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Influenza vaccine effectiveness estimates in the Dutch population from 2003 to 2014: The test-negative design case-control study with different control groups

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ABSTRACT

Information about influenza vaccine effectiveness (IVE) is important for vaccine strain selection and immunization policy decisions. The test-negative design (TND) case-control study is commonly used to obtain IVE estimates. However, the definition of the control patients may influence IVE estimates. We have conducted a TND study using the Dutch Sentinel Practices of NIVEL Primary Care Database which includes data from patients who consulted the General Practitioner (GP) for an episode of acute influenza-like illness (ILI) or acute respiratory infection (ARI) with known influenza vaccination status. Cases were patients tested positive for influenza virus. Controls were grouped into those who tested (1) negative for influenza virus (all influenza negative), (2) negative for influenza virus, but positive for respiratory syncytial virus, rhinovirus or enterovirus (non-influenza virus positive), and (3) negative for these four viruses (pan-negative). We estimated the IVE over all epidemic seasons from 2003/2004 through 2013/2014, pooled IVE for influenza vaccine partial/full matched and mismatched seasons and the individual seasons using generalized linear mixed-effect and multiple logistic regression models. The overall IVE adjusted for age, GP ILI/ARI diagnosis, chronic disease and respiratory allergy was 35% (95% CI: 15–48), 64% (95% CI: 49–75) and 21% (95% CI: −1 to 39) for all influenza negative, non-influenza virus positive and pan-negative controls, respectively. In both the main and subgroup analyses IVE estimates were the highest using non-influenza virus positive controls, likely due to limiting inclusion of controls without laboratory-confirmation of a virus causing the respiratory disease.

1. Introduction

The most effective way to prevent influenza virus infection and (severe) illness is by vaccination [1]. However, the composition of the influenza vaccine should be reconsidered annually, and eventually updated, due to amino acid substitutions causing antigenic drifts of the hemagglutinin and neuraminidase virus surface proteins which occurs continually over time to escape neutralization by the immune response [2,3]. Despite the yearly update, the ability of the vaccine to prevent influenza virus infection in the general population during an influenza season (vaccine effectiveness [VE]) varies each year [4]. Hence, VE information is important for immunization policy decision makers, e.g. to decide which type of vaccine should be used (i.e. inactivated or live attenuated virus, with or without adjuvant) and who should be immunized (e.g. health care workers, children, elderly) [5]. However, it is not possible to determine the VE before an influenza season. Therefore, retrospective studies using observational data are performed to estimate the VE annually [4,6].

The test-negative design (TND) case-control study is a commonly used study design to estimate influenza VE (IVE). In this study design, patients seeking medical care for influenza-like illness (ILI) are tested for influenza virus infection [7]. The IVE is

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determined by comparing the prevalence of influenza vaccination between ILI patients who tested positive for influenza [cases] and those who tested negative for influenza [controls] [7,8]. As both cases and controls are selected from patients seeking medical care for ILI, the study design is assumed to minimize confounding by health care-seeking behavior or functional status compared to other types of observational studies [9–11]. Moreover, laboratory tests are used to define the influenza outcome which, compared to other study designs using non-specific influenza outcomes (e.g. ILI symptoms), reduces misclassification bias [9–11].

Several studies have shown that the definition of the control group in TND studies may influence the estimates of the IVE [12–16]. Three types of control groups have been used in TND studies: (1) all ILI patients tested negative for influenza virus infection (all influenza negative), (2) ILI patients tested negative for influenza virus but positive for another respiratory virus (non-influenza virus positive), and (3) ILI patients tested negative for both influenza virus and other respiratory viruses (pan-negative) [11–18]. Although all influenza negative controls are commonly used, in several studies non-influenza virus positive controls have been used arguing that if another respiratory virus than influenza virus could be detected in the control group, the presence of misclassification is highly unlikely, as there is a confirmed infectious cause of ILI in both cases and controls. This is based on the fact that the same laboratory tests for influenza virus are used for both cases and controls [13,15,16]. On the other hand, other investigators argued that the presence of a non-influenza respiratory virus infection could be partly explained by the association between influenza vaccination and the increased risk of another respiratory virus infection due to a temporary nonspecific immune response [10–12,18,19]. Consequently, the definition of the second control group could lead to selection bias and thereby an overestimation of IVE since the risk of ILI symptoms caused by another pathogen would be higher in the vaccinated patients than in unvaccinated patients, resulting in a higher proportion of vaccinated individuals in the control group [11,12,14,17,18]. As a consequence, several studies have used pan-negative controls.

The aim of the present study is to estimate the IVE over ten influenza epidemic seasons in The Netherlands (from 2003/2004 to 2013/2014) using the three most commonly applied definitions of TND control groups and evaluate the differences among the IVE estimates.

2. Methods

2.1. Study database

We used data from the Sentinel Practices of NIVEL Primary Care Database [20,21]. Sampling of patients with ILI or another acute respiratory infection (ARI) for laboratory diagnostics started in 1992. Since 2003 participating general practitioners (GPs) are asked to take nose and throat swabs from two ILI patients each week. Since 2005/2006 with the additional instruction to sample preferably one patient less than 10 years of age. If no ILI patients are encountered, the GP is asked to swab patients with another ARI instead [22]. The official standard definition of ILI was used in the GP offices to diagnose a patient with ILI, namely an acute onset of symptoms (full development of typical symptoms in $\leq$4 days) including a rectal temperature of at least 38 °C and at least one respiratory or systemic symptom (i.e. cough, nasal catarrh, sore throat, frontal headache, retrosternal pain, myalgia) [21]. ARI is defined as an acute respiratory illness other than ILI, such as acute sinusitis or pneumonia, and with at least one of the following symptoms; coughing, rhinorrhea or sore throat [23]. Both ILI and ARI patients were included in this study to maximize the power. Patient information is registered on the sample form, e.g. personal information (gender, age), date of symptoms onset and swabbing, use of antiviral medication and underlying medical conditions. The surveillance study has been registered in the Personal Data Protection Act Register of the Dutch Personal Data Protection Commission [No. RIVM/EPI-043]. No further ethical approval was needed since only anonymized data was used for the current study.

2.2. Laboratory testing

Collected samples from all swabbed subjects were sent to the National Institute for Public Health and the Environment (RIVM) for laboratory tests for a number of pathogens. These pathogens were identified using virus isolation and/or reverse transcription polymerase chain reaction (RT-PCR). RT-PCR changed over time from conventional block-based to real-time format with necessary adjustments in primer and probe design. Laboratory tests for the respiratory viruses influenza virus, respiratory syncytial viruses (RSV), rhinovirus (RV) and enterovirus (EV) were performed throughout the study period from 2003 to 2014. Laboratory tests for other pathogens differed per season: the identification of parainfluenza virus (PIV) type 1–4, coronavirus (CoV) (229E, OC43 and NL63) and metapneumovirus (hMPV) stopped after the 2007/2008 influenza season and adenovirus (ADV) was tested only from 2005 until the 2007/2008 season. We used information on these other pathogens for sensitivity analyses only.

2.3. Selection of cases and controls

For each influenza season from 2003/2004 through 2013/2014 patients were selected when they were swabbed between week 48 and week 14 of the following year. Patients were excluded if (1) the vaccination status was unknown, (2) time between symptoms onset and swabbing was more than seven days, (3) a patient had received antiviral medication within the two weeks prior to the GP visit, (4) the date of swabbing was before the first of December of each season to make sure vaccination was given 14 days before symptoms onset, or (5) data was missing on other variables (i.e. gender, age, ILI/ARI diagnosis, underlying chronic disease and respiratory allergy) [7,24]. Patients swabbed in the season 2009/2010 were excluded since this was an atypical (pandemic) influenza season. Eligible swabbed patients who tested positive for influenza virus A(H1N1), A(H1N1)pdm09, A(H3N2) or B were regarded as cases. Controls were defined as those patients tested (1) negative for influenza virus (all influenza negative) (2) negative for influenza virus, but positive for RSV, RV or EV (non-influenza virus positive), and (3) negative for these four respiratory viruses (pan-negative). We included RSV, RV and EV since only these viruses were tested throughout the whole study period.

2.4. Statistical analysis

Chi-square tests were used to test for significant differences in proportions of categorical covariates, and *T*-tests for differences in mean age between cases and control groups. A P-value <0.05 was considered statistically significant.

IVE was calculated by IVE = $(1 - \text{OR}) \times 100\%$ with influenza vaccine status as the exposure [7]. The unadjusted and adjusted IVE for potential confounders were estimated, i.e. age, ILI/ARI diagnosis, respiratory allergy, underlying chronic disease (e.g. asthma, chronic obstructive pulmonary diseases, diabetes mellitus and cardiovascular diseases), influenza season and level of vaccine match. Variables that were associated with the outcome (changed the OR > 5%) were retained in the final generalized linear mixed-effect model (GLMM) or multiple logistic regression model. When

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