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Editorials

Collaborative efforts are needed to improve use of influenza immunisation in Europe

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This week's special issue of Eurosurveillance highlights various aspects and challenges related to the prevention of influenza by vaccination. Influenza is among the infectious diseases with the highest incidence and associated serious morbidity and mortality that can be prevented by vaccination. In the article of the Vaccine European New Integrated Collaboration Effort (VENICE), investigators report details of vaccine coverage among different segments of the target population in the European Union (EU) and European Economic Area (EEA) Member States. Among elderly persons, only the Netherlands succeeded in reaching vaccine uptake levels above 75%, the 2010 target of the World Health Organization (WHO); twelve countries reported 50% to 75% coverage, nine countries were even below the 2006 target of 50% and seven countries could not report any data. Importantly, vaccine uptake among clinical risk groups and health care workers was even lower. In a detailed report from France, F. Rance *et al.* reported that only 17% of asthmatic children were vaccinated against influenza. Furthermore, on behalf of the European Vaccine Manufacturers, M. Rodriquez de Azero *et al.* showed that the vaccine doses per capita only marginally increased from 17% to 20% in the years 2003 to 2006. So how can we be more successful in the prevention of influenza?

In the United States (US), it has been estimated that on average 51,000 persons die from influenza during epidemics each year [1]. Based mostly on figures from the US, most of the influenza burden is among persons with risk-elevating medical conditions such as chronic respiratory, cardio- or cerebrovascular or renal disease, diabetes and immunodeficiency, and among infants, older adults and residents of long-term health care settings [2]. Similar epidemiological studies in Europe could be of use to convince local politicians about the need to reduce the burden among these vulnerable groups. The Health Council of the Netherlands, for example, decided to lower the age threshold for vaccination from 65 to 60 years in 2007 based on the large excess in the number of primary care visits, hospitalisations and mortality among the healthy aged 60 to 64 years during epidemics [3]. Indeed, the lack of data on influenza burden at the more severe end of the clinical spectrum in many European countries probably contributes to the large variations in vaccine uptake reported to the VENICE investigators.

The success of vaccination is largely determined by its impact on disease burden in the target group when applied in practice. Recently, the effects of influenza vaccination on the incidence of pneumonia and mortality from all causes among the elderly have been debated. In the US, the influenza-associated mortality among elderly persons has not declined over the last decades despite increase in vaccine uptake, whereas in the Netherlands a clear reduction in mortality seems to have taken place after the national influenza vaccination campaign [4,5]. These contrasting findings have led to much discussion mainly about the potential for confounding in non-randomised observational studies, which may have had an impact on the validity of reported effect estimates so far.

An important feature of randomisation is that it removes all kinds of biases; hence randomised controlled trials (RCTs) are considered the paradigm to study vaccine effects. Many RCTs have been conducted among healthy adults showing that vaccination prevented a considerable part of proven influenza infections [6]. Also, a landmark trial among elderly persons demonstrated a 50% reduction in influenza illness [7]. However, such trials with death as an outcome are unlikely to be carried out in Europe. Influenza vaccines are currently recommended for a wide variety of patients, and serious outcomes such as deaths due to infection are infrequent. Thus the design of an RCT would require very large representative study samples. Also the vaccines can only be effective when patients are actually exposed to the virus and the vaccine matches circulating strains neither of which can be predicted. Finally, placebo-controlled influenza vaccine trials in the elderly and most high-risk groups are usually considered unethical in Europe, since as the VENICE survey found vaccinating these persons is recommended in immunisation guidelines in most countries.

Non-randomised case-control or cohort vaccine effectiveness studies are feasible alternatives to RCTs. They have the advantages of applicability in different patient populations, timeliness, reduction of costs, and increased feasibility. However, in observational studies the selection of patients for vaccination is influenced by their risk profile, which may lead to 'confounding by indication'. Typically, the vaccinated group comprises patients with more severe disease or higher risk than the unvaccinated group. Crude, uncontrolled, estimates of the association between vaccination and outcome in such studies, therefore, lead to an underestimation of vaccine effectiveness. Conversely, if refusal of vaccination is typically associated with low functional health status, the unvaccinated group may comprise persons with a worse prognosis than the control group. This so-called 'healthy user bias' will lead to an overestimation of the true vaccine effectiveness. Both types of biases can be present in influenza vaccine studies and it is therefore a challenge to the investigator to prevent and adjust for the confounding in the design of data collection and analysis, and, if possible, to quantify its potential magnitude [8-10].

The report by M. Valenciano *et al.* provides the reader with a very complete overview of the observational studies that were conducted

in the EU Member States and the potential for confounding bias. The authors suggested that in designing studies aimed at measuring accurately and in a timely manner the vaccine effectiveness in Member States, based on an extensive literature review and expert meetings, case-control and cohort studies should be set up, and in the case-control study the main outcome should be laboratory-confirmed influenza. In the same paper much attention has been given to measure as many potential confounding factors as possible. To quantify potential unmeasured bias it was suggested to also conduct cohort studies during pre- and post-influenza seasons. However, pre-influenza seasons are invalid reference seasons because influenza can still be present. Also, terminal patients may be included in cohorts evaluating the pre-influenza season, which can also induce selection bias such that vaccine effects are overestimated, because these patients may refrain from vaccination. These limitations notwithstanding and although more methods are available to quantify the potential impact of unmeasured confounding, the proposed studies are essential attempts to maintain confidence in the benefit of the vaccine programme.

Furthermore, country-specific data on influenza burden and European estimates of the effectiveness of vaccination are needed to estimate the cost-effectiveness of the vaccination programmes. Based on data from the Dutch PRISMA nested case-control study [11] and the abovementioned excess study [3], it was estimated that the vaccination programme in the Netherlands certainly resulted in saving money and concluded that it was cost-effective to vaccinate all adults aged between 60 and 64 years [12]. Consequently, the Dutch ministry of health decided to extend the vaccination programme to the lower age limit of 60 years. However, since the use of resources is different from country to country, such analysis should be initiated in each country or undertaken at an EU level to support the actual implementation of the vaccination programme.

Alarming reports of sudden cardiac failure after influenza vaccination in Israel [13] and the Netherlands [14] during the 2007 influenza season had a negative impact on vaccine acceptance, even though national surveillance data indicated that these few fatal cases could be explained by chance alone and no causative relationship was found. Undoubtedly, more potent adjuvanted vaccines will replace current conventional vaccines in the next few years and many countries are currently considering stockpiling (pre)pandemic vaccines for use on a large scale in a pandemic. For these reasons, a carefully developed risk management plan is necessary to be able to prevent potential harm during mass vaccination campaigns [15].

Finally, it needs to be acknowledged that the development of immunisation recommendations even when supported by, preferably local, evidence does not necessarily lead to acceptance of the vaccine by the public. Various factors determine the uptake of vaccination and educational programmes should be based on evidence from surveys that attempt to predict vaccine acceptance according to health behavioural and implementation models [16-19]. National commitment by government and professionals is crucial and this partly explains the successful performance of countries with better vaccination coverage. Such commitment is now needed at an EU level so that all countries can achieve such results. To conclude, collaborative action involving experts from the fields of public health, clinical epidemiology, psychology and health economy is needed to set up a European-wide infrastructure for studies on the epidemiology, (cost-)effectiveness, risk management and acceptance to further improve confidence and coverage in the influenza immunisation programmes. Reports published in this issue of Eurosurveillance provide useful guidance how to proceed.

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National Seasonal Influenza Vaccination Survey in Europe, 2008

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A cross-sectional survey was undertaken with the European Union (EU) Member States and Norway and Iceland to describe seasonal influenza immunisation in the 2006-7 season, in particular to identify country-specific recommendations for risk groups, obtain vaccine uptake information and allow comparison with global recommendations. A standardised questionnaire was completed electronically by each country's project gatekeeper. Of the 29 countries surveyed, 28 recommended seasonal influenza vaccination for older age groups (22 for those aged > 65 years), and in one country vaccine was recommended for all age groups. All countries recommended vaccinating patients with chronic pulmonary and cardiovascular diseases and most countries advised to immunise patients with haematologic or metabolic disorders (n=28), immunologic disorders (n=27) and renal disease (n=27), as well as residents of long-term care facilities (n=24). Most countries recommended vaccination for staff in hospitals (n=25), long-term care facilities (n=25) and outpatient clinics (n=23), and one-third had such recommendations for workers in essential (n=10), military (n=10) and veterinary services (n=10) and poultry industry (n=13). Eight countries recommended vaccine for pregnant women; and five advised to vaccinate children (with age limits ranging from 6 months to 5 years). Twenty countries measured influenza vaccine uptake among those aged > 65 years (range 1.8%-82.1%), seven reported uptake in healthcare workers (range 14%-48%) and seven assessed coverage in persons with underlying medical conditions (range 27.6%-75.2%). The data provided by this study can assist EU states to assess and compare their influenza vaccination programme performance with other countries. The information provides a comprehensive overview of policies and programmes and their outcomes and can be used to inform joint discussions on how the national policies in the EU might be standardised in the future to achieve optimal coverage. Annual surveys could be used to monitor changes in these national policies.

Background

Although immunisation against influenza is believed to benefit the elderly, measuring precise effectiveness of vaccine against morbidity and mortality in this group is difficult. Several recent studies and reviews have calculated widely varying levels of effectiveness and have described methodological hurdles for making accurate measurements [1,2]. One randomised study among older adults found that vaccine efficacy was 57% for preventing laboratory-confirmed influenza infection among adults aged 60-69 years and 23% among a small number of persons aged 70 years and older [3].

In May 2003, the World Health Assembly (WHA) recommended vaccination for all people at high risk, which it defined as the elderly and persons with underlying diseases. The participating countries, including all European Union (EU) Member States, also committed to the goal of attaining vaccination coverage of the elderly population of at least 50% by 2006 and 75% by 2010 [4].

The Vaccine European New Integrated Collaboration Effort (VENICE, http://venice.cineca.org/) project was launched in January 2006. It is funded by the European Commission Directorate General for Health and Consumer Protection (DG SANCO) within the framework of the EU Public Health Programme and supported by the European Centre for Disease Prevention and Control (ECDC). Currently 27 EU Member States and two EEA countries (Norway and Iceland) participate in the project whose aim is to establish a European network of experts who work with national immunisation programmes. Immunisation programmes and vaccination policies in Europe differ from country to country, partially reflecting the differences in healthcare delivery systems [5]. Prior to this work there had only been one European wide survey published in 2003 and there was no information routinely available to policy makers on the current status of influenza programmes and how they were implemented and monitored [6]. There is a need to improve knowledge on which population groups are targeted for vaccination, how immunisation programmes are resourced and which indicators are (or could be) used for monitoring vaccine uptake.

We conducted a web-based survey to describe the policies and practices of seasonal influenza immunisation programmes in the European Union and two countries of the European Economic Area (EEA), Norway and Iceland, for the 2006-7 influenza season.

This survey may establish the basis for conducting annual surveys of influenza vaccination policies and practices.

More information on the project and detailed results are presented in the "Final Report. National Seasonal Influenza Vaccination Survey in Europe, 2007" (henceforth referred to as: "Final report"), available from: http://venice.cineca.org/Influenza_Study_Report_v1.0.pdf

Methods

The survey was a collaborative study between the ECDC, VENICE project and EU and EEA countries. Each country had previously identified and enrolled gatekeepers responsible for conducting all VENICE surveys inside their countries.

A standardised questionnaire was developed predominately using close-ended questions. Information was sought to describe seasonal influenza vaccination policies during the 2006-7 influenza season; to identify influenza recommendations for different risk groups and the general population; to determine data sources, capacity and feasibility for routine seasonal influenza vaccination coverage monitoring; and to obtain the most recent vaccination coverage results for the general population and for the risk groups targeted by the recommendations. As vaccination coverage is estimated through a variety of means, we asked for information on the methodology used by each country to make these estimates: administrative methodologies (using some kind of information from those who are responsible for delivering vaccination to calculate the numerator and denominator); survey methodologies (using a sample of those targeted for vaccination); or by using pharmaceutical distribution or sales data. In addition information was collected on the form of payment for the costs of vaccine and its administration. The questionnaire is available in the "Final report", Appendix 2.

The questionnaire was piloted by three VENICE project-leading partners: Italian Istituto Superiore di Sanitá (ISS), the French Institut de Veille Sanitare (INVS) and the Irish Health Protection Surveillance Centre (HPSC). After the pilot, the questionnaire was reviewed and amended. The questionnaire was deployed as a cross-sectional web-based survey in January 2008 and was available for all participating countries on VENICE website. Gatekeepers in each participating country entered data directly on-line. The data were analysed using the computer-based EpiInfo (version 3.3.2) software. Gatekeepers in each country were asked to validate the results.

Not all countries were able to provide data on influenza vaccine uptake in our survey, but information on some countries was available from a study undertaken by the University of Zurich for the 2006-7 season [7]. In this study a population-based computer-assisted telephone survey was carried out in eleven countries. These data were used for vaccine coverage comparisons in our study and are presented here.

Results

Response rate and results of data validation

The response rate to the survey was 100% (29/29). Response rate to data validation was 83% (24/29) as of 2 April 2008.

Recommendations for specific target groups

All countries reported having recommendations on influenza immunisation for specific target groups in the population.

Age groups

The elderly were included in vaccination recommendations in all 29 countries (100%). Twenty-two countries reported specific recommendations for those aged 65 years or older, in six countries immunisation was recommended from the age of 50 (Poland), 55 (Malta) or 60 years (Germany, Greece, Hungary and Iceland). Austria was the only country in the survey which recommended influenza vaccination for all age groups. Besides Austria, five countries (Estonia, Finland, Latvia, Slovakia and Slovenia) recommended routine immunisation of children (with the age limits varying from six months to five years). Detailed information regarding vaccination recommendations for various age groups is presented in "Final report" Table 1.

People with chronic medical conditions

Seasonal influenza vaccine for patients with chronic pulmonary and cardiovascular diseases was recommended by all countries (100%). Nearly all countries recommended vaccinating individuals with haematological or metabolic disorders (n= 28, 97%), those with immunologic disorders (with or without HIV/AIDS) (n=27, 93%) and those with renal diseases (n= 27, 93%). Eight countries (28%) recommended vaccine for pregnant women (Table 1).

Other groups

Twenty-four participating countries (83%) recommended vaccination for residents of long-term care facilities. Fourteen countries (48%) advised to vaccinate household contacts of persons for whom vaccination was recommended.

Occupational groups

Most countries indicated that influenza immunisation was recommended for healthcare staff working in occupational settings such as hospitals (n=25, 86%), long-term care facilities (n=25, 86%) and outpatient care clinics (n=23, 79%). Some countries recommended vaccination for poultry industry workers (n=13, 45%) and essential, military and veterinary services (each n=10, 34%) (Figure 1). Three countries, Denmark, Finland and Sweden (10%) did not have recommendations for vaccination in any occupational setting.

Table 1

Influenza immunisation recommendations for persons with chronic medical conditions (without regard to age) or pregnancy. National seasonal influenza vaccination survey in Europe, January 2008 (n=29)

Condition	Number of countries (%)
Pulmonary diseases	29 (100)
Cardiovascular diseases	29 (100)
Haematologic or metabolic diseases	28 (97)
Renal diseases	27 (93)
Diseases of the immune system	27 (93)
HIV/AIDS	26 (90)
Children on aspirin	17 (59)
Hepatic diseases	14 (48)
Any condition that can compromise respiratory function	11 (38)
Pregnancy	8 (28)

Monitoring vaccine coverage

All countries except one have mechanisms to monitor influenza vaccination coverage. Most (n=14) measure uptake in both the general population and selected target groups, some (n=7) only in target groups, some (n=7) only in the general population. One country does not have any means of monitoring influenza vaccine coverage.

Concerning monitoring vaccination coverage in specific risk groups targeted by vaccine recommendations, only one country, the United Kingdom reported having mechanisms to monitor influenza vaccination coverage in each of the recommended target groups by actively collecting immunisation data. Further 20 countries had mechanisms for monitoring coverage in some selected risk groups, including 18 countries that monitored uptake in the elderly. Norway reported monitoring influenza vaccination coverage in a combined group including those aged ≥65 years and persons with underlying clinical conditions.

Monitoring coverage in groups other than the elderly was uncommon. Aside from the UK only the Netherlands, Hungary and Iceland reported having mechanisms for monitoring uptake among clinical risk groups and Hungary, Portugal and Iceland had mechanisms to monitor vaccine coverage among staff working in occupational settings. Seven countries reported they had no mechanisms to monitor influenza vaccine coverage in risk groups: Austria, Bulgaria, Czech Republic, Greece, Latvia, Spain and Poland. However, with the exception of Greece these countries monitored coverage rates in the general population. ("Final report", Table 5).

Methods of monitoring coverage

The mechanisms used to measure vaccination coverage vary by country and include health record data, surveys or pharmaceutical data.

Eight countries reported using only administrative methods (number of vaccines administered, payment reimbursement claims) to monitor vaccination coverage. Fourteen countries combined administrative with other methods (surveys or pharmaceutical data), one country combined survey and pharmaceutical data, one used only survey, and four only pharmaceutical data. Only one country does not have any method and does not monitor vaccine coverage.

Twenty-seven (93%) countries reported using one or several methods to measure the numerator (number of people vaccinated) for assessing influenza vaccine coverage in recent years (2004-2007). Sources used most frequently were health record data (medical documentation and/or computerised medical records and/or immunisation registries/data) which were used in 20 countries. Other countries used pharmaceutical data, surveys or other administrative methods.

Eleven countries (39%) collected data for numerator assessment annually and ten (36%) collected this data once at the end of season (Table 2). Only six countries attempted to monitor coverage during the season.

Eight countries used administrative methodology to estimate the denominator (number of people who should be vaccinated) for the occupational target groups and the group comprising persons with underlying clinical conditions, and ten countries have some information on other group categories. ("Final report" Table 9)

Seven countries used survey methods to estimate vaccination coverage, including household surveys (Germany), telephone surveys (Germany, Ireland, Portugal, Sweden, and France), mail surveys (Cyprus, Sweden) or individual interviews (Belgium).

Pharmaceutical distribution or sales data were formally collected in sixteen countries ("Final report", Table 6)

Vaccination coverage results

The elderly

Influenza vaccination coverage among those aged > 65 years age group was measured in nineteen countries (65%). The range of uptake in this age group varied from 1.8% to 82.1%. In addition, Norway provided combined vaccine uptake for those aged > 65 years

Figure 1

Vaccination recommendations for occupational groups. National seasonal influenza vaccination survey in Europe, January 2008 (n=29)

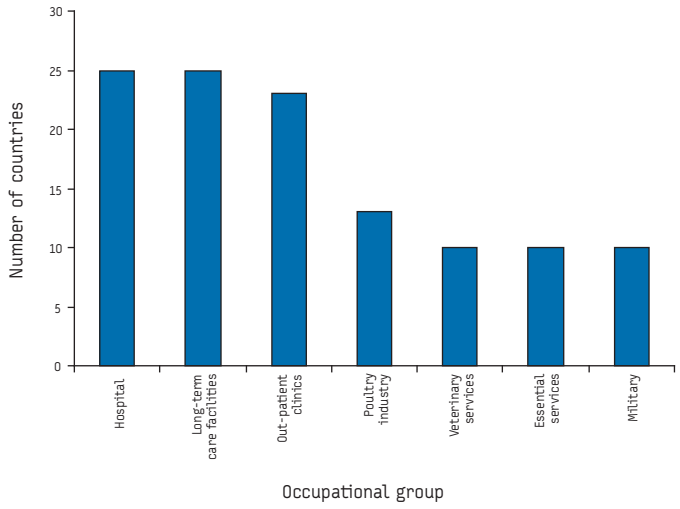


Table 2

Frequency and time of collecting numerator data for assessing influenza vaccine coverage. National seasonal influenza vaccination survey in Europe, January 2008 (n=28)

Frequency of numerator assessment	Countries
Monthly	Latvia, Lithuania, United Kingdom
Every two months	Ireland
Every three months	Estonia, Poland
Once, at the end of influenza season	Cyprus, Czech Republic, Hungary, Germany, Luxemburg, Norway, Romania, Slovenia, Malta, Portugal
Annually (specify date/time)	Austria (spring) Bulgaria (April) Denmark (first quarter of the year) Finland (April) Iceland (December) Italy (late spring) Netherlands Slovakia (May) Spain (first quarter of the following year) Sweden (end of summer, before next season) France (September)
Never	Greece

and clinical risk groups (50%) (Figure 2). Generally, members of EU-15 had better coverage than the 12 countries which joined the EU more recently. In the former, vaccine coverage in the elderly ranged from 32.1% to 82.1%, while in the latter coverage ranged from 1.8% to 34.1% (Figure 2).

Healthcare workers and clinical risk groups

Nine countries were able to report vaccination coverage for either healthcare workers or persons with underlying clinical conditions. Five countries reported coverage for both risk groups, two countries reported coverage of healthcare workers only and two countries had data on clinical risk group coverage only. Coverage in these groups ranged from 14% to 48% for healthcare workers and 27.6% to 75.2% for clinical risk groups (Figure 3).

Payment for vaccination

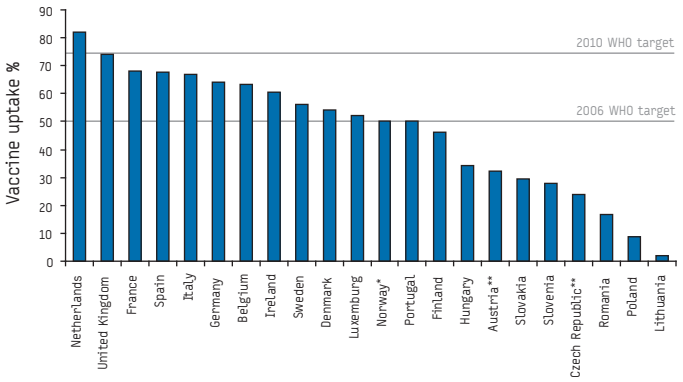
People aged > 65 years received the influenza vaccine free of charge in 13 (45%) countries, eight of which had achieved coverage > 50%. In three countries the elderly paid the full cost of vaccine and administration. In 12 countries the vaccine was free of charge for some people in the older age groups or there were partial subsidies for this age group, whereas in one (Sweden) the form of payment varied by county. (Figure 4)

Most countries offered free or partially refunded vaccination for other target groups:

In 12 countries vaccination was free for all and in five for some of the patients with underlying chronic illness. Nine countries offered free vaccination to all recommended occupational groups, 12 countries to some recipients in these groups. All children received the vaccine free of charge in three countries and some

Figure 2

Vaccination coverage in those aged ≥ 65 years. National seasonal influenza vaccination survey in Europe, January 2008 (n=22)



* Vaccination coverage in combined group of those aged ≥ 65 years and those with underlying clinical conditions
**Vaccination coverage estimated through telephone surveys; source: University of Zurich [7]
Note: Data on vaccination coverage in season 2006-7, except for Germany and Poland (season 2005-6) and Belgium (season 2003-4)

Figure 3

Vaccination coverage in clinical risk groups and healthcare workers. National seasonal influenza vaccination survey in Europe, January 2008 (n=9)

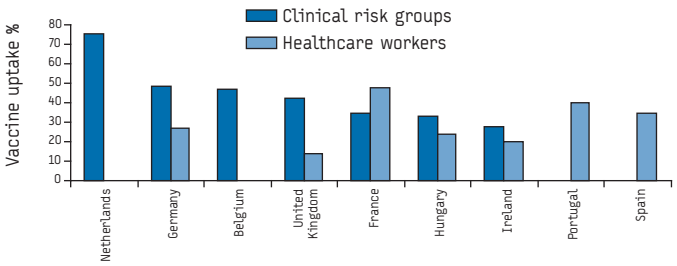
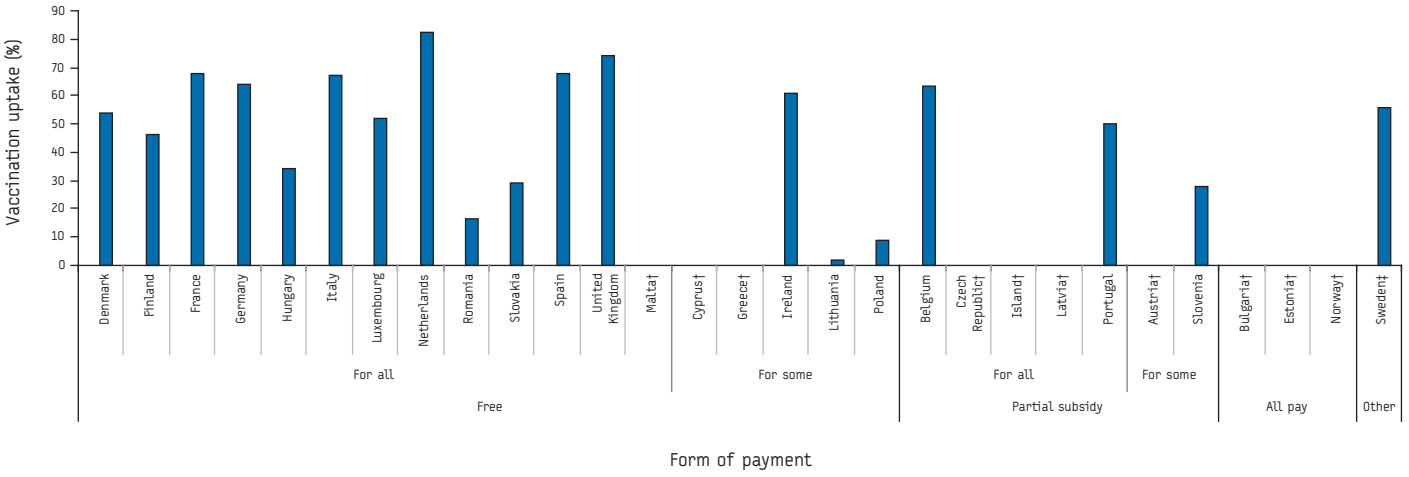


Figure 4

Costs of vaccination and vaccination coverage for persons aged ≥ 65 years, by country. National seasonal influenza vaccination survey in Europe, January 2008 (n=29)



Note: Data on vaccination uptake in season 2006-7, except for Germany and Poland (season 2005-6) and Belgium (season 2003-4)
† Countries unable to provide data on vaccination coverage in persons aged > 65 years
‡ In Sweden subsidies vary by county, approximately two-third of counties give free vaccination to this age groups

children in 10 countries. (Figure 5, more details in "Final report" Table 13).

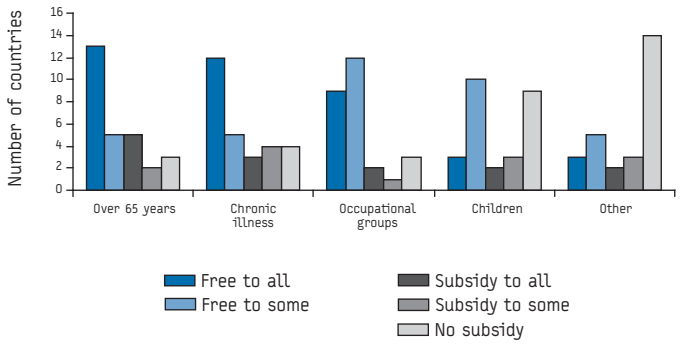
Discussion

This is the second published study which investigates influenza vaccination policy across all EU Member States, Norway and Iceland simultaneously, and reflects most up to date information available from each country [6]. ECDC undertook a smaller study with its Advisory Forum members in 2006 that served as a model to develop this study. Validation for the results is afforded by comparison with a recent population-based computer-assisted telephone survey carried out in eleven European countries for 2006-7 influenza season [7]. The coverage results were similar except for two countries. The VENICE approach involving gatekeepers already engaged in immunisation services would seem to be successful although validation and 'sign-off' by the authorities themselves was more difficult. It was impressive that this survey, despite its complexity, was completed in a short time (12 weeks from start to finish). A strong conclusion would be that ECDC and VENICE could make this an annual survey. Annual completion would become easier as it would simply be a matter of updating the previous years' results and noting differences. The standardised information that this could provide would enable the EU Member States, ECDC, other EU institutions and WHO to assess their progress towards achieving implementation of internationally accepted recommendations on influenza prevention and control.

Our study highlights the challenges facing those authorities in Europe that have to implement the 2003 WHA resolution. The health systems in Europe are quite different. Some countries have different policies regarding influenza vaccination between different regions/counties within national borders. Vaccine coverage is measured by different methods (medical records, surveys, data from the pharmaceutical industry) in different countries making direct comparisons difficult. However this survey shows that all EU countries, Norway and Iceland have adopted the 2003 WHA recommendation that vaccine should be offered to the elderly. All countries offer influenza vaccine for those aged 65 years and older, with a few countries lowering the age limit to 50, 55 or 60 years. What countries are finding hard is to monitor and achieve performance when compared against the WHA targets (coverage in the elderly of 50% by 2006 and 75% by 2010).

Figure 5

Costs of vaccination by group. National seasonal influenza vaccination survey in Europe, January 2008 (n=29)



In the 2003 survey of 26 European countries, 18 countries reported having mechanism for monitoring vaccination coverage, and 14 could monitor coverage in the elderly with an uptake ranging from 25% to 81% [6]. In our survey, 19 of the 29 countries monitored uptake specifically in the elderly obtaining a range of 2% to 82%. Norway measured it combined with risk groups. Comparison of the results for the nine countries that participated in both surveys is encouraging, with all countries improving coverage, some dramatically, which suggests that an ability to monitor uptake results in improvement ("Final report" Table 10). The fact that more countries were able to provide vaccine coverage data this year is also encouraging and suggests that countries are striving to obtain this data. However extrapolation of the trend data from the telephone surveys conducted by the University of Zurich [7] suggest that unless there is a radical improvement in the next two seasons only two or three of the 29 EU/EEA countries are likely to achieve the 2010 WHA target. Coverage in the elderly and those with chronic illnesses will become ever more important in the EU. Population projections for the 25 EU countries indicate that the proportion of the elderly population that was 17% in 2003 will rise to 29% by 2050 [8].

Currently only five countries recommend vaccination for young children and one country recommends vaccination for all age groups (Austria). Increasingly, children are seen as a group that bears substantial morbidity from influenza and plays a role in transmitting influenza to vulnerable contacts. Vaccination of this age group is already recommended in some countries outside Europe [9,10]. The limited effectiveness of the currently available vaccines in young children may have been an impediment for many countries to embark on such a strategy. However an ECDC convened panel noted few data from Europe itself and that information is now urgently needed [11].

The European situation regarding vaccination coverage among other groups for whom vaccination is recommended (occupational groups, people with underlying medical conditions, residents of long stay care facilities, household contacts of persons to whom vaccination is recommended etc.) is highly variable. Influenza vaccine is recommended for these groups in many countries but monitoring and data for vaccine coverage was available for less than one-third of the countries. It seems a major challenge for monitoring vaccine coverage are the difficulties in obtaining information on the denominator, i.e. the size of these risk groups, which can be inaccurate due to the lack of registries for target groups, population movement, or inaccurate census.

Another issue regarding influenza vaccine coverage is assessment of the numerator, i.e. the number of those who are vaccinated. All, except two, countries assess some numerator, but have to use different methods to obtain this information: health records, pharmaceutical distribution and sales data or surveys (telephone, mail, household). As different methods are used it is challenging to harmonise vaccine coverage monitoring and to compare vaccine coverage rates between countries. Numerators can be underestimated due to underreporting, incomplete reporting and failure to include information from all relevant sources. The numbers can also be overestimated, such as when vaccine sales data are used, as these data may not necessarily reflect the number of actually administered doses. Because of the demonstrated diversity of European immunisation delivery and monitoring systems it may be worth to consider obtaining comparable influenza vaccine

coverage data through the utilisation of a standard sampling methodology across all countries.

Vaccination of healthcare workers was recommended in the WHA in 2003 [12]. This is based on a number of reasons. There is good evidence that vaccination of staff provides indirect protection to vulnerable elderly patients in care homes, a group at high risk of the severe effects of influenza [13,14]. Vaccination of healthcare workers also has direct benefit for this occupational group as it provides individual protection and reduces absenteeism from work, and fewer working days are lost [15,16]. Our study found that most of the countries recommended vaccination for staff working in healthcare facilities but vaccine coverage was known only in one–third of the countries and, as seen in other studies, the uptake was very low [7].

Thirteen of the 20 countries which were able to estimate vaccine uptake among those aged 65 years or older achieved the 2006 WHO target. One country (the Netherlands) has already achieved the 2010 WHO target uptake in this group. The fact that nine EU/EEA countries still in early 2008 did not have any system in place with which they could estimate uptake in this high risk group is worrying and suggests that Europe will struggle to achieve the WHA target for 2010 or even to produce good statistics. Therefore a strong conclusion of this study is the need for all European authorities to have information systems in place that can monitor influenza vaccine coverage.

Previous studies have shown that subsidising the cost of vaccination increases the uptake rate [7]. Costs associated with vaccination can be a deterrent to the uptake, particularly if borne by the individual. This survey reports that half of the countries have adopted a policy of provision of free vaccine, in total or in part, predominantly for the elderly, individuals with chronic disease, occupational groups. Only three countries reported that the costs of vaccine and its administration are borne fully by recipients >65 years and these countries had noticeably low uptake.

Increasingly, European states are appreciating the need to have in place systems and processes to deal with the emergence of a pandemic strain including use of specific vaccines when these become available [17]. All countries should have the ability to deliver and monitor influenza vaccination programmes in the non-emergency setting (seasonal influenza programme) to be able to build on these well established, tested systems to prepare for the potential pandemic.

Conclusion

The limitations of our results predominantly relate to factors which make comparison of data between countries difficult but which are beyond the control of this study. As demonstrated, there is substantial variation in health systems, delivery of immunisation programmes and immunisation recommendations between and, sometimes, within countries. Various methodologies are used to measure immunisation coverage, and even when similar methodologies are described, it is possible that the accuracy of such estimates may vary between countries depending on the strength of information systems (ability to calculate numerator and denominator, target population groups etc.). However, having identified these differences, European countries are now better informed to identify how they can standardise their approach and in future provide more easily comparable data. The importance of high quality and comprehensive information systems in identifying populations targeted for influenza vaccine and in then monitoring uptake in these groups has been highlighted in this study. Countries can benefit by learning from each other; how some countries achieved high uptake, whether related to additional immunisation resources, social mobilisation, or incentives.

This is one of the first EU-wide surveys on influenza vaccination programmes and shows variability between countries with regard to recommendations for vaccine usage and uptake rates. Our survey revealed that there is substantial gap between recommendations and real vaccine uptake. Vaccine uptake in most countries needs to be improved.

However the data provided by this study can assist in standardising national and EU-level policies and recommendations and monitoring influenza immunisation programmes in future years. Survey results have shown that achieving high vaccine coverage for those who are at risk remains a serious public health challenge. We believe that European countries can use the results of our study to assess their own progress towards achieving WHO goals of influenza vaccine uptake and identify local obstacles that must be overcome if these goals are to be met. Policies and resources of countries that perform best can provide insight to guide other states struggling to achieve high uptake rates.

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Trends in influenza vaccination coverage rates in the United Kingdom over six seasons from 2001-2 to 2006-7

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In order to understand motivations and barriers to vaccination, and to identify people's intentions to get vaccinated for season 2007-8, influenza vaccination coverage was assessed in the United Kingdom (UK) from 2001 to 2007. Between 2001 and 2007 representative household surveys were performed by telephone interview with 12,143 individuals aged 16 or older. The overall influenza vaccination coverage rate dropped non-significantly from 25.9% in 2005-6 to 25.0% in 2006-7 (p=0.510). In the elderly (≥65 years) the rate decreased from 78.1% to 65.3% (p=0.001), and the odds ratio of being vaccinated compared to those not belonging to any of the risk groups targeted by vaccination decreased from 36.6 to 19.9. Healthcare workers and chronically ill persons had odds ratios of 2.0 and 15.5, respectively. The most important reason for getting vaccinated was a recommendation by the family doctor or nurse, and this was also perceived as the major encouraging factor for vaccination. No recommendation from the family doctor was the main reason for not getting vaccinated. A total of 38.4% of the respondents intended to get immunised against influenza in 2007-8. From 2001 to 2006 a slightly increasing trend (p for trend across seasons <0.0001) in vaccination coverage was observed in the UK, but in 2006-7 the rates returned to the level of 2004-5. Less media attention to the threat of avian influenza after 2005 may have contributed to the recent decrease of vaccination rates.

Introduction

Experts at the World Health Organization and elsewhere agree that the world is now closer to another influenza pandemic than at any time since the 1968 pandemic which was the last of the three influenza pandemics that occurred in the twentieth century [1]. This underlines the importance of achieving sufficiently high immunisation coverage in the general population and above all in sub-populations at high risk of influenza complications.

There is ample evidence in the medical literature that vaccination is an efficacious and safe preventive measure against seasonal influenza [2-4]. It not only provides substantial health benefits, but may also be associated with significant economic benefits [5,6], particularly among the elderly, healthy working adults and children. In the United Kingdom (UK), where complications of influenza cause 3,000 to 4,000 deaths every year, the government policy [7] is to vaccinate: i) all people aged 65 years and over (age-related policy introduced in 2000–1), ii) individuals aged 6 months and over who fall into a clinically defined risk group (chronic respiratory disease, including asthma, chronic heart disease, chronic renal disease, diabetes and immunosuppression), iii) individuals living in long-stay, residential-care institutions, iv) health and social-care professionals involved in direct care. Despite the relatively high influenza vaccination coverage of the target groups in UK, continuing efforts by physicians, the National Health Service and policy makers, are needed to contain the burden of the disease.

Earlier publications based on cross-sectional data have reported influenza vaccination rates in the UK [8-10]. However, the availability of a consistent dataset for six consecutive seasons permits us to expand the usual cross-sectional approach for the analysis of vaccination rates.

In this study we analyse influenza vaccination coverage and related trends in the UK over six consecutive vaccination seasons, with special regard to high-risk group coverage. Further objectives are to elucidate the motivations for being or not being vaccinated, and to reveal the intentions to get vaccinated for the season 2007-8.

Methods

The present survey is part of an ongoing international assessment of influenza immunisation uptake in five European countries, France, Germany, Italy, Spain and UK [11-14]. During six influenza seasons, from 2001-2 to 2006-7, a population–based telephone survey addressing different topics was carried out in December and January among UK households. Computer Assisted Telephone Interviews (CATI) were conducted, and the interviewees' consent was obtained at the beginning of each call. There was no study intervention. Using quotas and weights based on data from official national sources guaranteed that the reported sample of the survey (completed interviews) was representative of the non-institutionalised UK population aged 16 years or older [15]. The weighting was applied in terms of sex, age, profession, geographic region and town size.

Four target groups based on national recommendations were specified [7]:

1. Individuals aged 65 years or older
2. Individuals who suffer from a chronic illness
3. Individuals who work in the medical field
4. Individuals belonging to one or more of the above groups 1, 2 and 3 (composite target group)

The non-target group comprised individuals belonging to neither of groups 1, 2 and 3. The survey questionnaire has been published before [15]. The questions covered vaccination uptake, reasons for and against vaccination, as well as the intention to get vaccinated the next season. In order to assess the gap between actual and intended vaccination rates, the ratios between the actual coverage level in a given season and the intended level in the same or the next season were calculated. Since 2003-4, supplementary information on the chronic illness status of the interviewees was collected. Data comparing target groups with the non-target group were obtained from season 2003-4 to 2006-7. Starting with season 2005-6, the questionnaire also included questions on pandemic and avian influenza.

Sample weights were applied, and the annual datasets were pooled to correct for small deviations from the age and sex quotas requested. SPSS® version 14 for Windows was used for the statistical evaluation. The chi-square test was used to assess bivariate associations of categorical variables and the chi-square test for trends was used for assessing time trends of categorical variables. For all statistical tests two-sided $p \leq 0.05$ was set as the level of statistical significance. If available, exact p-values were displayed. Ninety-five percent confidence intervals (CI) were reported where appropriate. Expected predictor variables were considered candidates for multivariate analysis, and logistic regression was used to identify independent correlates of the outcome of interest, i.e. vaccination coverage. The following variables were regarded as potential predictors of vaccination coverage: sex, age, chronic illness, working in the medical field, educational level, and income. Multivariate logistic regression analysis was used to assess the independent explanatory value of these covariates. A full model (containing all covariates) was first fitted from the 2006-7 data. Non-significant predictors ($p > 0.05$) were subsequently removed on a stepwise basis. The regression models for all other seasons were based on the remaining set of influential covariates identified from the 2006-7 dataset. Due to the descriptive nature of this data, no correction for multiple testing was made.

Results

Response rate

In the 2006-7 coverage study 2,037 individuals completed the interview (6.0% of responses). A total of 12,143 persons were interviewed since 2001. An overview of the samples is shown in Table 1. The samples were composed similarly over the years and are representative of the population aged 16 or older [15,16].

Vaccination coverage rate

Figure 1 shows the actual as well as the intended influenza vaccination rates over time. Overall vaccination coverage rates declined non-significantly from 25.9% (95%CI: 23.9;27.9) in season 2005-6 to 25.0% (95%CI: 23.0;27.0) in season 2006-7 (p=0.510). With regard to the coming season of 2007-8, 38.4% (95% CI: 36.8-40.1) of the interviewees intended to get immunised against influenza (Figure 1). The ratio of actual and intended vaccination rates ranged between 0.58 and 0.69 over the years. Throughout, the intention to get vaccinated was much higher than the actual rate in the current or in the previous season (Figure 1).

In 2006-7, the proportion of vaccinated persons who had also been vaccinated in the past (22.4%) was very similar as in the previous season (22.6%), but significantly higher than in the seasons before 2005-6 (19.8% to 20.4%). At the same time, the proportion of individuals who had been vaccinated in the past, but not in the current season, decreased from 17.6% in 2005-6 to 16.9% in 2006-7 (not statistically significant), possibly a fluctuation of an increasing vaccination trend since season 2001-2. In 2006-7, the proportion of respondents who were vaccinated for the first time

Table 1

Overview of samples included in the influenza vaccination coverage surveys, United Kingdom, from 2001-2 to 2006-7 (n = 12,143)

	2001-2	2002-3	2003-4	2004-5	2005-6	2006-7
Total sample size (N)	2,023	2,028	2,026	2,005	2,024	2,037
Mean age (years)	44.5	45	44.9	45.2	44.8	45
(95% CI)	(43.7- 45.4)	(44.2- 45.8)	(44.1- 45.7)	(44.4- 46.0)	(44.0- 45.6)	(44.1- 45.8)
Male	48.8%	48.8%	48.9%	48.8%	48.9%	48.6%
(95% CI)	(48.3%- 49.1%)	(48.3%- 49.1%)	(48.4%- 49.4%)	(48.3%- 49.1%)	(48.4%- 49.4%)	(46.7%- 50.5%)
N	987	989	991	978	990	990
Age ≥ 65 years	18.1%	18.7%	19.2%	18.7%	19.0%	18.9%
(95% CI)	(17.9%- 18.3%)	(18.5%- 18.9%)	(19.0%- 19.4%)	(18.5%- 18.9%)	(18.8%- 18.9%)	(18.7%- 19.1%)
N	366	380	389	375	384	384
Work in the medical field	6.8%	8.2%	7.1%	6.8%	6.6%	6.4%
(95% CI)	(4.9%- 8.7%)	(6.3%- 10.1%)	(5.2%- 9.0%)	(4.9%- 8.7%)	(4.7%- 8.5%)	(4.5%- 8.3%)
N	138	167	144	136	133	130
Chronic illness	-	-	12.0%	14.0%	14.2%	14.4%
(95% CI)			(10.1%- 13.9%)	(12.1%- 15.9%)	(12.3%- 16.1%)	(12.6%- 16.3%)
N			243	281	288	294
Combined target group*	-	-	33.0%	33.2%	33.1%	33.2%
(95% CI)			(31.0%- 35.1%)	(31.1%- 35.2%)	(31.1%- 35.2%)	(31.1%- 35.2%)
N			669	665	671	676

*Includes people aged 65 years and over, suffering from chronic illnesses or working in medical field

(2.6%) was one fifth lower than in the preceding season (3.3%), whereas the proportion of those who had never been vaccinated increased from 57.1% to 58.1%. In spite of this small increase, there is no statistical evidence for a reversal of the decreasing trend in the long-term (p for trend across seasons <0.0001).

Vaccination coverage in target groups

For the target groups, changes in vaccination coverage over time are shown in Figure 2. In the group aged 65 years or older, coverage peaked in season 2005-6 at 78.1% (CI: 73.1%;83.1%), and then returned to 65.3% (95% CI: 60.3-71.3) in 2006-7 (p=0.001). Statistical significance in this case indicates that there may be a long-term upwards trend despite a substantial degree of yearly variation. In every season, coverage in this group was at a significantly higher level than in the non-target group (p<0.0001).

Figure 1

Actual vaccination rate and intended vaccination rate; influenza vaccination coverage surveys, United Kingdom, from 2001-2 to 2007-8

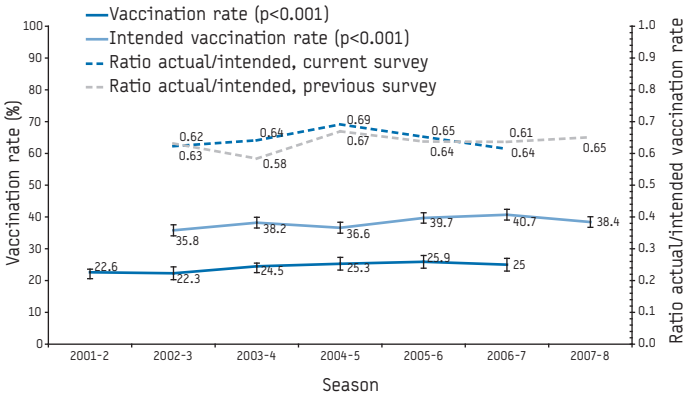
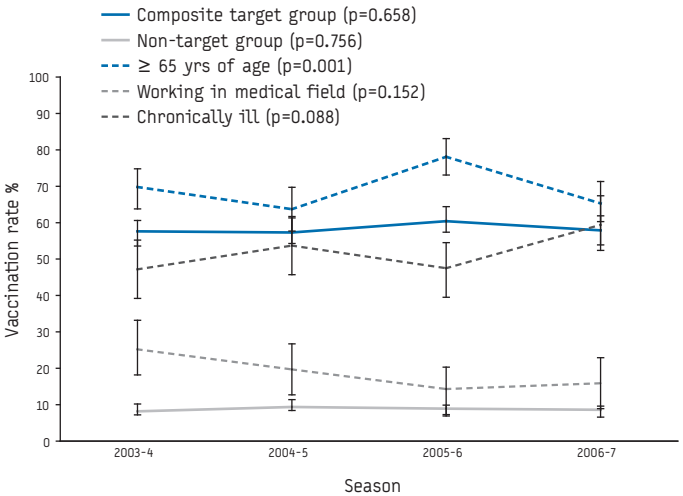


Figure 2

Trend curves of actual vaccination rates in high-risk target groups and in the non-target group; influenza vaccination surveys, United Kingdom, from 2003-4 to 2006-7 (p-values for trends across seasons)



Age-related differences in vaccination coverage over time were shown in Figure 3. Being elderly (≥65 years) was associated with the highest coverage (Figure 3). The lowest values were seen in the 16-39 years old.

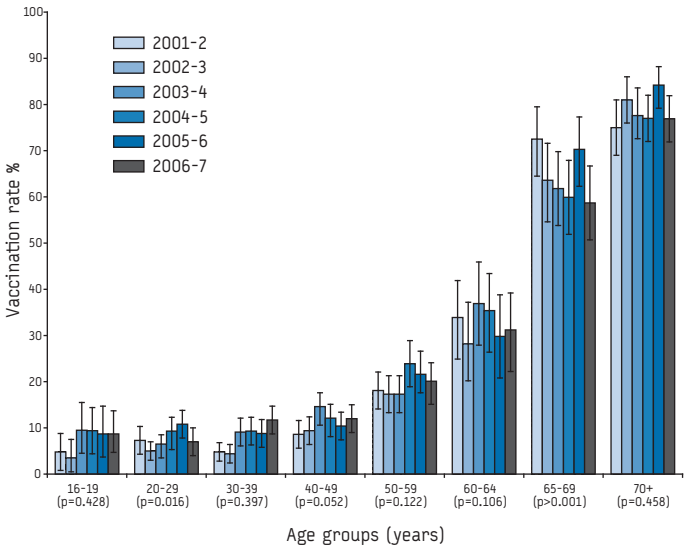
A question exploring the prevalence of chronic illness was included in the questionnaire from season 2003-4 onwards. Over the four observed seasons, significantly higher vaccination rates were found among the chronically ill, compared to the non-target group. In season 2006-7, an increase to 59.4% (95% CI: 52.4-67.4) was seen in this group, contrasting with values of 47.2% (95% CI: 39.2-55.2) in 2003-4 and 47.5 (95% CI: 39.5-54.5) in season 2005-6. Vaccination coverage in the group of healthcare professionals tended to decline over the years (p for trend = 0.152) but after the lowest value of 14.3 (95% CI: 7.3-20.3) in season 2005-6 rose to 15.9% (95% CI: 8.9-22.9) in season 2006-7. Even though the coverage in this group is the lowest among target groups, it still is about twice as high as in the non-target group (8.6%; 95% CI: 6.6-9.6). In the composite target group, vaccination coverage was essentially stable in the period from 2003-4 to 2006-7, with three seasons in the range from 57.3% to 57.9% and a peak of 60.4% (95% CI: 57.4-64.4) in season 2005-6.

Factors influencing vaccination coverage

Multivariate analysis of immunisation coverage accounted for membership in one or several target groups covering age, sex, educational level, and income. Since target group membership was the only covariate that showed a statistically significant effect in season 2006-7, the other potential influences (some of which suffered from considerable numbers of missing values) were excluded from the final logistic regression models (Table 2). A sex difference was apparent over time, with men being moderately less likely than women to be vaccinated (unadjusted odds ratio for women in season 2006-7: 1.2; CI 1.0; 1.5; p=0.062). However, no sex difference was present after adjusting for age, chronic illness, healthcare work and income. In 2006-7, the percentage of men in

Figure 3

Vaccinated population by age groups and influenza seasons; influenza vaccination coverage surveys, United Kingdom, from 2001-2 to 2006-7 (p-values for trends across seasons)



the non-target group was 52%, in the elderly it was 39.6%, in the chronically ill 48.5% and in the healthcare workers 30.8%.

Age 65 years or older was a significant predictor of vaccination (adjusted OR in 2006-7, compared to the non-target group: 19.9; odds ratios (ORs) ranging from 16.8 in season 2004-5 to 36.6 in season 2005-6). Individuals in the chronically ill target group had an odds ratio of 15.5 in season 2006-7, which was higher than in the previous three seasons (OR ranging from 9.3 to 11.2). Being aged 65 years or older and chronically ill raised the prediction of getting vaccinated distinctively in all seasons, with a maximum of 76.4 in season 2004-5. The likelihood of vaccination of health-care professionals was in the range of 1.8 and 3.8, and was 2.0 in season 2006-7.

The probability of vaccination for the composite target group (at least one of age ≥65 years, chronic illness, health-care worker) was 14.6 (CI: 11.5; 18.7) in season 2006-7, which was equal to the average of the four seasons from 2003-4 (data not shown). The highest probability of getting vaccinated was seen in season 2005-6 (OR 15.8; CI: 12.4; 20.1), and there was no trend over the four seasons covered (p for trend = 0.658, data not shown).

Motivations and barriers to vaccination

Table 3 shows reasons for getting or not getting vaccinated and how frequently they were named. In all seasons between 2001-2 and 2006-7 the reasons most frequently stated by those who had been vaccinated were "My family doctor/nurse advised me to do it" and "Because the flu is a serious illness and I did not want to get it". The media coverage of avian influenza and influenza pandemics had influenced the decision of 6.7% of the vaccinated respondents in 2006-7. This subgroup was not statistically different from the other vaccinated in terms of age, sex and belonging to a target group.

In season 2006-7 the most common reason for having never been vaccinated was "My family doctor did not recommend it to me" (38%, Table 3). Individuals previously vaccinated, but not in the current season (2006-7), most frequently said "I didn't think about it, I forgot it" (27.8%, previous season 28.1%), followed by "I do not feel concerned" (23.8%, same as in previous season).

There was little change in the knowledge about influenza vaccination in season 2006-7 compared to the previous seasons. Three-quarters of the surveyed were aware that it is possible to catch influenza even if vaccinated, and about two-thirds knew that

Table 2

Adjusted odds ratios of vaccination coverage in target groups vs. the non-target group (adjusted for age ≥ 65 years, chronic illness, working in the medical field); influenza vaccination coverage surveys, United Kingdom, from 2003-4 to 2006-7 (n = 8,048)

Target group	2003-4 n=2,013*	2004-5 n=1,994*	2005-6 n=2,015*	2006-7 n=2,026*
Age ≥ 65 years				
OR	25.9	16.8	36.6	19.9
(95% CI)	(18.8; 35.6)	(12.3; 23.0)	(25.9; 51.7)	(14.6; 27.3)
p-value	<0.001	<0.001	<0.001	<0.001
N	266	282	248	258
Chronic illness				
OR	10.0	11.2	9.3	15.5
(95% CI)	(6.8; 14.6)	(7.8; 16.1)	(6.5; 13.4)	(10.8; 22.2)
p-value	<0.001	<0.001	<0.001	<0.001
N	144	169	179	186
Chronic illness and age ≥ 65 years				
OR	42.8	76.4	46.2	51.9
(95% CI)	(24.3; 75.3)	(40.3; 144.7)	(27.1; 78.5)	(30.1; 89.6)
p-value	<0.001	<0.001	<0.001	<0.001
N	83	103	105	119
Work in medical field				
OR	3.8	2.4	1.8	2.0
(95% CI)	(2.4; 6.0)	(1.5; 3.9)	(1.0; 3.1)	(1.1; 3.4)
p-value	<0.001	<0.001	0.055	0.017
N	134	123	117	118
Work in medical field or chronic illness or age ≥ 65 years				
OR	18.0	13.0	12.6	3.9
(95% CI)	(17.1; 45.4)	(4.4; 38.6)	(5.5; 28.8)	(1.4; 10.9)
p-value	<0.001	<0.001	<0.001	0.01
N	20	14	24	17

* n< total sample for the season due to missing covariate values
Reference category: non-target group (persons who do not belong to any target group)

the infection is then less severe. A third of the interviewed persons agreed with the statement that the influenza vaccine would protect them against avian influenza, whereas a weak majority disagreed (52.5%).

The survey also showed that most people would be encouraged to get vaccinated in the future:

- "If my family doctor/nurse recommended it to me" (rank 1, 72%),
- "If I had more information on the vaccine regarding efficacy and/ or tolerance" (rank 2, 46%),
- "If my pharmacist recommended it to me" (rank 3, 35%),
- "If I knew more about the disease" (rank 4, 37%),
- "If there were other ways of administering the vaccine (orally, injection without needle)" (rank 5, 34%).

Discussion and conclusion

Telephone interviews have been used on a number of occasions to study vaccination coverage in the UK [9]. The random drawing of telephone numbers has been shown to be a good basis for a high quality selection process [17].

Despite correct sampling non-response is the major potential reason for selection bias. Comparisons of telephone, mail and face-to–face surveys on health-related issues, however, revealed only minor differences between modes of administration and modest non-response effects with respect to prevalence estimates [16,18]. In comparison with mailed surveys, non-response was found to be less content-oriented in telephone surveys [19]. Furthermore, bias due to dissimilar sociodemographic characteristics of individuals not reachable by telephone only slightly affected reporting of illness and related use of medical services, as long as the general population was addressed, and telephone coverage exceeded 90% [19,20]. These reports support the validity of our approach, even though we had no ways to independently confirm self-reported vaccination status. An earlier publication has described the limitations of the present data collection in greater detail [15]. The use of wireless telephones is a growing problem. In the United States (US) persons with landlines were shown to have higher odds of being vaccinated than those with exclusive access to wireless telephones (OR 1.27) [21]. If the same is true in the UK where mobile phones are even more common than in the US [22-24], our reported vaccination rates may have been slightly over-estimated.

The decrease in overall vaccination coverage in the UK in season 2006-7, compared to seasons 2004-5 and 2005-6, was not statistically significant. Coverage was still higher than in the seasons before 2004-5 and there is no strong evidence for a long-term change of trend. In 2006-7, 38.4% of the respondents expressed the intention to get vaccinated in season 2007-8. Thus, in the UK there may be a potential to increase future vaccination coverage provided that those who intend to get vaccinated but in the end do not are better targeted. Additionally, the increasing trend of those who had been vaccinated in the past but not in the current season could be explained by a failure of vaccine campaigns to maintain their trust in vaccination. A decreasing trend, however, was apparent in the age group of 65 to 69 years old respondents whose coverage dropped to the lowest level since season 2001-2 (Figure 3). As vaccinations are offered free of charge by the UK National Health Service, and as it is government policy to vaccinate all people aged 65 years and older we have no explanation for the decreasing trend in this particular age group. No trend over all seasons was apparent in the age group of 70 years or older, although the vaccination coverage in this group also reached the peak level in season 2005-6 and in 2006-7 returned to similar value as in season 2004-5.

In the two years before season 2006-7, the UK media have frequently reported on avian influenza and a potential shortage of antiviral agents. This may have increased the primary care providers' awareness of the risk of influenza pandemic and, by consequence, may have positively affected vaccination coverage in one of the high risk groups, namely the elderly, in season 2005-6. However, after season 2005-6 avian influenza lost the focus of the media [25], which may be a possible cause of the coincident decline in vaccination rates in 2006-7 to levels observed before the 2005-6 season. However, only less than 7% of respondents

Table 3

Ranking of reasons for and against vaccination; influenza vaccination coverage surveys, United Kingdom, from 2001-2 to 2006-7 (n = 10,252)

Motivations to get vaccinated (among those vaccinated in the current season)	2001-2 n=458 Rank (%)	2002-3 n=451 Rank (%)	2003-4 n=497 Rank (%)	2004-5 n=507 Rank (%)	2005-6 n=524 Rank (%)	2006-7 n=509 Rank (%)
My family doctor/nurse advised me to do it	2 (70)	2 (75)	1 (49)	1 (60)	1 (51)	1 (60)
Because flu is a serious illness and I did not want to get it	1 (73)	1 (82)	2 (47)	2 (46)	2 (42)	2 (50)
Because of my age	3 (59)	4 (56)	3 (41)	3 (39)	3 (40)	3 (42)
Because I am not in a very good health	6 (34)	6 (33)	5 (25)	4 (30)	5 (25)	4 (32)
So I do not pass the flu bug to my family and friends	4 (56)	3 (57)	4 (28)	5 (28)	4 (27)	5 (32)
Because the social security system pays for it	5 (40)	5 (36)	6 (25)	6 (26)	6 (24)	6 (29)
Reasons for not getting vaccinated (among those never vaccinated)	**2001-2 n=1,281 Rank (%)**	**2002-3 n=1,274 Rank (%)**	**2003-4 n=1,228 Rank (%)**	**2004-5 n=1,185 Rank (%)**	**2005-6 n=1,155 Rank (%)**	**2006-7 n=1,183 Rank (%)**
My family doctor did not recommend it to me	1 (56)	1 (54)	2 (33)	1 (37)	2 (37)	1 (38)
I have never considered it before	2 (56)	2 (51)	3 (33)	2 (34)	1 (37)	2 (35)
I do not think I am very likely to catch the flu	4 (32)	3 (41)	1 (34)	3 (33)	3 (30)	3 (33)
I am too young to be vaccinated	3 (34)	4 (37)	4 (29)	4 (31)	4 (29)	4 (32)
My pharmacist did not recommend it to me	-	5 (34)	5 (17)	5 (18)	5 (19)	5 (21)

listed the media as one of the factors influencing the decision to get vaccinated. Also, it neither explains the transitory decline in vaccination coverage in the chronically ill group in season 2005-6, nor the more long-term decrease in the healthcare professionals' vaccination rates. Working as health professional in the UK did not distinctly encourage vaccination as the adjusted odds were several magnitudes lower than those of the other defined target groups. Furthermore, the rate of vaccinated healthcare workers seemed to be decreasing (although statistically non-significant). Previous publications on influenza vaccination coverage [26-31] found low coverage rates in healthcare workers in Germany, ranging from 8% to 26% [27]. In comparison, in the UK surveys from 2001-2 to 2006-7 we obtained vaccination coverage in healthcare workers ranging between 14.3% and 25.2%, whereas the rates in non-target group never exceeded 9.4%.

Our observations on immunisation uptake in the UK population are largely consistent with findings from studies performed in the UK using a representative general practice database [32]. One notable difference regarding coverage trends is that in contrast with our findings the study by Coupland et al. found invariably increasing vaccination rates from every season to the next in all risk groups. The reason for these divergent results may primarily lie in the different approaches to collecting data; while Coupland's data were sampled from a subset of the population that visited a general practitioner (QRESEARCH database [33,34]), our data were sampled from the entire population accessible by telephone, irrespective of whether the respondents visited a physician or not.

Vaccination rates of children and young people under 16 years of age were not covered by our article. However, high vaccination coverage in children will be difficult to achieve at least in some countries, as paediatric recommendations for influenza vaccination in healthy children in most countries are nonexistent. This is why reaching high vaccination levels in the risk populations is even more important.

The overall vaccination rate in eleven European countries was 20.2% in season 2006-7 [our survey series, unpublished data]. Thus, in season 2006-7 the vaccination rate in the UK (25.0%) was higher than the European average. In previous seasons, the UK rates were above or slightly below the average of five European countries [13,19,35].

Regarding individual motivations for vaccination, our data confirm that the recommendation from the family doctor or nurse is the most important encouraging factor. Other publications support this finding [15,26,31,36-38]. A better understanding of the disease and administration of the vaccine without needle would generally encourage a third of the surveyed, and more information on the vaccine would encourage two-fifths of the respondents to get vaccinated in the future.

In order to achieve higher vaccination coverage, dealing with barriers to vaccination and enhancing positive motivations remain an important undertaking in the UK. This challenge should be accepted not only by the patients' key motivators, the primary care professionals, but also by government agencies, health professional organisations and independent media, which could all contribute to bridging the knowledge gap.

According to the WHO, the influenza pandemic risk remains on a high level [1]. Efforts should be made at national and international levels to raise coverage as set out in the WHO objectives (i.e. 50% vaccination coverage in the elderly to be reached in 2006 and 75% in 2010 [39]). As in the years before, the UK exceeded the 2006 goal with the 2006-7 vaccination rate reaching 65.3% in those aged 65 years and older. To arrive at the WHO objectives for 2010, though, additional efforts are required, and this remains a challenge for health organisations, primary healthcare providers, government, and the media.

Competing interests

This study was made possible by an educational grant from the European Vaccine Manufacturers Group of the European Federation of Pharmaceutical Industries and Associations (EFPIA), Brussels, Belgium.

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Trends in seasonal influenza vaccine distribution in the European Union: 2003-4 to 2007-8

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Seasonal influenza is widely regarded as a continuing threat to public health, with vaccination remaining the principal measure of prophylaxis. In 2003, the World Health Organization issued targets for influenza vaccine coverage in the elderly of at least 50% by 2006 and 75% by 2010, endorsed by the European Parliament in two resolutions in 2005 and 2006. However, a number of European public health systems lack mechanisms to assess progress in influenza vaccine uptake. The European Vaccine Manufacturers group (EVM) undertook a Europe-wide survey of vaccine distribution over the last five seasons (between 2003 and 2008) to provide baseline data from which vaccination trends may be extrapolated. The survey data showed that the dose distribution level *per capita* in the 27 EU countries increased from 17% in 2003-4 to 20% in 2006-7; this growth was not maintained in the season 2007-8. Even without information on which age or risk groups received the vaccine, an immunisation rate of approximately 20% of the whole population falls short of the public health goal by more than half: an estimated 49% of the total population fall into risk groups recommended to receive the influenza vaccine in Europe. These data provide the only systematic review of vaccine dose distribution across Europe from a uniform source. Although they represent an important baseline parameter, age- and risk-group related vaccine uptake data with sufficient detail are needed to assist public health policy decision making, immunisation planning and monitoring. In light of this situation, and to support the improvement of immunisation rates across the EU, EVM aims to provide dose distribution data for each influenza season to assist Member States in the implementation of local immunisation policies.

Introduction

Annual influenza epidemics continue to pose a substantial threat to public health. In Europe, estimates suggest that influenza is responsible for between 40,000 excess deaths in a moderate season and up to 220,000 during a severe epidemic [1]. Despite the recent focus on pandemics and accompanying extensive coverage in the media, seasonal influenza is responsible for many more deaths than those caused by influenza pandemics [1]. Consequently, the World Health Organization (WHO) and the Member States of the European Union (EU) recommend annual influenza vaccination for those at high risk of complications. A survey conducted in 2006 by the European Centre for Disease Prevention and Control (ECDC) among EU and European Economic Area (EEA) countries found that in the 23 Member States that responded, immunisation was recommended for the two largest groups targeted by WHO: the elderly above a nationally defined age limit (often 65 years but in some cases 60 or 50 years) and those over the age of six months with chronic illnesses such as heart or lung disease [1,2].

In 2003, the 56th World Health Assembly (WHA) recognised that influenza epidemics "cause fatal complications in up to one million people each year" and "that many of these deaths could be prevented through increased use, particularly in people at high risk, of existing vaccines, which are safe and highly effective". The WHA urged its member states to increase immunisation against seasonal influenza, and set a coverage target of at least 50% of the elderly by 2006, rising to 75% by 2010 [3]. In October 2005 and June 2006 the European Parliament adopted resolutions calling on the Member States to increase influenza vaccination in line with the WHO recommendations [4,5]. With these guidelines in place, Ryan et al. estimated that risk groups recommended for vaccination against influenza every year accounted for up to 49% of the population of the 25 EU countries in 2006, or 223 million people [6].

Despite these guidelines and targets, no Europe-wide systematic data are available to monitor vaccine uptake. Monitoring is conducted in only some Member States. Furthermore, there is no system to allow performance comparisons across the EU. Consequently, following a request from the European Commission, the European Vaccine Manufacturers group (EVM) surveyed suppliers in the region to provide baseline data on influenza vaccine distribution in the EU. These data represent a valuable indirect measure of vaccine use, and as such can be utilised by public health policy makers in conjunction with information on local vaccination recommendations, implementation measures and reimbursement criteria to assess gaps in provision and improve coverage where necessary.

Methods

In 2008, EVM issued a standardised, retrospective survey to its member companies (Baxter, Crucell, GlaxoSmithKline Biologicals, Novartis Vaccines, Sanofi Pasteur, Sanofi Pasteur MSD, Solvay, and Wyeth) and the Australian company CSL Biotherapies, who collectively supply nearly all of the influenza vaccines distributed in Europe, with the exception of Hungary and Romania, which each have a national producer. The survey was designed to assess the total number of doses supplied to each of the 27 EU Member States during the last five influenza seasons. The supply period was defined by influenza seasons rather than calendar years to reflect immunisation practise: in temperate zones influenza occurs in

epidemics during the winter and each influenza season consequently straddles the end of one calendar year and the beginning of the next. In the United Kingdom (UK), the study utilised data provided by the local national vaccine industry group (UVIG), which were collected by a similar methodology.

Data were collected covering the five influenza seasons from 2003-4 to 2007-8, which represent the period since the establishment of the WHA targets for influenza vaccine coverage in the elderly. To ensure full compliance with competition law, the manufacturers submitted dose distribution information to a single, independent collection point, where the data were aggregated and anonymised before further analysis was undertaken by the survey group. To determine the level of dose distribution per unit of population, the Eurostat database was accessed to ascertain the number of inhabitants of each of the 27 EU countries on the first of January each year during the survey period (1/1/2003; 1/1/2004; 1/1/2005; 1/1/2006; and 1/1/2007).

Results

The five-year dataset generated by the survey provides a comprehensive picture of influenza vaccine distribution and supply trends in the EU.

Dose distribution: macro-analysis

Throughout the study period, the total number of doses distributed across the region showed a general growth trend, rising from 81.1 million at the lowest point in 2004-5 to a peak of 98.6 million in 2006-7 (Figure 1). However, this overall trend was non-uniform with a slight drop in supply between the first and second year of the surveyed period, and a similar decrease in the last two years of the study (2006-7 to 2007-8).

When comparing these data against the number of doses that would be required to cover the proportion of the population at risk that is recommended for vaccination in Europe (up to 49.1% for the EU25; ranging from 41.6% in Cyprus to 56.4% in the UK [6]) it became clear that neither the EU Member States collectively (Figure 2) nor any individual country (Figure 3) sustained this level. Throughout the survey period, sufficient doses to immunise the entire at-risk population were available only during one season in a single country: during a substantial increase in supply in Malta in the 2005-6 season (Figure 3). Across the EU as a whole, the dose distribution level *per capita* reached above 20% in a single season during the study period; the level of supply required to immunise all those in at-risk groups was not reached in any of the years (Figure 2).

Dose distribution: by country

The country data show wide variations in distribution between different EU Member States. Not surprisingly, the five largest countries (France, Germany, Italy, Spain and the UK) accounted for the majority of doses distributed in the EU region. Regarding the number of distributed doses, these countries received a consistent share of the total, amounting to approximately 75% in each season (ranging from 74.7% in 2004-5 to 76.6% in 2005-6). Based on the population of these countries, this corresponds to a greater than representative proportion as their aggregate population remained steady during the period, with just over 62% of the total inhabitants of the 27 EU countries.

Disproportionate vaccine distribution is even more evident when the data are analysed in conjunction with the Eurostat database; the supply per unit of population shows wide variance between countries, in some Member States from year to year (Figure 3). Of particular note is the dramatic, albeit unsustained, increase in dose distribution in Malta in 2005-6, during a season of robust policy support targeting at-risk groups. Also noteworthy is the trend towards higher distribution in the EU15 countries versus the newer Member States. However, this is confounded to some degree by the relatively lower supply in some of the Nordic countries.

Discussion

This study provides for the first time a systematic view, drawn from a uniform source, of seasonal influenza vaccine distribution across Europe. While a number of methodological limitations

Figure 1

Total number of seasonal influenza vaccine doses distributed in the 27 EU countries, seasons 2003-4 to 2007-8 (n= 450.069 million)

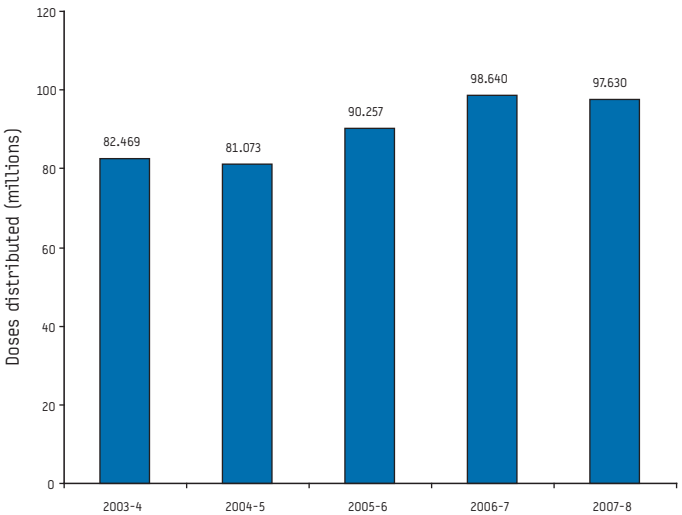
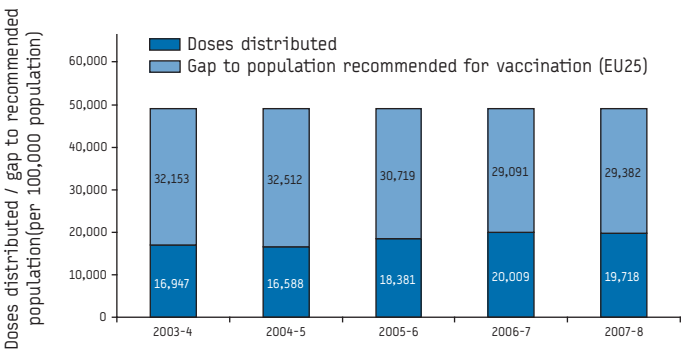


Figure 2

Influenza vaccine doses distributed per 100,000 inhabitants of the EU27 countries versus proportion of the population recommended for vaccination (EU25)*, seasons 2003-4 to 2007-8



* [6]

necessarily exist, these data nonetheless represent an important baseline against which the implementation of immunisation guidelines in the Member States may be assessed.

The survey group performed a number of quality audits, including an assessment against information compiled by national vaccine industry groups. However, a number of methodological limitations remain:

- Although vaccine supply and coverage are likely to be inextricably linked, the survey data represent the total number of doses distributed per country rather than the direct uptake in specific groups recommended for immunisation.
- The data necessarily provide an overestimation of vaccine coverage as a small percentage of doses remain unused and/or are returned each year. This proportion varies from year to year and by country (ranging from approximately 0 to 10%) and can be determined accurately only for those territories with centralised purchasing systems.
- The data for Hungary and Romania include the doses supplied by EVM survey participants, but not those supplied by local Hungarian and Romanian manufacturers.

Notwithstanding, the study reveals a clear variance in vaccine distribution between the 27 EU countries, with a trend towards greater provision in the EU15 Member States. However, it is noteworthy that these generally higher levels of supply *per capita* are not consistent, and whilst detailed economic analysis is beyond the scope of this paper, distribution levels do not appear to follow a simple direct correlation with economic development status. For instance, during the last three years of the study, Malta consistently achieved the highest levels of supply *per capita* throughout the EU27, while Cyprus and, in the latter years of the survey, Romania had a performance similar to those of several EU15 countries. Similarly, distribution levels in Denmark and Sweden were below those in many other EU15 Member States, including the five largest (France, Germany, Italy, Spain and the UK). These confounders suggest that a more subtle blend of factors relating to immunisation policy implementation influence overall vaccine supply, rather than a simple linear correlation with income.

At the macro level, the data collected over the 2003-4 to 2007-8 influenza seasons describe a modest growth in the dose distribution level *per capita* (from approximately 17% to just under 20%). However, while this trend is encouraging, the distribution rates both at the European and Member State level remain substantially below the rates required to immunise the estimated 49% of the population recommended for seasonal influenza vaccination [6].

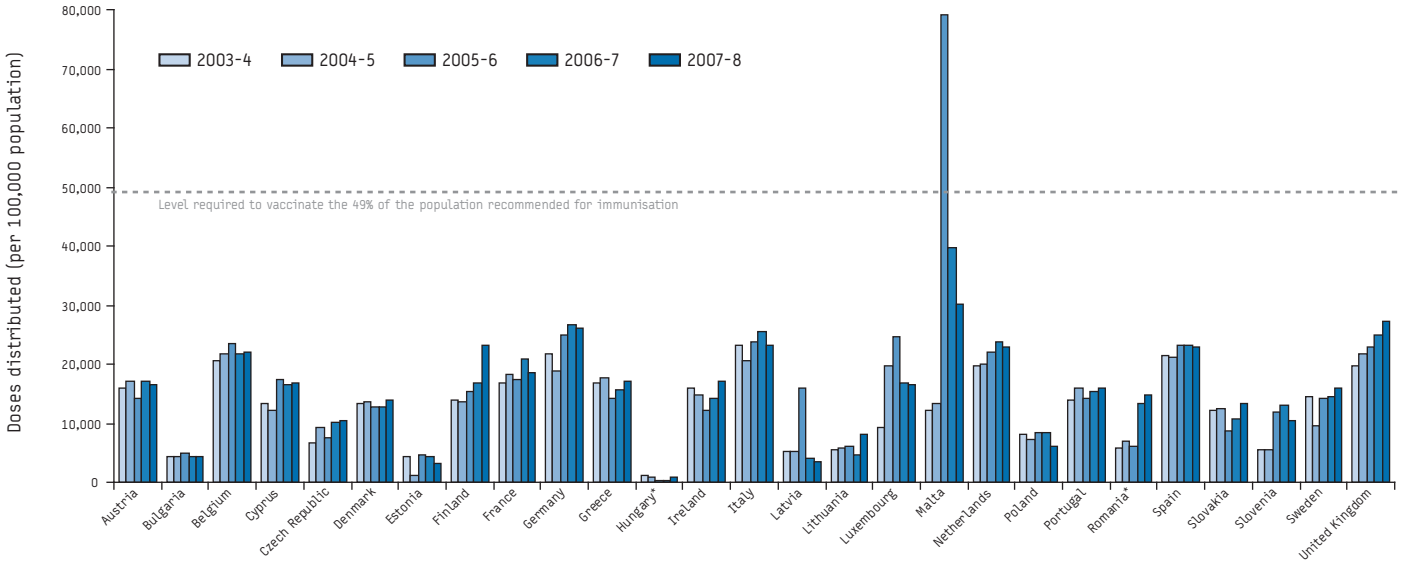
Given the serious and ongoing threat posed by annual influenza epidemics, improving immunisation coverage remains an important policy objective for WHO and the EU. Achieving this will require concerted efforts at the national level to ensure the effective implementation of existing guidelines. In some countries the current recommendations will need to be adapted to encompass all those who are at risk.

Previous research conducted in 11 European countries identified a number of key factors that would motivate at-risk populations to seek influenza vaccination [7]. Most important was the proactive recommendation by a healthcare professional, followed by information on the disease and the vaccine, and adequate funding to reimburse patients for vaccination or to make it cheaper. Notably, the three countries in which authorities provided low or no funding for seasonal influenza vaccination achieved the lowest coverage levels [7].

Based on a recognition at the national level of the need for robust vaccination policies, combined with long-term commitment to their effective implementation, vaccine production and distribution capacity can expand to meet the challenge of improving coverage

Figure 3

Distribution of seasonal influenza vaccine doses per 100,000 inhabitants in EU27 countries, seasons 2003-4 to 2007-8 (compared with the level required to immunise those in recommended groups in the EU25 assuming no wastage or return of doses)



*The numbers for Hungary and Romania do not take into account the doses distributed from the national vaccine manufacturers in these countries

rates. While increasing capacities is a long-term process requiring significant investment, it is clear from historical data that vaccine distribution can increase dramatically to meet demand: notably, during the period 1994-2003, global distribution of influenza vaccines more than doubled [8].

Conclusion

With influenza continuing to pose a public health challenge, the introduction of robust vaccine monitoring systems represents an important step to assess progress in reaching immunisation goals in Europe, and to inform public health decision making for improving protection across the region. This survey provides for the first time a unique view of vaccine supply throughout the EU. The data demonstrate significant differences in vaccine distribution between European countries. With some variation, the results indicate that immunisation in many countries often does not even reach half of those who are considered by national authorities to be at high risk of complications from influenza infection. However, complementary surveys with age- and risk-group specific information will be needed to focus national health interventions on the specific drivers and hurdles for influenza immunisation. Analysis of the study data in conjunction with local recommendations, reimbursement processes and public health communication campaigns should provide valuable insights into the efficacy of vaccination policies in the Member States. EVM aims to provide systematic supply data on a regular basis which will complement national efforts to assist policy makers in determining the most effective approaches to improving vaccination levels amongst those at risk from seasonal influenza.

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Low influenza vaccination coverage in asthmatic children in France in 2006-7

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In France, annual seasonal influenza vaccination has been recommended since 2000 for patients suffering from chronic respiratory diseases, including asthma. Since 1988, each year from September to December, a free influenza vaccination voucher is sent by the French Public Health Insurance authorities to patients with chronic respiratory disease, including severe asthma. In November 2006, this measure was extended to all asthmatic patients, irrespective of asthma severity. The present paper examines the 2006-7 influenza vaccination coverage rate (VCR) in 433 asthmatic children aged 6 to 17 years (mean age: 9.5 years; male: 61%) who consulted a paediatric pulmonologist between March and September 2007 in eight hospitals throughout France. The influenza VCR was 15.7% for the 2006-7 season (13.9% for the 2005-6 season and 10.9% for the 2004-5 season). General practitioners vaccinated 72.1% of the children. "Lack of information" (42%) was the most frequently reported reason for non-vaccination. Vouchers (received by 39.6% of the children) significantly increased the VCR (31% versus 5.9%; p<0.001). In France, in 2006-7, the influenza VCR in asthmatic children was far below the national public health objective (at least 75% for the year 2008). Concerted action is needed to improve the influenza VCR in asthmatic children.

Introduction

Influenza can be a serious infection for patients with asthma because it may trigger or exacerbate asthma symptoms. About 80% of acute exacerbations in asthmatic children are triggered by a respiratory virus infection, and influenza virus is one of the most common viruses affecting the respiratory tract together with rhinovirus, respiratory syncytial virus and coronavirus, particularly during winter epidemics [1,2]. For the 2003-4 season, Bhat *et al.* reported that 12 of 132 (9%) US children over six months of age with fatal influenza disease had asthma without other pulmonary disease [3].

Influenza vaccines are safe and effective in children [4,5], and recommended by the World Health Organization (WHO) for all children aged over six months with chronic conditions such as pulmonary and cardiovascular illness [6]. Most European countries have introduced annual influenza vaccination recommendations for high-risk patients from six months of age [7,8].

In France, annual seasonal influenza vaccination has been recommended since 2000 for patients of any age from six months old suffering from diverse chronic diseases including respiratory disorders such as asthma [9]. One of the French national public health objectives for 2008 is to achieve a 75% influenza vaccination coverage rate (VCR) for all high-risk patients, including asthmatic patients [10]. In France, asthma prevalence reaches 10% in children and 5% in adults [11]; in 1998, 3.5 million people were suffering from asthma [12].

Since 1988 [13], each year from September to December a free influenza vaccination voucher is sent by the French Public Health Insurance authorities to patients with chronic respiratory disease, including severe asthma. In November 2006, this measure was extended to all asthmatic patients, irrespective of asthma severity [14].

There is only very limited specific data available on influenza vaccination coverage in French asthmatic children [15]. To the best of our knowledge, the present study is the first to specifically assess influenza VCR in French asthmatic children. The primary objective was to estimate the VCR for the 2006-7 season in French asthmatic children. The secondary objectives were to examine factors influencing vaccination uptake and reasons for non-vaccination for the 2006-7 season and to estimate the VCR for the previous two influenza seasons.

Methods

Study design

This descriptive observational study was performed in France from March to September 2007 (i.e. after the 2006-7 influenza season). The study was initially submitted to 11 investigators (paediatric pulmonologists) from nine French academic hospitals.

A total of nine paediatric pulmonologists from eight academic hospitals agreed to participate in the study. The eight academic hospitals were located throughout France (Bordeaux, Clermont-Ferrand, Grenoble, Lille, Marseille, Paris, Strasbourg and Toulouse) and represented two thirds (N=8/12) of the French hospitals with a paediatric pulmonology unit.

Being an observational study which did not change the patient's usual medical management, the study protocol was not submitted to an ethics committee for approval, in line with current French legislation. Patients and their parents (or guardians) were provided by the paediatric pulmonologist with oral and written information, and oral consent was obtained from the parents before children were included in the study. Only patients whose parents gave their oral consent were included in the study. They were informed of their rights under the French information protection law. All questionnaire data were rendered anonymous using the Mapi-Naxis procedure validated by the *Commission Nationale de l'Informatique et des Libertés* (French Information Protection Commission) [16].

Study population

Each paediatric pulmonologist participating in the study consecutively included all children (girls and boys) who met the following inclusion criteria:

- aged ≥6 and ≤17 years in September 2006,
- seen at hospital by a paediatric pulmonologist,
- suffering from asthma diagnosed for at least six months,
- having a vaccination card enabling influenza vaccination status to be checked.

Diagnosis of asthma in children aged five and younger is considered to be difficult and unreliable according to the Global Initiative for Asthma (GINA) report, therefore only children ≥6 years were included in the present study [17,18].

Data collection

The paediatric pulmonologist filled in an anonymous questionnaire for each child included. The following demographic and clinical data were collected: birth date, sex, date of asthma diagnosis and asthma severity evaluated at inclusion according to the GINA classification [18] (i.e., intermittent, mild persistent, moderate persistent and severe persistent asthma). Parents were asked for the 2006-7 influenza season vaccination status of their children (yes or no) and receipt of a voucher for free influenza vaccination from the National Public Health Insurance authority for the 2006-7 season (yes or no). For vaccinated patients, the parents were asked for the identity of the vaccinator (i.e. health care professional who had administered the vaccine). The influenza vaccination date was recorded from the vaccination card. For children who had not been vaccinated parents were asked for the reasons for non-vaccination. Parents could give one or more than one reason for non-vaccination. The following reasons were specified in the questionnaire: lack of information, vaccine useless (disease considered as benign), forgotten or lack of time, vaccine considered as ineffective, vaccine considered as dangerous, allergy to egg, other allergy, vaccine contraindication, concomitant disease, current asthma exacerbation, afraid of injection. Parents could spontaneously report reasons for non-vaccination via the item "other reasons". Status and date of vaccination were recorded from the vaccination card for the 2004-5 and 2005-6 seasons.

Statistical Methods

All data were analysed by Mapi-Naxis (Lyon, France). Statistical analyses were performed on SPSS 14.0 software. A descriptive analysis for all the variables of the questionnaire was performed. For each variable, percentages were calculated using available data (missing data ignored). The influenza VCR value was given with its 95% confidence interval (95% CI). The chi-square test was used for comparison of VCRs in asthmatic children with and without free vouchers; the significance threshold was set at 0.05.

Results

Study population characteristics

Paediatric pulmonologists collected data for 435 asthmatic children. Data for two children were excluded from the analysis because they had been vaccinated against influenza before the official availability of the 2006-7 influenza season vaccine in France on 12 October 2006 [19]). Finally, data from 433 children were analysed.

In September 2006, at the beginning of the 2006-7 influenza season, the mean age of the analysed study population (N=433) was 9.5 ± 2.9 years (mean ± standard deviation). The distribution according to age groups was as follows: 6-9 years of age, 56.4% (N=244); 10-13 years of age, 30.9% (N=134); 14-17 years of age, 12.7% (N=55). The children were mainly boys (61%). There were more boys than girls in the 6-9 year age group (N=145 versus 90, respectively) and in the 10-13 year age group (N=88 versus 42, respectively) and fewer in the 14-17 year age group (N=22 versus 31, respectively) (Table 1).

TABLE 1

Study population characteristics

Demographic and clinical characteristics	All (N = 433)	Male (N = 255)	Female (N = 163)
Male: N (%)	255 (61.0)	-	-
Age (years): Mean ± SD	9.5 ± 2.9	-	-
Asthma duration (years): Mean ± SD	6.1 ± 3.5	-	-
Age at diagnosis (years): Mean ± SD	3.6 ± 2.6	-	-
Asthma severity, Global Initiative For Asthma (GINA) classification: N (%)[a,b]			
6-9 year old patients	244 (56.4)	145	90
Intermittent Mild persistent	64 (26.2) 110 (45.1)	38 (26.2) 65 (44.8)	22 (24.4) 40 (44.4)
Moderate persistent	60 (24.6)	38 (26.2)	22 (24.4)
Severe persistent	10 (4.1)	4 (2.8)	6 (6.7)
10-13 year old patients	134 (30.9)	88	42
Intermittent Mild persistent	33 (24.8) 43 (32.3)	26 (29.9) 27 (31.0)	7 (16.7) 13 (31.0)
Moderate persistent	41 (30.8)	23 (26.4)	17 (40.5)
Severe persistent	16 (12.0)	11 (12.6)	5 (11.9)
14-17 year old patients	55 (12.7)	22	31
Intermittent Mild persistent	14 (25.5) 17 (30.9)	8 (36.4) 8 (36.4)	6 (19.4) 9 (29.0)
Moderate persistent	20 (36.4)	5 (22.7)	13 (41.9)
Severe persistent	4 (7.3)	1 (4.5)	3 (9.7)

Missing data:
[a]For 15 patients data on sex missing
[b]For 1 patient asthma severity data missing

In September 2006, the mean duration of asthma in the analysed study population was 6.1±3.5 years. Mean age at diagnosis was 3.6±2.6 years. The severity of asthma according to the GINA classification [18] was known for all but one patient: 111 (25.7%) had intermittent, 170 (39.4%) mild persistent, 121 (28.0%) moderate persistent and 30 (6.9%) severe persistent asthma. In boys the highest proportion of intermittent asthma was found in 14-17 year-olds, mild persistent asthma in 6-9 year-olds and severe asthma in 10-13 year-olds. In girls the proportion of patients with severe persistent asthma increased with age and was highest in the age groups 10-13 and 14-17 years (Table 1).

Influenza VCRs for the 2006-7, 2005-6 and 2004-5 seasons

Of the 433 children analysed, 68 were vaccinated against influenza during the 2006-7 season. The global 2006-7 VCR was 15.7% (CI 95%: 12.6%-19.3%). The VCRs for the previous two seasons (2005-6 and 2004-5) were 13.9% (CI 95%: 10.9%-17.3%) (60 vaccinated children) and 10.9% (CI 95%: 8,2%-14.0%) (47 vaccinated children), respectively.

Influenza VCR for the 2006-7 season according to age, sex and severity of asthma

A total of 29/244, 24/134, and 15/55 children from the 6-9, 10-13, and 14-17 age groups, respectively, were vaccinated during the 2006-7 season. The influenza VCRs increased with age: 11.9% in the 6-9, 17.9% in the 10-13, and 27.3% in the 14-17 age group (Table 2).

Girls aged 6-9 years were less frequently vaccinated than boys in the same age group (7.8% versus 13.8%), whereas girls aged 10-13 years and 14-17 years were more frequently vaccinated than boys in the same age groups (21.4% and 35.5% versus 15.9% and 18.2%, respectively) (Table 2).

A total of 7/111 patients with intermittent asthma, 25/170 patients with mild persistent asthma, 25/121 patients with moderate persistent asthma and 10/30 patients with severe persistent asthma were vaccinated for the 2006-7 season. The influenza VCR increased with asthma severity, from 6.3% in children with intermittent asthma to 33.3% in those with severe persistent asthma (chi-square test: p<0.001) (Figure 1 and Table 2).

Influenza VCR for the 2006-7 season according to free vaccination voucher reception

Data regarding the receipt of a free vaccination voucher for the 2006-7 season were available for 424 children (nine missing

TABLE 2

Vaccination coverage against influenza among asthmatic children according to age, sex, and asthma severity, France, influenza season 2006-7

Groups	Number	Vaccinated	%	CI 95%
Total	433	68	15.7	(12.6; 19.3)
Age				
6-9 years	244	29	11,9%	(7,8% - 16,0%)
10-13 years	134	24	17,9%	(11,4% - 24,5%)
14-17 years	55	15	27,3%	(16,1% - 41,0%)
Sex: female				
6-9 years	90	7	7,8%	(3,1% - 15,4%)
10-13 years	42	9	21,4%	(10,3% - 36,9%)
14-17 years	31	11	35,5%	(19,2% - 54,7%)
Sex: male				
6-9 years	145	20	13,8%	(8,1% - 19,5%)
10-13 years	88	14	15,9%	(8,9% - 25,3%)
14-17 years	22	4	18,2%	(5,1% - 40,3%)
Asthma severity				
Intermittent	111	7	6,3%	(1,7% - 10,9%)
Mild persistent	170	25	14,7%	(9,3% - 20,1%)
Moderate persistent	121	25	20,7%	(13,4% - 27,9%)
Severe persistent	30	10	33,3%	(17,2% - 52,9%)

FIGURE 1

Vaccinated asthmatic children according to asthma severity (Global Initiative For Asthma - GINA classification), 2006-7 influenza season, France (n=432)

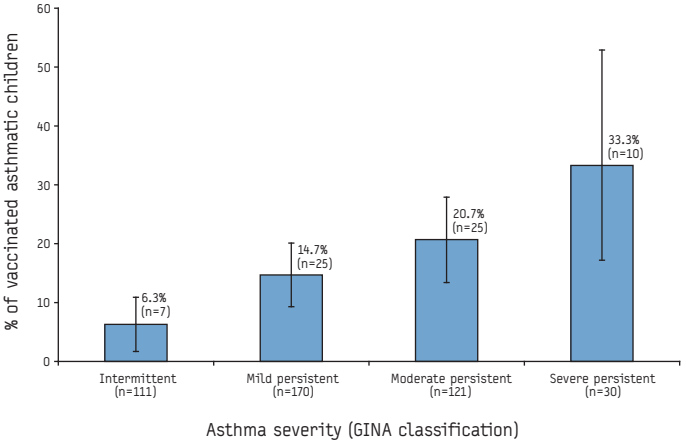
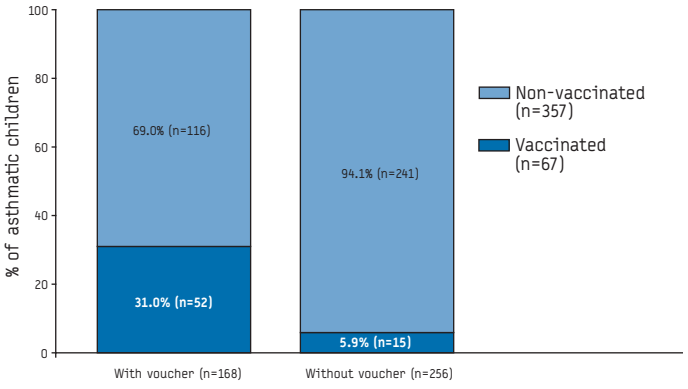


FIGURE 2

Vaccinated and non-vaccinated asthmatic children according to reception of voucher*, 2006-7 influenza season, France (n=424)



* A voucher for free influenza vaccination is provided by the French Public Health Insurance authorities to all asthmatic patients, irrespective of asthma severity

values). According to the information provided by parents, 168 (39.6%) children had received a voucher.

A total of 52 (31.0%) of the 168 children who received a free voucher were vaccinated compared to 15 (5.9%) of the 256 children who did not receive any voucher (Figure 2): Receiving a free vaccination voucher increased vaccination coverage in asthmatic children (31.0% versus 5.9%; chi-square test: p<0.001). A total of 116 of the 168 children who received a free voucher (69.0%) were not vaccinated.

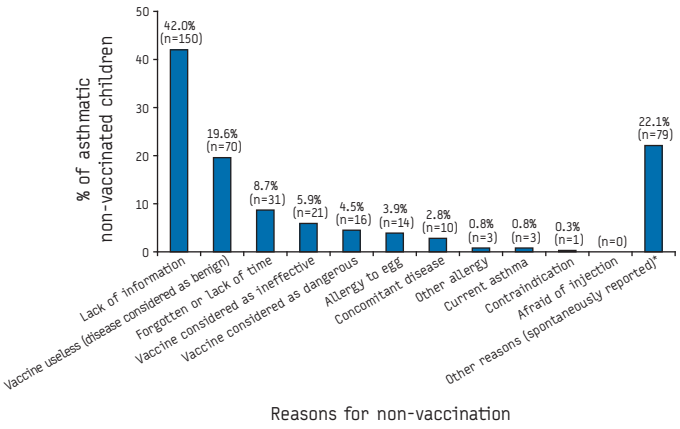
Vaccinators and reasons for non-vaccination in the 2006-7 season

The vaccination was mainly performed in private practice: 49 of the 68 children (72.1%) vaccinated for the 2006-7 influenza season were vaccinated by a general practitioner (GP), seven (10.3%) by a family paediatrician, and three (4.4%) by a hospital practitioner. Others were vaccinated by a nurse (N=5; 7.4%), their parents (N=3; 4.4%), or a pharmacist (N=1; 1.5%).

Reasons for non-vaccination were given for 357 of the 365 non-vaccinated children for the 2006-7 season. Among the reasons specified in the questionnaire, "Lack of information" (N=150; 42.0%), "Vaccine useless (disease considered as benign)" (N=70; 19.6%), "Vaccine considered as ineffective or as dangerous" (globally 10.4% of cases: for each item N=21, 5.9% and N=16, 4.5% respectively), and "Forgotten or lack of time" (N=31; 8.7%) were the most frequently reported reasons for non-vaccination (Figure 3). Allergy was a major motive for influenza non-vaccination for 17 children: 14 children (3.9%) declared an "Allergy to egg". Among them, there was one case of egg allergy with clinical signs of anaphylactic shock and 13 with egg allergies but no history of anaphylactic shock. "Other allergy" was reported as reason for non-vaccination for three children (0.8%). No allergy to one of the vaccine components was reported. A case of permanent rhinitis was considered as vaccine contraindication. The most frequent spontaneously reported reasons for non-vaccination were: "Vaccine not proposed" (N=26, 32.9%), "No medical indication" (N=15, 19.0%), and "No favourable opinion of this vaccine by the family practitioner" (N=10, 12.7%).

Figure 3

Reasons for non-vaccination of asthmatic children, 2006-7 influenza season, France (n=357, info missing for 8 children, multiple answers possible)



* The first three spontaneously reported reasons were: vaccine not proposed, no medical indication, no favourable opinion of this vaccine by the family practitioner

Discussion

Our study provides the first estimates of influenza VCR in France among asthmatic children.

It shows that the influenza VCR in asthmatic children was very low for the 2006-7 influenza season, as it had been over the previous two seasons. Only 15.7% of 433 asthmatic children ≥6 years of age seen in a hospital by a paediatric pulmonologist were vaccinated against influenza for the 2006-7 season, the percentages were even lower for the 2005-6 and 2004-5 seasons: 13.9% and 10.9%, respectively. These results are consistent with previous studies that have shown low VCRs in children with chronic respiratory diseases. In a recent French study conducted in the Parisian Region (seven general paediatric wards) in 239 children with underlying chronic disease, Weil-Olivier *et al.* reported a 12.8% VCR for the 2003-4 influenza season in the subset of 39 children suffering from a chronic respiratory disorder, of whom 33 were asthmatic [15]. In Spain, Lopez de Andres *et al.* observed an influenza VCR of 19.9% in 2003 in 6,869 children suffering from a chronic respiratory disorder [20]. In the United States (US), a 29% influenza VCR in asthmatic children for the 2004-5 season and a 36.2% influenza VCR in asthmatic patients (children and adults) for the 2005-6 season were reported [21,22].

In our study, for the 2006-7 season, the influenza VCR did increase with the severity of asthma; one third of children with severe persistent asthma were vaccinated. In the US, for the 2004-5 season, children with current asthma who experienced an asthma attack or episode in the past 12 months had higher VCRs than those without an attack or episode (35.9% versus 20.0%, respectively); children with current asthma who had ≥10 health-care visits had higher VCRs than children without current asthma (42.0% versus 14.6%, respectively) [21].

Influenza VCR remained far below the French national public health objective of at least 75% for the year 2008. Our study took place the year after the sending of a free influenza vaccination voucher to all asthmatic patients, irrespective of the severity of asthma, was implemented. Provision of a free voucher has already been shown to significantly improve VCR in children with cystic fibrosis in France [23]. According to the parents, only two in five asthmatic children have received a voucher for free vaccination and as the receipt of a voucher significantly improved VCR in asthmatic children, the reasons for non-receipt need to be analysed. Possible reasons are: asthma not declared to the Public Health Insurance authorities, lack of update of the database by the Public Health Insurance authorities, parents not remembering they had received the voucher, etc. After a period of adjustment, including provision of information about the voucher for free vaccination to the asthmatic children and their parents and updating of the database by the Public Health Insurance authorities, the decision to deliver a voucher to all asthmatic patients promises to help improve influenza VCR in asthmatic children in the near future. However, this measure, although necessary, will probably not be sufficient to reach the stated national objective, because receipt of a voucher during the 2006-7 season was not followed by influenza vaccination in as many as 69% of children.

The most frequently reported reasons given for non-vaccination were "Lack of information" (42.0%), "Vaccine useless (disease considered as benign)" (19.6%), "Vaccine considered as ineffective or dangerous" (in 10.4% of cases: 5.9% and 4.5% respectively), and "Forgotten or lack of time" (8.7%). These findings emphasise

the need for parents of asthmatic children to receive targeted information on the potential seriousness of influenza in asthmatic patients and on the tolerance and efficacy of influenza inactivated vaccine in children [4]. In conjunction with the voucher sent to all asthmatic patients, this information should also improve influenza VCR. Indeed, Schoeffer *et al.* [24] found that the clinical impact of influenza was underestimated or insufficiently well known to young people. These results were obtained from a study involving 2,131 German patients over 18 years of age, seen at a specialised medical centre for chronic respiratory disorders (asthma or chronic obstructive respiratory disease).

Anaphylactic hypersensitivity reaction to eggs or to one of the vaccine components is the only absolute contraindication to vaccination with trivalent inactivated influenza vaccine [25]. In the present study, 14 children (3.9%) declared an "allergy to egg" as reason for non-vaccination against influenza. However, only one of these 14 children had ever presented clinical signs of anaphylactic shock subsequent to exposure to egg, a contraindication to inactivated influenza vaccine, suggesting that the other 13 may have been eligible for influenza vaccination. This illustrates that some children may have failed to be vaccinated because the specific contraindications for inactivated influenza vaccine are not well known.

The vaccinator was a GP in around two in three children and a family paediatrician for around one in ten. This result should be interpreted with caution taking into account the fact that included children were ≥6 years old, an age which requires fewer visits to the paediatricians. Information on the potential seriousness of influenza in asthmatic patients and on the tolerance and efficacy of inactivated influenza vaccines in children should be provided by health care professionals during GP/paediatric consultations and/or in the waiting room via posters, leaflets, etc. especially during the last trimester of the year.

One limitation of our study could refer to the nature of the asthmatic children enrolled. Investigators were strictly limited to paediatric pulmonologists to ensure the accurate recruitment of children with asthma. Since the study included only children seen in a hospital, it could have been possible that there were more severe persistent asthma cases in this population than in general practice; nevertheless 7% of asthma cases were severe persistent in the present study compared with 10% in asthmatic general population [12].

Conclusions

In France, the 2006-7 influenza VCR in asthmatic children was substantially lower than the national target of at least 75% by 2008. The recent decision (November 2006) to deliver a free influenza vaccination voucher to all asthmatic patients, irrespective of asthma severity, has shown to improve the VCR in our study. To reach the national objective, however, this promising measure needs to be accompanied by timely information on the potential seriousness of influenza in asthmatic patients and by information about the tolerance and efficacy of inactivated influenza vaccines in children. Such information should be provided to, and by, health care professionals to parents of asthmatic children.

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First steps in the design of a system to monitor vaccine effectiveness during seasonal and pandemic influenza in EU/EEA Member States

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Estimating influenza vaccine effectiveness (IVE) early in the season helps measuring the consequences of a mismatch between the vaccine and the circulating strain and guiding alternative or complementary interventions. The European Centre for Disease Prevention and Control is funding a project to develop pilot studies to monitor IVE in the Member States (MS) of the European Union and European Economic Area (EU/EEA) during seasonal and pandemic influenza. To identify key methodological and practical issues in developing protocols for pilot studies, we conducted a survey among EU/EEA MS, a literature review on IVE methods, and consultations of experts. The survey and literature review highlighted the variety of the data sources used to estimate IVE and the difficulty to interpret data on IVE, which varies with age, risk group, outcome specificity and virus-vaccine mismatch. We also found that negative and positive confounding can bias IVE. The experts consultations lead to the following recommendations: to measure IVE in the same population in various seasons; to control for positive/negative confounding (including pre- and post-influenza season IVE estimates); and to include laboratory confirmation as outcome in various study designs. In the 2008-9 influenza season, two cohort studies using general practitioners' databases and six case control studies will be piloted in EU/EEA MS and will adhere to the above recommendations. The pilot studies will be the basis for the development of robust methods to monitor IVE in EU/EEA MS.

Background

Because influenza viruses are constantly changing and vaccines are reformulated every year, the influenza vaccine effectiveness (IVE) estimates from previous years cannot be used to estimate IVE in the subsequent years. Having annual IVE estimates at European level available as soon as possible after the start of a seasonal influenza epidemic or pandemic and monitoring it along the course of the epidemic/pandemic is essential in order to:

- decide on recommendations for the use of the vaccine by specific age and risk groups,
- target complementary or alternative public health measures (e.g. antivirals) to population segments in which the vaccine is less effective,
- estimate more precisely the impact of current vaccination strategies on the burden of disease with a view to supporting vaccination campaigns,
- provide some quantification to the current virological system of comparing antigenic matches of vaccine and circulating viruses,
- trigger further investigations on seasonal and pandemic vaccines (improving their composition, use of adjuvants, need for booster doses),
- better manage and respond to eports of vaccine failures (especially during a pandemic),
- counterbalance the reports of adverse events following immunisation by providing a basis for adequate risk management and cost-effectiveness analysis.

In addition, in order to be able to measure IVE for the pandemic vaccine it is necessary to develop already now a robust method that provides early estimates of IVE.

As the vaccine is recommended for risk groups, clinical trials to estimate IVE in Europe would not be ethical. Only observational studies can be considered when trying to obtain IVE estimates early in the season [1]. It is therefore necessary to define which observational study designs can be adopted in the Member States (MS) of the European Union and European Economic Area (EU/EEA) that would provide IVE estimates during an ongoing influenza season and allow monitoring it through consecutive seasons. These methods need to take into account the specific situation of each MS in terms of resources and available data.

The European Centre for Disease Prevention and Control (ECDC) is funding the development and piloting of study protocols for monitoring IVE in EU/EEA MS in the context of seasonal and pandemic influenza. A consortium of 18 European public health institutes coordinated by EpiConcept is carrying out this project. The first phase (January-July 2008) consisted of the development of protocols for the pilot studies. To identify key methodological and practical issues to be considered in the study protocols, we conducted a survey among EU/EEA MS, a literature review on methods used to estimate IVE, and three consultations of experts. These three approaches are described in the following sections of this article.

Survey

Survey methods

We carried out a survey among EU/EEA Member States to identify, in each MS, observational IVE studies and available data sources that could be used for real-time IVE studies.

We contacted 29 experts from 29 EU/EEA MS involved in influenza surveillance. The experts were the representatives of the institutions included in the consortium and, for MS not participating in the consortium, the epidemiologist focal point of the European Influenza Surveillance Scheme (EISS) or the gatekeeper of the Vaccine European New Integrated Collaboration Effort (VENICE). The experts were given the options either to provide information through a self-completed questionnaire or during a telephone or face to face interview. In addition, we reviewed available reports from EISS and VENICE, web pages from European institutions involved in influenza surveillance and articles on IVE studies conducted in EU/EEA MS.

We collected data on IVE studies conducted in the MS, available data sources for case identification (identification of influenza cases, death registries, hospital registries, general practitioners' (GP) databases, other) and for documenting influenza vaccination status, as well as potential interest in conducting a pilot study during the season 2008-9.

Survey results

Among the 29 MS we contacted, 24 (83%) accepted to participate in the survey. In four MS, we interviewed the experts face to face, in 12 by telephone and in eight MS, the experts self-completed the questionnaire we sent them.

Of the participating 24 MS, ten had conducted IVE studies in the past. We identified 43 published articles reporting results of case control studies (12 articles), of cohort studies (28 articles) and of studies using a screening method (three articles). Additional details on the studies including data sources and study outcomes are reported in the Table. A complete survey report is also planned to be published on the ECDC website.

In most of these studies, the study population and data sources had been identified through health delivery services. In the Czech Republic, Italy and Portugal, other data sources had been used for IVE studies as reported in the Table.

Computerised databases

Malta, Norway and Sweden have population registries including an individual unique identifier which allows linking existing databases (e.g. death registers, in-patient registers, vaccination registers if available). The linkage of the various databases is not immediate and an ethical or a personal protection approval is needed.

In Finland, France, Ireland, the Netherlands, Norway, and the United Kingdom (UK), various GP networks have computerised databases. Computerised GP databases are also available in some regions in Spain and in some counties in Sweden.

Computerised GP databases allow evaluating various outcomes: influenza-like illness (ILI)/acute respiratory infections (ARI), death, hospitalisation, vaccine status and some confounding factors (e.g. co-morbidities). However, certain issues need to be considered when using computerised databases for IVE studies, such as the representativeness, completeness, timeliness and quality of the data. For some of the databases, *ad hoc* studies may be necessary to further evaluate data quality.

Computerised databases have been used in the Netherlands, Spain, Sweden and the UK to conduct IVE cohort studies. They can provide rapid estimates for some outcomes (e.g. ARI/ILI) and more solid estimates at the end of the season (e.g. estimates adjusted for confounding factors, estimates for severe clinical outcomes).

Sentinel surveillance

In all 24 responding MS, the main source to identify clinical cases of influenza on a real-time basis was the virological or epidemiological sentinel influenza surveillance system. Case definitions vary from MS to MS but most sentinel networks report cases of ILI symptoms or ARI [44].

Laboratory confirmation of influenza cases is usually done in a subset of patients consulting the sentinel practitioners. In most MS, the decision of which patients to collect laboratory specimens from is based on clinical criteria. Thus, patients with laboratory tests are not a representative sample of all patients consulting a GP because of influenza symptoms [45]. In Denmark and France, the patients to be sampled are selected in a systematic way. Following EISS recommendations, laboratory request forms include the patients´ vaccination status.

Sentinel surveillance systems have been used to conduct case control studies of IVE in Denmark, France, Germany, the Netherlands, and the UK (Table).

Hospitalisation discharge databases

In most MS, cases with severe clinical influenza outcome (hospitalisations, deaths) are not identified in real time. Hospitalisation discharge databases are available with delays varying from three months to two years. In France, hospitals report on a daily basis to the Institut de Veille Sanitaire individual data from in-patients and out-patients consulting emergency rooms.

Various MS have developed or are developing real-time mortality monitoring [46]. Mortality has not yet been used in Europe to estimate real-time IVE.

Influenza vaccination status

Sources to document influenza vaccination status include medical records, computerised medical records, immunisation registries, surveys, and pharmaceutical data [47]. Vaccination registries allowing the extraction of real-time vaccination status are currently available at regional level in Finland, in some counties in Sweden and in some regions in Spain. In 2008-9, Spain plans to estimate real-time vaccination coverage using vaccination coverage reported by the sentinel practitioners.

Literature review

In addition to the survey described above, a literature review was conducted to identify the key elements to be considered in the design of the pilot studies. In particular, we focused on factors affecting IVE estimates and on methods described to control them. In the following paragraphs, we summarise factors that will have an influence on the choices made when developing the pilot study protocols: outcomes and confounding factors.

Table

Influenza vaccine effectiveness studies conducted in EU/EEA Member States, by study design and country

Country	Reference	Data source	Outcome
Cohort Studies			
Czech Republic	Chlíbek 2002 [2]	Mail questionnaire to volunteers	Influenza-like illness
	Berran 2003 [3]	Medical records employees Skoda Auto factory	Influenza-like illness
Italy	Comeri 1995 [4]	Questionnaire to a sample of the elderly population in one city	Clinical influenza
	Consonni 2004 [5]	Phone interviews, ambulatory patients	Influenza-like illness, acute respiratory infection
	Pregliasco 2002 [6]	Interviews, medical records geriatric units	Acute respiratory infection, hospitalisation
	Rizutto 2006 [7]	Interviews volunteer participants from Ministry of Health	Influenza-like illness
	Landi 2003 [8], Landi 2006 [9]	Minimum data Set for home care, Italian 'Silver Network' home careproject	Death (2003), hospitalisation (2006)
The Netherlands	Smits 2002 [10]	Computerised primary care practices	Low respiratory tract infection, otitis media
	Tacken 2004 [11]	GP database	Primary care contact rate during influenza epidemics
	Voordow 2003 [12], 2006 [13]	GP database	Influenza, pneumonia, death, low respiratory tract infection, hospitalisation for pneumonia
Portugal	2006-7, 2007-8 (unpublished data)	Pharmacies, voluntary recruiters	Laboratory-confirmed influenza
Spain	Castilla, 2006 [14]	Sentinel GPs	Clinical influenza
	Gené Badía 1991 [15]	Records from five health centres, hospital, death register	Death, all hospitalisations, hospitalisations for respiratory diseases
	López Hernández 1994 [16]	Records from one health centre, hospital records, death register	Hospitalisation, death
	Salleras, 2006 [17]	Questionnaires in clinics	Acute febrile illness, influenza-like illness, laboratory-confirmed influenza
	Vila-Córcoles 2007 [18]	GP electronic files, demographic database, death registry	Death
Sweden	Christenson 2001 [19], Christenson 2004 [20], Orktvist 2007 [21]	Population register, vaccination database, discharge diagnosis database	Influenza hospitalisation, hospitalisation for pneumonia
UK	Fleming 1995 [22]	GP database	Death, death or severe respiratory illness, death or any respiratory illness without further specification
	Armstrong 2004 [23]	GPs, Office for National Statistics	Death attributable to influenza
	Mangtani 2004 [24]	General Practice Research Database	Hospitalisation for respiratory disease, death from respiratory disease
Cohort studies during outbreak investigations			
France	Aymard 1979 [25]	Geriatric hospital	Disease, death
Italy	Caminiti 1994 [26]	Medical charts, hospital records, death certificates	Influenza-like illness, hospitalisation for influenza-like illness, hospitalisation for all respiratory illness, death from respiratory illness
UK	Arroyo 1984 [27]	One nursing home	Influenza-like illness, pneumonia, death from respiratory disease
	Mukerjee 1994 [28]	14 nursing homes	Upper respiratory tract infection
	Nicholls 2004 [29]		Influenza-like illness
Case control studies			
Denmark	Mazick 2006 [30]	GP surveillance network	Influenza-like illness laboratory-confirmed
France	Carrat 1998 [31]	GP practices	Acute respiratory infection, influenza-like illness laboratory-confirmed
	Lavallée 2002 [32]	Medical records of hospitalised cases, interviews	Hospitalisation for acute respiratory infection and hospitalisation for brain infarction
Germany	Grau 2005 [33]	Hospital records, patient interviews	Hospitalisation for ischaemic or haemorrhagic stroke / transient ischaemic attack
	Uphoff 2006 [34]	Sentinel GPs cases: influenza-like illness influenza-positive controls: influenza-like illness influenza-negative	Influenza-like illness laboratory-confirmed
Italy	Crocetti 2001 [35]	Discharge diagnoses, mailed questionnaire, telephone interviews	Hospitalisation for pneumonia or influenza
The Netherlands	Hak 2002 [36]	Administrative and medical databases from a health plan	GP visit and hospitalisations for acute respiratory disease and cardiovascular disease
	RIVM 2006-7 (unpublished data)	Sentinel GPs cases: influenza-like illness influenza-positive controls: influenza-like illness influenza-negative	Influenza-like illness laboratory-confirmed
Spain	Puig-Barberá 1997 [37], 2004 [38], 2007 [39]	Hospital emergency logs and records	Hospitalisation for acute coronary syndrome, hospitalisation for cerebrovascular accident, hospitalisation for pneumonia
UK	Ahmed 1995 [40]	Death certificates, GP records	Certified influenza death
	Jordan 2007 [41]	GP practice registries and hospital discharge registries	Hospitalisation for acute respiratory infection
UK (Scotland)	Health Protection Scotland, 2005-6 and 2006-7 (unpublished data)	Sentinel GPs cases: influenza-like illness influenza-positive controls: influenza-like illness influenza-negative	Influenza-like illness laboratory-confirmed
Screening			
France	Carrat 1998 [42]	Cases: sentinel GPs; vaccine coverage: national health survey	Influenza-like illness
	Legrand 2006[43]	Cases: sentinel GPs; vaccine coverage: national health survey	Influenza-like illness
Germany	Uphoff 2006[34]	Cases: sentinel GPs; vaccine coverage: national health survey	Influenza-like illness laboratory-confirmed
Spain	Instituto de Salud Carlos III (unpublished data)	Cases: sentinel GPs; vaccine coverage: national health survey	Influenza-like illness

GP: General Practitioner

Literature review methods

To identify relevant papers, we searched the Cochrane database and consulted Cochrane reviews on influenza vaccine effectiveness [48,49]. Additionally, we reviewed the Health Technology Assessment report "Systematic review and economic decision modelling for the prevention and treatment of influenza A and B" [50]. We also included a recent Sanofi Pasteur-MSD review [51]. Finally, we also reviewed references from each of the selected articles.

We selected studies providing IVE estimates. We also included studies addressing methodological aspects of IVE estimates and certain studies addressing the methodology of VE measurements for infectious diseases.

Literature review results

Overall, we reviewed 284 scientific articles and of them selected 93 descriptive observational studies (34 cohort studies, 26 outbreak investigations, 31 case control studies and two studies using the screening method). In addition we consulted 23 articles focusing on methodological issues.

Clinical outcome

The main clinical outcomes reported in the literature were hospitalisations for all or specific causes (e.g. pneumonia and influenza), deaths from all or specific causes (e.g. pneumonia and influenza), ILI, ARI and laboratory-confirmed cases of influenza.

IVE studies using non-specific clinical outcomes will include as cases individuals with clinical symptoms unrelated to influenza, leading to an underestimation of the IVE [52,53]. The influenza case definition combined with laboratory confirmation results has the highest specificity for influenza, and laboratory confirmation is therefore essential to estimate the true IVE [54]. Due to the costs involved, some authors have suggested to perform laboratory tests only in a small proportion of the study participants (validation set) [55].

Confounding factors

Comparing the crude IVE estimates and the IVE estimates adjusted for confounding factors reported in the literature provides an overview of the magnitude of confounding in IVE studies. We found a difference in percentage between crude and adjusted IVE in case control studies (Figure 1) and cohort studies (Figure 2) that ranged from -220% to 21%.

The list of potential confounding factors reported in the literature is very long (Box).

The main confounding factors discussed in the literature are factors resulting either in an underestimation of the IVE (negative confounding) or in an overestimation of the IVE (positive confounding factors). Negative confounding is the result of 'confounding by indication': Individuals that are at high risk of influenza are more likely to be vaccinated than individuals that are at low risk, and consequently, IVE is underestimated. Positive confounding is the consequence of healthier individuals being more conscious about their health, more motivated to accept vaccination and therefore more likely to be vaccinated than unhealthier individuals. An alternative explanation for positive confounding is the fact that critically ill patients are not offered (or refuse) to be vaccinated. Therefore, vaccinated individuals have a better baseline health status than the unvaccinated group leading to an overestimation of the IVE ('healthy vaccinee' effect).

Different alternatives have been proposed to adjust for the 'healthy vaccinee' and 'confounding by indication' effects. Some authors restricted the study population to groups that were more homogeneous with regard to the potential confounding factor. Others stratified the results according to risk groups. A majority of the studies reviewed included the potential confounders as covariates in a regression model. Some authors controlled for confounding using propensity scores, the conditional probability of being vaccinated given observed covariates [11,18,39,56-58]. They are used to group individuals at levels of the propensity score or as a covariate in the regression model.

Comparison with non-influenza season data

Some authors considered those adjustment methods insufficient to adjust for the 'healthy vaccinee' effect and suggest that residual confounding may persist. They proposed to compare the IVE estimates in the influenza season with estimates from periods with

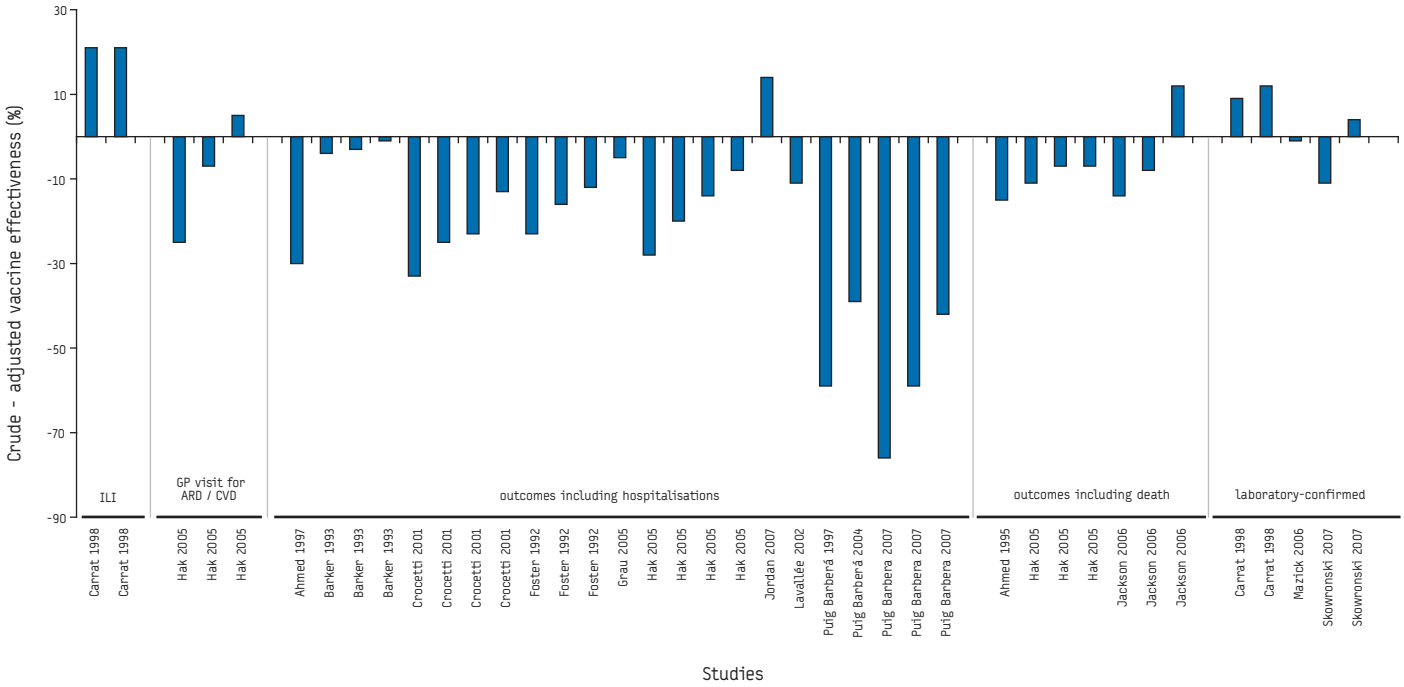
Box

List of potential confounding factors in influenza vaccine effectiveness studies reported in the literature

- Age
- Allergy to egg protein
- Asthma
- Diabetes mellitus and other endocrine diseases
- Disease severity
- Education level
- Functional status
- Former Influenza vaccination
- Former Pneumococcal vaccination
- Health medical organisation
- Health-related behaviours
- Heart diseases
- House heating
- Immunosuppression including haematopoietic malignant diseases and steroid and immunosuppressive treatment
- Index case in the family
- Length of hospital stay
- Level of social interaction
- Lifestyle factors
- Living together with grandchildren
- Malignant disorders
- Marital status
- Medication prescribed and number of repeat prescriptions
- Musculoskeletal and connective tissue diseases
- Neurological diseases (including dementia, Parkinson's disease and cerebrovascular diseases)
- Number of co-habitants
- Number of hospital admissions and out-patient visits
- Other pulmonary diseases
- Physical activity
- Place of residence: nursing and residential care homes; non-institutional
- Pre-school attendance
- Preventive care practices
- Propensity score
- Renal diseases
- Sex
- Smoking
- Socio-economic status
- Type of medical coverage
- Underlying chronic conditions
- Vaccination of caregiver
- Washing hands and gargling

Figure 1

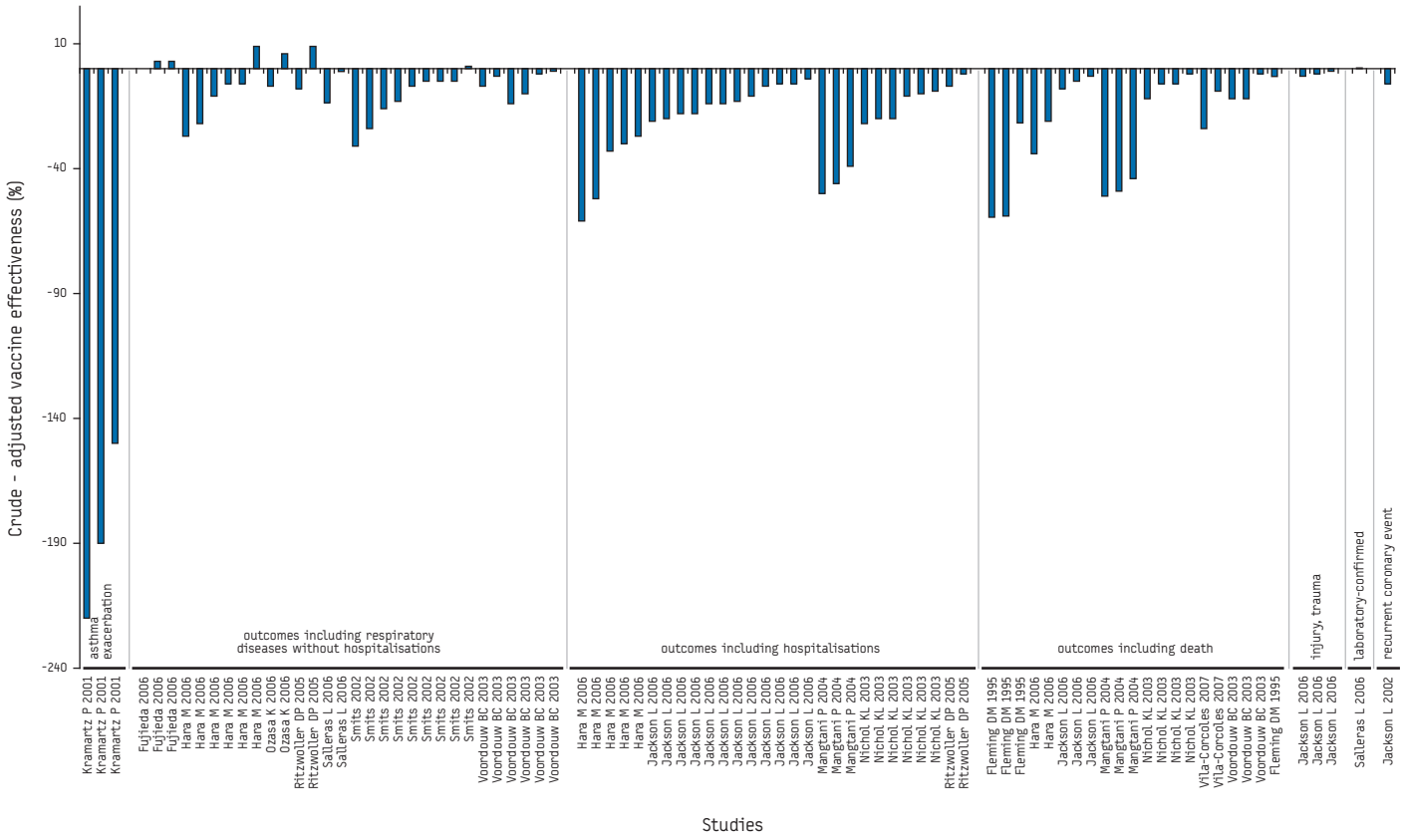
Difference between crude and adjusted influenza vaccine effectiveness estimated in case control studies, by study outcome



ARD, acute respiratory disease including acute bronchitis or exacerbations of chronic lung disease, influenza, pneumonia, and acute otitis media;
CVD, cerebrovascular disease including myocardial infarction, stroke, and heart failure;
GP, general practitioner;
ILI: influenza-like illness

Figure 2

Difference between crude and adjusted influenza vaccine effectiveness estimated in cohort studies, by study outcome



no influenza. The rationale behind this is that the vaccine should not have an effect in non-influenza seasons.

Several studies using this approach compared IVE during and after the influenza season. Most of the results showed a lower IVE after the season suggesting that there was no positive confounding [21,24,59-61]. Other authors, however, found a greater reduction in the risk of death and pneumonia hospitalisation in the period before the influenza season compared to the time during the influenza season, suggesting positive confounding [62]. They argue that studies that did not find an association between vaccine and disease outcome (low IVE) after the influenza season had assumed the difference in underlying characteristics to be constant over time. They suggest that the differences between vaccinated and unvaccinated individuals may diminish over time and the data should therefore be compared not only with the post-influenza season, but also with the pre-influenza season.

Expert consultations

During the first phase of the project, we organised several workshops for experts participating in the consortium and additional invited influenza experts.

The first workshop was held in April 2008. The aim was to present and discuss the results of the literature review and survey as described above and to consider the feasibility of the various observational methods to estimate real-time IVE at EU/EEA level. The participants included 25 experts from institutions participating in the consortium, four external influenza experts (London School of Hygiene and Tropical Medicine, Instituto de Salud Pública de Castellón, Sanofi Pasteur MSD, United States-Centers for Disease Control and Prevention Influenza division), four staff members from the ECDC Scientific Advice Unit and two EpiConcept epidemiologists.

The participants worked in three groups to discuss cohort studies, case control studies, and screening method studies. For each study design, the groups made recommendations to be considered in the development of generic protocols for the pilot studies. The experts' recommendations were to determine IVE in various population subgroups, to control for positive and negative confounding and to use laboratory-confirmed influenza as outcome. The group recommended measuring IVE in a homogenous population for a period of several years, using the same design each year. The participating MS and ECDC expressed their interest in supporting this project in the long term.

Following the first workshop, we developed two generic protocols (see below) for case control and cohort studies to be adapted to the situation of each MS.

The second set of consultations was held in June 2008 with the MS that were interested in conducting pilot studies in the season 2008-9. The objective was to further discuss methodological issues related to the two generic protocols for measuring IVE. Specific sessions were held for each study design.

The group agreed that, during the first season of the pilot phase, 2008-9, the following study designs were to be considered:

- Case-control studies based on influenza sentinel surveillance systems with laboratory-confirmed influenza-positive ILI as cases and influenza-negative ILI as controls.
- Prospective cohort studies using computerised databases and providing IVE estimates for different periods (pre-/during/post-influenza season). At least a subset of the cases would be laboratory-confirmed.

Conclusion

The survey showed that data sources to conduct IVE studies vary from MS to MS and in some MS from region to region. Computerised databases are available in few countries and, where available, are a good basis for cohort studies as they include large populations. Sentinel GP networks are present in all 24 EU/EEA MS that participated in the survey; they include laboratory confirmation of influenza cases and data on vaccination status for a subset of the population.

The literature review underlined the difficulty to interpret IVE estimates. IVE estimates vary with age, risk group and the specificity of the disease outcome. In addition, IVE estimates can be heavily biased by positive or negative confounding.

The expert consultations led to specific recommendations to be applied in the next phase of the project. Eight studies will be piloted in the 2008-9 season: two cohort studies, one case control nested in one of the cohorts, and five case control studies.

The two cohort studies will be conducted in England and Scotland, and in the Comunidad Autónoma de Navarra, Spain, using GP databases. These two studies will provide IVE for the pre- and post-influenza season and will allow to further analyse confounding factors included in the GP database. IVE will be estimated against ILI (both studies), all respiratory infections (England and Scotland), pneumonia and influenza hospitalisations (Navarra), all respiratory hospitalisations (Navarra), and all deaths (Navarra). In Navarra, a subset of patients will be laboratory-confirmed.

A case control study with laboratory-confirmed outcome will be nested in the England and Scotland cohort.

In addition, five case control studies among the elderly population will be conducted during the influenza season in Denmark, Hungary, Portugal, Romania and Spain. The vaccine status of ILI cases that are laboratory-confirmed for influenza will be compared to various sets of controls including influenza-negative ILI cases, controls from GP patients and controls from GP catchment areas.

The five studies will use the recommended European Commission case definition for ILI and a common definition for potential confounding factors such as functional status, underlying diseases, severity, smoking, previous influenza vaccination and pneumococcal vaccination. Therefore, the possibility of pooling the results from those five studies to have a multicentre IVE estimate will be explored.

Results of the 2008-9 pilot studies will be presented in an expert meeting in June 2009. Based on those results, amendments to the protocols will be proposed and implemented in the next round of pilot studies in the same eight countries in the season 2009-10. Subject to available resources, at least two additional pilot studies will start in 2009.

The results of the pilot studies will guide the establishment of a system capable to provide and share rapid and reliable information on IVE on an annual basis. The intention is for this information to be integrated as an essential part of the routine influenza surveillance outputs/data. In order to achieve the successful inclusion of IVE

data in regular influenza surveillance, sustained commitment from all partners as well as secured funding is fundamental.

Working group influenza vaccine effectiveness:

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The scientific basis for offering seasonal influenza immunisation to risk groups in Europe

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This paper summarises the scientific evidence supporting selection of risk groups that would benefit from annual seasonal influenza immunisation in European Union (EU) countries. Risk groups are defined restrictively as *persons in Europe at higher than average risk of adverse outcomes should they be infected with seasonal influenza and for whom use of vaccine is demonstrated to be effective in reducing the risk of those outcomes*. Existing evidence indicate that older people and those with chronic disease are at higher risk of severe adverse outcome and that immunisation reduces this risk. There is thus good scientific evidence for routinely offering annual immunisation to all older people (at least those aged 65 years and older), and people with certain groups of chronic medical conditions. We estimated that these two groups account for between 19% and 28% of the population of EU countries. Thus in 2006, an estimated 84 million older people aged 65 years and over and 41 million people younger than 65 years of age with chronic conditions were living in these countries. There is also strong evidence for immunising staff caring for patients belonging to these two risk groups in residential (care home) settings in order to protect the patients. There are as yet no strong data on whether or not immunising other healthcare workers and carers protect patients though immunisation of healthcare workers can be justified on occupational health grounds. At present the scientific evidence for immunising other suggested risk groups, notably children and pregnant women is not strong for Europe though equally there is no evidence against immunising these groups.

Introduction

Most people are susceptible to influenza infection and there are various estimates of the numbers that are infected each year, the resulting burden of ill-health and to what extent this burden can be reduced. All of these conclude that human seasonal influenza is a serious public health threat which occurs annually but can be significantly ameliorated [1,2]. Influenza vaccines are the most effective preventive tools available for reducing that burden and the risk to individuals [3-5]. The immunisation strategy for preventing human seasonal influenza aims at protecting vulnerable individuals, rather than trying to achieve herd immunity and reduce transmission in the community [6]. Some individuals and groups are more likely to develop severe disease and even die as a result of their infection [2,7-12]. Hence, since the first influenza vaccines were developed the strategy has been to immunise certain so-called 'risk groups' rather than whole populations [13].

Another reason for this selective strategy is the frequent change in circulating viruses and subsequently the need to regularly review the composition of influenza vaccines and to conduct immunisation annually. This introduces an unusually high level of expense and logistical considerations into vaccine production and delivery [14]. In addition to the traditional 'risk groups' (older people and people with chronic illnesses [6]) influenza vaccination is sometimes recommended to other groups and individuals who may or may not be at any higher than average risk of severe disease should they be infected. According to the VENICE study these groups in different EU countries include: pregnant women, children (under age of two or five years), persons living with those at higher risk, healthcare and other care workers, those working in essential, military and veterinary services, and poultry workers [15].

In 2003 the World Health Assembly (WHA) in a resolution concerning pandemic and seasonal influenza urged all its member states *"to establish and implement strategies to increase vaccination coverage of all people at high risk, including the elderly and persons with underlying diseases"* [16]. The resolution neither specified the age of the elderly nor any list of these underlying diseases and the scientific and public health background for the recommendation from the Assembly's secretariat in the World Health Organization (WHO) is unrecorded. Some subsequent specification can be found on the WHO web, where the high risk groups are described as: *the elderly, people with weakened immune systems and those with underlying chronic diseases where influenza often leads to severe pneumonia and other serious illness due to pre-existing chronic diseases* [17]. The WHA also recommended a coverage target for immunisation of the elderly of 50% by the year 2006 and 75% by the year 2010 [16]. No target for those with chronic illness was specified. All European Union (EU) countries are members of the WHA and none expressed a reservation to the resolution.

This paper is one of a series of outputs by the European Centre for Disease Prevention and Control (ECDC) providing scientifically-based public health information and advice concerning seasonal influenza vaccination in Europe, and its main aim is to summarise the scientific evidence supporting selection of risk groups. It also seeks to estimate the number of people in the two main identified risk groups and the proportion they constitute of the population in the EU countries and in EU as a whole.

Methods

The term risk groups has been used in various ways in literature, e.g. persons at higher risk than average for acquiring influenza, persons at higher than average risk of transmitting influenza, persons at higher risk of having an adverse outcome (severe disease or death) should they acquire infection or persons who if they acquire influenza are more likely to transmit the infection to others who will then develop severe disease.

In this paper we employ a restrictive definition, namely *"persons in Europe at higher than average risk of adverse outcomes should they be infected with seasonal influenza and for whom use of seasonal influenza vaccination is demonstrated to be effective in reducing the risk of those outcomes"*.

We did a review of published scientific literature in the field. The literature search firstly focused on articles mentioning risk factors for experiencing severe outcomes following influenza infection. Secondly publications were sought that investigated whether influenza immunisation reduced risks of severe outcome or that it was at least protective against any influenza infection. It was also investigated whether the literature supported the view that immunisation of others, notably healthcare staff and other carers, protected people in the risk groups.

The strategy was to search the PubMed database without date restriction up to September 2008, for relevant articles in English, using medical subject headings (MESH) identifying the disease (Human Influenza, Flu), the clinical outcome (hospitalisation/hospital*, mortality, death, pneumonia, morbidity) and a list of pre-identified possible broad risk factors (cardiovascular, chronic respiratory/COPD, diabetes, immunosuppression/immunodeficiency, HIV, transplant, pregnancy/pregn*, renal failure/dialysis/haemodialysis, elderly/old, child*/infant). To select the subset of studies also reporting "vaccine effectiveness" estimates we included this term in each search considering only articles where vaccine effectiveness was mentioned in the title or abstract. We screened the retrieved articles by reading their abstracts and selected those that were most relevant in terms of article type (reviews, guidelines, large cohorts, meta-analyses) and appropriateness of the content. The literature was screened to select studies based on European populations, and where possible we gave more emphasis to European studies on increased risk of severe clinical outcome in the various risk groups studies as there may be European specific features in terms of prevalence of risk factors and burden of disease that make the results of non-European studies difficult to generalise. This is less the case for vaccine effectiveness studies.

Articles included in the references of reviews, guidelines and meta-analyses were added where they had not been retrieved by the PubMed search. In addition, we drew on a review undertaken for an ECDC-convened scientific panel on immunisation of children in 2006-7 [18] and a systematic review commissioned by ECDC on methods for measuring influenza vaccine effectiveness and undertaken by the organisation Epiconcept (http:www.epiconcept.fr) [19].

The planning estimates of the size of population in the risk groups were made for the elderly and for those with chronic conditions in younger years. For the population aged 65 years and older we used published European population statistics for the year 2004 and with projections made forward to 2050 [20]. Estimating the number of people with chronic conditions in the influenza risk groups was more difficult, as estimates of chronic ill-health are usually not available in the routine statistics and what exists does not conform to the risk groups for influenza which do not comprise all persons with chronic medical and physical conditions.

A specific issue to address was to avoid double counting of persons both aged 65 years and older and with chronic conditions. A large cohort study in Sweden showed that the prevalence of multiple morbidity among older individuals reaches 55% [21]. To overcome this, we excluded European studies where the distribution of chronic conditions was not stratified by age or where double counting due to co-morbidity was not eliminated [22,23], which in some studies resulted in implausible differences between neighbouring countries [24]. Data available from the Global Burden of Disease and Risk Factors (GBD) project which overcomes double counting could not be used either because it does not directly describe the distribution of risk factors relevant to influenza in the general population [25].

The only survey identified that avoided double counting and selected the risk factors for influenza was the one undertaken in the United Kingdom, which used primary care data specifically for planning the needs for influenza vaccine [26]. This study was therefore selected as most likely to provide the accurate age-specific estimates of the proportion of the population suffering from relevant chronic diseases in the EU countries. The survey was undertaken with government support, gave age-stratified results, avoided double counting and included medical validation through doctors' opinions on whether a patient's illness was significant enough to deserve immunisation. These age-specific proportions were then applied to the 2006 populations of all EU countries (derived from Eurostat; http://epp.eurostat.ec.europa.eu/) to provide country-specific estimates of those under age 65 with one or more conditions that would put them into the chronic disease risk group category. These totals were added to the Eurostat estimates of the number of the elderly aged 65 years and older to estimate the proportion of the population that was either suffering from one or more chronic diseases or was aged 65 years and older for each EU country and the EU as a whole.

Results

Literature providing evidence on whether persons in certain categories are at higher than average risk of experiencing severe disease when infected with influenza are summarised in Table 1 along with relevant studies showing the effectiveness of vaccination in reducing this risk. The Table does not attempt to show all the studies but selects typical studies or describes the conclusions of reviews.

Older people

The data strongly support the WHO position that older people are at higher risk of severe illness, hospitalisation and death if they are infected with influenza, compared to younger adults. The data also show that immunisation significantly reduced this risk of adverse outcomes, though the protection afforded is lower than for younger people. The protection was somewhat less for the more severe outcomes (hospitalisation, pneumonia and death) than it is for all influenza but it was still significant both statistically and from a public health perspective.

Table 1

Selected articles providing evidence on the risk groups for influenza vaccination

Target population Risk group	Study type	Outcome measure provided	Comments
Individuals aged 65 years and older (Group 1)			
	Guidelines [27]	Not applicable	US-CDC updated recommendations for seasonal vaccination. Includes a comprehensive review of articles supporting vaccination of various risk groups. It is mainly based on evidence coming from the United States (US).
	Cohort [5]	VE against hospitalisation 21% (95% CI: 17%-26%). VE against death 12% (95% CI: 8%-16%).	Large cohort study conducted in the United Kingdom (UK) covering a 10-year period. Provides robust data on the effectiveness of vaccination in the elderly (≥65 years old) against hospitalisation and death.
	Cohort [3]	Incidence of hospitalisation for pneumonia/ influenza or death: 8.2/1,000 for healthy and 38.4/1,000 for high-risk individuals. VE against hospitalisation 48% (95% CI: 42%-52%)	Large cohort study conducted in the US. Provides rates of death/hospitalisation for healthy and high-risk elderly as well as VE data.
	Time series analysis [28]	Excess hospitalisations higher in persons ≥65 years old (10 per 100,000)	Large study based on hospital discharge records from all public hospitals in Spain covering four influenza seasons. Excess hospitalisations attributable to influenza significantly higher in those ≥65 years old.
Chronic illness (Group 2)			
Chronic respiratory diseases	Review [29]	Influenza vaccination reduced the development of severe respiratory complications and hospitalisation by 50-80%, and death from both respiratory disease and all causes by 40-55%.	
	RCT [8]	VE against influenza-confirmed ARI 76% among individuals with COPD.	VE was not influenced by the severity of COPD. None of the vaccinated patients required mechanical ventilation because of influenza-related ARI. By contrast, all the unvaccinated patients with moderate-to-severe COPD who were hospitalised because of influenza-related ARI needed assisted ventilation.
Chronic cardiovascular disease	Cohort [8]	Vaccination reduced the risk of cardiovascular death - RR 0.34 (95% CI: 0.17%-0.7%1) in individuals with stable coronary hearth disease.	
	Restrospective cohort [30-32]	Higher risk of acute myocardial infarction shortly after an acute respiratory infection (not necessarily influenza) RR 4.95 (95% CI: 4.43%-5.53%)	The study was based on the United Kingdom General Practice Research Database, which contains computerised medical records of more than five million patients.
Metabolic disorders (Including diabetes mellitus)	Case control [10-11]	Influenza vaccine effectiveness in diabetics was 79% (95% CI: 19%-95%)	
	Cohort [9]	Higher risk of hospitalisations, OR: 2.19 (95% CI: 1.08%-4.47%), and of any complication, OR: 1.74 (95% CI: 1.16%-2.61%), among non-elderly adults with diabetes.	
Chronic renal and hepatic diseases	Case series analysis [33,34]	Excess influenza-attributable mortality in patients on dialysis.	
	Literature review [34]	Increased incidence of respiratory infections in patients with chronic kidney disease.	
Immunosuppressed	Review [35]	Higher incidence of complication among organ and haematopoietic stem cell recipients.	
HIV	Meta-analysis [36-38]	Pooled relative risk reduction of 66% (95% CI: 36%-82%).	The study of the highest quality, an RCT, yielded the most conservative estimate (RRR 41%; 95% CI: 2%-64%)
	Cohort [37]	Influenza accounted for 42% of ARI among HIV-infected individuals followed up in a single clinic.	Probably high incidence of disease, but no evidence of more severe disease than in healthy population.
Young people taking salicylates long-term	Review [39]	Theoretical risk of developing severe disease (Reye syndrome) among people under the age of 20 taking salicylates.	A causal association was never established.
Other groups			
Pregnant women (Group 3)	Review [12]	Not applicable	Evidence is contradictory on pregnancy as risk factor for more severe influenza disease in women who are otherwise healthy.
Pregnant women with risk factors (Group 3)	Review [12]	Occurrence of acute respiratory illness was more likely than among healthy pregnant women OR: 3.2 (95% CI: 3%-3.5%). Influenza-attributable rate of hospital admission was increasing with pregnancy trimester: 3.9 (-6.4 to 14.2), 6.7 (-4.1 to 17.5), and 35.6 (21.1 to 50·1) respectively/per 10,000 woman-months.	
Children (Group 4)	ECDC technical report [18]	Data for young children, particularly under two years of age, are scant from European countries. Routine immunisation of school-age children has an indirect beneficial effect for adults and the elderly in terms of reduced disease burden.	This report was developed by a panel of experts who reviewed the available literature up to January 2007.

Abbreviations: ARI, acute respiratory tract illness; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ECDC, European Centre for Disease Prevention and Control; HIV, human immunodeficieancy virus; OR; odds ratio; RCT, randomised controlled trial; RR, relative risk; RRR, relative risk reduction; US-CDC, United States Centers for Disease Control and Prevention; VE, vaccine effectiveness;

There is uncertainty concerning the age 'cut-off', the lower age threshold above which all people should be recommended the vaccine and the data are not consistent with any precise age although as people get older the risk rises [28,40]. The age group most commonly stated as being routinely offered immunisation is of persons aged 65 years and older [15]. There are some exceptions to this and a few European countries have adopted policies for immunising younger persons and have lower age thresholds, others still are at present reviewing their policies with a view to lowering their age-limits [15]. One analysis sponsored by industry suggested reducing the age cut-off to 50 years [24].

Children

In 2006-7, an independent scientific panel convened by ECDC found there was then insufficient data to support starting widespread immunisation of children though the vaccines did induce immunity [18]. That review found considerable data from outside Europe but little that was from Europe itself, notably on the burden of disease in children. Our present review finds that this has not changed, although there is equally no evidence against immunising children.

Table 2

Country-specific estimates of the population in the two major risk groups for European Union countries*, 2006

	Number aged 65 years or over[1]		Number under 65 years-old with one or more risk morbidities[2]		Total "at risk"	
Country	No. of people	% of country's population	No. of people	% of country's population	No. of people	% of country's population
Austria	1,403,000	16.9	689,000	8.3	2,091,000	25.2
Belgium	1,810,000	17.1	879,000	8.3	2,689,000	25.4
Bulgaria	1,325,000	17.3	637,000	8.3	1,962,000	25.6
Cyprus	96,000	12.3	65,000	8.3	160,000	20.6
Czech Republic	1,482,000	14.4	853,000	8.3	2,336,000	22.7
Denmark	835,000	15.3	452,000	8.3	1,287,000	23.6
Estonia	229,000	17.1	111,000	8.3	340,000	25.4
Finland	869,000	16.5	437,000	8.3	1,306,000	24.8
France	10,277,000	16.2	5,262,000	8.3	15,539,000	24.5
Germany	16,299,000	19.8	6,832,000	8.3	23,131,000	28.1
Greece	2,074,000	18.6	927,000	8.3	3,001,000	26.9
Hungary	1,605,000	15.9	835,000	8.3	2,441,000	24.2
Ireland	478,000	11.1	358,000	8.3	836,000	19.4
Italy	11,772,000	19.9	4,907,000	8.3	16,681,000	28.2
Latvia	389,000	17.1	189,000	8.3	579,000	25.4
Lithuania	527,000	15.6	280,000	8.3	808,000	23.9
Luxemburg	67,000	14.0	40,000	8.3	106,000	22.3
Malta	56,000	13.8	34,000	8.3	91,000	22.1
Netherlands	2,368,000	14.5	1,358,000	8.3	3,726,000	22.8
Poland	5,116,000	13.4	3,164,000	8.3	8,280,000	21.7
Portugal	1,828,000	17.3	879,000	8.3	2,708,000	25.6
Romania	3,204,000	14.9	1,789,000	8.3	4,993,000	23.2
Slovakia	640,000	11.9	447,000	8.3	1,087,000	20.2
Slovenia	320,000	15.9	166,000	8.3	486,000	24.2
Spain	7,407,000	16.7	3,691,000	8.3	11,098,000	25.0
Sweden	1,581,000	17.4	756,000	8.3	2,338,000	25.7
United Kingdom	9,752,000	16.0	5.051,000	8.3	14,802,000	24.3
Total EU 27	**83,813,000**	**16.9%**	**41,095,000**	**8.3%**	**124,909,000**	**25.2%**

* Note numbers have been rounded to the nearest thousand so column totals will not necessarily add up.
[1] Eurostat data, average population by sex and five-year age groups, 2006 (date of extraction: 11 Feb 2008)
[2] Based on methodology of Fleming and Elliot (2006) [26]

Two other sources of information show similar estimates for specific countries:
Belgium: Based on the Health Interview Survey (HIS) last conducted in 2004 in Belgium [46], where people at risk were elderly or those with a chronic disease, 30.2% of the total population were at risk and considered for immunisation in 2004 which is consistent with the estimate applying Fleming and Elliot's findings of 25.4%. In absolute numbers, the population aged 65 years or older amounted to 1,789,812 individuals in 2004, and the population between 15- and 64-years-old with chronic health problems was estimated at 1,353,366 individuals. People with more than one chronic disease are not counted twice. Chronic conditions that were taken into consideration were similar to the ones counted in Fleming and Elliot (2006) [26].
France: The estimated number of people aged 65 years or older was around 9,100,000 (14.4% of the population of France) in 2007. The number of people who have used the social security system (because of chronic illness) was estimated at 7,700,000 (13.6%) in 2006 (L'assurance maladie, Caise national 2007 [47]). This means that the proportion of people in risk groups was about 28.0% of the total population which is close to the ECDC estimate of 24.5% applying Fleming and Elliot's data.

Persons with chronic medical conditions

Our review also supports the position that people of all ages with certain broad categories (as listed in Table 1) of chronic medical conditions are at higher risk for severe disease. However, there are much fewer published data that demonstrate that vaccination can reduce the risk of adverse outcomes in this group than there are for the older age-groups. When it comes to specific conditions (rather than broad groups), there is usually insufficient epidemiological scientific information to support immunisation, unless the condition is relatively common such as diabetes.

Our review of the literature also found that patients with more common milder conditions such as mild hypertension, mild asthma, asymptomatic HIV infection or controlled HIV disease with normal immune function have not been investigated for either an increased risk from influenza infection or the impact of vaccination.

Healthy pregnant women

Healthy pregnant women are another group where the case has been made for offering immunisation. It is policy in eight EU countries to offer the vaccine to healthy pregnant women [12,15], based on more complex arguments than in the case of children, reflecting both whether there is evidence of increased risk of severe disease in the women and whether or not this is a mechanism for providing direct and indirect protection of newborn babies by protecting their pregnant and nursing mothers [27]. There is only limited evidence from Europe of increased risk for severe disease in healthy pregnant women and hardly any evidence as yet of impact of immunisation, though the vaccines do induce immunity [12]. What evidence exists is conflicting and much of it is from outside Europe [12]. There are no data against immunising healthy pregnant women, but equally few data from Europe on the burden of influenza in pregnant women and none on the effectiveness of vaccination in reducing that burden. One recent blinded randomised trial of immunisation of pregnant women showed benefit for both mother and child in terms of reduced acute respiratory infection. But that study was conducted in a tropical country [41].

Other groups to whom vaccination is recommended

Many countries recommend immunising healthcare workers and there are occupational health reasons for doing so in order to protect the health of staff themselves [15], but that issue is outside the scope of this paper [42,43]. However immunisation of staff to protect people in risk groups is important to recognise. Randomised community trials (one conclusive community trial and another giving supportive evidence) of immunising care home staff have convincingly demonstrated that this reduces mortality in the elderly and chronically ill patients and therefore can be recommended [44,45]. In terms of protecting risk groups, we could identify no conclusive data that would support or refute policies for immunising other groups of staff or family carers.

Proportion of the population targeted by immunisation

Broad estimates of the number of people and the proportion of the population falling under the two main risk groups for influenza in EU countries and in the EU as a whole are shown in Table 2. The national range is from 19% to 28% depending on the proportion of the elderly in the population in each country. The EU total is estimated to be around 125 million people, with around 84 million persons aged 65 years or older and around 41 million younger persons living with chronic illness.

Discussion

Although there are a number of published studies on burden of disease and vaccination effectiveness in risk groups, relatively few of these are based on data from European countries. Therefore, evidence was considered also from other countries, especially on the effectiveness of vaccination in protecting risk groups. A particular gap is the lack of data on burden of severe disease due to influenza in Europe and surveillance for so called severe acute respiratory infection (SARI) in particular in children and pregnant women. It is notable that while there is good laboratory surveillance and surveillance of those presenting to primary care services with influenza in Europe (so far undertaken through the European Influenza Surveillance System (EISS; http://www.eiss.org/) and WHO National Influenza Centres (http://www.who.int/csr/disease/influenza/centres/en/index.html) working with WHO Global Influenza Surveillance Network (GISN; http://www.who.int/csr/disease/influenza/influenzanetwork/en/index.html) there are no routine European systems of surveillance for persons with severe adverse outcomes due to influenza. Similarly, there is no routine evaluation of influenza vaccine effectiveness in Europe. Therefore, the task of objectively determining the burden of influenza disease, which groups are at risk of severe disease from influenza in Europe and of these which would gain most from immunisation is not as straightforward an exercise as it could be. This is especially pertinent as the characteristics of influenza can change annually leading to significant short term and perhaps longer term variations in the severity of disease and the vaccine effectiveness [6].

Estimates of the impact of influenza vaccines on morbidity and mortality are variable [4,5,48,49]. This is inevitable when citing studies with non-specific outcomes (e.g. all cause or respiratory-related deaths) which always dilute the effects generally found in studies with laboratory-confirmed outcomes. Even in the latter studies it is important to allow for the role of confounding factors. Both positive confounding due for example to the "healthy vaccinee effect", as well as negative confounding associated with serious pre-existing medical conditions being more frequent among vaccinees (counfounding by indication) can bias vaccine effectiveness up- and downwards respectively. The diluting effect and the predominance of negative confounding in a particular study population explains why some reviews of effect from the influenza vaccine may conclude by showing no protection [48].

That said, the evidence supporting the WHA policy for selectively immunising the two risk groups: older people and those with chronic ill-health in Europe is sufficiently strong. Though immunising older people is not a panacea in protecting them against influenza, on balance, it certainly reduces their risk of infection and the more severe outcomes. There is no consensus on what exactly is the age cut-off for 'older people' in Europe and there has been no EU level debate on this subject. Defining a cut-off is beyond the scope of this paper. It also needs to be borne in mind that the age-structure varies across EU countries as do the costs of healthcare and income levels and with these the relative costs and benefits of influenza disease and immunisation respectively. Hence it could be quite reasonable for national age cut-offs to differ. However what data and analyses there are suggest the age of 65 years and over as the current threshhold and this is at least a reasonable minimum recommendation for policy decisions. Concerning the youngest age groups the lack of data from Europe makes decisions over childhood vaccination difficult. It should be noted that three counties, Finland and neighbouring Estonia and Latvia have

recently started immunising children routinely and it is expected that this will provide information on both the burden and impact of immunisation [15].

There are difficulties in defining the chronic conditions. Some national authorities take the approach of coming up with lists of medical and physical conditions for which immunisation is recommended. Others have taken the more pragmatic approach of defining broad categories, e.g. "all chronic metabolic conditions" [50,51]. In our view, the latter broad brush approach is preferable for two reasons. When it comes to individual rare conditions the numbers are always too low to research and so there can only be presumed evidence of increased risk, and even less of the effectiveness of vaccination in reducing that risk. Also there are always uncommon conditions that may have been omitted from the lists. Finally comparison between various EU countries show differences between the detailed national lists while the broad-brush lists all look the same along the lines of Table 1. A problem with both approaches is whether to include mild conditions that are technically chronic diseases but for which there is in fact no demonstrated evidence of increased risk of benefit from immunisation.

When it comes to estimating the number of persons at risk, more credibility should be afforded to the data in our review for the elderly population than that for the people under age of 65 years with chronic illnesses, since the latter data rely on application of results obtained from one country's survey to all other countries. However, the results for chronic illness are similar to what is found in an independent study undertaken by Ryan *et al.* though the overall estimates are greater in Ryan *et al.* because they include people down to the age of 50 years [24] and prevalence surveys in Belgium [46] and France [47] came up with results that were within a few percentage points of what we derived for those countries applying Flemings estimates (Table 2). Both the two independent country estimates were somewhat higher than our estimate but that may reflect that their surveys were without medical verification.

Our calculations suggest that EU countries would currently need to immunise about one quarter of their population annually covering the two major risk groups. Projections of expected demographic trends to 2050 indicate that the absolute numbers and proportions of the older age groups will rise inexorably over time in Europe because of aging populations; from the range of 11-19% in 2004 to 22-35% in 2050 [20,52] (Figure 1). It is less clear what will happen with the size of younger populations with chronic illness. Common sense suggests that the success of modern medicine in permitting people with chronic illness like HIV infection to live productive lives will also result in the increase of the proportion of the population with chronic illnesses. Also some secular changes like increasing obesity and declining levels of exercise may independently increase the prevalence of conditions like maturity onset diabetes and cardiovascular disease. Some limited confirmation of this hypothesis comes from the surveys undertaken by the University of Zurich which show a slow increase in prevalence of people with self-reported ill-health in telephone surveys [53].

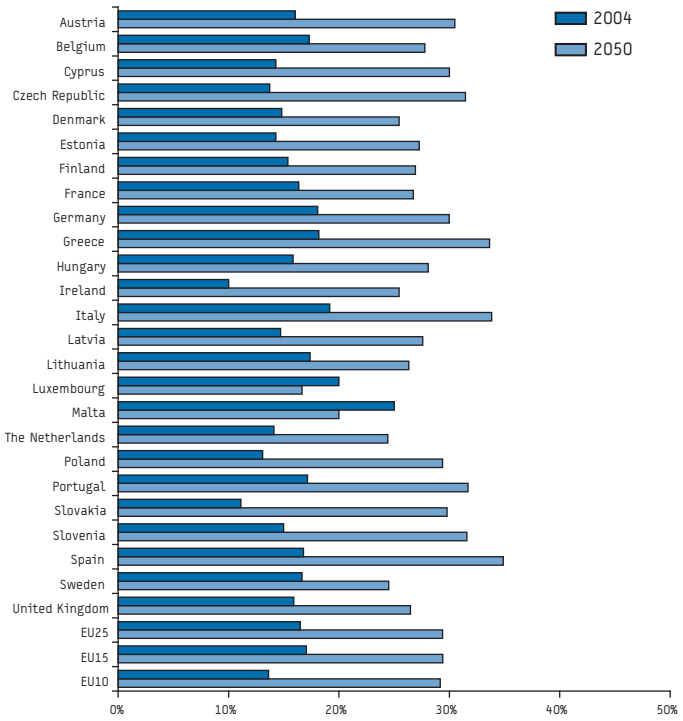
Despite the limited scientific basis for recommending influenza vaccination to healthcare workers in general there is no evidence against it either. Therefore the decisions taken by some countries to recommend immunisation to such groups are reasonable, even if they cannot yet be scientifically supported and conclusively shown to protect patients [54].

In conclusion, existing evidence indicate that the elderly and people with chronic diseases are at higher risk of severe adverse outcome of influenza and that immunisation reduces this risk. Our work has also highlighted a number of gaps in the evidence thus suggesting a number of obvious priorities for studies that could be performed in individual countries or at EU level. Specifically these are:

- Surveillance development – routine surveillance for severe manifestations of influenza and other respiratory infections in Europe (hospitalisations and death). This can be referred to as severe acute respiratory infection (SARI).
- Routine monitoring of the effectiveness of influenza vaccination against different outcomes. Such monitoring is currently piloted by ECDC, Epiconcept and EU Member States [55].
- Estimation of the burden of disease from influenza in pregnant women and children and evaluation of the impact of immunising these groups.
- Development of projects for stronger promotion of influenza immunisation among healthcare workers both for their own benefit and for that of their patients coupled with studies to investigate whether or not immunisation of healthcare staff and household members reduces risk in vulnerable people in the two main risk groups.

Figure 1

Percentage of population aged 65 years and older: 2004 census data compared with 2050 projected data



Data not stated for: Bulgaria, Romania (joined EU in 2007), Iceland and Norway
Data as published for Luxembourg and Malta
Source: The Economic Policy Committee (EPC) and European Commission (EC), December 2005 [20]

- Specific investigation as to whether or not there are higher levels of risk of severe disease from influenza infection in HIV-infected persons in Europe and similar studies for other more common conditions such as mild asthma.
- Development of cross-European health impact and health economic frameworks for policy-informing studies on influenza immunisation, for example regarding the cut-off ages of immunisation in the elderly recognising that there may be reasons for variation between countries.

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