

Relative effectiveness of cell-cultured versus egg-based influenza vaccines, 2017-18

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Disclaimer

The findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of FDA, CMS, ACUMEN or any other organization

Background

A CDC-sponsored interim analysis of the A(H3N2)-dominated 2017-18 influenza season showed a low (18%) vaccine effectiveness (VE) among individuals ages ≥ 65 years in the U.S.

One hypothesis is that egg-adaptation led to lower VE during 2017-18, so we studied the relative effectiveness of inactivated influenza vaccines prepared in mammalian cells (cell-cultured) versus embryonated chicken eggs (egg-based) among Medicare beneficiaries ages ≥ 65 years

Methods

OBSERVATION PERIOD

August 6, 2017 to April 20, 2018

EXPOSURES

Cell-cultured quadrivalent
Egg-based quadrivalent
Egg-based high-dose trivalent
Egg-based adjuvanted
Egg-based standard-dose trivalent

POPULATION

Medicare Fee-for-service beneficiaries who received the cell-cultured or any of four egg-based influenza vaccinations

OUTCOMES

Primary: Influenza hospital encounters (inpatient + ER)
Secondary: Office Visit (RIT + antiviral)
Post-hoc: Inpatient only
All during high circulation periods

Selection Process for Beneficiaries Included in the Study

Base Population: Beneficiaries who received an influenza vaccination within the specified time period for the season



Beneficiaries at least 65 years of age with continuous Medicare Part A/B enrollment for the 6 months prior to their vaccination date



Beneficiaries who received only one influenza vaccine type on index day, were not in a nursing home facility on vaccination day, and did not receive any influenza vaccine prior to index date in the season



Beneficiaries residing in one of the ten HHS regions

Final Study Populations

Cell-Cultured Quadrivalent (ccIIV4):	N= 653,099
Egg-Based Quadrivalent (IIV4):	N= 1,844,745
Egg-Based High-Dose Trivalent (IIV3-HD):	N= 8,449,508
Egg-Based Adjuvanted (aIIV3):	N= 1,465,747
Egg-Based Standard-Dose Trivalent (IIV3):	N= 1,007,082

Covariate Balance

We used standardized mean differences (SMDs) to determine cohort balance for 62 covariates

Approximately half of the 62 demographics and health utilization covariates were initially imbalanced

Stabilized inverse probability of treatment weighting (IPTW) was used to address imbalance in all measured covariates

Following IPTW, cohort balance was achieved with SMDs <0.05 for all covariates

Selected (Imbalanced) Covariates

Covariates	ccIIV4	IIV4	IIV3-HD	aIIV3	IIV3	<i>Pre-Weight Max SMD</i>	<i>Post-Weight Max SMD</i>
Vaccinated at Pharmacy	19.2%	9.2%	44.4%	67.5%	11.7%	1.39	0.03
Dual Eligible	13.3%	11.3%	6.9%	6.8%	16.3%	0.22	0.05
Month of Vaccination: August & September	27.4%	26.1%	33.6%	30.9%	22.6%	0.25	0.03
No Prior Outpatient Non-ER Visits	43.5%	32.2%	36.9%	40.4%	37.5%	0.14	0.02

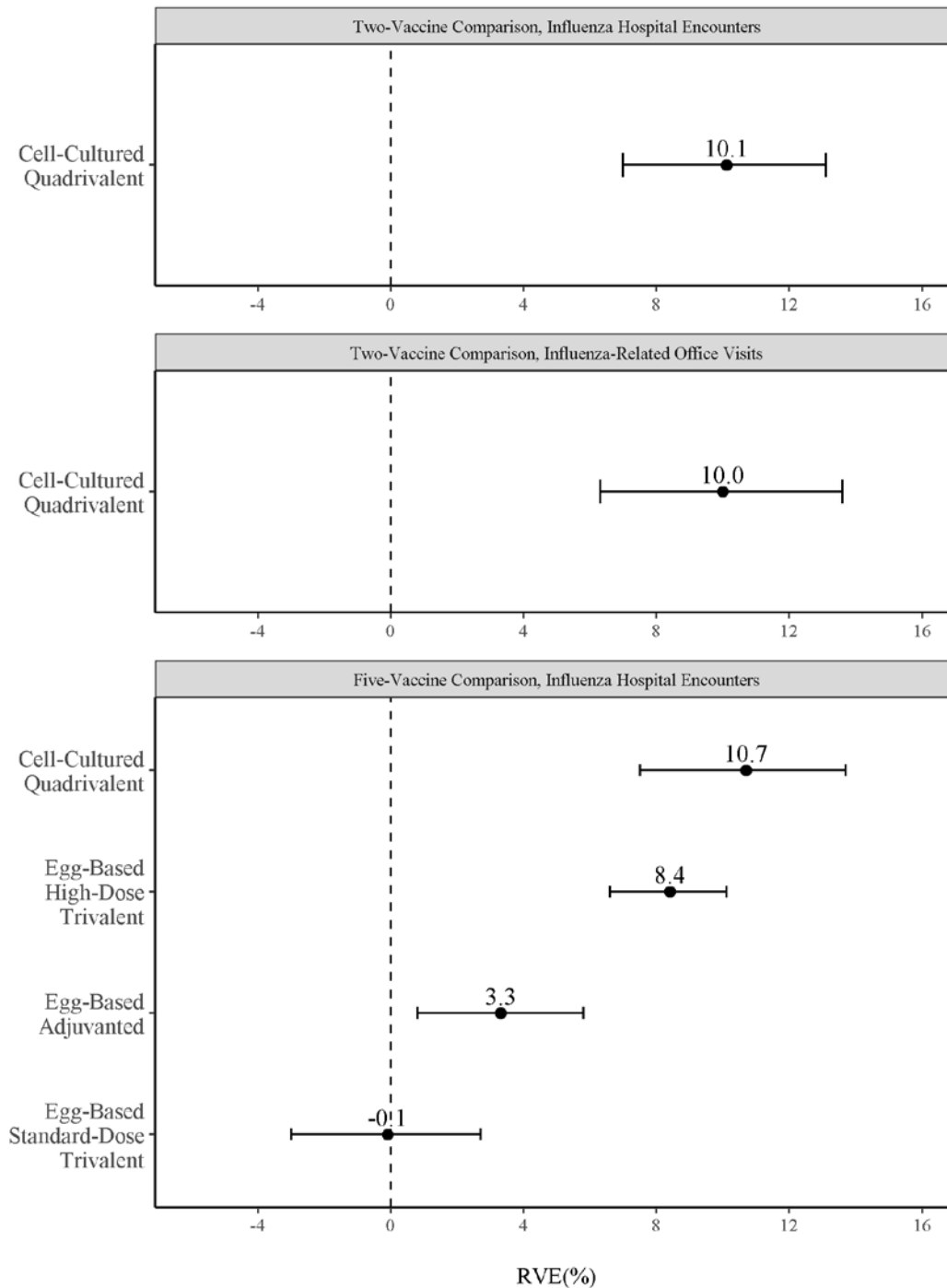
Addressing Potential Sources of Bias

- Used IPTW to address imbalance in all measured covariates
- IPTW did not necessarily address imbalance for unmeasured potential confounders, an issue often found when real world data are used
- IPTW adjusted relative vaccine effectiveness (RVE) was obtained using univariate Poisson regression



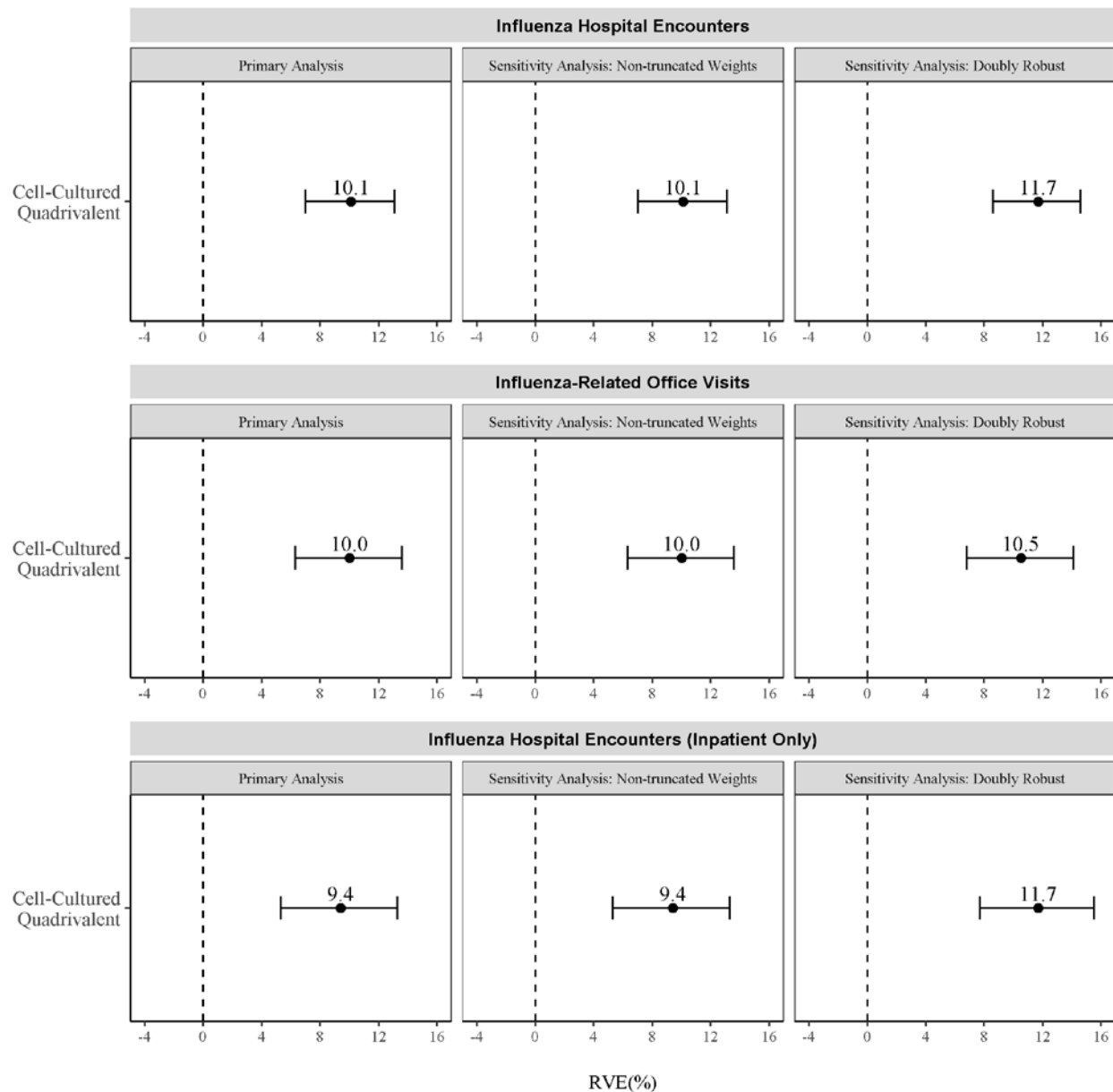
**IPTW
Adjusted
Poisson
Regression
RVE:
Two and Five-
Vaccine
Comparisons

(Egg-Based
Quadrivalent
Vaccine
Cohort as
Reference)**

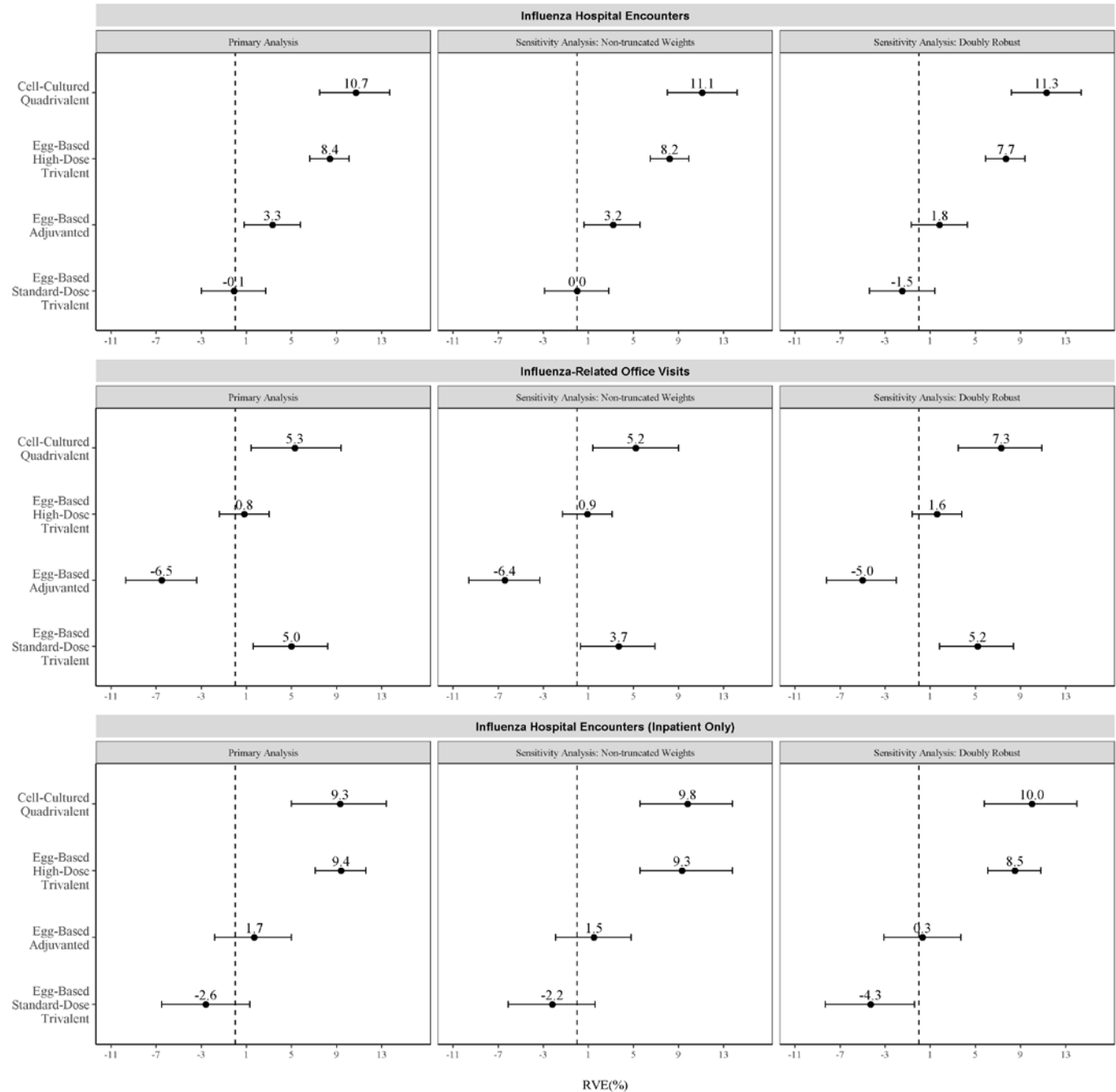


IPTW
Adjusted RVE:
Two-Vaccine
Comparison
Sensitivity
Analysis

(Egg-Based
Quadrivalent
Vaccine
Cohort as
Reference)



IPTW Adjusted RVE: Five-Vaccine Comparison, Sensitivity Analysis (Egg-Based Quadrivalent Vaccine Cohort as Reference)



Strengths

- These real world data include nearly all of the actual vaccine recipients ages 65+ nationally
- Data reflect the exposure and outcome experiences during routine clinical practice
- Unlike clinical trials, Medicare beneficiaries have a wider range of health conditions
- Large dataset provides power to detect small but clinically relevant differences and analyze rare serious outcomes

Limitations

- Real world data “are not collected or organized with the goal of supporting research, nor have they typically been optimized for such purposes”[†]
- Potential exposure and outcome misclassification
- Potential unmeasured confounding even after adjusting for measured covariates
- Influenza-related office visit results were inconsistent
- No virologic case confirmation, and can not differentiate between A(H3N2), A(H1N1), or B infections
- Processing delay for exposure and outcome codes

[†]N Engl J Med 2016; 375:2293-2297 DOI: 10.1056/NEJMs1609216

Summary 1

- In this analysis, the cell-cultured and high-dose vaccines were marginally more effective than the egg-based quadrivalent vaccines for hospital outcomes among U.S. people 65+ years during the 2017-18 season
 - Cell-cultured vaccines were 10.7% (95% CI 7.5, 13.7) more effective
 - High-dose vaccines were 8.4% (95% CI 6.6, 10.1) more effective

- These findings contribute to a growing evidence base about new and enhanced vaccines compared to traditional vaccines
 - This is the first comparison of several new and enhanced vaccines to both egg-based traditional vaccines and to each other
 - We will continue to monitor RVE for additional seasons

Summary 2

- Findings from this single observational study should be considered as part of the entire body of evidence
- While cell-cultured and high-dose influenza vaccines appear to offer some additional benefit to older adults, further efforts are needed to improve influenza vaccine effectiveness
- RVE could vary from season to season, data from more seasons are needed
- The results from similar studies conducted in different settings or health systems would provide important context for our results
- We continue to investigate ways to minimize and quantify potential sources of bias in real world evidence studies

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