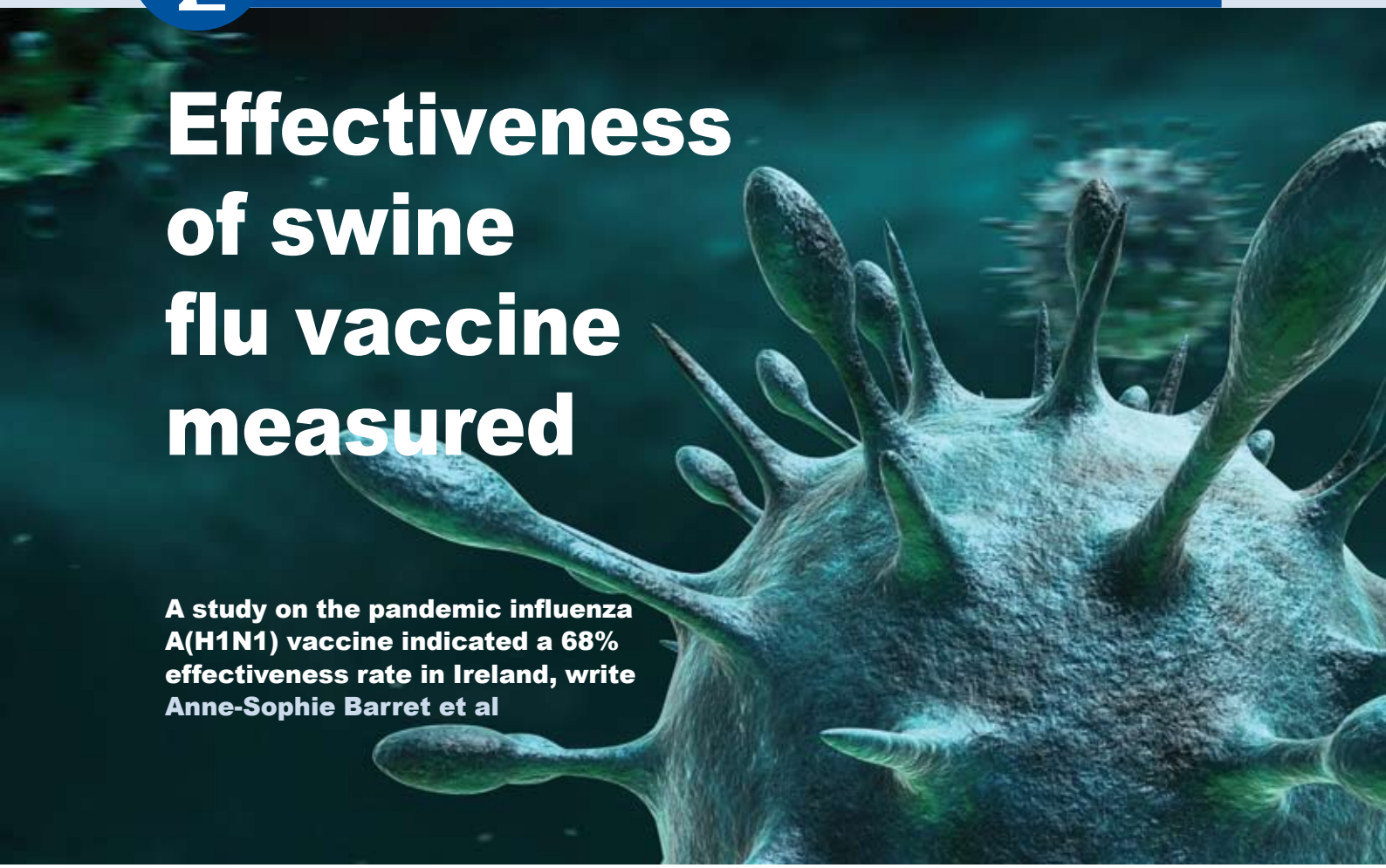

Effectiveness of swine flu vaccine measured

A study on the pandemic influenza A(H1N1) vaccine indicated a 68% effectiveness rate in Ireland, write Anne-Sophie Barret et al

IN APRIL OF LAST YEAR, the 2009 pandemic influenza A(H1N1) virus was identified in Mexico and subsequently spread worldwide. In June, the World Health Organization declared phase six of the influenza pandemic.

As part of the global pandemic response, vaccines were developed against the virus. As of October 6, 2009, three vaccines were granted a marketing authorisation from the European Commission, based on a scientific recommendation from the European Medicines Agency's Committee for Medicinal Products for Human Use. This recommendation was based on the review of data on quality, safety and immunogenicity of the vaccines. Early clinical trials showed good immune responses after the administration of the pandemic vaccines. However, clinical trials were conducted on healthy individuals and did not consider the vaccine impact on circulating strains in the population. Observational studies were needed to estimate the pandemic influenza vaccine effectiveness (PIVE) at population level.

In Ireland, the vaccination campaign against pandemic influenza started on November 2, 2009. It initially targeted people who had chronic medical conditions, as listed in the recommendations of the National Immunisation Advisory Committee;[1] pregnant women, immunosuppressed individuals and their household contacts, residents of disability units and individuals with significant physical or intellectual disability. The vaccination was then expanded to all healthcare staff, and to children aged between six months and five years and their household contacts, children aged between five and 18, adults aged 65 years and over and finally, all others. Two pandemic vaccines were marketed in Ireland, one with an adjuvant and one without.

The main objective of our study was to estimate the effectiveness of the 'swine flu' vaccine in Ireland in order to target public health measures, estimate the impact of vaccination on disease burden and provide some guidance on recommendations for vaccine use and composition.

Our secondary objective was to explore the feasibility of using the Irish GP influenza sentinel surveillance system for monitoring influenza vaccine effectiveness (IVE) every year. This study was part of a multi-centre European study (I-MOVE: Influenza Monitoring Vaccine Effectiveness in Europe). The I-MOVE 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.[2, 3]

Methods

A case-control study was conducted between November 2009 and May 2010 within the Irish influenza sentinel surveillance system. The sentinel system comprises approximately 135 sentinel GPs grouped in 60 practices that weekly report influenza-like illness (ILI) consultations and swab specimens from up to five ILI patients per week. All sentinel GPs were invited to participate in the study. Those who expressed interest in participating were provided with instruction materials.

The study population comprised all individuals with no contraindications for either pandemic and seasonal influenza vaccine(s), who were consulting at a participating sentinel GP practice and presenting with ILI. As part of routine influenza surveillance, participating GPs collected

swabs from five patients presenting with ILI per week. They were also asked to complete a standardised questionnaire with the patient's influenza vaccination history and other individual characteristics (age, underlying medical conditions, smoking status, antiviral treatment, number of GP visits in the previous year).

Specimens were sent to the National Virus Reference Laboratory (NVRL) as per routine procedure and were tested for influenza A and B and pandemic influenza using real-time PCR. Specimens positive for influenza A and negative for 2009 pandemic influenza A(H1N1) were sub-typed using a real-time type specific RT-PCR H1 and H3 subtyping assay for seasonal human H1 and H3 strains.

Cases were those individuals with laboratory-confirmed pandemic influenza. Controls were those who tested negative for all influenza viruses. The exposure of interest was a history of vaccination with the pandemic vaccine during the 2009/10 season. Patients were considered as immunised if they had received one dose of vaccine more than 14 days before the disease onset. Data were entered in Epi-Data Entry and analysed in Stata 11.0. Univariable and multivariable analyses were performed to compare the odds of vaccination among cases and controls. Variables were included in the logistic regression model if there was a relative difference of at least 15% between the crude and the adjusted odds-ratio (OR). Age group and risk factor were forced into the model as they are known as important confounders for IVE. The PIVE was computed as 1–OR.

A molecular analysis was performed on the first two positive isolates per week and whenever there were vaccine failure(s). This comprised nucleotide sequencing and phylogenetic analysis of the haemagglutinin (HA) gene using Paup version 4.0b104.

Results

GP participation

Of the 60 practices contacted, 24 expressed interest in participating in the study. The population covered by the 24 practices is estimated at 102,798 persons and covers approximately 2.4% of the Irish population. Of these 24 practices, 16 (66.6%) recruited ILI patients.

Recruiting patients

From week 45 2009 to week 20 2010, 168 ILI patients were recruited into the study. The majority of patients (42%) were recruited in weeks 46 and 47. The last pandemic influenza case was notified in week 2 2010 (with symptom onset in week 1). Of the 168 patients, 71 patients were excluded from the analyses. Of 97 patients, 32 (33.0%) were confirmed with pandemic influenza and 65 had a negative result. The only influenza virus detected among study participants was the pandemic virus.

The positivity rate for pandemic influenza did not vary significantly with the month of symptom onset. It was 31% in November, 38% in December and 20% in January. There were no significant differences between cases and controls for all baseline characteristics, except for age group; cases were more likely than controls to be aged between five and 14 years old. Of 96 patients for whom the information was available, fourteen (14.6%) had received one pandemic vaccine shot and six (6.3%) had received it more than 14 days before symptom onset and so were considered immunised against pandemic influenza. Of these, five had

received the adjuvanted vaccine and one had received the non-adjuvanted vaccine. All were aged between 15 and 64 years and four had a medical risk factor (diabetes mellitus, heart disease, chronic respiratory disease and asthma). The crude OR for the association between pandemic vaccination and confirmed influenza was 0.38 [95% CI:0.01;3.64].

Vaccine effectiveness

The crude PIVE was 62% [95% CI:-264%;99%] (Fisher's exact test, p=0.66). After adjusting for age group and presence of at least one risk factor, the PIVE was 68% [95% CI:-251%;97%] (Wald Test, p=0.35).

Phylogenetic analyses

Amplification and sequencing of a HA fragment was successful for 18 of 19 positive isolates selected for the phylogenetic analyses. All Irish isolates formed a monophyletic group with a set of H1v sequences from America, Asia and Europe including the vaccine strain, supported with a bootstrap value of 100%. When compared to the amino acid sequence of the vaccine strain A/California/07/2009, all Irish isolates presented a substitution at S203T. Two isolates had another substitution at D222E.

Discussion

The estimated PIVE was 68%, suggesting a protective effect of the recommended pandemic vaccines against medically-attended ILI pandemic influenza. However, this estimate is not statistically significant and should be interpreted with caution. Our findings are consistent with the immunogenicity data which indicated a good antibody response, obtained in the first clinical trials of the two vaccines licensed in Ireland.[5,6] According to national influenza laboratory surveillance, the pandemic influenza virus was the only virus detected during the 2009/10 season (Personal communication HPSC/NVRL). The phylogenetic analyses demonstrated a very good match between the circulating and the vaccine strain. None of the isolates had the D222G mutation reported by the Norwegian Institute of Public Health to the WHO in November 2009.[7,8] In particular, no specific mutation was identified in the 128 amino-acid sequence of the strain isolated from the patient with vaccine failure in the study.

We were limited in the statistical analyses due to the small sample size. The study started after the pandemic peak in Ireland. During the period of inclusion of patients into the study, the ILI rate in Ireland was declining as the vaccine coverage was increasing. Thus the probability of recruiting vaccinated ILI patients in the study was low. This situation was reflected in all European countries participating in the study.

The IVE can be estimated using different study designs (cohort, outbreak investigation, case-control or screening) according to the available data sources (computerised immunisation registries, sentinel GP network or national vaccination survey).[9,2] In Ireland, there is no national formal immunisation coverage register for influenza vaccine which could be used to undertake a cohort study. The national influenza vaccination coverage telephone survey, needed for the screening method, is not systematically conducted every year. In light of this, we decided to use the GPs' influenza surveillance system to undertake a case-control study. One advantage of the case-control design is that the selection bias is minimised since GPs do not know the case and

control status of the patients at recruitment. Moreover, the laboratory-confirmation of influenza cases has been showed to be an important parameter in IVE studies. Studies using less specific clinical outcomes without laboratory confirmation could underestimate the IVE.[10,11] Another advantage of the case-control design is that cases and controls are selected from the same population (GP attending patients). In our study, cases and controls did not differ significantly in the number of GP consultations in the previous year.

As systematic sampling is not routinely applied in the influenza sentinel network, participating GPs could decide which ILI patients to recruit. Some preliminary results from French studies suggest that GPs are more likely to select vaccinated patients over unvaccinated patients (personal communication I-MOVE). However, it is unlikely to produce a biased IVE estimate since GPs do not know the case or control status of patients at recruitment.

We conclude that the Irish GP influenza sentinel surveillance network can be used to monitor the IVE in Ireland. Efforts should be made to increase the number of participating GPs and the sample size to allow for more power in the analyses. Methods should be better harmonised within the European I-MOVE project. For the coming season, we will endeavour to implement the EU ILI case definition and systematic sampling of ILI patients.

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