



# Childhood & Adolescent Influenza Vaccination in Europe: A Review of the Evidence

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## CONTENTS

Executive Summary.....	4
1. Introduction and Methods.....	5
2. Rationale for Seasonal Vaccination of Children and Adolescents .....	6
2.1. Direct Protection.....	6
2.2. Indirect Protection .....	7
3. European Policy Landscape.....	10
3.1. Policy Considerations for European Countries .....	14
3.1.1. Demographic Factors .....	14
3.1.2. Treatment Factors.....	16
3.1.3. Health System Factors .....	17
3.1.4. Cultural Factors .....	22
4. Conclusions and Recommendations .....	24
References .....	25

## EXECUTIVE SUMMARY

- Children, in particular those aged less than two years old, 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 disease.
- Additional benefits may include reductions in absenteeism due to the need for parents/carers to take time of work to care for sick children and reduced pressure of health care services during peak circulation.
- Large developed countries such as the USA, Canada and the UK now recommend the vaccination of healthy children. However, the vast majority of European countries have chosen not to implement their own versions of these programmes.
- 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 which programmes will be able to achieve and the amount of indirect protection that they will provide.
- There are also likely to be concerns regarding the additional resources required to expand seasonal influenza vaccination to children in countries where programmes are publicly funded.
- The ethics of vaccinating children to protect vulnerable adults is also a subject of debate for decision makers.
- Despite these concerns, there remains a persuasive argument for vaccinating children against influenza, especially in countries with the existing infrastructure to deliver such programmes and suboptimal uptake among at risk groups with their current programmes.
- As more data becomes 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 or focus more on those most responsible for onward transmission.

# 1. INTRODUCTION AND METHODS

Influenza is a highly infectious virus which affects the respiratory tract. After an incubation period commonly lasting one to two days<sup>1</sup>, infected individuals can experience a sudden onset of symptoms including fever, headache, chills, sore throat, dry cough, runny nose and fatigue<sup>2</sup>. Influenza viruses are categorized as either type A, B or C, with the majority of clinical illness caused by types A and B<sup>2</sup>.

Otherwise healthy individuals who contract the virus can usually expect to make a full recovery<sup>3</sup>. However, for some groups, such as the very young, the elderly and those suffering from chronic illnesses, the virus may have serious consequences<sup>4</sup>. Its impact on morbidity and mortality amongst these groups is significant; the ECDC estimates that each year the average number of people in Europe who die prematurely due to influenza infection is 40,000<sup>5</sup>. The virus also places significant strain on health systems when its circulation is at its peak<sup>6</sup>.

Historically, the goal in countries which attempt to control the health and economic burden of influenza through mass vaccination has understandably been directly protecting those most at risk of serious complications. In the last ten years some health authorities have also opted to vaccinate healthy children in addition to the traditional approach of targeting at risk groups. Children experience some of the highest attack rates during influenza outbreaks and also play a key role in the spread of the virus, although they do not experience the same rates of complications or death as at risk-groups. 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.

The inclusion of healthy children and adolescents within seasonal influenza vaccination programmes hitherto remains far less widespread than for the elderly or people with predisposing conditions. There are a number of historical reasons for this, including concerns over safety, effectiveness, and cost-effectiveness. This review looks at the history of seasonal influenza vaccination programmes which have included healthy people under the age of 18 and discusses whether the policy should be employed more widely in European countries.

The report is broken down into three sections. In the first section we examine the data which provided the rationale for childhood and adolescent vaccination in countries where programmes are already in place, as well as what comparable information is available for other European countries who do not yet recommend vaccinating this age group. The second section attempts to place this data in the broader health policy landscape and outline the key factors which must be considered in relation to the expansion of vaccination to younger age groups. Finally, we conclude with some recommendations for European policy makers based on our findings.

## 2. RATIONALE FOR SEASONAL VACCINATION OF CHILDREN AND ADOLESCENTS

The earliest instance of a universal influenza vaccination programme for healthy children began in Japan in 1962<sup>7</sup>, although this was halted in 1994. More recently other large developed countries such as the USA, Canada and the UK have all issued recommendations for the vaccination of healthy children and adolescents of varying ages. The detailed reasons underpinning vaccination policy differ between countries but can nonetheless be grouped into two broad categories: reducing the burden of disease in younger age groups through direct protection and indirectly protecting high risk groups from disease by disrupting community transmission.

### 2.1. 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<sup>8</sup>. Common symptoms seen in children are fever, cough, rhinorrhoea and rhinitis<sup>9,10</sup>, with the potential for serious complications such as acute otitis media<sup>11,12,13</sup>, an infection of the middle ear, bacterial co-infection with streptococcus pneumoniae<sup>8</sup> or methicillin-resistant staphylococcus aureus<sup>14,15</sup> and febrile seizures<sup>16,17</sup>. The impact of uncomplicated and complicated influenza in children and adolescents on health-related quality of life (HRQoL) has not been widely reported but data for other generally self-limiting childhood infections suggest that the adverse effects can be very distressing for both children and their families<sup>18,19</sup>. A recent study from Australia showed that parents of children with influenza like illness reported HRQoL scores that were significantly below those who did not, the authors concluding that “the public health impact of ILI in children on the QoL in families is far from negligible<sup>20</sup>.”

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 2002-03 and 2003-04 flu seasons showed that the rates for visits to medical clinics and emergency departments due to laboratory confirmed influenza in children <5 were in the range of 50 to 95 and 6 to 27 per 1,000 children, respectively<sup>10</sup>. The risk of hospitalisation for healthy children decreases with age, with children aged <2 years old experiencing rates similar to other groups which have been traditionally been targeted for vaccination<sup>12,21,22,23,24</sup>.

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)<sup>25,26,27</sup>. The specific impact that childhood influenza has on the wider economy due to parents and responsible individuals having to take time off work to care for those who become sick has also been investigated. A prospective cohort study carried out in three large American companies found that employees with at least one child in their household with self-reported acute respiratory tract infection reported significantly higher levels of absenteeism due to household illness (0.8 versus 0.3

days) than those with no children reporting ARI<sup>28</sup>. Those with children who had ARI which met the criteria for ILI also had greater lengths of absence due to household illness than others (0.9 versus 0.5 days). 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 children at risk of complications, provided the rationale for the Advisory Committee on Immunization's (ACIP) decision to recommend all American children aged 6 months to be vaccinated on an annual basis<sup>29</sup>. A similar argument was put forward by the Canadian National Advisory Committee on Immunisation (NACI) in recommending the vaccination of children in aged 6 months to less than two years in the 2011-12 season<sup>30</sup>, with the upper age limit extend to less than five years in the following season<sup>31</sup>.

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<sup>32,33</sup>. For example, data drawn from England<sup>34</sup> over the course of eight consecutive seasons (2000-01 to 2007-08) show similar rates of GP consultations (61 per 1,000) and hospitalisations (2 per 1,000) for children aged 6 months to four years as 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<sup>32</sup>. The observed average number of days absent fell in the range of 1.3 to 6.3 (median range 2 to 4). Absenteeism due to childhood influenza is expected to increase as female labour market participation for those aged between 20 and 64 moves towards the 75% target set by the European Commission in 2010<sup>35</sup>.

## 2.2. INDIRECT PROTECTION

Influenza is transmitted when a susceptible individual comes into contact with droplets produced by someone who has already become infected<sup>36</sup>. In modelling the impact of influenza vaccination, 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) and the effectiveness of available vaccines<sup>37</sup>. Further exploration of the technical aspects of infectious disease modelling are beyond the scope of this paper but in order to highlight the role that indirect protection plays in the overall effect of influenza vaccination programmes we will briefly discuss the concept of the basic reproductive number, otherwise known as  $R_0$ .

$R_0$  is defined as the average number of secondary infections due to a single case when placed in an entirely susceptible population<sup>38</sup>. The  $R_0$  for influenza has historically ranged anywhere from 1.2 to 9<sup>39</sup> and it is intuitively evident that each case of an infection must lead to at least one additional case ( $R_0 \geq 1$ ) in order for it remain in circulation. From this observation, 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 virus means that the degree of susceptibility within populations remains high from year to year, particularly for Type A viruses<sup>40</sup>. Some mutations can also make the virus more infectious which in turn increase the value of  $R_0$ <sup>40</sup>. 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 in decline such as the elderly<sup>29</sup>. As the critical threshold for protection is proportional to the effectiveness of vaccination, low values for the latter can mean prohibitively high values for the former<sup>39</sup>.

Some research has suggested that the levels of population coverage which would be achieved in the event that all Europeans recommended to receive a vaccination were actually vaccinated would still be insufficient to disrupt transmission<sup>39</sup>. However, this is based on a strong assumption of homogenous mixing in the population i.e. all individuals are equally likely to come into contact with one another<sup>41</sup>. Other studies have demonstrated the increased frequency of contacts amongst children as well as between them and adults, relative to other age groups<sup>42</sup>. This gives rise to the possibility of targeting children and adolescents for influenza vaccination in order to maximise the impact of the programme through reduced transmission<sup>43</sup>. This argument is further strengthened by data on higher vaccine efficacy for newer influenza vaccines (e.g. live attenuated<sup>44</sup> and adjuvanted<sup>45</sup> influenza vaccines) delivered to children, meaning lower coverage rates within the subpopulation may still be able to induce noticeable decreases in incidence among other age groups.

There is data derived from a number of observational studies which demonstrates the impact that vaccinating younger age groups can have on influenza transmission<sup>46,47,48</sup>. 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<sup>7</sup>. Over the period where the routine programme was in operation, mortality attributable to influenza and pneumonia fell by 10,000 while all cause-mortality declined by 37,000. Importantly, no comparable decline was observed in the United States over the same period and deaths promptly rose after the programme was discontinued, which when taken together appear to suggest that the decline was strongly associated with the childhood influenza vaccination.

For observational studies of the effect of influenza vaccines the main sources of uncertainty for decision makers to take into account are potential confounding by indication and the lack of laboratory confirmed viral endpoints<sup>49</sup>. As a result, there has been a desire for randomised clinical trials (RCTs) to be carried out to confirm the presence of herd immunity. The authors are aware of only one such study: a cluster randomised 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 offers similar conclusions to the studies named above, showing that the vaccine was 61% effective at preventing influenza among unvaccinated persons in communities randomised to receive the vaccine<sup>50</sup>. Despite there being a vibrant debate over the validity of data generated from observational studies relative to that from RCTs with conflicting data on the level of agreement between the two<sup>51,52,53</sup>, it is clear that the results of this study along with those from the various



non-randomised studies influenced the decisions in both the US and Canada to recommend the vaccination of healthy children.

Further randomised trials would be of great assistance to other countries considering whether to introduce routine vaccination of children and adolescents. However, the scope to conduct such trials in the future is heavily constrained on the grounds of practicality (randomising entire communities is unfeasible) and cost<sup>49</sup>. A solution to this problem is to utilise mathematical modelling techniques to produce estimates for likely impact of vaccination programmes on seasonal influenza epidemics<sup>37</sup>. 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<sup>54</sup>. The Joint Committee on Vaccination and Immunisation (JCVI), the UK's national immunisation technical advisory group (NITAG), 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<sup>55</sup>. An additional benefit of mathematical models is that economic data can simultaneously be integrated to with effectiveness estimates to provide a measure of cost-effectiveness for new programmes.

In the context of influenza, 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 to include those aged from 2 to 18 years (using a live attenuated influenza vaccine (LAIV)) was likely to be highly cost-effective based on the UK threshold<sup>56</sup>. A similar analyses 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%)<sup>57</sup>. In 2012, the JCVI considered the evidence and recommended a staggered roll out of an extended programme from those aged 2 to 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<sup>58</sup>.

Mathematical models are nonetheless imperfect reflections of reality and overreliance on their findings for decision making has been criticised, especially in cases where the inclusion of economic data has been seen to act as a barrier to the introduction of new vaccines<sup>59</sup>. However, although the UK has implemented their programme with limited direct evidence of its likely impact, the phased roll out has allowed for early assessment of its effects, with early evidence suggesting indirect protection may be occurring<sup>60</sup>. 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.

### 3. EUROPEAN POLICY LANDSCAPE

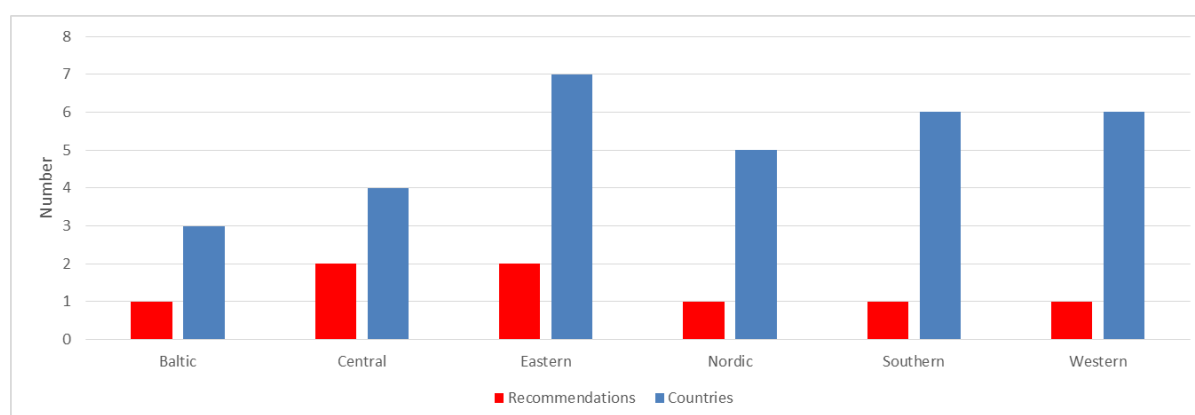
For the purposes of reviewing current vaccination policy towards influenza among all European countries, we have placed them into six regions based on geographical proximity. The groups and their constituent countries can be found in Table 1.

**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			

Only eight countries currently have a general recommendation for the vaccination of children and/or adolescents: Austria, Finland, Latvia, Malta, Poland, Slovakia, Slovenia and the United Kingdom. Of these, only Finland, Latvia and the United Kingdom provide the vaccine free of charge. Figure 1 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 European Centre for Disease Prevention and Control (ECDC)<sup>61</sup> and the Vaccine European New Integrated Collaborative Effort (VENICE) survey of counties for the 2011-12 influenza season<sup>62</sup>.

**Figure 1: Number of countries with a general recommendation for the vaccination of children and adolescents by geographical region**



### Baltic Countries

Latvia is the only Baltic country with a positive recommendation for the young. They provide TIV free of charge to all children aged  $\geq 6$  months and  $< 3$  years, as well as to those aged  $\geq 65$ . This is in keeping with its general approach to vaccination policy which is amongst the most aggressive in Europe<sup>63</sup>. For example, vaccination is mandatory for all state employees and 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 very low according to the most recent VENICE group survey. Although Estonia and Lithuania also recommend that those aged  $\geq 65$  are vaccinated, they do not provide public funding for the programme. The latter has higher uptake in the elderly than Latvia but coverage is still well below recommended levels.

**Table 2: Age groups with a general recommendation for seasonal influenza vaccination and coverage rates in 2011-12 for countries in the Baltic region** - Fields highlighted in red indicate that public funding is available for the vaccine while fields in blue receive no public funding

Age Groups with General Recommendation <sup>61</sup>	Vaccination Coverage 2011-12 Season (%) <sup>62</sup>		
	Estonia	Latvia	Lithuania
6 to 23 months		0.1	
65+ years	-	1.7	18.5

### Central European Countries

Both Poland and Austria recommend the vaccination of children and adolescents using TIV, the latter opting to vaccinate from  $\geq 7$  months to  $< 16$  years and the former from  $\geq 13$  months to  $< 18$  years. The recommendations in both countries were originally made in 2010<sup>64</sup>, although Austria subsequently reduced the upper limit from  $< 18$  years to  $< 16$ <sup>65</sup>. Neither country provides public funding for these programmes nor has a high vaccination coverage rate. Germany and Liechtenstein both provide vaccine free of charge for persons aged  $\geq 60$  and  $\geq 65$ , respectively, with the German state of Saxony including those aged  $\geq 6$  months within their recommendations<sup>66</sup>.

**Table 3: Age groups with a general recommendation for seasonal influenza vaccination and coverage rates in 2011-12 for countries in the Central region** - Fields highlighted in red indicate that public funding is available for the vaccine while fields in blue receive no public funding

Age Groups with General Recommendation <sup>61</sup>	Vaccination Coverage 2011-12 Season (%) <sup>62</sup>			
	Austria	Germany	Liechtenstein	Poland
7 to 12 months	-			
13 months to 4 years	-			1.4*
5 to 14 years	-			2.4
15 years	-			-
16 to 19 years				-
50 to 54 years	-			
55 to 59 years	-			-
60 to 64 years	-	-		-
65+ years	-	-	-	14.2

\*Includes children aged 6 to 12 months although they are not recommended to receive the vaccine.

### Eastern European Countries

In Eastern Europe, Slovenia and Slovakia recommend seasonal vaccination of children, the latter for ages  $\geq 6$  months to  $< 13$  years and the former for ages  $\geq 6$  months to  $< 3$  years, with no reimbursement of vaccine costs. Slovenian vaccination policy differs from most other European countries in that childhood vaccination across nine disease areas is mandatory, with no exceptions based on religious belief and fines for those who fail to comply<sup>63</sup>. The remaining countries have the following recommendations: those aged  $\geq 18$  in the Czech Republic, aged  $\geq 60$  in Hungary and  $\geq 65$  in Bulgaria, Croatia and Romania. Only Romania provides public funding for the vaccine and no countries are close to reaching the 75% target for at risk groups.

**Table 4: Age groups with a general recommendation for seasonal influenza vaccination and coverage rates in 2011-12 for countries in the Eastern region** - Fields highlighted in red indicate that public funding is available for the vaccine while fields in blue receive no public funding

Age Groups with General Recommendation <sup>61</sup>	Vaccination Coverage 2011-12 Season (%) <sup>62</sup>						
	Bulgaria	Croatia	Czech R.	Hungary	Romania	Slovakia	Slovenia
6 months to 2 years						2.7**	0.14*
3 years to 12 years							
18 to 59 years			-				
60 to 64 years			-	31.9		21.9	
65+ years	-	-	-		20.9		16.2

\*Data is only for those aged up to 23 months; \*\* Data includes children aged 13 to 15 years despite this groups not being recommended.

### Nordic Countries

Finland has had a publicly funded vaccination programme for all healthy children aged  $\geq 6$  months to  $< 3$  years since 2007/08<sup>67</sup>. Importantly, this is part of their routine schedule and as a result they have achieved higher levels of uptake than other countries with a childhood recommendation (36.2% in 2007-08)<sup>68</sup>. Iceland also provides reimbursement for vaccine but only for those aged  $\geq 60$ . The remaining countries all recommend that persons aged  $\geq 65$  be vaccinated but do not provide funding.

**Table 5: Age groups with a general recommendation for seasonal influenza vaccination and coverage rates in 2011-12 for countries in the Nordic region.** Fields highlighted in red indicate that public funding is available for the vaccine while fields in blue receive no public funding.

Age Groups with General Recommendation <sup>61</sup>	Vaccination Coverage 2011-12 Season (%) <sup>62</sup>				
	Denmark	Finland	Iceland	Norway	Sweden
6 months to 3 years		-			
60 to 64 years			-		
65+ years	51	-	-	36	44

### Southern European Countries

Among Southern European countries only Malta has a positive recommendation for childhood influenza vaccination ( $\geq 6$  months to  $< 3$  years) but this is not part of the routine schedule. Cyprus has no general age group recommendations and Greece has a publicly funded seasonal programme for

those aged  $\geq 60$ . Italy, Spain and Portugal all advise the vaccination of the  $\geq 65$  population, with funding provided in both Iberian countries. Uptake in those aged  $\geq 65$  ranges from 43.4% in Portugal to 62.7% in Spain.

**Table 6: Age groups with a general recommendation for seasonal influenza vaccination and coverage rates in 2011-12 for countries in the Southern region** - Fields highlighted in red indicate that public funding is available for the vaccine while fields in blue receive no public funding

Age Groups with General Recommendation <sup>61</sup>	Vaccination Coverage 2011-12 Season (%) <sup>62</sup>					
	Cyprus	Greece	Italy	Malta	Portugal	Spain
6 months to 5 years				-		
55 to 59 years				-		
60 to 64 years		-		-		
65+ years		-	62.7	-	43.4	57.7

#### Western European Countries

As previously mentioned, the Joint Committee on Vaccination and Immunisation (JCVI), the UK government's advisory body on vaccine policy, issued a recommendation that all healthy children and adolescents aged  $\geq 2$  years to  $< 17$  years be vaccinated using the live attenuated influenza vaccine<sup>56</sup>. The intention is for the programme to be phased in over a number of years, with the first pilot programmes that were introduced during the 2013/14 season delivering promising results<sup>60</sup>. Belgium recommends that persons aged  $\geq 50$  are vaccinated while Luxembourg has limited its recommendation to  $\geq 65$ , but the programmes are not funded in either country. On the other hand, France ( $\geq 65$ ), Ireland ( $\geq 65$ ) and The Netherlands ( $\geq 60$ ) all have fully funded routine seasonal vaccination, with the latter achieving the highest uptake in  $\geq 65$  of all European countries.

**Table 7: Age groups with a general recommendation for seasonal influenza vaccination and coverage rates in 2011-12 for countries in the Western region** - Fields highlighted in red indicate that public funding is available for the vaccine while fields in blue receive no public funding

Age Groups with General Recommendation <sup>61</sup>	Vaccination Coverage 2011-12 Season (%) <sup>62</sup>					
	Belgium	France	Ireland	Luxembourg	Netherlands	United Kingdom
2 to 16 years						-
50 to 59 years	-					
60 to 64 years	-				-	
65+ years	-	54	56.3	45.1	77.2	-

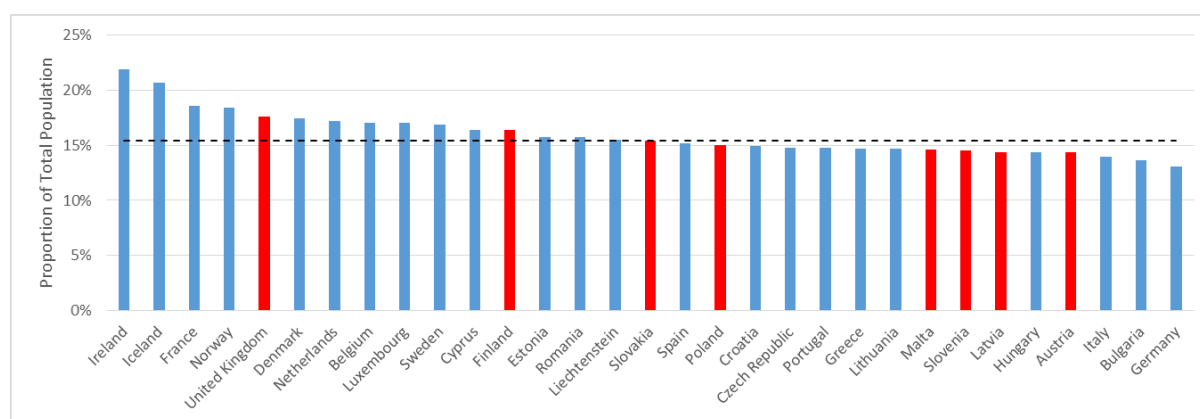
### 3.1. POLICY CONSIDERATIONS FOR EUROPEAN COUNTRIES

The limited rollout of influenza vaccination for healthy children along with the variation in recommendations among countries who have them is confirmation that a consensus has yet to be reached over the policy<sup>69</sup>. In an attempt to explain this variation, we have identified four main policy considerations around both the recommendation and subsequent implementation of influenza vaccination for children and adolescents: demographic factors, treatment factors, health system factors and cultural factors.

#### 3.1.1. 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 2 shows the proportion of the population aged 0 to 14 years for selected European countries. Of the countries with a recommendation for childhood vaccination (those highlighted in red), the UK has the highest share of school-aged children with 17.6%, with Finland being the only other country above the median of 15.4%.

**Figure 2: 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

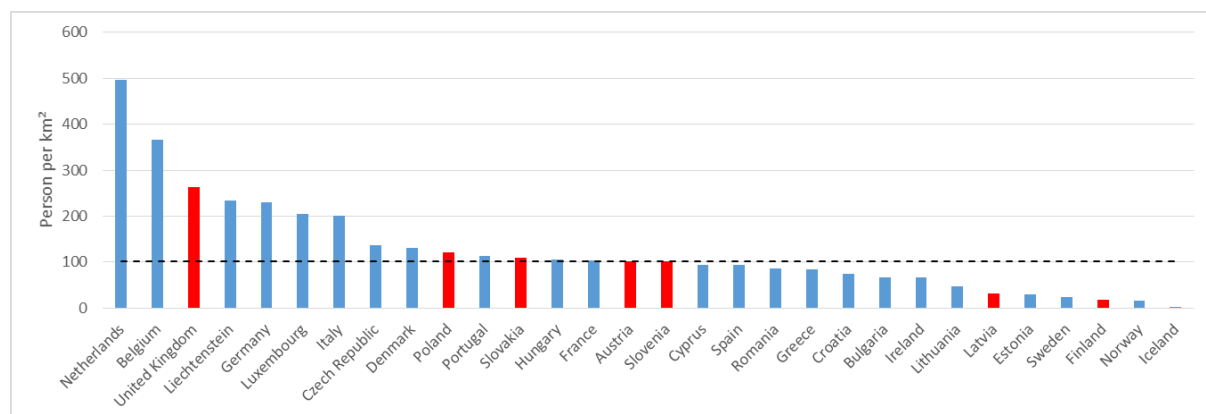


However, a relatively large young population does not guarantee that the burden of influenza among them will be significant, with variables which influence this also having important implications for whether vaccinating children can provide indirect protection to at risk groups. As was briefly touched upon during previous section, a distinction has been drawn between high risk groups and high transmission groups. The former generally encompasses those who traditionally have been recommended for seasonal vaccination, such as the elderly, infants and those with predisposing health conditions, while the group most frequently associated with the latter are

school age children<sup>70</sup>. In some circumstance both groups may overlap (for example in the season following the pandemic outbreak), 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 urbanisation and social contact patterns<sup>42</sup>.

Europe is one of the most densely populated regions in the world, with 116.9 persons per square kilometre (km<sup>2</sup>) in 2012<sup>71</sup>, although substantial intra and inter country variation exists. Most recent estimates show Malta has the highest population density at 1327.4 persons per km<sup>2</sup> kilometre and Iceland had the lowest at 3.2 person per km<sup>2</sup>. Figure 3 shows all the countries, with the exception of Malta included in the review ranked from highest to lowest. Among countries recommending some form of childhood vaccination, the UK again has the highest population density with Poland the only other country above the median. Although variations in density appear to have an impact on the frequency of contacts, a large scale study in a sample of European countries found the age and intensity of contact patterns to be highly consistent<sup>42</sup>. This is important as it allows evidence generated on the impact of childhood influenza vaccination in countries which have already instituted programmes to potentially be used to inform decisions elsewhere.

**Figure 3: European countries (excluding Malta) ranked by their population density 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



The profile of national workforces is another important influence on the potential benefit of vaccinating children against influenza. Female labour market participation has been steadily increasing since the early 1990s<sup>72,73</sup>. There are many reasons for this trend, however, the driver which holds the most importance in the context of childhood influenza vaccination is the squeeze that ageing European populations place on labour supply. This 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 the appeal of protecting children against influenza much greater 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.

### 3.1.2. TREATMENT FACTORS

The starting point for decision makers when evaluating whether a new vaccine or new indication should be recommended and introduced into the schedule is evidence of efficacy and safety. Evidence on this is usually provided through an RCT of the protection that the vaccine provides against pre-determined clinical endpoints, with the results then scrutinised by national and international regulatory agencies during the marketing authorisation process<sup>74</sup>. The need for rapid evaluation of influenza vaccines due to changing compositions from season to season and infeasibility of carrying out annual RCTs has led the EMA to develop a unique set of processes for their authorisation 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.

A number of different meta-analyses of RCTs examining the efficacy (i.e. level of immune response to vaccination) of inactivated and live attenuated influenza vaccines administered to healthy children have been carried out<sup>75,76,77</sup>. These studies suggest that 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. However, one study found LAIV to be superior to TIV in terms of efficacy in children aged ≥2 years (80% versus 48%)<sup>75</sup>, with the pooled estimate of efficacy of LAIV in children aged between 6 months and seven years from another providing similar results (VE 83%: 95% CI 69–91%)<sup>76</sup>. A phase III trial of an adjuvanted inactivated influenza vaccine carried out in 2011 found it to provide 86% 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<sup>78</sup>.

Normally this type of data from Phase III clinical trials, along with evidence of cost-effectiveness where applicable, would be sufficient to guide decisions over whether a treatment should be introduced. This has not been the case for influenza vaccines, however, as the trials which measure efficacy are usually of relatively short duration and do not fully account for effect modifiers which may be present in routine practice. In contrast to efficacy, effectiveness measures the protection provided by the vaccine when used in the field and are usually provided through non-randomised, observational studies.

A number of such observational studies have been carried out in European children. 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 to 50 months<sup>79</sup>. Another similar Finnish study of TIV showed effectiveness against influenza A to be 84% (95% CI 40–96%) and 45% (95% CI -34–78%) for influenza B<sup>80</sup>. A multi-centre case-control study of vaccine effectiveness during the 2012-13 season found that, after adjusting for the impact of comorbidities, the vaccine effectiveness in those aged 0 to 14 years was 22% (95% CI -37-56%), 37% (95% CI -44-72%) and 36% (95% CI -41-71) against influenza B, influenza A (H1N1) and influenza A (H3N2), respectively<sup>81</sup>.

There is currently no effectiveness data for live attenuated and adjuvanted vaccines in European populations due to their limited usage in routine practice. Preliminary data from the early phases of the UK programme has recently been published; a comparison of cumulative disease incidence in areas where the delivery of LAIV to children aged between 4 and 11 years old has been piloted and



those which have not showed the vaccine impact to be 66%, although this did not reach statistical significance<sup>60</sup>.

The apparent lack of data on effectiveness of both inactivated and live attenuated influenza vaccines in healthy children has been cited as a significant barrier to wider implementation of childhood influenza vaccination<sup>33,82</sup>. 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 officials in the UK to introduce the vaccine based on current evidence suggests that in the meantime other countries may choose to implement their own programmes rather than wait for this information to become available.

### 3.1.3. HEALTH SYSTEM FACTORS

The structure of a country's health system places a number of constraints on decision makers when determining optimal vaccine policy<sup>83</sup>. Important considerations include whether policies are made at the national or local level<sup>83</sup>, the availability of funding and reimbursement for vaccines and existing capacity to deliver vaccination programmes<sup>84</sup>, for example through schools. There are also 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<sup>85</sup>. 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<sup>86</sup>.

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<sup>87</sup>. The JCVI is also supported by staff from Public Health England, the national agency responsible for health protection and promotion, who have access to high quality virological surveillance data along with extensive information on resource use<sup>58</sup>. This is made possible by the highly centralised nature of the NHS in England, along with the long-term investment that has been made in the infrastructure to allow both epidemiological data collection and analysis<sup>88</sup>. Centralised systems can also take advantage of their monopsony powers to negotiate lower vaccine prices<sup>89</sup> and, as has been the case in England as well as the other UK territories, has helped foster a system of school nurses who are able to facilitate mass vaccination of children in schools<sup>90</sup>.

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 consequently for the benefits from herd immunity to be realised<sup>39</sup>. 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<sup>91</sup>. Schools based programmes of mass vaccination can potentially deliver higher levels of uptake, although robust data of their actual effect is limited<sup>92</sup>, with the added benefit that the vaccine can

be delivered prior to onset of the influenza season. They 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<sup>93</sup>. However, there are barriers to implementing schools based systems such as the high capital expenditure required to create the necessary infrastructure or existing healthcare and/or educational provider arrangements making such programmes impossible.

Providing vaccine free of charge has also been shown to be an important influence on uptake<sup>94,95</sup>. In countries where the assessment process for vaccines contains a health economic component, the cost-effectiveness of new programmes, such as influenza vaccine for health 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 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, possibly leading to lower coverage. In this case decision makers might view a recommendation as tautological and therefore 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<sup>96</sup>. 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 especially important in the context of an intervention with low perceived health benefit for the recipient, which some may regard influenza vaccination, regardless of age, to be, as this makes the decision to substitute more palatable. As a result of this, many countries offer financial incentives to physicians to ensure sufficient levels of coverage can be reached<sup>94</sup>, although research on the effectiveness of such incentives, despite showing these types of incentives to be effective, is generally of a low quality<sup>97</sup>. These create an additional cost for vaccination programmes which become part of the implementation decision.

Table 8 gives an overview of health system and vaccination policy features for a sample of European countries<sup>85</sup>. Data on whether or not schools based immunisation takes place were taken from a review of human papillomavirus vaccination programmes<sup>98</sup>. 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.

**Table 8: Overview of health system and vaccine policy making features for a sample of European Countries**

Country	Main system of finance	Final decision maker on immunisation	Funding source for immunisation schedule	Tender system in place	Main provider of immunisations	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

Country	Main system of finance	Final decision maker on immunisation	Funding source for immunisation schedule	Tender system in place	Main provider of immunisations	NITAG	Consideration of cost-effectiveness required
UK	Taxation	Ministry of Health	Tax-funded	National level	Public providers, including school nurses	Yes	Yes

### 3.1.4. CULTURAL FACTORS

Deaths due to influenza among healthy children remain rare<sup>99</sup>. Hospitalisation is also uncommon compared to elderly populations and at risk groups, with the exception of children aged <2 years. These have perhaps been the driving factors behind many countries' decision to focus their limited resources on directly protecting these individuals. However, as further evidence emerges regarding the benefits for those most at risk of complications and death due to the disruption of transmission associated with childhood and adolescent influenza vaccination, the validity of this argument becomes more uncertain<sup>58</sup>.

Nonetheless, even in situations where robust data on the effectiveness and efficiency of vaccinating children and adolescents exists, the question remains as to whether exposing otherwise healthy young people to the risks associated with the vaccine, no matter how small, in order to protect others is justifiable from both an ethical and practical standpoint<sup>100</sup>. The answers from both perspectives depend largely on the prevailing cultural trends in the countries in question<sup>101</sup>. Taking ethics firstly, it could be argued that countries with existing vaccine schedules which 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 disease within combination vaccinations, which distributes the disutility of adverse events across diseases, may explain why uptake has not fallen.

Beyond ethical considerations, which are largely linked to the empirical estimation of individual risk trade-offs, another important practical consideration is the sensitivity of public opinion regarding the utility of vaccination to external messaging regarding safety and efficacy<sup>102</sup>. The agency model of medicine in which patients pass responsibility for decisions over their own care or the care of those for whom they are responsible based on their expert knowledge can become problematic when the views of these perceived sources of expertise, such as media outlets, are not supported by empirical evidence<sup>103,104</sup>. As the downstream effects of falls in coverage can be highly detrimental for public health<sup>105</sup>, the impact that any change to the existing schedule might have on the likelihood of declines in public confidence due to inaccurate information regarding the safety and/or effectiveness of vaccination is an important consideration for decision makers. 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...”<sup>56</sup>

Quantifying the risk that changes to the schedule pose to public confidence is extremely difficult, even more so when it is not formally part of the decision making criteria but may still have some subconscious influence on levels of risk aversion among decision makers themselves. Therefore it is not possible to say with any assurance how important a role it has played in influencing the speed of adoption of childhood influenza vaccination in Europe. What is clear is that the UK in particular has had success in expanding its schedule while maintaining high levels uptake. It remains to be seen

whether this will continue with the roll out of childhood seasonal influenza programme and, if so, whether other European countries attempt to replicate the approach.

## 4. CONCLUSIONS AND RECOMMENDATIONS

The unpredictability of the influenza virus continues to present a major challenge to health professional and policy makers alike. Vaccination nonetheless remains the most effective means of reducing the incidence and severity of influenza<sup>2</sup>, yet uptake 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 <2 years old, 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.

Childhood influenza vaccination also highlights some of the key themes which belie decisions regarding whether to implement public health interventions in general, and vaccination programmes in particular. Unlike most pharmaceuticals, the benefits of vaccination are not entirely confined to those who receive them directly. As such, indirect protection can form a substantial part of their value from both public health and finance perspectives. Assessment criteria and impact models which fail to capture this reality are destined to misrepresent the true value of vaccination. However, there are moral and ethical issues with placing too great an emphasis on indirect protection. These can only be removed through strict assurance regarding safety otherwise the negative impacts for public confidence in vaccination may be catastrophic.

Closely related to the issue of indirect protection is the level of evidence required to justify the introduction of public health programmes. The variables influencing the success or failure of public health interventions are numerous, with the added complication that many are difficult to observe and measure. This can lead to decision makers favouring the status quo rather than choosing to make decisions over policies for which there are clear losers and opaque winners. This is particularly true of vaccination, where an individual would never know if they would have become sick had they not been vaccinated but are fully aware of whether they are denied resources as the result of the investment decision. Novel approaches to implementation of such programmes which aim to mitigate risks, as has been done in the UK, are therefore required to guard against these inertial forces.



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