Optimal Strategies to Estimate the Relative Effectiveness of Influenza Vaccines (SERVE)

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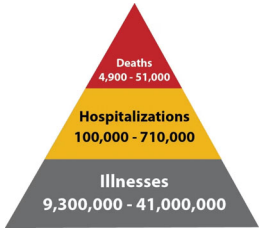
Background

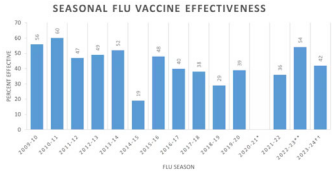
- Influenza virus infection causes hundreds of thousands of hospitalizations and tens of thousands of deaths in the United States each year (Figure 1).
- Influenza vaccines are the best available tool for preventing influenza.
- Influenza vaccine effectiveness typically ranges from 40% to 60% when circulating viruses are well matched to the vaccine, but can be far lower when not well matched (Figure 2).
- There are 9 influenza vaccines licensed for use in the United States for 2024-2025 (Table 1).
- High Dose, Adjuvanted, or Recombinant vaccines are preferentially recommended for adults ≥65 years.
- Comparative effectiveness data are very limited, and there are several new vaccines on the horizon.

Figure 1. Annual Influenza Burden in the United States.



https://www.cdc.gov/flu/about/burden/index.html

Figure 2. Annual Influenza Vaccine Effectiveness.



https://www.cdc.gov/flu/vaccines-work/effectiveness-studies.htm

Table 1. Influenza Vaccine Products Licensed for the 2024-2025 Influenza Season.

Manufacturer	Trade Name (Abbreviation)	How Supplied	Age Range	Technology
AstraZeneca	FluMist (LAIV)	0.2 mL (single-use nasal spray)	2 – 49 years	Egg-grown, live-attenuated virus
GSK	Fluarix (IIV)	0.5 mL (single-dose syringe)	≥6 months	Egg-grown, inactivated virus
	Fluarix (IIV)	0.5 mL (single-dose syringe)	≥6 months	Egg-grown, inactivated virus
Sanofi	Flublok (RIV)	0.5 mL (single-dose syringe)	≥18 years	Recombinant
	Fluzone (IIV)	0.5 mL (single-dose syringe)	≥6 months	Egg-grown, inactivated virus
		0.5 mL (single-dose vial)	≥6 months	Egg-grown, inactivated virus
		5.0 mL multi-dose vial (0.25 mL dose)	6 – 35 months	Egg-grown, inactivated virus
		5.0 mL multi-dose vial (0.5 mL dose)	≥6 months	Egg-grown, inactivated virus
	Fluzone High-Dose (hdIIV)	0.5 mL (single-dose syringe)	≥65 years	Egg-grown, inactivated virus
CSL Seqirus	Afluria (IIV)	5.0 mL multi-dose vial (0.25 mL dose)	6 – 35 months	Egg-grown, inactivated virus
		5.0 mL multi-dose vial (0.5 mL dose)	≥3 years	Egg-grown, inactivated virus
		0.5 mL (single-dose syringe)	≥3 years	Egg-grown, inactivated virus
	Fluad (aIIV)	0.5 mL (single-dose syringe)	≥65 years	Adjuvanted, egg-grown, inactivated virus
	Flucelvax (ccIIV)	0.5 mL (single-dose syringe)	≥6 months	Cell-grown, inactivated virus
		5.0 mL multi-dose vial (0.5 mL dose)	≥6 months	Cell-grown, inactivated virus

Adapted from: https://www.immunize.org/wp-content/uploads/catg.d/p4072.pdf

Objectives

The overall aim of this study is to develop strategies for estimating the relative effectiveness (rVE) of influenza vaccines by completing the following objectives:

- Identify challenges and propose solutions for timely and efficient estimation of the rVE of influenza vaccines.
- Develop a protocol for estimating the rVE of licensed influenza vaccines in preventing medically-attended influenza using electronic health records (EHR).
- Prepare a strategy to rapidly estimate the real-world rVE of novel influenza vaccines as compared to other, currently licensed influenza vaccines.

Methods

Multiple Sources of EHR Data will be Evaluated across Multiple GPC Sites

Criteria for participating sites:
- Individual-level EHR data with sufficient sample size.
- Data from 2021-2022 influenza season or more recent.
- Required data elements: influenza vaccination, influenza testing, healthcare encounters, demographics.

Table 2. Analytic Study Designs.

	Retrospective Cohort	Retrospective Test-Negative Design
Population	Medically-homed individuals receiving influenza vaccine product A or B in study period.	Medically-homed individuals receiving influenza vaccine product A or B AND tested for influenza in study period.
Outcome	Primary Analysis: Influenza diagnosis (ICD-10) Secondary Analysis: Laboratory-confirmed influenza	Case: Influenza test positive Control: Influenza test negative
Exposure	Age 18 to 64: RIV vs IIV & ccIIV vs IIV Age ≥65: hdIIV vs aIIV	Age 18 to 64: RIV vs IIV & ccIIV vs IIV Age ≥65: hdIIV vs aIIV
Analysis	Cox-proportional hazards models	Logistic regression models

Control of Confounding and Bias Assessment

- Doubly-robust estimation, combining outcome regression with propensity score weighting
- Negative Control Outcomes
  - Urinary Tract Infection; Non-Influenza Respiratory Virus; Acute Gastroenteritis; Cellulitis
- Negative Control Exposures
  - Tdap Vaccination; COVID-19 vaccination
- Quantitative Bias Analyses

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