Effectiveness of 2010/2011 Seasonal Influenza Vaccine in Ireland

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Abstract
We conducted a case-control study to estimate the 2010/2011 trivalent influenza vaccine effectiveness (TIVE) using the Irish general practitionersâ influenza sentinel surveillance scheme. Cases were influenza-like illness (ILI) patients with laboratory-confirmed influenza. Controls were ILI patients who tested negative for influenza. Participating sentinel general practitioners (GP) collected swabs from patients presenting with ILI along with their vaccination history and other individual characteristics. The TIVE was computed as (1 â odds ratiofor vaccination) x100%. Of 60 sentinel GP practices, 22 expressed interest in participating in the study and 17 (28%) recruited at least one ILI patient. In the analysis, we included 106 cases and 85 controls. Seven controls (8.2%) and one influenza case (0.9%) had been vaccinated in 2010/2011. The estimated TIVE against any influenza subtype was 89.4% [95% CI: 13.8; 99.8%], suggesting a protective effect against GP-attended laboratory confirmed influenza. This study design could be used to monitor influenza vaccine effectiveness annually but sample size and vaccination coverage should be increased to obtain precise and adjusted estimates.

Introduction
As influenza viruses constantly evolve, influenza vaccines have to be reformulated every year to contain representative circulating virus strains. Clinical trials can provide data on the efficacy of vaccines but they cannot be conducted yearly and are usually limited to healthy adults. Therefore observational studies are needed to monitor influenza vaccine effectiveness (IVE) annually at population level. Various study designs can be used according to the epidemiology of influenza, available data sources and available resources [1,2]. In February 2010, the World Health Organization (WHO) recommended the following viruses to be used for influenza vaccines in the 2010/2011 influenza season in the northern hemisphere: an A/California/7/2009 (H1N1)-like virus, an A/Perth/16/2009 (H3N2)-like virus and a B/Brisbane/60/2008-like virus [3]. Following these recommendations, trivalent influenza vaccines were developed by manufacturers. In Ireland, the seasonal influenza vaccination campaign started on 6th October 2010. Two vaccines were marketed, both were non-adjuvanted. Vaccination was recommended for persons aged 50 years and over, adults and children aged over 6 months with underlying medical conditions or morbid obesity, immunosuppressed individuals, children on long-term aspirin therapy, pregnant women, health care workers, residents of nursing homes and other long stay facilities, and individuals with close contact with pigs, poultry or water fowl. Vaccines could be administered either in general practitioner (GP) practices, occupational health departments or in selected Boots pharmacies.

The first study measuring IVE in Ireland was conducted in 2009/2010. This study was part of a multicentre European study within the I-MOVE network (I-MOVE: Influenza Monitoring Vaccine Effectiveness in Europe). This network was established in 2007 by the European Centre for Disease Prevention and Control (ECDC) with the aim of monitoring seasonal and pandemic IVE in Europe [4]. It successfully provided IVE estimates during the 2008/2009 and 2009/2010 seasons [5,6]. The main objective of our study was to estimate the 2010/2011 trivalent influenza vaccine effectiveness (TIVE) in Ireland. This study was again part of the I-MOVE multicentre study based on sentinel GP surveillance networks from seven other European countries. This article presents the results of the study conducted in Ireland.

Methods
We conducted a case-control study between October 2010 and May 2011 within the framework of the Irish College of General Practitioners (ICGP) influenza surveillance scheme. This system has been in operation since October 2000 and comprises 135 sentinel GPs from 60 practices who each week report on influenza-like illness (ILI) consultations. They also take nasal and throat swabs from one to five ILI patients weekly for influenza testing. The group covers 6.2% of the national population (based on the 2006 census). All sentinel GPs were invited to participate in the study. The study population comprised all individuals with no contraindications for seasonal influenza vaccine who consulted a participating sentinel GP practice with ILI. We used the European Union (EU) ILI definition: sudden onset of symptoms and at least one systemic symptom (fever, malaise, headache and myalgia) and at least one respiratory symptom (cough, sore throat or shortness of breath) [7]. Each participating GP practice was asked to recruit the first three patients aged less than 65 years old presenting with ILI each week and all ILI patients aged 65 years or over. Patients were eligible if they met the EU ILI definition and presented within seven days of symptom onset and gave oral consent to participate.

As well as swabbing ILI patients, GPs also completed a standardised questionnaire (paper or web-based) collecting the patientâ s influenza vaccination history and individual characteristics (age, underlying medical conditions and related hospitalisations, smoking status, functional status, antiviral treatment, number of GP visits in the previous year). Specimens were sent to the NVRL as per routine procedure and were tested for influenza A and B using real-time PCR. Specimens positive for influenza A were further sub-typed using a real-time type specific RT-PCR for seasonal influenza A(H1), A(H3) or pandemic influenza A(H1N1)2009. Cases were patients with laboratory-confirmed influenza. Controls were those who tested negative for all influenza viruses. The exposure of interest was a history of vaccination with the 2010/2011 trivalent influenza vaccine more than 14 days before symptom onset. Vaccination status was ascertained by GPs through the patient medical records or by asking the patient directly. Data were entered into EpiData Entry and analysed in Stata 11.0. Univariable analysis was performed to compare the odds of vaccination among cases and controls. The TIVE was computed as [1â Odds Ratio (OR)]x100%. Molecular analysis was performed on the first positive isolate per week for each circulating subtype and whenever there were vaccine failures. This comprised nucleotide sequencing and phylogenetic analysis of the haemagglutinin (HA) gene using Paup version 4.0b108. Ethical approval was obtained from the ICGP Research Ethics Committee.

Results
GP participation
Of 60 practices contacted, 22 expressed an interest in participating in the study and 17 (28%) recruited at least one ILI patient. The population covered by the 17 practices is estimated at 1.8% of the Irish population (based on the 2006 census). The geographical distribution of the GPs is shown in Figure 1.

Figure 1: Geographical distribution of the17 GP practices participating in the influenza vaccine effectiveness study in Ireland, 2010/2011

Recruitment of patients
GP practices recruited on average one patient per week (min: 0; max: 9) during the period of high influenza activity (when the sentinel ILI consultation rate wasover the baseline threshold). Over the study period, 288 ILI patients were recruited but 97 (34%) did not meet the inclusion criteria and were excluded from the analysis. The main reasons for exclusion were: week of symptom onset prior to the first or after the last confirmed influenza case recruited into the study (n=32, 33%), delay greater than seven days between symptom onset and swabbing (n=17, 18%) or reported symptoms did not fulfil the EU ILI definition (n=35, 36%).

Description of patients
Of 191 patients included in the analysis, 85 tested negative for any influenza virus and 106 (55%) were confirmed with influenza, of whom: 56 (53%) with influenza A(H1N1)2009, 47 (44%) with influenza B, 2 with influenza A (unsubtyped) and one with influenza A(H3). The epidemic peak of the ILI consultation rate occurred in week 1-2011 (Figure 2). Of 191 patients, 45 (23.5%) were reported as belonging to a target group for influenza vaccination. Eight patients (4.2%) had received the 2010/2011 influenza vaccine more than 14 days before symptom onset.

Figure 2: Distribution of ILI patients (N=191) and positivity rate by week of onset of symptoms (ISO week number) and by virus subtype, Influenza vaccine effectiveness study in Ireland, 2010/2011

Comparison of influenza cases and controls
Influenza B cases were significantly younger than controls (median age: 12 years versus 31 years, p=0.001) whereas influenza A(H1N1)2009 had a similar age distribution to controls (median age: 29 years versus 31 years, p=0.76). Controls were more likely to have diabetes than influenza cases. There were no significant differences between cases and controls for other baseline characteristics. Regarding history of vaccination in previous years, controls were significantly more likely than cases to have received the seasonal vaccine in 2009/2010 but the difference in terms of the 2009/2010 pandemic vaccine was not significant (Table 1).

Vaccine effectiveness
Seven controls (8.2%) and one influenza case (0.9%) had received the 2010/2011 influenza vaccine. The vaccinated case was confirmed as influenza B. This patient was aged 15-24 years and had a chronic neurological disease. The crude TIVE was 89.4% [95%CI: 13.8; 99.8%] against any influenza subtype, 100% [95%CI: -8; 100%] against influenza A(H1N1)2009 and 77% [95%CI:-90.0; 99.5%] against influenza B.

Phylogenetic analyses
Amplification and sequencing of a HA fragment was successful for 18 positive isolates: 11 influenza A(H1N1)2009 and 7 influenza B. The specimen isolated in the patient with vaccine failure could not be sequenced. All influenza A(H1N1)2009 isolates formed a monophyletic group with a set of reference sequences from America, Asia and Europe including the vaccine strain. Regarding influenza B, six sequences were clustered as Victoria-like strains (genetically similar to the 2010/2011 influenza vaccine strain) and one was clustered as Yamagata-like strain.

Discussion
The 2010/2011 TIVE against any influenza subtype was estimated to be 89.4%, suggesting a protective effect of the vaccines against medically-attended laboratory-confirmed influenza. However, this result should be interpreted with caution given the wide confidence interval around the estimates. Our findings are consistent with the phylogenetic analyses which demonstrated a good match between the vaccine and the circulating strain. The TIVE point estimate in Ireland was higher than the preliminary estimates reported from studies conducted in other European countries. The adjusted TIVE against laboratory-confirmed influenza (any subtype) was 50% [95%CI: -6; 77%] and 58% [95% CI: 11; 80%] in two case-control studies conducted in Spain and 42% [95% CI: -7; 69%] in the I-MOVE multicentre case-control study [9-11]. However, comparison is limited by the low precision and the fact that no adjustment for potential confounders could be done in Ireland. In all other studies, the adjusted TIVE was lower than the crude TIVE. Major confounders identified were seasonal influenza vaccination in 2009/2010 and age group. The main limitation of the study was the small sample size coupled with low vaccination coverage which decreased the precision of the TIVE estimate and precluded the possibility of conducting multivariable and stratified analysis. The number of participating GP practices, number of patients recruited by week and vaccination coverage were all lower than expected. Moreover, a substantial number of recruited patients did not meet the inclusion criteria.

Various study designs have been described to estimate IVE [2]. Cohort, case-control or screening methods can be used depending on the available data sources. Given the absence of a national immunisation register in Ireland, we decided to use the sentinel GP influenza surveillance system to undertake a case-control study (also called test-negative design). One advantage of this design is that the selection bias is minimised since GPs do not know the case and control status of the patients at recruitment. Moreover, laboratory-confirmation of influenza cases has been shown to be an important parameter in IVE studies [11]. Another advantage of the test-negative design is that cases and controls are selected from the same population (GP attending patients) and are assumed to have the same health-seeking behaviour and the same chances of being vaccinated [12]. In our study, cases and controls did not differ significantly in the number of GP consultations in the previous year.

The influenza sentinel GP surveillance system is a unique network for estimating IVE at population level in Ireland. Some improvements have already been achieved following the 2009/2010 study, in particular the implementation of the EU ILI definition in the influenza sentinel GP surveillance system and the use of systematic sampling to recruit ILI patients. For coming influenza seasons, the priority would be to increase the power of the analyses, by increasing both sample size and vaccination coverage, in order to obtain precise IVE estimates for Ireland. All sentinel GPs are encouraged to participate in this research study. Changes in the recruitment strategy will be explored in order to increase sample size. Inclusion criteria should also be better explained and emphasised during the planning phase in order to optimise recruitment.

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