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## Research articles

# 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 reports 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
<b>Cohort Studies</b>			
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], Orkqvist 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
<b>Cohort studies during outbreak investigations</b>			
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
<b>Case control studies</b>			
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
<b>Screening</b>			
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

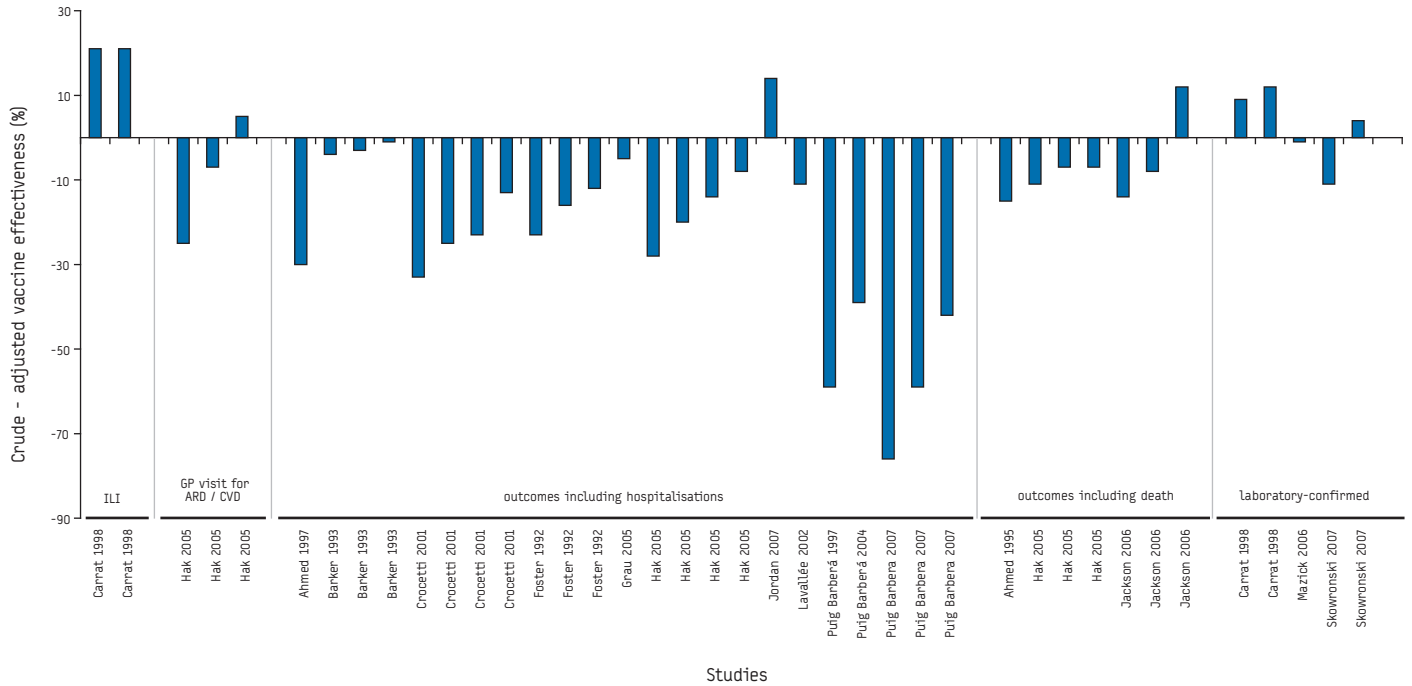
## Box

### 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**

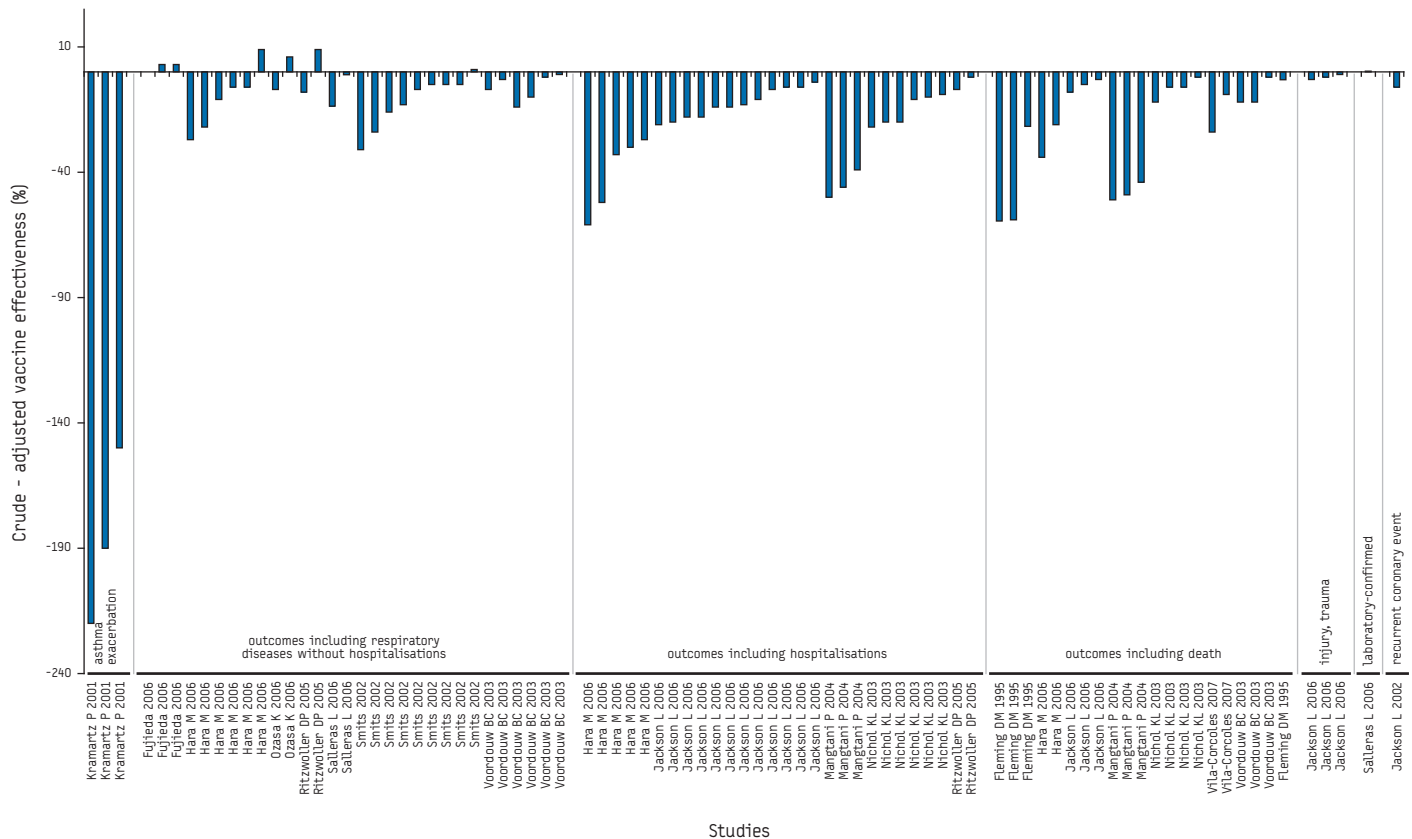
**Difference between crude and adjusted influenza vaccine effectiveness estimated in case control studies, by study outcome**



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.

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