Vaccine 32 (2014) 6440–6444

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Can the rolling cross-sectional survey design be used to estimate the effectiveness of influenza vaccines?

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ARTICLE INFO

Article history:
Received 22 April 2014
Received in revised form
12 September 2014
Accepted 22 September 2014
Available online 3 October 2014

Keywords:
Rolling cross section
Influenza vaccine
Vaccine effectiveness

ABSTRACT

Introduction: Observational studies of influenza vaccine effectiveness often study persons seeking medical care for acute respiratory infection (ARI). We conducted a pilot study to determine if vaccine effectiveness could be estimated in the general population with a novel rolling cross-sectional survey sampling design and laboratory confirmation of influenza.
Methods: Cross-sectional samples were selected weekly from defined populations in Marshfield, Wisconsin and Monroe County, New York from January through April, 2011 (12 weeks). Persons were telephoned and asked about the occurrence of ARI in the past week. Nasal and throat swabs were obtained from consenting individuals with ARI and tested by real-time reverse transcription polymerase chain reaction (RT-PCR). Vaccine effectiveness (VE) was defined as $(100 \times [1 - OR])$ for vaccination in a logistic regression model that adjusted for age, calendar week, and site. The comparison group included all study participants without RT-PCR confirmed influenza, including those who were not ill.
Results: Study personnel contacted 9537 (62%) of 15,303 persons sampled; the primary analysis included 5678 subjects. Of these, 193 (3%) reported an ARI and agreed to be tested for influenza; 13 (7%) were influenza positive. The adjusted effectiveness of the influenza vaccine was 1% (95% confidence limits −239–70%).
Conclusions: The rolling cross-sectional design is methodologically feasible and may be useful as a complement to clinic-based VE studies. This pilot study did not have sufficient power to detect significant vaccine effectiveness during a mild influenza season, but this approach may facilitate rapid estimation of VE in a pandemic setting when normal patterns of health care utilization are disrupted.

1. Introduction

Current recommendations call for nearly all persons aged six months and older in the United States to be vaccinated annually with influenza vaccine [1]. Consequently, observational studies of vaccine effectiveness (VE) have largely replaced randomized, placebo-controlled clinical trials to assess efficacy [2]. One observational study design to estimate VE is the "test-negative design" in which vaccination rates are compared for influenza-positive versus influenza-negative patients who are receiving medical care for an acute respiratory illness (ARI). This design is commonly used because it is logistically simple with cases and comparison subjects enrolled in the same process and it may reduce bias due to health care seeking behavior [3,4]. However, the test negative design estimates vaccine effectiveness based on a combination of effectiveness against infection and effectiveness against severity (with health care seeking used as a surrogate for severity) [3]. Therefore, results from such studies may not be directly comparable to vaccine efficacy estimates derived from clinical trials, although VE estimates from observational studies have yielded results that are similar to those obtained in trials [5,6].

Abbreviations: ARI, acute respiratory illness; RCS, rolling cross-sectional; RT-PCR, real-time reverse transcription polymerase chain reaction; MESA, Marshfield Epidemiologic Study Area; VE, vaccine effectiveness.

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http://dx.doi.org/10.1016/j.vaccine.2014.09.051
0264-410X/

A cohort sampled prospectively from the general population can be used to generate VE estimates from persons with symptomatic influenza, regardless of whether they sought care for their illness. However, such studies are logistically difficult, expensive to implement, and may be subject to bias if the study's frequent follow-up methods affect subject behavior. Thus, it is important to assess other study designs for evaluating VE. In this report, we describe a pilot study in which we assess the methodological feasibility of estimating the effectiveness of the influenza vaccine for preventing laboratory-confirmed, symptomatic influenza during the 2010–2011 influenza season in two well-defined community populations using a design similar to a *rolling cross-sectional (RCS) survey*. The RCS design, first described by political scientists, consists of a series of cross-sectional samples in which each sample is representative of the source population [7,8].

2. Methods

For each of the 12 weeks in the study period (mid-January to early April, 2011) a cross-sectional sample was selected from population-based cohorts in Rochester, NY and Marshfield, WI. The Rochester population comprised 90,245 persons who received medical care at 12 primary care practices within the Greater Rochester Practice-Based Research Network. The Marshfield population comprised 48,969 residents of the Marshfield Epidemiologic Study Area (MESA) in central Wisconsin [9]. Potential participants were included in the sampling frame if they were at least six months old on January 1, 2011, had one or more medical care encounters in the prior 24 months, and were residents of Monroe County (Rochester) or MESA (Marshfield) for at least 12 continuous months before January 1 (children less than 12 months of age were residents since birth). All individuals meeting these criteria were eligible each week to be randomly sampled except those who had refused a previous invitation. Each sampled person was assigned a day on which attempts ($\leq$3/day) to reach them by telephone would begin; calls continued for two additional days (including weekends) if needed. A new sample was processed each Monday.

Subjects who verbally consented to participate in the telephone survey were asked about recent respiratory illness. If the subject answered affirmatively, information on signs and symptoms were collected. Those who reported onset of feverishness or cough within the previous seven days (including the day of contact) were defined as having an ARI. Parents were interviewed for children 12 years old or younger (Marshfield) or 17 years old or younger (Rochester). Influenza immunization status for the current season was determined by interview (Marshfield) or from the medical record (Rochester).

Nasal and throat swabs were collected either at the subject's home or a clinical facility by a research coordinator within seven days of illness onset. Written informed consent (and assent for children aged 7–17 years) was obtained at the time of swab collection. The two swabs were combined and tested for influenza using real-time reverse transcription polymerase chain reaction (RT-PCR) with primers and probes from the Centers for Disease Control and Prevention (CDC); further information is available from the Influenza Division, CDC.

To estimate VE we conducted logistic regression analyses on pooled data containing all study participants across the weekly samples. RT-PCR-confirmed influenza was the outcome studied, influenza vaccination was the exposure, and time (seven-day subject recruitment periods), age, and community were adjusted for in the models. VE was defined as $(100 \times [1 - \mathrm{OR}])$ where OR is the adjusted odds ratio from the model. The non-influenza group comprised subjects without recent ARI symptoms (i.e., study participants who were not tested) along with those who had ARI and a negative RT-PCR test.

This study can be conceptualized as approximating a series of 1-week cohort studies where each subject was sampled one week before their interview date and followed for seven days. To account for the fact that some participants with ARI were not tested for influenza, the following weights were applied in the analysis: (a) people with ARI and RT-PCR results were assigned a weight of [(number of people with ARI)/(number with ARI and RT-PCR results)], (b) people with ARI and no RT-PCR results were assigned a weight of zero, and (c) people without ARI were assigned a weight of 1. Robust variance estimation was incorporated in the model to account for the weighting [10]. The OR from the model estimated the risk ratio if the following assumptions were satisfied: (1) subjects were representative of the underlying cohort and participation did not depend on either vaccination or influenza status, (2) the number of people who died or were otherwise unavailable for sampling due to influenza was small, (3) the risk of influenza during any week was small in both vaccinated and unvaccinated people, (4) people with ARI and RT-PCR results were representative of people with ARI and no RT-PCR results, and (5) the RT-PCR test was sensitive and specific [11].

For this pilot study, budgetary constraints dictated that approximately 1275 persons could be sampled each week, resulting in study power of 0.27 to detect a VE of 60% after accounting for an overall participation rate of ~40%. Since an RCS study can be conceptualized as approximating a series of cohort studies, and case-control studies with 100% sampling fractions can be viewed as cohort studies, standard formulas for an unmatched case-control study can be used to generate sample size estimates for a VE study employing the RCS design described above. The estimate should be inflated by the inverse of both the proportion with ARI expected to consent to influenza testing and the expected response rate to determine the number of people to sample in order to achieve the calculated sample size. The control:case ratio in the calculations is $[1 - p]/p$ where p is the expected influenza positivity rate in the pooled RCS sample; p can be estimated as the assumed overall influenza cumulative incidence divided by the number of sampling periods.

All participants provided informed consent. The study was approved by the University of Rochester Research Subjects Review Board and the Marshfield Clinic Research Foundation Institutional Review Board.

3. Results

During the study period 15,303 persons were randomly sampled, including 7500 in Marshfield and 7803 in Rochester. Study personnel successfully contacted 9537 (62%) who were invited to participate; just under 94% were eligible (Fig. 1). After excluding those who refused, those with an illness onset greater than or equal to 192 h before the interview, and partial vaccinees there were 5761 individuals enrolled in the study resulting in a 64% enrollment rate. The primary analysis was restricted to 5678 participants after excluding an additional 83 persons who reported an ARI, but who were not swabbed. Of the participants, 51% were females, 54% were less than 50 years old, and 62% were from Marshfield.

Overall, 276 (4.8%) of the individuals enrolled reported an ARI; 193 (69.9%) of these were swabbed and tested for influenza. The ARI rate varied by week, with the highest rate (6.2%) occurring in week 4 and the lowest (3.3%) in week 12. ARI was reported by 4.3% and 5.5% of all respondents in Marshfield and Rochester, respectively. The clinical features of ARI did not vary substantially by vaccination status (Table 1). Of the 193 persons with ARI who were tested, 13 (6.7%) were influenza positive. Influenza cases were detected in all