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Within-season influenza vaccine waning suggests potential net benefits to delayed vaccination in older adults in the United States

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ABSTRACT

Background: There is growing evidence that there is within (intra-) season waning of influenza vaccine protection in older adults, suggesting there may be a benefit to giving influenza vaccine closer to the time of increased infection risk. We aimed to quantitatively evaluate the impact of modifying the timing of influenza vaccination in U.S. older adults.

Methods: Using historical data (2010/2011–2015/2016, inclusive) on influenza activity and vaccine uptake, we explore the optimal time to begin vaccinating older adults (≥65 years) in the U.S. to maximize prevention of influenza. We modelled the effect of changing the timing of vaccination by estimating the percentage change to the current disease burden and used this to calculate the estimated optimal week to begin vaccination in the U.S.

Results: When we assumed a relatively slower waning protection rate (over 52 weeks), the estimated optimal time to begin vaccinating those aged ≥65 years varied between mid-August (week 34, 2012–2013) and mid-late October (week 43, 2011–2012) depending on the season, resulting in 0.44% and 5.11% of the current disease burden prevented respectively. Under faster waning (over 26 weeks), the estimated optimal week varied between early September (week 37, 2012–2013) and mid-November (week 47, 2011–2012), resulting in 3.69% and 11.97% of the current disease burden prevented respectively.

Conclusions: While it is difficult to determine the ideal time to start to vaccinate due to substantial variation in timing of individual seasons, we found that there are potentially substantial benefits to minimizing the time between vaccination and influenza activity in U.S. older adults. Modest delays in immunization were beneficial in the seasons we evaluated. If further evidence suggests fast waning, longer delays may be warrant as in these scenarios the timing of the current vaccination was often very suboptimal.

1. Introduction

While debate remains, for older adults there is growing evidence that there is within (intra-) season waning of influenza vaccine protection [1–6]. This suggests there may be a benefit to giving influenza vaccine closer to the time of potential infection risk. However, when considering the best time to start vaccination, there is a trade-off between reducing the opportunity for waning to occur (by delaying vaccination) and increasing the possibility that people are vaccinated too late after influenza is circulating or miss being vaccinated altogether. This trade-off is further complicated by between (inter-) seasonal variation in the timing of influenza circulation.

Influenza vaccine is typically first available from mid-late July to early August in the U.S. [9]. The specific date that it becomes available can vary from year to year and the availability in specific regions can be affected by local delays [8]. The current overall uptake of influenza vaccination in those ≥65 years in the U.S. is approximately 65% [7]. However, vaccination uptake in the population occurs over time, with vaccination starting to from the first availability but with most vaccine uptake in those ≥65 years happening in the months following and continuing to accrue throughout the influenza season. This means that some older adults are not vaccinated until after influenza has started to circulate widely in the population.

The U.S. Advisory Committee on Immunization Practices (ACIP) currently recommendation influenza vaccination "...by the end of

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October, if possible" [9]. However, the trade-offs related to waning protection are noted by ACIP [9] and have led to various revisions of the recommendations over time [10]. For example, prior ACIP recommendations have suggested vaccination "…soon after vaccine becomes available and, if possible, by October" [10,11]. As new data emerges [1–3] on intra-season waning of influenza vaccine protection, questions are again being raised as to when to start influenza vaccination to maximum protection in older adults.

To date no published studies have quantitatively assessed the impact (positive and negative) of modifying the timing of influenza vaccination of older adults. Using historical data on influenza activity and vaccine coverage, we explore the optimal time to begin vaccinating older adults in the U.S. to maximize prevention of influenza.

2. Methods

We estimated the timing of influenza vaccination coverage in the U.S. using publicly available monthly data on influenza vaccination coverage for older adults (≥65 years) from FluVaxView over the last 6 years of seasonal influenza 2010/2011 to 2015/2016, inclusive [12]. For adults, FluVaxView provides data on influenza vaccination coverage from the Behavioral Risk Factor Surveillance System (BRFSS), an on-going monthly telephone survey of ~400,000 randomly selected persons aged ≥18 years. The national estimates we used from BRFSS were based on data collected from all 50 states and the District of Columbia. The monthly uptake estimates were interpolated using cubic splines, with the exception of joining the initial and final time points where linear interpolation was used to prevent negative coverage values. The fitted cubic spline was used to provide weekly coverage estimates under the assumption that the monthly uptake represented estimates for the mid-point in each month. We assumed that vaccination begins at the start of August (surveillance week 31) as coverage in July was only available for some years and was reported as below 1% in other seasons considered.

To establish the timing of seasonal influenza burden in the U.S., we used publicly available weekly data on laboratory confirmed influenza (irrespective of type) for those ≥65 years from FluViewInteractive between 2010/2011 and 2015/2016, inclusive [13]. The age grouped data from FluViewInteractive come from (approximately 100) public health laboratories who report to the CDC as part of the U.S. World Health Organization Collaborating Laboratories System/National Respiratory and Enteric Virus Surveillance System (NREVSS), which includes laboratories in all 50 states, Puerto Rico, and the District of Columbia. Each season was defined as starting from the surveillance week 27 (early July) and ending on the 26 week in the following year. Each surveillance week starts on Sunday and week 1 is the first week of the year with at least 4 days [14]. In each season, we assumed that the timing of these influenza reports would reflect the *distribution* of the disease burden within that season.

To assess the effect of changing the timing of vaccination, we estimated the percentage change to the current disease burden under alternative strategies (i.e. the % of the current disease burden prevented by the new vaccination approach, beyond that which is prevented by current vaccination efforts). Based upon these results, we calculated our primary outcome, the predicted optimal week to begin vaccination at a population level under the assumption that current patterns of uptake persist (i.e. from the start of August) but are shifted to start later in the season ('gradual vaccination'). We also as a secondary outcome calculated the week of vaccination that offered maximum protection to an individual (assuming 'immediate vaccination'). Finally, as a shift to later vaccination may reduce opportunities for immunization and the total cumulative coverage in older adults, we estimated the relative percentage *decrease* in total cumulative uptake that could be sustained under a new population strategy before it offers less protection than the current uptake strategy. For details on the specific methods to calculate results see Appendix 1.

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.08.007.

To determine the best *overall* timing of vaccination we calculated results using the same start week for each season and identified the week that produced the highest overall net benefit, firstly assuming that each season had equal weight (unweighted). However, as the influenza burden is not the same in each season and there may be a relationship between the timing of influenza notifications and disease burden (e.g. with more severe seasons may be more likely to occur early) we also estimated weighted results. As there have been changes in laboratory surveillance system overtime, it is not appropriate to use influenza reports to establish trends in influenza burden between seasons [13]. Instead, we weighted the benefits (in terms of % change in disease burden) for each season by the relevant Centers for Disease Control and Prevention (CDC) estimates of influenza hospitalization rates for each season [15] as a proxy measure of disease burden (Appendix 1, Table A1). Here the optimal overall timing was defined as that which maximizes this weighted % of current burden prevented across the 6 seasons.

Influenza vaccine efficacy was used in two ways in the analyses. First, it was used to establish a hypothetical no vaccination baseline (i.e. where we model a removal of the impact of current vaccination efforts in older adults), to estimate what the distribution of influenza reports would be without the current vaccination uptake. To do this, influenza laboratory confirmed reports in each given week for those ≥65 years-old were inflated by a factor of (1−coverage * efficacy) to account for the impact of the current vaccination uptake, adjusting the time dependence of efficacy and uptake (Appendix 1). This baseline was then used to model alternative vaccination strategies and evaluate their impact in comparison to the current coverage distribution. Vaccine efficacy was then also used to calculate the benefits in terms of % change in the disease burden when implementing a modified uptake distribution.

Influenza vaccine efficacy in older adults is likely to be lower than in other adults [16] and we assumed 50% efficacy against influenza for those aged over 65 years. We assumed that there was a 2-week delay between vaccination and protection being achieved. The rate of decline in influenza vaccine efficacy in older adults over time is uncertain; with some studies finding that protection declines within 6 months [1] and others suggesting that protection may decline over 12 months [2]. We compare two waning scenarios in which efficacy declines linearly from 50% efficacy at 2 weeks post-vaccination to 0% efficacy by either 52 weeks post-vaccination ('slower waning') or to 0% efficacy at 26 weeks post-vaccination ('faster waning').

All analyses were performed in the statistical software R.

3. Results

We found substantial variation in the timing of influenza activity between seasons in those aged ≥65 years (Fig. 1, left panel). The peak of reports (i.e. the week of highest number of laboratory reports) varied by year from surveillance week 1 (January 2015, 2014–2015) to week 10 (March 2016, 2015–2016). In three seasons (2012–2013, 2013–2014, 2014–2015), 10% of total influenza reports had been accrued by the end of the year (week 52), whereas in some others this did not occurred until February (week 7, 2015–2016 and week 8, 2011–2012; see Appendix, Table A2).