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Original Study

Cost Benefit of High-Dose vs Standard-Dose Influenza Vaccine in a Long-Term Care Population During an A/H1N1-Predominant Influenza Season

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A B S T R A C T

Objectives: Influenza is a leading cause of *avoidable* admissions for nursing home (NH) residents. We previously evaluated the effectiveness of a high-dose trivalent influenza vaccine (HD) compared to a standard-dose influenza vaccine (SD) through a cluster-randomized trial of NH residents. Fewer residents from facilities randomized to HD were hospitalized. In this article, we extend our analyses to consider direct medical care costs relative to vaccine costs for HD ($31.82/dose) as compared to SD ($12.04/dose).
Design: Post hoc, cost-benefit analysis.
Setting and participants: From the participating NH facilities (n = 817), we identified Medicare fee-for-service enrollees who were long-stay residents (>100 days) at the start of the 2013-2014 influenza season (November 1–May 31). The intervention was residence in a facility randomized to HD or SD influenza vaccine.
Methods: We summed expenditures from long-stay NH residents' Medicare Part A, B, and D fee-for-service claims and compared person-level expenditures between residents of facilities offering HD vs SD. Expenditures were adjusted for clustering of residents within NHs, person-time, and prespecified covariates using 2-part, generalized linear models with bootstrapped standard errors. We examined the incremental cost-benefit of HD vs SD vaccines from a payer perspective.
Results: There were 18,605 and 18,658 Medicare fee-for-service long-stay residents in facilities offering HD and SD, respectively. Person- and facility-adjusted total expenditures differed by $546 ($P = .006$). The $20 incremental cost of HD to SD offset adjusted expenditures for a net benefit of $526 per NH resident and a financial return on investment of 546/20 = 27:1.
Conclusions/implications: The use of HD influenza vaccine in long-stay NH residents reduced total health care expenditures for a net benefit despite HD being more expensive per dose. These cost offsets applied to Medicare beneficiaries residing in NHs could result in important savings to the Medicare program.

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Influenza is the second most costly, vaccine-preventable illness among older adults and a leading cause of *avoidable* admissions for nursing home (NH) residents.[1,2] Immunosenescence and various comorbidities that increase with age not only increase the morbidity and mortality of infections and vaccine-preventable diseases, but also affect the efficacy and effectiveness of vaccines. Most influenza vaccines include 15 μg of each of 3 (trivalent) or 4 (quadrivalent) antigens and are purified from egg-grown virus for intramuscular injection. Because of declining effectiveness with age, more immunogenic vaccines have been developed and are specifically approved for adults aged 65 years and older. Among these is a vaccine that contains 4 times the usual amount of each antigen, 60 μg. This high-dose vaccine has demonstrated reduced laboratory-confirmed protocol-defined influenza-like illness by about 24% in both a prospective randomized controlled trial and claims-adjudicated influenza in metadata-type studies among outpatient elderly.[3–5] High-dose vaccine costs twice as much per dose, though, and with the large population at risk for influenza, its economic impact becomes salient. More recently, Chit et al[3] suggested that the high-dose vaccine was less costly and more effective than standard-dose vaccine for an outpatient older population, driven by lower hospital admissions among high-dose vaccine recipients. However, as vaccine response declines both as a function of age and disease, the question remains as to whether in a frail, NH older population the high-dose vaccine could still provide superior, cost-effective protection.

We previously conducted a cluster-randomized trial to evaluate long-stay residents living in 823 US NHs over the 2013-2014 influenza season. From that trial, we reported that fewer long-stay residents aged 65 years and older of facilities offering a high-dose trivalent influenza vaccine (HD) were hospitalized (adjusted risk ratio 0.873, 0.776-0.982) than those in facilities offering standard-dose influenza vaccine (SD),[6] similar to the earlier completed feasibility study.[7] Centers for Medicare & Medicaid Services–approved prices are double for the HD vaccine as compared to the SD vaccine, and with more than 1.7 million NH residents in the United States, the incremental cost should be evaluated relative to its net benefits. Because we have complete data on Medicare expenditures across all service categories, the goal of this study is to calculate the actual cost differential of medical care relative to the incremental vaccine cost.

Methods

We derived our study population from a prior cluster-randomized controlled study evaluating the comparative effectiveness of high- vs standard-dose (HD vs SD) influenza vaccine in a long-term care population for the 2013-2014 influenza season using an institutional review board-–approved protocol.[6] The methods are fully described elsewhere.[8] Briefly, we randomized vaccine assignment of a large number of facilities. We evaluated outcomes on an intent-to-treat basis, treating the 15% or so who were not vaccinated as if they received the vaccine offered by randomization at their facility as the care standard and not changing how refusals or other aspects were handled within facilities. We evaluated direct medical costs from a payer (Medicare) perspective and included individual service category costs as well as their sum.

Our analytic sample included individuals who met inclusion requirements based on long-stay status, age minimum, and status as a Medicare beneficiary in a setting where similar number of staff at the facility level received SD vaccine between treatment groups. Individuals were deemed long-stay residents if they were residing at the facility for at least 90 days by October 1: we limited to long-stay residents to avoid heterogeneous, exogenous factors driving hospitalizations and adverse health events for the shorter-stay Medicare skilled nursing facility population. Because the HD vaccine was Food and Drug Administration approved only for use in individuals aged 65 years and older, we required study subjects to have achieved age 65 by October 1 to be included in the analytic sample. Finally, the analytic sample for this report was restricted to the subset of residents who were Medicare fee-for-service (FFS) beneficiaries, allowing us to assess direct health care costs. The numbers of cases differed slightly from the previously published trial results because we extended the mandatory FFS enrollment period to encompass the entire influenza season, rather than the baseline months. We evaluated the data on these long-stay NH residents of the 823 participating facilities from November 1, 2013 through May 31, 2014, the influenza season of interest, establishing a short-run time horizon for the cost analyses.

Our data sources included data collected directly from each NH, such as vaccine lot numbers and staff vaccination rates, along with data reported to the federal government, including the Minimum Data Set resident assessments, the Online Survey Certification and Reporting, and Medicare Parts A, B, and D claims. The Online Survey Certification and Reporting contains facility-level characteristics, including information on staffing. The Minimum Data Set assessments and Medicare claims contained diagnosis codes, and Medicare claims also contained hospital, hospice, and posthospitalization rehabilitation costs in Part A; physician and other providers visits, certain medications, and procedures in Medicare Part B; and medications and their costs in Medicare Part D. Costs, defined as provider-reimbursed amounts, were tabulated from the payer perspective, specifically Medicare, and excluded patient and facility out-of-pocket costs, productivity costs, and NH costs not directly covered under Medicare.

Costs were summarized at the individual service level by claim type: inpatient acute, other inpatient, emergency room/observation, post-acute skilled nursing facility, outpatient rehabilitation, and outpatient provider services (Part B), hospice, home health, and outpatient prescription medications (Part D). We then summed all expenditures over the study period (November-May). We compared the person-level expenditure between residents of facilities offering HD vs SD using the intent-to-treat approach. In accordance with the study design, these unadjusted costs accounted for NH assignment. Vaccine costs (per dose) were from the Centers for Medicare & Medicaid Services pricing schedule: HD, $31.82; and SD, $12.04. Results were reported as net monetary benefit (resource cost differences between SD and HD minus vaccine costs) and as the return on investment, consistent with cost-benefit analysis.

As in the comparative effectiveness analysis,[6] we adjusted expenditures for clustering of residents within NHs, person-time, and prespecified covariates. Person-level and facility-level covariates included age and average age of facility residents, activities of daily living and average activities of daily living of facility residents, cognitive function and average cognitive function of facility residents, chronic heart failure and prevalence of heart failure in the facility, and facilities' prior years' hospitalization rates. To model direct medical costs, we employed 2-part models (logit of any utilization followed by a generalized linear model among those with utilization) with bootstrapped standard errors (1000 replications for each model). The 2-part model allowed for less biased estimates due to large numbers of zero costs (no utilization) in some of the service categories. The generalized linear model used the gamma distribution to account for skewed costs, with the log of person time as an offset term to account for varying resident follow-up times, and accounting for clustering at the facility level. Given the high degree of skewness with cost data, we reran the total expenditure analyses by down-weighting the top percentile (1%) of outliers as a sensitivity analysis. As the original trial was powered to detect a difference in hospital admissions, it potentially would be underpowered to determine cost differences.

Finally, we plotted average weekly expenditures by treatment group across the period of the trial and included the Centers for Disease Control and Prevention (CDC)–confirmed influenza hospitalization

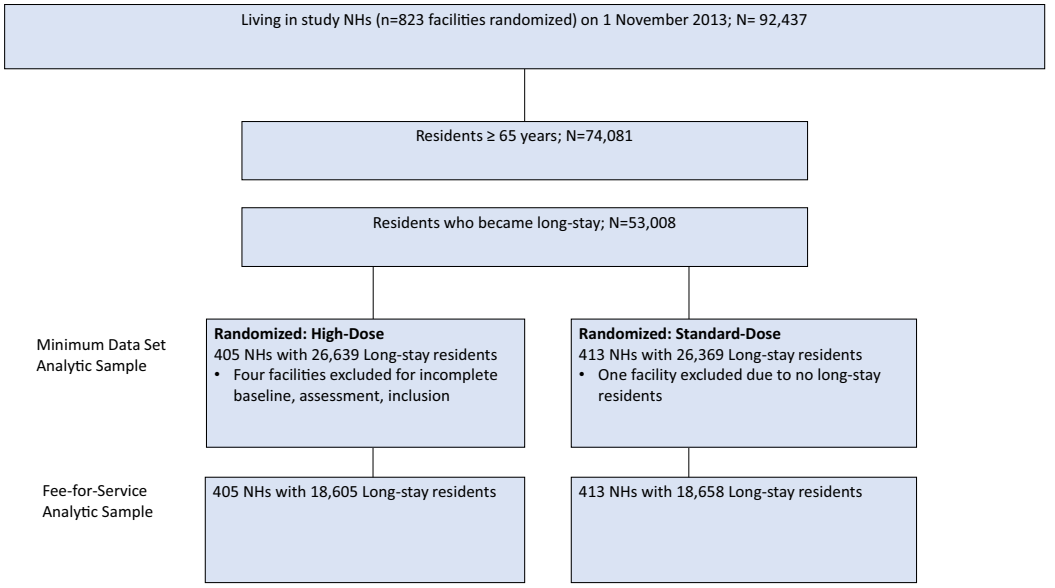

Fig. 1. Consort diagram.

rates for adults older than 65 years, reported as admissions per 100,000 population. This allowed us to show how expenditures compared to the timing of influenza events. Week zero (0) corresponded to the first week in November, capturing the start of the month after which vaccinations were given in the NHs.

Ethics Committee Approval

The original trial was approved by the New England Institutional Review Board.[6,8] Our Institutional Review Board approved the cost analysis of the secondary data under a data use agreement (DUA 24928) from the Centers for Medicare and Medicaid Services.

Table 1
Subject Characteristics by Treatment Arm

	High-Dose Vaccine Group (n = 18,605)	Standard-Dose Vaccine Group (n = 18,658)
Mean age, y	83.8 (8.7)	83.9 (8.8)
Female, n (%)	13,468 (72.4)	13,495 (72.3)
Ethnic origin, n (%)		
African American	2524 (13.6)	2677 (14.3)
White	14,395 (77.3)	14,238 (76.3)
Hispanic	860 (4.6)	889 (4.8)
Married	3443 (18.7)	3432 (18.6)
Cognitive function scale, n (%)		
Intact or no impairment	4935 (26.5)	4821 (25.8)
Mild impairment	3990 (21.5)	3955 (21.2)
Moderate impairment	6940 (37.3)	7226 (38.7)
Severe impairment	2606 (14.0)	2534 (13.6)
Missing	134 (0.7)	122 (0.7)
Baseline ADL scale score (of 28 points)	17.0 (6.7)	17.3 (6.5)
Previous conditions, n (%)		
Heart failure	3792 (20.4)	3832 (20.5)
Cerebrovascular accident or event	3643 (19.6)	3772 (20.2)
Hypertension	14,718 (79.1)	14,784 (79.2)
Diabetes mellitus	6219 (33.4)	6358 (34.1)
Chronic lung disease	3716 (20.0)	3800 (20.4)

ADL, activities of daily living.
Data are mean (standard deviation) unless otherwise noted. Cerebrovascular accident or event includes prior stroke and transient ischemic attacks; chronic lung disease includes chronic obstructive pulmonary disease and asthma.

Role of the Funding Source

Sanofi Pasteur provided funding for this post hoc cost analysis through an investigator-initiated grant. All data collection, analysis, and interpretation was done by the investigative team. The manuscript was also written by the investigative team. The corresponding author and collaborators had full access to the data and maintains final responsibility for the decision to submit for publication.

Results

There were 18,605 and 18,658 FFS long-stay residents included from facilities offering HD and SD, respectively (Figure 1). Subject characteristics are shown in Table 1. There were no important differences between HD and SD participants: their average age was 83.6 years, they included a high proportion of females (72%) and a high proportion of whites (77%). Predominant comorbidities included hypertension, diabetes mellitus, heart failure, cerebrovascular disease, and lung disease (ie, asthma or chronic obstructive pulmonary disease). Mortality was similar between groups (0.812 per 1000 resident-days, 15.9% HD, over 6 months vs 0.829 per 1000 resident-days, 16.2% SD, over 6 months).

Table 2
Per-Participant Direct Medical Costs ($) for HD vs SD Flu Vaccine

Service Category	High-Dose Vaccine Group (n = 18,605)		Standard-Dose Vaccine Group (n = 18,658)	
	Mean ($)	95% Confidence Interval	Mean ($)	95% Confidence Interval
Acute inpatient	3043	2773, 3313	3255	2998, 3512
Other inpatient	338	248, 427	419	324, 513
Emergency department/ observation	133	122, 144	135	123, 148
Skilled nursing facility	686	613, 758	723	642, 803
Outpatient rehabilitation	1257	1181, 1334	1280	1207, 1353
Physician/other provider	1887	1779, 1995	1951	1862, 2041
Hospice	2167	2000, 2333	2123	1947, 2300
Home health	47	38, 55	42	35, 50
Outpatient medications	1528	1470, 1586	1560	1508, 1612
Total	11084	10628, 11541	11490	11034, 11946

Table 3
Adjusted Differences per Participant Direct Medical Costs ($) for HD vs SD Flu Vaccine

Service Category	Standard-Dose Minus High-Dose Vaccine Group Costs ($), Mean Difference (95% CI)
Acute inpatient	262 (−0.06, 524)
Other inpatient	85 (2, 168)
Emergency department/observation	6 (−7, 18)
Skilled nursing facility	52 (−24, 129)
Outpatient rehabilitation	43 (−3, 89)
Physician/other provider	106 (44, 160)
Hospice	−33 (−158, 91)
Home health	4 (−14, 7)
Outpatient medications	30 (−16, 76)
Total	546 (153, 939)

Marginal effects at overall means, adjusted for facility clusters, patient- and facility-level characteristics were derived from 2-part model with bootstrap standard errors (1000 replications); positive values indicate higher costs in the SD group. Individual values do not sum to the total because of varying levels of zero costs within each category.

Direct medical costs per NH resident were $406 higher for SD vs HD residents (Table 2), more than half ($212) of which was attributable to lower inpatient hospital costs. The second highest cost service category was hospice, though it was slightly lower for the SD residents.

The fully adjusted, 2-part model (Table 3), results show per-resident health care expenditures significantly lower for the HD group (Δ = $546, P = .006). Reductions in inpatient hospital costs accounted for almost half (48%) of the overall savings, with lower physician services accounting for another 19% of the savings.

Figure 2 shows the week-by-week relative costs (colored lines, left axis) between the HD and SD treatment groups alongside national CDC confirmed influenza hospitalization rates for adults over age 65 years (dashed line, right axis). The savings accrued during the weeks where SD costs exceed HD costs. There is a short period, just after the 12th week of the season, where HD costs exceeded SD costs. The peak rate for CDC-confirmed influenza hospitalizations occurred at around the 10th week of the trial, with hospitalizations remaining elevated through the end of the trial period.

Considering that HD vaccine costs $20 more than the SD vaccine, the adjusted expenditures resulted in a net financial savings to Medicare of $526 = ($546 minus $20) per NH resident for a vaccine's costs to health system savings ratio of 546/20 = 27:1. These financial savings to Medicare are in addition to the net loss of health or healthy time experienced by individuals receiving SD instead of HD.

Discussion

As a follow-up to our previously reported cluster randomized trial of HD vs SD vaccination in NH residents, we demonstrated that the ~$20/dose higher HD vaccine price offered a 27-fold return to Medicare. The largest dollar savings came from reduced inpatient service costs and physician and other provider (Part B) costs even though these costs did not differ significantly between treatment arms. Indeed, the hallmark impact of influenza in the NH setting is the need to hospitalize for severe respiratory symptoms. Even in this relatively mild 2013-2014 season, acute inpatient costs were $262 lower in the HD group. Furthermore, there was little difference in emergency department utilization. As both treatment groups experienced similar mortality, no quality-adjusted life years analysis was applied.

Our results are consistent with other cost-effectiveness analyses of various high-dose vaccination strategies in older adults. Izurieta et al[5] conducted a retrospective analysis of Medicare claims during the 2012-2013 influenza season and found a 22% reduction in hospital admissions in individuals aged 65 years and older receiving the high-dose vaccine compared to those receiving standard-dose vaccine in the community setting. Chit and colleagues[3] applied a cost-effectiveness analysis to a randomized controlled trial of high-dose influenza vaccine compared to standard dose over 2 influenza seasons (2011-2012 and 2012-2013), and also found high dose to be cost effective in an ambulatory ≥65-year-old population. Their mean participant medical costs were $1376 (standard deviation, $6857) in

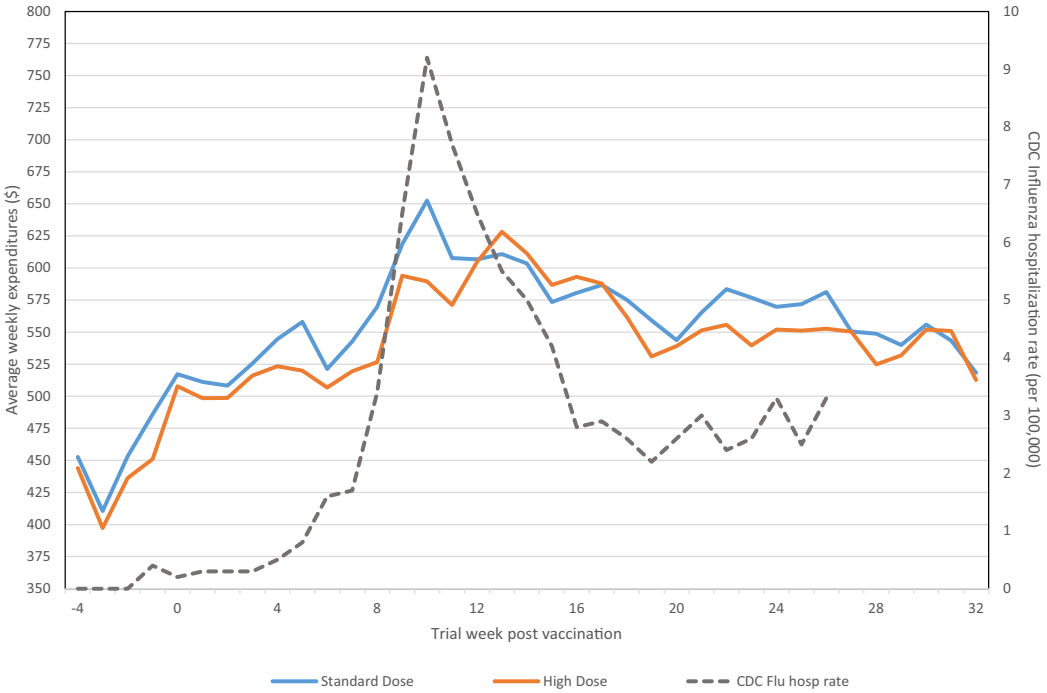

Fig. 2. Weekly total expenditures by treatment arm and CDC influenza hospitalization rates.

the high-dose compared to $1492 (standard deviation, $7447) in the standard-dose group. As our study involved long-stay NH residents as opposed to community dwellers, our population was older with a higher burden of illness, and total expenditures were an order of magnitude greater, >$11,000 per average patient.

In 2010, the CDC's Advisory Committee on Immunization Practices announced its recommendation to expand influenza vaccination to include all adults.[9] The recommendation was made based on the opportunity to reduce the substantial public health care burden of influenza and advance vaccine coverage. Clements et al demonstrated the cost-effectiveness of universal mass vaccination in the United States compared to the previous targeted vaccine program and determined that mass vaccination would be cost saving using reasonable assumptions for coverage, cost, and efficacy.[10] Prior evaluations of influenza vaccination in noninstitutionalized older adults have also demonstrated reductions in hospital admissions and cost-effectiveness. Our study and the analyses of Chit et al[3] and Izurieta et al[5] contribute significantly to the body of literature on cost-effectiveness of high-dose influenza vaccine, particularly, in older adults and older adults in the NH setting.

Limitations

We did not conduct local influenza testing to confirm the diagnoses, but given that randomization balanced study arms, the impact of such misclassification bias would have been minimized. A similar proportion of HD and SD long-stay residents were not vaccinated, about 15%, so our effect estimates do not reflect the full potential impact if vaccination rates were 100%. We did not correct for the lack of difference in vaccine costs for this unvaccinated subset. The season evaluated was considered a mild season in terms of influenza hospitalizations compared with the recent predominantly A/H3N2 seasons. The CDC reported the 2013-2014 season as relatively mild compared to adjacent 2012-2013 and 2014-2015 seasons (cumulative incidence rates by week 17 of laboratory-confirmed influenza hospitalizations for those aged 65 years and older, 84.8 per 100,000 for 2013-2014 vs 183.9 in 2012-2013 and 308.8 in 2014-2015) among individuals aged 65 years and older, suggesting our cost-benefit estimate is conservative.[11] Our primary cost analysis was limited to Medicare FFS beneficiaries, potentially limiting generalizability to Medicare Advantage beneficiaries and non-Medicare residents. As the relative proportions of Medicare Advantage enrollment did not differ significantly between treatment arms, we do not anticipate that Medicare Advantage costs would have differed between arms, but they might have been lower/higher than FFS costs. We did not have access to other costs incurred by facilities or individual residents, so our estimates did not reflect any cost shift to facilities for residents who may have been ill and required additional nursing time or other nonbillable services but did not require hospitalization. There was no reason to expect that the HD and SD facilities would change their threshold for sending sick residents to the hospital merely because of awareness of having administered one vaccine over the other. We did not include short-stay residents who also could have received vaccine at the facility, and whose known high rehospitalization risk may have further contributed to differences between the net benefit to high-dose vaccination in this setting. Finally, this cost analysis may not be generalizable to a noninstitutional older population, though as noted previously the vaccine has been evaluated in that population.

Conclusion and Implications

The use of HD influenza vaccine in long-stay NH residents reduced hospitalizations and resulted in lower Medicare expenditures. The magnitude of the estimated savings overwhelmed the incremental cost of the HD relative to SD vaccine. These savings applied across all Medicare beneficiaries residing in NHs could result in important savings to the Medicare program.

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