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Optimal timing of influenza vaccination in patients with human immunodeficiency virus: A Markov cohort model based on serial study participant hemoagglutination inhibition titers

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ABSTRACT

Background: Seasonal influenza vaccination offers one of the best population-level protections against influenza-like illness (ILI). For most people, a single dose prior to the flu season offers adequate immunogenicity. HIV+ patients, however, tend to exhibit a shorter period of clinical protection, and therefore may not retain immunogenicity for the entire season. Building on the work of Nosyk et al. (2011) that determined a single dose is the optimal dosing strategy for HIV+ patients, we investigate the optimal time to administer this vaccination.
Methods: Using data from the "single dose" treatment arm of an RCT conducted at 12 CIHR Canadian HIV Trials Network sites we estimated semimonthly clinical seroprotection levels for a cohort ($N = 93$) based on HAI titer levels. These estimates were combined with CDC attack rate data for the three main strains of seasonal influenza to estimate instances of ILI over different vaccination timing strategies. Using bootstrap resampling of the cohort, nine years of CDC data, and parameter distributions, we developed a Markov cohort model that included probabilistic sensitivity analysis. Cost, quality adjusted life-years (QALYs), and net monetary benefits are presented for each timing strategy.
Results: The beginning of December is the optimal time for HIV+ patients to receive the seasonal influenza vaccine. Assuming a willingness-to-pay threshold of $50,000, the net monetary benefit associated with a Dec 1 vaccination date is $19,501.49 and the annual QALY was 0.833744.
Interpretation: Our results support a policy of administering the seasonal influenza vaccination for this population in the middle of November or beginning of December, assuming nothing is know about the upcoming flu season. But because the difference in between this strategy and the CDC guideline is small—12 deaths averted per year and a savings of $60 million across the HIV+ population in the US—more research is needed concerning strategies for subpopulations.
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1. Introduction

Regular and widespread coverage of vaccination is a cornerstone of public health policy in most developed healthcare systems. In this context, one of the primary public health strategies for reducing seasonal influenza incidence is annual immunization [1,2]. With timely influenza vaccination, seroprotective antibody titers are achieved in responders within two to four weeks. The duration of retention of seroprotection typically persists for several months. If timed optimally, immunization provides protection during the winter and early spring when influenza has the highest attack rates [3,4]. People with the Human immunodeficiency virus (HIV) are particularly vulnerable and are also less likely to achieve seroprotective titers after influenza immunization and furthermore, maintain these titers for a shorter time [5].

Since both cell-mediated and humoral immunity is compromised in HIV-infected individuals, this population is at risk for severe illness from common infectious diseases including influenza

Abbreviations: ILI, influenza-like-illness; CIHR, Canadian Institutes of Health Research; QALY, quality adjusted life-years; HAI, hemoagglutination inhibition; NMB, net monetary benefit; QoL, quality of life; WtP, willingness-to-pay.

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[6]. Among patients with HIV/AIDS, influenza symptoms are prolonged and the risk for complications is increased [7,8]. The risk of influenza-related death is seven to fourteen times greater among AIDS patients than in the general population [9]. Additionally, there is an increased risk of heart- and lung-related hospitalizations in HIV/AIDS patients during influenza season [6,9]. Therefore the correct timing of influenza vaccination among HIV+/AIDS patients is of critical importance and should be based on factors that maximize protection, and therefore the quality and quantity of life, of this population.

To date, there is a paucity of literature and very limited information concerning the optimal strategy for initiating the seasonal influenza vaccine among HIV+ patients [6]. Among the various vaccination strategies available, such as larger or multiple doses, the most cost-effective overall strategy for HIV+ adults has been demonstrated to be "single-dose" vaccination [10]. However, timing of the implementation of the optimal strategy is still unknown. Crane et al. [11] described this uncertainty related to the timing of the seasonal influenza vaccine as one of the major shortcomings in studying vaccine effectiveness among immune-compromised patients.

Optimal timing for routine vaccinations such as Hepatitis B and A, tetanus, and pneumococcal vaccines among HIV+ individuals has been developed according to the known long-term antibody response of these vaccines [11,12]. In this context, while several studies have investigated the immunogenicity of the influenza vaccine in the HIV+ population [7,8], recent systematic reviews argue that these studies cannot be used for the development of a public strategy due to (a) the small sample sizes of individual studies, and (b) the lack of generalizability of the studies as they do not incorporate the uncertainties associated with varying immune response and attack rates of influenza in specific populations [5,6]. Within the general population the determinants of flu vaccine timing have been studied from a health economic perspective by modeling incentives for early vs. later flu shots [13,14], and simulation and optimization models have been used to determine optimal vaccine strategies during an influenza pandemic [15]. In other vulnerable populations there are several studies examining the timing of seasonal influenza vaccination. For pregnant women and infants, vaccination should occur as soon as the seasonal vaccine is available [16]. Children should be vaccinated by September or October [17].

The US Centers for Disease Control and Prevention (CDC) provide recommendations regarding seasonal influenza vaccination timing [18]. These recommendations, perhaps considering the logistics of vaccinating millions of people, suggest administering the vaccine to the general public as soon as it becomes available, and if possible by October. Because the peak of the season can occur in or after January, the recommendation is to continue offering the vaccine through December or even later. The recommendations acknowledge that it is difficult to determine the optimal policy for any given year, because of the variation from season to season. Finally, the vaccine should be offered during healthcare visits and hospitalizations as long as it is available. With respect to HIV+ patients, the CDC recommends that these patients be given priority when vaccine supplies are limited.

It would be impractical to conduct an RCT that includes a dozen different timing strategies. Furthermore, unless that RCT were conducted over a number of years in order to capture the variation in influenza from year to year, the results would not be generalizable. While the costs associated with actually implementing different vaccination strategies do no vary from month to month, there are cost implications through differences in healthcare visits and hospitalizations. The motivation behind this study was therefore the lack of clear evidence concerning the most cost-effective timing of the seasonal influenza vaccination for HIV+ individuals. Accordingly, we investigated different timing strategies with respect to both cost and health outcomes. Due to the highly variable behavior of the virus from season to season, along with the genetic drift of the individual influenza strains, we utilized a probabilistic mathematical model that used the seroprotection levels inferred from hemoagglutination inhibition (HAI) titer measurements taken over a number of weeks in an RCT of HIV+ patients who had been administered a single-dose seasonal influenza vaccine. Combined with historical attack rates over nine years—and information on costs, mortality rates, and health outcomes—we were able to determine the optimal timing strategy.

2. Methods

We utilized a Markov cohort model combined with Monte Carlo simulation to estimate the population-level clinical protection under different influenza attack rates and seasonal variation in order to determine cost and quality adjusted life year (QALY) estimates. We used the HAI titer (antibody response) as a surrogate measure to reflect the response of a participant to the vaccine and ultimately of his/her protection level against influenza. Few studies have used mathematical modeling to estimate seroprotection and to assess the clinical protection level, measured as a function of HAI among the HIV+ population [4,19]. Nosyk et al. [10] expanded on the approach in Nauta et al. [19] and estimated the probability of influenza-like illness (ILI) by calibrating influenza exposure using attack rate parameters from annual surveillance data. Our decision analytic model is a modified and expanded version of [10] that uses some of the same participant-level cohort data but that is able to address the question of vaccine timing.

2.1. Subjects

During the 2008–2009 influenza season, a randomized controlled trial of 298 subjects evaluated three different seasonal influenza vaccination dosing strategies in HIV+ participants [20]. Informed consent was obtained for all participants. One study arm consisting of 93 subjects received a single 15 μg dose of the 2008 trivalent killed split non-adjuvanted seasonal influenza vaccine (FluviralTM, GSK, Laval, Canada) containing A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and B/Florida/4/2006. To assess immunogenicity, HAI titers were measured at baseline, week 4, week 8, and week 20 [20]. We utilized HAI titers, participant characteristics, and participant-reported quality of life (QoL) measures from this study.

2.2. Decision model

Nosyk et al. used data from all three treatment arms of the aforementioned study in a Markov cohort model to determine which of three dosing strategies is optimal for HIV+ patients [10]. We used a similar overall approach, but—in addition to addressing the optimal timing question—altered the model as follows: (1) we used bootstrap case resampling instead of parametric bootstrapping so that fewer distributional assumptions were necessary; (2) probabilistic sensitivity analysis was built into the model; (3) annual attack rates more accurately reflected historical data, in that some years were higher or lower than others; and (4) a net monetary benefit (NMB) approach including probabilistic sensitivity analysis (via Monte Carlo simulation) incorporating parameter uncertainties [21] allowed us to more easily compare the timing strategies.

2.2.1. Participant data and attack rates

The original data included HAI titer measurements for baseline, week 4, week 8, and week 20, for the three predominant strains of the seasonal influenza virus: A(H1N1), A(H3N2), and B. Ten

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