"I-MOVE" towards monitoring seasonal and pandemic influenza vaccine effectiveness: lessons learnt from a pilot multi-centric case-control study in Europe, 2008-9

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Within I-MOVE (European programme to monitor seasonal and pandemic influenza vaccine effectiveness (IVE)) five countries conducted IVE pilot case-control studies in 2008-9. One hundred and sixty sentinel general practitioners (GP) swabbed all elderly consulting for influenza-like illness (ILI). Influenza confirmed cases were compared to influenza negative controls. We conducted a pooled analysis to obtain a summary IVE in the age group of ≥65 years. We measured IVE in each study and assessed heterogeneity between studies qualitatively and using the I2 index. We used a one-stage pooled model with study as a fixed effect. We adjusted estimates for age-group, sex, chronic diseases, smoking, functional status, previous influenza vaccinations and previous hospitalisations. The pooled analysis included 138 cases and 189 test-negative controls. There was no statistical heterogeneity (I2=0) between studies but ILI case definition, previous hospitalisations and functional status were slightly different. The adjusted IVE was 59.1% (95% CI: 15.3-80.3%). IVE was 65.4% (95% CI: 15.6-85.8%) in the 65-74, 59.6% (95% CI: -72.6 -90.6%) in the age group of ≥75 and 56.4% (95% CI: -0.2-81.3%) for A(H3). Pooled analysis is feasible among European studies. The variables definitions need further standardisation. Larger sample sizes are needed to achieve greater precision for subgroup analysis. For 2009-10, I-MOVE will extend the study to obtain early IVE estimates in groups targeted for pandemic H1N1 influenza vaccination.

Introduction

The influenza virus has a high genetic mutation rate that frequently determines antigenic drifts and occasionally antigenic shifts. To achieve a good match between circulating and vaccine viruses, the composition of the vaccine has to be reformulated each season based on the recommendations of the World Health Organization (WHO) Global Influenza Surveillance Network [1]. Therefore, influenza vaccine effectiveness (IVE) can vary from year to year according to the degree of match between the selected vaccine strains and those actually circulating. Hence, IVE should be measured and monitored every year. In a pandemic situation, strain specific vaccines become available only four to six months after beginning the development of the vaccine. Consequently, when the vaccines start to be administered, the virus is already circulating and IVE results are needed rapidly. In addition, vaccine availability is likely to increase over time according to the speed of vaccine production and the licensing of additional vaccines, meaning that IVE measurements need to be repeated over time during the pandemic.

Many factors affect IVE in observational studies. IVE estimates vary according to the specificity of the outcome, the influenza incidence, the population targeted for vaccination and the confounding factors taken into account. Many of the case-control studies reported in the literature measured IVE against clinical outcomes (i.e. hospitalisations for pneumonia or influenza, acute respiratory infections, influenza-like illness (ILI)). Clinical outcomes for influenza are non-specific and likely to underestimate the IVE [2]. To minimise bias, laboratory-confirmed influenza is now being used as outcome in case-control studies in Canada, Australia and the USA [3-5].

Confounding affects IVE observational studies. IVE is underestimated when individuals at higher risk of acquiring influenza are more likely to be vaccinated than individuals at lower risk (negative confounding by indication) [6,7]. IVE is overestimated if individuals more cautious about their health and at lower risk of acquiring influenza are more likely to be vaccinated (positive confounding due to healthy vaccinee effect) [7,8].

In general practitioners (GP) based case-control studies, individuals who use health services more often are more likely to be vaccinated and more likely to consult their GP with influenza symptoms. Vaccinated individuals with influenza symptoms will have a higher probability of being included in the study than vaccinated individuals with no influenza symptoms. This would underestimate the IVE. To control for health seeking behaviour, recent studies suggested comparing individuals who consult for ILI and are influenza positive to individuals consulting for ILI who test negative for influenza (test-negative controls) [3-5;9]. The assumption is that test-negative controls have the same vaccination coverage as the source population giving rise to the influenza cases detected at the GP practice.

I-MOVE started in 2007 with the aim to measure IVE against seasonal and pandemic influenza in the European Union (EU) and the European Economic Area (EEA). Two cohort and five case-control studies to measure IVE were piloted in the 2008-9 season. In order to develop a sustainable system, the studies were conducted in the framework of existing GP-based influenza sentinel surveillance systems. All the country teams conducting I-MOVE pilot studies are members of the European Influenza Surveillance Network (EISN) (the successor of the Commission-funded network, EISS). EISN collects and exchanges timely information on influenza activity in Europe [11]. National Reference Laboratories participating in EISN are evaluated periodically through external inter-laboratory quality control assessments. All the EU Member States recommend seasonal vaccine for the elderly either defined as 65 years old and older or as 60 years old and older [12].

In the pilot case-control studies, we measured IVE against laboratory-confirmed influenza and collected variables to control for positive and negative confounding in the analysis. We restricted the study population to community-dwelling elderly. To increase the precision of the estimates and to provide a summary IVE for the five studies, we explored the feasibility of conducting a pooled analysis. We present here the pooled results of the pilot case-control studies conducted in Denmark, Hungary, Portugal, Romania, and Spain. We assumed that if the pooled case-control design was feasible for seasonal vaccine, the study population could later be expanded to include the age groups targeted for the pandemic vaccine.

Methods

The study population consisted of community-dwelling elderly living in selected sentinel GP practice catchment areas in the five participating European countries. Age groups included were 60 year-olds and older in Hungary and 65 year–olds and older in the other four countries. Participating sentinel GPs swabbed all community-dwelling elderly individuals consulting for ILI during 2008-9 influenza season.

For the first time, in Denmark, Hungary, and Romania sentinel GPs used the EU ILI case definition [13]. In Spain, the ILI EU case definition was used with an additional stated criterion "without any other suspected diagnosis". In Portugal, ILI was defined as in the routine sentinel surveillance, according to GPs´ criteria. Clinical symptoms were collected for all ILI cases.

ILI patients were not eligible for the study if they were institutionalised, had evidence of dementia, did not speak the local language or refused participation.

A case of influenza was defined as an ILI patient who was swabbed and tested positive for influenza using real-time polymerase chain reaction (RT-PCR) or culture. Test-negative controls included in the five studies were ILI patients who were swabbed and tested negative for influenza.

To check if vaccination coverage observed among ILI patients testing negative for influenza was different from that observed in other potential control groups, we measured vaccination coverage among systematic samples of patients from participating GPs who had not had ILI since the beginning of the influenza season (non-ILI controls; up to two controls selected around the time of occurrence of a case) (Hungary, Portugal, Spain), in the community (Denmark, Portugal) and in the participating GPs' catchment area (Hungary, Romania, Spain).

A person was considered vaccinated if s/he had received the 2008-9 influenza vaccine more than 14 days before date of onset of ILI symptoms or of selection as a control.

The minimum set of common confounding variables for the five countries included age, sex, presence of chronic conditions and their respective severity measured in number of hospitalisations for the chronic diseases in the previous 12 months or any hospitalisation in the previous 12 months (Hungary and Portugal), smoking history (none, past, current smoker), functional status (help for bathing and/or help for walking), and influenza vaccination in the previous two seasons.

All ILI patients had a nasal or throat swab taken, which was tested for influenza at the respective countries' National Influenza Reference Laboratory (in Spain, all laboratories integrated in the Spanish Influenza Sentinel Surveillance System) using RT-PCR techniques and/or culture. In each country, all or a subset of influenza isolates were antigenically characterised. Laboratory viral detection, typing, subtyping and variant analysis performed in each of the National Reference Laboratories are described elsewhere [14].

The sentinel GPs carried out face-to-face interviews with ILI patients and non-ILI control patients using country-specific standardised questionnaires. Trained interviewers conducted telephone interviews with community controls using a standardised questionnaire in Denmark and Portugal. Each country study team entered and validated data.

A previously agreed minimum dataset for pooling, including information on case or control status and exposure status and several covariates, was sent to EpiConcept, the I-MOVE coordination focal point. EpiConcept checked the data again for inconsistencies, outliers and logical errors and conducted the pooled analysis.

We created a common restricted dataset of ILI patients meeting the EU case definition, older than 64 years and with a delay between onset of symptoms and swabbing of less than eight days. For each of the country specific datasets, we excluded the controls identified before the week of the first case and after the week of the last case, in order to include only ILI cases within the influenza season.

IVE estimates were obtained using the formula: 1- odds ratio, with 95% exact confidence intervals (CI) [10,15].

We computed study specific crude IVE and adjusted for the pre-defined set of confounders (including age, sex, chronic disease, smoking, previous influenza vaccination and functional status) where possible, using logistic regression. We evaluated heterogeneity between studies qualitatively by assessing the standardisation of the case and covariate definitions. We evaluated statistical heterogeneity using the Q-test and the I2 index [16,17]. To estimate a pooled IVE, we used a one-stage method with study as fixed effect in the model. Results were stratified according to influenza strain and two age groups: 65-74 and >74 years.

According to country specific requirements for ethical approval, all participants provided oral or written consent.

Figure 1

Influenza-like illness (ILI) incidence (cases per 100,000 population) reported by the national influenza sentinel surveillance systems in Denmark, Hungary, Portugal, Romania, and Spain, influenza season 2008-9*

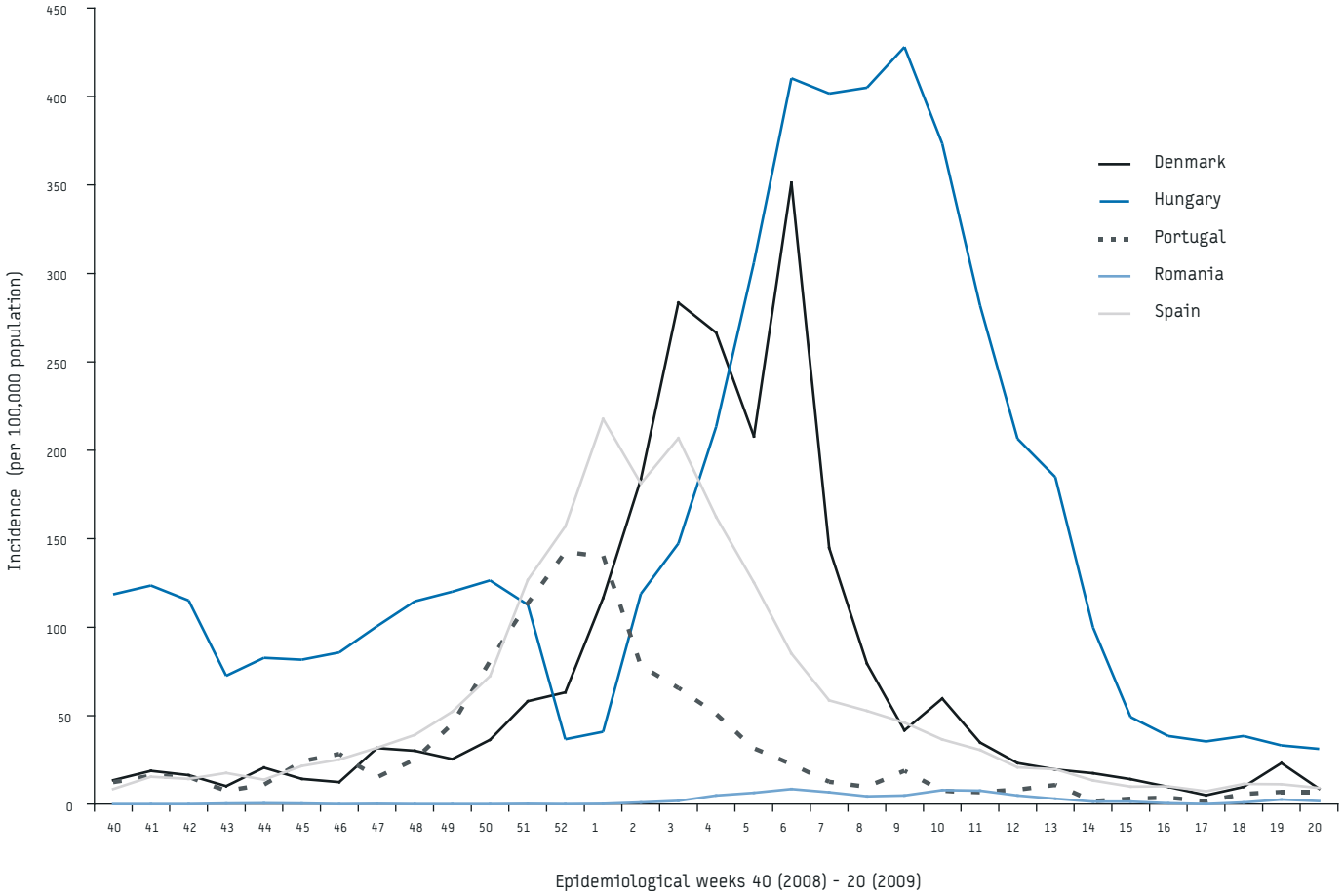

Table 1

General practitioner (GP) participation and influenza-like illness (ILI) cases recruitment by study, Denmark, Hungary, Portugal, Romania, and Spain, influenza season 2008-9

Study	Number of GPs accepting to participate	Number of GPs recruiting at least one ILI patient (%)	Number of ILI patients recruited by GPs	Number of ILI patients positive to influenza (%)	Number of non-ILI GP patients	Number of community controls
Denmark	40	29 (73)	63	25 (40)	N/A	80
Hungary	50	27 (54)	144	45 (32)	89	N/A
Portugal	42	9 (21)	42	15 (36)	40	136
Romania	47	28 (60)	103	30 (29)	N/A	N/A
Spain	164	67 (40)	103	44 (43)	88	N/A
Total	**343**	**160 (47)**	**455**	**159 (35)**	**217**	**216**

Figure 2

Diagramme with study exclusion criteria, Denmark, Hungary, Portugal, Romania, and Spain, influenza season 2008-9

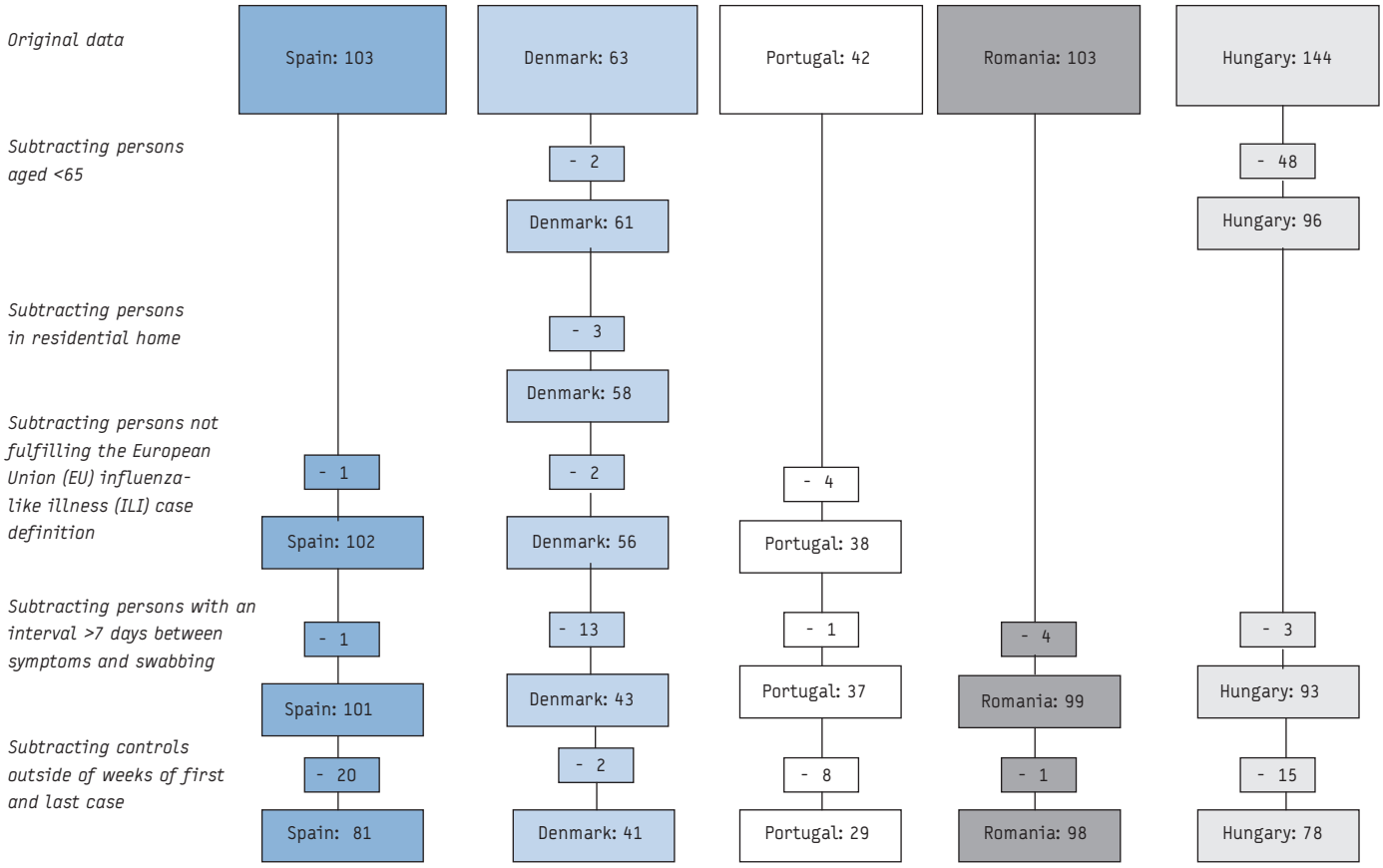

Table 2

Influenza cases and test-negative controls by study and characteristic, Denmark, Hungary, Portugal, Romania, and Spain, influenza season 2008-9

Characteristics	Country	ILI patients		p
		Influenza cases	Test-negative controls	
Interval from symptom onset to swab sample collection (mean in days)	Denmark	3.05	4.25	0.001*
	Hungary	2.1	3.08	0.036*
	Portugal	1.5	2.33	0.030*
Mean age	Portugal	70	75	0.040*
		Number with characteristic / total	Number with characteristic / total	
Any influenza vaccination in past 2 seasons	Portugal	4/14	10/14	0.023**
	Spain	28/43	33/36	0.005**
Fever	Denmark	19/20	14/21	0.022**
	Romania	30/30	57/68	0.019**
Cough	Denmark	20/20	16/21	0.020**
Chronic pulmonary disease	Romania	1/30	13/68	0.040**

*Mann-Whitney U test, **Chi square

Results

In the participating pilot countries, the 2008-9 seasonal influenza epidemic started in Portugal at the end of 2008 (epidemiological week 49) and spread to the east of Europe (Hungary) in spring 2009 (week 4) (Figure 1).

The duration of the epidemic period ranged from seven weeks in Denmark to 13 weeks in Romania. The influenza peaks were reached between week 52 in 2008 (Portugal) and week 10 in 2009 (Romania).

In the five participating countries, the population was vaccinated with a trivalent inactivated influenza vaccine. In the 2008-9 influenza season, different vaccine brands were used in each of the countries. The number of GPs enrolled in each of the studies ranged from 40 in Denmark to 164 in Spain. Overall, 160 GPs recruited at least one patient ranging from 21% in Portugal to 73% in Denmark (Table 1). GPs swabbed and interviewed a total of 455 ILI patients. Among them, 159 (35%) were positive for influenza (from 29% in Romania to 43% in Spain). The completeness of the variables in the returned questionnaires varied from 85% to 100%.

Among 147 isolates typed before the restriction criteria were applied, 131 (89%) were influenza A and 16 (11%) B. Ninety-five of the A isolates were H3N2. All H3N2 strains genetically characterised were A/Brisbane/10/07 similar to the H3N2 vaccine component of the 2008-9 northern hemisphere vaccine. The B strain included in the 2008-9 vaccine did not match the circulating strain. Eight out of the 16 type B isolates were from cases enrolled in Hungary.

After applying the study restriction criteria we included 138 cases and 189 test-negative controls in the analysis (Figure 2).

Table 3

Vaccination coverage for the seasonal 2008-9 influenza vaccine by control group and country study, Denmark, Hungary, Portugal, Romania, and Spain, 2008-9

Study	Vaccine coverage (%) in ILI positive cases	Vaccine coverage (%) in test-negative controls	Vaccine coverage (%) in non-ILI GP patients	Vaccine coverage in community controls	Vaccine coverage in participating GPs catchment area
Denmark	55	71.4	N/A	53.6**	N/A
Hungary***	41.9	48.7	42.7	N/A	38.5
Portugal	42.9	53.3	70	54.4*	N/A
Romania	46.7	67.6	N/A	N/A	86.9
Spain	61.4	89.2	80.7	N/A	65.3

N/A : not applicable
*Community controls sample selected for national telephone survey (Lisboa: Instituto Nacional de Saúde Dr. Ricardo Jorge. Observatório Nacional de Saúde)
** Community controls randomly selected from the Danish population register
*** Results apply to ages 65 years and above, apart from Hungary where the study was carried out for 60 year-olds and older

Table 4

Country specific and pooled crude and adjusted vaccine effectiveness (VE), Denmark, Hungary, Portugal, Romania, and Spain, influenza season 2008-9

		Crude analysis			Adjusted analysis			Variables used for adjustment
		N	VE	95% CI	N	VE	95% CI	
Country specific estimates	Spain	81	80.8	36.0 - 94.2	76	82.9	30.6 - 95.8	age, sex, chronic disease, smoking, functional status
	Portugal	29	34.4	-184.3 - 84.9	28	82.3	-70.5 - 98.2	age, sex, chronic disease, smoking
	Denmark	41	51.1	-78.2 - 86.6	34	90.9	-43 - 99.4	age, sex, chronic disease, smoking, previous influenza vaccination
	Romania	98	58.2	-0.8 - 82.6	92	86.8	38.0 - 97.2	age, sex, chronic disease, smoking, previous influenza vaccination
	Hungary	78	28.6	-78.6 - 71.5	72	43.6	-119.8 - 85.6	age, sex, chronic disease, smoking, previous influenza vaccination
Pooled estimates	65+	327	55.1	27.8 - 72.1	292	59.1	15.3 – 80.3	study, age, sex, chronic disease, smoking, previous influenza vaccination, functional status, previous hospitalisation
	65-74 years				196	65.4	15.6 - 85.8	study, sex, chronic disease, smoking, previous influenza flu vaccination, functional status, previous hospitalisation
	75+ years				96	59.6	-72.6 - 90.6	study, sex, chronic disease, smoking, previous influenza vaccination, functional status, previous hospitalisation
	A(H3) strain				259	56.4	-0.2 - 81.0	study, age, sex, chronic disease, smoking, previous influenza vaccination, functional status, previous hospitalisation

In Romania and Denmark, the proportion of ILI patients presenting with fever was higher among cases than among test-negative controls (Table 2). In Denmark, all of the cases and three quarters of the controls had a cough (p=0.02). In Romania, the proportion of ILI patients with pulmonary chronic disease was lower among cases than among controls (3% vs. 19%).

The mean delay between onset of symptoms and swab collection was shorter for cases than for test-negative controls in Portugal, Denmark and Romania (Table 2). In Spain and Portugal, the proportion of people having received influenza vaccines in at least one of the two previous seasons was lower among cases than among test-negative controls.

Vaccination coverage among controls varied according to country and control group; no specific pattern was identified (Table 3).

The country specific adjusted VE estimates ranged from 43.6% (95% CI: -119.8 - 85.6) in Hungary to 90.9% (95% CI: -42.6 - 99.4) in Denmark (Table 4).

In terms of heterogeneity between studies, two out of the five studies used a different ILI definition. Three variables (number of hospitalisations, presence of chronic diseases and functional status) were collected differently in the five studies. The Q test for heterogeneity was 2.87 (p = 0.579) and the I2 index was 0%.

In the pooled analysis the crude IVE was 55.1% (95% CI: 27.8-72.1%). The IVE adjusted for study, age, sex, presence of chronic conditions, previous hospitalisations, smoking history, functional status, and previous influenza vaccination was 59.1% (95% CI: 15.3-80.3%) (Table 4).

The adjusted IVE was 65.4% (95% CI: 15.6-85.8%) in the 65-74 year-olds and 59.6% (95% CI: -72.6 -90.6%) in the age-group of ≥75 years. The adjusted IVE against the A(H3) strain was 56.4% (95% CI: -0.2-81.0%).

Discussion

We estimated influenza VE against laboratory-confirmed medically attended influenza using test-negative controls, within existing sentinel GP networks in five EU countries. The country specific and the pooled IVE estimates suggest a protective effect of the 2008-9 seasonal vaccine in the elderly population in a year with a good match between the seasonal vaccine and the A(H3) strain predominantly circulating in Europe [18]. However, the estimates have wide confidence intervals.

The case-control design using test-negative controls was performed easily in the framework of the established GP sentinel surveillance networks. Participating GPs had previous experience in collecting swabs and in completing a form for each patient swabbed. Among the GPs who accepted to participate in the study, less than half interviewed and swabbed ILI patients. This may be explained by the overall low incidence of ILI in the elderly in 2008-9 [18] rather than a low acceptability of GPs, as swabbing and interviewing ILI patients is a simple way of recruiting cases and test- negative controls. The questionnaires used for data collection were short leading to a high completeness of all variables. At the end of the season, the study coordinators in Denmark, Romania, and Spain interviewed GPs who participated in the 2008-9 study. Most of them (95% in Spain, 78% in Romania, 74% in Denmark) would be willing to participate in the study in 2009-10 (data not shown). In 2006 in Denmark (one of the current study sites), Mazick *et al.* showed similar acceptability results following an influenza VE case-control study based on the sentinel GP network [19].

The recruitment procedure minimised selection bias as all ILI cases were swabbed. Furthermore, GPs did not know the case or control status when recruiting ILI patients. This was the first season in which the EU ILI case definition was introduced into the sentinel GP networks. For most ILI patients recruited, the case definition was correctly used: of 455 ILI patients reported, only 17 were excluded because they did not match the EU ILI case definition. However, we cannot rule out that some GPs did not include all patients corresponding to the EU case definition. If the sensitivity of GPs´ ILI case definition were dependent on the vaccination status, IVE might have been over- or underestimated.

Various studies suggest that ILI test-negative controls represent the source population of influenza cases seen at GPs offices and that the study design adjusts for propensity to seek care. This would mean that the propensity to seek care is equal between ILI patients who test positive and those testing negative for influenza. Our results indicate that in three out of the five studies, the delay between onset of symptoms and swabbing was shorter for cases than for test-negative controls. Similar results were found in the Wisconsin study [3]. This may indicate a different health-seeking behaviour or a different severity of ILI in cases and in controls. Health-seeking behaviour of ILI cases and ILI test-negative controls should be further studied and compared.

To further assess the representativity of test-negative controls, we measured the vaccine coverage in other potential control groups. The vaccine coverage differed by control group (test-negative controls, non-ILI GP controls, community controls) and between countries with no specific pattern. This could suggest that the source population of influenza cases consulting a GP may be country specific. In general, the vaccine coverage in the community or in the GPs catchment area was lower than the vaccine coverage of GP clients indicating that community controls do not represent a good control group for medically-attended ILI influenza cases. In a recent study in Wisconsin, VE for laboratory confirmed medically attended-ILI was estimated for three seasons using two control groups: test-negative controls and controls randomly selected from individuals in the source population who did not have a clinical encounter for acute respiratory illness prior to the week of recruitment [3]. In the three seasons, the vaccination coverage of the test-negative controls was higher than among the other controls.

We took into account the main confounding factors identified in the literature. Most of them were based on patients´ report for which validity is unknown. The pooled crude and adjusted IVE were similar suggesting a low distortion of effect due to confounding. In our study, a small proportion of ILI patients had indicators of frailty (4.3% had poor functional status and 6.4% were hospitalised in the previous year). Elderly ILI patients consulting GPs at their office may have a better health status than those not consulting. Therefore, functional status and severity may not be relevant confounding factors within this study population and study design. Our results may also reflect that using specific outcomes decrease the amount of confounding observed [5,7]. In Canada, using the same study design, IVE did not change when adjusting for chronic diseases [20].

The excellent collaboration between the study teams made the pooling of data from the five studies possible. Pooling increased the precision of the estimates. Given the small samples sizes of the individual studies, we used a one-stage pooling model that assumes that the effect of the exposure (the seasonal vaccine) and the effect of the covariates are the same in all the studies. We do not know if the difference in virus circulation in the various countries and a potential different health-seeking behaviour may violate this assumption. The pooled estimates of the pilot phase have to be interpreted with caution as heterogeneity between studies may exist. Futhermore, different vaccine brands were used. However, the aim of I-MOVE is not to guide the Member States in deciding which seasonal vaccine to purchase. In order to assess VE for the various vaccine brands, the sample size would have to be increased significantly. The definitions of some covariates were not exactly the same in the different studies. Tests for interaction between study and covariates did not suggest the presence of heterogeneity. However, the small sample size may have led to an insufficient power to detect heterogeneity.

Conclusions

In 2008-9 the match between the seasonal influenza vaccine and the predominant circulating strains was good and the IVE in the elderly relatively high. Our results suggest that GP based case-control studies using test-negative controls to estimate seasonal IVE against laboratory-confirmed medically- attended influenza, are feasible in Europe. The use of a laboratory confirmed outcome may reduce the magnitude of confounding. If other studies confirm this, the number of confounders documented may be reduced, thus simplifying the data collection. The representativity of test-negative controls should be further evaluated.

Pooling of country specific data is needed to have early seasonal or pandemic VE estimates and to increase the precision of the estimates for subgroup analysis. In 2009-10 we will increase the sample size, by increasing the number of countries participating in the study and including more GPs per country. The larger sample size will allow the use of a two-stage model that better takes into account the potential heterogeneity between studies [18,21]. The studies will use common definitions for all variables to minimise heterogeneity between studies. During H1N1 influenza pandemic, interim analyses will be conducted in different periods according to the available sample size. The timing for conducting each of the interim analyses will depend on the time necessary to reach the appropriate sample size. This will depend mainly on the ILI incidence, the influenza incidence and the vaccination coverage.

The suitability of the case-control studies based on sentinel GPs to measure pandemic IVE will depend on the vaccination and control strategy. If pandemic cases are seen by the sentinel GPs and GPs have the possibility to ascertain patient vaccination status, then the case-control design piloted in 2008-9 would be adequate to estimate pandemic VE. All age and risk groups targeted by the vaccine should be included in the study. The design will be adapted to reduce the GPs' workload by simplifying the questionnaire and revising the procedure to select patients to swab.

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-All participating GPs in Denmark, Hungary, Portugal, Romania, and Spain.

*Erratum: The x-axis in Figure 1 indicated the wrong weeks and this was corrected on 6 November 2009.

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