination programmes may have additional benefits, including reductions in absenteeism resulting from parents/carers taking time off work to care for sick children and reductions in pressure on healthcare services during peak influenza circulation.

- Large developed countries such as the USA, Canada and the UK now recommend influenza vaccination of healthy children and many have school-based influenza vaccination programmes.

- However, the vast majority of European countries have chosen not to implement their own versions of these programmes, and only a minority of countries with recommendations have public funding for influenza vaccines. Possible explanations for this include continuing uncertainty regarding the burden of influenza among children in some countries, the field effectiveness of inactivated and live attenuated vaccines when administered to children, the level of uptake achievable by national programmes and the amount of indirect protection that they will provide.

- There are also likely to be concerns regarding the resources required to expand

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seasonal influenza vaccination to children in countries where programmes are publicly funded.

- Despite these concerns, there remains a persuasive argument for vaccinating children against influenza, especially in countries with the existing infrastructure to deliver such programmes but where there has been suboptimal uptake among at risk groups with their current programmes.

- As more data become available on the effectiveness of vaccinating European children against influenza, for example through the UK programme, European countries are likely to be faced with the decision whether to continue the traditional approach of targeting groups at the highest risk of complications (and for whom the response to the vaccine is potentially poorest) or focus more on those most responsible for onward transmission.

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* Of interest

** Of considerable interest

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Table 1. Regions and their constituent countries

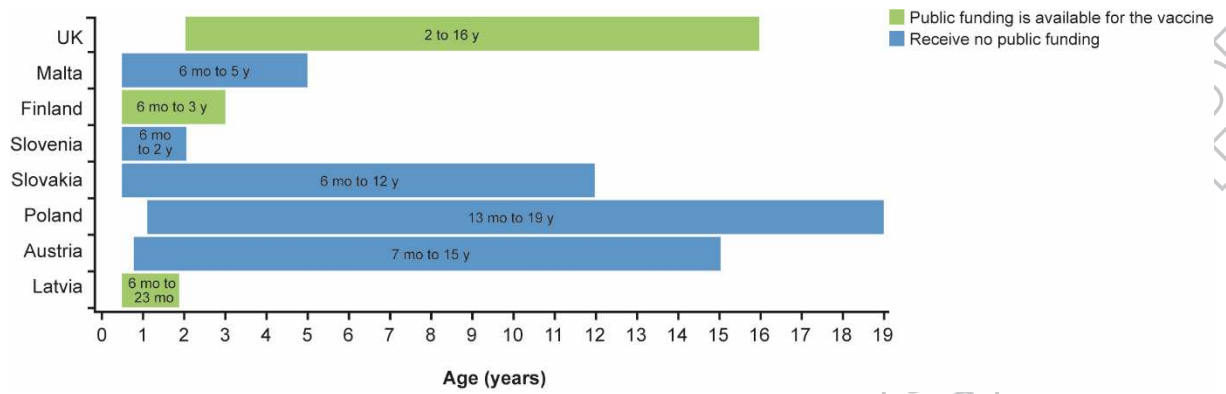| Regions					
Baltic	**Central**	**Eastern**	**Nordic**	**Southern**	**Western**
Estonia	Austria	Bulgaria	Denmark	Cyprus	Belgium
Latvia	Germany	Croatia	Finland	Greece	France
Lithuania	Liechtenstein	Czech R.	Iceland	Italy	Ireland
	Poland	Hungary	Norway	Malta	Luxembourg
		Romania	Sweden	Portugal	Netherlands
		Slovakia		Spain	United Kingdom
		Slovenia			

Table 2. Overview of health system and vaccine policy making features for a sample of European countries

Country	Main system of finance	Final decision maker on immunization	Funding source for immunization schedule	Tender system in place	Main provider of immunizations	NITAG	Consideration of cost-effectiveness required
Austria	Compulsory social insurance	Ministry of Health after negotiations with other stakeholders	Mixed	National level	Private practice	Yes	Yes
Belgium	Compulsory social insurance	National and regional Ministries of Health	Mixed (childhood vaccines tax-funded)	Regional level	Private practice	Yes	No
Denmark	Taxation	Parliament	Tax-funded	National level	Public providers	Yes	Yes
Finland	Taxation	Parliament with recommendation from Ministry of Finance	Tax-funded	National level	Public providers	Yes	Yes
France	Compulsory social insurance	Ministry of Health	Mixed	National level	Private practice	Yes	Yes
Germany	Compulsory social insurance	NITAG	Social insurance	Regional level (for some vaccines)	Private practice	Yes	Yes
Greece	Taxation	Ministry of Health	Tax-funded	National level	Private practice	Yes	No
Ireland	Taxation	Ministry of Health	Tax-funded	National level	Public providers, including school nurses	Yes	Yes
Italy	Taxation	National and regional Ministries of Health	Tax-funded	National, regional and local level	Public providers	Yes	Yes
Netherlands	Mixed	Ministry of Health	Tax-funded	National level	Public providers	Yes	Yes
Portugal	Taxation	Ministry of Health	Tax-funded	No system in place	Public providers	Yes	Yes
Spain	Taxation	National and regional Ministries of Health	Tax-funded	No system in place	Public providers, including school nurses	Yes	Yes
Sweden	Taxation	Government	Tax-funded	Regional and local level	Public providers, including school nurses	No	Yes
UK	Taxation	Ministry of Health	Tax-funded	National level	Public providers, including school nurses	Yes	Yes

Data on whether or not school-based immunization takes place were taken from a review of human papillomavirus vaccination programmes [94]
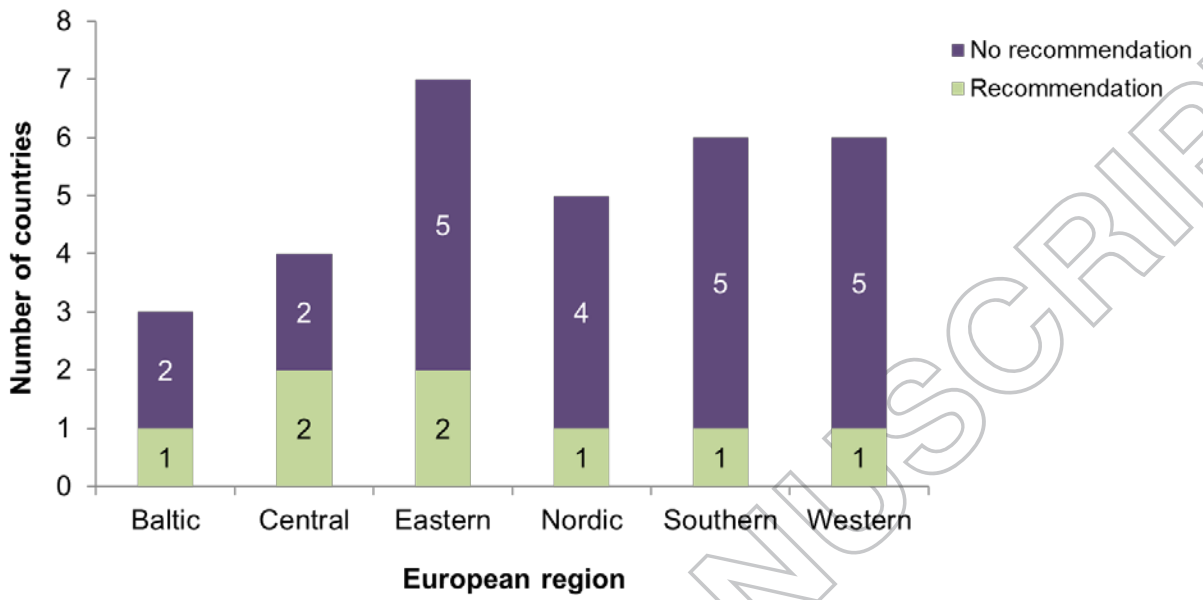
NITAG: National Immunisation Technical Advisory Groups

1

Figure 1. Childhood and adolescent age groups with a general recommendation for seasonal influenza vaccination in Europe
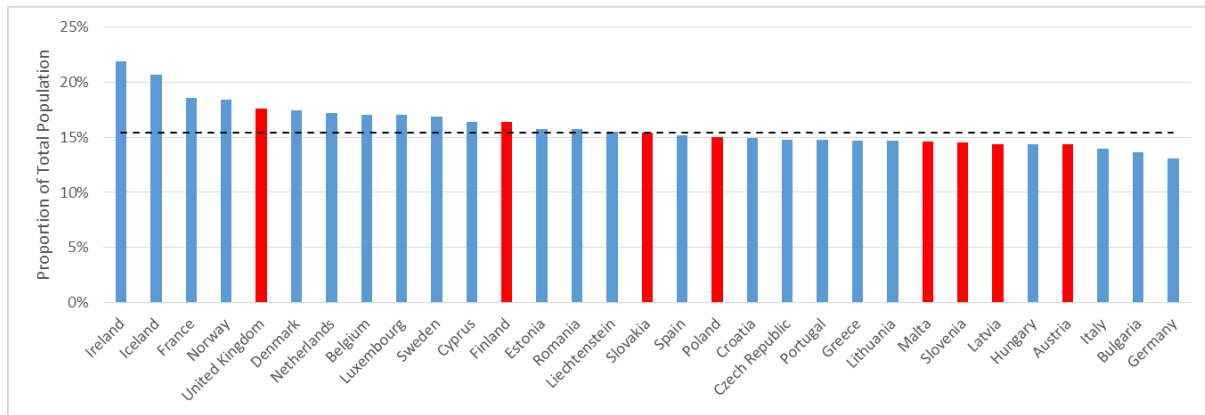
Figure 2. Number of countries with a general recommendation for the vaccination of children and adolescents by geographical region

Figure 3. European countries ranked by the proportion of their population aged between 0 and 14 years in 2012

Countries with a recommendation for healthy children to be vaccinated against influenza are in red, with the dashed line representing the median for all countries