An economic assessment of high-dose influenza vaccine

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GENERAL DISCUSSION

Main findings
Adults 65 years and older (hereinafter referred to as seniors) are at greater risk for complications following influenza infection compared with younger adults, due in part to immunosenescence and increased prevalence of chronic medical conditions with increasing age, leading to decreased vaccine efficacy and increased severity of influenza-related complications [1, 2]. Our research in the Veterans Health Administration (VHA) showed the influenza-attributable hospitalization rates of senior Veterans to be 2.8 times higher than rates of Veterans aged between 50 and 64 years, and 6.5 times higher than rates of Veterans aged between 18 and 59. Vaccination is the best strategy to prevent influenza infection [3].

Standard dose (SD) inactivated influenza vaccines are derived from egg-grown viruses and contain 15 µg of hemagglutinin (HA) from each of three (trivalent, SD-IIV3, 45 µg HA total) or four (quadrivalent, SD-IIV4, 60 µg HA total) strains and are licensed in the U.S. for use in individuals 6 months of age or older. Due to immunosenescence and prevalence of chronic medical conditions, there is a need for vaccines that provide better protection than SD among seniors. Currently in the U.S., two influenza vaccines are licensed exclusively for use in seniors: an egg-grown trivalent inactivated high dose (HD-IIV3) influenza vaccine (Fluzone® High-Dose, Sanofi Pasteur) and an egg-grown trivalent inactivated adjuvanted (aIIV3) influenza vaccine (Fluad®, Seqirus). HD-IIV3 aims to improve protection through quadrupling the dose per influenza strain from 15 µg HA to 60 µg HA (180 µg total) whereas aIIV3 is an SD-IIV3 vaccine to which an oil-in-water emulsion of squalene oil (MF59) adjuvant is added.

HD-IIV3 is often offered at a price premium compared to SD-IIV3 and aIIV3. In this thesis we attempted to answer if this premium is worthwhile. Based on our research in two specific sub-populations in the United States – Veterans receiving care through VHA and members of a large national managed care company affiliated with Optum – the answer is “yes”. HD-IIV3 is cost saving compared to SD-IIV3 or aIIV3 due to additional hospitalizations avoided. More precisely, we compared the cost of influenza vaccination and acute hospitalization for either cardiovascular or respiratory disease of 158,636 HD-IIV3 and 3.6 million SD-IIV3 recipients vaccinated in VHA facilities during five respiratory seasons and found that HD-IIV3 vaccination resulted in average
net cost savings of $202 (95% CI: $115 – $280) per recipient. These savings were achieved by a relative vaccine effectiveness (rVE), or additional reduction, of HD-IIV3 versus SD-IIV3 of 14% (95% CI: 8% - 19%) for cardio-respiratory disease-associated acute hospitalizations. This may be interpreted as a net cost saving of $202 for each patient that received HD-IIV3 instead of SD-IIV3. In addition, we analyzed 1,900,920 HD-IIV3 and 223,793 aIIV3 recipients in senior members of a large national managed care company in the U.S. and found that – pooled over two predominantly A/H3N2 influenza seasons – HD-IIV3 vaccination resulted in net cost savings of $50 (9$ - $100) per HD-IIV3 recipient due to reduced hospitalizations for either respiratory or cardiovascular disease. These savings were achieved based on an rVE, or additional reduction, of HD-IIV3 versus aIIV3 of 7% (2.3 – 12%) for cardio-respiratory disease-associated acute hospitalizations. This may be interpreted as a net cost saving of $50 for each patient that received HD-IIV3 instead of aIIV3.

Limitations of study design and methods
For our analyses we used real-word data (RWD): health insurance claims data and electronic medical records from VHA, Medicare and Optum. The availability of large databases with data of millions of people makes affordable retrospective cohort studies possible. In addition, it allows for studies in populations not represented in the gold standard: a randomized controlled trial (RCT). Compared to an RCT, retrospective cohort studies are more prone to information bias, confounding, and selection bias that could potentially lead to incorrect estimates and conclusions. It is reassuring, however, that our cost-saving estimate of $202 per patient in the Veteran population is between the net savings of $91 that Chit and colleagues calculated in a RCT for cardio-respiratory hospitalizations, and the $262 per patient Shireman et al. estimated for acute hospitalizations in the US nursing home population using a cluster-randomized study design when comparing HD-IIV3 with SD-IIV3 [4, 5]. RCT participants were drawn from the general, relatively healthy population. The Veteran patient population, in contrast, is on average older, predominantly male, has a higher prevalence of comorbid conditions and poorer health status than the general population [6]. If patients with a poorer health status benefit more from HD than healthy patients, it is logical that the estimated savings found in our study are closer to the savings observed for nursing home residents than to those in the general population.
In all our analyses we made various design choices and applied various methods to minimize information bias, confounding, and selection bias. A very important reason not to include an unvaccinated control group in our analysis was to reduce misclassification of vaccination status, a form of information bias. Indeed, the absence of a vaccination record or insurance claim can mean the person did not receive a vaccination, or received the vaccine through means not captured in the available database (e.g., additional private insurance, attendance of a free-of-charge vaccination campaign). Another reason not to include an unvaccinated control group was to minimize confounding. Confounding is the distortion of the association between vaccination and outcome (for example a hospitalization) by a third variable, the confounding factor. Examples of confounding factors are risk factors like chronic lung disease, heart disease, liver disorders and endocrine disorders like diabetes mellitus, but also the level of education a person has, their personal hygiene practices (e.g., hand washing), and trust in healthcare providers. Some of these confounding factors are very hard to obtain from insurance claims data and can be very different between vaccinated and unvaccinated people [7]. Selection bias arises from the tendency to reserve better treatment for sicker patients, resulting in confounding. That is why this type of selection bias is also known as confounding by indication. Another way is self-selection of the treatment by patients, potentially associated with education level or other confounding factors.

We applied two different methods to minimize the effect of confounding when estimating the relative vaccine effectiveness of HD-IIV3: an instrumental variable (IV) analysis, and the prior event rate ratio (PERR) method. Both methods have in common that they can adjust for measured and unmeasured confounding factors. Measured confounding factors are patient characteristics that we were able to observe in our databases (e.g., age and diagnosis for chronic lung disease), while unmeasured confounding factors are patient characteristics that were missing in our databases (e.g., frailty, personal hygiene practice and trust in healthcare providers). An important reason to use these methods was the fact that when we used standard regression methods that only adjust for measured confounding factors, we observed significant residual confounding. An important assumption for standard regression methods to reduce confounding is that all confounding factors are sufficiently observed and measured. Baseline hospitalization rates during the summer period were at least 20% higher in the HD-IIV3 group compared with the SD-IIV3 or aIIV3 groups.
IV analysis and PERR do have important assumptions as well, and we cannot be 100% certain that all assumptions have been met. To name a few, IV analysis assumes that the instrumental variable – in our case the proportion of HD-IIV3 recipients in a certain VHA facility – is not directly associated with the outcome, a hospitalization. In theory, this assumption could be violated if high-functioning facilities with the best healthcare would not only provide vaccine A, but already have much lower hospitalization rates to begin with compared to the facilities who provide vaccine B. Reassuringly, we did not find differences between facilities with high and low HD-IIV3 proportions for facility characteristics like quality scores, complexity of care available, serving a rural or urban area, and overall health status of the patient population.

The PERR method, on the other hand, assumes that the hospitalization rate-change (from summer period to influenza season) in the aIIV3 group can be used as a proxy for the rate-change in the HD-IIV3 group, had they received aIIV3 instead. If, however, HD-IIV3 recipients are more likely to decrease their health status from summer period to influenza season compared to aIIV3 recipients, PERR underestimates the treatment effect. Here, it is helpful to remember that baseline hospitalization rates during the summer period were 20% higher in the HD-IIV3 group compared with the aIIV3 group, suggesting that HD recipients were sicker or frailer than aIIV3 recipients. Going into the influenza season, the winter, this decrease in health status is not an unlikely scenario.

Both IV analysis and PERR are unable to adjust for regional variations in viral activity. In theory, our estimates could be biased if HD-IIV3 recipients lived in areas with significantly higher or lower viral activity than SD-IIV3 or aIIV3 recipients. Matching cohorts on geographic location is a common method to adjust for geographic heterogeneity. In the VHA study we matched the cohorts on 1,347 facilities before applying PERR, and in the Optum study we matched on 48 States – the most granular data available to us, but potentially too coarse to adjust for within-state viral heterogeneity.

**Generalizability of the results**

The results of our studies have limited generalizability to the general population. First, some of our design choices to reduce confounding and increase internal validity came at the cost of generalizability. As a result, our findings cannot be generalized to
unvaccinated people. In addition, we cannot rule out heterogeneity of the treatment effect of HD-IIV3 which further limits generalizability outside of the studied study population. For example, if the VHA population is generally sicker and frailer than the general population and if the rVE of HD-IIV3 is different for healthy compared to sicker people, then we cannot use the findings in the VHA population to estimate the number of additionally prevented hospitalizations in the general population. On top of that, we observed different cost of similar hospitalizations and vaccines in different health systems. This greatly limits generalizability of net cost savings or cost avoided due to additionally prevented hospitalizations. Fortunately, by now the comparative vaccine effectiveness of HD-IIV3 versus SD-IIV3 has been studied in different populations and seasons, supporting our findings [8]. Based on these studies, health systems could pick an rVE from a study that closely resembles their population (e.g., nursing home) and apply their own vaccination rates, hospitalization rates and cost structure to estimate the budget impact of switching from SD-IIV3 to HD-IIV3. The recent introduction of SD-IIV4 and the upcoming introduction of HD-IIV4 and aIIV4 might warrant a repetition of these studies comparing the quadrivalent vaccines.

Because aIIV3 has been introduced so recently in the US market (our study comparing HD-IIV3 with aIIV3 was during the first two season that aIIV3 was available), more seasons need to be studied to see the effect of viral heterogeneity from one season to the other on the relative vaccine effectiveness of HD-IIV3 and HD-IIV4 compared to aIIV3 and aIIV4.

Proposal for future research

The regulatory body in the US, the Food and Drug Administration (FDA) is currently developing a framework for evaluating RWD and RWE in regulatory decisions [9]. It is to be expected that the potential sources in retrospective cohort studies mentioned earlier need to be addressed convincingly: information bias, confounding, and selection bias. One potential way to do this is to use RWD to replicate the results of an RCT, or more convincingly, predict the results of an ongoing RCT. In a future study, methods need to be applied or developed that: select RCT-eligible people in claims databases; compare baseline characteristics and health profiles between treatment and control groups; and estimate the level of residual confounding after adjusting for confounding factors. The ongoing pragmatic cluster randomized trial comparing a recombinant
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quadrivalent influenza vaccine (RIV4) with SD-IIV4 in the Kaiser Permanente healthcare system is a potential candidate for such a study [10].

In addition, the theoretical work we did on rate-change methods (including PERR) is still in its early phase and could benefit from additional attention. More precisely, an efficient estimator needs to be defined for the number of events prevented that adjust for all measured confounding factors, and how to estimate bias parameter $u$ is still largely unclear.

Conclusions

HD-IIV3 is associated with less hospitalizations compared to SD-IIV3 and aIIV3. Because HD-IIV3 prevents more hospitalizations than the other vaccines, the avoided hospitalization costs more than offset the often higher price of HD-IIV3, resulting in net cost savings. Generalizability of these results outside of our study populations is limited because of healthcare system specific factors like cost of vaccination and hospitalization, and overall health status of the patient population. Our studies do provide tools for individual healthcare systems to estimate the effect of switching from one vaccine to the other on their budget applying a published rVE in a population closely resembling their own. Additional research is needed to include more influenza seasons for the recently introduced aIIV3, and to compare the upcoming quadrivalent versions of the vaccines studied in this thesis.
REFERENCES


