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Seasonal influenza vaccine effectiveness estimates: Development of a parsimonious case test negative model using a causal approach

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ABSTRACT

Background: Influenza vaccine effectiveness (VE) is increasingly estimated using the case-test negative study design. Cases have a symptom complex consistent with influenza and test positive for influenza, while non-cases have the same symptom complex but test negative. We aimed to determine a parsimonious logistic regression model for this study design when applied to patients in the community.
Methods: To determine the minimum covariate set required, we used a previously published systematic review to find covariates and restriction criteria commonly included in case-test negative logistic regression models. Covariates were assessed for inclusion using a directed acyclic graph. We used data from the Victorian Influenza Sentinel Practice Network from 2007 to 2013, excluding the pandemic year of 2009, to test the model. VE was estimated as (1 – adjusted OR) * 100%. Changes in model fit from addition of specified covariates were examined. Restriction criteria were examined using change in VE estimate. VE was estimated for each year, all years aggregated, and for influenza type and sub-type.
Results: Using publicly available software, the directed acyclic graph indicated that covariates specifying age, time within the influenza season, immunocompromising comorbid conditions and year or study site, where applicable, were required for closure. The inclusion of sex was not required. Inclusions and exclusions were validated when testing the variables (when collected) with our data. Restriction by time between onset and swab was supported by the data. VE for all years aggregated was estimated as 53% (95%CI 38, 64). VE was estimated as 42% (95%CI 19, 59) for H3N2, 75% (95%CI 51, 88) for H1N1pdm09 and 63% (95%CI 38, 79) for influenza B.
Conclusion: Theoretical covariates specified by the directed acyclic graph were validated when tested against surveillance data. A parsimonious model using the case test negative design allows regular estimates of VE and aggregated estimates by year.

1. Introduction

Circulating influenza viruses can change every year, often requiring reformulated vaccines. Since these vaccines are considered to be variations of a licensed vaccine rather than a new vaccine, annual trials to establish efficacy are not required and would moreover be impractical [1]. However, monitoring of the potential impact of publicly funded influenza vaccination campaigns by estimating the effectiveness of annual influenza vaccines is an important programme evaluation strategy and has become increasingly common in recent years.

Timely evaluation has been made possible by the development of a study design, known variously as the test negative design [2] or the case test negative design [3]. In this study design, cases have a symptom complex consistent with influenza and test positive for influenza while non-cases, often referred to as controls, have the same symptom complex but test negative for influenza. In published studies, testing has been almost uniformly performed by reverse transcriptase polymerase chain reaction (RT-PCR) assays. The study design, where cases and non-cases are ascertained throughout the season before their case status is known, together with the use of PCR assays, allows for rapid annual influenza vaccine effectiveness (VE) estimates. This design, although similar to a prospective case control study, is not strictly a case control study because case status is not known, and cases

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and non-cases are both still theoretically at risk of influenza, at ascertainment.

The first study using this design was based on data from a Canadian sentinel practice network and was published in 2005 [4]. Four years later, similarly designed exploratory studies were published from Australia [5], the United States [6] and Europe [7]. Since then the number of studies using variations of this method have expanded with more than 85 studies published by September 2014 [8]. Increasing sample sizes and improved analytic approaches have allowed many study sites to report interim estimates of influenza VE before the end of the influenza season in temperate northern [9,10] and southern hemispheres [11].

The early test negative studies used a modelling study, which had aimed to determine the utility of rapid tests for estimating influenza VE, as their theoretical justification [12]. The modelling study explored VE estimates using cohort, case control and test-negative designs and showed the latter design gave comparable estimates of VE to the two conventional study designs when test specificity was high. PCR tests in good laboratories approach 100% specificity [13].

Since the modelled justification for the test negative design, studies estimating VE have been published in parallel with studies validating the design [2,3]. It has been further shown that, in the absence of selection bias, the test negative design results in VE estimates that are not different from the gold standard randomised controlled trial [14].

Not surprisingly for a novel study design, there is inconsistency in the model specifications used to estimate VE, with 85 recently reviewed studies using 68 different statistical covariate sets [8]. In this study we aimed to review the covariates used in published test-negative community-based studies and to assess their theoretical relevance using a directed acyclic graph. We further aimed to test the theoretical conclusions from the directed acyclic graph against seven years of data from the Victorian Sentinel Practice Influenza Network (VicSPIN) and to estimate VE each year, a global VE over specified aggregated years and influenza type and sub-type estimates for aggregated years.

2. Methods

2.1. Development of a directed acyclic graph

Using a recent systematic review we determined the most common covariates used by published test negative design studies that estimated influenza VE amongst patients presenting in the community [8]. We then constructed a directed acyclic graph, including potential confounders and explanatory variables that were used in >10% of published studies [8], without considering selection bias. Directed acyclic graphs can provide a visual representation of complex causal relationships between measured or unmeasured variables in a study. Closure of a directed acyclic graph involves the identification of a minimum set of variables that must be conditioned on, such as through adjustment, stratification or restriction, to provide an unbiased estimate of the causal relationship between an exposure and an outcome, given the assumptions contained in the graph. We tested our directed acyclic graph for closure using DAGitty, a software package available in the public domain [15].

2.2. Data source: the Victorian Sentinel Practice Influenza Network

General practitioners (GPs) were recruited to the Victorian Sentinel Practice Influenza Network (VicSPIN, formerly the General Practice Sentinel Surveillance System) as described elsewhere [16]. Participants were recruited by the GPs based on patient influenza-like illness (ILI) symptoms defined loosely as fever, cough and fatigue [17]. Participants were selected for swabbing at the discretion of the GP, with guidelines to swab only when four or fewer days had elapsed between symptom onset and consultation. GPs were asked to collect data on the patient's date of symptom onset, age, sex, influenza vaccination status (based on patient recall or general practice record) and current year (season) date of vaccination. From 2011 onwards binary variables indicating seasonal influenza vaccination in the previous year, based on patient report, and the presence of comorbidities were also collected.

Participants were included in this study if they presented to a VicSPIN general practitioner with ILI during the 2007–2013 influenza surveillance periods (weeks 18–44) and provided a nasal or throat swab for testing. Participants were excluded if they presented during the pandemic year of 2009, if they reported vaccination with H1N1 monovalent vaccine in 2010, if they tested positive for influenza C, or if data on vaccination status, age or sex were missing. We assumed vaccination more than 14 days prior to onset where current season vaccination date was missing.

Nose and/or throat swabs were tested for influenza at the Victorian Infectious Diseases Reference Laboratory (VIDRL) using a variety of PCR assays, which evolved over the study period, as described elsewhere [18–20]. Influenza type and sub-type were also recorded.

2.3. Testing the causation model from the directed acyclic graph

We used the case-test negative design to estimate influenza VE. We used seven years of VicSPIN data, 2007–2013 inclusive but omitting the pandemic year of 2009, to derive a series of regression models, based on the directed acyclic graph (Fig. 1). Crude and adjusted odds ratios (OR) and 95% confidence intervals were calculated using logistic regression. VE was estimated as (1 − OR)*100%. For covariates, adjustment was assessed through changes in model fit, and restriction criteria through changes in VE estimate, as described below.

To assess covariates for adjustment, a series of bivariate models were created beginning with a crude estimate and incorporating each covariate required by the directed acyclic graph, where collected by VicSPIN. We tested the change in VE estimates due to each covariate using the likelihood ratio (LR) test. This process was repeated with data stratified by year and influenza type or subtype. Covariates were retained in the model where adjustment was considered to improve model fit, because the covariate was a confounder or predictor of influenza, where the LR test was conventionally significant ($p < 0.05$), or the resulting VE differed by 10 or more percentage points from the crude estimate in any overall, year specific or subtype specific estimate. p-Values were adjusted using the Bonferroni correction to account for multiple testing. Covariates were assessed as above both pre and post the application of retained restriction criteria, to maximise the available sample size. Finally, stepwise regression was performed, to assess the change in VE from the removal of each covariate.

Potential restriction criteria, specifically time between vaccination and onset and time between onset and swab, were applied after covariate adjustment. Time between vaccination and onset was required to be >14 days, the consensus on time needed for protective antibody production to occur. Time between onset and swab was restricted based on the observation of decreased viral shedding with time since symptom onset [21]. We assumed decreased viral shedding with time may decrease the likelihood of viral RNA detection and hence the classification as influenza-infected. As restriction criteria aim to exclude patients where non-differential misclassification is thought to have occurred, resulting in a VE estimate biased towards the null, restriction criteria were retained if they appeared to be working as hypothesised and increased the

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