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Original Report

Potential Cost-Effectiveness of a Universal Influenza Vaccine in Older Adults

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Abstract

Background and Objectives: "Universal" vaccines that could have multistrain and multiyear effectiveness are being developed. Their potential cost-effectiveness in geriatric populations is unknown.

Research Design and Methods: A Markov model estimated effects of a theoretical universal influenza vaccine compared with available seasonal vaccines in hypothetical cohorts of U.S. 65+-year olds followed over a 5-year time horizon to capture potential multiyear protection. Outcomes included costs per quality-adjusted life-year gained and influenza cases avoided.

Results: Using hypothetical universal vaccine parameter values (cost $100, vaccine effectiveness 39%, uptake 64%, effectiveness duration 5 years), universal vaccine was less costly than seasonal influenza vaccination strategies. High-dose trivalent influenza vaccine, compared with universal vaccine, gained 0.0028 quality-adjusted life-years and cost $82 more, or $28,700 per quality-adjusted life-year gained. Other seasonal vaccines were not favorable economically. Five-year influenza risk with universal vaccination was 32.3% under base case assumptions, compared with <30% with adjuvanted or high-dose vaccine use. In sensitivity analyses, universal vaccine was favored when uptake or vaccine effectiveness was greater than standard-dose influenza vaccine. If absolute universal vaccine effectiveness was 10% less than standard-dose vaccine, universal vaccine could be cost-saving but not more effective than other strategies. Universal vaccine was not favored if its effectiveness duration was <3 years.

Discussion and Implications: Universal vaccine use in older persons could be either cost effective or cost saving when universal vaccine parameters are within plausible ranges. However, if its effectiveness is substantially less than current vaccines, its use would probably not be favored in geriatric populations.

Translational Significance: If universal influenza vaccine effectiveness is less than that seen with the standard-dose vaccines, then universal vaccine use in seniors would likely be unfavorable from economic or public health standpoints, with high-dose or adjuvanted vaccines favored instead. Universal vaccine could be favored if its effectiveness is comparable or better than standard-dose vaccine.

Keywords: Decision making, Economics, Health care policy

Suboptimal influenza vaccine effectiveness during the past few influenza seasons has heightened urgency for development of more effective influenza vaccines (Flannery et al., 2017, 2018). One of these efforts, and an NIH priority, is development of a universal influenza vaccine that protects against multiple influenza virus subtypes, potentially over several years (Paules, Sullivan, Subbarao, & Fauci, 2018). Universal influenza vaccines are currently being developed by several manufacturers, but it is unclear when these vaccines will become available or how effective they may be. Development costs have been considerable and these costs will likely be reflected in the price of the universal vaccine, which is likely to be greater than the prices of currently available seasonal vaccines (Lee et al., 2012). Early candidate universal vaccines have shown lower vaccine effectiveness than that seen with seasonal vaccines (Krammer & Palese, 2015). However, fear or dislike of needles is a known barrier to vaccine acceptance (Nowalk et al., 2010; Zimmerman et al., 2003). A multiyear universal vaccine could reduce the number of vaccine administrations required to prevent influenza, leading to greater cumulative uptake. If vaccine effectiveness with universal vaccine is reduced compared with seasonal vaccines, this reduction could be offset by higher uptake, potentially resulting in greater herd immunity as well as longer-lasting protection against multiple influenza virus strains. It should be noted that a recent NIH strategic plan calls for a universal vaccine that is at least 75% effective against symptomatic influenza (Erbelding et al., 2018); whether this is a realistic or achievable goal in geriatric populations, with considerably less vaccine effectiveness in recent seasons, is unclear (Flannery et al., 2017, 2018). Thus, the conflicting benefits and disadvantages of introducing a universal influenza vaccine raise questions regarding whether it could be a reasonable use of limited health care resources, particularly in older age groups.

A previous cost-effectiveness analysis (Lee et al., 2012) of lifetime universal influenza vaccine use starting in childhood found that it could be economically reasonable if its vaccine effectiveness was >50%, its effectiveness duration was >5 years, or its cost was <$200. In this study, we seek to establish boundaries for cost, vaccine effectiveness, and uptake in which a universal influenza vaccine could be an economically viable option for adults aged ≥65 years. In view of the universal vaccine's unknown cost, vaccine effectiveness, acceptability, and uptake, a decision analysis model can offer insight into the level of potential benefits necessary to consider it a good health care investment.

Research Design and Methods

A Markov state transition model was used to estimate characteristics of a theoretical universal influenza vaccine that would favor its use in adults aged 65 years and older compared with currently available seasonal influenza vaccines. The analysis modeled plausible parameter ranges for vaccine effectiveness, uptake, and cost that would result in a universal vaccine costing less than $100,000 per quality-adjusted life-year gained (the commonly accepted U.S. cost-effectiveness threshold; Neumann, Cohen, & Weinstein, 2014) or being cost saving ($0 per quality-adjusted life-year gained threshold) when considering all vaccination and influenza illness costs. The model followed identical hypothetical cohorts of 65-year-olds over a 5-year time horizon in annual cycles. A 5-year time horizon was chosen to capture potential multiyear protection from universal vaccination. Available seasonal vaccines used for comparison were standard-dose trivalent inactivated influenza vaccine, high-dose trivalent vaccine, standard-dose quadrivalent vaccine, and adjuvanted influenza vaccine. Strategy effectiveness was measured as quality-adjusted life-years, to account for both time and quality of life, and as influenza cases prevented. The analysis took a societal perspective, following recommendations of the Panel on Cost-Effectiveness in Health and Medicine, discounting costs and effectiveness by 3% per year (Sanders et al., 2016). In following these updated recommendations, indirect costs of illness are accounted for by estimates of productivity lost by patients and their caregivers, which are included in our influenza cost parameters.

Cohorts entered the model either vaccinated or unvaccinated (Figure 1), based on the strategy-specific likelihood of vaccination. Portions of the cohort could contract influenza, with the likelihood of infection in the vaccinated dependent on vaccine effectiveness. Varying influenza season severity was modeled through variation of influenza frequency, hospitalization, and mortality rates in sensitivity analyses. The yearly probability of influenza disease without vaccination was derived from CDC estimates of influenza cases and averted cases (Molinari et al., 2007; Reed et al., 2014). Influenza cases could result in hospitalization or death. Influenza illness, hospitalization, death, and adverse events were assigned disutility values (loss of quality and/or duration of life), as shown in Table 1. For patients with fatal influenza, disutility was the discounted quality-adjusted life expectancy loss for their remaining life span (i.e., not limited by the model's 5-year time horizon).

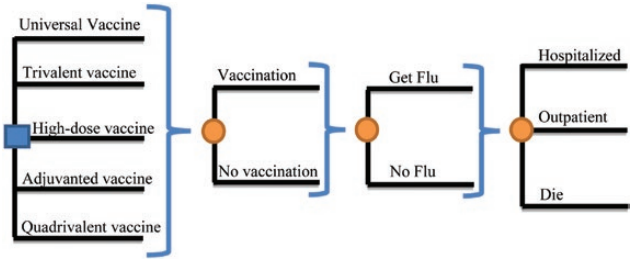

Figure 1. Schematic diagram of the Markov model decision tree. *Note.* Trivalent vaccine = trivalent inactivated influenza vaccine; high-dose vaccine = high-dose trivalent inactivated influenza vaccine; adjuvanted vaccine = adjuvanted influenza vaccine; quadrivalent vaccine = quadrivalent inactivated influenza vaccine.

Mechanistically, the Markov model had two states (alive and dead), with influenza and its consequences (costs and disutilities) modeled as tolls within the model that could occur during each modeled year. Outcomes in high-risk and nonhigh-risk proportions of the cohort were accounted for using weighted averages for risk group-specific frequencies, durations, and costs.

Other parameter values used in the model are shown in Table 1. Influenza costs, utilities, and outcomes were obtained from the medical literature, as were values for seasonal influenza vaccines' effectiveness and uptake. A cost base year of 2016 was used, with prior costs inflated using the U.S. Consumer Price Index. Influenza vaccination costs included vaccine cost derived from CDC vaccine price lists (private sector cost; CDC, 2016) plus administration costs from Centers for Medicare and Medicaid Services data (CMS, 2016). The base case analysis assumed a universal vaccine cost of $100.

For the universal vaccination strategy, patients were vaccinated once over the 5-year time horizon, with the likelihood of receiving universal vaccine set to 64% (similar to current seasonal vaccination rates), then varied widely in sensitivity analyses. We assumed that the universal vaccine was effective for 5 years, with vaccine effectiveness remaining constant over that time; this assumption was tested further in sensitivity analysis. For vaccination strategies using currently available seasonal vaccines, vaccination likelihood was the current uptake, 64.7%. We assumed that vaccine effectiveness for all seasonal vaccines did not wane over time, and that vaccine effectiveness was the combined effectiveness against all circulating influenza strains. Vaccine effectiveness for universal vaccine was set to 39%, the same as that of standard-dose trivalent vaccine, then varied ±10 percentage points (i.e., absolute effectiveness differences) in sensitivity analyses. Influenza case–hospitalization and case–fatality rates were assumed to be identical regardless of vaccination status or strategy. We also assumed that other noninfluenza causes of death were not affected by vaccination. The model accounted for vaccine adverse events, assuming them to be the same for all vaccines (DiazGranados et al., 2014). Vaccination strategies assumed exclusive use of that strategy's vaccine to highlight universal vaccine characteristics compared with currently available seasonal vaccines. A sensitivity analysis relaxing this assumption and allowing mixed use of universal and current seasonal vaccines was also performed.

In sensitivity analyses, vaccine effectiveness, uptake, and costs were varied widely over ranges shown in Table 1. One-way sensitivity analyses were performed, individually varying all parameter values over their listed ranges. Parameters found to be individually sensitive to variation (i.e., would change the favored strategy) were then included in deterministic multiway sensitivity analyses, simultaneously varying those parameters in analyses examining where the universal vaccine would be favored at a $100,000 per quality-adjusted life-year gained threshold (a commonly cited U.S. cost-effectiveness benchmark; Neumann et al., 2014) or at a cost-savings ($0 per quality-adjusted life-year gained) threshold. Probabilistic sensitivity analyses were then performed, where universal vaccine cost and effectiveness values were held at various hypothetical values while simultaneously varying all other parameter values over distributions 5,000 times. In these analyses, universal vaccine costs were fixed at $50, $100, and $150, and universal vaccine effectiveness varied ±10% from base values using normal distributions; base universal vaccine effectiveness values used were absolute differences of 0%, –10%, or +10% compared with standard-dose trivalent vaccine. In the probabilistic sensitivity analyses, all other probability, effectiveness, and utility parameters were varied over beta distributions fitted to approximate ranges listed in Table 1, while cost parameters were similarly varied over gamma distributions. Finally, in a separate set of sensitivity analyses, we considered shorter (<5 years) effectiveness durations for universal vaccine.

Results

In the base case cost-effectiveness analysis, using hypothetical values for universal vaccine cost, vaccine effectiveness, effectiveness duration, and uptake, the universal vaccine strategy was less costly ($1,647 total per person vaccination and illness costs over 5 years) than all of the seasonal influenza vaccination strategies but less effective than high-dose vaccine, quadrivalent vaccine, and adjuvanted vaccine (Table 2). Adjuvanted vaccine was eliminated from consideration due to extended dominance, that is, it cost more per quality-adjusted life-year gained than high-dose vaccine, a more effective strategy (Cantor, 1994). High-dose trivalent vaccine, compared with universal vaccine, cost $82 more and gained 0.0028 quality-adjusted life-years (about 1 day), or about $28,700 per quality-adjusted life-year gained. Both standard-dose trivalent vaccine and quadrivalent vaccine were dominated from a cost-effectiveness standpoint—they were more costly and less effective than other strategies. From a public health standpoint, the 5-year probability of influenza with universal vaccination was 32.3%, compared with <30% with annual high-dose vaccine or adjuvanted vaccine use.

In one-way sensitivity analyses, we found only two parameters (the likelihood of receiving universal vaccination and the effectiveness of the universal vaccine) whose individual variation led to universal vaccination being favored over other strategies at a $100,000 per quality-adjusted life-year gained threshold. Universal vaccination was favored at this threshold if its likelihood of receipt was >70.7% (base case value 64%) or its vaccine effectiveness was >43.3% (base case 39%). Individual variation of universal vaccine cost defined as a multiple of high-dose vaccine cost ($36.85) found that the universal vaccine strategy remained less costly than other strategies when universal vaccine was varied to six times high-dose vaccine cost

Table 1. Model Parameter Values

Model parameters	Base case	Ranges	Reference
Probabilities (%)			
Influenza illness			
Influenza	9.0	7.8–10.2	Molinari et al. (2007)
High-risk elderly proportion	51.2	23.5–78.5	Molinari et al. (2007)
High-risk elderly seeking office visits	82.0	58.7–96.3	Molinari et al. (2007)
Nonhigh-risk elderly seeking office visits	62.0	56.6–67.0	Molinari et al. (2007)
Case–hospitalization	4.21	3.51–4.91	Molinari et al. (2007)
Case–fatality	1.17	0.0078–1.56	Molinari et al. (2007)
Vaccine effectiveness			
Universal	39.0		Assumption
Trivalent	39.0	0.0–65.0	Reed et al. (2014)
Proportion uncovered influenza B	7.7	3.85–20.0	Reed et al. (2014)
Quadrivalent	42.0		Calculated
Relative effectiveness increase of adjuvanted vaccine over trivalent	22.6	21.5–22.0	McElhaney et al. (2013)
Relative effectiveness increase of high-dose vaccine over trivalent	24.2	9.7–36.5	DiazGranados et al. (2014)
Vaccination			
Seasonal vaccines	64.7	64.1–65.3	Reed et al. (2014)
Universal vaccine	64.0	0.0–100.0	Assumption
Vaccination adverse event	8.3	0.0–8.3	DiazGranados et al. (2014)
Cost and resource utilization			
Adverse events			
Cost of any nonhospitalized adverse event	$2.80	$1.40–$4.20	Ibuprofen cost Walgreens
Illness costs			
Lost productivity—1 day	$190.60	$81–$243	Molinari et al. (2007)[a]
Death from flu—high-risk	$43,392	$21,696–$65,088	Molinari et al. (2007)[a]
Death from flu—nonhigh-risk	$55,139	$27,570–$82,709	Molinari et al. (2007)[a]
Lost productivity cost from mortality	$244,289	$122,145–$366,434	Molinari et al. (2007)[a]
Antiviral medication	$120.60	$60–$182	Medical Letter (2014)
Hospitalization—high-risk	$25,007	$12,503–$37,510	Molinari et al. (2007)[a]
Hospitalization—nonhigh-risk	$17,228	$8,614–$25,842	Molinari et al. (2007)[a]
Influenza with no office visit	$4.09	$2.05–$6.15	Molinari et al. (2007)[a]
Flu requiring office visit (incl productivity)			
High-risk	$1,947	$973–$2,921	Molinari et al. (2007)[a]
Nonhigh-risk	$883	$441–$1,325	Molinari et al., (2007)[a]
Vaccination costs			
Adjuvanted vaccine	$32.17	$10–$50	Medical Letter, (2016)
Quadrivalent	$16.62	$8.08–$24.23	CDC (2016)
Trivalent	$14.41	$7.20–$21.61	CDC (2016)
High dose trivalent	$36.85	$20–$40	Medical Letter (2016)
Universal	$100	$0–$500	Assumption
Vaccine administration	$25.08	$12.54–$37.62	CMS (2016)
Durations and utilities			
Outpatient			
Days of lost productivity—high-risk elderly	7.0	3.5–10.5	Molinari et al. (2007)
Days of lost productivity—nonhigh-risk elderly	3.0	1.5–4.5	Molinari et al. (2007)
Hospitalization			
Days of lost productivity—high-risk elderly	18	10–27	Molinari et al. (2007)
Days of lost productivity—nonhigh-risk elderly	13	6–20	Molinari et al. (2007)
Disutilities (quality-adjusted life-years lost)			
Vaccination adverse event	0.00274	0.0–0.005	Assumption
Death	9.0216	5.0–16.0	Arias (2014)

Table 1. *Continued*

Model parameters	Base case	Ranges	Reference
Utilities			
Well	0.84	0.70–0.95	Gold, Franks, McCoy, and Fryback (1998)
Influenza	0.558	0.30–0.80	Luce et al. (2008)
Discount rate	3%	Not varied	

[a]Listed values are inflated to 2016 U.S. dollars using the U.S. Consumer Price Index.

Table 2. Base Case Cost-Effectiveness Analysis Results—Strategies Rank-Ordered by Cost

Strategy	Cost	Incremental cost	Effectiveness (QALY)	Incremental effectiveness (QALY)	Incremental C/E ratio
Universal vaccine	$1,647	—	3.8164	—	—
Adjuvanted vaccine	$1,723	$77	3.8190	0.0026	Ext Dom
High-dose trivalent vaccine	$1,729	$82	3.8192	0.0029	$28,719
Quadrivalent vaccine	$1,758	$29	3.8169	-0.0023	Dominated[a]
Trivalent vaccine	$1,796	$67	3.8159	-0.0034	Dominated[a]

Note. C/E = cost effectiveness; Ext Dom = extended dominance (strategy has a higher C/E ratio than a more effective strategy); QALY = quality-adjusted life-year.
[a]More costly and less effective than other strategies.

($221.10), with the high-dose vaccine strategy remaining favored at a $100,000 per quality-adjusted life-year threshold throughout. Individual variation of all other parameter values over the ranges listed in Table 1 did not result in the universal vaccination strategy being favored. For example, jointly varying influenza hospitalization cost parameters from the low to high ends of their ranges resulted in high-dose vaccine costing $27,893–$44,010/quality-adjusted life-year gained compared with universal vaccination. In general, parameter variations where the effects of influenza illness were worsened, in terms of greater suffering, disability, or utilization due to influenza, favored the more effective influenza prevention strategy (in the base case, high-dose vaccine) more strongly.

Figure 2 depicts a deterministic multiway sensitivity analysis, which plots the universal vaccine costs and uptake at which its use was favored at three levels of universal vaccine effectiveness. When universal vaccine effectiveness is 10 percentage points less than standard-dose trivalent vaccine effectiveness (i.e., 39% minus 10% = 29%), universal vaccine was cost saving only when universal vaccine uptake was high and its cost was relatively low (top left panel, Figure 2) and was never favored at a $100,000 per quality-adjusted life-year threshold (bottom left panel). When no effectiveness difference was assumed between universal vaccine and trivalent vaccine, cost savings with universal vaccine use were seen over larger ranges (top middle panel), but universal vaccination was not favored at a $100,000 per quality-adjusted life-year threshold unless uptake was >70% (bottom middle panel). If universal vaccine effectiveness was 10 percentage points more than trivalent vaccine

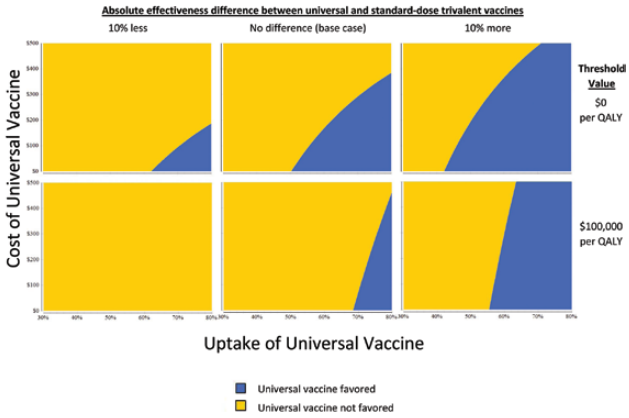

Figure 2. Sensitivity analysis of universal vaccine parameters. *Note.* Simultaneous variation of universal vaccine uptake and cost (*x*- and *y*-axes of individual panels), as well as universal vaccine effectiveness (columns of panels) for two cost-effectiveness threshold values (rows of panels). Shaded areas depict values where strategies are favored for each cost-effectiveness threshold. QALY = quality-adjusted life-year gained.

(right panels), comparable to the vaccine effectiveness of high-dose or adjuvanted vaccines, then larger ranges where universal vaccine was favored were seen under both thresholds. If universal vaccine effectiveness was increased to 75%, the NIH goal (Erbelding et al., 2018), universal vaccine was favored at a $100,000/quality-adjusted life-year threshold if its uptake was >40.5% and its cost was <$500 (not shown in the figure). When the universal vaccine was not favored, the favored seasonal influenza vaccine depended on the increase in relative effectiveness

(compared with standard-dose trivalent vaccine) of high-dose vaccine (base case 0.242) and the increase in relative effectiveness of adjuvanted vaccine (base case 0.226). At a $100,000/quality-adjusted life-year threshold, adjuvanted vaccine was favored over high-dose vaccine if adjuvanted vaccine relative effectiveness is >0.234; at $0/quality-adjusted life-year, adjuvanted vaccine was favored if its relative effectiveness was >0.216.

Probabilistic sensitivity analysis results are shown in Figures 3–5, with universal vaccine costs fixed at $50, $100, and $150, and universal vaccine effectiveness less than (Figure 3), greater than (Figure 4), or the same as (Figure 5) standard-dose trivalent vaccine. Universal vaccine effectiveness was varied ±10 percentage points in each analysis. In each of these figures, all other model parameter values, including universal vaccine uptake, are simultaneously varied over distributions, and the likelihood of strategies being considered cost-effective is approximated by the proportion of model iterations where strategies are favored at a given willingness-to-pay threshold value. When universal vaccine effectiveness is lower than the trivalent vaccine, it is less likely to be favored even at the low range cost, $50 (Figure 3), and even less likely to be favored when universal vaccine costs are higher at this level of effectiveness (not shown). If universal vaccine effectiveness is higher than trivalent vaccine, it is favored at the higher universal vaccine cost, $150 (Figure 4), and favored even more if its costs are lower (not shown). When universal vaccine effectiveness is the same as trivalent vaccine (Figure 5), universal vaccination becomes slightly less favorable as universal vaccine cost increases (in successive columns of Figure 5).

In a separate sensitivity analysis, we examined results when universal vaccine effectiveness duration was less than 5 years, finding that universal vaccination, under base case assumptions, was dominated (both more costly and less effective) by seasonal vaccination strategies if its effectiveness duration is less than 3 years. In scenarios depicted in Figure 2, areas favorable to universal vaccine grew progressively smaller as its effectiveness duration decreased. In another analysis, we allowed mixed use of universal vaccine and other seasonal vaccines, finding that varying relative likelihoods of universal vaccine use led to cost-effectiveness ratios comparable to those seen in the base case analysis.

Discussion and Implications

Development of a universal influenza vaccine is an NIH priority due to its great potential for multiyear protection and recent disappointments with diminished effectiveness of seasonal vaccines (Erbelding et al., 2018; Paules et al., 2018). In this analysis, we found that a universal vaccine, when used in adults aged 65 years or older, could be either cost saving or cost-effective (at a $100,000 per quality-adjusted life-year gained threshold) when universal vaccine effectiveness, uptake, and costs are within plausible ranges. However, if universal vaccine effectiveness is less

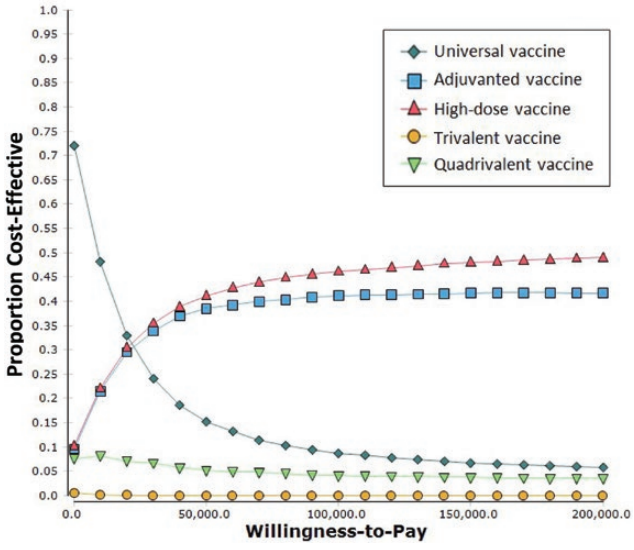

Figure 3. Probabilistic sensitivity analysis, less effective universal vaccine that costs $50. *Note.* Curves track the likelihood that strategies are favored (*y*-axis) over a range of willingness-to-pay quality-adjusted life-year thresholds (*x*-axis) when universal vaccine cost is fixed at $50, absolute universal vaccine effectiveness is 10% less (varied from 0% to 20% less) than trivalent standard-dose influenza vaccine, and all other model parameters are simultaneously varied over distributions. Universal vaccine was unlikely to be favored if willingness-to-pay thresholds are $30,000 per quality-adjusted life-year gained or more, and would be less likely to be favored if universal vaccine costs were $100 or $150 (not shown).

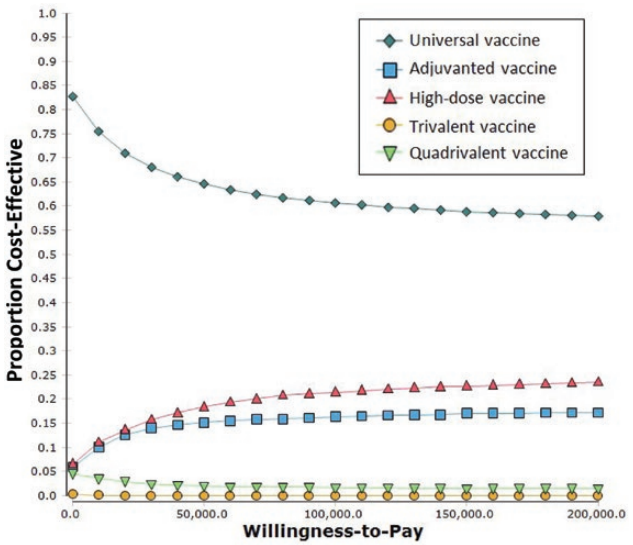

Figure 4. Probabilistic sensitivity analysis, more effective universal vaccine that costs $150. *Note.* Likelihood that strategies are favored (*y*-axis) over a range of willingness-to-pay thresholds (*x*-axis) when universal vaccine cost is fixed at $150, absolute universal vaccine effectiveness is 10% greater (varied from 0% to 20% more) than trivalent standard-dose influenza vaccine, and with simultaneous variation of all other model parameters. Universal vaccine was likely to be favored over the entire range of willingness-to-pay thresholds, and would be more likely to be favored if universal vaccine costs were $50 or $100 (not shown).

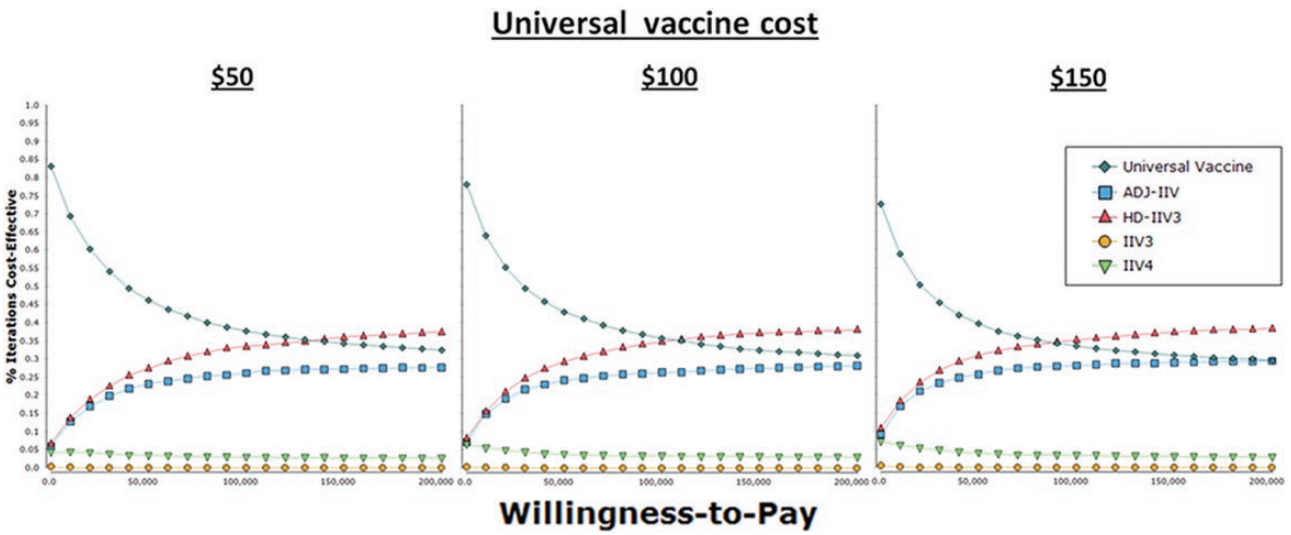

Figure 5. Probabilistic sensitivity analysis, equally effective universal vaccine. *Note.* Chart columns depict differing universal vaccine costs when universal vaccine effectiveness is assumed to be equal to trivalent standard dose vaccine (absolute effectiveness difference = 0%, varied from −10% to 10% difference). Individual charts show the likelihood that strategies are favored (*y*-axis) over a range of willingness-to-pay (or acceptability) thresholds per quality-adjusted life-year gained (*x*-axis) when all remaining model parameters are varied over distributions.

than that seen with the standard-dose trivalent vaccine, then universal vaccine use in U.S. seniors would likely not be favored from economic or public health standpoints, with high-dose or adjuvanted vaccines favored for this population instead. These findings suggest that universal vaccine effectiveness compared with available seasonal vaccines will be a crucial factor in vaccination policy decisions regarding future universal vaccine use in U.S. seniors.

Variation in influenza vaccine effectiveness and recent ineffectiveness has become a major impetus for universal vaccine development (Paules et al., 2018). If universal vaccines are more reliably effective on a season-to-season basis than seasonal vaccines, then their broad use in all populations could be justified. However, considerations of universal vaccine use in populations aged 65 years and older, compared with other age groups, are more complicated. High-dose and adjuvanted vaccines are licensed for use in older adults, and variability in their effectiveness is not as clearly delineated as that observed with standard-dose vaccines. In addition, seasonal influenza vaccine uptake in seniors is greater than that seen in younger adults, potentially diluting the multiyear and multiple strain protection advantages of a universal vaccine. However, if universal vaccine effectiveness is consistent and comparable to seasonal vaccines, the costs and convenience of a multiyear universal vaccine could be advantageous for influenza prevention in older population groups.

A prior analysis of potential universal vaccine use in pediatric age groups throughout their lifetimes found that universal vaccination could be cost-effective or cost-saving under some universal vaccine effectiveness, cost, and uptake scenarios (Lee et al., 2012). Our analysis, although limited to consideration of adults aged ≥65 years, generally agreed with those results. In both analyses, universal vaccine became less favorable if its cost was >$200 or its uptake was ≤50%. In the prior analysis, results with universal vaccine effectiveness of <50% were not reported. The prior analysis also considered the potential for 10 years of protection from universal influenza vaccination. Our analysis only considered a maximum of 5 years protection, due to doubts raised about the durability of protection beyond that point, due to the high immunogenicity of hemagglutinin from wild virus exposure that may overwhelm the response to a conserved epitope from a universal vaccine (Park et al., 2018). Thus, a 5-year effectiveness assumption may be overly optimistic.

We did not model mixed use of different seasonal vaccines as it currently occurs in older adults, a potential limitation. However, with observed increasing use of high-dose vaccine in older populations, this modeling choice should not materially affect results favoring high-dose vaccine use. Modeling of mixed use of universal and seasonal vaccines did not substantially affect results. Seasonal influenza vaccination in seniors has decreased effectiveness compared with vaccination in younger groups. Differential universal vaccine effectiveness by age is presumed but is, at present, uncertain. Our model did not account for potential indirect effects of vaccination in seniors, another limitation, which could affect estimates of cost-effectiveness and public health impact, with prior analyses tending to overestimate cost-effectiveness ratios compared with no vaccination strategies. It is not clear, when modeling competing vaccination strategies, how consideration of indirect effects might affect results. Another limitation of the analysis is the assumption that universal vaccine will equally prevent

all aspects of influenza (i.e., prevention of infection, severity of disease, speed of recovery), when such vaccines rely on conserved virus epitopes, which might be less protective against infection than conventional vaccines. Finally, this analysis may be limited by not considering behavioral aspects of influenza vaccination, such as potential differences in vaccination uptake between seasonal and universal vaccines due to differences in vaccine convenience, which could play a crucial role in this decision.

Universal influenza vaccines have proven challenging to develop, but several companies have candidate vaccines in development. Challenges also await in developing policies regarding universal vaccine use once it becomes available. Our analysis suggests that, in older adults, universal vaccine use could be clinically and economically reasonable if its effectiveness and uptake were comparable to or better than available seasonal vaccines and its effectiveness duration was 3 years or more. Vaccination policy decision making regarding universal vaccine use in geriatric populations will be complicated by their greater likelihood of seasonal vaccine uptake and the more potent vaccines available for this group.

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Conflict of Interest

Richard Zimmerman has no active research grants from industry but within 3 years had grants from Sanofi Pasteur, Pfizer Inc., and Merck & Co., Inc. Jonathan Raviotta has no active research grants from industry but within 3 years had grants from Pfizer, Inc. and Merck & Co., Inc. Mary Patricia Nowalk has grant funding from Merck & Co., Inc. on an unrelated topic and within 3 years had received grant funding from Pfizer, Inc. The remaining authors have no conflicts to disclose.

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