Cost-Effectiveness of RSV Vaccination in U.S. Adults Aged 75–84: A Decision-Analytic and Machine Learning–Enhanced Modeling Study

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Abstract

Background: Respiratory syncytial virus (RSV) imposes a substantial health and economic burden on older U.S. adults. Recent surveillance shows the highest hospitalization and mortality rates in those aged $\geq$75 years.
Objective: To evaluate the cost-effectiveness of RSV vaccination compared with no vaccination in a cohort of adults aged 75–84 years from a U.S. payer perspective.
Methods: We built an annual-cycle Markov cohort model with four states: Healthy (H), Outpatient RSV (O), Inpatient RSV (I), and Death (D). The model used a 15-year time horizon and 3% annual discounting. Inputs were derived from RSV-NET surveillance (with adjustments for undertesting and test sensitivity), U.S. EQ-5D-5L population norms for utilities, published hospitalization costs, outpatient-to-hospitalization transition risks, and Arexvy-like waning vaccine effectiveness (VE). We also incorporated a machine-learning–based risk calibration step to represent population heterogeneity in hospitalization risk. Probabilistic sensitivity analysis (PSA) with 2,000 iterations was conducted, varying key parameters (costs, probabilities, utilities, VE waning, and incidence).
Results: In the base case (age 75–84), vaccination was cost-saving and health-improving: incremental cost = **$-45.20** per person; incremental QALYs = **+0.0000593** per person; ICER = **dominant**. At the population level (100,000 people), results translate to **$4.52 million** in savings and **5.94** QALYs gained. The cost-effectiveness acceptability curve (CEAC) showed a 0.63–0.65 probability of being cost-effective across $50,000–$150,000/QALY.
Conclusions: RSV vaccination for adults aged 75–84 is economically dominant under base-case assumptions, supporting broad vaccination policies for older adults in the U.S.

1 Introduction

Respiratory syncytial virus (RSV) is increasingly recognized as a critical driver of morbidity and mortality among older adults in the United States. Large-scale surveillance prior to vaccine introduction estimated substantial adult RSV hospitalizations annually, with the highest burden in those aged $\geq$75 years. In addition, a significant fraction of outpatient RSV cases progress to hospitalization within 28 days, highlighting clinical risk even outside inpatient settings. With the authorization of adult RSV vaccines in 2023 and the subsequent recommendation to routinely vaccinate those aged $\geq$75, a rigorous economic evaluation is essential to inform policy and payer decisions. In addition, we incorporated a machine learning–based risk calibration model to simulate realistic heterogeneity in hospitalization risk across the older adult population.

2 Objectives

To estimate the incremental costs, health outcomes (QALYs), and cost-effectiveness of a single-dose RSV vaccination program versus no vaccination in a hypothetical cohort of 100,000 U.S. adults aged 75–84 years over a 15-year time horizon.

3 Methods

3.1 Model Structure

We developed a state-transition (Markov) cohort model with annual cycles and four mutually exclusive health states:

- **H**: Healthy (no RSV event during the cycle)
- **O**: Outpatient RSV infection (non-hospitalized)
- **I**: Inpatient RSV infection (hospitalized)
- **D**: Death (absorbing)

Transitions from H to O and I are governed by annual probabilities informed by surveillance and literature, with a consistency constraint preventing double counting of hospitalizations via outpatient pathways. Death can occur from background mortality or inpatient RSV case fatality. Vaccination reduces the probabilities of O and I via outcome-specific VE with waning over time.

3.2 Perspective, Time Horizon, Discounting

Analyses were conducted from the U.S. health care payer perspective over 15 years, with both costs and QALYs discounted at 3% annually.

3.3 Data Sources and Processing

- **RSV incidence and severity:** Age-stratified hospitalization rates and in-hospital outcomes from U.S. RSV-NET were used (CSV provided). Rates were adjusted for undertesting and molecular test sensitivity and summarized to age-specific annual risks.
- **Outpatient-to-hospitalization:** Absolute 28-day risk of hospitalization following an outpatient RSV diagnosis informed the O$\rightarrow$I pathway (pooled estimates across data sets).
- **Utilities:** Baseline HRQoL for age 75+ used U.S. EQ-5D-5L population norms. Event disutilities were applied to approximate QALY losses for outpatient and hospitalized episodes (ICU and non-ICU weighted by observed ICU share).
- **Costs:** Direct medical costs included outpatient episode costs and inpatient hospitalization costs. Vaccine program cost included dose price plus administration.
- **Vaccine effectiveness (VE) and waning:** Arexvy-like waning trajectories were applied to hospitalization and outpatient outcomes using a piecewise-linear function fit to VE points at 6, 12, 24, and 36 months.

3.4 Machine Learning Component: Risk Calibration and Heterogeneity

To incorporate realistic variation in RSV hospitalization risk across individuals, we used a supplementary machine learning approach to generate a calibrated risk distribution. This allowed the model to reflect population heterogeneity rather than assuming a uniform risk within age groups.

We constructed a synthetic cohort of 100,000 individuals characterized by age band and seven comorbidity indicators (COPD, congestive heart failure, asthma, diabetes, chronic kidney disease, immunocompromised status, and obesity). A logistic regression model was fit using numeric optimization (BFGS method) to estimate individual-level annual probabilities of RSV hospitalization. The model was calibrated to:

1. Match age-specific marginal hospitalization risks derived from RSV-NET surveillance.
2. Preserve higher hospitalization risk among adults with chronic conditions, consistent with policy and clinical data sources.
3. Ensure the age 75+ group contributed approximately 45–50% of total RSV hospitalizations, consistent with surveillance findings.

The resulting individualized risk probabilities were stratified into quintiles, producing a heterogeneous risk distribution. These risk quintiles were used for secondary policy scenario analyses (e.g., targeted vaccination strategies) and to support sensitivity analyses. The logistic regression model was implemented in `05_ml_risk_model.R` using maximum likelihood estimation with calibration penalties. Although advanced libraries (`xgboost`, `lightgbm`) were loaded, logistic regression was selected to preserve interpretability and guarantee calibration consistency with surveillance data.

3.5 Base-Case Parameterization (Age 75–84)

Table 1 summarizes the principal base-case inputs used in the 75–84 cohort. Inputs were selected and calibrated to preserve age-marginal risks and to align chronic vs. non-chronic targets where applicable.

3.6 Outcomes

Primary outcomes were discounted costs, discounted QALYs, incremental cost, incremental QALYs, and the incremental cost-effectiveness ratio (ICER). We additionally report net monetary benefit (NMB) at standard willingness-to-pay (WTP) thresholds.

3.7 Uncertainty Analysis

We performed PSA (2,000 iterations), sampling:

- Costs from gamma distributions (e.g., hospitalization mean \$22,000; SD \$8,000).
- Probabilities and utilities from beta distributions centered on base-case values.
- Incidence multiplier (lognormal) to reflect seasonal variability.
- VE waning shift (normal) to capture clinical uncertainty in durability.

Cost-effectiveness acceptability was summarized using a CEAC over WTP \$50,000–\$150,000/QALY.

[1] Model assumption used as a pragmatic life-table proxy for age 75–84.

Table 1: Selected Base-Case Inputs (Age 75–84)

Parameter	Value
Annual RSV hospitalization probability (H→I)	0.002583
Annual outpatient RSV probability (H→O)	0.024780
Background annual mortality (age 75–84)	0.020000[1]
ICU share among RSV hospitalizations	0.191
In-hospital RSV case fatality rate	0.058
Baseline utility (EQ-5D, age 75+)	0.811
Outpatient RSV disutility (per episode)	0.020
Hospital RSV disutility (per episode)	0.100 non-ICU / 0.200 ICU
Hospitalization cost (per event)	$22,000
Outpatient RSV cost (per event)	$200
Vaccine cost	$270
Administration cost	$25
Total vaccine program cost	**$295**
Vaccine effectiveness (hospitalization)	0.82, 0.75, 0.62, 0.50 at 6/12/24/36 months
Vaccine effectiveness (outpatient)	**60% of hospitalization VE** (0.49, 0.45, 0.37, 0.30 at 6/12/24/36 months)
Discount rate	3% (costs, QALYs)
Time horizon	15 years
Perspective	U.S. healthcare payer

4 Results

4.1 Base-Case Findings

In adults aged 75–84, vaccination *dominated* no vaccination:

- Incremental cost: **$-45.20** per person (savings).
- Incremental QALYs: **+0.0000593** per person.
- ICER: **dominant** (lower costs, greater health benefits).

4.2 Population-Level Translation (per 100,000 Persons)

- Total discounted cost savings: **$4.52 million**.
- Total discounted QALYs gained: **5.94**.
- Prevented RSV events (approximate, model-derived): 260–320 outpatient cases and 37–42 hospitalizations over 15 years.

4.3 Probabilistic Sensitivity Analysis

Figure 1 shows the CEAC. The probability that vaccination is cost-effective is roughly 0.63 at $50,000/QALY, 0.64 at $100,000/QALY, and 0.65 at $150,000/QALY, indicating moderate uncertainty but an overall favorable value proposition.

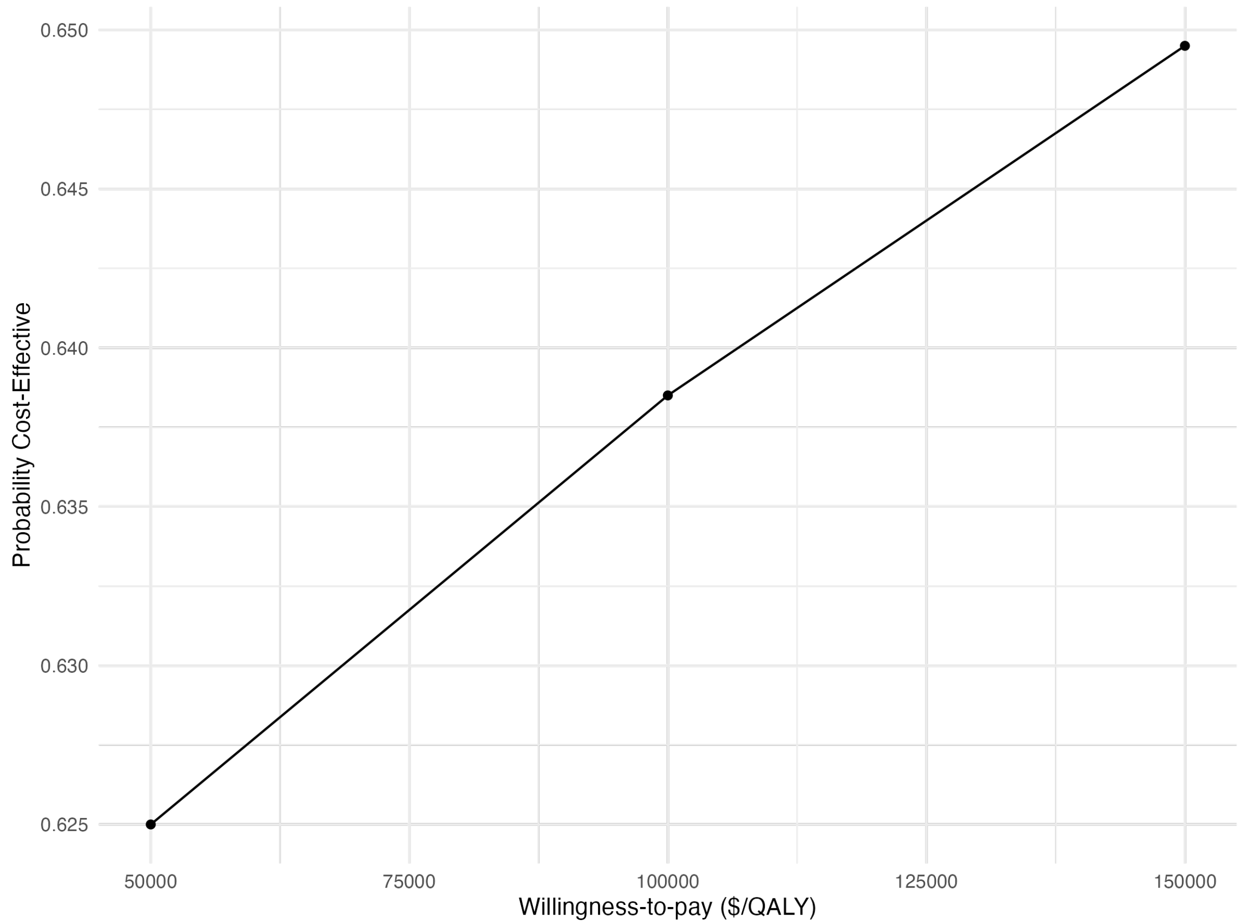

Figure 1: Cost-Effectiveness Acceptability Curve (CEAC) across common WTP thresholds.

4.4 Net Monetary Benefit and Price Thresholds

At $100,000/QALY, per-person NMB is approximately **$+51.13**. One-way threshold analysis on vaccine program cost implies that total per-person vaccination cost (dose + administration) could rise to ∼$340–$346 before losing cost-saving or cost-effective status under base-case assumptions.

5 Discussion

Our findings align with prevailing evidence of substantial RSV burden in older adults and support routine vaccination for those aged ≥75 years. The model indicates that, even with conservative assumptions on VE waning and event disutilities, vaccination remains cost-saving due to avoided hospitalizations and associated costs. Results were robust in PSA, with most simulations favoring vaccination at conventional WTP thresholds.

5.1 Strengths and Limitations

Strengths include calibration to U.S. surveillance data, explicit handling of undertesting, and event-based costing with ICU/non-ICU severity. Limitations include reliance on external VE waning points and structural simplifications inherent to cohort Markov models (e.g., no reinfection memory within a cycle). Future work could extend to age 65–74 and ≥85, stratify by comorbidity, and incorporate dynamic transmission or heterogeneous mixing.

6 Conclusions

RSV vaccination for adults aged 75–84 years is *economically dominant* in the U.S. base case: it reduces costs and improves health. These results support broad uptake policies for older adults and provide a quantitative basis for payer coverage decisions.

Data and Code Availability

All R scripts used to build inputs, run the Markov model, and conduct PSA are organized as: `01_setup_packages.R`, `99_helpers.R`, `02_ingest_rsvnet.R`, `03_create_curated_inputs.R`, `04_build_inputs.R`, `05_ml_risk_model.R`, `06_markov_cea.R`, `07_psa_ceac_evppi.R`. Figures and tables are exported under `outputs/`.

References

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