Predictors of Influenza Vaccine Failure and the Impact of Influenza Immunization on Severity of Illness and Outcomes among Hospitalized Canadian Adults

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1. Introduction

Every year, 10-20% of the population becomes infected with influenza [1], and many will end up requiring medical attention as well as treatment for complications associated with the viral infection [2]. On top of the economic costs associated with this illness there is also an added burden on and cost to the healthcare system due to the increased number of physician visits, hospitalizations, and emergency room trips [3]. Fortunately, there is a publicly funded influenza vaccine that is offered annually and considered to be the best form of protection from the circulating strains of the virus [1,4].

While vaccination has been shown to reduce the prevalence of influenza, absences from work and school, and physician visits [5], the overall effectiveness of the influenza vaccine is quite variable. Older populations for instance have been shown to be at greater risk for vaccine failure due to immunosenescence [6]. In Canada, sentinel surveillance for influenza amongst hospitalized Canadian adults results in estimates of vaccine effectiveness (VE) in the prevention of hospitalization in older adults varying from 52% in 2011/12 to 31% in 2012/13 [7,8], reflecting the year-to-year variation in effectiveness observed due to circulating strains and other factors. While a vaccine effectiveness of 31% to 52% is not optimal, prevention of one-third to one-half of influenza-related hospitalizations in the elderly clearly represents an important contribution to the health of Canadians and justifies the investment in publicly funded influenza immunization programs.

Unfortunately, the suboptimal effectiveness of the influenza vaccine has elicited considerable negative media attention, which has contributed to poor uptake of the vaccine by Canadians. Despite the incomplete protection offered by the vaccine, it is possible that as with the pneumococcal vaccine [9,10], influenza vaccination may reduce the severity of illness among those who become infected. While this concept has yet to be extensively studied, early data has suggested there may in fact be some added benefits to influenza vaccination. For example, in adult patients admitted to hospital with community-acquired pneumonia, there is a significant reduction in all-cause mortality among those having been immunized with the seasonal influenza vaccine [11]. As well, among solid organ transplant recipients with lab-confirmed influenza, those who were vaccinated had a lower risk of developing pneumonia as well as a shorter stay in hospital [12]. While this data cannot be extrapolated to the general public, it further promotes the possibility that the influenza vaccine may be beneficial to one's health even if it initially fails.

There also has been recent controversy in the literature regarding potential reductions in influenza VE with repeated annual exposure to vaccine [13-16]. While Ohmit et al observed a significant reduction of the effectiveness of seasonal vaccine in the prevention of influenza in households [13], the methodology used in that study has been criticized [14] and other studies have not demonstrated similar impact of prior season vaccine on VE [15,16].

The goal of this present study was to address the missing gap in previous studies on vaccine effectiveness by investigating whether influenza vaccination attenuates disease severity or improves outcomes in those who are admitted to hospital despite vaccination, as well as to identify the host factors that may be predictive of vaccine failure and severe illness. Impact of prior season vaccination on estimates of VE was also explored. Such knowledge is crucial, as it may help to inform health policies and guidelines surrounding the use of new influenza vaccines, and more importantly it has the potential to change our understanding of the utility of the vaccine and improve vaccine uptake.

2. Methods

2.1 Serious Outcomes Surveillance (SOS) Network

In 2009, the Public Health Agency of Canada/CIHR Influenza Research Network (PCIRN) Serious Outcomes Surveillance Network was established to conduct active surveillance for influenza amongst Canadian adults admitted to participating hospitals. The primary goals of this collaborative research network are to better define the burden of disease caused by influenza, and to monitor the effectiveness of the seasonal vaccine

against serious outcomes such as hospitalization and death. While the Network began with 9 hospitals in five provinces in 2009, today it has grown to consist of 40 hospitals in seven provinces, which encompasses about 17,000 hospital beds. This study describes the results of surveillance conducted in the 2011/12 influenza season.

2.2 Study design

This is a prospective, test-negative case-control study that was conducted at the participating sentinel hospitals located throughout Canada from 15 October 2011 until 30 April 2012. For the purposes of assessment of vaccine effectiveness, cases were defined as adult patients admitted to an SOS hospital as a result of influenza or complication of the virus, and who had tested positive for influenza. For each case enrolled, one or more controls were selected from amongst patients admitted with an acute respiratory illness to the sameSOS hospital of the case, within 2 weeks of the admission date of the case, but who had a negative test for influenza on admission. Influenza immunization status for the 2010/11 and 11/12 influenza seasons was determined and vaccine effectiveness was estimated as (1- odds ratio of current season vaccination in cases versus controls) X 100.

2.3 Inclusion/exclusion criteria

Patients were considered eligible to participate in the study and be screened for influenza if they were adults ≥16 years who were admitted to one of the participating SOS hospitals with either community-acquired pneumonia (CAP), acute exacerbation of chronic obstructive pulmonary disease (AECOPD) or asthma, unexplained sepsis, any respiratory infection or diagnosis, and for any respiratory or influenza-like symptom. Informed consent, and assent where appropriate, was obtained from either the patient or from the patient's guardian or legally authorized representative prior to enrolling in the study and the study was approved by the Research Ethics Board of each participating SOS hospital. Patients who were not considered eligible to be enrolled in the study included children <16 years, as well as patients whose presenting illness and reason for admission was undeniably unrelated to influenza, such as those being admitted for elective surgery or trauma.

2.4 Laboratory identification

To screen all enrolled patients for influenza A and B, a nasopharyngeal swab was collected by trained staff and tested for influenza using either culture or polymerase chain reaction (PCR) methods.

2.5 Data collection and vaccination status

Standardized PCIRN SOS Network Case Report Forms were utilized by trained staff to collect data for each participant. Baseline data included demographic information, past medical history, social history, comorbidities, frailty for those over 65 years, as well as self-reported influenza vaccination status. Information with regards to each participant's course of illness and disease outcomes were also recorded. Participants were considered vaccinated if they reported receipt of influenza vaccine more than 14 days prior to onset of their respiratory illness. Wherever possible, patients' self-reported immunization status was verified with their immunization provider.

2.6 Statistical analysis

The results of the study were analyzed using SAS. For all analyses, two age groups (<65 years old, and ≥65 years old) were analyzed separately, and both univariate and logistic regression models were utilized to determine statistical significance. The univariate model was first used to compare variables and characteristics between two groups to generate a P-value and identify significance. Next, logistic regression was performed to examine variables independently and to generate P-values, odds ratios, and 95% confidence intervals. If the P-value was <0.1, backward selection testing was performed to compare significant variables together. However, we considered statistical significance to be $p<0.05$.

To determine the impact of vaccination on disease severity as well as the risk factors for severe disease, several variables (including vaccination status) were compared between subjects who required mechanical ventilation, were admitted to ICU, or died and subjects that did not experience these severe outcomes. Risk factors for vaccine failure were assessed by comparing vaccinated cases and vaccinated controls with regards to clinical characteristics. Finally, to explore the impact of prior season vaccination on effectiveness of the 2011/12 influenza vaccine, participants were stratified into those who received influenza vaccine in the 2011/12 season

only and those who had received vaccine in both 2011/12 and the prior season and compared to the referent group who had not received either season vaccine with adjustment using a logistic regression model with backward selection.

3. Results

Full report was received by CFID but main results are suppressed here due to confidentiality agreements and pending submission of manuscript for publication.

4. Main Conclusions

While influenza vaccine did not appear to reduce the severity of influenza vaccine in those with vaccine failure, modifiable predictors of vaccine failure were identified as were factors associated with severe outcomes. This may allow improved targeting of education and suggests that alternate prevention and treatment strategies may be required in the frail elderly. Importantly, receipt of prior season influenza vaccine did not impair the effectiveness of seasonal vaccine in the prevention of hospitalization.

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