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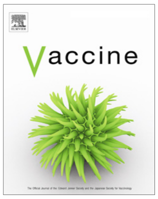

Impact of seasonal influenza vaccination in the presence of vaccine interference

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ABSTRACT

Background: Annual influenza vaccination is a key to preventing widespread influenza infections. Recent reports of influenza vaccine effectiveness (VE) indicate that vaccination in prior years may reduce VE in the current season, suggesting vaccine interference. The purpose of this study is to evaluate the potential effect of repeat influenza vaccinations in the presence of vaccine interference.

Methods: Using literature-based parameters, an age-structured influenza equation-based transmission model was used to determine the optimal vaccination strategy, while considering the effect of varying levels of interference.

Results: The model shows that, even in the presence of vaccine interference, revaccination reduces the influenza attack rate and provides individual benefits. Specifically, annual vaccination is a favored strategy over vaccination in alternate years, as long as the level of residual protection is less than 58% or vaccine interference effect is minimal. Furthermore, the negative impact of vaccine interference may be offset by increased vaccine coverage levels.

Conclusions: Even in the presence of potential vaccine interference, our work provides a population-level perspective on the potential merits of repeated influenza vaccination. This is because repeat vaccination groups had lower attack rates than groups that omitted the second vaccination unless vaccine interference was at very high, perhaps implausible, levels.

1. Introduction

Annual influenza vaccination is a critical public health measure for preventing widespread influenza infections and their attendant morbidity and mortality. The United States (U.S.) Advisory Committee on Immunization Practices (ACIP) recommends annual influenza vaccination for all individuals six months of age and older [1]. However, in Canada, the United States, and Europe, lower vaccine effectiveness (VE) estimates against influenza A (H3N2 and H1N1) virus illness have been observed [2–11] among those vaccinated during the previous season(s), compared to those not vaccinated. Similar results were reported in another multi-season analysis where the highest protection against influenza A (H3N2) illness was observed among vaccinees who had been not been vaccinated in the previous 5 years (VE = 65%, 95% CI = 36–80) and the lowest VE was among those repeatedly vaccinated in 4 or 5 recent seasons (VE = 25%, 95% CI = 3–41%) [8]. Such findings are also consistent with results from a household cohort study, which indicated lower VE against A (H3N2) illness among those vaccinated in both the current and prior year than those only vaccinated in the current season [12]. Additionally, in a prospective cohort study of healthcare personnel (HCP) ages 18–65 years, the magnitude of immune response indicated by geometric mean titer or geometric mean ratio declined with the number of inactivated trivalent influenza vaccine(s) (IIV3) received during the prior 4 years, among all age groups [7]. In contrast, a recent meta-analysis found interference only for influenza A (H3N2) and actually found enhanced responses for influenza A (H1N1) and B with repeat vaccination [13]. However, it was also suggested that caution is required in the interpretation of pooled results across multiple seasons,

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because pooling can mask important variation in repeat vaccination effects among seasons [14].

Taken together, there exists some evidence on negative interference, namely a negative effect of prior vaccination on the current season's VE that reduces protection against influenza infection (i.e., a lower but still positive vaccine effectiveness point estimate). Furthermore, previous prospective studies have suggested that negative interference from prior influenza vaccination may be especially pronounced when the composition of vaccine antigens has been unchanged and the match with circulating strains is not strong [8,9,12].

These findings raise questions about standard flu vaccination recommendations, i.e., should individuals be revaccinated annually to be protected against ever-mutating viruses?

In this study, we sought to assess the impact of annual influenza vaccination in the presence of vaccine interference to address this question.

2. Methods

To assess the epidemiological impact of revaccination at various levels of vaccine interference (VI), we present an age-structured model of influenza dynamic transmission and vaccination in which an individual's VE was assumed to be dependent on age and vaccination status in a prior season (Table S1) [3,9]. Specifically, the model assumed that the VE in individuals who received influenza vaccine in two consecutive years was generally lower than that of vaccine recipients who were unvaccinated in the prior season [8,9]. Dynamic models implicitly capture the herd protection conferred by vaccination and thus the incorporate vaccine-induced indirect protection. Model parameters were based on the current age distributions in the U.S. and vaccination rates in age groups [15], and estimated the influenza incidence levels [16].

2.1. Susceptibility and infectivity

The influenza-related epidemiologic status of individuals was tracked in eight age-dependent classes. All individuals in the population are (partially) susceptible to infection prior to the influenza season. Specifically, individuals in age group k at time t are divided into four epidemiological classes depending on their vaccination status: individuals vaccinated prior season only ($T_k(t)$), individuals vaccinated in current and prior seasons ($W_k(t)$), individuals not vaccinated in either season ($S_k(t)$), and individuals vaccinated in current season only ($V_k(t)$). We assumed that vaccination provides partial protection, thus resulting in vaccinated individuals being less susceptible than unvaccinated ones.

In addition to these four (partially) susceptible classes, the model has four additional epidemiological classes: exposed individuals who are not infectious yet ($E_k(t)$), individuals who are infectious and asymptomatic ($A_k(t)$), individuals who are infectious and symptomatic ($I_k(t)$), and recovered individuals ($R_k(t)$). Each epidemiologic class was subdivided into five age groups, which are denoted by the subscript k ($k = 1, \ldots, 5$) and correspond to 0–8 years, 9–17 years, 18–49 years, 50–64 years, and ≥65 years. Those who received an influenza vaccine in a prior season were assigned to the epidemiological class T_k, whereas the others were assigned to the class S_k. Thus, consistent with recent observations [17], the following values were assigned: $T_1(0) = 0.62n_1$, $T_2(0) = 0.53n_2$, $T_3(0) = 0.33n_3$, $T_4(0) = 0.44n_4$, $T_5(0) = 0.63n_5$; $S_k(0) = n_k - T_k(0) - I_{k0}$; $W_k(0) = 0$; $V_k(0) = 0$; $E_k(0) = 0$; $A_k(0) = 0$; $I_k(0) = I_{k0}$; and $R_k(0) = 0$ where n_k denotes the size of age group k [8,17].

2.2. Vaccine effectiveness (VE) and vaccine interference (VI)

We assumed that VE is dependent on both an individual's age and on his or her history of vaccination (Table 1). For instance, the model assumes that individuals in age group k who were vaccinated in both current and prior seasons would become infected at a fraction $(1 - \varepsilon_{W,k})$ of the rate at which unvaccinated susceptible individuals (S_k) become infected. Here $\varepsilon_{W,k}$ denotes the VE against infection for individuals who were vaccinated in both prior and current seasons. Similarly, we define $\varepsilon_{V,k}$ as the VE among individuals who are vaccinated in the current season only, while $\varepsilon_{T,k}$ denotes the VE among individuals who are vaccinated in the prior season only. In other words, the level of residual protection by vaccination in the prior year is represented by $\varepsilon_{T,k}$. For our simulations, we fixed the values of $\varepsilon_{V,k}$ and $\varepsilon_{T,k}$ at baseline values shown in Table 1, and let $\varepsilon_{W,k}$ be determined by various levels of VI. Specifically, to measure the degree of VI, we defined the level of VI as one minus the relative VE of repeat vaccinees compared to that of vaccine recipients who skipped the influenza vaccine in a prior season: $VI = 1 - \frac{\varepsilon_{W,k}}{\varepsilon_{V,k}}$. Thus, at high level of VI, the protection conferred among repeat vaccinees, $W_k(t)$, is assumed to be minimal compared to individuals who are vaccinated in the current season only, $V_k(t)$.

Table 1
Baseline age-specific efficacy of current and prior vaccination against influenza [30,32,33].

Age	Vaccination history	Vaccine efficacy (%)	
		Notation	Baseline value
<9 years	Vaccinated both current and prior season	(1-*VI*) $\varepsilon_{V,1}$	Varied between 0 and 0.69
	Vaccinated current season only	$\varepsilon_{V,1}$	0.69
	Vaccinated prior season only	$\varepsilon_{T,1}$	0.50
9–17 years	Vaccinated both current and prior season	(1-*VI*) $\varepsilon_{V,2}$	Varied between 0 and 0.74
	Vaccinated current season only	$\varepsilon_{V,2}$	0.74
	Vaccinated prior season only	$\varepsilon_{T,2}$	0.61
18–49 years	Vaccinated both current and prior season	(1-*VI*) $\varepsilon_{V,3}$	Varied between 0 and 0.63
	Vaccinated current season only	$\varepsilon_{V,3}$	0.63
	Vaccinated prior season only	$\varepsilon_{T,3}$	0.33
50–64 years	Vaccinated both current and prior season	(1-*VI*) $\varepsilon_{V,4}$	Varied between 0 and 0.80
	Vaccinated current season only	$\varepsilon_{V,4}$	0.80
	Vaccinated prior season only	$\varepsilon_{T,4}$	0.50
≥65 years	Vaccinated both current and prior season	(1-*VI*) $\varepsilon_{V,5}$	Varied between 0 and 0.46
	Vaccinated current season only	$\varepsilon_{V,5}$	0.46
	Vaccinated prior season only	$\varepsilon_{T,5}$	0.73

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