Letter to the editor: influenza vaccine effectiveness: heterogeneity in estimates for the 2012/13 season

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To the editor: In the past few weeks, there have been several publications on influenza vaccine effectiveness (VE) during the 2012/13 influenza season. Having robust VE estimates as soon as possible during the season is of great public health benefit. Indeed, to optimise the design of such studies and increase the precision of (early) estimates by pooling of data, the European Centre for Disease Prevention and Control (ECDC) has supported the European Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) network [1].

However, the recently published studies provide very different estimates: A study from the United Kingdom (UK) showed a VE against laboratory-confirmed influenza in a general practitioner (GP) network of 51% (95% confidence interval (CI): 27% to 68%) [2]. In contrast, a study from Denmark using national registries showed a dramatically low VE of -11% (95% CI: -41% to 14%) against laboratory-confirmed influenza A among those aged 65 years and over [3]. VE against influenza B in the Danish study was much higher at 69% (95% CI: 26% to 87%).

Both studies used the test-negative case–control method, which has become a standard method for estimating influenza VE and in which the study population consists of people tested for suspected influenza [4]. Those with a positive test for influenza virus are cases and those with a negative test are controls. VE is then calculated based on the influenza vaccination status of cases and controls. Most studies estimate VE from GP networks, in which patients presenting with influenza-like illness (ILI) are swabbed for surveillance purposes. In the Netherlands, we routinely estimate VE with the test-negative approach from the sentinel GP network of the NIVEL Netherlands Institute for Health Services Research [5]. The information it collects is indicative only, as the number of swabs from ILI patients is often too low to obtain robust estimates.

The Table shows the most recent VE estimates for the Netherlands for the 2012/13 season. VE was estimated using logistic regression on all medically attended ILI patients in the sentinel GP network swabbed between 3 December 2012 and 3 February 2013. We excluded cases if the period between disease onset and date of swabbing was seven days or more. For type- and subtype-specific VE, controls were defined as negative for any influenza virus. The adjusted VE point-estimates for all ages early in the 2012/13 influenza epidemic

Table

Influenza vaccine effectiveness estimates in all age groups for the 2012/13 influenza epidemic in the Netherlands

Number of ILI patients swabbed[a]	Influenza virus (sub)type	Crude VE (95% CI)	Age- and comorbidity- adjusted VE (95% CI)[b]
176	All (sub)types	59% (15% to 81%)	90% (68% to 97%)[c]
117	A(H1N1)pdm09	82% (35% to 95%)	96% (79% to 99%)[d]
111	A(H3N2)	42% (-51% to 78%)	82% (17% to 96%)[e]
100	B	39% (-82% to 80%)	87% (20% to 98%)[d]

CI: confidence interval; ILI: influenza-like illness; VE: vaccine effectiveness.

[a] Numbers represent all influenza virus-negative patients plus the patients positive for the indicated influenza virus type and subtype.

[b] Adjusted for age and the following comorbidities reported by the general practitioner on the swabbing form: respiratory allergy including asthma, immunodeficiency, and chronic diseases including chronic obstructive pulmonary disease.

[c] Information on comorbidity missing for three patients.

[d] Information on comorbidity missing for two patients.

[e] Information on comorbidity missing for one patient.

were remarkably high, suggesting that the vaccine was effective against all circulating influenza virus (sub) types in the Netherlands. Adjusted VE for those aged 60 years and older was also high, although the confidence interval was very wide and included zero (VE: 92%; 95% CI: -27% to 99%).

The Danish study by Bragstad et al. is unique, in that it used laboratory and vaccination registries with nationwide coverage [3]. These are generally not available in other countries and provide exciting opportunities for epidemiological studies. However, as the authors indicated, information on some important variables such as comorbidity was not available from the national registries. The authors argue that comorbidity is unlikely to be an important confounder and that selection bias is unlikely to have played a role. However, our data showed a significant effect after correction for comorbidity, and other Dutch data show that influenza vaccination coverage is likely to be higher among elderly with underlying medical conditions compared to elderly who consider themselves healthy. In the Netherlands, over the past few years, this difference has consistently been larger than 20% [6].

One could further speculate that in comparison with healthy elderly peoply, those with underlying medical conditions are more likely to seek medical care in case of acute febrile illness, more likely to be admitted to hospital, and more likely to get an influenza diagnostic laboratory test. If this is true, then a larger proportion of influenza virus infections would be detected in the vaccinated group compared to the non-vaccinated group, and the VE estimate would be biased. Such bias is less likely when the study population consists of patients visiting their GP for ILI.

In the context of ongoing controversies about the usefulness of influenza vaccination, there is a great need to further develop optimal methodologies for the rapid assessment of influenza VE. The Innovative Medicines Initiative, a public-private partnership of the European Union and the pharmaceutical industry aims to develop a framework for rapid assessment of vaccination benefit/risk in Europe over the coming years. For influenza VE, the I-MOVE network has already shown that significant progress and harmonisations across the participating European countries was feasible [4]. Considering the heterogeneity in VE estimates that to some extent may depend on the used methodology and the sources of information, this process of harmonisation needs to continue to provide optimal and rapid assessment of influenza vaccine effectiveness.

Conflict of interest

None declared.

Authors' contributions

W van der Hoek, MA van der Sande, F Dijkstra and MM de Lange conceived the idea to respond to the recent articles on influenza vaccine effectiveness in Eurosurveillance. A Meijer provided the virological test data and MM de Lange and F Dijkstra did the data analysis for the Dutch VE estimates. W van der Hoek drafted the letter. The text was revised by the co-authors, and all authors approved the final version of the letter.

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