THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

Durability of Covid-19 Vaccines

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Outline

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The Journal of Infectious Diseases

PERSPECTIVE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

Reliably Assessing Duration of Protection for Coronavirus Disease 2019 Vaccines

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Decision making about vaccination and boosting schedules for coronavirus disease 2019 (COVID-19) hinges on reliable methods for evaluating the longevity of vaccine protection. We show that modeling of protection as a piecewise linear function of time since vaccination for the log hazard ratio of the vaccine effect provides more reliable estimates of vaccine effectiveness at the end of an observation period and also detects plateaus in protective effectiveness more reliably than the standard method of estimating a constant vaccine effect over each time period. This approach will be useful for analyzing data pertaining to COVID-19 vaccines and other vaccines for which rapid and reliable understanding of vaccine effectiveness over time is desired.

Keywords. booster vaccination; clinical trials; Cox model; hazard ratio; observational studies; vaccine efficacy; vaccine effectiveness; waning effects.

Existing Methods

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Table 1: Vaccine Efficacy (VE) against COVID-19 in Phase 3 Trials

Vaccine	Time since full vaccination	VE_{Const} (95% CI)
Pfizer[1]	7 days – 2 months	96.2% (93.3%, 98.1%)
	2 months – 4 months	90.1% (86.6%, 92.9%)
	4 months – 6 months	83.7% (74.7%, 89.9%)
Moderna[2]	14 days – 2 months	94.1% (89.3%, 96.8%)
	14 days – 6 months	93.2% (91.0%, 94.8%)

Note: VE_{Const} estimates are obtained under the standard Cox or Poisson model, assuming a constant hazard ratio over each time period.

[1] *Thomas et al., NEJM, 2021*

[2] *Sahly et al., NEJM, 2021*

Existing Methods

- Weighted average of the time-varying VE over the time period
- Time points with more cases receive greater weights
- Limitations
  - tends to be higher than the true VE at the end of the time period
  - vulnerable to changes in disease incidence over calendar time
  - not precise when the time period is short
  - not informative when the time period is long

Proposed Methods

- Notation
  - S: calendar time of vaccination
  - T: calendar time of disease occurrence
  - X: baseline risk factors (e.g., age, occupation, health conditions)
- New Cox model

$$\lambda(t|S,X) = \lambda_0(t)\exp\left\{\beta^{\mathsf{T}}X + \eta(t-S)I(S<t)\right\} \tag{1}$$

  - $\lambda_0(\cdot)$: baseline hazard function
  - β: log hazard ratios for baseline risk factors
  - $\eta(\cdot)$: log hazard ratio for vaccination
  - $I(\cdot)$: indicator function
- Two time indexes
  - baseline hazard function depends on calendar time
  - vaccine effect depends on time elapsed since vaccination
- $\mathrm{VE}_{\mathrm{HR}}(t) = 1 - e^{\eta(t)}$

Proposed Methods

- Advantages
  - VE_{HR} measures the vaccine effect on the current risk and thus is more sensitive to the level of waning
  - adjust for changes in disease incidence over calendar time
  - allow us to compare disease incidence between the vaccinated and unvaccinated groups at the same calendar time
- Parameterization
  - B-splines for $\eta(\cdot)$: continuous piecewise linear

$$\eta(t) = \sum_{\ell=0}^{L} \gamma_\ell B_\ell(t) = \gamma_0 t + \gamma_1 (t - t_1)_+ + \cdots + \gamma_L (t - t_L)_+$$

  - Write $\gamma = (\gamma_0, \ldots, \gamma_L)^\mathsf{T}$ and $Z(t) = (B_0(t - S), \ldots, B_L(t - S))^\mathsf{T} I(S < t)$
  - (1) becomes

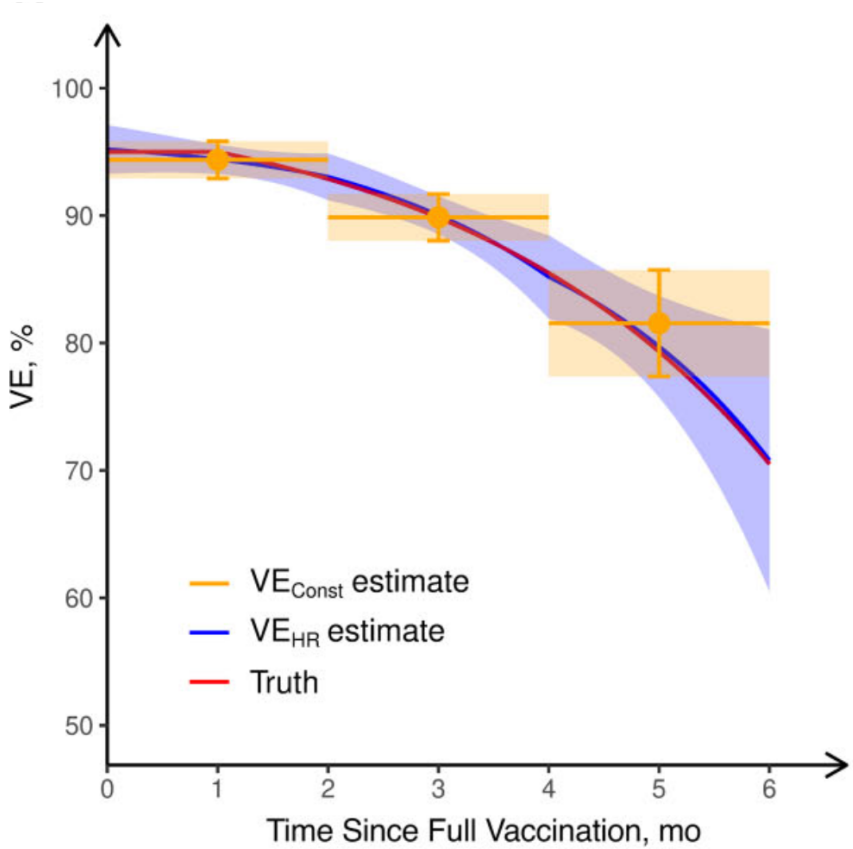
$$\lambda(t|S, X) = \lambda_0(t) \exp\left\{\beta^\mathsf{T} X + \gamma^\mathsf{T} Z(t)\right\}$$

Simulation Results

VE_{Const}: over 0–2, 2–4, and 4–6 months after full vaccination

VE_{HR}: change points placed at 0, 2, and 4 months after full vaccination

Truth: decreases from a peak of 95% that lasts 1 month to 70% at 6 months after full vaccination.



ORIGINAL ARTICLE

Effectiveness of Covid-19 Vaccines over a 9-Month Period in North Carolina

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ABSTRACT

BACKGROUND

The duration of protection afforded by coronavirus disease 2019 (Covid-19) vaccines in the United States is unclear. Whether the increase in postvaccination infections during the summer of 2021 was caused by declining immunity over time, the emergence of the B.1.617.2 (delta) variant, or both is unknown.

METHODS

We extracted data regarding Covid-19–related vaccination and outcomes during a 9-month period (December 11, 2020, to September 8, 2021) for approximately 10.6 million North Carolina residents by linking data from the North Carolina Covid-19 Surveillance System and the Covid-19 Vaccine Management System. We used a Cox regression model to estimate the effectiveness of the BNT162b2 (Pfizer–BioNTech), mRNA-1273 (Moderna), and Ad26.COV2.S (Johnson & Johnson–Janssen) vaccines in reducing the current risks of Covid-19, hospitalization, and death, as a function of time elapsed since vaccination.

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Data Sources

North Carolina COVID-19 Surveillance System: person-level information about Covid-19 and clinical outcomes (hospitalization, death)

COVID-19 Vaccine Management System: person-level vaccination histories

Population Census: 2020 Bridged-Race Population estimates

Study Period: December 11, 2020 – September 8, 2021

Statistical Methods

- Notation
  - S: calendar time of vaccination
  - T: calendar time of clinical outcome of interest
  - V: vaccine type (1/2-dose Pfizer, 1/2-dose Moderna, Janssen)
  - X: demographic variables (age, sex, race/ethnicity, geographic regions, county-level vaccination rate)
- Revised Cox model

$$\lambda(t|S,V,X) = \lambda_0(t)\exp\left\{\beta^{\mathsf{T}}X + \sum_{k=1}^{5}\eta_k(t-S)A_k(t)\right\}$$

  - $\lambda_0(\cdot)$: baseline hazard function
  - β: log hazard ratios for confounders
  - $\eta_k(\cdot)$: log hazard ratio for the k-th vaccine type
  - $A_k(t) = I(S < t, V = k)$
  - baseline hazard function depends on calendar time
  - vaccine effect depends on time elapsed since vaccination

Statistical Methods

- $\mathrm{VE}_k(t) = 1 - e^{\eta_k(t)}$, $k = 1, \ldots, 5$
- Parameterization
  - piecewise linear approximation for $\eta_k(\cdot)$
  - change points at every month
  - constrain the first spline parameter to be the same between 1-dose and 2-dose regimens for mRNA vaccine

Statistical Methods

- The partial likelihood takes the form

$$L(\beta, \gamma) = \prod_{i=1}^{n} \left\{ \frac{e^{\beta^{\mathsf{T}} X_i + \gamma^{\mathsf{T}} Z_i(\widetilde{T}_i)}}{S^{(0)}(\beta, \gamma; \widetilde{T}_i)} \right\}^{\Delta_i},$$

  where $S^{(0)}(\beta, \gamma; t) = \sum_{j=1}^{n} I(\widetilde{T}_j \geqslant t) \exp\{\beta^{\mathsf{T}} X_j + \gamma^{\mathsf{T}} Z_j(t)\}$
- individual-level information is not available for those who have neither been vaccinated nor developed COVID-19
- Divide these individuals into G strata according to X
- n_g individuals in the gth stratum, each has $X = X_g$
- $\tilde{n}$ individuals with individual-level information
- $S^{(0)}(\beta, \gamma; t) = \sum_{j=1}^{\tilde{n}} I(\widetilde{T}_j \geqslant t) \exp\{\beta^{\mathsf{T}} X_j + \gamma^{\mathsf{T}} Z_j(t)\} + \sum_{g=1}^{G} n_g \exp\{\beta^{\mathsf{T}} X_g\}$

Results

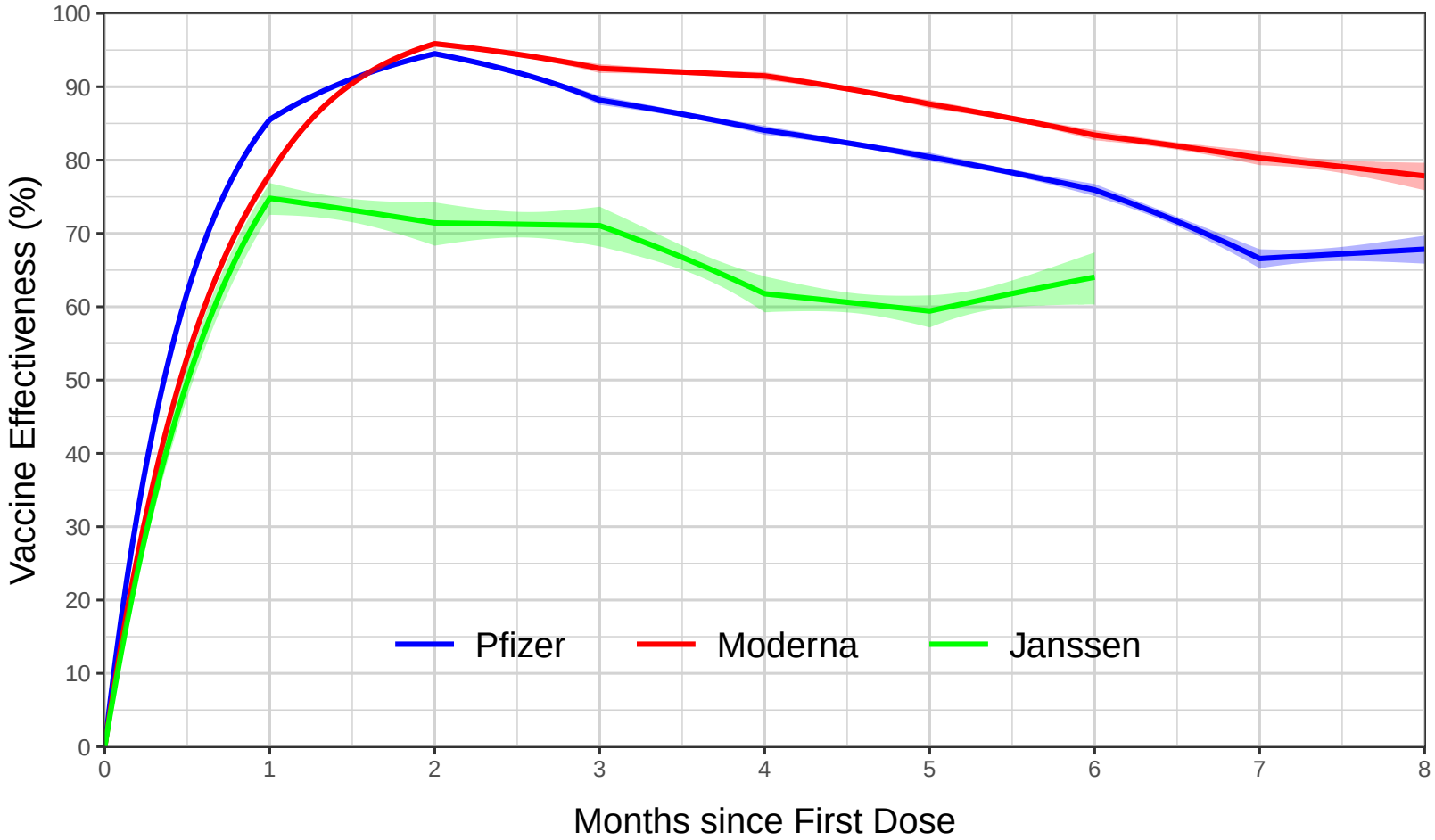

Figure 1: VE against COVID-19

Results

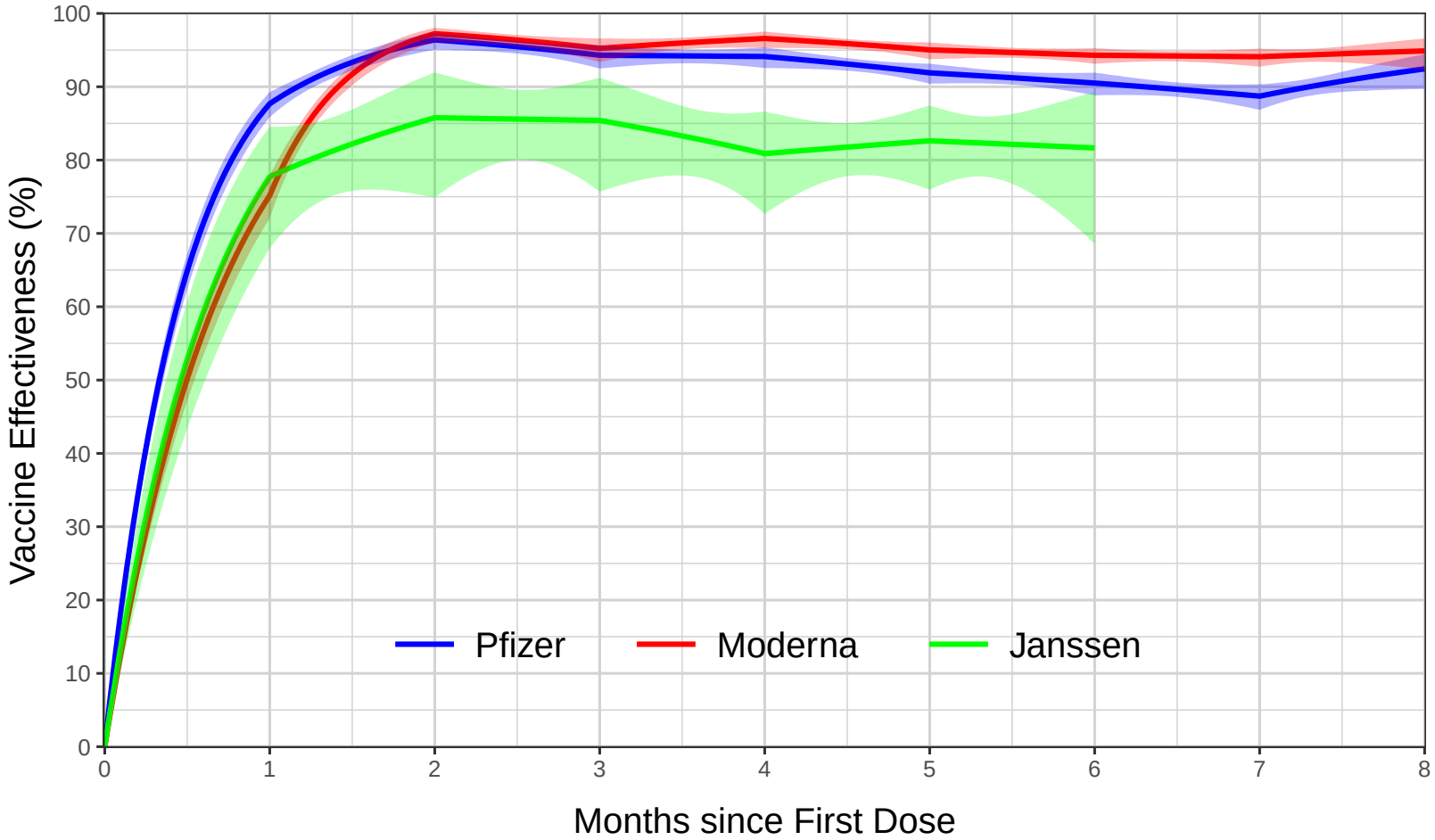

Figure 2: VE against Hospitalization

Results

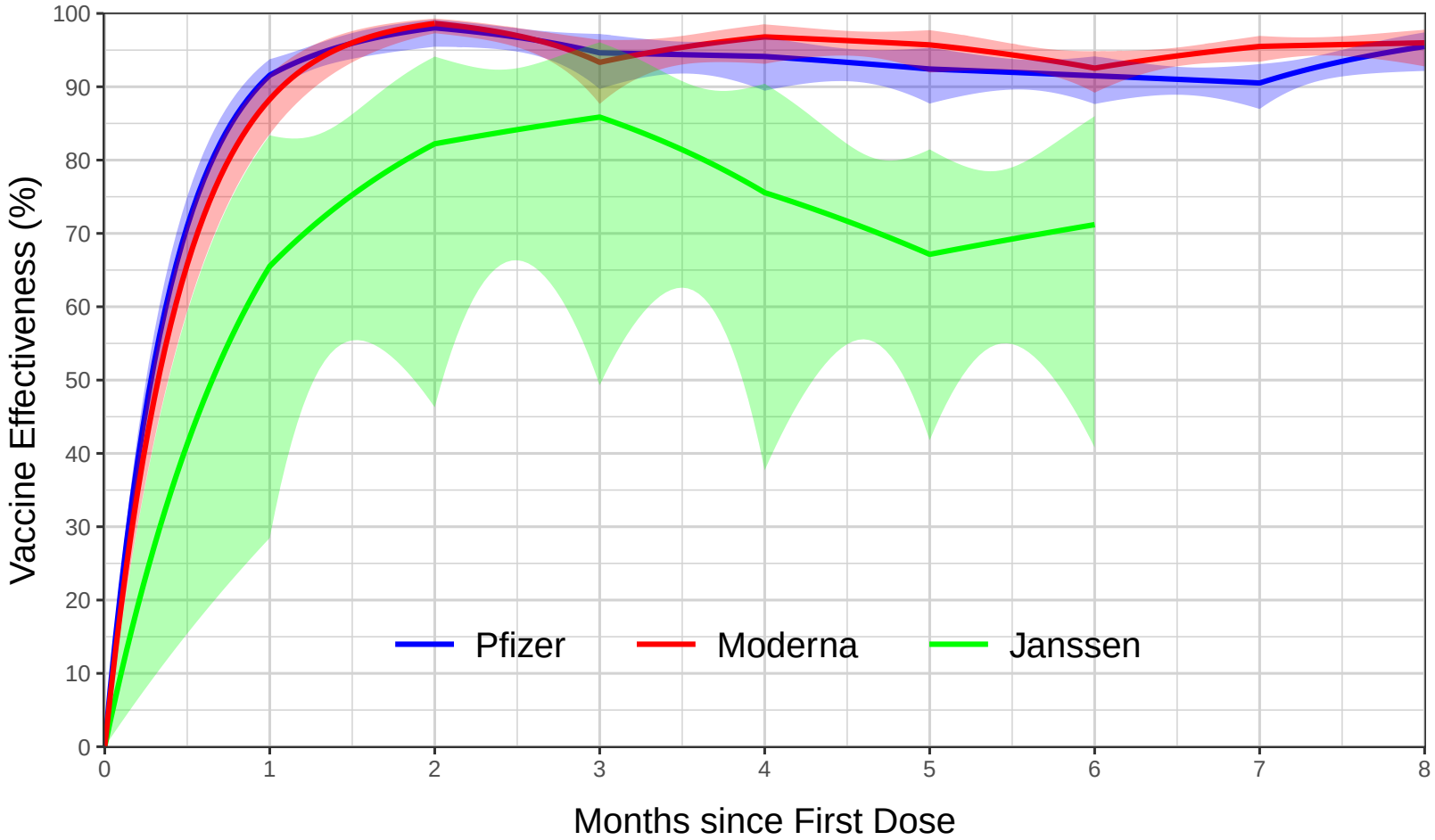

Figure 3: VE against Death

Implications

- Vaccines are durably effective against hospitalization and death
- Booster shots should be given earlier for Janssen and Pfizer recipients

Subgroup Analysis

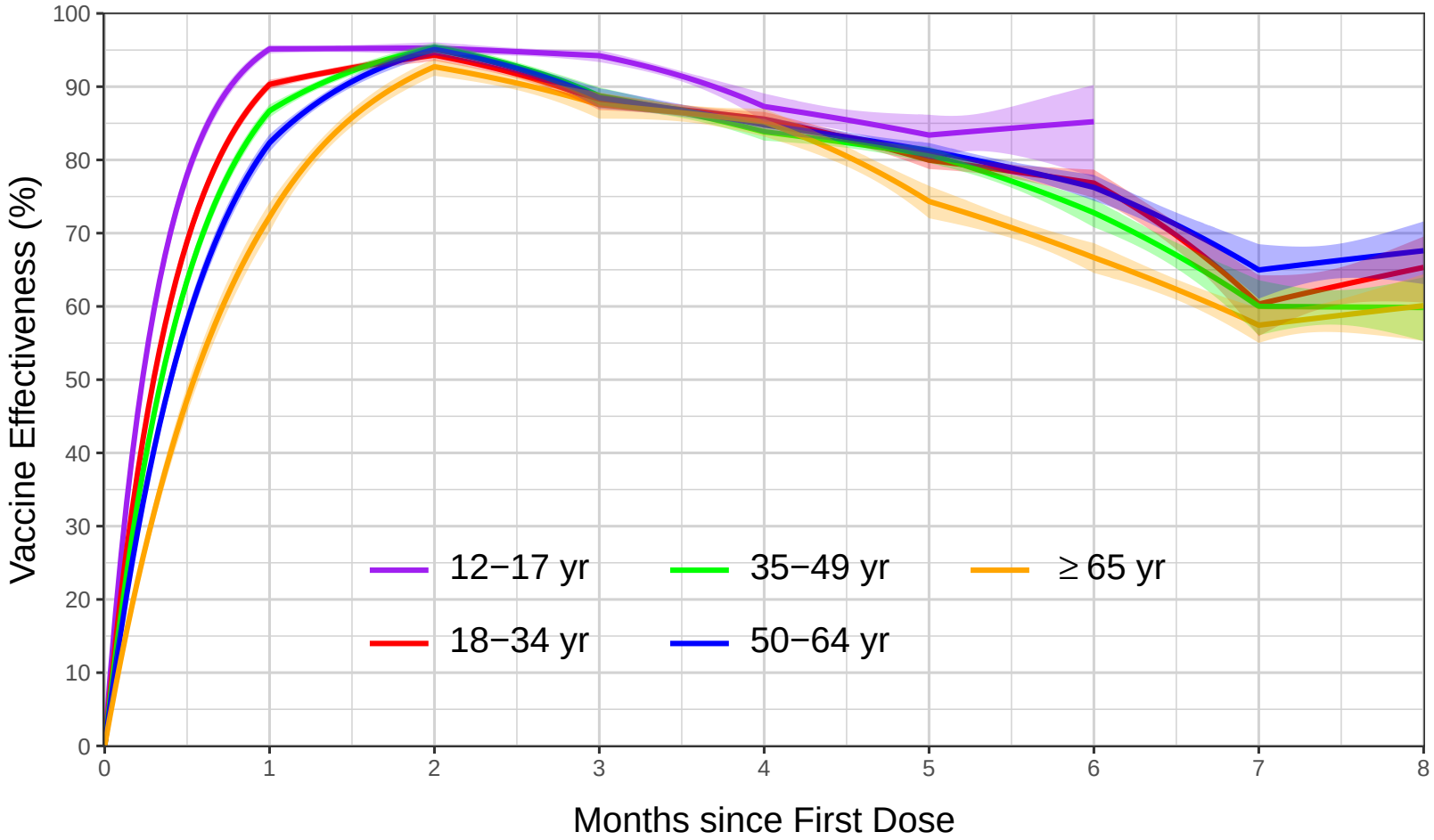

Figure 4: VE of Pfizer Vaccine against COVID-19 by Age Group

Subgroup Analysis

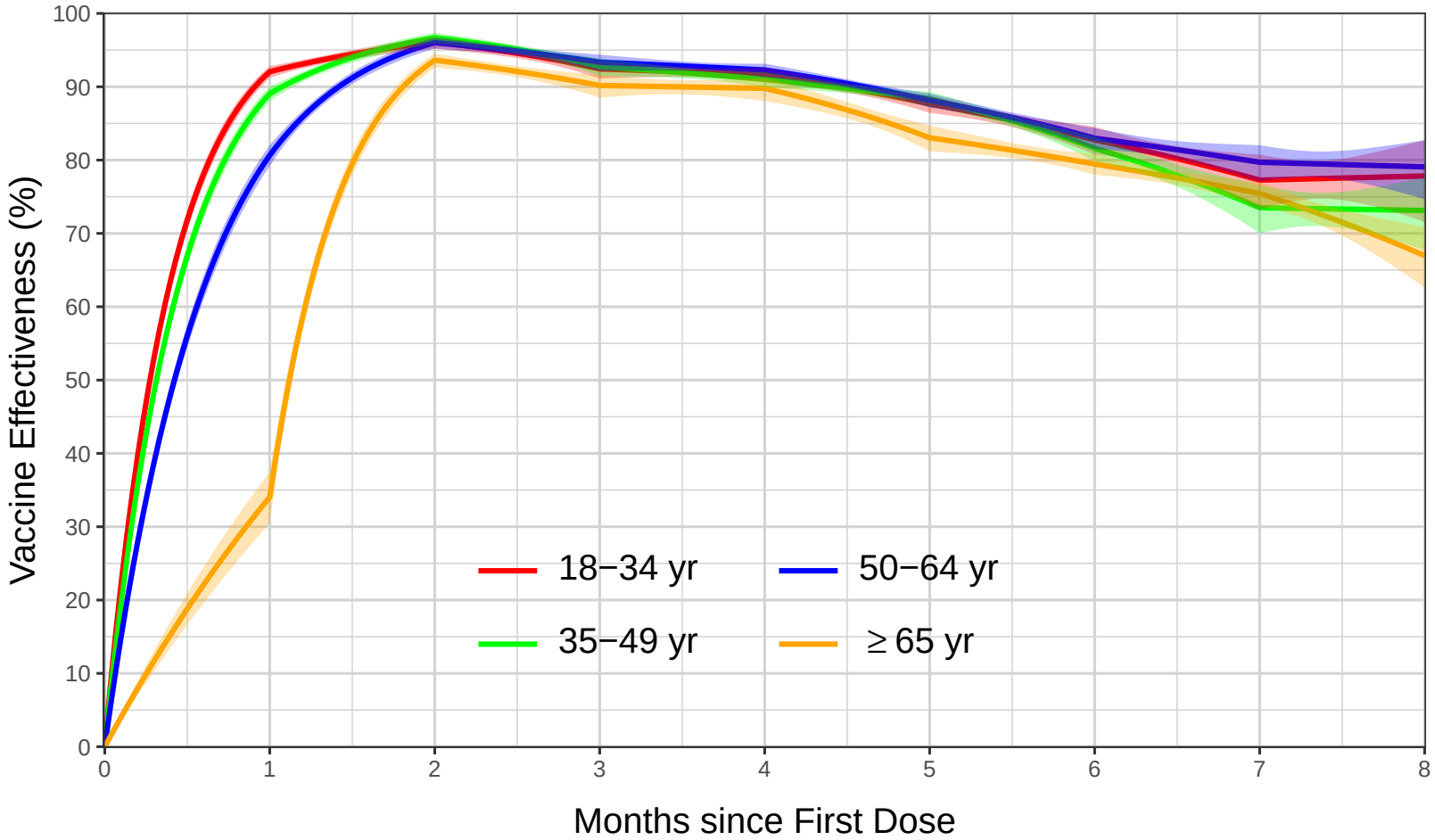

Figure 5: VE of Moderna Vaccine against COVID-19 by Age Group

Subgroup Analysis

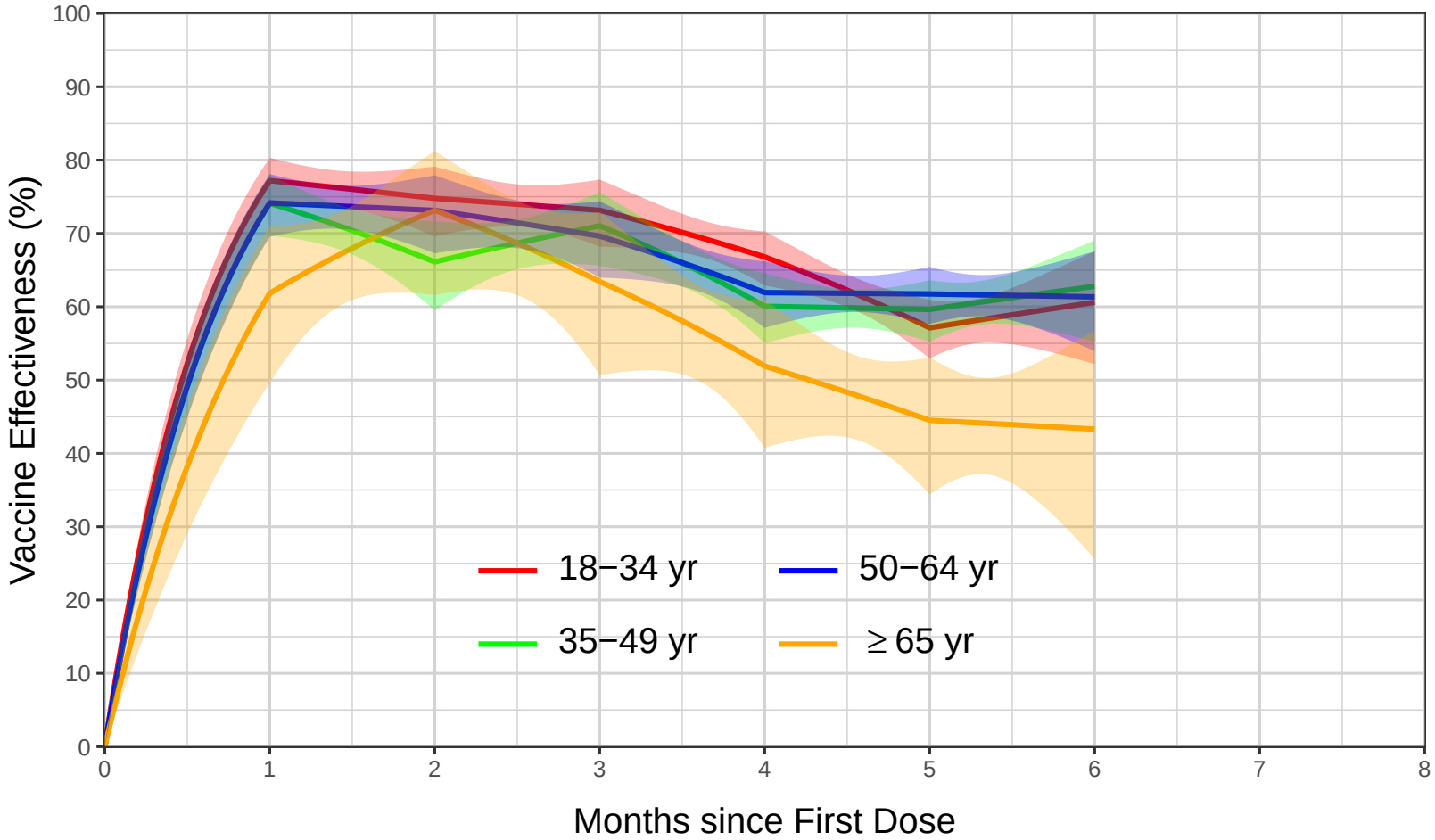

Figure 6: VE of Janssen Vaccine against COVID-19 by Age Group

Current Research

- Effectiveness against omicron infection
- Multiplicative intensity models to account for reinfections
- Effectiveness of primary series over 15 months
- Effectiveness of boosters/second boosters/prior infection

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