

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: 0.17-0.71) in individuals with stable coronary heart 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 immunodeficiency 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

Country	Number aged 65 years or over ¹		Number under 65 years-old with one or more risk morbidities ²		Total "at risk"	
	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, Caisse nationale 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/influenzane트워크/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 (confounding 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].

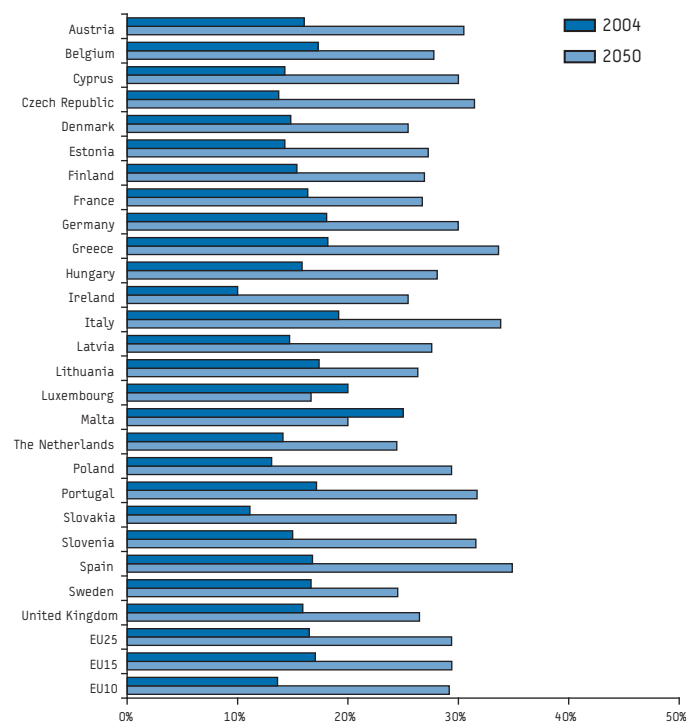
That said, the evidence supporting the WHA policy for selectively immunising the two risk groups: older people and those with chronic ill-health in Europe is sufficiently strong. Though immunising older people is not a panacea in protecting them against influenza, on balance, it certainly reduces their 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 threshold 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 countries, 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

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]

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.

- 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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